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Evaluating HIV drug resistance in the middle East and North Africa and its associated factors: a systematic review

Nastaran Khodadad[1], Ava Hashempour[1*], Mohamad Matin Karbalaei Ali Nazar[1] and Farzaneh Ghasabi[1]

Abstract

Objective One of the obstacles to achieving successful treatment of HIV infections is the development and spread of mutations linked to resistance. Thus, it is important to monitor the prevalence and occurrence of drug resistance in HIV consistently. This study aimed to investigate how drug resistance affects the effectiveness of ART.

Methods This systematic review focused on surveying ART resistance in both treatment-naïve and treatment-experienced PWH from 2004 to 2024.

Results Out of 101 potential publications, 41 studies were included in this review. ART-experienced PWH in MENA countries commonly receive a regimen consisting of two NRTI drugs in combination with one NNRTI drug. The most frequent mutations were found in NRTIs (M184V, D67N, V75M, M41L, and T69N), NNRTIs (K103N, K101E, V106A, and G190S), and PIs (M36I and H69K). The ART-experienced groups in Israel and Iran presented the highest rates of resistance, reaching 52.78% and 43.03%, respectively, whereas the ART-naïve group in Turkey presented a resistance rate of 53.57%. The most prevalent HIV-1 subtypes in the region were B, CRF35-AD, CRF01-AE, A1, CR02-AG, C, and D. A high frequency of drug resistance mutations, such as M184V and K103N/S, was observed in the CRF35-AD, A, and C subtypes.

Conclusion This is the first report to provide deep insight into ART resistance patterns in the MENA region among both ART-naïve and ART-experienced PWH. The results revealed a significant occurrence of drug resistance to RTIs, PIs, and INSTIs among both groups. This finding highlights the importance of prescribing the INTIs in native and PWH with resistance to RTIs and/or PIs to increase the chance of response to ART as well as regular monitoring of resistance to ART in MENA countries. This also involves identifying the key factors contributing to drug resistance, including inadequate adherence to ART and a lack of adequate monitoring systems to prevent treatment failure. Since the MENA region is significant as an economic challenge, PWH with poor adherence to ART medication and insufficient monitoring systems may hinder successful infection control; therefore, HIV control strategies may prevent viruses from spreading in other countries.

Clinical trial number Not applicable.

Keywords HIV, ART, Mutation, Drug resistance, Middle east, North Africa, MENA region

*Correspondence:
Ava Hashempour
thashem@sums.ac.ir
[1]HIV/AIDS Research Center, Institute of Health, Shiraz University of Medical Sciences, Shiraz, Iran

Introduction

In developing countries, infectious diseases are the primary reason for morbidity and mortality. These infections can result in numerous difficulties and potentially cause serious health problems, disrupt daily routines, and strain healthcare systems, highlighting the importance of prevention and prompt treatment [1–4].

Currently, antiretroviral drugs are easily accessible to people living with HIV (PWH) worldwide who are living with human immunodeficiency virus (HIV) [5]. According to the World Health Organization (WHO), by the end of 2023, approximately 30.7 million out of 39.9 million people with HIV were receiving antiretroviral therapy (ART), accounting for 77% of the total. Furthermore, the HIV viral loads of nearly 72% of these were successfully suppressed [6]. At present, there are six distinct classes of HIV treatment plans globally, with the most prevalent being nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and integrase strand transfer inhibitors (INSTIs) [7].

ART reduces the spread of HIV and delays the progression of acquired immunodeficiency syndrome (AIDS), resulting in a longer lifespan [8–10]. Nevertheless, the increasing utilization of ART has played a role in the development of HIV drug resistance epidemics [5]. The increase in drug resistance can greatly limit the treatment options available for ART and increase the risk of virological treatment failure in PWH who are not yet diagnosed and receiving treatment [11–13]. Therefore, additional accumulation of mutations that are resistant to drugs could use up the available drug choices and result in a worse outlook for PWH, as well as the spread of drug-resistant strains to the general population [14]. The WHO recommends regular follow-up of the viral load, but it does not recommend routine resistance testing. This is especially true given the widespread use of integrase strand transfer inhibitors (INSTIs) and their endorsement as a first-line treatment option by the WHO [15].

This review aimed to thoroughly evaluate drug resistance patterns in the Middle East and North Africa (MENA) region. The MENA region has been identified as having insufficient data and a lack of understanding of the HIV/AIDS epidemic [16]. The first case of HIV-1 infection was reported in the mid-1980s in this region [17]. Although HIV-1 rates are less than 0.1–0.3% in most countries in MENA [18], between 2010 and 2023, there was a 116% increase in the number of new cases in the region [19]. In addition, the high prevalence of HIV among at-risk populations in the MENA region, such as injecting drug users (IDUs) and men who have sex with men (MSM), is a major cause of concern [20]. These groups not only have a greater likelihood of contracting HIV but also have the potential to spread drug-resistant strains if access to and adherence to ART are not optimal [21].

