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ORIGINAL ARTICLE

Prevalence of low-level viremia and its association with virological failure among adolescents living with HIV in Eastern Cape, South Africa

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Abstract

Objectives: Low-level viremia (LLV) has been associated with an increased risk of virological failure among adults on antiretroviral therapy (ART). However, evidence on the clinical implications of LLV among adolescents living with HIV remains limited. This study aimed to assess the prevalence and predictors of LLV and to determine the association between LLV and subsequent virological failure.

Methods: We analysed data from an integrated prospective cohort of adolescents living with HIV linked to the National Institute for Communicable Diseases (NICD) data warehouse in South Africa. Using routine viral load data from 2015 to 2021, we estimated the prevalence of LLV at the first test. We then used mixed-effects logistic regression to identify socio-demographic factors associated with LLV. Among adolescents with at least three viral load measurements, we assessed the association between LLV and subsequent virological failure using a Cox proportional hazards model in RStudio.

Results: Among 730 adolescents, the prevalence of LLV ranged between 10.4% and 20.1%. Older adolescents aged 15–19 years (aOR: 1.92; 95% CI: 1.44–2.55) and those ≥20 years (aOR: 1.69; 95% CI: 1.12–2.57) had significantly higher odds of LLV compared to those 10–14 years. Among 617 adolescents, 13.3% had LLV, of which 17.1% subsequently progressed to virological failure. Those experiencing LLV were associated with a four-fold (aHR 4.91; 95% CI:

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2.46–9.79) increased hazard of virological failure compared to suppressed adolescents.

Conclusions: The prevalence of LLV among adolescents living with HIV on ART is high and LLV strongly predicts virological failure. Enhanced adherence support for adolescents with LLV is needed to minimize the risk of long-term virological failure.

KEYWORDS

adherence, adolescent, antiretroviral therapy, HIV, low-level viremia, virological failure

INTRODUCTION

Persistent challenges with adherence to antiretroviral therapy (ART) among adolescents living with HIV (ALHIV) on ART have been shown to be prevalent [1], leading to higher levels of non-suppressed viremia and virological failure among them, compared to adults [2, 3]. While recent studies have shown increases in levels of viral load suppression among ALHIV in recent years [4, 5], partly due to the transition to dolutegravir [5], ALHIV still remain less likely to achieve viral load suppression compared to their adult counterparts and continue to fall short of achieving the UNAIDS third 95 target [2]. This disparity highlights an urgent need for tailored strategies to improve treatment adherence and reduce the risk of virological failure among adolescents on ART.

Low-level viremia (LLV), defined by the World Health Organization as a viral load between 51 and 999 copies/mL [6], has been shown to be associated with sub-optimal adherence among adults [7, 8]. LLV has also been shown to be an important predictor of progression to viral non-suppression, virological failure and the development of drug resistance mutations [9–14]. Among adults on ART, the prevalence of LLV has been shown to be high; for example, a study in Nigeria between 2016 and 2021 found that LLV ranged between 12% and 24% [9]. Despite high levels of ART adherence challenges among ALHIV in sub-Saharan Africa, little is known about the prevalence of LLV among them. Moreover, there is also limited data on the predictors and long-term ART consequences of LLV among ALHIV.

Few studies have explored LLV among children and adolescents on ART in sub-Saharan Africa. Children and adolescents (0–19 years) on ART in Zimbabwe were more likely to experience LLV compared to adults (>19 years) [15]. In Cameroon, adolescents (10–19 years) with LLV and those with virological failure had similar levels of HIV drug resistance mutations [16].

While data on the prevalence of LLV in sub-Saharan Africa remains limited, studies from other regions provide some insight. In a multicentre cohort study in Asia, up to 17% of children (<18 years) living with HIV experienced LLV, with 37% of them having multiple episodes [17]. The study also identified female sex, not having a biological parent as a caregiver and having had a low baseline CD4 count as predictors of LLV [17]. In another study in the United States, adolescents with perinatally acquired HIV on ART with LLV and fewer clinic visits were more likely to have virologic failure [18].

While studies outside sub-Saharan Africa provide important insights about LLV among ALHIV, their findings may not be generalizable to sub-Saharan African settings with high HIV prevalence. Using data from an integrated prospective cohort of ALHIV in the Eastern Cape province in South Africa, linking self-reported data to routine laboratory data from the country's National Health Laboratory Service, we aimed to assess the prevalence and predictors of LLV among ALHIV, then further explored the impact of LLV on progression to virological failure.

METHODS

Data sources

We conducted a longitudinal observational cohort study of adolescents living with HIV (ALHIV)—all initiated on ART before 2014—recruited from 52 clinics in the Eastern Cape province of South Africa. The cohort included 1107 ALHIV, aged 10–19 years at baseline (2014), who were followed up for three rounds of interviews between 2014 and 2018 [19]. Data included interviews with ALHIV merged with clinical tests available in the national data warehouse. Study interviews assessed participants' sociodemographic information, self-reported past-week ART adherence using validated tools and

social and family experiences using scales and measures with strong psychometric and contextual validity [20, 21].

