BMC Infectious Diseases

https://doi.org/10.1186/s12879-026-12916-4

Article in Press

Genetic diversity and drug resistance mutations of HIV-1 in Ghana: a systematic review of two decades

Received: 14 May 2025

Accepted: 15 February 2026

Published online: 26 February 2026

Cite this article as: Appiah P., Adusei-Poku M., Obeng B.M. *et al.* Genetic diversity and drug resistance mutations of HIV-1 in Ghana: a systematic review of two decades. *BMC Infect Dis* (2026). https://doi.org/10.1186/s12879-026-12916-4

Pious Appiah, Mildred Adusei-Poku, Billal Musah Obeng, Richard Osei-Yeboah, Gaspah Gbassana, Seth Agyemang, Lennox Mac-Ankrah, Ibrahim Jamfaru, Makafui Seshie, Isaac Kwame Sraku, Samuel Ankamah, Kwabena Obeng Duedu & Kwamena William Coleman Sagoe

Genetic diversity and drug resistance mutations of HIV-1 in Ghana: a systematic review of two decades

Pious Appiah[1]*, Mildred Adusei-Poku[1]*, Billal Musah Obeng[2], Richard Osei-Yeboah[3], Gaspah Gbassana[4], Seth Agyemang[5], Lennox Mac-Ankrah[6], Ibrahim Jamfaru[6], Makafui Seshie[1], Isaac Kwame Sraku[1], Samuel Ankamah[7], Kwabena Obeng Duedu[8], and Kwamena William Coleman Sagoe[1]

Authors Affiliations

1 Department of Medical Microbiology, Medical School, College of Health Sciences, University of Ghana, Accra, Ghana.

2 Immunovirology & Pathogenesis Program, Kirby Institute, University of New South Wales, South Wales, NSW, Australia.

3 Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, Edinburgh, United Kingdom.

4 Department of Laboratory Medicine, University of Liberia, Monrovia, Liberia.

5 Yemaachi Biotechnology, Accra, Greater Accra, Ghana.

6 Department of Microbiology and Immunology, School of Medicine, University of Health and Allied Sciences, Ho, Ghana.

7 University of Ghana Library System, University of Ghana, Accra, Greater Accra, Ghana.

[8] College of Life Sciences, Birmingham City University, City South Campus, Birmingham, B15 3TN, United Kingdom.

Pious Appiah, piousedu19@gmail.com

Mildred Adusei-Poku, madusei-poku@ug.edu.gh

Billal Musah Obeng, bobeng@kirby.unsw.edu.au

Richard Osei-Yeboah, Richard.Osei-Yeboah@ed.ac.uk

Gaspah Gbassana, gbassanaga@ul.edu.lr

Seth Agyemang, seth@yemaachi.com

Lennox Mac-Ankrah, lankrah@uhas.edu.gh

Ibrahim Jamfaru, ijamfaru@uhas.edu.gh

Makafui Seshie, amaseshie@gmail.com

Isaac Kwame Sraku, iksraku@ug.edu.gh

Samuel Ankamah, sankamah@ug.edu.gh

Kwabena Obeng Duedu, kwabena.duedu@bcu.ac.uk

Kwamena William Coleman Sagoe, ksagoe@ug.edu.gh

***: Corresponding Authors**

Abstract

Background: Since the roll-out of antiretroviral therapy (ART), there has been a significant reduction in Human Immunodeficiency Virus 1 (HIV-1) related mortality and morbidity. Nonetheless, drug resistance has emerged significantly, affecting treatment outcomes, but there is limited surveillance of HIV-1 drug resistance and subtype diversity, which is critical for clinical decision-making on therapeutic choices as well as public health control measures. The goal of this systematic review was to analyze data from 2004 to 2024 on subtype diversity and drug resistance mutations (DRMs) among persons living with HIV-1 in Ghana.

Methods: We searched PubMed, Scopus, Cochrane CENTRAL, CINAHL Complete, Web of Science, and Google Scholar for cross-sectional and longitudinal studies reporting on HIV-1 subtype diversity, drug resistance, or both among individuals in Ghana published from 2004 to 2024 and reviewed according to PRISMA guidelines. The protocol for this review was registered with PROSPERO (CRD42024529606).

Results: A total of 2472 studies were screened, 28 were selected for full-text review, and 18 were included. The overall sample size was 2001 individuals. HIV-1 subtypes observed were CRF02_AG (68.9%), A (2.2%),

A3 (1.7%), B (2.1%), C (0.6%), G (3.5%), CRF06_cpx (3.3%), CRF09_cpx (0.6%), and other recombinant forms (16.8%). Only one occurrence was observed each for Subtypes D and K. Key DRMs for NRTIs were documented, with M184V/I detected at 41.2%, followed by M41L (15.4%) and T215Y/F (11.8%). For NNRTIs, DRMs were in the set as K103N (28.4%), G190A/S (10.1%), and V106I/AT (10.7%). The DRMs for PI were primarily marked by M46I/L and L90M (25.0% each), while I54V, I84V, and V82A were each identified in 12.5% of cases. The INSTIs accessory mutations observed were L74I/M (46.7%), E157Q (20.0%), G163R/K and T97A (13.3% each). Only two studies analyzed sequences for DRMs from the integrase gene; however, these were accessory DRMs and are not known to produce resistance to the current INSTI regimen. Also, mutational profiles varied notably by ART history, and key mutations in NRTIs, NNRTIs, and INSTIs were significantly associated with ART experience.

Conclusion: The findings reveal CRF02_AG predominance and a considerable increase in NNRTI DRMs, highlighting the need for tailored therapies and continued surveillance to address emerging resistance in Ghana.

Keywords: HIV-1, Subtype diversity, Drug resistance mutation, Ghana

INTRODUCTION

Human immunodeficiency virus (HIV) is a global threat, with 39.9 million [36.1 million–44.6 million] persons living with HIV (PLWH) worldwide in 2023, and approximately 65% of this burden was found in Africa [1]. In Ghana, HIV was reported in 1986 after the global discovery in the early 1980s, marking the beginning of a long and complex battle against the virus in the country [2,3]. After confirming the first case in Ghana, national efforts to combat the epidemic have been through awareness campaigns, improved access to testing, the establishment of treatment centres aimed at providing care for those affected, and the recommendation of effective antiretroviral therapy (ART) to suppress viral replication and improve the quality of life for PLWH. These activities have been coordinated through the Ghana AIDS Commission and the National AIDS Control Programme [4]. The management and control efforts have also been largely influenced by global recommendations led by the World Health Organization (WHO). For instance, the WHO recommends testing and treating all cases, and hence, the use of ARTs has increased significantly in Ghana [5,4], thereby exerting selective pressure on the virus, leading to genetic evolution.

There are two forms of HIV: HIV-1 and HIV-2. Of the two types, HIV-1 is the predominant form and is mostly responsible for the HIV/AIDS pandemic [6]. It is further divided into groups M, N, O, and P, with members of group M being the main form of the virus that infects humans. Subtypes of HIV-1 group M include A-D, F-H, J, and K. Additionally, the subtypes have been further classified into sub-subtypes A1-A4, A6, F1, and

F2, circulating recombinant forms (CRFs), and unique recombinant forms (URFs) [6,7]. The reported sub-types in Ghana include CRF02_AG, CRF06_cpx, A, G, A3, C, B and different circulating recombinant forms [8,9], are similar to those reported in neighbouring countries, Togo [10], and Burkina Faso [11,12], as well as other African nations, including Nigeria, [13], Cameroon [14], and Egypt [15]

Efforts to obtain an HIV cure have been ongoing since its discovery. However, the desired results have not been obtained due to the continuous evolution of HIV-1 genetic diversity and associated drug resistance mutations (DRMs) and latency within the genomes of long-lived host cells [7,16]. Despite this setback, the introduction of ART has rendered HIV a manageable chronic infection, reducing HIV-1-related mortality and morbidity. To keep the prospects of finding a cure and/or elimination alive, it is important to keep up to date with continuous surveillance of the evolution of genetic diversity and its association with drug resistance.

Using the available data from HIV genetic surveillance activities globally, the World Health Organization (WHO) has led the cause with member states to modify ART guidelines to address emerging resistance and treatment failures. The main approaches to addressing this have been the introduction of newer drugs as alternatives and combination therapy to enhance the efficacy of existing regimens [17]. To ensure therapeutic practices and recommendations are always relevant, the WHO recommends surveillance of HIV DRMs as ART is used [17]. Implementing this recommendation has, however, not been successful in Ghana and

several other resource-limited settings that share a high burden of disease. The reasons are multifaceted but mostly due to cost and infrastructure, hence data is only available from individual, mostly non-coordinated studies [8]. This gap in national data also hinders the ability to formulate tailored, effective national strategies and policies to combat the epidemic locally and inform translational efforts like drug discovery and therapeutic development. This systematic review, therefore, aimed at consolidating and analyzing all the published data on HIV-1 genetics from 2004, when the first study was carried out in Ghana, to 2024, to describe the dynamics of subtype diversity and associated DRMs.

METHODS

Study design and protocol registration

We analyzed data from published studies on HIV-1 genetics to explore the changes in HIV-1 subtypes and drug resistance mutations from its inception in Ghana. A systematic literature search was performed to identify studies published since 1986, when HIV was first reported in Ghana. As per the inclusion criteria for study selection, data were available from 2004 to 2024 [Supplementary material 1]. Two investigators independently searched records to be included in the study by screening the titles and abstracts of each paper. Conflicts due to the inclusion and exclusion of the study were resolved by a third reviewer. This systematic review was completed according to PRISMA guidelines using Covidence. The protocol for this review is registered with PROSPERO (CRD42024529606).

