

HIV susceptibility to second-generation integrase strand transfer inhibitors among people with multidrug resistance: a systematic review and meta-analysis protocol

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Abstract

Background: With the rapid scale-up of dolutegravir-based regimens, there is a declining trend of HIV drug resistance in several resource-limited settings. However, treatment success using second-generation integrase strand-transfer inhibitors (2nd-Gen INSTI) among people living with HIV with long therapeutic experience could be jeopardized by pre-existing drug resistance mutations to first-generation INSTI or even to other drug class.

Objectives: The aim of this systematic review and meta-analysis will be to provide a summary of existing evidence on the HIV susceptibility to 2nd-Gen INSTI among people with multidrug resistance.

Design: This will be a systematic review and meta-analysis.

Methods and analysis: This systematic review will include randomized and non-randomized trials, experimental studies, cohorts, cross-sectional studies, and governmental notices focusing on HIV susceptibility to 2nd-Gen INSTI. The search will consider studies conducted all over the world and published from 2013 to 2024, retrieved from PubMed/MEDLINE, Cochrane Central Register of Controlled Trials, Google scholar, African journals online, and Cumulative Index to Nursing and Allied Health Literature. Hand searching of the reference lists of relevant reviews and trials will be conducted, and we will also look for conference abstracts. We will include studies of adults and/or children exposed to dolutegravir, bictegravir, or cabotegravir following treatment failure to more than one drug class. The primary outcomes will be "the level of sensitivity to 2nd-Gen INSTI" and the "rate of viral suppression following exposure to 2nd-Gen INSTI." The secondary outcomes will essentially consist of the determinants of a good virological response (viral load < 1000 copies/mL at 48 weeks) under 2nd-Gen INSTI among participants with a history of multidrug resistance. Two reviewers will independently screen titles and abstracts, assess the full texts for eligibility, and extract data. If data permit, random-effects models will be used where appropriate. Subgroup and additional analyses will be conducted to explore the potential sources of heterogeneity (e.g., age, sex, baseline clinical data, treatment duration, and adherence level).

Discussion: This review will help to strengthen evidence on the effectiveness of 2nd-Gen INSTI by contributing to current knowledge concerning people living with HIV with long therapeutic exposure. The results will, therefore, contribute to set up baseline data for optimal management of people living with HIV harboring multidrug-resistant viruses.

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Introduction

In the African's context, transitioning from efavirenz/nevirapine (EFV/NVP)-based therapy to dolutegravir (DTG)-based regimens was of paramount importance.^{1–7} Of note, DTG is a very potent integrase strand transfer inhibitor (INSTI), which also has a strong genetic barrier. It is widely marketed as a fixed-dose combination of tenofovir (TDF) + lamivudine (3TC) + DTG (TLD),^{1,8–10} and is currently the preferred model for initiation to antiretroviral treatment (ART) in resource-limited settings (RLS) in replacement to TDF + 3TC + EFV (TLE) combination.^{2,11} Importantly, ART guidelines in Cameroon, like many other RLS, followed a World Health Organization (WHO) public health approach and consisted of two nucleoside reverse transcriptase inhibitors (NRTIs) and one non-nucleoside reverse transcriptase inhibitors (NNRTI) as a preferred first-line regimen before 2020 and second-line regimens consisting of two NRTIs and one ritonavir-boosted protease inhibitor (PI/r) in the event of first-line ART failures.¹² The introduction of TLD as a first-line regimen for treatment initiation was officially launched for people newly diagnose with HIV as of January 1, 2020,¹³ and the transition of the formal first-line regimen (like TLE) was done in health facilities at the discretion of clinicians. Notably, many authors have already reported early findings on the effectiveness of DTG-based first-line ART, including modeling studies and clinical trials in sub-Saharan Africa and beyond.^{3,11,14–16}

