# CONCEPT SHEET: MULTI-REGIONAL ANALYSES OF HIV-1 DRUG RESISTANCE IN PATIENTS FAILING DTG-BASED ART (V. 5)

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| **Date of EC approval:** | *8 July 2019* |
| **Tracking number:** | *MR151* |
| **Title:** | **HIV-1 subtype specific drug resistance in patients failing DTG-based 1st, 2nd or 3rd line regimens: multiregional cross-sectional study** |
| **Concept Lead:**<br>Email: | Roger Kouyos and Matthias Egger on behalf of the HIV Resistance Working Group of IeDEA-SA.<br>roger.kouyos@uzh.ch |
| **Collaborators:** | Richard Lessells and Tulio de Oliveira, University of KwaZulu-Natal<br>Gary Maartens, University of Cape Town<br>Representatives from all regions |
| **IeDEA Correspondents:**<br>Email: | Matthias Egger, ISPM, University of Bern, Switzerland<br>matthias.egger@ispm.unibe.ch<br>Mary-Ann Davies, CIDER, University of Cape Town, South Africa<br>mary-ann.davies@uct.ac.za. |
| **Data Manager:**<br>Email: | Tbd |
| **Lead Statistician:**<br>Email: | Tbd |
| **Bioinformatician:**<br>Email: | Tbd |
| **Where will data be merged?** | Tbd |

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| **Where will statistical analyses be done?** | Tbd |
| **Abstract:**<br>(±200 words) | **Background**<br>The success of the global scale-up of antiretroviral therapy (ART) is threatened by rising HIV resistance to non-nucleoside reverse transcriptase inhibitors (NNRTI). The next phase of the global HIV response will therefore rely on dolutegravir (DTG), an HIV integrase strand transfer inhibitor (InSTI) with a high genetic barrier to resistance. Resistance to DTG is unlikely if combined with other active drugs but may emerge in pretreated patients on second- and third-line ART.<br>**Research questions**<br>This multi-regional project of IeDEA aims to<br>1. Determine the prevalence of HIV-1 drug resistance mutations, including in minority variants,<br>2. Investigate differences in DTG and other resistance patterns across different HIV-1 subtypes, including B, C, A, D and circulating recombinant forms, including CRF01_AE and CRF02_AG<br>in adult patients failing 1st, 2nd or 3rd line DTG-based ART regimens.<br>**Hypotheses**<br>1. DTG resistance will emerge in treatment-experienced individuals failing 2nd or 3rd line DTG-based ART but rarely be observed in patients failing 1st line DTG ART.<br>2. Minority variants and subtype-specific polymorphisms are prevalent in patients failing 2nd and 3rd line DTG-based, high-genetic barrier regimes.<br>3. The spectrum/distribution of resistance mutations differs across subtypes.<br>**Data source**<br>IeDEA cohort databases, enriched with cross-sectional resistance testing based on plasma or DBS samples. |

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| **Project outline:**<br>(±1000 words) | **Background**<br>The expansion of access to antiretroviral therapy (ART) has been one of the most successful public health interventions in history, but the emergence and spread of HIV drug resistance (HIVDR) is a major barrier to ending the HIV epidemic [1]. The next phase of the global HIV response will rely on dolutegravir (DTG), a potent integrase strand-transfer inhibitor (InSTI) with a high genetic barrier to resistance [2]. So far, the evidence suggests that if used in combination with other active antiretroviral drugs, resistance to DTG is extremely uncommon [3]. However, the emergence of resistance has been documented with DTG monotherapy [4-6], and in treatment-experienced individuals, particularly if previously exposed to other INSTIs [7-11].<br>Evidence to inform the rational use of antiretrovirals beyond first-line therapy in low-income and middle-income countries (LMIC) is limited, yet by 2020 more than three million people are expected to be on second-line and third-line ART regimens. Current WHO guidelines recommend the use of DTG in first-line, second-line and third-line ART regimens [2]. This multiplicity of roles of DTG in the public health approach to ART employed in LMIC, with standardized regimens, limited monitoring, and recycling of drugs creates further potential for the emergence of DTG resistance.<br>In this proposal, we plan to leverage the International epidemiology Databases to Evaluate AIDS (IeDEA) research consortium to address critical questions around DTG and HIV drug resistance. We will invite IeDEA cohorts from all seven regions to participate in this study: Central, Eastern Western and Southern Africa, NA-ACCORD, and the Caribbean, Central and South America network for HIV epidemiology (CCASAnet). This brings four key strengths to the proposal:<br>i) Pooling of data across a network of research cohorts to explore the determinants of rare events, in particular DTG resistance,<br>ii) Harmonizing collection of clinical and drug resistance data across IeDEA cohorts,<br>iii) Inclusion of multiple HIV-1 subtypes across geographic areas (Figure 1), |  <br>RE IEDEA response.msg |

iv) Combining expertise in the clinical, epidemiological, biological, and computational fields.

