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Longitudinal Trajectories of Antiretroviral Treatment Adherence and Associations With Durable Viral Suppression Among Adolescents Living With HIV in South Africa

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Background: Compared with other age groups, adolescents living with HIV (ALHIV) are estimated to have lower levels of adherence to antiretroviral treatment. Despite this, we lack evidence on adolescents' adherence patterns over time to inform the customization of intervention strategies.

Setting: Eastern Cape province, South Africa.

Methods: We analyzed data from a cohort of ALHIV (N = 1046, aged 10–19 years at baseline) recruited from 53 public health facilities. The cohort comprised 3 waves of data collected between 2014 and 2018 and routine viral load data from the National Institute for Communicable Disease data warehouse (2014–2019). Durable viral suppression was defined as having suppressed viral load (<1000 copies/mL) at ≥2 consecutive study waves. Group-based multitrajectory model was used to identify adherence trajectories using 5 indicators of self-reported adherence. Logistic regression modeling evaluated the associations between adherence trajectories and durable viral suppression.

Results: Overall, 933 ALHIV (89.2%) completed all 3 study waves (55.1% female, mean age: 13.6 years at baseline). Four adherence trajectories were identified, namely, "consistent adherence" (49.8%), "low start and increasing" (20.8%), "gradually decreasing" (23.5%), and "low and decreasing" (5.9%). Adolescents experiencing inconsistent adherence trajectories were more likely to be older, live in rural areas, and have sexually acquired HIV. Compared with the consistent adherence trajectory, the odds of durable viral suppression were lower among adolescents in the low start and increasing (adjusted odds ratio [aOR]: 0.62, 95% CI: 0.41 to 0.95), gradually decreasing (aOR: 0.40, 95% CI: 0.27 to 0.59), and the low and decreasing adherence (aOR: 0.25, 95% CI: 0.10 to 0.62) trajectories.

Conclusions: Adherence to antiretroviral treatment remains a challenge among ALHIV in South Africa. Identifying adolescents at risk of nonadherence, based on their adherence trajectories may inform the tailoring of adolescent-friendly support strategies.

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INTRODUCTION

Advances in access to antiretroviral treatment (ART) have led to global reductions in AIDS-related mortality and improved quality of life for people living with HIV.[1] Consistent adherence to ART is essential to achieve and sustain viral suppression and maintain the health and well-being of an individual.[2,3] Despite the successful rollout of ART in sub-Saharan Africa (SSA),[4,5] adolescents living with HIV (ALHIV) continue to demonstrate poor adherence[6,7] and fall behind global targets on viral suppression (UNAIDS 95–95–95 targets).[8–10] For example, approximately 78% of adolescents on ART are estimated to be virally suppressed (defined as <1000 copies/mL).[11] Moreover, sub-optimal adherence to ART is high among ALHIV compared with adults, with adolescents estimated to be 50% less likely to maintain optimal adherence.[12,13]

Several studies have examined ART adherence among adolescents in SSA[14–18] and demonstrated the utility of self-reported measures in adherence monitoring. However, less attention has been given to understanding variations in patterns of adherence over time in this group. Most studies on adherence among adolescents are largely cross sectional, which does not appropriately reflect changes in patterns of adherence over time.[19] Existing longitudinal evidence on adolescents has mostly used aggregate methods, dichotomized adolescents as adherent versus nonadherent, and examined within-person patterns of adherence, which is insufficient to capture the dynamic nature of long-term adherence.[7,20–22] Therefore, there is a need for additional longitudinal analyses to distil variability in adherence patterns both between and within adolescents, as these variations can influence the likelihood of sustaining viral suppression.[20,23]

One analytic approach to address this gap is group-based trajectory model (GBTM), a novel data-driven approach used for modeling developmental trajectories (ie, changes of an outcome over time).[24] Unlike traditional analytic methods, GBTM can be used to categorize trajectories (distinct patterns over time) of ART adherence and can use multiple indicators of an outcome of interest simultaneously.[25] This element of GBTM is essential in ART adherence literature, particularly for adolescents, as it captures the variability in their long-term adherence behavior. To date, few studies in SSA (mostly among adult populations) have used GBTM to describe ART adherence trajectories.[26–28] Applying GBTM to identify these trajectories among adolescents may be useful in the tailoring and targeting of adherence support interventions and focusing on adolescents at risk of poor adherence and subsequent treatment failure rather than all ALHIV.[29] Given that adolescence is a period characterized physical, sexual, emotional, and psychological development, which may influence adherence and changes over time,[30] we hypothesize that GBTM will delineate distinct trajectories of adherence over time among ALHIV. We further examine the relationship between ART adherence trajectories and durable viral suppression.

METHODS

Study Design

This analysis is based on a three-wave cohort study of ALHIV conducted in the Eastern Cape province of South Africa between 2014 and 2018. In the Buffalo City District in the Eastern Cape province, we identified 53 health facilities (community health care centers, hospitals, and primary health clinics) that provided HIV care to adolescents. In each facility, all patient files were reviewed to identify adolescents who had initiated ART and were aged 10–19 years. Eligible ALHIV (n = 1176) were approached for study participation and recruited in health facilities, or traced back into their home communities,[31] to ensure the inclusion of those no longer engaged in care. Of all study-eligible adolescents, 1046 were recruited and participated at the baseline of the study in 2014–2015, 979 (94.0%) of these were followed up at the second wave (2016–2017) of the study, 953 (91.1%) at the third wave (2017–2018), and 35 (3.4%) died during the study period. A more detailed description of the study design and data collection procedures is available elsewhere,[32,33] and further study information, including study protocol, is available at www.mzantsiwakho.org.za.

