Patterns of Adherence and Loss to Follow-Up in Pediatric Patients on ART in Nigeria

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Abstract: *Introduction*: High levels of adherence to antiretroviral therapy (ART) and retention in treatment programs are required for successful virologic suppression and treatment outcomes. While there have been numerous studies focusing on adherence and loss to follow-up (LTFU) in adults, studies in children and young adolescents are limited. For this study, we examined patterns of adherence and LTFU in HIV-infected pediatric patients receiving ART in PEPFAR-funded sites in Nigeria.

Methods: We conducted a retrospective observational study utilizing data that had been collected during the course of care in a large pediatric ART program in Nigeria.

Results: A total of 3,513 children ages 0-14.9 years enrolled at 31 different sites between June 2005 and March 2011 were included in the study. Of the enrolled patients, 1,987 (56%) were LTFU by the end of the study period. LTFU was highest in those ages<2 years and those ≥13 years (*versus* aged 2-12.9 years). Year of ART initiation was a strong predictor of LTFU across all age groups. For those patients retained to 12 months, less than half showed optimal adherence (≥95%). While there were no differences in adherence rates at month 12 by age group, those aged 10 years and older did have declining adherence starting at 18 months.

Discussion: Adherence is critical for optimal ART patient outcomes. We found both low adherence and high LTFU rates in our study cohort. Additional studies focused on barriers to adherence and development of age-specific intervention programs are critical to improving overall pediatric outcomes.

Keywords: Children, HIV, loss to follow-up, pediatric ART, young adolescents.

INTRODUCTION

It has been well documented that high levels of adherence to antiretroviral therapy (ART) and follow-up visit schedules are required for successful virologic suppression and treatment outcomes and retention on ART regimen is critical for prevention of HIV-related morbidity and mortality [1-9]. Several ART adherence studies from sub-Saharan Africa (SSA) revealed rates in adults ranging from 5.8% to 94.7% [10]. There is evidence that adherence rates in youth are lower than adults [11,12]. In systematic reviews that included ART programs in youth from low- and middle-income countries (LMIC), researchers revealed a median adherence rates from 49%-100% [13,14]. In addition, it is understood that compliance with drug regimens can worsen as a child gains increasing independence from parental control and risk of loss to follow-up increases as a child moves into adolescence [15], yet there are scant data on pediatric patients that are transitioning to adult care [16,17]. Retention, specifically due to loss to follow-up, has been examined in a few studies and values vary for children; one recent study examining retention rates in four countries, Kenya, Mozambique, Rwanda, and Tanzania, found that retention rates at 24 months ranged from 62% to 93%, depending on the country [12].

Since data on adherence and LTFU patterns for pediatric patients in RLS are limited, we chose to assess patterns of adherence and LTFU in pediatric patients receiving ART across various HIV care centers across Nigeria. We hypothesized that adherence and LTFU patterns might differ by age groups and evaluated various age strata to assess these variances. Additionally, we examined predictors of overall LTFU patterns by age group in order to better understand factors impacting these measures across age strata. Finally, we evaluated adherence patterns longitudinally, as a function of the age at which ART was initiated, to examine adherence patterns over long periods of time.

MATERIALS AND METHODS

Study Design and Participants

We conducted a retrospective evaluation of HIV-infected pediatric patients enrolled on ART between April 2005 and June 2011 in the Harvard/APIN PEPFAR Program in

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Nigeria. Data were collated from patients seen at a combination of 31 secondary and tertiary hospitals located in 9 states across Nigeria. The study patients ranged in age from 0-14.9 years; they entered the program either following identification of HIV infection through the prevention of mother-to-child transmission (PMTCT) clinics or through voluntary testing and counseling services (VCT). Upon enrollment in the Harvard/APIN PEPFAR HIV care program and following completion of informed consent, all patients were assessed for ART eligibility according to Nigerian National Guidelines in place at the time the patient was under treatment, which followed the relevant implemented WHO guidelines [18,19]. The recommendations utilized were as follows: 1) patients enrolled prior to 2006 were treated following the 2003 WHO recommendations; 2) patients enrolled between 2006-2010 were treated using the 2006 WHO recommendations; and, 3) those in care following adoption of the 2010 guidelines were treated following the 2010 guidelines. The study and consent forms were approved by the institutional review boards at Harvard, APIN and all of the participating Harvard/APIN PEPFAR HIV care and treatment sites.

