Review

Mapping HIV-1 Genetic Diversity and Drug Resistance in Central Africa (2020–2025): A Systematic Review and Meta-Analysis Protocol

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Mapping HIV-1 Genetic Diversity and Drug Resistance in Central Africa (2020–2025): A Systematic Review and Meta-Analysis Protocol

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Abstract

Central Africa exhibits the highest genetic diversity of HIV-1 globally, reflecting its role as the region where the virus first emerged. A product of this diversity is the increased prevalence of drug resistance mutations (DRMs), which has been documented in the region, particularly to NRTIs and NNRTIs, highlighting the importance of studying this diversity. This has led to a significant amount of literature being produced on the topic, although it is scattered throughout multiple niche sources, investigates different populations and reports variable outcomes. This review aims to compile this information, offering pooled regional and country-level proportions of subtypes, recombinant forms and individual DRMs, exploring their evolution from 2000 to 2025. To achieve these objectives, a meta-analysis will be performed for each subtype classification and individual DRM, with a subgroup analysis using the country of origin of the samples and a meta-regression analysis using the sample collection date. Methodological quality of the studies will be addressed using a proper tool for systematic reviews of prevalence, heterogeneity using the I^2 statistic, and publication bias using Egger's regression test. Finally, a bibliometric analysis will provide an overview of the research landscape in HIV-1 molecular epidemiology in Central Africa and enhance the understanding of subtype distribution and diversity hotspots.

Keywords: Central Africa; drug resistance mutations; HIV; molecular epidemiology; recombinant forms; subtypes

1. Introduction

1.1. Rationale

By the end of 2024, an estimated 40.8 million people were living with HIV globally, and approximately 630,000 deaths were attributed to AIDS-related complications, more than 60% of which occurred in sub-Saharan Africa. Within this region, Central and Western Africa account for approximately 19% of global HIV-related deaths despite representing only 13% of global HIV cases [1]. In addition to this discrepancy, Central African countries present a markedly diverse HIV-1 genetic landscape, defined by the circulation of multiple subtypes. These conditions favour the emergence of complex recombinant mosaic viruses, in which genomic segments from different subtypes are combined within a single genome. When applying formal diversity metrics such as the Shannon Index, Central Africa emerges as the region with the highest genetic diversity worldwide, with the five most diverse countries being Chad, the Democratic Republic of the Congo (DRC), Angola, the Republic of the Congo, and Equatorial Guinea [2]. This extensive diversity of genetic forms can be explained in part by the fact that the earliest human infections with simian

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immunodeficiency viruses, the ancestor lineages of HIV-1, occurred in Central Africa, making this region the cradle of the HIV-1 pandemic [3].

Regarding resistance to antiretrovirals (ARVs), this problem is exacerbated in contexts of economic vulnerability, where increasing resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) has been reported [4]. This is largely attributable to the fact that both classes of inhibitors were, until recently, used as first-line treatment regimens in these regions, which may also explain the relatively low prevalence of resistance mutations to protease inhibitors (PIs). In high-income countries, where subtype B predominates, a stabilisation of the previously declining trend in resistance to several classes of ARVs has been observed, suggesting that, despite the availability of more advanced treatments with higher genetic barriers, the emergence of drug-resistance mutations (DRMs) remains a growing concern [5]. The recent modernisation of ARV therapies in sub-Saharan Africa, particularly through the implementation of the integrase strand transfer inhibitor (INSTI) dolutegravir and the licensing of generic lenacapavir, a novel capsid inhibitor [6], has further increased interest in ARV resistance. Consequently, a growing body of literature has emerged on the occurrence of DRMs in the region, creating favourable conditions for conducting a systematic review of the literature.

The recent funding cuts to the U.S. President's Emergency Plan for AIDS Relief (PEPFAR), which currently supports three Central African countries - Angola, Cameroon, and the DRC - underscore the urgent need to compile and consolidate research in the region. Among these, the DRC is the most dependent on PEPFAR funding for HIV medicines, while Angola ranks ninth in terms of reliance [7].

1.2. Objectives

- To characterise the diversity and geographic distribution of HIV-1 subtypes and recombinant forms circulating in Central Africa between 2000 and 2025;
- To assess the presence and distribution of drug resistance mutations (DRMs) associated with all classes of antiretroviral drugs reported in Central Africa between 2000 and 2025.

2. Materials and Methods

This systematic review protocol was developed in accordance with the PRISMA-P 2015 guidelines [8] to ensure a transparent and reproducible methodology and has been registered in the Open Science Framework [9].

