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Virologic response of adolescents living with perinatally acquired HIV receiving antiretroviral therapy in the period of early adolescence (10–14 years) in South Africa

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Background and objectives: Adolescents living with perinatally acquired HIV (ALPHIV) on antiretroviral therapy (ART) have been noted to have poorer adherence, retention and virologic control compared to adolescents with non-perinatally acquired HIV, children or adults. We aimed to describe and examine factors associated with longitudinal virologic response during early adolescence.

Design: A retrospective cohort study

Methods: We included ALPHIV who initiated ART before age 9.5 years in South African cohorts of the International epidemiology Database to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration (2004–2016); with viral load (VL) values <400 copies/ml at age 10 years and at least one VL measurement after age 10 years. We used a log-linear quantile mixed model to assess factors associated with elevated (75th quantile) VLs.

Results: We included 4396 ALPHIV, 50.7% were male, with median (interquartile range) age at ART start of 6.5 (4.5, 8.1) years. Of these, 74.9% were on a non-nucleoside reverse transcriptase inhibitor (NNRTI) at age 10 years. After adjusting for other patient characteristics, the 75th quantile VLs increased with increasing age being 3.13-fold (95% CI 2.66, 3.68) higher at age 14 versus age 10, were 3.25-fold (95% CI 2.81, 3.75) higher for patients on second-line protease-inhibitor and 1.81-fold for second-line NNRTI-based regimens (versus first-line NNRTI-based regimens). There was no difference by sex.

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Conclusions: As adolescents age between 10 and 14 years, they are increasingly likely to experience higher VL values, particularly if receiving second-line protease inhibitor or NNRTI-based regimens, which warrant adherence support interventions.

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Introduction

The success of pediatric antiretroviral therapy (ART) has led to better survival with a growing number of adolescents living with perinatally acquired HIV (ALPHIV) surviving through to adulthood [1–3]. In 2018, there were 1.6 million (1.1–2.3 million) adolescents living with HIV (ALHIV) worldwide, and of these, 1.5 million (970 000–2.0 million) were living in sub-Saharan Africa [4]. Despite these reported successes, ALPHIV who enter adolescence virologically suppressed may experience deteriorating outcomes as they progress through adolescence [5].

ALPHIV usually have long prior treatment histories and have been noted to have poorer adherence, retention and deteriorating virologic control as they start to become autonomous regarding their healthcare [6,7]. Several studies have reported higher rates of non-adherence, virologic failure, drug resistance, faster disease progression, and higher rates of mortality and loss to follow-up among ALPHIV compared to either children or adults with non-perinatally acquired HIV [8–12]. Among ALPHIV in Cameroon, only 36% self-reported being adherent to their medications in the previous 14 days, 71% achieved virologic suppression, and only 52% had sustained virologic suppression [13]. Among ALPHIV initiating ART before the age of 20 years in Europe, the cumulative incidence of triple-class virologic failure increased from about 10% within 3 years of follow-up to about 30% within 5 years compared to <9% among adults [8].

ALPHIV on second-line regimens have also been reported to be more likely to experience virologic failure compared to young children [14,15]. For example, in multicenter aggregate analysis of second-line treatment outcomes for children living with HIV, one in six children on second-line protease inhibitor (PI)-based therapy experienced virologic failure, with adolescents having higher failure rates than young children [16]. Among older adolescents, boys may have poorer virologic response compared to girls [17,18] but it is not clear if this is the same among younger adolescents, and especially among ALPHIV. There are also limited data on the age at which the virologic response begins to deteriorate and whether this differs by sex.

Most studies assessing virologic outcomes in this age group have either looked at the most recent viral load (VL), examined changes in mean VL, or considered the binary outcome of virologic suppression versus non-suppression [8,13,19]. VLs are time-varying and usually follow a bimodal distribution [20]. Therefore, analyzing VL at a single time point or grouping data into a binary outcome will likely result in significant loss of information. Even modeling longitudinal VLs using normal linear models is inappropriate, given the bimodal distribution of VL measurements, and may not identify risk factors for the clinically relevant outcome of escalating VLs. Our study aims to describe the longitudinal VL trajectories of ALPHIV in the period of early adolescence (10–14 years). Our research will explicitly assess differences in virologic suppression between girls and boys along with other factors associated with elevated VL values during this period using log-linear quantile mixed methods which do not rely on the normal distributional assumptions of the linear mixed model framework.