We matched participants' sociodemographic information to their laboratory records from the South African National Institute for Communicable Diseases (NICD) data warehouse, a division of the National Health Laboratory Service (NHLS), which manages and archives laboratory results for over 80% of the South African population. The NHLS conducts record linkage at the national level, tracking laboratory tests for individuals across all healthcare facilities, not just within the study region. This allowed us to identify participant records even when individuals had transferred care outside the study area. Study participants were considered matched to an NICD data warehouse record if their personal identifying details (name, surname and date of birth) were an exact match, and an additional matching criterion was developed to account for minor variations likely due to human error [22]. The inability to match some participants to the NICD data warehouse records may be attributed to variations in name entry, record-keeping inconsistencies and the absence of a unique national identifier, all of which routinely constrain record linkage in the local data ecosystem [23]. Laboratory test results, including viral load tests for matched study participants, were then extracted and linked to their self-reported data. The cohort data linkage process and participant profile are described in more detail elsewhere [22]. Data from the NICD data warehouse do not include information on participant ART or TB treatment regimens, regimen switches, records of adherence counselling or support or drug resistance mutations. For LLV analyses, inclusion was restricted to participants who were successfully matched to laboratory test records obtained from the NICD data warehouse and had at least one viral load test recorded from 2015 to 2021 ($N = 730$). Virological failure analyses were further restricted to participants with at least three documented viral load tests ($n = 617$) (Figure 1).

Study measures

In this analysis, our virologic outcomes and explanatory variables are defined according to standard thresholds of plasma HIV-1 RNA quantification. Viral suppression was defined as ≤50 copies/mL. LLV was defined as a viral load measurement from 51 to 999 copies/mL. Viral non-suppression was defined as a viral load ≥1000 copies/mL. Virological failure was defined as two consecutive episodes of viral load ≥1000 copies/mL. These outcomes were used as the primary explanatory variables explored in this study.

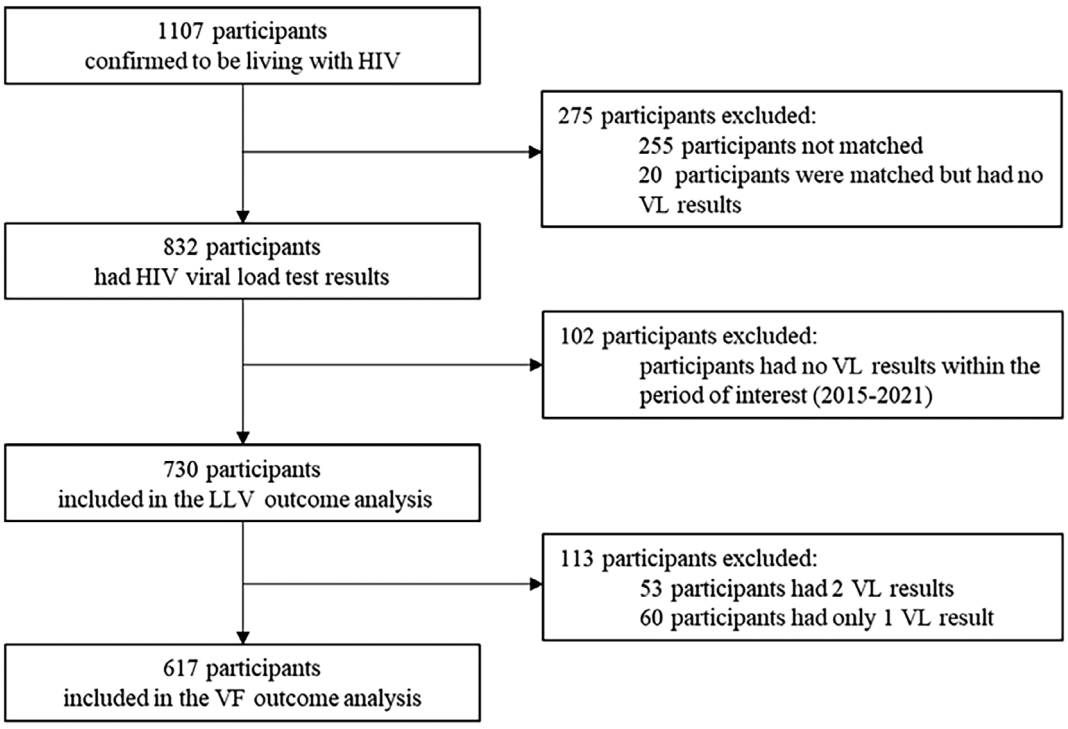

FIGURE 1 Flow chart of included study participants. Participants matched without any viral load results had biomedical tests non-specific to HIV, including anatomical pathology, chemical pathology, haematology and microbiology. There were no significant sociodemographic differences between the matched and unmatched participants. LLV, low-level viremia; VF, virological failure; VL, viral load.

