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Breaking barriers, bridging gaps: UN World AIDS Day 2023

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Published in
Frontiers in Public Health
Frontiers in Psychiatry

ISSN 1664-8714
ISBN 978-2-8325-7188-0
DOI 10.3389/978-2-8325-7188-0

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Breaking barriers, bridging gaps: UN World AIDS Day 2023

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Citation

Gesesew, H. A., Lambert, J. S., eds. (2025). *Breaking barriers, bridging gaps: UN World AIDS Day 2023*. Lausanne: Frontiers Media SA.

doi: 10.3389/978-2-8325-7188-0

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frontiers | Frontiers in Public Health

TYPE Editorial
PUBLISHED 10 November 2025
DOI 10.3389/fpubh.2025.1728931

OPEN ACCESS

EDITED AND REVIEWED BY
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RECEIVED 20 October 2025
ACCEPTED 24 October 2025
PUBLISHED 10 November 2025

CITATION
Gesesew HA and Lambert JS (2025) Editorial: Breaking barriers, bridging gaps: UN World AIDS Day 2023.
Front. Public Health 13:1728931.
doi: 10.3389/fpubh.2025.1728931

Editorial: Breaking barriers, bridging gaps: UN World AIDS Day 2023

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KEYWORDS

UN Day, AIDS, stigma, HIV diagnosis, HIV prevention, HIV incidence, health systems, HIV delivery

Editorial on the Research Topic
Breaking barriers, bridging gaps: UN World AIDS Day 2023

Background

World AIDS Day is a moment to reflect on both the achievements and the ongoing challenges of the global HIV response—including the decline in new HIV infections and HIV-related deaths, the expansion of antiretroviral therapy (ART) coverage, and the growing concern of drug resistance. At the same time, it reminds us of the remaining obstacles: persistent new infections, unequal progress among populations such as those in conflict-affected or vulnerable settings, and the continuing need for sustained funding and political commitment.

As part of this exploration and in recognition of the United Nations World AIDS Day 2023, by 22 of December 2023, a Research Topic of the Frontiers in Public Health entitled "*Breaking barriers, bridging gaps: UN World AIDS Day 2023*," was opened and a team of scholars has handled the editorial work as guest editors to facilitate the timely peer-review and publication of relevant manuscripts from multiple studies. The Research Topic brings together global scholarship and local experience to reflect on the progress and ongoing challenges in the HIV response.

A total of 19 manuscripts were submitted of which seven were rejected. Twelve manuscripts from 46 contributing authors from Ethiopia (four), Uganda (one), Zambia (one), Kenya (one), Namibia (one), South Africa (one), Thailand (one), and China (two), represent Africa and Asia, two most affected contents by the HIV epidemic, were published between 22 December 2023 and 22 June 2024. Population in the studies included adults living with HIV, adolescents living with HIV and their caregivers, other high-risk populations and older people living with HIV/AIDS.

Together, these works advance our understanding of the multifaceted determinants of HIV care and the innovative approaches being adopted to close gaps in health systems, psychosocial support, and community engagement. By October 2025, the Research Topic achieved 30,000 views and downloads. In this Research Topic, key thematic areas were discussed including but not limited to:

1. Health system readiness and differentiated service delivery (DSD)—Research from Africa, for example, Kaonga et al. from Zambia identified that less than 50% of the facilities had all indicators of availability and readiness, respectively. These findings underscore the importance of capacity building, infrastructure investment, and decentralized care in improving retention and treatment adherence. Community-based DSD models evaluated in Ethiopia (e.g. Merid et al.) and Zambia (e.g. Kaonga et al.) illustrate how such innovations enhance convenience and continuity, particularly for populations with limited access to traditional health facilities.
2. Treatment outcomes, viral suppression, and survival—Research from Ethiopia, Namibia, and China focuses on time to viral load suppression, rapid ART initiation, and determinants of time to death. For example, Chen et al. from China revealed a significant association between rapid ART initiation and reduced risk of viral failure; and Abeje et al. from Ethiopia found that the change in increasing in viral load was high during the latter follow-up period compared to the beginning of the follow-up period.
3. Psychosocial dimensions and stigma—Some contributions explore the complex psychosocial terrain of living with HIV. For example, analyses of body mass index (BMI) and perceived stigma by Desta et al. found that patients with non-adherent to HAART and poor social support were more likely to suffer from HIV-related perceived stigma. Studies on mental phenotypes among individuals with well-controlled HIV by Rubin et al. and on psychosocial and mental health challenges of perinatally infected adolescents by Wanjala et al. bring attention to an often-overlooked aspect of the epidemic—the cognitive, emotional, and developmental impacts that persist even in the era of effective treatment. Work on unsuppressed adolescents and their caregivers further illuminates how familial and community support are essential to sustained engagement in care.
4. Prevention, retention, and the power of hope—Prevention continues to evolve, as reflected in research examining pre-exposure prophylaxis (PrEP) uptake and retention among high-risk populations by Rayanakorn et al.. These insights reinforce the value of differentiated prevention strategies to meet the needs of diverse communities. Finally, a study on hope levels among older people living with HIV by Yu et al. from China captures an important, humanistic dimension of the response—reminding us that the goal of HIV care is not only biological control but also psychological resilience, social inclusion, and dignity in aging.

Conclusion

We hope that our Edited Research Topic provides multidimensional evidence to enhance understanding of the factors affecting HIV care and highlights effective approaches to close gaps within the HIV care system.

Author contributions

HG: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. JL: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – review & editing.

Acknowledgments

We thank all contributing authors and reviewers, and the Frontiers in Public Health journal for offering the Research Topic, and the staff of the publishing house. Their work continues to inspire hope and action toward a more equitable, stigma-free world.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Publisher's note

frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 17 April 2024
DOI 10.3389/fpubh.2024.1371675

OPEN ACCESS

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RECEIVED 16 January 2024
ACCEPTED 29 March 2024
PUBLISHED 17 April 2024

CITATION
Yu C, Wu Y, Zhang Y, Li M, Xie X and Xie L (2024) Hope level and associated factors among older people living with HIV/AIDS: a cross-sectional study.
Front. Public Health 12:1371675.
doi: 10.3389/fpubh.2024.1371675

Hope level and associated factors among older people living with HIV/AIDS: a cross-sectional study

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Background: In China, little is known about the hope level of older people living with HIV/AIDS (PLWHA).[1] This study was to examine the hope level of older PLWHA in China and identify related factors.

Methods: This cross-sectional study was conducted in Sichuan province in China among older PLWHA.[2] A standardized self-report questionnaire, the Herth Hope Index, was adopted. Multiple linear regression was used to identify factors influencing hope level. p-values <0.05 were considered statistically significant.

Results: There were 314 participants with an average age of 64.5 (SD ± 8.7). Most of the participants were males (72.6%), primary school and below (65.9%), rural household registration (58.6%) and married (64.3%). More than half of the older adults had pension insurance, had a monthly income of more than RMB 1,000 and considered themselves to be in good health. About 80% confirmed being diagnosed for more than a year and disclosed their HIV status to family and friends. The majority of the population had low medium social support (79%). More than 80% had moderate and severe HIV stigma. Many older PLWHA had medium and high levels of hope, with an average score of 34.31 (SD ± 4.85). Multiple linear regression showed that having pension insurance ($\beta = 1.337$, $p = 0.015$), longer diagnosis ($\beta = 0.497$, $p = 0.031$), better self-reported health ($\beta = 1.416$, $p<0.001$) and higher levels of social support ($\beta = 2.222$, $p < 0.001$) were positively associated with higher levels of hope. HIV stigma ($\beta = -1.265$, $p < 0.001$) was negatively correlated with hope level.

Conclusion: The hope level of older PLWHA is good, but there is still room for improvement, and its hope is related to multiple factors. Therefore, the AIDS-related healthcare sector should pay special attention to the hope of older PLWHA, help them to improve their health, provide financial assistance and social aid to those with financial difficulties, and take measures to reduce HIV stigma, improve family support for the older adults, and guide the older adults to adopt a positive approach to life.

KEYWORDS

older people, HIV, hope, stigma, social support

1 PLWHA: People living with HIV/AIDS.

2 older PLWHA: Older people of living with HIV/AIDS.

Introduction

There is an increasing trend toward an aging population of people living with HIV/AIDS (PLWHA). Highly active antiretroviral therapy (HAART)[3] has extended the life expectancy of people living with HIV, making AIDS a chronic disease (1). Additionally, HIV infections are soaring among people over the age of 50. According to China CDC Weekly, the proportion of newly HIV-positive males aged 60 and above increased to 18.21% in 2020 (2). There is a growing body of research focusing on issues related to older people living with HIV (PLWHA).

As the UNAIDS 90–90-90 goal for people living with HIV is increasingly being realized in many contexts, the fourth 90, which is to give 90% of people living with AIDS a normal quality of life, has gained increased attention (3). This makes improving the quality of life of people living with AIDS a hot and difficult issue facing public health. One of the challenges in achieving the 4th 90 goal is the mental health of this group. Mental health issues have become the biggest challenge to improving the quality of life of people living with HIV.

AIDS is an incurable, transmissible and stigmatized disease which has a huge physical and emotional impact on those who suffer from it. Mental health problems are common among older PLWHA. Research (4) indicates that older PLWHA are more likely to experience HIV-related stigma and co-morbid mental illness than their younger counterparts. Past studies (5–7) have observed that factors such as HIV stigma, sexual stigma, and age discrimination cause many older PLWHA to experience mood disorders such as anxiety and depression, and that social discrimination and family isolation cause them to lose hope for survival, develop suicidal thoughts, and commit suicidal behavior.

Hope is recognized as an important determinant of mental health recovery (8), which motivates patients to seek treatment. Although hope does not promote healing, it provides the courage to continue to fight for improvement (9). For hopeful patients, the process of facing the disease may be more enjoyable. Hope is a multidimensional and dynamic life force that enables people to look forward to and achieve their individual goals with a positive and optimistic attitude (10). Hope is a protective factor that is thought to be associated with better psychological mental and physical health, better quality of life and well-being, and greater life and happiness (9).

Given the aging trend in PLWHA and the importance of hope, there is a need to understand the level of hope among older people living with HIV which could help healthcare workers take targeted measures to improve their level of hope to promote physical and mental health. To date, almost no studies in China have measured the hope of HIV-infected older people. Thus, the implications of investigating the level of hope among older PLWHA were profound. This study aimed to assess the hope level and related factors for older people in China.

Methods

Study design

This cross-sectional study was conducted in Luzhou City, Sichuan Province from May to October 2021, using the Chinese version Herth Hope Index (HHI), Social Support Revalued Scale (SSRS), simplified Berger HIV Stigma Scale (SBHSS) and questions about the demographic information. The study data were collected in the HIV treatment and management departments of health services. Please refer to the Supplementary material for specifics of the questionnaire.

Participants

Convenience sampling was used in this study because of the state's protection of PLWHA privacy and the difficulty of the general population to have direct access to this group. Due to the necessity of the study, we obtained permission from the regional CDC to sign a privacy and confidentiality agreement and conducted the questionnaire collection in the field with the assistance of the community HIV follow-up manager. We recruited eligible participants on-site, and the researcher provided instructions for completing the questionnaire. After completing the questionnaire, participants were given some household items as a gift for participation. Inclusion criteria for the research subjects: HIV-positive, aged 50 years or older, having clear consciousness and ability to communicate and understand questions, and being willing to participate in research. People with a mental disorder or poor mental health status were excluded.

Ethical approval

The study was approved by the research institution's Human Research Ethics Committee. The researchers signed an AIDS confidentiality agreement. The researcher explained the purpose of the study and its procedures to the participants before the survey. Participants participated in the study voluntarily and could withdraw from the study at any time.

Measures

Chinese version Herth Hope Index (HHI), Social Support Revalued Scale (SSRS) and simplified Berger HIV Stigma Scale (SBHSS) were used. HHI is currently the most widely used scale. It was translated and introduced by Chinese scholar Professor Zhao Haiping in 1999 and has been widely used in research on hope levels in China (11). The scale consists of 3 dimensions and 12 items, which include temporality and future (T), positive readiness and expectancy (P), and inter-connectedness (I). Each question had four Likert-type options: completely disagree, disagree, agree and completely agree, scoring 1–4 respectively, with a total score of 12–48. Questions 3 and 6 had inverted scores. A higher score means a higher level of hope. Levels of hope were classified according to hope scores. A total score of 12–23 is defined as a low level of hope, 24–35 as a medium level of hope and 36–48 as a high level of hope. SSRS was developed by Chinese scholar Xiao (12). The scale has 10 items with a total score of 12–66, which can be divided into three levels of social support: low (≤22), medium (23–33) and high (>45). SBHSS was derived from the Berger HIV Stigma Scale and scholars from Peking University in China simplified the scale (13). The scale has 15 items with a total score of 15. A score of 0 indicated no HIV stigma, 1–5 indicated mild

3 HAART: Highly active antiretroviral therapy.

HIV stigma, 6–10 indicated moderate HIV stigma, and 11–15 indicated severe HIV stigma.

Statistical analysis

The data were analyzed using SPSS version 21. All variables involved in the study and measurement results were analyzed by descriptive statistics according to the type of variables. The continuous variables were subject to normal distribution using Mean and Standard deviation (SD). Categorical variables were statistically described by frequency (percentage). The dependent variable in this study was the total score of hope which was a normal continuous variable. First, the univariate Pearson correlation test was used to screen statistically significant variables. Then the variables that were statistically significant in the correlation analysis were included in the multivariate linear regression analysis. All analyses were two-sided, and p-values <0.05 were considered statistically significant.

Results

A total of 338 questionnaires were distributed in this study, of which 314 were valid, with a valid response rate of 92.9%. Table 1 shows the characteristics of the participants and univariate correlation analysis of hope level. There were 314 participants with an average age of 64.5 years (SD ± 8.7). Most of the participants were males (72.6%), primary school and below (65.9%) and rural household registration (58.6%). 64.3% of participants were married. Older people living alone had a high proportion (32.8%). Most old people had a monthly income of more than 1,000 yuan and more than half of them had pension insurance. About 80% had been diagnosed for more than 1 year. More than half of the older adults rated their health as good and only 28.7% were in the stage AIDS. Nearly 80% had disclosed their HIV status to family and friends. The average score of social support was 28.8 (SD ± 6.9). The majority of the population had low and medium social support. More than 80% had moderate and severe HIV stigma. A majority of participants had medium and a high level of hope. The average score of hope level was 34.31 (SD ± 4.85).

From Table 1, univariate correlation analysis showed that education level ($r = 0.185$, $p = 0.001$), monthly income ($r = 0.241$, $p < 0.001$), having pension insurance ($r = 0.235$, $p < 0.001$), the time diagnosis ($r = 0.120$, $p = 0.034$), self-reported health ($r = 0.410$, $p < 0.001$), and level of social support ($r = 0.237$, $p < 0.001$) were positively associated with higher levels of hope. Gender ($r = -0.115$, $p = 0.041$), household registration ($r = -0.155$, $p = 0.006$) and degree of HIV stigma ($r = -0.269$, $p = 0.015$) were negatively correlated with hope level.

Multivariate analysis: factors influencing hope level of older PLWHA

Multiple linear regression identified factors associated with hope level in older PLWHA (Table 2). Having pension insurance ($\beta = 1.337$, $p = 0.015$), longer diagnosis ($\beta = 0.497$, $p = 0.031$), better self-reported health ($\beta = 1.416$, $p < 0.001$), and higher levels of social support ($\beta = 2.222$, $p < 0.001$) were positively associated with higher levels of hope. HIV stigma ($\beta = -1.265$, $p < 0.001$) was negatively correlated with hope level. The D-W test value is 1.950.

Discussion

The study was special which was conducted during the COVID-19 pandemic, which may have had an impact on participants' psychological states. During the COVID-19 pandemic, factors such as substance use, antiretroviral adherence, social support, financial hardship and economic vulnerability were associated with increased psychological distress of HIV-positive people (14). A study (15) noted that in the COVID-19 epidemic, the occurrence of three negative emotions, inner restlessness, forgetfulness, and exhaustion, were more severe in older AIDS patients than in young and middle-aged patients. Although the COVID-19 epidemic had a negative impact on the psychological status of people living with HIV, the level of hope for older PLWHA in this study remained good.

Our findings suggested that the majority of older PLWHA had moderate or high levels of hope. This is consistent with the results of Chinese studies on the level of hope for PLWHA (16, 17). This result may be due to these facts. First, our study site was in Luzhou, not the center of the COVID-19 outbreak, and the outbreak was not severe. As a result, the local government did not strictly control the city, and ART follow-up treatment of older PLWHA was largely unaffected. Second, ART makes AIDS a chronic disease and reduces the incidence of mortality and related complications. In China, AIDS care policy enables PLWHA to receive free antiviral treatment. In this study, 71.3% of older PLWHA did not progress to the stage of AIDS due to long-term ART. Third, the anti-discrimination publicity of AIDS in various countries around the world has made people have a certain understanding of AIDS, reduced social discrimination of the public against AIDS patients, and thus relieved the psychological pressure on patients. In addition, with the advocacy of the concept of humanistic care, society and AIDS-related healthcare workers (18) attach more importance to the psychological care of PLWHA.

In this study, pension insurance, time of diagnosis, self-reported health status, and level of social support were independent influencing factors for the level of hope. Pension insurance is an important living guarantee for older PLWHA, and those who have it have a stable income every month. As AIDS patients live longer, the potential for other complications and risk factors arises, leading to costly medical care. Studies (19, 20) have shown that complications of AIDS can lead to impaired immune function, which in turn can increase hospitalization rates, hospital expenses, and patients' financial burden. Pension insurance is a crucial financial security. Many older PLWHA no longer have a source of income from work because of their age, and pension insurance may be their main source of income. Therefore, it is necessary to pay attention to the pension insurance situation of older adults PLWHA, and for those who have no pension insurance and are in poor economic conditions, the government and society could provide economic assistance and social aid, to help the patients raise their level of hope and to promote the

10.3389/fpubh.2024.1371675

TABLE 1 Characteristics of the participants and univariate correlation analysis of hope level (n = 314).

Variables	Frequency, n (%)	Pearson's correlation (r)	p-value
Gender		−0.115	0.041
Male	228 (72.6)		
Female	86 (27.4)		
Age (years)		−0.012	0.832
50–59	105 (33.4)		
60–69	113 (36.0)		
70–79	84 (26.8)		
≥80	12 (3.8)		
Education level		0.185	0.001
Primary school and below	207 (65.9)		
Junior high school	76 (24.2)		
Senior high school	24 (7.6)		
Junior college and above	7 (2.2)		
Household registration		−0.155	0.006
Urban	130 (41.4)		
Rural	184 (58.6)		
Marital status		−0.064	0.259
Married	202 (64.3)		
Divorced or widowed	99 (31.5)		
Unmarried	13 (4.1)		
Whether is living alone		−0.034	0.544
Yes	103 (32.8)		
No	211 (67.2)		
Monthly income (yuan)		0.241	<0.001
<1,000	116 (36.9)		
1,001–2000	89 (28.3)		
2001–3,000	44 (14.0)		
3,001–4,000	40 (12.7)		
>4,000	25 (8.0)		
Pension insurance		0.235	<0.001
Not have	117 (37.3)		
Have	197 (62.7)		
Diagnosis (years)		0.120	0.034
<1	61 (19.4)		
1–3	140 (44.6)		
3–5	43 (13.7)		
>5	70 (22.3)		
Self-rated health		0.410	<0.001
Very poor	11 (3.5)		
Poor	46 (14.6)		
Fair	85 (27.1)		
Good	109 (34.7)		
Very good	63 (20.1)		
Whether is in the stage of AIDS?		0.047	0.404

(Continued)

TABLE 1 (Continued)

Variables	Frequency, n (%)	Pearson's correlation (r)	*p*-value
No	224 (71.3)		
Yes	90 (28.7)		
Have you disclosed your HIV status to family and friends?		0.000	0.998
No	69 (22.0)		
Yes	245 (78.0)		
Social support level		0.237	<0.001
Low (score ≤ 22)	63 (20.0)		
Medium (score 23–44)	248 (79.0)		
High (score > 45)	3 (1.0)		
Degree of HIV stigma		−0.269	<0.001
No (score = 0)	1 (0.3)		
Mild (score 1–5)	42 (13.4)		
Moderate (score 6–10)	119 (37.9)		
Severe (score 11–15)	152 (48.4)		
Level of HIV hope		-	-
Low (score 12–23)	6 (1.9)		
Medium (score 24–35)	177 (56.4)		
High (score 36–48)	131 (41.7)		

TABLE 2 Multivariate analysis of hope level in patients with older PLWHA ($n = 314$).

Variables	β	SE	β′	t	*p*-value
(Constant)	25.188	2.202	–	11.437	<0.001
Gender	−0.356	0.533	−0.033	−0.668	0.505
Education level	0.180	0.367	0.027	0.489	0.625
Household registration	0.328	0.565	0.033	0.581	0.562
Monthly income (yuan)	0.311	0.225	0.083	1.387	0.167
Endowment insurance	1.337	0.547	0.133	2.444	0.015
Diagnosis (years)	0.497	0.229	0.106	2.167	0.031
Self-rated health	1.416	0.236	0.314	5.996	<0.001
Level of social support	2.222	0.566	0.191	3.926	<0.001
Degree of HIV stigma	−1.265	0.337	−0.187	−3.757	<0.001

$F = 10.372$, $p < 0.001$; VIF: 1.029–1.314; $R^2 = 0.235$; D-W test value is 1.950.

patients' mental health, which in turn will improve their ability to cope with the disease.

In this study, the duration of HIV diagnosis was a protective factor affecting the level of hope. This is contrary to the findings of another study (21) that the longer the disease, the lower the level of hope. Firstly, this may be because, as the disease progresses, older PLWHA have a reduced fear of AIDS, revisit the issue of life and death, and value life more, hence their level of hope is higher. Secondly, compared to other diseases, the country has invested a lot of resources in AIDS prevention and control, and infected people can receive free AIDS treatment drugs. Therefore, even if the duration of the disease is prolonged, patients have basic guarantees for medical treatment and thus have a higher level of hope. This suggests that we can use peer support to conduct a hope intervention for older PLWHA with low hope (22). Let the older PLWHA with long diagnosis and high hope participate in peer assistance and encouragement of the older PLWHA with low hope.

The better the self-reported health status of the older PLWHA, the higher their level of hope. Scioli et al. (23) demonstrated that the total hope scores and hope sub-scores were significantly correlated with various dimensions of self-reported health status, which is consistent with our findings. This may be because the better the self-rated health of the older adults, the less burden of AIDS-related symptoms they are likely to bear and the less impact the disease has on the older adult person's life. Hope is an emotion that may exert powerful effects on health (23, 24). Health

promotes hope and hope influences health, thus achieving a virtuous circle. Therefore, AIDS healthcare personnel should pay attention to the self-reported health status of older adult patients to help patients improve their health and reduce the impact of the disease, to increase their level of hope.

HIV stigma and discrimination are widespread, and older PLWHA are more likely to experience ageism and sexual stigma (the sexual life of older people is considered shameful and indecent) than younger people living with HIV (5, 6).

Poor mental health due to stigma and discrimination has been well documented among people living with HIV. Thus older PLWHA with higher HIV stigma had lower level of hope. We found that older PLWHA with higher HIV stigma and lower social support have lower hope levels. Hope was also found to be positively associated with social support in other studies (24, 25). Older PLWHA have limited social networks, and in the cultural context of family responsibilities in China, family support is an important resource for older adults, who rely heavily on their families for psychosocial, financial, and caregiving support (6). Therefore, there is a need for interventions to reduce HIV discrimination in society and reduce the HIV stigma of older PLWHA. It is also important to improve family support for older PLWHA, and there is a need to monitor family members' fulfillment of their maintenance obligations to the older adults (especially older PLWHA with low family support) and to develop family-centered measures to cope with HIV infection, to increase the level of hope for the older adults.

Our study has several strengths and limitations. To our knowledge, our study is the first study to examine the hope level of older PLWHA. But as a cross-sectional study design, this study also has several limitations. First, a definite causal relationship is difficult to obtain from a cross-sectional analysis. Second, the study was conducted in one city in China and used convenience sampling, which made the sample underrepresentative. Finally, this study ignored the possible effect of the COVID-19 epidemic on participants' hope levels. In the future, multi-center large-scale research could be conducted in conjunction with other institutions. And longitudinal studies could be taken to track hope over time with age. Exploring the role of hope in the HIV care continuum for older PLWHA would also be meaningful.

Conclusion

Older PLWHA had medium and high levels of hope. The AIDS healthcare health sector could use the factors influencing the level of hope of older PLWHA as an entry point to take effective measures to provide financial assistance to those in financial difficulty, help patients improve their health, reduce HIV stigma, and improve family support, thereby increasing the level of hope of patients.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Ethics Committee of the Affiliated Hospital of Southwest Medical University. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

CY: Writing – original draft, Methodology, Funding acquisition. YW: Writing – review & editing, Validation, Resources. YZ: Writing – review & editing, Conceptualization, Software. ML: Writing – review & editing, Methodology, Formal analysis, Software. XX: Writing – review & editing, Supervision, Project administration. LX: Writing – review & editing, Data curation, Investigation.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This research was supported by the Primary Health Development Research Center of Sichuan Province Program (SWFZ21-Q-51) and the Sichuan Hospital Management and Development Research Center, Southwest Medical University (SCYG2021-21).

Acknowledgments

The authors are grateful to all patients who participated in this study and the Centers for Disease Control and Prevention for their support of this program.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1371675/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 15 May 2024
DOI 10.3389/fpubh.2024.1366754

OPEN ACCESS

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RECEIVED 18 January 2024
ACCEPTED 03 May 2024
PUBLISHED 15 May 2024

CITATION
Rayanakorn A, Chautrakarn S, Intawong K, Chariyalertsak C, Khemngern P, Olson D and Chariyalertsak S (2024) Experiences and challenges of pre-exposure prophylaxis initiation and retention among high-risk populations: qualitative insights among service providers in Thailand.
Front. Public Health 12:1366754.
doi: 10.3389/fpubh.2024.1366754

Experiences and challenges of pre-exposure prophylaxis initiation and retention among high-risk populations: qualitative insights among service providers in Thailand

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Objectives: Pre-exposure prophylaxis (PrEP) has been an essential element of the national combination prevention package and included in the Universal Health Coverage (UHC) of Thailand since 2019. As a part of the national monitoring and evaluation framework, this qualitative study aims to describe experiences and barriers concerning PrEP initiation and retention among service providers from both hospital and Key Population Led Health Service (KPLHS) settings under the country's UHC roll-out.

Methods: Between September and October 2020, ten focus group discussions with PrEP service providers from both hospitals and KPLHS across Thailand were conducted of which there were six hospitals, one health service center, three KPLHS. All interviews were recorded and transcribed *verbatim* to identify providers' experiences, attitudes, and perceived barriers regarding PrEP service delivery in Thailand.

Results: Among the 35 PrEP service providers, most of them reported positive attitudes toward PrEP and believed that it is an effective tool for HIV prevention. Men who have sex with men were perceived to be the easiest group to reach while PrEP uptake remains a challenge in other key populations. Integration of a PrEP clinic with other HIV services at hospitals made most healthcare providers unable to adopt an active approach in recruiting new clients like at KPLHS settings. Challenges in delivering PrEP services included lack of public awareness, high workload, limited benefit package coverage, structural and human resources.

Conclusion: Additional services to address different health needs should be considered to increase PrEP uptake among harder-to-reach populations. Novel approaches to PrEP service integration and close collaboration between hospitals and KPLHS would be essential in optimizing PrEP uptake and retention. Support regarding raising awareness, expanding service coverage and access, improving facilities and workforce, and providers' capacities are crucial for the success of the national PrEP programme.

KEYWORDS
HIV, prevention, pre-exposure prophylaxis, PrEP, service provider, Thailand

1 Introduction

In the past three decades, Thailand has made remarkable progress toward Human Immunodeficiency Virus (HIV) treatment and prevention. These include the "100 Percent Condom Program" among commercial sex workers in 1991 (1) and the country's clinical trials of antiretroviral therapy (ART) to prevent mother-to-child HIV transmission (2). This has culminated in a significant reduction in HIV incidence rates and made Thailand the first country in Asia to eliminate new HIV infections among newborns in 2016 (1, 3). In 2005, the Thai government included ART into the Universal Health Coverage (UHC)'s benefit package, followed by compulsory licensing for the antiretroviral drugs (ARV), efavirenz (EFV) and the lopinavir/ritonavir (LPV/r) ARV combination in 2006 and 2007, respectively (4).

Despite numerous achievements, there has been slow progress in scaling up the service. HIV prevalence has been increasing among key populations who have high risk of HIV infections, including men who have sex with men (MSM), transgender women (TGW), sex workers (SWs), and people who inject drugs (PWID) while the proportion of people living with HIV (PLWHIV) who achieved virological suppression is still relatively small (5, 6). In 2021, with the total population of 71.6 million, it has been estimated that there were around 530,000 PLWHIV, 6,500 new HIV infections, and 9,300 HIV-related deaths in Thailand (7). HIV prevalence among adults aged 15–49 years old was around 1% (7) with higher proportions among individuals who are at high risk: 1.1% among female sex workers, 3.8% among male sex workers, 4.2 among TGW, 7.3 among MSM, and 7.8% among PWIDs (8). As part of the country's commitment to end AIDS epidemic by 2030 following the World Health Organization (WHO) and the Joint United Nations Programme on HIV/AIDS (UNAIDS)' global strategy initiative, the Thai government has set a number of priorities within the National AIDS Strategic and Operational Plan including expanding ARV access to all HIV-infected Thai nationals regardless of CD4+ level (9) and initiating the first fee-based HIV pre-exposure prophylaxis (PrEP) program in 2014 (10). Since then, PrEP has been an essential element of the national combination prevention package and included into the UHC in 2019 (5, 11). PrEP service in Thailand can be provided either from healthcare providers at hospitals or at Key Population Led Health Services (KPLHS) where the service is usually delivered by trained lay providers who are members of key populations. The KPLHS model was established in 2015, under the context of KP-leadership which means the services addressing key health issues identified KP members were provided under a "needs-based, demand-driven, and client-centred" approach to ensure non-judgmental and stigma-free environment (12–14). Currently, KPLHS provide the majority of PrEP services accounting for 82% of PrEP users in Thailand (15). The number has increased more than double since the introduction of KPLHS in 2019.

In 2020, the National Health Security Office (NHSO) launched a pilot project to provide PrEP for 2,000 new clients at 50 PrEP service centers across the country. To date, few qualitive studies have been conducted on PrEP services and are largely based on patients' perspective (16, 17). This qualitative study was conducted to explore insights of service providers across Thailand from two PrEP service delivery models (hospital and KPLHS settings). As a part of the national monitoring and evaluation framework to evaluate early adoption of the country's PrEP service under the UHC, this qualitative study aims to describe experiences and barriers concerning PrEP initiation and retention under service providers' perspectives from both hospital and KPLHS settings as well as their foreseeable challenges in scaling up PrEP service and suggestions to overcome them. This is critical to inform the improvement of the national PrEP service and the development of a combined HIV prevention package, especially among individuals at high risk and key populations.

2 Methods

2.1 Study settings

We conducted 10 focus group discussions (FDGs) with 35 service providers from 10 PrEP centers participating in the NHSO's PrEP pilot project: 6 hospitals, 1 health service center, 3 KPLHS. These facilities were from 5 provinces (Chiang Mai, Udonthani, Songkla, Ratchaburi, and Bangkok) across 4 regions in Thailand. The study was reviewed and approved by the Research Ethics Committee, Faculty of Public Health, Chiang Mai University (Document No. ET017/2020).

2.2 Data collection

We conducted focus group discussions from September to October 2020 using a semi-structured interview guide developed by the research team to capture further insights not covered in the quantitative self-administered online survey (18). The earlier quantitative study included service providers from all 50 active PrEP centers across the country (18). The main content of the predetermined interview guides is presented in Table 1.

A purposive sampling was used to recruit participants from PrEP service centers with over 10 active PrEP clients and 1 year of experience from different service delivery models and geographical settings. Eligibility criteria included presently providing PrEP service at either hospital or KPLHS with PrEP clients' engagement for over 6 months. All participants were contacted through their center contact lists, provided by the Center for Disease Control and Prevention, Ministry of Public Health (MoPH) and screened for eligibility. Sample size was determined by saturation of information, and extensive discussions with the study team members which would be finalized by the principal investigator (SC) who has extensive experience in this area.

Each focus group was comprised of 2 to 6 service providers working at the selected PrEP centers. All interviews were conducted in Thai either face-to-face or virtually led by the principal investigator. Interviewers explained about the study, objectives, and asked for participants' consent verbally before starting the interview. Each interview lasted between 60 to 120 min and was recorded. The audio recordings were transcribed *verbatim*. Each participant was compensated with 300 Thai Baht ($8.66 USD) for their time.

TABLE 1 Interview guides.

(1)	When did your center start providing PrEP service? Why did your center decide to participate as a PrEP service center?
(2)	What are the sources of funding for PrEP service at your center?
(3)	How many personnel are responsible for PrEP service at your center? Who are they?
(4)	How often does your center provide PrEP service? How many days per week? Do you think this is too much or too little?
(5)	What is the service delivery model used by your center? What are the pros and cons to the use of this model?
(6)	Who are your main clients?
(7)	How do you generally recruit PrEP clients at your center?
(8)	Which population groups are the most difficult to reach for your center? Why?
(9)	How does your center perform in terms of recruitment and retention?
(10)	How do you work with hospitals/KPLHS in your area? In your opinion what improvements are needed to fill gaps in PrEP service delivery?
(11)	How do you evaluate the candidate's eligibility if they want to take PrEP? Do you think the criteria should be made easier or harder? Why?
(12)	How do you monitor and follow up on your PrEP clients?
(13)	What are challenges and barriers in providing PrEP service?
(14)	What kind of support would be helpful to improve the PrEP programme?

2.3 Data analysis

Analyses of transcripts to identify providers' perceived barriers concerning PrEP services and PrEP users' perceptions were reviewed and summarized by two project team members in which disagreements were resolved through discussion and consensus. Braun and Clarke's thematic approach involving six steps (familiarization with the data, generating codes, searching for themes, reviewing themes, defining and naming themes, and locating exemplars) was applied where the data was initially given a new thematic code without having to fit any pre-existing themes. The themes later emerged and were linked through the data (19). Transcription relating to barriers and key success/failures concerning PrEP implementation were listed. The completed list of categories and data extraction were reviewed by an additional investigator for clarification, presentation, and detail. Then the final list and transcripts were summarized for write-up.

3 Results

3.1 Respondent characteristics

Ten focus groups were conducted among 35 service providers engaging in PrEP services from Chiang Mai, Udonthani, Songkla, Ratchaburi, and Bangkok. Among these, 21 participants were from hospital or government health service centers whereas 14 were from KPLHS which were Rainbow Sky Association of Thailand (RSAT), Service Workers in Group (SWING), and MPlus (Table 2). More than half of the participants reported as female (54.3%) while 45.7% reported as males. Forty percent of the participants were PrEP counselors from KPLHS settings (14 of 35) whereas all participants from hospitals were reported as healthcare practitioners (HCPs) of which the majority were nurses (16 of 35; 45.7%), followed by physicians (3 of 35; 8.6%) and pharmacists (2 of 35; 5.7%) respectively.

TABLE 2 Respondent demographics.

Sociodemographic characteristics ($N = 35$)	Overall (%) ($N = 35$)
Settings	
Hospital	17 (48.57)
Health service center	4 (11.43)
Key Population Led Health Service (KPLHS)	14 (40.00)
Gender	
Male	16 (45.71)
Female	19 (54.29)
Primary occupation role	
Nurse	16 (45.71)
Physician	3 (8.57)
Pharmacist	2 (5.71)
Others, e.g., PrEP counselor/coordinator, KPLHS manager	14 (40.00)

*At KPLHS, PrEP counseling is generally provided by trained lay providers who are not HCPs whereas blood collection/sampling is done separately by technicians who are not engaged in PrEP counseling.

3.2 Qualitative findings

Five thematic areas emerged: Decision to engage in PrEP service, service delivery, clients' recruitment, monitoring and retention, and challenges and recommendations to improve PrEP program. The key insights of each thematic area are detailed below.

3.2.1 Decision to engage in PrEP service

The main reasons to participate as a PrEP service center were high-HIV prevalence, high proportion of key population who are at high risk, no other PrEP center in the area, and proximity to key populations. Some hospitals were selected to join the pilot program because they had experience in offering HIV and sexual transmitted disease (STD) services with availability of ARV clinic in place. Most providers reported that PrEP service was an effective tool to prevent HIV transmission:

> *'PrEP is another tool apart from condoms to prevent HIV infection'.* (Male PrEP counsellor).

> *'We have many HIV cases. Prescribing medication for prevention should be better than taking ARV'*. (Female HCP).

> *'The center was selected to join the pilot program because we are close to BTS [convenient for key populations]'*. (Female HCP).

3.2.2 Service delivery

At the hospital setting, PrEP service was generally integrated with HIV Voluntary Counseling and Testing and ARV clinic while at KPLHS, PrEP clinic was usually run separately. All KPLHS offered same day PrEP service where providers dispensed PrEP medication to the clients on the first visit date and PrEP users would be later contacted in case there were any abnormal laboratory findings while some hospitals dispensed PrEP on the next day after obtaining the laboratory results. This was raised as a limitation in recruiting new clients by some providers:

> *'The distinction between two service delivery models is that at hospital, we have limited medication supplies unlike at KPLHS that PrEP can be offered on the same day without having to wait for lab results [which is more convenient]. On the next day, patients may not come back'*. (Female HCP).

Many providers noted 'same day PrEP' as an advantage in reaching and recruiting new cases:

> *'Same day PrEP helps to close the gap and make PrEP more accessible to potential clients'*. (Male PrEP counsellor).

Most KPLHS started their PrEP clinic in the afternoon until evening while majority of hospitals' PrEP clinic operated during office hours. The clinic's working hours were also crucial to make the service accessible to clients, especially key populations:

> *'It takes a long time to wait at the public hospital. The operation time [which is the office hours] is not convenient for clients [who are key population]'*. (Male HCP).

> *'Apart from convenience, visiting the clinic after office hours can also avoid stigmatization'*. (Male HCP).

Both hospital and KPLHS providers agreed that pharmacies might not be appropriate for PrEP provision due to their concerns regarding venue space to allow privacy and confidentiality and monitoring of laboratory tests:

> *'VCT [Voluntary Counseling and Testing] is needed for screening. I am concerned about how this will be done at pharmacies'*. (Male KPLHS provider).

> *'It is possible [to have PrEP delivered at pharmacies] among those who have good adherence. However, I think they'd prefer [receiving PrEP] at hospital because of their concern regarding confidentiality'*. (Female HCP).

> *'[At pharmacy], it can be double-edged sword as we do not know their blood testing results. It may be fine for refilling medication, but clients still need to visit hospital to follow up on their laboratory tests…'*. (Male HCP).

3.2.3 Clients' recruitment and target PrEP users

Different PrEP client recruitment strategies were employed (Figure 1). PrEP clients were referred from hospital STD/ARV, and antenatal care (ANC) clinics as well as recruited from KPLHS via Voluntary Counseling and Testing (VCT), friend's referral and social media platforms. PrEP counselors at KPLHS actively screened and identified high-risk populations through mobile VCT and multiple social media platforms while healthcare providers at hospitals generally adopted a passive approach preferring potential PrEP users to present themselves at the facilities or having them referred from other clinics, e.g., STD/ARV clinic and ANC. Few hospital providers mentioned their involvement in mobile VCT with limited success as many potential PrEP users were concerned about HIV testing and were unprepared to know their infection status:

> *'We've been to many places [to promote PrEP] including military barracks, 5 schools/vocational institutions, and juvenile observation and protection centers. The only places left [that we have not been to] are entertainment venues [but no one was interested in taking PrEP]'*. (Female HCP).

> *'Some people are afraid to have their blood taken for HIV testing. When they were told that they needed to undergo HIV testing [before being prescribed PrEP], they said no.'* (Female HCP).

Sex workers and people who use drugs were perceived to be the most difficult to reach groups. Many providers expressed challenges in reaching these populations:

> *'The form of commercial [sex] service has been changed. They are now online instead of physically available at entertainment venues [so it is harder to reach sex workers for Voluntary Counseling and Testing].'* (Male PrEP counsellor).

> *'We tried to convince all cases we have at drug addiction clinic to take PrEP but no one was interested'*. (Male HCP).

> *'People who use drugs are the most unprepared [among all high-risk groups]. They are not ready to cooperate and adhere to medication. It is also not convenient for them to come to hospital'*. (Female HCP).

> *'Currently, we do not have any PrEP users who are drug users. They are a very closed group [not open to any outsiders]'*. (Female HCP).

Apart from that, some providers reported having new clients through friends' referrals and individuals who were HIV Post-exposure Prophylaxis (PEP) users:

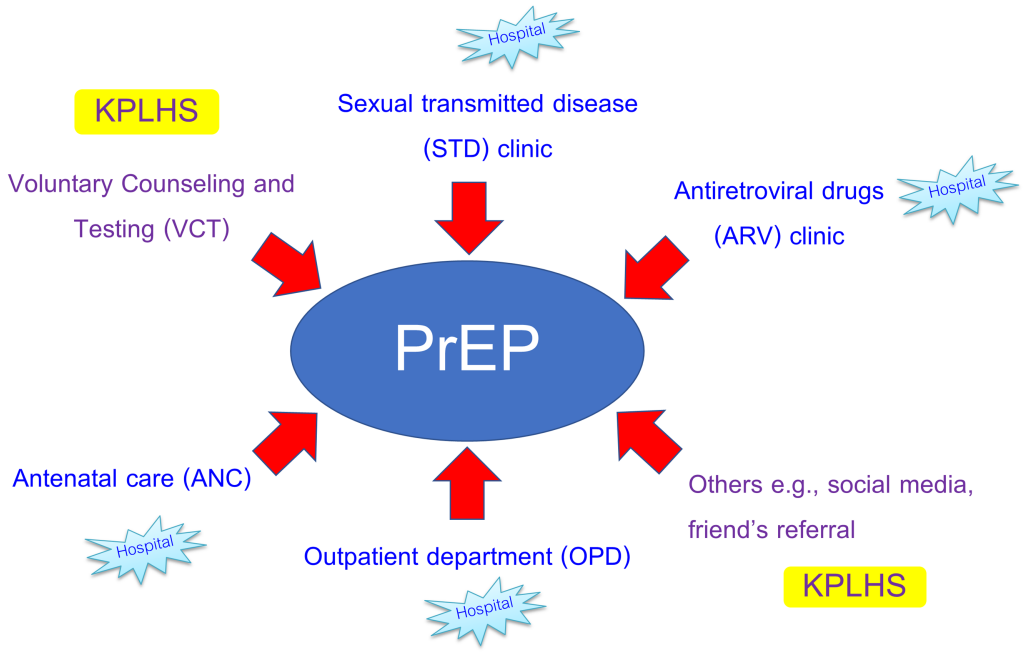

FIGURE 1
Channels for PrEP client recruitment between hospital and KPLHS settings.

> *'We will tell them [PEP users] that it is the continuing program from PEP to PrEP among those who are interested. We will convince most of our PEP clients to continue taking PrEP'*. (Male PrEP counsellor).

> *'I normally inform my clients that they will be prescribed PrEP after taking PEP medication and ask whether they agree with that. This is because they are at high risk and may continue having that risk [of HIV infection]. That's why they take PEP. If they are ok, I will dispense PEP. It is like we have an agreement together'*. (Male PrEP counsellor).

Most PrEP users at hospitals were heterosexual individuals who had HIV-positive partners or were referred from other clinics including STD and ANC. On the contrary, most clients at KPLHS were from key populations mainly men who have sex with mem (MSM) individuals followed by transgender women (TGW). Most KPLHS providers felt that MSM were the easiest to reach group as they generally had good knowledge about PrEP and perceived themselves as having a high risk of HIV infection.

> *'MSM are the easiest. They are the majority of our clients. They are knowledgeable, educated and have a wide network where they also refer their friends to take PrEP. Taking PrEP is even a plus to their profiles in some online dating applications'*. (Male PrEP counsellor).

Most counselors recognized TGW as a more difficult to reach group due to their usage of hormone therapy which might be a barrier to concomitantly take PrEP in the long term:

> *'TGW are afraid that they may forget to take PrEP because they take a lot of medications [including hormone therapy] concomitantly and have concern that they cannot adhere to medication'*. (Male PrEP counsellor).

Some KPLHS counselors mentioned that TGW perceived that they had lower risk for HIV acquisition compared to MSM:

> *'TGW have undergone sex reassignment surgery. They have sexual intercourse through their vagina and consider themselves to have lower risk [compared to MSM] in acquiring HIV infection'*. (Male PrEP counsellor).

In contrast, healthcare providers from hospital settings who also provided PrEP to inmates discerned TGW in prison to be an easier to reach population as they did not take any hormone therapy and felt comfortable talking to female healthcare providers:

> *'TGW are easier to reach [compared to other key populations]. They see us as their sisters'*. (Female HCP).

3.2.4 PrEP clients' monitoring and retention

Most participants reported that over half of their clients could stay on PrEP for over 6 months of which the majority were MSM, followed by negative partners of serodiscordant couples. At hospitals, PrEP users were usually followed up according to routine practice without any reminders/frequent contacts whereas at KPLHS, PrEP clients were followed up more closely through online platforms:

> *'Patients can book their appointments through the website [take me now] and they will get SMS to confirm their appointments'*. (Male KPLHS provider).

> *'We do not have any reminders, but we phone them if they do not show up at their follow-up visit'*. (Female HCP).

> *'We also have line official where we work with the responsible pharmacist to respond to their inquiries regarding medication(s)'*. (Male HCP).

The main reasons for loss to follow-up reported were relocation and changes of sexual risk behaviors:

> *'Relocation of their workplace is one of the major problems that make them (PrEP users) cannot come for follow-up visit'*. (Female HCP).

Most providers expressed the sentiment that maintaining good relationships and rapport with clients was essential for retention.

> *'Building good relationships is key to engage them to come back for follow-up'*. (Female HCP).

3.2.5 Challenges and recommendations to improve PrEP program

Many providers from hospital settings expressed the lack of structural resources and manpower as significant issues hindering PrEP service delivery. Integration of PrEP service with ARV, STI clinics and Voluntary Counseling and Testing at hospital settings had culminated in high workloads which impeded active screening and counseling of high-risk individuals for PrEP initiation and retention:

> *'At hospital, we have limited manpower, so the provider-client relationship is not as close as at KPLHS'*. (Female HCP).

> *'Our center is a two-storey building which has very limited space but serving over a thousand of patients'*. (Male HCP).

> *'The service at hospital usually has very limited space which does not allow enough privacy [for key population]'*. (Male KPLHS provider).

Most providers felt that PrEP was not widely known and there was a need to raise awareness about PrEP among healthcare providers and the general population:

> *'PrEP is something new to healthcare providers who are not involved in PrEP. Even hospital staff who are not involved [in PrEP] do not know anything about it. We need to raise awareness and educate HCPs more'*. (Female HCP).

> *'Very few people know about PrEP and have access of which most users are MSM. Promoting and publicizing [PrEP] might have been done too little. PrEP is not available at all hospitals. Therefore, access is limited in some settings. As many people are not aware about PrEP, when we promote it to outsiders, we can only get some certain groups and cannot make it accessible to a wider population'*. (Female, HCP).

Notably, some providers were concerned about the perception of other healthcare providers regarding PrEP that it might result in sexual risk compensation:

> *'[Some] doctors disagree to use PrEP. They think this will make clients less likely use condoms'*. (Female HCP).

Healthcare providers additionally expressed their high workload concerning data entry in different programs and called for a single system to avoid repetitions of work and overlapping data as well as the need for condoms and lubricant supplies:

> *'The programs were complicated, and I had to work outside of office hours to enter similar information'*. (Male HCP).

> *'Condoms are sufficient for the size that we do not want (49″) while the size that we want (52″, 54″, and 56″) are not provided'*. (Female HCP).

To increase PrEP uptake, healthcare providers suggested a seamless process to allow same day PrEP and a referral system in case of clients' relocation:

> *'[I] would like the hospital to have more supplies in our stock so that we can dispense PrEP right away […] Then we only phone them in case of abnormal laboratory findings such as […]. This should be more convenient for clients as they may not come back to be informed about the results of their blood test'*. (Female HCP).

To increase PrEP uptake among TGW, some providers suggested having additional services such as feminizing hormone therapy counseling for TGW and emphasized the need for training of PrEP providers to support TGW's specific health concerns:

> *'There should be educational materials concerning feminizing hormone therapy and its potential drug interactions [with PrEP] for TGW'*. (Male KPLHS provider).

Finally, when asked about prioritizing groups to receive PrEP, participants reported that PrEP should be given to all high-risk individuals or any person who would like to take it including a non-Thai citizen:

> *'PrEP should be available to all who want to take it even non-Thai citizens as [some] of these individuals also have Thai partners. In case we do not do well for preventive measures, this can also be the burden of our health system'*. (Female HCP).

4 Discussion

The aim of this study is to understand how to improve the national PrEP service and overcome foreseeable challenges in scaling up PrEP services in Thailand. Our findings have identified themes which have promising implications for improvement and expansion of the PrEP program among key populations and individuals at high-risk. Overall,

most service providers reported positive attitudes toward PrEP and perceived it as an effective tool for HIV combination prevention program. This is consistent with the previous quantitative study (18). However, challenges remain at the micro-level management and service integration with opportunities to scale up the service among key populations.

Differences between the delivery model used at KPLHS and the model used at hospital settings have significant impact on their PrEP service operation and approach in reaching new clients. KPLHS's primary focus on PrEP allows KPLHS providers to adopt an active approach in reaching and recruiting potential new users through VCT and mobile PrEP. In addition, extensive PrEP promotion through social media/online platforms and availability of 'same day PrEP' at KPLHS are also their key success factors in recruiting many new clients. On the contrary, the integration of PrEP service with HIV and STD services at hospital settings may impose a high workload on healthcare providers making them prefer a more passive approach which may be ineffective for PrEP uptake. More collaboration between hospitals and nearby KPLHS for cases' referral and recruitment is essential for a seamless process and expansion of PrEP service access.

The hours that PrEP service is available is also important in engaging potential clients. Flexible operation times at KPLHS makes the service more accessible among key populations compared to hospitals where PrEP service is usually provided only during office hours. According to some service providers in our study, accessing PrEP service outside office hours is a feasible way to avoid stigmatization. HIV-related stigma and discrimination have been a significant obstacle to health services access leading to poor disease outcomes (20). HIV-stigma is also negatively associated with mental health and health-related quality of life (HRQoL) (20). Negative self-image or internalized stigma has been noted as the cause to avoid visiting a healthcare facility by one-third of people living with HIV (21). In our study, fear of knowing HIV serostatus has been reported as a key obstacle in reaching key populations for VCT which could impede PrEP uptake. This emphasizes the need for social empowerment and interventions to eliminate HIV-related stigma particularly negative self-image which has been recognized as more impactful than external stigma (22).

Differential PrEP service delivery models with client-focus are essential to enhance HIV-prevention efforts (Figure 2). Despite the availability of PrEP service to all populations at risk in Thailand, access to service is still a problem for some key populations especially transgender women and people who use drugs who may have specific health needs. Transgender women's desire for additional services based on their needs were noted in a number of previous studies (23, 24). Although clinical data in Thai transgender women suggested no significant drug–drug interactions between female hormone therapy and PrEP that would impact on PrEP protection level (25), this is still a major concern that has hampered the uptake and adherence of PrEP among this population. Additional services to address female hormone therapy as well as sensitizing and gender affirming therapy trainings to strengthen capacities of healthcare providers and KPLHS providers to better serve this group of clients are needed to increase PrEP uptake among transgender women. In response to the unmet health needs of TGW population, the first transgender-led sexual health clinic in Thailand named "Tangerine Community Health Clinic" was established in 2015 to offer comprehensive healthcare services through lay providers who are members of transgender community and gender sensitive healthcare providers. Up to March 2021, Tangerine Clinic has served over 3,900 TGW (26) with significant reduction in the annual HIV prevalence and syphilis from 2016–2019 (27). This stresses the imperative role of this specialized service model as a key component of HIV prevention to achieve HIV epidemic control.

All service providers in our study reported they had no PrEP experience in dealing with people who use drugs. Our respondents consistently remarked that people who use drugs were the most difficult to reach population due to being unprepared for medication adherence and the inconvenience of visiting PrEP clinics. Integrating PrEP services into existing access venues such as methadone maintenance programs which already require routine behavioral

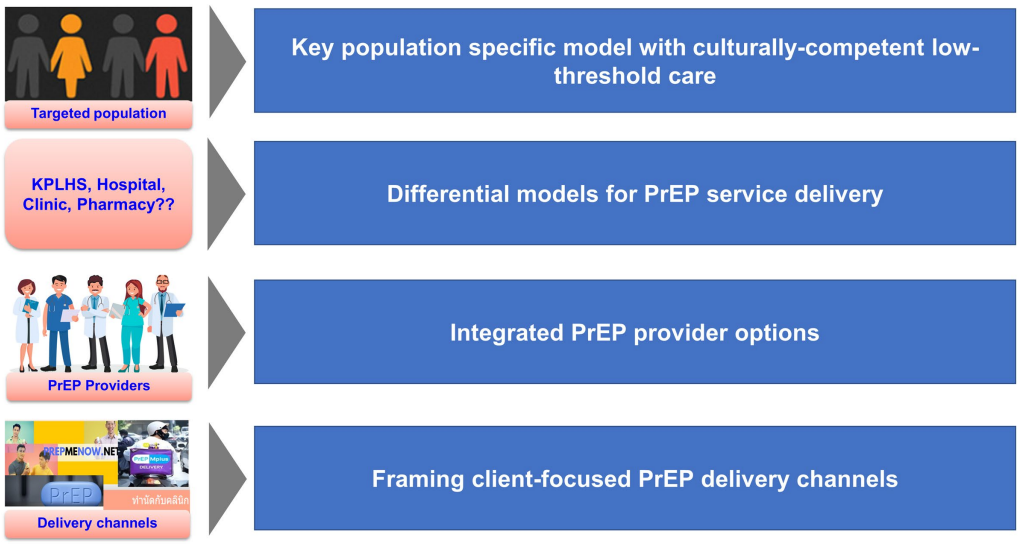

FIGURE 2
Novel approaches for differentiated PrEP service delivery.

counseling in place may have a profound impact on HIV prevention efforts. Long-acting PrEP formulations such as injectable carbotegravir (CAB-LA) which can be given once every 8 weeks can be a viable option to improve uptake and retention among this population whose adherence to daily oral PrEP imposes significant challenges.

Community pharmacies have been suggested as promising additions to the delivery of PrEP services to reduce the burden on the rest of the PrEP service system. This has been well accepted in the USA (23, 28). However, both hospital and KPLHS providers reported that PrEP delivery at pharmacies might not be exclusive enough to enable privacy for PrEP provision. Some providers also raised their concerns about the issue regarding blood collection for routine laboratory monitoring which may not be viable at pharmacies. As novel approaches are needed to expand service access, providing PrEP at pharmacies may be a potential alternative under the service integration model where PrEP is delivered by trained pharmacists working in partnership with hospitals.

Several major challenges were raised by healthcare providers from hospital settings. The repetition of work requiring data entry into different programs is one of the main causes of their excessive workload outside office hours. Therefore, a single user-friendly system for PrEP program data entry regardless of sources of fundings should be considered to enable efficient operation and monitoring and evaluation processes. Limited space for service delivery could compromise privacy for PrEP provision, emphasizing the need to improve infrastructure and healthcare facilities. The limited coverage of the UHC's benefit package for laboratory tests, insufficient condoms, lubricant supplies, and medications remain challenges in PrEP service delivery. Increasing coverage for some specific cases that require additional laboratory tests, sufficient medications and supplies are essential to enable same-day PrEP and enhance service efficiency. The limited-service coverage for non-Thai populations is also a barrier that hampers the country's ambitious goal to end HIV/AIDS by 2030. Thus, expanding health services access as well as education to improve the public's attitude about migrants as a "temporary source of labor" (29) are needed.

Although respondents reported good knowledge about PrEP and none of them reported increases in risky behavior among their clients, most of them agreed that there was a need to raise awareness among HCPs who are not involved in PrEP. This awareness should include an improved understanding that PrEP has not led to an increase in high-risk behavior. HCPs at hospital settings are in a position to counsel and refer potential clients for PrEP initiation. A lack of HCPs' understanding has been associated with never having HIV testing (30), increased sexual behavior risk (31), and reduced healthcare service utilization (32). Therefore, educating HCPs outside PrEP service is crucial to improve efficiencies of service integration and facilitate patients' referrals to PrEP uptake.

This study provides comprehensive insights from PrEP service providers in Thailand from both hospital and KPLHS settings. However, there are several limitations in our study to be noted. As this is a qualitative study, the data produced might be subjective and may impose transferability limits. Most of the study participants were experienced with good knowledge about PrEP. Therefore, the generalizability may be limited and may not be applicable for settings at the early stage of PrEP implementation. We did not collect the information concerning sexual orientation and age of the participants as the main purpose of the study is to collect insights and challenges regarding PrEP service in Thailand. The use of thematic analysis in this study can impose challenges concerning differentiations between codes and themes where different types of themes could be generated. However, this also allows more flexibility and application of researchers' experiences to gain deeper understanding of the insights. Finally, to get different points of view, we included multiple staff involved in PrEP from the same center in each focus group. Hence, it is possible that the influence of different hierarchies and powers might have undermined candid conversations. Nevertheless, we did not identify any significantly different opinions or attitudes among participants within the same setting in the analyses.