2.1. Framework and Review Question

The review question and eligibility criteria were structured according to the CoCoPop (Condition, Context, Population) framework (Table 1), which is recommended for systematic reviews addressing prevalence and epidemiological questions [10,11].

Table 1. Definition of the CoCoPop framework elements.

Element	Definition	Solution
Co (Condition)	*What is the condition/problem/symptom being studied?*	HIV-1 genetic diversity and antiretroviral drug resistance
Co (Context)	*What is the context? Which qualifiers or factors are key for understanding? When or where?*	Central Africa, 2000-2025.
Pop (Population)	*What is the population being examined?*	People living with HIV-1.

Review question: What is the proportion of HIV-1 subtypes and antiretroviral drug-resistance mutations among people living with HIV-1 in Central Africa between 2000 and 2025?

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2.2. Eligibility Criteria

- Types of studies: Observational studies with cross-sectional data, published in English, French, Portuguese, or Spanish;
- Target population: Individuals of any age diagnosed with HIV-1 at any stage of treatment (treatment-naïve, treatment-experienced, or heavily treatment-experienced), residing in a Central African country as defined by the United Nations "Middle Africa" region (Angola, Cameroon, Central African Republic, Chad, DRC, Equatorial Guinea, Gabon, Republic of the Congo, and São Tomé and Príncipe), with blood, plasma or serum samples collected between 2000 and 2025;
- Outcomes of interest: The proportion of HIV-1 subtypes and recombinant forms, determined using automated subtyping tools or phylogenetic inference methods, and/or the presence of DRMs associated with antiretroviral drug classes, including NRTIs, NNRTIs, PIs, INSTIs, entry inhibitors (EIs), and capsid inhibitors (CIs), identified using internationally recognised interpretation algorithms (e.g., Stanford HIVdb, ANRS-MIE, IAS-USA). Acceptable automated subtyping tools include: COntext-based Modeling for Expeditious Typing (COMET HIV-1), jumping profile Hidden Markov Model (jpHMM), REGA HIV subtype tool (REGA), Stanford University HIV Resistance Database (HIVdb), Subtype Analyser (STAR), and Subtype Classification Using Evolutionary Algorithms (SCUEL).

2.3. Information Sources

- Databases: PubMed/MEDLINE and the Cochrane Library will be used as primary health science databases, Scopus as a broader multidisciplinary database to include other relevant publications in virology, and AJOL to identify publications by African authors that may not be indexed in the aforementioned databases;
- Grey literature: The repositories Limo (https://kuleuven.limo.libis.be/), Theses.fr (https://theses.fr), RCAAP (https://www.rcaap.pt/), TESEO (https://aplicaciones.ciencia.gob.es/teseo/#/home), E-Theses Online Service (EThOS) or the British Library catalogue (https://www.bl.uk/), and the Research Portal of the Institute of Tropical Medicine of Antwerp (Belgium) (https://research.itg.be/) will be used to identify master's dissertations and doctoral theses. These repositories were selected because Central African countries were historically colonised by Belgium, France, Portugal, Spain, or the United Kingdom, resulting in a considerable body of literature about this region produced in the former colonial countries. In addition, the websites of the Ministries of Health of the "Middle Africa" countries will be consulted for reports on HIV-1 molecular epidemiology, as well as the websites of international organisations such as WHO, UNAIDS, PANGEA HIV, and Africa CDC. Major HIV-related meetings will also be searched to identify relevant oral and poster presentations, including the Conference on Retroviruses and Opportunistic Infections (CROI), the International AIDS Society Conference on HIV Science, HIVR4P – the HIV Research for Prevention Conference, the European Meeting on HIV & Hepatitis, the International Conference on HIV Treatment, Pathogenesis, and Prevention Research (INTEREST), AIDS – the International AIDS Conference, HIV Glasgow and the European AIDS Conference. Preprints.org, medRxiv, and bioRxiv will be searched to capture articles that have not yet undergone formal publication. This is particularly relevant given the focus on low- and middle-income settings, where research dissemination may be slower due to financial constraints;
- Additional searches: A manual search will also be conducted using the "similar articles" suggestions, citation tracking, and direct contact with leading scientists in the field to identify potential additional publications.

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2.4. Search Strategy

Database searches will be conducted according to the strategies detailed in Table 2, with filters applied, when supported by the database, to limit results to publications from 2000 onwards, published in English, French, Portuguese, or Spanish.

Table 2. Research strategies to be used in databases.