In MENA countries, obstacles related to cultural and social norms may hinder marginalized groups from easily accessing healthcare services, potentially worsening the issue of drug resistance in HIV treatment [22]. The insufficient amount of research specifically addressing ART resistance in the MENA region hampers the comprehension of region-specific factors that lead to resistance. This gap emphasizes the critical necessity for specialized studies that can clarify the occurrence, causes, and consequences of ART resistance in MENA. On the basis of the cases discussed, examining the ART resistance pattern in this region is necessary. This study also aimed to survey the effects of subtypes on ART resistance in both treatment-naïve and treatment-experienced PWH in countries within the area to guide future interventions for HIV care.

Methods

Search strategy

A systematic literature review was conducted to identify articles published in the MENA region between 2004 and 2024 documenting HIV drug resistance. Herein, a digital search was carried out by introducing the following terminology to various databases, including Scopus, Web of Science, PubMed, and Google Scholar: ("HIV" OR "Human immunodeficiency virus" OR "HIV-1" OR "HIV infection*" OR "HIV/AIDS" OR AIDS OR "AIDS infection*") AND ("antiretroviral therapy" OR "ART" OR HAART OR "ARV therapy" OR "antiretroviral drug*" OR "treatment") AND ("drug resistance" OR "HIV drug resistance" OR "Transmitted Drug Resistance" OR TDR OR "Multidrug Drug Resistant" OR MDR OR "transmitted mutation*" OR "response" OR "outcome") AND ("MENA" OR "Middle East*" OR "North Africa*"). Additionally, the reference lists of the studies that were included were meticulously reviewed to detect any further pertinent publications.

Study selection

A standardized protocol was developed prior to the study selection process to minimize discrepancies in the reviewers' procedures. All the references identified through the comprehensive search strategy were imported into EndNote 21.4, and duplicates were removed. The inclusion criteria were subsequently established as cross-sectional, cohort, or case–control studies that reported quantitative data concerning the rates or determinants of drug resistance among treatment-naïve, treatment-experienced, or both populations. Owing to the heterogenicity of citations, no limitations regarding the patient's age, sex, or viral load were imposed. Each

reviewer independently assessed the title and abstract of each report according to the mentioned inclusion criteria. The full texts of the final selected studies were meticulously examined by two other investigators to exclude reports that focused on treatment interruptions or programmatic outcomes lacking clinical metrics.

Data extraction

Two examiners extracted the data separately, and any discrepancies were resolved through discussion with a third investigator. A database was established to document the study period, publication year, location, and design. Additionally, the transmission route, HIV subtypes, circulating recombinant factors (CRFs), treatment approach, and type of treatment failure (virological, immunological, or clinical response) were recorded. Finally, quantitative data, including the population mean age, sex ratio, viral load, and number of resistance mutations, were noted. Any complementary findings were also added on the basis of the investigator's judgment.

Analysis approach

The mutation frequency leading to drug resistance was compared between two groups, ART-naïve (those who never received ART) and ART-experienced (those who received ART), to differentiate transmitted and acquired mutations. Additionally, the study compared the resistance rates within each category of ART and regional rates with those of other countries worldwide to describe contributing factors. Finally, the most frequent treatment regimens and related mutations in different countries of MENA were discovered.

Results

Demographic data

This review assessed 41 included studies from 12 different countries in MENA—a total of 5523 samples from ART-naïve and ART-experienced PWH (Fig. 1) were subjected to drug resistance analysis with the following distributions: Israel ($n = 2067$, 37.42%), Iran ($n = 1804$, 32.66%), Pakistan ($n = 590$, 10.68%), Turkey ($n = 334$, 6.04%), Saudi Arabia ($n = 212$, 3.83%), and Tunisia ($n = 110$, 1.99%). The approximate male-to-female ratio was 2.3 (3612 males and 1563 females). With the exception of 3 studies conducted on pediatric PWH, the remaining studies examined an adult population with a mean age of 32–45 years. The major routes of transmission were sexual intercourse, mother-to-child, and drug abuse.

Subtype distribution

On the basis of phylogenetic analysis, the subtype predominance reported in most publications was as follows: CRF35_AD in Iran, B in Turkey, CRF01_AE in Kuwait and Israel, A1 in Pakistan, and non-B subtypes such as CR02_AG, C, and D in North African countries. Additionally, there are reports of fewer subtypes, such as CRF03_AB, CRF06_cpx, F, and J, in this region.

Treatment approach

The target populations of the studies included ART-naïve PWH ($n = 9$), ART-experienced PWH ($n = 19$), or both ($n = 13$). Samples from 36 publications were subjected to genome sequencing to identify mutations in NRTIs, NNRTIs, and PIs in associated regions. Eight studies were also aimed at detecting mutations in the INSTI class. Among ART-experienced PWH, a combination of two NRTI drugs, lamivudine (3TC), zidovudine (AZT), tenofovir (TDF), and abacavir (ABC), and one NNRTI drug, efavirenz (EFV) or nevirapine (NVP), is the first choice in the majority of countries.