Other explanatory variables which were assessed in this analysis include age, sex and mode of HIV acquisition. Age at each test was categorized as younger adolescents (10–14 years), older adolescents (15–19 years) and adulthood (≥20 years). Mode of HIV acquisition (vertical vs. horizonal) was determined using ART initiation age ≤10 years as a proxy for vertical transmission [24, 25]. Where clinical documentation was unavailable, an extended algorithm was applied to refine the classification, incorporating additional indicators such as reported sexual activity and parental mortality and validated using supporting evidence such as history of parental death, maternal HIV status and self-reported sexual history [26]. Other factors including residing location (defined as rural vs. urban area), orphanhood (both maternally and paternally orphaned), food insecurity (at least 1 day in the past week without enough food for three meals in the home) and household poverty were also measured. Household poverty was defined as the lack of seven basic essentials described in a South African survey: clothing, shoes, toiletries, a doctor, school fees, uniforms and school supplies [27]. ART duration was defined as the difference between the viral load test date and ART initiation date measured in months and categorized as <12 months, 12–24 months, 24–60 months and >60 months. Mental health symptomology was defined as a CDI (Children's Depression Inventory) score >6, self-reported suicidal ideation or attempt and elevated symptoms across three Child PTSD Checklist subscales (negative cognitions, hyper-arousal and avoidance; scores >0) [28, 29]. HIV-related stigma included experienced and perceived stigma. Social support was measured using the Medical Outcomes Study Social Support Survey (MOS-SSS), assessing emotional/informational, tangible, affectionate and positive social interaction support [30]. Timing relative to the DTG rollout was derived from viral load test dates and defined as ≤2019 (before rollout) or >2019 (after rollout). South Africa transitioned to dolutegravir (DTG)-based first-line ART in late 2019, replacing non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimens due to DTG's higher genetic barrier to resistance, improved tolerability and superior virological efficacy [31, 32]. Finally, two testing interval variables were created: Test interval 1–2 (time between the first and second viral load tests), and Test interval 2–3 (time between the second and third tests). Guideline-concordant monitoring was defined as both intervals meeting recommended timing. Concordance was determined according to national ART guidelines applicable at the time of testing, allowing a 1-month grace period beyond recommended testing intervals to account for routine scheduling variability [33, 34]. Relevant guideline thresholds and monitoring intervals are summarized in Table S1. Participants were classified as non-concordant if either interval fell outside recommended timeframes.

Statistical analysis

First, we estimated the prevalence of LLV among those with viral load test results in a given calendar year (by calculating the proportion of ALHIV with LLV at their first viral load test in a year among all those who had a test within that specific year). We also calculated binomial confidence intervals for the prevalence proportions. The rationale for the selected time period (2015–2021) was to analyse only the most recent linked test results and retain as much of the sample as possible. Results from 2022/2023 were excluded due to the disproportionately small subgroup sizes within those years when compared to those from 2015 to 2021, which would compromise the reliability and comparability of the year-specific prevalence analysis [22].

Second, to assess the factors associated with low-level viremia, we used a mixed-effects logistic regression model including an individual-level random intercept to account for repeated measures over time. The study outcome was LLV at any given time point, and explanatory variables assessed were sociodemographic and clinical characteristics identified from our conceptual framework (Figure S1). We reported crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CIs).

Third, we examined the longitudinal transitions of virological categories among adolescents who presented with LLV at the first test between 2015 and 2021 ($n = 82$). All participants with LLV at the first test were evaluated for their subsequent virological outcomes at the second test. Only those who had not achieved suppression at the second test were followed up to the third test.

Fourth, to assess if ALHIV with LLV are more likely to progress to virological failure, we restricted the analysis to ALHIV with at least three viral load test results between 2015 and 2021. We used the Cox proportional hazards model with time defined as the duration between the date of the first and third viral load result. Participants who did not experience viral failure were censored at their third viral load result date. Kaplan-Meier survival curves were used to estimate the probability of progressing to virological failure over time, and differences between viremia categories were assessed using the log-rank test. Cox proportional hazards regression was employed to evaluate the association between LLV and virological failure, adjusted for variables identified as potential confounders from our conceptual framework. We report hazard ratios (HR) with 95% confidence intervals (CI).

Lastly, we calculated the proportion of individuals receiving guideline-concordant viral load monitoring within each viral load category across sequential testing intervals. Differences in monitoring frequency across categories were assessed using Pearson's chi-square tests.

Statistical significance was set at a level of 5%. Analyses were conducted in R (version 4.3.1) and STATA/SE 15.1.

Ethics statement

Ethics approval for this study was granted by the ethical review boards from the University of Cape Town (UCT/CSSR/2013/4) and (UCT/CSSR/2019/01), Oxford University (Oxford/CUREC2/12-21), provincial Departments of Health and Education, Imperial College Research Governance and Integrity Team (ICREC Ref: 20IC6451) and the ethical review boards of participating healthcare facilities. Data release authorization was approved by the NHLS Academic Affairs and Research Management System (2019/08/07) and written informed consent to access and extract clinic records was obtained from study participants, and parents (or caregivers) if those eligible were below the age of 18 years.