Data sources

The article search was performed on 24th July 2024, using keywords related to the subject, "HIV-1 genetic diversity and Drug Resistance Mutations in Ghana". The search was conducted using the following databases: PubMed, Scopus, Cochrane CENTRAL, CINAHL Complete, Web of Science, and Google Scholar. No language or regional restrictions were applied to the search. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords to identify relevant studies. Search terms included: “People living with HIV”, PLWHIV, “HIV Patients”, “Genetic diversity”, “drug resistance mutation”, DRM, “antiretroviral therapy”, “antiretroviral treatment”, “antiretroviral resistance”, as well as geographic terms such as Ghana, Accra, Kumasi, Greater Accra, Tamale, and Sunyani. These terms were used in various combinations, applying the Boolean operators “AND” and “OR” to structure and refine the search. All relevant original research articles meeting the inclusion criteria were selected for title and abstract, and full-text screening. When the thesis work had subsequently been published as a peer-reviewed journal article, we included only the journal article and excluded the corresponding thesis to avoid duplicate inclusion of the same data. The extracted data included the study title, year of publication, study objectives, study sites, sampling date, study population, sample size, HIV-1 subtypes, and DRMs based on the genomic region of HIV-1.

Study bias assessment

Risk of bias for each included study was assessed using the Joanna Briggs Institute checklist, which evaluates eight domains including clarity of inclusion criteria, description of the study setting and participants, validity and reliability of exposure and outcome measurements, consideration of confounding, and appropriateness of statistical analysis. Two reviewers independently applied the tool and resolved any disagreements by discussion and consensus. Study-level ratings for each domain are presented in Supplementary Material 2.

Inclusion and exclusion criteria

We included observational studies (cross-sectional surveys, routine surveillance, and cohort studies) that reported HIV-1 subtype or DRM data from individuals in Ghana and excluded review articles, mathematical modelling studies, qualitative studies, policy analyses, and studies that focused on other infections aside from HIV-1.

Data analysis

Descriptive statistics were utilized to summarize the prevalence of HIV-1 subtypes and associated DRMs. The DRM data were categorized by antiretroviral therapy classes, including nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs). The frequency of each subtype and DRM was calculated to provide insights into the distribution and patterns of resistance. Polymorphisms were removed from the mutational profile to emphasize the major DRMS. HIV-1 subtypes and DRM pattern were

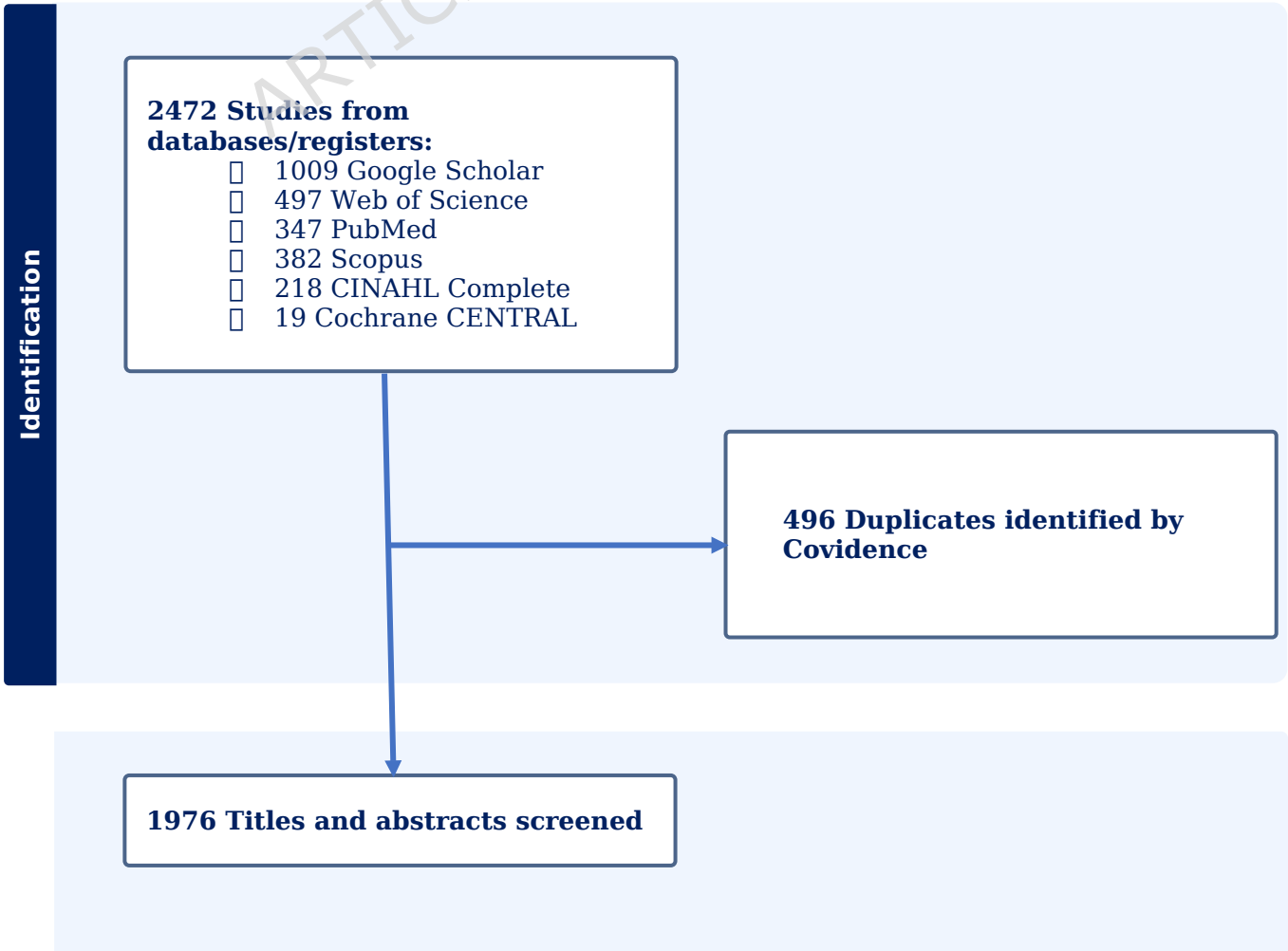
analyzed using three temporal groups: <2007 (Early ART phase), 2007-2018 (ART expansion with NNRTI/NRTI-based treatment), and 2019-2024 (DTG-based regimen scale-up). DRMs had only two temporal groups (2007-2018 and 2019-2024) since the first report was in 2007. These intervals enabled temporal comparisons based on clinical guidelines changes and molecular epidemiology milestones in Ghana. To assess the association between DRM prevalence and ART status, participants with successful sequences were stratified into ART-experienced and ART-naive groups. Statistical comparisons were performed using Fisher's exact test to evaluate significance in the frequency of specific DRMs between these groups. All tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. A formal meta-analysis with pooled prevalence estimates was considered but not undertaken because of substantial clinical and methodological heterogeneity across studies. This included differences in study design (routine surveillance vs treatment-failure cohorts), genomic regions sequenced (partial versus more extensive pol, with or without integrase), sequencing platforms (Sanger vs next-generation sequencing), and resistance interpretation algorithms and thresholds. Because these factors directly influence the detection and classification of DRMs, any pooled prevalence estimate was judged likely to be difficult to interpret and potentially misleading.

RESULTS

Study characteristics

We identified 2,472 publications and removed 496 duplicates. The titles and abstracts of the remaining 1,976 were screened according to the inclusion and exclusion criteria. Following this, 28 studies were selected for full-text review, of which 18 met the eligibility requirements for inclusion in this review [Figure 1]. The final analysis comprised a cumulative sample size of 2,001 individuals living with HIV-1 in Ghana. Out of the 18 studies, 9 reported on sex, and the majority (340/559, 60.8%) were females. The majority of the studies were carried out in Greater Accra (41.7%) and Eastern (29.2%) regions, with no study conducted in the Ahafo, Bono East, Western, Western North, Upper East, Savanna, Volta, and Oti regions [Figure 2]. The Summary data of all included studies have been summarised as supplementary material 1 (Title: HIV-1 among people living with HIV in Ghana).

Overall, the included studies were of moderate to high methodological quality. Most studies clearly defined inclusion criteria and described the study setting and participants in sufficient detail, and all used validated methods to measure HIV-1 subtypes and DRMs. However, some studies relied on convenience sampling and had relatively small sample sizes, and items related to the identification and management of confounding were frequently rated as not applicable. In addition, most studies originated from facilities in Greater Accra and Eastern regions, indicating regional clustering. These patterns suggest a potential for selection bias and limited generalisability beyond clinic-attending populations in data-rich regions (supplementary material 2).