Drug resistance

Among the 22 studies with an ART-naïve population, 13 reported drug resistance mutation rates against NNRTIs, NRTIs, and PIs ranging from 5.6 to 22.4%, with the lowest rates observed in Pakistan and the highest in Turkey. Additionally, one single study reported 8.1% resistance to INSTIs in Turkey. The amounts of resistance for NNRTI, NRTI, PI, and INSTI were 6.1–21%, 5.2–12.2%, 2.4–9.1%, and 0–8.1%, respectively.

Among the 32 studies involving ART-experienced PWH, 18 evaluated overall resistance to NNRTIs, NRTIs, and PIs, with the lowest rate recorded in Pakistan (30.6%) and the highest in Israel and Iran (52.78% and 43.03%). Two studies examined only PI fragments and reported resistance rates of 8.33 and 21%, respectively. Resistance to INSTIs was demonstrated in two studies conducted in Iran [23, 24], with rates of 4% and 6.41%, and in one study carried out in Israel, with a rate of 8.33% [25]. Additionally, the rate of resistance was 50–78.8% for NRTIs, 16–53% for NNRTIs, 2–26% for PIs, and 4–8.3% for INSTIs.

Additionally, the most frequently detected mutations for each class were as follows: M184V, D67N, V75M, M41L, and T69N in the NRTI group; K103N, K101E, V106A, and G190S in the NNRTI group; and M36I and H69K in the PI group.

Discussion

This systematic review involves 5523 samples that have been successfully categorized into different subtypes, sourced from 41 studies conducted between 2004 and 2024. The primary objective of this study was to explore the degree of resistance to antiretroviral medication among various populations in the MENA region.

