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Follow-Up Outcomes of Children, Adolescents, and Young People on Darunavir-Based Third-Line Antiretroviral Therapy: Observational Cohort From 9 African Countries

Vincent J. Tukei, MBChB, MMed, MPH,[a] Rhoderick Machekano, PhD,[b] Boris K. Tchounga, MD, PhD,[c] Philisiwe Ntombenhle Khumalo, BA Soc. Sci, PGDipPH, MSW,[a] Rachel Tumwebaze, MPH,[d] Mildrate Murandu, Bsc Applied Maths, Msc Epi,[e] Shannon Viana, MA,[b] Rose Otieno Masaba, MD MSc-Epi,[f] Majoalane Mokone-Mwape, BSN, MPH,[g] Lameck Chirwa, MSc,[h] Simba Mashizwa, MB ChB, MPH,[e] Natella Rakhmanina, MD, PhD,[b] and Appolinaire Tiam, MD, PhD,[b] The New Horizon's Study Team

Background: We assessed clinical outcomes among children, adolescents, and people younger than 25 years on darunavir-based antiretroviral therapy (ART) in 9 sub-Saharan African countries.

Setting: Third-line ART centers in Cameroon, Eswatini, Kenya, Lesotho, Nigeria, Rwanda, Uganda, Zambia, and Zimbabwe.

Methods: From January 2019 to December 2022, we collected data from a cohort of children, adolescents, and young people receiving third-line ART from 9 sub-Saharan African countries. Data on treatment continuity, viral suppression, death, and clinic transfers were extracted from medical records and summarized. Cox proportional hazards models were used to identify factors independently associated with retention in care.

Results: Of 871 participants enrolled, the median age was 14.8 (range: 0.2–24.7) years and 488 (56.0%) were male; 809 (92.9%) [median duration of follow-up of 28.3 months (interquartile range: 17.5–45.2)] had final outcomes after initiating third-line ART. Of these, 711 (87.9%) were alive and in care at the end of study follow-up, 29 (3.6%) died, 30 (3.7%) were transferred to other facilities, and 39 (4.8%) were lost to follow-up. Retention in care was less likely among male patients compared with female patients [aHR: 0.85, 95% confidence interval: 0.72 to 1.0] and in 10–14-year-old children compared with younger children. Adolescents (15–19 years old) had higher mortality compared with children younger than 10 years (aSHR: 4.20, 95% confidence interval: 1.37 to 12.87). Viral suppression was seen in 345/433 (79.7%), 249/320 (77.8%), and 546/674 (81.0%) patients with results at 6 months, 12 months, and study end, respectively.

Conclusions: A high proportion of children and young people receiving third-line ART in sub-Saharan Africa remain in care and attain viral suppression during follow-up.

Key Words: children, adolescents, HIV, darunavir, third-line antiretroviral therapy

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INTRODUCTION

Sub-Saharan Africa has the largest HIV epidemic in the world. The region is home to an estimated 25.6 million people living with HIV (PLHIV), which corresponds to two-thirds of the global estimates.[1] By the end of 2022, 83% of patients with PLHIV in East and Southern Africa and 78% in Central and West Africa were on antiretroviral therapy (ART). As governments in the region strive to achieve the Joint United Nations Programme on HIV/AIDS (UNAIDS) 95-95-95 targets, the number of people on ART is expected to rise. Most of these patients will continue with their first-line ART; however, patients with treatment failure will need second and third-line ART. As ART programs improve on viral load testing and identification of treatment failure, the number of patients requiring third-line ART is likely to increase.[2–5]

There are a few options for third-line ART. Clinical trials and cohort data, mainly from treatment-experienced adult populations, have shown that second-generation non-

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From the [a]Elizabeth Glaser Pediatrics AIDS Foundation, Mbabane, Eswatini; [b]Elizabeth Glaser Pediatrics AIDS Foundation, Washington, DC; [c]Elizabeth Glaser Pediatrics AIDS Foundation, Yaounde, Cameroon; [d]Elizabeth Glaser Pediatrics AIDS Foundation, Kampala, Uganda; [e]Elizabeth Glaser Pediatrics AIDS Foundation, Harare, Zimbabwe; [f]Elizabeth Glaser Pediatrics AIDS Foundation, Nairobi, Kenya; [g]Elizabeth Glaser Pediatrics AIDS Foundation, Maseru, Lesotho; and [h]University Teaching Hospital, Lusaka, Zambia.