Ethical approvals were granted by University of Cape Town (UCT/CSSR/2013/4) and (UCT/CSSR/2019/01), the Oxford University (Oxford/CUREC2/12-21), provincial Departments of Health and Education, NHLS Academic Affairs and Research Management System (August 07, 2019) and the ethical review boards of participating health care facilities. At all study waves, adolescent participants and their caregivers (when adolescents were <18 year old) provided voluntary written informed consent for participation in their language of choice (Xhosa or English), including interviews and access to adolescents' medical records.

Study Data and Procedures

The sample for the current analysis included adolescents who participated at all 3 study visits. At each study visit, data were collected using tablet-based standardized questionnaires (translated to local language: Xhosa) that assessed adolescents' experiences at home, in their communities, and health care settings, including self-reported ART adherence. The questionnaires were designed to be nonstigmatizing through extensive consultation with South African ALHIV, included graphics and vignettes to introduce questions about sensitive topics. Tools were prepiloted on n = 25 adolescents at baseline.[34] Adolescents then completed the questionnaire at each study visit—in their communities or at clinics—in their preferred language (English or Xhosa), with the help of trained research assistants.

Data were collected on sociodemographic characteristics, including age (divided into 10–14 and ≥15 year age groups), sex, urban/rural residence, and access to 8 socially perceived necessities for children and adolescents validated in

a nationally representative South African Social Survey (eg, enough food).[35] HIV treatment factors included knowledge of HIV status,[36] estimated or self-reported time on ART (years), and mode of HIV acquisition. Mode of HIV acquisition (perinatally versus sexually acquired HIV) was defined following existing sub-Saharan African pediatric cohorts: age of ART initiation cutoff [≤10 years][37] validated and updated with a detailed algorithm that considered other strong evidence (ie, self-reported sexual history and parental death) in the absence of definitive clinic notes ascribing mode of HIV acquisition.[38]

Self-reported data on ART adherence were also collected at each visit using various measures on missed doses—with varying recall time frames—and missed clinic appointments. The measures used in this analysis included 4 on missed doses *in the past 3 days*, *past week,* and *past month and any past-month days missed* adapted from the Patient Medication Adherence Questionnaire,[39] and 1 on *missed clinic appointments*, which was added into the questionnaire based on recommendations from other studies.[34,40] All adherence measures were dichotomized and positively coded to represent adherence. These 5 measures showed good test accuracy against viral load (VL) ≥ 1000 copies per milliliter and have been described in full elsewhere.[41]

Following the completion of the study waves, adolescents' VL tests data (2014–2019) were obtained through the National Health Laboratory Services routine laboratory data at the National Institute for Communicable Disease data warehouse of South Africa. The National Institute for Communicable Disease archives all routine laboratory data from public-sector health facilities, including from facilities outside the study catchment area. Demographic information (name, surname, sex, and date of birth) for adolescents in the cohort was used to link laboratory test records in the National Institute for Communicable Disease data warehouse. Given that the dates of VL test results were in line with the participant's clinic VL monitoring schedule and did not always match the study visit dates, VL results were assigned to at each visit if they were within 12 months from the adolescents' interview date. For participants with more than 1 result within this window, we selected the VL result closest to the study visit date. The median interval between the date of the selected VL result and the study visit was 2 months (interquartile range [IQR]: 1–5 months), across all 3 study visits. The mean interval between VL records assigned at Wave 1 and Wave 2 was 19 months; for those at Wave 2 and Wave 3, the interval was 15 months. Each of these align with the mean interval between study visits: 18 and 14 months, respectively. We defined viral suppression as VL <1000 copies per milliliter.

Data Analysis

Primary exposure: ART adherence trajectories as categorized by GBTM based on 5 self-reported adherence measures.

Outcome measure: The outcome measure was durable viral suppression, defined as having a suppressed VL (<1000 copies/mL) at 2 or more consecutive study waves.

Statistical Analysis

Group-Based Trajectory Modeling

We used the group-based trajectory model (GBTM), a specialized finite mixture model first introduced by Nagin and Odgers[25] to identify groups of adolescents that follow similar longitudinal progressions of adherence over time.[24] This model assumes that the overall population is made up of distinct, unobserved subpopulations that follow different behavioral patterns.[25] To identify adolescent groups that follow joint adherence trajectories using multiple (5 binary measures) indicators over 3 time points, we performed a multitrajectory analysis, which is an extension of the GBTM that simultaneously estimates joint trajectories for multiple indicators.

The following steps were taken to identify the number and shape of adherence trajectory groups. Because the number of groups and the order of the trajectory polynomials (ie, linear, quadratic, cubic) are not actually known a priori, we first tested a series of model specifications with varying the number of groups systematically to determine the appropriate number of trajectory groups. The second step entailed visual inspections for interpretability of the trajectories and determining trajectory shapes across a series of model specifications. To determine model fit, consistency, and the optimal number of trajectory groups, we considered the following criteria: (1) Bayesian information criteria (BIC) with smaller values indicating better fit, (2) within each group, the average posterior probability of group membership was compared 0.7 threshold (values greater than 0.7 indicate adequate internal reliability or acceptable classification), (3) assessed the tightness of the confidence intervals around the estimated group membership probabilities, (4) compared the odds of correct classification with a minimum threshold of 5, (5) compared the probability that a model with j groups is the correct model from a set of J different models (the best-fitted model has a probability close to 1).[24] In addition, we aimed for the smallest group to have at least 5% of the sample.[42] Because our 5 adherence measures were all dichotomous, adherence was modeled, assuming a binomial distribution and a logit link function. The GBTM model was estimated using *Traj* plugin in Stata version 17.1 (StataCorp, College Station, TX).

Descriptive Statistics

First, we assessed differences between trajectory groups by sociodemographic and HIV-related characteristics using the χ^2, Kruskal–Wallis, or Fisher exact tests. Second, we used multinomial logistic regression to assess the association between baseline factors and trajectory group membership. Our model included an interaction between age group and sex. We estimated predictive margins to report the results as the expected distribution of trajectory across baseline characteristics.