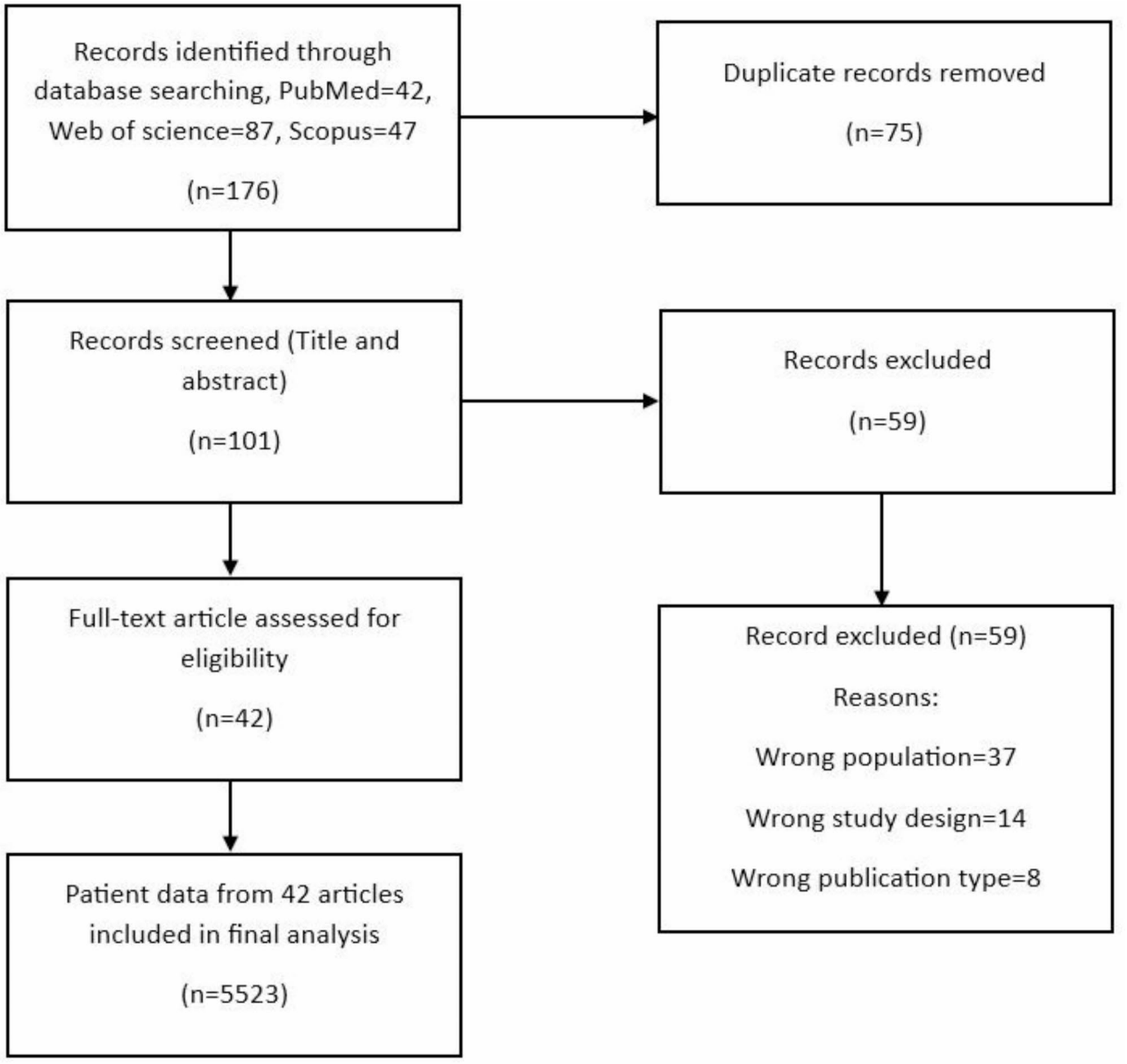

Fig. 1 PRISMA flowchart describing the article selection process

Investigating HIV treatment classes in ART-naïve and ART-experienced PWH

Our research revealed a high prevalence of drug resistance in Israel, Pakistan, and Iran, with rates of 53.85%, 47.52%, and 25.07%, respectively. In the case of PWH who had first experience with ART, a common practice in many countries was to prescribe a combination of two NRTI drugs (such as 3TC, AZT, TDF, and ABC) along with one NNRTI drug (EFV or NVP). Additionally, the highest level of drug resistance in ART-experienced PWH was observed in those taking NRTI medications. This was followed by PWH taking NNRTI drugs and then PIs, with INSTIs showing a lower level of drug resistance. In ART-naïve PWH, the highest resistance rates were reported in the NNRTI, NRTI, PI, and INSTI drug groups. INSTIs were given to PWH in eight studies, four of which were conducted in Iran [8, 9, 27, 29] and one each in Sudan [39], Israel [32], Kuwait [40], and Turkey [41]. The most commonly prescribed drugs are raltegravir (RAL), elvitegravir (EVG) and dolutegravir (DTG). These medications have not been widely used for long periods, resulting in the development of less resistance within the community. To address this issue, although naïve PWH have not previously received any drugs, the higher rate of drug resistance mutations related to RTIs and PIs than to INSTIs may be attributed to the longer history of RTI and PI usage in HIV-infected PWH, as opposed to the more recent emergence of INSTIs. Consequently, there

is a greater likelihood of resistance mutations developing in PWH undergoing treatment and the subsequent transmission of mutant viruses to naïve PWH. Notably, HIV-1 evolution under the influence of drug selection pressure and internal epistatic constraints in HIV-1 causes related mutations that result in changes in the frequency of drug resistance mutations in the population over time. Research studies indicate that the timeline for the emergence of drug-selected mutations in PWH who have not been exposed to drugs can range from a few weeks to more than a year after they start ART [26].

Examining drug resistance mutations in ART-naïve and ART-experienced PWH

In general, both study groups in Pakistan presented the lowest levels of drug resistance to NNRTI, NRTI, and PI medications. However, the highest resistance rates were reported in the ART-experienced group in Israel (52.78%) and Iran (43.03%), as well as in the ART-naïve group in Turkey (53.57%). In Iranian PWH, the mutations M184V [13, 27–29] and T215Y [27, 30] were observed more frequently in NRTIs, whereas D67N, K101E [13, 27, 30], K103N [13, 27, 30, 31], and P225H [27, 31] were common in NNRTIs, and M46L [13, 32], I47V [32, 33], and V82A [13, 30] were prevalent in PIs. Additionally, R263K, G163R [23], L74I [23, 34], and V72I [23] were noted in INSTIs [24]. These mutations resulted in resistance to drugs such as 3TC + emtricitabine (FTC) + EFV, ABC + NVP, fosamprenavir (FPV), tipranavir (TPV), RAL, and EVG during the initial stage of treatment. Resistance to drugs such as ABC, AZT, 3TC, FTC/TDF (corresponding mutations: M41L, A62V, M184IV, and T215DE) [35–37], EFV, NVP (related mutations: K101E, K103N, and E138A) [25, 35, 36], and lopinavir/ritonavir (LPV/r)/FPV/r (frequent mutations: I47V and L90M) [25, 36] was more commonly observed in four studies conducted in Israel. In Turkey, the most significant drug resistance is associated with drugs such as AZT/stavudine (d4T) [38, 39], FTC/3TC + LPV/r [40], FTC/TDF + EFV [41], RAL, and EVG [42] during first-line treatment. The mutations M41L, M184V, and V75I were more common in NRTIs; E138A and K103N were more common in NNRTIs; Q58E and V82I were more common in PIs; and L68V and L74I were more common in INSTIs. In conclusion, in the ART-experienced population, the resistance rate was 50–78.8% for NRTIs, 16–53% for NNRTIs, 2–26% for PIs, and 4–8.3% for INSTIs. However, ART-naïve PWH presented resistance rates of 6.1–21% for NNRTI drugs, 5.2–12.2% for NRTI drugs, 2.4–9.1% for PI drugs, and 0–8.1% for INSTI drugs. Therefore, it appears more beneficial to prescribe INSTIs to newly diagnosed PWH. Furthermore, PWH with good adherence to RTIs and PIs who have developed resistance to RTIs and PIs should switch to INSTIs. In the following paragraph, we provide more details on resistance mutations related to ART drugs.