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Correspondence to: Vincent J. Tukei, MBChB, MMed, MPH, Elizabeth Glaser Pediatric AIDS Foundation, Second Floor, Sicenphetelo MVA Fund Office Park, Mbhilibhi Road, Mbabane, Eswatini (e-mail: vtukei@pedaids.org).

nucleoside reverse transcriptase inhibitors (NNRTIs) such as etravirine (ETR), second-generation protease inhibitors (PIs) such as darunavir (DRV), and integrase strand transfer inhibitors (InSTIs) such as raltegravir (RAL) are efficacious options for third-line ART.[6–10] Over the last decade, the World Health Organization, while acknowledging the limited evidence available, has encouraged national programs to develop third-line ART policies that include new drugs such as INSTIs and second-generation NNRTIs and PIs with minimal risk of cross-resistance to previously used regimens.[11–13] Many HIV programs in sub-Saharan Africa have implemented treatment protocols based on these World Health Organization guidelines; however, evidence on the effectiveness of these third-line ART options in a region with little access to genotypic resistance testing remains scarce. There is a paucity of evidence on patient outcomes, particularly among children and adolescents who are often disadvantaged by unavailability of age-appropriate drug formulations. This study assessed clinical outcomes of children, adolescents, and people younger than 25 years, who ever received a DRV or ETV-based ART regimen from 9 sub-Saharan African countries. Specifically, we report on viral suppression, treatment continuity, death, clinic transfers, tuberculosis, and other infections among patients receiving DRV and/or ETV ART from public and private health facilities in the 9 countries.

METHODS

Study Design and Setting

This was an observational cohort study of children, adolescents, and young people receiving third-line ART in 9 sub-Saharan African countries that included Cameroon, Eswatini, Kenya, Lesotho, Nigeria, Rwanda, Uganda, Zambia, and Zimbabwe. These countries were part of a collaborative program (the New Horizons Pediatric Care Collaborative) that provided no-cost access to darunavir and etravirine as second and third-line treatment for children, adolescents, and young adults. Transition to third-line treatment was based on individual country protocols. In general, patients on at least 6 months of second-line ART who had viral loads greater than 1000 copies/mL received intensified or enhanced adherence counseling and a repeat viral load test after 3 months. Genotypic tests, whenever available, were performed on patients with persistent viremia. A multidisciplinary team of expert clinicians discussed and determined the appropriate third-line options for such patients based on the information available.

We collected cohort data from all HIV treatment centers providing third-line ART to children, adolescents, and young people living with HIV (CAYPLHIV) and offering DRV or ETV as part of third-line HIV treatment for CAYPLHIV in the 9 sub-Saharan African countries. Information on health facilities offering third-line ART and on the number of CAYPLHIV receiving treatment in the facilities was obtained from the Ministries of Health of the participating countries. The health facilities included health centers, hospitals, and specialized ART centers where third-line ART was offered to CAYPLHIV. Information on children receiving treatment at each health facility and details of their medical records were provided by the health facilities.

Participants

We included all HIV-positive patients younger than 25 years who were on DRV and/or ETV or had ever received these drugs as part of their ART at the study facilities. From January 2019 to December 2022, we reviewed health facility records and extracted relevant study data for all eligible study participants. At study initiation, we extracted cohort data to cover the period of DRV/ETV treatment before participant enrollment; thereafter, prospective follow-up data were collected from health facility records every 6 months for the duration of the study.

Data Sources and Study Variables

We used a structured electronic questionnaire to collect data from paper and electronic source documents used at the health facilities. Study information was extracted from individual patient charts/cards, electronic medical records, and registers used for patient care and follow-up. Registers were reviewed to identify all patients who had ever received DRV or ETV at the facilities. Patient files were assigned unique study numbers, and relevant study information was extracted. Information on patient demographics (age and gender), anthropometry, ART regimen, duration on DRV and/or ETV, and follow-up outcomes, including loss to follow-up, transfer to nonstudy sites, and death, was extracted and entered into a secure study database. Loss to follow-up was defined based on individual country protocols for patient follow-up and the records in the source documents. Patients with viral loads of less than 1000 copies/mL were considered to have attained viral suppression,[14] and death among cohort participants was defined based on the information available in the health facility documents.

