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REVIEW ARTICLE

Human Immunodeficiency Virus (HIV) Drug Resistance: A Global Narrative Review

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ABSTRACT

Background: Antiretroviral Therapy (ART) has significantly improved Human Immunodeficiency Virus (HIV) patients' survival rates. However, the emergence of HIV Drug Resistance (HIVDR) has markedly reduced the effectiveness of Antiretroviral Therapy (ART).

Aim: This narrative review was conducted to review published studies on HIV drug resistance and its consequences.

Materials and methods: A literature search for this narrative review was carried out and the following databases were used PubMed, Google Scholar, and The Lancet. The cited articles were published from 1999 to 2021. The keywords used in the search of literature included 'Antiretroviral therapy', 'resistance', and 'Human Immunodeficiency Virus drug resistance', 'HIV', 'HIV drug resistance', 'HIV vaccines', and the Boolean word 'AND'.

Results: There is a high prevalence of HIV drug resistance globally that has been associated with some factors such as older age, non-adherence to treatment, long treatment duration, lower cell count and high viral load. HIV drug resistance may lead to treatment failure, prolongation of the time required to achieve viral suppression and leads to increased mortality. Increasing access to viral load monitoring can help mitigate HIV drug resistance.

Conclusion: HIV drug resistance is a global threat to public health and has been associated with increased morbidity and mortality. Therefore, there is a need for more research to be carried out and various strategies like the use of antiretrovirals with a high genetic barrier to resistance need to be put in place to prevent further spread resistance. HIVDR must be monitored frequently taking into consideration the geographic variability. There is an urgent need for the development of anti-HIV vaccines that will help to prevent further transmission and spread of HIV.

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INTRODUCTION

Human Immunodeficiency Virus (HIV) is a global public health issue that has led to increased morbidity and mortality [1-3]. The rapid expansion of Antiretroviral Therapy (ART) has significantly improved the prognosis of HIV positive patients, by reducing the morbidity and mortality rates in both developed and resource-limited countries [4-6]. The effectiveness of ART has been markedly reduced by the development of HIV Drug Resistance (HIVDR), which is a major factor in the failure of ART [7,8].

HIVDR occurs because of one or more changes in the genetic structure of HIV that affects the ability of a specific drug or combination of drugs to block the replication of the virus [9]. HIVDR is also observed when the ART fails to suppress the viral load [10,11]. Besides, HIVDR has been reported due to the widespread usage of ART to treat HIV [12]. HIVDR has become a significant barrier to reaching the Joint United Nations Programme on HIV and AIDS (UNAIDS) Fast-Track goal of ending Acquired

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Immune Deficiency Syndrome (AIDS) by 2030 [13]. The threat of HIVDR is high, especially in sub-Saharan Africa and other low and middle-income countries where weak health systems and poor access make managing HIV more challenging [14,15]. The rise in HIVDR rates has mostly been against Nucleoside Reverse Transcriptase Inhibitors (NRTIs) and Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs) [16]. This is of particular concern because these drug classes are part of the first or/and second-line ART regimens.

Factors associated with the development of HIV drug resistance include; poor adherence, suboptimal ART doses, initiation of therapy late in the course of HIV infection, use of substandard antiretroviral regimens, lack of plasma viral load monitoring, the transmission of drug-resistant HIV, treatment interruptions, high replication rates of the virus, selective pressure caused by the Antiretrovirals (ARVs), and initial infection by resistant strains of HIV [17-21].

The World Health Organisation (WHO) commonly classifies HIVDR into three major categories; Acquired HIV Drug Resistance (ADR), Transmitted HIV Drug Resistance (TDR), and Pretreatment HIV Drug Resistance (PDR) [9]. Transmitted HIV drug resistance occurs when previously uninfected individuals are infected with a drug-resistant virus [22]. Acquired HIV drug resistance is Drug-Resistant Mutations (DRMs) that are selected during antiretroviral therapy, which can happen when viral replication is not fully suppressed in the drug's presence [23]. Pretreatment drug resistance refers to the resistance detected among ARV drug naïve people initiating ART or people with previous ARV drug exposure initiating or re-initiating first-line ART [9]. PDR is either TDR or ADR or both and it is associated with poor response to first-line treatment, premature virological failure, and accumulation of DRMs [9,24,25].

