Time to First-Line ART Failure and Time to Second-Line ART Switch in the IeDEA Pediatric Cohort

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Background: Globally, 49% of the estimated 1.8 million children living with HIV are accessing antiretroviral therapy (ART). There are limited data concerning long-term durability of first-line ART regimens and time to transition to second-line.

Methods: Children initiating their first ART regimen between 2 and 14 years of age and enrolled in one of 208 sites in 30 Asia-Pacific and African countries participating in the Pediatric International Epidemiology Databases to Evaluate AIDS consortium were included in this analysis. Outcomes of interest were: first-line ART failure (clinical, immunologic, or virologic), change to second-line, and attrition (death or loss to program). Cumulative incidence was computed for first-line failure and second-line initiation, with attrition as a competing event.

Results: In 27,031 children, median age at ART initiation was 6.7 years. Median baseline CD4% for children ≤5 years of age was 13.2% and CD4 count for those >5 years was 258 cells per microliter. Almost all (94.4%) initiated a nonnucleoside reverse transcriptase inhibitor; 5.3% a protease inhibitor, and 0.3% a triple nucleoside reverse transcriptase inhibitor–based regimen. At 1 year, 7.7% had failed and 14.4% had experienced attrition; by 5 years, the cumulative incidence was 25.9% and 29.4%, respectively. At 1 year after ART failure, 13.7% had transitioned to second-line and 11.2% had experienced attrition; by 5 years, the cumulative incidence was 31.6% and 25.9%, respectively.

Conclusions: High rates of first-line failure and attrition were identified in children within 5 years after ART initiation. Of children meeting failure criteria, only one-third were transitioned to second-line ART within 5 years.

Key Words: HIV, children, ART, failure, first-line, second-line

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BACKGROUND

As of 2015, globally, 1.8 million children were living with HIV, most of whom resided in low- and middle-income countries (LMIC).[1] Of these children (ages 0–14), 49% were accessing treatment, ranging from 20% in West and Central Africa to >95% in Europe and North America.[1,2] The effectiveness of combination antiretroviral therapy (ART) in children is undisputed, with 12-month viral suppression rates ranging from 49% to 83.3%.[3–10] However, there are limited data from LMIC concerning the long-term durability of first-line ART regimens. Because children in LMIC HIV treatment programs tend to start treatment at older ages with significant immune compromise, and are often monitored in the absence of virologic data, estimates of first-line ART durability taken from high-income settings may not be generalizable to these programs.[9,11,12] Although targeted viral load (VL) testing is currently recommended to confirm suspected failure, many

public-sector programs still rely on clinical and immunologic criteria to detect therapeutic failure, and are likely to continue to do so in full or in part because of issues with access to equipment, reagents, or availability of consistent specimen transport to reference laboratories.[13] Within this context, it is important to understand the cumulative incidence of failure and the time to transition to second-line ART.

The cumulative incidence of switch to second-line ART in children has been assessed in both clinical trials and cohort studies. However, studies vary regarding the initial ART regimen, monitoring strategy, and definitions for the switch to a second regimen. The proportion switched to second-line after 5 years on treatment in the EPPICC cohort and the PENPACT trial were 35% and 29%, respectively.[4,6] In Asia, the proportions of switch to second-line have been reported at 22% and 17.6% in cohorts with median on ART observation periods of 4.5 and 4.9 years, respectively.[14,15] However, much lower rates of switch have been reported from Sub-Saharan Africa, with one observational cohort from South Africa reporting a 3-year estimated probability of switch of only 6.2%, and the ARROW trial reporting switch rates at approximately 2 years on ART of 5%–6%.[10,16] With the exception of the ARROW trial, which identified failure based on clinical or immunologic criteria, the above studies predominately or exclusively used VL criteria for failure. As the positive predictive value of the WHO's immunologic criteria for failure has been estimated to range from 20.0% to 54.9% in children, there is a high likelihood that first-line failure is significantly underdiagnosed in studies and programs using CD4 monitoring in the absence of VL.[17] Of note, although the South African cohort only had a 6.2% cumulative incidence of switch, the cumulative incidence of virologic failure was 19.3%, thus suggesting that even in the face of virologic failure there may be issues with transitioning antiretroviral regimens.[16]

In light of the complex environment in which HIV-infected children in LMIC are being assessed for failure and transitioned to second-line regimens, the International Epidemiology Databases to Evaluate AIDS (IeDEA) consortium sought to explore the time to and factors associated with ART failure as well as change to second-line in children initiating ART between 2 and 14 years of age.