Statistical Methods

We summarized baseline patient characteristics using frequencies and proportions for categorical variables and means (with standard deviations) or medians (with interquartile ranges) for continuous variables. Treatment outcomes were also summarized using frequencies and proportions. We used Kaplan–Meier graphs to describe retention in care and time to death. For each baseline characteristic, we evaluated the proportional hazards assumption by checking for parallel lines in plots of –log{–log(survival) versus log(time) for each category before fitting a bivariable Cox regression model. For the final multivariable models, we performed a universal test for proportional hazards based on testing for association between scaled Schoenfeld residuals and time using a χ^2 test as well as visual inspection of the scatterplot of scaled Schoenfeld residuals and time. We identified factors independently associated with retention in care using a multivariable Cox proportional hazards model. Hazard ratios and associated 95% confidence intervals (CI) were used to assess the strength of association. Unverified loss to follow-up is

sometimes due to patient death. We therefore used a competing-risk Fine and Gray model to examine factors associated with mortality, in which mortality and loss to follow-up are considered competing events.

Ethics

Thirteen institutional review boards and ethics committees reviewed and approved the study protocol. They included the Advarra Institutional Review Board (United States), the National Committee of Research Ethics for Human Health (Cameroon), the National Health Research Review Board (Eswatini), the Baylor College of Medicine Children's Foundation—Eswatini IRB, the Kenyatta National Hospital-University of Nairobi Ethics and Research Committee (Kenya), the Ministry of Health Research and Ethics Committee (Lesotho), the Baylor College of Medicine Institutional Review Board (Lesotho), the National Health Research Ethics Committee of Nigeria, the National Ethics Committee (Rwanda), Makerere University Higher Degrees, Research, and Ethics Committee (Uganda), the Uganda National Council for Science and Technology, the University of Zambia Biomedical Research Ethics Committee, and the Medical Research Council of Zimbabwe.

The study focused on the review of participant records and did not involve any direct interaction with the participants. A waiver of consent was granted by the institutional review boards and ethics committees. All study staff were trained on human subject protections, and confidentiality of patient records was maintained by use of unique identification numbers assigned to each record.

RESULTS

A total of 871 participants enrolled in the study; 488 (56.0%) were male, 178 (21.2%) were children younger than 10 years , 248 (29.5%) were 10–14 years old, 268 (31.9%) were 15–19 years old, 146 (17.4%) were young people aged 20–24 years, and 31 had no records of age. Before initiation of third-line ART, nearly one-half (48.3%) of participants received an NRTI combination that consisted of tenofovir (TDF) and lamivudine (3TC) or emtricitabine (FTC) while a few participants received an NRTI backbone that consisted of 3TC/FTC (3.8%) or TDF (1.5%) (Table 1).

TABLE 1. Baseline Characteristics of 871 Children, Adolescents, and Young People Who Received DRV or ETV ART From 9 African Countries

Baseline Characteristic	N (%)
Sex	
Female	383 (44.0)
Male	488 (56.0)
Age category (yr)	
<10	178 (21.2)
10–14	248 (29.5)
15–19	268 (31.9)
20–24	146 (17.4)
Missing	31
Country	
Cameroon	18 (2.1)
Eswatini	106 (12.2)
Kenya	68 (7.8)
Lesotho	14 (1.6)
Nigeria	13 (1.5)
Rwanda	5 (0.6)
Uganda	465 (53.4)
Zambia	46 (5.3)
Zimbabwe	136 (15.6)
NRTI backbone before third-line ART	
TDF + 3TC/FTC	421 (48.3)
ABC + 3TC/FTC	79 (9.1)
AZT + 3TC/FTC	72 (8.3)
3TC/FTC only	33 (3.8)
TDF only	13 (1.5)
Other	253 (29.0)
Agents combined with NRTI backbone	
LPV/r	478 (54.9)
NVP	18 (2.1)
ATV/r	216 (24.8)
EFV	54 (6.2)
DTG	57 (6.5)
Other	48 (5.5)
Had a baseline viral load	
No	105 (12.1)
Yes	766 (87.9)
Viral suppression reported within 6 months before DRV/ETV initiation (copies/mL)	
≤1000	75 (10.5)
>1000	636 (89.5)
Missing	55

Follow-Up Outcomes

Of 871 study participants, 11 did not have baseline data and another 51 had no follow-up information. Baseline and follow-up outcomes were available for 809 (92.9%) participants; the median duration of follow-up was 28.3 months [interquartile range (IQR): 17.5–45.2]. Figure 1 shows the patient flow from DRV and/or ETR initiation to study end.