5 Conclusion

Most service providers have positive attitudes and good knowledge about PrEP service in Thailand. Despite success in HIV combination prevention and PrEP service implementation, large opportunities to scale up remain among key populations. The innovative PrEP service delivery model that focuses on clients' specific needs is essential to increase PrEP uptake among harder-to-reach populations. The KPLHS reach-recruit to hospital model should be adopted to optimize PrEP uptake. Support regarding raising awareness, improving facilities and human resources, service coverage and providers' capacities are important for the success of the national PrEP programme.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by the Research Ethics Committee, Faculty of Public Health, Chiang Mai University. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because this is a focus group discussion among service providers. There is no involvement of any patient information or personal information. The study participants provided verbal informed consent before completing study procedures. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

AR: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. SiC: Data curation, Project administration, Writing – review & editing. KI: Data curation, Writing – review & editing, Project administration. CC: Project administration, Resources, Writing – review & editing. PK: Funding acquisition, Resources, Writing – review & editing. DO: Supervision, Writing

– review & editing. SuC: Conceptualization, Funding acquisition, Resources, Supervision, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The work is supported by The Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), Department of Disease Control, Ministry of Public Health (Grant No. 7/2563) and The Joint United Nations Programme on HIV/AIDS (Grant No. 2020/1025705). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgments

The authors gratefully thank all study participants who provided invaluable insights on PrEP delivery service in Thailand and Department of Disease Control, Ministry of Public Health for their support in reaching the interview participants. Furthermore, authors also appreciate Chutima Charuwat and Nuttakan Aussawakaewfa for their great coordination throughout the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 13 June 2024
DOI 10.3389/fpubh.2024.1380027

OPEN ACCESS

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RECEIVED 31 January 2024
ACCEPTED 03 June 2024
PUBLISHED 13 June 2024

CITATION
Munyayi FK and van Wyk B (2024) Experiences of support by unsuppressed adolescents living with HIV and their caregivers in Windhoek, Namibia: a qualitative study.
Front. Public Health 12:1380027.
doi: 10.3389/fpubh.2024.1380027

Experiences of support by unsuppressed adolescents living with HIV and their caregivers in Windhoek, Namibia: a qualitative study

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Background: Adolescents living with HIV (ALHIV) lag behind younger children and adults in the achievement of HIV care and treatment targets for HIV epidemic control. Treatment outcomes for adolescents may be influenced by their experiences with the support provided in HIV programs. We report on the experiences of virally unsuppressed adolescents and their caregivers with the current support in primary healthcare settings in Namibia.

Methods: A qualitative descriptive and exploratory study was conducted in 13 public primary healthcare facilities in Windhoek, Namibia. A total of 25 in-depth interviews were conducted with unsuppressed adolescents ($n = 14$) and their caregivers ($n = 11$) between August and September 2023. The audio-recorded interviews were transcribed verbatim, and uploaded into ATLAS.ti software, and subjected to thematic content analysis.

Findings: Three main support domains for the unsuppressed adolescents emerged from our analysis, namely: psychosocial, clinical and care, and socioeconomic support. The psychosocial support was delivered through peer support (teen clubs and treatment supporters) and enhanced adherence counselling mostly. The clinical and care support included implementing adolescent-friendly HIV services, differentiated service delivery approaches, and caregivers and healthcare worker care support for improved ART adherence, clinic attendance and continuous engagement in care. Socioeconomic support was provided for nutritional support, transport to access clinics, and school supplies, as well as income-generating projects.

Conclusion: Psychosocial, clinical and care, and socioeconomic support are key elements in addressing the needs of adolescents challenged with achieving viral suppression. Health systems may benefit from whole-of-society and whole-of-government approaches to meet the needs of ALHIV that are beyond the scope of health service delivery such as nutritional, education and socioeconomic influences on both the health and well-being of ALHIV.

KEYWORDS

adolescents, HIV, viral suppression, antiretroviral therapy, fast-track city

1 Introduction

Adolescents living with HIV (ALHIV) lag behind younger children and adults in the attainment of the Joint United Nations Program on HIV/AIDS (UNAIDS) and World Health Organization (WHO) targets for HIV epidemic control. Approximately 1.65 million [1.18 million-2.19 million] adolescents between the ages of 10 to 19 years were living with HIV globally in 2022 (1). Substantial resources have been committed through multi-national and country programs to reach the 95-95-95 targets (2). However, reaching these goals remains elusive, especially in children, adolescents and young adults living with HIV. Worldwide, treatment coverage lags for children and adolescents, and by 2022 only 63% [49–86%] of children living with HIV knew their HIV status, 57% [44–78%] of them were on ART, and only 46% [36–63%] were virally suppressed (81% of children on ART) (3).

An estimated 27,000 AIDS-related deaths (4% global AIDS-related mortality) were reported globally in 2022, with more than 80% of them in sub-Saharan Africa (1). Viral non-suppression is a risk factor for mortality (4), and a recent systematic review reported ART adherence levels and viral suppression for ALHIV in sub-Saharan Africa at 65 and 55%, respectively (5). An estimated 11,057 adolescents are living with HIV in Namibia, with a prevalence of 1.9% among the 10–14 years age group and 3.7% among older adolescents aged 15–19 years (6). The Namibia Population-based HIV Impact Assessment (NAMPHIA) of 2019 reported the highest annual HIV incidence among adolescents and young women aged 15–24 years (0.99% vs. 0.36% for all adults aged 15–64 years) (6). Adolescents disproportionately lag behind the adults, with a recent analysis of treatment outcomes in ALHIV in Windhoek reporting a 12 and 15% gap in viral suppression and retention in care, respectively, whilst the viral suppression gap in adults is less than 5% (7, 8).

The lower viral suppression rates in adolescents compared to adults can be attributed to the unique challenges that adolescence presents in addition to being HIV positive (9). These challenges are related to adolescence as a developmental stage that is associated with rapid physiological, psychological and physical changes, fluctuating emotions and boundary-testing behaviour (9). Barriers to achieving viral suppression include non-disclosure-related issues, stigma, lack of psychosocial support, reliance on caregivers, childhood forgetfulness, unfavourable school schedule, unavailability of transport money, medication stockouts, side effects, prolonged clinic waiting time, unfriendly health settings and socioeconomic challenges (poverty, lack of food) (5, 9–13). Noted enablers of good adherence to ART and staying engaged in HIV care include access to adolescent-friendly services, reliable drug supply chain, good attitude from healthcare workers, financial support, and family and positive peer support among others (5, 14).

The United Nations Children's Fund (UNICEF), WHO, UNAIDS and other international partners have launched several global initiatives to end AIDS by 2030 (15), and provided some recommendations for the provision of adolescent-friendly HIV services and best practices on peer-led interventions for adolescents in HIV care. Namibia has adopted several of the international recommendations for addressing the gaps in managing ALHIV including the "*Global Plan towards ending new HIV infections among children by 2015 and keeping their mothers alive,*" and the "*2016 Political Declaration on HIV and AIDS goals*" (16, 17). Some of the most notable interventions included in the national HIV response are adolescent-friendly HIV services, differentiated care models, multi-month dispensing (MMD), peer-led interventions such as the Namibia Adolescents Treatment Supporters (NATS) and teen clubs, enhanced adherence counselling (EAC), and optimization of treatment with introduction of dolutegravir (DTG)-based regimens, as recommended by UNICEF, WHO and UNAIDS (18, 19). Despite the successes observed over the past decade to reach the 90-90-90 goals set by UNAIDS for 2020, a persistent gap remains to reach the new target of 95% viral suppression for adolescents on HIV treatment.

In 2017, Namibia attained 86-96-91% of the initial 90-90-90 UNAIDS and WHO targets for epidemic control (6). However, the most recent modelled spectrum estimates for 2023 reported that Namibia has achieved approximately 95 -97% -94% of the revised 95-95-95 UNAIDS targets. Windhoek, with an estimated population of 431,000 people, has one of the highest burdens of HIV in Namibia, and a high population of ALHIV. The estimated HIV prevalence for the younger population of 15 to 24 years is 4.0%, whereas for younger adolescents aged 10–14 years, it is estimated to be at 1.7% (20). Considering the high HIV burden among adolescents in Windhoek, the city joined the joint Fast-Track Cities Initiative, which aspires to optimize HIV service delivery, including improving treatment outcomes for ALHIV (21). A recent retrospective analysis of viral suppression among ALHIV at all the Windhoek healthcare facilities ($n = 13$) reported 12% of all the 695 adolescents on ART in Windhoek to be virally unsuppressed (1,000 copies/ml threshold) and approximately 94, 90 and 85% retention in care rates at 12, 24 and 36 months, respectively (7, 8). In this study, we report on the experiences of unsuppressed ALHIV and their caregivers with the current support in primary healthcare settings, and identify remaining, persistent gaps in service delivery to ALHIV. We believe the findings can assist with the identification of potentially modifiable determinants for enhancing viral suppression among ALHIV (22).

2 Methods

2.1 Study setting

This study was conducted in Windhoek, the capital city of Namibia. Windhoek has two main referral hospitals, two middle-level health centers, and nine primary healthcare clinics. All the 13 facilities in Windhoek were included in the study.

2.2 Research design, sample size, and sampling

A qualitative descriptive and exploratory study was performed. Adolescent participants (10–19 years) were obtained from the high viral load registers maintained at each health facility ART clinic. For every high viral load result received (>1,000 copies/ml), the client is enrolled into Enhanced Adherence Counselling (EAC) and registered either in the adult (>15 years) high viral load register or the paediatric (<15 years) high viral load register. The Namibia Adolescent Treatment Supporters (NATS) based at ART clinics also generate lists of adolescents with high viral loads (from the high viral load registers)

who need standard or enhanced care. We generated a list of potential participants using the high viral load registers and the NATS lists for enhanced care. Adolescent participants were recruited into the study during their routine follow-up visits, with their caregivers, or the caregivers were contacted in consultation with the adolescent and clinic staff. A purposive sampling approach was utilized to enrol unsuppressed adolescents and their respective caregivers into the study, considering those in EAC and enhanced NATS care, the number of younger and older adolescents, and male and female adolescents. Written informed consent was obtained from the caregivers and older adolescents aged 18 years and above whilst younger adolescents aged less than 18 years had to assent to participate with caregiver consent. A total of 14 in-depth interviews (IDIs) were conducted with unsuppressed adolescents as well as 11 of their caregivers (Table 1), guided by the data saturation concept. Through the in-depth interviews, we explored sensitive and personal themes concerning the individual experiences of adolescents on HIV treatment, and the meanings of the disease to them. We used the interviews with caregivers to triangulate the responses of the adolescents – to enhance the credibility of the findings of this qualitative study (23).

2.3 Data collection

Separate interview guides were developed for adolescents and their caregivers and administered in person by the first author. The interview guides were developed based on the research question related to the experiences of adolescents and their caregivers with the health system, driven by preliminary quantitative analyses of determinants of viral suppression and retention in care among ALHIV in Windhoek, a review of policy and guidelines for management of ALHIV in Namibia, and key informant interviews with HIV program managers and service providers. The interview guides were piloted at two of the 13 facilities to ascertain the reliability of the guides. The interviews took place between August and November 2023. Before each interview, each participant was taken through the participant information sheet and the written informed consent for participation. All 25 IDIs were conducted in person at the ART clinics, in either English or any of the local languages, and audio recorded with the participant's consent. The recorded interviews were transcribed verbatim and translated to English (where required).

2.4 Data analysis

The interview transcripts were uploaded into ATLAS.ti v8 software and we performed thematic content analysis. We developed codes from the participants` responses using an inductive approach, whereby rather than using a theoretical framework, the codes and themes emerged from the transcribed data (24). The first author first reviewed 3 adolescent transcripts and 2 caregiver transcripts (21% of all transcripts) to develop the codebook. The transcripts and codebook were reviewed by the second author and inter-coder disagreements were discussed. A comprehensive codebook was created through an iterative engagement process between the two authors, emanating in agreed codes with definitions by consensus. The emerging codes, sub-themes and themes were further reviewed, refined and verified by the authors and applied to the rest of the transcripts. Data triangulation between the adolescents and caregiver codes and themes, as well as second author checks, were employed for data validation. A final matrix of themes, sub-themes and codes describing the barriers/challenges to ART adherence and enablers/facilitators of good adherence, from the perspective of unsuppressed ALHIV and their caregivers, was developed (Supplementary materials S1, S2).

2.5 Rigor and trustworthiness

The credibility and trustworthiness of the research were enhanced through prolonged engagement with the healthcare facilities in Windhoek. We continuously engaged with the facilities throughout the different preceding phases of the research. We initially conducted a baseline analysis of all adolescents enrolled in ART services in all the Windhoek facilities. We then conducted a policy and programmatic documents review which involved consulting the management of the MoHSS and facility-based management and staff. During the qualitative phase of the research, we engaged with managers of adolescent-focused HIV programs and the healthcare workers providing HIV services to ALHIV. The ongoing engagement throughout the preceding data collection periods, and piloting of the interview guides helped refine the quality of questions in the data collection tools for the adolescents and their caregivers, as well as the quality of information obtained from the interviews. A participatory approach, persistent observation, and prolonged engagement

TABLE 1 Summary characteristics of unsuppressed adolescent participants and their caregivers.

	Female		Male		Total
Age group (in years)	**10–14 (n = 1)**	**15–19 (n = 6)**	**10–14 (n = 2)**	**15–19 (n = 5)**	
In school	1	3[a]	2	3[a]	**9**
Employed				2	**2**
In teen club	1	3	2	4	**10**
Caregiver interviewed					
Father		2		1	**3**
Mother		2	1	3	**6**
Aunt			1		**1**
Grandmother	1				**1**

[a]2 (1 female and 1 male) adolescents are staying in the hostels in boarding school.

enhances familiarity and understanding of contexts for the researcher, and develops a sense of ownership and involvement in the outcome of the research for the participants (25). These measures add more value for fulfilling the trustworthiness criteria in terms of the credibility of the research, and ensuring dependability, confirmability, and transferability of findings (26). The researchers also familiarized themselves with key concepts related to barriers, enablers and interventions for improving viral suppression rates, by conducting a systematic review to identify effective interventions for improving viral suppression for ALHIV. The mixed methods research design of the project, which also included a policy and programs documents review, facilitated the development of an interview guide well informed by findings from the preceding phases. As already mentioned, we also employed triangulation to analyse responses from the unsuppressed adolescents and their caregivers to compare responses to reach as rich a picture of their perspectives, experiences and different dynamics, to the extent possible and to increase credibility (23). Credibility was also enhanced by meticulous identification of unsuppressed adolescents from records and confirmed by NATS as part of the sampling process and recruitment of participants.

2.5.1 Ethical approval and informed consent

The ethical clearance was obtained from the University of the Western Cape Biomedical Research Ethics Committee (ref. no. BM21/5/7) and the Namibia Ministry of Health and Social Services (MHSS) Research Management Committee (ref. no. 17/3/3/FKM). The study was carried out in compliance with the Helsinki Guidelines Declaration of 1964 and its subsequent amendments. Written consent was obtained from adolescents aged 18 years and above and parents or caregivers, and assent was obtained from adolescents under 18 years, prior to participation in the study. No personal identifying information such as names, surnames or identity numbers, was collected to ensure respect for the privacy and dignity of the participants and the confidentiality of participants' information. All data was stored on a password-protected tablet and backed up on a password-protected computer.

3 Findings

Table 1 outlines the key demographics of the adolescents who participated in the study and the relations with the caregiver participants who were interviewed. A total of 25 participants were interviewed: 14 unsuppressed ALHIV and 11 caregivers of unsuppressed adolescents. Nine adolescents were in school (4 of the 7 females, 5 of the 7 males) and 2 older male adolescents were employed. All the younger adolescents (10–14 years) were in school. Ten out of the 14 adolescents were in Teen Clubs (6 males and 4 females). Their caregiver participants included mothers ($n = 6$), fathers ($n = 3$), and an aunt ($n = 1$) and a grandmother ($n = 1$).

Three main adolescents' support domains emerged from the analysis of the interview data, namely: *psychosocial*, *clinical and care*, and *socioeconomic* support (Table 2). We describe each of these themes in turn, and note the interventions that related to each domain, as sub-themes, with verbatim quotes where appropriate to illustrate authenticity of the coding process.

TABLE 2 Support domains for ALHIV with unsuppressed viral load.

Domain	Intervention
Psychosocial support	Teen Club Peer support Namibia Adolescent Treatment Supporters (NATS) Advice on avoiding alcohol Adherence counselling Motivational interviewing
Clinical and care support	Adolescent-friendly clinic services Medication delivery at home Home visits Healthcare workers support HIV/AIDS education Facilitated medication pick-ups Introduction of long-acting injectables for HIV Weekend and after-hours clinic services Flexibility in clinic visits scheduling Receive reminders Receiving follow-up calls Caregiver support for ART adherence and clinic attendance Tracing and post-tracing services
Socioeconomic support	Food and transport support Financial support for school Savings project Accessibility of healthcare facilities

3.1 Psychosocial support

Adolescents who have high viral loads are enrolled for enhanced adherence counselling (EAC) and motivational interviewing, receive advice on avoiding alcohol and are enrolled in the Namibia Adolescent Treatment Supporters (NATS) enhanced care. They are also invited to the teen clubs to facilitate peer support. Both the adolescents and their caregivers described the counselling received as excellent. However, there were concerns about the availability of adequate counselling services for ALHIV with disabilities.

> He is a disabled person, he is deaf. I don't know if he receives counselling because I don't think there are counsellors who know sign language. Long back they used to tell me, and I translate to him, for now I do not know how they do it because now he comes alone – Caregiver.

The teen clubs provide a safe environment for the adolescents to share their experiences, to support each other and learn from the facilitators (clinic staff, NATS and peers). Most adolescents reported good experiences in the teen clubs, learning the basics about HIV and AIDS, dealing with stigma and discrimination, and how to cope with their HIV status and be resilient. The caregivers concurred that the teen clubs were excellent platforms for building confidence and providing emotional support to the adolescents.

> Meeting my age mates with the same status as me kept me strong, it made me to be strong, I now know that I am not alone. Sharing

> their stories and how they take their medicine, we seriously learn a lot – ALHIV.
>
> This group trains them very well how to have confidence and self-competency. Giving them emotional and physical support knowing there is someone there for them. I think this group is doing the most. Knowing her she always come home hyper and energetic, I think this also boosts her – Caregiver.

However, some challenges persisted with the teen clubs. Some adolescents stopped attending the teen clubs because they felt that other members did not like them or were rude to them; or the stories shared affected them emotionally. Others stopped attending because they were staying in the hostels, or their parents refused to approve their participation in teen clubs. Some indicated that the clinic stopped calling them to come for the teen club meetings whilst others have many responsibilities at home that prevent them from attending teen club meetings.

> I was introduced to it [teen club] but their dates are always not good for me. It's either I am busy or home alone or with the kids and there is no one I will leave them with – ALHIV.

The NATS were successful in closing the gaps that existed between the adolescent clients and healthcare workers. The adolescents preferred getting assistance from the NATS at the facilities because they get preferential treatment and are fast-tracked through different service delivery points. The NATS also motivated the virologically unsuppressed adolescents to take their medication as prescribed and were role models as teenagers who overcame challenges with adherence and reached viral suppression through individual resilience. In general, most adolescents reported that the clinic staff provided excellent counselling services, as did the NATS.

> I didn't want to be seen, until one of the guys who works for NATS came in the clinic, lucky enough we know each other from school. He asked why I am leaving, and I said no I am going because your people here are acting otherwise. He was like no come let me help you they are busy. Unfortunately, he travelled, and things are now hard for me – ALHIV.

3.2 Socioeconomic support

Provision of food, transport money and financial support for school emerged as key enablers for adolescents struggling with adherence to treatment and clinic appointments. Nutritional support was previously provided by non-governmental organizations (NGOs) but has ceased. At the time of the study responsibility for food, transport money and school funds fell to the families – which was difficult for some (or most). An initiative to have a savings project for the adolescents was initially useful in providing transport money for clinic visits. However, it seems to have faced sustainability problems as it did not last long because of accountability concerns.

> I think I should always drink them [tablets] after a meal, because sometimes there is no food, and I feel dizzy, nausea, headaches and sometimes vomit them [tablets]. Sometimes I find myself not having transport money, but facility staff members can give me – ALHIV.
>
> The government should take it seriously. Just to provide healthy foods to our children because I don't think these foods we are feeding them are all healthy – Caregiver.

For most of the adolescents, the clinics are quite accessible as there are short distances from their homes to the healthcare facilities. However, for those who stay longer distances from the clinics, lack of transport money becomes a barrier to accessing the clinic HIV services.

> The clinic is not far, because some time I can even walk to the clinic if I do not have taxi money, the facility is just near – ALHIV.

3.3 Clinical and care support

Clinical services support ranged from facility-based adolescent-friendly HIV services to community-based differentiated care services. Many of the participants appreciated the prioritization of adolescents in often busy and crowded facilities, with facilitated quick medication pick-ups, especially when their clinic visits occur during school times. Some facilities have adolescent corners, which provide focused attention to the adolescents. However, participants suggested that the clinics should have more flexibility in scheduling of clinic visits, especially by involving the adolescents in decision-making on convenient times for them to come for their follow-up visits. It was also suggested to have afterhours and weekend clinic visits so as to minimize disruption of the school attendance. In addition, some participants expressed the desire to have long-acting injectables, to address the ART regimen-related challenges of taking daily medication and treatment fatigue.

> The solution, what I am suggesting is the clinic should be able to provide injection for each and every month for it to replace tablets. It is irritating for the child to be responsible for taking medication each and every day – Caregiver.

Healthcare worker support through education on HIV and AIDS basics, provision of reminders (such as pill boxes, wristwatches, and sending text message reminders) are key support mechanisms offered at some of the clinics. Despite their utility, these reminders are not readily available at all facilities.

> I need somewhere to check time because my father who has a phone, so I check the time is not always home. He comes late from work; I just want reminders. The support I want is to be helped with a watch – ALHIV.

Many participants indicated that the healthcare workers are friendly, supportive, helpful and always kind. However, some participants indicated that sometimes the service is slow and the clinics are often crowded with long queues.

> One visit I met sister [name provided]. Mind you I used to feel guilty of not taking my medication and not coming to the clinic and everything was not up to date. When I met her, she was very understanding, nice to me, and she was encouraging me, so I told her my problem and she agreed to help me, now she went to another clinic – ALHIV.

Some of the clinics have nurses and health assistants who make follow-up calls to remind the adolescents of their upcoming clinic visits or when they have missed an appointment, which triggers the activation of tracing and post-tracing services. Receiving follow-up calls is an essential measure that helps the adolescents to comply with their visit schedules. Healthcare workers play a crucial role in promoting caregiver support and involvement in the care of the adolescents whenever such intervention is needed. It was clear from the caregivers' responses that caregiver absence in the care of most of the unsuppressed adolescents was a key barrier to good ART adherence and clinic attendance.

> If I am not around everything is messed up. That undetected condition [viral suppression] used to happen when she was under my care. I always make sure he attends his appointment. I have to keep monitoring that he takes his medication on time. The problem is mostly when I am staying in the north – Caregiver.

The NATS have been helpful in delivering medication at home for adolescents who are having problems with going to their clinics. Other adolescents who are challenged with accessing their nearest health facilities also suggested that the clinic staff should have a schedule for delivering medication at home or in the community.

> I wish the nurses could bring my medication at home, then I don't have to come here. They once told us that NATS people will be taking care of that issue. Like if you tell them your situation and they will deliver our medication at our places. I want that to be implemented – ALHIV.

The community-based support would also include conducting home visits to assess the home environment and identify and address the needs of the adolescents who are struggling because of some socioeconomic or family challenges at home, as part of the comprehensive post-tracing services.

> They are even approaching exams, I need someone to come in our house and see what he is doing because I have been trying to talk to him, maybe he is hiding the medication – Caregiver.

4 Discussion

In this study, we qualitatively explored the experiences of unsuppressed adolescents in HIV care and their caregivers with the current support in primary healthcare settings in Windhoek, Namibia. We identified the remaining, persistent gaps in service delivery to ALHIV that related to the main barriers to ART adherence namely, psychological, social, behavioural, structural, clinical care, ART regimen-related, and socioeconomic challenges. We identified enablers such as psychosocial support, individual resilience, clinical care and structural support, which serve as the basis for our recommendations for the optimization of the HIV program for ALHIV in Namibia.

Our findings suggest that there are several good practices implemented to provide psychosocial support to ALHIV and their caregivers. The results indicate that unsuppressed ALHIV are enrolled in EAC as standard practice, and receive motivational interviewing, to motivate them to adhere to treatment (27). The counselling services provided by the clinic staff and NATS were described as excellent. Studies investigating the association between EAC and viral suppression in individuals on ART have found mixed and inconclusive results (28, 29). Nonetheless, other studies found EAC and routine viral load monitoring to be potentially effective interventions to improve viral suppression levels in individuals living with HIV (30, 31). Counselling sessions include discouraging adolescents from drinking alcohol and taking other recreational drugs which may exacerbate cognitive function and mental health impairments (32). However, there are indications that the counselling services, including EAC, are insufficient to address some unique challenges that adolescents may be facing. Concerns were raised about the accessibility of the counselling services to adolescents living with disability. The healthcare providers may not be adequately equipped to provide the necessary counselling services to clients that are deaf. A study in Kenya recommended deaf-friendly HIV services that are also supplemented by peer education programs (33).

The WHO recommends the implementation of peer support programs for adolescents and young people living with HIV (AYPLHIV) aged between 10 to 24 years, and recognizes teen clubs and community adolescent treatment supporters (CATS) as some of the best practices (34). Namibia has adopted some of these best practices and counselling services are also extended to peer support interventions such as the NATS (adopted from CATS) and teen clubs. The teen club intervention model in Namibia is primarily designed to deliver psychosocial support only, and includes unsuppressed adolescents (35). Namibia has been scaling up establishment of teen clubs and promoting greater uptake of this intervention among all ALHIV who are aware of their HIV status. Ten (71%) of the unsuppressed ALHIV who participated in our study were members of a teen club and evidently appreciate the peer support and good learning experiences in such safe spaces, as observed in a study conducted in Cape Town, South Africa (36). Great potential to improve treatment outcomes for ALHIV has been observed in group-based peer support interventions such as teen clubs. An evaluation of a teen club intervention in Malawi reported that adolescents who were not exposed to teen clubs were less likely to be retained in care than those in teen clubs (aOR 0.27; 95% CI 0.16, 0.45) (37). A 2019 evaluation in Malawi of a teen club intervention reported improved ART adherence in teen clubs (38). However, no significant association has been reported between attending a teen club and viral suppression or retention in care among ALHIV in Namibia (35, 39).

Nevertheless, several country programs are scaling up the teen club intervention, albeit as a differentiated service delivery model which includes ART refills and other clinical services (38). The teen club model in Namibia which focuses on psychosocial support only may be inadequate and could benefit from incorporating ART refills and other clinical services. Attrition from the teen clubs needs to

be addressed as a number of the participants in our study indicated that they stopped attending because of negative experiences with peers (attitude, relations and emotional triggers). Other barriers to attending the teen club such as parents refusing to approve participation, staying in the hostel or being busy also need to be addressed. Adding other clinical services to the teen club and prioritizing the unique needs for each adolescent (case management for unsuppressed ALHIV), may possibly improve retention in teen clubs, and consequently their treatment outcomes. A study in Kenya recommended that facilities or organizations dealing with ALHIV should consider case management interventions to address determinants influencing adolescents` resilience in HIV treatment and care programs (40).

The NATS play a crucial role in closing some of the care gaps between adolescents, caregivers and the healthcare workers. Many of the unsuppressed adolescents have been enrolled in the NATS enhanced care and indicated that the support they get from the NATS includes facilitated pill pick-ups, being fast-tracked through the clinic during visits, encouragement to adhere to their medication, and medication deliveries at home when the adolescent cannot physically go to the clinic for their appointment. Peer-led differentiated service delivery (DSD) models have been recognised as promising interventions for improving viral suppression among ALHIV (41–43). Namibia is one of the countries currently scaling up the peer-led DSD models, and plans are underway to evaluate the effectiveness of the intervention in achieving viral suppression in unsuppressed adolescents (44). However, the NATS intervention may be inadequately implemented in Namibia, as only a few of the unsuppressed adolescents indicated that they were enrolled in the program. Concerns about the reach of the program needs further interrogation as all adolescents with unsuppressed viral loads at the study sites are expected to be under NATS enhanced care.

With the emphasis on client-centred care, it has become increasingly essential for DSD models to focus healthcare services designs on patient preferences which will promote better retention in care and is amenable to lifelong care (45). Many of the adolescent and caregiver participants suggested that medication be delivered at home, either by healthcare workers or the NATS. As mentioned earlier, NATS have taken up this responsibility especially for adolescents in enhanced care challenged with accessing the clinic, but structured community based DSD approaches for this population seems to be missing.

However, there are some **clinical and care support** best practices implemented at facility level. The clinics provide adolescent friendly services, including dedicated spaces within the facilities in the form of adolescent corners. The WHO recommends implementation of adolescent-friendly health services that improve acceptability, equity, accessibility, effectiveness, and appropriateness of ART services to ALHIV (19). Our results indicate that these services enable smoother interactions with the clinic for most adolescents, with reduced clinic waiting times and adequate clinician consultation time as needed. Yet at some health facilities, often times the clinics would be crowded and very busy, such that the service would be slow. Without prioritized assistance, long clinic waiting time becomes a significant barrier for adolescents to adhere to their clinic visit appointments, especially when they occur during school hours. Both adolescents and caregivers indicated that scheduling of some of the clinic visits was disruptive of their school attendance, with 9 of the 14 adolescents still in school. Consultations with the adolescents and caregivers gives them an opportunity to participate in the decision-making process concerning conducive scheduling of their visits. There is growing evidence that adolescents can be agents of positive change to improve their treatment outcomes and they should be critically engaged in decision-making process throughout the continuum of care (46). Suggestions to implement more flexibility in scheduling clinic visits could address clashing clinic schedules with school attendance, and this could be through after school hours and weekend scheduled visits (47).

Tracing services are key to returning clients who miss their appointments back into care. Namibia has developed a tracing and post-tracing services standard operating procedure (SOP) to guide healthcare providers on mechanisms to reduce interruption in treatment. Adolescents appreciated follow-up calls from clinicians and health assistants (lay counsellors) to remind them of upcoming appointments or if they miss their clinic visit date. Poor clinic attendance consequently predicts viral non-suppression and tracing interventions should incorporate post-tracing services that recognize the adolescent-specific individual, structural, and social barriers to uninterrupted treatment engagement (48). Our observations suggest that these services may be insufficiently implemented as some of the unsuppressed adolescents had interrupted treatment for long periods and their missed appointments should have triggered tracing services.

Our results also highlighted the great interest from adolescents and their caregivers to get assistance with reminders for taking medication. As one of the observed best practices, Namibia has introduced and distributed wristwatches and pill boxes to adolescents to facilitate timely taking of medication, although the reach of the intervention has been limited to selected facilities due to inadequate resources. Anecdotally, service providers have seen improvements in adherence in adolescents that were previously struggling with taking their medication in a timely manner. However, the effectiveness of this intervention has not been empirically established yet. Studies investigating the effectiveness of reminders (mobile phone text messages) on ART adherence have reported mixed results and recommended larger studies to be conducted (36). The Namibia HIV program plans to evaluate the effectiveness of the reminders that have been distributed to ALHIV in selected facilities.

It was apparent that some adolescents rely on their caregivers to remind them to take their medication, and in the absence of the caregiver, adherence was poor. For this reason, a few caregivers suggested the introduction of long acting injectables for HIV treatment (49). Observations from our study suggest that caregiver support, in the form of reminders, psychosocial, food and transport money, is key for adolescents to take their medication on time and to attend their clinic appointments. However, caregivers also experience challenges associated with family, psychological and social needs that require social networking and financial resources support to be strengthened as a coping mechanism for most caregivers (50). For these reasons, healthcare workers at Windhoek facilities have introduced caregivers' clubs to provide support to the caregivers of adolescents, especially those taking care of unsuppressed ALHIV. Caregiver involvement in the treatment and care of the adolescents is key and it was apparent that problems often surfaced during caregiver absence. A caregiver has the potential to be a powerful ally for their child and family centred approaches that include socioeconomic and health needs should be prioritized to improve ART adherence and resilience among ALHIV (51).

Healthcare worker support to both the caregivers and to adolescents is essential and several participants expressed their appreciation of good support they were receiving from healthcare workers regarding psychosocial wellbeing, emotional support, motivation and encouragement to stay engaged in care and taking their medication as prescribed. Evidence suggests that health education on HIV and AIDS basics is a crucial component for improving treatment literacy among adolescents (52). HIV and AIDS education is delivered through healthcare workers, NATS and as part of the teen club activities. Interventions that target treatment literacy in ALHIV and their caregivers can address immediate determinants of poor adherence and facilitate achievement of undetectable viral loads (53). The HIV and AIDS education sessions seem to be successful in improving the understanding of HIV and AIDS basics by both adolescents and their caregivers, evidenced by the acceptance of HIV status, understanding self-management and coping mechanisms, as well as great desire to achieve viral suppression.

As alluded to earlier, structured DSD models are inadequately implemented for this population and some caregivers suggested that healthcare workers should conduct home visits to support the adolescents and their families. Addressing the socioeconomic needs of the adolescents is an essential component of managing the holistic needs of adolescents, which includes their immediate home environment. Programs providing **socioeconomic support** for ALHIV and their families have been scarce and limited. Although most of the participants stayed near the clinics, transport money was a challenge for those who stayed longer distances from the clinic. Support with transport money and food previously came through NGOs whose programs have since ended. The Bantwana Initiative provided similar support for ALHIV and their caregivers through a combination of financial literacy, savings groups, and income-generating skills to improve their financial and nutritional status, as well as food security (51). Although a savings project was initiated for some of the adolescents and caregivers in Windhoek, it was not sustainable.

Because of the socioeconomic challenges raised by participants, we observed that there is a significant gap in addressing nutritional, transport, and financial support for school supplies. Designing programs specifically addressing socioeconomic challenges for ALHIV may go a long way in addressing some of the structural determinants of poor adherence and viral non-suppression. In addition, it appears support from social workers is missing or inadequate, at most, as there were no clear engagements mentioned specifically with social workers by the adolescents nor their caregivers. Overall, it is essential to involve the adolescents and their caregivers in designing programs that are concerned with their care, and utilizing the whole-of-society and whole-of-government approaches to address the holistic needs of ALHIV (54).

The limitations of our study included the smaller number of younger adolescent participants compared to the older adolescents, and our findings may be predominantly the experiences of older adolescents who are challenged with attaining and maintaining viral suppression. Our study setting was also limited to Windhoek, with facilities in urban and peri-urban settings. The experiences of adolescents in rural settings may be different. Our study focus was on unsuppressed adolescents and did not include interviews with suppressed adolescents.

5 Conclusion

Psychosocial, clinical and care, and socioeconomic support are key elements in addressing the needs of adolescents challenged with achieving viral suppression. We recommend that the involvement of ALHIV and their caregivers should be part of a whole-of-society approach for health service delivery. In addition, direct involvement of other sectors such as education, social welfare, and poverty eradication through a whole-of-government approach, is essential to meet the needs that are beyond the scope of health services, but directly impact the health and well-being of ALHIV such as nutritional, education and socioeconomic determinants of health. Practices of adolescent HIV care should be holistic and participatory for both ALHIV and their caregivers to achieve optimum outcomes, including sustained viral suppression.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by University of the Western Cape Biomedical Research Ethics Committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

FM: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Writing – original draft, Writing – review & editing. BW: Conceptualization, Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to acknowledge the Ministry of Health and Social Services management, Khomas Health Regional Management Team, and the Windhoek district management for granting us access to the facilities for this study. We also acknowledge the management of the facilities and staff, and the adolescents and their caregivers who participated in this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1380027/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 25 June 2024
DOI 10.3389/fpubh.2024.1393627

OPEN ACCESS

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RECEIVED 29 February 2024
ACCEPTED 07 June 2024
PUBLISHED 25 June 2024

CITATION
Ogutu S, Mohammed M and Mwambi H (2024) Investigating the effects of cytokine biomarkers on HIV incidence: a case study for individuals randomized to pre-exposure prophylaxis vs. control.
Front. Public Health 12:1393627.
doi: 10.3389/fpubh.2024.1393627

Investigating the effects of cytokine biomarkers on HIV incidence: a case study for individuals randomized to pre-exposure prophylaxis vs. control

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Introduction: Understanding and identifying the immunological markers and clinical information linked with HIV acquisition is crucial for effectively implementing Pre-Exposure Prophylaxis (PrEP) to prevent HIV acquisition. Prior analysis on HIV incidence outcomes have predominantly employed proportional hazards (PH) models, adjusting solely for baseline covariates. Therefore, models that integrate cytokine biomarkers, particularly as time-varying covariates, are sorely needed.

Methods: We built a simple model using the Cox PH to investigate the impact of specific cytokine profiles in predicting the overall HIV incidence. Further, Kaplan-Meier curves were used to compare HIV incidence rates between the treatment and placebo groups while assessing the overall treatment effectiveness. Utilizing stepwise regression, we developed a series of Cox PH models to analyze 48 longitudinally measured cytokine profiles. We considered three kinds of effects in the cytokine profile measurements: average, difference, and time-dependent covariate. These effects were combined with baseline covariates to explore their influence on predictors of HIV incidence.

Results: Comparing the predictive performance of the Cox PH models developed using the AIC metric, model 4 (Cox PH model with time-dependent cytokine) outperformed the others. The results indicated that the cytokines, interleukin (IL-2, IL-3, IL-5, IL-10, IL-16, IL-12P70, and IL-17 alpha), stem cell factor (SCF), beta nerve growth factor (B-NGF), tumor necrosis factor alpha (TNF-A), interferon (IFN) alpha-2, serum stem cell growth factor (SCG)-beta, platelet-derived growth factor (PDGF)-BB, granulocyte macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and cutaneous T-cell-attracting chemokine (CTACK) were significantly associated with HIV incidence. Baseline predictors significantly associated with HIV incidence when considering cytokine effects included: age of oldest sex partner, age at enrollment, salary, years with a stable partner, sex partner having any other sex partner, husband's income, other income source, age at debut, years lived in Durban, and sex in the last 30 days.

Discussion: Overall, the inclusion of cytokine effects enhanced the predictive performance of the models, and the PrEP group exhibited reduced HIV incidences compared to the placebo group.

KEYWORDS

cytokine biomarkers, HIV incidence, pre-exposure prophylaxis, stepwise Cox PH, Kaplan–Meier

1 Introduction

HIV continues to be a serious worldwide health concern, with South Africa having the world's highest HIV epidemic, with an estimated 8.45 million people living with HIV (1). The primary mode of transmission in this endemic setting is heterosexual intercourse, and women 18–40 years account for more than 60% of new infections where the young women bear the greatest burden (2). It is well known that sex workers are at a greater risk of HIV acquisition (3). Significant effort has been made in South Africa over the last decade to search for new technologies that prevent sexually transmitted HIV infections in women such as the pre-exposure prophylaxis (PrEP) products. Initiatives have been undertaken to scale up education and access to these products for example the tenofovir gel an antiretroviral microbicide that can be applied to the vagina or rectum with intentions of reducing the acquisition of HIV (4).

The initial stages of HIV infection are characterized by inflammation and profound immune dysregulation in the gut mucosa (5, 6) and genital inflammation at this stage also correlates with an increased plasma viral load (7). Taken together, inflammation is a key mediator of HIV pathogenesis. The levels of inflammatory cytokines and chemokines, which signal the presence of infection and recruit activated immune cells to the mucosa, are frequently used as biomarkers of inflammation in the female reproductive tract (FRT) (8). As such, we hypothesize it might be expected that elevated mucosal cytokines would be correlated with increased rates of HIV acquisition. The increased levels of pro-inflammatory cytokine is associated with increased rates of HIV acquisition (9) and cytokine profile is a strong predictor of subsequent HIV acquisition. Understanding the interplay between cytokine biomarkers and HIV incidence by identifying specific cytokine profiles associated with increased or decreased HIV susceptibility is crucial for optimizing PrEP strategies.

Cytokines serve a vital role in maintaining immune system homoeostasis (10), and HIV infection causes dysregulation of the cytokine profile (11). Changes in the cytokine signature directly affect HIV disease progression (12), with an intense cytokine "storm" during acute HIV infection (13). T-helper type 1 (Th1) cytokines such as interleukin (IL)-2 and antiviral interferon (IFN)-gamma are generally decreased during HIV infection, whereas T-helper type 2 (Th2) cytokines such as IL-4, IL-10, pro-inflammatory cytokines (IL-1, IL-6, IL-8) and tumor necrosis factor (TNF)-alpha are increased (10). IFN-alpha, IFN-beta, and IL-16 are HIV-suppressive cytokines that inhibit HIV replication in T cells while IFN-gamma, IL-4, and granulocyte-macrophage colony-stimulating factor, for example, have been demonstrated to have both inhibitory and stimulatory effects on HIV (14).

In clinical research, it is a common phenomenon for covariate data to be collected longitudinally and for the covariates to change over time during the follow up period. For example, patients in a clinical trial to asses the safety and effectiveness of tenofovir gel, a vaginal microbicide in sexually active women at risk for HIV, cytokine profiles were measured repeatedly up to infection or until censorship (4). In many instances, while examining the relationship between time to HIV infection and covariate(s), investigators will only consider the baseline covariates, leaving out covariates that change over time hence failing to consider the relation of the survival outcome as a function of the change of the time dependent covariates (15). It appears natural and suitable to use time-varying covariate information in an appropriate statistical model. The Cox PH model can be used to link survival times with either fixed covariates whose values remain constant during the follow-up period or predictor variables that fluctuate over time (16). The mentioned covariates can be dealt with as a time dependent covariates into the Cox PH model or incorporated as a derived longitudinal variables as further elaborated in the Section 2.2.

A previous analysis was conducted by Abdool Karim et al. (4) and Mansoor et al. (17) to investigate the effectiveness, safety and adherence in the CAPRISA 004 tenofovir gel microbicide trial. They used Proportional Hazards (PH) regression model to calculate the hazard ratios while adjusting for potentially important baseline covariates (age, site, anal sex history, contraceptive method, HSV-2, antibody status and condom use). They reported a hazard ratio of 0.63 (CI: 0.42,0.94, $p = 0.025$). In their analysis they did not include cytokine profile neither did they report on significant baseline covariates associated with HIV incidence. Masson et al. (18) used the same dataset to investigate whether genital inflammation influenced HIV acquisition in women. Their study selected 12 cytokines for their analysis. They employed conditional logistic regression and unsupervised hierarchical clustering in their statistical analysis.

Naranbhai et al. (19) investigated the role of immune activation in HIV acquisition in the CAPRISA 004 trial. They selected 13 cytokines and used logistic regression and principal component analysis (PCA) in their statistical analysis. On the other hand, Ngcobo et al. (20), in their study examining whether pre-infection plasma cytokine concentrations predicted the rate of HIV disease progression in the same study cohort, considered all 48 cytokines. They used linear regression to assess the impact of each cytokine on viral load (VL) and the CD4:CD8 ratio in both bivariate and multivariable models, adjusting for age, contraceptive use, HSV-2 status at baseline, study site, and study arm at randomization. Ignacio et al. (21) used the Sabes dataset and LASSO machine learning algorithms to study how dynamic immune markers predict HIV acquisition and strengthen associations with sociobehavioral factors related to HIV exposure. They selected 10 cytokines for their analysis. Other studies (22, 23) that have utilized CAPRISA 004 data set to investigate HIV progression, did not include time varying cytokine profile as a covariate in their analysis. To the best of our knowledge, cytokine profile as a time-varying covariate or as derived covariate has not been used with baseline covariate in previous studies to identify significant predictors of HIV incidence.

This study therefore, seeks to investigate the effect of time-varying cytokine biomarkers in determining significant predictors of HIV incidence among individuals randomized to PrEP vs. control exposure. We achieved that by building a series of Cox PH models that include different forms of the covariates that change over time and further asses the overall effectiveness of the tenofovir treatment by comparing the two groups using Kaplan–Meier estimator and survival curves. The variations in individual immune responses, particularly in cytokine profiles, may influence the efficacy of PrEP therefore this research aims to contribute to

the development of personalized PrEP interventions tailored to individual immune responses.

2 Materials and methods

2.1 Dataset

The data was accessed from Center for the Aids Programme of Research in South Africa (CAPRISA 004) (4), a two arm double blinded randomized trial, placebo and tenofovir group conducted on HIV negative and sexually active women aged 18–40 years in South Africa for a period of 30 months; 18 months Accrual period and 12 months follow up. It was conducted between May 2007 and March 2010, and the dataset consist of survival and longitudinal data. The variables considered in this study were baseline characteristics and longitudinally measured cytokine profiles as described in the Supplementary Table S1.

2.1.1 Cytokine measurement

Plasma samples and cervicovaginal lavage specimens from cases and control were collected and stored for assessment. There were a total of 48 cytokines from 812 (tenofovir group = 405, placebo group = 407) women with 96 HIV infections (tenofovir group = 37, placebo = 59). The measurements were taken at irregular follow up times as shown in Figure 1 where majority of patients had their cytokine measurements recorded three times during the course of study. The average interval between the first and second cytokine measurements was 12 months, while the interval between subsequent cytokine measurements was 6 months.

2.1.2 Data pre-processing

The data underwent pre-processing to prepare it for subsequent analysis. The pre-processing steps involved eliminating variables with excessive missing values (Figure 2) i.e with more than 50% missingness and very small frequency percentages for the levels of some categorical variables. Additionally, in our efforts to enhance the robustness of our statistical analysis, we appropriately combined certain levels of categorical variables and renamed the strings. This step is crucial because a categorical variable with too many levels can compromise the model's performance due to small frequencies in some of the levels (24). Moreover, variables with only one level fail to positively impact the model due to very low variation, while levels that rarely occur have minimal chance of significantly affecting the model fit (25). These adjustments ensure that our analysis accurately captures the relationships within the data. Furthermore, Figure 2 demonstrates the completeness of our dataset, with almost 84.93% of variables containing no missing information, 10.46% missing income value data, and the remaining variables displaying other missing patterns.

The data preparation and the statistical analysis was done using the *R* version (R-4.3.2). The R code file for this analysis is available in the Supplementary Table S2. As a result of the pre-processing step, 24 baseline characteristics and 48 cytokines covariates were used as initial variables at the start of the analysis. The categorical variables were summarized using frequency and percentages depicted in the Supplementary Table S2. The patient baseline characteristics in relation to HIV status and treatment group is summarized in Table 1, where the number of years with stable partner ($p = 0.034$) and the patients receiving income from husband ($p = 0.026$) were significantly associated with HIV status and treatment group. The statistical analysis was conducted on complete cases only in two stages; the first is survival analysis on baseline covariates without the cytokine covariates effects then survival analysis when including the cytokine covariate effects. Cytokine variable profiles are time-varying covariates since they change over time through the follow-up period. Therefore, the cytokine information was included in three ways; firstly we averaged all measurements throughout the follow-up time to better capture their average effects, secondly we took the difference between the last and first measurement to model the effect of change and lastly we treated the cytokine as a time-dependent covariate.

2.2 Statistical methods

Four separate Cox PH models were fitted in an increasing complexity based on how the cytokine effects are included. Model 1 (Equation 8): Cox regression model with baseline variables only, model 2 (Equation 9): Cox regression model with baseline variables plus cytokine effects using the mean value of the cytokine measurements as covariate, model 3 (Equation 10): Cox regression model with baseline variables plus cytokine effects using the difference between the last observed cytokine value and the first value as covariate in the model and model 4 (Equation 11): Cox regression model with baseline variables plus time dependent cytokine effects.

2.2.1 Kaplan–Meier survival curves

The Kaplan–Meier estimator is a non-parametric statistic that is used to estimate the survival function based on lifetime data (26). The estimate is frequently used in medical research to examine recovery rates, likelihood of deaths and whether or not a treatment was effective. Furthermore, it is used to compare two groups of subjects, the control group and treatment group (27). The Kaplan–Meier survival curve is a graphical representation of the survival function defined as the probability of surviving in a given length of time while considering time in many small intervals (28).

To estimate the survival function $S(t)$ (the probability that life is longer than t), we consider survival time $t_i = t_1, t_2, ..., t_n$ including censored observations (ordered by increasing observation) of a group of n subjects. The proportion of individuals, $S(t)$, who survive after any follow up time t_i is estimated by (Equation 1)

$$S(t) = \prod_{t_i<t} \frac{n_i - d_i}{n_i} = \prod_{t_i<t} \left(1 - \frac{d_i}{n_i}\right) \quad (1)$$

where t_i is the largest survival time less than or equal to t, n_i is the number of individuals uninfected just before time t_i (the i^{th} ordered survival time) and d_i denotes the number who got HIV infection at time t_i (29). $S(t_0) = 1$ before the first infection of

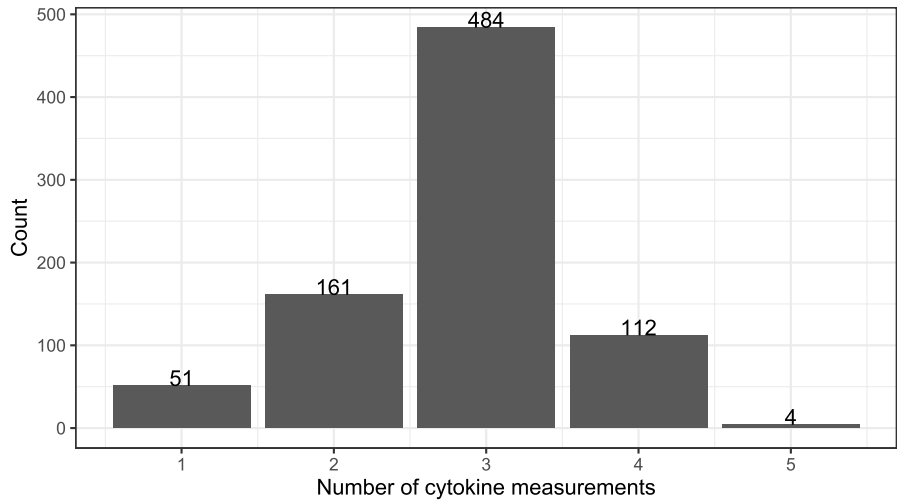

FIGURE 1
Total count for the frequency of cytokine profile measurements.

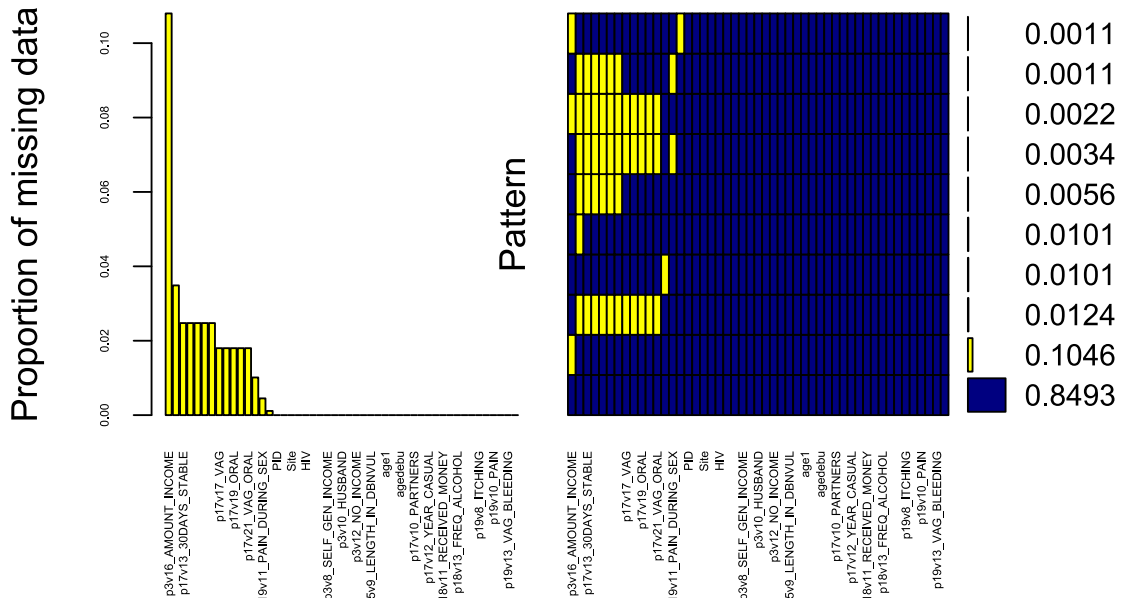

FIGURE 2
Missing data aggregation plot. Proportion of missing values for all variables in the dataset, sorted by decreasing order **(left)**. Combinations of missing values **(right)**: yellow squares in a matrix entry denote the presence of missing values for the variable associated to the column in the samples corresponding to the row; the bars on the right show the cardinality of each set of points. The *x*-axis displays the variable names (not all variables are displayed due to limited space).

HIV. The survival $S(t)$ at time t_i given the number of infections d_i and the number of uninfected patients n_i just before t_i is given by (Equation 2),

$$S(t_i) = \frac{n_i - d_i}{n_i} \times S(t_{i-1}). \tag{2}$$

Maximum likelihood estimation of the discrete hazard function h_i, (the probability of an individual experiencing an event at time t_i), yields the Kaplan–Meier estimator as shown (Equation 3),

$$\hat{S}(t) = \prod_{i\,:\,t_i \le t} \left(1 - \hat{h}_i\right) = \prod_{i\,:\,t_i \le t} \left(1 - \frac{d_i}{n_i}\right). \tag{3}$$

Moreover, The Kaplan–Meier estimator is a statistic, and its variance is approximated by numerous

TABLE 1 Summary description of patient's baseline characteristics stratified by HIV status and treatment group.

Variables	0:Placebo	1:Placebo	0:Tenofovir	1:Tenofovir	*p*
n	327	51	353	33	
Treat = Tenofovir (%)	0 (0.0)	0 (0.0)	353 (100.0)	33 (100.0)	<0.001
Site = Vulindlela (%)	215 (65.7)	33 (64.7)	239 (67.7)	21 (63.6)	0.917
months (mean [SD])	19.25 (5.86)	8.54 (5.52)	19.25 (5.57)	10.86 (7.28)	<0.001
Partner live together = No (%)	288 (88.1)	46 (90.2)	298 (84.4)	30 (90.9)	0.367
Highest education (%)					0.262
High school	289 (88.4)	46 (90.2)	311 (88.1)	26 (78.8)	
Primary	12 (3.7)	1 (2.0)	21 (5.9)	4 (12.1)	
Tertiary	26 (8.0)	4 (7.8)	21 (5.9)	3 (9.1)	
Self generated Income = Yes (%)	19 (5.8)	1 (2.0)	19 (5.4)	0 (0.0)	0.361
Salary = Yes (%)	38 (11.6)	6 (11.8)	36 (10.2)	6 (18.2)	0.565
Husband's income = Yes (%)	49 (15.0)	4 (7.8)	39 (11.0)	9 (27.3)	0.026
Social grants = Yes (%)	257 (78.6)	42 (82.4)	283 (80.2)	24 (72.7)	0.701
Other income source = Yes (%)	30 (9.2)	5 (9.8)	27 (7.6)	5 (15.2)	0.499
Income amount = < R10001 (%)	293 (89.6)	46 (90.2)	321 (90.9)	29 (87.9)	0.908
Years in Durban (mean [SD])	16.49 (9.05)	17.94 (7.94)	17.23 (9.46)	15.48 (8.55)	0.466
Age at enrollment (mean [SD])	24.02 (5.11)	22.63 (3.55)	24.60 (5.37)	23.64 (4.74)	0.053
Marital status (%)					0.761
Casual	7 (2.1)	2 (3.9)	6 (1.7)	0 (0.0)	
Married	20 (6.1)	2 (3.9)	25 (7.1)	1 (3.0)	
Stable & Casual	11 (3.4)	4 (7.8)	16 (4.5)	2 (6.1)	
Stable	289 (88.4)	43 (84.3)	306 (86.7)	30 (90.9)	
Age at debut (mean [SD])	6.53 (2.03)	6.16 (1.86)	6.43 (2.24)	6.24 (1.92)	0.618
Number of partners (mean [SD])	3.53 (12.45)	3.06 (3.16)	3.12 (6.50)	2.45 (1.70)	0.893
Years with stable partner (mean [SD])	1.02 (0.21)	1.06 (0.31)	1.06 (0.28)	1.18 (1.04)	0.034
Years with casual partner (mean [SD])	0.77 (6.51)	0.31 (0.73)	0.56 (4.50)	0.15 (0.57)	0.865
Stable partners in 30 days (mean [SD])	0.99 (0.11)	0.98 (0.14)	0.99 (0.13)	1.00 (0.00)	0.867
Casual partners in 30 days (mean [SD])	0.17 (1.23)	0.12 (0.38)	0.41 (4.20)	0.12 (0.33)	0.712
Times sex in 30 days (mean [SD])	8.71 (10.19)	7.20 (4.85)	8.91 (8.99)	7.58 (6.52)	0.573
Age of oldest sex partner (mean [SD])	27.69 (6.30)	26.24 (3.82)	28.20 (6.75)	26.88 (5.02)	0.149
Sex partner have other partner (%)					0.228
No	53 (16.2)	2 (3.9)	56 (15.9)	5 (15.2)	
Don't know	199 (60.9)	35 (68.6)	232 (65.7)	21 (63.6)	
Yes	75 (22.9)	14 (27.5)	65 (18.4)	7 (21.2)	
Frequency of condom use = Occasionally (%)	227 (69.4)	37 (72.5)	254 (72.0)	20 (60.6)	0.533
Vaginal abnormal discharge = Yes (%)	97 (29.7)	16 (31.4)	114 (32.3)	17 (51.5)	0.085

0: HIV negative, 1: HIV positive.

estimators such as Greenwoods's formula (30) that gives (Equation 4),

$$\hat{Var}\left(\hat{S}(t)\right) = \hat{S}(t)^2 \sum_{i:t_i \le t} \frac{d_i}{n_i(n_i - d_i)} \quad (4)$$

The log-Rank test: Is used to compare the hazards between two groups or more by testing the null hypothesis that the probability of an event at any time point between the two or more populations do not differ. Thus, log-rank test compares the survival function of the two groups (27). The null hypothesis will be rejected if the *p*-value is <0.05.

2.2.2 Stepwise Cox proportional hazard model (Cox PH)

Stepwise Cox proportional hazards regression is a method of selecting a subset of relevant variables for a Cox regression

model from a larger set (31). Cox PH is the most widely used statistical method for analyzing the time-to-event data (16). The Cox PH model assesses the impact of multiple factors on survival simultaneously. Essentially, it enables one to investigate how specified predictors influence the rate of a specific event happening such as infection or death at a given point in time (32). This rate is commonly known as hazard rate.

In order to evaluate the association of the baseline and cytokine effects covariate and survival time, consider sample size n from sample $k = 1, 2, ..., n$ and $C_k = (C_{k1}, C_{k2}, ..., C_{kp})$ is a vector of p covariates (baseline plus cytokine effect covariates) of the different models. The k^{th} patient survival data can be represented by (T_k, θ_k, C_k), where T_k and θ_k are the survival time and censor status, respectively. Mathematically, the general Cox PH (33) in Equation 5 is represented as

$$h_k(t; C_k) = h_0(t)e^{\beta' C_k} \tag{5}$$

where β is the parameter vector of the regression coefficients and $\boldsymbol{C_k}$ is the covariate (baseline and cytokine effects) vector. $h_0(t)$ is an unspecified baseline hazard function that corresponds to the value of the hazard if all C_k are equal to zero. The hazard ratio for two patients (Equation 6), k and i is

$$\frac{h_k(t; C_k)}{h_i(t; C_i)} = \frac{e^{\beta' C_k}}{e^{\beta' C_i}} \tag{6}$$

and is independent of time t. Cox PH model parameters are estimated by the maximum partial likelihood method given below (Equation 7);

$$L(\beta) = \prod_{r \in E} \frac{e^{\beta^T C_r}}{\sum_{i \in R_r} e^{\beta^T C_r}} \tag{7}$$

where E is the indices of the HIV infection and R_r represent vector of indices for individuals at risk at time t_r.

