THERAPEUTIC ADVANCES in
*Infectious Disease*

*Study Protocol*

# HIV drug resistance following pre-exposure prophylaxis failure among key populations in sub-Saharan Africa: a systematic review and meta-analysis protocol

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**Ezechiel Ngoufack Jagni Semengue, Evariste Molimbou, Naomi-Karell Etame, Christelle Aude Ka'e, Collins Chenwi Ambe, Alex Durand Nka, Pamela Patricia Tueguem, Aurelie Minelle Kengni Ngueko, Rachel Audrey Nayang Mundo, Désiré Takou, Jean-De-Dieu Anoubissi, Zacheaus Zeh Akiy, David Anouar Kob Ye Same III, Duplextine Aimée Ngougo, Serges Billong, Carlo-Federico Perno, Nicaise Ndembi and Joseph Fokam**

***Abstract***

**Background:** Key populations (KP) are highly vulnerable to HIV acquisition and account for 70% of new infections worldwide. To optimize HIV prevention among KP, the World Health Organization recommends the combination of emtricitabine plus tenofovir disoproxil fumarate for pre-exposure prophylaxis (PrEP). However, PrEP failure could be attributed to drug resistance mutations (DRMs) but this is unexplored in sub-Saharan Africa (SSA).

**Objectives:** We aim to conduct a systematic review that will provide evidence on the prevalence of HIV drug resistance (HIVDR) following PrEP failure among KP in SSA.

**Design:** This will be a systematic review and meta-analysis of studies conducted in sub-Saharan Africa.

**Methods and Analysis:** This systematic review will include randomized and non-randomized trials, cohorts, case controls, cross-sectional studies, and case reports evaluating the prevalence of HIVDR following PrEP failure among KP (i.e., gay men and men who have sex with men, female sex workers, transgenders, people who inject drugs, prisoners, and detainees) in SSA. Results will be stratified according to various KP, age groups (adolescents and adults), and geographic locations. Primary outcomes will be "the prevalence of PrEP failure among KP" and "the prevalence of HIVDR after PrEP failure" in SSA. Secondary outcomes would be "the prevalence of DRMs and drug susceptibility" and "the level of adherence to PrEP." A random-effects model will be used to calculate pooled prevalence if data permit and we will explore potential sources of heterogeneity.

**Discussion:** Our findings will provide estimates of HIVDR following PrEP failure among KP in SSA. In addition, determinants of PrEP failure and driving factors of the emergence of DRMs will also be investigated. Evidence will help in selecting effective antiretrovirals for use in PrEP among KP in SSA.

**Registration:** PROSPERO: CRD42023463862.

***Keywords:*** drug resistance mutations, HIV-1, key population, pre-exposure prophylaxis, sub-Saharan Africa

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Correspondence to:
**Ezechiel Ngoufack Jagni Semengue**
Chantal BIYA International Reference Centre for Research on HIV/AIDS Prevention and Management, Yaoundé, Cameroon

National HIV Drug Resistance Working Group, Ministry of Public Health, Yaoundé, Cameroon
**ezechiel.semengue@gmail.com**

**Joseph Fokam**
Chantal BIYA International Reference Centre for Research on HIV/AIDS Prevention and Management, Yaoundé, Cameroon

National HIV Drug Resistance Working Group, Ministry of Public Health, Yaoundé, Cameroon

National AIDS Control Committee (NACC), Yaoundé, Cameroon

Faculty of Health Sciences, University of Buea, Buea, Cameroon
**josephfokam@gmail.com**

**Evariste Molimbou**
**Aurelie Minelle Kengni Ngueko**
Chantal BIYA International Reference Centre for Research on HIV/AIDS Prevention and Management, Yaoundé, Cameroon

Faculty of Medicine and Surgery, University of Rome "Tor Vergata," Rome, Italy

**Naomi-Karell Etame Christelle Aude Ka'e Alex Durand Nka Pamela Patricia Tueguem Rachel Audrey Nayang Mundo**
Chantal BIYA International Reference Centre for Research on HIV/AIDS Prevention and Management, Yaoundé, Cameroon