Table 1 Classification of drug resistance data by year

Year	ARTs categories	Number of studies	Resistance mutations to ART
2004–2008	NNRTI, NRTI, PI	2	M184V, K70R, T215Y
2009–2013	NNRTI, NRTI, PI	7	M184V, T215Y, M41L, K103N, L90M, D30N
2014–2018	NNRTI, NRTI, PI, INSTI	15	M184V, K103N, M41L, D67N, L74I, E138A, G73S
2019–2024	NNRTI, NRTI, PI, INSTI	17	M184V, K103N, M41L, V75M, R263K, G163R, L74I, M50I

In a report by Tekin et al., ART-naïve and ART-experienced PWH underwent genome sequencing for the purpose of detecting mutations related to NRTIs, NNRTIs, PIs, and INSTIs in specific regions [43]. In our study, the most common mutations were identified in the NRTI group, the mutations M184V, D67N, V75M, M41L, and T69N; in the NNRTI group, the mutations K103N, K101E, V106A, and G190S; and in the PI group, the mutations M36I and H69K. In addition, the prevalent resistance mutations to INSTIs included major and minor mutations such as R263K [24, 43], L74I [24, 44, 45], T66A/I [43, 46], Y143R, and T97A [46], as well as polymorphism mutations such as G163R [23, 24], S230N [24], E157Q [45], V72I [23, 24], Q216H [23], and M50I/L/R [24, 44]. These mutations led to resistance against RAL and EVG in two groups of PWH [23, 24, 46]. The classification of NNRTI, NRTI, PI, and INSTI drugs and resistance mutations has been clarified annually. Over time, there has been an increase in drug resistance, as shown by the data in Table 1, which demonstrates an increase in the prevalence of drug resistance.

HIV subtyping assessment in the MENA region

Drug resistance in HIV can develop due to genetic differences that are already present and can be exacerbated by the selective pressure used in ART, especially in cases where only one or two drugs are being used [47]. The HIV-1 outbreak in the MENA area is characterized by a wide range of subtypes, including a significant presence of particular variations. Recognizing these subtypes is essential for successful public health interventions. Sallam and colleagues (2017) reported that the most common subtypes in this area were B (39%), CRF35-AD (19%), and CRF02-AG (14%) [18]. The geographical distribution of subtyped sequences in the MENA region according to the HIV database was obtained from the HIV sequence database (https://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.html) (Fig. 2). Our study results confirmed the presence of prevalent HIV-1 subtypes such as B, CRF35-AD, CRF01-AE, A1, and (CR02-AG, C, and D) in Turkey, Iran, Kuwait/Israel, Pakistan,