Methods

Study population and inclusion criteria

We included data from ALPHIV who initiated ART from 2004 to 2016 at age <9.5 years (a proxy for perinatally acquired HIV infection [5]) at eight South African cohorts that contribute data to the International epidemiology Database to Evaluate AIDS-Southern Africa (IeDEA-SA) collaboration [21,22]. These cohorts include both urban and rural populations across three provinces and have been described in detail elsewhere [23–30].

Patients eligible for this study had to be virologically suppressed (VL < 400 copies/ml) at age 10 years and have at least one VL measurement after 10 years of age.

We, therefore, excluded all adolescents who had initiated ART after 9.5 years. We also excluded all adolescents who had a non-suppressed VL (≥400 copies/ml) at the start of adolescence and those that initiated ART before 2004 or after 2016.

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ART was defined as a three-drug regimen containing two nucleoside reverse transcriptase inhibitors (NRTIs) and either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a PI. The outcome of interest was time-updated $\log_{10}$VL, measured between 10.5 and 14.5 years of age.

Analysis

We used descriptive statistics of proportions, medians and interquartile ranges (IQRs), means and standard deviations to summarize the data [31]. We then used density plots to visualize the estimated probability distribution of VLs. VL values recorded as the lower limit of detection (LLD) were assigned the value of the assay LLD value minus one (e.g. 399 if the LLD was 400) or assigned a conservative value of 399 if the LLD value was not provided. Because the 75th quantile of the $\log_{10}$ VL distribution marked approximately the start of virologic non-suppression (VL $\geq$ 400 copies/ml) across all VL measurements, we chose to use this threshold as an outcome in a random intercept linear quantile mixed-effects model (LQMM) [32,33]. Because the outcome is measured on a log-scale, the exponentiated coefficients of this model can be interpreted as relative changes in the 75th quantile VL over time. The statistical model included the following explanatory variables: sex, age, World Health Organization (WHO) clinical stage (stages I and II and stages III and IV), $CD4^+$ cell count, and calendar year of ART initiation as well as healthcare facility at ART start and time-varying age. In a sensitivity analysis, we restricted the cohort to ALPHIV who had been on treatment for at least 2 years to assess if increasing age remained a risk factor for elevated VL in adolescents who had been on treatment for more extended periods and were more stable at the start of adolescence (Supplemental Digital Content, Table 1, http://links.lww.com/QAD/B991).

We used multiple imputations (MI) using the Amelia II package in *R* to account for missing observations of $CD4^+$ cell count and WHO stage, using the complete data in sex, age, cohort and calendar year of ART start in the MI model [34]. Results were combined according to Rubin's rules [35]. The remaining analyses were performed in *R* and Stata 15.1 (StataCorp. 2017 Stata Statistical software Release 15. StataCorp LLC, College Station, Texas, USA).

Ethics statement

IeDEA-SA cohorts have ethical approval to collect and transfer anonymized patient data to the IeDEA Data Centers at the Universities of Bern and Cape Town. The data centers have approval from their respective institutions for curation and analysis of the combined anonymized data.

Results

Patient characteristics

Of 4396 adolescents included, 50.7% were male with a median age at ART start of 6.5 (IQR: 4.5, 8.1) years (Table 1). At ART start, 2145 (66.2%) of the adolescents with WHO staging measures were in stage III/IV. The majority of adolescents had initiated ART between 2004 and 2009 (76.0%) and had been on treatment for at least 2 years. Over 85% of all adolescents had been initiated on an NNRTI-based regimen. By the age of 10 years, 570 (13.0%) had switched treatment to a second-line regimen, and the majority (2457, 73.9%) had $CD4^+$ cell count >500 cells/μl. Median follow-up in the 10–14-year period was 2.2 (IQR: 1.0, 3.9) years.