**Collins Chenwi Ambe**
Chantal BIYA International Reference Centre for Research on HIV/AIDS Prevention and Management, Yaoundé, Cameroon

National HIV Drug Resistance Working Group, Ministry of Public Health, Yaoundé, Cameroon

Faculty of Medicine and Surgery, University of Rome "Tor Vergata," Rome, Italy

**Désiré Takou**
Chantal BIYA International Reference Centre for research on HIV/AIDS prevention and management, Yaoundé, Cameroon

National HIV Drug Resistance Working Group, Ministry of Public Health, Yaoundé, Cameroon

**Jean-De-Dieu Anoubissi**
National HIV Drug Resistance Working Group, Ministry of Public Health, Yaoundé, Cameroon

National AIDS Control Committee (NACC), Yaoundé, Cameroon

**Zacheaus Zeh Akiy**
U.S. Agency for International Development (USAID), Yaounde, Cameroon

**David Anouar Kob Ye Same III**
Joint United Nations Programme on HIV/AIDS (UNAIDS), Country Office, Yaounde, Cameroon

**Duplextine Aimée Ngougo**
Cameroon National Association for Family Welfare (CAMNAFAW), Yaounde, Cameroon

**Serges Billong**
Faculty of Medicine and Biomedical Sciences, University of Yaoundé I, Yaoundé, Cameroon

**Carlo-Federico Perno**
Bambino Gesu' Children's Research Hospital, Rome, Italy

## Background

The human immunodeficiency virus (HIV/AIDS) remains a public health threat in every country in the world, with over 70% of people living with HIV in sub-Saharan Africa (SSA).[1,2] In Cameroon, the prevalence of HIV/AIDS is 2.7% among people aged 15–49 and 1.2% among children and adolescents.[1–3] According to UNAIDS, key populations (KP) particularly vulnerable to HIV infection represent less than 5% of the world's population and account for 70% of new HIV infections in all regions of the world.[6] Specifically, men who have sex with men (MSM) and female sex workers (FSW) are 13 times more likely to be living with HIV than the general population in SSA.[4–7]

Current recommendations from the World Health Organization (WHO) suggest the combination of two antiretroviral drugs, emtricitabine 200 mg (FTC) and tenofovir disoproxil fumarate 300 mg (TDF) as pre-exposure prophylaxis in the context of HIV/AIDS prior to potential exposure to the risk of HIV infection.[10] HIV pre-exposure prophylaxis (PrEP) is the use of antiretroviral in uninfected people at high risk of HIV acquisition and is one of the most effective methods of achieving the ambitious public health goals of ending AIDS by 2030.[8–10] Clinical studies have shown that the use of TDF with or without FTC as PrEP can reduce the risk of HIV acquisition in MSM and transgender women when adherence is respected.[11,12] However, some authors report HIV infection in a small proportion of MSM on PrEP despite confirmed adherence to daily regimens.[13–15] Therefore, people failing PrEP with subsequent HIV infection are not just a result of very short periods of PrEP adherence with high-risk sexual activity[12,16,17] but this could also be attributed to existing HIV drug resistance (HIVDR).[12,16]

To the best of our knowledge, there is no summary of the prevalence of HIVDR in the frame of PrEP failure among KP in SSA. Global and regional data on HIVDR following PrEP failure among KP are crucial for better management of the regimens used for PrEP. Thus, this systematic review and meta-analysis will provide estimates of HIVDR following PrEP failure among KP in SSA. In addition, determinants of PrEP failure and factors leading to the emergence of DRMs will also be investigated in the meta-analysis. Evidence will help in selecting effective antiretrovirals for use in PrEP among KP in SSA.

## Methods/design

This protocol has been registered in the PROSPERO database (registration number CRD42023463862) and was drafted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement[18] (Additional File 1 in the Supplemental Material presents complete PRISMA-P 2015 checklist). PRISMA focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews and meta-analyses.

### *Eligibility criteria*

*Type of studies to be included.* We will include cohort and cross-sectional studies, randomized and non-randomized trials, and case reports evaluating the prevalence of HIVDR following PrEP failure among KP in SSA.