All ART-eligible patients were placed on treatment following a clinical examination and a set of baseline laboratory tests, which included hematology, clinical chemistries, CD4+ cell count, and plasma viral load (VL) measurements. All patients seen at tertiary-level sites were provided treatment by a pediatrician through pediatric HIV services while patients at secondary sites were provided care within the general HIV care and treatment clinic. All services provided to pediatric patients, regardless of site type, were standardized and followed a prescribed regimen outlined in the Harvard/APIN Pediatric Care Guidelines that was developed by a core team of expert clinicians from Harvard, APIN and a selection of the affiliated program sites. The majority of patients were provided a 30-day supply of antiretroviral (ARV) medications. Following the first prescription pick-up, refills were obtained monthly and patients returned to the clinics every 6 months for routine laboratory monitoring unless an earlier evaluation was medically indicated. All patient data were entered and stored in electronic databases [20].

For these analyses, we included patients who initiated ART between April 2005-March 2011 to ensure at least 3 months of follow-up time for adequate determination of LTFU. All newly enrolled patients were ≤14 years of age at the time of enrollment. We excluded patients who had previous ARV experience prior to enrolling in the Harvard/APIN program and those placed on protease-inhibitor-containing regimens.

Definition of Loss to Follow-Up

Patients were classified as LTFU if, at the end of the study (29 June 2011), at least two months had elapsed since the patient's last scheduled pick-up date and they did not subsequently return. Patients who died, withdrew, or transferred to non-Harvard/APIN sites during the period of evaluation were not considered LTFU and were censored at time of discontinuation for the analyses.

Factors Associated with LTFU

For the analyses, age was stratified; after evaluating impact of age in 2-year increments and by quartiles and examining differences by categories, age was stratified into categories that were guided by clinical and developmental relevance for the general overview of demographic data, as follows: <2 years, 2-4.9 years (i.e., pre-schoolers), 5-9.9 years (i.e., early primary school-aged), 10-12.9 years (i.e., "tweens), 13-16.7 years (i.e., teenagers), which is similar to those used by another group examining LTFU in pediatric cohorts [12]. Following initial bivariate analyses and evaluations of outcome differences by age categories, groups were further collapsed to: <2 years, 2-12.9 years, 13+ years for the time to LTFU analyses; these categories were determined following within group comparisons and assertion of no difference between the collapsed groups. A number of covariates were evaluated as possible factors that might influence risk of LTFU. The demographic factors included were: sex, enrollment site (secondary *vs* tertiary site), and enrollment year (i.e., calendar year). The clinical factors considered were: ART regimen (AZT-containing regimen *vs* other), baseline CD4+ cell count (<200 cells/μL, 200-349 cells/μL, 350-499 cells/μL, 500-749 cells/μL, 750-999 cells/μL, ≥1,000 cells/μL) and baseline VL (≤400 copies/μL, 401-9,999 copies/μL, 10,000-99,999 copies/μL, ≥100,000 copies/μL), where baseline was defined as the time of ART initiation.

Measurement of Adherence

We used prescription refill timeliness (i.e., pill coverage between drug refill pick-ups), which has been validated in multiple studies as a strong surrogate for adherence [21-26], to quantify adherence patterns. To compute pill coverage, we divided the total number of pills provided during the previous pick-up by the number of days in the time period between drug pick-ups and then multiplied by 100 for an average percent adherence for the time period. Average percent adherence values were stratified into clinically relevant categories for analyses; they were stratified as optimal (≥95%), suboptimal (80%-94%), and poor (<80%), based on previously established thresholds [4].

Statistical Analyses

Bivariate comparisons of categorical variables were performed using the Chi-squared and Fisher's exact tests, as relevant, and of continuous variables using Student's t-test and the Wilcoxon rank sum test, as relevant. Statistical significance was established at an α-level of 0.05. Categorical variables were further stratified based bivariate outcomes.