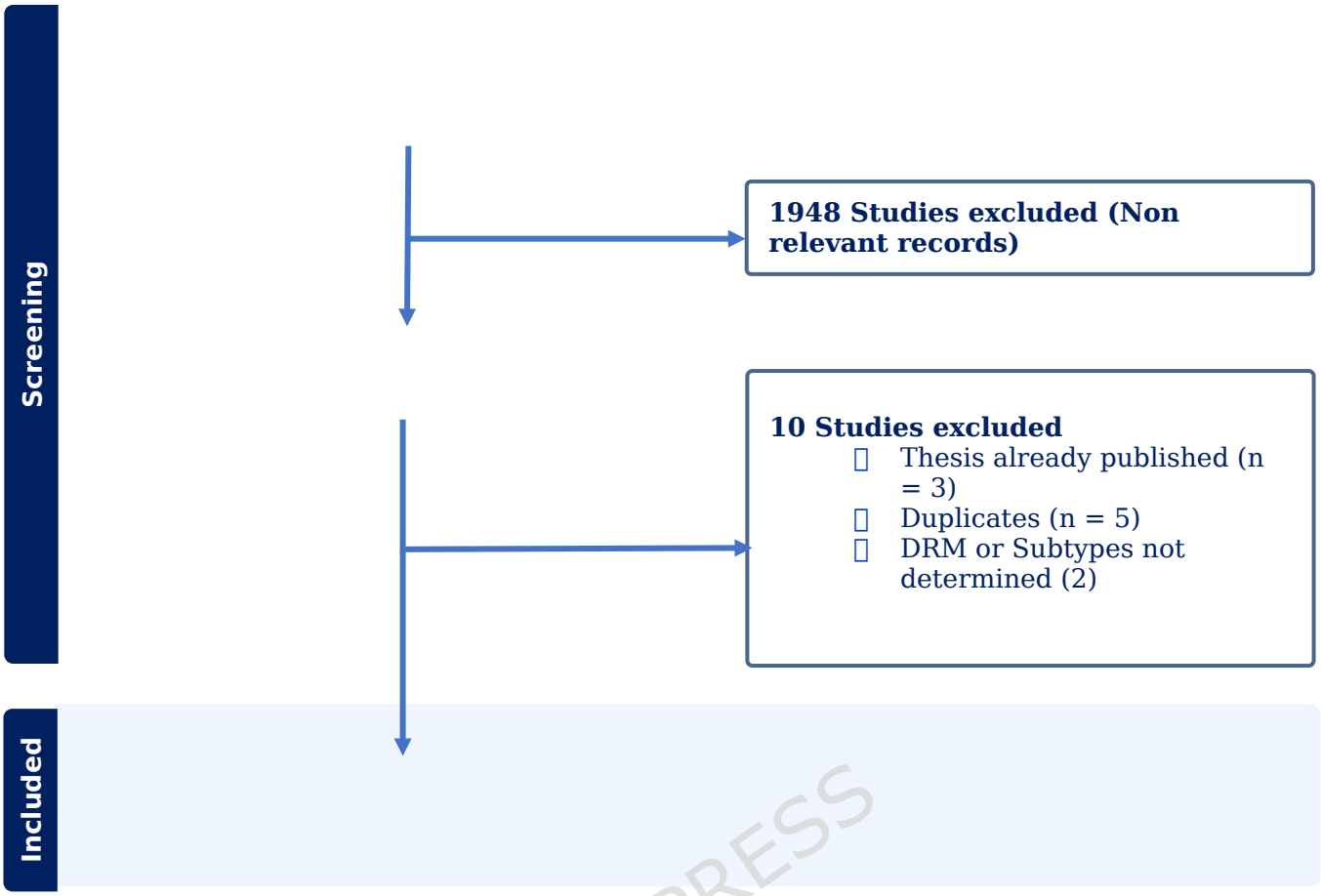


Figure 1: PRISMA Flow Diagram of Study Selection. This figure illustrates the systematic review process for identifying studies on HIV-1 genetic diversity and drug resistance mutations in Ghana. A total of 2,472 studies were screened, leading to 28 selected for full-text review, with 18 ultimately included in the analysis.

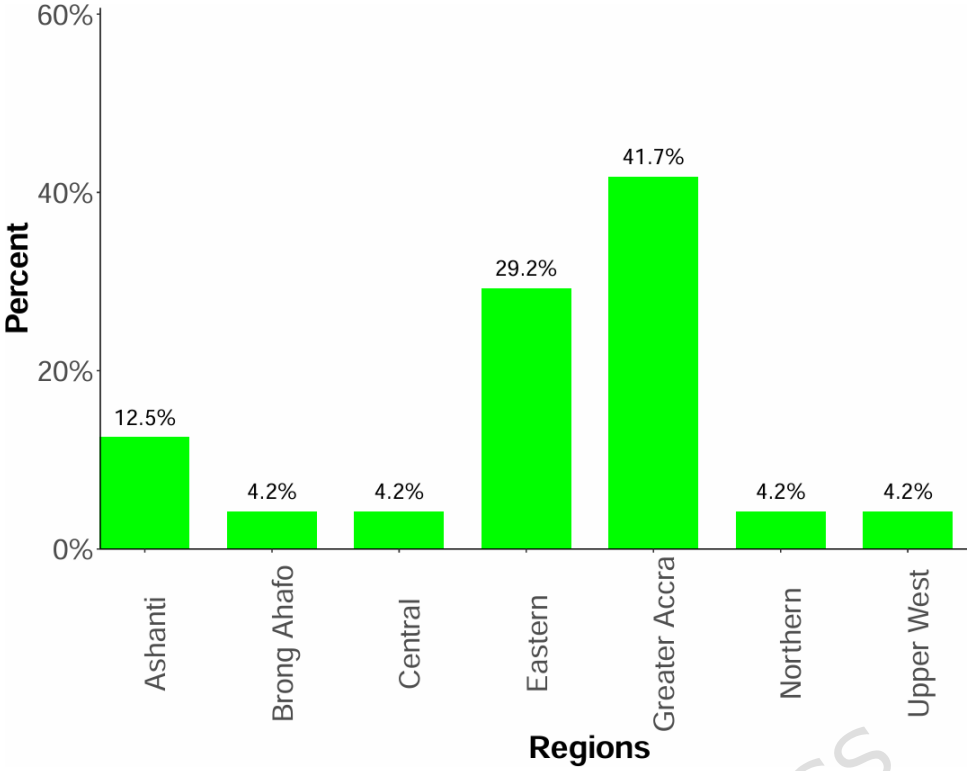


Figure 2. Regional distribution of included studies. For studies with multiple sites from different regions, each region was marked as an individual study in this analysis. Only regions with at least one study site from the included articles were considered. Among the included studies, no study was conducted in Ahafo, Bono East, Western, Western North, Upper East, Savannah, North East, Volta, or Oti regions. Two studies did not specify the region or study sites. The majority of the studies were carried out in the Greater Accra (41.7%) and Eastern (29.2%) regions.

HIV-1 genetic diversity

The predominant HIV-1 subtype identified was CRF02_AG (68.9%). Other subtypes included G (3.5%), CRF06_cpx (3.3%), A (2.2%), B (2.1%), A3 (1.7%), C (0.6%), CRF09_cpx (0.6%), and other recombinant forms (16.8%). Only one occurrence was observed each for D and K subtypes [Figure 3]. The occurrence of the CRF02_AG strain has shown a consistent prevalence over the years (above 50%), with 37.5% only in 2016, indicating its entrenched position within the local epidemic. A 66.8% frequency of CRF02_AG was published in 2004, and 84.6% in 2024 [Figure 4].

