New Horizons Advancing Pediatric HIV Care Collaborative

Demographic, Clinical, and Laboratory Characteristics and Outcomes of Patients Who Ever Received Etravirine and/or Darunavir – Multi-country Data Abstraction

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I. Acronyms

ANC:	Antenatal Care
ART:	Antiretroviral Therapy
CDC:	Centers for Disease Control and Prevention
CIPHER	Collaborative Initiative for Paediatric HIV Education and Research
CHAI:	Clinton Health Access Initiative
CTC:	Care and Treatment Clinic
CTX:	Cotrimoxazole
DHMT:	District Health Management Team
DRV:	Darunavir
EGPAF:	Elizabeth Glaser Pediatric AIDS Foundation
EID:	Early Infant Diagnosis
EFV:	Efavirenz
ETR:	Etravirine
HCW:	Health Care Workforce
HIV:	Human Immunodeficiency Virus
IAS:	International AIDS Society
IRB:	Institutional Review Board
KG:	Kilogram
LPV:	Lopinavir
LPV/r:	Lopinavir/ritonavir
M&E:	Monitoring and Evaluation
MOH:	Ministry of Health
MSD:	Medical Stores Department
NRTI:	Nucleoside Reverse Transcriptase Inhibitor
NNRTI:	Non-Nucleoside Reverse Transcriptase Inhibitor
OGAC:	Office of the Global AIDS Coordinator
PFSCM:	Partnership for Supply Chain Management
PI:	Protease Inhibitor
RAL:	Raltegravir
RAMs:	Resistance Associated Mutations
R&R:	Reporting and Requesting
sdNVP:	Single Dose Nevirapine
SOP:	Standard Operating Procedures
TA:	Technical Assistance
TAMs:	Thymidine Analogue Mutations
TLE:	Tenofovir/Lamivudine/Efavirenz
TWG:	Technical Working Group
UNAIDS:	Joint United Nations Programme on HIV/AIDS
USAID:	United States Agency for International Development
WHO:	World Health Organization

II. Introduction

Background

Rapid scale-up of antiretroviral therapy (ART) for HIV-infected children and adolescents is anticipated in the near future in response to UNAIDS 90-90-90 fast-track global HIV targets. As more children and adolescents with HIV infection receive first-line ART and many subsequently face the challenge of the treatment failure, the need for second- and third-line ART will also increase.[i,ii] Barriers to adherence, poor retention in care, gaps in available data and research, as well as limited second- and third-line options for children and adolescents highlight the need to address the issue of treatment failure in these vulnerable sub-groups.[iii,iv,v,vi,vii,viii,ix] The 2015 World Health Organization (WHO) consolidated treatment guidelines recommend that national HIV/AIDS programs develop third-line ART guidance specifying regimens that include antiretroviral drugs (ARVs) unlikely to have cross-resistance with currently recommended first- and second-line ART regimens, such as integrase inhibitors, second-generation non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI).[x] Limited data from randomized clinical trials, mainly conducted in high and middle-income countries and among adult populations, demonstrate that etravirine (ETR), darunavir boosted with ritonavir (DRV/r), and raltegravir (RAL) used alone or in combination with other ARVs are efficacious when used in treatment-experienced patients with an optimized backbone. For example, twice daily DRV/r plus an optimized nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone was shown to be virologically and immunologically superior to the control regimen consisting of an investigator-selected control PI plus an optimized backbone in treatment-experienced adults with HIV as shown by a pooled subgroup analysis.[xi] In treatment-experienced adults with viremia and NNRTI and PI resistance, ETR paired with a background regimen of DRV/r and optimized backbone had improved durable rates of viral suppression and CD4 increase at 96 weeks compared to a similar regimen with ETV-placebo.[xii] Finally, in patients with multiple drug mutations with limited options for treatment, combination therapy including DRV/r, ETR, and RAL has been associated with high rates of virological suppression at 48-96 weeks. [xiii,xiv]

Programmatic Response

Janssen (the Pharmaceutical Companies of Johnson & Johnson), the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF), the Partnership for Supply Chain Management (PFSCM), the Collaborative Initiative for Pediatric HIV Education and Research (CIPHER) of the International AIDS Society (IAS), Right to Care, and The Relevance Network have partnered to implement the *New Horizons Advancing Pediatric HIV Care Collaborative* (New Horizons Collaborative) to improve and scale-up pediatric HIV/AIDS care and treatment through increased awareness, research, health systems strengthening, and improved access to HIV/AIDS medicines.