Kaplan-Meier methods were employed to evaluate the cumulative probability of follow-up for patients that enrolled on ART in the Harvard/APIN PEPFAR Program from June 2005-February 2011. For the model, patients were viewed as at risk for LTFU starting at the time they initiated treatment to the date of their last pick-up, transfer, withdrawal or death. Patients were censored at the time of their last record in the databases, meaning date of death for those that died or date of last visit for those that transferred or withdrew. Cox proportional hazards models were fit to investigate

associations between baseline and demographic factors with LTFU. The log-rank test was utilized to evaluate equality across strata. Because we found significant differences in rate of LTFU by collapsed age categories (<2 years, 2-12.9 years, 13+ years), we generated separate multivariate models to better examine factors associated with LTFU by age group. Covariates that were significant at the α-level$\leq$0.20 were considered for inclusion in the multivariate models. Variables were deleted from the models in a stepwise procedure to ascertain the best fit. Random effects methods were used to control for unmeasured heterogeneity between sites.

We had previously found that adherence in the early part of treatment is a strong predictor of LTFU in adults [27] and wanted to better understand adherence patterns in pediatric patients. While we recognized that rates of LTFU were high during the first year of treatment, we wanted to examine adherence patterns in those patients that had not discontinued. For those patients that did not discontinue during the first year of ART, we examined adherence patterns by age strata. For this evaluation, we further stratified the 2-12.9 year age group to allow for further elucidation of developmentally relevant age groups. A logistic regression model was used to evaluate factors associated with non-adherence at month 12. Variables considered for inclusion in multivariate modeling were those found to be associated with non-adherence at the α-level $\leq$ 0.2 in bivariate analyses. Variables were deleted in a stepwise fashion to select the best fit. Finally, to examine the hypothesis that longitudinal adherence patterns might differ by age groups, we also evaluated average percent adherence patterns in six-month increments out to 24 months in patients, where each increment included those that were retained to the measured time point.

Because there were considerable missing CD4+ cell count data, we compared those with CD4+ cell counts to those without on the various predictor variables; overall, we found significant differences in ART initiation year, enrollment site type, and whether or not they were on an AZT-containing regimen between the two groups and, therefore, controlled for these variables in multivariate analyses examining predictors of LTFU. Since the number of patients missing VL data were also substantial, we chose to force VL in the multivariate analyses, while controlling for the variables that differed between those that had *versus* those that were missing data (i.e., ART initiation year and AZT-containing regimen). To further investigate the potential bias due to missing data, 10 rounds of multiple imputations of missing values were performed using chained equations with the assumption of missingingness at random. We found no difference in significance of covariates or overall models following multiple imputations and, therefore, present values from complete case data.

All statistical analyses were conducted using Stata version 10 (Stata Corporation, College Station, Texas, USA).

RESULTS

A total of 3,513 children, ages 0-14.9 years, enrolled between June 2005 and February 2011, were included in the study. The median age of the cohort was 3.7 years (IQR: 1.7-7.1; data not shown). Baseline demographic and clinical characteristics of the study cohort were stratified by age category (Table **1**). The cohort was 47% (N=1,649) female. The majority of patients were treated at a tertiary level hospital (91%). The median baseline CD4+ cell count was 442 cells/μL (IQR: 211-777 cells/μL) and a substantial proportion (49%) had known baseline viral loads ≥10,000 copies/μL. The majority (83%) of the patients were on AZT-containing ART regimens.

Bivariate analyses indicated that there were statistically significant differences in various patient characteristics across age groups (Table **1**). The most notable clinical differences across age groups were the baseline CD4+ cell counts; we found that younger children (<2 years) tended to have higher baseline counts than the older children. We also found a statistically significant difference in VL levels across age strata; however, these were not of high clinical relevance when actual values were compared. While there was a statistically significant difference in type of site at which patients were enrolled by age group, there were no discernible trends across groups. We found no differences in gender or ART initiation year by age category.

Patterns and Predictors of LTFU in Pediatric Patients

Overall, 1,966 (56.0%; 95% CI: 54.3%-57.6%) of the pediatric patients that initiated ART were LTFU at the end of the study period, with 26.7% (95%CI: 25.2%-28.2%) lost by month 12 and 39.7% lost by month 24 (95% CI: 38.1%-41.3%). There was an interesting trend in the LTFU rates, where the youngest (<2 years) and oldest (≥13 years) groups had higher percentages of LTFU patients than those in the age groups ranging from 2-12.9 years. In Kaplan-Meier analysis, the risk of LTFU was highest for those in the age group ≥13 years (Fig. **1**); risk was lowest for those aged 2-12.9 years.