Distribution and completeness of viral load measurements

Overall, 612 (13.9%) of the adolescents had at least one VL $\geq$400 copies/ml. Among those followed up for 4 years or more, over 80% had five or more VL measurements (Fig. 1). By 11 years of age, two-thirds of the adolescents had at least one VL measurement, with nearly a third having two measurements. For those followed up until age 14 years or longer, over 80% had at least five VL measurements. The median (IQR) number of VL measurements per year of follow up was 1.89 (1.42, 2.49). Supplemental Digital Content, Figure 1 (http://links.lww.com/QAD/B990) shows the bimodal distribution of VL measures stratified by sex with a cut-off line at VL = 400 copies/ml. Overall, VL values increased with age with an emerging hump in the distribution of high VL values between 10 000 and 100 000 copies/ml by the age of 14 years. There was no evidence of a crude difference in VL values by sex (Supplemental Digital Content, Figure 1, http://links.lww.com/QAD/B990).

Factors associated with high viral load values at the 75th quantile

There was a consistent increase in VLs as age increased (Table 2). Compared to age 10 years, there was a 2.10-fold [95% confidence interval (CI): 1.89–2.33] increase in the 75th quantile VLs at 11 years, and a 3.13-fold (2.66, 3.68) increase in the 75th quantile VLs at 14 years, having adjusted for all other measured patient characteristics. The 75th quantile VL was similar for girls and boys [exponentiated β coefficient: 0.98 (95% CI 0.92, 1.06)]. In comparison to ALPHIV who were on NNRTI-based first-line regimens, those on other regimens had higher 75th quantile VL values as follows: first-line PI-based 1.29-fold higher (95% CI 1.15; 1.45); NNRTI-based second-line 1.81-fold higher (95% CI 1.48, 2.22) and second-line PI-based 3.25-fold higher (95% CI: 2.81, 3.75) There was an increase in the 75th quantile VLs among those starting ART in more recent years (2013–2016 versus 2004–2006, 1.48, 95% CI 1.22, 1.78).

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Table 1. Characteristics of adolescents living with perinatally acquired HIV at ART start and start of adolescence (age 10 years).

Patient characteristics	Number ($N = 4396$)	Percentage
Sex		
Male	2227	50.7%
Age at ART start, years, median (IQR)	6.5 (4.5, 8.1)	
WHO stage at ART start[a]		
I/II	1093	33.8%
III/IV	2145	66.2%
Missing	1158	26.3%
Calendar year of ART start		
2004–2006	1627	37.0%
2007–2009	1718	39.1%
2010–2012	876	19.9%
2013–2016	175	4.0%
Time on treatment, years		
<1	699	15.9%
1–2	736	16.7%
3–5	1730	39.4%
>5	1231	28.0%
Third drug in regimen at ART start		
Non-nucleoside reverse transcriptase inhibitor (NNRTI)	3798	86.4%
Protease inhibitor (PI)	598	13.6%
Ever switched from regimen by the age of 10 years		
Yes	570	13.0%
$CD4^+$ cell count (cells/μl) at age 10 years[a]		
≤250	352	10.6%
251–350	138	4.2%
351–500	376	11.3%
≥500	2457	73.9%
Missing	1073	24.4%
Time of follow up, years, median (IQR)	1.7 (0.5, 3.4)	
Third drug in regimen at age 10 years		
First line NNRTI	3294	74.9%
First line PI	532	12.1%
Second line (PI to NNRTI)	65	1.5%
Second line (NNRTI to PI)	505	11.5%

ART, antiretroviral therapy; IQR, interquartile range.
[a]Denominator for the stage and $CD4^+$ cell count categories is those with complete records.