The stepwise Cox proportional hazards regression method adds or removes predictor variables from the model based on some criteria, such as the Akaike information criterion (AIC) or the Bayesian information criterion (BIC) (34). The AIC and BIC are measures of how well the model fits the data, and they penalize models that have too many parameters. The lower the AIC or BIC, the better the model (35). The stepwise Cox PH regression method can be performed using different methods, such as forward selection, backward elimination, bidirectional selection, or score selection (36). Forward selection starts with an empty model and adds one variable at a time until it reaches a stopping criterion, such as a minimum AIC or BIC value. Backward elimination starts with a full model and removes one variable at a time until it reaches a stopping criterion. Bidirectional selection starts with an empty model and adds one variable at a time in both directions until it reaches a stopping criterion. Score selection starts with an empty model and adds one variable at a time based on its score in terms of AIC or BIC.

We used the packages *StepReg* (37) to implement stepwise regression, *Survival* and *survminer* to implement Cox PH model in R. The specific Cox PH models for model 1, model 2, model 3, and model 4, as described above, are formulated as follows:

2.2.3 Model 1

The model that includes the baseline covariates only. We call this the naive Cox PH model. The assumption is that regression parameters remain constant over time (38). Consequently, the hazard ratio for any two individuals remains constant over time. The Model is given by,

$$h_k(t; X_k) = h_0(t) \times exp(\beta' X_k) \tag{8}$$

with $h_0(t)$ as the baseline hazard function, β is the vector of regression coefficients for baseline covariates X_k.

2.2.4 Model 2

The model that includes the baseline covariates plus cytokine effects using the mean value of the cytokine measurements as the covariate. Here the derived cytokine is the average of all the cytokine measurements for an individual patient recorded at different follow up time. It models the average effect of the time-varying cytokine covariate (15). The Cox model is;

$$h_k(t; X_k, G_k) = h_0(t) \times exp\left(\beta' X_k + \delta' \bar{G}_k\right) = h_0(t) \times exp\left(\beta' X_k + \sum_{j=1}^{v} \delta_j \bar{G}_{kj}\right) \tag{9}$$

where $h_0(t)$ is the baseline hazard function, β is the regression coefficient vector for time invariant covariates X_k, $\bar{G}_{kj} = \frac{1}{m_{kj}} \sum_{r=1}^{m_{kj}} G_{krj}$ for $r = 1, 2, ..., m_{kj}$, represents the average value of the cytokine level measured longitudinally for the k^{th} subject with m_{kj} observations for cytokine j ($j = 1, 2, ..., v$). The scalar $\delta_j \in \mathbb{R}$ is the parameter that links the average to the hazard.

2.2.5 Model 3

The model that includes the baseline covariates plus cytokine effects using the difference between the last observed cytokine value and the first value as the covariate in the model. It models the effect of change in the cytokine covariates (39).

$$h_k(t; X_k, D_k) = h_0(t) \times exp\left(\beta' X_k + \delta' D_k\right) = h_0(t) \times exp\left(\beta' X_k + \sum_{j=1}^{v} \delta_j D_{kj}\right) \tag{10}$$

where $h_0(t)$ is the baseline hazard function, β is the regression coefficient vector for the time invariant covariates X_k, $D_{kj} = \left[G_{km_{kj}} - G_{k1j}\right]$ represents the difference between the last and first cytokine levels observed longitudinally for the k^{th} subject, with m_{kj} measurements for cytokine j ($j = 1, 2, ..., v$). The scalar $\delta_j \in \mathbb{R}$ is the parameter that links the change to the hazard. The model answers the question whether a big or small change in cytokine has an effect on HIV acquisition.

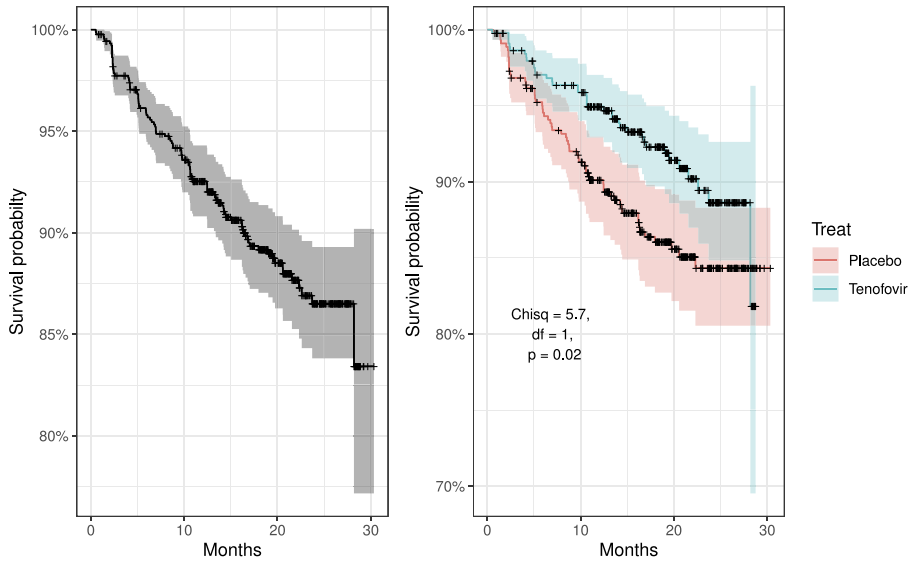

FIGURE 3
Kaplan–Meier survival curves: left panel showing overall survival curve for all participants and right panel compares overall survival curves by treatment groups, placebo vs. tenofovir participants.

2.2.6 Model 4

The model that includes the baseline covariates plus time dependent cytokine effects. When a covariate changes over time throughout the follow-up period, this is referred to as time-varying/time dependent covariate (40). For this it is critical to structure the data in a counting process format. We code the time-dependent covariate using time intervals (41). The hazard is assumed to be proportional to the instantaneous probability of an event at a specific time conditional on the variables at that time (42). The interpretation of the results of this approach is more complicated than a naïve baseline approach as the covariate information changes over time. Here we consider sample size n subjects, consisting of $\left[T_k, \theta_k, \left[G_k(t), 0 \leq t \leq T_k\right], k = 1, 2, ..., n\right]$, T_k is the time-to event for the kth subject, θ_k is the event indicator and $G_k(t)$ is the time varying covariate. The Cox PH model becomes,

$$h(t; X_k, G_k) = h_0(t) \times exp\left(\beta' X_k + \delta' G_k(t)\right) = h_0(t) \times exp\left(\beta' X_k + \sum_{j=1}^{v} \delta_j G_{kj}(t)\right) \quad (11)$$

where $h_0(t)$ is the baseline hazard function, β is the regression coefficient vector for time invariant covariates, $G_{kj}(t) = \left[G_{k1j}(t), G_{k2j}(t), ..., G_{km_{kj}}(t)\right]$ is a set of covariates for the number of longitudinal measures m_{kj} for the k^{th} subject of cytokine j ($j = 1, 2, ..., v$). The scalar $\delta_j \in \mathbb{R}$ represent the parameter that links the time dependent covariates to the hazard.

3 Results

3.1 Kaplan–Meier survival curves analysis

Figure 3 shows the overall survival curve over time and the overall survival comparison between the two treatment group. It is clear that patients from Tenofovir treatment arm have a better chance of surviving (less probability of HIV acquisition) more than the patients from placebo group. The placebo curve has a steeper slope indicating a higher HIV infection rate, therefore a worse survival prognosis. The curve have plateaus from 24th month indicating no change in survival. The curves comparing the two treatment cross in the first few months and consistently separate afterwards. The log-rank test performed gives $\chi^2 = 5.7$, $df = 1$ and p-value = 0.02. Since p-value is <0.05 we reject the null hypothesis to conclude that there is sufficient evidence indicating that the two treatment groups are significantly different in terms of survival.

3.2 Stepwise Cox proportional hazard analysis

The results of the survival problem based on the effects of cytokine biomarkers (mean, difference, and time dependent effect) were obtained. As a first step, we employed the stepwise regression using the *stepwiseCox* function. Within the function we specified the following arguments; model selection procedure to be bidirectional, model selection metric as the AIC, significance level of entry and exit value in the model as 0.15 and model approximation method as Efron. Bidirectional selection procedure is the appropriate since it adds variables in both directions. Moreover, backward selection produces same results as bidirectional while forward selection produces results with more covariates and larger AIC. The model selection criterion AIC was used to determine the order in which effects enter and leave at each step of the specified model selection procedure (bidirection). The value 0.15 is a commonly used p value threshold which is a statistical significance level that a predictor variable must meet to be included or to stay in the model. Several

TABLE 2 Multivariable Cox PH results for predictors of HIV survival among women aged 18–40 years (model 1).

Variable	HR (SE)	95% CI	*p*-value
Age at enrollment	0.949 (0.026)	(0.902, 0.998)	0.042*
Treatment group			
Placebo	1.000		
Tenofovir	0.6286 (0.225)	(0.405, 0.977)	0.039*
Self generated income			
No	1.000		
Yes	0.225 (1.013)	(0.031, 1.634)	0.140
Vaginal abnormal discharge			
No	1.000		
Yes	1.431 (0.225)	(0.920, 2.226)	0.112
Salary			
No	1.000		
Yes	1.658 (0.322)	(0.882, 3.116)	0.116
Sex partner have other partner			
No	1.000		
Don't know	1.849 (0.403)	(0.840, 4.072)	0.127
Yes	2.280 (0.438)	(0.966, 5.383)	0.060

*p-value < 0.05.

approximation methods have been proposed to handle tied events in cox regression such as Breslow, Efron, and Exact (methods of obtaining Cox partial likelihood estimate of the baseline hazard function). However, the Efron method performs better in terms of time, fit statistics, and differences in parameters estimates (43). We then tested the Cox PH assumption of the selected covariates using Schoenfeld residuals test (44) by applying the *cox.zph* function. The analysis of the results for model 1-4 are shown in Tables 2–5.

The analysis result of model 1 in Table 2 indicates that age at enrolment was the only significant predictor of HIV hazard. Tenofovir treatment group reduced the hazard of HIV infection as compared to the Placebo treatment group (HR: 0.629, 95% CI: 0.405,0.977). The adjusted hazard ratio for a 1 year increase in age at enrolment is 0.949 (95% CI: 0.902, 0.998). This implies that HIV incidence decreases with increasing age.

Model 2 results in Table 3 shows that tenofovir treatment group reduced the hazard of HIV infection as compared to the placebo treatment group (HR: 0.486, 95% CI: 0.296, 0.798). For every average unit increase of the cytokines IL-12P70, IL-16, B-NGF, SCGF-B, IL-17A and IL-3 there is a decrease of HIV hazard by 2.32% (HR: 0.977, 95% CI: 0.968, 0.986), 0.44% (HR: 0.996, 95% CI: 0.999, 0.999), 19.3% (HR: 0.807, 95% CI: 0.670, 0.973), 0.07% (HR: 0.995, 95% CI: 0.993, 0.999), 2.14% (HR: 0.979. 95% CI: 0.965, 0.992) and 1.1% (HR: 0.989, 95% CI: 0.982, 0.996) respectively. On the other hand for every average unit increase of the cytokines SCF, TNF-A, CTACK, IL-10, IL-5 and IFN-A2 there is an increase of HIV hazard by 11.31% (HR: 1.113, 95% CI: 1.077, 1.151), 1.77% (HR: 1.018, 95% CI: 1.009, 1.027), 3.94% (HR: 1.039, 95% CI: 1.016, 1.063), 4.9% (HR: 1.049, 95% CI: 1.013, 1.086), 10.6% (HR:

TABLE 3 Multivariable Cox PH results for predictors of HIV survival among women aged 18–40 years (model 2).

Variable	HR (SE)	95% CI	*p*-value
Age of oldest sex part	0.945 (0.026)	(0.898, 0.995)	0.031*
Treatment group			
Placebo	1.000		
Tenofovir	0.486 (0.253)	(0.296, 0.798)	0.004**
M-CSF	1.004 (0.001)	(1.002, 1.006)	0.000***
Salary			
No	1.000		
Yes	2.474 (0.358)	(1.227, 4.987)	0.011*
Frequency of condom use			
Always	1.000		
Occasionally	1.543 (0.272)	(0.905, 2.632)	0.111
Age at debut	0.884 (0.069)	(0.772, 1.012)	0.073
Number of stable partner (past year)	1.480 (0.188)	(1.025, 2.138)	0.037*
Vaginal abnormal discharge			
No	1.000		
Yes	1.513 (0.249)	(0.930, 2.463)	0.096
Sex partner have other partner			
No	1.000		
Don't know	2.948 (0.441)	(1.241, 7.001)	0.014*
Yes	2.613 (0.492)	(0.996, 6.854)	0.051
Self generated income			
No	1.000		
Yes	0.261 (1.040)	(0.034, 2.005)	0.197
MIG	1.000 (0.000)	(1.000, 1.000)	0.001**
MIP-1B	1.001 (0.000)	(1.001, 1.001)	0.000***
MCP-1	0.991 (0.005)	(0.982, 1.000)	0.053
SCF	1.113 (0.017)	(1.077, 1.151)	0.000***
IL-12P70	0.977 (0.005)	(0.968, 0.986)	0.000***
IL-16	0.996 (0.002)	(0.992, 1.000)	0.034*
MIF	1.000 (0.000)	(1.000, 1.0000)	0.001***
B-NGF	0.807 (0.095)	(0.670, 0.973)	0.024*
SCGF-B	0.995 (0.000)	(0.993, 0.999)	0.000***
TNF-A	1.018 (0.005)	(1.009, 1.027)	0.000***
IL-17A	0.979 (0.007)	(0.965, 0.992)	0.002**
MCP-3	0.982 (0.011)	(0.961, 1.004)	0.110
CTACK	1.039 (0.012)	(1.016, 1.063)	0.001***
IL-10	1.049 (0.018)	(1.013, 1.086)	0.007**
IL-5	1.106 (0.049)	(1.004, 1.218)	0.041*
G-CSF	1.000 (0.000)	(1.000, 1.000)	0.034*
IL-3	0.989 (0.004)	(0.982, 0.996)	0.003**
IL-2RA	1.023 (0.013)	(0.997, 1.049)	0.085
IFN-A2	1.028, (0.011)	(1.006, 1.050)	0.012*

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001.

TABLE 4 Multivariable Cox PH results for predictors of HIV survival among women aged 18–40 years (model 3).

Variable	HR (SE)	95% CI	*p*-value
Age of oldest sex partner	0.946 (0.023)	(0.903, 0.990)	0.017*
Sex partner have other partner			
No	1.000		
Don't know	2.6235 (0.441)	(1.106, 6.223)	0.029*
Salary			
No	1.000		
Yes	1.887 (0.330)	(0.988, 3.607)	0.055
Yes	3.991 (0.487)	(1.535, 10.373)	0.005**
Treatment group			
Placebo	1.000		
Tenofovir	0.652 (0.238)	(0.409, 1.039)	0.072
Husband's income			
No	1.000		
Yes	1.901 (0.316)	(1.023, 3.534)	0.042*
Self generated income			
No	1.000		
Yes	0.267 (1.028)	(0.036, 2.003)	0.199
IL-1RA	1.000 (0.000)	(1.000, 1.000)	0.004**
MIF	1.000 (0.000)	(1.000, 1.000)	0.000***
B-NGF	0.896 (0.026)	(0.851, 0.943)	0.000***
CTACK	1.022 (0.005)	(1.013, 1.032)	0.000***
IL-5	0.923 (0.023)	(0.882, 0.966)	0.001***
IL-2	1.106 (0.033)	(1.037, 1.179)	0.002**
IL-1A	1.000 (0.000)	(0.999, 1.000)	0.106
TRAIL	0.997 (0.001)	(0.995, 0.999)	0.014*
PDGF-BB	1.005 (0.002)	(1.002, 1.008)	0.003**
EOTAXIN	0.977 (0.012)	(0.954, 1.000)	0.052
IL-16	0.999 (0.000)	(0.998, 0.999)	0.028*
SCF	1.0138 (0.009)	(0.997, 1.030)	0.107

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001.

TABLE 5 Multivariable Cox PH results for predictors of HIV survival among women aged 18–40 years (model 4).

Variable	HR (SE)	95% CI	*p*-value
Other income source			
No	1.000		
Yes	2.807 (0.480)	(1.095, 7.197)	0.032*
Age of oldest sex partner	0.920 (0.033)	(0.862,0.982)	0.012*
Vaginal abnormal discharge			
No	1.000		
Yes	1.688 (0.318)	(0.906, 3.146)	0.099
Age at debut	0.824 (0.080)	(0.704, 0.963)	0.015*
Treatment group			
Placebo	1.000		
Tenoofovir	0.652 (0.185)	(0.454, 0.938)	0.021*
Sex in last 30 days	0.930 (0.035)	(0.868, 0.995)	0.037*
Salary			
No	1.000		
Yes	2.186 (0.454)	(0.899, 5.320)	0.085
Years lived in Durban	1.039 (0.019)	(1.001, 1.080)	0.045*
Site			
eThekwini			
Vulindlela	0.487 (0.411)	(0.218, 1.089)	0.080
SCF	1.040(0.009)	(1.022, 1.058)	0.000***
IL-15	0.909 (0.034)	(0.851, 0.971)	0.004**
MIP-1B	1.001 (0.000)	(1.000, 1.001)	0.001***
SCGF-B	0.994 (0.000)	(0.992, 0.999)	0.028*
GM-CSF	0.993 (0.003)	(0.988, 0.999)	0.018*
G-CSF	0.999 (0.000)	(0.999, 1.000)	0.098

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001.

1.106, 95% CI: 1.004, 1.220), and 2.75% (HR: 1.028, 95% CI: 1.006, 1.050) respectively.

After including the mean value of the cytokine measurements as covariate, the Cox model showed that age of the oldest sex partner, salary, years with stable partner and sex partner have other partner variables were significant baseline predictors associated with HIV infection. For every year increase for the age of the oldest sex partner, the hazard of HIV decreases by 5.47% (HR: 0.945, 95% CI: 0.898, 0.995). Patients who earned salary had a higher risk of HIV infection (HR: 2.474, 95% CI: 1.227, 4.987) compared to their counterparts who did not earn salary. It was surprising to note that, for every one additional stable partner there was about a 1.5 fold increase in hazard of HIV infection (HR: 1.480, 95% CI: 1.023, 2.138). Moreover, the patients whom did not know if their sex partners had other sex partners had a higher HIV hazard (HR: 2.948, 95% CI: 1.241, 7.001) than those who knew their sex partners did not have other sex partners. Testing the PH assumption using the Scaled Schoenfeld test for the significant variables indicated that CTACK (χ^2: 4.710, df: 1, p: 0.03) did not meet the Cox PH assumptions.

The results of model 3 shown in Table 4 depicts that Tenofovir treatment group reduced the hazard of HIV infection as compared to the placebo treatment group (HR: 0.652, 95% CI: 0.238, 1.039). For every unit change (difference) of the cytokines B-NGF, IL-5, IL-16 and TRAIL there is a decrease of HIV infection by 10.38% (HR: 0.896, 95% CI: 0.851, 0.943), 7.7% (HR: 0.923, 95% CI: 0.882, 0.966), 0.08% (HR: 0.999, 95% CI: 0.998, 0.999) and 0.3% (HR: 0.997, 95% CI: 0.995, 0.999) respectively while for the same change in the cytokine CTACK, IL-2 and PDGF-BB there is an increase of HIV infection by 2.23% (HR: 1.022, 95% CI: 1.013, 1.032), 10.59% (HR: 1.106, 95% CI: 1.037, 1.179) and 0.49% (HR: 1.005, 95% CI: 1.002, 1.008) respectively. After including the difference value (between last observed and first value) of the cytokine measurements as covariate, the Cox model showed that

TABLE 6 Comparative tests to evaluate Cox PH model performances.

	Model 1	Model 2	Model 3	Model 4
AIC (df)	1,064.5 (7)	919.3 (30)	955.3 (19)	531.4 (14)
Likelihood ratio test (df)	22.1 (7)	185.9 (30)	127.4 (19)	70.0 (14)
Wald test (df)	19.1 (7)	168.3 (30)	119.6 (19)	67.1 (14)
Logrank test (df)	19.9 (7)	248.9 (30)	136.9 (19)	102.4 (14)

sex partner have other partner, husband's income and age of the oldest sex partner covariate were significant baseline predictors associated with HIV infection. For every year increase of age for the oldest sex partner, HIV risk decreases by 5.47% (HR: 0.945, 95% CI: 0.898, 0.995). Both patients who did not know if their partners had other sex partners (HR: 2.948, 95% CI: 1.241, 7.001) and those who knew their sex partners had other partner (HR = 3.991, 95% CI: 1.535, 10.373) had a higher HIV hazard compared to those who knew their partners had no other sex partners. Additionally, the ones who received income from husband (HR: 1.901, 95% CI: 1.023, 3.534) had a higher hazard of HIV than those who did not receive any income from their husband. Testing the PH assumption using the Scaled Schoenfeld test indicated that all the significant variables from the model met the PH Cox assumptions.

Table 5 presents the analysis results of model 4 which indicates that tenofovir treatment group reduced the hazard of HIV infection as compared to the placebo treatment group (HR: 0.652, 95% CI: 0.454, 0.938). The cytokines IL-15, SCGF-B and GM-CSF had an instantaneous decrease of HIV incidence by 9.11% (HR: 0.909, 95% CI: 0.851, 0.971), 0.07% (HR: 0.994, 95% CI: 0.992, 0.999), and 0.68% (HR: 0.993, 95% CI: 0.988, 0.998) respectively at a particular time t. Conversely, SCF had an instantaneous increase of HIV incidence by 4.02% (HR: 1.040, 95% CI: 1.022, 1.058) at a particular time *t*. When using the cytokines as time dependent covariate, the Cox PH analysis indicated that significant baseline predictors were; age of oldest sex partner, other source of income, age at debut, sex in the last 30 days, and years lived in Durban. For every year increase of the age of the oldest sex partner and patient's age at debut, the hazard of HIV infection increases by 7.99% (HR: 0.920, 95% CI: 0.862, 0.982) and 17.63% (HR: 0.824, 95% CI: 0.704, 0.963) respectively. The less sex the patient had in the previous 30 days, the lower the patient's HIV risk by 7.04% (HR: 0.930, 95% CI: 0.868, 0.995). Furthermore, for every extra year the patient spends in Durban, the chance of HIV infection rises by 3.94% (HR: 1.039, 95% CI: 1.001,1.080). Likewise individuals with other sources of income had an increased risk of HIV infection by 180.68% (HR: 2.807, 95% CI: 1.095, 7.197) compared to those without. Upon testing the PH assumption on significant variables using scaled Schoenfeld residual test, other sources of income (χ^2: 5.288, df: 1, p: 0.022) and age of oldest sex partner (χ^2: 5.426, df: 1, p: 0.020) violated the PH assumption.

The overall performance of the models (model 1–4) shown in Table 6 indicate that model 4 had the lowest AIC, while model 1 the highest AIC. The overall survival of the models over time are depicted in Figure 4.

The plot in Figure 5 show how the effects of the covariates in model 4 (with the lowest model fit scores as shown in Table 6) change over time. The intercept of the model 4 in Figure 5 had a smooth increasing slope over time. The time dependent cytokine covariates; G-CSF, GM-CSF, IL-15, MIP-1B, SCGF-B, and baseline covariates; age at debut, sex in the last 30 days, age of oldest sex partner and site had a decreasing slope over time. Increasing slope over time is observed in the time-dependent covariate SCF and baseline covariates; abnormal discharge, other income source, salary and years lived in Durban. Table 7 indicate which cytokines overlap between model 2–4, or which are no longer significant in the subsequent models. Figure 6 illustrates the direction of change for the significant cytokines identified in the analysis of models 2–4.

4 Discussion

The global HIV pandemic remains a significant public health challenge, necessitating the continuous exploration of innovative preventive strategies (45). Pre-exposure prophylaxis (PrEP) particularly Antiretroviral Microbicide has emerged as a promising intervention for individuals at high risk of HIV acquisition (4). However, variations in individual immune responses, particularly in cytokine profiles, may influence the efficacy of PrEP. It is known that dynamic changes in immune states are linked with HIV acquisition, and biomarkers, demographic and behavioral data add complementary details to HIV risk (21). Recent research has highlighted the potential of cytokines as biomarkers in the Pre-exposure prophylaxis. Cytokines have been suggested as potential predictors of HIV acquisition.

This study investigated the effect of individual cytokine biomarkers that changes over time in determining HIV incidence among individuals randomized to PrEP vs. control exposure by building a series of Cox Proportional Hazard models. The Cox PH is essentially a regression model commonly used statistical method in medical research and in other applications for investigating the association between the survival time and one or more predictor variables (16). The simple form of Cox model is when it models time fixed covariates. One of the strengths of the extended Cox model is its ability to incorporate covariates that change over time. This functionality is practical because, at each event time, the Cox model compares the current covariate values of the subject experiencing the event with the current values of all other subjects who were at risk at that time (41). We incorporate stepwise regression in the Cox PH model to eliminate noisy variables and remain with the best model fit (31).

The cytokine biomarkers in our data set changes over time i.e they were longitudinally measured, indicating the presence of a time-varying covariates. When such covariates exist, an analyst should consider taking them into account in survival modeling in order to improve estimation (15). The presence of time-dependent covariates in a model offers exciting opportunities for exploring associations and potentially causal mechanism (46). However, the use of these variables is technically difficult in the choice of covariate form, might have great potential for bias and violates the assumption that the hazard ratio for any two individual remains constant over time. We therefore, improve the model fit by using derived cytokine variables from the longitudinal measurements. As

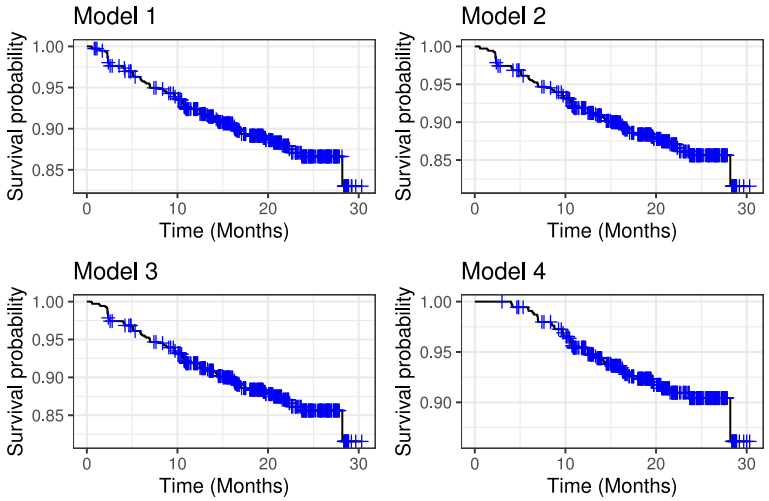

FIGURE 4
Comparative overall survival curves for model 1 (upper left panel), model 2 (upper right panel), model 3 (lower left panel) and model 4 (lower right panel).

a starting point in modeling, we started with Model 1 (Equation 8), a traditional time-invariant (baseline covariates) Cox PH model. In this model the initial variables were 24 which were further reduced to seven variables that contributed to the best model fit and it estimated age at enrollment as the only significant predictors of HIV risk.

The first improved model (model 2-Equation 9) we used baseline covariates plus the individual level average of the cytokine measurements to better describe the average effect of the time-varying cytokine covariate. Through stepwise regression the covariates were reduced from 72 to 30 in the final best fit model. When comparing model 1 with model 2 we are able to identify four other different baseline covariate (Age of oldest sex partner, salary, years with stable partner and sex partner having other sex partner) and twelve individual average cytokines (IL-3, IL-5, IL-10, IL-16, IL-17A, IL-12P70, CTACK, SCF, B-NGF, SCGF-B, TNF-A, IFN-A2) that are significantly associated with HIV risk. Therefore, the predictive performance of model 2 was better than model 1 with lower AIC (919.3) in comparison to model 1 AIC (1,064.5). This clearly showed that not accounting for cytokine effect in model 1 confounded the effect of other significant baseline characteristics.

Model 3 (Equation 10) is the second improved Cox PH model which consisted of baseline covariates plus individual cytokine difference between the first and the last observed measurement. The final best model fit in model 3 had 19 covariates from an initial total of 72. Notably the model had a better predictive performance compared to model 1 as it had three additional baseline covariates (sex partner having other partners, husband's income, age of the oldest sex partner) and seven individual difference cytokines (IL-2, IL-5, IL-16, CTACK, PDGF-BB, BNG-F and TRAIL) that were significant predictors of HIV infection. Furthermore, when compared to model 2, there were three similar baseline covariates (age of the oldest sex partner, treatment group and sex partner having other partner) that were significant predictors in both models. However, there were fewer cytokine covariates than in model 2, with IL-5, IL-16, CTACK, and BNG-F all being significant cytokine covariates in both models. When compairing the AIC of the models, model 3 had a lower AIC than model 1 but slightly higher than AIC of model 2. Model 3 predicted the individual level changes of the cytokines and its association with HIV risk therefore accounting for time. The major drawback of the model was some individuals had single measurements hence no change effect observed. Additionally, the model ignores the intermediate changes between the first and the last observed cytokine measurement which implies loss of information within individual cytokine measurements.

The last improved Cox PH model fit was model 4 (Equation 11) that used baseline covariates plus time-dependent cytokine covariates. The final best model fit consisted of 14 variables out of 72. When compared to model 1, there were five additional baseline covariates (age of oldest sex partner, age at debut, other income source, sex in the last 30 days and years lived in Durban) and four time-dependent cytokines (SCF, IL-5, SCGF-B and GM-CSF). Moreover, Age of oldest sex partner and IL-5 were significant predictors estimated by all the improved models while SCF and SCGF-B were both predictors by model 2 and 4. Likewise CTACK, IL-5, IL-16 and B-NGF were significant predictors estimated in both model 3 and 4. Table 7 indicate which cytokines overlap between models 2–4, or which are no longer significant in the subsequent models.

Overall, model 2 produced the greatest number of significant cytokine predictor variables, giving a wider perspective to a researcher which cytokine biomarkers are associated with HIV Hazard. However, there is loss of time information in this model for the derived cytokine variables. Model 4 on the other hand had the lowest AIC compared to the other models making it the best model. This emphasizes that time-dependent covariates is a powerful tool for exploring predictive relationships. Nevertheless, their use and interpretation is much more complicated in practice than the fixed (baseline) covariates.

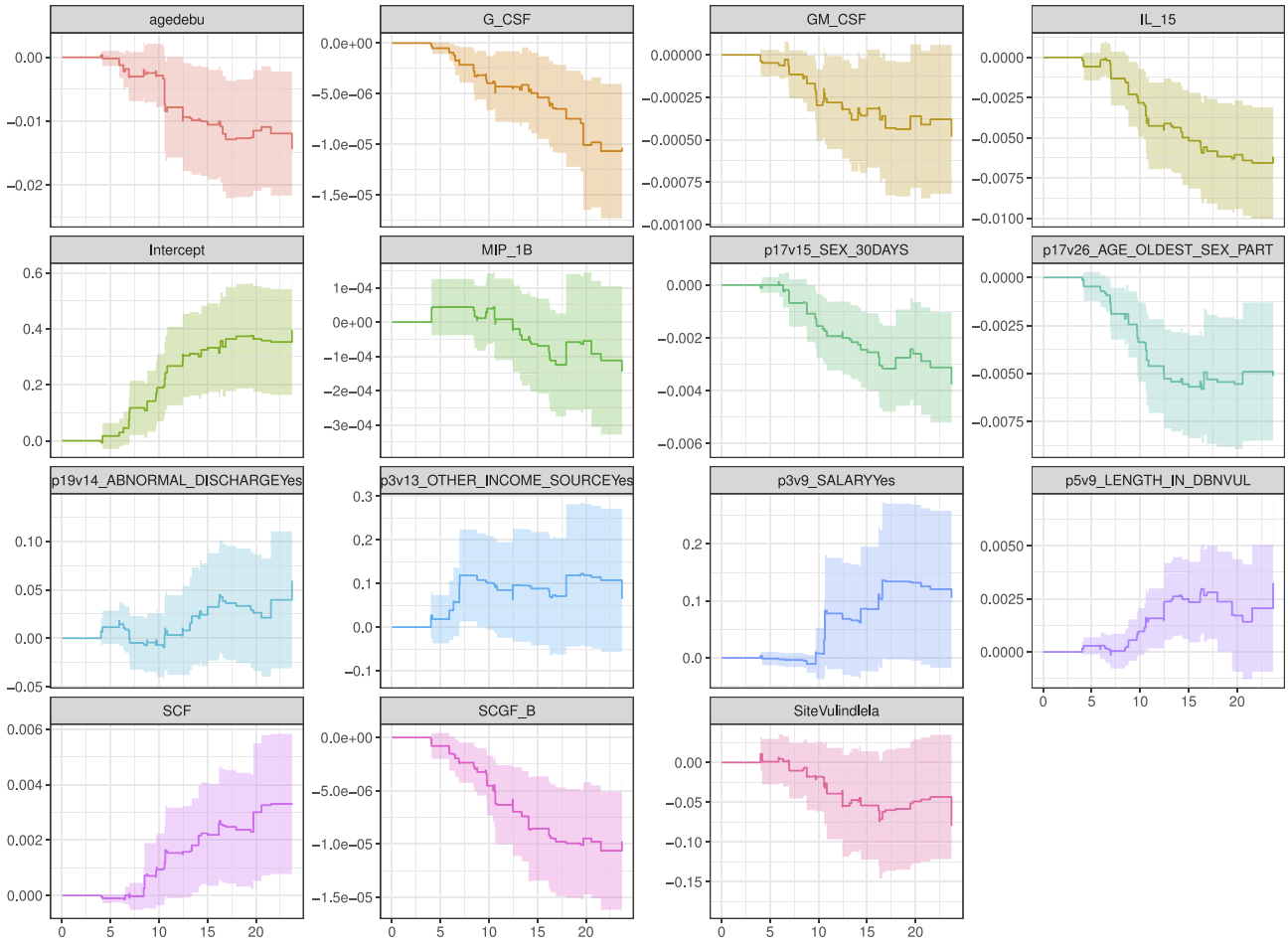

FIGURE 5
Overall trend of the covariate effects (only significant baseline and cytokine covariates) for model 4 over time. Abreviations of the baseline characteristics: agedebu, age at debut; p17v15_SEX_30DAYS, number of times had sex in 30 days; p17v26_AGE_OLDEST_SEX_PART, age of oldest sex partner; p19v14_ABNORMAL_DISCHARGEYes, abnormal discharge variable for yes category; p3v13_OTHER_INCOME_SOURCEYes, other income sources for category yes; p3v9_SALARYYes, salary variable for category yes; p5v9_LENGTH_IN_DBNVUL, number of years lived in Durban Vulindlela area; SiteVulindlela, site variable for category Vulindlela.

Furthermore the potential for erroneous inference and modeling is increased (46).

Our findings reveal that incorporating cytokine biomarkers into the PH regression model not only enhances the model's predictive performance but also provides more insightful information about significant predictors linked to HIV incidence. These results are consistent with a recent study by Ignacio et al. (21), which found that changes in cytokine levels over time are highly predictive of HIV acquisition and that cytokines influence the effects of sociobehavioral risk factors on HIV acquisition. Although Ignacio et al. (21) used a different model (LASSO machine learning algorithms), a different dataset (Sabes study), and selected fewer biomarkers (10 cytokines), their study also highlighted the importance of immune activation markers in predicting HIV beyond traditional demographic and behavioral factors, aligning with our objective. Our analysis identified and reported several baseline predictors such as the age of the oldest sex partner, participant's age at enrollment, earning a salary or not, years with a stable partner, income source, whether the sex partner has other partners, and frequency of sex in the last 30 days as significantly associated with HIV incidence. These findings align with those of other research studies (47–55).

In the previous analysis by Masson et al. (18) to investigate whether genital inflammation influenced HIV acquisition in women, they used 12 cytokines out of 48 available cytokine measurements. This selection was disadvantageous as it excluded other potentially relevant cytokine covariates. They utilized conditional logistic regression which has limitations because the risk sets and time-dependent covariates are predefined, unlike in Cox regression, where these factors are calculated at the time of each case failure (56). Moreover, Cox models that was employed in our study, offers more statistical power than logistic regression models because they account for the time until the event occurs (57). Naranbhai et al. using the same dataset, employed logistic regression and PCA to investigate the role of immune activation in HIV acquisition. The PCA's assumption of linearity limits its effectiveness in interpreting the components, as they are linear combinations of the original variables (58). Ngcobo et al. (20), in

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TABLE 7 Significant predictors of HIV survival among women aged 18–40 years for model 2–4.

Variable	Model 2	Model 3	Model 4
IL-16	✓	✓	
MIF	✓	✓	
B-NGF	✓	✓	
CTACK	✓	✓	
IL-5	✓	✓	
MIG	✓		✓
SCGF-B	✓		✓
SCF	✓		✓
MIP-1B	✓		
MCP-1	✓		
IL-12P70	✓		
TNF-A	✓		
IL-17A	✓		
MCP-3	✓		
IL-10	✓		
G-CSF	✓		
IL-3	✓		
IL-2RA	✓		
IFN-A2	✓		
IL-1RA		✓	
IL-2		✓	
TRAIL		✓	
PDGF-BB		✓	
IL-15			✓
GM-CSF			✓

The table indicate which cytokines overlap between the different models, or which are no longer significant in the subsequent models.
Blank: cytokine absent in the model.
✓: cytokine was significant in the model.

their study of examining whether pre-infection plasma cytokine concentrations predicted the rate of HIV disease progression in the same study cohort, used linear regression to assess the impact of each cytokine on viral load (VL) and the CD4:CD8 ratio in both bivariate and multivariable models. The major drawback of linear regression is its lack of consideration for time continuity (56). Notably, none of the previous studies exploring predictors of HIV progression (20, 22, 23) using CAPRISA 004 trial considered cytokine biomarkers as time-varying covariates. This study underscores the importance of incorporating longitudinal risk factor information in predicting HIV incidence.

Our study results successfully confirmed the cytokines Interleukin (IL-2, IL-3, IL-5, IL-10, IL-16, IL-12P70, and IL-17 alpha), Stem cell factor (SCF), Beta Nerve growth factor (B-NGF), Tumor necrosis factor alpha (TNF-A), interferon (IFN) alpha-2, serum stem cell growth factor (SCG)- beta, platelet-derived growth factor (PDGF)-BB, Granulocyte macrophage colony stimulating factor (GM-CSF), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and cutaneous T-cell-attracting chemokine (CTACK) are associated directly to HIV infection and identified new cytokine biomarkers to enrich the field's literature further. Figure 6 shows the direction of change for the cytokines mentioned. Therefore, better understanding of the role of cytokines before, during, and after HIV infection could enable for the development of new therapeutic approaches based on the use of either recombinant cytokines or particular antagonists, with the goal of limiting both HIV spread and clinical manifestations of this infection (59).

Different cytokines play significant roles in HIV prevention and management with PrEP. Interleukins (ILs) such as IL-2 enhance T-cell proliferation and activation, aiding the immune response against HIV, and its levels can help assess immune activation efficacy in PrEP users. IL-3 and IL-5 regulate hematopoiesis and immune responses, with elevated levels indicating an ongoing immune response relevant for those exposed to HIV (60). IL-10, an anti-inflammatory cytokine, prevents excessive inflammation, with high levels suggesting reduced inflammation in PrEP patients. IL-12P70 and IL-17 alpha aid in differentiating and activating T-helper cells, promoting cell-mediated immunity, and protecting mucosal barriers, respectively (60). Monitoring these cytokines helps understand immune modulation in PrEP users. IL-16 attracts T-cells and other immune cells to infection or inflammation sites, a marker for immune activation in PrEP.

SCF and SCG-beta are essential for hematopoietic stem cell proliferation and differentiation, indicating bone marrow activity and the ability to replenish immune cells in PrEP users (61). B-NGF supports neuron survival and maintenance and has immunomodulatory effects. In PrEP users, B-NGF might influence neuroimmune interactions, affecting the nervous system's response to HIV exposure. TNF-A and TRAIL are significant in immune regulation and inflammation (10). TNF-A, a pro-inflammatory cytokine, indicates inflammation and immune activation, which is crucial for those at risk of HIV. TRAIL induces apoptosis in cancer and infected cells, helping eliminate HIV-infected cells in PrEP users. IFN Alpha-2 has antiviral properties, inhibiting HIV replication and modulating the immune response, providing additional protection in PrEP users. PDGF-BB aids in wound healing and tissue repair, helping maintain mucosal integrity and prevent HIV entry through mucosal surfaces in PrEP users. GM-CSF stimulates granulocyte and macrophage production, providing insights into immune readiness (62). CTACK directs T-cells to the skin, indicating immune surveillance at mucosal and skin surfaces to prevent initial HIV infection.

In clinical practice, these cytokines are useful biomarkers to monitor individuals' immune status and response using PrEP. Regularly measuring cytokines like IL-2, IL-10, TNF-A, IFN Alpha-2, IL-12P70, IL-17 alpha, and TRAIL can help assess immune activation, regulation, and the body's response to HIV exposure (60). This monitoring allows clinicians to evaluate the balance between immune activation and regulation, ensuring optimal immune response without excessive inflammation (11). Personalized PrEP strategies

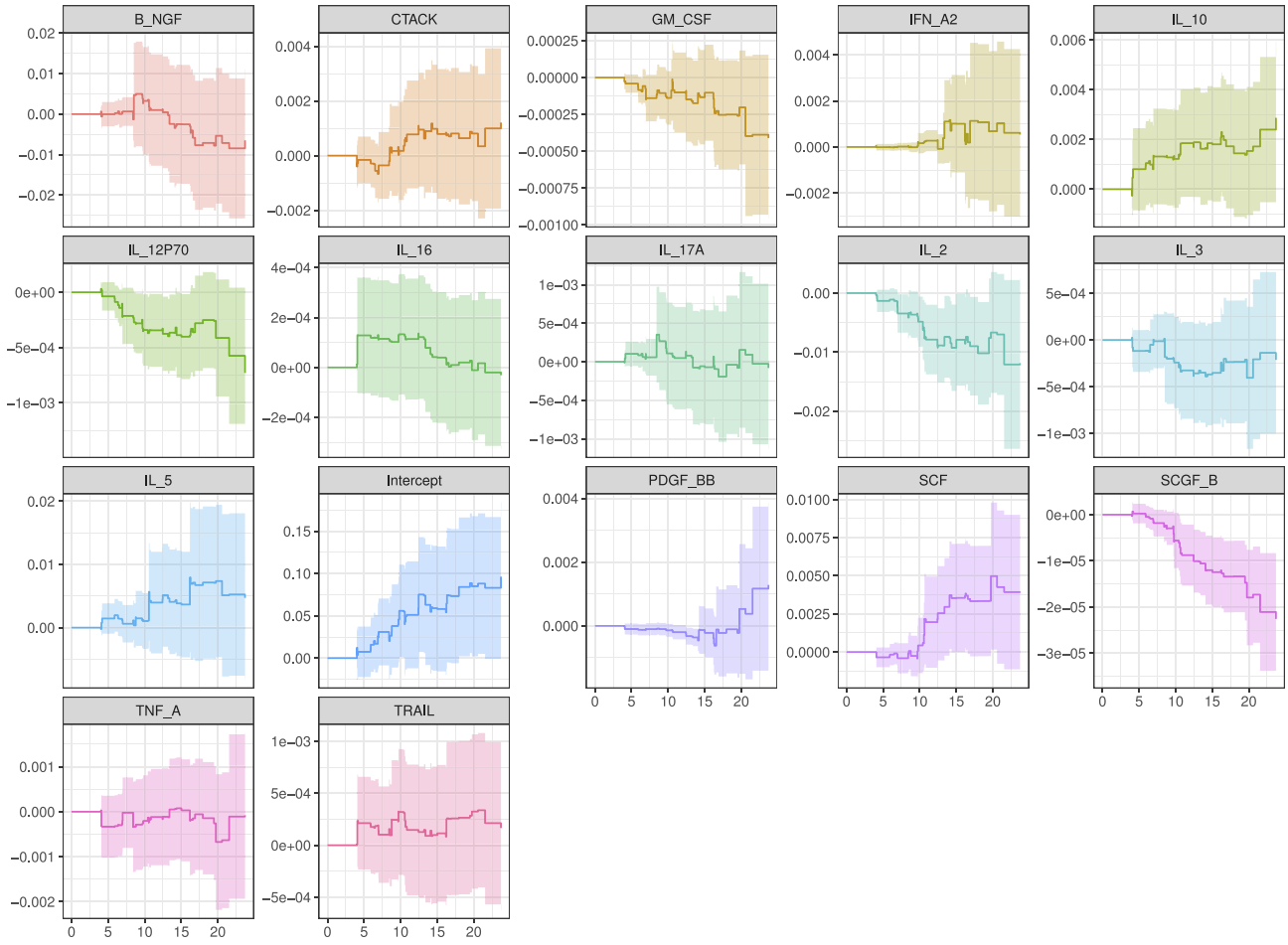

FIGURE 6
Direction of change for the cytokines of interest confirmed by our study results.

can be developed based on individual cytokine profiles, optimizing dosages and combinations of PrEP medications to enhance protection. Additionally, certain cytokines can indicate adverse immune reactions or inflammation, enabling timely interventions to manage side effects. Integrating cytokine monitoring into PrEP care enhances HIV prevention strategies, tailored interventions to individual needs, and improves clinical outcomes.

5 Conclusion

In this article we investigated the effect of individual cytokine biomarker, a time varying covariate, where we provided ways of handling the covariate in the stepwise Cox PH modeling by using a derived variable from the longitudinal measurements (mean and difference) and as a time dependent covariate (model 2–4). The presence of a cytokine effect in a model improved the predictive performance of the model hence the improved models were more informative about predictors that are associated with HIV hazard. Moreover, the tenofovir treatment exposure significantly lowered the hazard of HIV compared to the Placebo treatment group. Furthermore, Kaplan–Meier estimator indicated that the patients who received tenofovir antiretroviral microbicide treatment had a significantly lower risk of HIV infection compared to the placebo group hence an effective treatment in reducing the risk of HIV in women between the age of 18–40 years.

Further investigation of the cytokine biomarker could involve utilizing the standard deviation of longitudinal measurements or lagged observations. Additionally, with internal time-varying covariates, one might explore employing joint modeling of longitudinal and survival data. The aim is to apply a model to a continually changing covariate that is measured longitudinally, potentially with error. This longitudinal model is linked to survival times by modeling the joint distribution of longitudinal and survival data.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions. Researchers wanting to access data from the completed CAPRISA studies are requested to

complete a data request form. Requests to access these datasets should be directed to https://www.caprisa.org/Pages/CAPRISAStudies.

Author contributions

SO: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. MM: Writing – review & editing, Visualization, Validation, Supervision, Software, Formal analysis. HM: Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. This research was funded in whole or in part by Science for Africa Foundation to the Sub-Saharan Africa Consortium for Advanced Biostatistics (SSACAB II) programme [Grant Number DEL-22-009] with support from Wellcome Trust and the UK Foreign, Commonwealth & Development Office and is part of the EDCPT2 programme supported by the European Union. For purposes of open access, the author has applied a CC BY public copyright license to any Author Accepted Manuscript version arising from this submission.

Acknowledgments

The authors extend their sincere appreciation to CAPRISA for graciously granting permission to access and utilize the dataset in our research.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1393627/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 23 July 2024
DOI 10.3389/fpubh.2024.1379262

OPEN ACCESS

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RECEIVED 16 February 2024
ACCEPTED 04 July 2024
PUBLISHED 23 July 2024

CITATION
Wanjala SW, Nyongesa MK, Luchters S and Abubakar A (2024) Psychosocial and mental health challenges facing perinatally HIV-infected adolescents along the Kenyan coast: a qualitative inquiry using the socioecological model.
Front. Public Health 12:1379262.
doi: 10.3389/fpubh.2024.1379262

Psychosocial and mental health challenges facing perinatally HIV-infected adolescents along the Kenyan coast: a qualitative inquiry using the socioecological model

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Background: The advent of antiretroviral therapy has led perinatally HIV-infected (PHI) adolescents to live long, fulfilling lives through lifelong treatment. However, there is limited knowledge about the lived experiences and psychosocial and mental health challenges faced by PHI adolescents in sub-Saharan Africa, where 80% of PHI adolescents reside. To address this gap, we adapted the socioecological model to investigate the challenges and lived experiences of PHI adolescents in rural coastal Kenya.

Methods: Between October and November 2018, a sample of 40 participants (20 PHI adolescents and their 20 primary caregivers) participated in a qualitative study using an H-assessment data collection approach for adolescents and focus group discussions with caregivers. Data analysis was conducted using a framework approach on NVIVO 11 software.

Results: PHI adolescents from this setting experience many challenges across various levels of the ecosystem. At the individual level, challenges include living in denial, HIV status disclosure, antiretroviral adherence, internalized stigma, and mental health issues. Within the family, challenges such as parental loss, insufficient care from parents, and unacceptance lead to threats of harm. In the broader community, key challenges such as gossip, unsupportive community members, long waiting times at the health facility, isolation, rejection, and an unresponsive school system fail to address the needs of PHI adolescents. Finally, HIV-related stigma and discrimination manifested across different levels of the socioecological framework. To cope with these challenges, PHI adolescents often rely on privacy and social support from their families.

Conclusion: The findings underscore the need to develop and implement multi-level adolescent-friendly interventions to address PHI adolescent challenges and guide future investment in adolescent's health. Furthermore, there is a need to address internalized and interpersonal stigmas through individual-level interventions that promote resilience and the active involvement of adolescents, their caregivers, peers, and teachers who are their social support system.

KEYWORDS

perinatal HIV infection, adolescents, socioecological model, HIV-related stigma, qualitative inquiry, focus group discussion (FGD), H-Assessment

1 Introduction

Adolescence, aged 10 to 19 years old as defined by the World Health Organization, represents a developmental and transitional phase between childhood and adulthood characterized by rapid growth and significant biological, psychological, and socioemotional transformations that support significant health implications (1–3). Furthermore, adolescence can be divided into early (10–14 years) and late (15–19 years) adolescence, each characterized by unique physical, emotional, cognitive, and social changes (4, 5). Over 16% of the world's population are adolescents, emphasizing their pivotal role in achieving the 2030 sustainable development goals (1). Moreover, adolescents account for approximately 5% of all people living with HIV (PLWHA) and 11% of new HIV infections (6).

In 2022, an estimated 1.65 million adolescents were living with HIV infection across the world, the majority (85%) of them resided in sub-Saharan Africa (sSA) (6). Moreover, more than 80% of adolescents living with HIV (ALHIVs) acquired the infection through mother-to-child transmission (7). However, despite extensive efforts to prevent the vertical transmission of HIV, millions of children and adolescents in sSA remain perinatally infected (8). The majority of children infected perinatally with HIV are now in adolescence and early adulthood phases with a stigmatizing, potentially fatal, and chronic illness (9). Owing to the increased survival of ALHIVs due to antiretroviral therapy (ART) and vertically transmitted HIV among adolescents, the rate of increased survival continues to rise (10, 11). Relatedly, ALHIVs are the fastest-growing subgroup of PLWHA (11).

Living with HIV poses both psychosocial and socioeconomic challenges related to HIV and its care (12, 13). Particularly for PHI adolescents, the prolonged survival with HIV/AIDS (9) aggravates these challenges, impeding their ability to seek treatment and recommend for themselves (14, 15). The struggles these adolescents face extend beyond accepting their seropositive status and dealing with family members with positive status, and they struggle with the memories of deceased parents and uncertainties about their future, health, education, career, and marriage (16). Additionally, adolescence, marked by risk-taking and transitioning to greater independence, magnifies these challenges for adolescents. Parental influence diminishes risky behavior, which is prevalent, and the imperative to establish an identity and fit in with peers takes precedence (4, 5). Coping with a seropositive status becomes difficult during adolescence, necessitating a different management approach compared with adults.

The present study aimed at getting a nuanced understanding of the lived experiences and challenges faced by PHI adolescents. Understanding HIV-infected adolescents' unique challenges is crucial in designing and developing effective interventions tailored to improve their quality of life. However, there is a shortage of data available on this population, and previous studies have mostly focused on quantitative research. While there are some existing qualitative studies on this topic, the data is still limited, and our study adds to the growing body of knowledge on this important topic by using an adaptation of the socio-ecological framework (17–20), which recognizes that the experience of health and illness transcends individual characteristics and examines the interplay between individual, interpersonal, community, and policy-level factors that shape the experiences of HIV-infected adolescents in a rural Kenyan setting. However, our study does not focus on the challenges at the public policy level. The socioecological model has been extensively applied in various fields, especially in public health, as it conceptualizes health broadly and focuses on the understanding how layered social environments impact individual behaviors and health outcomes. Since its conception in the 1970s, the socioecological model has been adapted to develop multilevel approaches in areas such as safe practices in primary care (21), violence prevention (22), immunization uptake (23), barriers to HIV clinic attendance (24), and psychosocial and mental challenges faced by people living with HIV (17).

Adolescents between 12 and 17 years old are typically belong to upper primary school to secondary school experience the same developmental phases. Compared with a wider age range of 10–19 years, including pre-adolescents and emerging adults who may be going through different life and developmental stages such as attending tertiary institutions or having a full-time job, adolescents aged 12–17 years share more homogenous emotional, cognitive, and social issues. This study was designed to explore challenges faced by PHI adolescents aged 12 to 17 years living with HIV in rural Kenya (at the intrapersonal/individual, interpersonal/family, and community levels) and understand the lived experiences of PHI African adolescents in a rural Kenyan setting.

2 Methods

We describe study methods and findings following the guidelines outlined in the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (25) (see Supplementary Table S3). This checklist comprises 32 items that must be addressed to ensure explicit and comprehensive reporting of qualitative studies (25).

2.1 Study design and setting

In the context of HIV, this is a nested sub-study that is a part of baseline data collected from an ongoing larger longitudinal observational cohort study, the Adolescent Health Outcomes Study (AHOS), examining the neurocognitive and mental health outcomes among adolescents aged 12–17 years (26). The baseline data were collected between November 2017 and October 2018. The current study qualitatively examines the lived experiences and psychosocial and mental health challenges faced by PHI adolescents who participated in the baseline phase of the main study. This qualitative study was conducted at the Comprehensive Care and Research Clinic

(CCRC) located in the Kilifi County Hospital, a public healthcare institution. The study was carried out by the Center for Geographic Medicine Research, Coast (CGMR-C), which is a part of the Kenya Medical Research Institute—Wellcome Trust Research Programme (KEMRI/WTRP) located in Kilifi County. Kilifi County is mostly a rural setting with an estimated population of 1.5 million, predominantly rural dwellers (27) with almost half of this population comprising individuals who are younger than 15 years old (28). Additionally, Kilifi County is among the poorest counties in Kenya (29), and the main economic activities of the residents of Kilifi County include subsistence farming, small-scale trading, and fishing (30). The county has low literacy levels and high rates of school dropouts (31).

2.2 Study participants and recruitment

In this sub-study, we recruited 20 PHI adolescents and their primary caregivers participating in the present study. These adolescents needed to be aware of their HIV status, receiving treatment at the CCRC. The caregivers were supposed to be aware of their HIV status and the primary carers of the PHI adolescents, willing to accompany them for assessments. Recruitment was carried out by a trained research assistant collaborating with experienced healthcare workers involved in the participating HIV treatment facilities. The emergence of data saturation (32, 33) determined the sample size during the data collection exercise in our study. The larger AHOS study recruited participants through consecutive sequential sampling from all families attending HIV clinic days at eight HIV treatment and care clinics in Kilifi County until the targeted number was achieved. The selection of the clinics was purposively done based on their distribution and client capacity of the HIV-specialized clinics in the Kilifi Health and Demographic Surveillance System (KHDSS) (30). In total, AHOS comprised 558 (201 perinatally HIV infected, 158 perinatally HIV exposed but uninfected, and 199 HIV unexposed and uninfected) adolescents. Further details about the AHOS study and its procedures have been described elsewhere (26).

2.3 Data collection materials and procedures

H-Assessments (Supplementary Table S1) were used to collect data from all adolescents, whereas Focus group discussions (FGDs) (Supplementary Table S2) were conducted on the caregivers of these adolescents. The H-assessment is pivotal for qualitative data collection as it engages respondents actively, not passively, and can be used to help children assess the strengths and weaknesses of their environment and the support they receive through pictures (34). Though ideal for children, the H-assessment can be adapted for adults. Using the H-assessment to begin a FGD with the adolescents gave them a chance to record their thoughts and experiences before discussing them with the larger group. FGDs were used to elicit responses from parents/caregivers about the lived experiences of PHI adolescents. In total, three H-assessments and three FGDs were held between October and November 2018.

After obtaining informed consent from caregivers and assent from adolescents, the FGDs and the H-assessments were audio-recorded. A trained facilitator and note-taker led the discussions in Kiswahili, one of the two national languages of Kenya and the most widely spoken language along the coast of Kenya. H-assessments lasting for 45–55 min were conducted on PHI adolescents by SWW and MKN in a spacious private room located in the neuro assessment offices at KEMRI. Furthermore, FGDs lasting for approximately 2 h were held with the caregivers of the PHI adolescents in a quiet spacious private room located in the neuro assessment offices at KEMRI. All interviews were conducted in Kiswahili, the official national language, and were recorded digitally after obtaining consent from all participants. The interviews were conducted by a team of researchers with different expertise: (1) a medical sociologist specialized in HIV/AIDS stigma (SWW), (2) an expert in mental health with expertise in global health (MKN), and (3) three trained fieldwork assessors (R.M., G.S., and A.C.) (see Supplementary Table S4). Facilitators of the FGDs and H-assessment used a semi-structured interview guideline containing open-ended questions to guide the discussions. The authors formed the interview guidelines with questions informed by the grounded theory. Separate interview guidelines were used for H-assessments on PHI adolescents and FGDs on their caregiver, and these interview guidelines were developed to delve deeply into stigma and discrimination challenges such as challenges experienced by PHI adolescents, their experiences of HIV stigma and discrimination and spaces where stigma takes place, and the perpetrators of stigma carrying toward PHI adolescents in the community.

