Association of Antiretroviral Drug Regimen With Viral Suppression in HIV-positive Children on Antiretroviral Therapy in Eswatini

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Background: Global pediatric treatment goals are for 90% of known children living with HIV to be on antiretroviral therapy (ART), with 90% having viral suppression. We used enrollment data from a study evaluating a family-centered HIV care program in Eswatini to describe the ART histories and virologic outcomes of enrolled children living with HIV and identify factors associated with viral suppression (<1000 RNA copies/mL) and undetectability (<400 RNA copies/mL).

Methods: Factors associated with viral suppression and undetectability were identified using Pearson χ^2 for categorical variables and Wilcoxon rank sum tests for continuous variables.

Results: Three hundred seventy-seven children were enrolled, median age 8.5 years. Median age at HIV diagnosis was 2.1 years; at ART initiation, 2.6 years; and ART duration at enrollment, 4.1 years. Ninety-nine percent were receiving ART; 95.2% were on first-line ART and 4.8% on second-line ART. Most children (43.1%) were receiving nevirapine-based ART (median age 9.2 years), with 31.3% on lopinavir-ritonavir-based (median age 5.4 years) and 25.5%, efavirenz-based ART (median age 10.3 years). Viral suppression (<1000 copies/mL) was observed in 77.9% and undetectability (<400 copies/mL) in 73.5% of children. The only factor significantly associated with viral suppression was ART regimen, with 72.1% of children on nevirapine-based ART versus 86.7% on efavirenz-based ART virally suppressed.

Conclusions: Although 99% of children enrolled in the study were receiving ART, viral suppression was observed in only 77.9%, with lowest rates among children receiving nevirapine-based ART. These findings highlight the critical importance of monitoring treatment regimen for optimizing treatment outcomes for pediatric HIV.

Key Words:HIV, pediatric, antiretroviral, viral suppression

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An estimated 1.8 million children under the age of 15 years were living with HIV globally by the end of 2017, with most, 90%, residing in sub-Saharan Africa.[1] Globally, children under 15 years of age account for 5% of all people living with HIV, but 12% of AIDS-related deaths.[1,2] Scale-up of treatment in children has lagged behind adults; the World Health Organization (WHO) estimates only 52% of children living with HIV are receiving antiretroviral therapy (ART) despite current guidelines recommending treatment for all individuals living with HIV.[3]

Eswatini has recommended universal ART for all children under age 5 years since 2015 and rapidly adopted revised WHO guidelines in October 2016 with initiation of the "Test and Start Initiative," promoting early initiation of ART among all people living with HIV regardless of CD4 cell count or age.[4] The Eswatini Ministry of Health reported that 86% of adults and 75% of children under 15 years of age living with HIV were receiving ART in 2017.[5] Eswatini pediatric guidelines changed over time, with ART guidelines in 2010[6] recommending a nucleoside reverse transcriptase inhibitor (NRTI) backbone of zidovudine [azidothymidine (AZT)]/lamivudine (3TC), modified in 2015 to abacavir (ABC)/3TC for those <12 years and tenofovir disoproxil fumarate (TDF)/3TC for those ≥12 years and ≥40 kg.[4] The preferred third drug also changed. In 2010, nevirapine (NVP) was preferred for most children [if exposed to NVP prophylaxis and <2 years, then lopinavir/ritonavir (LPV/r) was preferred] until age ≥12 years and ≥40 kg, after which efavirenz (EFV) was preferred. In 2015, LPV/r moved to being preferred for children through age <5 years, with EFV preferred for ≧5 years. The 2010 and 2015 guidelines also specifically note that once started on ART, children should continue on their initial regimen for life unless a switch specifically indicated for toxicity, treatment failure, tuberculosis disease or simplification.[4,6]

The Elizabeth Glaser Pediatric AIDS Foundation, in collaboration with the Eswatini Ministry of Health, is conducting an evaluation of a family-centered HIV care program on pediatric viral suppression and retention in the Hhohho district of Eswatini. We used enrollment data from this study to describe the HIV and ART histories and virologic outcomes of children living with HIV enrolled in the study and to identify factors associated with viral suppression (<1000 RNA copies/mL) and undetectable viral load (<400 RNA copies/mL).