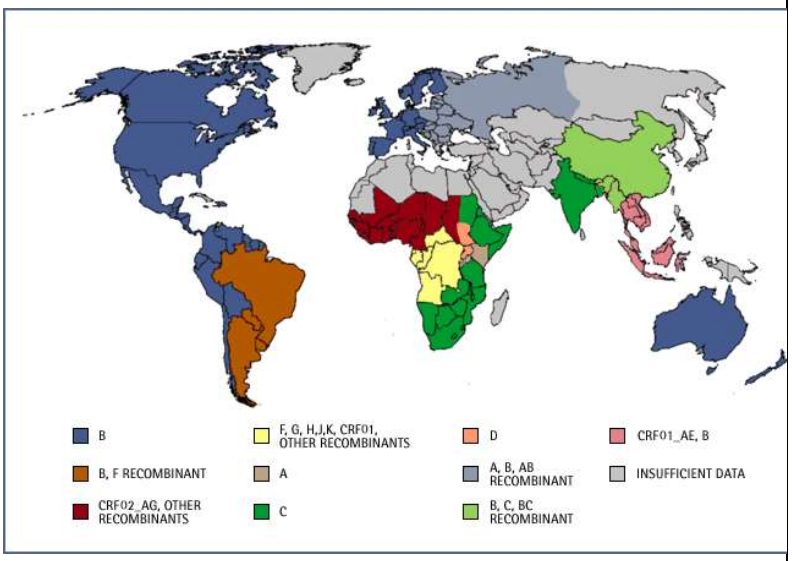


**Figure 1:** Distribution of major HIV subtypes and CRFs. IeDEA is represented in all regions except Europe. See also table below (after references).
Source: Francine E. McCutchan, Henry M. Jackson Foundation (Rockville, Maryland). https://to.pbs.org/2T7oEPZ.

## Research questions

There are three research questions:

1. Determine the prevalence of HIV-1 drug resistance mutations, including in minority variants, in patients failing 1st, 2nd or 3rd line DTG-based ART regimens.
2. Investigate differences in DTG and other resistance patterns across different HIV-1 subtypes, including B, C, A, D and circulating recombinant forms, including CRF01_AE and CRF02_AG.

## Methods

We will collate clinical data and perform genotypic resistance tests (GRT) in adults aged 18 years or above failing 1st, 2nd and 3rd line DTG-based ART. We will perform next-generation sequencing (NGS) using the Illumina Miseq platform on samples at virological failure (Illumina, San Diego, CA). We will thus identify minority variant drug resistance mutations (MV-DRMs) in *RT*, *protease* and *integrase*. We will estimate the prevalence of MV-DRMs at failure (mutational load). We will characterize the phenotypic

effects of genotypic resistance patterns by performing the PhenoSense assays (Monogram Biosciences, San Francisco, CA) on selected samples. Based on this data, we will be able to determine the patterns of clinically relevant HIV-1 drug resistance mutations across different HIV-1 subtypes, with a focus on DTG resistance.

**Hypotheses**

1. DTG resistance will emerge in treatment-experienced individuals failing 2nd or 3rd line DTG-based ART but rarely be observed in patients failing 1st line DTG ART.
2. Minority variants and subtype-specific polymorphisms are prevalent in patients failing 2nd and 3rd line DTG-based, high-genetic barrier regimes.
3. The spectrum/distribution of resistance mutations differs across subtypes.

**Objectives**

The overarching goals of this project are to discover the contexts in which DTG and other resistance emerges across subtypes and settings and to establish the prevalence of different resistance patterns. The results from this study will inform HIV treatment strategies and contribute to safeguarding the long-term sustainability of the global HIV response.

**Eligibility, recruitment and sample size**

1. Age 18 years (or age of legal majority).
2. Treatment failure on a 1st, 2nd, 3rd, or salvage ART regimen including DTG (based on clinical, immunological or virological criteria).
3. Informed consent (if required).

Patients will be enrolled consecutively. We aim to achieve a total of 100-200 patients per subtype, and a total sample size of 700-1400 patients:

| **Subtype/CRF** | **No. failing 1st/2nd/3rd line** | **IeDEA countries/ regions** |
|---|---|---|
| B | 100-200 | USA, Canada, Australia |
| C | 100-200 | East Africa, Southern Africa |

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|---|---|---|
| A | 100-200 | Rwanda |
| D | 100-200 | Burundi |
| CRF01_AE | 100-200 | Thailand, Vietnam, Cambodia, Indonesia, Malaysia, Singapore |
| CRF02_AG | 100-200 | West Africa<br>Cameroon |
| B, F recombinant | 100-200 | Brazil, Argentina |
| **All** | **700-1400** | **All** |

*See also Figure 1 and supplementary table after references.*

Enrolment will be open for two years or until the enrolment, targets are reached. Enrolment targets refer to number of patients per region with the subtypes in table 1 indicating the most frequent subtype in each region. Samples not matching the indicated subtypes will be included nevertheless as this may help to reach enrolment targets for some subtypes and as having samples from the same subtype across different settings or from different subtypes in the same setting may allow to disentangle the impact of region and subtype.