Database	Research strategy
PubMed	("HIV-1"[MeSH Terms] OR "acquired immunodeficiency syndrome"[MeSH Terms] OR "HIV infections"[MeSH Terms] OR "people living with HIV"[Title/Abstract] OR "HIV-positive"[Title/Abstract] OR "VIH"[Title/Abstract] OR "VIH-1"[Title/Abstract] OR "SIDA"[Title/Abstract]) AND ("Angola"[MeSH Terms] OR "Cameroon"[MeSH Terms] OR "Cameroun"[Title/Abstract] OR "Chad"[MeSH Terms] OR "Tchad"[Title/Abstract] OR "Central African Republic"[MeSH Terms] OR "Republique Centrafricaine"[Title/Abstract] OR "Centrafrique"[Title/Abstract] OR "Congo"[MeSH Terms] OR "Congo-Brazzaville"[Title/Abstract] OR "Democratic Republic of the Congo"[MeSH Terms] OR "DR Congo"[Title/Abstract] OR "Congo-Kinshasa"[Title/Abstract] OR "Republique Democratique du Congo"[Title/Abstract] OR "Sao Tome and Principe"[MeSH Terms] OR "São Tomé e Príncipe"[Title/Abstract] OR "Equatorial Guinea"[MeSH Terms] OR "Guinea Ecuatorial"[Title/Abstract] OR "Gabon"[MeSH Terms] OR "Gabonese Republic"[Title/Abstract] OR "République Gabonaise"[Title/Abstract] OR "Africa, Central"[MeSH Terms] OR "Middle Africa"[Title/Abstract] OR "Afrique Centrale"[Title/Abstract] OR "África Central"[Title/Abstract]) AND ("phylogeny"[MeSH Terms] OR "phylogenie" [Title/Abstract] OR "filogenia" [Title/Abstract] OR "molecular epidemiology"[MeSH Terms] OR "epidemiologie moleculaire"[Title/Abstract] OR "epidemiologia molecular"[Title/Abstract] OR "genetic variation"[MeSH Terms] OR "genetic diversity"[Title/Abstract] OR "diversité genetique"[Title/Abstract] OR "diversidade genética"[Title/Abstract] OR "diversidad genética"[Title/Abstract] OR "drug resistance"[MeSH Terms] OR "drug resistance, microbial"[MeSH Terms] OR "antiviral agents"[MeSH Terms] OR "drug resistance, viral"[MeSH Terms] OR "drug resistance, multiple, viral"[MeSH Terms] OR "drug resistance, multiple"[MeSH Terms] OR "antiretroviral resistance"[Title/Abstract] OR "résistance aux antirétroviraux"[Title/Abstract] OR "resistência aos antirretrovirais"[Title/Abstract] OR "subtyping"[Title/Abstract] OR "subtype"[Title/Abstract] OR "subtipo"[Title/Abstract] OR "sous-type"[Title/Abstract] OR "genotyping"[Title/Abstract] OR "genotypage"[Title/Abstract] OR "genotipagem"[Title/Abstract] OR "genotipificar"[Title/Abstract])
Cochrane Library	#1 MeSH descriptor: [HIV-1] explode all trees #2 MeSH descriptor: [HIV] explode all trees #3 MeSH descriptor: [Acquired Immunodeficiency Syndrome] explode all trees #4 MeSH descriptor: [HIV Infections] explode all trees #5 (People living with HIV):ti,ab,kw #6 (HIV-positive):ti,ab,kw #7 (VIH):ti,ab,kw #8 (VIH-1):ti,ab,kw #9 (SIDA):ti,ab,kw #10 MeSH descriptor: [Angola] explode all trees #11 MeSH descriptor: [Cameroon] explode all trees