The development of anti-HIV vaccines is crucial in preventing HIV transmission and containing the HIV pandemic. However, the variability in the HIV-1 envelope proteins of more than 30% of the amino acids makes it difficult for anti-HIV vaccine development [8]. Currently, the development of broadly neutralizing anti-HIV antibodies (bNAbs) may help stimulate the immune response against HIV [26]. Vaccine candidates such as polyvalent envelope glycoprotein vaccines have shown greater success in the development of anti-HIV vaccines [27,28]. Despite much good progress made in anti-HIV vaccine development, no known vaccine has prevented HIV transmission to date [29].

The rise in HIV drug resistance is a great threat to global health, and if it is not urgently addressed, it may result in millions of deaths and an increase in new HIV infections. Therefore, the purpose of this narrative review was to review the published studies on HIV drug resistance to ART.

MATERIALS AND METHODS

A literature search for this narrative review was conducted from November 2019 to September 2020 with the following databases: PubMed, Google Scholar, and The Lancet. Keywords used in the search were 'antiretroviral therapy', 'resistance', 'HIV vaccines', 'HIV drug resistance, 'HIVDR', and the Boolean word 'AND'. Articles were read and assessed for relevance. The inclusion criteria included articles published from 1999 to 2021 and focused on HIV drug resistance. Exclusion criteria included editorials, commentaries, and conference abstracts. A total of 133 articles were retrieved but only 77 were included in this review. Five major themes were identified; mechanisms of HIV drug resistance, factors leading to HIV drug resistance, the prevalence of HIV drug resistance, the impact of HIV drug resistance on HIV/AIDS and strategies to mitigate HIV drug resistance.

Mechanisms of HIV drug resistance

Resistance occurs because of alterations called mutations in the HIV's genetic structure which lead to changes in certain proteins, most commonly enzymes that regulate the production of infectious viruses [30]. The mechanisms of resistance to antiretroviral drugs differ from one drug class to another [31]. The available classes of HIV drugs include Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), Intergrase Inhibitors, Fusion Inhibitors, and CCR5 Antagonists [32]. Resistance to NRTIs occurs through modification of the reverse transcription enzyme allowing it to discriminate between NRTIs and analogue substrates which results in reduced incorporation of the NRTIs into the growing chain [32]. Another way in which resistance to NRTIs occurs is through enhanced removal of the drug from its site of attachment at the end of the Deoxyribonucleic Acid (DNA) chain [7]. The table 1 shows the major NRTI resistance mutations.

These mutations allow Adenosine Triphosphate (ATP) to bind to the active site which liberates the drug and terminates its effects [7]. The most common mutations of NRTIs include M184V, K65R and Thymidine Analogue Mutations (TAMs). The TAMs include; M41L, D67N, K219Q, and T215F [33].

NNRTIs resistance occurs due to single mutations around the reverse transcriptase pocket which decreases the binding of the drug [34]. The most common NNRTI mutations are K103N, G190A, Y181C, and Y188L [33]. Protease Inhibitors (PIs) resistance occurs primarily as a result of amino acid mutations that arise within or proximal to the catalytic binding site to the drug [7]. Intergrase inhibitors resistance occurs due to mutations in residues surrounding the intergrase active site. Fusion inhibitors mechanism of resistance occurs because of mutations in the gp41 transmembrane protein that interfere with the association of

Table 1: Major NRTI Resistance Mutations.

	Non- TAMs				TAMs				
	184	65	74	115	41	67	70	215	219
Cons	M	K	L	Y	M	D	K	T	K
3TC	VI	R							
FTC	VI	R							
ABC	VI	R	VI	F					
TDF		R							
ZDV					L	N	R	YF	Q

Heptad Repeat 1 (HR1) and HR2 required for virus-cell fusion [35]. Recent resistance of HIV to Dolutegravir (DTG) HAS has been reported [36]. Table 2 shows the major resistance mutations to NNRIs, PIs and intergrase inhibitors.