2.4 Data management and analysis

Data were managed using NVivo qualitative data indexing software (version 11 Pro, QSR international). The audio-recorded interviews were transcribed verbatim, with all identifying information removed, translated into English, proofread, and uploaded to NVivo. Additionally, as described by Ritchie and Spice, data were analyzed using the framework approach (35), constantly applying comparative techniques (36) and resolving coding differences through mutual agreement. Codes were inductively generated by the analysis of transcripts by two researchers (SWW and MKN) and deductively generated by drawing on data from the interview guidelines.

An initial coding scheme was generated, expanded, and refined through additional coding against transcripts to incorporate emerging themes. Subsequently, data were summarized, categorized, and exported into matrices to compare themes systematically. Investigator triangulation (37) was used to ensure the credibility of the results (37), whereby two researchers (SWW and MKN) coded and analyzed the data. Regular meetings were held during data analysis to discuss emerging codes, and any discrepancies were resolved through discussion before updating the codebook. We achieved data saturation (32, 33), as sufficient information on our research question was collected.

2.5 Theoretical framework

The data analysis and reporting were based on an adaptation of the socioecological model (18, 19). This theory-based framework recognizes that health and illness experiences are frequently influenced by factors within and beyond an individual (18, 19). The application of this framework was intended to provide a robust platform for the

investigation of challenges that PHI adolescents experience not only at the individual level but also at the interpersonal and community levels. This study aims to comprehend the challenges that PHI adolescents experience at the intrapersonal (individual) and interpersonal levels (family and community levels), as the latter covering the spaces in which PHI adolescents spend the maximum time (schools, healthcare facilities, and the playground). By using this framework and identifying the challenges occurring at multiple levels at which they occur, this study has the potential to provide recommendations that integrate health services to serve PHI adolescents more effectively.

2.6 Ethics statement

This study adhered to the ethical principles and guidelines for studies involving human participants as outlined in the Declaration of Helsinki. The local institutional review board, Scientific and Ethics Review Unit (SERU) of the Kenya Medical Research Institute (KEMRI), granted the ethical approval to recruit and interview participants (Ref SERU; KEMRI/SERU/CGMR-C/084/3454). Additionally, permission to work in the HIV care and treatment clinic was sought from and granted by the Department of Health, County government of Kilifi (Ref HP/KCHS/VOL.VIX/80). A legal caretaker collected data of all eligible adolescents at the CGMRC-KEMRI. Eligible adolescents provided written assent, whereas their caregiver/legal guardian provided written informed consent for their participation. Adolescents and caretakers were reimbursed for their travel costs depending on their residence.

3 Results

3.1 Participants' characteristics

In this study, the analysis incorporated 6 transcripts, including 3 H-assessments with 20 PHI adolescents and 3 FGDs with 20 primary caregivers. The sociodemographic characteristics of the participants are presented in Table 1.

TABLE 1 Summary of participants' socio-demographic characteristics.

Sample characteristics	Frequency (%)
Socio-demographic characteristics	
PHI Adolescents (n = 20)	
Age (12–17 years)	
Mean (SD)	14.35 (1.63)
Sex	
Female	8 (40%)
Male	12 (60%)
Number of years in school	
Mean (SD)	5.40 (2.35)
Religion	
Christianity	16 (80%)
Islam	4 (20%)
Caregiver Participants (n = 20)	
Age (32–56 years)	
Mean (SD)	44.35 (7.84)
Sex	
Female	16 (80%)
Male	4 (20%)
Education	
Primary	17 (85%)
Secondary	3 (15%)
Religion	
Christianity	16 (80%)
Islam	4 (20%)

3.2 Challenges faced by adolescents living with HIV

Figure 1 presents an overview of the challenges faced by PHI adolescents in our setting, which is categorized according to various levels of the adapted socioecological system, including individual-level challenges, family-level challenges, and community-level challenges (general community, school, HIV clinic, and playground). Furthermore, this challenge illustrates both the emerging challenges specific to each level and overlaps across multiple levels within the socioecological system (see Figure 1).

3.2.1 Individual-level challenges

3.2.1.1 Acceptance of HIV-positive status

Caregivers and adolescents noted the challenges faced by adolescents living with HIV in accepting their positive HIV status. These challenges impacted their self-perception and overall well-being. Some adolescents may find it difficult to accept their HIV status, leading to a negative mindset and doubts about their ability to succeed in different areas of life. The constant reminder of their HIV status likely contributes to this negative self-perception, potentially affecting their motivation and confidence.

> *If a PHI adolescent has not come to terms with their diagnosis, they might hold the belief that their efforts will not lead to success. Consequently, they consistently remind themselves of their HIV status, creating a perception that their goals are unattainable whenever they attempt to pursue a goal (Female HIV-infected adolescent, 13 years old).*

One participant shared their daughter's experience, emphasizing the detrimental effects of living in denial on mental health, such as insanity indicating profound psychological distress. However, they emphasized the significance of accepting the HIV-positive status of an individual, receiving appropriate medical treatment, and adhering to antiretroviral (ARV) medications for maintaining the health and well-being of individuals living with HIV.

> *Until last year but one, my daughter had been living in denial about her HIV status. Subsequently, her viral load was extremely*

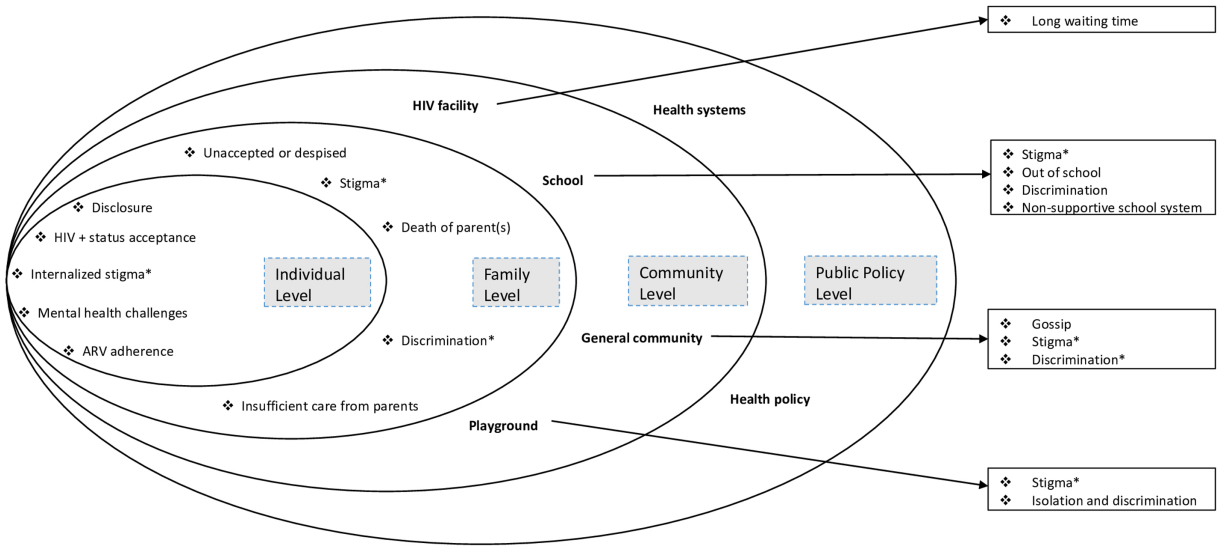

FIGURE 1
Challenges facing perinatally HIV-infected adolescents from coastal Kenya, mapped onto the socioecological model. In asterisk (*) are the inter-level challenges. Adapted from Nyongesa et al. (17).

> *high, and she eventually went 'insane' at some point. However, after she started adhering to her ARVs, she recently gave birth to a healthy baby (Female caregiver of an HIV-infected adolescent, 38 years old).*

3.2.1.2 Disclosure of HIV status to others

Participants discussed how the disclosure of HIV-positive status had been a challenge because of the fear of being judged, too many questions (e.g., what the ARV medication was used to treat and why they carried it daily), the worry about the reactions they might face from people close to them, and fear of their HIV status spreading beyond those with whom they shared it.

> *Moderator: You do not tell people at home that you are taking medicine. And why do not you tell them?*
>
> *It's your secret.*
>
> *Moderator: What will they do if you tell them?*
>
> *They will tell others (Female HIV-infected adolescent, 14 years old).*
>
> *What will I tell my girlfriend if she discovers I am on ARVs? (Male HIV-infected adolescent, 15 years old).*

3.2.1.3 Poor adherence to antiretroviral medication

PHI adolescents struggled to adhere to their prescribed medication regimen. They were involved in improper medication practices, such as taking ARVs at the wrong time, missing doses, and taking more than the prescribed or incorrect dosages. Managing ARV schedules, dealing with disclosure stigma, and the impact of non-disclosure on treatment adherence were additional challenges encountered by these adolescents.

> *Taking ARVs in front of your peers is challenging because you are unsure how to do it discreetly without them noticing (Female HIV-infected adolescent, 14 years old).*

To avoid taking ARVs at a prescribed time during the day, some adolescents opted to take all the day's ARVs once:

> *Another challenge is overdosing. For instance, if the prescription is for two pills in the morning and two pills in the evening, he might inadvertently take all four at once, exceeding the recommended dosage. This could occur either in the morning or evening to eliminate the need to carry the ARVs to school (Male HIV-infected adolescents, 15 years old).*

The lack of disclosure of adolescents' HIV-positive status to others created a dilemma for them as they were hesitant to take their ARVs in front of their classmates for fear of inadvertent disclosure. Consequently, this might result in skipping doses or stop taking ARVs.

> *Adhering to ARV medication schedules is a challenge. If you carry your ARVs to school, you will face inquiries about the purpose of the ARVs and why you always have them every day. When faced with such situations, you will begin skipping doses or completely discontinue using your ARVs (Male HIV-infected adolescent, 13 years old).*

A caregiver suggested his child to carefully take the ARV at a water tap to avoid inadvertent disclosure of the HIV-positive status.

> *The challenge he experiences is at school because his class schedule conflicts with his medication schedule. They leave for school at 6 am and return home at 8 pm. He is supposed to take his ARVs at 6 am and 6 pm. Sometimes he takes it (ARVs) around 8:30 pm when he arrives home from school. He is in a dilemma as he wants to take his ARVs but does not know how to do so without his friends*

> *knowing. I always advise him to take his ARVs at the tap so his peers think he is just getting water (Female caregiver of an HIV-infected adolescent, 49 years old).*

Despite adherence to medication practices proving to be a challenge, one adolescent expressed no fear in taking their ARVs and other prescribed drugs in front of other classmates. However, as a strategy to avoid stigma, discrimination, judgment, and unwanted attention associated with being HIV-positive, as well as to maintain a sense of privacy and protection from prejudice, they utilized the purpose of their medication by attributing it to a more socially acceptable disease, such as malaria.

> *I do not fear taking my drugs in front of other people, when they ask what they are for I lie that they treat other diseases like malaria (Male HIV-infected adolescent, 16 years old).*

A participant described how disagreements or conflicts within a household, where the parents appeared indifferent or unconcerned about the situation, would potentially lead to an approach of an adolescent refusing to take their prescribed ARV medications, with severe consequences that could even lead to death.

> *If disagreements occur at home and the parents seem like they do not care, it might lead to him refusing to take his meds which might lead to death (Female Parent of HIV-infected adolescent, 35 years old).*

3.2.1.4 Mental health challenges

The death of parent(s) due to HIV/AIDS, stigma, and discrimination associated with HIV/AIDS, adolescents not accepting their positive HIV status, facility-level challenges such as long waiting times and inadvertent disclosure of HIV status may lead to adolescents experiencing common mental health problems, such as depression and anxiety. These mental health problems were expressed using some phrases such as "thinking too much" and "feeling sad," which are similar to how these common mental health problems are understood locally. In addition, due to the fear of being judged or rejected by their peers, adolescents may isolate themselves and avoid social interactions. This self-imposed isolation can further exacerbate feelings of sadness, rumination (repetitive negative thinking), and self-loathing.

> *This child was being discriminated against at home. His status was being disclosed to everyone in the community. As a result, the child was not at peace, he was thinking too much and isolated himself as he was uncomfortable associating with other people. He was filled with sadness, and constantly ruminated because he thought if he associated with his peers, he will labelled as someone suffering from HIV (Female caregiver of an HIV-infected adolescent, 34 years old).*

The psychological distress experienced by adolescents with HIV has detrimental effects on their lives. Some adolescents may stop following their antiretroviral medication while others may have suicidal thoughts. Excessive rumination results in difficulties concentrating in class, ultimately leading to poor academic performance.

> *Due to constant rumination, a HIV-infected adolescent is likely to perform poorly in their exams. Additionally, discrimination at home and lack of enough personal time might lead to suicidal ideation as a means of finding solace from their worldly struggles (Male HIV-infected adolescent, 12 years old).*
>
> *Discrimination might lead you to have suicidal thoughts (Female HIV-infected adolescent, 14 years).*

Another HIV-infected adolescent reported experiencing sadness when they take their ARVs after the prescribed time had lapsed because the person who usually reminds them to do so was not present.

> *Maybe your parent has gone somewhere, and they are the ones who remind you when it is time to take your ARVs. If they return late past my time to take ARVs, I always feel sad because I am taking my drugs past the appointed time (Female HIV-Infected adolescent, 14 years old).*

3.2.1.5 Internalized stigma

Participant narratives revealed that HIV-infected adolescents isolated themselves from peers due to a fear of transmitting the virus to them. In addition, the internalization of stigma revealed that adolescents may have concerns about potential discrimination, stigma, or negative treatment if their HIV status was known. Accordingly, adolescents preferred to remain their HIV-positive status a secret.

> *We do not disclose our HIV positive status to others in the community because it is our secret (Female HIV-infected adolescent, 15 years old).*
>
> *Interviewer: Does the teacher know that your child is living with HIV?*
>
> *Participant: The teacher is unaware…my child told me, "I do not want my teacher to find out about my HIV status." (Female caregiver of an HIV-infected adolescent, 36 years old).*
>
> *Adolescents infected with HIV isolate themselves because they think if they interact with their peers, they might infect them (Female HIV-infected adolescent, 16 years old).*

3.2.2 Family-level challenges

3.2.2.1 Parental loss

A few participants mentioned that they were either full or partial orphans. Additionally, some participants revealed that the loss of parent(s) can be challenging to HIV-infected adolescents. Specifically, one HIV-infected adolescent can overcome by emotional distress following the loss of a parent.

> *For example, if your mother or father has passed away, you are overcome with grief (Female HIV-infected adolescent, 14 years old).*

3.2.2.2 Unacceptance leading to death threats

During the interviews, a participant described a scenario in which a group of adolescents contemplated killing of an HIV-infected adolescent (their cousin). This act was not only illegal but also morally abhorrent, driven by the fear of contracting the virus due to a lack of understanding about its transmission.

> *In the homestead where I live, a lady died from AIDS and left a child with HIV. Some kids (cousins to the infected adolescent) in that homestead hatched a plan to kill him by mixing his food with rat poison. They feared they might contract the virus from interacting with him by playing or eating together. Fortunately, one of the children informed his father (uncle to the HIV-infected adolescent) about the plan, who then punished them for hatching such a plan. The uncle then sent the HIV-infected adolescent to live with an aunt in another town as his cousins had negative thoughts and feelings about him (Female caregiver of an HIV-infected adolescent, 38 years old).*

3.2.2.3 Insufficient care from parents

According to a participant, adolescents living with HIV faced challenges such as unmet basic needs because their parent(s) were unable to provide adequate care. This necessitated committed caregivers to involve and fulfill the crucial caregiving role. In addition, siblings played an important role in recommending the well-being of adolescents living with HIV, as highlighted in the following quote:

> *……. the kid used to live with his father since I am just a caregiver and not the parent. When my sister died, her husband had to care for the children. However, after some time, her siblings came to me and reported that their sister was suffering because when their father leaves, he does not leave food for her (Female caregiver of an HIV-infected adolescent, 45 years old).*

3.2.3 Community-level challenges

3.2.3.1 Health facility challenges

3.2.3.1.1 Long waiting time

A caregiver of an HIV-infected adolescent expressed that long waiting times at the health facility posed a challenge. The adolescent consistently urged his mother to request for a prompt attention from the doctors, as he desired to go back to school and continue his education. If he did not attend quickly, he would become annoyed and angry due to missing out on lessons. The interruption in his education and the potential consequences on his academic advancement resulted in a significant frustration.

> *……. My son always tells me to tell the doctors to attend to him quickly and give him his medication refills so that he can return to school and continue learning. As a result, if I accompany him to the clinic and he is not attended to promptly, he becomes irritable and angry because he has missed some lessons. However, if he is quickly attended to and returns to school, he is a happy boy because he will be able to study alongside other students (Female caregiver of an HIV-infected adolescent, 36 years old).*

3.2.3.2 School environment challenges

Based on our interviews, it was found that school-going children faced institutional barriers when it came to following through with their medical appointments, particularly when they had to be absent from school to attend their clinic appointments.

3.2.3.2.1 School system is unresponsive to the needs of HIV-infected adolescents

HIV-infected adolescents faced the difficulties of navigating an unresponsive school system that did not cater to their medical and educational needs. Before the teachers being informed of their HIV status, they consistently received punishment for their school absences when they had to go to the hospital for medical appointments. These adolescents encountered the challenge of regularly missing school whenever they needed to attend the clinic for their medical appointments. Other students reported difficulties in navigating issues how to coordinate with their medical appointments, especially when disclosure had not been made to the school authorities.

> *Before the teacher knew what he was suffering from, he was always punished when he used to miss school because he had gone to the hospital for his ARV refill. However, I intervened and advised him to go and disclose his status to his class teacher and tell him that whenever he misses school, he is always at the hospital for his ARV refill. Nowadays, when he is not in school, they know he has gone to pick up his medication, and nobody punishes him as they know his status (Female caregiver of an HIV-infected adolescent, 38 years old).*

Other challenges at school included, among other things, non-consensual/inadvertent disclosure of status, missing classes for clinic appointments, experiencing discrimination and isolation at school (as discussed in the stigma section), and constantly being interrogated by their peers about the purpose of their medication and why they had to carry it with them to school daily.

> *Other students always want to know why they are taking medication, and once they know, they refuse to sit close to them because of their HIV status (Female caregiver of an HIV-infected adolescent, 42 years old).*

The fear of unintended/non-consensual disclosure at school was a major concern for HIV-infected adolescents, especially the deterioration of their relationship with fellow students. HIV-related stigma and discrimination could extend beyond personal opinions and disagreements because even within a close friendship, knowledge of the adolescent's HIV status might have been used as a means to exclude and socially isolate them.

> *If you disagree with a friend who is aware of your HIV status at school, they might disclose your status to others and tell them not to interact with you because of your HIV status (Male HIV-infected adolescent, 15 years old).*

3.2.3.3 Playground challenges

3.2.3.3.1 Isolation and rejection

Some participants described experiences of frequently feeling unloved and being excluded from social activities, such as playing football during playtime, by their peers due to their HIV status. They were consistently instructed to play alone first and then promised for the inclusion, which led to the feelings of isolation and rejection.

> *When people are playing football, they will refuse to play with me because of my HIV status, and thus they discriminate against me (Male HIV-infected adolescent, 16 years old).*

> *They do not love me. When we are playing together, they always tell me to play alone then later; we will play together (Male HIV-infected adolescent, 14 years old).*

3.2.4 Inter-level challenges

Various forms of HIV-related stigma (enacted, internalized, perceived, and anticipated) and discrimination against adolescents living with HIV were mentioned by the study participants at various levels of the socioecological system. HIV-related stigma was experienced at individual, family, and community levels (general community, school, and playground). HIV-related discrimination was mentioned at the family and community levels (general community, playground, and school). Table 2 presents the various forms of HIV-related stigma and discrimination experienced by these adolescents living with HIV.

At the family level, HIV-related discrimination was marked by insufficient care from parents, including denial of food, cessation of education, and isolation and separation of utensils.

> *They isolated him and did not want to eat together with him. Relatives looked at him as a dog and gave him his own bowl. Initially, they used to eat together, but now they have been told that if he is given food, let him eat his food, and do not use or even touch them (Female caregiver of an HIV-infected adolescent, 36 years old).*

In the community, HIV-related discrimination resulted in the exclusion and isolation of HIV-infected adolescents, particularly when their peers became aware of their HIV status.

> *When our peers become aware of our HIV status, they might stop interacting with us as they will think that they can contract the virus through interaction (HIV-infected adolescent).*

From our discussions, it became evident that both teachers and fellow students carried out HIV-related discrimination within the school environment. However, a parent warned the teacher about the potential consequences if her child were to complain again, implying that the teacher would face undesirable repercussions as a result.

> *The challenge was that his peers and teachers gossiped about him having the virus (HIV), but I solved that. I warned the teacher that if it ever happened again, he would not like the consequences that would befall him. Right now, my child studies with no problem (Female caregiver of an HIV-infected adolescent, 40 years old).*

During our discussions with adolescents and their caregivers, we encountered various types of HIV-related stigma. At the family and community levels, participants discussed the presence of enacted and perceived stigma, while at an individual level, there was evidence of internalized HIV-related stigma (see Table 2 for selected excerpts). In the community, particularly on the playground, the manifestation of HIV stigma was observed as HIV-positive adolescents being excluded from playing with their peers solely because of their HIV status.

> *When people are playing football, they will refuse to play with me because of my HIV status, and thus they discriminate against me (Male HIV-infected adolescent, 14 years old).*

3.3 Coping strategies

Although participants were not asked about the coping strategies they used for positive living, these adolescents mentioned several sources of support that aided their coping.

3.3.1 Social support

Our findings suggest that HIV-related social support in this setting involved a wide range of supportive measures. In addition, practical assistance was mobilized through social support to promote medication adherence, which included reminders for adolescents to take their medication as prescribed and in handling school-related consequences, such as obtaining permissions for those adolescents who were unable to disclose their condition to the school authority (teachers).

> *I had to talk to the teachers and the headmaster, explaining that my child needs to take medications. So if they notice he was absent from school, they should know that he had gone for his clinic appointment (Female caregiver of an HIV-infected adolescent, 53 years old).*

> *Your parents are the ones who remind you when it is time to take your ARVs (Female HIV-Infected adolescent, 14 years old).*

3.3.2 Secrecy

Respondents indicated that adolescents used various coping mechanisms, including HIV status concealment through either partial disclosure or complete non-disclosure. In one instance, a caregiver suggested to an adolescent that, to prevent their peers from discovering their status, they should discreetly take their medication from the water tap in school. Other participants chose to isolate themselves to avoid persistent inquiries about the purpose of their medication.

> *He is in a dilemma as he wants to take his medication but does not know how to do so without his friends knowing. I always advise him to take his medication, go to the tap, and take it from there, as his peers would think he has just gone to drink water (Female caregiver of an HIV-infected adolescent, 36 years old).*

To maintain their medication routine while keeping their HIV status a secret, one participant chose to take their ARVs but resorted to deception by providing false information about the purpose of their

TABLE 2 Types of HIV-related stigma and discrimination experienced by adolescents living with HIV from Kilifi, Kenya.

Level of social ecosystem	Forms of HIV–related stigma	Data sources	Select illustrative quote(s)	Forms of HIV discrimination	Data sources	Select illustrative quote(s)
Individual level	• Internalized stigma	4 HIV-infected adolescents, 2 caregivers	*We do not disclose our HIV-positive status to others in the community because it is our secret (HIV-infected adolescent)* *I: Does the teacher know that your child is living with HIV?* *P: The teacher is unaware…my child told me, "I do not want my teacher to find out about my HIV status." (Caregiver of an HIV-infected adolescent)* *What will I tell my girlfriend if she discovers I am on ARVs?(HIV-infected adolescent)* *When children get to know about their HIV status, they might self-isolate as they will think their peers will reject them. They isolate themselves and live like a lone ranger. (HIV-infected adolescent)*	–	–	–
Family level	• Enacted stigma • Perceived stigma	3 Perinatally HIV-infected adolescents	*When one wants to use the water closet seat, they are told not to use it as they can infect others who use the same toilet. A separate toilet will be constructed for their use (an HIV-infected adolescent)*	• Isolation • Parental neglect • Denied food • Separate utensils	6 Caregivers, 4 Perinatally HIV-infected adolescents	*They isolated him and did not want to eat together with him. They looked at him as a dog and gave him his own bowl. Initially, they used to eat together, but now they have been told that if he is given food, let him eat his food, and do not use or even touch them. (Caregiver of an HIV-infected adolescent)* *However, after some time, her siblings came to me and reported that their sister was suffering because when their father leaves, he does not leave food for her (Caregiver of an HIV-infected adolescent)*
Community level						
a) General community	• Enacted stigma • Perceived stigma	4 Perinatally HIV-infected adolescents, 4 Caregivers	*I went to the neighbour's house and found them eating. The mother told me to excuse them for some time. Why is it that everywhere I go, I feel like I am being discriminated against (HIV-infected adolescent)* *Some neighbours warn their children against playing with HIV-infected adolescents because they might contract HIV through contact. (Caregiver of an HIV-infected adolescent)* *For example, when you pass near where your neighbours are seated, and they start gossiping about your HIV status (HIV-infected adolescent)*	• Neighbour not wanting my child to sit next to her kids • Denied food • Friends refuse to associate with you once HIV status is known/Rejection	7 Caregivers, 5 Perinatally HIV-infected adolescents	*If my neighbour is serving her children food, then she sees my child, she will ask her what she wants and then send her back home, promising to share leftovers, but this is a ploy so that my child does not interact with her children (Caregiver of an HIV-infected adolescent)* *When our friends get to know of our HIV status, they might stop interacting with us as they will think that they can contract the virus through interaction or through sharing what we have with them (HIV-infected adolescent)* *Someone living with HIV is discriminated against by others in the community as they refuse to play with him and they cannot involve him in anything happening in the community (HIV-infected adolescent)*

(Continued)

10.3389/fpubh.2024.1379262

TABLE 2 (Continued)

Level of social ecosystem	Forms of HIV–related stigma	Data sources	Select illustrative quote(s)	Forms of HIV discrimination	Data sources	Select illustrative quote(s)
b) Health facility			–	–	–	–
c) Within the school environment	• Enacted stigma • Perceived stigma • Anticipated stigma	10 Perinatally HIV-infected adolescents 5 Primary caregivers	*If you disagree with a friend who is aware of your HIV status at school, they might disclose your status to others and tell them not to interact with you because of your HIV status (HIV-infected adolescent)* *When people start discussing HIV in school, you isolate yourself because you think they might mention you or a family member (HIV-infected adolescent)* *Whenever my child seeks permission from the teacher to go to the clinic, his peers always want to know where he is headed. Recently, a fellow student snatched his bag leading to his medicines spilling on the ground (caregiver of an HIV-infected adolescent)*	• Other students are reluctant to sit next to an adolescent living with HIV/Isolation	2 Primary caregivers	*Other students always want to know why they are taking medication, and once they know, they refuse to sit close to them because of their HIV status (Caregiver of an HIV-infected adolescent)*
d) At the Playground	• Enacted stigma • Perceived stigma	4 Perinatally HIV-infected adolescents	*They do not love me. When we are playing together, they always tell me to play alone, then later; we will play together (HIV-infected adolescent)* *When people are playing football, they will refuse to play with me because of my HIV status, and thus they discriminate against me (HIV-infected adolescent)*	• Isolation; peers avoiding contact with HIV-infected adolescents	3 Perinatally HIV-infected adolescents	*Our peers isolate us (PHI adolescents) and do not want to play with us who are infected (HIV-infected adolescents)*

10.3389/fpubh.2024.1379262

medication. They attributed their medication intake to a more socially acceptable illness such as malaria, to conceal their actual HIV status. By doing so, they aimed to create the perception that their medication was for a less stigmatized condition.

> *I do not fear taking my drugs in front of other people, when they ask what they are for I lie that they treat other diseases like malaria (Male HIV-infected adolescent, 15 years old).*

4 Discussion

4.1 Summary of key findings

This qualitative study aimed to gain a comprehensive and nuanced understanding of the day-to-day challenges encountered by PHI adolescents from rural coastal Kenya. We utilized an adaptation of the socioecological model as a framework to guide the analysis and reporting of these challenges. Various challenges emerged from the interviews with adolescents and their caregivers at different levels of the socioecological model. At the individual level, psychosocial and mental health issues emerged as significant challenges that greatly hampered the well-being and interaction of PHI adolescents. At the family level, participants mentioned challenges, such as death of parent(s), insufficient care from parents, and unacceptance leading to death threats. Within the general community, they experienced challenges, such as gossip and a lack of support from community members. Long waiting times at the HIV clinic was also mentioned as a challenge. Inflexible or strict school schedules and policies and disclosure to teachers led to absence in class for medical appointments, facing constant questioning from peers regarding the purpose of their appointments. Isolation and rejection by peers were mentioned as frequent challenges experienced by the adolescents within the playground. Finally, HIV-related stigma and discrimination in various forms were prevalent experiences for PHI adolescents across multiple levels of the socioecological framework. These negative attitudes and behaviors further aggravated the challenges they faced in their daily lives and affected their sense of belonging.

4.2 Comparison of study findings with previous research

Despite numerous studies documenting the psychosocial challenges affecting ALHIV (13, 38–41), there is a growing need to comprehend their lived experiences and contextual circumstances to address the obstacles hindering their uptake of HIV-related services and overall well-being (42), especially in resource-constrained settings. Our study builds upon the existing literature about challenges experienced by ALHIV by presenting a rich contextualized account of the psychosocial and mental health challenges faced by PHI adolescents in a resource-limited setting. The most common psychosocial challenges encountered by younger ALHIV (aged 12–19 years), as identified in a systematic review of qualitative studies from East Africa (13), include HIV-related stigma and discrimination in different manifestations, concerns regarding HIV disclosure, difficulties in adhering to ARV, and struggling with the implications of having an HIV-positive identity. In our study, in a similar study conducted within our setting among adolescents of the same age group (38), these challenges also emerged as frequent challenges faced by PHI adolescents.

The coping strategies utilized by respondents to positively cope with these challenges in the present study reflect what has been reported in previous studies (17, 39, 40, 43). For instance, social support can help adolescents adhere to their medication because peers who are aware of the status might remind them to take their medication. Similar to our findings, as reported in a previous study, caregivers were found to be a strong pillar of support and played an important role in navigating school permissions for students who were unable to face their teachers (44). Furthermore, disclosure by these adolescents can also help them get guidance on a healthy living (17). On the other hand, secrecy and describing as healthy as a coping strategy which impacted adherence to ART was used to avoid the inadvertent disclosure of their HIV status and subsequent stigmatization, especially in the school setting (38, 39).

In the absence of support through resilience strategies, stigma can manifest in different contexts, such as home or in school, having negative implications for the health outcome of adolescents (45). We found that experiences of internalized, enacted, perceived, and anticipated stigma were common in the daily life experiences of ALHIV in Kenya, similar to other studies (17, 38, 39). Anticipated stigma and the fear of rejection due to the internalization of stigma and the inevitability of enacted stigma which are pervasive in society were shown to influence ART adherence and disclosure to both peers and teachers within the school setting, a phenomenon that has been documented in other studies (17, 39). Enacted stigma was highlighted in respondents' narratives of non-consensual disclosure by peers due to a disagreement, separation of utensils, bedding, sanitation facilities (toilet), and limited socialization within the home and school environments. This led to psychological distress, non-adherence to ART, and non-disclosure of HIV status.

The internalization of stigma and the negative inferences that respondents attributed to themselves coupled with misconception about HIV transmission led to the concealment of HIV status and non-adherence to ART similar to other studies (46). Self-imposed isolation due to internalized stigma have negative consequences on their mental health and social well-being through reduced social support, loneliness, and limited opportunities for social development. Finally, although not adversely mentioned, perceived stigma was evident in respondent narratives of peers who were advised against interacting with HIV-infected adolescents when HIV-infected adolescents were excluded from social activities. This limited their social interactions, resulting in a reduction in their support network. The outcomes of HIV-related stigma observed in this study are congruent with the findings from the previous research, which include psychological distress (38, 39, 47), reluctance to disclose HIV status (38, 48), suboptimal adherence to antiretroviral therapy (ART) (17, 49), and limited access to social support (39). HIV-infected adolescents lacking sufficient social support might face difficulties in building resilience, leading to challenges in adhering to ART and experiencing social isolation (45).

The anticipation of stigma coupled with the fear of constant questioning from peers about their medication, concerns about the spread of their HIV status beyond those they had shared with, and worries about the potential reactions from loved ones contributed to non-disclosure. Furthermore, our data suggest that the fear of

disclosure contributes to sub-optimal adherence to ART, an issue that has been reported elsewhere (50). In addition, the timing of disclosure to adolescents by their caregivers has been shown to have detrimental effects on the adherence to medication as they questioned about the reason of taking the medication. Status disclosure, in the context of a chronic condition, has the potential to generate social support which has been demonstrated to play a crucial role in fostering resilience and motivating adherence (45) while also empowering adolescents to combat HIV-related stigma and actively engage in treatment support (51). Furthermore, it strengthens individual-level resilience factors including self-efficacy (51, 52), increasing self-confidence and motivation (52). Furthermore, research conducted in sSA demonstrates that disclosure to close family members and friends positively impacts the well-being and outcomes of ALHIV (53) but, if not rightly done, can lead to undesired outcomes.

Our findings revealed that medication adherence was a problem perceived by both caregivers and their PHI adolescents with some caregivers expressing challenges in ensuring medication adherence. Existing research suggests that interventions should prioritize addressing adolescents' need for peer acceptance and social connection by teaching them effective disclosure methods to trusted individuals and providing guidance on navigating social situations (54). We propose interventions aimed at addressing interpersonal stigma that involves active engagement of both adolescents and individuals within their support system to address misconceptions and stigma while also enhancing psychosocial support and promoting adherence to treatment similar to recommendations in a previous study (55).

Even though not so many participants considered coming to terms with their HIV-positive status a challenge, others found this challenging as was mentioned by their caregivers. In the present study, the lack of acceptance about their HIV-positive status led them to have a perception which negatively impacts their motivation and self-confidence, resulting in a negative mindset and doubt about their ability to become successful life. Additionally, living in denial caused these adolescents psychological distress and contributed to sub-optimal adherence to ART. This could be attributed to the fact that they might have lost hope in life due to the chronic nature of HIV. Adolescents with an HIV-positive status including identity issues have been reported as a challenge in previous studies (17, 40, 43).

As reported before, within the sSA context, mental health issues are often expressed using local terms or idioms (56), necessitating the localized understanding (57) of mental health and illness for meaningful investigation (17). Our data suggest that the fear of judgment or rejection makes adolescents isolate themselves, avoiding social interactions and intensifying feelings of sadness, rumination, and self-hatred. Some participants used local idiomatic expressions to describe their experience of mental health issues such as anxiety and depression. In our study, mental health problems such as anxiety and depression that have been associated with suicidal tendencies and thoughts are similar to previous studies conducted among younger adolescents (aged 12–17 years) (38) and emerging adults (18–24 years) (17) in this setting. Furthermore, our findings reflect the conclusions drawn from a quantitative study indicating that mental health problems are prevalent among adolescents (58). It is worth noting that psychosocial issues contribute to mental health problems in PLWHA (17, 45).

At the family level, though not common, a participant reported that an adolescent who had not been accepted by peers due to the fear of HIV infection had considered being killed through poisoning. Unacceptance among emerging adults has been reported in a previous study (17). Other challenges that emerged within the family have previously been reported in other studies, such as parental neglect/insufficient care from parents and parental loss (17, 40, 43). While grieving following the loss of a loved one is a universal experience across different cultures (43), complications arise when prolonged grieving starts to have a detrimental effect on the individual's life. The death of parents and extended periods of grieving among adolescents may be attributed to their anticipation of a bleak future in the absence of their primary caregivers. As with other studies, we recommend continued counseling support to assist these adolescents in effectively navigating the stages of grief (17).

Our findings that gossip and non-supportive community members are some of the community-level challenges reflect results from another study conducted in South Africa (43). In this study, HIV status disclosure as a result of gossip and rumor-mongering had the potential to contribute to stigma and discrimination. The non-supportive nature of community members deprives adolescents from the social support they require to navigate life with a chronic ailment. In line with previous studies conducted in Kenya (38, 44, 45, 49), Uganda (39), and South Africa (59), our analysis revealed that the school environment was notably unresponsive to the needs of PHI adolescents. Furthermore, our data suggest that stigma emerged as a significant obstacle faced by these adolescents in the school eco-system as they lacked a safe space to build community, disclose their status, and take their medication corroborating findings of a study conducted in Uganda (39). Participant narratives illuminate how some adolescents felt about teachers who were not particularly responsive to their needs as they were punished for school absences due to medical appointments.

Furthermore, the inflexibility of school schedules and policies and disclosure to teachers and PHI adolescents to adjust to when, where, and how often they took their medication to avoid inadvertently disclosing their HIV status were evident in our findings in case of the other studies carried out in sSA (39–44, 49, 60, 61). The experience of stigma has far-reaching consequences on the well-being of adolescents in the school, including their ART adherence and school engagement (44, 49). From our findings, as a result of stigma, some PHI adolescents admitted to being unable to concentrate in class and poor class participation. Poor concentration in class could lead to poor academic performance. Our findings suggest that psychosocial development of PHI, adolescents, e.g., their academic achievement may be compromised due to stigma. There is a need for future research to reduce HIV-related stigma within the school environment and mobilize social support apart from home; the school is also one of the most important socioecological contexts for well-being and development where adolescents spend most of their time.

Finally, our data indicated that the sentiments expressed by PHI adolescents regarding the playing field indicated the primary challenges they faced, such as feelings of isolation and rejection. Their attempts to join their peers in playing met the instructions to play alone with the promise of inclusion at a later time. Peers of PHI adolescents, possibly influenced by misconceptions or fear associated with HIV, expressed hesitation in engaging in close contact or playing with them. As a result, adolescents living with HIV experienced a sense of isolation and rejection as has been reported elsewhere (13, 38).

Stigma and discrimination continue to be significant factors in the daily life experiences of ALHIV. Despite four decades having passed since its emergence, the persistence of HIV stigma (62) still presents a perplexing challenge both for ALHIV and policymakers (38). Previous research has found that HIV-related stigma influences disclosure

practices, uptake of HIV-related services, ART adherence, and social relationships and interactions (17, 38). Therefore, there is a need for the development of intervention initiatives specifically addressing HIV-related stigma, particularly among adolescents. A previous study among emerging adults living with HIV (17) emphasized the importance of considering the complex interplay between psychosocial issues when prioritizing HIV-related interventions. Our findings reported that struggling with an HIV-positive identity contributed to sub-optimal adherence to ART, negative self-perception, disclosure difficulties, and psychological distress among adolescents living with HIV. Therefore, it is crucial to recognize the interconnected nature of these factors when designing interventions to address psychosocial challenges faced by PHI adolescents.

4.3 Strengths and limitations of the study

This qualitative study used data triangulation to present a comprehensive analysis of the daily life experiences of PHI adolescents facing psychosocial and mental health challenges, offering in-depth insights into their thoughts and beliefs, as well as daily life experiences of their caregivers. However, several limitations should be taken into account when interpreting our findings. First, the study utilized a convenience sample consisting of PHI adolescents and their caregivers, which may restrict the generalizability of the results, although this is not atypical in qualitative research. Moreover, the perspectives gathered were specific to a population in rural coastal Kenya, and caution should be exercised when applying these findings to other regions in sSA or resource-limited settings. Finally, although we used the socioecological model, our study did not focus on the challenges at the public policy level.

5 Conclusion

Our findings indicated the fact that PHI adolescents experience several challenges at the individual, family, and community levels of the socioecological spectrum. Of note, HIV stigma and discrimination were manifested in various forms with far-reaching consequences at multiple levels of the socioecological framework. To effectively tackle these challenges and enable PHI adolescents to flourish and realize their full potential, it is crucial that stigma is understood and addressed at the different levels of the socioecological framework as it links directly to treatment adherence, disclosure, HIV status acceptance, and schooling. In addition, it is essential to develop and implement customized multi-level adolescent-friendly interventions accommodating the unique needs of adolescents. Additionally, these programmatic or policy interventions should incorporate relevant context-specific coping mechanisms and support structures to facilitate a smooth transition into adulthood. Finally, addressing internalized stigma necessitates individual-level interventions that promote resilience, while tackling interpersonal stigma requires the active involvement of adolescents and individuals in their support systems.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study adhered to the ethical principles and guidelines for studies involving human participants as outlined in the Helsinki Declaration. The local institutional review board, Scientific and Ethics Review Unit (SERU) of the Kenya Medical Research Institute (KEMRI) granted the ethical approval to recruit and interview participants (Ref SERU; KEMRI/SERU/CGMR-C/084/3454). Additionally, permission to work in the HIV care and treatment clinic was sought from and granted by the Department of Health, County government of Kilifi (Ref HP/KCHS/VOL.VIX/80). All eligible adolescents were accompanied by a legal caretaker for data collection at the CGMRC-KEMRI. Eligible adolescents provided written assent, whereas their caregiver/legal guardian provided written informed consent for their participation. Adolescents and caretakers were reimbursed for their travel costs depending on their residence.

Author contributions

SW: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. MN: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Software, Supervision, Writing – review & editing. SL: Conceptualization, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. AA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Resources, Software, Supervision, Validation, Writing – review & editing.

Funding

The author(s) declare financial support was received for the research, authorship, and/or publication of this article. The funding for this research was provided by the Medical Research Council (Grant number MR/M025454/1) awarded to AA. This grant is a collaboration between the UK Medical Research Council (MRC) and the UK Department for International Development (DFID) under the MRC/DFID concordant agreement. It is also part of the EDCTP2 program, which is supported by the European Union.

Acknowledgments

The authors express our sincere gratitude to all the adolescents who willingly participated in this study and invested their time and effort. Additionally, the authors acknowledge the valuable support provided by health facility managers, staff, and the caregivers of the adolescents' for their support during this study. The authors would like to extend their thanks to Anderson Charo (AC) and Gladys Sanga (GS) for their role in data collection. Finally, the authors sincerely appreciate the Kenya Medical Research Institute (KEMRI) Director for granting permission to publish this study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1379262/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 08 August 2024
DOI 10.3389/fpubh.2024.1390538

OPEN ACCESS

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RECEIVED 23 February 2024
ACCEPTED 22 July 2024
PUBLISHED 08 August 2024

CITATION
Merid F, Toma TM, Anbesie A and Guyo TG (2024) Uptake of community-based differentiated antiretroviral therapy service delivery and associated factors among people living with HIV in Ethiopia: a multicenter cross-sectional study.
Front. Public Health 12:1390538.
doi: 10.3389/fpubh.2024.1390538

Uptake of community-based differentiated antiretroviral therapy service delivery and associated factors among people living with HIV in Ethiopia: a multicenter cross-sectional study

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Background: Achieving the 95–95–95 targets require an efficient and innovative person-centered approach, specifically community-based differentiated service delivery (DSD), to improve access to human immunodeficiency virus (HIV) services and reduce burdens on the health system. Therefore, this study aimed to assess the uptake of community-based DSD models and associated factors among people living with HIV (PLHIV).

Methods: A multicenter cross-sectional study was conducted among PLHIV in public health facilities in South Ethiopia. Data were collected and entered into EpiData version 3.1 before being exported to Stata version 14 for further analysis. In the bivariable logistic regression analysis, variables with a p-value of ≤ 0.25 were included in the multivariable logistic regression analysis. A p-value of <0.05 was used to identify statistically significant factors.

Results: Among 381 stable PLHIV, 55.91% were women. The median age (interquartile range) was 40 years (27–53). The uptake of community-based DSD models was 19.16%. Residence and disclosure were the two independent factors significantly associated with the uptake of community-based DSD models.

Conclusion: One out of five stable PLHIV on antiretroviral therapy uptake the community-based DSD models. Improvement in uptake is needed in Ethiopia's resource-limited healthcare system to better achieve the 95-95-95 targets.

KEYWORDS

community-based DSD models, uptake, factors associated, PLHIV, CAG, PCAD

Introduction

Globally, by the year 2022, ~39 million people were living with HIV, of which 29.8 million had access to life-saving antiretroviral therapy (ART), and ~630,000 died from acquired immunodeficiency syndrome (AIDS)-related illnesses (1). Africa is among the primarily affected continents by HIV, with 20.8 million people living with the virus and 260,000 deaths due to AIDS-related illnesses in the southern and eastern regions of the continent (1). Ethiopia is one of the sub-Saharan African countries with 610,350 people living with HIV (PLHIV) (2, 3). The prevalence of HIV in the country was higher (2.9%) in urban areas (4). There were ~11,000 AIDS-related mortalities in Ethiopia (2).

The United States Agency for International Development (USAID) offers differentiated service delivery (DSD) to improve care retention and address barriers to HIV treatment. The DSD models cater to unique population needs, focusing on client-centered care. Options include multi-month drug dispensing and decentralized drug distribution, reducing healthcare visits, and allowing clients to pick up drugs at home (5). Differentiated HIV care and treatment involves strategic modifications to client flow, schedules, and location of services to improve access, coverage, and quality of care for specific HIV subgroups (6, 7). This approach has the potential to overcome obstacles that clients face in adhering to medication schedules and visits (7).

Ethiopia implements less-intensive and more-intensive HIV treatment DSD models for established HIV patients. Less-intensive models include facility- and community-based approaches, while more-intensive models are implemented at the health facility level for those with advanced HIV disease, adolescents, key populations, and maternal and child health (8). Community-based differentiated service delivery (C-DSD) is a person-centered approach to improving access to HIV services and reducing burdens on the health system. It includes the Health Extension Professional-Managed Community ART Group (CAG) and Peer-Led ART Distribution (PCAD) (8, 9). These models were piloted in some areas of Ethiopia in 2019 but are currently under-implemented throughout the country (8).

Evidence from the studies conducted in Uganda (10–13), Malawi (14), and South Africa (15, 16) showed that the uptake of differentiated community ART models, including community client-led ART delivery (CCLAD), CAG, and Central Chronic Medication Dispensing and Distribution (CCMDD), ranged from 6 to 55%. A report from the evaluation of the DSD model in Kenya revealed that the overall uptake of the DSD model increased from 53% in 2018 to 85% in 2019 (17). In addition, a prospective comparative analysis conducted on client preference and viral suppression among PLHIV enrolled in the DSD model in Ethiopia showed that 59% of the PLHIV enrolled in the community DSD model preferred PCAD, while 41% preferred CAG (9).

In 2022, the global progress toward the 95–95–95 targets for testing, treatment, and viral load suppression showed that 86% of PLHIV know their HIV status, 89% of people who know their HIV status are on treatment, and 93% of PLHIV on treatment have suppressed viral loads (18). Ethiopia has nationally achieved the second and third 95 targets. A total of 84% of PLHIV know their status; 98% are on ART, and 98% of PLHIV on ART are virally suppressed (19). To achieve the 95–95–95 targets and to ensure that PLHIV are aware of their status, receive and maintain ART, and achieve viral suppression, community-based and health facility HIV service delivery points must provide effective, efficient, and high-quality services (20).

To achieve the 95–95–95 ambitious targets of UNAIDS, adopting efficient and innovative mechanisms for providing HIV treatment, care, and prevention services that meet the needs of various types of clients is essential (21). Community ART models aim to enhance patients' quality of services, optimize national ART program effectiveness, and minimize the need for clinic visits and system and patient difficulties (22–24). Community ART model uptake had a significant effect on removing obstacles to accessing care (25), reducing mortality, and reducing loss to follow-up (LFTU) (26). In addition, the uptake of community ART models can also improve retention in care (27) and contribute to money savings, which makes it a cost-effective intervention and reduces healthcare workforce requirements compared to individual care provision (28). In addition to the abovementioned benefits, a qualitative study conducted in three African countries, South Africa, Uganda, and Zimbabwe, reported that community ART models can enhance time-saving, support adherence, improve peer support, and reduce stigma (22). In Africa, community-based ART delivery had the potential to improve HIV care engagement, and outcomes related to ART in terms of adherence to ART, viral suppression, retention in care, and ART uptake were good among key populations (29).

Previous studies conducted on the uptake of different community-based DSD models showed that some sociodemographic and clinical factors like age, marital status, educational status, occupational status, duration on ART, and missed clinical appointment were associated with the uptake of community-based DSD models (10, 15, 16).

Expanding ART access to community-based ART service delivery programs resulted in remarkable achievement in poor resource settings (30). However, with the implementation of the community-based DSD model in Ethiopia, there is a lack of evidence regarding the uptake of the community-based DSD models and responsible factors, and no study was conducted in the study settings. Therefore, this study aimed to assess the uptake of community-based DSD models and associated factors among PLHIV in South Ethiopia.

Methods and materials

Study setting and period

The study was conducted at public health hospitals of Wolaita Sodo University Comprehensive Specialized Hospital, Arba Minch General Hospital, and Jinka General Hospital from June to September 2023. The hospitals are located in the administrative cities of the South Ethiopia Region, Wolaita Sodo, Arba Minch, and Jinka.

Study design and participants

A facility-based, multicenter cross-sectional study was conducted among stable adult patients on ART for at least 1 year. Eligible participants include those with no adverse drug reactions requiring regular monitoring; a good understanding of lifelong adherence; evidence of treatment success (i.e., two consecutive VL measurements <1,000 copies/ml, rising CD4 cell counts, or CD4 counts above 200 cells/mm^3); no acute illness; those who were not pregnant or breastfeeding (4), and those who visited ART clinics in selected public hospitals during the data collection period.

Eligibility criteria

The inclusion criteria were stable HIV clients on ART who were at least 18 years old. Those who provided incomplete information from other health facilities were excluded from the study.

Sample size determination and sampling technique

A single population proportion formula with a 50% prevalence, a 95% confidence interval, and a 5% margin of error was used to calculate the sample size, resulting in 384 participants. Since the total population was less than 10,000, a correction formula was applied, yielding a sample size of 350. Adding 10% to account for the non-response rate resulted in a final sample size of 385. The sample size was proportionally allocated among the selected public health hospitals, and a systematic sampling technique was used to select study participants.

Data collection method

A predetermined structured questionnaire was used, and the data collection tool consisted of sociodemographic, behavioral-related, health service delivery-related, clinical, and treatment-related characteristics. An interview and medical chart observation of clients were used to collect the data. The client records were reviewed manually. Six BSc nurses collected the data, and three public health professionals supervised the data collection process.

Study variable

The dependent variable was the uptake of community-based DSD models. Independent variables were sociodemographic characteristics (age, sex, residence, marital status, educational status, occupation, and monthly income), behavioral-related and health service delivery-related characteristics (khat chewing, alcohol use, frequency of condom use, and number of the sexual partner, facility type, ART facility catchment, and distance), and clinical and treatment characteristics (duration on ART, WHO clinical stage, viral load, CD4 count, regimen change, missed clinical appointment, disclosure status, history of tuberculosis infection, and social support).

Data quality assurance

Before the data collection process, a pretest was conducted on 5% of the sample size, and 2 days of training were provided to data collectors and supervisors. The supervisors checked the completeness and consistency of the questionnaire filled out daily, and any necessary corrections were made.

Data processing and analysis

The collected data were entered using Epi-Data version 3.1 and exported to Stata version 14 for further analysis. A descriptive statistical analysis was conducted, including frequency, percentage, median, and interquartile range. A bivariable logistic regression analysis was conducted to examine the relationship between the uptake of the community-based DSD models and independent variables such as age, sex, residence, marital status, educational status, occupation, monthly income, khat chewing, alcohol use, frequency of condom use, number of the sexual partner, facility type, ART facility catchment, distance, duration on ART, WHO clinical stage, viral load, CD4 count, regimen change, missed clinical appointment, disclosure status, history of tuberculosis infection, and social support. Variables with p-values of ≤ 0.25 were considered candidates for the multivariable logistic regression analysis.

The backward likelihood ratio was used to build the model. In the multivariable analysis, variables with a p-value of <0.05 and an adjusted odds ratio (AOR) with a 95% CI were considered statistically significant. Multicolinearity and model adequacy were assessed using the variance inflation factor (mean VIF = 1.00) and the Hosmer and Lemeshow goodness of fit test (prob > chi^2 = 0.5708).

Results

Among the total sample size, 381 participants were included in the analysis, with a response rate of 98.96% (Figure 1).

Sociodemographic, behavioral-related, health service delivery-related, and clinical characteristics

The median age of the study participants was 40 years, with an interquartile range of 27–53 years. The majority of the participants, 255 of them (66.93%), were older than 35 years. More than half (55.91%) of the participants were women, and three-fourths of the participants (75.85%) were urban residents. Among 381 study participants, one-fourth of the participants (93 participants, 24.41%) had no formal education. Nearly one-fifth of the participants (16.8%) had alcohol use problems. Moreover, 24 participants (6.3%) had a history of TB co-infection, and 361 participants (94.75%) had undetectable viral loads. The baseline regimen was changed for the majority (87.93%) of the study participants. Additionally, one-fifth of the participants (19.69%) missed their clinical appointments, and 345 participants (90.55%) disclosed their serostatus (Table 1).

Uptake of community ART model

The uptake of the community-based ART DSD model was 19.16% (95% CI: 15.19%, 23.13%); (Figure 2).

Factors associated with community ART model uptake

Residence, educational status, occupational status, number of sexual partners, duration of ART, and disclosure were the factors associated with the uptake of community-based ART DSD models

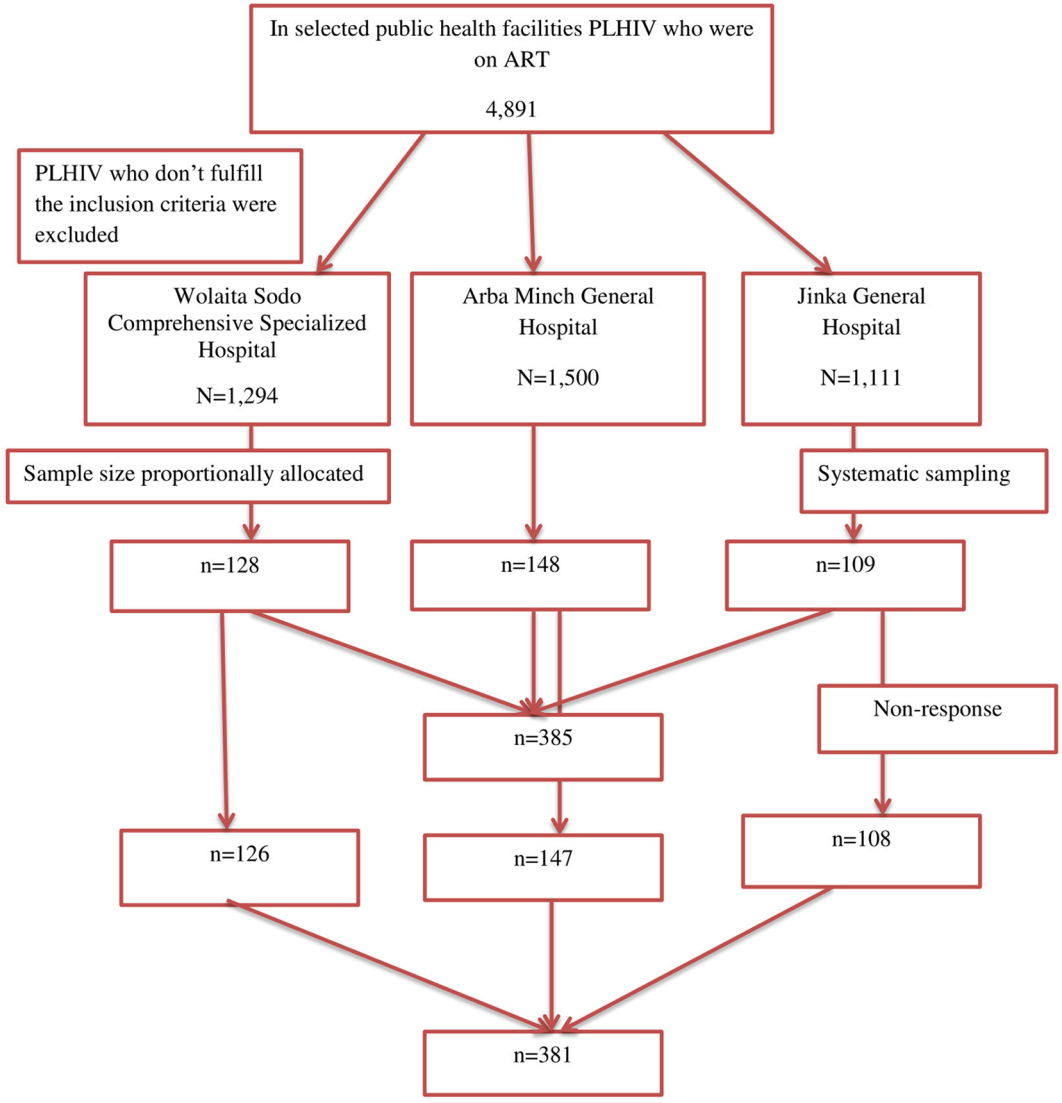

FIGURE 1
A flow diagram of the included study participants.

in the bivariable logistic regression analysis. The multivariable logistic regression analysis showed that residence and disclosure with were significantly associated factors with the uptake of the community-based models among PLHIV, with a p-value of <0.05.

The odds of uptake of the community-based ART DSD models for patients in urban areas were two times higher than those of patients in rural areas (AOR 2.30, 95% CI: 1.12, 4.70). Additionally, patients who disclosed their HIV status were 4.44 times more likely to utilize the community-based ART DSD models compared to those who never disclosed their HIV status (AOR: 4.44, 95% CI: 1.04, 18.97); (Table 2).

Discussion

This study aimed to explore the uptake and associated factors of community-based DSD models among PLHIV. The uptake of the community-based DSD models was nearly 20%. Residence and serostatus disclosure were statistically significant factors associated with the uptake. These findings indicate that the uptake of community-based DSD models requires attention from policymakers and program planners. Efforts should be made to address the barriers faced by stable PLHIV on ART to enhance the uptake of these models, which are crucial for improving adherence, retention in care, and decongesting healthcare facilities.

Our study showed that the proportion of uptake of the community-based DSD model was 19.16%. This finding is lower than that of studies conducted in KwaZulu-Natal, South Africa (16) and Durban, South Africa (15). The sample size, study design, and participants' eligibility criteria could explain this variation. The study conducted in Durban, South Africa, used a randomized controlled trial design. Another possible explanation might be that PLHIV on ART in our setting might prefer a facility-based DSD model over community-based DSD models. These findings have significant implications for decreasing the

TABLE 1 Sociodemographic, behavioral-related, health service delivery-related, and clinical characteristics of PLHIV in public health facilities in South Ethiopia, 2023 ($n = 381$).