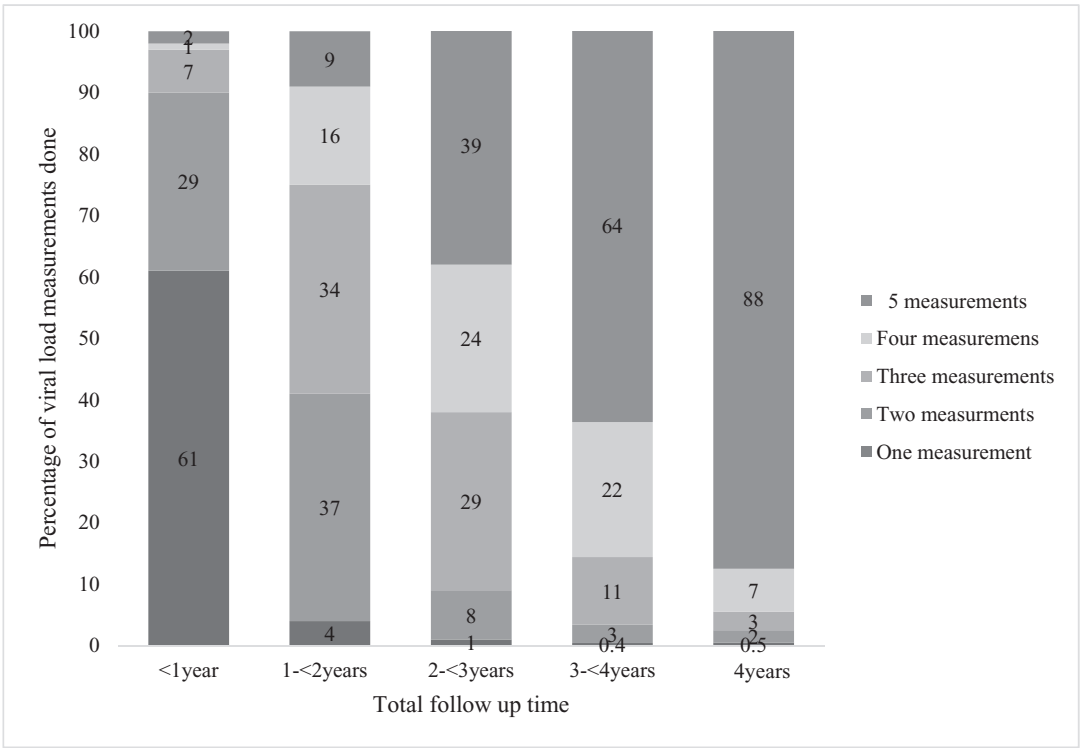


Fig. 1. Proportion of viral load measurements done per year stratified by total follow up time in the 10–14-year period.

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Table 2. Factors associated with high VL values *f* at the 75th quantile between 10 and 14 years.

Patient characteristics	CR[a]: adjusted relative changes* in 75th quantile VL (95% CI)	MI[b]: adjusted relative changes in 75th quantile VL (95% CI)
Age, years		
10	1	1
11	1.65 (1.45, 1.88)	2.10 (1.89, 2.33)
12	1.73 (1.52, 1.99)	2.38 (2.12, 2.67)
13	1.88 (1.68, 2.10)	2.71 (2.39, 3.08)
14	2.10 (1.82, 2.39)	3.13 (2.66, 3.68)
Sex		
Male	1	1
Female	1.00 (0.93, 1.07)	0.98 (0.92, 1.06)
WHO clinical stage at ART start		
Stages I and II	1	1
Stages III and IV	1.07 (0.92, 1.25)	1.06 (0.99, 1.14)
Calendar year of ART start		
2004–2006	1	1
2007–2009	1.09 (0.97, 1.23)	1.27 (1.17, 1.37)
2010–2012	1.51 (1.25, 1.84)	1.60 (1.38, 1.84)
2013–2016	1.60 (1.21, 2.10)	1.48 (1.22, 1.78)
'Third' drug in regimen at age 10 years		
First line NNRTI	1	1
First line PI	1.15 (0.97, 1.36)	1.29 (1.15, 1.45)
Second line NNRTI	1.75 (1.39, 2.23)	1.81 (1.48, 2.22)
Second line PI	2.53 (2.16, 1.94)	3.25 (2.81, 3.75)
Time on treatment before age 10		
<1 year	1	1
1–2 years	1.07 (0.88, 1.31)	0.98 (0.85, 1.12)
3–5 years	1.05 (0.88, 1.25)	1.04 (0.91, 1.18)
>5years	0.92 (0.89, 1.23)	1.11 (0.94, 1.31)
$CD4^+$ cell count (cells/μl) at age 10 years		
≤250	1	1
251–350	0.92 (0.73, 0.86)	1.01 (0.80, 1.26)
351–500	0.99 (0.77, 1.27)	0.96 (0.82, 1.14)
>500	0.99 (0.81, 1.21)	0.87 (0.75, 1.00)

ART, antiretroviral therapy; CR, complete record; NNRTI, non-nucleoside reverse transcriptase inhibitor; MI, multiple imputations; VL, viral load. *f* 612 (13.9%) adolescents experienced a non-suppressed VL, *β* adjusted for health facility where the patient was receiving care.
[a]Complete records analysis.
[b]Multiply imputed analysis.
*Number of times that the 75th quantile VL is bigger or smaller for different values of the independent variable.