RESULTS

A total of 832 out of 1107 (75%) ALHIV from the 'Mzantsi Wakho' cohort were successfully linked to data received from the NICD data warehouse, of which 730 (87.7%) had at least one viral load test result between 2015 and 2021 (Figure 1). The median age of included participants at their first viral load result between 2015 and 2021 (baseline) was 15 years (interquartile range (IQR): 12–17), and the majority were female (52.9%). Other baseline characteristics of participants are presented in Table 1.

There were no significant differences in age, sex, mode of HIV acquisition, residing location, orphanhood, ART duration, food insecurity, household poverty, mental health symptomology, social support, HIV-related stigma or viral load testing period, between ALHIV who were matched to NICD data warehouse records and those who were not [22]. Using the proportion of ALHIV with LLV at their first viral load test in a year among all those who had a test in that year, the prevalence of LLV ranged between 10.4% (95% CI: 7.8–13.1) and 20.1% (95% CI: 10.3–17.3). The point prevalence of LLV increased between 2015 and 2019, where it peaked and declined thereafter (Figure 2).

TABLE 1 Sample characteristics at first viral load test between 2015 and 2021 among adolescents living with HIV in a South African cohort.

Characteristics	Analytic sample ($n = 730$)
Viremia category, *n* (%)	
Suppressed	435 (59.6%)
LLV	94 (12.9%)
Non-suppressed	201 (27.5%)
Age in years, median (IQR)	15 (12–17)
Age category in years, *n* (%)	
10–14	357 (48.9%)
15–19	299 (41.0%)
≥20	74 (10.1%)
Sex, *n* (%)	
Females	386 (52.9%)
Males	344 (47.1%)
Mode of HIV acquisition, *n* (%)	
Vertical	597 (81.8%)
Horizonal	123 (16.8%)
Missing	10 (1.4%)
Residing location, *n* (%)	
Rural	183 (25.1%)
Urban	537 (73.6%)
Missing	10 (1.4%)
Orphanhood, *n* (%)	
Orphaned	106 (14.5%)
Not orphaned	614 (84.1%)
Missing	10 (1.4%)
ART duration in months, *n* (%)	
<12	46 (6.3%)
12–24	43 (5.9%)
24–60	169 (23.2%)
60+	472 (64.7%)
Food insecurity, *n* (%)	
No food insecurity	604 (82.7%)
Food insecurity	116 (15.9%)
Missing	10 (1.4%)
Household poverty, *n* (%)	
No household poverty	469 (64.2%)
Household poverty	251 (34.4%)
Missing	10 (1.4%)
Mental health symptomology, *n* (%)	
No mental health symptomology	595 (81.5%)

(Continues)

TABLE 1 (Continued)

Characteristics	Analytic sample ($n = 730$)
Mental health symptomology	125 (17.1%)
Missing	10 (1.4%)
Social support, *n* (%)	
High social support	516 (70.7%)
Low social support	204 (27.9%)
Missing	10 (1.4%)
Stigma, *n* (%)	
No HIV-related stigma	466 (63.8%)
HIV-related stigma	264 (36.2%)
Viral load testing period, *n* (%)	
Tested before DTG rollout (≤2019)	716 (98.1%)
Tested after DTG rollout (>2019)	14 (1.9%)

Abbreviation: LLV, low-level viremia.

ALHIV aged 15–19 years had nearly double the odds of LLV compared to those under 15 years (aOR: 1.92; 95% CI: 1.44–2.55), and those aged 20 years and older also showed increased odds (aOR: 1.69; 95% CI: 1.12–2.57). Those tested before DTG rollout were also more likely to experience LLV (aOR: 1.35; 95% CI: 1.02–1.77) compared to those tested after DTG rollout. While ART duration, sex, residing location, orphanhood, food security, household poverty, mental health symptomology, social support, stigma and non-concordant monitoring were not significant predictors of LLV (Table 2).

Viral load status was assessed among 617 adolescents with at least three consecutive viral load test results from 2015 to 2021. At the first test, 13.3% exhibited low-level viremia, 60.9% were virologically suppressed and 25.8% were virologically non-suppressed. Longitudinal analysis of the subgroup with LLV at first test ($n = 82$) revealed considerable variability in subsequent viral load categories. Specifically, at second test, 26.8% of these adolescents maintained LLV, and 23.2% were virologically non-suppressed, whereas only 50.0% achieved virological suppression. Among those with LLV at the first test, 13.4% experienced persistent LLV, having experienced LLV at both the first and second tests, and then continued to exhibit LLV at the third test, while 9.8% reverted to virological suppression and 3.7% remained non-suppressed. Importantly, 17.1% of those who had experienced LLV at first test went on to subsequently progress to virological failure by third test (Figure S2).