Variables	Categories	*n* (%)
Age (in years)	≤25	27 (7.09)
	26–35	99 (25.98)
	>35	255 (66.93)
Sex	Male	168 (44.09)
	Female	213 (55.91)
Residence	Urban	289 (75.85)
	Rural	92 (24.15)
Marital status	Single	29 (7.61)
	Married	222 (58.27)
	Divorced/separated	65 (17.06)
	Widowed	65 (17.06)
Education	No formal	93 (24.41)
	Primary	142 (37.27)
	Secondary	97 (25.46)
	Tertiary	49 (12.86)
Occupation	Daily laborer	63 (16.54)
	Merchant	83 (21.78)
	Government employee	82 (21.52)
	Housewife	86 (22.57)
	Farmer/student	39 (10.24)
	Other*	28 (7.35)
Monthly income (Ethiopian Birr)	≤5,000	341 (89.50)
	>5,000	40 (10.50)
Facilities type	General hospital	255 (66.93)
	Comprehensive specialized hospital	126 (33.07)
ART facility catchment	Within the catchment	296 (77.69)
	Out of the catchment	85 (22.31)
Distance (in minutes)	≤10	6 (1.57)
	11–50	236 (61.94)
	>50	139 (36.48)
kchat chew	Yes	72 (18.90)
	No	309 (81.10)
Alcohol use problem	Yes	64 (16.80)
	No	317 (83.20)
Condom use	Always	57 (14.96)
	Sometimes	127 (33.33)
	Never	197 (51.71)
Number of sexual partners	No sexual partner	149 (39.11)
	One sexual partner	210 (55.12)
	≥2 sexual partner	22 (5.77)
Duration (in years)	≤5	86 (22.57)
	>5	295 (77.43)
WHO clinical stage	I	195 (51.18)
	II	74 (19.42)
	III/IV	112 (29.40)
Recent viral load	Undetectable	361 (94.75)
	Detectable	20 (5.25)
Baseline CD4 count	<500 cell/mm^3	315 (82.68)
	≥500 cell/mm^3	66 (17.32)
Regimen Change	Yes	335 (87.93)
	No	46 (12.07)
History of TB co-infection	Yes	24 (6.30)
	No	357 (93.70)
Missed clinical appointment	Yes	75 (19.69)
	No	306 (80.31)
Disclosure status	Yes	345 (90.55)
	No	36 (9.45)
Social support	Poor	195 (51.18)
	Intermediate	149 (39.11)
	Strong	37 (9.71)

*Pastoralist, retired, self-employed, NGO, driver, unemployed, evangelist.

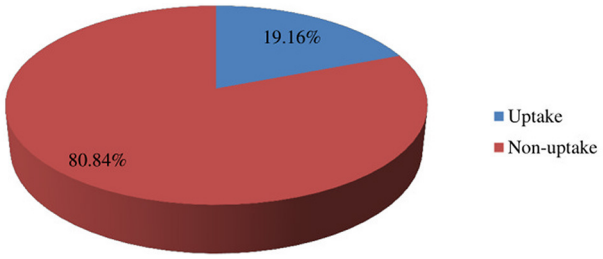

FIGURE 2
The uptake of community-based DSD models among people living with PLHIV in public health facilities in South Ethiopia, 2023 ($n = 381$).

burden on health facilities by promoting the community-based DSD model (31).

However, our study's findings are higher than those from previous studies conducted in Malawi (14), Kampala, Uganda (10), Mulago, Uganda (12), and Arua district, Uganda (13). The difference might be due to study setting variations, health service delivery systems, and eligibility criteria, and the definition used for the outcome could also contribute to the differences observed. In our study, the uptake of community-based DSD models refers to the uptake of either community ART groups

10.3389/fpubh.2024.1390538

TABLE 2 Bivariable and multivariable logistic regression analyses for factors associated with the uptake of community-based DSD models among PLHIV in public health facilities of South Ethiopia, 2023 ($n = 381$).

Variables	Community-based DSD model uptake		COR (95% CI)	AOR (95% CI)	*p*-value
	No (%)	Yes (%)			
Residence					
Urban	226 (78.20)	63 (21.80)	2.29 (1.12, 4.67)	2.30 (1.12, 4.70)	0.023
Rural	82 (89.13)	10 (10.87)	Reference	Reference	
Education					
No formal	77 (82.80)	16 (17.20)	Reference	Reference	
Primary	115 (80.99)	27 (19.01)	1.13 (0.57, 2.24)	1.03 (0.48, 2.13)	0.939
Secondary	73 (75.26)	24 (24.74)	1.58 (0.78, 3.21)	1.99 (0.85, 4.66)	0.111
Tertiary	43 (87.76)	6 (12.24)	0.67 (0.24, 1.84)	0.76 (0.22, 2.65)	0.663
Occupation					
Daily laborer	51 (80.95)	12 (19.05)	2.06 (0.61, 6.91)	1.46 (0.41, 5.23)	0.562
Merchant	70 (84.34)	13 (15.66)	1.63 (0.49, 5.35)	1.07 (0.31, 3.77)	0.911
Government employee	67 (81.71)	15 (18.29)	1.96 (0.60, 6.35)	1.25 (0.36, 4.38)	0.729
Housewife	63 (73.26)	23 (26.74)	3.19 (1.02, 9.98)	2.07 (0.63, 6.86)	0.232
Farmer/student	35 (89.74)	4 (10.26)	Reference	Reference	
Other	22 (78.57)	6 (21.43)	2.39 (0.60, 9.42)	1.68 (0.39, 7.15)	0.484
Catchment of ART facility					
Within	232 (78.38)	64 (21.62)	2.33 (1.11, 4.90)	1.67 (0.69, 4.09)	0.258
Outside	76 (89.41)	9 (10.59)	Reference	Reference	
Number of sexual partners					
No sexual partner	124 (83.22)	25 (16.78)	4.23 (0.54, 32.94)	3.08 (0.37, 25.37)	0.295
One sexual partner	163 (77.62)	47 (22.38)	6.06 (0.79, 46.20)	4.93 (0.61, 39.60)	0.133
≥2 sexual partner	21 (95.45)	1 (4.55)	Reference	Reference	
Disclosure					
Yes	274 (79.42)	71 (20.58)	4.41 (1.03, 18.78)	4.44 (1.04, 18.97)	0.045
No	34 (94.44)	2 (5.56)	Reference	Reference	
Duration on ART					
≤5	65 (75.58)	21 (24.42)	Reference	Reference	
>5	243 (82.37)	52 (17.63)	0.66 (0.37, 1.18)	0.62 (0.34, 1.11)	0.109

(CAG) or peer lead community ART distribution (PCAD), whereas studies conducted in Malawi and Uganda indicate the uptake of CAG.

The findings of this study revealed that urban residents living with HIV are more likely to uptake community-based DSD models than rural residents. The possible explanation might be the better socioeconomic status, good adherence, and disclosure status of clients in urban areas than those in rural areas. A systematic review and meta-analysis revealed that clients living in urban areas have better adherence than those living in rural areas (32). However, this study finding is inconsistent with early programmatic data from Zimbabwe, which indicates that the uptake of community-based DSD models is highest in rural areas (33). This result suggests that urban resident clients are more likely to utilize community-based DSD models. Further studies are needed to identify the association between the place of residence and the uptake of community-based DSD models.

Furthermore, in this study, HIV-positive patients who disclosed their status were significantly more likely to uptake community-based DSD models. The reason might be that patients who disclose their HIV status may have strong social support and better adherence to ART services. Serostatus disclosure of HIV is significantly associated with better engagement in medical care, reduced HIV transmission, improved ART adherence, decreased psychological distress, and enhanced social support opportunities (34). PLHIV who disclosed their HIV status demonstrated better adherence than those who did not (35). In addition, the community-based DSD model may increase the risk of serostatus

disclosure, which poses a significant challenge to the uptake of these models (36, 37). This finding suggests that disclosing HIV serostatus enhances the uptake of community-based DSD models.

Strengths and limitations of the study

The study was conducted at multicenter public health facilities, enhancing its generalizability. However, due to the cross-sectional study design, the study's limitations include the difficulty in establishing cause-and-effect relationships.

Conclusion

One out of five PLHIV utilizes the community-based DSD models. Urban residence and serostatus HIV disclosure were significantly associated with the uptake of community-based DSD models. Increasing the uptake of community-based DSD models might improve ART outcomes and the efficiency of the healthcare system by improving adherence, viral suppression, and retention in care and service delivery efficiency among PLHIV. Therefore, to increase adherence and retention in ART, efforts should be made to improve the uptake of community-based DSD models by encouraging HIV serostatus disclosure. Improvement in uptake is essential for the resource-limited healthcare system of Ethiopia.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Institutional Review Board of Arba Minch College of Health Science. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

FM: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. TT: Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. AA: Project administration, Supervision, Validation, Visualization, Writing – review & editing. TG: Data curation, Formal analysis, Investigation, Methodology, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 01 October 2024
DOI 10.3389/fpubh.2024.1420609

OPEN ACCESS

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RECEIVED 24 April 2024
ACCEPTED 19 September 2024
PUBLISHED 01 October 2024

CITATION
Chen H, Tao R, Wu L, Chen C and He J (2024) Rapid antiretroviral therapy and treatment outcomes among people living with HIV: exploring the mediating roles of medication adherence.
Front. Public Health 12:1420609.
doi: 10.3389/fpubh.2024.1420609

Rapid antiretroviral therapy and treatment outcomes among people living with HIV: exploring the mediating roles of medication adherence

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Introduction: The rapid initiation of antiretroviral therapy (ART) and its impact on treatment outcomes have been a subject of global public health interest. However, the precise mechanisms underlying the effects of rapid ART initiation remain unclear.

Methods: This retrospective cohort study examined data from 1846 HIV-infected individuals in Jiulongpo District, Chongqing, China, spanning from 2016 to 2022. Logistic regression models and serial mediation analysis were used to explore the influence of rapid ART initiation on treatment outcomes and the role of medication adherence as a mediating factor.

Results: The findings revealed a significant association between rapid ART initiation and reduced risk of viral failure (adjusted odds ratio [OR] = 0.320, 95% confidence interval [CI] = [0.161, 0.637]), as well as an increased likelihood of improved adherence (adjusted OR = 2.053, 95% CI = [1.226, 3.438]). Medication adherence was identified as a partial mediator in the relationship between rapid ART initiation and viral failure, explaining 10.5% of the total effect.

Discussion: In conclusion,rapid initiation of antiretroviral therapy was found to enhance treatment outcomes, emphasizing the importance of early adherence education. The study recommends early initiation of ART coupled with adherence education and psychological counseling for HIV-infected individuals.

KEYWORDS

HIV, rapid ART initiation, medication adherence, viral failure, mediation effect

Introduction

HIV/AIDS remains a critical global public health challenge and a predominant cause of mortality worldwide. In 2022, there were 39 million people globally living with HIV/AIDS, with 1.3 million new HIV infections, and 630,000 deaths attributed to HIV/AIDS-related illnesses (1). Despite the HIV epidemic has largely improved since the introduction of antiretroviral therapy (ART) (2), ongoing efforts to achieve the goal of ending AIDS require continuous adaptation of treatment protocols. Initially, the initiation of ART for people living with HIV (PLWH) relied on CD4 cell count thresholds (3). Subsequently, the World Health Organization (WHO) issued the "treat all" policy, advocating for HIV treatment regardless of CD4 cell count or clinical symptoms (4). Presently, the WHO recommends the rapid initiation of antiretroviral therapy (Rapid ART), which defined as the initiation of ART within 7 days of diagnosis and recommends that prepared individuals should begin treatment on the same day of diagnosis (5).

The mechanism by which rapid ART enhances treatment outcomes may be associated with the reduction of the viral reservoir. Clones of infected cells can arise as early as 20 days after HIV infection (6), and a viral reservoir of long-lived, transcriptionally silent cells is established very early in the peripheral blood, lymphoid tissue, lungs, brain, spleen, and gut (7). This reservoir remains despite ART and leads to viral rebound when ART is discontinued. While rapid ART can reduce the plasma viral load, lower the viral set point, and limit the size of the latent HIV reservoir (8–10). Additionally, Lee et al. found very limited identical viral sequences after early ART initiation, which might imply that there is little clonal proliferation of CD4+ T-cells, an important mechanism fueling persistence of the HIV reservoir (11).

Numbers of evidence suggest that the rapid initiation of treatment can yield both clinical and public health benefits. Rapid ART has been demonstrated to increase ART initiation rates (12, 13), shorten the time to achieve viral suppression (13–16), reduce the risk of HIV transmission (12, 17, 18), decrease morbidity and mortality (19, 20), and mitigate patient loss to follow-up (17, 21). Furthermore, it has shown potential in decreasing the incidence of tuberculosis and severe bacterial infections (22). Epidemiological and economic analyses conducted in Spain have indicated that rapid ART initiation could prevent approximately 992 potential HIV infections and result in an estimated €323 million in potential savings over the next two decades (23).

Treatment adherence is a backbone for the success of ART (24). A retrospective cohort study conducted in Uganda demonstrates that individuals with better adherence are more likely to achieve viral suppression (24). Additional research suggests poor adherence is associated with ART failure and the occurrence of drug resistance (25, 26). Furthermore, adherence appears to be a crucial factor in the relationship between rapid ART and treatment outcomes. On the one hand, rapid ART can reduce treatment loss (27) and maintain treatment retention (12); on the other hand, hasty rapid ART may decrease willingness to be treated (5). However, there is limited research in real-world settings on the mechanisms linking adherence to rapid ART and treatment outcomes.

In China, the comprehensive implementation of the "treat all" policy began in 2016, laying the groundwork for rapid ART, which commenced in 2021. The purpose of this study is to (1) explore the association between rapid ART and viral suppression in real world, and (2) investigate the role of medication adherence among these two factors.

Materials and methods

Data source and collection

This observational retrospective study examined a cohort of patients diagnosed with HIV from January 2016 to December 2022. Data were sourced from the China Information System for Disease Control and Prevention, which record diagnosis and treatment details through reporting agencies and designated treatment facilities. This study was conducted in the Jiulongpo District of Chongqing, where three government-designated healthcare institutions (Chongqing Public Health Medical Center (CMC), The First Public Hospital in Jiulongpo (FPH) and The Second Public Hospital in Jiulongpo (SPH)) provided antiretroviral therapy services for HIV/AIDS and authorized healthcare personnel inputted information of PLWH, including personal, treatment, and epidemiological data.

Study population

We included patients who registered for HIV diagnosis and treatment in the information system and screened the study population based on the following criteria. Inclusion criteria: (1) Current address was in Jiulongpo District of Chongqing; (2) ART initiation occurred between January 2016 and December 2022. Exclusion criteria: (1) Age < =15; (2) Duration of ART less than 24 weeks; (3) Patients without CD4 test results before ART initiation; (4) Absence of at least one viral load test per year after 24 weeks of ART, with a total number of viral load tests less than two; (5) Indications of inappropriateness for rapid ART, including pulmonary tuberculosis, extrapulmonary tuberculosis, mycobacterium avium complex infection, cryptococcal meningitis, serious chronic diseases, hepatic and renal insufficiency, nervous system diseases, pneumocystis carinii pneumonia, Penicillium marneffei. The filter process is shown in Figure 1.

Measures

Outcome-The outcome of interest was viral failure (VF), defined dichotomously as two consecutive plasma HIV-1 RNA measurements exceeding 200 copies/ml after 24 weeks of ART, according to the latest manual on free antiviral drug treatment in China (2023), as opposed to viral suppression (*VS*). An increasing number of studies utilized continuous measurements of viral load to define VF (28, 29).

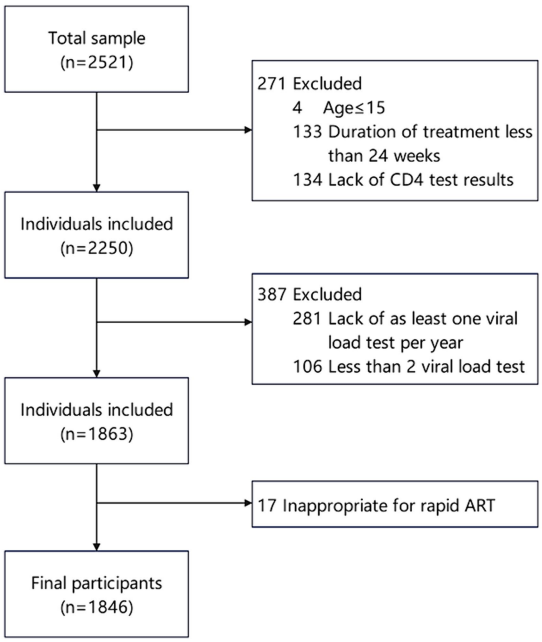

FIGURE 1
Flow of participant inclusion among PLWH initiating antiretroviral therapy in Jiulongpo District from 2016 to 2022.

Predictor-The predictor of interest was rapid ART, defined as the initiation of ART within 30 days of diagnosis. Currently, there is no unified consensus on the timing of treatment initiation, and the Chinese Guidelines for Diagnosis and Treatment of Human Immunodeficiency Virus Infection /Acquired Immunodeficiency Syndrome (2021 edition) do not provide specific regulations regarding the initiation timing for confirmed cases. Furthermore, due to the relatively late introduction of Rapid ART in China, with only 18.7% of patients starting ART within 7 days (30), we defined rapid ART initiation as treatment initiation within 30 days to align with some nationwide studies (20, 27).

Mediators-The focus mediator was medication adherence, determined by the adherence rate calculated as the number of days medication was taken divided by the prescribed number of days. Adherence was classified into two groups: optimal medication adherence (≥95% adherence) and poor medication adherence (<95% adherence) (31, 32).

Covariates-Covariates were chosen *a priori* based on their potential for confounding. Covariates included sex, age, marital status, CD4 cells count, occurrence of related symptoms, WHO clinical stage, ART regimen, and duration of ART at baseline. Age was dichotomized into two groups: <50 years old and ≥ 50 years old. ART regimen are categorized into first-line, second-line, and others. The first-line treatment includes two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitor (NNRTI). The second-line treatment substitutes the NNRTI with either an integrase strand transfer inhibitor (INSTI) or a protease inhibitor (PI).

Analyses

Descriptive analyses were conducted to summarize participant characteristics. To test for differences, we used chi-square or Fisher test for independence for categorical variables and Mann–Whitney U test for continuous variables.

To evaluate the relationship between rapid ART and VF, logistic regression was used to estimate the total effect of rapid ART on VF. In these models, we initially included only rapid ART to estimate the crude odds ratios (COR), then all covariates were adjusted to calculate adjusted odds ratios (AOR). Furthermore, to explore the roles of medication adherence as mediators, we estimated indirect and direct effects along possible pathways using mediation analysis with 95% confidence intervals (95%CI), generated from bias-corrected bootstrapped standard errors.

All analyses were conducted using R4.1.0. Statistical significance was considered at $p < 0.05$.

Results

Participant characteristics

From 2016 to 2022, a total of 2,521 people living with HIV (PLWH) initiated antiretroviral therapy, and finally, 1846 of them were included in the present study (Figure 1). The participant characteristics of the included PLWH are presented in Table 1. The majority of PLWH were male (77.2%), with 39.4% of participants aged 50 and above, and 44.5% married.

In terms of baseline clinical presentation, the majority of individuals (93.9%) had no related symptoms, with over half (60.9%) being at WHO clinical stage 2. Additionally, the median CD4 count prior to treatment initiation was only 207, and during the treatment process.

Regarding treatment aspects, the majority of individuals (81.0%) were prescribed first-line treatment regimens, with 96.4% exhibiting optimal medication adherence. The median duration of treatment was 1,296 days, and 60.4% of PLWH initiated treatment within 30 days.

The total viral failure rate was 2.11%. Compared to cases with *VS*, patients experiencing VF appeared to have poor medication adherence, lower baseline CD4 counts, longer treatment durations, and a lower proportion of rapid ART initiation (all $p < 0.05$).

Effect of rapid ART on vial failure

In the crude model, rapid ART had a significantly association with VF, such that rapid ART was associated with lower odds of VF (COR = 0.359, 95% CI = [0.185, 0.696]). These results were similar with those of the fully adjusted model. Specifically, rapid ART was associated with a 68% decrease in the odds of VF (AOR = 0.320, 95% CI = [0.161, 0.637]). In addition, there was an association between VF and baseline CD4 levels, with odds ratios and 95% CI of 0.995 (0.992, 0.998), as showed in Table 2.

Effect of rapid ART on adherence

The results indicated that, without adjusting for confounding factors, rapid ART could significantly increase medication adherence (COR = 1.761, 95% CI = [1.076, 2.882]). Correspondingly, after controlling for all confounding variables, the AOR for rapid ART improving adherence was 2.053 (95% CI = [1.226, 3.438]). Additionally, WHO stage 4 was associated with decreased adherence (AOR = 0.195, 95% CI = [0.064, 0.592]), as showed in Table 3.

The moderate effect of adherence

Figure 2 displayed the findings of serial mediation analyses, presenting total effects as differences in log-odds for comparison. After accounting for potential mediators, rapid ART was found to exert a statistically significant negative direct effect on VF ($\beta = -0.019$, 95% CI = [−0.034, −0.01]), and this direct effect was of lesser magnitude compared to the estimated total effect of rapid ART ($\beta = -0.021$, 95% CI = [−0.039, −0.01]).

The indirect effect of Rapid ART on reducing the risk of VF through enhancing medication adherence was also significant ($\beta = -0.002$, 95% CI = [−0.008, 0.000]). 10.5% of the total effect could be attributed to the mediating role of adherence.

Discussion

In present study, nearly 60% of participants initiated rapid ART, which was lower than the data from a recent study conducted in China, where the ART initiation rate within 30 days for newly diagnosed HIV-infected individuals in China was reported to be close to 75%

TABLE 1 Baseline characteristics of patients and the differences between viral failure and viral suppression.

Variables	Total (n = 1,846)	*VS* (n = 1,807)	VF (n = 39)	*P*	Z/χ^2
Sex, *n* (%)				0.967	0.002
Male	1,425 (77.2)	1,395 (77.2)	30 (76.9)		
Female	421 (22.8)	412 (22.8)	9 (23.1)		
Marital status, *n* (%)				0.692	0.736
Single	703 (38.1)	690 (38.2)	13 (33.3)		
Married or cohabiting	822 (44.5)	802 (44.4)	20 (51.3)		
Divorced, widowed or unknown	321 (17.4)	315 (17.4)	6 (15.4)		
Occurrence of related symptoms, *n* (%)				0.557	0.345
No	1734 (93.9)	1,696 (93.9)	38 (97.4)		
Yes	112 (6.1)	111 (6.1)	1 (2.6)		
WHO clinical stage, *n* (%)				0.069	
Stage 1	385 (20.9)	379 (21)	6 (15.4)		
Stage 2	1,125 (60.9)	1,105 (61.2)	20 (51.3)		
Stage 3	115 (6.2)	112 (6.2)	3 (7.7)		
Stage 4	221 (12)	211 (11.7)	10 (25.6)		
Adherence, *n* (%)				< 0.001	51.623
Optimal	1779 (96.4)	1751 (96.9)	28 (73.7)		
Poor	66 (3.6)	56 (3.1)	10 (26.3)		
Baseline CD4 count, cells/μl, Median (Q1, Q3)	207 (116.25, 318)	210 (120, 319.5)	123 (47, 218.5)	< 0.001	−3.659
Duration on ART, Median (Q1, Q3)	1,296 (766, 1887.75)	1,293 (759, 1885.5)	1,642 (1,152, 1930)	0.009	−2.625
Age group, *n* (%)				0.9	0.016
<50	1,118 (60.6)	1,094 (60.5)	24 (61.5)		
≥50	728 (39.4)	713 (39.5)	15 (38.5)		
Initiation time of ART, *n* (%)				0.002	10.001
Rapid ART(<30d)	1,115 (60.4)	1,101 (60.9)	14 (35.9)		
Delayed ART(≥30d)	731 (39.6)	706 (39.1)	25 (64.1)		
ART regimen, *n* (%)				0.064	
First-line treatments	1,496 (81.0)	1,459 (80.7)	37 (94.9)		
Second-line treatments	91 (4.9)	90 (5)	1 (2.6)		
Others	259 (14.0)	258 (14.3)	1 (2.6)		

(33). Furthermore, individuals initiating rapid ART were more likely to exhibit optimal medication adherence and lower risk of viral failure. Mediation analysis revealed that medication adherence partially mediated the association between rapid ART initiation and viral failure.

In this study, we found a significant association between rapid ART and a lower likelihood of viral failure, even when adjusting for potential confounders. This discovery was consistent with findings from previous studies involving PLWH. For instance, A large retrospective observational cohort study conducted in China found that patients who received immediate ART (within 30 days of diagnosis) had a lower rate of viral failure compared to those who initiated ART later (27). In a prospective randomized controlled trial, the viral suppression rate at 12 months of treatment was 50.4% in the rapid initiation group, compared to only 34.3% in the standard protocol group (12). And another comprehensive retrospective analysis of newly diagnosed PLWH in high-income countries has demonstrated that immediate initiation of antiretroviral therapy (ART) accelerates viral suppression during follow-up (34).

Some studies suggested that rapid initiation of treatment might lead to decreased adherence, which contradicted our research findings (31, 35). This discrepancy could be attributed to the definition of rapid initiation treatment as initiating treatment on the same day of diagnosis in their studies, whereas PLWH might not psychologically accept the fact of infection in a short period of time and might harbor biases against treatment due to lack of information about antiretroviral therapy. In contrast, a retrospective cohort study conducted in China suggested that rapid ART within 7 days may actually improve adherence (36). This suggests that newly diagnosed patients require a certain degree of buffering before initiating treatment.

Numerous studies had demonstrated that medication adherence is a key influencing factor for the success of antiviral therapy (24, 37), yet few explored the role of adherence in the causal pathway between rapid treatment initiation and treatment outcomes. This study indicated that

10.3389/fpubh.2024.1420609

TABLE 2 The association between rapid ART and viral failure.

Variables	Model 1		Model 2	
	COR (95%CI)	*P*	AOR (95%CI)	*P*
Initiation time of ART				
Delayed ART(≥30d)	1		1	
Rapid ART(≤30d)	0.359 (0.185–0.696)	0.002	0.320 (0.161–0.637)	0.001
Sex				
Male			1	
Female			0.935 (0.42–2.078)	0.868
Marital status				
Single			1	
Married or cohabiting			1.218 (0.521–2.848)	0.650
Divorced, widowed or unknown			0.892 (0.298–2.676)	0.839
Weather occur HIV-related diseases				
No			1	
Yes			0.217 (0.028–1.679)	0.143
WHO clinical stage				
WHO clinical stage 1			1	
WHO clinical stage 2			1.71 (0.611–4.787)	0.307
WHO clinical stage 3			2.042 (0.47–8.883)	0.341
WHO clinical stage 4			3.133 (0.984–9.976)	0.053
ART regimen				
First-line treatments			1	
Second-line treatments			0.505 (0.066–3.851)	0.510
Others			0.268 (0.034–2.097)	0.210
Age group				
Age < 50			1	
Age ≥ 50			0.894 (0.411–1.945)	0.778
Baseline CD4 count			0.995 (0.992–0.998)	0.002
Duration on ART			1.001 (1–1.001)	0.054

COR: crude odds ratios; AOR: adjusted odds ratios; 95%CI: 95% confidence interval. Model 1: Crude model with no covariates were adjusted. Model 2: Fully adjusted model with adjusted for sex, age, marital status, CD4 cells count, occurrence of HIV-related diseases, WHO clinical stage, ART regimen, and duration of ART at baseline.

good adherence served as a mechanism for the reduction of viral failure risk associated with rapid ART, with the mediating effect accounting for 10.5%. Although more and more drugs are now being used for HIV treatment, some of which have a high genetic barrier to maintain a good virological response, a large proportion of patients are still on previous regimens. Therefore, to enhance the effectiveness of rapid treatment initiation, it is imperative to strengthen education on communication methods for healthcare professionals, and this will enable them to accurately and effectively convey the benefits of rapid treatment initiation to New HIV-infected individuals within limited time frames. Additionally, providing psychological counseling for patients can help improve their acceptance and adherence to treatment.

This study also has some limitations. Firstly, only a small proportion of patients underwent viral load testing before treatment initiation, thus the confounding effect of baseline viral load could not be controlled. Additionally, there were other potential confounding factors that were not documented systematically, such as alcohol consumption and AIDS related knowledge. Secondly, this study was conducted in one district and the same participants could not represent all PLWH in China; however, it is possible that an even larger sample and multi-center approach may have been necessary.

Conclusion

In summary, during the study period, the rate of rapid ART was 60.4%, and those who experience rapid ART are more likely to exhibit good adherence and less likely to be VF, indicating that rapid treatment initiation continues to be a crucial strategy. Additionally, improving medication adherence is a partial pathway through which rapid treatment initiation reduces the risk of viral failure. Therefore, this study suggests that adherence counseling should be particularly emphasized for individuals starting ART. Capacity building of healthcare workers in adherence counseling and deploying counselors to ART clinics could help improve adherence and consequently enhance viral load suppression.

TABLE 3 The association between initiation time of ART and medication adherence.

	Model 1		Model 2	
Variables	COR (95%CI)	*P*	AOR (95%CI)	*P*
Initiation time of ART				
Delayed ART(≥30d)	1		1	
Rapid ART(≤30d)	1.761 (1.076–2.882)	0.024	2.053 (1.226–3.438)	0.006
Sex				
Male			1	
Female			1.068 (0.579–1.969)	0.834
Marital status				
Single			1	
Married or cohabiting			0.836 (0.404–1.733)	0.630
Divorced, widowed or unknown			0.577 (0.257–1.296)	0.183
Weather occur HIV-related diseases				
No			1	
Yes			1.105 (0.4–3.055)	0.848
WHO clinical stage				
WHO clinical stage 1			1	
WHO clinical stage 2			0.48 (0.187–1.233)	0.127
WHO clinical stage 3			0.395 (0.103–1.515)	0.176
WHO clinical stage 4			0.195 (0.064–0.592)	0.004
ART regimen				
First-line treatments			1	
Second-line treatments			0.704 (0.266–1.863)	0.480
Others			2.158 (0.86–5.413)	0.101
Age group				
Age < 50			1	
Age ≥ 50			0.682 (0.368–1.264)	0.224
Baseline CD4 count			0.999 (0.997–1.001)	0.209
Duration on ART			1 (1–1.001)	0.140

COR: crude odds ratios; AOR: adjusted odds ratios. Model 1: Crude model with no covariates were adjusted. Model 2: Fully adjusted model with adjusted for sex, age, marital status, CD4 cells count, occurrence of HIV-related diseases, WHO clinical stage, ART regimen, and duration of ART at baseline.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Author contributions

HC: Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. RT: Data curation, Writing – original draft, Writing – review & editing. LW: Data curation, Writing – original draft. CC: Data curation, Formal analysis, Writing – review & editing. JH: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. The study was funded by the Public Health Key Discipline Construction Program of Chongqing (NO. YWBF2022072).

Acknowledgments

We would like to thank the Public Health Key Discipline Construction Program of Chongqing, which funded the study. We would also like to thank Chongqing Public Health Medical Center (CMC), The First Public Hospital in Jiulongpo (FPH) and The Second Public Hospital in Jiulongpo (SPH) for their efforts in information collection, testing, and treatment of PLWH.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

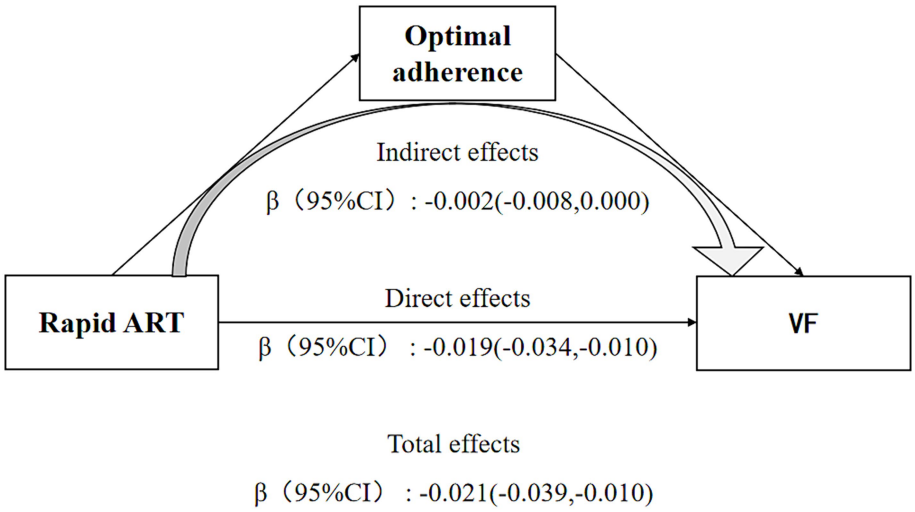

FIGURE 2
Direct and indirect effects of rapid ART on viral failure depending on the moderator medication adherence. Sex, age, marital status, CD4 cells count, occurrence of HIV-related diseases, WHO clinical stage, ART regimen, and duration of ART at baseline were controlled in the model.

Publisher's note

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 28 October 2024
DOI 10.3389/fpubh.2024.1384787

OPEN ACCESS

EDITED BY
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RECEIVED 10 February 2024
ACCEPTED 20 September 2024
PUBLISHED 28 October 2024

CITATION
Chirnet AT, Habtewold EM, Aman H, Wakwoya EB and Workie SG (2024) Time to viral load suppression and its predictors among people living with HIV on antiretroviral therapy in Gebi Resu zone, Afar Region, Ethiopia, 2023.
Front. Public Health 12:1384787.
doi: 10.3389/fpubh.2024.1384787

Time to viral load suppression and its predictors among people living with HIV on antiretroviral therapy in Gebi Resu zone, Afar Region, Ethiopia, 2023

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Objective: This study aimed to estimate the time to viral load suppression and identify its predictors among HIV patients receiving antiretroviral therapy (ART) in the Gebi Resu zone, Afar Region, Ethiopia, 2023.

Setting: The study was conducted at public health facilities in the Gebi Resu zone of the Afar region.

Study design: This study is a facility-based, retrospective follow-up study.

Study participants: This study included 298 people living with HIV who were receiving ART services at selected health facilities in the Gebi Resu zone. Data were collected by reviewing patient records using a structured checklist. Bivariate and multivariate Cox regression analyses were conducted to assess the relationship between variables and control for confounders.

Results: The incidence rate of viral load suppression was 9.46 per 100 person-months. The median time to viral load suppression was 7.7 months, with an interquartile range of 3.8 months (IQR = 6.47–10.27). Patients at clinical stages 3 and 4 [AHR = 0.67, 95%CI (0.47, 0.96)], those who received cotrimoxazole prophylaxis therapy [AHR = 1.47, 95%CI (1.12, 1.92)], and patients with poor drug adherence [AHR = 0.40, 95%CI (0.18, 0.90)] were significantly associated with time to viral load suppression among people on antiretroviral therapy.

Conclusion: The time to viral load suppression and the median time to viral load suppression among people living with HIV on ART were shorter than those observed in many developing and developed countries. Clinical stage, cotrimoxazole prophylaxis therapy, and drug adherence were significant predictors of viral load suppression.

KEYWORDS

time to viral load suppression, antiretroviral therapy, predictors, Afar, Ethiopia

Introduction

Antiretroviral therapy (ART) for HIV infection aims to achieve and maintain viral load suppression. This can, in turn, prevent further immune system damage, reduce acquired immune deficiency syndrome (AIDS)-associated morbidity and mortality, restore immune function, and lower the risk of HIV transmission to uninfected individuals. Together, these effects contribute to reducing the overall incidence of HIV (1–4). In Ethiopia, ART became available free of charge in 2005, and antiretroviral treatment was first introduced in 2003 (5). Monitoring the response to ART is critical for determining treatment outcomes in people living with HIV (PLWH). Treatment outcomes are assessed using immunological markers (CD4 T-cell count), World Health Organization (WHO) clinical staging, and routine viral load suppression monitoring. Among these methods, viral load suppression monitoring is considered to be more accurate, timely, and reliable for detecting treatment failure compared to clinical monitoring or CD4 count (immunologic monitoring) (6).

According to WHO guidelines, viral load monitoring should be conducted annually for stable individuals and every 6 and 12 months after beginning ART (7, 8). Viral load suppression is defined by the WHO as the reduction of the virus's ability to replicate to less than 1,000 copies/ml of plasma after a sufficient duration of ART (9).

The international community has established a global goal to ensure that 95% of all patients undergoing antiretroviral therapy achieve viral suppression by 2025. However, as of 2020, only 66% of the approximately 26 million PLWH on ART had achieved viral load suppression. In 2021, this figure increased to 68% of the 28.7 million PLWH worldwide. Similarly, in Ethiopia, only 72% of HIV-positive patients on ART achieved viral suppression (10, 11).

Multiple factors can lead to an unsuppressed viral load, including patients' sociodemographic characteristics, treatment adherence, ART regimens, and other clinical factors (4, 12–14).

After a patient has been on ART for at least 6 months, an elevated or unsuppressed viral load could indicate poor adherence to treatment or therapeutic failure due to antiretroviral resistance (7, 15). The probability of CD4 T-cell destruction, the rate at which AIDS advances, and the ease of virus transmission all increase with the number of viral particles in the blood (16). In Ethiopia, among people starting highly active antiretroviral medication, an unsuppressed viral load was found to be a significant predictor of mortality (17). Additionally, studies have shown that 91.5% of new HIV infections were caused by PLWH who were either undiagnosed or did not receive medical attention, that is, those who did not achieve viral load suppression (18).

Despite its importance, only a few studies were conducted in Ethiopia to estimate the time to viral load suppression and its predictors (12, 14, 19, 20), and the time for viral load suppression ranged from a minimum of 3 months in Arba Minch to a maximum of 9 months in Hossana (12, 19).

Given the wide range of findings, conducting a study to assess the median time to viral load suppression in the study area is crucial for improving patient quality of life.

In addition, to the best of our knowledge, very little research has been conducted in the current study region, and there are no data regarding the time to viral load suppression and its predictors for the Afar region, which has been identified as having significantly high clusters of PLWH (21). Therefore, this study was designed to estimate the time to viral load suppression and its predictor in the Gebi Resu zone.

Methods and materials

Study design, setting, and population

The facility-based retrospective follow-up study was conducted in ART clinics of public health facilities in Gebi Resu (Zone 3), Afar National Regional State, Ethiopia.

The zone has 11 health centers and 1 general hospital, but only 8 health centers and 1 hospital offer ART services. The study was conducted among PLWH receiving ART services at selected health facilities in the Gebi Resu zone from 11 September 2017 to 10 September 2022. All PLWH who initiated ART for the first time during this period were eligible for inclusion. Since at least two consecutive measurements are required to declare viral load suppression, individuals with less than two consecutive viral load measurements were excluded from the study.

Sample size, sampling procedure, and measurement

The sample size was calculated using the formulas designed for survival analysis through STATA statistical software, the log-rank test, and the Cox proportional hazard model. The following assumptions were taken into consideration: confidence level = 95%, power = 90%, sample size allocation ratio = 1:1, the hazard ratio of patient's baseline CD4 level of less than 200 compared to their counterpart 0.683, the hazard ratio of good ART adherence level 2.648, and 1.85 of hazard ratio among patients having opportunistic infection taken from the study conducted in Arba Minch (12) and West Gojam zone (14). Finally, a sample of 298 PLWH was determined after comparing the calculated sample sizes.

Based on the difference in the level of care, we stratified them into hospitals and health centers from a total of nine public health facilities providing ART service in the Gebi Resu zone of the Afar regional state. Only one hospital (Mohammed Akle Referral Hospital) in the zone provided ART service. In addition, three health centers were selected from the seven listed health centers by employing a simple random sampling method. Then, according to the inclusion criteria, eligible PLWH who started ART from 11 September 2017 to 10 September 2022, were identified from the registration book of each selected ART clinic. Finally, study units and selected PLWH receiving ART were randomly selected and allocated proportionally to each selected health facility.

Operational definition

Viral suppression refers to a viral load less than or equal to 1,000 copies/mL.

The adherence level is classified as good if average adherence is >95% or the patient misses ≤2 from 30 doses and < 3 from 60 doses, fair if the average adherence is 85–94% or the patient misses 3–5

from 30 doses and 3–9 from 60 doses, and poor if the average adherence is <85% or the patient misses ≥6 from 30 doses and > 9 from 60 doses.

Body Mass Index (BMI) is categorized as follows: underweight <18.5 kg/m2, normal weight 18.5–24.99 kg/m2, overweight 25–29.99 kg/m2, and obesity > = 30 kg/m2.

Data collection procedure and quality assurance

The data for the study were collected by four data collectors who were working on ART service provision, and the collection process was supervised by four trained clinical officers. Data were collected using a structured data abstraction checklist that included sociodemographic variables, clinical factors, and treatment-related variables. The data abstraction format was prepared in the English language. The data were collected through a review of patient medical records, electronic ART databases, and other related registration books (ART registration book, viral load registration book, and HIV-positive tracking registration book) at the selected facilities.

The study's objectives, purposes, questionnaire, data collection procedures, roles in the evaluation, best practices for high-quality data, confidentiality, and supervision techniques were all covered in a 2-day training session for all data collectors (ART providers) and supervisors (clinical officers). Additionally, the data-gathering tool was pre-tested, and supervisors monitored and verified the data collection procedures. Before processing, the gathered data were stored in a secure location and verified every day for accuracy. After the data were collected, each questionnaire was coded separately.

Patient and public involvement

Patients were not involved in this study.

Data analysis

The collected data were coded and entered into Epi-Info version 7.2. These data were then exported to STATA version 16 for processing and analysis. Descriptive statistics such as frequency distribution, percentage, median, and interquartile range were calculated to summarize the characteristics of the study participants. The results of the variables were displayed using frequency tables and graphs. Kaplan–Meier survival curves were used to compare the event times between two or more groups. Observed survival differences were assessed using log-rank tests, with a significance level set at 5%.

Cox proportional-hazard regression was used to identify the predictors of time to viral load suppression among PLWH on ART. The event of interest under this particular objective was viral load suppression after enrolling in ART. The proportional hazard assumption was checked statistically using the global goodness-of-fit test proposed by Schoenfeld. The proportional hazard assumption was fulfilled with a global test value of 0.5661. The assumption was also checked for each predictor with minimum and maximum *p*-values of 0.2350 and 0.9753, respectively. The goodness of fit was checked using the Cox-Snell residual test.

Predictors with *p*-value of less than 0.25 in the bivariate Cox regression analysis were selected as candidates for multiple regression analysis. All predictors were then included in the multiple regression model to identify those independently associated with the outcomes of interest, adjusting for potential confounding variables. Variables with a *p*-value of less than 0.05 were considered as significantly associated with the dependent variable. The strength of the association between dependent and independent variables was expressed as a hazard ratio with a 95% confidence interval.

Results

Sociodemographic characteristics of patients

A total of 812 PLWH received ART at public health facilities in the Gebi Resu zone during the data collection period. Of these, 298 participants who fulfilled the inclusion criteria were randomly selected (Figure 1). From a total of 298 PLWH on ART, 204 participants (68.5%) were male individuals, 136 (45.6%) of them were married, 107 participants (35.9%) had no formal education, 205 participants (68.8%) resided in urban areas, 151 participants (50.7%) were Orthodox Christians, 88 participants (29.4%) were private employees, 39 participants (13.1%) were government employees, 27 participants (9.1%) were merchants, and 11 participants (3.7%) were pastoralists. (Table 1).

Treatment-related characteristics of patients

Of the 298 study participants, 109 participants (36.6%) were on a baseline ART regimen of ABC/3TC/NVP or EFV, 254 participants (85.2%) demonstrated good medication adherence, 162 participants (54.4%) received cotrimoxazole prophylaxis therapy (CPT), 195 participants (65.4%) received isoniazid preventive therapy (IPT), and 216 participants (72.5%) disclosed their HIV status to family and friends (Table 2).

Clinical characteristics of patients

Of the 298,298 study participants, 208 participants (69.8%) were at WHO clinical stages 1 and 2, 98 participants (32.9%) had previously developed an opportunistic infection, 78 participants (26.2%) had a tuberculosis co-infection, and 213 participants (71.55%) had a baseline CD4 count of greater than or equal to 200 cells/mm.^{3} Additionally, 275 participants (92.3%) had a baseline viral load of less than 1,000 copies/ml, and 208 participants (69.8%) had a baseline body mass index (BMI) greater than 18.5 kg/m^2 (Table 3).

Time to viral load suppression and incidence among PLWH on ART

The incidence proportions of people who have achieved first viral load suppression were 83.89% (95% CI (79.25, 87.66)). The total

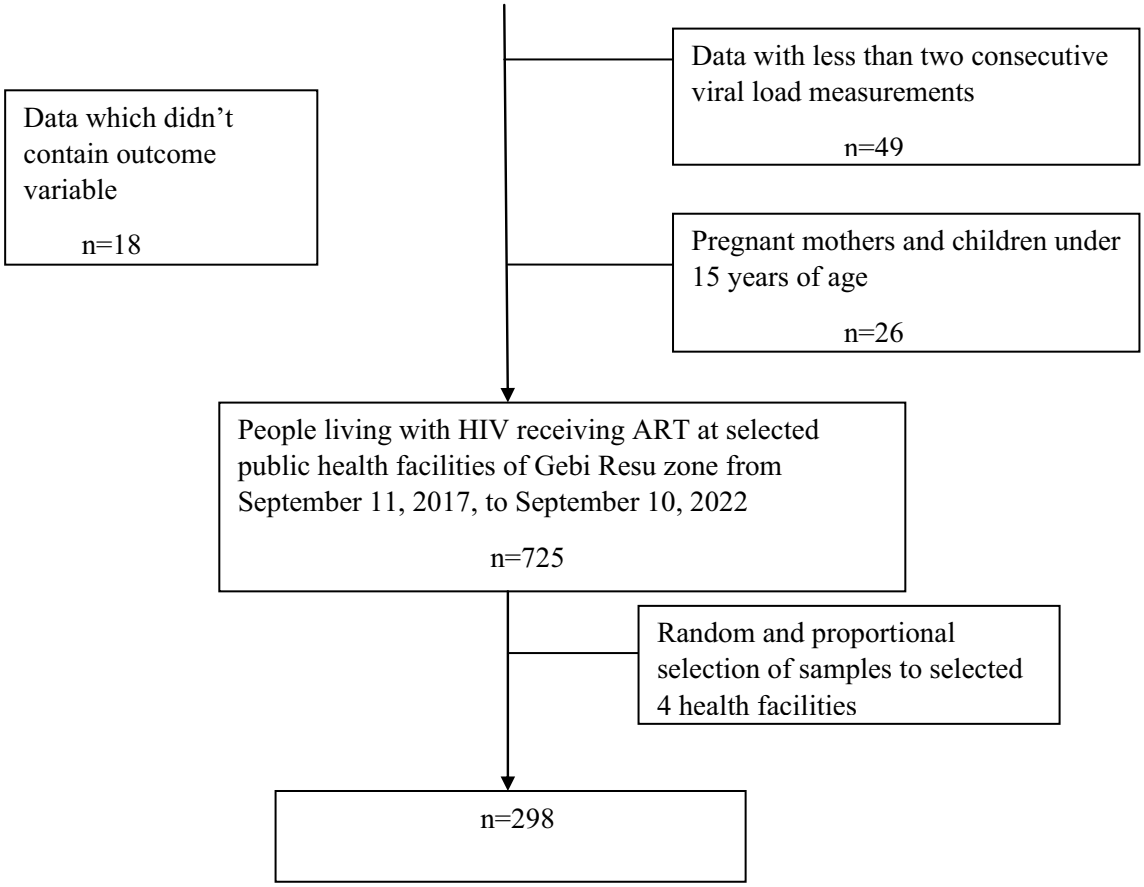

FIGURE 1
Flow diagram of patient selection to determine the time to viral load suppression and its predictors among PLWH on ART in Gebi Resu zone, Afar region, Ethiopia 2023.

observation time for the 298 patients was 2,644 person-months, and the viral load suppression incidence rate was 9.46 per 100 person-months. The median time to viral load suppression was 7.7 months with an interquartile range of 3.8 months (Q1 = 6.47 and Q3 = 10.27).

The Kaplan–Meier survival function graph presents the overall time to viral load suppression, with a median survival time of approximately 8 months, indicating that 50% of PLWH achieve viral load suppression approximately 8 months after initiating ART (Figure 2).

The Kaplan–Meier survival estimate and log-rank test were used to compare the probability of time to viral load suppression across different variable groups. Significant differences in time to viral load suppression were observed between the categories of WHO clinical stage, CPT use, baseline CD4 count, and drug adherence groups (Figures 3–6).

Predictors of time to viral load suppression among PLWH on ART

Variables with a *p*-value of <0.25 in the bivariate Cox regression analysis, such as sex, age, residence, BMI, WHO clinical stage, adherence, CPT, IPT, baseline CD4, and past opportunistic infection, were included in the multivariate Cox regression model (Table 4).

In the multivariate Cox regression model, WHO clinical stage, CPT, and drug adherence were significant predictors of viral load suppression among PLWH with a *p*-value of <0.05 within a 95% confidence interval.

Patients at WHO clinical stages 3 and 4 had lower hazards of achieving viral load suppression by 33% compared to patients at clinical stages 1 and 2 (AHR = 0.67, 95%CI (0.47, 0.96)). Patients who received CPT had 1.47 times higher probability of achieving viral load suppression (AHR = 1.47, 95%CI (1.12, 1.92)). Patients with poor drug adherence had a reduced hazard of viral load suppression by 60% compared to patients with good drug adherence (AHR = 0.40, 95%CI (0.18, 0.90)) (Table 5).

Discussion

This research aimed to assess the time to viral load suppression and its predictors among PLWH on ART in the Gebi Resu zone, Afar Region, Ethiopia. The incidence proportions of people who have achieved their first viral load suppression were 83.89% (95% CI (79.25, 87.66)). The result aligned with studies conducted in Arba Minch, Ethiopia, and the United States of America (12, 22, 23).

On the other hand, the result was higher than the findings from studies conducted in East Shewa and West Gojjam zones in Ethiopia, Kenya, and Uganda (14, 20, 24, 25). On the other hand, the result was lower than that of a study conducted in Hossana, Ethiopia, Nigeria,

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TABLE 1 Sociodemographic characteristics of PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023.

Variable categories	Frequency	Percent (%)
Sex		
Female	94	31.5
Male	204	68.5
Age		
15–24	37	12.4
25–34	127	42.6
35–44	93	31.2
>=45	41	13.8
Marital status		
Single	49	16.4
Married	136	45.6
Divorced	87	29.2
Widowed	26	8.7
Religion		
Orthodox	151	50.7
Muslim	116	38.9
Protestant	31	10.4
Education		
No formal education	107	35.9
Primary	108	36.2
Secondary	52	17.4
Tertiary	31	10.4
Occupation		
Private employee	88	29.5
Government employee	39	13.1
Merchant	27	9.1
Farmer	10	3.4
Pastoralist	11	3.7
Student	46	15.4
Housewife	48	16.1
Not working	29	9.7
Residence		
Urban	205	68.8
Rural	93	31.2

TABLE 2 Treatment-related characteristics of PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023.

Variable categories	Frequency	Percent (%)
Antiretroviral therapy regimen		
ABC/3TC/NVP or EFV	109	36.6
AZT/3TC/NVP or EFV	25	8.4
TDF/3TC/NVP or EFV	164	55.0
Adherence level		
Good	254	85.2
Fair	25	8.4
Poor	19	6.4
Cotrimoxazole preventive therapy		
No	136	45.6
Yes	162	54.4
Isoniazid preventive therapy		
No	103	34.6
Yes	195	65.4
Disclosure status		
Disclosed	216	72.5
Not disclosed	82	27.5

ABC, Abacavir; 3TC, Lamivudine; AZT, Zidovudine; TDF, Tenofovir Disoproxil Fumarate; NVP, Nevirapine; EFV, Efavirenz.

and Brazil (19, 26, 27). This discrepancy might be due to the differences between the study areas in sociodemographic, infrastructural, and healthcare provision.

The incidence rate of viral load suppression was 9.46 per 100 person-months. This finding was similar to the results from a study conducted in Hossana, Ethiopia, higher than that of a study conducted in Kenya and lower than that of a study conducted in West Gojjam Zone, Ethiopia (14, 19, 24). The difference might be due to the enhancement in the ART service over time and the difference in socioeconomic status of the participants.

The median time for viral load suppression was 7.7 months (IQR: 6.47–10.27). It aligned with studies conducted in Hossana, Ethiopia, and Italy (19, 28). On the contrary, the median time was longer than studies conducted in Arba Minch and the East Shewa zone in Ethiopia and Switzerland (12, 20, 29). The discrepancy might be due to differences in weather conditions between the study areas. The weather conditions in Afar are very difficult to cope with since it is deserted and sandy (30). It affects the nutritional status of the population, especially PLWH, which would lead to lower antiretroviral adherence and, finally, longer duration of viral load suppression (30, 31). The other reason for the inconsistency might be the socioeconomic differences between the study areas.

The likelihood of achieving viral load suppression among PLWH at WHO clinical stages 3 and 4 was 33% lower than for those at clinical stages 1 and 2. This result aligns with studies conducted in Hossana and Arba Minch in Ethiopia, Kenya, and Nigeria (12, 19, 24, 27). This finding could be explained by the fact that, as HIV progresses to advanced stages, opportunistic infections occur due to immune suppression, which can increase morbidity and mortality rates due to complications (32). Additionally, the suppressed immunity in PLWH at clinical stages 3 and 4, where they develop AIDS, likely contributes to increased viral replication (33).

PLWH who received CPT had a 1.47 times higher likelihood of achieving viral load suppression compared to patients who did not receive CPT. This result is consistent with studies conducted in Arba Minch, Ethiopia (12), Uganda (34), and China (35).

The likely explanation is that CPT reduces susceptibility to bacterial infections, providing an advantage over those not on prophylaxis (36). It is advised that PLWH in clinical stages 3 and 4 take prophylaxis to suppress high viral loads and prevent various

TABLE 3 Clinical-related characteristics of PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023.

Variable categories	Frequency	Percent (%)
WHO clinical staging		
Stages 1 and 2	208	69.8
Stages 3 and 4	90	30.2
History of opportunistic infections		
No	200	67.1
Yes	98	32.9
History of tuberculosis		
Negative	220	73.8
Positive	78	26.2
Baseline CD4		
<200	85	28.5
>=200	213	71.5
Baseline viral load		
<10,000	275	92.3
>=10,000	23	7.7
Body mass index		
Underweight	90	30.2
Normal	208	69.8
Functional status		
Working	244	81.9
Ambulatory	31	10.4
Bedridden	23	7.7

opportunistic infections. Additionally, CPT may improve survival rates by reducing malaria and opportunistic infections, thereby strengthening the immune system (37). Studies have also shown that CPT is associated with a slower decline in CD4 levels and a faster reduction in viral load (34, 38).

Patients with poor drug adherence were 60% less likely to achieve viral load suppression compared to those with good drug adherence. The result aligns with the findings from studies conducted in Kenya (24). The observed outcome may be attributed to the critical role of ART in suppressing HIV replication and improving patient outcomes. Good adherence to ART is essential for prolonging the life of PLWH, while poor adherence can have the opposite effect (39–41). Poor adherence diminishes the patient's immune response, creating opportunities for viral replication, which may also lead to the emergence of drug-resistant strains (42).

The main limitations of the study include the exclusion of important behavioral factors that could directly or indirectly affect the time to viral load suppression, such as alcohol use, smoking, nutritional status, and the patients' economic conditions. These factors were not accounted for due to the retrospective nature of the study.

Conclusion

The time to viral load suppression and the median time to viral load suppression among PLWH on ART in the Gebi Resu zone, Afar Region, Ethiopia, were shorter compared to results from both developing and developed countries. The patient's baseline HIV clinical stage, use of CPT, and adherence to antiretroviral medication were significant predictors of time to viral load suppression in this region in 2023.

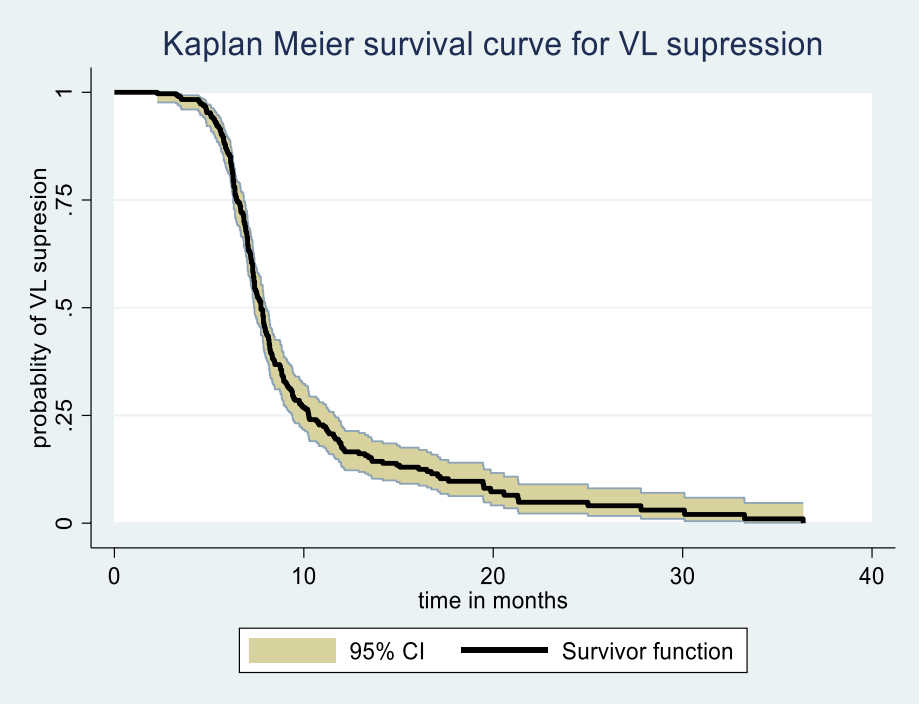

FIGURE 2
Overall Kaplan Meier survival curve of time to viral load suppression among PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023.

