CONCEPT SHEET: MULTIREGIONAL ANALYSIS

Date of EC approval:	*26 October 2021*
Tracking number:	*MR190*
Title:	Transition to dolutegravir-based ART regimens at ART programs in low- and middle-income countries participating to the IeDEA global consortium
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Where will data be merged?	No
Where will statistical analyses be done?	Bern, Switzerland
Abstract: (±200 words)	**Background and objectives** In 2017, the increasing resistance to nucleoside reverse transcriptase inhibitors (NRTIs) led WHO to recommend the use of dolutegravir (DTG) in

	the 1st-, 2nd and 3rd-line ART for adults and adolescents living with HIV.[3] Due to its good tolerability and high barrier to resistance, DTG-containing ART regimens are being rolled out in the low- and middle-income settings, including at many IeDEA sites. The objectives of this concept are: - To determine the proportion of sites having introduced DTG-based regimens over time, overall and by region; - To describe the eligibility criteria for DTG-based regimens, overall and by region; - To explore if viral load monitoring and resistance testing are considered before switching to a DTG-based regimen; - To identify programme-level factors which are associated with the implementation of DTG-based regimens. **Methods** Site Assessment 4.0: Cross-sectional survey to be completed by all sites participating in IeDEA in 2020-2021.
Project outline: (±1000 words)	**Background** HIV drug resistance has grown with the expansion of ART in low- and middle-income countries (LMIC).[1,2] In 2017, the increasing resistance to nucleoside reverse transcriptase inhibitors (NRTIs) led WHO to recommend the use of dolutegravir (DTG) for 1st-, 2nd and 3rd-line ART for adults and adolescents.[3] DTG is a potent integrase strand transfer inhibitor (InSTI), which has better efficacy and safety profiles than efavirenz in 1st-line therapy and lopinavir/ritonavir in 2nd-line therapy.[4–6] Due to its good tolerability and high barrier to resistance, DTG-containing ART regimens are being rolled out in low- and middle-income settings, including at many IeDEA sites. **Objectives and hypotheses** We hypothesize that the rollout of DTG-based regimen will have been initiated at most participating sites but that the modalities vary across IeDEA regions. In particular, we hypothesize that there are differences in which groups of patients receive a DTG-based regimens. Our objectives are the following: 1. To determine the proportion of sites having introduced DTG-based regimens as first-line, second- or third-line therapy and when they were introduced, overall and by region; 2. To describe the eligibility criteria for DTG-based first-, second-, and third-line regimens, overall and by region; 3. To explore if the decision to switch clients to a DTG-based regimens is based on viral load monitoring, overall and by region; 4. To explore if the switch to a DTG-based regimen is based on drug resistance testing, overall and by region; 5. To explore the use of other InSTI drugs (Elvitegravir, Raltegravir,

Bictegravir) in first-line regimens, overall and by region;

6. To identify site-level factors that are associated with the implementation of DTG as first-, second-, and third-line regimens.

Study design

Site Assessment 4.0: Cross sectional survey to be completed by all sites participating in IeDEA.

Parent concept sheet: MR155

Eligibility criteria

All active IeDEA sites that provide direct clinical care and contribute patient data that can be linked to a particular clinical site (as opposed to a clinical or programmatic cohort) will be requested to participate in the survey.

Key variables and definitions

Our analysis will focus on the variables collected in the Site Assessment 4.0:

- Section 1 (respondent information): Q 1.3
- Section 2 (patient population in care): Q 2.1, 2.2, 2.3
- Section 6 (ART monitoring, including resistance testing): Q 6.6, Q 6.7
- Section 7 (fees related to ART and lab tests): Q 7.5, Q 7.6
- Section 11 (rollout of DTG-based regimens): Q 1.1 – Q 1.18

We will use the following definitions:

A site will be defined as having transitioned to DTG from the time DTG-based regimens were introduced in routine care, for first-, second- or third-line treatment.

Outcomes

This analysis will provide a unique overview of the extent to which DTG has been rolled out at ART programs globally, as per the recommendation of WHO. This analysis will be published in a peer-reviewed, open access, journal.

Data collection and statistical methods

Data will be collected centrally for the Site Assessment 4.0.

We will use descriptive statistics to characterize the participating ART programs (IeDEA region, country (map), setting, population in care at the program, availability of viral load testing, cost-models).

We will use Kaplan-Meier curves to show the cumulative implementation of DTG-based regimens at participating sites, distinguishing the use of DTG in first-, second- and third-line regimen.

We will show in what proportion of the sites, different population groups are currently eligible for DTG-based regimens, distinguishing first-, second- and third-line regimen.