Of the participants with follow-up outcomes, 449 (55.5%) were male; the median age was 14.8 years (range: 2 months–24.7 years), with the majority (61.5%) being older children, adolescents and young people aged 10–19 years (Table 2). Approximately 80% of participants had previously been on a PI-based ART regimen before starting DRV and/or ETR, of which 451 (55.7%) had been on lopinavir/ritonavir (LPV/r) and 190 (23.5%) on atazanavir/ritonavir (ATV/r). Most (87.9%) of the participants had a baseline viral load performed within a 12-month period before DRV and/or ETR initiation, and 89.5% of those with viral load results were unsuppressed (Table 2). At the end of the study, 711 (87.9%) participants were alive and in care, 29 (3.6%) had died, 30 (3.7%) transferred to other health facilities, and 39 (4.8%) were lost to follow-up.

Figure 2A shows retention in care over time. At 6 months following initiation of DRV and/or ETR, 98.4% of the participants remained in care, with the proportion gradually reducing to 97.4% at 12 months and 86.8% at 5 years of

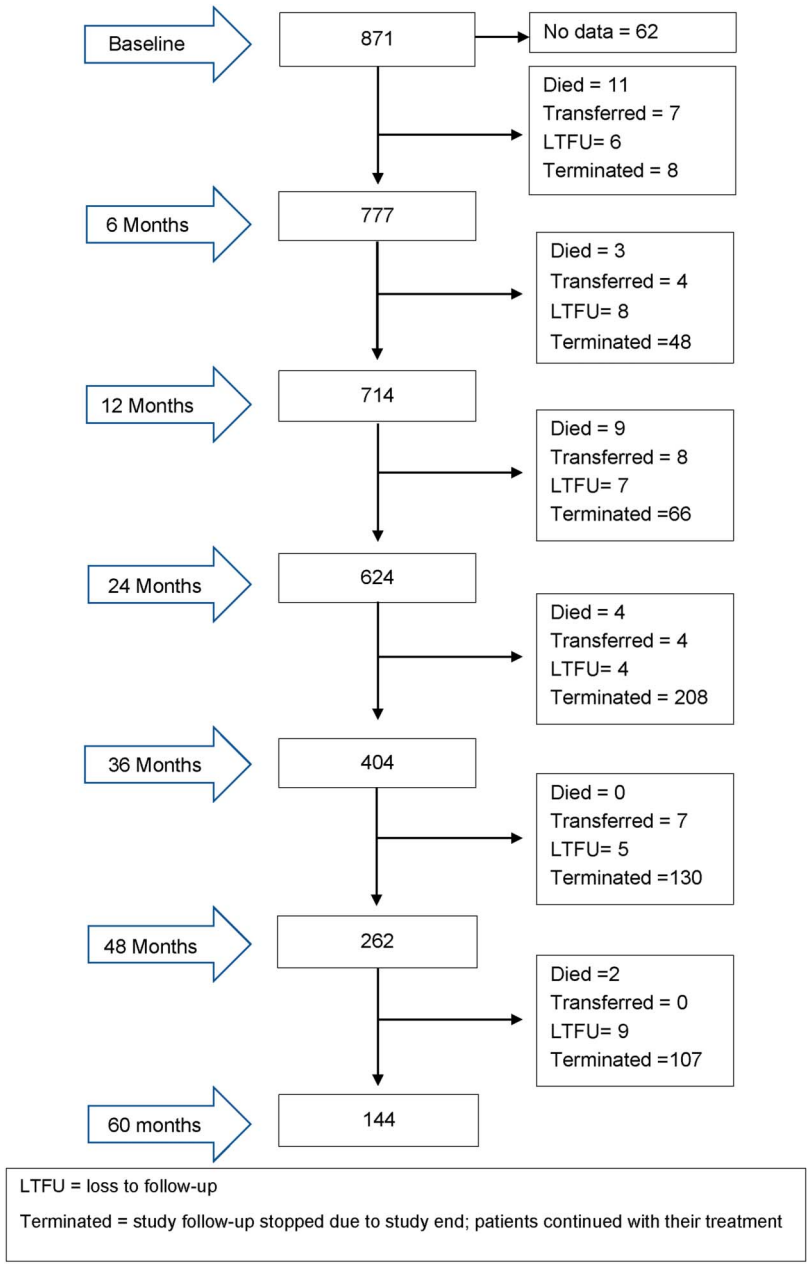

FIGURE 1. Follow-up outcomes of 871 children, adolescents, and people younger than 25 years receiving DRV and/or ETV ART in 9 sub-Saharan African countries.

treatment follow-up. Figure 2B displays the mortality rate from DRV and/or ETR initiation by age group. Almost half of the total deaths were observed in the first year of DRV and/or ETR initiation (14/29). There were no significant differences in the mortality rates across age categories (log-rank $P = 0.158$). Among participants who died, 24 of 29 had baseline viral load tests and none had viral suppression at the time of DRV and/or ETV initiation (Table 2).