METHODS

Study Design and Setting

This retrospective cohort study used deidentified patient-level and site-level data drawn from the IeDEA Pediatric Cohort. The IeDEA consortium is composed of 7 regional data centers that collect, harmonize, and analyze data drawn from HIV care and treatment programs within their region. Data from 5 of the IeDEA Pediatric Cohorts (Asia-Pacific; East Africa; West Africa; Central Africa; and Southern Africa) are represented in this analysis.[18] The Central African clinics are represented twice as Central Africa 1.0 and Central Africa 2.0 because the clinics within the region differ between 2 periods.

This analysis was approved, as part of East Africa IeDEA, by the Indiana University Institutional Review Board as well as local, and where required, national regulatory bodies affiliated with the participating programs and regional data centers. Most of the participating sites and regulatory bodies do not require written informed consent for the use of deidentified routinely collected patient-level data.

Study Population

ART-naive HIV-infected children enrolling in care before 10 years of age and initiating their first ART regimen with a nonnucleoside reverse transcriptase inhibitor (NNRTI)–based, triple nucleoside reverse transcriptase inhibitor (NRTI)–based, or protease inhibitor (PI)–based 3–4 drug regimens between the ages of 2 and 14 years were included in this analysis. Children younger than 2 years of age were ineligible because the WHO clinical and immunologic criteria for failure were not well defined for this age group when the study was designed. Many HIV programs transition children from the pediatric to the adult clinic at 14 years and so 14 years was chosen as the upper age limit for inclusion. Children were excluded if they did not initiate a standard and consistent ART regimen, VL data were inconsistent (2 VL tests on the same day with different values), there were no visits after ART initiation, or if their age was inconsistently documented (Fig. 1).

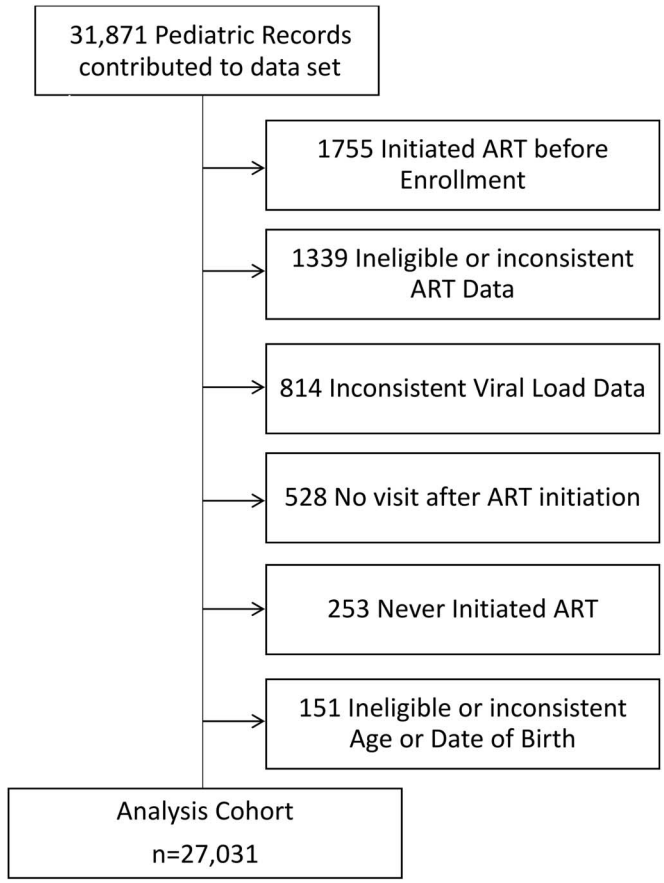

FIGURE 1. Cohort composition.

Data Collection and Management

Data were collected as part of routine clinical care using locally designed data collection instruments and then transcribed into the local electronic patient database. Laboratory studies, such as HIV VL and CD4 cell counts, were analyzed by local clinical laboratories using local protocols and procedural standards. Vital status ascertainment was variable across sites with some sites having active tracing programs for those loss to program (LTP) and other sites relying on passive death reporting.