In a sensitivity analysis including only those who had been on ART for at least 2 years by age 10 years, the effects of age, being on a second-line regimen, and calendar year on the 75th quantile VL were attenuated but similar to the primary analysis (Supplemental Digital Content, Table 1, *http://links.lww.com/QAD/B991*).

Discussion

In our analysis, ALPHIV on ART entering adolescence with VL <400 copies/ml experienced increasing VLs with age up to 14 years. Adolescents on second-line PI-based regimens were especially vulnerable and had three-fold higher 75th quantile VL values compared to those on first-line NNRTI-based regimens. There was, however, no particular age at which the VLs sharply increased, and the virologic response was similar for boys and girls.

Our results are consistent with other studies which have found deteriorating virologic and immunologic outcomes among ALPHIV [8–10]. Although our study was restricted to ALPHIV who had a suppressed VL at the time they entered into adolescence, there was a progressive increase in the 75th quantile of the VL distribution between 10 and 14 years of age. Adherence challenges brought about by changes in HIV care offered, the increased responsibility for their own health decisions and the usual social and developmental changes of adolescence may partly explain the increasing VL. In a study among ALPHIV in Thailand, almost half reported having suboptimal adherence measured as a composite outcome of self-reported missed doses in the previous seven days and caregiver rating of overall adherence [36]. Similar to our study, 18% of the adolescents in that study were virally non-suppressed (VL ≥ 1000 copies/ml). The main barriers to adherence in this age group, as highlighted by a systematic review done in low and middle-income countries, were non-disclosure to the adolescent themselves of serostatus, coming from a 'broken' family structure or having non-biological parents as caregivers, the impact of burdensome ART regimens, having had missed clinic appointments in the past as well as coming from rural versus urban locations [37].

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Other authors point out the need for greater adherence and psychosocial support during the adolescent period, especially as adolescents grow older and get more independent with their healthcare needs [7,36]. Denison *et al.* also highlighted the importance of families and home environments in supporting adolescent adherence to treatment and disclosure in Zambia [38]. Conversely, a study in the USA did not find any association of age with virologic non-suppression among ALPHIV and adolescents with non-perinatally acquired HIV [39]. However, lack of ascertaining an age-related association could be due to differences in study design, as the US study used a cross-sectional design, unlike our longitudinal design.

In our study, 13% of adolescents who had switched to second-line regimens by age 10 years experienced far greater increases in the 75th quantile VLs than those on first-line NNRTI-based regimens. This finding is in line with other studies that have reported ALPHIV being at high risk of treatment failure and multiclass drug resistance [14,16]. Similar results were observed in a study done among Asian ALPHIV on stable ART to assess incidence and predictors of post suppression virologic rebound; 13% of the adolescents experienced postsuppression virologic rebound at a rate of 3.4 (95% CI 2.9–3.9) per 100 person-years, which was consistent over time [40]. A Kenyan study reported over one-third of children experiencing virologic failure among those that underwent routine VL testing, with children that had switched ART regimen having higher odds of having unsuppressed VL [15]. In a Tanzanian study, among the 25% of children identified with virological failure, 90% had ART-associated drug resistance mutations, and almost 80% had multiclass resistance [41].

Notwithstanding, in our study, 88% of adolescents on second-line were on a PI-based regimen following NNRTI-based first-line and these children had the highest 75th quantile VL values, which may indicate non-adherence and not necessarily resistance. These adolescents probably had suboptimal adherence and viral failure before adolescence, which led to switching in regimens. For example, in a study done among Tanzanian children, suboptimal adherence to the first-line regimen was a predictor of suboptimal adherence to the second line [42]. In their study, Mocroft *et al.* also found that patients on the second line were more likely to experience virologic rebound compared to those on the first line [43]. Furthermore, even adolescents on first-line PI-based regimens had higher 75th quantile VL values compared to those on first-line NNRTI-based regimens, also suggesting non-adherence especially as there is a high genetic barrier to PI resistance. PI regimens have also been recorded to have severe side effects like gastrointestinal effects compared to NNRTIs [44].

The median number of VL measurements per year of follow up was approximately two measurements/year of follow up. This is in line with what the VL monitoring guidelines in South Africa recommend. This finding suggests that despite the increased number of patients in the healthcare system, on average, VL testing is being done as per guidelines.