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#12 MeSH descriptor: [Chad] explode all trees
#13 MeSH descriptor: [Central African Republic] explode all trees
#14 MeSH descriptor: [Congo] explode all trees
#15 MeSH descriptor: [Democratic Republic of the Congo] explode all trees
#16 MeSH descriptor: [Sao Tome and Principe] explode all trees
#17 MeSH descriptor: [Equatorial Guinea] explode all trees
#18 MeSH descriptor: [Gabon] explode all trees
#19 MeSH descriptor: [Africa, Central] explode all trees
#20 (Middle Africa):ti,ab,kw
#21 (DR Congo):ti,ab,kw
#22 (Congo-Kinshasa):ti,ab,kw
#23 (Gabonese Republic):ti,ab,kw
#24 (Congo-Brazzaville):ti,ab,kw
#25 (Guinea Ecuatorial):ti,ab,kw
#26 (Cameroun):ti,ab,kw
#27 (Republique Centrafricaine):ti,ab,kw
#28 (Centrafrique):ti,ab,kw
#29 (République Démocratique du Congo):ti,ab,kw
#30 (São Tomé e Principe):ti,ab,kw
#31 (République Gabonaise):ti,ab,kw
#32 (Afrique Centrale):ti,ab,kw
#33 (África Central):ti,ab,kw
#34 MeSH descriptor: [Molecular Epidemiology] explode all trees
#35 MeSH descriptor: [Genetic Variation] explode all trees
#36 MeSH descriptor: [Drug Resistance] explode all trees
#37 MeSH descriptor: [Drug Resistance, Microbial] explode all trees
#38 MeSH descriptor: [Antiviral Agents] explode all trees
#39 MeSH descriptor: [Drug Resistance, Viral] explode all trees
#40 MeSH descriptor: [Drug Resistance, Multiple, Viral] explode all trees
#41 MeSH descriptor: [Drug Resistance, Multiple] explode all trees
#42 MeSH descriptor: [Anti-Retroviral Agents] explode all trees
#43 MeSH descriptor: [Phylogeny] explode all trees
#44 (phylogénie):ti,ab,kw
#45 (filogenia):ti,ab,kw
#46 (subtyping):ti,ab,kw
#47 (genotyping):ti,ab,kw
#48 (subtype):ti,ab,k
#49 (genetic diversity):ti,ab,kw
#50 (resistance mutation):ti,ab,kw
#51 (antiretroviral resistance):ti,ab,kw
#52 (épidémiologie moléculaire):ti,ab,kw
#53 (résistance aux antirétroviraux):ti,ab,kw
#54 (génotypage):ti,ab,kw
#55 (diversité génétique):ti,ab,kw
#56 (sous-type):ti,ab,kw
#57 (epidemiologia molecular):ti,ab,kw
#58 (resiste^ncia aos antirretrovirais):ti,ab,kw
#59 (diversidade genética):ti,ab,kw
#60 (genotipagem):ti,ab,kw
#61 (subtipagem):ti,ab,kw
#62 (resistencia a los antirretrovirales):ti,ab,kw
#63 (diversidad genética):ti,ab,kw
#64 (genotipificar):ti,ab,kw

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	#65 (subtipo):ti,ab,kw #66 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 #7 OR #8 OR #9) AND (#10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33) AND (#34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65)
Scopus	TITLE-ABS-KEY (phylogeny OR phylogenie OR filogenia OR “genetic diversity” OR “diversite genetique” OR “diversidade genetica” OR “diversidad genetica” OR “molecular epidemiology” OR “epidemiologie moleculaire” OR “epidemiologia molecular” OR “drug resistance” OR “antiretroviral resistance” OR “resistance aux antiretroviraux” OR “resistencia aos antirretrovirais” OR “resistencia a los antirretrovirales” OR subtyping OR subtype OR “sous-type” OR subtipo OR genotyping OR genotypage OR genotipagem OR genotipificar) AND TITLE-ABS-KEY (Angola OR Cameroon OR Cameroun OR Chad OR Tchad OR “Central African Republic” OR “Republique Centrafricaine” OR Centrafrique OR “Democratic Republic of the Congo” OR “Republique Democratique du Congo” OR Congo OR “Sao Tome and Principe” OR “Sao Tome e Principe” OR “Equatorial Guinea” OR “Guinea Ecuatorial” OR Gabon OR “Gabonese Republic” OR “Republique Gabonaise” OR “Central Africa” OR “Middle Africa” OR “Afrique Centrale” OR “Africa Central”) AND TITLE-ABS-KEY (“HIV-1” OR AIDS OR VIH OR “VIH-1” OR SIDA)
AJOL	A free search will be performed using: “HIV”, “subtype”, “Central Africa”, “Angola”, “Cameroon”, “Central African Republic”, “Chad”, “Democratic Republic of the Congo”, “Congo”, “Equatorial Guinea”, “Gabon”, “Sao Tome and Principe” and other adjacent terms.

Searches in grey literature sources will be conducted using combinations of keywords related to HIV-1, together with terms addressing genetic diversity and drug resistance, combined with the names of the countries included in this review, following a strategy analogous to the database searches. These searches will adhere to the same conceptual framework as the database search strategies but will be adapted to the functionality and capabilities of each source. The Internet Archive will be used to access older conference proceedings that may no longer be available.