MATERIALS AND METHODS

The Elizabeth Glaser Pediatric AIDS Foundation and the Eswatini Ministry of Health are piloting a family-centered care (FAM-CARE) model in the Hhohho region of Eswatini. In this model, the child living with HIV along with other members of the household with HIV are seen together to receive HIV care and counseling services. The pilot goal is to increase initiation and adherence to ART and improve retention in care and viral suppression for children and their adult family members. The FAM-CARE study will compare viral suppression and retention in care in children in family-centered care pilot sites to those receiving the usual standard of care, with separate HIV clinics for children and adults. Eight healthcare facilities in the Hhohho region were randomized to initiate the family-centered care pilot (4 sites) or remain providing standard HIV care (4 sites).

Enrollment eligibility criteria for children included confirmed HIV infection, age <15 years and residing in a family with

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at least one other household member living with HIV; if the family included more than one child with HIV, all children were eligible to be enrolled. Caregivers, defined as the person who takes primary care responsibility for the child (not necessarily a biological parent), were eligible regardless of their HIV status. Study visits are conducted at enrollment, 3, 6, 12 and 18 months, and each visit includes caregiver interview and medical record abstraction from the child and other family members with HIV; DBS specimen is drawn from the child for HIV viral load testing at enrollment, 6, 12 and 18 months. The study protocol was reviewed and approved by the Eswatini Ministry of Health National Health Research Review Board and the Population Council Institutional Review Board.

Between September 2017 and October 2018, the study enrolled 377 children with HIV age <15 years and their 363 caregivers. The current study reports on combined enrollment interview and medical record abstraction data and enrollment viral load from children from all sites. Variables of interest included age at HIV diagnosis and ART initiation, duration of time on ART, current ART regimen and viral load. Viral load suppression was defined as plasma HIV RNA <1000 copies/mL and undetectable viral load as HIV RNA <400 RNA copies/mL.

Summary statistics were used to describe the characteristics of children (gender, age and school attendance), caregivers (gender, age, education, marital status and household composition) and HIV history of children including age at HIV diagnosis, disclosure, age at ART initiation and time on ART. ART history data including drug regimen, adherence (defined as good, 95%; moderate, 85%–95%; and poor, <85% of doses), interruptions in care, timeliness of drug pick-ups and virologic outcomes were summarized for children. Factors associated with viral load suppression and undetectable viral load in children were identified using Pearson χ^2 for categorical variables and Wilcoxon rank sum tests for continuous variables.

RESULTS

Children's characteristics and HIV history are shown in Table 1. The median age at enrollment was 8.5 years, with nearly 80% of children 6–15 years of age and only 4.1% age <3 years. All children were on ART at enrollment except one child. The median age at ART initiation was 2.6 years and median time on ART was 4.1 years. The vast majority (95.2%) were receiving first-line ART at enrollment, with only 4.8% receiving second line and none receiving third-line regimens. Figure 1 presents ART regimens among children. Among children receiving ART, 43.1% were receiving NVP-based ART regimen, most (90.0%) with a dual NRTI backbone of AZT/3TC and the remainder with ABC/3TC; 31.3% were receiving a LPV/r-based regimen (66.1% with an NRTI backbone of ABC/3TC and the remainder with AZT/3TC) and 25.5% were receiving an EFV-based regimen (68.0% with ABC/ 3TC, 27.1% with AZT/ 3TC and 5.2% with TDF/3TC. Children receiving LPV/r-based ART regimens were younger (mean age 5.4 years) than those receiving NVP (mean age 9.2 years) or EFV (mean age 10.3 years). According to medical records, 93.0% had good-to-moderate adherence to ART. Viral suppression was observed at enrollment in 77.9% (279/358) of children and undetectable viral load in 73.5% (263/358).

Caregiver characteristics are outlined in Table 2. The median age was 36 years, 92.0% were women and 44.2% married. Only 10 of 363 caregivers were HIV negative. All caregivers with HIV were receiving ART at enrollment except for one. CD4 count and viral load data, abstracted from the medical chart for caregivers, were missing for 39.2% and 51.4% of 352 caregivers living with HIV, respectively. For the 49.0% of caregivers with viral load data, rates of viral suppression (89.5%) and undetectability (87.7%) were higher than in children.