Deidentified data were transferred from the local programs to the affiliated regional data center where data were harmonized and transfered to the East African Regional data center for creation of a single analysis data set. Data quality checks were incorporated into each step of the process. This analysis used patient-level data collected from February 1994 to February 2015 depending on region-specific data availability. Additional data were collected through 2 site-level surveys, which assessed programmatic factors such as recommended first- and second-line ART regimens, antiretroviral availability, monitoring strategies (clinical, immunologic, and/or virologic monitoring) and criteria for failure over the life of the program, as well as site characteristics such as facility type (public, academic, nonprofit/private), location (urban, rural, in-between), and population served (family [adults and children] or children only). The site-level data were assessed up to 2011-2012 for most of the programs.

Analysis

The primary outcome of interest was the time to first-line ART failure. A minimum of 24 weeks on ART were required before being eligible for an assessment of failure. Clinical failure was defined as the appearance or reappearance of a WHO stage 3 or 4 condition. Immunologic failure was defined as the development or return to age-associated CD4 cell thresholds including an absolute CD4 count of less than 200 cells per microliter or a CD4 percent of less than 10% for children aged between 2 and 5 years, as well as a CD4 count less than 100 cells per microliter for children aged 5 years or older. Virologic failure was defined as a single VL measurement exceeding 5000 copies per mL, consistent with the WHO guidelines when this analysis was designed.[13]

Throughout this analysis, the decision hierarchy for failure assumed that virologic parameters superseded immunologic parameters, which in turn superseded clinical parameters. The first VL measurement within 6 months after an immunologic or clinical failure event was used to determine the failure status. Likewise, if the first CD4 count within 2 months after a clinical failure did not meet immunologic criteria for failure, then the clinical failure was superseded by immunologic status. If a clinical failure event was documented and no immunologic or VL data were available, then the patient was considered to have failed. An example of the decision analysis: If a patient had a WHO stage-4 event and a CD4 cell count less than 100 cells per microliter but had an undetectable VL (within 6 months after the failure events) in the absence of a change in ART regimen, they were not considered to have failed their ART regimen.

The secondary outcome of interest was the time from first-line ART failure to change to second-line ART, defined as a class change in the base component (eg, NNRTI to PI or vice versa) and a change in at least one NRTI. Attrition (death or LTP) was used as a competing risk in both the time to first-line ART failure and time to change to second-line analyses. Death and LTP were viewed as the composite variable attrition in both analyses, because death is frequently underreported within Sub-Saharan African ART programs and consequently may be misclassified as LTP.[19] LTP was defined as no visit during the 6 months before database closure in the absence of documented death, transfer, or relocation outside the clinic catchment.

Covariates assessed at ART initiation included sex, WHO stage, age, CD4 and weight-for-age Z-score (WAZ), facility location, facility type, population served, whether the site began providing ART before or after 2004, site virologic monitoring (confirmatory VL, routine VL, or no VL), and composition of the first-line regimen (NNRTI versus PI-based). WHO stage was converted into a binary variable WHO-stage1–2 versus 3–4. WAZ was defined using the 2000 CDC Growth Charts for ages 0 to $<$20 years.[20] Sites that monitored VL every 6–12 months were defined as routine VL sites, whereas sites that used VL to confirm clinical or immunologic failure were defined as confirmatory VL sites. Neither the IeDEA region nor the country were included as factors in the proportional hazards model due to colinearity with other variables (eg, type of monitoring strategy).

Missing CD4 counts were imputed using a mixed-effects model with a spline in the time factor, where the outcome was the longitudinal CD4 count and the predictors included a random intercept, baseline age, sex, and the spline basis functions. The subject-specific effect was estimated from the above model, and it was used to estimate the corresponding subject's missing CD4 cell count adjusting for age at ART initiation and sex. Missing WAZ and WHO stage at ART initiation were similarly imputed using a linear regression model, where the outcome was the WAZ at ART initiation or the WHO stage, and the predictors included sex, age, and CD4 cell count at ART initiation. Children missing, at baseline, both CD4 count and WHO stage or missing both CD4 count and WAZ, as well as those with no CD4 data at any time during follow-up were excluded from the multivariable analysis but included in the univariate analysis. It should be noted that imputed quantities were used only in the multivariable models as risk factors of failure and switch to second-line ART after failure but were not used to define treatment failure (clinical or immunologic).

Medians and interquartile ranges (IQRs) for continuous variables and frequency percentages for categorical factors were calculated based on the observed data. Cumulative incidence was computed for first-line failure and second-line regimen initiation. Attrition was treated as a competing event as described earlier.