In general, the WHO has recommended the use of DTG-based regimens as first-line treatment and in cases of multidrug resistance (MDR) in RLS.¹⁷ All second-generation integrase strand-transfer inhibitors (2nd-Gen INSTI) have superior efficacy, a higher genetic barrier to resistance and a better safety profiles than most antiretrovirals (ARVs) used in RLS, including first-generation INSTIs such as raltegravir and elvitegravir.^{18,19} However, some in vitro trials have revealed that

mutations located outside the integrase gene can confer a high level of resistance to all INSTIs.²⁰ This implies that HIV may use an alternative mechanism to develop resistance to INSTIs by selecting mutations in regions coding for reverse transcriptase²⁰ and envelop²¹; otherwise, people harboring MDR would be less susceptible to DTG and other INSTIs. Despite the predicted high effectiveness of TLD,^{3,11,14–16} the effect of previous exposure to the same backbone (TDF + 3TC) gives room for possible existing drug-resistant mutants in the current transition from TLE to TLD (specifically with the K65R and M184V mutations known as major drug resistance mutations (DRMs) to TDF and 3TC/FTC, respectively). In effect, Inzaule et al. have recently reported that high levels of resistance to the NRTI backbone were common among those failing NNRTI-based first-line ART in RLS.²² Moreover, accumulation of NRTI resistance mutations, while transitioning to regimen with DTG, would lead to a "functional" monotherapy and eventually failure of that molecule,²³ which would further enhance the rapid emergence of DTG resistance among such people. The same would occur among those previously treated (and failed) with first-generation INSTI. Thus, the transition to regimen with INSTI with prior exposure to TLE may be accompanied by a suboptimal response in RLS and sub-Saharan Africa in particular, especially considering the risk of pre-existing DRMs other drug class and even to first-generation INSTI. The aim of this systematic review and meta-analysis will, therefore, be to provide a summary of existing evidence on the HIV-susceptibility to 2nd-Gen INSTI among people living with HIV harboring MDR.

Methods

Design and recording

This protocol was written following the guidelines of the Preferred Reporting Items for

Systematic Reviews and Meta-Analysis- Protocol (PRISMA-P)²⁴ (Supplemental Additional File 1) and has been registered within the PROSPERO database (registration number (CRD42023470922)). We will include randomized and non-randomized trials, cohorts, and cross-sectional studies underlining the use of 2nd-Gen INSTI among participants with history of MDR. In vitro assays evaluating the susceptibility of the virus in the presence of second-generation INSTI will also be included and analyzed separately.

Eligibility criteria

1. Participants: We will consider studies focusing on adults and/or children living with HIV with available history of therapeutic failure or MDR to prior antiretroviral therapies.
2. Exposure: Our main interest will be the exposure to 2nd-Gen INSTI among participants living with HIV. All studies on participants without exposure to 2nd-Gen INSTI will not be included. We would assess susceptibility to 2nd-Gen INSTI among participants with history of therapeutic failure or MDR to NRTI, NNRTI, PI, and even INSTI.
3. Outcomes: The primary outcome will be “the level of sensitivity to 2nd-Gen INSTI” and the “rate of viral suppression following exposure to 2nd-Gen INSTI.” Secondary outcomes will be the determinants of viral suppression under 2nd-Gen INSTI among participants with history of multiclass drug-resistant viruses.
4. Report characteristics: We will include studies that were published in English or French from 2013 to 2024; as the first 2nd-Gen INSTI (DTG) was approved in 2013.

Search strategy

We will carry out a comprehensive literature search in public and online databases and also search within the grey literature whenever possible. In addition, we will contact experts in the field for other potentially eligible studies we may have missed.

Electronic databases. We will be carrying the search out in PubMed/MEDLINE, Cochrane

Central Register of Controlled Trials (CENTRAL), Science direct, Google scholar, African journals online (AJOL) and Cumulative Index to Nursing and Allied Health Literature (CINAHL).

Trial registers. Ongoing trials will be sought in the WHO International Clinical Trials Registry Platform (ICTRP) and ClinicalTrials.gov (<https://clinicaltrials.gov/>).

Conference abstracts. We will search conference abstract archives on the websites of the Conference on Retroviruses and Opportunistic Infections (CROI); the International AIDS Conference (IAC); the International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention (IAS), and all Virology Education conferences, for all available abstracts presented at all conferences from 2013 onwards.

Other sources. Hand searching of the reference lists of relevant reviews and trials will be conducted. In addition, we will contact experts in the field for other potentially eligible studies we may have missed. The Medical Subject Headings (MeSH terms) for HIV and AIDS and key terms “antiretrovirals,” “ARVs,” “antiretroviral therapy,” “ART,” “drug susceptibility” “INSTI,” “integrase strand transfer inhibitors,” “integrase inhibitors,” “dolutegravir,” “cabotegravir,” “bictegravir,” “drug resistance,” “multi-drug resistance,” “multi-class resistance,” “dual-class resistance” and “triple-class resistance” will be cross referenced (Supplemental Additional File 2 shows the detailed search strategy for Pubmed and CINAHL). We will update the search prior to publication to include any additional eligible papers published recently.