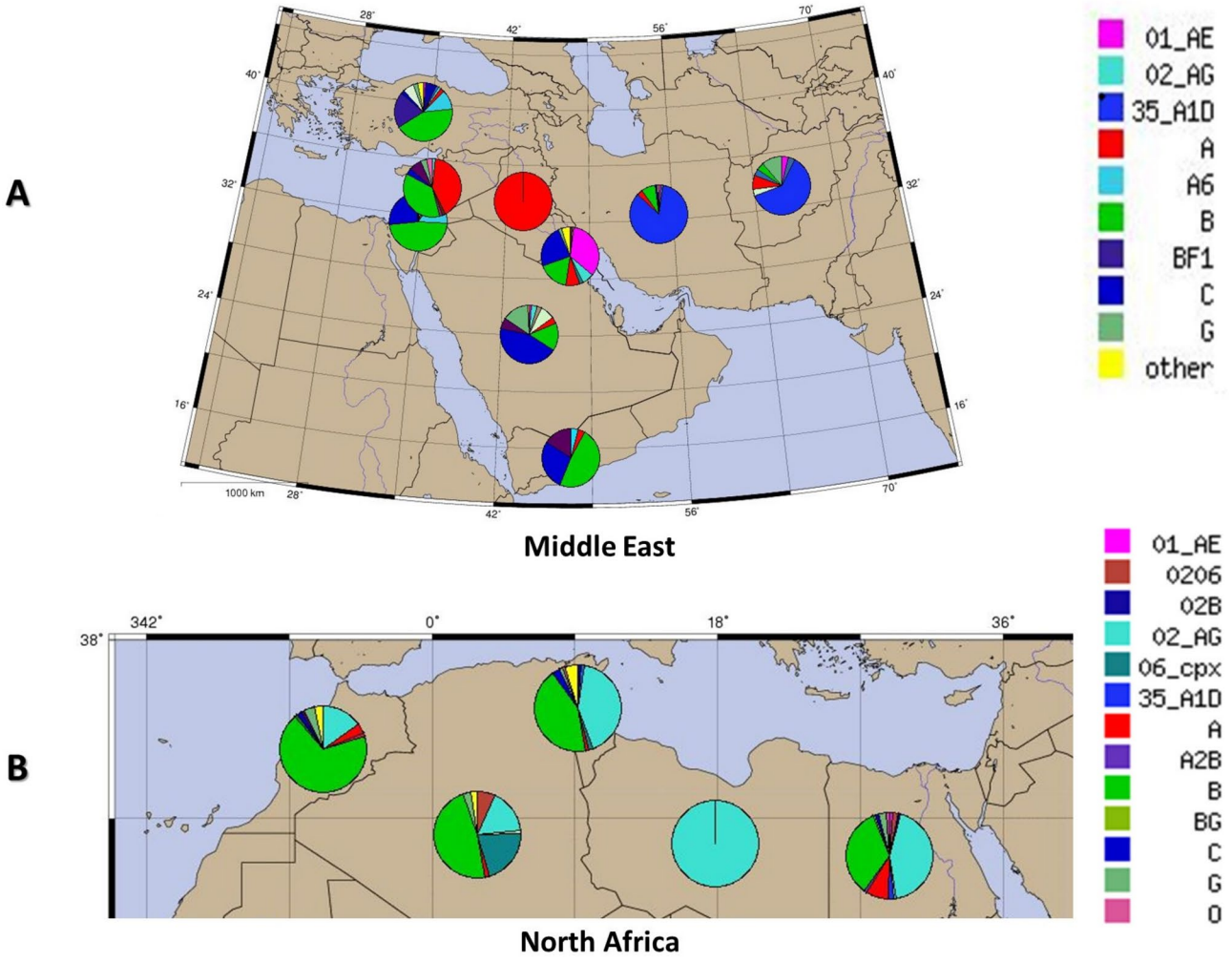

Fig. 2 Geographical distribution of HIV subtypes in the Middle East (**A**) and North Africa (**B**) regions on the basis of the HIV sequence database

and North African countries, which are associated with HIV drug resistance. While there is a predominance of subtype B and CRF35_AD, the existence of various subtypes circulating concurrently underscores the necessity for customized prevention approaches. Understanding these patterns is crucial for effectively combating the increasing prevalence of HIV-1 in this area [48].

Relationship between resistance mutations and HIV subtypes

Research suggests that different subtypes of HIV, specifically subtypes A, C, and F, exhibit unique mutation patterns in response to ART. Subtype C is more likely to experience mutations at codons 65 and 106 in the reverse transcriptase gene when exposed to ART pressure [49]. Additionally, subtype B is the most common subtype at 74% in Morocco, and there are noticeable mutations associated with drug resistance, especially in strains other than type B, in which 50% of PWH are ART resistant [50]. Another study in Kuwait revealed various subtypes (B, C, CRF01_AE) and identified nonpolymorphic resistance mutations in ART-naïve PWH, emphasizing the importance of continuous monitoring [51]. On the other hand, subtype A was the prevalent strain in Pakistan, accounting for 82% of the cases, whereas only 7% of the sequences presented significant mutations, indicating a lower resistance level [52]. It is important to understand resistance patterns specific to different subtypes to create successful ART regimens. Customizing treatment according to the most common subtypes in a particular area can reduce the development of drug resistance [53, 54]. In our research, the M184V (NRTI) and K103N/S (NNRTI) mutations occurred in all the subtypes identified in the region, with the highest frequency in the CRF35-AD, A, and C subtypes. There was a greater occurrence of the mutations M41L, M184V, T215C, V75I, T69N (NRTI), E138A, K103N (NNRTI), and Q58E and V82I (PI) in subtype B than in the other subtypes. In contrast, the occurrence of M184V, D67N, K219E, K103N, and G179I mutations was more frequent in