TABLE 1. Characteristics and HIV History of Children at Enrollment

	Children (N = 377) Median (IQR) or Number (%)	
Age (yr)		
Median (IQR)	8.5 (5.6–11.0)	
	N	%
Age (yr) (N = 372)		
0–1	7	1.9
2–3	8	2.1
4–5	60	16.1
6–10	177	47.6
11–15	120	32.3
Gender		
Female	186	49.3
Male	191	50.7
Child in school (N = 299)		
Yes	278	93.0
No	21	7.0
Days missed school in past 3 mo (N = 278)		
Did not miss school	177	63.7
<7 d	97	34.9
7–14 d	3	1.1
15+ d	1	0.4
Age at HIV diagnosis (yr)		
Median (IQR)	2.1 (0.8 – 5.6)	
Ever been hospitalized (N = 374)		
Yes	106	28.3
No	268	71.7
Number of hospitalizations (N = 96)		
1	73	76.1
2	17	17.7
3	6	6.2
Child knows HIV status (all ages) (N = 376)	159	42.3
Knowledge of HIV status by age (yr) (N = 371)		
0–5	75	1.8
6–10	176	31.3
11–15	120	82.5
Currently on ART		
Yes	376	99.7
No	1	0.3
Age at ART initiation (yr)		
Median (IQR)	2.6 (1.1–7.1)	
Viral load (plasma HIV RNA copies/mL)		
Missing	19	5.0
Undetectable (<400 copies/mL)		
<400 copies/ mL	263	73.5
≥400 copies/ mL	95	26.5
Viral suppression (<1000 copies/mL)		
<1000 copies/ mL	279	77.9
≤1000 copies/ mL	79	22.1

IQR, interquartile range.

Only ART regimen was statistically significantly associated with viral suppression in children. Children receiving EFV-based regimens were more likely to be suppressed (86.7%) than those on NVP- (72.1%) or LPV/r (79.1%)-based regimens ($P = 0.032$) (Table 3). Children on LPV/r were statistically significantly more likely to be suppressed when combined with the NRTI backbone of AZT/3TC versus ABC/3TC, 92.1% versus 72.7%, respectively ($P = 0.013$), although the sample size was small. While a similar trend was observed for association of regimen with undetectable viral load (80.0% EFV, 70.1% NVP and 73.0% LPV/r), this was not statistically significant ($P = 0.20$). Children receiving LPV/r were statistically significantly more likely to have undetectable viral load when combined with AZT/3TC versus ABC/3TC (86.8% vs. 66.2%, $P = 0.015$). No demographic characteristics of the

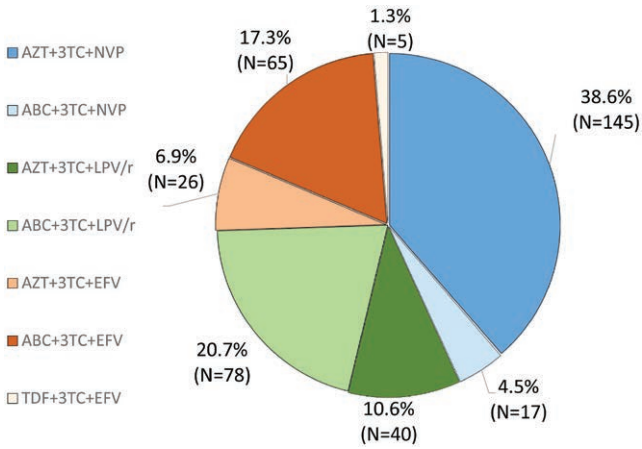

FIGURE 1. Antiretroviral treatment regimens at enrollment in study children.