Factors leading to HIV drug resistance

Understanding the interplay of factors that are associated with HIV drug resistance is an important factor, especially in Low to Middle-Income Countries (LMIC) [37]. In China, Xing and colleagues studied the incidence and factors associated with HIV drug resistance in patients. The independent factors that were associated with the development of resistance included initial ART regimen, ART distribution institution, a high baseline viral load (≥ 1000 copies/ml), and low baseline CD4 counts (0-199 cells/µl) [38]. A cross-sectional study by Zhou, et al. [39] showed that gender and treatment time were factors associated with the development of drug resistance. A comparison of the risk of drug resistance between patients treated for 1-2 years (RR = 13.616, 95% CI: 1.715-108.109), 2-3 years (RR = 19.556, 95% CI: 2.278-167.857), and more than 3 years (RR = 50.579, 95% CI: 4.855-526.891) was made and it was found that there was a greater possibility of HIV drug resistance emerging with longer treatment duration.

A study conducted by Ekong and colleagues on epidemiologic and viral predictors of antiretroviral drug resistance in Nigeria evaluated 159 cases with ADR and 299 cases without ADR. The factors that were associated with ADR included older age (age group 31-40) (OR = 2.35 [95% CI: 1.29, 4.27], age group 41 + OR = 2.31 [95% CI: 1.11, 4.84], being unmarried (single) (OR = 0.40 [95% CI: 0.24-0.67], higher education level (secondary) (OR = 2.14 [95% CI: 1.11-4.13]), non adherence to care (OR = 2.48 [95% CI: 1.50-4.00]), long treatment duration (> 3 years) (OR = 1.80 [95% CI: 1.37-2.35]), lower CD4 count and a higher viral load (OR = 1.97 [95% CI: 1.44-2,54]) [40].

Ekong, et al. and Xing, et al. [38,40] both observed that low CD4 cell count and high viral load were associated with drug resistance development. Their results showed that patients with a low CD4 count were more likely to develop resistance. These results are consistent with Jose, et al. [41] whose results also demonstrated that resistance was more likely to occur in patients with a low CD4 count than those with a high cell count (> 350 cells/µL). High viral load was associated with resistance development because there is incomplete viral suppression in patients, which increases the risk of drug resistance [42]. Longer treatment duration (> 3 years) was found to be a risk factor of HIV drug resistance development by both Ekong *et al.* and Zhou *et al.* thus, showing that patients who have been on ART for a longer time are at risk of HIV developing resistance [39,40].

Ekong, et al. [40]. were able to associate more factors with the development of resistance because they conducted a case-control study between 2004-2011. Therefore, with the longer duration of the study, they were able to associate other factors with the development of drug resistance such as age, being unmarried and high education, non-

Table 2: Major NNRTIs, PIs and Integrase Inhibitor Resistance Mutations.

	47	50	54	82	92	101	103	106	132	181	188	190
Cons	I	I	I	V	E	K	K	V		Y	Y	G
NVP						P	N	AM		C	L	ASE
EFV						P	N	AM			L	ASE
ETR						P				C		EQ
RPV						P				C	L	EQ
ATV/r		L	VTAM	ATSF								
DRV/r	VA	V	LM	F								
LPV/r	VA	V	VTAM	ATSF								
RAL					Q				KA			
EVG					Q				KA			

adherence. Being unmarried was associated with the risk of HIVDR development because the support that married individuals have makes them adhere to treatment more [40]. Higher education was associated with increased risk of drug resistance, but this differs from Boateng and Awunyo-Vitor who found that a high education level led to good knowledge on HIV/AIDS and ART, it influenced motivation and uptake of ART, thus making the patients more adherent and reducing the risk of HIV drug resistance [43]. Non-adherence to ART increases the possibility of HIV drug resistance and factors that are associated with poor adherence include gender, age, employment, marital status, and health status [44].

2.3. Stigma and social backgrounds among infected individuals are other factors that can lead to HIV drug resistance. This is because stigma and social backgrounds can affect access to ART and compliance [45]. A study conducted by Denison and colleagues found that self-stigma was associated with incomplete adherence among patients on ART. Due to self-stigma, some patients avoided attending nearby clinics for fear of being identified as HIV infected by the community and health care workers whom they know [46,47].

Prevalence of HIV drug resistance

The prevalence of HIVDR has been increasing over the past few years. Moreover, HIVDR has been reported among the first- and second-line ART [48]. This called for the third-line of treatment more especially in low- and middle-income countries [49]. In 1999, the prevalence of HIVDR was reported to be 16.3% among newly infected individuals sampled between 1994 and 1999 in the United States of America [12]. In 2010, the WHO reported the prevalence estimates for HIV drug resistance to NNRTIs to be 5.5% in Low and Middle-Income Countries (LMICs), and by 2015 Transmitted Drug Resistance (TDR) levels had risen in the ranges of 1-12.3% in different regions [22,50].