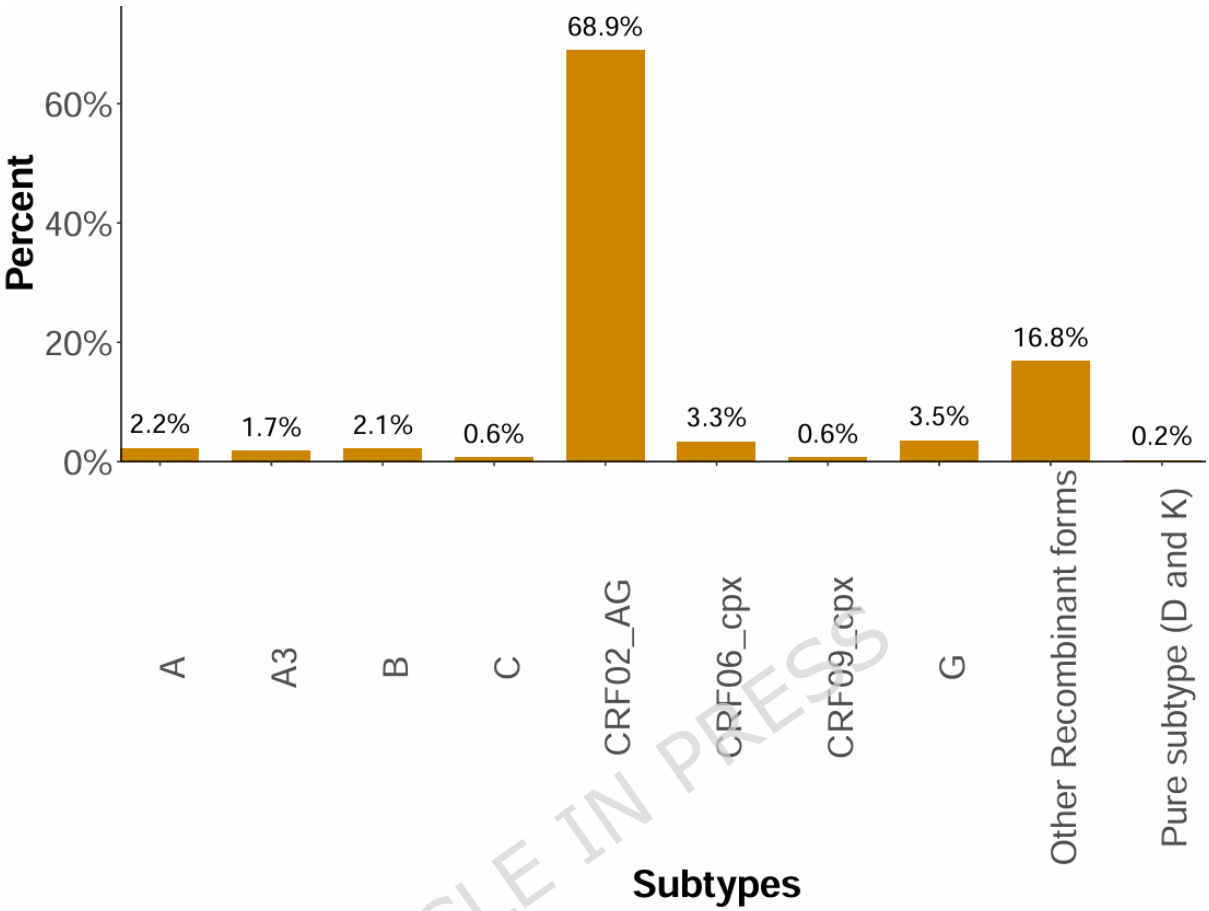


Figure 3: Distribution of HIV-1 Subtypes Among Individuals in Ghana. This figure presents the prevalence of various HIV-1 subtypes identified in individuals living with HIV in Ghana. The data indicate that CRF02_AG is the predominant subtype, comprising 68.9% of cases, followed by subtypes G (3.5%), CRF06_cpx (3.3%), A (2.2%), B (2.1%), A3 (1.7%), and other recombinant forms.

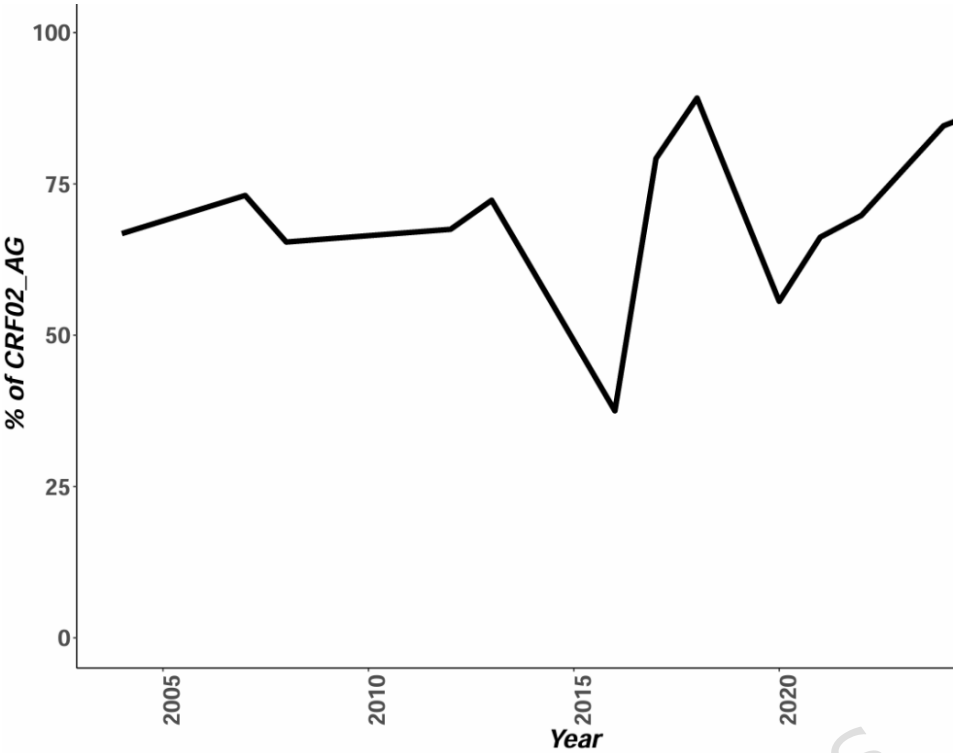


Figure 4: Occurrence of CRF02_AG Strain over the years

HIV-1 mutational patterns

In the category of nucleoside reverse transcriptase inhibitors (NRTIs), we documented 12 major DRMs with the most frequent, M184V/I detected at 41.2%, followed by M41L (15.4%) and T215Y/F (11.8%) [Figure 5]. For non-nucleoside reverse transcriptase inhibitors (NNRTIs), 14 major DRMs were in the set as K103N (28.4%), G190A/S (10.1%), and V106I/AT (10.7%). Protease inhibitor (PI) resistance was primarily marked by M46I/L and L90M, each present in 25.0% of samples, while I54V, I84V, and V82A were each identified in 12.5% of cases. For INSTIs accessory mutations, L74I/M was the most common (46.7%), followed by E157Q (20.0%) and G163R/K and T97A (13.3% each). Notably, only two studies

included sequence analysis for DRMs in the integrase gene, indicating limited data for INSTI mutation patterns [Figure 5].

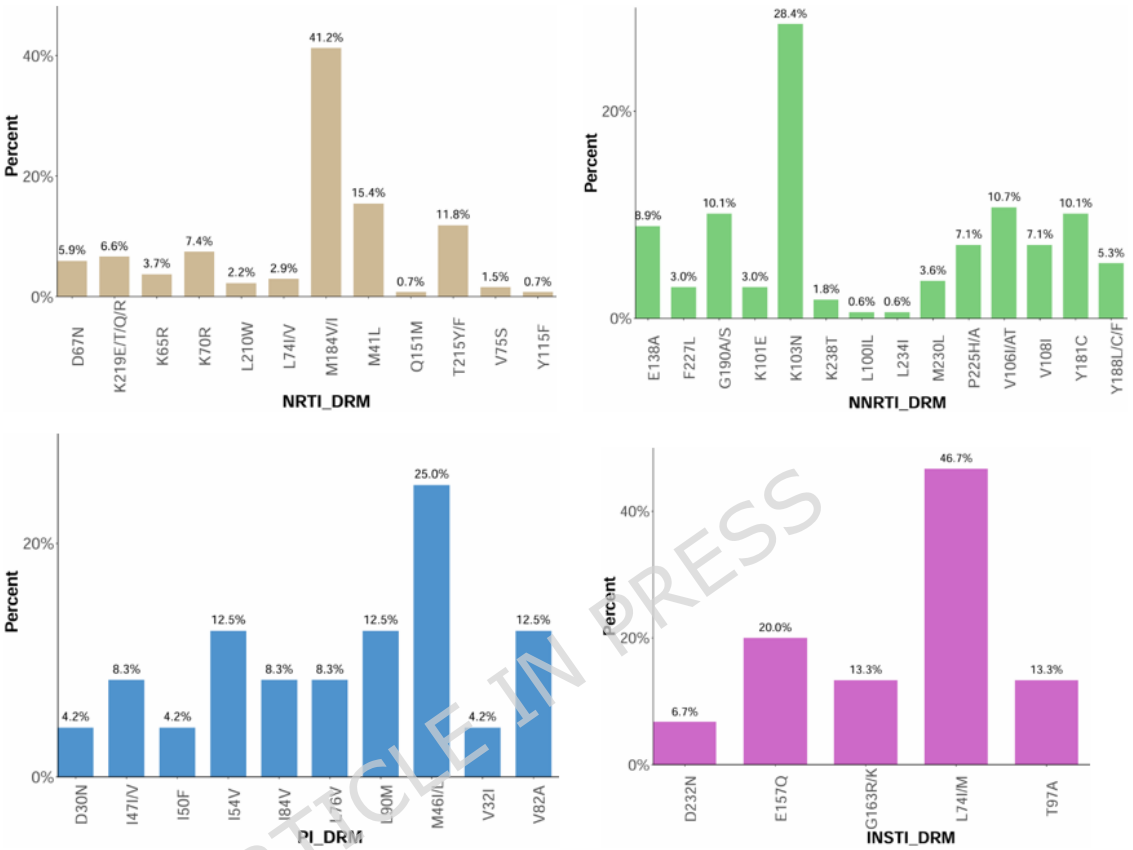


Figure 5: Occurrence of NRTI, NNRTI, PI, and INSTI Mutations. This figure illustrates the prevalence of drug resistance mutations linked to nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) among people living with HIV in Ghana. Notable mutations for NRTI include M184V/I (41.2%), M41L (15.4%) and T215Y/F (11.8%), NNRTI: K103N (28.4%), G190A/S (10.1%), V106I/AT (10.7%), and E138A (8.9%) PI: M46I/L and L90M (25.0% each), with I54V, I84V, and V82A each at 12.5%and INSTI accessory mutations: L74I/M (46.7%), E157Q (20.0%) and G163R/K (13.3%).

HIV-1 mutational patterns per ART history

Drug resistance mutations (DRMs) were significantly more prevalent in ART-experienced versus ART-naive participants across key antiretroviral drug classes [Table 1]. Among NRTIs, major mutations M184V/I (13.1% vs 1.2%, p<0.0001), M41L (4.1% vs 1.0%, p=0.007), T215Y/F (3.8% vs 0.0%, p<0.0001), D67N (1.9% vs 0.0%, p=0.008), K70R (2.1% vs 0.2%, p=0.021), and K219E/Q/R (1.9% vs 0.0%, p=0.015) were significant in treatment experienced participants. L74V/I and L210W showed no significant difference. For NNRTIs, mutations K103N (9.5% vs 1.9%, p<0.0001), V106A/T (2.4% vs 0.0%, p=0.002), Y181C (3.3% vs 0.7%, p=0.012), P225H (2.4% vs 0.2%, p=0.011), G190A/S (3.1% vs 1.0%, p=0.047), and M230L (1.4% vs 0.0%, p=0.031) were significantly associated with ART experience. Mutations such as Y188L/C/F and K101E had no significant difference. PI mutations were detected mainly in ART-experienced patients but lacked statistical significance, possibly due to the smaller occurrence of PI mutations in the participants. INSTI accessory mutations L74I/M (22.2% vs 1.1%, p=0.001), E157Q (11.1% vs 0.0%, p=0.01), and T97A (7.4% vs 0.0%, p=0.048) were significantly more frequent in experienced participants [Table 1].