Adherence Trajectories and Durable Viral Suppression

We used multivariate logistic regression model to assess the association between adherence trajectory groups

and durable viral suppression, controlling for known confounders measured at baseline. Potential confounders were selected based on the literature and expert knowledge. This analysis was limited to participants with VL data at 2 or more study visits during the study period. A sensitivity analysis of the associations between adherence trajectories and durable viral suppression using alternative VL cutoffs (50 and 400 copies/mL, respectively) to define durable viral suppression was conducted. We also used the χ^2 test to compare the baseline characteristics of those participants included in the outcome versus those who did not meet the criteria for durable viral suppression. All analyses were conducted with Stata version 17.1 (Stata Corp LLC, College Station, TX).

RESULTS

Participant Characteristics

Of the 1046 ALHIV recruited in this study, N = 933 (89.1%) completed all 3 study waves, which formed our analytic sample. The analytical sample comprised 55.1% females, and the mean age of 13.6 years (SD = 2.9) at baseline. Approximately one-third resided in rural areas and two-thirds reported lacking at least 1 of the 8 basic necessities. The majority (78.7%) had acquired HIV sexually, and median time on ART was 4.7 years (IQR: 2.7–7.3 years). Two-thirds of the participants knew their HIV status (Table 1). Among female participants, 105 (20.4%) had been ever pregnant across the 3 waves, with 63.8% of these reported at baseline.

Description of Adherence Trajectory Groups

Based on the 5 self-reported adherence measures, GBTM revealed 4 distinct trajectories of adherence to ART (Fig. 1). The first trajectory group "consistent adherence" was made up of adolescents who were more likely to report adherence across all measures at all 3 waves, accounting for 49.8% of the sample. The second trajectory group "low start and increasing adherence," 20.8% of the sample, was made up of adolescents who were less likely to report adherence early in the period, who then improved after baseline. The third group "gradually decreasing adherence," 23.5% of the sample, were adolescents who reported adherence early in the period (on all measures) but then decreased gradually after baseline. The fourth group "low and decreasing adherence," 5.9% of the sample, comprised adolescents who were less likely to report being adherent across all measures throughout the study period. The model with 4 trajectory groups was identified as optimal based on the information criterion, good separation of groups, and interpretability (see Table 1, Supplemental Digital Content, http://links.lww.com/QAI/C261). The average posterior probabilities for each group were greater than 0.7 and ranged from 0.94 to 0.97. Odds of correct classification, measuring improvement in membership probability of individuals belonging to trajectory group 1 compared with all other trajectory groups, which were all greater than 5, suggest a reasonable fit for the model (see Table 2, Supplemental Digital Content, http://links.lww.com/QAI/C261).

Baseline Factors Associated With Trajectory Group Membership

The distribution of adolescents' characteristics in each trajectory group is shown in Tables 2 and 3. Overall, age, sex, place of residence, access to 8 basic necessities, mode of HIV acquisition, and time on ART were statistically significantly different between the trajectory groups. In multinomial logistic regression, participants in the "consistent adherence" group were most likely to be younger adolescents (<15 years) with perinatally acquired HIV (Table 3). Participants in the "low start and increasing adherence" group were more likely to be older females, to reside in a rural residence at baseline, and to have sexually acquired HIV. Participants in the "gradually decreasing adherence" group were most likely to be older males (≥15 years) at baseline. Participants in the "low and decreasing adherence" group were more likely to be older females with sexually acquired HIV and shorter time on ART. However, despite these patterns, overall differences in the distribution of distinct trajectory groups across baseline characteristics were small.

Durable Viral Suppression by Trajectory Group Membership

Of the 933 ALHIV, 655 participants (70.2%) had VL data at 2 or more visits across the study period, thus had sufficient VL tests to be included in this analysis. A comparison between those included versus those excluded showed no differences (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/C261), except that those excluded were likely to be older and not aware of their HIV-positive status. The rates of viral suppression decreased over time across all trajectory groups, and the decrease was higher among adolescents in the inconsistent adherence trajectories

TABLE 1. Baseline Participant Characteristics, (N = 933)

Characteristic	N (%)
Age (mean/SD), yr	13.6 (2.9)
Age group	
<15 yrs	609 (65.3)
≥15 yrs	324 (34.7)
Sex	
Male	419 (44.9)
Female	514 (55.1)
Place of residence	
Urban	684 (73.3)
Rural	249 (26.7)
Socioeconomic factors	
Access to 8 basic necessities	300 (32.2)
HIV treatment factors	
Knowledge of HIV status	627 (67.2)
Mode of HIV acquisition	
Perinatally	734 (78.7)
Sexually	199 (21.3)
Time on ART (median/IQR: years)	4.7 (2.2–7.3)

(see Figure 1, Supplemental Digital Content, http://links.lww.com/QAI/C261). The "low and decreasing adherence" group had the lowest rates of viral suppression at all study waves. Of those with sufficient VL data (N = 655), 359 (54.8%) had durable viral suppression. Table 4 summarizes the unadjusted and adjusted estimates of the association between adherence trajectory membership and durable viral suppression from the logistic regression model. Compared with the "consistent adherence" group, the "low start and increasing adherence" group (adjusted odds ratio [aOR]: 0.62, 95% CI: 0.41 to 0.95, $P = 0.029$), the "gradually decreasing adherence" group (aOR: 0.40, 95% CI: 0.27 to 0.59, $P < 0.001$), and the "low and decreasing adherence" group (aOR: 0.25, 95% CI: 0.10 to 0.62, $P = 0.003$) had significantly lower odds of durable viral suppression.

A sensitivity analysis of the associations between adherence trajectories and durable viral suppression using alternative VL cutoffs—50 and 400 copies per milliliter, respectively—to define durable viral suppression showed similar and consistent results (see Table 4, Supplemental Digital Content, http://links.lww.com/QAI/C261).