Transmitted Drug Resistance (TDR) levels have been rising over the past few years. A meta-analysis by Rhee, et al. [50] found the median overall TDR prevalence in sub-Saharan Africa and South/Southeast Asia to be 2.8% and 2.9% respectively and it was accompanied by an estimated 1.1-fold yearly increase in NRTI and NNRTI-associated TDR since the antiretroviral scale-up began. The TDR prevalence in upper-income Asian countries, Latin America/Caribbean, Europe, and North America was 5.6%, 7.6%, 9.4%, and 11.5% respectively with an estimated 1.1-fold yearly increase in TDR in North America and Latin America/Caribbean. In upper Asian countries, the estimated yearly increase of NNRTI associated TDR was 1.2-fold, while in Europe there was a 0.9-fold yearly decrease in NRTI-associated TDR. A study in Brazil also reported an increase in the overall TDR prevalence to be 16.3% (95% CI: 8.1-30.0) and the highest prevalence was against NNRTI (11.6%), with K103N being the most frequently identified mutation [51]. A 7.21% TDR was reported recently in China in which HIV was resistant to NNRTI, NRTI, PIs, and PIs + NNRTI [52].

The findings from these studies on TDR show an increase in TDR with Brazil reporting the highest prevalence of 16.3%. The high prevalence rate reported in Brazil was because the study focused on patients with acute/recent HIV infection while the meta-analysis focused on recently and chronically infected ARV-naïve individuals. TDR studies focusing on chronically HIV-infected patients, usually have lower TDR detection because of the overgrowth of more fit, drug-sensitive viral quasi-species in such individuals [51].

The rise in TDR can at times be exceeded by a rise in acquired drug resistance as seen from a meta-analysis in China. The meta-analysis reported a pooled TDR prevalence of 3.0% including 0.3% for NRTIs, 1.4% for NNRTIs, and 0.5% for PIs, and a pooled ADR prevalence of 44.7% including 31.4% for NRTIs, 39.5% for NNRTIs, and 1.0% for PIs. The difference in HIVDR prevalence observed was regional due to the variable coverage rates and durations of ART since its introduction in China [53].

The prevalence of Pretreatment Drug Resistance (PDR) has been rising in many LMICs especially in sub-Saharan [54]. This rise in prevalence is high for the most commonly used first-line NNRTIs, namely efavirenz, and nevirapine. A meta-analysis done in 64 LMIC reported the estimated annual increase of PDR for NNRTIs of 23% in Southern Africa, 17% in Eastern Africa, 17% in Western and Central Africa, 11% in Latin America and the Caribbean, and 11% in Asia. The most common mutations reported in the study were K103N, Y181C, and G190A [55]. Similar findings for increased levels of prevalence of PDR for NNRTIs were reported in other studies. In a study done in West Africa and Southeast Asia, the recorded overall PDR prevalence was 15.9% (95% CI: 13.8–18.3) for any drug-resistant mutation, ranging from 9.6% and 10.2% in Burkina Faso and Thailand, respectively, 14.7% in Vietnam, 15.4% in Mali, 16.5% in Coˆ te d'Ivoire and 19.3% in Cameroon, to 24.6% in Togo. The prevalence by ARV drug class was 3% for PI, 4% for NRTI, and 12% for NNRTI [56]. Bisso, et al. [57] from Argentina reported 14% PDR prevalence with 2%, 3%, and 11% prevalence for PIs, NRTIs, and NNRTIs respectively. The highest drug-specific prevalence was against NNRTIs then NRTIs and the most frequently associated mutations were M184V for NRTIs and K103N for NNRTIs. The high prevalence of NNRTIs observed is because in patients who have a virological failure the earliest mutations to emerge are NNRTI mutations and so transmission of these resistant variants is greater. The NRTI mutation does emerge early as well, but it is not commonly transmitted because of its significant fitness cost to the virus [55].

HIV drug resistance rates in African countries have also been reported. A study in sub-Saharan Africa on men who have sex with men (MSM) and transgender women found that 63 (34.4%) of 183 participants were infected with HIV.