TABLE 2. Characteristics and HIV History of Caregivers at Enrollment

	Caregivers, N = 363 (352 HIV positive)	
	Number	%
Gender (N = 362)		
Female	333	92.0
Male	29	8.0
HIV status (N = 362)		
Positive	352	97.2
Negative	10	2.8
Marital status (N = 362)		
Married	160	44.2
Living with partner	21	5.8
Single	118	32.6
Divorced, separated, widowed	63	17.4
Number of HIV-positive adults in caregiver household (N = 362)		
0	5	1.4
1	209	57.7
2+	148	40.9
Number of HIV-positive children (<15 yr) in caregiver household (N = 362)		
1	326	90.1
2	29	8.0
3 or 4	7	1.9
Number of HIV-positive members in caregiver household on ART (N = 362)		
1	198	54.7
2	134	37.0
3+	30	8.3
Currently on ART (N = 352)		
Yes	351	99.7
No	1	0.3
CD4 count (N = 352)		
Missing	138	39.4
<200	14	6.5
200–499	69	32.2
≥500	131	61.2
Viral load (plasma HIV RNA copies/mL) (N = 352)		
Missing	181	51.6
Undetectable (<400 copies/mL)		
<400 copies /mL	150	87.7
≥400 copies/mL	21	12.3
Viral suppression (<1000 copies/mL)		
<1000 copies/mL	153	89.5
≥1000 copies/mL	18	10.5

child or caregiver were associated with suppression or undetectable viral load, and neither age at ART initiation or ART duration was associated with either suppression or undetectable viral load. Reported adherence, interruptions in care, missed doses in the past 2 months and the last 2 drug pick-ups on time were not statistically significantly associated with suppression or undetectable viral load, although most children had moderate-to-good adherence (93.0%) and few reported missing doses (5.1%) or drug pick-ups (12.0%).

DISCUSSION

This analysis of cohort data of children age <15 years living with HIV in Eswatini showed a median age at HIV diagnosis of 2.1 years and at ART initiation of 2.6 years, and median time on ART at 4.1 years. Viral suppression was observed in 77.9% of children, similar to a large meta-analysis in children, where the rates of suppression in most recent years (since 2010) were 72.7%.[11] Although >99% of children were receiving ART at enrollment, 43.1% were receiving a suboptimal NVP-based regimen. The only factor statistically significantly associated with viral suppression was ART regimen. Children receiving EFV-based ART were more likely to have achieved viral suppression (86.7%) than children on NVP-based (72.1%) or LPV/r-based (79.1%) ART ($P = 0.032$).

Eswatini pediatric treatment guidelines have changed over time as WHO guidelines were changed.[3,4,6–10] In 2010, the preferred first-line NRTI backbone in Eswatini pediatric ART guidelines was AZT/3TC, which changed in 2015 to ABC/3TC.[4,6] The first-line preferred third ART drug also changed: in 2010, guidelines recommended NVP for most children until age ≥12 years and weight ≥40 kg (LPV/r was preferred for children <2 years with prior NVP exposure for perinatal prophylaxis).[6] In 2015, this changed to LPV/r for all children <3 years and EFV for older children.[4] Because the median age of children was 8.5 years, the majority had initiated ART under the 2010 guidelines and hence AZT/3TC/NVP predominated; only 4.0% were <3 years of age and may have started on ART with the more recent guidelines. The Eswatini guidelines do not recommend modification of an existing regimen with age, and specifically state that children already on ART should remain on their current regimen unless switch indicated for toxicity, tuberculosis, simplification or treatment failure. Thus, a significant proportion of children likely initiated ART under the 2010 guidelines and never had their regimen modified despite aging-up and guidelines changes. Limited access to viral load testing and detection of treatment failure may be another reason such a high proportion of children are still on NVP-based ART. Only 17 (4.5%) of the 379 children in this cohort were on second-line treatment and no children were on third-line treatment. A recent global analysis of the incidence of switching to the second-line therapy in children found a 3-year incidence in the African setting to be only about 2%, compared with 26% in the United States and 12% in Europe.[12]

Age at ART initiation in children has improved over time. In a multiregional study from the International Epidemiologic Data for Evaluation of AIDS including 13,611 children living with HIV from Asia-Pacific and East, Southern and Western Africa in care between 2000 and 2009, the median age at ART initiation was 5 years, with only 22% of children initiating ART before age 2 years.[13] In a separate analysis of 5485 children from the International Epidemiologic Data for Evaluation of AIDS Southern African region followed between 2007 and 2008, the median age at ART initiation was 3.5 years.[14] Age at ART initiation has further improved in our cohort, with a median age at diagnosis of 2.1 years and at ART initiation of 2.6 years, demonstrating improvement in earlier detection and treatment compared with earlier studies.