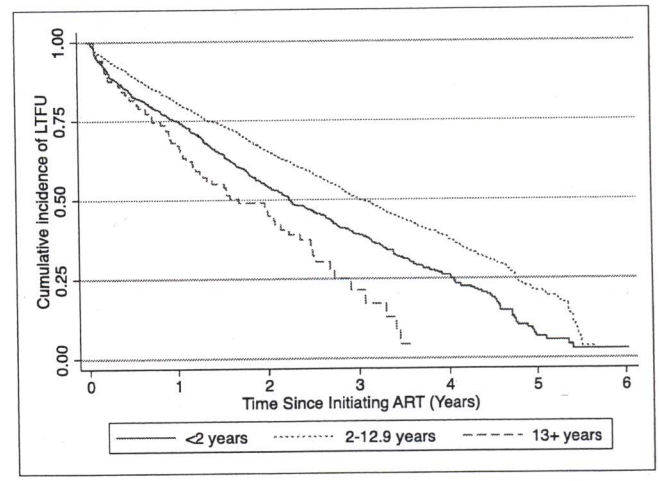

Fig. (1). Cumulative incidence of LTFU by age category.

In Cox proportional hazards models examining predictors of LTFU by age group (Table **2**), we found that the significant predictors of LTFU in those aged <2 years in unadjusted analyses were: being treated at a secondary (*vs* tertiary) site and later ART initiation year. However, following adjustment, later ART initiation year remained the only significant predictor of LTFU for those under 2 years of

Table 1. Characteristics of the HIV-infected Nigerian children that initiated ART during June 2005-March 2011, by age at ART initiation.

		Age, Years						
Variable	**Total n=3,513**	**<1 n=498**	**1-1.9 n=515**	**2-4.9 n=1,128**	**5-9.9 n=955**	**10-12.9 n=292**	**13-14.9 n=125**	**p**
Sex, n (%)								
Female	1,649 (47)	249 (50)	228 (44)	514 (46)	459 (48)	138 (47)	61 (49)	0.41
Male	1,857 (53)	247 (50)	286 (56)	613 (54)	494 (52)	153 (53)	64 (51)	
Site Type, n (%)								
Tertiary	3,184 (91)	432 (87)	461 (90)	1,015 (90)	894 (94)	263 (90)	119 (95)	<0.001
Secondary	329 (9)	66 (13)	54 (10)	113 (10)	61 (6)	29 (10)	6 (5)	
ART Initiation Year, n (%)								
2005-2006	352 (10)	44 (9)	42 (8)	126 (11)	106 (11)	27 (9)	7 (6)	0.08
2007	646 (18)	85 (17)	84 (16)	229 (20)	172 (18)	57 (20)	19 (15)	
2008	756 (22)	93 (19)	124 (24)	250 (22)	206 (22)	56 (19)	27 (22)	
2009	819 (23)	125 (25)	128 (25)	257 (23)	216 (23)	61 (21)	32 (26)	
2010-2011	940 (27)	151 (30)	137 (27)	266 (24)	255 (27)	91 (31)	40 (32)	
Baseline CD4+ Cell Count, n (%)								
<200 cells/μL	678 (19)	46 (9)	37 (8)	109 (10)	272 (28)	153 (52)	59 (47)	<0.001
200-349 cells/μL	495 (14)	44 (9)	42 (8)	141 (13)	188 (20)	55 (19)	25 (20)	
350-499 cells/μL	445 (13)	37 (7)	49 (10)	187 (17)	143 (15)	17 (6)	12 (10)	
500-749 cells/μL	507 (14)	42 (9)	94 (18)	231 (20)	112 (12)	20 (7)	8 (6)	
750-999 cells/μL	300 (9)	53 (11)	63 (12)	129 (11)	45 (5)	8 (3)	2 (2)	
≥1,000 cells/μL	461 (13)	136 (27)	119 (23)	146 (13)	53 (5)	4 (1)	3 (2)	
Missing	627 (18)	140 (28)	109 (21)	184 (16)	142 (15)	35 (12)	16 (13)	
Median (IQR)	*442 (211-777)*	*801 (349-1,365)*	*694 (398-1,083)*	*533 (338-811)*	*302 (138-504)*	*138 (51-307)*	*186 (64-325)*	
Baseline Viral Load, n (%)								
≤400	172 (5)	27 (5)	24 (5)	47 (4)	49 (5)	17 (6)	8 (7)	<0.001
401-9,999 copies/μL	302 (8)	23 (5)	39 (7)	105 (9)	88 (9)	34 (12)	13 (10)	
10,000-99,999 copies/μL	600 (17)	42 (8)	65(13)	209 (19)	197 (21)	62 (21)	25 (20)	
≥100,000 copies/μL	1,113 (32)	192 (39)	184 (36)	361 (32)	256 (27)	79 (27)	41 (33)	
Missing	1,326 (38)	214 (43)	203 (39)	406 (36)	365 (38)	100 (34)	38 (30)	
Drug Regimen, n (%)								
AZT-containing	2,913 (83)	365 (73)	376 (73)	955 (85)	860 (90)	251 (86)	106 (85)	<0.001
Other	600 (17)	133 (27)	139 (27)	173 (15)	95 (10)	41 (14)	19 (15)	
Lost to Follow-Up, % (95%CI)	56 (54-58)	60 (55-64)	59 (55-63)	54 (51-57)	54 (51-57)	57 (51-62)	63 (54-71)	