Of the 63 participants, 11 (17.5%) had at least one major drug-resistant mutation, and the most frequently detected mutations were M184V for NRTI and K103N for NNRTI [58]. From Zimbabwe, Kouamou, et al. [59] detected HIV drug-resistant mutations in 97% (72/74) of the participants, with NNRTI drug-resistant mutations at 97%, and NRTI drug-resistant mutations at 84%. The most frequently identified mutations were M184V, K65R, and TAMs, also, two-class resistance was detected in 84% (62/74) of the participants owed to NRTIs and NNRTIs. In Kenya, the prevalence of drug resistance was reported to be 23.1% among the studied population with M184V and K103N been the most prevalent drug mutations [45]. Overall, Zimbabwe had the highest prevalence of HIV drug resistance. This could be because, in many LMICs, there is a lack of differentiation between patients who are being initiated on first-line ART and those who are being re-initiated on first-line ART [55]. The risk of HIV drug resistance is high in those who have previous exposure to ART [55].

Impact of HIV drug resistance on HIV/AIDS

Phillips, et al. [60] studied the impact of HIV drug resistance on HIV/AIDS and found that a high level of HIVDR indicates gaps in ART service delivery. Furthermore, the study brought to light that in situations where pretreatment drug resistance is over 10% the impact is great with an estimated 8,90,000 AIDS deaths and 45,000 new infections. This shows that HIV drug resistance causes attenuation of the potential full health benefits of ART and adds costs to the programs. Besides, the consequences of HIV drug resistance include treatment failure, the spread of drug-resistant HIV strains and increased mortality [60,61].

HIV drug resistance can cause ART failure, which may make the treatment of HIV more challenging [61,62]. It also leads to limitations in the choice of effective treatment regimens and increases costs switches to second and third-line therapy and routine laboratory monitoring of patients [20,63,64]. Furthermore, it can prolong the time required to achieve viral suppression and shorten the time to virological failure when compared to infections with a non- drug-resistant viral strain [65,66].

Strategies of mitigating HIV drug resistance

With the rise in NNRTI Pretreatment Drug Resistance (NNRTI PDR), WHO launched a Global Action Plan where it recommended that countries with high levels of NNRTI PDR defined by a PDR above 10% in populations starting ART, use a first-line regimen that remains active against HIV [67,68]. As of July 2018, WHO ART guidelines recommended the use of Dolutegravir (DTG)–based regimen as the preferred first-line antiretroviral therapy [68]. DTG is an integrase inhibitor with superior efficacy, tolerability and has a high genetic barrier to resistance than NNRTI, so the use of a DTG- based first-line regimen reduces the risk of HIV drug resistance [69]. The most commonly used DTG- based regimen is Tenofovir Disoproxil Fumarate (TDF) + Lamivudine (3TC) + Dolutegravir (DTG) as first-line therapy [68,70,71].

Other ways of mitigating HIV drug resistance in patients on ART include increasing and improving access to viral load monitoring, enhancing HIV drug resistance testing services for individuals, improving adherence by providing person-centred care, enhancing research into long-acting ART formulations and functional care, encouraging ART programmes for implementation and promotion of good practices, increasing knowledge for better understanding of biological determinants of drug resistance, using ARVs with a high genetic barrier to resistance in first-line therapy [56,69,72,73].

The development of anti-HIV vaccines is urgently needed [74-77]. The HIV vaccines will prevent the new transmission and spread of HIV and HIV drug resistance. Despite a lot of challenges being faced in developing HIV vaccines, a breakthrough vaccine will change the disease burden across the globe.

CONCLUSION

HIV infections remain a global health problem that has been worsened by the development of HIV drug resistance. The current prevalence of HIV drug resistance is widespread in the world and it is a global threat to the treatment of HIV/AIDs. HIV drug resistance can cause attenuation of the potential full health benefits that people on ART can experience. Therefore, more research must be carried out to come up with various strategies like the use of ARVs with a high genetic barrier to resistance. This may help prevent the further spread of HIV drug resistance. Besides, HIVDR must be closely monitored so that treatment can be according to HIV susceptibility. Moreover, the development of HIV vaccines is urgently needed across the globe to contain the HIV pandemic.

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