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ORIGINAL ARTICLE

HIV-1 drug-resistance mutations and related risk factors among HIV-1-positive individuals receiving first-line antiretroviral therapy

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ABSTRACT

BACKGROUND
Acquired immunodeficiency syndrome (AIDS) remains a global health issue. Antiretroviral therapy (ART) controls HIV progression, but widespread use had led to drug resistance mutations (DRMs) such as M184V and K103N, compromising treatment efficacy. This study assessed the prevalence of these mutations and identified associated risk factors in patients with first-line nucleoside reverse transcriptase inhibitor (NRTI)-based ART.

METHODS
A cross-sectional study was conducted involving 80 HIV patients aged > 18 years who had been on NRTI and non-NRTI (NNRTI) therapy for >6 months. Data included sociodemographic characteristics, ART adherence, opportunistic infections, viral load, CD4 count, treatment duration, ART regimen, and presence of M184V and/or K103N mutations. Genetic analysis was performed and statistical associations were assessed using simple and multivariate logistic regression.

RESULTS
M184V and/or K103N mutations were detected in 8 patients (10%), significantly associated with poor ART adherence ($p<0.01$), detectable viral load ($p<0.01$) and male gender ($p=0.048$), but not with age ($p=0.653$), body mass index ($p=0.661$), opportunistic infections ($p=0.938$), CD4 count ($p=0.265$), and treatment duration ($p=0.365$). Multivariate logistic regression analysis showed that poor ART adherence was associated with a decreased risk of mutations compared to good adherence (OR = 0.73, 95% CI:0.012-0.427) and male patients had a 10-fold higher risk compared to females (OR = 10.03, 95% CI:1.033-97.350).

CONCLUSION
This study demonstrated that male gender was significantly associated with an increased risk of mutations, while poor ART adherence showed an unexpected inverse association. Strengthening adherence support programs remains essential to preventing drug resistance mutations and ensuring treatment efficacy.

Keywords: ART, adherence, drug resistance mutation, HIV

INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) remains a global health issue. According to World Health Organization (WHO) data, an estimated 39.9 million people worldwide were living with human immunodeficiency virus (HIV), with 1.3 million new cases and 630,000 deaths from HIV-related causes in 2023.[1] In Indonesia, the number of HIV infections continues to rise annually, with an estimated 543,100 individuals living with HIV in 2020.[2] West Sumatra ranks eighth nationally in cumulative HIV and AIDS cases, with 3,338 HIV cases and 2,087 AIDS cases recorded as of 2019.[2]

The WHO and the Joint United Nations Program on HIV/AIDS (UNAIDS) have set a global objective to end the AIDS pandemic as a public health threat by 2030. This goal follows the "95-95-95" strategy: ensuring that 95% of people living with HIV are aware of their status, that 95% of diagnosed individuals receive antiretroviral therapy (ART), and that 95% of those on ART achieve viral suppression.[3] To achieve this target, the WHO recommended in 2016 that all HIV patients should receive immediate ART upon diagnosis.[4] Combination ART has proven to be highly effective in suppressing viral load and reducing HIV transmission compared to monotherapy.[5] With advancements in ART, life expectancy among people living with HIV has significantly improved.[6] However, long-term therapy increases the risk of drug-related side effects and treatment failure.[6] Additionally, HIV drug resistance has emerged as a major challenge to epidemic control, as it compromises the effectiveness of ART and increases the risk of treatment failure and the transmission of resistant strains.[7]

A meta-analysis of ART failure rates in China reported a treatment failure rate of approximately 14.4%, which is lower than rates observed in Haiti (15%), Ethiopia (15.3%), and Uganda (43%).[8] A study by Kurniawan et al.[9] found that around 10.7% of patients experienced virological failure (defined as a viral load >400 copies/mL), while research by Fibriani et al.[10] reported a similar rate of 9.1%. Treatment failure can lead to the development of ART resistance, increasing the risk of mortality due to drug resistance mutations (DRMs). [11] Antiretroviral therapy resistance is influenced by both viral and host factors. The HIV virus has a high mutation rate, while host-related factors include low drug susceptibility (regimen potency and toxicity), suboptimal drug selection (inappropriate regimen, incorrect dosage, low drug potency, poor absorption, and drug interactions), delays in drug delivery, and inadequate adherence monitoring. [12] Antiretroviral therapy resistance can negatively impact treatment response, increase mortality rates, and complicate disease management, requiring careful consideration to prevent further treatment failure.[13]