It is concerning that adolescent who had started ART in more recent calendar years appear to have higher 75th quantile VL values compared to those who began ≤2006. However, a high proportion of the children who started in the first 2–3 years of ART roll-out were long term survivors of perinatally acquired HIV in the era before ART was widely available. Our finding may reflect a survival bias favoring the most adherent and least sick among that cohort. In addition, there was no evidence of a deteriorating trend in viral outcomes over calendar time beyond 2006. The children who initiated in more recent years may carry drug-resistant strains from being exposed to maternal ART hence having a higher risk of rebound. A study conducted in the United Kingdom and Ireland among children on ART [45] showed this result, although they did not have sufficient power to evaluate this. Another plausible explanation is that in more recent years, with the overcrowding of the health system due to increased survival of patients, VL monitoring has targeted high-risk patients. This could mean that the stable patients may have their VLs done less frequently, and could have been excluded or be under-represented in our analysis due to our strict exclusion criteria.

Our study concurs with others which showed no strong association in virologic response between younger adolescent boys and girls [13]. A study comparing retention and virologic suppression among adolescents and young adults attending either an adolescent-friendly clinic or standard pediatric care reported no major differences by sex in either model of care, having adjusted for all other measured patient characteristics [46]. Sex differences in adolescent outcomes have mostly been reported among those with horizontally acquired HIV and in older adolescents of ≥15 years [18,46].

Our study was limited by the lack of data on resistance, treatment interruptions and adherence; hence we were unable to assess an association between elevated VLs and resistance or adherence in this population. We also made assumptions about the actual VL value when VL was reported as below the LLD. Although the LLD of assays has dropped in more recent years, it is unlikely to have affected the 75th quantile values themselves as the 75th quantile value from 11 years of age onwards was >400, the lowest LLD. A further limitation is our use of starting ART before age 9.5 years as a proxy for perinatally acquired HIV as there may be adolescents commonly referred to as 'slow progressors' who were missed in our definition of perinatal infection [7,47]. The inclusion of children who survived into adolescence and had a VL measurement in the 10–14-year age period may have

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introduced selection and survival bias and hence an overestimation of the high VL trajectories. However, there was no difference in the median number of VL measurements/year of adolescent follow-up by calendar year of ART start suggesting minimal/no selection bias by the calendar year in those whose VL was measured.

We used linear quantile mixed regression modeling that considers the bimodal distribution as the longitudinal nature of the VL data instead of cross-sectional analyses, modeling of dichotomized virologic outcomes (VL suppression versus non-suppression) or longitudinal analyses based on assuming a normal distribution of VL measures. We also used MI for missing observations. We presented both results from complete record analysis (CR) and MI, which provides a more robust comparison and generalizability of the results [35]. Our analysis is further strengthened by the large sample size and the broad geographic coverage of our cohort, comprising adolescents from a wide range of public-sector patients from hospitals and health centers in three provinces of South Africa. The results may be generalizable to other routine care settings in Sub-Saharan Africa, where VL monitoring is available.

Conclusions

In our study, ALPHIV experienced deteriorating VL outcomes as they aged from 10 to 14 years, especially if on any second-line or a PI-based first-line regimen with no major/relevant differences by sex. Using the quantile regression allowed for a more granular understanding of the factors that cause higher VL values in the most clinically relevant upper end of the range. Adherence support in early adolescence is critical, with a particular focus on ensuring regular VL monitoring and adherence interventions for those on second-line treatment.

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Author contributions: P.N. conceptualized the idea, wrote the first draft, did the analysis, interpreted the results, and wrote the final draft. M.S. conceptualized the idea, advised on methods of analysis, interpreted the results, and revised all the manuscript drafts. N.S. reviewed and edited the final manuscript. K.-G.T. revised and edited the final manuscript. G.F. revised and edited the final manuscript. H.R. revised and edited final manuscript. F.T. revised and edited final manuscript. B.E. revised and edited final manuscript. J.E. revised and edited final manuscript. R.W. revised and edited final manuscript. P.R.T. revised and edited final manuscript. C.T.Y. advised on methods of analysis, revised, and edited all manuscript drafts. M.C. revised and edited all manuscript drafts. M.A.D. conceptualized the idea, interpreted the result, and revised and edited all manuscript drafts.

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Conflicts of interest

There are no conflicts of interest.

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