### *Characteristics of the participants*

*Population.* We will include studies carried out among KP (i.e., gay men and MSM, FSW, transgenders, people who inject drugs, prisoners, and detainees) who have failed PrEP and stratify these studies by age (adolescents and adults) and geographic location (country).

*Exposure.* PrEP use will be our main exposure of interest.

*Outcomes.* Primary outcomes will be "the prevalence of PrEP failure" among KP and "the prevalence of HIVDR after PrEP failure" in SSA. Secondary outcomes would be "the prevalence of DRMs and drug susceptibility" and "the level of adherence to PrEP." Of note, PrEP failure refers to the proportion of individuals found HIV positive after documented exposure to PrEP.

*Report characteristics.* We will include peer-reviewed articles and abstracts from conference presentations published in English or French from 2010 to 2024 to have the most updated and contextual data on the subject (considering that 2010 was when the first oral PrEP trials were conducted). Pre-prints and reviews will not be included in the data synthesis of this systematic review.

### *Information sources*

We will carry out a comprehensive literature search in public and online databases and also

search within the gray literature whenever possible. In addition, we will contact experts in the field for other potentially eligible studies we may have missed.

*Electronic databases.* Online databases that will be consulted will be PubMed/MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Science Direct, Google Scholar, African Journals Online, and Cochrane Central Register of Controlled Trials.

*Trial registers.* Ongoing trials will be searched in the WHO International Clinical Trials Registry Platform 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; the International AIDS Conference; the International AIDS Society Conference on HIV Pathogenesis, Treatment, and Prevention, and all relevant Virology Education conferences, for all available abstracts presented at all conferences from 2010 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. We will update the search prior to publication to include any additional eligible papers published recently.

*Search strategy.* Briefly, The Medical Subject Headings (MeSH terms) for "HIV" or "AIDS," "drug resistance," "Pre-exposure prophylaxis," "Sexual and gender minorities," and key terms "Pre-exposure prophylaxis," "Key population," "HIV drug resistance," "PrEP-failure," and "Sub-Saharan Africa" will be cross-referenced with terms associated with 56 African countries (Additional File 2 in the Supplemental Material shows the detailed search strategy for PubMed and CINAHL).

### Study records

*Data management.* All documents from the various sources included in our search strategy will be combined and uploaded into the Mendeley reference management software (version 2.83.0). Duplicates will be eliminated from the analysis. After checking the eligibility of published articles from titles and abstracts, a Google questionnaire will be used to extract relevant data and information from full-text manuscripts. We will use Microsoft Excel (version 2016 for Windows, Microsoft Corp., Redmond, WA, USA) to record the outcomes of the selection process.

### Selection of eligible studies

Articles extracted from the databases will be selected independently by three reviewers (E.M., N.K.E., and A.M.K.). Any disagreements will be resolved by discussion or consensus or will involve a fourth reviewer (E.J.N.S., A.N.D., or C.C.A.) as referee. Three reviewers (E.M., P.P.T., and R.A.N.M.) will independently evaluate the full text of selected papers. Differences will be resolved by consensus or by the arbitration of a fourth reviewer (E.N.J.S. or J.F.). Studies that are being conducted at the time of the review and which do not yet have results will be identified as ongoing. Excluded studies and their reasons for exclusion will be described. The PRISMA-P[19] study flow diagram will reflect this process and detail the reasons for the exclusion of studies.

### Data collection

After checking the eligibility of published articles, a Google questionnaire will be used to extract relevant data and information. Two or three reviewers will independently read each eligible full-text article and extract the relevant data. Both sets of data 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 (J.F., J.D.D.A., D.A.N., and S.B.) if necessary.

### Data items

We will extract the following from the included studies:

- Study characteristics (year of publication, country, study design and study period, and aims of study).
- Characteristics of the study population (sample size, age, sex, and inclusion and exclusion criteria).
- Prevalence of HIV infection among KP in SSA.

**Nicaise Ndembi**
Africa Centres for Disease Control and Prevention (Africa CDC), Addis Ababa, Ethiopia

Carlo-Federico Perno is also affiliated to Chantal BIYA International Reference Centre for research on HIV/AIDS prevention and management, Yaoundé, Cameroon

- HIV types and subtypes among infected individuals.
- Adherence to PrEP.
- DRMs following PrEP failure.