Cox proportional hazards regression revealed that initial virological status emerged as the most significant predictor of virological failure. Adolescents with LLV (aHR 4.91; 95% CI: 2.46–9.79) were associated with an increased hazard of virological failure compared to those with suppressed viral loads (Figure 3). Those with virological non-suppression had the highest hazard both when unadjusted (HR: 13.66; 95% CI: 8.42–22.17) and adjusted (aHR: 15.60; 95% CI: 9.11–26.74). Adolescents aged 15–19 years had a significantly higher hazard of virological failure compared to those younger than 15 years (HR: 1.92; 95% CI: 1.30–2.85), and those ≥20 were also associated with a higher hazard of virological failure (HR: 1.83; 0.98–3.41) though significance weakened when adjusted. Those tested before DTG rollout had a six-fold higher hazard of virological failure compared to those tested after (aHR: 6.76; 95% CI: 2.74–16.68) (Table 3).

Guideline-concordant viral load monitoring was substantially lower among virologically non-suppressed individuals compared with suppressed individuals, both between the first and second viral load tests (25.8% vs. 65.4%) and between the second and third tests (23.4% vs. 64.4%; $p < 0.001$ for both comparisons). In contrast, individuals with LLV had monitoring frequencies comparable to those who were virologically suppressed (63.4% vs. 65.4% between the first and second tests, and 67.6% vs. 64.4% between the second and third tests; $p < 0.001$).

DISCUSSION

This study provides important insights into the prevalence, predictors and consequences of LLV among ALHIV on ART in South Africa. The findings indicate that LLV is common, more likely among older adolescents, and significantly associated with progression to virological failure. This underscores the clinical importance of addressing LLV as a key risk factor and indicator for poor treatment outcomes in this vulnerable population.

The prevalence of LLV at the first viral load test ranged between 10.4% and 20.1% across the study years, indicating a substantial proportion of adolescents experiencing LLV during their ART treatment. The increase in LLV from 2015 to 2019 may reflect adolescents transitioning from paediatric to adult care since our sample has a median age of 15 at baseline. This explanation is further strengthened by analyses of this cohort, which found that the median age at first transition out of paediatric care was 14 years (IQR: 11–15) [35]. Early transition is often influenced by service delivery constraints in public healthcare settings and the introduction of simplified treatment regimens designed to support long-term adherence [36]. A similar trend in overall prevalence is observed with studies in adults showing that

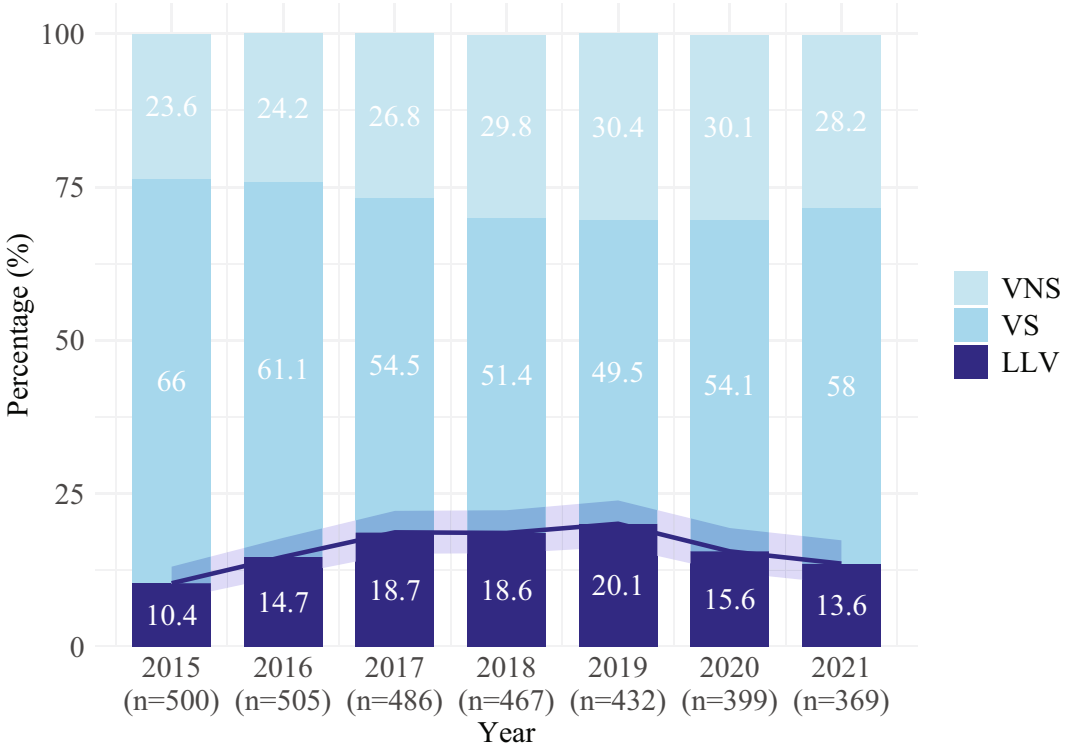

FIGURE 2 Annual distribution of viremia categories and prevalence of low-level viremia. Stacked bars depict the percentage distribution of viremia categories by year. The solid line represents low-level viremia (LLV) prevalence with shaded areas indicating 95% confidence intervals. Prevalence was calculated using the first viral load test result for each participant within a given year. VNS, virological non-suppression; VS, virological suppression.