DISCUSSION

GBTM revealed 4 latent trajectories of adherence to ART among South African ALHIV, with approximately 5.9% in the low and decreasing adherence group and approximately half (49.8%) classified in the consistent adherence group. The rest of the adolescents were grouped into the low start and increasing adherence (20.8%) and the gradually decreasing adherence trajectories (23.5%). Although it is encouraging that approximately half of the ALHIV in this study were classified in the consistent adherence group, the remaining trajectories reflected inconsistent adherence over time. These inconsistent adherence trajectories had lower odds of durable viral suppression compared with adolescents who followed the consistent adherence trajectory. Given the lack of evidence on adherence trajectories among adolescents, these findings provide initial evidence on the evolution of adherence (self-reported) over time and its effects on VL outcomes among ALHIV in South Africa.

Our study further identified a few baseline characteristics associated with adherence trajectory group membership.

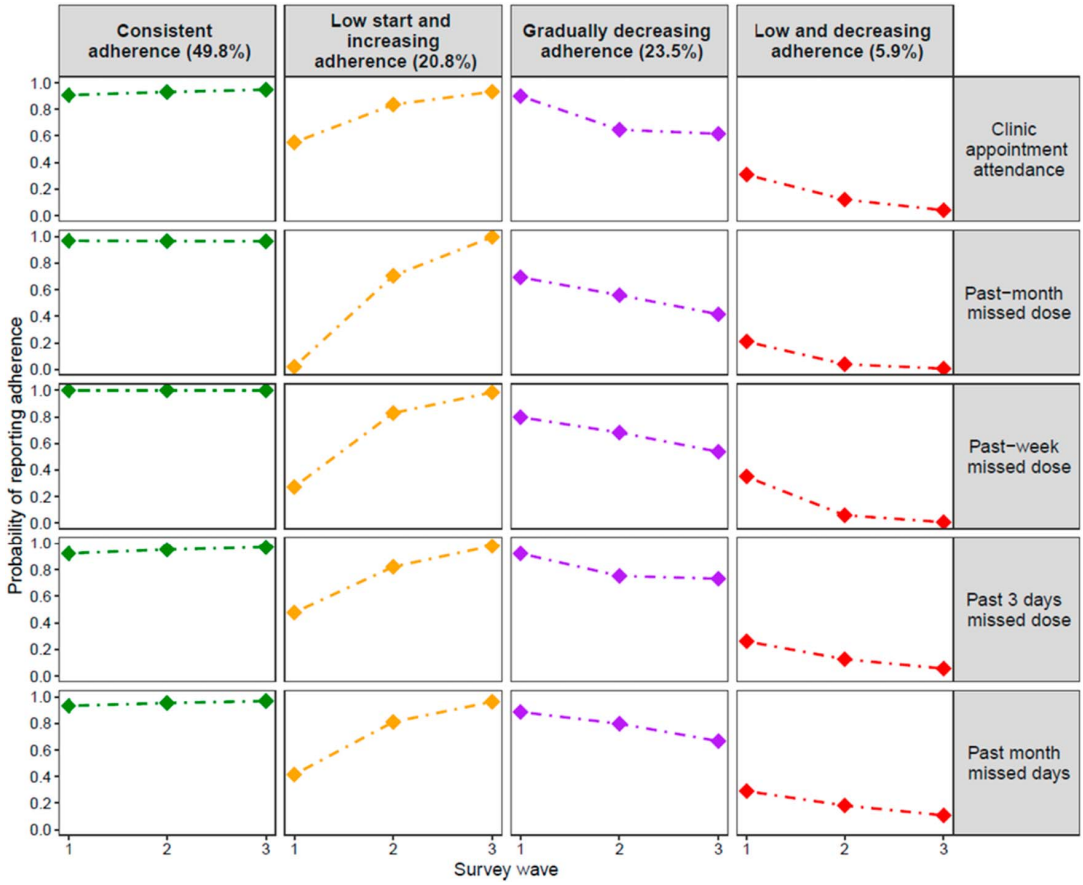

FIGURE 1. Longitudinal adherence trajectories by adherence measure (4-group model). Estimated longitudinal trajectories for adolescents that were categorized into 4 groups based on group-based multitrajectory analysis. Because the adherence measures were dichotomous, the y-axis represents the percentage who reported adherence based on each item in each trajectory group. All adherence measures were coded positively, 1 (adherence) and 0 (nonadherence). Columns represent trajectory groups, whereas rows represent adherence indicators.

Participants in the "consistent adherence" group were more likely to be younger adolescents (<15 years) with perinatally acquired HIV, whereas those in the "low and decreasing adherence" group were more likely to be older females (≥15 years) with the least median time on ART, who acquired HIV sexually. These findings corroborate existing evidence, which show that younger adolescents rely more on their primary caregivers for clinic visits and ART uptake,[43] whereas recent HIV diagnosis coupled with increasing responsibility for self-health care among older adolescents[44] can result in failure to adapt to medication routines[31] contributing to poor adherence. Participants in the "gradually decreasing adherence" group were more likely to be older males (≥15 years). This may be explained in part by societal norms of manhood and health care engagement,[45] and increased mobility associated with older adolescents as they transition out of school toward a search for livelihoods leading to disengagement from HIV care.[46] Participants in the "low start and increasing adherence" group were more likely to be older females (≥15 years) who sexually acquired HIV and live in rural residences. This group may have poor access to care, which may lead to delays in establishing workable ART medication routines and hence poor adherence at the start.[47] There was no significant association between knowledge of HIV status and the categorization into 4 adherence trajectories. This may be partly explained by the fact that the majority of adolescents already knew their HIV status at baseline[36] and the potential confounding effects of age at ART initiation and the duration of ART[48] or that the disclosure process or pattern may influence adherence more than knowledge of status.[49]