Patients not experiencing the outcome of interest or a competing event were censored on the database closure date. A cause-specific proportional hazards model was used to

identify factors associated with each outcome. Hazard ratios were calculated for each covariate in the cause-specific proportional hazards model. Because available data spanned more than 2 decades in some cases, there was the concern that some of the results of these analyses might not be generalizable to more recent calendar periods. To address this potential concern, we performed a sensitivity analysis where data were restricted to persons initiating ART during the most recent 5 years of available data (ART initiation no earlier than December 31, 2010). All analyses were implemented in R, Version 3.0.2. *P* values less than 0.05 were considered significant.

RESULTS

Data were contributed by 208 clinical sites from 30 countries. Of the 31,871 records received by the East African Regional Data Center, 4840 were not included in the analysis for one or more of the following reasons: ART initiated before enrollment; never initiated ART; ART regimen was incomplete or inconsistent; age data were inconsistent; or there were insufficient visit data (Fig. 1). Of the remaining 27,031 children, 52.8% were from Southern Africa, 27.8% from East Africa, 7.2% from Asia-Pacific, 6.4% from West Africa, and 5.9% from Central Africa (Table 1). Children came predominately from clinics that were pediatric-specific (69.1%), were publicly operated (59.4%), were located in between an urban and rural area (49.3%), and began operation before 2004 (62.9%).

The proportion of clinics reporting use of routine VL monitoring increased from 7% for 2004 to 21.2% for 2011–2012. For 2004, 99.4% of clinics reported the use of an NNRTI, 6.6% a PI, and 3.0% an NRTI-based first-line regimen. For 2011–2012, 100% of clinics reported the use of an NNRTI, 47.5% a PI, and 1.0% an NRTI-based first-line regimen. For 2004, 95.8% of clinics reported that they had access to second-line ART regimens, whereas 99.0% reported that they had access for 2011–2012.

Among the 27,031 children included in this analysis, there were nearly equal proportions of male and female children. The median age at first visit was 6.1 years (IQR: 3.5–9.1), whereas the median age at ART initiation was 6.7 years (IQR: 4.2–9.7) (Table 1). At ART initiation, the median CD4 percent for children aged <5 years was 13.2% (IQR 8.7–19.0) and the median CD4 count for children aged ≥5 years was 258 cells per microliter (IQR: 112–444). The majority (94.4%) of children initiated an NNRTI-, 5.3% a PI-, and 0.3% an NRTI-based regimen.

During 19.5 months of median follow-up after ART initiation, 4763 children were identified as having failed first-line ART with the mode of ascertainment for the earliest failure event being 32.4% by clinical, 22.2% by immunologic, and 45.4% by virologic criteria. During the same period, 6037 children experienced an attrition event. The cumulative incidence of any type of failure at 1 and 5 years after ART initiation was 7.7% [95% confidence interval (CI): 7.4–8.1] and 25.9% (95% CI: 25.6–27.0), respectively (Fig. 2A). At 1 and 5 years after ART initiation, the cumulative incidence of attrition was 14.4% (95% CI: 14.1 to 15.0) and 29.4% (95% CI: 29.1 to 30.5), respectively (Fig. 2A).

TABLE 1. Patient Demographics and Distribution by Site Characteristic

Characteristic	N	(%)
Region		
Asia-Pacific	1935	(7.2)
Central Africa 1.0	49	(0.2)
Central Africa 2.0	1550	(5.7)
East Africa	7511	(27.8)
Southern Africa	14,270	(52.8)
West Africa	1716	(6.4)
Affiliation		
Academic	2225	(8.2)
Public	16,055	(59.4)
Nonprofit	8239	(30.5)
Missing	512	(1.9)
Location		
Urban	12,413	(45.9)
Rural	860	(3.2)
In-between	13,321	(49.3)
Missing	437	(1.6)
Type		
Children only	18,685	(69.1)
Family clinics	7088	(26.2)
Missing	1258	(4.7)
Year started providing ART		
Before 2004	16,993	(62.9)
2004 and after	10,038	(37.1)
Female	13,339	(49.4)
Initial regimen type		
NNRTI-based	25,512	(94.4)
NRTI-based	80	(0.3)
PI-based	1439	(5.3)
	Median	**(IQR)**
Age at first visit	6.1	(3.5–9.1)
Age at ART start	6.7	(4.2–9.7)
CD4 count at ART start (cells/μl)*	258	(112-444)†
CD4% at ART start‡	13.2	(8.7–19.0)†

*Patients ≥5 years old.
†Closest within 90 days before and 7 days after ART initiation.
‡Patients <5 years old.