age. In the 2-12.9 years age group, the significant predictors of LTFU in unadjusted models were: receiving treatment at a secondary *versus* tertiary site, later ART initiation year, baseline CD4+ cell count ≥200 cells/μL (*vs* <200 cells/μL), and starting on an AZT-containing (*vs* other) regimen; following adjustment, all of those variables except site type remained significant predictors of LTFU. Finally, in the age group ≥13 years, the significant predictors of LTFU in unadjusted modeling were: receiving treatment at a secondary (*vs* tertiary) site and later ART initiation year; in the adjusted model, site type no longer remained a significant predictor. While those age <2 years and those aged ≥13 years had similar predictors of LTFU, those aged 2-12.9 years had additional covariates of CD4 count and ART regimen that can also be considered significant predictors of LTFU.

Adherence Patterns in Pediatric Patients

In an evaluation of patients that did not discontinue during the first year of ART, we found that the rates of optimal adherence were quite low across all the age groups, ranging from 35.2% (95%CI: 31.9%-38.6%) in those ages 2-4.9 years to 45.7% (95%CI: 34.4%-57.5%) in those aged 13 years-14.9 years (Fig. **2a**). Nearly one-quarter of children in each of the age groups demonstrated a poor level of adherence (i.e, <80% adherence). Interestingly, for those that remained on treatment through the first year, we found no significant differences in adherence patterns across age groups.

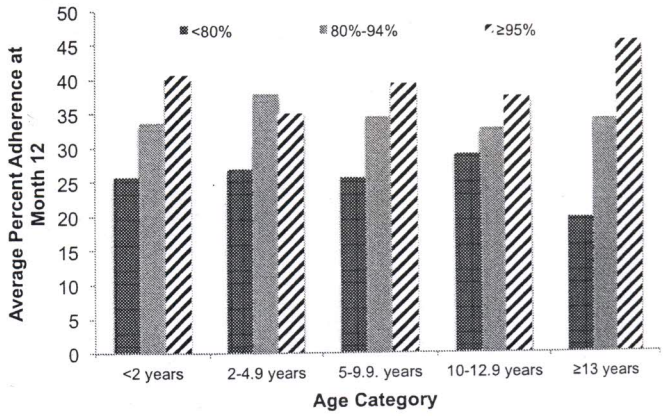

Fig. (2a). Average percent adherence from ART initiation to M12 by age group.

In the unadjusted logistic regression modeling examining predictors of optimal (≥95%) adherence at month 12 for those that did not discontinue prior to month 12, significant predictors

Table 2. Predictors of LTFU by age.