Table 1: DRMs for NRTIs, NNRTIs, PIs, and INSTIs according to treatment history

Mutations	ART-Experienced n (%)	ART-Naive n (%)	P-Value
NRTI	**n=419**	**n=417**	
M41L	17 (4.1)	4 (1.0)	0.007*
M184V/I	55 (13.1)	5 (1.2)	0.0001*
T215Y/F	16 (3.8)	0 (0.0)	0.0001*
D67N	8 (1.9)	0 (0.0)	0.008*
K70R	9 (2.1)	1 (0.2)	0.021*

L74V/I	4 (1.0)	1 (0.2)	0.124
K219E/Q/R	8 (1.9)	0 (0.0)	0.015*
L210W	2 (0.5)	2 (0.5)	0.686
V75S	1 (0.2)	2 (0.5)	0.624
K65R	4 (1.0)	2 (0.5)	0.686
Q151M	1 (0.2)	1 (0.2)	1.000
Y115F	1 (0.2)	1 (0.2)	1.000
NNRTI	**n=419**	**n=417**	
K103N	40 (9.5)	8 (1.9)	0.0001*
Y188L/C/F	5 (1.2)	4 (1.0)	1.000
G190A/S	13 (3.1)	4 (1.0)	0.047*
K101E	4 (1.0)	1 (0.2)	0.374
P225H	10 (2.4)	1 (0.2)	0.011*
V106A/T	10 (2.4)	0 (0.0)	0.002*
Y181C	14 (3.3)	3 (0.7)	0.012*
F227L	5 (1.2)	0 (0.0)	0.062
M230L	6 (1.4)	0 (0.0)	0.031*
L100IL	1 (0.2)	0 (0.0)	1.000
PI	**n=342**	**n=361**	
V82A	3 (0.9)	0 (0.0)	0.115
M46I/L	4 (1.2)	2 (0.6)	0.44
V32I	1 (0.3)	0 (0.0)	0.486
I47V	2 (0.6)	0 (0.0)	0.236
I54V	3 (0.9)	0 (0.0)	0.115
L90M	3 (0.9)	0 (0.0)	0.115
D30N	0 (0.0)	1 (0.3)	1.000
I84V	2 (0.6)	0 (0.0)	0.236
L76V	2 (0.6)	0 (0.0)	0.236
INSTI	**n=27**	**n=95**	
G163R/K	0 (0.0)	2 (2.1)	1.000
L74I/M	6 (22.2)	1 (1.1)	0.001*
E157Q	3 (11.1)	0 (0.0)	0.01*
T97A	2 (7.4)	0 (0.0)	0.048*
D232N	1 (3.7)	0 (0.0)	0.221

The table presents the frequency and percentage of key drug resistance mutations (DRMs) in nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) stratified by antiretroviral therapy (ART) status. Comparisons between ART-experienced and ART-naive groups were performed using Fisher's Exact test, with p-values indicating statistical significance of mutation differences between these groups. Significant associations (P-value < 0.05) are marked with an asterisk (*).

Temporal trends of HIV-1 diversity and mutational patterns

Across all three time periods (<2007, 2007-2018, 2019-2024), CRF02_AG remained the predominant HIV-1 subtype in Ghana, constituting approximately 67-70% of cases in each era. Subtypes A, A3, B, C, G, D, K, and circulating recombinant forms (CRF06_cpx, CRF09_cpx) were consistently low in frequency, with an observed increase in subtype B (<1% to 8%) and G (4% to 7%). The proportion of “Other recombinant forms” declined steadily from 29% (<2007) to 6% (2019-2024) [Figure 6].

The analysis of DRMs revealed differences between the 2006-2018 and 2019-2024 periods. NRTI mutations such as M184V/I was most prevalent, increasing from 42% to 45%. Key mutations M41L (18% to 11%) and T215Y/F (18% to 4%) decreased over the period. NNRTI mutations, K103N, showed a notable decline from 34% to 27%. V106I/AT and P225H/A showed moderate increases (P225H/A: 6% to 8%). PI mutations, M46I/L and I54V, increased in 2019–2024, while the percentage of “other PI mutations” dropped from 40 to 16 [Figure 7].

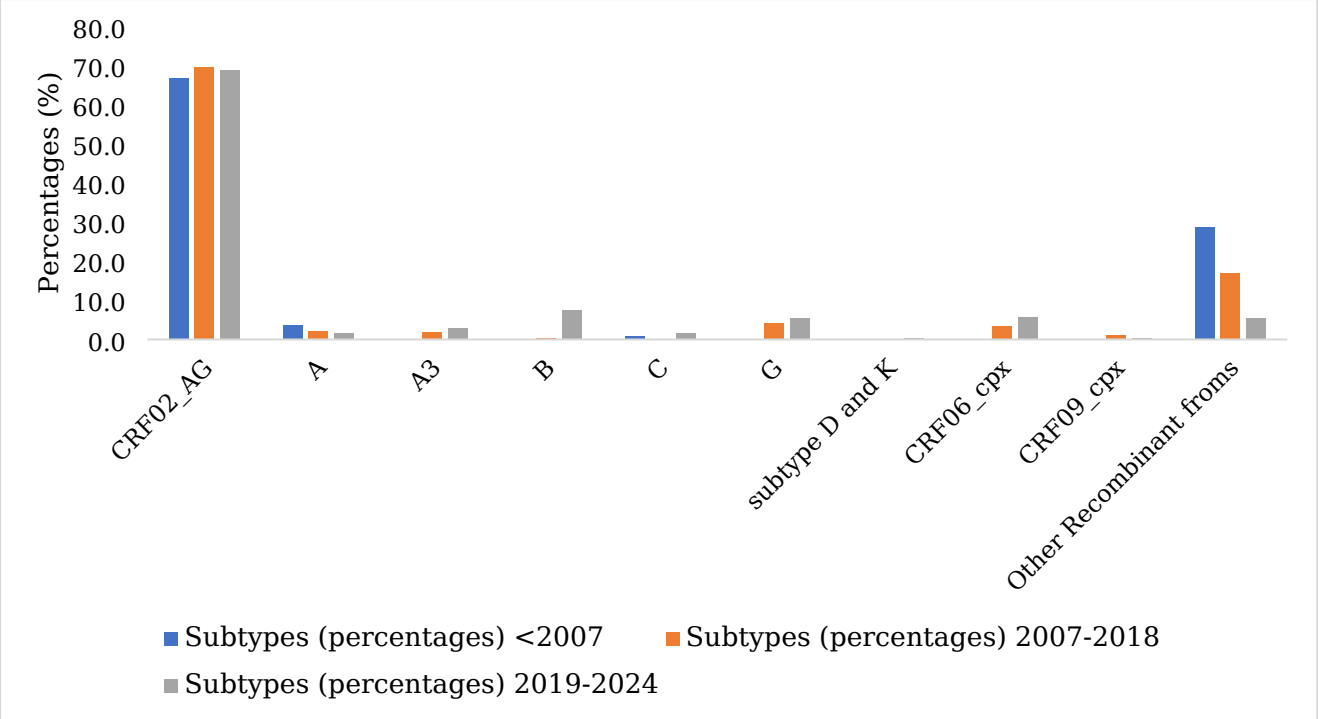


Figure 6. Temporal distribution of HIV-1 subtypes and recombinant forms in Ghana across three periods: <2007, 2007–2018, and 2019–2024. CRF02_AG remains the predominant subtype throughout, while minor subtypes (A, A3, B, C, G) and circulating recombinant forms (CRF06_cpx and CRF09_cpx) show limited but evolving variability.