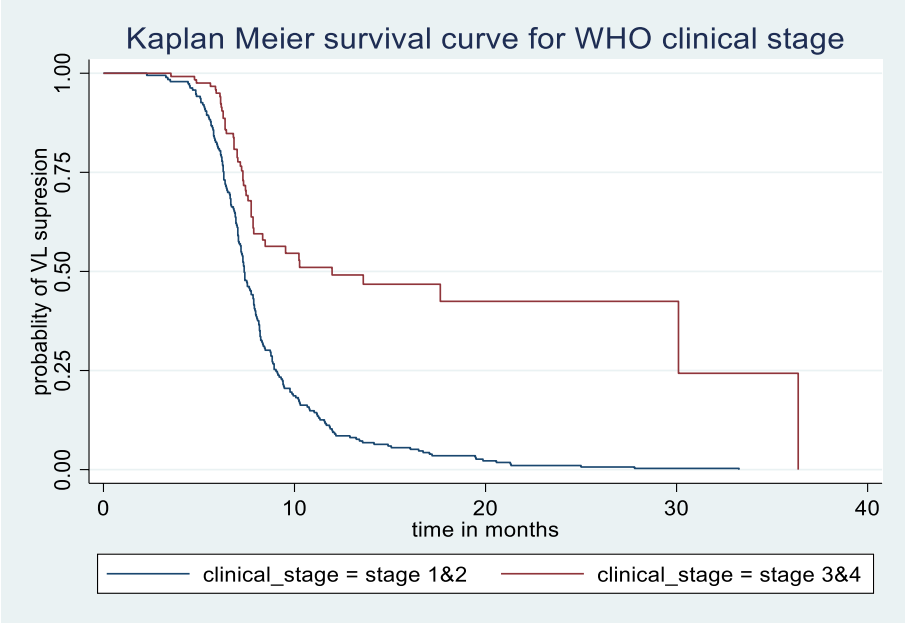

FIGURE 3
Kaplan Meier survival curve by WHO clinical stage among PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023. Log-rank test *p*-value = 0.0001.

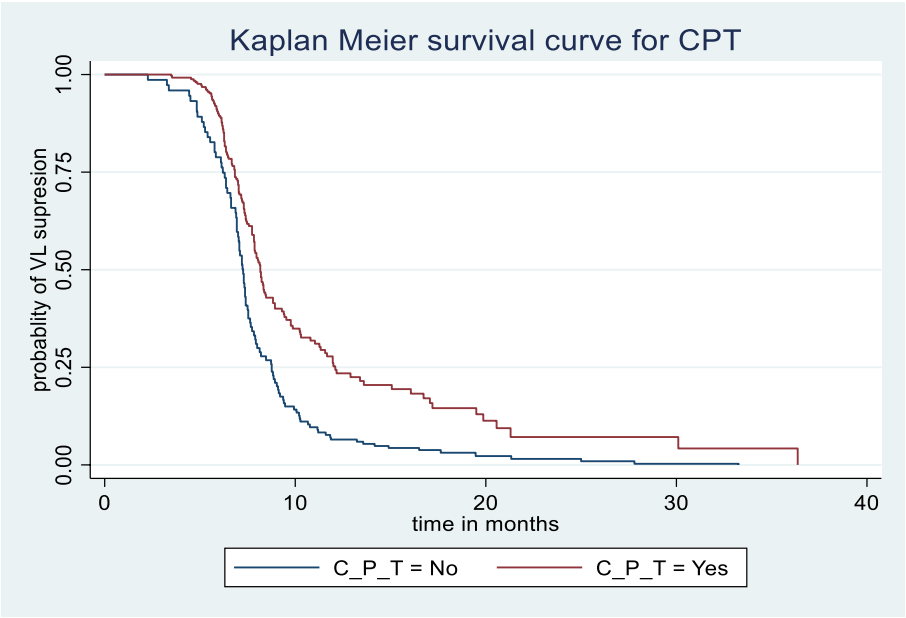

FIGURE 4
Kaplan Meier survival curve by Cotrimoxazole Prophylaxis Therapy among PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023. Log-rank test with a *p*-value of 0.0008.

Our findings indicate that interventions aimed at improving clinical management, enhancing adherence to ART, and ensuring access to cotrimoxazole prophylaxis for individuals with unsuppressed viral load can significantly contribute to achieving the Joint United Nations Programme on HIV/AIDS (UNAIDS) "last 95%" target in Ethiopia. By focusing on these areas, healthcare providers and policymakers can work toward a more effective response to the HIV epidemic in Ethiopia. This aligns with global initiatives to end AIDS as a public health threat by 2030, reinforcing the need for continued investment in healthcare infrastructure, education, and support systems that empower

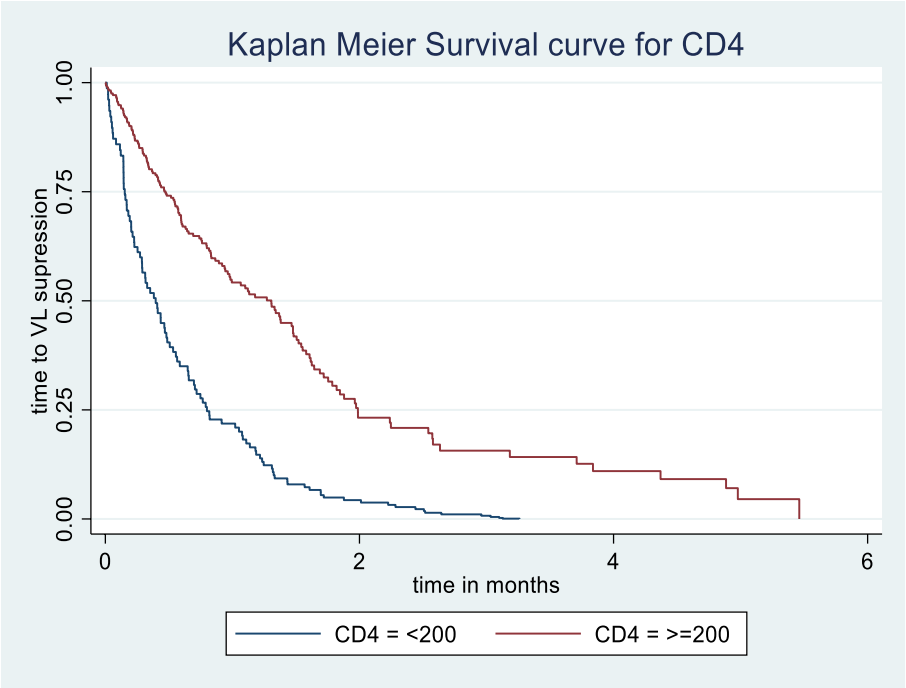

FIGURE 5
Kaplan Meier survival curve of time to viral load suppression among PLWH on ART by baseline CD4 in Gebi Resu zone, Afar Region, Ethiopia, 2023. Log-rank test with a *p*-value of 0.0143.

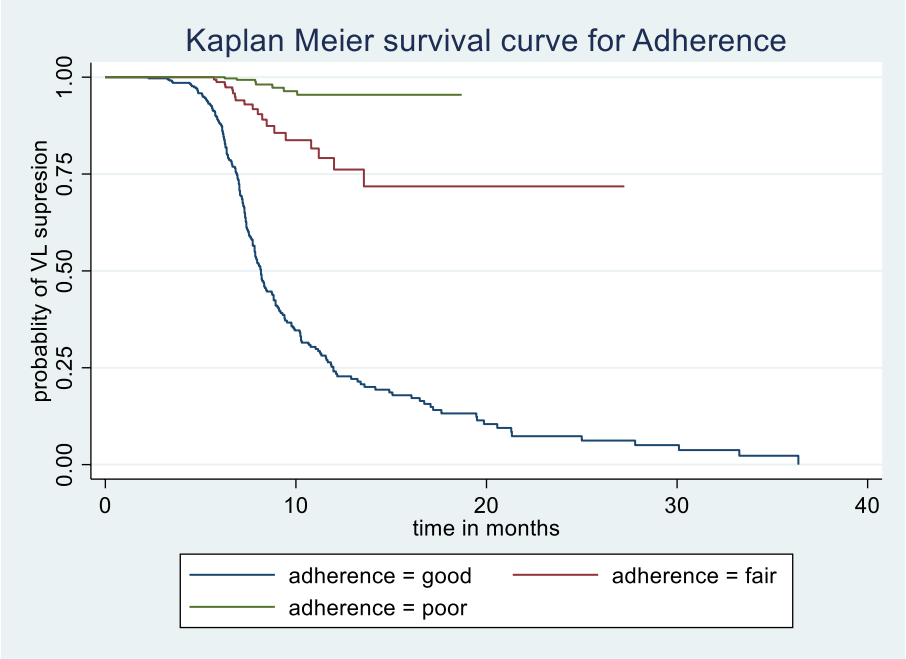

FIGURE 6
Kaplan Meier survival curve of time to viral load suppression among PLWH on ART by Adherence level in Gebi Resu zone, Afar Region, Ethiopia, 2023. Log-rank test with a *p*-value of 0.0015.

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TABLE 4 Bivariate cox regression analysis of predictors of time to viral load suppression among PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023.

Variable categories	Outcome		CHR (95%CI)	*p*-value
	VL suppressed	Censored		
Sex				
Female	83 (88.3%)	11 (11.7%)	1	
Male	167 (81.9%)	37 (18.1%)	0.84 (0.64, 1.09)	0.186
Age				
15–24	30 (81.1%)	7 (18.9%)	1	
25–34	111 (87.4%)	16 (12.6%)	1.00 (0.66, 1.51)	0.196
35–44	78 (83.9%)	15 (16.1%)	1.21 (0.79, 1.86)	0.379
>=45	31 (75.6%)	10 (24.4%)	0.89 (0.53, 1.48)	0.250
Marital status				
Single	42 (85.7%)	7 (14.3%)	1	
Married	116 (85.3%)	20 (14.7%)	0.76 (0.53, 1.09)	0.133
Divorced	71 (81.6%)	16 (18.4%)	0.88 (0.60, 1.29)	0.515
Widowed	21 (80.8%)	5 (19.2%)	0.67 (0.40, 1.14)	0.141
Religion				
Orthodox	130 (86.1%)	21 (13.9%)	1	
Muslim	94 (81.0%)	22 (19.0%)	0.90 (0.69, 1.18)	0.447
Protestant	26 (83.9%)	5 (16.1%)	0.97 (0.63, 1.48)	0.879
Education				
No formal education	89 (83.2%)	18 (16.8%)	1	
Primary	92 (85.2%)	16 (14.8%)	0.93 (0.69, 1.25)	0.625
Secondary	45 (86.5%)	7 (13.5%)	1.00 (0.70, 1.44)	0.991
Tertiary	24 (77.4%)	7 (22.6%)	0.82 (0.52, 1.29)	0.391
Occupation				
private employee	74 (84.1%)	14 (15.9%)	1	
Government employee	31 (79.5%)	8 (20.5%)	0.75 (0.49, 1.14)	0.182
Merchant	21 (77.8%)	6 (22.2%)	1.02 (0.63, 1.66)	0.923
Farmer	6 (60.0%)	4 (40.0%)	0.76 (0.33, 1.74)	0.515
Pastoralist	8 (72.7%)	3 (27.3%)	1.08 (0.52, 2.25)	0.836
Student	41 (89.1%)	5 (10.9%)	1.05 (0.72, 1.54)	0.798
Housewife	43 (89.6%)	5 (10.4%)	1.08 (0.74, 1.58)	0.690
Not working	26 (89.7%)	3 (10.3%)	1.08 (0.69, 1.70)	0.726
Residence				
Urban	188 (91.7%)	17 (8.3%)	1	
Rural	62 (66.7%)	31 (33.3%)	0.83 (0.62, 1.10)	0.102
WHO clinical staging				
Stages 1 and 2	198 (95.2%)	10 (4.8%)	1	
Stages 3 and 4	52 (57.8%)	38 (42.2%)	**0.52 (0.38,0.72)****	0.000
Body mass index				
Underweight	66 (73.3%)	24 (26.7%)	1	
Normal	184 (88.5%)	24 (11.5%)	1.43 (0.96, 1.90)	0.097
Functional status				
Working	215 (88.1%)	29 (11.9%)	1	

(Continued)

TABLE 4 (Continued)

Variable categories	Outcome		CHR (95%CI)	*p*-value
	VL suppressed	Censored		
Ambulatory	21 (67.7%)	10 (32.3%)	0.66 (0.42, 1.05)	0.077
Bedridden	14 (60.9%)	9 (39.1%)	0.63 (0.37, 1.08)	0.095
History of tuberculosis				
Negative	203 (92.3%)	17 (7.7%)	1	
Positive	47 (60.3%)	31 (39.7%)	0.62 (0.02, 1.06)	0.324
Past opportunistic infection				
No	178 (89.0%)	22 (11.0%)	1	
Yes	72 (73.5%)	26 (26.5%)	**0.65 (0.50, 0.85)***	0.043
Cotrimoxazole prophylactic therapy				
No	96 (70.6%)	40 (29.4%)	1	
Yes	154 (95.1%)	8 (4.9%)	**1.54 (1.19, 1.99)****	0.001
Isoniazid prophylactic therapy				
No	80 (77.7%)	23 (22.3%)	1	
Yes	170 (87.2%)	25 (12.8%)	1.24 (0.95, 1.63)	0.111
Disclosure status				
Disclosed	184 (85.2%)	32 (14.8%)	1	
not disclosed	66 (80.5%)	16 (19.5%)	0.98 (0.74, 1.30)	0.901
Adherence level				
Good	224 (88.2%)	30 (11.8%)	1	
Fair	19 (76.0%)	6 (24.0%)	0.66 (0.41, 1.05)	0.107
Poor	7 (36.8%)	12 (63.2%)	**0.25 (0.12, 0.53)****	0.006
Antiretroviral therapy regimen				
ABC/3TC/NVP or EFV	95 (87.2%)	14 (12.8%)	1	
AZT/3TC/NVP or EFV	13 (52.0%)	12 (48.0%)	1.01 (0.56, 1.81)	0.972
TDF/3TC/NVP or EFV	142 (86.6%)	22 (13.4%)	0.18 (0.91, 1.54)	0.211
Baseline CD4				
<200	52 (61.2%)	33 (38.8%)	1	
> = 200	198 (93.0%)	15 (7.0%)	**1.22 (0.95, 1.57)***	0.018

*Significant variables with a *p*-value of < 0.05.
**Significant variables with a *p*-value of < 0.001.

individuals living with HIV. Further studies should consider assessing behavioral factors that could affect the time to viral load suppression by conducting prospective studies using primary data.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the [patients/ participants OR patients/participants legal guardian/next of kin] was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

AC: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EH: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. HA: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology,

10.3389/fpubh.2024.1384787

TABLE 5 Bivariate and multivariate Cox regression of predictors of time to viral load suppression among PLWH on ART in Gebi Resu zone, Afar Region, Ethiopia, 2023.

Variable categories	Outcome		CHR (95%CI)	AHR (95%CI)	*p*-value
	VL suppressed (%)	Censored (%)			
Sex					
Female	83 (88.3%)	11 (11.7%)	1	1	
Male	167 (81.9%)	37 (18.1%)	0.84 (0.64, 1.09)	0.85 (0.65, 1.12)	0.315
Age					
15–24	30 (81.1%)	7 (18.9%)	1	1	
25–34	111 (87.4%)	16 (12.6%)	1.00 (0.66, 1.51)	0.69 (0.44, 1.06)	0.279
35–44	78 (83.9%)	15 (16.1%)	1.21 (0.79, 1.86)	0.88 (0.56, 1.39)	0.157
>=45	31 (75.6%)	10 (24.4%)	0.89 (0.53, 1.48)	0.69 (0.41, 1.19)	0.482
Residence					
Urban	188 (91.7%)	17 (8.3%)	1	1	
Rural	62 (66.7%)	31 (33.3%)	0.83 (0.62, 1.10)	0.87 (0.64, 1.19)	0.361
Body mass index					
Underweight	66 (73.3%)	24 (26.7%)	1	1	
Normal	184 (88.5%)	24 (11.5%)	1.43 (0.96, 1.90)	1.08 (0.79, 1.47)	0.162
WHO clinical staging					
Stages 1 and 2	198 (95.2%)	10 (4.8%)	1	1	
Stages 3 and 4	52 (57.8%)	38 (42.2%)	0.52 (0.38, 0.72)**	**0.67 (0.47, 0.96)***	0.026
Functional status					
Working	215 (88.1%)	29 (11.9%)	1	1	
Ambulatory	21 (67.7%)	10 (32.3%)	0.66 (0.42, 1.05)	0.77 (0.47, 1.25)	0.258
Bedridden	14 (60.9%)	9 (39.1%)	0.63 (0.37, 1.08)	0.85 (0.48, 1.50)	0.189
History of opportunistic infections					
No	178 (89.0%)	22 (11.0%)	1	1	
Yes	72 (73.5%)	26 (26.5%)	0.65 (0.50, 0.85)*	0.79 (0.59, 1.05)	0.085
Cotrimoxazole prophylaxis therapy					
No	96 (70.6%)	40 (29.4%)	1	1	
Yes	154 (95.1%)	8 (4.9%)	1.54 (1.19, 1.99)**	**1.47 (1.12, 1.92)***	0.013
Isoniazid prophylaxis therapy					
No	80 (77.7%)	23 (22.3%)	1	1	
Yes	170 (87.2%)	25 (12.8%)	1.24 (0.95, 1.63)	1.08 (0.82, 1.43)	0.504
Baseline CD4					
<200	52 (61.2%)	33 (38.8%)	1	1	
>=200	198 (93.0%)	15 (7.0%)	1.22 (0.95, 1.57)	1.00 (0.76, 1.30)	0.629
Adherence level					
Good	224 (88.2%)	30 (11.8%)	1	1	
Fair	19 (76.0%)	6 (24.0%)	0.66 (0.41, 1.05)	0.79 (0.48, 1.31)	0.187
Poor	7 (36.8%)	12 (63.2%)	0.25 (0.12, 0.53)**	**0.41 (0.18, 0.90)***	0.017

*Significant variables with a *p*-value of < 0.05.
**Significant variables with a *p*-value of < 0.001.

Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EW: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. SW:–.

Funding

The author(s) declare that no financial support was received for the research, authorship, and/or publication of this article.

Acknowledgments

We would like to acknowledge Adama Hospital Medical College for their support during this research. We would also like to express our gratitude to health institutions, data collectors, friends, family, and supervisors for their full support during the whole process of the study.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 06 November 2024
DOI 10.3389/fpubh.2024.1396590

OPEN ACCESS

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RECEIVED 05 March 2024
ACCEPTED 18 October 2024
PUBLISHED 06 November 2024

CITATION
Kaonga P, Sampa M, Musukuma M, Mulawa MJ, Mulavu M, Sitali D, Moonga G, Mweemba O, Matenga TF, Zyambo C, Hamoonga T, Phiri H, Halwindi H, Chavula MP, Zulu JM and Jacobs C (2024) Availability and readiness of public health facilities to provide differentiated service delivery models for HIV treatment in Zambia: implications for better treatment outcomes.
Front. Public Health 12:1396590.
doi: 10.3389/fpubh.2024.1396590

Availability and readiness of public health facilities to provide differentiated service delivery models for HIV treatment in Zambia: implications for better treatment outcomes

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Background: There is persistent pressure on countries with a high burden of HIV infection to reach desired targets for HIV treatment outcomes. This has led to moving from the "one-size-fits-all" model to differentiated service delivery (DSD) models, which are meant to be more patient-centered and efficient but without compromising on the quality of patient care. However, for DSD models to be efficient, facilities should have indicators of HIV services available and ready to provide the DSD models. We aimed to assess the availability of HIV service indicators and the readiness of facilities to provide DSD models for HIV treatment in selected public health facilities in Zambia.

Methods: We conducted a nationwide cross-sectional survey among public health facilities in Zambia that provide antiretroviral therapy (ART) services. We used an interviewer-administered questionnaire based on a World Health Organization (WHO) Service Availability Readiness Assessment (SARA) tool to assess the availability of HIV service indicators and the readiness of facilities to implement DSD models for HIV treatment. Availability and readiness were considered latent constructs, and therefore, we used structural equation modeling (SEM) to determine the correlations between them and their respective indicators.

Results: Of 60 public health ART facilities, the overall availability of HIV service indicators was 80.0% (48/60), and readiness to provide the DSD models was 81.7% (48/60). However, only 48 and 39% of the facilities had all indicators of availability and readiness, respectively. Retention in care for HIV multidisciplinary teams was more likely to occur in urban areas than in rural areas. SEM showed that the standardized estimate between availability and readiness was

significantly and positively correlated ($r = 0.73$, $p < 0.0001$). In addition, both availability and readiness were significantly and positively correlated with most of their respective indicators.

Conclusion: Although most facilities had available HIV service indicators and were ready to provide DSD models, most facilities did not have all indicators of availability and readiness. In addition, there were differences between rural and urban facilities in some indicators. There is a need for persistent and heightened efforts meant to implement DSD in HIV treatment, especially in rural areas to accelerate reaching the desired HIV treatment outcomes.

KEYWORDS

HIV, differentiated service delivery, availability, readiness, Zambia

Introduction

There has been mounting pressure to meet global targets for HIV treatment, such as the 95-95-95 goals, while also reducing unnecessary burdens and costs for both patients and the healthcare system. In addition, there is a need to better titrate limited healthcare system resources to diverse client needs and improved treatment outcomes, better retention in care, increased peer support, higher viral load suppression, reduced waiting time and clinic visits, and extended time for ART refill (1, 2). This requires a shift away from the traditional "one-size–fits-all" model to alternative approaches such as HIV differentiated service delivery (DSD) models that are more patient-centered and efficient while not compromising patient care (3). DSD models are meant to simplify HIV treatment services across the HIV cascade to better reflect the preferences, expectations, and needs of people living with HIV (4, 5). As almost every country in sub-Saharan Africa is scaling up the DSD models, with a decline in funding, various funders, policymakers, and governments are questioning which models are more efficient and effective for greater client treatment uptake and coverage and better HIV treatment outcomes (6, 7). The DSD models offer an exciting and promising alternative to HIV treatment, but it is unclear which models are most effective and relevant given the diverse settings and populations. To maximize the effect and impact of DSD models, healthcare workers need to acknowledge and appreciate patient-centered and adaptive approaches and employ quality improvement processes. However, routine implementation of DSD models, in most instances, does not align with monitoring and evaluation strategies needed to assess the impact of DSD models on key HIV treatment outcomes. The pressure to roll out DSD models, especially in public health facilities, poses valid questions bordering on the availability of HIV service indicators and the readiness of health facilities to provide DSD models.

In 2017, Zambia adopted the DSD strategy, and the models recommended in the country for stable clients (clients with no adverse drug reactions that require regular monitoring, no current illnesses, and evidence of treatment success: two consecutive viral load measurements of <1,000 copies/mL and a CD4 count of 200 cells/mm^3) (8) are:

- Multi-month dispensing: Clients are given ART from a health facility lasting for several months.
- Fast track: Clients are given ART from a facility or dispensing point without being attended to by a clinician or it could be from a separate queue or kiosk, at a facility to speed up service delivery.
- After hours: It denotes additional hours to a facility's operations to facilitate access for clients who cannot manage normal working hours, such as on evenings or weekends.
- Home delivery: This refers to delivering ART to patients' homes (e.g., by a community health worker). Community delivery ART points to a variety of models that bring both clinical care and medications into the community, such as nurse-led outreach.
- Scholar: This is a model for those in schools or learning institutions where ART pickup and other appointments are provided during the holidays, weekends, or after hours.
- Dedicated pediatric ART day: Dedicated day for pediatrics clinics and medication pickups timed to coincide with school holidays.
- Adolescent support: This is a facility-based model for adolescents and young women/men aged 10–24 years. The model aims to ensure uninterrupted, age-appropriate, and comprehensive care before, during, and after the transition to adult care.
- Men's clinic: A facility-based model for men aged 15 years and older, featuring a separate space away from the main clinic. This model is combined with various integrated services such as prostate screening, male circumcision, erectile dysfunction, and condom distribution (1).

Empirical evidence suggests that core healthcare services, such as infrastructure, key health personnel, and service utilization, along with facility readiness components, including medicines, standard precautions, basic equipment, laboratory tests, and commodities, are essential prerequisites for optimal healthcare delivery. Assessment of these indicators is more feasible and cost-effective than downstream outcome indicators of service quality (9, 10). The World Health Organization (WHO) recommends the use of the Service Availability and Readiness Assessment (SARA) tool to assess healthcare service availability and readiness. Utilization of this tool can inform planners and implementers of health programs in terms of human resources, supplies, and essential services (6).

Both availability and readiness have many facets and are latent constructs. Therefore, the use of structural equation modeling (SEM) could provide a more reliable measure of the relationship between indicators of availability and readiness with these latent constructs. We hypothesized that there is a relationship between availability and readiness since the availability of the required HIV service indicators at a facility could suggest readiness and vice versa. The premise is that the absence of components of availability or readiness would negatively affect the implementation and later adoption of the DSD models.

In Zambia, as far as we searched the literature, we did not come across any study that assessed the availability of HIV service indicators and readiness to provide DSD models in public health facilities. We anticipated differences between rural and urban facilities rather than by type of facility based on the implementation and scaling-up of the DSD models (1). Therefore, this study set out to assess the availability of HIV service indicators and the readiness of public health facilities to provide DSD models. This was performed to identify gaps in the current implementation strategies as the first step toward strengthening indicators and tracking the availability of HIV service indicators and the readiness of facilities to effectively provide differentiated service delivery for HIV treatment and adoption.

Methods

Study setting and design

Zambia is a landlocked, lower-middle-income country located in Southern Africa with an estimated population of 20 million people. Most (60%) of the population reside in rural areas, and the country is divided into 10 provinces. Approximately half (50%) of the population is under the age of 15 years, and only 3% are above the age of 65 years (11). The country has an HIV prevalence of 11% among adults (15+ years), and women are disproportionately affected, with a 1.7 times higher prevalence than men (12).

The government of Zambia through the Ministry of Health together with implementing partners launched its first DSD models as a pilot in 2016 and began scaling up in 2017 (1). DSD models are implemented with an emphasis on increasing community DSD coverage following the rollout of updated consolidated HIV guidelines. The President's Emergency Plan for AIDS Relief (PEPFAR) and the Ministry of Health together with other partners aim to provide and scale HIV services to achieve HIV epidemic control. In this regard, Zambia has made tremendous progress, where 88.7% of adults (15+ years) living with HIV are aware of their HIV status; among adults living with HIV who are aware of their status, 98.0% are on ART, and among adults who are on ART, 96.3% have viral load suppression (1). The country has over 1996 ART facilities, which are supported by PEPFAR to provide HIV services through several implementing partners.

This was a cross-sectional survey conducted in 10 selected districts across 8 provinces, namely, Solwezi, Ndola, Kabwe, Mansa, Choma, Livingstone, Kapiri Mposhi, Luangwa, Chipata, and Lusaka districts.

Recruitment of study sites

This study included public health facilities providing HIV treatment. In Zambia, the delivery system of the healthcare service has three levels: (i) First level: community-level health facilities including district hospitals, health centers, and health posts; (ii) second-level: provincial or general hospitals; and (ii) third level: central or specialist hospitals. This study included facilities in the first level (health posts, health centers, level 1 hospitals, and level 2 hospitals) serving both rural and urban populations. We included facilities that were providing HIV prevention, testing, and treatment services. There were major differences in terms of patients' volume, facility organization, and staffing levels. These differences may affect patients' acceptability of DSD models. According to the Ministry of Health records, there were 1992 public ART facilities at the time of the study. We excluded low-volume facilities (<500 clients on ART), facilities with less than three DSD models implemented, and those with less than 12 months of experience providing ART and DSD models.

Sample size

We adopted a multi-stage cluster sampling. Our initial stage involved the random selection of 10 districts in 8 provinces. We anticipated a minimum sample size of five facilities in each district with an expected deviation of <4, level of confidence = 95%, precision = 1, inter-class correction coefficient of <0.02, power = 80%, and cluster size of 4 (13). We increased the number of facilities to 20 per district based on the information from the Ministry of Health (approximately 25% would be high-volume facilities with >500 clients and at least 3 DSD models implemented), which would meet the inclusion criteria. Based on this information, the number of facilities increased from 5 to 6. Then, 60 facilities were randomly chosen in the second stage using probability proportional to size.

Measurement of variables

In this study, there were two latent constructs as outcome variables, namely, availability and readiness based on the WHO recommendations for assessing facility services availability and readiness. Therefore, the availability of HIV service indicators was considered as the physical presence of the delivery of HIV services (14), while readiness is the capacity of health facilities to provide specific healthcare services (15); in this case, it was DSD models for HIV treatment. Both constructs can be measured through tracer items such as guidelines, trained staff, and commodities (16). In this study, the availability of HIV service indicators was measured by the following nine items: "an existing HIV multidisciplinary team", "latest ART orientation guidelines rolled out", "adequate storage space for additional commodities related to HIV services", "implemented the Zambian HIV quality improvement framework", "achieved a routine viral load monitoring uptake of ≥90%", "established a facility-based system for fast-track ART distribution", "had ≥ 3 months of ART available on site", "established system to monitor patients level outcomes specifically retention, lost to follow-up, mortalities and viral load suppression", and "established recording and reporting systems for community ART." Readiness was measured using the following indicators: "presence of community health workers in all departments offering HIV services oriented on the latest ART guidelines for the year 2022", "had a commodity management or commodity security committee", "does the facility have a quality improvement team", "had an HIV multidisciplinary team to review clinical cases and provide support to patients failing HIV treatment or with advanced disease", "healthcare workers trained on the revised HIV monitoring and evaluation tools", "identified a focal person to oversee community-based ART distribution", "identified appropriate personnel to distribute ART", "had staff and resources to train ART distributors", and "identified a focal person to pre-pack and label ART for community distribution". The outcome variables were then

created as composite scores by adding the presence of each indicator (present = 1; not present = 0), and for both, if all indicators were present, a maximum score of nine was given and if all indicators were not present, a score of zero was given. Facilities with 50% or more available HIV service indicators and readiness were categorized as available and ready, respectively.

Data collection procedure

Data were collected using KOBO Collect (17), a mobile platform based on the WHO health facility SARA assessment tool. All the questions contained in the tool regarding service availability and readiness had Yes/No responses. Data on both availability and readiness were collected from the ART department of the facilities. In addition, we obtained information regarding the number of clients per facility, average waiting time for clients to be seen at the ART clinic, whether the facility is rural or urban, ART operational times, average distance clients cover to get to the facility, ART regimen dispensed, and types of DSD models implemented at the facility.

Development and validation of the availability and readiness tool

Briefly, we conducted a literature search for availability of HIV service indicators and readiness to implement DSD models instrument, no prior validated tool was found. Thus, local Zambian experts in HIV DSD models and HIV services were engaged in brainstorming session to evaluate whether the questions effectively captured availability and readiness of facilities to implement DSD models. This was followed by a psychometrician checking for any errors and later was piloted in five facilities and assessed face validity of the questions to confirm clarity and the meaning of the questions. Data from these facilities was not included in the final analysis. Internal consistency was assessed using Cronbach Alpha coefficient and items with at least 0.70 or higher value were returned.

Data quality assurance and management

A 4-day training was conducted for research assistants together with supervisors regarding the objectives of the study, data collection techniques, and ethical conduct of research. During training, important information on the availability of HIV service indicators and readiness was emphasized. During data collection, supervisors checked the consistency, completeness of collected data, and facility coverage. On average, data collection took 2 days at each facility, and information regarding availability and readiness for the facility was provided by the ART in-charge. Two investigators (PK and MS) were responsible for daily checks of data submitted online. Detailed data cleaning and validation checks were conducted before analysis.

Data analysis

We used nine indicators each to measure availability and readiness. A facility was considered to have a given indicator item if it was reported to be present or observed to be available. Aggregates of availability and readiness were calculated from nine indicators for the items present, and the overall proportion of facilities indicating the presence of all items was calculated. Categorical data were described using frequencies and percentages, while continuous variables were described using the median and intertitles ranges. Chi-square tests were used to compare differences between facilities in rural and urban areas.

Since availability and readiness are latent constructs, the relationship with their respective indicators was modeled using the SEM. The model fit was assessed using the chi-square value, root mean square error of approximation (RMSEA), and comparative fit index (CFI). The test level was 0.05 and $p < 0.05$, suggesting significant differences. All statistical analyses were performed using Stata version 17 (Stata Corp., College Station, Texas, United States).

Ethical considerations

The study was reviewed and approved by the University of Zambia Research Ethics Committee (approval number: 2999-2022), and further permission was obtained from the National Health Research Authority. The study took into consideration procedures to safeguard participants' confidentiality and privacy. Participants were informed that they were free to withdraw from participating or skip certain questions they felt uncomfortable without any consequences.

Results

There were 60 public health ART facilities with a median number of clients on ART of 1,225 (interquartile range [IQR], 442-2692). The median number of clients seen per day was 15 (10–20), and the waiting time to be seen was 20 min (10–30). The majority (34, 57.6%) of the facilities were health centers, and 49 (81.7%) had operational hours between 07:00 and 16:00 h. Close to two-thirds 38 (63.3%) were urban facilities and the facilities indicated that 27 (45.0%) of lived more than 5 km from the facilities. Regarding DSD models that were offered by the facilities, all had multi-months dispensing (100%), more than half (6.2%) were offering fast-track, community delivery ART points (46.7%) and only less than one-fifth (15.0%) had family-based model (Table 1).

Availability of HIV service indicators

Facilities with 50% or more availability of HIV service indicators were 81.7% (49/60). The facilities with 50% or more availability of HIV service indicators in rural areas were 74.8%, while for urban facilities, they were 88.7%. Slightly above two-thirds (40, 67.8%) of the facilities reported that they had existing HIV multidisciplinary teams, 56 (94.2%) rolled out the latest ART orientation guidelines, 54 (91.5%) implemented the Zambian HIV quality improvement framework, 53 (88.1%) established a facility-based system for fast-track ART distribution, and almost all facilities (58, 98.3%) had established systems to monitor patient-level HIV treatment outcomes, specifically retention, lost to follow-up, mortalities, and viral load suppression. When different questions about the availability of HIV service indicators were compared between rural and urban facilities, significant differences were found with questions related to the existence of HIV multidisciplinary teams ($p = 0.002$) and the

10.3389/fpubh.2024.1396590

TABLE 1 Characteristics of selected ART facilities where DSD models were implemented in Zambia, March 2023 ($n = 60$).

Characteristics	Median/ Frequency	IQR/ Percentage
Clients seen per day in ART, median (IQR)	15	10–20
Waiting time for clients to be seen at ART in minutes, median (IQR)	20	10–30
Number of clients on ART, median (IQR)	1,225	442–2,692
Type of facility		
Level-2 hospital	3	5
Health center	34	57.6
Health post	14	23.7
Level-1 hospital	9	15.3
ART operational times		
07:00–13:00 h	4	6.7
07:00–16:00 h	49	81.7
Anytime	7	11.7
Region		
Rural	22	36.7
Urban	38	63.3
Average distance of clients to the facility (km)		
< 3	6	10
3–5	27	45
> 5	27	45
DSD models offered by facilities*		
Multi-month dispensing	60	100
Fast track	37	61.7
After hour/weekend	26	43.3
Adolescent support	16	26.7
Men's clinic	13	21.7
Dedicated pediatric ART day	24	40
Community delivery ART points	28	46.7
Scholar model	12	20
Family-based model	9	15
Home ART delivery	17	28.3

ART, antiretroviral; IQR, interquartile range; * multiple response question.

establishment of systems to monitor patient-level outcomes on retention in care, lost to follow-up, mortalities, and viral load suppression ($p = 0.043$), which were more likely to be in urban facilities than in rural facilities (Table 2).

Facility readiness to provide DSD models

Facility readiness with 50% or more indicators was 81.3% (49/60). The readiness for rural facilities was 73.6%, while for urban facilities, it was 88.8%. The majority (55, 93.2%) of the facilities had community health workers in all departments offering HIV services oriented on the latest ARV guidelines for the year 2022, and quality improvement teams were present in all urban facilities. In addition, HIV multidisciplinary teams that review clinical cases and provide support to patients failing treatment or with advanced disease were more likely to be in urban facilities than in rural facilities (84.2% versus 71.4%). Above three-quarters (47, 79.7%) of the facilities reported that they had identified a focal person to pre-pack and label ART for community distribution, and slightly above half (31, 52.5%) of the facilities had staff and resources to train ART distributors with no difference between rural and urban facilities (Table 3).

Structural equation modeling

The SEM was designed to model a relationship between the availability of HIV service indicators and readiness of DSD model provision as well as the moderation effects through the existence and functional structures of ART health facilities. The correlation between availability and readiness was assessed. Taking availability and readiness as latent variables, path analysis of the model showed that the relationship between availability and readiness had a significant positive effect on each other ($r = 0.73$). The presented model suggested an acceptable fit, with RMSEA = 0.012 (<0.08), CFI = 0.96 (>0.95), and an overall chi-square value = 0.09 (>0.05) (18). The coefficients representing the relationships between the variables are indicated by the numbers on the arrows. Direct arrows indicate the direct effect of an explanatory variable on its respective latent variable. There was a significant correlation between the direct effect of the existing HIV multidisciplinary team (r = 0.18), orientation in the latest ART guidelines (r = 0.72), the HIV multidisciplinary team's role in reviewing clinical cases and supporting patients failing treatment or with advanced disease (r = 0.51), and the identification of appropriate personnel to distribute ART (r = 0.21) with HIV service indicators availability. For readiness, all coefficients were positive and significant. The notable ones were community health workers in all departments offering HIV services having been oriented on the latest ART guidelines for the year 2022 (r = 0.97), the presence of a quality improvement team (r = 0.51), healthcare workers trained in revised HIV monitoring and evaluation tools (r = 0.52), and the identification of a focal person to pre-pack and label ART for community distribution (r = 0.4), as shown in Figure 1.

Discussion

This study set out to assess the availability of HIV service indicators and readiness to provide DSD models in selected public health facilities in Zambia. The results from the SEM analysis showed that there was a significant correlation between the availability of HIV service indicators and facility readiness to provide DSD models, suggesting that facilities that were considered to have HIV service indicators available were more likely to be ready for the provision of DSD models and vice versa. Availability and readiness of facilities to provide DSD models as defined in this study were above average. There were still gaps in the provision of both indicators for availability and readiness, which requires significant strengthening in equipment, staffing, commodities, and amenities. We believe that a comprehensive assessment of availability and readiness could be maximized by including the qualitative study to show an in-depth understanding of these two constructs that were measured. This is because there is a limitation in the validity of the facility availability and readiness

TABLE 2 Availability of basic packages of essential DSD in HIV treatment offered by selected public ART facilities in Zambia, March 2023.

	Questions/Variables	Total $N = 60$	Rural $n = 22$	Urban $n = 38$	p-value
Availability, n (%) answered Yes					
A1	Does the facility have an existing HIV multidisciplinary team?	40 (67.8)	9 (42.9)	31 (81.6)	0.002
A2	Are the latest ARV orientation guidelines being rolled out at the facility?	56 (94.2)	20 (95.2)	36 (94.7)	0.933
A3	Does the facility have adequate storage space for additional commodities related to HIV services?	43 (72.9)	17 (80.9)	26 (68.4)	0.300
A4	Has the facility implemented the Zambian HIV quality improvement framework?	54 (91.5)	19 (90.5)	35 (92.1)	0.810
A5	Has the facility achieved a routine viral load monitoring uptake of ≥90%?	52 (88.1)	19 (90.5)	33 (86.8)	0.679
A6	Has the facility established a facility-based system for fast-track ART distribution?	53 (89.8)	18 (85.7)	35 (92.1)	0.437
A7	Currently, does the facility have ≥3 months of ART available on site?	56 (94.9)	19 (90.5)	37 (97.4)	0.249
A8	Does the facility have an established system to monitor patient-level outcomes on retention, lost to follow-up, mortalities, and viral load suppression?	58 (98.3)	20 (95.2)	38 (100)	0.175
A9	Is the facility able to establish recording and reporting systems for community ART?	44 (74.6)	18 (85.7)	26 (68.4)	0.144
	Facilities with all indicators available			**23/60 (38.3%)**	
	Facilities with 50% or more indicators			**49/60 (81.7%)**	

ART, antiretroviral therapy; HIV, human immunodeficiency virus. Bold values are facilities with all indicators available and facilities with at least 50% of the indicators available respectively.

TABLE 3 Readiness of selected ART facilities to offer DSD in HIV treatment in Zambia, March 2023.

	Statements/Variables	Total	Rural	Urban	p-value
Readiness, n (%) answered Yes					
R1	Have community health workers in all departments offering HIV services been oriented on the latest ARV guidelines for the year 2022?	55 (93.2)	19 (90.5)	36 (94.7)	0.048
R2	Does the facility have a commodity management/commodity security committee?	41 (69.5)	15 (71.4)	26 (68.4)	0.810
R3	Does the facility have a quality improvement team?	55 (93.2)	17 (80.9)	38 (100)	0.005
R4	Does the facility have an HIV multidisciplinary team to review clinical cases and provide support to patients failing treatment or with advanced disease?	47 (79.7)	15 (71.4)	32 (84.2)	0.040
R5	At this facility, have the healthcare workers been trained on the revised HIV M&E tools?	43 (72.9)	13 (61.9)	30 (78.9)	0.159
R6	Has the facility identified a focal person to oversee community-based ART distribution?				
R7	Has the facility identified appropriate personnel to distribute ART?	44 (74.6)	17 (80.9)	27 (71.1)	0.403
R8	Does the facility have staff and resources to train ART distributors?	31 (52.5)	12 (57.1)	19 (50.0)	0.599
R9	Has the facility identified a focal person to pre-pack and label ART for community distribution?	47 (79.1)	17 (80.9)	30 (78.9)	0.855
	Facilities with all readiness indicators			**29/60 (48.0%)**	
	Facilities with 50% or more indicators			**49/60 (81.7%)**	

ART, antiretroviral therapy; HIV, human immunodeficiency; M&E, monitoring and evaluation. Bold values are facilities with all indicators available and facilities with at least 50% of the indicators available respectively.

assessment tool (19). Facilities utilized other models apart from the "one-size fits-all," including the multi-month dispensing model to accelerate the attainment of desired HIV treatment outcomes. The findings continue to highlight essential efforts made in the provision of HIV treatment services to achieve the second and third 95% targets in order to end HIV/AIDS as a public health threat by 2030 (20). DSD model approaches should be adaptive to address specific barriers for all individuals living with HIV to enable them to access treatment easily. Access to treatment is still not equally accessible or used, with some groups encountering specific difficulties. For instance, male individuals with HIV are less likely to access treatment compared to their female counterparts (21). Similarly, adolescents have lower 95-95-95 targets than the general population (22–24). In this regard, specific DSD models for specific groups are essential to assist in

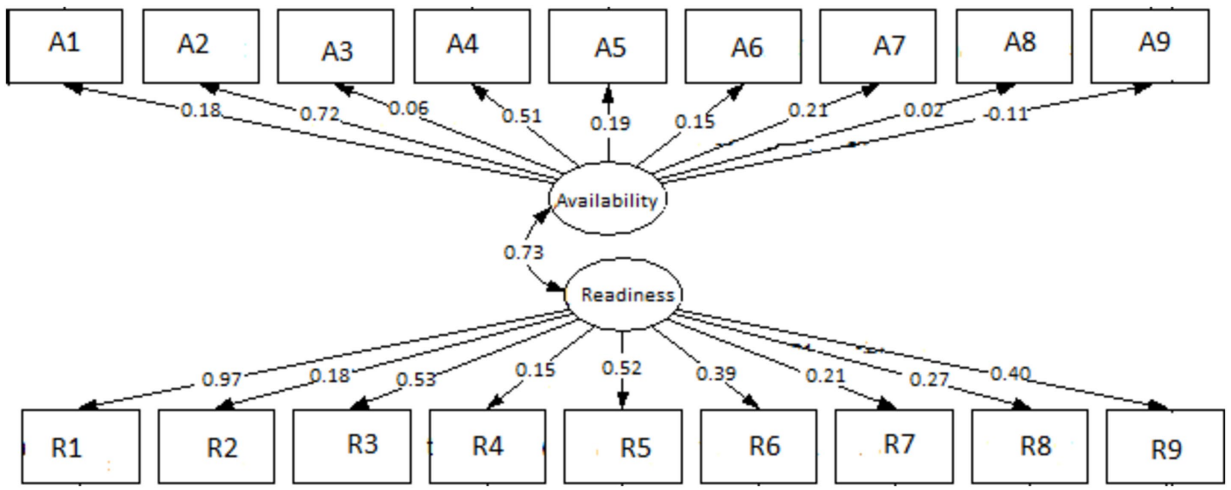

FIGURE 1
Structure equation modeling (SEM) on the availability and readiness of ART facilities to implement DSD for HIV treatment in selected health facilities in Zambia. A1–A9 are questions on availability, and R1– R9 are questions on readiness.

closing the gap in the HIV treatment response and can facilitate early access to treatment.

The results of this study showed that the availability of HIV service indicators may culminate in greater provision of DSD models, especially in a more favorable environment due to the observed results from SEM, which showed significant and positive direct standardized effects of some of its indicators. This finding is consistent with another study that demonstrated that the presence of HIV treatment indicators resulted in better provision of treatment (25). However, this is speculative since availability and readiness do not equate to actual implementation of DSD models and desired results, which this study did not assess. In addition, some indicators of availability such as adequate storage space for additional commodities related to HIV services and identification of a focal person to pre-pack and label ART for community distribution were insignificant or negative, suggesting mixed results on their impact on the provision of DSD models. This is not to say they are not important in the provision of the DSD models but could be that on their own or their components may not have a direct association with availability as a latent construct. One plausible explanation could be that each indicator captured a partial aspect that may not be sufficient to represent what the availability of HIV service indicators contains in its entirety. A combination of different important aspects is required for HIV service indicators. For example, although approximately three-quarters of the facilities reported that they had adequate storage space for additional commodities related to HIV services and established recording and reporting systems for community ART, their positive impact may be countered by unfavorable aspects, which could be either missing in the indicators or resulting in the estimated impact of the dimension being insignificant. In this instance, just adequate space for HIV services and having recording and reporting systems for community ART is not sufficient to culminate in the availability of HIV service indicators, especially if the space is not stocked with essential commodities or a non-functional recording and reporting system, respectively.

Determination of a health facility readiness to provide a health service is essential indicator for identification of weaknesses and opportunities for continued improvement (15). This study found that facilities that reported 50% or more of the indicators present were 81.7% suggesting that facilities were ready, and further comparisons showed that urban facilities were more likely to be ready than rural facilities. As suggested by a previous study (26), the observed difference between rural and urban facilities in readiness might be due to a lower supply of resources and essential commodities in rural facilities, which is common in low-resource settings and may contribute to insufficiencies and inequities. Thus, more concerted efforts are needed by all relevant stakeholders to make all indicators of readiness available in rural facilities (27, 28), which serve approximately 60% of Zambia's population in order to accelerate and increase better HIV treatment outcomes necessary to attain an HIV-free generation and quality care for those living with HIV.

Community health workers oriented in the latest HIV guidelines are important in the provision of HIV treatment services (29, 30). Our study showed that having community health workers oriented in the latest HIV guidelines significantly and positively correlated with the availability of HIV service indicators. In addition, the SEM results showed that the indicator related to the community health workers' orientation in the latest HIV guidelines had the highest correlation with readiness to implement DSD models. A plausible explanation could be due to the ability of health workers to periodically monitor and provide feedback to improve the quality of services being offered (31), an aspect that may not be possible to implement for health facilities with health workers that have not been oriented in the latest HIV guidelines. Generally, community health workers have been shown to play a pivotal role in the provision of HIV services for better treatment outcomes (32).

Consistent with previous studies (33, 34), this study showed that having a quality improvement team significantly and positively correlated with readiness to provide DSD models. It is possible that facilities with quality improvement teams reviewed and improved signal functions that enhanced DSD models, availability, and readiness. Despite the concerted and innovative efforts in the fight against the HIV pandemic and as a requirement for an HIV

framework to improve treatment outcomes, the results showed that all facilities in urban areas but not all in rural areas had quality improvement teams. This could have negatively impacted the readiness and ultimately the ability of facilities in rural areas to effectively provide the DSD models. Ensuring the presence of quality improvement teams in rural facilities may improve service delivery.

This study has several limitations. First, availability and readiness constructs measured may vary significantly depending on the educational, training, and personnel values of individuals who were working in these facilities or interviewed. Second, the degree to which different facilities embraced change, implementation, and adoption of the DSD models for HIV treatment could have varied due to resistance or acceptance at different degrees by staff at each facility. Third, we only used quantitative design to obtain the absence or presence of elements that may influence availability and readiness. This method may make it challenging to accurately measure certain using a binary checklist, potentially leading to underreporting or overreporting of other elements. Future studies should consider including qualitative design to provide a more comprehensive assessment. Moreover, we used the WHO SARA tool, which has been criticized in other studies for reducing the assessment of availability and readiness to a binary checklist. This approach tends to focus heavily on "hardware" systems while neglecting "software" systems, such as interactions among people, values, and norms (35, 36). Therefore, our findings should be interpreted with caution.

In summary, our study suggests some disparities in the availability of HIV service indicators and the readiness of different health facilities to provide the DSD models. Although both availability and readiness were above average, the study highlighted the gaps that exist in certain indicators between rural and urban facilities, such as the availability of quality improvement teams and orientation of community health workers in the latest HIV guidelines. With respect to readiness, differences were noted in the area of existence of HIV multidisciplinary teams to review clinical cases and provide support to patients who are failing treatment or those with advanced disease. This calls for training and the provision of guidelines to strengthen HIV service necessary for HIV treatment and care for better treatment outcomes. Therefore, the stakeholders and the government should prioritize the training and orientation of community health workers, the establishment of quality improvement teams, and the setting up of multidisciplinary teams to review HIV clinical cases. Future studies should consider longitudinal or panel data collection to strengthen the non-experimental approach to causal analysis (37) and may be useful to ensure the effective implementation of signal functions of the availability and readiness of health facilities to provide HIV DSD models. The evidence in this study could inform onward planning with respect to strengthening areas that are negatively affecting the effective provision of DSD of HIV treatment. Indicators that were positive and significant in SEM would potentially improve DSD models and probably better HIV treatment outcomes.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by University of Zambia Biomedical Research Committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

PK: Methodology, Validation, Conceptualization, Data curation, Formal analysis, Investigation, Project administration, Software, Supervision, Visualization, Writing – original draft. MS: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. MwM: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. MuM: Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Writing – review & editing. MaM: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Validation, Writing – review & editing. DS: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing. GM: Conceptualization, Methodology, Writing – review & editing. OM: Conceptualization, Investigation, Methodology, Validation, Writing – review & editing. TM: Conceptualization, Investigation, Methodology, Writing – review & editing. CZ: Conceptualization, Investigation, Validation, Writing – review & editing. TH: Investigation, Writing – review & editing. HP: Writing – review & editing. HH: Funding acquisition, Methodology, Project administration, Resources, Supervision, Validation, Writing – review & editing. MC: Investigation, Writing – review & editing. JZ: Investigation, Writing – review & editing. CJ: Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. This study was funded by the Global Fund.

Acknowledgments

The authors are grateful to the research assistants who participated in data collection and all health facilities and ART in-charges who responded to the questionnaire. Furthermore, the authors would like to acknowledge the Global Fund for funding the study through the Ministry of Health, Zambia.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 28 January 2025
DOI 10.3389/fpubh.2024.1407413

OPEN ACCESS

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RECEIVED 04 June 2024
ACCEPTED 16 December 2024
PUBLISHED 28 January 2025

CITATION
Rubin LH, Cho K, Bolzenius J, Mannarino J, Easter RE, Dastgheyb RM, Anok A, Tomusange S, Saylor D, Wawer MJ, Nakasujja N, Nakigozi G and Paul R (2025) Mental health phenotypes of well-controlled HIV in Uganda.
Front. Public Health 12:1407413.
doi: 10.3389/fpubh.2024.1407413

Mental health phenotypes of well-controlled HIV in Uganda

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Introduction: The phenotypic expression of mental health (MH) conditions among people with HIV (PWH) in Uganda and worldwide are heterogeneous. Accordingly, there has been a shift toward identifying MH phenotypes using data-driven methods capable of identifying novel insights into mechanisms of divergent MH phenotypes among PWH. We leverage the analytic strengths of machine learning combined with inferential methods to identify novel MH phenotypes among PWH and the underlying explanatory features.

Methods: A total of 277 PWH (46% female, median age = 44; 93% virally suppressed [<50copies/mL]) were included in the analyses. Participants completed the Patient Health Questionnaire (PHQ-9), Beck Anxiety Inventory (BAI), and the PTSD Checklist-Civilian (PCL-C). A clustering pipeline consisting of dimension reduction with UMAP followed by HBDScan was used to identify MH subtypes using total symptom scores. Inferential statistics compared select demographic (age, sex, education), viral load, and early life adversity between clusters.

Results: We identified four MH phenotypes. Cluster 1 (n = 76; *PTSD phenotype*) endorsed clinically significant PTSD symptoms (average PCL-C total score > 33). Clusters 2 (n = 32; *anxiety phenotype*) and 3 (n = 130; *mixed anxiety/depression phenotype*) reported minimal PTSD symptoms, with modest BAI (Cluster 2) and PHQ-9 (Cluster 3) elevations. Cluster 4 (n = 39; *minimal symptom phenotype*) reported no clinical MH symptom elevations. Comparisons revealed higher rates of sexual abuse during childhood among the *PTSD phenotype* vs. the *minimal symptom phenotype* (p = 0.03).

Discussion: We identified unique MH phenotypes among PWH and confirmed the importance of early life adversity as an early risk determinant for unfavorable MH among PWH in adulthood.

KEYWORDS

mental health, global, Uganda, HIV, cognition, depression, anxiety, PTSD

1 Introduction

Human immunodeficiency virus (HIV) and depressive disorders are highly prevalent, co-occurring conditions, that remain among the top 10 causes of disability among people living in the eastern, Sub-Saharan Africa country of Uganda (1). According to the 2020 Uganda Population-based HIV Impact Assessment, a nationwide survey to estimate the prevalence and incidence of HIV, approximately 1.3 million adults are living with HIV (2). The prevalence of current depressive disorders among Ugandan adults is reported to range between 14 and 21% (3). Notably, people with HIV (PWH) are disproportionately affected by depressive disorders (estimates of 21–28%) (4–6). Thus, there remains an urgent need to better understand and treat depressive disorders in PWH in this region of the world.

In the "Treat All era," HIV studies in Uganda have primarily focused on depression as a unidimensional disease entity, and most commonly as an isolated mental health (MH) disorder in PWH. There is ample evidence from the field of psychiatry that there is considerable heterogeneity in the clinical presentation and course of depression (7, 8). However, this multidimensionality is rarely examined in HIV epidemiological studies (6) even though PWH with depressive disorders exhibit markedly different profiles of somatic (e.g., sleep, appetite) and non-somatic symptoms (e.g., anhedonia, feelings of sadness or loss) (9). For example, depressed PWH could lose or gain weight, sleep too much or too little, or experience psychomotor agitation or retardation, each of which likely have different underlying mechanisms and unique treatment considerations. Furthermore, depression often does not occur in isolation, with high comorbidity observed in the context of anxiety disorders (e.g., phobias, generalized anxiety disorder) and post-traumatic stress disorder (PTSD) (10). Data from the United States National Comorbidity Survey Replication indicates that 72.1% of individuals with a depressive disorder also meet criteria for at least one other MH disorder over a 12 month period, including 59.2% with anxiety disorders (10). This co-occurrence is also common among PWH living in sub-Saharan Africa (11).

While most studies have focused on diagnostic prevalence or total symptom burden, there has been a shift toward identifying MH phenotypes. To date, few studies have employed data-driven methods to identify and characterize MH phenotypes among PWH (12–18). Early efforts outside of neuroHIV have defined MH phenotypes based on clinical symptoms, an approach that has yielded novel insights into the neurobiological basis underlying the heterogeneity of depression as well as potential therapeutic targets. For example, one study using data-driven approaches identified and validated three depression phenotypes based on item level responses to self-report questionnaires (insomnia, affective, and atypical symptoms) (19). When considering treatment response, antidepressants were most effective for individuals with the affective phenotype compared to the other two groups.

In the context of HIV, a recent large-scale, multi-site study used latent class analysis to empirically identify MH phenotypes based on current symptoms of emotional distress and substance use as well as childhood trauma, which is known to predict MH disorders and substance use disorders in adulthood (20, 21). Recent studies using data driven methods have also provided new insights into the mechanism of divergent HIV disease outcomes. For example, Chan *et al.* used group-based trajectory analysis to identify three distinct longitudinal cognitive phenotypes among PWH who initiated ART during acute infection (22). Interestingly, more severe symptoms of depression at the start of ART was the only variable that differed between the groups, with more depression evident among those in the lowest performing cognitive group. In the same cohort of PWH, Paul et al. reported that item-level responses on traditional MH questionnaires at the time of HIV diagnosis and treatment onset predicted CD4/CD8 T-cell inversion after 144 weeks of suppressive ART (23).

Clinical characteristics of PWH in cohorts in the global south differ from cohorts in the global north. In the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD), which represents HIV care in the United States and Canada, the prevalence and multimorbidity of age-associated conditions, substance use, and polypharmacy is high and is forecasted to increase by 2030 in PWH (24, 25). In contrast, neuroHIV studies in Uganda indicate minimal medical comorbidities (e.g., obesity, diabetes, hypertension), no psychiatric medication use (e.g., antidepressants, anxiolytics), balanced proportions of females and males, a different HIV subtype distribution [primarily D (59%) and A (23%)], and a preponderance of heterosexual HIV transmission with virtually no injection drug use (9, 14, 26). Furthermore, the way in which individuals experience symptoms of mental distress is intimately bound to their cultural context. As such, MH phenotypes among PWH described in studies in western countries may not generalize to PWH in Uganda. Understanding the constellation of factors that explain unique MH phenotypes among PWH, including factors that are potentially modifiable vis-à-vis prevention and/or intervention, has the potential to inform the development and implementation of tailored therapeutic strategies capable of improving the MH of PWH in Uganda and other regions of the world.

In this study, we first aimed to identify MH phenotypes among PWH in Uganda. We focused on symptoms of depression, anxiety, and PTSD given the high prevalence of these MH conditions among PWH globally (6, 11, 27–29). Second, we aimed to understand the unique attributes of each phenotype by interrogating symptom (i.e., item) level data from each MH measure. Third, we aimed to identify and characterize the sociodemographic (including history of early life adversity), HIV disease indices and cognitive factors that correspond to specific MH phenotypes.