Selection of studies for inclusion in the review

Two reviewers (VKM and ENJS) will independently review titles and abstracts to identify potentially eligible studies using an eligibility form. Disagreements will be resolved by consensus, if necessary, in discussion with a third reviewer (BY or JF). Full texts of potentially eligible articles will be obtained and independently reviewed by two authors (VKM and ENJS) to identify included studies. Discrepancies will be resolved by consensus and, if necessary, by discussion with a third reviewer (ACK, AND, BY, JF or DT). Studies in progress at the time of

review and which have not yet produced results will be identified as ongoing. Studies that have been completed without results could be classified as studies awaiting classification. Excluded studies and the reasons for their exclusion will be described. The study flowchart will reflect this process and detail the reasons for excluding studies.²⁴

Data extraction and management

All documents from the various sources included in our search strategy will be combined, downloaded into Zotero reference management software (version 7.0.7, Virginia, USA) and de-duplicated. We will use Microsoft Excel (version 2016 for Windows, Microsoft Corp., Redmond, WA, USA) to record the results of the selection process.

We will develop a data extraction sheet to guide data extraction. This sheet will be tested by two reviewers (ENK and AMN) on a random sample of 05 articles and revised if necessary. Two reviewers will independently read each eligible full-text article and extract the relevant data. Both data sets will be entered into Microsoft Excel (version 2016 for Windows, Microsoft Corp.). Any discrepancies in the extracted data will be resolved by consensus, in discussion with a third reviewer if necessary.

Data elements. We extract the following elements from the included studies:

- ✓ study characteristics (year of publication, study period, study population, study design, study objective, geographical location, and duration of follow-up)
- ✓ characteristics of the study population (sample size, age, gender, and period of enrolment).
- ✓ 2nd-Gen INSTI-based regimens
- ✓ duration of 2nd-Gen INSTI-based treatments
- ✓ INSTI sensitivity level; this will be taken into consideration after at least 48 weeks of exposure to 2-Gen INSTI
- ✓ virological (viral responses) and immunological (CD4) follow-up data after at least 48 weeks of exposure to 2-Gen INSTI
- ✓ failed drug classes
- ✓ DRMs reported in the history
- ✓ level of compliance
- ✓ variants involved.

Good virological response or viral suppression is here defined as a plasma viral load <1000 copies of viral RNA/mL at 48 weeks as stated by WHO for RLS. In case any study reports viral suppression levels < 50 or < 200 or < 400 copies/mL, we will categorize all data with the same threshold to avoid confounding assumptions. Immune recovery corresponds to a CD4 count > 500 cells/mm³ after treatment, according to individual studies. Subtypes or recombinants refer to viral strains identified in a patient sample.

The various timepoints (be it for the sensitivity or the viral response) will be analyzed subsequently in subgroup analyzes depending on what is reported in studies included.

Data synthesis

The main characteristics of all included studies will first be summarized in narrative form (year of publication, study period, study population, study design, study objective, geographical location, and duration of follow-up). A descriptive analysis of study characteristics will be undertaken to explore study heterogeneity. Summary statistics will then be used to describe study results, including means or medians and frequencies. Proportions and exact 95% binomial confidence intervals (95% CI) will be calculated for each result and presented in forest plots. We will calculate variance between the study (tau-squared) and *p*-values for heterogeneity tests between the study. We expect significant heterogeneity between studies, and subsequent analyses will, therefore, focus on identifying and exploring sources of heterogeneity. Finally, we will explore the associations that may exist between proportions in countries, contexts (e.g., urban, rural), and study outcomes (i.e., viral suppression rate and level of drug resistance) using random intercept (binomial-normal) logistic meta-regression models. These models avoid the biases that arise when normal-normal models are applied to logit or square root transformed proportions. Where appropriate, we will use the same models to calculate combined estimates of proportions.