The heterogeneity observed in the adherence trajectories among ALHIV in this study is very relevant to improving their HIV-related health outcomes, given that it is highly associated with VL outcomes. This study showed that, compared with the group who were more likely to report adherence consistently over time ("consistent adherence"), the remaining groups were associated with significantly lower odds of durable viral suppression. Therefore, the extent to which the variations in long-term adherence influence adolescents' health treatment outcomes is noteworthy. These findings highlight the importance of understanding the dynamics of adherence to anticipate changes in adolescents' capacity to sustain adherence. Moreover, it is important that we support adolescents to adhere to their ART treatment at the start and retain adherence over time, which is associated with improved HIV-treatment outcomes. Overall, current strategies targeting high-risk adolescents should use this understanding of longitudinal adherence trajectories to guide the development of tailored support and intervention strategies—which are critical to improving adolescents' treatment outcomes.[12,50]

Characterizing longitudinal trajectories of adherence provides a more nuanced understanding of adolescents' ART adherence than more traditional metrics. However, little is known about the dynamics of adherence among adolescents over time. Previous research using self-reported measures of ART adherence[44,51] mostly employed traditional metrics, such as proportions, which may mask heterogeneity and inconsistencies in adherence over time.[52] Even in longitudinal studies, heterogeneity between adolescents is obscured by

TABLE 2. Distribution of Baseline Participant and HIV-Related Characteristics by Trajectory Group (N = 933)

Baseline Characteristics	Consistent Adherence (N = 465, 49.8%) N (%)	Low Start and Increasing Adherence (N = 194, 20.8%) N (%)	Gradually Decreasing Adherence (N = 219, 23.5%) N (%)	Low and Decreasing Adherence (N = 55, 5.9%) N (%)	*P*
Age (mean/SD), yr	13.1 (2.69)	14.1 (3.02)	13.6 (2.89)	15.3 (2.95)	**<0.001**
Age group					**<0.001**
<15 yrs	143 (65.3)	112 (57.7)	333 (71.6)	21 (38.2)	
≥15 yrs	76 (34.7)	82 (42.3)	132 (28.4)	34 (61.8)	
Sex					**<0.001**
Male	114 (52.1)	73 (37.6)	218 (46.9)	14 (25.5)	
Female	105 (47.9)	121 (62.4)	247 (53.1)	41 (74.5)	
Place of residence					**0.007**
Urban	175 (79.9)	126 (64.9)	344 (74.0)	39 (70.9)	
Rural	44 (20.1)	68 (35.1)	121 (26.0)	16 (29.1)	
Socioeconomic factors					
Access to 8 basic necessities	160 (34.4)	47 (24.2)	78 (35.6)	15 (27.3)	**0.037**
HIV-related factors					
Knowledge of HIV status	155 (70.8)	128 (66.0)	311 (66.9)	33 (60.0)	0.440
Mode of HIV acquisition					**<0.001**
Perinatally	169 (77.2)	140 (72.2)	400 (86.0)	25 (45.5)	
Sexually	50 (22.8)	54 (27.8)	65 (14.0)	30 (54.5)	
Time on ART (median/IQR: years)	5.1 (2.8–7.8)	4.2 (1.8–6.9)	4.4 (1.8–7.3)	2.6 (1.4–5.2)	**0.001**

Bold denotes 5% significance level.

TABLE 3. Predicted Probabilities of Trajectory Group Distribution Across Baseline Adolescent's Characteristics From Multinomial Logistic Regression (N = 933)

Baseline Characteristics	Consistent Adherence (N = 465, 49.8%)	Low Start and Increasing Adherence (N = 194, 20.8%)	Gradually Decreasing Adherence (N = 219, 23.5%)	Low and Decreasing Adherence (N = 55, 5.9%)
Age group				
<15 yrs male	53.6 (48.1–59.1)	16.5 (12.5–20.5)	27.8 (22.8–32.7)	2.2 (0.8–3.5)
<15 yrs female	53.9 (48.5–59.3)	21 (16.6–25.5)	21.2 (16.9–25.6)	3.9 (1.8–5.9)
≥15 yrs male	45.8 (38.4–53.2)	21.4 (15.2–27.5)	27.4 (20.7–34.2)	5.4 (1.8–9.1)
≥15 yrs female	44.3 (37.6–51.1)	26.2 (20.1–32.3)	20.2 (15–25.3)	9.3 (4.9–13.8)
Place of residence				
Urban	49.7 (46.1–53.4)	18.7 (15.7–21.6)	25.4 (22.2–28.7)	6.1 (4.3–7.9)
Rural	50.2 (44.1–56.4)	26.4 (21–31.9)	18 (13.2–22.8)	5.4 (2.9–7.9)
Socioeconomic factors				
Access to 8 basic necessities	53.4 (47.6–59.1)	16.7 (12.3–21.1)	26.2 (21.1–31.3)	3.7 (1.4–6.1)
HIV-related factors				
Knowledge of HIV status				
Yes	45.7 (40.1–51.3)	22.2 (17.2–27.2)	20.8 (16.1–25.6)	11.3 (6.8–15.7)
No	51.5 (47.6–55.4)	19.7 (16.6–22.8)	24.4 (21.1–27.8)	4.4 (2.9–5.8)
Mode of HIV acquisition				
Perinatally	53.7 (50–57.4)	19.9 (16.9–22.9)	22.7 (19.6–25.7)	3.7 (2.2–5.1)
Sexually	35.8 (28.4–43.2)	24.2 (17.9–30.6)	27.6 (20.6–34.5)	12.4 (7.4–17.4)

population-level averages.[53] Moreover, most of these studies use single or composite measures of adherence. A few studies among adult populations living with HIV have assessed adherence trajectories over time.[26–28] For example, a study among adults in the Swiss HIV Cohort Study using data on self-reported missed doses identified 4 behavioral groups associated with specific adherence patterns, namely, good, worsening, improving, and poor adherence.[54] The adherence trajectory groups identified in these previous studies are generally comparable with those in this study, although most of these studies use singular indicators to define trajectories and among adult populations. This study extends this work in 3 ways: first, by applying multitrajectory GBTM to examine adherence trajectories among ALHIV—a group with relatively poor HIV-related outcomes and high mortality;[12,41] second, by using multiple (5) indicators of self-reported adherence, which may reduce measurement bias; and third, by conducting these analyses using cohort data from resource-limited settings in South Africa.