Factors Associated With Retention in Care and Death During Follow-Up

Compared with their female counterparts, male participants were less likely to be retained in care (aHR: 0.85, 95% CI: 0.72 to 1.0), although the difference was of borderline statistical significance. Children aged 10–14 years were less likely to remain in care compared with younger children; however, no significant differences in retention were seen with other age categories (Table 3). Conversely, participants receiving the DRV + DTG–based third-line regimen were more likely to be retained in care compared with participants on other third-line ART regimens (aHR: 4.38, 95% CI: 3.48 to 5.53).

Adolescents aged 15–19 years had significantly higher mortality compared with children younger than 10 years (aSHR: 4.20, 95% CI: 1.37 to 12.87), and patients on DRV + DTG had significantly lower hazards of death compared with patients on other third-line regimens (aSHR: 0.20, 95% CI: 0.09 to 0.45).

TABLE 2. Baseline Characteristics of 809 Participants With Follow-Up Outcomes From a Cohort of Children, Adolescents, and Young People on Third-Line ART in 9 Sub-Saharan African Countries

	Follow-Up Outcomes				
	Alive and in Care (n = 711)	Died (n = 29)	Transferred (n = 30)	Lost to Follow-Up (n = 39)	Total (n = 809)
Variable	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Sex					
Female	321 (45.1)	10 (34.5)	11 (36.7)	18 (46.2)	360 (44.5)
Male	390 (54.9)	19 (65.5)	19 (63.3)	21 (53.8)	449 (55.5)
Age (yrs)					
<10	151 (22.0)	4 (13.8)	8 (27.6)	4 (10.5)	167 (21.4)
10–14	207 (30.2)	7 (24.1)	8 (27.6)	12 (31.6)	234 (30.0)
15–19	205 (29.9)	15 (51.7)	9 (31.0)	17 (44.7)	246 (31.5)
20–24	122 (17.8)	3 (10.3)	4 (13.8)	5 (13.2)	134 (17.1)
Missing	26	0	1	1	28
ART before DRV and/or ETR					
LPV/r	395 (55.6)	20 (69.0)	15 (50)	21 (53.8)	451 (55.7)
NVP	14 (2.0)	0 (0.0)	1 (3.3)	2 (5.1)	17 (2.1)
ATV/r	167 (23.5)	7 (24.1)	6 (20.0)	10 (25.6)	190 (23.5)
EFV	47 (6.6)	0 (0.0)	2 (6.7)	4 (10.3)	53 (6.6)
DTG	46 (6.5)	1 (3.4)	2 (6.7)	1 (2.6)	50 (6.2)
Other	42 (5.9)	1 (3.4)	4 (13.3)	1 (2.6)	48 (5.9)
Regimen at enrollment to DRV or ETR-based third line					
DRV/r + DTG + NRTI	381 (53.6)	7 (24.1)	14 (46.7)	13 (33.3)	415 (51.3)
DRV/r + DTG only	109 (15.3)	1 (3.4)	4 (13.3)	5 (12.8)	119 (14.7)
DRV/r + 2 NRTIs	72 (10.1)	5 (17.2)	6 (20.0)	3 (7.7)	86 (10.6)
DRV/r+ RAL only	24 (3.4)	2 (6.9)	0 (0.0)	2 (5.1)	28 (3.5)
DRV/r + ETR + RAL + NRTI	39 (5.5)	7 (24.1)	1 (3.3)	4 (10.3)	51 (6.3)
DRV/r + ETR + RAL only	31 (4.4)	4 (13.8)	4 (13.3)	5 (12.8)	44 (5.4)
ETR + DTG + DRV/r	24 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	24 (3.0)
Other	31 (4.4)	3 (10.3)	1 (3.3)	7 (17.9)	42 (5.2)
Baseline viral load a year before or up to 1 mo after DRV and/or ETV					
Viral load test not performed	79 (11.1)	5 (17.2)	6 (20.0)	8 (20.5)	98 (12.1)
Viral load test performed	632 (88.9)	24 (82.8)	24 (80.0)	31 (79.5)	711 (87.9)
Viral suppression at baseline (before DRV and/or ETV) (copies/mL)					
≤1000	72 (11.4)	0 (0.0)	2 (8.3)	1 (3.2)	75 (10.5)
>1000	560 (88.6)	24 (100.0)	22 (91.7)	30 (96.8)	636 (89.5)