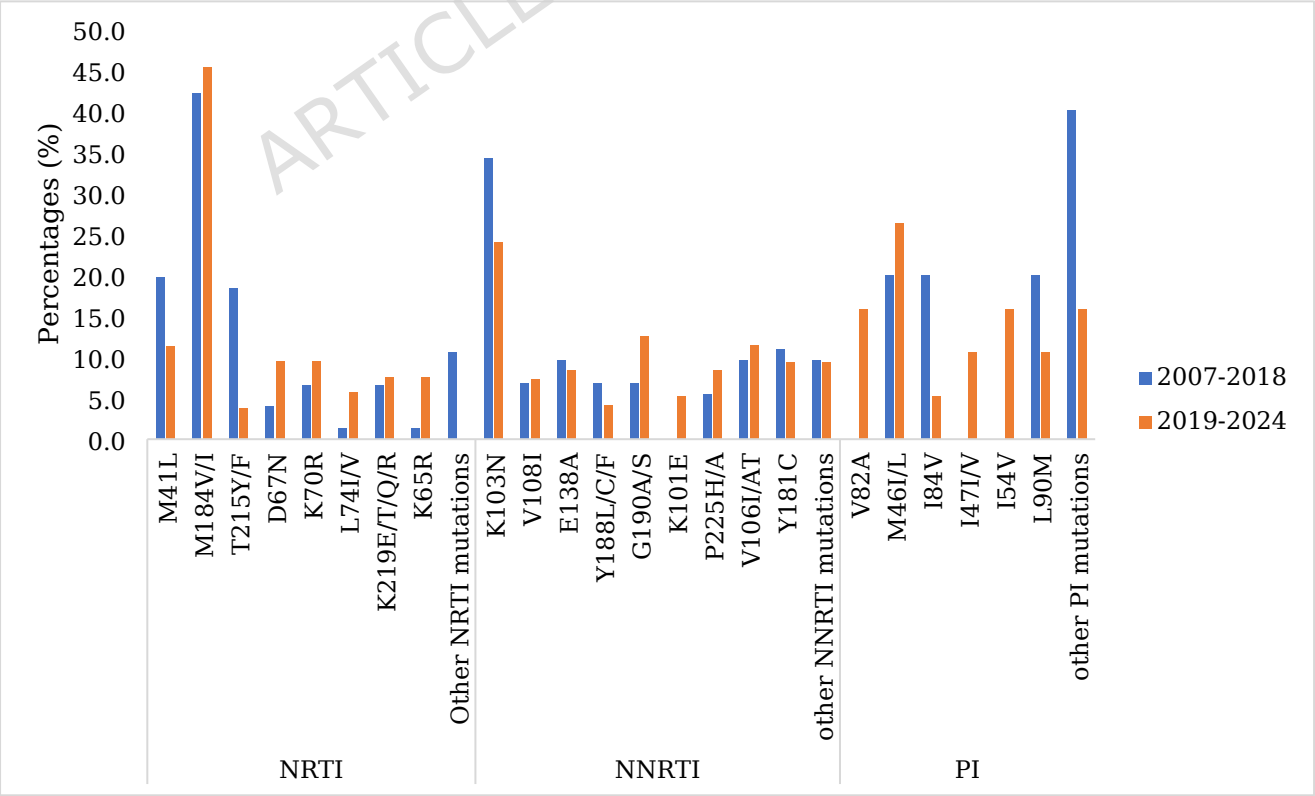


Figure 7. Distribution of HIV-1 drug resistance mutations (DRMs) detected in Ghana during two treatment eras: 2006–2018 (blue) and 2019–2024 (orange). The chart illustrates frequencies of specific nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI) mutations, highlighting changes in key variants such as M184V/I, K103N, and M46I/L over time.

DISCUSSION

We synthesized data on HIV-1 genetic diversity and DRMs among individuals living with HIV in Ghana and highlighted critical insights into the evolving landscape of the epidemic [8, 9, 18-33]. The findings indicate a predominance of the CRF02_AG strain, alongside a notable presence of DRMs that pose significant challenges to effective treatment regimens. The observed trends in subtype diversity and the presence of recombinant forms underscore the emerging complexity of managing HIV-1 in Ghana. While we reported predominant CRF02_AG, other subtypes, including A, A3, B, C, G, and circulating recombinant forms such as CRF06_cpx and CRF09_cpx, were present at much lower frequencies. CRF02_AG has been consistently predominant relative to other subtypes over the past two decades [8,9,24]. The trend in the subtypes' distributions over time underscores the need for continued genomic surveillance, as new recombinants may impact transmission dynamics and treatment outcomes.

The predominance of the CRF02_AG subtype in Ghana aligns with patterns observed in other African countries, where this subtype is frequently reported as the dominant form [11,13,34]. This widespread prevalence may be attributed to historical transmission dynamics, including sexual

networks, migration patterns, and social behaviours that facilitate the spread of this recombinant form. In comparison to neighbouring countries like Nigeria [13], and Togo [10], Ghana's subtype distribution shows similarities but also notable differences. For instance, Nigeria has reported a higher prevalence of subtype G alongside CRF02_AG [13], while Togo has documented similar patterns with CRF02_AG being predominant among men who have sex with men [10]. In Côte D'Ivoire, studies have also highlighted a diverse mix of subtypes, including A, G, and CRFs, indicating a complex transmission network across West Africa [35].

The presence of CRF02_AG as a circulating recombinant form indicates that it has likely emerged from the mixing of subtypes A and G from different individuals, reflecting the complex interplay between viral evolution and human behaviour [6,36]. This dynamic and active process of viral evolution can lead to the emergence of new variants that may evade immune responses or develop resistance to ART. Countries outside Africa with frequent migration to Ghana, such as the United Kingdom [37], the United States of America [38], Germany [39], and Canada [40], predominantly report subtype B. Ghana's situation is markedly different; however, there were reports of CRF02_AG. The trend of subtype B has increased recently among the Ghanaian population [Figure 6]. The extensive recombination observed within HIV-1 subtypes raises concerns about rapid viral evolution, whose clinical and epidemiological implications are still under study.

The high diversity observed among HIV-1 subtypes in Ghana is further supported by whole genome next-generation sequencing (NGS) data [8], which revealed multiple circulating recombinant forms, including CRF02_AG and CRF06_cpx, illustrating the extensive genetic variability present within the population. This whole-genome NGS approach suggests that traditional Sanger sequencing methods may underreport this diversity [41]. This limitation highlights the necessity for continuous monitoring of HIV-1 diversity in Ghana to review treatment protocols effectively and ensure that ART remains potent against emerging variants.

The high prevalence of K103N and M184V/I mutations, though expected, poses serious challenges for first-line ART regimens. K103N confers resistance to NNRTIs, particularly efavirenz (EFV), which is included in the first-line regimens in Ghana [4,5]. Similarly, M184V/I affects NRTIs, particularly lamivudine (3TC) and emtricitabine efficacy, both integral components of combination therapies [43,44]. Notably, NNRTI DRMs remained high over time, indicating an increased resistance pattern that may further compromise the efficacy of NNRTI-based regimens. These mutations can lead to virologic failure and increase the risk of transmission of resistant strains. Also, NRTI/NNRTI-based regimens, as shown in several clinical trials, such as the D2EFT study, concluded that recycling NRTIs as DTG+TDF+3TC/FTC without any NNRTI is effective in persons failing first-line therapy [44].

Moreover, additional mutations such as T215Y/F and M41L further complicate treatment protocols by affecting other NRTIs. Specifically,

T215Y mutations are associated with resistance to zidovudine (AZT) and 3TC, both commonly used in first-line ART regimens [45]. The M41L mutation also contributes to reduced susceptibility to AZT [46]. As these mutations dominate, they can significantly undermine existing first-line therapies. The high prevalence of major PI resistance mutations such as M46I/L and L90M raises concern for the efficacy of second-line ART regimens in Ghana. These mutations are known to reduce susceptibility to commonly used PIs, including lopinavir/ritonavir and atazanavir, with M46I/L particularly impacting drug binding and viral suppression rates. The presence of I54V and V82A further complicates the resistance profile, collectively diminishing the potency of these agents and increasing the likelihood of treatment failure among individuals requiring PI-based therapy [47]. Consequently, patients experiencing treatment failure on first-line regimens may find limited options available for effective second-line therapy due to existing resistance patterns.

The lack of comprehensive data on INSTI resistance patterns is of concern, given the increasing adoption of DTG as a first-line treatment option in Ghana [4]. Although studies have indicated that the presence of some mutations against other antiretrovirals, like M184V/I, may not adversely affect the efficacy of DTG [48,49], regional surveillance is still critical. Our analysis demonstrates a significantly higher prevalence of key DRMs in ART-experienced individuals across NRTI and NNRTI classes, emphasizing the selective pressure exerted by prior treatment. These findings align with global data highlighting the accumulation of resistance mutations

following ART exposure, which challenges long-term treatment effectiveness and supports the need for routine resistance monitoring to inform therapeutic choices. The lack of significant PI mutation associations may be due to smaller sample sizes, suggesting further investigation [8,17,33,45].

While many high-income countries have established systematic monitoring frameworks that facilitate timely detection and management of drug resistance [50], such as Canada's policy change to conduct routine drug resistance testing [51], low- and middle-income countries like Ghana often struggle with inadequate resources for comprehensive surveillance programs. This gap hinders effective responses to emerging resistance patterns and compromises patient care. The findings from this review emphasize the critical need for enhanced surveillance systems to monitor both HIV-1 subtype diversity and drug resistance patterns in Ghana. The national database for tracking these parameters, such as the e-tracker, should be improved for this purpose. Such a system would facilitate data-driven decision-making and timely responses to emerging threats [4,50]. Furthermore, integrating routine drug resistance testing into clinical practice is essential to inform ART regimens tailored to individual patient needs. By prioritizing research initiatives focused on understanding both genetic diversity and DRMs, Ghana can better position itself to combat the evolving challenges posed by HIV.

Clinical data such as CD4+ T cell counts, viral load measurements, and adherence information were often incompletely reported, limiting our

ability to link specific DRMs with clinical outcomes. Also, many studies used convenience samples of patients engaged in care at specific facilities, which may introduce selection bias and limit generalizability to individuals not in regular care or living in rural areas. Again, the lack of longitudinal follow-up in most studies precluded assessment of the evolution of resistance within individuals over time. Finally, as noted above, the geographic concentration of data in a few regions constrains our ability to draw truly national inferences.