This study is not without limitations. First, we use self-reported adherence measures, which are prone to social desirability bias and recall bias.[55–59] However, the questionnaire was administered by research assistants trained to work with adolescents, and outside of routine HIV care reducing the risk of social desirability bias. Second, the assignment of adolescents into distinct trajectory groups only represent systematic attempts to characterize and classify adolescents based on the available data, which may lead to classifications that do not seem intuitive. However, model fit diagnostics indicated a good fit for the data with clear distinct trajectory groups. Third, VL data used in this analysis did not match the questionnaire dates exactly, and 29.8% did not have sufficient VL data to be included in the analysis of durable suppression, which may bias the relationship between adherence trajectories and viral suppression. Fourth, this study excluded adolescents who died (N = 35, 3.4%) or were lost-to-study follow-up (N = 78, 7.5%) in estimating trajectories, which may underestimate the extent of inconsistent adherence over time. However, there were no significant differences between participants excluded in the analysis and those retained, other than that those excluded were likely to be older.[41] Fifth, the age of the data may impact the relevance of these findings to current practice. The strength of this study is that it is longitudinal and included multiple self-reported indicators of adherence from a sample of ALHIV. Therefore, findings from this study may be generalizable to other countries in sub-Saharan Africa as well as other resource-constrained settings. Overall, these findings demonstrate the utility of self-reported measures for adherence monitoring among ALHIV over time. Future research should seek to understand why adolescents fall into these adherence trajectory groups and identify malleable factors contributing to the distinct groups of ALHIV over time. Additional research is also needed to establish at what point in the care of an adolescent trajectories can be assigned.

In conclusion, our study demonstrates that adherence to ART remains a major challenge among ALHIV in the Eastern Cape province in South Africa because approximately half (50.2%) of the adolescents reflected inconsistent adherence trajectories over time. Our analysis further shows that the adolescent population is composed of distinct groups with different adherence behavior trajectories and varying degrees of risk of viral nonsuppression over time. This nuanced understanding of the heterogeneity in adolescent ART adherence behaviors over time, ultimately paves the way to a shift from one-size-fits-all approaches and may be useful in

TABLE 4. Logistic Regression Models of the Association Between Trajectory Membership and Durable Viral Suppression (N = 655)

Outcome	Durable Viral Suppression*			
Characteristic	OR (95% CI)	*P*	aOR (95% CI)	*P*
Trajectory group				
Consistent adherence (reference)	1		1	
Low start and increasing adherence	**0.54 (0.36 to 0.81)**	**0.003**	**0.62 (0.41 to 0.95)**	**0.029**
Gradually decreasing adherence	**0.40 (0.27 to 0.59)**	**<0.001**	**0.40 (0.27 to 0.59)**	**<0.001**
Low and decreasing adherence	**0.18 (0.07 to 0.43)**	**<0.001**	**0.25 (0.10 to 0.62)**	**0.003**
Baseline characteristics				
Age (15+ yrs)	—	—	**0.66 (0.44 to 0.98)**	**0.042**
Female	—	—	1.18 (0.85 to 1.65)	0.322
Rural residence	—	—	**0.66 (0.46 to 0.96)**	**0.030**
Access to 8 basic necessities	—	—	1.29 (0.92 to 1.83)	0.144
Knowledge of HIV status	—	—	0.79 (0.54 to 1.17)	0.247
Sexually acquired HIV	—	—	0.71 (0.43 to 1.16)	0.174
Time on ART (yrs)	—	—	1.03 (0.98 to 1.08)	0.325

*Subsample analysis of those with at least 2 VL measurements. Durable viral suppression was defined as having at least 2 viral loads <1000 copies per milliliter across the 3 study waves. A comparison of the participants included (N = 655) and (N = 278) not included (see Table 3, Supplemental Digital Content, http://links.lww.com/QAI/C261) showed no differences on most baseline characteristics, except that participants excluded were more likely to be older and less likely to know their HIV status.

OR, odds ratio.

Bold denotes 5% significance level.

developing tailored behavioral interventions or support programs for ALHIV.