In an analysis involving the 22,257 children with available data, factors at ART initiation associated with failure or attrition, in the univariate analyses, are outlined in Table 2. In a multivariable analysis, the factors at ART initiation that were associated with a lower hazard of any type of failure were higher WAZ, higher CD4 count, enrollment at a private clinic, or a clinic starting ART provision after 2004, whereas a higher hazard of failure was associated with being male, having a higher WHO stage, initiating a PI-based regimen, or enrollment at an in-between clinic. A lower hazard of attrition was significantly associated with older age, higher WAZ, higher CD4 cell count, enrollment at a rural clinic, a family clinic, a clinic starting ART provision after 2004, or a clinic using any VL testing. Higher

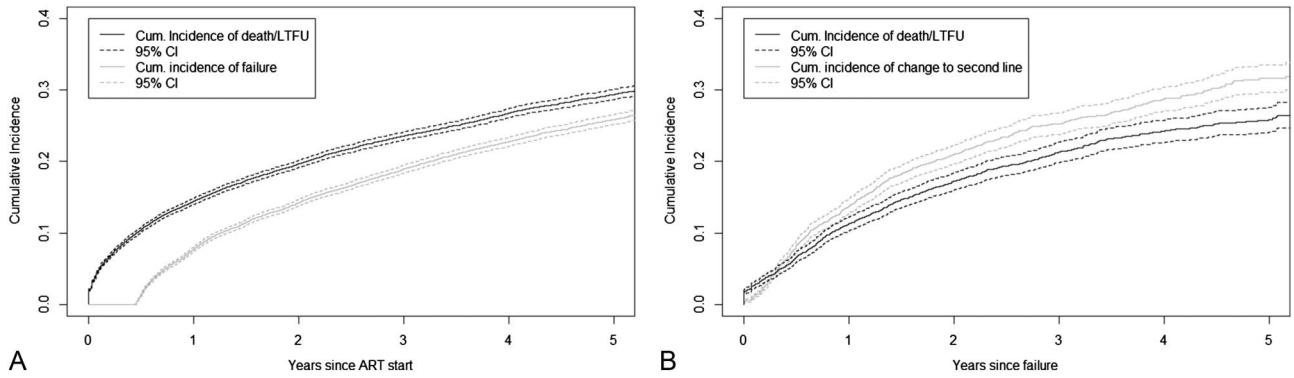

FIGURE 2. A, Cumulative incidence of failure and death/LTP after ART initiation. B, Cumulative incidence of change to second-line and death/LTP after a failure event. LTFU, lost to follow-up.

WHO stage and being enrolled at a private clinic were significantly associated with a higher hazard of attrition. In the analyses based on data from the most recent 5 years (sensitivity analyses described in the Methods, not shown), the results were virtually identical with those of the overall multivariable analyses presented above.

The 4763 patients identified with first-line ART failure were followed for a median of 14.3 months after a failure event during which 990 (20.8%) were transitioned to second-line and 833 (17.5%) had an attrition event. The cumulative incidence of switch to second-line ART for the entire cohort (irrespective of failure) at 1 and 5 years after ART initiation was 0.38% (95% CI: 0% to 1%) and 0.49% (95% CI: 0% to 1%), respectively. Among those with a documented failure event, the cumulative incidence of change to second-line at 1 and 5 years after failure was 13.7% (95% CI: 12.9 to 15.0) and 31.6% (95% CI: 30.9 to 32.4), respectively (Fig. 2B). The cumulative incidence of attrition at 1 and 5 years after failure was 11.2% (95% CI: 10.5 to 12.4) and 25.9% (95% CI: 25.1 to 28.8), respectively (Fig. 2B).

Among 4120 children with available data, factors at ART initiation associated with change to second-line ART or attrition, in the univariate analyses, are outlined in Table 3. In a multivariable analysis, baseline factors that were associated with a lower hazard of change to second-line ART after failure included a higher CD4 cell count, PI-based first-line, and enrollment in a family clinic, an in-between clinic, or an academically affiliated clinic. Being male, older, and enrolled in a clinic with confirmatory VL testing was associated with a higher hazard of switch to second-line ART. Baseline factors that were associated with a lower hazard of attrition after first-line ART failure included higher WAZ, higher CD4 cell count, enrollment in a family clinic, or an academically affiliated clinic. Receiving care at a private clinic was significantly associated with a higher hazard of attrition after failure (Table 3). In the analyses based on data from the most recent 5 years (not shown), the results were virtually identical with those of the overall multivariable analyses presented above.