**Key variables and definitions**

*Outcomes:*

DTG and other resistance mutations in genotypic resistance test (by NGS; including minority variants) in patients developing virological failure.

*Other data:*

Age, sex, previous ART regimens, adherence (based on pharmacy refill measures), clinic and region

**Sample and data collection and ethical consideration**

The core data for this concept sheet will be cross-sectional genotypic resistance tests, which will be combined with the routinely collected clinical and epidemiological data from the IeDEA cohorts. A plasma or DBS sample will be collected at failure. In sites where plasma samples are possible, we suggest that a DBS sample is also obtained.

As this study will be performed in a research context, samples will be tested batch-wise for logistic reasons. Thus, routine clinical practice will not be affected by this study. However, results will be reported back to sites as soon as they become available.

**Statistical methods**

Descriptive statistics to describe prevalence of resistance mutations and patterns. Regression models for the impact of viral subtype and previous failure (i.e. 1st vs. 2nd / 3rd line DTG-based ART) on the prevalence of resistance (logistic regression for individual mutations, truncated regression models for susceptibility scores as outcome variables). Multivariable (linear) regression for the impact of resistance mutations on phenotypic resistance. Potentially, machine learning approaches (regression trees, ridge-regression), and conjunctive-Bayesian-Network models for the accumulation of resistance mutations.

A detailed statistical analysis / bioinformatics pipeline plan will be written.

**Power considerations**

With 100-200 patients per HIV-1 subtype / CRF we will be able to describe drug resistance mutations and have reasonable power to detect meaningful differences in resistance patterns across type of failure and subtype/CRF. Should the enrolment targets not be reached for some subtypes, we will consider pooling subtypes with sample sizes below the target (<50 patients per subtype) or compare the subtype with largest sample size (most likely subtype C) to the remaining subtypes combined, as has been done in studies of subtype B (12). Note that due to the descriptive nature of this study and the lack of information on DTG resistance, the collected data will be very valuable even if enrolment targets are not reached for all subtypes. As failure under DTG-based combination therapy and resistance to DTG are rare, pooling such rare events across different sites is the only approach to address the knowledge gaps on DTG-resistance evolution. The large IeDEA network is therefore in a very good position to make an important contribution.

**References**

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**Supplementary table: Distribution of HIV-1 subtypes**

**across IeDEA regions / countries.**

Source: Francine E. McCutchan, Henry M. Jackson Foundation (Rockville, Maryland). https://to.pbs.org/2T7oEPZ.

| Region | Country | Dominant subtype |
|---|---|---|
| Asia Pacific | Australia | B |
| | Cambodia | CRF01_AE, B |
| | China and Hong Kong SAR | B, C, BC recombinant |
| | India | C |
| | Indonesia | CRF01_AE, B |
| | Japan | |
| | Malaysia | CRF01_AE, B |
| | New Zealand | |
| | Philippines | |
| | Singapore | CRF01_AE, B |
| | South Korea | |
| | Taiwan | |
| | Thailand | CRF01_AE, B |
| | Vietnam | CRF01_AE, B |
| CCASAnet | Argentina | B, F recombinant |
| | Brazil | B, F recombinant |
| | Chile | B |
| | Haiti | |
| | Honduras | B |
| | Mexico | B |
| | Peru | B |
| NAACCORD | USA | B |
| | Canada | B |
| Central Africa | Burundi | D |
| | Cameroon | CRF02_AG, other recombinants |
| | Democratic Republic of Congo | F, G, H, J, K, CRF01, other recombinants |
| | Republic of Congo (RoC) | F, G, H, J, K, CRF01, other recombinants |
| | Rwanda | A |

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|---|---|---|---|
| | East Africa | Kenya | C |
| | | Tanzania | C |
| | | Uganda | C |
| | Southern Africa | Lesotho | C |
| | | Malawi | C |
| | | Mozambique | C |
| | | South Africa | C |
| | | Zambia | C |
| | | Zimbabwe | C |
| | West Africa | Benin | CRF02_AG, other recombinants |
| | | Burkina Faso | CRF02_AG, other recombinants |
| | | Cote d'Ivoire | CRF02_AG, other recombinants |
| | | Ghana | CRF02_AG, other recombinants |
| | | Mali | CRF02_AG, other recombinants |
| | | Senegal | CRF02_AG, other recombinants |
| | | Togo | CRF02_AG, other recombinants |

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| **Ethics:** | ☐ This concept uses only the IeDEA standard dataset and is covered by the core IeDEA ethics approvals.<br>☒ 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. |
| **Dataset:** | ☒ This concept requires a new dataset.<br>☐ This concept uses an existing dataset that was issued for: |
| **Target journal(s):** | Leading specialist journal, for example Lancet ID, Lancet HIV, CID etc. |
| **Milestones:** | Circulation of concept sheet: April 2019<br>Funding for feasibility phase is available. Possible submission as unsolicited R01 to NIH 7th of May or 7th of September, and potentially for specific drug-resistance calls by NIH if reopened. Possible submission to SNSF 1 October 2019. |