CONCLUSION

Our systematic review examines HIV-1 subtype diversity and DRMs in Ghana from 2004 to 2024. CRF02_AG remains the predominant subtype, with no significant change over time. The widespread use of NNRTI-based regimens has led to a significant increase in NNRTI mutations. In contrast, PI mutations showed no temporal trend due to limited use in first-line treatments. NRTI mutations, such as M184V/I, remained consistent, reflecting common use in combination therapies. Geographically, most studies were conducted in the Greater Accra and Eastern regions, with a notable lack of data from other areas. Whole genome Next-generation sequencing (NGS) could provide deeper insights into complex recombinant forms and emerging resistance patterns, emphasizing the importance of broader surveillance efforts. The findings highlight the importance of comprehensive national data on HIV-1 subtypes and DRMs, and possibly the e-tracker, as suggested earlier, should be improved to manage the data. These are essential for formulating effective public health strategies

and achieving the UNAIDS 95-95-95 targets aimed at eradicating the HIV epidemic by 2030.

List of abbreviations

Abbreviation	Full Term
HIV	Human Immunodeficiency Virus
HIV-1	Human Immunodeficiency Virus Type 1
PLWH	People Living with HIV
ART	Antiretroviral Therapy
ARV	Antiretroviral
DRM(s)	Drug Resistance Mutation(s)
NRTI(s)	Nucleoside Reverse Transcriptase Inhibitor(s)
NNRTI(s)	Non-Nucleoside Reverse Transcriptase Inhibitor(s)
PI(s)	Protease Inhibitor(s)
INSTI(s)	Integrase Strand Transfer Inhibitor(s)
CRF	Circulating Recombinant Form
URF	Unique Recombinant Form
PMTCT	Prevention of Mother-To-Child Transmission
WHO	World Health Organization
UNAIDS	Joint United Nations Programme on HIV/AIDS
JBI	Joanna Briggs Institute

Abbreviation	Full Term
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
NGS	Next-Generation Sequencing
3TC	Lamivudine
FTC	Emtricitabine
AZT	Zidovudine
DTG	Dolutegravir
NACP	National AIDS/STI Control Programme (Ghana)
GHS	Ghana Health Service

Ethical approval

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Competing interests

The authors declare that they have no competing interests.

Funding

There was no funding for this study.

Contributors

PA, MAP, GG and KWCS conceptualized this review and drafted the protocol. PA, SA, GG, ROY and BMO did the literature search and independently did all stages of screening. PA, MAP, KWCS, BMO, ROY, SA, LMA, IJ, MS, IKS, SA, and KOD directly accessed and validated the data. PA and GG independently extracted data, and PA and BMO conducted all formal analyses. MAP, BMO, KOD and KWCS double-checked the data extraction. MAP, SA, LM, IJ, MS, and IKS checked the data analysis. PA, BMO and MAP interpreted the results and wrote the original draft of the review. KOD, KWCS, MAP, ROY, GG and LMA made substantial contributions to the interpretation of the results and edited the manuscript. KWCS, KOD, MAP, BMO and ROY supervised the review. All authors had full access to all data in the study, reviewed, edited and approved the final version of the manuscript for submission.

Acknowledgements

We acknowledge the collaboration of the HIV-REST group at the University of Ghana Medical School. The platform provided by the BANGA-Africa Team Grant is acknowledged.

References

[1] UNAIDS, “FACT SHEET 2024: Global HIV statistics.” UNAIDS, 2024. Accessed: Oct. 20, 2024. [Online]. Available: https://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf

[2] N. A. Addo, A. E. Yawson, A. S. Addo, B. T. Dornoo, and H. N. A. Seneadza, “A Review of National Programme Data on the HIV Epidemic in Ghana: 2005-2010,” *gcps*, vol. 3, no. 2, pp. 73–81, Jul. 2022, doi: 10.60014/pmjg.v3i2.65.

[3] J. Neequaye *et al.*, “Sexual habits and social factors in local Ghanaian prostitutes which could affect the spread of human immune deficiency virus (HIV),” *Ghana Med J*, vol. 1987; 21, no. 12–15, 1987, [Online]. Available: https://journal.gcps.edu.gh/index.php/pmjg/article/view/65/57

[4] NACP and GHS, “CONSOLIDATED GUIDELINES FOR HIV CARE IN GHANA: Test, Treat & Track.” National AIDS/STI Control Programme, 2022. [Online]. Available: https://www.differentiatedservicedelivery.org/wp-content/uploads/Consolidated-Guidelines-For-Hiv-Care-In-Ghana.pdf

[5] WHO, *Consolidated guidelines on HIV prevention, testing, treatment, service delivery and monitoring: recommendations for a public health approach*, 2nd ed. Geneva: World Health Organization, 2021.

[6] P. M. Sharp and B. H. Hahn, “Origins of HIV and the AIDS pandemic,” *Cold Spring Harb Perspect Med*, vol. 1, no. 1, p. a006841, Sep. 2011, doi: 10.1101/cshperspect.a006841.

[7] N. Bbosa, P. Kaleebu, and D. Ssemwanga, “HIV subtype diversity worldwide,” *Current Opinion in HIV and AIDS*, vol. 14, no. 3, pp. 153–160, May 2019, doi: 10.1097/COH.0000000000000534.

[8] A. Appah *et al.*, “Molecular Epidemiology of HIV-1 in Ghana: Subtype Distribution, Drug Resistance and Coreceptor Usage,” *Viruses*, vol. 15, no. 1, p. 128, Dec. 2022, doi: 10.3390/v15010128.

[9] L. Fischetti, O. Opare-Sem, D. Candotti, F. Sarkodie, H. Lee, and J. P. Allain, “Molecular epidemiology of HIV in Ghana: Dominance of CRF02_AG,” *Journal of Medical Virology*, vol. 73, no. 2, pp. 158–166, Jun. 2004, doi: 10.1002/jmv.20070.

[10] A. A. Konou *et al.*, “Genetic diversity and transmission networks of HIV-1 strains among men having sex with men (MSM) in Lomé, Togo,” *Infection, Genetics and Evolution*, vol. 46, pp. 279–285, Dec. 2016, doi: 10.1016/j.meegid.2016.05.030.

[11] D. M. Tebit *et al.*, “Analysis of the diversity of the HIV-1 pol gene and drug resistance associated changes among drug-naïve patients in Burkina Faso,” *Journal of Medical Virology*, vol. 81, no. 10, pp. 1691–1701, Oct. 2009, doi: 10.1002/jmv.21600.

[12] S. T. Soubeiga *et al.*, “Human immunodeficiency virus type 1 drug resistance in a subset of mothers and their infants receiving antiretroviral treatment in Ouagadougou, Burkina Faso,” *J Public Health Afr*, Jul. 2018, doi: 10.4081/jphia.2018.767.

[13] J. Nazziwa *et al.*, “Characterisation of HIV-1 Molecular Epidemiology in Nigeria: Origin, Diversity, Demography and Geographic Spread,” *Sci Rep*, vol. 10, no. 1, p. 3468, Feb. 2020, doi: 10.1038/s41598-020-59944-x.

[14] L. E. Abongwa, A. K. Nyamache, J. N. Torimiro, P. Okemo, and F. Charles, “Human immunodeficiency virus type 1 ((HIV-1) subtypes in the northwest region, Cameroon,” *Virol J*, vol. 16, no. 1, p. 103, Dec. 2019, doi: 10.1186/s12985-019-1209-6.

[15] A. N. Amer, A. Gaballah, R. Emad, A. Ghazal, and N. Attia, “Molecular Epidemiology of HIV-1 Virus in Egypt: A Major Change in the Circulating Subtypes,” *CHR*, vol. 19, no. 5, pp. 448–456, Sep. 2021, doi: 10.2174/1570162X19666210805091742.
[16] U. Mbonye and J. Karn, “The cell biology of HIV-1 latency and rebound,” *Retrovirology*, vol. 21, no. 1, p. 6, Apr. 2024, doi: 10.1186/s12977-024-00639-w.
[17] WHO, “HIV drug resistance.” World Health Organization, 2024. Accessed: Oct. 20, 2024. [Online]. Available: https://www.who.int/news-room/fact-sheets/detail/hiv-drug-resistance
[18] J. A. M. Brandful *et al.*, “Phenotypic characterization of HIV type 1 isolates from Ghana,” *AIDS Res Hum Retroviruses*, vol. 23, no. 1, pp. 144–152, Jan. 2007, doi: 10.1089/aid.2007.23.144.
[19] K. W. C. Sagoe *et al.*, “Variability of the human immunodeficiency virus type 1 polymerase gene from treatment naïve patients in Accra, Ghana,” *Journal of Clinical Virology*, vol. 40, no. 2, pp. 163–167, Oct. 2007, doi: 10.1016/j.jcv.2007.07.016.
[20] E. Delgado *et al.*, “High Prevalence of Unique Recombinant Forms of HIV-1 in Ghana: Molecular Epidemiology From an Antiretroviral Resistance Study,” *JAIDS Journal of Acquired Immune Deficiency Syndromes*, vol. 48, no. 5, pp. 599–606, Aug. 2008, doi: 10.1097/QAI.0b013e3181806c0e.
[21] J. A. M. Brandful, D. Candotti, and J.-P. Allain, “Genotypic diversity and mutation profile of HIV-1 strains in antiretroviral treatment (ART) -Nave Ghanaian patients and implications for antiretroviral treatment (ART),” *J. AIDS HIV Res.*, vol. 4, no. 7, pp. 187–197, Jul. 2012, doi: 10.5897/JAHR12.008.
[22] N. I. Nii-Trebi *et al.*, “HIV-1 Drug-Resistance Surveillance among Treatment-Experienced and -Naïve Patients after the Implementation of Antiretroviral Therapy in Ghana,” *PLoS ONE*, vol. 8, no. 8, p. e71972, Aug. 2013, doi: 10.1371/journal.pone.0071972.
[23] E. Y. Bonney *et al.*, “Low level of transmitted HIV Drug resistance at two HIV care centres in Ghana: a threshold survey,” *Ghana Med J*, vol. 47, no. 2, pp. 82–86, Jun. 2013.
[24] N. I. Nii-Trebi, B. Js, B. M. Obeng, and A. Wk, “Epidemiologic dominance of HIV-1 subtype CRF02_AG in Ghana: preliminary virological evidence of increasing association with new infections,” *IJVSR*, pp. 22–28, Apr. 2016, doi: 10.19070/2330-0027-160004.
[25] A. Martin-Odoom, T. Adiku, E. Delgado, M. Lartey, and W. K. Ampofo, “Occurrence of transmitted HIV-1 drug resistance among Drug-naïve pregnant women in selected HIV-care centres in Ghana,” *Ghana Medical Journal*, vol. 51, no. 1, p. 20, Apr. 2017, doi: 10.4314/gmj.v51i1.4.
[26] A. Martin-Odoom *et al.*, “Emergence of HIV-1 drug resistance mutations in mothers on treatment with a history of prophylaxis in Ghana,” *Virol J*, vol. 15, no. 1, p. 143, Dec. 2018, doi: 10.1186/s12985-018-1051-2.
[27] S. D. Deletsu, E. K. Maina, O. Quaye, W. K. Ampofo, G. A. Awandare, and E. Y. Bonney, “High resistance to reverse transcriptase inhibitors among persons infected with human immunodeficiency virus type 1 subtype circulating recombinant form 02_AG in Ghana and on antiretroviral therapy,” *Medicine (Baltimore)*, vol. 99, no. 7, p. e18777, Feb. 2020, doi: 10.1097/MD.0000000000018777.
[28] B. M. Obeng *et al.*, “Transmitted drug resistance mutations and subtype diversity amongst HIV-1 sero-positive voluntary blood donors in Accra, Ghana,” *Virol J*, vol. 17, no. 1, p. 114, Dec. 2020, doi: 10.1186/s12985-020-01386-y.

