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Characteristics of Treatment-Experienced HIV-infected African Children and Adolescents Initiating Darunavir and/or Etravirine-based Antiretroviral Treatment

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ABSTRACT

Background: Data are limited on the selection and sequencing of second and third-line pediatric antiretroviral treatment (ART) in resource-limited settings. This study aimed to evaluate characteristics of African pediatric patients initiated on darunavir (DRV) and/or etravirine (ETR) through a specific drug donation program.

Methods: This was a cross-sectional study of baseline immunologic, virologic and demographic characteristics of children and adolescents initiating DRV- and/or ETR-based ART. Descriptive statistics were used.

Results: Study enrolled 48 patients (45.8% female; median age=15 years (IQR 17.7-10.3)) at nine clinical sites in Zambia, Swaziland, Kenya and Lesotho. The majority (87.5%; n=42) had received ≥ 2 prior ART regimens; most (81.2%) had received lopinavir/ritonavir-based ART prior to switch. All patients had detectable HIV RNA (median=56,653 copies/mL). Forty seven (98.9%) patients had HIV genotype results: 41 (87.2%) had ≥1 nucleos(t)ide reverse transcriptase inhibitor (NRTI)-resistance mutation (RM), predominantly M184V (76.6%; n=36); 31 (65.9%) had ≥1 non-NRTI-RM, including 27 (57.4%) with ≥1 ETR-RM; 30 (63.8%) had ≥ 3 protease inhibitor RM, including 20 (42.6%) with ≥ 1 DRV-RM. For new ART regimens, DRV and raltegravir were most frequently prescribed (83.3%; n=40 on DRV and raltegravir, each). Eighteen patients (37.5%) were initiated on the NRTI-sparing ART.

Conclusions: In our study, a significant proportion of treatment-experienced African children and adolescents had one or more DRV-RM and ETR-RM. For the new regimen, more than a third of pediatric patients failing second-line ART, were prescribed NRTI-sparing regimens. Better understanding of the current approaches to pediatric ART sequencing in resource-limited settings is needed.

INTRODUCTION

Pediatric antiretroviral treatment (ART) programs have experienced steady growth during the last decade; however, as of 2015, it was estimated that only approximately half of 1.8 million children living with HIV had access to ART.[1] Inadequate capacity to evaluate and support ART adherence, insufficient access to and utilization of viral load testing and limited availability of pediatric antiretroviral (ARV) drugs formulations for young infants continue to hamper the efficacy and success of ART among children and adolescents.[1, 2] In recent years, scale-up of pediatric ART for has become a priority of national HIV/AIDS programs in response to the The Joint United Nations Programme on HIV and AIDS (UNAIDS) 90-90-90 targets, the 2016 recommendations for universal ART by the World Health Organization (WHO), and the Accelerating Children's HIV/AIDS Treatment (ACT) initiative.[2-4] As more children and adolescents are initiated on treatment, the number of pediatric patients living with HIV who require second- or third-line ART is likely to increase.[5-11]

The 2016 WHO consolidated HIV treatment guidelines recommend that national HIV/AIDS programs address treatment failure and develop ART sequencing guidance that include ARV drugs unlikely to have cross-resistance with currently recommended first- and second-line ART regimens.[3,12-13] To date, evidence on current WHO-recommended second- and third-line ART regimens for pediatric patients is limited.[14] The protease inhibitor (PI) darunavir (DRV) boosted with ritonavir (RTV) (approved for use in children ≥3 years)[15] and non-nucleoside reverse transcriptase inhibitor (NNRTI) etravirine (ETR) (approved for use in children ≥6 years)[16] were both recommended for consideration for second- and third-line ART agents for adults and children in the 2010 and 2013 editions of the WHO ART guidelines.[17, 18]

Since then, ETR moved to the role of an alternative NNRTI, while RTV-boosted DRV retained its role in the updated 2016 version.[3]