There are various ways that Ministries of Health (MOH) can access DRV and/or ETR, such as through the Global Fund to Fight AIDS, Tuberculosis, and Malaria or other global donors, as well as direct purchase from the manufacturer. However, a primary source of DRV and ETR for pediatric populations in sub-Saharan Africa is through the New Horizons DRV/ETR *Donation Program*. Under the New Horizons Collaborative, a DRV/ETR Donation Program was launched in 2014 to increase access to pediatric HIV medicines for children experiencing ART failure. Under this program, Janssen provides DRV (PREZISTA®) and/or ETR (INTELENCE®) free of charge to eligible national HIV/AIDS programs in sub-Saharan Africa, for use in children and adolescents up to 25 years of age. Upon turning 25 years (or before as required by the national HIV/AIDS program), patients using donated products will be transitioned into the countries' HIV treatment programs for adults as designated by the national HIV program. Under this Donation Program, DRV in combination with ritonavir (RTV) may be used for either second- or third-line treatment after failure on lopinavir/ritonavir (LPV/r) and/or in individuals with virus that has multiple PI resistance mutations. Of note, the Donation Program does not endorse the use of DRV (along with RTV) as second- or third-line therapy for patients who have previously received only NNRTI-based ART regimens (e.g., 2 NRTIs plus nevirapine or efavirenz).

In order to be eligible for participation in the New Horizons Collaborative, countries must satisfy the following criteria:

1. Applicant country must be located in sub-Saharan Africa or else considered to be a Least Developed Country as defined by the United Nations
2. Medicine donation is legal in the applicant country
3. Adult second - and third-line HIV treatment is part of the national HIV program (or will be put in place within 6 months of the applicant country's acceptance into the donation program)
4. The applicant country has national guidelines for second- and third-line pediatric HIV treatment
5. DRV is approved for use in children in the applicant country
6. ETR is approved for use in children in the applicant country
7. There is demonstrated need for second – and third-line ARVs for children, adolescents, and young people
8. The applicant country has necessary clinical expertise to identify children experiencing HIV treatment failure and manage children on second- and third-line treatment
9. Other ARVs, including RTV, needed to create an active regimen with DRV and/or ETR, are available in country

Countries currently participating in the New Horizons Collaborative include:

- Cameroon

- Eswatini
- Ethiopia
- Kenya
- Lesotho
- Nigeria
- Rwanda
- Uganda
- Zambia
- Zimbabwe

Any country that applies and is approved for receipt of donated product will become eligible for this study when they begin offering donated product to patients.

Following acceptance of eligible countries into the New Horizons Donation Program, Janssen and PFSCM have worked with the Ministries of Health (MOH) to forecast and order needed product. Orders of DRV and ETR are shipped to a central warehouse in South Africa, managed by Imperial Health Sciences. Following receipt and processing into South Africa, individual country orders are then sent to the respective MOH.

EGPAF has been provided with funding by Johnson & Johnson Services to manage the country application process and convene the third-party review committee for country selection. EGPAF is also responsible for provision of technical assistance (TA) to national HIV/AIDS programs engaged in the New Horizons Collaborative. In 2014, EGPAF volunteered to conduct a collection of baseline demographic and clinical data for patients receiving DRV and/or ETR through in New Horizons Collaborative countries. The evaluation included 48 patients (45.8% female; median age=15 years) from nine clinical sites in Zambia, Swaziland, Kenya and Lesotho.[vi] Most children (87.5%) had received ≥ 2 prior ART regimens; 81.2% had received lopinavir/ritonavir-based ART prior to switch. ARV drug resistance was common; of 47 patients with genotype results, 87.2% had ≥1 NRTI-resistance mutation (RM), predominantly M184V; 65.9% had ≥1 non-NRTI-RM, including 57.4% with ≥1 ETR-RM; 63.8% had ≥ 3 protease inhibitor RM, including 42.6% with ≥ 1 DRV-RM. For new ART regimens, DRV and RAL were most frequently prescribed (83.3%; n=40 on DRV and raltegravir, each). Eighteen patients (37.5%) were initiated on the NRTI-sparing ART.[vi] These data reflect baseline information on children receiving DRV and/or ETR through New Horizons but did not capture new ART regimen treatment response. Hence, EGPAF is proposing to conduct a similar data collection from children and adolescents receiving DRV and/or ETR. For each patient, we will collect demographic, clinical and laboratory data (1) as recorded at the time of initiation on DRV and/or ETR, and (2) updated information approximately every six months, through 2021. New patients will be added to the dataset who have been enrolled since the previous data collection point.