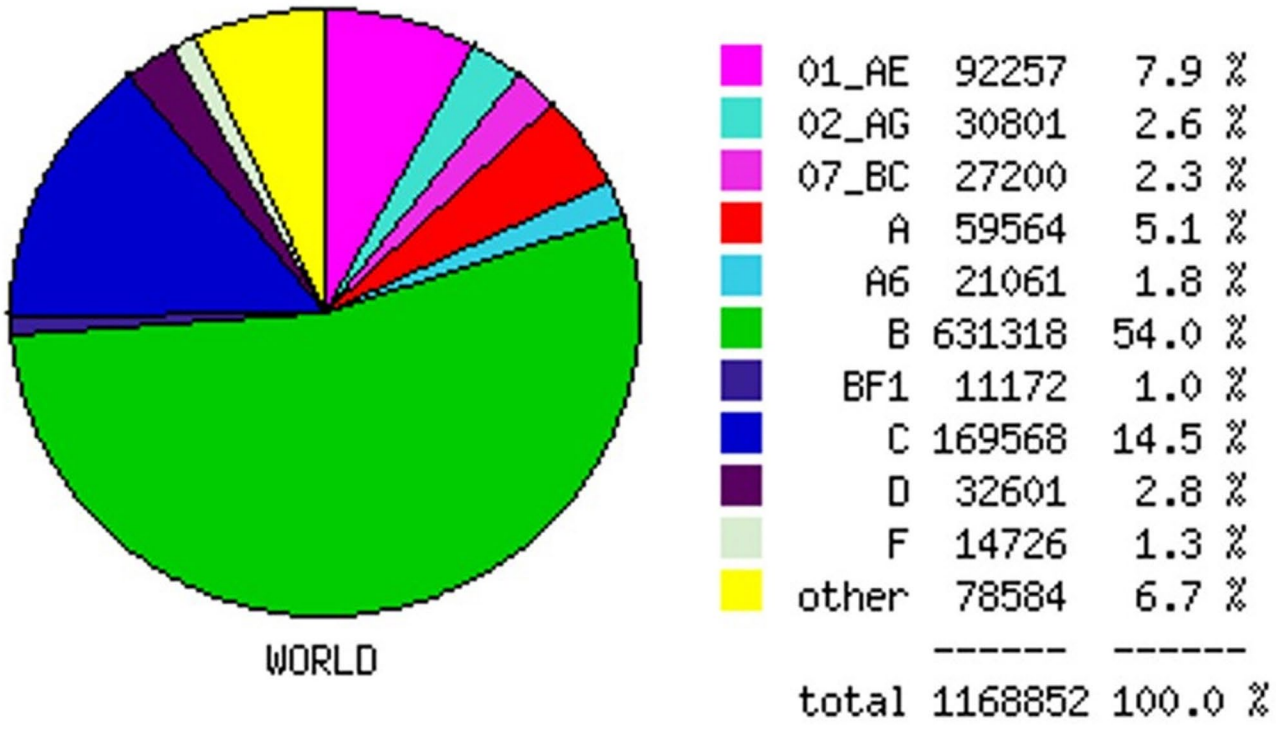

Fig. 3 Prevalence of HIV subtype distributions worldwide on the basis of the HIV database

subtype A than in CRF01-AE. In addition, the mutations causing resistance to INSTIs were primarily observed in the CRF35-AD subtype, with fewer occurrences in the D and B subtypes. A majority of the studies examining these mutations were conducted in Iran [23, 24, 46]. Notably, databases such as Stanford (https://hivdb.stanford.edu/) and ANRAS (https://hivfrenchresistance.org/) primarily focus on subtype B for analyzing drug resistance in HIV. On the basis of the HIV sequence database (https://www.hiv.lanl.gov/components/sequence/HIV/geo/geo.html), subtype B is the most prevalent HIV subtype in the world (Fig. 3). However, alongside subtype B, CRF35-AD, CRF01-AE, and A are also prevalent in MENA countries. This could impact the accuracy of drug resistance analysis for non-B subtypes in these databases, rendering the results invalid.

HIV transmission routes in the MENA region

In this region, there are high concentrations of epidemics, especially among IDUs, MSM, and sex workers [21, 55]. The occurrence of HIV among IDUs in the region is concerning, with certain areas such as Libya reporting rates as high as 87.1%. Risky behaviors such as sharing needles (18–28%) and the limited use of condoms (20–54%) worsen the problem [16]. On the other hand, our results revealed that the main routes of transmission include sexual contact, transmission from mother to child, and IDU.

Relationships between age, sex, and the development of drug resistance mutations

Our findings indicated that, in addition to 3 studies focusing on pediatric PWH, the remaining studies investigated adults with average ages ranging from 32 to 45 years, and the ratio of men was greater than that of women. On the other hand, in 2024, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported that approximately 20% of the recent HIV cases in the area were found in PWH between the ages of 15 and 24, with the majority being males (55%) [19]. Since the male-to-female patient ratio is approximately 2.3, gender differences may impact resistance to HIV medication; therefore, the correlation is complex and influenced by various factors. Research suggests that there may be differences in the progression of HIV disease and treatment outcomes between women and men due to biological, hormonal, social, and behavioral factors [56]. For example, women often show more favorable initial responses to ART, achieving undetectable viral loads more frequently than men do. However, over time, women may experience lower levels of immunological recovery, which could indirectly influence resistance patterns [57].

Nonadherence to ART and its impact on drug resistance

Insufficient information regarding drug resistance creates challenges in treating this condition. Inadequate adherence to ART and a lack of adequate monitoring

systems are factors that lead to the development of drug-resistant strains [21]. Moreover, comprehensive monitoring and customized strategies are essential for effectively addressing these issues. There are various reasons why HIV-1 patients may struggle with ART, including the side effects of ART drugs, stigma, mental health problems, complex treatment plans, socioeconomic obstacles, lack of knowledge, and forgetfulness. In contrast to the belief that the MENA region is not heavily impacted by HIV, the actual situation shows a rising epidemic, especially among vulnerable groups, highlighting the need for immediate measures to prevent more transmission and drug resistance [21]. Nonadherence to ART significantly impacts the development of HIV resistance, affecting both individual and public health outcomes. When ART is not performed as prescribed, inadequate drug levels in the body allow the virus to replicate. This replication increases the risk of genetic mutations, which can lead to drug-resistant strains of HIV [58, 59]. Drug resistance reduces the effectiveness of current ARTs, which require the use of more advanced and expensive second- or third-line therapies [60]. Moreover, nonadherence to ART can lead to the transmission of drug-resistant HIV strains to other strains and increase the likelihood of genetic recombination between strains, leading to the introduction of new CRFs and complicating treatment efforts on a broader scale. Thus, poor adherence to ART leads to unfavorable health consequences, such as accelerated disease progression and increased mortality rates [59].