In 2013, the New Horizons (NH) Advancing Pediatric HIV Care Collaborative drug donation program was launched by the Janssen Pharmaceutical Companies of Johnson & Johnson (Janssen) to provide access to DRV and/or ETR for treatment-experienced HIV-infected children and adolescents through eligible national HIV/AIDS programs in Sub-Saharan African and/or least developed countries as per the United Nations.[19] The Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) provides coordination and technical support to the NH Collaborative since its inception in 2013. As of July 2016, the NH Collaborative drug donation program had been implemented in Zambia, Swaziland, Kenya and Lesotho. This study aimed to evaluate the ART, immunologic, virologic and demographic characteristics of children and adolescents with who were initiated on DRV and/or ETR through the NH Collaborative donation program.

METHODS

Study Design

This was a cross-sectional study of baseline data from children and adolescents in four African countries (Zambia, Swaziland, Kenya and Lesotho) who became recipients of DRV and ETR through the NH donation program. The participating health care facilities (HCFs) and eligible patients were identified through collaboration with relevant Ministries of Health (MOHs).

Eligibility Criteria

The study protocol received approvals from the central ethics committees in each country. Patient and/or guardian consent was waived, as study data collection did not involve direct contact with any patient, neither did it collect any personally identifying information. All

patients aged 0 up to 24 years who were prescribed the NH donated DRV and/or ETR were eligible for study data collection.

Data Source and Variables

Individual patient level data were extracted from medical charts at the participating pediatric and adult healthcare facilities in relevant countries. Demographic data included age and gender. ARV characteristics included prior ART regimens (up to five most recent ART combinations) and concomitantly prescribed ARV drugs. Virologic characteristics included most recent HIV RNA viral load and HIV resistance results (including drug specific mutations). Immunologic characteristics included most recent CD4 cell count and CD4%. All laboratory parameters were collected at the closest time point prior to initiation on DRV- and/or ETR-based ART. History of concomitant tuberculosis at the time of DRV and/or ETR initiation was also recorded. A designated EGPAF study coordinator conducted review of medical charts and data extraction at all sites. Aggregated de-identified data were entered into a single electronic secure database stored at EGPAF.

Data Analysis

Data were analyzed in aggregate across all sites and countries. Descriptive statistics were used for analyses of ART, demographic, immunologic and virologic characteristics. HIV drug resistance mutations (DRM) were interpreted according to the Stanford University HIV Drug Resistance (ttps://hivdb.stanford.edu).

RESULTS

During the period between November 2015 and June 2016, data were collected on 48 children and adolescents (45.8% female, 54.2% male; median age=15 years; 4 patients >19 years

of age) participating in the NH program from nine urban HCFs in Zambia, Swaziland, Kenya and Lesotho. (Table 1)

The majority (87.5%; n=42) of patients had received ≥ 2 ART regimens prior to initiation on DRV and/or ETR. (Table 1) The median duration of most recent ART regimen was 23 months; most patients (81.2%) had received lopinavir/ritonavir (LPV/RTV) based ART. There was no history of PI exposure other than LPV/RTV among participants. HIV RNA viral load testing was performed among all patients (n=48) at a median of 138 days (IQR 280-58 days) prior to initiation on DRV and/or ETR. Viremia with a median HIV RNA of 56,653 copies/mL was present in the majority (95.8%; n=46) of patients. Two patients had HIV RNA <1000 copies/mL. No patient was documented to have active tuberculosis at the time of the ART regimen change.