REFERENCES

1. Oguntibeju OO. Quality of life of people living with HIV and AIDS and antiretroviral therapy. *HIV AIDS (Auckl)*. 2012;4:117–124.
2. World Health Organization. *Viral Suppression for HIV Treatment Success and Prevention of Sexual Transmission of HIV*. WHO News; 2018. Available at: https://www.who.int/news/item/20-07-2018-viral-suppression-for-hiv-treatment-success-and-prevention-of-sexual-transmission-of-hiv. Accessed January 02, 2024.
3. Johnson LF. Access to antiretroviral treatment in South Africa, 2004-2011. *South Afr J HIV Med*. 2012;13:22–27.
4. Myburgh H, Reynolds L, Hoddinott G, et al. Implementing 'universal' access to antiretroviral treatment in South Africa: a scoping review on research priorities. *Health Policy Plan*. 2021;36:923–938.
5. Venter F. HIV treatment in South Africa: the challenges of an increasingly successful antiretroviral programme. *South Afr Health Rev*. 2012;2012:37–47.
6. Hudelson C, Cluver L. Factors associated with adherence to antiretroviral therapy among adolescents living with HIV/AIDS in low-and middle-income countries: a systematic review. *AIDS Care*. 2015;27:805–816.
7. Zhou S, Cluver L, Shenderovich Y, et al. Uncovering ART adherence inconsistencies: an assessment of sustained adherence among adolescents in South Africa. *J Int AIDS Soc*. 2021;24:e25832.
8. Maskew M, Fox MP, Evans D, et al. Insights into adherence among a cohort of adolescents aged 12–20 years in South Africa: reported barriers to antiretroviral treatment. *AIDS Res Treat*. 2016;2016:4161738.
9. UNAIDS/UNICEF. *All in to End the Adolescents AIDS Epidemic*; 2016. Available at: https://www.unaids.org/sites/default/files/media_asset/ALLIN2016ProgressReport_en.pdf. Accessed November 27, 2020.
10. Zanoni BC, Archary M, Buchan S, et al. Systematic review and meta-analysis of the adolescent HIV continuum of care in South Africa: the Cresting Wave. *BMJ Glob Health*. 2016;1:e000004.
11. Marinda E, Simbayi L, Zuma K, et al. Towards achieving the 90–90–90 HIV targets: results from the South African 2017 national HIV survey. *BMC Public Health*. 2020;20:1375.
12. Nachega JB, Hislop M, Nguyen H, et al. Antiretroviral therapy adherence, virologic and immunologic outcomes in adolescents compared with adults in Southern Africa. *J Acquir Immune Defic Syndr*. 2009;51:65–71.
13. Reif LK, Abrams EJ, Arpadi S, et al. Interventions to improve antiretroviral therapy adherence among adolescents and youth in low-and middle-income countries: a systematic review 2015-2019. *AIDS Behav*. 2020;24:2797–2810.
14. Arage G, Tessema GA, Kassa H. Adherence to antiretroviral therapy and its associated factors among children at South Wollo Zone Hospitals, Northeast Ethiopia: a cross-sectional study. *BMC Public Health*. 2014;14:365–367.
15. Bijker R, Jiamsakul A, Kityo C, et al. Adherence to antiretroviral therapy for HIV in sub-Saharan Africa and Asia: a comparative analysis of two regional cohorts. *J Int AIDS Soc*. 2017;20:21218.
16. Brittain K, Asafu-Agyei NA, Hoare J, et al. Association of adolescent-and caregiver-reported antiretroviral therapy adherence with HIV viral load among perinatally-infected South African adolescents. *AIDS Behav*. 2018;22:909–917.
17. Casale M, Carlqvist A, Cluver L. Recent interventions to improve retention in HIV care and adherence to antiretroviral treatment among adolescents and youth: a systematic review. *AIDS Patient Care STDS*. 2019;33:237–252.
18. Chandwani S, Koenig LJ, Sill AM, et al. Predictors of antiretroviral medication adherence among a diverse cohort of adolescents with HIV. *J Adolesc Health*. 2012;51:242–251.
19. Kim H. *Longitudinal Patterns of HIV Medication Adherence at an Urban HIV Clinic*. Johns Hopkins University; 2016. Available at: https://jscholarship.library.jhu.edu/bitstream/handle/1774.2/39484/KIM-THESIS-2016.pdf?sequence=1&isAllowed=y. Accessed May 11, 2022.
20. Carrieri P, Cailleton V, Le Moing V, et al. The dynamic of adherence to highly active antiretroviral therapy: results from the French National APROCO cohort. *J Acquir Immune Defic Syndr*. 2001;28:232–239.
21. Meloni ST, Agaba P, Chang CA, et al. Longitudinal evaluation of adherence, retention, and transition patterns of adolescents living with HIV in Nigeria. *PLoS One*. 2020;15:e0236801.
22. Ross JL, Teeraananchai S, Lumbiganon P, et al. A longitudinal study of behavioral risk, adherence, and virologic control in adolescents living with HIV in Asia. *J Acquir Immune Defic Syndr*. 2019;81:e28–e38.
23. Bastard M, Fall MB, Laniece I, et al. Revisiting long-term adherence to highly active antiretroviral therapy in Senegal using latent class analysis. *J Acquir Immune Defic Syndr*. 2011;57:55–61.
24. Nagin DS, Jones BL, Passos VL, et al. Group-based multi-trajectory modeling. *Stat Methods Med Res*. 2018;27:2015–2023.
25. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol*. 2010;6:109–138.
26. de Oliveira Costa J, Schaffer AL, Medland NA, et al. Adherence to antiretroviral regimens in Australia: a nationwide cohort study. *AIDS Patient Care STDS*. 2020;34:81–91.
27. Furtado dos Santos S, Almeida-Brasil CC, Costa JDO, et al. Does switching from multiple to single-tablet regimen containing the same antiretroviral drugs improve adherence? A group-based trajectory modeling analysis. *AIDS Care*. 2020;32:1268–1276.
28. Storholm ED, Bogart LM, Mutchler MG, et al. Antiretroviral adherence trajectories among Black Americans living with HIV. *AIDS Behav*. 2019;23:1985–1997.