Coinfection and resistance to ART

Coinfections may result in inadequate adherence to ART, which can increase the likelihood of developing drug-resistant strains of HIV. Inconsistent adherence is a recognized contributor to the development of resistance mutations [61]. The WHO has reported a prevalence of ART resistance ranging from 3 to 29%, suggesting that coinfections may worsen this problem, especially in areas with high rates of coinfection [62]. In addition, research conducted in Brazil revealed that the rate of transmitted drug resistance (TDR) was 14.1%. Some identified mutations did not seem to have a significant effect on the effectiveness of ART. This finding indicates that coinfections could complicate treatment but may not always result in resistance development [63]. Multiple studies in our study reported the occurrence of HIV coinfection with HBV/HCV, TB, and syphilis at rates of 50.55%, 2.86%, and 3.14%, respectively [13, 28, 34, 35]. However, a considerable proportion of PWH are resistant to ART [12, 33, 46, 64].

Relationship of CD4 T cells with ART treatment

Antiretroviral medications are commonly used to prevent immunologic failure and manage HIV-related illnesses rather than completely eliminating the virus [65]. CD4 + T-cell counts are frequently used as important markers by healthcare providers when determining the need to start ART [66]. This test can also help predict the likelihood of developing AIDS or succumbing to other causes of death [67, 68]. Despite this, many areas with limited resources continue to rely on the WHO clinical staging system for making treatment decisions [69]. In the majority of countries, more than half of PWH qualify for ART because they have CD4 counts of ≤ 350 cells/mm3 at the time of diagnosis [70, 71]. It is essential to establish or enhance surveillance systems in places with access to CD4 measurements as a top priority in the region [72]. In this review, some publications reported the CD4 count, with an average of approximately 432 PWH in both groups (ART-naïve PWH and ART-experienced PWH).

Limitations and suggestions

This study is the first to consider 41 studies regarding ART resistance profiles in both ART-naïve and ART-experienced HIV-positive populations and incorporates profiles for more than 5500 PWH across 12 MENA countries between 2004 and 2024. The review has large and diverse sample sizes across the world and 20 years of data to distinguish regional differences in ART responses. However, it is important to acknowledge that some related publications may not have been included despite extensive search methods. The review was also unable to factor in some effects that could have contributed to these results, such as socioeconomic factors, because not all the studies used in the review reported these effects. Furthermore, few studies have been conducted in rural areas, leading to analyses that have focused mainly on ART resistance profiles in urban and peri-urban regions. The analysis disproportionately relies on data from Israel and Iran, whereas contributions from other countries are minimal and may imbalance the interpretations of regional resistance patterns. To avoid ART resistance data imbalance, it is important to use statistical methods such as weighted sampling. Weighted sampling can help compensate for the overrepresentation of specific regions, ultimately leading to decreased bias and a more even accurate analysis. Moreover, to mitigate bias, future studies should prioritize underrepresented regions and discuss how current sampling limitations affect generalizability. While the review offers valuable insights at the population level, determining causal relationships solely from observational data poses challenges. In the future, conducting larger prospective studies that establish standardized outcomes and gather extensive information on

clinical and socioeconomic factors could provide more insight into the factors that can be modified to improve treatment responses in the MENA region. Notably, current databases, such as Stanford and ANRAS, have focused primarily on drug resistance in HIV subtype B. In the MENA region, subtype B is predominant, but other subtypes are also widespread. To improve the efficiency of these databases, the inclusion of drug resistance data from other subtypes or ORFs identified by different countries in the databases mentioned is suggested.

Moreover, in several MENA countries, routine HIV drug resistance testing for individual patient care is not common [73, 74]. The WHO recommends annual monitoring of certain factors that indicate early warning signs of HIV drug resistance at all ART clinics, including executing strategies to increase adherence to ART, which can lead to better control of viral loads; promoting widespread use of viral load testing; establishing a procedure to facilitate the prompt transition to second-line ART when necessary; enhancing communication and coordination between pharmacy and clinic records to identify PWH at risk of developing HIV drug resistance owing to missed medication pickups; and providing support and improvement of supply chain management [12]. This should be done by following comprehensive strategic information protocols about HIV within the healthcare domain [75, 76].

Conclusions

As the first report from MENA, our data revealed a greater occurrence of drug resistance in Israel, Pakistan, and Iran, with percentages of 53.85%, 47.52%, and 25.07%, respectively. Furthermore, the greatest level of resistance to drugs in both ART-naïve and ART-experienced PWH was found among those who were using RTIs, followed by PIs and INSTIs. Owing to high rates of resistance to RTIs and PIs, it seems more advantageous to recommend the INSTI drug class for PWH who are newly diagnosed and/or developed resistance to RTIs and/or PIs. Furthermore, HIV subtypes such as B, CRF35-AD, CRF01-AE, A1, CR02-AG, C, and D are linked to a greater likelihood of developing drug resistance. The most reliable HIV databases (Stanford and ANRAS) focused on the analysis of HIV drug resistance are focused primarily on subtype B. However, in the MENA region, along with subtype B, other subtypes comprising CRF35-AD, CRF01-AE, and A1 are prevalent. Hence, to enhance and refine the functionality of these databases, considering drug resistance findings related to other subtypes or ORFs is highly recommended. Furthermore, coinfection with HIV may lead to an increased occurrence of drug resistance among infected PWH. Given the economic situation of the countries in the MENA region, it is essential that both the treatment and all HIV-related tests, including drug resistance testing, be provided free of charge.

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Declarations

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The authors declare no competing interests.

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