The majority (98.9%; n=47) of patients had an HIV genotype test performed prior to DRV and/or ETR initiation. (Table 2) Thirty (63.8%) patients had ≥ 3 PI-resistant mutations (RMs), of whom 42.6% (n=20) had ≥ 1 DRV- RM. The most predominant PI-RMs were M46I (38.3%; n=18), V82A (38.3%; n=18), and I54V (36.2%; n=17). A majority of patients (87.2%; n=41) had ≥ 1 nucleos(t)ide reverse transcriptase inhibitor (NRTI)-RM, predominantly M184V (76.6%; n=36). The most common thymidine analogue mutations (TAMs) were D67N (51.1%; n=24) and M41L (38.3%; n=18). More than half (65.9%; n=31) of patients had ≥ 1 NNRTI-RM, among them 57.4% (n=27) had ≥ 1 ETR-RM. Three out of four younger patients (≤5 years of age) had at least one nevirapine (NVP) RM documented; all four received prior LPV/RTV-based ART, and data on maternal single-dose NVP exposure for any patient were not available.

New ART regimens contained an average of 4 ARVs. DRV and the integrase inhibitor (INSTI) raltegravir (RAL) were the most frequently prescribed ARVs (83.3%; n=40 started on

DRV and RAL, each). DRV/RTV/ETR/RAL (33%; n=16), DRV without NNRTI or INSTI (12.5%; n=6), and ETR without PI or INSTI (2.1%; n=1). In one patient (14.8 years) DRV was prescribed without RTV boosting. Eighteen patients (37.5%) were initiated on the NRTI-sparing ART regimens.

DISCUSSION

Consistent with current WHO HIV treatment guidelines [3] in our study, treatment-experienced African children and adolescents underwent viral load testing prior to the second and third-line ART switch. Equally consistent with the 2013 and 2016 WHO HIV treatment guidelines, [3, 18] DRV was primarily used in pediatric patients with treatment failure and prior exposure to a PI-based regimen (LPV/RTV). As reported in other studies, treatment-experienced children with viral failure in our cohort had high rates of multidrug resistance as evidenced by genotype testing.[5-11]

There was a single patient who received DRV without recommended pharmacokinetic (PK) boosting with RTV. DRV dosing without RTV PK boosting results in suboptimal plasma DRV exposure [3, 15, 20] and NH Collaborative country program eligibility criteria included documentation of the ability to provide RTV for DRV boosting.[19] The importance of PK boosting and proper DRV dosing is critical, since both ensure optimal plasma DRV exposure in patients with usually less than optimal backbone regimens. In addition to the challenge of a separate formulation RTV booster, pediatric dosing of current formulations of DRV is complex and requires close follow-up for weight-based dose adjustments. [3, 15] Moreover, in our cohort of treatment-experienced pediatric and adolescent patients with a median 23 months of LPV/RTV exposure, close to half (43%) had ≥ 1 DRV-RM, further increasing the risk for developing DRV resistance with suboptimal DRV exposure. Recently approved generic formulation of pediatric

RTV tablets [20] and ongoing efforts in developing generic DRV/RTV co-formulations are expected to simplify dosing and boosting of this PI in children and adolescents.

The presence of NNRTI RMs and specific ETR-RMs in large proportion (65.9% and 57.4%, respectively) of our patients, is consistent with published data reporting high rates of DRM in children.[21, 22] Since the data on pediatric use of ETR are limited to studies in combination with boosted PIs in treatment-experienced children and adolescents,[22-24] current US national pediatric HIV treatment guidelines recommend using ETR as part of an ART regimen which includes a boosted PI.[25] Therefore, the observed use of ETR/RAL without a boosted-PI in our study is concerning, particularly when used in a dual ART regimen without an NRTI backbone. In fact, more than one third (37.5%) of pediatric patients in our cohort were initiated on NRTI backbone-sparing ART regimens, contrary to the 2016 WHO consolidated HIV treatment guidelines recommending that patients with NRTI resistance remain on an NRTI backbone when switching ART regimens due to treatment failure.[3]

We observed limited, unstandardized documentation in patient medical charts regarding reasons for ART switch and justifications for the new regimen selection. Across the four study countries, there was no standardized approach to third-line ART management. In some, a national third-line ART expert committee was relied upon to interpret genotype and virologic tests and to recommend ART sequencing. Other countries had decentralized third-line management, and some relied on the expertise of a single center of excellence. Some countries allowed clinical officers and nurses to manage third-line ART under the guidance of a third-line committee. In all countries, practitioners interacting with study team expressed desire to gain more expertise for management of pediatric treatment failure and had interest in support tools and capacity building.