2.5. Study Selection

Articles identified in the initial search will be imported into Mendeley (v2.132.2) for reference management and duplicate detection. Rayyan [12] will be used for article selection at all stages, conducted independently and in parallel by two reviewers. In the event of disagreement, consensus will first be sought through discussion and if it is not reached a third reviewer will make the final decision.

The first stage of screening will involve reviewing titles and abstracts, applying the eligibility criteria broadly to exclude studies outside the scope of this review, such as systematic reviews, clinical trials, or studies that do not include samples from individuals in Central Africa. The second stage will consist of a full-text review, during which the eligibility criteria will be applied in detail to determine final study inclusion. The screening process will be reported using a PRISMA flow diagram [13].

2.6. Data Extraction

Data extraction will be performed by one reviewer using Microsoft Excel. The following variables will be collected:

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- Publication details:
  - Year of publication
  - Study type
- Sample information:
  - Country of origin of the samples
  - Date of sample collection
  - Sample size
  - Sampling method
  - Type of biological sample (blood, plasma, serum)
- Target population:
  - Definition and description of the population
  - Characteristics of the study participants:
    - Age
    - Sex or gender
    - Other relevant criteria (e.g., pregnancy status, STI coinfection, intravenous drug use)
- Laboratory and genomic data:
  - Genomic region analysed
  - Sequencing method
  - Evidence of APOBEC-derived hypermutation
  - Algorithm used for resistance mutation analysis
  - Technique used for subtyping

Considering the two primary review objectives previously defined, the following outcomes will also be extracted:

- Proportion and number of sequences of each reported subtype and recombinant form
  - When available, description of the genetic structure of unique recombinant forms
- Proportion and number of sequences carrying each individual resistance mutation

2.7. Risk of Bias

For each included study, a critical appraisal of methodological quality and risk of bias will be conducted using an appropriate checklist for cross-sectional epidemiological studies [11]. As in the previous stage, this assessment will be carried out by one reviewer. The results will be reported and considered in the interpretation of the review findings.

2.8. Meta-Analysis

Studies reporting data on HIV-1 subtype distribution will be included in meta-analyses of proportions, conducted using the latest available version of JASP [14]. A random-effects model will be applied, as substantial heterogeneity across studies is anticipated given the diversity of study designs and settings.

To address variance instability when proportions are close to 0 or 1, proportions will be stabilised using the Freeman-Tukey double arcsine transformation [15]. This approach ensures that model assumptions are met and that pooled estimates and confidence intervals are reliable. Following analysis, the results will be back-transformed to the 0-1 scale for interpretation.

Separate meta-analyses will be conducted for each subtype with sufficient data to estimate pooled proportions in Central Africa, together with the corresponding 95% confidence intervals. Subgroup analyses will be performed by "country of origin of the samples" to estimate pooled subtype proportions for each country included in the review. In addition, potential temporal trends in subtype distribution will be explored at the regional level using a univariate meta-regression, with "date of sample collection" as the explanatory variable.

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For studies reporting data on drug resistance mutations, additional meta-analyses of proportions will be conducted following a similar approach. In this case, pooled proportions of individual drug resistance mutations in Central Africa will be estimated. Subgroup analyses by country and meta-regression analyses exploring temporal trends will also be carried out.

Statistical heterogeneity among studies will be assessed using the I^2 statistic [16], with values above 70% considered indicative of substantial heterogeneity. Where such heterogeneity is identified, additional subgroup analyses and meta-regression models will be conducted to explore potential sources of heterogeneity.

Potential publication bias will be assessed using Egger's regression test [17] and by visual inspection of funnel plots when at least 10 studies are available. If asymmetry is detected, the trim-and-fill method [18] will be applied to evaluate its potential impact on pooled estimates.

Finally, sensitivity analyses will be performed by excluding studies assessed as having a high risk of bias in order to evaluate the robustness of the pooled estimates.

2.9. Bibliometric Analysis

To complement the systematic review and meta-analysis, a bibliometric analysis will be conducted using VOSviewer [19]. Bibliographic metadata, including authors, institutions, countries, keywords, and citations, from all the included studies will be analysed through network analysis. This approach will facilitate the visualisation of patterns of collaboration among authors and institutions, as well as country contributions and keyword co-occurrence. The identification of clusters and trends will provide an overview of the research landscape in HIV-1 molecular epidemiology in Central Africa and enhance the understanding of its distribution and key research hotspots.

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