Characteristic	Age Category					
	<2 years		2-12.9 Years		13-14.9 Years	
	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	Unadjusted HR (95%CI)	Adjusted HR (95%CI)	Unadjusted HR (95%CI)	Adjusted*** HR (95%CI)
Female Sex	1.02 (0.86-1.22)		0.96 (0.86-1.09)		1.21 (0.76-1.92)	
Tertiary Site	**0.41 (0.21-0.77)**	0.97 (0.39-2.40)	**0.35 (0.17-0.70)**	0.73 (0.31-1.73)	**0.43 (0.13-1.43)**	1.03 (0.31-3.44)
ART Initiation Year						
2005-2006	**0.02 (0.01-0.03)**	**0.03 (0.001-0.010)**	**0.003 (0.002-0.005)**	**0.001 (0.0003-0.002)**	**0.09 (0.03-0.27)**	**0.09 (0.03-0.27)**
2007	**0.06 (0.04-0.10)**	**0.02 (0.01-0.05)**	**0.02 (0.01-0.02)**	**0.005 (0.003-0.009)**	**0.09 (0.04-0.22)**	**0.09 (0.04-0.22)**
2008	**0.15 (0.11-0.21)**	**0.08 (0.05-0.13)**	**0.07 (0.05-0.09)**	**0.04 (0.03-0.06)**	**0.15 (0.07-0.32)**	**0.15 (0.07-0.33)**
2009	**0.38 (0.28-0.50)**	**0.27 (0.19-0.40)**	**0.23 (0.19-0.28)**	**0.17 (0.13-0.22)**	**0.26 (0.13-0.52)**	**0.27 (0.13-0.54)**
2010-2011	Reference	Reference	Reference	Reference	Reference	Reference
Baseline CD4 Count≥200 cells/μL*	1.09 (0.80-1.49)	1.11 (0.72-1.73)	**0.74 (0.64-0.86)**	**0.85 (0.72-1.00)**	1.37 (0.82-2.30)	
Baseline VL≥10,000 copies/μL**	0.82 (0.62-1.09)	0.82 (0.61-1.11)	0.99 (0.84-1.19)	1.00 (0.84-1.20)	1.00 (0.51-1.97)	
AZT-containing regimen	0.77 (0.62-1.00)	0.96 (0.71-1.30)	**0.58 (0.48-0.71)**	**0.74 (0.59-0.92)**	0.64 (0.34-1.23)	0.90 (0.45-1.77)

* Comparator group: CD4 count<200 cells/μL.
** Comparator group: VL<10,000 copies/μL.
*** Model simplified due to requirement for optimization.

of optimal adherence were later ART initiation year, baseline CD4+ cell count <200 cells/μL (*vs* ≥200 cells/μL) and being on a non-AZT containing regimen. Following adjustment, being ages <2 or ≥13 years at ART initiation, ART initiation year, being seen at a secondary care site, and CD4 count <200 cells/μL at baseline were significant predictors of optimal adherence.

Table 3. Predictors of Adherence at Month 12 Post-initiation of ART.

Predictor	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Age		
<2 years	1.16 (0.95-1.41)	**1.17 (1.15-1.19)**
2-12.9 years	Reference	Reference
≥13 years	1.42 (0.88-2.30)	**1.22 (1.17-1.28)**
Sex		
Male	Reference	
Female	1.13 (0.95-1.35)	
Site Type		
Tertiary	Reference	Reference
Secondary	1.26 (0.86-1.83)	**2.13 (2.09-2.17)**
ART Initiation Year		
2005-2006	Reference	Reference
2007	**1.66 (1.19-2.33)**	**1.21 (1.19-1.22)**
2008	**1.90 (1.37-2.65)**	**1.53 (1.33-1.75)**
2009	**3.92 (2.84-5.43)**	**2.62 (2.39-2.88)**
2010-2011	**5.75 (3.71-8.89)**	**4.62 (4.42-4.83)**
Baseline CD4 Count		
<200 cells/μL	**1.28 (1.02-1.61)**	**1.30 (1.08-1.57)**
≥200 cells/μL	Reference	Reference
Baseline VL		
<10,000 copies/μL	Reference	Reference
≥10,000 copies/μL	1.12 (0.86-1.45)	1.14 (0.95-1.38)
Drug Regimen		
AZT-containing	Reference	Reference
Other	**1.37 (1.08-1.74)**	1.11 (0.93-1.32)

In our evaluation of longitudinal adherence patterns by age groups, we found no major differences in overall adherence at the end of year 1, but did find an interesting trend as we moved towards year 2, where patients aged ≥10 years started showed declining rates of adherence starting at month 18 (Fig. **2b**). This pattern was maintained to month 24 following initiation of ART, while adherence seemed to increase slightly for those aged <10 years. Overall, we found that only 47%-58% of children maintained a ≥95% adherence rate even at just 6 months post-initiation of ART.