2 Methods

2.1 Participants

We evaluated 277 PWH at the Rakai Health Sciences Program (RHSP)-supported HIV clinics and the Rakai Community Cohort Study. This open, community-based cohort includes participants residing in 40 communities in rural Rakai District, Uganda. Eligible participants were PWH aged 18 or older at the time of enrollment. Additional exclusion criteria for the overall study included severe cognitive or psychiatric impairment precluding written informed consent (participants answered questions to demonstrate their ability to understand the nature of the study and their competency to provide informed consent), physical disability preventing travel to the RHSP clinic for study procedures, known central nervous system (CNS) opportunistic infections, or prior CNS disease. This study was

reviewed and approved by the Western Institutional Review Board (IRB00209786), the Uganda Virus Research Institute Research Ethics Committee (GC/127/789), and the Uganda National Council for Science and Technology (HS634ES).

2.2 Study visit assessments

Consenting participants were administered a comprehensive assessment battery that required approximately 5 h to complete. In brief, the battery consisted of a structured questionnaire to record sociodemographic characteristics, substance use, medical history, ART and non-ART medication use, MH and cognitive assessments, functional status assessments, and a neuromedical exam. HIV status was confirmed by rapid test, and CD4 cell count and plasma viral load were assessed.

2.2.1 MH, cognitive, and motor assessments

Participants completed the Patient Health Questionnaire-9 (PHQ-9) (30) to assess depressive symptoms, the Beck Anxiety Inventory (BAI) (31) to assess anxiety symptoms, the PTSD Checklist–Civilian Version (PCL-C) to determine PTSD symptoms (32), and the sexual and physical abuse subscales on the Childhood Trauma Questionnaire to determine early life adversity (33). Translation and back-translation between English and Luganda were performed for each questionnaire. Prior studies demonstrate that PHQ-9 has high sensitivity and specificity in PWH in Uganda (34, 35). The CTQ has also been validated within adults in northern Uganda (36). While the PCL-C has not been validated in Uganda or other East African sample; the PCL-5 which is an updated version of the PCL-C for the DSM-V was validated in college students in Rwanda (37). For cognition and motor function, participants completed tests of psychomotor speed (Color Trails 1, Symbol Digit Modalities Test), cognitive flexibility (Color Trails 2), fine motor speed and dexterity (Grooved Pegboard), verbal learning and memory (WHO-UCLA Auditory Verbal Learning Test [AVLT]), and gross motor function (Timed Gait) that had been previously translated into Luganda and successfully employed in our prior studies (14, 38). Raw test scores were used in subsequent analyses. Research nurses administered and scored the tests after completing a thorough training and certification program (14).

2.2.2 Neurological evaluation and functional assessments

The neuro evaluation included a structured questionnaire of neurological symptoms employed in our prior studies (14, 38) and a neurologic exam to document extrapyramidal signs, gait, strength, reflexes, and neuropathy signs (39). Karnofsky Performance Status (40) was used to measure functional status.

2.3 Statistical analyses

The analytic approach involved several steps. First, hierarchical density-based spatial clustering of applications with noise (HBDScan) (41) after dimension reduction with the UMAP algorithm (42) was implemented to identify MH phenotypes using total scores from the BAI, PHQ-9 and PCL-C. HDBScan is a hierarchical, density-based clustering method that utilizes a proximal distance to the nearest neighbor approach. In contrast to common clustering methods (e.g., K-means), HDBScan does not require *a priori* determination of the expected number or shape of the clusters. Additionally, outliers are defined as a unique cluster rather than forced integration into an otherwise homogeneous cluster. The UMAP algorithm is a flexible non-linear dimension reduction method that estimates the topology of the data (including nonlinear interactions) to maintain the structure of complex data even at lower levels of dimensionality.

Second, we utilized inferential univariate statistical methods to determine if the clusters differed (from the referent Cluster) on a select number of variables informed by the results of prior research studies (demographics, viral load, and early life adversity). Early life adversity was examined as categorical (none or minimal, low to moderate, moderate to extreme). *T*-tests were employed for continuous variables and Chi-Square tests were used for categorical variables where applicable.

Third, we employed a machine learning approach to investigate a much larger array and dimensionality of variables (Table 1) that could help explain differences in the MH clusters identified in the first statistical step. Given the homogeneity of Clusters 1 (*PTSD phenotype*) and 4 (*minimal symptom phenotype*), we focused the classification analysis on these two subgroups. Specifically, we applied gradient boosted multivariate regression (GBM) (43, 44) a form of ensemble machine learning that yields similar classification accuracy to more computationally intensive methods, such as Super Learner (45), while minimizing the risk of overfitting (17, 46–51). CatBoost (43, 44) was utilized to build the classification model in Python. Feature selection was completed using an in-house program based on SciKit-learn (52) and PDPBox (53). Class membership was determined using a probability score based on the sigmoid function (1/(1 + e^(−x))), 0.5 decision boundary, and gradient descent to minimize prediction error. Highly correlated features ($r > 0.65$) were managed by selecting the feature with the highest maximal information coefficient (MIC) value. We examined two classification models, one that allowed two-way interactions and one that did not allow interactions among the features. Our prior studies have consistently revealed that inclusion of two-way interactions provides unique insights regarding potential mechanisms that underlie more complex clinical phenotypes (17, 23, 47–49).

Multiple steps were employed to reduce overfitting. First, as noted above we employed a classification method that is more robust to overfitting than other methods such as support vector machines. Second, we focused on parsimonious models. Specifically, the number of features in the final algorithms was determined by model saturation, at which point the inclusion of additional features did not improve model performance by more than 1 SD from the base model. Third, model performance was determined using the F1 score which is a more conservative approach to determine model performance in unbalanced designs compared to AUC. F1 is the harmonic mean of the precision (i.e., positive predictive value; PPV) and recall (i.e., sensitivity). The highest possible value is 1.0, indicating perfect PPV and sensitivity. Fourth, we employed five-fold cross validation repeated five times (total of 25 trials) and utilized the average F1 score as the final metric of model performance. Five-fold cross validation is recommended over higher fold options in cases where the sample sizes are restricted (54, 55).

TABLE 1 Input features for the gradient boosted machine learning (GBM) analyses.

Demographics	Age at time of most recent seizure	Grooved pegboard non-dominant time to completion
Sex	# of seizures inpast 12 months	Grooved pegboard non- dominant total # of drops
Age	Seizures with febrile illness	Color Trails 1 time to completion
Marital status	Anti-seizure medication use	Color Trails 1 # of prompts
Educational attainment (years)	Hypertension medication use	Color Trails 1 # sequence errors
Currently taking ART (yes/no)	Cholesterol medication use	Color Trails 1 # near misses
History of brain infection	ART duration (months)	Color Trails 2 time to completion
Medical history	History of stroke	Color Trails 2 # of prompts
History of diabetes	History of meningitis	Color Trails 2 # sequence errors
History of hypertension	Smoke cigarettes, tobacco, or pipe	Color Trails 2 # near misses
TB medicine use (Niazid; historical and current)	Illicit drug use in past 2 years (yes/no?)	Symbol Digit Modalities total correct
Dapsone use	ART adherence	Timed Gait average time to completion
Flagyl use	Karnofsky	Mental Health
Sensory Symptoms (tingling, burning, numbness in hands or feet)	Karnofsky score	Childhood Trauma Questionnaire (CTQ) – item level responses
Balance difficulty or unsteadiness	Cognitive/Motor testing	CES-D positive affect – item level responses
History of fit or seizure	WHO Verbal Learning & Memory: Trials I-V, # Correct	Hopkins Symptom Checklist-25 – item level responses for depression subscale
History of epilepsy or epileptic fits	Grooved pegboard dominant time to completion	
Age at time of first seizure	Grooved pegboard dominant # of drops	

3 Results

3.1 Demographic characteristics at enrollment

The sample was comprised of 277 PWH (127 males, 150 females). The median age of the participants was 44 [interquartile range (IQR) = 38–50], and the median years of educational attainment was 6 (IQR = 4–8). Most individuals (94%) had an undetectable viral load (<50 copies/mL), and the majority (81%) were on the ART regimen efavirenz+ lamivudine+ tenofovir. Overall, 15.2% of the sample had PCL-C scores ≥33 which is considered indicative of possible PTSD. Eight percent of the sample met criteria for mild anxiety on the BAI, 3% moderate anxiety, and 1.4% severe anxiety. For depressive symptoms, 12% met criteria for mild, 4% moderate, and 1.1% moderately severe depression. Overall, self-reported comorbidities were low (see Supplementary Figure S1).

3.2 MH phenotypes defined by the clustering analysis

As depicted in Figure 1, the clustering algorithm identified four MH phenotypes. Cluster 1 ($N = 76$) included participants who endorsed a high frequency of PTSD symptoms on the PCL-C, with an average total score that was above the clinical threshold. Individuals in this cluster also reported symptoms on the BAI and the PHQ-9; however, the average total scores were below the clinical thresholds. Cluster 1 was designated as a *PTSD-phenotype*. Clusters 2 ($N = 32$) and 3 ($N = 130$) included individuals who reported minimal to mild levels of anxiety on the BAI and/or depression on the PHQ-9, with modestly higher scores on the BAI reported by individuals in Cluster 2 [mean (M) = 5.03, standard deviation (SD) = 1.91] compared to individuals in Cluster 3 ($M = 1.15$, SD = 1.54). As such, Cluster 2 was designated as an *anxiety phenotype* and Cluster 3 was designated as a *mixed anxiety/depression phenotype*. Cluster 4 ($n = 39$) was comprised of individuals who reported no clinical elevations on the BAI, PHQ-9, or the PCL-C. Cluster 4 was designated as a *minimal symptom phenotype*. Clustering analysis metrics indicated good cluster cohesiveness and robustness based on analysis of Silhouette score (see Supplementary Figures S2–S4).

Overall, Cluster 1 (*PTSD phenotype*) exhibited higher scores on the PCL-C, PHQ-9, BAI total scores (p's < 0.001) compared to Cluster 4. Cluster 2 (*anxiety phenotype*) reported higher scores on the PCL-C, PHQ-9, and BAI total scores (p's < 0.01) compared to Cluster 4. Finally, Cluster 3 (*mixed anxiety/depression phenotype*) exhibited higher PHQ-9 ($p = 0.03$) and PCL-C ($p < 0.001$) total scores compared to Cluster 4.

3.3 Item-level analysis of MH symptoms by cluster

As expected from the primary clustering results, individuals in Cluster 1 reported a high burden of symptoms on the PCL-C, consistent with a *PTSD phenotype* (Figure 2A). Of interest, cognitive symptoms on the PCL-C (e.g., difficulty concentrating) were infrequently endorsed by individuals in this cluster. It is of note that the average age of individuals in Cluster 2 is 49, nearly 5 years older than the average age of study participants in the other three clusters. On the PHQ-9, individuals in Cluster 1 endorsed more severe ratings of anhedonia (Figure 2B) compared to the other groups. Similar to the

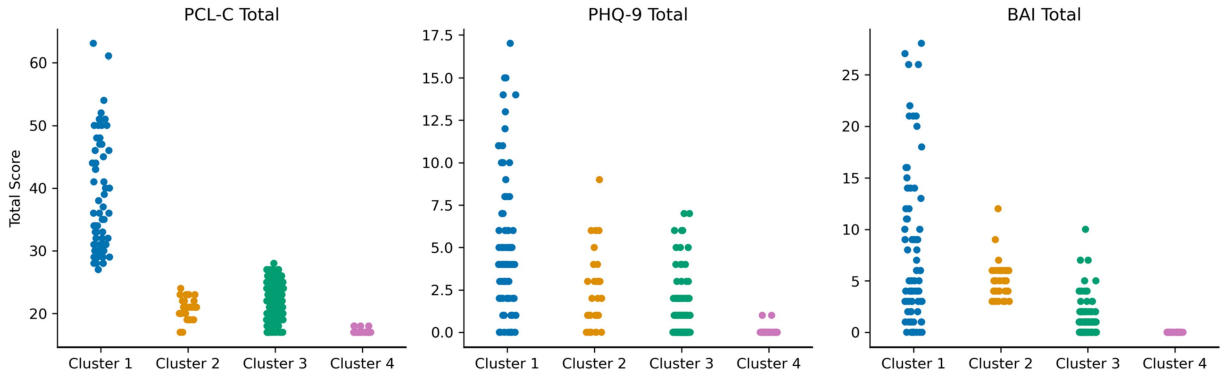

FIGURE 1
Scores on the PTSD checklist-civilian version (PCL-C), Patient health questionnaire-9 (PHQ-9), and Beck anxiety inventory (BAI) among the four mental health clusters in Figure. Strip plot demonstrating spread of scores on mental health inventories across the four clusters. Four mental health subtypes were identified. Cluster 1 (blue; PTSD phenotype) reported clinically elevated symptoms on the PCL-C, with a wide distribution of scores on the BAI and PHQ-9. Cluster 2 (orange; anxiety phenotype) reported lower PTSD symptoms, but depressive and anxiety symptoms in the mild–moderate range. Cluster 3 (green; mixed anxiety/depression phenotype) reported lower PTSD symptoms, with depressive and anxiety symptoms in the minimal-mild range. Cluster 4 (pink; minimal symptom phenotype) reported very low symptoms on all measures.

results of the BAI, individuals in Cluster 2 reported a high burden of vegetative symptoms of depression. Clusters 3 and 4 were similar in terms of item level responses on the PHQ-9. On the BAI, individuals in Cluster 1 reported more severe ratings than the other groups except for physical symptoms (e.g., "feeling hot"), which were more frequently reported by individuals in Cluster 2 (Figure 2C). Individuals in Cluster 2 reported a low rate of affective symptoms of anxiety (e.g., scared, fear of losing control), but a high rate of physical symptoms.

3.4 Inferential comparisons between MH phenotypes

Comparisons between cluster group 1, 2, and 3 and Cluster 4 (*minimal symptom phenotype*) were examined for differences in demographic, viral load, and early life adversity variables. Cluster 1 (*PTSD phenotype*) exhibited a higher rate of childhood sexual abuse ($p = 0.03$), but not physical abuse ($p = 0.26$) versus Cluster 4. Cluster 2 (*anxiety phenotype*) was older ($p < 0.001$) and reported lower rates of childhood sexual abuse ($p = 0.04$) versus Cluster 4. Cluster 3 (*mixed anxiety/depression phenotype*) did not differ from Cluster 4 on these factors. See Table 2 for full descriptive statistics per Cluster.

3.5 Machine learning classification of PTSD vs. minimal symptom phenotype

The algorithm to classify individuals into Cluster 1 (*PTSD phenotype*) vs. Cluster 4 (*minimal symptom phenotype*) yielded an F1 score of 79% for the model without interactions (see Supplementary Table S1 for full model performance metrics). The classification algorithm was built from 10 features (Figure 3; Supplementary Table S2) including (1) tingling, burning, or numbness in the feet or hands; (2) response to CES-D item, "During the past week, I was happy."; (3) response to CTQ item, "When I was growing up, someone tried to make me do sexual things or watch sexual things."; (4) number of near misses on Color Trails 2; (5) response to CES-D item, "During the past week, I enjoyed life."; (6) response to CES-D item, "During the past week, I felt hopeful about the future."; (7) taking tuberculosis medication (i.e., niazid); (8) Karnofsky score; (9) history of hypertension; and (10) response to CES-D item, "During the past week, I felt I was just as good as other people." The classification algorithm allowing for two-way interactions (see Figure 3; Supplementary Table S3) yielded an F1 score of 81% using the following 10 features: (1) happiness over the past week and tingling, burning, or numbness in the feet or hands; (2) use of Metronidazole and happiness over the past week; (3) use of tuberculosis medication and tingling, burning, or numbness in feet or hands; (4) smoking cigarettes, tobacco, or a pipe and happiness over the past week; (5) tingling, burning, or numbness in feet or hands and hopefulness over the past week; (6) hypertension and happiness over the past week; (7) hypertension medication and happiness over the past week; (8) tingling, burning, or numbness in feet or hands and balance difficulty or unsteadiness when walking; (9) tingling, burning, or numbness in feet or hands (a non-interactive feature); (10) time taking ART and tingling, burning, or numbness in feet or hands. Partial dependency plots in Figure 4 depict the directionality of each feature in relation to cluster classification (*PTSD phenotype* vs. *minimal symptom phenotype*). The heatmaps depicted in Figure 5 visualize the interactions as they relate to the classification results.

4 Discussion

Using novel analytic techniques, this study examined depression, anxiety, and PTSD symptoms within a sample of PWH in Uganda, with the aim of identifying distinct MH phenotypes. We identified four phenotypes: high PTSD symptoms, moderate anxiety, mixed anxiety/depression, and minimal clinical symptoms. Prior research suggests that internalizing disorders are highly heterogenous and that individuals can present with varied profiles of physical and psychological symptoms. For example, there are over 14,000 symptom combinations and over 200 ways that individuals can meet symptom criteria for major depressive disorder (MDD) (56, 57). Additionally,

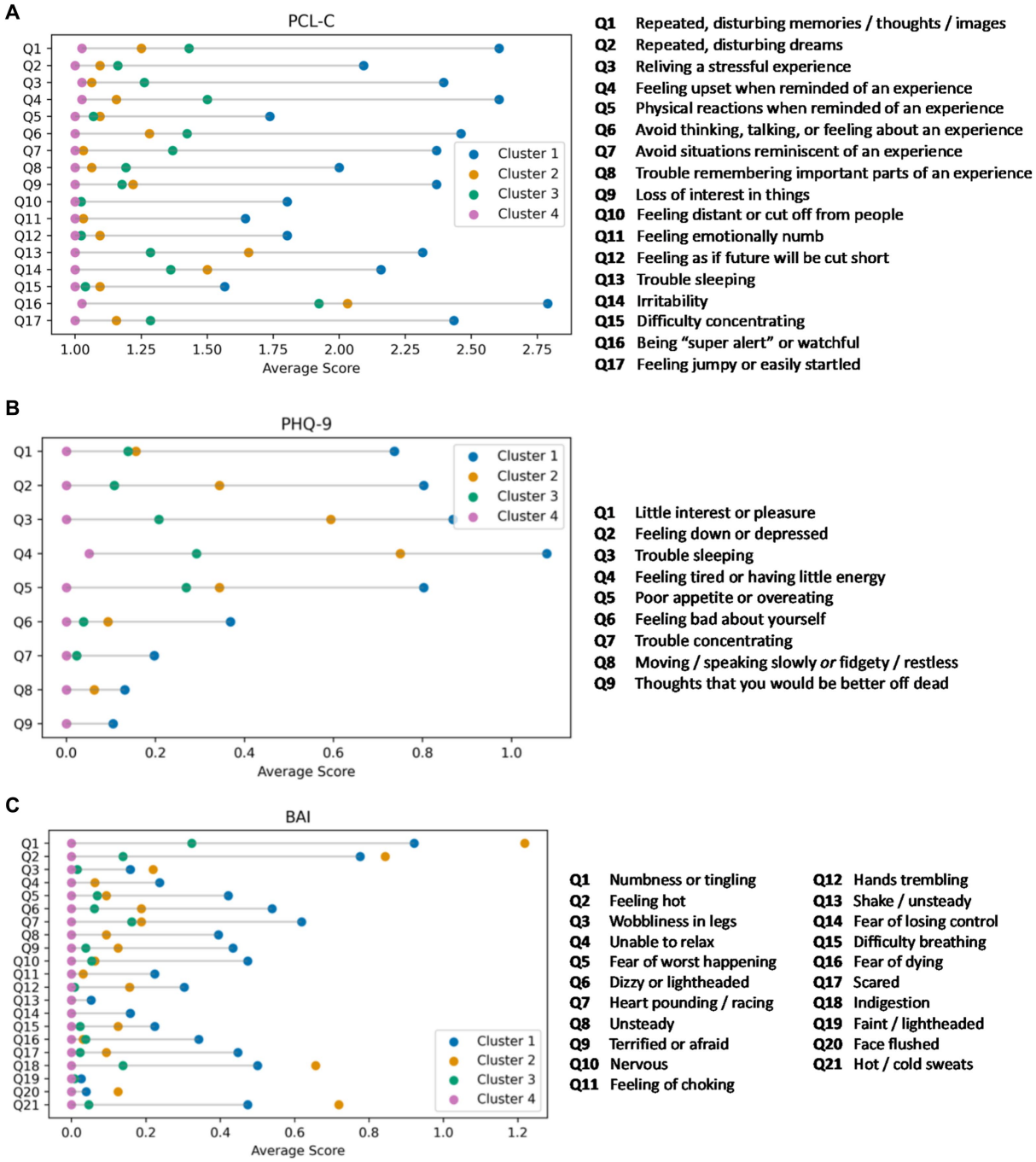

FIGURE 2
(A) Item level responses on the PTSD Checklist-Civilian version (PCL-C) by cluster. Lollipop plots displaying the mean scores on individual PCL-C items for each of the mental health clusters. Cluster 1 (blue; PTSD phenotype) reported clinically elevated PCL-C symptoms. Clusters 2 (orange; anxiety phenotype), 3 (green; mixed anxiety/depression phenotype), and 4 (pink; minimal symptom phenotype) reported lower scores in stepwise fashion on each item as well as the PCL-C total score. **(B)** Item level responses on the Patient Health Questionnaire-9 (PHQ-9) by cluster. Lollipop plots displaying the mean scores on the item level responses to the PHQ-9. Cluster 1 (blue; PTSD phenotype) reported, on average, clinically elevated PHQ-9 symptoms. Cluster 2 (orange; anxiety phenotype) reported somatic symptoms, while Clusters 3 (green; mixed anxiety/depression phenotype), and 4 (pink; minimal symptom phenotype) endorsed few symptoms. **(C)** Item level responses on the Beck Anxiety Inventory (BAI) by cluster. Lollipop plots displaying the mean scores on individual BAI items for each of the mental health clusters. Clusters 1 (blue; PTSD phenotype) and 2 (orange; anxiety phenotype) reported greater total BAI symptom burden, but with distinct profiles between the two groups (more affective symptoms for Cluster 1 and more physical symptoms for Cluster 2). Clusters 3 (green; mixed anxiety/depression phenotype) and 4 (pink; minimal symptom phenotype) had low anxiety symptoms on each BAI item and on the BAI total score.

depression, anxiety, and PTSD are highly comorbid, with significant overlap in the diagnostic criteria of MDD, generalized anxiety disorder, and PTSD (58, 59). Our findings of four distinct MH phenotypes support prior work on the heterogeneity of internalizing disorders and highlights the importance of taking a multidimensional approach to understanding MH within HIV (Table 1).

10.3389/fpubh.2024.1407413

TABLE 2 Demographic and clinical characteristics for the total sample and by cluster.

	Total Sample (*n* = 277)	Cluster 1	Cluster 2	Cluster 3	Cluster 4
	M (SD)	(*n* = 76: 27%)	(*n* = 32: 12%)	(*n* = 130: 47%)	(*n* = 39: 14%)
		M (SD)	M (SD)	M (SD)	M (SD)
Variables used in the cluster analysis					
Mental health indices					
BAI total score	3.25 (5.12)	7.76 (7.46)	5.03 (1.91)	1.15 (1.54)	0 (0)
PHQ-9 total score	2.18 (3.17)	5.09 (4.19)	2.34 (2.22)	1.08 (1.60)	0.05 (0.22)
PCL-C total score	25.10 (9.11)	37.14 (8.80)	20.81 (1.67)	21.52 (3.1)	17.1 (0.31)
Variables used in inferential statistical and machine learning analyses					
Age	44.05 (8.77)	42.92 (9.54)	49.59 (8.08)	44.04 (8.49)	41.74 (6.86)
Male sex, *n* (%)	127 (46)	28 (37)	13 (41)	65 (50)	21 (54)
Years of education	6.21 (3.68)	6.00 (3.62)	6.47 (3.94)	6.03 (3.71)	6.97 (3.49)
Undetectable viral load, *n* (%)	259 (94)	67 (88)	30 (94)	124 (95)	38 (97)
Early life adversity-CTQ					
PA					
None or minimal	230 (83)	55 (72)	28 (88)	114 (88)	33 (85)
Low to moderate	26 (9)	10 (13)	3 (9)	9 (7)	4 (10)
Moderate to extreme	21 (8)	11 (15)	1 (3)	7 (5)	2 (5)
SA					
None or minimal	208 (75)	44 (58)	27 (84)	105 (81)	32 (82)
Low to moderate	33 (12)	11 (14)	5 (16)	15 (11)	2 (5)
Moderate to extreme	36 (13)	21 (28)	0 (0)	10 (8)	5 (13)
Variables used in machine learning analyses only					
Married, *n* (%)	162 (58)	37 (49)	13 (41)	89 (68)	23 (59)
CTQ-*item level scores*					
PA by family required medical	1.05 (0.35)	1.09 (0.50)	1.09 (0.53)	1.04 (0.23)	1.00 (0.00)
PA by family leaving marks	1.30 (0.76)	1.50 (0.90)	1.16 (0.45)	1.25 (0.74)	1.23 (0.67)
Punished with a hard object	1.26 (0.71)	1.32 (0.79)	1.22 (0.66)	1.22 (0.65)	1.31 (0.80)
Belief was PA	1.24 (0.66)	1.43 (0.85)	1.19 (0.54)	1.14 (0.51)	1.23 (0.67)
Others noticed PA	1.21 (0.65)	1.38 (0.85)	1.09 (0.39)	1.18 (0.59)	1.10 (0.50)
Any attempt at SA	1.20 (0.55)	1.45 (0.77)	1.00 (0.00)	1.09 (0.36)	1.23 (0.63)
Threatened if refused SA	1.13 (0.47)	1.20 (0.54)	1.03 (0.18)	1.08 (0.35)	1.23 (0.74)
Forced to do/watch sexual things	1.21 (0.62)	1.41 (0.82)	1.13 (0.49)	1.13 (0.46)	1.15 (0.67)
Molested	1.23 (0.64)	1.50 (0.95)	1.06 (0.25)	1.12 (0.41)	1.18 (0.56)
Belief was SA	1.20 (0.57)	1.38 (0.71)	1.06 (0.25)	1.14 (0.53)	1.15 (0.54)
Cognition					
WHO AVLT total learning	47.83 (8.05)	49.13 (8.10)	47.28 (8.10)	47.42 (8.32)	47.10 (6.97)
WHO AVLT delayed recall	10.00 (2.48)	10.42 (2.46)	9.56 (2.71)	10.02 (2.48)	9.46 (2.26)
WHO AVLT recognition	13.68 (1.83)	14.04 (1.25)	14.06 (1.13)	13.63 (1.64)	12.82 (3.17)
Pegs-dominant	81.40 (23.05)	83.95 (25.87)	88.26 (25.12)	79.60 (21.70)	77.00 (18.64)
Pegs-nondominant	94.28 (27.94)	97.84 (31.60)	105.50 (31.57)	89.34 (23.77)	94.32 (27.23)
Color Trails 1	90.32 (32.12)	92.59 (36.45)	99.90 (35.07)	89.33 (29.67)	81.57 (27.09)
Color Trails 2	188.37 (68.13)	196.33 (72.62)	197.86 (66.97)	186.40 (67.08)	172.19 (62.74)
Color Trails 1-near misses	0.16 (0.44)	0.19 (0.40)	0.06 (0.25)	0.13 (0.38)	0.26 (0.72)

(Continued)

TABLE 2 (Continued)

	Total Sample (*n* = 277)	Cluster 1	Cluster 2	Cluster 3	Cluster 4
	M (SD)	(*n* = 76: 27%)	(*n* = 32: 12%)	(*n* = 130: 47%)	(*n* = 39: 14%)
		M (SD)	M (SD)	M (SD)	M (SD)
Color Trails 2-near misses	0.31 (0.65)	0.30 (0.52)	0.48 (0.89)	0.30 (0.64)	0.18 (0.69)
Symbol digit	18.94 (10.24)	19.17 (10.60)	17.69 (9.62)	18.83 (10.17)	19.97 (10.59)
Timed gait	11.18 (1.62)	11.46 (1.85)	11.08 (1.28)	11.19 (1.55)	10.70 (1.55)
Medical history, *n* (%)					
Diabetes	2 (1)	1 (1)	0 (0)	1 (1)	0 (0)
Hypertension	14 (5)	7 (9)	1 (3)	6 (5)	0 (0)
Sensory Symptoms	82 (30)	38 (50)	15 (47)	27 (21)	2 (5)
Balance difficulty	6 (2)	4 (5)	2 (6)	0 (0)	0 (0)
Fit or seizure	4 (1)	3 (4)	0 (0)	1 (1)	0 (0)
Smoke	27 (10)	10 (13)	5 (16)	9 (7)	3 (8)
Medication use, *n* (%)					
Niazid	195 (70)	48 (63)	24 (75)	91 (70)	32 (82)
Dapsone	11 (4)	1 (1)	3 (9)	5 (4)	2 (5)
Flagyl	5 (2)	4 (5)	1 (3)	0 (0)	0 (0)
Antihypertensive	8 (3)	5 (7)	0 (0)	3 (2)	0 (0)

BAI, Beck Anxiety Inventory; CTQ, Childhood Trauma Questionaire; M, mean; PA, physical abuse; PCL-C, PTSD checklist-civilian version; PHQ-9, patient health questionnaire-9; SA, sexual abuse; SD, standard deviation; sensory symptoms include tingling, burning, numbness in hands or feet; WHO AVLT, World Health Organization Auditory Verbal Learning Test.

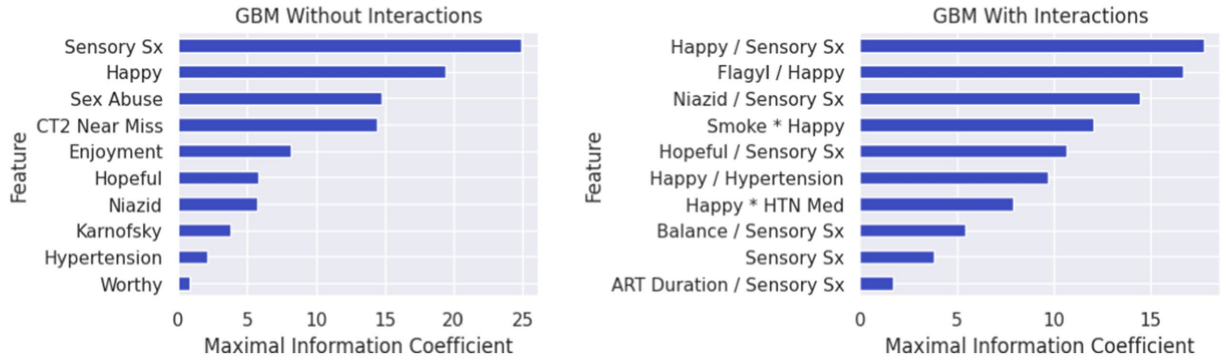

FIGURE 3
Feature lists depicting the rank order (highest to lowest) of variables classifying individuals in the PTSD phenotype (Cluster 1) vs. the minimal symptom phenotype (Cluster 4). In Figure Variables that collectively classified individuals into the PTSD phenotype (Cluster 1) versus the minimal symptom phenotype (Cluster 4) for the gradient boosted machine learning (GBM) without interaction features (left) and the GBM with interaction features (right). For the GBM with interaction features, multiplication between variables reflects synergies (risk linked to change in the same direction), whereas division between variables reflects divergence in the directionality. Features in rank order of relevance to classification without interactions include: **(Feature 1)** endorsing sensory symptoms (e.g., tingling, burning); **(Feature 2)** ratings of happiness over the past week; **(Feature 3)** belief that sexually abused in childhood; **(Feature 4)** near misses on Color Trails 2; **(Feature 5)** ratings of life enjoyment over the past week; **(Feature 6)** ratings of hopefulness over the past week; **(Feature 7)** taking Niazid; **(Feature 8)** Karnofsky score; **(Feature 9)** hypertension; **(Feature 10)** feelings of worthiness over the past week. The feature list for the model with interactions includes: **(Feature 1)** ratings of happiness over the past week and sensory symptoms (e.g., tingling, burning); **(Feature 2)** taking Flagyl and ratings of happiness over the past week; **(Feature 3)** taking Niazid and sensory symptoms (e.g., tingling, burning); **(Feature 4)** smoking and ratings of happiness over the past week; **(Feature 5)** ratings of hopefulness over the past week and sensory symptoms (e.g., tingling, burning); **(Feature 6)** ratings of happiness over the past week and hypertension; **(Feature 7)** ratings of happiness over the past week and taking anti-hypertensive medications; **(Feature 8)** balance difficulties and endorsing sensory symptoms (e.g., tingling, burning); **(Feature 9)** endorsing sensory symptoms (e.g., tingling, burning); **(Feature 10)** duration of ART and endorsing sensory symptoms (e.g., tingling, burning).

Within the study, 86% of the sample fell within one of the clinical phenotypes, with the remaining cases defined as outliers. The most common phenotype was *mixed anxiety/depression*, which comprised 47% of the sample. The second most common group was the *PTSD phenotype* (27%), followed by the *minimal symptom phenotype* (14%), and the *anxiety phenotype* (12%). These results suggest that the norm for PWH is to experience MH symptoms, most commonly mild anxiety and depression, followed by high levels of PTSD symptoms.

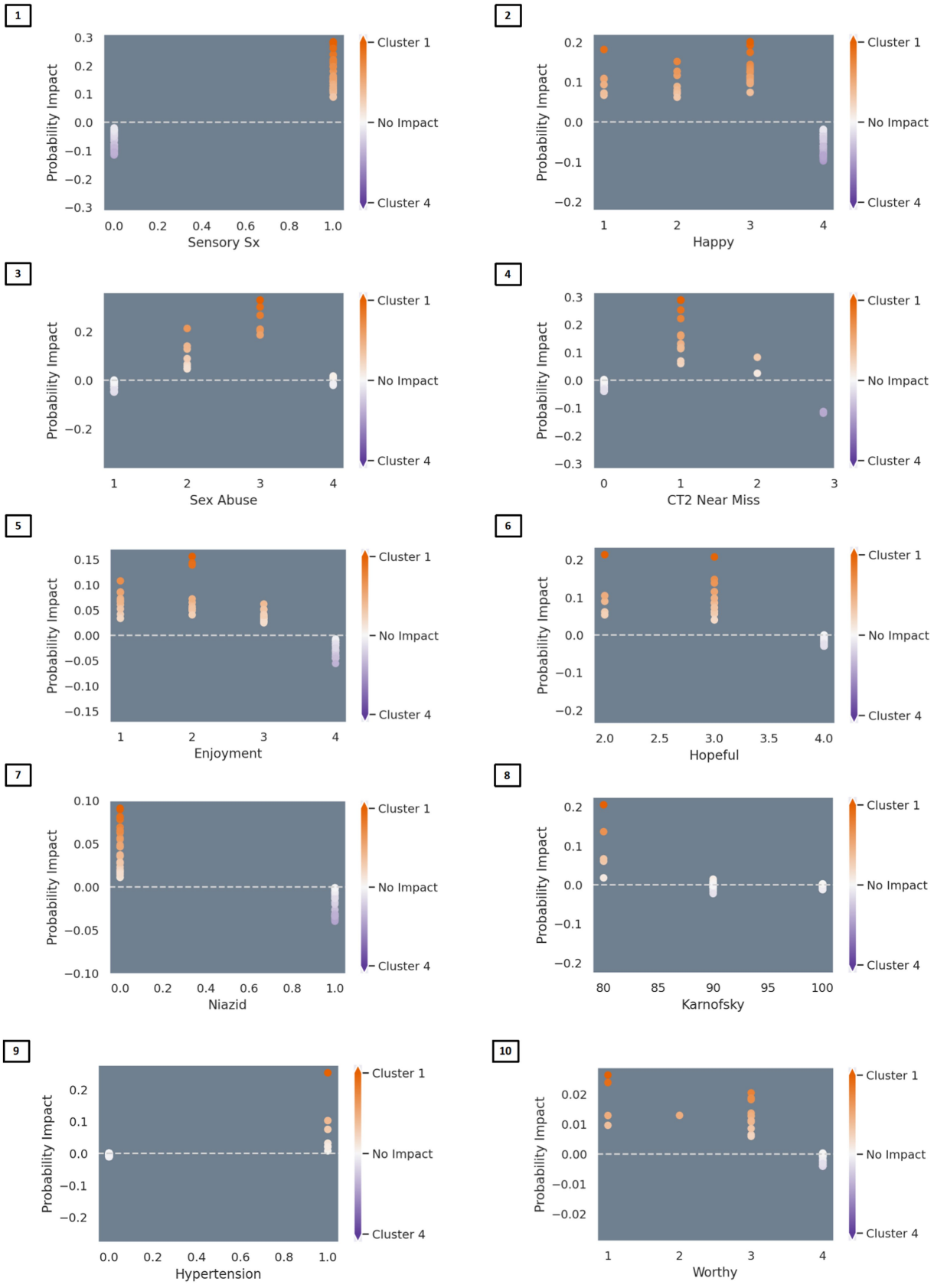

FIGURE 4
Partial dependency plots depicting the directionality of associations between variables and classification into the PTSD versus the minimal symptom phenotypes. In Figure Partial dependency plots depicting linear and nonlinear relationships between variables and classification into the PTSD versus

(Continued)

FIGURE 4 (Continued)
the normative MH phenotypes. Red represents association with the PTSD phenotype (Cluster 1) and blue represents association with the normative phenotype (Cluster 4). Predictors of classification into the PTSD phenotype included: **(Feature 1)** endorsement of sensory symptoms (e.g., tingling, burning); **(Feature 2)** lower ratings of happiness over the past week; **(Feature 3)** belief that sexually abused in childhood; **(Feature 4)** 1–2 near misses on Color Trails 2; **(Feature 5)** lower ratings of enjoying life over the past week; **(Feature 6)** lower ratings of hopefulness over the past week; **(Feature 7)** not taking medications for tuberculosis (i.e., niazid); **(Feature 8)** lower Karnofsky score; **(Feature 9)** history of hypertension; **(Feature 10)** lower ratings of worthiness/greater feelings of worthlessness.

In addition to cluster analyses, this study examined item-level responses to detect further distinctions in the MH phenotypes. The *PTSD phenotype* reported more physical symptoms, higher anhedonia, and fewer cognitive symptoms than the *anxiety phenotype*. Individuals in the *anxiety phenotype* reported fewer affective symptoms and more physical symptoms of anxiety. All four clusters endorsed histories of childhood physical and sexual abuse. However, childhood sexual abuse rates were higher in the PTSD phenotype.

Individuals in Clusters 2 and 3 (*anxiety* and *mixed anxiety/depression phenotypes*) reported similar levels of anxiety and depressive symptoms. However, upon inspection at the item level, the distinction between these groups becomes more apparent. Individuals in the *anxiety phenotype* endorsed somatic/physical BAI items at a higher rate than all other clusters. These items included experiencing numbness or tingling, feeling hot, indigestion, and hot or cold sweats. They were also more likely to endorse difficulty with sleeping or feeling tired on the PHQ-9. This finding suggests that while the total symptom burden may be similar between the *anxiety* and *mixed anxiety/depression* phenotypes, the nature of the symptoms is distinctive. It also highlights both the importance and benefits of conducting item-level analyses to discover the determinants of distinct MH phenotypes.

Additionally, our results are consistent with the well-documented finding that childhood trauma is a risk factor for MH disorders. Although individuals across all groups (including Cluster 4-*minimal symptom phenotype*) endorsed early life adversity, childhood abuse was only a significant risk factor for distinguishing Cluster 1 (*PTSD phenotype*) versus Cluster 4. Of note, the participants in Cluster 1 endorsed a high frequency of PTSD symptoms with an average total PCL-C score that was above the clinical threshold whereas Clusters 2 (*anxiety phenotype*) and 3 (*mixed anxiety/depression phenotype*) had total scores on the MH indices that were below the threshold. Thus, childhood abuse appears to be a risk factor only for PWH that report MH symptoms that are clinically significant. With respect to the *minimal symptom phenotype*, the higher endorsement of childhood sexual abuse suggests a level of resilience within some of the sample. Alternatively, this group may be underreporting their MH symptoms. Future research that examines factors that may predict whether PWH with histories of childhood sexual abuse experience elevated trauma symptoms as adults will be beneficial.

The average age of the moderate *anxiety phenotype* (49.59 years) was about 6–8 years older than the other phenotypes. Furthermore, the *anxiety phenotype* (59.4% female) comprised of 10–20% more women than the other clusters. When the item-level responses that distinguish the *anxiety phenotype* are examined within the context of these sociodemographic differences, it raises the possibility that these symptoms (numbness/tingling, feeling hot, indigestion, hot/cold sweats) may represent peri-menopausal features rather than anxiety. Thus, older women experiencing perimenopause may be potentially misclassified as falling within the anxiety group. Further examination of the symptom presentation of older women with HIV is therefore warranted.

To further understand differences between the *PTSD* and *minimal symptom phenotypes*, we utilized machine learning techniques to identify a combination of features that distinguished the two groups. Results from the models with and without interactions revealed that sensory symptoms (e.g., tingling, burning) and lower levels of happiness were prominent features associated with classification into the *PTSD phenotype*. Additionally, results from the models that allowed for up to two-way interactions revealed that use of Flagyl, Niazid, and hypertension medications in combination with sensory symptoms and lower ratings of happiness contributed to model performance. These findings emphasize the complexity of MH difficulties within the sample and the importance of understanding other components of health beyond those captured by traditional psychological measures in order to understand MH within the group.

Another important finding that warrants comment from the machine learning analysis is that the only cognitive feature that distinguished between the *PTSD* and *minimal symptom phenotypes* was the number of near misses on Color Trails 2. Typically, the only outcome examined on Color Trails is total completion time. Our finding suggests that the number of near misses should be considered as an additional cognitive outcome in neuroHIV studies.

Overall, results from this study highlight the frequent endorsement of somatic symptoms as a component of MH within a Ugandan sample. These findings are in line with prior research that suggests that individuals in Uganda are more likely to endorse somatic symptoms of MH (60–62). Similar findings have been reported in other low-income countries in the global south (63). This underscores the importance of taking a culturally sensitive and informed approach to MH assessment within this population.

This study had some limitations. First, we did not have a control group of people without HIV or those with other chronic disease who completed all three MH questionnaires. Without a comparison group, it is difficult to determine whether the observed MH phenotypes are unique to PWH or if similar patterns might be found in other populations, limiting the specificity of conclusions. Second, both the self-report measures and cognitive measures were designed using Western samples and therefore likely have cultural biases. Although many of these measures have been previously validated in Uganda or nearby countries, they likely still have some cultural bias such that some psychological and cognitive components of the Ugandan sample's presentations may be misrepresented or missed during measurement. Future research that involves cultural adaptations or of, or addendums to, mental health measures would be beneficial to offer further insight and understanding of mental health symptoms and phenotypes within Uganda. Additionally, information about adulthood trauma and exposure to types of childhood trauma beyond physical and sexual abuse was not collected; thereby we could not examine how these factors may relate to current MH symptoms or phenotype placement.

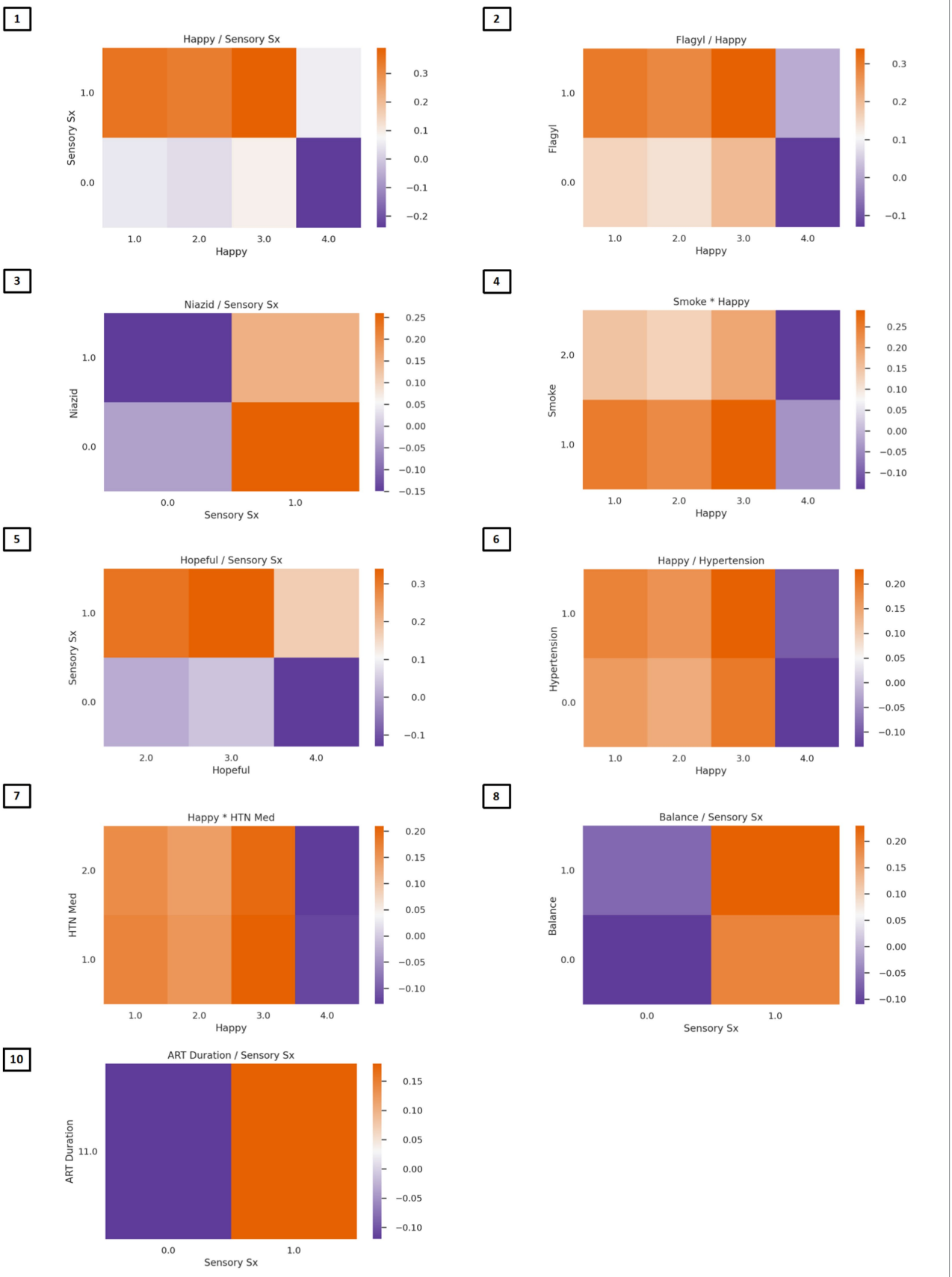

FIGURE 5
Heat maps depicting two-way associations between variables in the classification model. In Figure Heatmaps depict color-coded probabilities of classification in the PTSD phenotype (red) vs. the normative phenotype (blue). Predictors of PTSD phenotype membership are presented in descending

(Continued)

FIGURE 5 (Continued)
order of feature importance. Multiplication between variables reflects synergies (risk linked to change in the same direction), whereas division between variables reflects divergence in the directionality. **(Feature 1)** Lower ratings of happiness and endorsement of sensory symptoms; **(Feature 2)** Lower ratings of happiness and taking Flagyl; **(Feature 3)** Endorsement of sensory symptoms and not taking Niazid; **(Feature 4)** Lower ratings of happiness and smoking history corresponded to classification in the PTSD phenotype group; **(Feature 5)** Lower ratings of hopefulness and endorsement of sensory symptoms; **(Feature 6)** lower ratings of happiness and history of hypertension; **(Feature 7)** lower ratings of happiness and taking hypertensive medications; **(Feature 8)** endorsement of both sensory symptoms and balance problems corresponded to classification in the PTSD phenotype; **(Feature 9)** endorsement of sensory symptoms (no heat map); **(Feature 10)** endorsement of sensory symptoms and lower duration of ART corresponded to classification in the PTSD phenotype.

This study offers several treatment implications. Firstly, individuals reported high levels of somatic symptoms (e.g., tingling). Therefore, treatment on somatic concerns may offer some amelioration of MH distress. Additionally, difficulties with sleep was frequently reported across the clinical phenotypes; thus, sleep intervention may be a beneficial area of care for PWH in Uganda. Interactions identified in our model such as "happiness over the past week" combined with "sensory symptoms" help to emphasize the multifactorial relationship between clinical disorder and symptom manifestation, with the goal of using these findings both to corroborate existing clinical impression and to better focus future research efforts geared toward enhancing precision medicine. Additional studies of the features with and without interactions are needed to further interrogate clinical relevance (e.g., predicting response to PTSD treatment) are needed.

The results of this analysis highlight several critical observations that are directly relevant to ongoing NIH initiatives aimed at identifying, characterizing, and predicting unique biotypes among PWH. Specifically, we demonstrate compelling proof of concept that use of advanced data driven analyses can delineate distinct and clinically relevant subgroups among a large sample of PWH who are receiving suppressive ART. Further, our results underscore the importance of combining exploratory (hypothesis generating) and confirmation (hypothesis testing) analytic strategies to accurately characterize and explain differences between the data-driven MH phenotypes. Specifically, the results describe the potential misclassification/misdiagnosis of anxiety-related symptoms among select subgroups of PWH (e.g., older females). Finally, the results identify the importance of early life adversity, particularly sexual abuse in childhood as an early risk determinant for PTSD symptomology in adulthood. Additionally, individuals in Cluster 4 also reported a history of sexual abuse; yet they reported no elevations in depression, anxiety, or PTSD symptoms, consistent with resilience or under-reporting. Follow-up analyses will further investigate the stability of these groups over time as well as to further characterize explanatory mechanisms of risk vs. resilience in terms of MH phenotypes. Incorporating neurobiological (including CD4/CD8 T cell count), genetic, and/or physiological metrics could yield additional insights into MH phenotype mechanisms and support the clustering results.

In conclusion, these results underscore the significant heterogeneity in MH profiles reported by PWH who have achieved viral suppression with sustained use of ART. The clusters identify distinct clinical profiles that differ markedly in nature and severity of mental health symptoms. Importantly, the different mental health profiles were not discernible at the group level. Our findings underscore the need to conduct deeper phenotyping of mental health symptoms to discern unique risk profiles nested within large clinical cohorts. Furthermore, whereas prior studies have prioritized assessment of depression among PWH, our findings indicate that anxiety and PTSD symptoms are also prevalent among virally suppressed PWH and merit clinical attention.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Western Institutional Review Board, the Uganda Virus Research Institute Research Ethics Committee, and the Uganda National Council for Science and Technology. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

LR: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. KC: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing – review & editing. JB: Data curation, Formal analysis, Visualization, Writing – original draft, Writing – review & editing. JM: Visualization, Writing – original draft, Writing – review & editing. RD: Visualization, Writing – review & editing. AA: Investigation, Project administration, Writing – review & editing. ST: Investigation, Project administration, Writing – review & editing. DS: Writing – review & editing. MW: Project administration, Supervision, Writing – review & editing. NN: Investigation, Project administration, Supervision, Writing – review & editing. GN: Investigation, Project administration, Supervision, Writing – review & editing. RP: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. RE: Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research, authorship, and/or publication of this article. Research reported in this publication was supported by the National Institute of Mental Health (NIMH) under MH120693 and MH075673. The content is solely the responsibility of the authors and does not

necessarily represent the official views of the National Institutes of Health.

Acknowledgments

We would like to acknowledge the late Dr. Ned Sacktor who was instrumental in initiating this neuroHIV work in Rakai, Uganda. We also would like to acknowledge all of the study participants who have made this work possible. Part of this work was presented by LHR at the 2024 Conference on Retroviruses and Opportunistic Infections, Denver, Colorado.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The author(s) declared that they were an editorial board member of Frontiers, at the time of submission. This had no impact on the peer review process and the final decision.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2024.1407413/full#supplementary-material

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frontiers | Frontiers in Public Health

TYPE Original Research
PUBLISHED 18 March 2025
DOI 10.3389/fpubh.2025.1418999

OPEN ACCESS

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RECEIVED 24 April 2024
ACCEPTED 04 February 2025
PUBLISHED 18 March 2025

CITATION
Abeje ET, Agedew E, Endalew B and Alen GD (2025) Viral load change and time to death among adult HIV/AIDS patients on ART after test-and-treat in Northwest Ethiopia: a retrospective multi-center follow-up study using Bayesian joint modeling.
Front. Public Health 13:1418999.
doi: 10.3389/fpubh.2025.1418999

Viral load change and time to death among adult HIV/AIDS patients on ART after test-and-treat in Northwest Ethiopia: a retrospective multi-center follow-up study using Bayesian joint modeling

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Introduction: Among patients infected with Human Immunodeficiency Virus who are on antiretroviral therapy, nearly one-fifth develop viral load rebound within 2 years of initiation of therapy. Studies on viral load change are limited in Ethiopia. Previous studies have not adequately accounted the undetectable viral load in the analysis and the association between viral load change and time to death. This study assessed viral load change, its predictor variables, and the joint association between viral load change and time to death.

Methods: An institution-based retrospective follow-up study was conducted. The data were extracted from 24 April to 30 May 2022 using charts of 489 study participants selected using simple random sampling. OpenBUGS software from the R2OpenBUGS R package was used for model building. A joint Tobit skewed normal mixed effects model and survival analysis using a Bayesian approach was employed.

Results: The data were extracted from a total of 489 participants. Starting from six months post-treatment initiation (time zero), the log viral load decreased by 0.027 log units per month until 10.82 months of follow-up, while after 20.9 months, it increased by 0.034 log units per month. Participants who took ART medication outside of the catchment health facility had 0.29 log viral load unit higher than within the catchment health facility. The hazard of death was 3.5 times higher for individuals whose log viral load slope increased by one standard deviation from the population slope during the first 10.82 months of follow-up.

Conclusion: The change in log viral load increment was high during the latter follow-up period compared to the decrement in log viral load at the beginning of the follow-up period. Duration of treatment, taking ART medication outside the catchment area, baseline WHO stage three and four, poor adherence were associated with log viral load change. Addressing stigma and discrimination is essential to prevent ART patients from seeking treatment outside the catchment area, improve treatment outcomes and reduce viral load rebound.

KEYWORDS

viral load change, viral load pattern, time to death, HIV/AIDS, viral load rebound, survival analysis, Bayesian analysis

Introduction

Human Immunodeficiency Virus/Acquired Immunodeficiency Syndrome (HIV/AIDS) has become a global pandemic, infecting and killing millions since the 1980s. It destroys the immune system progressively and results in a condition called AIDS (1, 2). Highly Active Antiretroviral Therapy (HAART) has been taken by an estimated 27.5 million people living with HIV globally by the end of 2020. However, HIV remains a global health crisis: the world saw 1.5 million new HIV infections and 680,000 deaths from AIDS-related causes that occurred in 2020 (3, 4). In Ethiopia, besides the HAART, Pre-exposure prophylaxis (PrEP) for HIV is used by individuals who are not infected with HIV but are at a substantial risk to block the acquisition of HIV. HIV-negative female sexual workers (FSWs) and HIV-negative spouses of Sero-discordant couples are the intended recipients of PrEP services (5).

HIV viral load quantifies the amount of virus in the blood (viral RNA count in 1 mL of blood), which is then used to monitor treatment effectiveness and the progression of disease (1, 2). According to the 2021 World Health Organization (WHO) guidelines, routine viral load monitoring starts at 6 months after antiretroviral therapy (ART) initiation and is then followed up at 12 months and yearly thereafter for patients that have undetectable viral load until the occurrence of treatment failure. The new addition to this guidelines is the provision of enhanced adherence counseling if the viral load is between 50 and 1,000 copies/milliliter (ml) and repeat viral load testing after 3 months unlike the previous guidelines where enhanced adherence support has been done when viral load is greater than 1000 copies/ml (6, 7).

Now the world is aiming to achieve the 95–95-95 target for HIV issued by the Joint United Nations Program on HIV/AIDS (UNAIDS) on HIV/AIDS by the end of 2030. However, Ethiopia is one of the sub-Saharan countries short of achieving the 90–90-90 target with one-fourth of the population having a high viral load count (unsuppressed viral load) (3, 8). The median survival time was 8 years according to a meta-analysis study and only one-fourth survive past 12 years (9). In Ethiopia, the median survival time for HIV patients was three years, but this has improved in recent years. More than half of the participants were alive at the end of the follow-up period, with nearly equal follow-up durations observed due to the provision of free and accessible highly active antiretroviral therapy. Incidence of death was lowered from ten to three per hundred person years of follow-up for nearly equal length of follow-up time (10–14). However, nearly one out of five people die within 5 years of starting therapy even after the initiation of the test and treat program (13, 14). HIV/AIDS-related mortality has shown a declining trend over the years in Ethiopia. The decline was remarkable among the under-5 age group followed by the 15–49 age groups, whereas the age group 50–69 has shown an upward trend in recent years. In addition to this, the incidence-to-mortality ratio is now less than one due to high mortality (15).

To overcome this problem, there exist many interventions and strategies, from provision of higher-line therapies to the test and treat program in Ethiopia. Routine viral load testing and monitoring are done to identify treatment failure as early as possible and switch to higher-line therapy (6, 16–22). However, still nearly one-fifth of all patients in Ethiopia develop viral load rebound within 2 years of initiation of therapy, which in turn leads to treatment failure (drug resistance mutation) and death (23).

Different viral load measuring intervals based on the length of undetectable viral load and patient characteristics have shown better patient prognoses. However, in Ethiopia, emphasis and frequent measurements are given after they already have a high viral load count due to the cost of scaling up the viral load measurements (1, 6, 7, 18–21). After the provision of the test and treat program, viral load is used for treatment monitoring and treatment failure. However, there are study gaps on viral load change over time, predictors of viral load change, and the association between viral load change and time to death. Previous studies showed limitations, including an inability to incorporate undetectable viral load measurements into the analysis and had short follow-up time. This study has aimed to assess viral load change and its predictor variables as well as the joint association between viral load change and time to death among adult HIV/AIDS patients on ART after initiation of the test and treat program.

Abbreviations: AIDS, Acquired immunodeficiency syndrome; ART, Antiretroviral Therapy; BMI, Body Mass Index; CD4, Cluster of differentiation 4; CPT, Cotrimoxazole Prophylactic Therapy; IPT, Isoniazid Preventive Therapy; HIV, Human immunodeficiency virus; HAART, Highly Active Antiretroviral Therapy; Ml, Milliliter, mm3- Millimeter cued; TB, Tuberculosis; UTT, Universal Test and Treat; UNAIDS, Joint United Nations Program on HIV/AIDS; WHO, World Health Organization.

Methods

Study area and period

The study was conducted at three comprehensive specialized hospitals in the Amara region, Debre Markos, Debre Tabor, and Felege Hiwet comprehensive specialized hospitals in northwest Ethiopia. The patients newly registered for ART between 2017 and 2018 made up a total of 870 during the recruitment period. The study was conducted from 1 March 2017 to 13 April 2022. The data extraction period was from 24 April to 30 May 2022.