Limitations of our study include its retrospective design and small sample size. Data on patient response to DRV and /or ETR-based ART were not collected. We are in the process transitioning this study into a prospective protocol to collect outcome data on second-and third-line ART facilitated by the NH donation program.

CONCLUSIONS

Our study of HIV treatment-experienced pediatric and adolescent patients with virologic treatment failure who were initiated on third- line ART through the drug donation program, identified high rates of multidrug resistance including RMs for DRV and ETR. We also report a dual ETR/RAL regimen without RTV boosted PI, and use of NRTI sparing regimens currently not recommended by the WHO.

The availability of DRV/RTV, ETR and integrase inhibitors, provides new opportunities for optimizing ART options for treatment-experienced children. Managing treatment failure in children and adolescents requires expertise and experience different from managing HIV-infected adults. Our report underscores the importance of applied HIV virologic testing and integrated adherence support in the management of treatment failure and ART sequencing among pediatric and adolescent populations in the settings of overall low genotyping availability. Targeted technical assistance and capacity building in sequencing pediatric ART in low-resource settings can help optimize the management of treatment failure in children and adolescents.

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Table 1. Characteristics of patients in the study.

	Patients N=48
Country	
Zambia Swaziland Lesotho Kenya	23 (47.9%) 4 (8.3%) 6 (12.5%) 15 (31.2%)
Gender	
Male Female	26 (54.1%) 22 (45.8%)
Age	
Median age, years (IQR)	15 (17.7-10.3)
Age groups: < 5 years ≥ 5 to ≤ 10 years > 10 to ≤19 years > 19 years	 3 (6.2%) 11 (22.9%) 30 (62.5%) 4 (8.3%)
Antiretroviral (ART) history	
2 Prior ART regimens 3 Prior ART regimens	42 (87.5%) 21 (43.8%)
Immunologic and virologic parameters	
Median CD4 cell count (IQR)* Median HIV RNA viral load, copies/mL (IQR)**	91 (383-14) 56,653 (113,110-14,130)

*44 total patients had recent (within last 6 months) CD4 test results.
** All patients (n=48) had documented HIV RNA viral load results.

Table 2. HIV resistance mutations (RM) among patients (by antiretroviral drug class).

PI Mutations (% of 47 with RM)	**NNRTI Mutations (% of 47 with RM)**	**NRTI Mutations (% of 47 with RM)**
Any PI RM (70.2%)	**Any NNRTI RM (65.9%)**	**Any NRTI RM (87.2%)**
M46I (38.3%)	G190A (23.4%)	**M184V (76.6%)***
V82A (38.3%)	K103N (23.4%)	**D67N (51.1%)**
I54V (36.2%)	**Y181C (17.0%)***	**M41L (38.3%)**
L76V (19.1%)*	**K101E (10.6%)**	**T215Y (34.0%)**
I84V (10.6%)	K103S (8.5%))	**L210W (31.9%)**
L24I (8.5%)	E138A (4.3%)	**K70R (21.3%)**
M46L (6.4%)	F227L (4.3%)	**T215F (10.6%)**
I47A (4.3%)	**K101P (4.3%)**	**K219E (10.6%)**
L90M (4.3%)	V106M (4.3%)	**K219Q (8.5%)**
V32I (4.3%)	**Y181I (4.3%)**	K65R (8.5%)
I47V (2.1%)	E138G (2.1%)	L74V (8.5%)
I54L (2.1%)	**K101H (2.1%)**	Y115F (8.5%)
	L100I (2.1%)	

*Major RMs and TAMs in bold; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; RM=resistance mutation; TAMs – thymidine analogue mutations.