[29] D. N. K. Quansah, “Transmitted Drug Resistance and Co-Receptor Tropism of Circulating HIV-1 Subtypes in Art-NaÃ¯ve HIV Patients in Ghana,” University of Ghana, Ugspace, 2021. [Online]. Available: https://ugspace.ug.edu.gh/browse/author?value=Quansah,%20D.N.K.&bbm.return=1
[30] P. K. Parbie *et al.*, “High-level resistance to non-nucleos(t)ide reverse transcriptase inhibitor based first-line antiretroviral therapy in Ghana; A 2017 study,” *Front. Microbiol.*, vol. 13, p. 973771, Aug. 2022, doi: 10.3389/fmicb.2022.973771.
[31] P. Appiah, G. Gbassana, M. Adusei-Poku, B. M. Obeng, K. O. Duedu, and K. W. C. Sagoe, “Genetic landscape for majority and minority HIV-1 drug resistance mutations in antiretroviral therapy naive patients in Accra, Ghana,” *Heliyon*, vol. 10, no. 12, p. e33180, Jun. 2024, doi: 10.1016/j.heliyon.2024.e33180.
[32] M. Seshie *et al.*, “Resistance to protease inhibitors among persons living with HIV in Ghana: a case for viral load and drug resistance monitoring,” *Virol J*, vol. 21, no. 1, p. 159, Jul. 2024, doi: 10.1186/s12985-024-02354-6.
[33] N. I. Nii-Trebi *et al.*, “Dynamic HIV-1 genetic recombination and genotypic drug resistance among treatment-experienced adults in northern Ghana,” *Journal of Medical Microbiology*, vol. 66, no. 11, pp. 1663–1672, Nov. 2017, doi: 10.1099/jmm.0.000621.
[34] M. Giovanetti, M. Ciccozzi, C. Parolin, and A. Borsetti, “Molecular Epidemiology of HIV-1 in African Countries: A Comprehensive Overview,” *Pathogens*, vol. 9, no. 12, p. 1072, Dec. 2020, doi: 10.3390/pathogens9121072.
[35] F. E. T. Foka and H. T. Mufhandu, “Current ARTs, Virologic Failure, and Implications for AIDS Management: A Systematic Review,” *Viruses*, vol. 15, no. 8, p. 1732, Aug. 2023, doi: 10.3390/v15081732.
[36] I. Bulla *et al.*, “HIV classification using the coalescent theory,” *Bioinformatics*, vol. 26, no. 11, pp. 1409–1415, Jun. 2010, doi: 10.1093/bioinformatics/btq159.
[37] G. Yebra *et al.*, “A high HIV-1 strain variability in London, UK, revealed by full-genome analysis: Results from the ICONIC project,” *PLoS ONE*, vol. 13, no. 2, p. e0192081, Feb. 2018, doi: 10.1371/journal.pone.0192081.
[38] R. L. Kline, N. Saduvala, T. Zhang, and A. M. Oster, “Diversity and characterization of HIV-1 subtypes in the United States, 2008–2016,” *Annals of Epidemiology*, vol. 33, pp. 84–88, May 2019, doi: 10.1016/j.annepidem.2019.02.010.
[39] U. Fiebig *et al.*, “Transmitted drug resistance and subtype patterns of viruses from reported new HIV diagnoses in Germany, 2017–2020,” *BMC Infect Dis*, vol. 23, no. 1, p. 673, Oct. 2023, doi: 10.1186/s12879-023-08649-3.
[40] B. S. Akouamba *et al.*, “HIV-1 Genetic Diversity in Antenatal Cohort, Canada,” *Emerg. Infect. Dis.*, vol. 11, no. 8, pp. 1230–1234, Aug. 2005, doi: 10.3201/eid1108.040877.
[41] N. P. Pai, A. Karellis, J. Kim, and T. Peter, “Modern diagnostic technologies for HIV,” *The Lancet HIV*, vol. 7, no. 8, pp. e574–e581, Aug. 2020, doi: 10.1016/S2352-3018(20)30190-9.
[42] I. Mimtsoudis, O. Tsachouridou, K. Akinosoglou, and S. Metallidis, “Treatment Management Challenges in Naïve and Experienced HIV-1-Infected Individuals Carrying the M184V Mutation,” *Viruses*, vol. 16, no. 9, p. 1392, Aug. 2024, doi: 10.3390/v16091392.
[43] O. Stirrup *et al.*, “Continuation of emtricitabine/lamivudine within combination antiretroviral therapy following detection of the M184V/I HIV-1

resistance mutation," *HIV Medicine*, vol. 21, no. 5, pp. 309–321, May 2020, doi: 10.1111/hiv.12829.
[44] G. Matthews *et al.*, "Dolutegravir plus boosted darunavir versus recommended standard-of-care antiretroviral regimens in people with HIV-1 for whom recommended first-line non-nucleoside reverse transcriptase inhibitor therapy has failed (D2EFT): an open-label, randomised, phase 3b/4 trial," *The Lancet HIV*, vol. 11, no. 7, pp. e436–e448, Jul. 2024, doi: 10.1016/S2352-3018(24)00089-4.
[45] D. Siddiqui *et al.*, "Genetic and antiretroviral drug resistance mutations analysis of reverse transcriptase and protease gene from Pakistani people living with HIV-1," *PLoS ONE*, vol. 18, no. 8, p. e0290425, Aug. 2023, doi: 10.1371/journal.pone.0290425.
[46] P. L. Boyer, K. Das, E. Arnold, and S. H. Hughes, "Analysis of the Zidovudine Resistance Mutations T215Y, M41L, and L210W in HIV-1 Reverse Transcriptase," *Antimicrob Agents Chemother*, vol. 59, no. 12, pp. 7184–7196, Dec. 2015, doi: 10.1128/AAC.05069-14.
[47] S.-Y. Rhee *et al.*, "HIV-1 protease mutations and protease inhibitor cross-resistance," *Antimicrob Agents Chemother*, vol. 54, no. 10, pp. 4253–4261, Oct. 2010, doi: 10.1128/AAC.00574-10.
[48] G.-J. Chen *et al.*, "Effectiveness of switching from protease inhibitors to dolutegravir in combination with nucleoside reverse transcriptase inhibitors as maintenance antiretroviral therapy among HIV-positive patients," *International Journal of Antimicrobial Agents*, vol. 54, no. 1, pp. 35–42, Jul. 2019, doi: 10.1016/j.ijantimicag.2019.03.016.
[49] E. Ndashimye and E. J. Arts, "Dolutegravir response in antiretroviral therapy naïve and experienced patients with M184V/I: Impact in low-and middle-income settings," *International Journal of Infectious Diseases*, vol. 105, pp. 298–303, Apr. 2021, doi: 10.1016/j.ijid.2021.03.018.
[50] World Health Organization, "HIV drug resistance: brief report 2024," World Health Organization, Geneva, 2024. Accessed: Nov. 18, 2024. [Online]. Available: https://iris.who.int/bitstream/handle/10665/376039/9789240086319-eng.pdf
[51] L. Mbuagbaw *et al.*, "The impact of routine HIV drug resistance testing in Ontario: A controlled interrupted time series study," *PLoS ONE*, vol. 16, no. 4, p. e0246766, Apr. 2021, doi: 10.1371/journal.pone.0246766.