Study design

An institution-based retrospective follow-up study was conducted.

Population

Source population

All adult HIV/AIDS patients who newly started ART at Debre Markos, Debre Tabor, and Felege Hiwet comprehensive specialized hospitals after the initiation of the Universal Test and Treat (UTT) program were the source population.

Study population

All adult HIV/AIDS patients who newly started ART at Debre Markos, Debre Tabor, and Felege Hiwet comprehensive specialized

hospitals after initiation of the UTT program from 1 March 2017 to 1 April 2018 were the study population.

Eligibility criteria

Inclusion criteria

All adult HIV/AIDS patients who newly started ART at Debre Markos, Debre Tabor, and Felege Hiwet comprehensive specialized hospitals after initiation of UTT program and who had at least two total viral load measurements (the first viral load test at 6 months of treatment initiation and one additional viral load measurement) were included.

Exclusion criteria

Transferred-in patients after started treatment between March 01/2017 and April 01/2018 were excluded.

Sample size determination and sampling technique

Sample size determination

The two-step sample size calculation approach method was used for this study (24).

Sample size calculation for viral load change

GLIMMPSE version 3.0.0 software was used to calculate the sample size for viral load change. Longitudinal mixed-effects regression model sample size calculation requires the effect size between the comparison groups (−0.1298), treatment regimen (AZT-3TC-NVP vs. TDF + 3TC + NVP), correlation structure (6 × 6 correlation matrix), number of measurements of the outcome variable (6), group ratio (1.5:1, AZT-3TC-NVP to TDF + 3TC + NVP), standard deviation ratio over time (1.0, 1.15, 1.0, 0.84, 0.7, 0.8), within individuals variance of the outcome variable (0.4115), power (80%), and confidence level (95%) (25, 26). These parameters were obtained from a study conducted at Zewuditu Hospital (27). The largest sample size was obtained from the effect size of the treatment regimen (AZT-3TC-NVP vs. TDF + 3TC + NVP), and the sample size was 143. The treatment regimen variable has four categories: 25% of the sample was added and it became 179 (26). $N = \frac{n_0}{(1-q)}$, where $n_0$is the sample size through the assumption of complete cases = 179; q is the missing data due to death and loss to follow up from a study conducted at Addis Ababa after universal test and treat (=0.21 death +0.164 lost to follow-up = 0.374). $N = \frac{179}{(1-0.37)}$=286, and after the addition of 15% for incomplete data, it became 329.

Sample size calculation for survival data

For time-to-event data sample size calculation, the required parameters were significant effect size hazard ratio, event probability, withdraw probability, survival probability, group size ratio, confidence level, and power (28, 29). This information was obtained from a previous study in Addis Ababa on time to death after a universal test and treat program in public health hospitals (14). Stata 14 was used for sample size calculation. The event probability and withdrawal probability conducted in Addis Ababa after initiation of the test and treat program were 21.1 and 16.4%, respectively (14). The largest calculated sample size was obtained from the baseline CD4 independent variable (baseline CD4 200–350cells/mm3 versus baseline CD4 less than 200cells/mm3). Then, power logrank 0.84, hratio(0.257) power(0.8) wdprob(0.164) nratio(0.48) became 366. Because baseline CD4 was categorized into four groups, the sample size was increased by 25%, resulting in a final sample size of 458 (26). With 15% data incompleteness, it became 527. Then, the calculated sample size in the second stage was higher than the first stage (24). Therefore, the final sample size was declared to be 527.

Sampling technique and procedure

A simple random sampling technique was used. First, the number of newly registered patients from 1 March 2017 to 13 April 2018 in the logbook who had viral load measurements taken at 6 month of treatment initiation was selected based on their Medical Record Number (MRN). A sampling frame was developed for identified cards and a random computer-generated number was used to select the sampling units. The sampling frame was prepared from the eligible participants of Felege Hiwot (387), Debre Markos (198), and Debre Tabor (152). The final sample comprised 268 samples from Felege Hiwet, 145 from Debre Markos and 114 from Debre Tabor comprehensive specialized hospital.

Study variables

Outcome variables

The outcome variables were viral load change and time to death.

Independent variables

These are independent variables for both time to death and viral load change:

Demographic characteristics - gender, age, religion, marital status, employment, educational status.

Clinical characteristics - Cluster of Differentiation 4 (CD4), WHO clinical stage, baseline CD4, adherence, Co-trimoxazole Preventive Therapy (CPT), opportunistic infection, Tuberculosis (TB), anemia, Isoniazid Preventive Therapy (IPT), Body Mass Index (BMI). and weight.

Operational definition

Adherence

The extent to which a person's behavior on taking medications, following a diet, and executing lifestyle changes corresponds with agreed recommendations from a health care provider (7, 30):

Good- taken greater than 95% doses of prescribed drugs,

Fair- taken 85–94% doses of prescribed drugs, and.

Poor- taken less than 85% doses of prescribed drugs.

Catchment area

The geographic region served by a specific health facility, where patients receive ART (7, 12).

Within Catchment Area: Patients who receive ART at the nearest health facility designated for their region.

Outside Catchment Area: Patients who receive ART at a health facility other than the one nearest to them.

Treatment initiation

It refers to the time point at which participant commences their antiretroviral therapy (ART) regimen. This time point serves as the baseline for variables specifically measured at the start of treatment (5).

Six months post-treatment initiation

It refers to the time point at six months after the commencement of ART. At this time point, the initial viral load measurement was obtained to assess subsequent changes in viral load and treatment outcomes over time. Time zero for this study was set at six months post-treatment initiation. The follow-up time was measured starting from this point (5, 59).

Data extraction tools and procedure

The data extraction tool was developed from different kind of literature (10, 12, 27, 31–33). Three components made up the data extraction: clinical, behavioral, and demographic characteristics. Data extractors looked over the patient's card and the information was recorded into the data extraction tool until the patient passed away, was lost, transferred out, or the follow-up time ended.

Data quality management

The data extraction tool was tested for the availability of identified variables 2 weeks before the main data extraction period from 10 MRN charts at Debre Markos compressive specialized hospital on 18 April 2022. Based on the information gathered from the pretest, the data extraction tool was modified for main data extraction. The day before data extraction at each center, supervisors and data extractors attended a one-day training session. Supervisors and investigators reviewed and coded the completed data daily.

Data processing and analysis

The data was checked, refined, and entered into Epi-Data version 3.1 and imported to R software version 4.1.2 for graphical analysis and using OpenBUGS software from R2OpenBUGS R package for model building. Descriptive statistical analysis was done first, followed by Tobit skewed normal mixed effects model and piecewise constant cox proportional hazard model were analyzed separately. Finally, joint Tobit skewed normal mixed effects model and survival analysis was performed. The Bayesian Markov Chain Monte Carlo (MCMC) approach was used for estimation (34–40). DIC (deviance information criteria) was used for model selection. Finally, model diagnostics was done using posterior predictive model checking (29, 41–51). Improper (vague) priors were used for all parameters. The DIC was set after checking the convergence assessment based on Gelman and Rubin diagnostic plot, trace, history, and autocorrelation plots. A total of 125,000 initial iterations were used until all the parameters mixed well. This iteration was then discarded as burn-in and an additional 100,000 iterations were run before being declared as the final output. The Monte Carlo standard errors were less than 1/50th of the standard deviation for all the parameters.

Ethical approval and waived informed consent

Ethical approval was obtained from the Institutional Review Committee of the College of Health Sciences, Debre Markos University (Ref.No/HSC/R/C /Ser/co/101/ 11/14). Waived informed consent was obtained from the Institutional Review Committee of the College of Health Sciences, Debre Markos University, as it involved secondary data from the patients' charts. By collecting data in an entirely anonymous manner and not including the patients' names or MRN on the data extraction checklist, confidentiality of the information was guaranteed. Ultimately, the dataset was merely used for this study analysis. Every technique and material used was carried out in compliance with the instructions.

Results

The data was extracted from 489 participants with a data completeness rate of 92.7%.

Socio-demographic characteristics

Of the study participants, 53.2% were female, 48.3% were married, and 17.0% of the participants came from outside the catchment area. The mean age of the participants was 37.67 years with a standard deviation of 11.08 (Table 1).

Clinical characteristics

Of the study participants, 6.3% had poor adherence and 16.8% had fair. The mean weight of the participants was 52.44 with a standard deviation of 7.41 (Table 2).

Outcome variables

Of the study participants, 6.95% died before the follow-up period ended, 18.0% were lost to follow up, and 4.1% were transferred out (Table 3).

Survival probability

The overall survival probability was 0.918 with a maximum of 42.667 months of follow-up. The restricted mean survival time was 41.9 (41.58, 42.2). Half of the deaths occurred after 25 months of follow-up (Figure 1).

10.3389/fpubh.2025.1418999

TABLE 1 Socio-demographic characteristics.

Categorical variables		Proportion
Sex	Male	229 (46.83%)
	Female	260 (53.17%)
Occupation	Daily labor	89 (18.2%)
	Farmer	34 (7.0%)
	Government employee	91 (18.6%)
	Housewife	43 (8.8%)
	Merchant	103 (21.1%)
	Private	97 (19.8)
	Other	32 (6.5%)
Marital status	Never married	126 (25.8%)
	Married	214 (43.8%)
	Divorced	109 (22.3%)
	Widowed	40 (8.1%)
Religion	Orthodox	447 (91.4%)
	Protestant	11(2.3%)
	Muslim	31(6.3%)
Education status	No education	89 (18.2%)
	Prime education	130 (26.6%)
	Secondary education	142 (29.0%)
	Higher level	128 (26.2)
Catchment area	Outside	83 (17.0%)
	Within	406 (83.0%)
Continuous variable		
	Mean	Standard deviation
Age	37.67	11.08

TABLE 2 Clinical characteristics.

Clinical characteristics		Proportion
Baseline WHO	Stage 1	145 (29.7%)
	Stage 2	179 (36.6%)
	Stage 3	142 (29.0%)
	Stage 4	23 (4.7%)
CPT	No	260 (53.2%) 229
	Yes	229 (46.8%)
Baseline tuberculosis	No	458 (93.7%)
	Yes	31 (6.3%)
IPT	No	31 (6.3%)
	Yes	458 (93.7%)
Baseline regimen	AZT-3TC-EFV	11 (2.2%)
	AZT-3TC-NVP	37 (7.6%)
	TDF-3TC-EFV	438 (89.6%)
	TDF-3TC-NVP	3 (0.6%)
Adherence	Good	376 (76.9%)
	Fair	82 (16.8%)
	Poor	31 (6.3%)
Clinical characteristics		
	Mean	Standard deviation
Baseline CD4	397.1	205.5
Baseline hemoglobin	13.4	1.59
Weight	52.44	7.41
Height	165.0	6.10
BMI	19.30	2.09

TABLE 3 Outcome variables.

Variables		Proportion
Event status	Censor	455 (93.04%)
	Event	34 (6.95%)
Censor type	Lost	88 (18.0%)
	Period ends	355 (75.6%)
	Transfer out	20 (4.1%)

Explanatory analysis

Exploring viral load individual profile

Individual study participants had different viral loads at six months post-treatment initiation ranging from undetectable viral load to high viral load counts greater than 1,000 copies (random intercept). Individual viral load profiles show that individuals with high log viral load counts at 6 months of treatment saw a faster decrease in log viral load than low log viral load at 6 months of treatment (random slope) (Figure 2).

Exploring the mean

The mean profile shows a decreasing trend at the beginning of the follow-up period, remaining low with a curved transition, and then an increasing trend during the latter follow-up period (52–54) (Figure 3).

Summarizing the data exploration

Different viral loads at the start of the study and different viral load progressions indicate a random intercept and random slope. The mean profile shows a linear spline with bent cable transition.

Viral load

From 1,485 measurements, 586 (40.2%) showed an undetectable viral load, 189(12.7%) showed a viral load greater than 1,000 copies, and the rest 700 (47.1%) showed viral load measurements that fell somewhere in between. The lower detection limit was 150 copies per ml. After applying log10 transformation to the viral load, the distribution exhibit half-right skewed normal distribution.

Final joint model

From all the variables in the descriptive analysis, baseline CD4, age of the participant, baseline WHO stage, catchment area, and adherence were included in the final joint model. The posterior

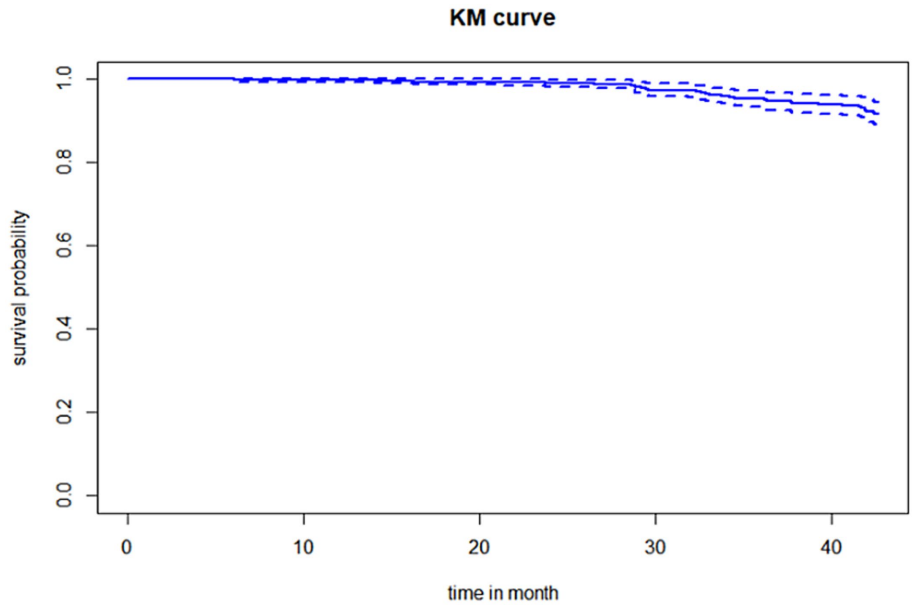

FIGURE 1
Survival probability.

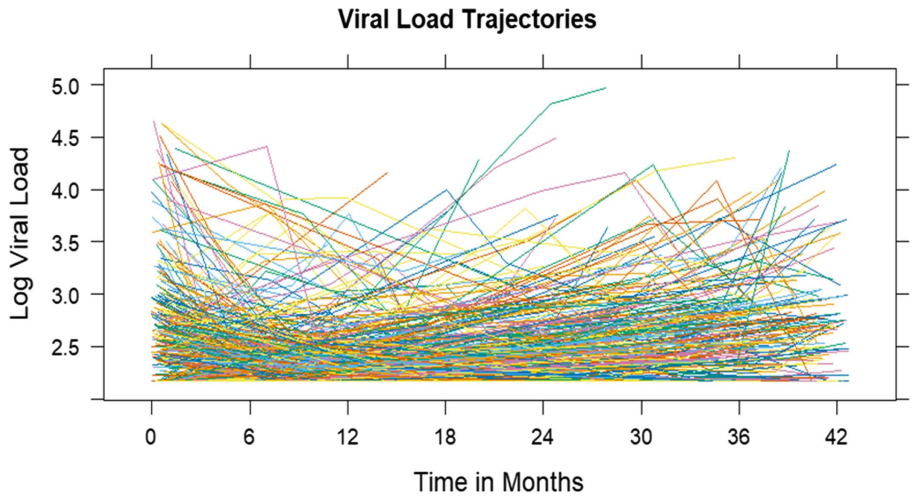

FIGURE 2
Viral load trajectory: individual profile plots.

mean 95% credible interval for the log viral load over time, both before and after the transition, indicates an association between time and log viral load. Log viral load decreased by 0.02675 ($10^{0.02675}$ = 1.06 viral load copies) when time increased by 1 month up to 10.82 months. Log viral load increased by 0.03384 ($10^{0.03384}$ = 1.08 viral load copies) when time increased by 1 month ((−0.02675) + 0.06059 = 0.03384) after 20.925 months of follow-up.

Participants who took ART medication outside of the catchment health facility had 0.29 log viral load unit higher than within the catchment health facility. Patients with WHO stages 3 and 4 showed an increase in the log viral load by 0.6078 and 0.738 respectively than WHO stage 1 at the start of the study. Poor adherence increases the hazard of death by 88.5% ($e^{0.634} = 1.885(1.20, 2.8)$) compared to good adherence. The hazard of death is increased by 1.34 times when the age of the patient increases by one standard deviation (11.08 years).

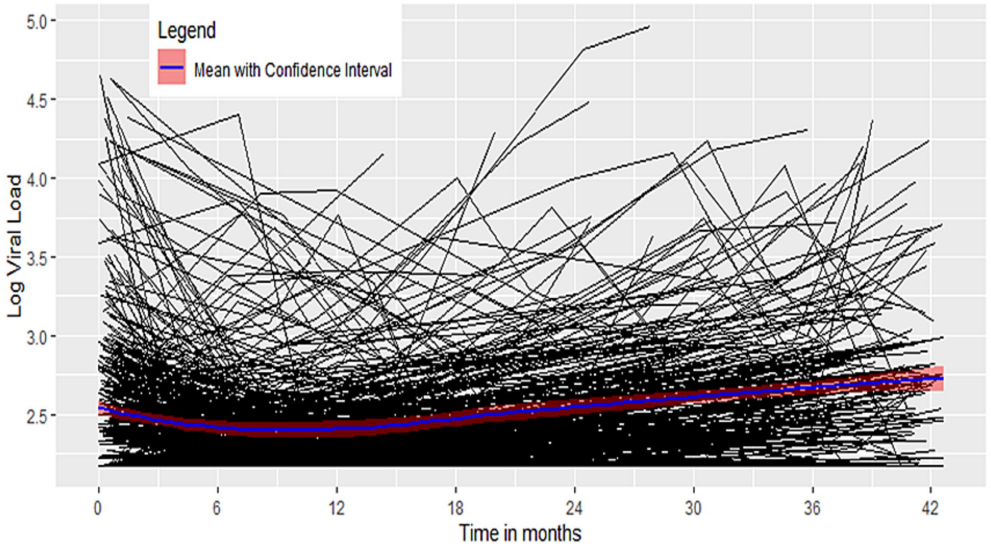

FIGURE 3
Mean structure using smoother.

The hazard of death was 3.5 times higher for individuals whose log viral load slope increased by one standard deviation from the population slope during the first 10.82 months of follow-up (Table 4).

Discussion

The log viral load showed a decreasing trend during the first eleven months of follow-up. This is supported by studies conducted in the United States, sub-Saharan Africa, Cameron, Arbanch, and Zewuditu Memorial Hospital in Ethiopia (27, 32, 55–59). This may be due to the HAART and adherence support. The log viral load remains low during the middle of the follow-up period. This is supported by studies done in the United States and sub-Saharan Africa (55, 56). This may be because better adherence to treatment and the effectiveness of HAART in reducing viral loads to their lowest achievable levels, beyond which further reduction is not possible under the current treatment regimen and guidelines.

The log viral load increases after 21 months of initiation of the study. This finding is supported by studies done in the United States and sub-Saharan Africa (55, 56). This may be due to treatment failure and non-adherence at the latter follow-up time. There is a discrepancy between this study and studies done in Arbanch and Zewuditu, Cameron, South Africa Memorial Hospital in Ethiopia (27, 32, 57–59). They concluded the viral load was decreasing over time. This may be due to methodological differences in the longitudinal growth curve model, inclusion of skewness, assumption of missing data, and incorporating undetectable viral load measures in this study. Even though the viral load follows similar trend, the effect size in this study is lower than the previous studies with the same pattern, mainly before the transition parameter. This may be because this study's viral load measurements were taken 6 months after treatment initiation. The viral load is low due to HAART and more frequent viral load monitoring in this study than in previous studies.

The correlation between baseline log viral load and log viral load change before 10.82 months of follow-up is negative. This finding is supported by studies done in South Africa and Zewuditu Memorial Hospital (27, 32, 59). This may be because individuals with a high viral load experience a more rapid decrease over time due to treatment effects and adherence to medication compared to those with a low viral load at six months post-treatment initiation. The correlation between log viral load change before 10.82 months of follow-up and after 20.92 months of follow-up is strongly negative. This may be because having a high viral load before transition becomes having a low viral load after a while due to adherence counseling and a next-line treatment switch.

Higher WHO stages (3 and 4) are associated with higher log viral load at six months post-treatment initiation. This finding is supported by studies done in Ethiopia at Zewuditu Memorial Referral Hospital, South Africa, sub-Saharan Africa (27, 32, 56). This may be due to the log viral load remaining high for those with advanced WHO stages even 6 months after initiation of treatment. On the other hand, there is a discrepancy between this study and a study done in Arbanchi, Ethiopia (58). This may be because the first viral load measurement was done at the same time as the initiation of treatment (prospective study up to 6 months) at the prior study. This means the viral load might be high irrespective of the WHO stage. As this study is conducted after 6 months of treatment initiation, having a low WHO stage may linked with sharp decrease of viral load over 6 months (60).

Taking ART service outside the catchment area was associated with a high log viral load at six months post-treatment initiation. This may be due to missing their appointment date and treatment interruption, which in turn leads to adherence problems and treatment failure. Another possible explanation may be fear of disclosure to the public due to discrimination and stigmatization (60).

Poor adherence level is associated with high log viral load at six months post-treatment initiation. This study is supported by studies conducted in Arbaminch and Zewuditu Memorial Hospital, Ethiopia (27, 58, 59). This may be due to the inability to take medication properly; this affects the efficacy of HAART medication on viral load reduction and leads to resistance to HAART medication that may result in treatment failure.

10.3389/fpubh.2025.1418999

TABLE 4 Viral load change sub-model and time-to-death sub-model.

Longitudinal sub-model		Mean	Sd	val2.5pc	Median	val97.5pc
Variables						
Intercept		1.557	0.1351	1.285	1.559	1.817
Time (slope one)		−0.02675	0.01091	−0.04883	−0.02664	−0.005678
Time (slope two)		0.06059	0.01556	0.02935	0.06034	0.09157
Variance intercept		0.1018	0.03429	0.05138	0.09629	0.1879
Cov. intercept and slope one		−0.0091	0.003678	−0.01632	−0.008903	−0.00192
Cov. intercept and slope two		0.0068	0.007598	−0.006808	0.006328	0.0232
Variance slope one		0.0130	0.002132	0.009558	0.01278	0.01796
Cov. slope one and slope two		−0.0106	0.002692	−0.01687	−0.01031	−0.006301
Variance slope two		0.0215	0.003996	0.01522	0.02105	0.03084
Skewness		0.0034	0.148	−0.2849	0.002816	0.3013
Base CD4		−0.0678	0.07832	−0.2221	−0.06724	0.08427
Age		0.1297	0.07449	−0.01762	0.13	0.2734
Catchment area	Within	Ref				
	Outside	0.2853	0.1527	0.02398	0.2768	0.6043
Base WHO	Stage 1	Ref.				
	Stage 2	0.2154	0.1559	−0.08851	0.2161	0.5252
	Stage 3	0.6078	0.1876	0.2452	0.6075	0.9767
	Stage 4	0.738	0.2564	0.2304	0.7374	1.244
Adherence	Good	Ref.				
	Fair	0.2859	0.1641	−0.03908	0.2855	0.6092
	Poor	0.7316	0.2636	0.212	0.7297	1.25
Variance		1.23	0.08177	1.082	1.226	1.401
Transition parameters						
Gam		5.425	1.75	1.995	4.801	8.85
Kappa		1.864	0.3746	1.129	1.793	1.92
Tau		15.5	0.7335	14.06	15.71	16.93

Survival sub-model							
Variables		**Mean**	**Sd**	**val2.5pc**	**Median**	**val97.5pc**	**Hazard ratio**
Catchment area	Within	Ref.					
	Outside	−0.1252	0.1353	−0.3954	−0.123	0.1371	0.88(0.67–1.15)
Base WHO	Stage 1						
	Stage 2	0.276	0.205	−0.1142	0.2695	0.6927	1.32(0.89–1.99)
	Stage 3	0.664	0.2216	0.2414	0.6573	1.098	1.94(1.27–2.99)
	Stage 4	1.214	0.2018	0.8187	1.209	1.624	3.37(2.27–5.07)
Adherence	Good	Ref.					
	Fair	0.06223	0.1512	−0.2323	0.06025	0.3677	1.06(0.79–1.44)
	Poor	0.6341	0.2101	0.1898	0.6421	1.031	1.89(1.21–2.80)
Base CD4		−0.1043	0.08636	−0.2749	−0.1061	0.06679	0.90(0.76–1.07)
Age		0.291	0.06659	0.1561	0.2912	0.4215	1.34(1.17–1.52)
Association intercept		0.1061	0.5812	−1.0330	0.111	1.248	1.11(0.36–3.48)
Association slope one		1.249	0.506	0.257	1.181	2.241	3.5 (1.29–9.40)
Association slope two		0.650	1.132	−1.562	0.6445	2.88	1.92(0.21–17.63)

Individual patient log viral load change before 10.82 months of follow-up deviates from the average population log viral load change is associated with time to death. This finding is supported by studies conducted in the United States, sub-Saharan Africa, and South Africa (32, 56, 61, 62). This may be due to differences in the viral load change between patients who survived and those who died (63, 64).

Strengths and limitations of the study

This study uses robust analysis without constraining the natural follow of the data using random visit times. This is achieved using Bayesian analysis, incorporating a skewness parameter, modeling undetectable viral load with the Tobit mixed-effects model, and handling missing data through joint analysis. The study findings apply to other ART treatment sites in Ethiopia since all study centers have similar findings on viral load change, given the generalizability to similar populations (proximal population generalizability). These findings may also be relevant for other developing countries that follow the WHO guidelines.

The weakness of this study is its inability to include time interaction effects of baseline covariates on viral load change due to the slow execution of the software. Few viral load measurements per participant may affect the findings. The viral load measurements were not measured at the planned time points (viral load measurements at 6 months, 12 months, and every 12 months since treatment initiation), and many patients had only two and three viral load measurements within a 4-year follow-up period. In fact, a minimum of five viral load measurements were considered, and more for those who showed immunologic, clinical, and virologic failure.

Implication of the study

The study may be used by policymakers for guideline revision or modification to incorporate the viral load change and factors associated with viral load rebound into the program to overcome resource-intensive viral load measurement as well as to prevent HIV transmission due to high viral load measures along with protective measures.

The study may be used by clinicians to assess the prognosis of their clients by observing the speed of viral load change, assess the clients in time to prevent transmission among couples and high-risk groups, identify treatment failure as early as possible, and highlight the factors associated with viral load change and survival. It will be used as a baseline for future studies on this area (viral load).

Conclusion

Duration of treatment, WHO stages 3 and 4, taking Art service outside the catchment area, and poor adherence are associated with log viral load change. Log viral load decreases up to 11 months of follow-up, remaining low at the transition point and rebounding after 21 months. Individual patient log viral load change deviation from the mean log viral load change of the population is associated with time to death. The log viral load decrement after six months post-treatment initiation is smaller compared to the log viral load increment after 21 months since six months post-treatment initiation (27 months since treatment initiation).

Data availability statement

The datasets presented in this article are available upon reasonable request. Requests to access the datasets should be directed to eyobt525152@gmail.com.

Ethics statement

The studies involving humans were approved by the Institutional Review Committee of the College of Health Sciences, Debre Markos University. Waived informed consent was granted, as the study used secondary data from patient charts. The studies were conducted in accordance with the local legislation and institutional requirements. The ethics committee/institutional review board waived the requirement of written informed consent for participation from the participants or the participants' legal guardians/next of kin because it is secondary data on patient chart.

Author contributions

ETA: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. EA: Conceptualization, Methodology, Project administration, Supervision, Visualization, Writing – review & editing. BE: Conceptualization, Project administration, Supervision, Validation, Visualization, Writing – review & editing. GA: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – review & editing.

Funding

The author(s) declare that no financial support was received for the research and/or publication of this article.

Acknowledgments

We would like to thank Debre Markos University College of Health Science for giving ethical approval for this research project. The authors would also like to extend their gratitude to Debre Markos, Debre Tabor, and Felege Hiwet for comprehensive specialized hospital stuffs, data collectors, and supervisors for their collaboration and contribution.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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TYPE Original Research
PUBLISHED 28 July 2025
DOI 10.3389/fpsyt.2025.1404896

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RECEIVED 21 March 2024
ACCEPTED 30 June 2025
PUBLISHED 28 July 2025

CITATION
Desta F, Zenbaba D, Sahiledengle B, Metaferia S, Desalegn T, Gomora D, Kene C, Beressa G, Mesfin T, Petruka P and Mwanri L (2025) Perceived stigma and the role of BMI on perceived HIV-related stigma among people living with HIV/AIDS in Southeast Ethiopia.
Front. Psychiatry 16:1404896.
doi: 10.3389/fpsyt.2025.1404896

Perceived stigma and the role of BMI on perceived HIV-related stigma among people living with HIV/AIDS in Southeast Ethiopia

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Background: People living with HIV/AIDS are at an increased risk of perceived HIV-related stigma. The effectiveness of social support for perceived HIV-related stigma is hampered by high depression. Although there is evidence that being underweight is associated with perceived HIV-related stigma, the mechanism is not well known. This study aimed to assess perceived HIV-related and the role of body mass index (BMI) on perceived HIV-related stigma in Southeast Ethiopia.

Methods: A hospital-based cross-sectional study design was conducted among 547 randomly selected HIV/AIDS patients in Southeast Ethiopia. Perceived HIV-related stigma was assessed using a 10-item perceived HIV stigma scale assessment tool. Descriptive statistics were computed, and the data were analyzed by logistic regression, correlation, and mediation model.

Results: The magnitude of perceived HIV-related stigma was found to be 68% [95% CI: (64.1%, 71.9%)] among participants. Patients with low social support [AOR=1.5, 95% CI: (1.05, 2.40)], a body mass index (BMI) of <18.5 kg/m^2 (kilogram per meter squared) [(AOR = 5, 95% CI: (2.30, 11.0)], and non-adherence to highly active antiretroviral therapy (HAART) [(AOR: 5, 95% CI: (1.03, 3.05)] were significantly associated with perceived HIV-related stigma. In mediation, the results indicated that the total mediation effect (*B* = -0.62, 95% CI [-0.828, 0.404]), direct effect (*B* = -0.30, 95% CI [-0.554, -0.046]), and depression played a chain mediating role (indirect effect) (*B* = -0.41, 95% CI [-0.557, -0.261]) were significant.

Conclusion: The prevalence of perceived HIV-related stigma was found high. Patients with poor social support and non-adherent to HAART were more likely to suffer from HIV-related perceived stigma. Our findings suggest that there is a relationship between body mass index and perceived HIV-related stigma, while depression can indirectly predict perceived HIV-related stigma.

KEYWORDS

perceived HIV-related stigma, HIV/AIDS, Ethiopia, PLWHIV, depression

Introduction

HIV/AIDS is a major public health concern across the world, particularly in low- and middle-income countries (LMICs) (1). More than 74.9 million people worldwide have been infected with HIV (2). Sub-Saharan Africa (SSA), the most affected region, is home to 76% PLWHIV (3). HIV/AIDS-related stigma is seen as prejudice, discounting, ridiculing, and discrimination aimed against those who are suspected of having HIV/AIDS (4, 5).

Perceived stigma describes how people living with HIV (PLWHIV) feel or fear when they are being treated unfavorably (6, 7). The United Nations Programme on HIV/AIDS (UNAIDS) report indicated that over 50% of people globally experience discriminatory attitudes because of their HIV status (8). A study conducted in the United States reported that 89% of PLWHA in the US experienced perceived stigma (9). A study conducted in Botswana and Venezuela reported stigma as a major obstacle to HIV testing (10, 11). The perceived stigma has a significant impact on the quality of life in PLWHIV (12). Stigma limits PLWHIV's access to care, which is a significant contributor to the global HIV pandemic (12–14).

Different studies conducted in Brazil (15), USA (16), South Africa (17), Zambia (18), and Southern Ethiopia (19) indicated an association between perceived HIV-related stigma and low birth weight. Other studies also revealed that a low BMI significantly increases the risk of developing antiretroviral drug-related liver injury (20) and tuberculosis (21) among people living with HIV patients. The findings from various studies highlight the importance of addressing perceived HIV-related stigma to improve the health outcomes for PWH, particularly in those with low BMI (22).

The national prevalence rate of HIV/AIDS in Ethiopia is 0.9% (23), and the number of PLWHA per region contributes to the varied prevalence rates (24). The Ethiopian Demographic and Health Survey (DHS) 2016 reported a low prevalence of HIV/AIDS (0.7%) in Oromia region (24) within and across nations. The low HIV prevalence may contribute to increased stigma toward PLWHA (25, 26).

In Ethiopia, about 16%–56% of PLWHA reported having perceived HIV-related stigma (27, 28). A stigma index survey done by networks of HIV-positive people in Ethiopia indicated that stigma is acquired and perpetuated through gossip, verbal insult, isolation, and rejection (6).

A recent systematic review indicated that an evidence-based effective programming to reduce stigmatizing and discriminatory attitudes has increased significantly (6, 29). However, money countries has not made reducing stigma a top priority in their national AIDS policies or programs (30), and HIV-related stigma continues to play a significant role in contributing to the spread of the epidemic (31). Although a substantial number of PLWHA live within the study area, the issue of HIV-related stigma has not been well addressed.

Therefore, this study primarily aimed at exploring BMI and its related mechanisms, which are essential to developing mental health interventions, which are becoming increasingly important to improve the mental and physical quality of life among HIV/AIDS patients. However, to the best of our knowledge, no studies have explored how and when BMI affects perceived HIV-related stigma in PLWHIV. Thus, this study also helps to determine whether depression mediates the association between BMI and perceived HIV-related stigma.

Methods

Study design and setting

A hospital-based cross-sectional study design was used to assess HIV-related perceived stigma and its associated factors among PLWHIV who receive treatment at antiretroviral therapy (ART) clinics. The Bale Zone is located approximately 412 kilometer (km) away from Addis Ababa. It has three government hospitals, one referral (Goba Referral Hospital), and two general hospitals (Dellomena and Robe General Hospitals) that are currently providing ART services in the Zone. During the period between February 1 and April 30, 2021, there were 3,308 adult HIV/AIDS patients who had registered for ART follow-up in these three public hospitals in the study hospitals.

Study population

All HIV-positive patients aged >18 years who were enrolled to receive ART treatment follow-up in public hospitals in Bale Zone

were the source population (32). The potential participants were randomly selected for inclusion in the study if they had been enrolled for ART for at least 6 months. Patients who were unable to communicate or had a serious medical condition were excluded.

Sample size determination and sampling technique

The sample size was determined using the single population proportion formula using EPI info version 7.2 assuming the following parameters: 95% level of confidence, 4% marginal error, and 49.4% proportion of HIV-related perceived stigma among PLWHA (4). Moreover, 10% of the potential participants were added to address the non-response rate yielding the total sample size as 559. The study participants were chosen using systematic sampling techniques. The sampling interval was calculated by dividing the total number of patients on ART (N = 3 308) by the total desired sample size of 559. As a result, the k number was six, and the fourth patient was chosen at random from the first six ART patients, and then every sixth patient was included in the study. The sample size was allocated proportionally to each hospital after obtaining lists of potential participants from the ART registers of each hospital.

Variables of the study

Dependent variable

The dependent variable is perceived HIV-related stigma.

Independent variables

The socio-demographic variables included (age, sex, religion, residence, marital status, education level, occupation, and monthly income). The psychosocial variables included living condition, social support, and lost job. Clinically related data were included such as WHO HIV/AIDS stage, current CD4 count, medication adherence, drug regimen, current drug side effect, duration of HAART treatment, and viral load.

Data collection, measurement, procedures, and quality control

A data collection tool (questionnaire) that included socio-demographic, psychosocial, and disease-related information was developed after reviewing relevant literatures. The questionnaire was originally developed in the English language and translated into Amharic and local language (Afaan Oromo) by language experts. The Amharic and Afaan Oromo version was translated back to English to verify the consistency by language experts. Both of the Amharic and the Afaan Oromo language questionnaires were used to collect data.

HIV-related perceived stigma occurs when PLWHA feel/perceive or believe that they are being negatively treated by others including partners, family, friends, healthcare providers, and members of their community because of their HIV status (6). Perceived stigma was assessed using the HIV-related stigma scale assessment tool which contains 10 stigma assessment questions with Likert scale. The agreement questions (strongly disagree–strongly agree) were assigned values 1–5 in order to determine the level of perceived stigma. Respondents who scored higher than the mean from the total were considered to have experienced perceived stigma, whereas those who scored lower than the mean were considered to have not experienced perceived stigma (33, 34).

Additionally, social support was assessed using the Social Support Questionnaire-6 (SSQ-6) which assessed the available social support (35). It had six assessment questions (help from no one, help from family, friends, organization, regions father/person, and unknown persons); those respondents who scored higher than the mean were considered to have good social support, while those who scored lower than the mean were considered to have poor social support. Thirdly, the structured Patient Health Questionnaires-9 (PHQ-9) was used to measure the depression status of HIV/AIDS patients (36). It had a potential total sum score of 27 from nine items; those respondents who scored 5 and above in the total sum were considered depressed, while those scoring below 5 were considered non-depressed. Fourthly, the adherence was assessed using the Morisky Medication adherence scale questions eight (MMAS-8) that had a total sum score of 8 from eight items (37, 38). Respondents who scored below six were considered non-adherent, while those who scored six and above were considered adherent.

Data were collected using interviewer-administered questionnaires and by extracting pertinent information from the patients' medical records. Four data collectors with bachelor of science (BSc) degrees prepared; nurses, midwifes, and public health were involved in data collection. A one-day intensive training was given on the objective of the study, how to fill the questionnaire, confidentiality of the information, and interviewing technique prior to their involvement for data collection. A pretesting of the questionnaire was done on 5% of the total sample size in a non-study area, and appropriate amendments were made before the actual data collection. The completed questionnaires were reviewed and checked for completeness, consistency, and relevance daily.

Data processing and analysis

The data were entered into Epi Data™ version 3.1 before being exported to Statistical Package for Social Science (SPSS ™) version 25 for cleaning, coding, and analysis. Descriptive statistics such as frequency, percentage, and mean were computed and presented by using text, tables, and graphs. Bivariable binary logistic regression was undertaken to see the association between dependent and independent variables. Those variables having a p-value of <0.25 in bivariable binary logistic regression were included in the multivariable logistic regression model. Both crude odds ratio (COR) and adjusted odds ratio along with 95% confidence interval (CI) were used to estimate the strength of the association between factors and outcome variable. In the multivariable logistic regression model, variables having a P-value of <0.05 were considered statistically significant. The Hosmer and Lemeshow

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TABLE 1 Socio-demographic and economic characteristics of people living with HIV/AIDS in public hospitals in Southeast Ethiopia, 2021 (n = 547).

Variables	Frequency	Percent
Sex		
Male	274	50.1
Female	273	49.9
Age category		
18–29	105	19.2
30–39	200	36.6
40–49	184	33.6
≥50	58	10.6
Residence		
Urban	402	73.5
Rural	145	26.5
Ethnicity		
Oromo	360	65.8
Amhara	164	30.0
Others*	23	4.2
Religion		
Protestant	91	16.6
Orthodox	240	43.9
Muslims	197	36.0
Catholic	16	2.9
Others**	3	0.5
Education status		
Unable to read and write	60	11.0
Able to read and write	104	19.0
Primary school	164	30.0
Secondary or preparatory	159	29.1
College and University	60	11.0
Marital status		
Single	67	12.2
Married	340	62.2
Widowed	73	13.3
Divorced	67	12.2
Occupation		
Farmer	126	23.0
Housewife	126	23.0
Government employee	114	20.8
Daily laborer	113	20.7
Others***	68	12.4
Income level		
≤500	94	17.2
501–1,500	133	24.3
1,501–2,500	119	21.8
2,501–3,500	80	14.6
≥3,501	121	22.1
Family size		
<5	448	81.9
5–7	79	14.4
≥8	20	3.7

*Dawuro, Woliyta.
**Jehovah's witness, Adventists, woqefeta.
***Merchants, non-governmental employee.

test was used to determine the final model's fitness, and the variance inflation factor was used to check for multi-collinearity among selected independent variables. We also used a mediation model in which body mass index served as the independent variable and perceived HIV-related stigma served as the dependent variable. In the model, depression was used as a mediating variable. Based on 5,000 bootstrap samples, the chain-mediating effect was estimated using the bootstrap 95% confidence interval (CI). All covariates were taken into account in the analysis.

Results

Socio-demographic and economic characteristics of study participants

A total of 547 study participants were included in the study, yielding an overall response rate of 97.8%. The respondents' mean age (+SD) was 38.1 (± 9.8) years. A total of 274 (50.1%) respondents were male, 340 (62.2%) were married, and 200 (36.6%) were between the ages of 29 and 39 years. Almost one-third, 164 (30.0%), of the respondents attended primary education, 240 (43.9%) were Orthodox religion followers, 126 (23.0%) were housewives, and 402 (73.5%) lived in urban areas (Table 1). This study also identifies a negative association between body mass index and perceived HIV-related stigma in PLWHIV.

Psychosocial and clinical-related characteristics of respondents

Of the 547 study participants, 437 (79.9%) lived with their families, 153 (28%) lost their jobs due to HIV/AIDS-related illness, and 375 (68.6%) received inadequate social support from their families or other supportive bodies. Most of the respondents, 434 (79.3%), were at WHO clinical stage I, whereas 12.4% were at WHO

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clinical stage II. About one-third [181(33.1%)] of the respondents had a CD4 count greater than 500 cells/μL. More than two-thirds of 442 (80.8%) respondents had good adherence to HAART. Of all the study participants, 151 (27.6%) had HAART-related side effects, 441 (80.6%) were on the first line of the drug, and 503 (92%) were on HAART for more than or equal to 2 months (Table 2).

Prevalence of perceived HIV-related stigma

The prevalence of perceived HIV-related stigma among people living AIDS was found to be 68% [95% CI: (64.1%, 71.9%)] (Figure 1).

Factors associated with HIV-related perceived stigma

The multivariable binary logistic regression analysis result showed that having a BMI <18.5 kg/m^2 [AOR = 5, 95% CI: (2.3, 11.0)], BMI 18.5–24.99 kg/m^2 [AOR = 3.6, 5, 95%: (1.88, 7.16), poor social support [AOR = 1.5, 95% CI: (1.05, 2.40)], and non-adherent to HAART [AOR=1.7, 95% CI: (1.03, 3.05)] were significantly associated with perceived HIV-related stigma (Table 3).

Correlation analysis of BMI, stigma, and depression

Table 4 shows Pearson partial correlations among key variables after controlling for all covariates. All key variables were significantly associated. BMI was negatively associated with stigma (r = -0.196, P < 0.001). Stigma was positively associated with depression (r = 0.518, P < 0.001).,

Mediating roles of depression

Table 5 shows the mediating roles of depression in the association between body mass index and perceived HIV-related stigma.

Discussion

Internationally, it has been acknowledged that stigma kills more people than the HIV virus itself (39). The study attempted to ascertain the prevalence of HIV-related perceived stigma and associated factors among HIV patients attending an anti-retroviral treatment follow-up clinic at public hospitals of Southeast Ethiopia. The finding showed that the prevalence of HIV-related perceived stigma was high (68%) among the participants. Variables like BMI <18.5 kg/m^2, BMI 18.5–24.99 kg/m^2, poor social support, and non-adherence to HAART were significantly associated with perceived HIV-related stigma.

This study revealed that the prevalence of perceived stigma was higher compared to studies conducted in the hospitals of Oromia

TABLE 2 Psychosocial and clinical characteristics of people living with HIV/AIDS in public hospitals in Southeast Ethiopia, 2021 (n = 547).

Variables	Frequency	Percent
Living condition		
Alone	89	16.3
Live with my families (like wife, mother, father, sister, brother)	437	79.9
Others*	21	3.8
Lost job due to HIV		
Yes	153	28.0
No	394	72.0
Opportunistic disease		
Do not have	469	85.7
Toxoplasma	17	3.1
Fungus	21	3.8
Tuberculosis	40	7.3
BMI category		
<18.5	112	20.5
18.5–24.99	390	71.3
25–29.99	45	8.2
Source of infection		
Blood contact	97	17.7
Unsafesexual intercourse	213	38.9
I do not know	237	43.3
Comorbidity		
No	482	88.1
Diabetes mellitus	26	4.8
Hypertension	39	7.1
Substance use		
Khat	87	15.9
Alcohol	135	24.7
Cigarettes	40	7.3
I do not use	285	52.1
Social support		
Poor social support	375	68.6
Good social support	172	31.4
Depression status		
Depressed	376	68.7
Non depressed	171	31.3
WHO clinical stage		
Stage I	434	79.3

(Continued)

TABLE 2 Continued

Variables	Frequency	Percent
WHO clinical stage		
Stage II	68	12.4
Stage III	45	8.2
CD4 count current		
<200	59	10.8
200–349	131	23.9
350–499	176	32.2
≥500	181	33.1
Adherence to medication		
Poor adherent	442	80.8
Good adherent	105	19.2
Drug side effect		
Yes	151	27.6
No	396	72.4
Drug regimen		
First line	441	80.6
Second line	106	19.4
Duration on HAART (in month)		
12	16	2.9
13-24	28	5.1
≥25	503	92.0

BMI, body mass index; HAART, highly active anti-retroviral therapy; CD4, cluster of differentiation four.
*Living with close friends.

and Dessie city health facilities in Ethiopia (28, 40) and Cameron (13); however, it was lower than studies conducted at Jimma in Ethiopia (6), Iran (12), and University of Washington (41). This discrepancy might be explained by time variation and differences in setting, particularly for research conducted outside of Ethiopia. It might also be attributed to various governmental and non-governmental efforts in the respective sites.

In the current study, PLWHIV with a BMI of less than 18.5kg/m^2 (underweight) were five times more likely to have perceived HIV-related stigma as compared to their counterparts. In the past, being underweight was used as a diagnostic criterion for HIV infection (42); hence, PLWHIV might be worrying about their body weight because as they become thinner or lose bodyweight they feel or fear discrimination.

In this study, social support was significantly associated with the level of perceived HIV-related stigma. Study participants with poor social support were 1.5 times more likely than their counter-parts to experience perceived stigma. However, there is evidence that social care and support should be provided in accordance with suitable social and ethical procedures rather than having PLWHIV being perceived as a distinct individual from the rest of the community sponsored by NGOs, which may result in significant stigma (6). Further investigation is needed to ameliorate this issue.

Despite this, the provision of ART was observed to increase the lifespan of people living with HIV/ADIS. Discrimination and a high burden of HIV/AIDS-related stigma, which is induced by socio-demographic, psychological, behavioral, and clinical variables, jeopardize this longer lifetime (43). This study also revealed that respondents who were non-adherent to HAART were 1.7 times more likely to have perceived HIV-related stigma. This could be due to stigma and discrimination, fear of being found, lack of social support, and poor health outcomes that may all play a role in emotional non-adjustment to HIV/AIDS, depression, and a loss of motivation in treatment; this would ultimately lead to poor treatment adherence among PLWHIV (44).

This study revealed a negative association between body mass index and perceived HIV-related stigma in PLWHIV (Figure 2). More importantly, the findings of this study suggest important roles for psychological status (depression) in the reduction of perceived HIV-related stigma in PLWHIV by body mass index. According to current studies, PLWHIV with a low body mass index (<18.5 kg/m^2) (42) experience more severe perceived HIV-related stigma because of higher depression.

This study suggests that body mass index affects perceived HIV-related stigma in PLWHIV with high depression (45), which adds numerical evidence to how body mass index affects perceived HIV-related stigma. PLWHIV who have a normal body mass index (18.5–24.9 kg/m^2) might not worry about their body weight, and they are

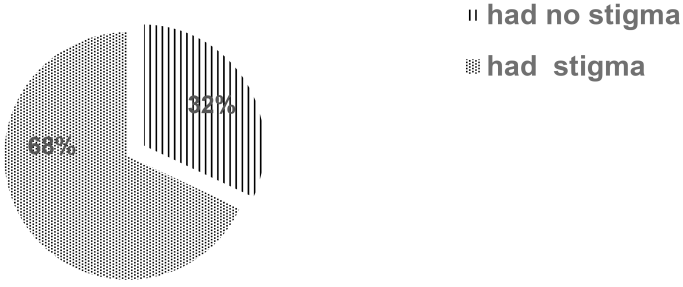

FIGURE 1
Prevalence of perceived HIV-related stigma among people living with HIV/AIDS at hospitals in Southeast Ethiopia.

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TABLE 3 Model for perceived HIV related-stigma and predictors among people living with HIV/AIDS in public hospitals of Bale Zone, Southeast Ethiopia, 2022 (n = 547).

Variables	Category	Stigma		COR (95% CI)	AOR (95% CI)
		No	Yes		
Sex	Male	81	193	1	1
	Female	94	179	0.79 (0.55, 1.15)	0.71 (0.46, 1.1)
Age	18–29	33	84	1	1
	30–39	58	130	0.88 (0.52,1.46)	0.93 (0.52, 1.65)
	40–49	61	109	0.70 (0.42,1.17)	0.66 (0.36, 1.20)
	≥50	23	49	0.44 (0.44, 1.58)	0.83 (0.39, 1.77)
Marital status	Single	21	46	1	1
	Married	10	236	1.03 (0.58, 1.82)	1.2 (0.62, 2.25)
	Widowed	30	43	0.65 (0.32, 1.31)	0.77 (0.33, 1.78)
	Divorced	20	47	1.07 (0.51, 2.23)	1.4 (0.60,3.25)
Substance use	Khat	30	57	0.89 (0.53, 1.4)	0.76 (0.42, 1.35)
	Alcohol	40	95	1.1 (0.71,1.73)	0.94 (0.57, 1.55)
	Cigarette	14	26	0.87 (0.43,1.74)	0.83 (0.37,1.84)
	Do not use	91	194	1	1
HIV stages	Stage I	125	309	1.8 (0.96,3.38)	1.78 (0.88, 3.58)
	Stage II	31	37	0.87 (0.40,1.86)	0.89 (0.39, 2.04)
	Stage III	19	26	1	1
CD4 counts	<200	18	41	1.24 (0.66, 2.34)	1.1 (0.54, 2.05)
	200–349	37	94	1.38 (0.85, 2.26)	1.4 (0.83, 2.43)
	350–499	56	120	1.17 (0.75, 1.8)	1.2 (0.75, 1.93)
	≥500	64	117	1	1
BMI (kg/m^2)	<18.5	27	85	5 (2.46, 10.89)*	5 (2.30, 11.0)*
	18.5–24.99	120	270	3.7 (1.95, 7.01)*	3.6 (1.88, 7.16)*
	>25	28	17	1	1
Level of depression	Depressed	130	246	1	1
	Non-depressed	45	16	1.4 (0.99, 2.21)	1.5 (0.96, 2.35)
Social support	Poor social support	109	266	1.5 (1.03, 2.22)*	1.5 (1.05, 2.40)*
	Good social support	66	106	1	**1**
HAART adherence	Adherent	147	295	1	**1**
	Non-adherent	28	77	1.3 (0.85, 2.2)	1.7 (1.03, 3.05)*

*p-value < 0.05.
BMI, body mass index; COR, crude odd ratio; AOR, adjusted odd ratio; HAART, highly active anti-retroviral therapy.

not feeling or fearing discrimination. These all contribute to a reduction in depression and thus a reduced risk of perceived HIV-related stigma. Thus, the study indicates that depression can be considered a potential psychological mechanism underlying the relationship between body mass index and perceived HIV-related stigma. Future researchers better explore other variables' roles in this association.

Limitation of the study

In a study area lacking previous data on the prevalence and risk factors associated with HIV/AIDS, the aim of this study was to investigate the role of BMI on perceived HIV-related stigma. The following limitations must be taken into consideration when interpreting the study's results, even though it employed primary

TABLE 4 Correlations matrix between stigma, body mass index, and depression.

	Mean (SD)	Stigma	BMICAT	Depression
Stigma	30.07 (9.4)	–		
BMI	20.98 (2.78)	-0.196***	–	
Depression	9.24 (7.13)	0.518***	-0.24***	–

All correlations were controlled for age, sex, education level, marital status, income, CD4 count, viral load, and time since HIV diagnosis.
BMI, body mass index.
***$P < 0.001$.

TABLE 5 The mediating roles of depression.

	Effect size	SE	Boot LLCI	Boot ULCI	$P > \|z\|$
Direct effect	-0.30	0.129	-0.554513	-0.045527	0.021
Indirect effect	-0.41	0.076	-0.557186	-0.261132	0.000
Total effect	-0.71	0.108	-0.827837	-0.403956	0.000

A model analysis was adjusted to age, sex, CD4 count, marital status, viral load, educational level, social support, and adherence to ART.
Indirect effect: body mass index → perceived HIV-related stigma
Indirect effect: body mass index → depression→perceived HIV-related stigma
Total effect: body mass index → perceived HIV-related stigma

data on the extent of perceived HIV-related stigma, depression, and social support with skilled data collectors and supervisors: First, a cause-and-effect relationship between the risk factors and perceived HIV-related stigma cannot be established due to the cross-sectional nature of the study. Second, self-reported surveys of social support, depression, and perceived stigma were used to evaluate the participants; however, these surveys may be liable to social desirability bias. Thirdly, because the study is centered in a hospital, the finding may not be generalizable to the total population.

Conclusion

This study showed that perceived HIV-related stigma was higher among people living with HIV/AIDS attending hospitals in Southeast Ethiopia due to low awareness of the impact of stigma. It is evident that PLWHIV can be stigmatized in a variety of ways, impacting treatment adherence and the mental health of patients living with HIV (46). As such, in order to address HIV management issues, in general, the impact of HIV-related stigma must be addressed with the same effort as vaccine trials and treatment development initiatives. The authors suggest that in all ART clinics, non-payment of services and free therapy should include education to increase awareness on the impact of stigma. The impact of HIV-related stigma including delayed testing, non-disclosure of HIV status, service access barriers, reduced treatment adherence, poor social support, and directly to the mental health among affected individuals and their families are detrimental to global efforts against HIV so far. In addition to addressing stigma in Ethiopia, the clinics should continue the promotion of HAART adherence to sustain people who are already affected by HIV. Our findings suggest that there is a relationship between body mass index and perceived HIV-related stigma, while depression can indirectly predict perceived HIV-related stigma. Importantly, the lessons learned from the findings

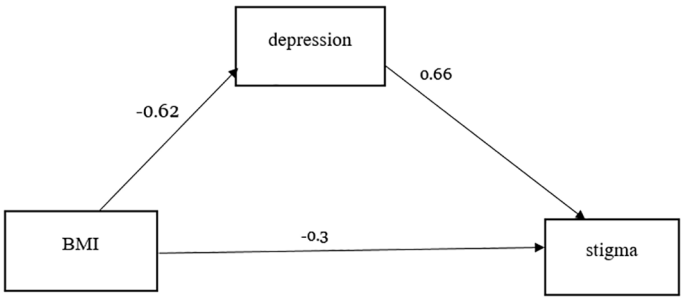

FIGURE 2
Specific path of the associations between body mass index and perceived HIV-related stigma (mediating effect).

of the current study need to be considered in the design and implementation of HIV initiatives, including policy making and programming in Ethiopia and related settings.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Madda Walabu University Ethics review committee. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided written informed consent to participate in this study.

Author contributions

FD: Conceptualization, Formal Analysis, Investigation, Methodology, Resources, Software, Supervision, Visualization, Writing – original draft, Writing – review & editing. DZ: Conceptualization, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. BS: Conceptualization, Formal Analysis, Investigation, Software, Validation, Writing – original draft, Writing – review & editing. SM: Formal Analysis, Methodology, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing. TD: Conceptualization, Data curation, Investigation, Software, Writing – original draft, Writing – review & editing. DG: Formal Analysis, Validation, Writing – original draft, Writing – review & editing. CK: Conceptualization, Investigation, Software, Writing – original draft, Writing – review & editing. GB: Conceptualization, Data curation, Investigation, Methodology, Software, Supervision, Writing – original draft, Writing – review & editing. TM: Conceptualization, Data curation, Investigation, Methodology, Supervision, Writing – original draft, Writing – review & editing. PP: Conceptualization, Data curation, Formal Analysis, Investigation, Methodology, Software, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. LM: Conceptualization, Data curation, Formal Analysis, Methodology, Resources, Software, Supervision, Validation, Writing – original draft, Writing – review & editing.

Funding

The author(s) declare that financial support was received for the research and/or publication of this article. Madda Walabu University funded this research after the proposal was passed through strong peer review process by a research committee organized in the University.

Acknowledgments

We would like to acknowledge, firstly, Madda Walabu University for the financial support. Secondly, we extend our gratitude to Donald E. Morisky, Sc.D., M.S.P.H., Sc. M. President, and Morisky Medication Adherence Research, LLC, dba adherence for providing us the permission. The MMAS-8 Scale (U.S. Copyright Registration No.TX0008632533), content, name, and trademarks are protected by US copyright and trademark laws. Permission for use of the scale and its coding is required. A license agreement is available from MMAR, LLC., www.moriskyscale.com.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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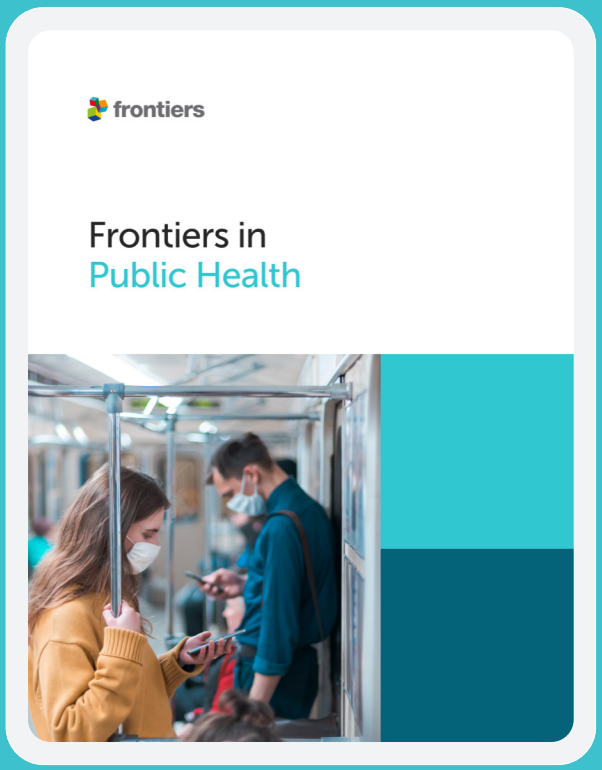

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