There is no pre-planned data assumption.

### *Data synthesis*

Data analysis will be performed using the "meta" and "metafor" packages of the R statistical software via the RStudio interface (V.4.3.1, R Foundation for Statistical Computing, Vienna, Austria),[20,21] and results will be considered statistically significant if $p < 0.05$. Study heterogeneity is estimated using the $H$ statistical test and quantified by the $I^2$ value.[22] The $I^2$ value is used to calculate the percentage of the total variation between studies due to genuine differences between studies rather than chance. The degree of heterogeneity with values of 0%, 18%, 45%, and 75% with $p < 0.05$ will designate zero, low, moderate, and high heterogeneity, respectively.[22,23] The prevalence of resistance following PrEP failure with 95% confidence intervals (95% CI) will be calculated with the "meta-prop" command using a random-effects model.[24] Subgroup analyses will be performed according to study design, defined geographic area, and duration of exposure to PrEP before failure[25]; further adjustments may be made for pooled prevalence estimates. The certainty of the evidence will be classified as "high," "moderate," "low," and "very low" following the GRADE approach. Detailed interpretation of each evidence and the respective recommendations are provided in Additional File 3 in the Supplemental Material.

### *Additional analyses*

Subgroup and further analyses will be performed after stratification of study participants. Results will then be sorted according to age (adults vs adolescents), key population subgroup with PrEP resistance, antiretrovirals used, level of adherence, and adverse events. This will enable us to adjust for potential confounding factors, for better estimation of the effect of each variable on the observed results. Data permitting, meta-regressions will be performed, and summary estimates will help explore the relationship between study variables and observed effects, to highlight any statistical significance.

### *Dealing with missing data*

If data on key variables are missing, we will contact the authors to obtain clarification of the study. A description of the missing data for each study will be provided and we will discuss the possible implications of the missing data.

### *Risk of bias and quality assessment*

The evaluation of included studies for the risk of bias will be done using ROBINS-1,[26,27] a tool for assessing the risk of bias in non-randomized trials for interventions. ROBIS [RoB 2.0],[26,27] will be used for randomized controlled trial studies. For observational studies, we will use the quality assessment tool (known as the Newcastle–Ottawa scale) for observational cohort and cross-sectional studies.[28] Discrepancy in the risk of bias assessment among the review authors will be solved by discussion and consensus, or by arbitration of a third review author.

### *Meta-biases*

The publication bias will also be assessed by visual inspection of the asymmetry of the funnel plot and the Egger test with the value of $p < 0.1$ indicating a potential bias.[29]

### *Statistical software*

All analyses will be done in Epi info™ version 7 (CDC Atlanta, Georgia USA) and Microsoft Excel version 2016 (Windows, Microsoft Corp.). Epi info™ will help us calculate means, medians, frequencies, percentages, confidence intervals, and assess primary associations between variables using statistical tests. R statistical software via the RStudio interface (V.4.3.1, R Foundation for Statistical Computing, Vienna, Austria)[20,21] will be used to assess study heterogeneity as well as for subgroup analyses. We will use a validated Excel spreadsheet for meta-analysis and forest plots, as previously described.[30]

## Discussion

This systematic review and meta-analysis will contribute to update the knowledge on DRMs emerging in KP who have failed PrEP in SSA countries. Our results will be useful for the appropriate and contextual management of PrEP among KP in these settings. They will also help us

to understand the determinants of PrEP failure and the emergence of DRM among KP, and thus help in developing new strategies to improve the prevention of HIV infection in this sub-population. Furthermore, considering the economic context of SSA which supports public health approaches over personalized strategies for ART programs, evidence that will be generated might also lead to the implementation of an efficient algorithm for HIVDR testing among KP in SSA. We are therefore convinced that our results will be useful to the scientific community and policy-makers to tailor specific health system interventions in SSA, and resource-limited settings in general.