Prior to the inception of the New Horizons Collaborative, no multi-country data were collected regarding the demographic or clinical characteristics of the target patient population (i.e., children, adolescents, and young people < 25 years in need of second- or third-line HIV/AIDS treatment). Therefore, the current activity proposes to collect cross-sectional demographic and clinical data at baseline and every six months for patients receiving DRV and/or ETR across participating New Horizons countries. This activity will comprise data abstraction of a key demographic, clinical, laboratory and case history indicators and outcomes on each patient who ever received DRV and/or ETR.

Objectives

The objectives of this data collection activity are to:

a) Describe the baseline demographics, clinical and laboratory profile of patients who ever received DRV and/or ETR, at the time of initiation on DRV and/or ETR,
b) Describe the clinical and laboratory profile of patients who ever received DRV and/or ETR every 6 months from the first data collection point through 2021,
c) Describe dynamics in HIV drug resistance mutations among patients who fail treatment on new regimens, including DRV and/or ETR.
d) Describe demographics, clinical and laboratory profile of young adults who transition out of the donation program after the age of 25 years at 12 months after their transition.

Use of Results of this Evaluation

The de-identified data from each participating country will be analyzed and reported to relevant MOH. These overall demographic and clinical findings will be used to describe the children and adolescents who have received DRV and/or ETR up through each time point of data collection. Data from this evaluation will be used as resource when countries review their national guidelines for second- and third-line ART.

The findings will be presented at regional and international scientific meetings or conferences.

Data summarized across New Horizons countries will be shared with programmatic stakeholders and potential New Horizons partners. These stakeholders include the Centers for Disease Control and Prevention (CDC), the United States Agency for International Development (USAID), the United States Office of the Global AIDS Coordinator (OGAC), IAS CIPHER, the Clinton Health Access Initiative (CHAI), PFSCM, various industry partners such as Janssen and Merck, and others.

III. Procedures and Methods

Targeted Facilities

Data collection will occur in the existing clinical programs that are currently managing patients on ART regimens, which include at least one product (i.e., DRV and/or ETR).

Sources of Data

Data will be abstracted from individual patient files/cards stored at the health facility. Only those patient files which represent recipients of DRV and/or ETR will be accessed for the purposes of this activity. All data collection tools and processes will be approved by the in-country IRB. Each patient will be assigned a unique Study identification (ID) number and data collection forms will be linked to the patient using this unique identifier only. The data abstraction team will maintain a master document ("link log") that allows linking of files of participants to the unique ID. Access to this document will be limited to members of the abstracting team and the evaluation team.

Methods and Timeline

The current data collection activity is intended to describe the demographic, clinical and laboratory characteristics of patients at the point of initiation on DRV and/or ETR and b) the most recently recorded data at the time of most recent data collection point (every six months). Patients will be stratified by the duration of time on ETR and/or DRV.

Members of the abstraction team will visit each participating facility which is handling patients who ever used DRV and/or ETR on a convenient and mutually agreeable day. Because the volumes of patients on DRV and/or ETR are anticipated to be low, data collection activities at each facility are not anticipated to take more than a few hours on a single day. Data abstraction from each patient is expected to be repeated approximately every six months from the last data collection point. The last data collection activity is anticipated to occur in December 2021.

Key Variables

Table 1: Key variables and data source.

Objectives	Variables	Data sources	Comment
a) Describe the demographics, clinical and laboratory profiles of patients who ever received DRV and/or ETR, at the time of initiation on DRV and/or ETR.	- Age - Gender - Weight - Height (when available)	- Clinical card - ART register - Lab register	Data collection team should use ART and Lab registers, among others, to complement data not found in the clinical cards

	- Viral load at the time of DRV and/or ETR initiation - Baseline ARV drug resistance mutations		
b) Describe clinical and laboratory profile of patients who ever received DRV and/or ETR every 6 months from the first data collection point through 2021.	- Weight - Height - Most recent viral load - Any new genotypic resistance assay results	- Clinical records - ART registers - Lab registers	Data collection team should abstract data from ART clinical file and ART and lab registers, among other registers. These data will be disaggregated by time duration from last visit as 6, 12, 18, 24, 30 and 36 months.
c) Describe dynamics in HIV drug resistance mutations among patients who fail treatment on new regimens, including DRV and/or ETR.	- Weight - Height - Viral load - Duration receiving DRV/ETR - Genotypic resistance test results - Lab based suggested regimen by clinical virologist	- Clinical records - Lab registers	These data will be abstracted from Laboratory form/register, among other registers.
d) Describe demographics, clinical and laboratory profile of young adults who transition out of the donation program after the age of 25 years at 12 months after their transition.	- Weight - Height - Most recent viral load - Any new genotypic resistance assay results	- Clinical records - ART registers - Lab registers	Data collection team should abstract data from ART clinical file and ART and lab registers, among other registers.