Further analysis

Subgroup and additional analyses will be performed after stratification of study participants. Specifically, a subgroup analysis will be done among studies reporting participants with MDR. Results will then be sorted according to age (adults vs adolescents vs children (<10 years)), gender (men vs women), INSTI regimens, prior DRMs to NRTI, NNRTI, PI and INSTI, level of compliance, and duration of follow-up under 2nd-Gen INSTI-based treatments. This will enable us to adjust for potential confounding factors, in order to better estimate the effect of each variable on the observed results. Data permitting, meta-regression will be performed, and summary estimates will be used to explore the relationship between study covariates and effect size, in order to highlight any statistical significance.

Handling missing data

If data are missing for key variables (primary and secondary outcomes), we will contact the study authors for clarification. In the absence of clarification of these key variables, studies will be excluded. A description of other non-essential missing data will be provided for each study as a supplementary material, and we will discuss the possible implications of these missing data.

Assessing risk of bias in individual studies

Two reviewers (ENJS and NAD) will evaluate eligible studies using ROBINS-I,²⁴ a tool for assessing the risk of bias in non-randomized intervention studies. ROBINS enables available data on the risk of bias in these studies to be systematically organized and presented. ROBIS (RoB 2.0)²⁴ will be used in parallel for randomized studies, which include randomized controlled trials. Risk of bias in cohort and case-control studies will be assessed using the Newcastle-Ottawa scale.²⁴ These tools will be used to assess studies, but not their results, and will be adapted to the context of this systematic review.

Meta-bias

Publication bias between individual studies will be assessed by visually inspecting the trace of asymmetry on the funnel plot; the logistic model will take account of study size; quality assessment

will be cross-checked; and any disagreements will be resolved within the assessment team.

Grading the evidence of the data

We will use the GRADE approach to classify the certainty of the evidence as “high,” “moderate,” “low,” and “very low.”²⁵ The main findings concerning INSTI resistance, drug susceptibility, and the association with second-generation INSTI therapy will be summarized in a table. This table will also present the quality of the evidence found, all sorted according to socio-demographic data, clinical and laboratory parameters. Although evidence from randomized trials is of the highest quality, it may be downgraded to moderate, low, or very low quality. Grading will depend on limitations in study design and implementation, indirectness of evidence, unexplained heterogeneity, imprecision of results, and high likelihood of publication bias.²⁵ Evidence from strong observational studies (cohorts and case-control studies) will be classified as low quality.²⁵ However, if these studies produce large effects, and there is no obvious bias explaining these effects, we will classify the evidence as moderate quality or—if the effect is large enough—even high quality.²⁵ Detailed interpretation of each piece of evidence and its respective recommendation is provided in Supplemental Additional File 3.

Statistical software

All analyses will be performed in Epi infoTM version 7 (CDC, Atlanta, USA) and Microsoft Excel (version 2016 for Windows, Microsoft Corp., Redmond, WA, USA). Epi infoTM will help us calculate means, medians, frequencies, percentages, confidence intervals, and assess primary associations between variables using statistical tests. We will use a validated Excel spreadsheet for meta-analysis and forest plots (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3296675/>), as previously described.²⁶

Discussion

This systematic review and meta-analysis will help to update knowledge of the susceptibility of integrase inhibitors in people living with HIV who have failed several classes of antiretroviral therapy

and to understand the difficulties that may arise in choosing the best therapies for this type of patient. Our results will first be useful for the appropriate and contextual management of people on second-generation INSTI-based treatment. They will also enable new strategies to be developed to improve the management of people living with HIV and to reduce the transmission of resistant viruses when new transmission of HIV occur. This study will, therefore, be very useful in informing health systems interventions and HIV prevention and treatment strategies in sub-Saharan Africa and, more generally, in regions where resources are limited. Among the potential limitations of this review, we may be faced with significant heterogeneity and incompleteness in the studies, but these will be taken into account in the statistical models during the meta-regression analysis; if this is not the case, the incompleteness of the studies can at least be resolved by contacting the study authors. Another limitation may lie in the review and inclusion of studies. In the process of resolving disagreements during the review of articles, all team members will be included in the decision-making process or at least aware of the disagreements discussed. We will try as far as possible to reach a consensus decision for each disagreement. Significant changes to the protocol will be documented, taken into account when analyzing the data and discussed accordingly in the final document. Our findings will be published in a peer-reviewed journal and then disseminated to policy-makers, first at national level through the submission of a government notice, and then at international level through conferences and stakeholder meetings.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Not applicable.

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Supplemental material

Supplemental material for this article is available online.

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