Surprisingly, children receiving LPV/r-based ART who received the dual NRTI backbone of AZT/3TC appeared to have

TABLE 3. Factors Associated With Viral Suppression (<1000 RNA copies/ mL) and Undetectable Viral Load (<400 RNA copies /mL) Among HIV-positive Children at Enrollment

	Viral Suppression N = 352)					Undetectable Viral Load (N = 352)				
	<1000 RNA copies/mL N = 280 Median or Number (%)		≥1000 RNA copies/mL N = 79 Median or Number (%)		*P*	<400 RNA copies/mL N = 264 Median or Number (%)		≥400 RNA copies/mL N = 95 Median or Number (%)		*P*
First-line regimen					0.55					0.78
Yes	261	95.6	74	93.7		245	95.3	90	94.7	
No, second- line	12	4.4	5	6.3		12	4.7	5	5.3	
Age at ART initiation					0.12					0.42
Median	2.8		1.7			2.7		1.7		
Duration on ART					0.26					0.05
Median	4.2		3.8			4.4		3.4		
ART regimen					0.03					0.20
EFV based (N = 90)	78	86.7	12	13.3		72	80.0	18	20.0	
ABC+3TC+EFV (N = 60)	50	83.3	10	16.7		45	75.0	15	25.0	
AZT+3TC+EFV (N = 25)	23	92.0	2	8.0		23	92.0	2	8.0	
TDF+3TC+EFV (N = 5)	5	100.0	0	0.0		4	80.0	1	20.0	
NVP based (N = 154)	111	72.1	43	27.9		108	70.1	46	29.9	
ABC+3TC+NVP (N = 17)	11	64.7	6	35.3		11	64.7	6	35.3	
AZT+3TC+NVP (N = 137)	100	73.0	37	27.0		97	70.8	40	29.2	
LPV/r based (N = 115)	91	79.1	24	20.9		84	73.0	31	27.0	
ABC+3TC+LPV/r (N = 77)	56	72.7	21	27.3	0.013*	51	66.2	26	33.8	0.015*
AZT+3TC+LPV/r (N = 38)	35	92.1	3	7.9		33	86.8	5	13.2	

**P* value for statistical significance of the test of independence of ABC+3TC+LPV/r and AZT+3TC+LPV/r, and viral suppression and undetectable viral load, respectively.

better suppression than those receiving ABC/3TC. While a South African study found that children receiving LPV/r- or EFV-based ART plus ABC/3TC were less likely to achieve viral suppression and higher rate of viral failure than those receiving stavudine (d4T)/3TC.[15] In contrast, a clinical trial children starting nelfinavir-based ART and randomized to AZT/3TC, AZT/ABC or ABC/3TC found ABC/3TC was virologically superior.[16] Neither d4T or nelfinavir is currently recommended antiretroviral drugs. In the CHAPAS-3 trial in Zambia and Uganda, there was no difference in virologic response in children randomized to NVP or EFV plus d4T/3TC, ABC/3TC or AZT/3TC.[17] In our study, of the 115 children receiving LPV/r-based ART, only 38 received AZT/3TC and 77 ABC/3TC, thereby limiting the sample size available for comparison and significant relationships should be interpreted with caution. Current Eswatini and WHO guidelines recommend an NRTI backbone of ABC/3TC for children age >4 weeks.[10]

A high percentage of caregivers did not have CD4 or viral load test results in their medical records, 39.2% and 52.0%, respectively. While viral load tests were obtained from children at enrollment, viral load results for caregivers were abstracted from medical records. It is not known for the caregivers if the test was conducted, but results were missing from the medical record, or if the test was not done. In either case, these findings point to an important area for improvement in HIV treatment services in study clinic sites.

While more than 99% of children enrolled in the study were receiving ART, these findings highlight the critical importance of monitoring treatment regimen for optimizing treatment outcomes for pediatric HIV and adoption and close monitoring of implementation of WHO guidelines. Programs must ensure children are initiated on and or transitioned to optimal ART regimen as recommended by WHO without delays.

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