DISCUSSION

This 5-region analysis of data from Sub-Saharan Africa and Asia demonstrated a high rate of first-line failure (25.9%) among children at 5 years after ART initiation. Data for comparison are limited because most studies use the rate of switch to second-line or VL failure as the outcome measures when assessing first-line ART durability, whereas our study uses a site-dependent composite failure variable that includes clinical, immunologic, and/or VL criteria. Although not directly comparable, our failure rates seem somewhat lower than those of the PENPACT trial, which reported a failure rate of 36% (VL ≥1000 copies/mL) at a median of 5 years after ART initiation.[21] Our results seem consistent with those of the ARROW trial, which reported virologic failure (>400 copies/mL) in approximately 23% of children at a median of 3.7 years and somewhat higher than data from Soweto reporting virologic failure (confirmed VL >1000) in 16.3% of children at a median of 36 months.[22]

In the multivariable analysis, failure was associated with a PI-based regimen but not with routine VL testing. This finding is counter to our a priori assumptions. An additional exploratory analysis showed that the proportion of patients on a PI-based regimen with a VL was significantly greater than individuals on an NNRTI-based regimen ($P < 0.001$). Based on this finding, we posit that there is confounding by site because the sites most likely to have routine VL testing, primarily in South Africa, also have a higher proportion of children on PI-based first-line ART. Other factors that may have contributed to the finding of an association between PI-based first-line regimen and failure include the possibility of colinearity with age (in South Africa, PI-based ART is initiated in children aged <3 years) and the use of unboosted PIs in the early phase of ART rollout in some countries. Additional factors associated with an increased hazard of failure were, not unexpectedly, related to the child's disease severity at ART initiation, including higher WHO stage, lower WAZ, and lower CD4 count. Results from the sensitivity analyses focusing on patients initiating ART during the most recent 5 years were identical to those involving the complete database. This suggests that the associations between various predictors and the cause-specific hazards of attrition or of treatment failure were generally consistent throughout the observation period and, more importantly, are still relevant in the current reality of HIV pediatric patient care.

TABLE 2. Cause-Specific Hazard Ratios and 95% Confidence Intervals for Factors Associated With First-Line ART Failure or Attrition in a Competing Risk Analysis

	Univariate			Multivariate		
Factor n = 22,257	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Failure						
Sex						
Female	Ref			Ref		
Male	1.092	1.031–1.156	0.003	1.100	1.034–1.169	0.002
Age per year	1.027	1.018–1.036	<0.001	0.999	0.988–1.009	0.788
WAZ per sd	0.945	0.931–0.960	<0.001	0.960	0.945–0.976	<0.001
CD4 count per 50 cells/μL	0.963	0.958–0.968	<0.001	0.960	0.954–0.965	<0.001
WHO per stage	1.222	1.146–1.304	<0.001	1.142	1.064–1.225	<0.001
Regimen						
NNRTI	Ref			Ref		
PI	1.090	0.964–1.232	0.169	1.482	1.284–1.712	<0.001
Clinic type						
Public	Ref			Ref		
Academic	1.183	1.083–1.292	<0.001	0.990	0.866–1.131	0.880
Nonprofit/ private	0.562	0.520–0.607	<0.001	0.375	0.320–0.440	<0.001
Clinic location						
Urban	Ref			Ref		
Rural	1.235	1.061–1.438	0.006	1.090	0.826–1.113	0.318
In-between	0.868	0.818–0.921	<0.001	1.121	1.039–1.208	0.003
Clinic type						
Children only	Ref			Ref		
Family clinic	1.328	1.249–1.412	<0.001	0.959	0.826–1.113	0.580
Clinic started providing ART						
Before 2004	Ref			Ref		
2004 or after	1.091	1.029–1.157	0.003	0.880	0.802–0.965	0.007
VL availability						
None	Ref			Ref		
Confirmatory	1.300	1.101–1.536	<0.001	1.638	1.349–1.989	<0.001
Routine	1.391	1.175–1.647	<0.001	1.078	0.878–1.323	0.475
Death/lost to program						
Sex						
Female	Ref			Ref		
Male	1.002	0.952–1.054	0.941	0.990	0.935–1.048	0.727
Age per year	0.987	0.979–0.995	0.001	0.980	0.971–0.989	<0.001
WAZ per sd	0.861	0.850–0.871	<0.001	0.893	0.880–0.906	<0.001
CD4 count per 50 cells/μL	0.990	0.986–0.994	<0.001	0.991	0.987–0.995	<0.001
WHO per stage	1.198	1.131–1.270	<0.001	1.112	1.042–1.186	0.001
Regimen						
NNRTI	Ref			Ref		
PI	1.023	0.915–1.144	0.689	1.008	0.868–1.171	0.918
Clinic type						
Public	Ref			Ref		
Academic	1.061	0.960–1.173	0.243	0.876	0.759–1.011	0.071
Nonprofit/ private	2.056	1.949–2.169	<0.001	1.431	1.264–1.621	<0.001
Clinic location						
Urban	Ref			Ref		
Rural	0.627	0.508–0.773	<0.001	0.626	0.493–0.796	<0.001
In-between	1.520	1.442–1.602	<0.001	1.033	0.953–1.119	0.435
Clinic type						
Children only	Ref			Ref		
Family clinic	0.791	0.745–0.841	<0.001	0.843	0.752–0.944	0.003
Clinic started providing ART						
Before 2004	Ref			Ref		
2004 or after	0.684	0.647–0.723	<0.001	0.874	0.792–0.964	0.007
VL availability						
None	Ref			Ref		
Confirmatory	0.691	0.625–0.764	<0.001	0.577	0.506–0.658	<0.001
Routine	0.442	0.397–0.492	<0.001	0.364	0.310–0.426	<0.001