A total of 433 participants had viral load tests 6 months after initiating DRV and/or ETR. Of these, 345 (79.7%) were virally suppressed. Viral suppression was seen in 249 (77.8%) of 320 participants with test results at 12 months of follow-up and in 546 (81.0%) of 674 participants with results at study end.

Comorbidities: Tuberculosis and Malaria

From the entire cohort of 871 CAYPLHIV on DRV and/or ETR-based ART, 55 (6.3%) participants were diagnosed with tuberculosis, 28 (3.2%) of them were diagnosed within the 6 months before transitioning to DRV and/or ETR ART while 27(3.1%) were diagnosed after initiation of DRV and/or ETR-based treatment. Of all cohort patients ever diagnosed with tuberculosis, 7 (12.7%) died, 4 (7.3%) were lost to follow-up, and 2 (3.6%) were transferred to other health facilities.

Fifty-four (6.2%) participants were reported to have had at least 1 malaria episode during follow-up. Of these, 29 (53.7%) had malaria in the 6 months preceding the transition to DRV and/or ETR ART while 25 (46.3%) had malaria episodes after initiation of DRV and/or ETV ART. Of the 25 diagnosed with malaria after transition to DRV and/or ETR ART, 3 (12.0%) died, 1 (4.0%) was lost to follow-up, and 1 (4.0%) transferred to another health facility.

DISCUSSION

This study evaluated outcomes of children, adolescents, and young people receiving third-line ART in 9 sub-Saharan African countries. Our results show favorable outcomes of