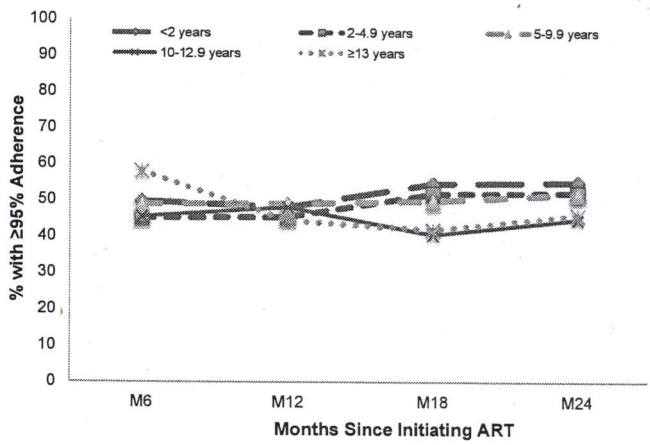

Fig. (2b). Percent of patients with optimal adherence (≥95%) by age group and time on treatment.

DISCUSSION

Our evaluation indicated an overall LTFU of 56% in pediatric patients, with approximately 27% lost by month 12 and 40% lost by month 24. We found that LTFU was higher in the youngest (<2 years) and oldest (≥13 years) age groups of pediatric patients. The overall LTFU rates in our cohort seemed to be similar [28] or higher [12,29-34] than those reported in other studies on pediatric ART patient cohorts in

SSA. It is noteworthy that some of the studies that found lower rates of LTFU used longer time windows for their definitions of LTFU; whereas our definition of LTFU required a drug refill pick-up within 2 months of the last scheduled visit, other studies defined LTFU as no recorded visit for 6 or 12 months after the last recorded visit. Interestingly, other groups have found a higher rates of LTFU in infants and/or adolescents and youth as compared to school-aged and younger adolescent children [30,35,36].

We found that ART initiation year was the only variable that remained a significant predictor of LTFU across all age groups. While most would expect that percent of patients LTFU in programs would decline with calendar year and program experience, we found the opposite to be true. We had a similar finding in another recent analysis we conducted examining LTFU in a cohort if adults receiving ART in Nigeria [27] and another group found an increasing trend in Cote d'Ivoire [34]. While we do not have qualitative data to explain reasons behind this association, we suspect that one reason might be due to decentralization as the program matured. Initially, the program enrolled patients at tertiary care sites, but then started moving towards decentralizing to secondary and primary care sites. It is possible that parents moved their children to care centers closer to their homes as more sites opened throughout the country. More focused qualitative research is required to better understand the reasons behind this trend of increased LTFU with calendar year. Furthermore, since we did find that there were additional factors associated with LTFU in children aged 2-12.9 years, future studies should also stratify by age category; this type of resolution by age group will assist programmatic staff in considering age-specific intervention strategies for reducing LTFU.

Of those retained to 12 months, less that 50% demonstrated an optimal average adherence of ≥95%. Average aggregate adherence during the first year of treatment did not appear to differ by pediatric age group. However, the proportion of patients ages ≥10 years achieving optimal adherence declined at 18 months post-initiation of ART. Rates of adherence in this evaluation, where an objective measure of adherence was used, were similar or lower than estimates from studies conducted in other pediatric populations, where more subjective measures of adherence (i.e., patient recall) were used [37-40]. Interestingly, we found that for those that were retained to 12 months, some of the predictors of having optimal adherence were in opposition to those predicting risk of LTFU. For example, children ages <2 years and ≥13 years as compared to those aged 2-12.9 years were more likely to be LTFU in the overall cohort, but amongst the retained up to 12 months, those aged <2 and ≥13 years were more likely to have optimal adherence when compared to those aged 2-12.9 years. Similarly, patients seen at secondary sites were more likely than those at tertiary sites to be LTFU, but amongst those retained to 12 months, those at secondary sites *vs* tertiary sites were more likely to demonstrate ≥95% adherence. It is interesting to note that while patients in the <2 and ≥13 year age groups are at higher risk of LTFU, they are capable of achieving levels of optimal adherence that are even better than those that are aged 2-12.9 years. That being said, the overall number of patients achieving ≥95% adherence during the first 12 months on treatment was still very low.

To date, there have been few studies focusing on older children that were transitioning to adult care. Of great concern was the high LTFU and poor adherence patterns that were documented in this vulnerable population of patients. In pediatric care services, there is a great deal of attention for a young child, but less focus as they transition to adult care. For children who do not establish strong adherence patterns while in pediatric care services, it is expected that adherence will worsen when they have less focused attention. It is of great concern that we found that nearly 50% of patients that enrolled at ages ≥13 years were LTFU within 2 years of initiating treatment. Efforts to develop focused and targeted interventions for this age group are critical to ensure a smooth transition into adult HIV treatment programs.