Table 2. Schedule of Evaluation data extraction from each clinical file

Study Activity	Baseline	6 months	12 months	18 months	24 months	30 months	36 months
Demographics	X						
Review Patient Clinical file	X	X	X	X	X	X	X
Record of co-morbidities, such as TB, etc.	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X

Height (if available)	X	X	X	X	X	X	X
Results of Viral Load	X[1]	X	X	X	X	X	X
Recorded Clinical diagnosis of Treatment Failure	X	X	X	X	X	X	X
Genotypic Resistance mutation	X	X	X	X	X	X	X
Records of pregnancy	X	X	X	X	X	X	X

Data Handling and Analysis

EGPAF will fund the data collection, data entry, analyses and reporting activities. Data will be abstracted from patient files, ART register or laboratory registers at participating facilities by an EGPAF staff member specifically trained in the objectives and methods of the current assessment (the "abstraction team"). All evaluation team members will be trained in patient confidentiality and human subject protection. Data abstraction will occur in a private location of the health facility to minimize any risk of unauthorized viewing of medical records.

Routinely collected patient-level data will be abstracted from patient files and recorded into a password protected database. Each patient will be assigned a unique study ID and data collection will be linked to the patient using this unique ID only. A master document, "link log" that permits linking of the patient's name to the unique identification number will be maintained in password protected files by the abstracting team, with access to this document limited to members of the abstracting team and the evaluation team only. Baseline demographic, clinical and laboratory data will be summarized using frequencies and percentages for categorical variables and mean (SD) or median (IQR) for continuous variables depending on their distributions.

Clinical and laboratory follow-up data will be summarized using appropriate descriptive statistics stratified by duration on DRV/ETR. In addition, patient records will be stratified by duration of time on DRV/ETR, and retention on DRV/ETR regimen will be described.

Other analyses may also be conducted using the de-identified data.

Ethical Considerations

Institutional Review Board and Informed Consent

This protocol will be reviewed by an Institutional Review Board (IRB) in the US and an ethical review committee in each of the project countries. The local in-country ethics committees will also receive and approve country-specific details about the evaluation.

This protocol will be conducted with human subject oversight locally in countries participating in the New Horizons Collaborative from the local Institutional Review Boards (IRBs) and in the United States from Advarra IRB (IORG0000635) (Formerly called "Chesapeake IRB"). We are requesting a waiver of consent to abstract data from routine clinic registers, forms, and charts for several reasons, all of which conform with United States (US) Federal regulations OHRP-45CFR46.116, DHHS- 45CFR46.117(c), and HIPAA-CFR 164.512(i)(2)(ii). According to US federal regulations, a waiver of consent is acceptable if the following criteria are met:

a) The research involves no more than minimal risk to the participants, and involves no procedures for which written consent is normally required outside of the evaluation/research context.
b) The waiver will not adversely affect the rights and welfare of the participants.
c) The research could not practicably be carried out without the waiver.
d) Whenever appropriate, the participants are provided with additional pertinent information after participation.

This evaluation and all the procedures involved with collecting and analyzing routinely program data impose minimal risk to participants because it does not involve direct interaction between the program evaluation staff and patients on DRV and/or ETV. Study numbers will be used and protocols put in place to protect patient identifiers from improper use and disclosure and reduce accidental disclosures. Patient identifiers will be redacted or destroyed at the completion of the study.

A waiver of consent would not adversely affect the rights and welfare of participants because no identifiable information will be recorded in the electronic database. Patient identifiers will only be recorded on an evaluation enrollment log during the data abstraction phase to link patient-level data across routine clinic registers, and clinical cards. When the data abstraction and data cleaning phases have been completed and patient identifiers are no longer required for research purposes, the enrollment log will be shredded. Because age and sex are important variables potentially associated with some of the outcomes to be measured, information on these two variables will be collected. All evaluation staff will be required to sign a confidentiality agreement prohibiting disclosure of any individual-level information including HIV status. The evaluation databases will be password-protected, and all electronic communications involving program evaluation data will be encrypted.

Risks

This study involves minimal risk to participants. All data collected are being abstracted from routinely-collected information in existing medical charts and no interactions

between patients and study staff are required. Key risks involve breaches of confidentiality but steps will be taken to ensure confidentiality and protect privacy.

Confidentiality/Privacy Protections

All evaluation staff members who collect identifiable patient level data or analyze collected data will complete training in human subjects' protections process prior to starting the study.

Standard operating procedures for data security and confidentiality will be implemented and staff will be trained on this protocol. In addition, during site visits, facility staff or MOH representatives may escort data collectors through the facilities, as appropriate. Any breaches of confidentiality will be immediately reported to the EGPAF regulatory officer and appropriate ethical committees, as required.

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