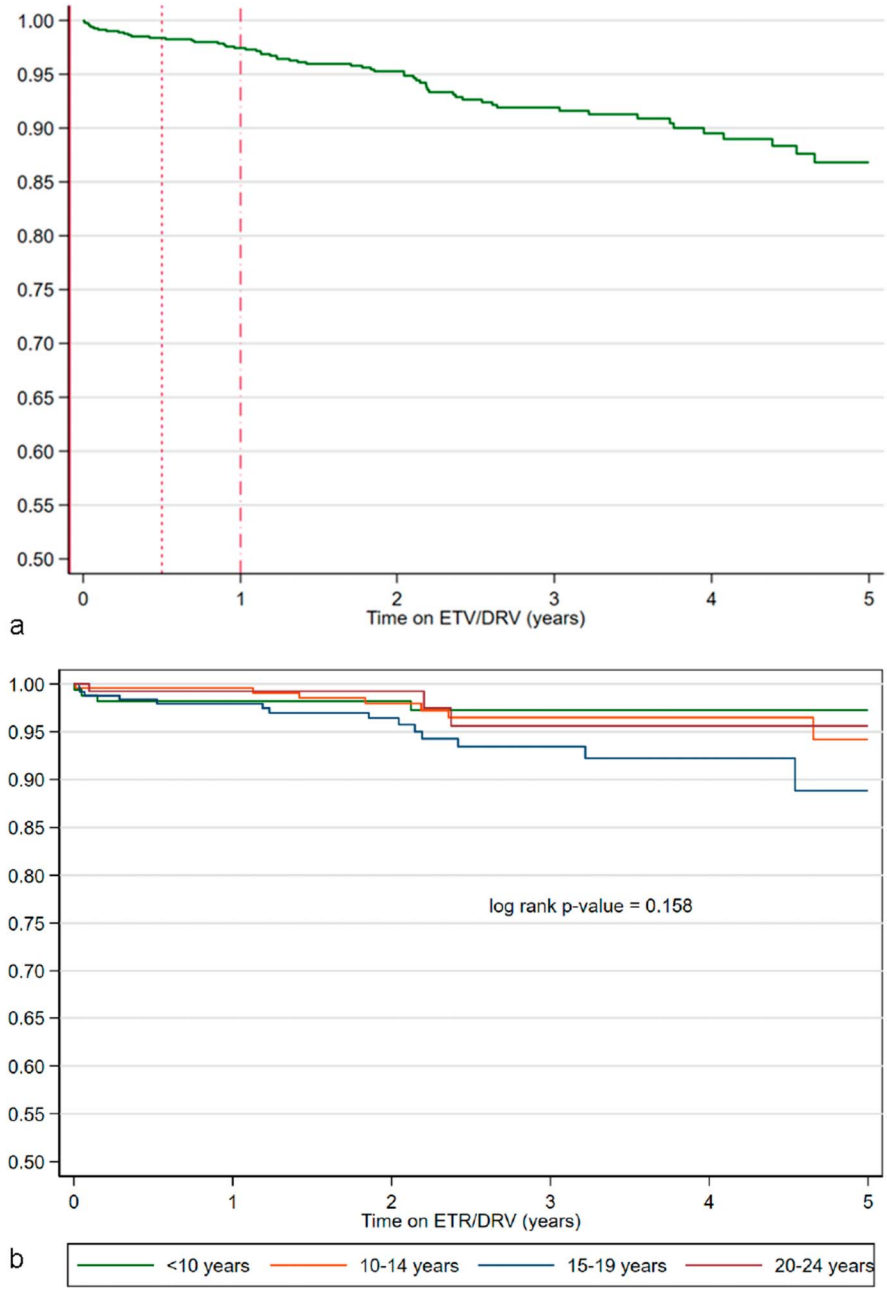

FIGURE 2. A, Retention in care among children, adolescents, and people younger than 25 years receiving DRV and/or ETV ART in 9 sub-Saharan African countries. B, Mortality over time in a cohort of children, adolescents, and young people (disaggregated by age group) on DRV and/or ETV ART from 9 Sub-Saharan African countries.

follow-up, as demonstrated by the high proportion (87.9%) of CAYPLHIV remaining alive and continuing with their third-line treatment and low mortality of 3.6% seen during follow-up. In addition, nearly 80% of patients who had a viral load test after 6 months of DRV and/or ETR ART attained viral suppression. This level of viral suppression was sustained at 12 months of follow-up, and by study end, most (81%) of the participants continued to have viral suppression.

Comparison data from other cohorts of children, adolescents, and young people on third-line ART are very scanty; however, the virologic response seen in our cohort is consistent with outcomes reported from several adult cohorts within sub-Saharan Africa. In Zimbabwe, 79% of adults in government clinics and 83% of similar patients from a private clinic attained viral suppression after 6 months of third-line ART.[15] In Zambia, the proportion with viral suppression seen among adult patients was 78.9%,[16] and in South Africa, 83% of adults from the public sector attained viral suppression.[17]

Because of limited access to effective medicines for the management of treatment-experienced patients in many resource-limited settings, national protocols for third-line ART often vary widely. Depending on drug availability, some protocols include DRV with or without ritonavir, RAL, and ETV combined with NRTIs that are often recycled from previous treatments. These variations in treatment protocols, coupled with the unavailability of services for HIV resistance

TABLE 3. Factors Associated With Retention in Care and Mortality in a Cohort of Children and Adolescents on Third-Line ART in 9 Sub-Saharan African Countries

	Retention in Care			Mortality		
Characteristic	**Unadjusted HR (95% CI)**	**Adjusted HR (95% CI)**	***P***	**Unadjusted SHR (95% CI)**	**Adjusted SHR (95% CI)**	***P***
Sex: Male	0.95 (0.82 to 1.10)	0.85 (0.72 to 1.0)	0.049	1.43 (0.66 to 3.10)	1.44 (0.67 to 3.11)	0.346
Age group: (ref <10 yrs)						
10–14	1.02 (0.83 to 1.26)	0.77 (0.60 to 0.98)	0.034	1.27 (0.37 to 4.38)	1.76 (0.51 to 6.08)	0.370
15–19	1,25 (1.01 to 1.54)	0.80 (0.62 to 1.03)	0.080	2.59 (0.84 to 8.03)	4.20 (1.37 to 12.87)	0.012
20–24	1.80 (1.42 to 2.28)	0.79 (0.59 to 1.06)	0.144	1.16 (0.25 to 5.32)	2.56 (0.60 to 10.90)	0.204
Baseline viral load: ≤1000 (reference >1000)	0.99 (0.78 to 1.26)	1.16 (0.89 to 1.50)	0.279	<<	<<	<0.001
DRV + DTG (reference other third-line regimens)	4.10 (3.41 to 4.93)	4.38 (3.48 to 5.53)	<0.001	0.26 (0.11 to 0.62)	0.20 (0.09 to 0.45)	<0.001
NRTI backbone						
TDF + 3TC/FTC	Ref	1.15 (0.87 to 1.53)	0.322	2.34 (0.80 to 6.84)		
ABC + 3TC/FTC	0.94 (0.73 to 1.23)	1.08 (0.76 to 1.52)	0.683	1.14 (0.31 to 4.29)		
AZT + 3TC/FTC	0.59 (0.45 to 0.77)	0.36 (0.23 to 0.57)	<0.001	0.58 (0.08 to 3.95)		
3TC/FTC only	0.26 (0.18 to 0.39)	1.12 (0.52 to 2.40)	0.765	<<		
TDF only	0.43 (0.21 to 0.87)	0.50 (0.41 to 0.62)	<0.001	0.81 (0.31 to 2.13)		
Other	0.48 (0.41 to 0.57)	1.15 (0.87 to 1.53)	0.322	2.34 (0.80 to 6.84)		