LLV is a frequent occurrence among individuals on ART, particularly in populations with suboptimal adherence [37, 38]. However, the prevalence recorded in this study may be particularly concerning given the well-documented challenges with ART adherence in adolescents, who face unique barriers such as psychosocial stressors and developmental transitions [39, 40]. Moreover, our study documents consistently high rates of both LLV and viral non-suppression (>1000 copies) for the cohort participants over time, with only half (53.4%) of the virological failure sub-sample being virologically suppressed at the last viral load.

Older adolescents (15–19 and ≥20 years) were more likely to experience LLV compared to their younger counterparts, suggesting that adherence challenges may escalate with age as adolescents transition to increased autonomy in managing their care [41]. Frequently missed or delayed doses result in intermittent adherence and lead to subtherapeutic antiretroviral drug levels, allowing viral replication to continue at low but detectable levels, manifesting as LLV. Testing before DTG rollout was also associated with LLV. This likely reflects prior reliance on NNRTI-based regimens, which have a lower genetic barrier to resistance and are more susceptible to resistance selection under suboptimal adherence [42, 43]. In contrast, DTG-based regimens demonstrate a greater genetic barrier and virological efficacy [44–46]. Prolonged NNRTI exposure combined with intermittent adherence can facilitate resistance mutations, which may reduce regimen effectiveness and contribute to LLV [43, 47]. However, this analysis cannot test this hypothesis due to lack of ART regimen data.

Among adolescents with LLV at the first test, only 50.0% achieved virological suppression at the second test. This finding underscores that nearly half of the adolescents with initial LLV either persisted with LLV or experienced virological rebound, thereby failing to reach optimal virological outcomes. By the third test, 34.1% of adolescents were either experiencing LLV, virological non-suppression, or failure, indicating that poor virological outcomes are not transient but persist across follow-up tests.

Adolescents with LLV had a four-fold higher hazard of progressing to virological failure compared to those who were virologically suppressed when adjusted for all variables. This aligns with adult studies, reinforcing that LLV serves as a critical early warning signal for virological failure [48, 49]. Evidence from the SESOTHO trial suggests that early regimen optimization can improve suppression in adults with persistent LLV, although

TABLE 2 Sociodemographic and clinical factors associated with low-level viremia.

Low-level viremia sub-sample analyses ($n = 730$)				
Factors	**OR (95% CI)**	***p*-value**	**aOR (95% CI)**	***p*-value**
Age, years (time updated)				
10–14	1 (ref)	1 (ref)	1 (ref)	1 (ref)
15–19	1.73 (1.33–2.26)	<0.001	1.92 (1.44–2.55)	<0.001
≥20	1.25 (0.89–1.77)	0.195	1.69 (1.12–2.57)	0.013
ART duration in months				
<12	1 (ref)	1 (ref)	1 (ref)	1 (ref)
12–24	1.24 (0.48–3.15)	0.658	1.23 (0.48–3.32)	0.643
24–60	0.94 (0.45–1.96)	0.868	0.87 (0.40–1.89)	0.724
>60	0.97 (0.48–1.97)	0.943	0.86 (0.40–1.84)	0.696
Baseline factors				
Male	1.09 (0.86–1.37)	0.491	1.04 (0.82–1.33)	0.736
Vertical HIV acquisition	1.21 (0.86–1.69)	0.280	1.39 (0.94–2.07)	0.103
Rural residence	0.99 (0.75–1.30)	0.924	1.00 (0.74–1.30)	0.883
Orphanhood	0.97 (0.69–1.36)	0.856	0.90 (0.63–1.27)	0.535
Food insecure	1.23 (0.89–1.70)	0.220	1.21 (0.86–1.71)	0.282
Household poverty	1.09 (0.85–1.40)	0.483	1.11 (0.86–1.45)	0.424
Mental health symptomology	0.94 (0.68–1.31)	0.740	0.89 (0.63–1.27)	0.521
Low social support	1.03 (0.80–1.35)	0.789	1.07 (0.81–1.41)	0.633
HIV-related stigma	1.08 (0.84–1.40)	0.548	1.09 (0.84–1.42)	0.521
Tested before DTG rollout	1.15 (0.91–1.46)	0.246	1.35 (1.02–1.77)	0.033
Non-concordant monitoring	1.15 (0.90–1.47)	0.273	1.12 (0.86–1.45)	0.388

Note: Crude and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) of factors associated with low-level viremia.

comparable data in adolescents remain limited. This result was further corroborated by a recent study among children and ALHIV in Tanzania [50]. The strong predictive value of LLV for virological failure highlights the urgent need for targeted interventions to support adherence and optimize ART outcomes among adolescents. The clinical significance of this relationship is multifaceted: First, it underscores that current virological failure thresholds in guidelines (World Health Organization's ≥1000 copies/mL at 2 consecutive tests) may be insufficiently sensitive for early intervention, especially in resource-limited settings where LLV monitoring is not prioritized [51, 52]. Second, LLV likely serves as a reservoir for viral evolution and resistance, as persistent low-level replication enables the accumulation of drug resistance mutations, undermining future regimen efficacy [38, 53].