At 1 year after first-line failure, the cumulative incidence of reaching one of the study endpoints of change to second-line ART (13.7%) or attrition (11.2%) was 24.9%. Thus, 75.1% of children, 1 year after meeting criteria for first-line failure, were still in care and on a first-line regimen. The 1-year rate of switch to second-line therapy in our analysis is significantly lower than that previously reported by the Southern Africa IeDEA region (38% within 1-year of virologic failure).[16] Although the data in this analysis are insufficient to explore factors contributing to a physician's assessment of failure, our findings that a lower CD4 count was associated with an increased probability of switch and that a PI-based regimen was associated with a lower probability of switch, similar to the South African analysis, suggest that multiple factors impact a clinician's decision to transition a patient to second-line ART.[16] Delays in switch to second-line may be related to clinician concerns about the diagnostic accuracy of the failure criteria, the availability or

TABLE 3. Cause-Specific Hazard Ratios and 95% Confidence Intervals for Factors Associated With Change to a Second-Line ART Regimen or Attrition in a Competing Risk Analysis

	Univariate			Multivariate		
Factor n = 4120	**HR**	**95% CI**	***P***	**aHR**	**95% CI**	***P***
Change to second-line ART						
Sex						
Female	Ref			Ref		
Male	1.287	1.133–1.463	<0.001	1.317	1.147–1.513	<0.001
Age per year	1.089	1.069–1.110	<0.001	1.043	1.020–1.067	<0.001
WAZ per sd	0.971	0.938–1.006	0.101	0.999	0.961–1.039	0.969
CD4 count per 50 cells/μL	0.925	0.911–0.937	<0.001	0.930	0.9176–0.946	<0.001
WHO per stage	0.990	0.858–1.143	0.895	0.969	0.818–1.126	0.613
Regimen						
NNRTI	Ref			Ref		
PI	0.387	0.260–0.576	<0.001	0.355	0.221–0.572	<0.001
Clinic type						
Public	Ref				Ref	
Academic	0.632	0.510–0.783	<0.001	0.354	0.254–0.494	<0.001
Nonprofit/private	1.149	0.964–1.369	0.121	0.839	0.594–1.186	0.321
Clinic location						
Urban	Ref				Ref	
Rural	0.553	0.361–0.847	0.006	0.709	0.443–1.136	0.152
In-between	0.889	0.780–1.012	0.076	0.839	0.705–0.997	0.046
Clinic type						
Children only	Ref				Ref	
Family clinic	0.720	0.627–0.827	<0.001	0.521	0.375–0.725	<0.001
Clinic started providing ART						
Before 2004	Ref				Ref	
2004 or after	0.782	0.687–0.891	<0.001	1.009	0.826–1.231	0.932
VL availability						
None	Ref				Ref	
Confirmatory	1.321	0.825–2.118	0.244	1.767	0.687–1.274	0.040
Routine	1.851	1.150–2.964	0.010	1.604	0.886–2.902	0.119
Death/lost to program						
Sex						
Female	Ref			Ref		
Male	1.042	0.908–1.194	0.563	1.049	0.901–1.221	0.539
Age per year	1.024	1.003–1.044	0.023	0.996	0.970–1.020	0.732
WAZ per sd	0.907	0.874–0.941	<0.001	0.921	0.885–0.959	<0.001
CD4 count per 50 cells/μL	0.979	0.968–0.990	<0.001	0.977	0.963–0.989	0.001
WHO per stage	0.980	0.836–1.149	0.803	0.900	0.756–1.071	0.236
Regimen						
NNRTI	Ref			Ref		
PI	0.923	0.691–1.232	0.585	0.842	0.587–1.208	0.351
Clinic type						
Public	Ref			Ref		
Academic	0.799	0.642–0.995	0.045	0.532	0.374–0.757	<0.001
Nonprofit/private	1.685	1.419–2.002	<0.001	1.447	1.033–2.029	0.032
Clinic location						
Urban	Ref			Ref		
Rural	0.695	0.453–1.067	0.096	0.714	0.439–1.161	0.175
In-between	1.010	0.877–1.162	0.893	0.747	0.614–0.910	0.004
Clinic type						
Children only	Ref			Ref		
Family clinic	0.766	0.659–0.890	<0.001	0.714	0.494–0.942	0.039
Clinic started providing ART						
Before 2004	Ref			Ref		
2004 or after	0.764	0.663–0.880	<0.001	0.921	0.695–1.115	0.487
VL availability						
None	Ref			Ref		
Confirmatory	0.805	0.549–1.179	0.265	0.828	0.541–1.267	0.385
Routine	0.835	0.568–1.228	0.360	0.624	0.379–1.027	0.064