This study has several strengths. First, the study had a large sample size with over 3,500 patients spread across 31 sites, allowing for more generalizability of the results. Second, the evaluation utilized prospectively-collected electronic patient-level data that were captured over a span of nearly six years, which allowed for monitoring of temporal trends in LTFU and predictors over a considerable period of time. Finally, with the volume of patients, we were able to stratify pediatric patient groups into developmentally-relevant categories to better examine predictors by age group.

The study also had a few limitations that are worthy of note; similar to other ART programs, ours obtained death and transfer information in a passive manner and did not actively trace all lost patients, Therefore, we were not able to capture and analyze additional qualitative predictors of loss. Some evaluations in which researchers were able to return and trace subsets of lost patients identified that as many as 50% of those recorded as lost had actually died [41-43] while others found that patients transferred to other HIV care sites or chose to stop their treatment due to inadequate funds, food insecurity issues, fear of stigma or backlash, or various other logistical concerns [44-46]. Thus, by invoking the composite LTFU outcome and passive methods of patient tracing, we have an underestimation of those that either died or left the program. If we had the capacity to actively trace patients that were LTFU, we would have further information for our clinics to enhance their abilities to retain patients. We would also have had better opportunity to investigate if decentralization of sites contributed to the association between LTFU and calendar year. It must also be noted that adherence data were also only computed for those patients that were retained to the measured time points, thus introducing a survivor bias and a "best-case scenario"; in reality, the adherence rates would have been worse if we included those that were LTFU, died, transferred or withdrew. Finally, because our analysis included only on ART patients and we focused on outcomes starting at ART initiation, we might have missed additional predictors associated with the pre-ART phase that could potentially have further explained LTFU patterns.

As maintenance of high level adherence is fraught with challenges, various other studies have been able to capture qualitative predictors of adherence and revealed that major barriers to retention and adherence include: non-availability

of drugs, stigma and discrimination, simultaneous substance abuse, forgetfulness, suspicion of therapy, complicated regimens, reduced quality of life, work and family concerns, non-disclosure of HIV status, pill burden, drug toxicity and cost of transportation to the health facility [47-50]. The issues facing HIV-infected young adolescents are different than those typically of adults, as they must also deal with additional adolescent concerns including issues with body image, first sexual experience, mental health issues, peer pressure and identity formation [51-59].

In another meta-analysis, factors associated with pediatric ART adherence included: stigma, caregiver issues, interactions between children and their caregivers, disclosure, complexity of regimens, issues with drug side effects, and financial concerns [13]. Additional challenges in children include dependence on the adult caregiver for drug administration, appropriate drug formulation, as well as socio-economic factors affecting the caregiver and/or the child [60-62]. In Zimbabwe, researchers confirmed an association between inadequate adherence and the environment in which a child was living, thus promoting a need for family-centered approaches to providing support, allowing for focus on issues of disclosure, stigma and mental health [63].

Our findings indicate an urgent need for interventions to assist children and young adolescents with HIV to adhere to their medication regimens. Based on our findings, interventions should be targeted by age group. Further studies that focus on the structural and societal barriers to adherence and retention are critical. Patient-level and group-level interventions to address social barriers to adherence might be very useful for children and should be explored. As some limitations of our study included that we were missing data on social, structural and clinical barriers to adherence, further studies elucidating these factors in this population will be useful and will serve as a critical source for developing strong interventions.

CONCLUSION

In this evaluation of a large number of pediatric patients across Nigeria, we found relatively high rates of LTFU and sub-optimal adherence. Further, the percent of patients LTFU appeared to increase with calendar year. While some of this loss might be due to decentralization of treatment sites, more research is needed to determine the structural, contextual and social issues that contribute to these losses so that interventions can be designed to mitigate these losses. Given that current ART is effective and outcomes for those retained and fully adherent on treatment can be so successful, barriers to achieving this success must be addressed rapidly to improve outcomes for children and young adolescents on ART.

SUMMARY

Evaluation of adherence and LTFU in a large pediatric HIV treatment program revealed high LTFU and low adherence rates. LTFU and adherence patterns were worst in those aged ≥13 years as compared to those <13 years.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

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