Despite updated recommendations for enhanced monitoring for individuals with viral loads of 50–999 copies/mL, our findings indicate that testing frequencies among adolescents with LLV remain suboptimal, ranging from 63.4% to 67.6% across consecutive viral load tests, consistent with other South African data [54]. Current practice often prioritizes intensified adherence support for individuals with virological non-suppression, potentially overlooking those with LLV. However, the heightened virological failure risk linked to LLV necessitates a paradigm shift in clinical practice. Towards enhanced viral load monitoring frequency, adherence support for at-risk populations and earlier regimen optimization. Addressing LLV is essential not only for individual outcomes but also for achieving global targets like UNAIDS 95–95–95, as uncontrolled viremia propagates both transmission and drug resistance [53].

Enhanced adherence counselling tailored to the developmental needs of adolescents is crucial. Peer support groups, mobile health interventions and community-based adherence programmes have shown promise in improving ART adherence in this population and should be expanded [55, 56]. Early identification of LLV through routine viral load monitoring may enable timely intervention before progression to virological failure. The limited data on LLV among adolescents necessitate further research to elucidate its underlying drivers and potential interventions.

TABLE 3 Sociodemographic and clinical factors associated with virological failure.

Virological failure sub-sample analyses ($n = 617$)				
Factors	**HR (95% CI)**	***p*-value**	**aHR (95% CI)**	***p*-value**
Virological status (time updated)				
VS	1 (ref)	1 (ref)	1 (ref)	1 (ref)
LLV	4.34 (2.20–8.54)	<0,001	4.91 (2.46–9.79)	<0.001
VNS	13.66 (8.42–22.17)	<0.001	15.60 (9.11–26.74)	<0.001
Age, years				
10–14	1 (ref)	1 (ref)	1 (ref)	1 (ref)
15–19	1.92 (1.30–2.85)	0.001	1.32 (0.85–2.06)	0.217
≥20	1.83 (0.98–3.41)	0.057	0.86 (0.35–2.07)	0.732
ART duration in months				
<12	1 (ref)	1 (ref)	1 (ref)	1 (ref)
12–24	1.27 (0.51–3.17)	0.606	0.35 (0.12–1.07)	0.066
24–60	1.29 (0.59–2.79)	0.527	0.69 (0.27–1.73)	0.425
>60	0.86 (0.41–1.80)	0.695	0.56 (0.23–1.39)	0.212
Baseline factors				
Male	1.10 (0.76–1.58)	0.613	1.14 (0.76–1.70)	0.526
Vertical HIV acquisition	0.74 (0.47–1.15)	0.181	0.95 (0.50–1.82)	0.882
Rural residence	1.18 (0.78–1.77)	0.432	0.98 (0.64–1.51)	0.938
Orphanhood	1.55 (0.95–2.52)	0.077	1.14 (0.67–1.93)	0.640
Food insecure	1.24 (0.78–1.98)	0.366	1.24 (0.71–2.17)	0.446
Household poverty	1.17 (0.79–1.75)	0.433	1.10 (0.71–1.71)	0.667
Mental health symptomology	1.20 (0.75–1.93)	0.447	1.51 (0.85–2.67)	0.157
Low social support	0.72 (0.47–1.10)	0.125	0.73 (0.45–1.18)	0.196
HIV-related stigma	1.06 (0.71–1.57)	0.793	0.76 (0.48–1.18)	0.214
Tested before DTG rollout	5.05 (2.13–11.99)	<0.001	6.76 (2.74–16.68)	<0.001
Non-concordant monitoring	3.52 (1.82–6.81)	<0.001	1.26 (0.61–2.61)	0.537

Note: Crude and adjusted hazard ratios of factors associated with virological failure assessed using a cox proportional hazards model.

Qualitative studies exploring adherence behaviours and access to care could provide valuable insights into the unique challenges faced by ALHIV [57]. Moreover, cost-effectiveness analyses of interventions targeting LLV could inform resource allocation within ART programmes. This study's findings support the inclusion of adolescents with LLV in enhanced monitoring and intervention frameworks to prevent virological failure and subsequent health complications.