We will show in what proportion of the sites viral load monitoring and resistance testing is considered to decide if a patient is switched to a DTG-based regimen.

All analyses will be done overall and by IeDEA region.

We will use univariable and multivariable models to explore site-level factors (e.g. IeDEA region, setting, availability of viral load monitoring, cost-models) associated with the availability of DTG-based regimens in general.

We will explore the site-level factors associated with the availability of DTG-based regimens, for first-, second-, and third-line separately.

Sample size considerations

All sites participating in the Site Assessment 4.0 will be eligible.

References

1. Gregson J, Tang M, Ndembi N, et al. Global epidemiology of drug resistance after failure of WHO recommended first-line regimens for adult HIV-1 infection: a multicentre retrospective cohort study. *The Lancet Infectious Diseases*. 2016;16(5):565-575. doi:10.1016/S1473-3099(15)00536-8

2. Gupta RK, Gregson J, Parkin N, et al. HIV-1 drug resistance before initiation or re-initiation of first-line antiretroviral therapy in low-income and middle-income countries: a systematic review and meta-regression analysis. *The Lancet Infectious Diseases*. 2018;18(3):346-355. doi:10.1016/S1473-3099(17)30702-8

3. World Health Organization. *WHO Updated Recommendations on First-Line and Second-Line Antiretroviral Regimens and Post-Exposure Prophylaxis and Recommendations on Early Infant Diagnosis of HIV. Interim Guidance.* World Health Organization; 2018.

4. Walmsley SL, Antela A, Clumeck N, et al. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J Med*. 2013;369(19):1807-1818. doi:10.1056/NEJMoa1215541

5. Aboud M, Kaplan R, Lombaard J, et al. Dolutegravir versus ritonavir-boosted lopinavir both with dual nucleoside reverse transcriptase inhibitor therapy in adults with HIV-1 infection in whom first-line therapy has failed (DAWNING): an open-label, non-inferiority, phase 3b trial. *Lancet Infect Dis*. 2019;19(3):253-264. doi:10.1016/S1473-3099(19)30036-2

6. Walmsley S, Baumgarten A, Berenguer J, et al. Brief Report: Dolutegravir Plus Abacavir/Lamivudine for the Treatment of HIV-1 Infection in Antiretroviral Therapy-Naive Patients: Week 96 and Week 144 Results From the SINGLE Randomized Clinical Trial. *J Acquir Immune*

	Defic Syndr. 2015;70(5):515-519. doi:10.1097/QAI.0000000000000790
Ethics:	X This concept uses only the IeDEA standard dataset and is covered by the core IeDEA ethics approvals. ☐ This concept requires additional collection of health-related data, measurements or tests, or sampling of biological material not included in the IeDEA standard dataset. Additional ethics approval is required. ☐ This concept does not fall into either ethics category above. *Describe*:
Dataset:	☐ This concept requires new patient-level datasets. ☐ This concept uses existing patient-level datasets submitted for a previous concept: *Concept title:* *Concept number*: MR_____ X This concept uses IeDEA Site Assessment or other IeDEA survey data. ☐ This concept does not use any IeDEA data (e.g., viewpoint paper).
Target journal(s):	TBD
Milestones:	Circulation of concept sheet: Oct 2020 Circulation of draft paper: Depending on the SA Submission to target journal: Depending on the SA

Next Steps

Thank you for preparing a concept proposal for an IeDEA Multiregional Analysis. All IeDEA Concept Sheets are reviewed by the IeDEA Executive Committee (EC). Here are the steps for submitting your concept:

1. Before submitting the concept sheet, please **ensure all sections have been completed** or marked not applicable, the document is clean (all edits and comments are removed), and references have been added. If you are participating in an IeDEA region, ensure your Regional Principal Investigator has reviewed and approved the concept prior to submission.
2. Concepts that are developed within or have relevance to one or more IeDEA Working Groups (see list of Working Groups here) may be required to **obtain approval from the relevant IeDEA Working Groups** before submission to the EC. Please contact Aimee Freeman (afreeman@jhu.edu) with questions on this requirement and to circulate the document to the appropriate Working Group.
3. Once the document is ready for circulation to the IeDEA Executive Committee, you can **upload it to the IeDEA Hub for EC review** at the following link:

http://bit.ly/iedeasubmit

The concept will be reviewed by IeDEA Administrators prior to circulation to the Executive Committee. If you have questions about the form content, contact Aimee Freeman. For questions about the IeDEA Hub upload process, contact the Harmonist team at harmonist@vanderbilt.edu.