testing in some settings, complicate the comparison of treatment outcomes. However, despite the variations in treatment, the favorable virologic outcomes seen in this cohort provide some optimism for the increasing number of growing children, adolescents, and young people in need of third-line ART.

Many of the third-line drug formulations available to our participants were single-agent formulations, which when taken together cause pill burden that potentially leads to poor adherence. This draws attention to the importance of developing fixed-dose antiretroviral combinations for children and adolescents on third-line therapy.

The high number of CAYPLHIV who remained alive and in care throughout the follow-up period was a key finding of this study. Nearly all participants remained in care 6 months after initiating third-line ART, and many continued to receive their ART at the health facility that initiated the third-line treatment. While it is important for all HIV-positive patients to continue with their ART, remaining in care is particularly critical for patients who are on third-line ART. For such patients, effective treatment options are markedly reduced, hence the need for strict adherence to clinic appointments and prescribed treatment. We observed better retention among participants on the DRV + DTG-based regimen compared with those on other regimens, in female patients compared with male patients, and in young children (0–9 years) compared with older children (10–14 years). It is possible that the DRV + DTG regimen may be better tolerated with less pill burden than other treatment options.

Challenges of retaining adolescents in HIV care and treatment have been well documented and are not unique to third-line therapy.[18,19] While the task of keeping young children in care is often the responsibility of adult caregivers, growing adolescents with increasing level of independence are often left to cater for their own health needs. The reduced adult supervision and care leads to poor adherence to medication and clinic visits, which subsequently results in loss from treatment programs. In addition, issues related to disclosure of HIV status may explain the disengagement from care seen in early adolescent years.[18,20,21] Previous studies have not demonstrated gender differences in retention in care for adolescents on HIV treatment[19]; in our study, male CAYPLHIV were less likely than female CAYPLHIV to be retained in care, though this difference was of borderline statistical significance.

Mortality among study participants was reassuringly low. We, however, note that nearly half of the deaths occurred within the first year of transition to DRV and/or ETV. These early deaths may be an indication of delays in transition of patients from the failing ART regimen to more effective treatments.[22] In addition, this early mortality underscores the need for close monitoring of patients who may be clinically unstable at the time of third-line ART initiation.

Tuberculosis diagnosed in the 6 months preceding DRV and/or ETV initiation, or during follow-up, was an important contributor to morbidity and mortality. The diagnosis of tuberculosis before switching to DRV and/or ETV ART indicates development of advanced HIV disease in patients who continued to take the failing ART regimen. This finding highlights the need for timely and prompt initiation of third-line ART.

Our study had several limitations. We relied on data from patient charts and health facility registers. The integrity of these data depended on the accuracy and completeness of information recorded in the source documents. Viral load coverage for patients on treatment was suboptimal. The treatment response of patients who did not get viral load tests remained unknown. In addition, differences in the regimen given to patients in clinics across the 9 countries may have distorted the magnitude of some of the outcomes

observed. Finally, due to the observational nature of the study, randomization of exposure was not conducted. The possibility of bias in the associations assessed cannot be eliminated.

The cohort includes participants of a wide age range, whose outcomes are often expected to differ widely. While this may potentially be a limitation, which was partly addressed in the statistical analysis used, the exceedingly large size of this cohort of CAYPLHIV receiving third-line ART from a region worst affected by HIV and least resourced to manage treatment-experienced patients living with HIV is a cardinal strength of this evaluation.

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