The limitations of this study must be acknowledged. First, we could not link the laboratory data of 25% of the eligible sample ($N = 1107$) and did not have viral load results for 12% of those linked; therefore, findings may not be generalizable to all ALHIV on ART. Second, reliance on routine viral load data may introduce variability in testing intervals and result accuracy. Thirdly, since the virological failure sub-sample was restricted to only three of the most recent viral load tests, the sample may not fully capture the longitudinal patterns of viral suppression or failure and may overrepresent those with stable care engagement, introducing selection bias. Inconsistent testing frequency may also introduce surveillance bias. Survival bias may be present, since participants could only reach virological failure after three consecutive measurements. Fourth, unmeasured confounders may have influenced the observed associations, including the absence of ART regimen data, co-morbidities and regimen changes over time and enhanced adherence counselling. Lastly, most adolescents (81.8%) were vertically infected and at increased risk of accumulated drug resistance due to prolonged ART exposure. However, resistance data were unavailable to differentiate adherence-related LLV from virological resistance. Further research is needed to map the contributions of different clinical

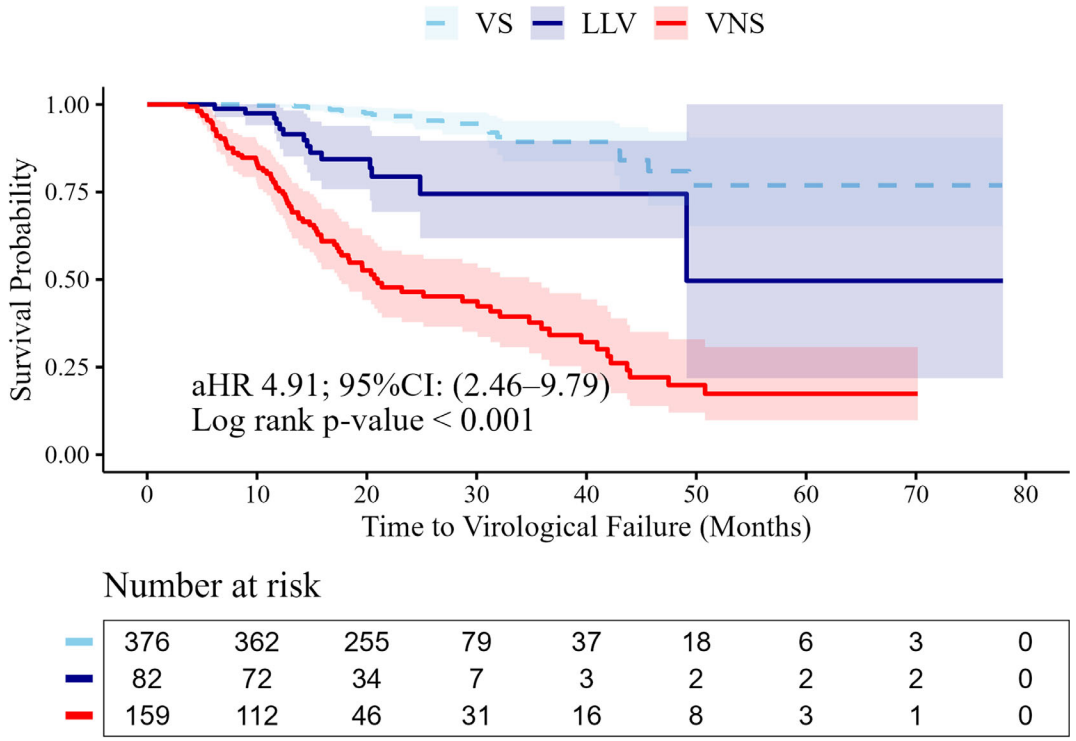

FIGURE 3 Kaplan-Meier plot illustrates the time to virological failure stratified by viremia category and measured between the first and third viral load tests. The Kaplan-Meier survival analysis demonstrates significant differences ($p < 0.0001$) in the time to virological failure across the three viremia categories: LLV, low-level viremia; and VNS, virologically non-suppressed; VS, virologically suppressed. Among adolescents with at least three viral load tests, the median time to virological failure was 14 months (IQR: 10–24 months). The graph indicates that patients with low-level viremia have a slower progression to virological failure compared to those virologically non-suppressed but faster than those with suppressed viral loads.

causes to LLV. The study's strengths include the use of a large longitudinal dataset and robust statistical methods to evaluate the relationship between LLV and virological outcomes.

CONCLUSIONS

This study provides evidence that LLV among adolescents is common and strongly predicts virological failure. Early identification of LLV may enable timely adherence support or regimen modification before failure [51]. Early identification of adolescents with LLV may allow for timely adherence support, resistance testing, or regimen modification before treatment failure occurs. The higher prevalence among older adolescents likely reflects age-related adherence challenges [58, 59]. Strengthening surveillance of LLV and integrating adolescent-specific adherence and psychosocial interventions may improve sustained suppression. Future research should define adolescent-specific LLV thresholds and evaluate targeted prevention strategies.

AUTHOR CONTRIBUTIONS

ZL conceptualized the study, performed and led the statistical analysis and drafted the initial manuscript. OE contributed to methodological guidance and reviewed the analysis outputs. ET, LC, OE, SZ, JT, GS and AM critically reviewed the manuscript and provided substantive feedback on its content. ET and LC led the overall study design and implementation. All authors read and approved the final version of the manuscript as submitted to JIAS.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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