29. Whiteley LB, Olsen EM, Haubrick KK, et al. A review of interventions to enhance HIV medication adherence. *Curr HIV/AIDS Rep*. 2021;18:443–457.
30. Kim SH, Gerver SM, Fidler S, et al. Adherence to antiretroviral therapy in adolescents living with HIV: systematic review and meta-analysis. *AIDS*. 2014;28:1945–1956.
31. Cluver L, Pantelic M, Toska E, et al. STACKing the odds for adolescent survival: health service factors associated with full retention in care and adherence amongst adolescents living with HIV in South Africa. *J Int AIDS Soc*. 2018;21:e25176.
32. Toska E, Zhou S, Chen-Charles J, et al. Factors associated with preferences for long-acting injectable antiretroviral therapy among adolescents and young people living with HIV in South Africa. *AIDS Behav*. 2023;27:2163–2175.
33. Cluver L, Shenderovich Y, Toska E, et al. Clinic and care: associations with adolescent antiretroviral therapy adherence in a prospective cohort in South Africa. *AIDS*. 2021;35:1263–1271.
34. Hodes R, Cluver L, Toska E, et al. Pesky metrics: the challenges of measuring ART adherence among HIV-positive adolescents in South Africa. *Crit Public Health*. 2020;30:179–190.
35. Pillay U, Roberts B, Rule S, et al. *South African Social Attitudes: Changing Times, Diverse Voices*. Cape Town, South Africa: HSRC Press; 2006.
36. Edun O, Shenderovich Y, Zhou S, et al. Predictors and consequences of HIV status disclosure to adolescents living with HIV in Eastern Cape, South Africa: a prospective cohort study. *J Int AIDS Soc*. 2022;25:e25910.
37. Sherr L, Cluver LD, Toska E, et al. Differing psychological vulnerabilities among behaviourally and perinatally HIV infected adolescents in South Africa - implications for targeted health service provision. *AIDS Care*. 2018;30:92–101.
38. He E, Tolmay J, Zhou S, et al. Mode of HIV acquisition among adolescents living with HIV in resource-limited settings: a data-driven approach from South Africa. *PLoS One*. 2023;18:e0281298.
39. Duong M, Piroth L, Grappin M, et al. Evaluation of the Patient Medication Adherence Questionnaire as a tool for self-reported adherence assessment in HIV-infected patients on antiretroviral regimens. *HIV Clin Trials*. 2001;2:128–135.
40. Magadzire BP, Mathole T, Ward K. Reasons for missed appointments linked to a public-sector intervention targeting patients with stable chronic conditions in South Africa: results from in-depth interviews and a retrospective review of medical records. *BMC Fam Pract*. 2017;18:82–10.
41. Zhou S, Toska E, Langwenya N, et al. Exploring self-reported adherence measures to screen for elevated HIV viral load in adolescents: a South African cohort study. *AIDS Behav*. 2023;27:3537–3547.
42. Ostbye T, Malhotra R, Landerman LR. Body mass trajectories through adulthood: results from the national longitudinal survey of youth 1979 cohort (1981-2006). *Int J Epidemiol*. 2011;40:240–250.
43. Nabukeera-Barungi N, Elyanu P, Asire B, et al. Adherence to antiretroviral therapy and retention in care for adolescents living with HIV from 10 districts in Uganda. *BMC Infect Dis*. 2015;15:520.
44. Kacanek D, Huo Y, Malee K, et al. Nonadherence and unsuppressed viral load across adolescence among US youth with perinatally acquired HIV. *AIDS*. 2019;33:1923–1934.
45. Ndiaye M, Nyasulu P, Nguyen H, et al. Risk factors for suboptimal antiretroviral therapy adherence in HIV-infected adolescents in Gaborone, Botswana: a pilot cross-sectional study. *Patient Prefer Adherence*. 2013;7:891–895.
46. Sawyer SM, Afifi RA, Bearinger LH, et al. Adolescence: a foundation for future health. *Lancet*. 2012;379:1630–1640.
47. Nsibandze BS, Downing C, Poggenpoel M, et al. "I have been rejected so many times" experiences of female adolescents living with HIV in rural Manzini, Eswatini: a case study. *Int J Afr Nurs Sci*. 2021;14:100307.
48. Sirikum C, Sophonphan J, Chuanjaroen T, et al. HIV disclosure and its effect on treatment outcomes in perinatal HIV-infected Thai children. *AIDS Care*. 2014/09/02 2014;26:1144–1149.
49. Mugo C, Njuguna IN, Beima-Sofie K, et al. Adolescent experiences, perceptions, and preferences for the process of HIV status disclosure in Kenya. *Front Public Health*. 2023;11:1165557.
50. Damulak PP, Ismail S, Abdul Manaf R, et al. Interventions to improve adherence to antiretroviral therapy (ART) in sub-Saharan Africa: an updated systematic review. *Int J Environ Res Public Health*. 2021;18:2477.
51. Lowenthal ED, Bakeera-Kitaka S, Marukutira T, et al. Perinatally acquired HIV infection in adolescents from sub-Saharan Africa: a review of emerging challenges. *Lancet Infect Dis*. 2014;14:627–639.
52. Mody A, Eshun-Wilson I, Sikombe K, et al. Longitudinal engagement trajectories and risk of death among new ART starters in Zambia: a group-based multi-trajectory analysis. *PLoS Med*. 2019;16:e1002959.
53. Haber N, Pillay D, Porter K, et al. Constructing the cascade of HIV care: methods for measurement. *Curr Opin HIV AIDS*. 2016;11:102–108.
54. Glass TR, Battegay M, Cavassini M, et al. Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr*. 2010;54:197–203.
55. Dziva Chikwari C, Ferrand RA, Simms V. Association between self-reported adherence and HIV viral load suppression among older children and adolescents. *J Acquir Immune Defic Syndr*. 2017;76:e87–e89.
56. Kim MH, Mazenga AC, Yu X, et al. High self-reported non-adherence to antiretroviral therapy amongst adolescents living with HIV in Malawi: barriers and associated factors. *J Int AIDS Soc*. 2017;20:21437.
57. Simoni JM, Kurth AE, Pearson CR, et al. Self-report measures of antiretroviral therapy adherence: a review with recommendations for HIV research and clinical management. *AIDS Behav*. 2006;10:227–245.
58. Wilson IB, Carter AE, Berg KM. Improving the self-report of HIV antiretroviral medication adherence: is the glass half full or half empty? *Curr HIV/AIDS Rep*. 2009;6:177–186.
59. Vreeman RC, Nyandiko WM, Liu H, et al. Measuring adherence to antiretroviral therapy in children and adolescents in western Kenya. *J Int AIDS Soc*. 2014;17:19227.