As potential limitations of this study, we may be confronted first with the limited data published and important study heterogeneity, but these will be considered in statistic models during meta-regression analysis; if not performed, study incompleteness at least would be solved by contacting study authors. Another limitation may be at the level of reviewing and including studies. In effect, in the process of resolving disagreements while reviewing articles, all team members will be included in the decision-making process or at least aware of the disagreements being discussed. Significant adjustments to the protocol will be documented, taken into consideration during data analysis, and discussed accordingly in the final manuscript. Our results will be presented at conferences and published in a scientific journal to guarantee the quality of our findings.

## Declarations

### *Ethics approval and consent to participate*

Not applicable.

### *Consent for publication*

Not applicable.

### *Author contributions*

**Ezechiel Ngoufack Jagni Semengue:** Conceptualization; Investigation; Methodology; Resources; Software; Supervision; Validation; Writing – original draft; Writing – review & editing.

**Evariste Molimbou:** Data curation; Formal analysis; Investigation; Methodology; Software; Writing – original draft; Writing – review & editing.

**Naomi-Karell Etame:** Formal analysis; Methodology; Software; Writing – original draft; Writing – review & editing.

**Christelle Aude Ka'e:** Data curation; Formal analysis; Writing – original draft; Writing – review & editing.

**Collins Chenwi Ambe:** Software; Writing – original draft; Writing – review & editing.

**Alex Durand Nka:** Formal analysis; Methodology; Writing – original draft; Writing – review & editing.

**Pamela Patricia Tueguem:** Formal analysis; Writing – original draft; Writing – review & editing.

**Aurelie Minelle Kengni Ngueko:** Data curation; Writing – original draft; Writing – review & editing.

**Rachel Audrey Nayang Mundo:** Formal analysis; Writing – original draft; Writing – review & editing.

**Desiré Takou:** Software; Validation; Writing – original draft; Writing – review & editing.

**Jean-de-Dieu Anoubissi:** Software; Writing – original draft; Writing – review & editing.

**Zacheaus Zeh Akiy:** Software; Writing – original draft; Writing – review & editing.

**David Anour Kob Ye Same III:** Software; Writing – original draft; Writing – review & editing.

**Duplextine Aimée Ngougo:** Software; Writing – original draft; Writing – review & editing.

**Serges Billong:** Software; Writing – original draft; Writing – review & editing.

**Carlo-Federico Perno:** Software; Validation; Writing – original draft; Writing – review & editing.

**Nicaise Ndembi:** Software; Validation; Writing – original draft; Writing – review & editing.

**Joseph Fokam:** Conceptualization; Project administration; Resources; Software; Supervision; Validation; Writing – original draft; Writing – review & editing.

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*Competing interests*
The authors declare that there is no conflict of interest.

*Availability of data and materials*
Data sharing is not applicable to this paper as no datasets were generated or analyzed during the write-up of the current protocol.

**ORCID iD**
Ezechiel Ngoufack Jagni Semengue https://orcid.org/0000-0001-8768-2371

**Supplemental material**
Supplemental material for this article is available online.

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## Appendix

### *Abbreviations*

| | |
|---|---|
| 3TC | Emtricitabine |
| AJOL | African Journals online |
| ART | Antiretroviral therapy |
| ARV | antiretrovirals |
| CENTRAL | Cochrane Central Register of Controlled Trials |
| CINAHL | Cumulative Index to Nursing and Allied Health Literature |
| CROI | Conference on Retroviruses and Opportunistic Infections |
| DRMs | drug resistance mutations |
| FDA | Food and Drug Administration |
| FSW | female sex workers |
| HIV/AIDS | Human immunodeficiency virus infection/acquired immune deficiency syndrome |
| HIVDR | HIV drug resistance |
| IAC | International AIDS Conference |
| IAS | International AIDS Society |
| ICTRP | International Clinical Trials Registry Platform |
| KP | key population |
| PrEP | Pre-exposure prophylaxis |
| MeSH | Medical Subject Headings |
| MSM | men having sex with men |
| PRISMA-P | Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols |
| SSA | Sub-Saharan Africa |
| TDF | tenofovir disoproxil fumarate |
| TG | transgender |
| WHO | World Health Organization |