effectiveness of subsequent ART regimens, as well as implementation of interventions to improve adherence.

The use of routine VL monitoring was not associated with a higher likelihood of switch after failure, but was associated with a trend toward a lower likelihood of attrition after failure. This finding persisted in the sensitivity analysis focusing on patients initiating ART during the most recent 5 years of data; thus, the increasing use of routine VL in the most recent period did not modify the association between various predictors and the likelihood (hazard) of initiating second-line ART regimens. Because the endpoint for this analysis was the first failure event, in neither the initial analysis nor in the sensitivity analysis did we assess whether or not patients subsequently suppressed their VL without a regimen change. It is possible that a detectable VL triggered an adherence intervention that subsequently led to

suppression, which obviated the need for a regimen change. In addition, academic and family-based clinics were less likely to transition patients to second-line, but also had lower hazards of attrition after failure compared with public or child-only clinics. This leads us to speculate that these clinics may implement adherence intervention strategies, triggered by identification of a failure event, before enacting a transition to second-line ART.

Because the data used in this analysis came from HIV clinical programs, there are a number of weaknesses in the study. Death was passively reported by most programs. Consequently, there is the potential for individuals who have died to be misclassified as being LTP.[23] In addition, individuals who are LTP may be engaged in HIV care at another program. As such, the composite attrition variable (death or LTP) constitutes a suboptimal summary of the patient experience after leaving a program. However, we anticipate that a significant proportion of patients classified as LTP either died or completely disengaged from care; given that both these events compete for the identification of failure, we believe that structuring the analysis in this way allows for the most conservative estimates, given the limitations of these data. In addition, this analysis may underestimate LTP as children who have no follow-up time on ART were excluded from this analysis; however, because retention was not the focus of this analysis, this does not impact the key findings of this article. As noted previously, failure was identified as the first episode of meeting clinical, immunologic, or viral criteria, and interventions other than a change to second-line therapy may have occurred (eg, adherence counseling, referral to a support group, assignment of a peer navigator, etc.). Unfortunately, alternative interventions could not be assessed in this analysis. In addition, missing data on clinical events and laboratory testing such as CD4 cell counts and VLs may have led to an underestimate of the cumulative risk of failure over time.

Despite these significant limitations, the strengths of this analysis are that the data are from a large geographically diverse cohort that is representative of the HIV-infected pediatric population receiving ART in Sub-Saharan Africa and Asia. In addition, this is one of the few studies that has been able to assess the incidence of failure, based on the monitoring strategies used by the programs, and assess time from an indication of failure to transition to second-line ART.

In conclusion, based on this analysis, approximately a quarter of pediatric HIV patients in Sub-Saharan Africa and Asia experience at least one failure event within 5 years of ART initiation. However, the rate of change to second-line ART regimens was low. Further studies are needed to understand how HIV program health care providers assess and respond to treatment failure events.

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