According to the WHO, ART resistance is defined by the presence of one or more mutations in the HIV genome that reduce the effectiveness of specific antiretroviral drugs in inhibiting viral replication.[11] A single mutation can confer resistance to certain ART drugs of the nucleoside reverse transcriptase inhibitor (NRTI) class, such as lamivudine, or of the non-nucleoside reverse transcriptase inhibitor (NNRTI) class. Zuo et al. [14] reported that the M184V mutation leads to lamivudine resistance, while the K103N mutation is the most frequently observed NNRTI-associated mutation at 54.5%. Zou et al. [15] found that the most common NRTI resistance mutation was M184V (62.04%), while NNRTI resistance was most frequently associated with K103N (41.90%). These mutations allow the virus to replicate despite ART, leading to increased HIV RNA levels and treatment failure.[15]

Previous studies have demonstrated that M184V and K103N mutations contribute to ART resistance, with a relatively high prevalence in certain countries, such as China.[15] The risk of developing drug resistance mutations (DRMs) depends on several factors, including the ART regimen used and its duration.[16] However, results from previous studies on ART resistance have shown variability, depending on the studied population, ART regimen, and adherence patterns. The heterogeneous nature of these studies makes summarizing and interpreting the evidence regarding acquired drug resistance (ADR) difficult. The present study aimed to analyze the risk factors contributing to the development of M184V and K103N mutations and identify the most dominant risk factor in a local Indonesian population.

METHODS

Research design

A cross-sectional study was conducted at the Voluntary and Counseling Testing (VCT) clinic of Dr. M. Djamil-Hospital Padang, from January to June 2022.

Research subjects

A total of 80 patients were included in the study. Patient were included if they were aged > 18 years and had been receiving NRTI and/or NNRTI therapy for more than 6 months. The exclusion criteria were patients with hepatitis B or hepatitis C co-infection, active pulmonary tuberculosis, autoimmune disease, or undergoing radiotherapy or chemotherapy. The selected sample was divided into two groups, namely patients with M184V and/or K103N mutations and those without mutations.

Data collection

Data collected included age, gender, BMI, ART regimen, opportunistic infections, viral load, CD4 count, treatment duration, ART adherence, and presence of M184V and/or K103N mutations. Blood specimens were obtained through venipuncture and processed for genetic analysis.

HIV genotyping and drug resistance mutations (M184V and K103N)

The HIV antiretroviral drug resistance mutations (DRMs) M184V and K103N were examined using a 5-mL venous blood sample from each subject. The examination was conducted by means of the RT-PCR technique, with first round primers consisting of forward primer 5'-TTTYAGRGARCTYAATAARAGAACTCA-3' and reverse primer (RT): 5'-CCTCITTYTTGCATAYTTYCCTGTT-3'. Second round primers comprised forward primer (RT): 5'-TTYTGGGARGTYCARYTAGGRATACC-3' and reverse primer (RT): 5'-GGYTCTTTGRTAAATTTGRATATGTCCA-3'. Data in the form of presence or absence of mutation of either one or both of these SNPs were tabulated and the respective percentages calculated.

Statistical analysis

The obtained data were processed using the IBM statistical package for the social sciences (SPSS) and analyzed using simple logistic regression test for bivariate analysis to assess the association between independent variables (age, gender, BMI, ART regimen, opportunistic infections, viral load, CD4 count, treatment duration, and ART adherence) and the presence of M184V and/or K103N mutations. Variables with p-value <0.25 were further analyzed using multivariate logistic regression to determine the most dominant risk factors. A p-value of < 0.05 was considered statistically significant.

Ethical clearance

This study was approved by the Health Research Ethics Committee of Dr. M. Djamil Hospital under No. LB.02.02/5.7/157/2022.

Table 1. Characteristics of study participants (n=80)

Characteristics	n	%
Age (years)		
<35	44	55.0
≥35	36	45.0
Gender		
Male	74	92.5
Female	6	7.5
Body mass index		
Underweight	32	40.0
Normal	37	46.3
Overweight	7	8.7
Obese	4	5.0
Separate drugs		
Yes	15	18.7
No	65	81.3
Comorbidity / opportunistic infection		
Yes	29	36.2
No	51	63.8
Viral load		
Detectable	35	43.8
Undetectable	45	56.2
CD4 (cells/mm^3)		
<200	25	31.3
>200	55	68.7
Treatment duration (months)		
<12	7	8.8
≥12	73	91.2
Therapy regimen		
AZT+3TC+EFV	7	8.7
AZT+3TC+NVP	6	7.5
EFV/FTC+TDF	46	57.5
TDF+3TC+EFV	17	21.3
TDF+3TC+NVP	4	5.0
M184V and/ or K103N mutation		
Present	8	10.0
Absent	72	90.0

Note: 3TC: lamivudine; AZT: zidovudine; EFV: efavirenz; FTC: emtricitabine; NVP: nevirapine.

Furthermore, 65 subjects (81.3%) did not receive separate ART drugs and 51 subjects (63.8%) did not have complications in the form of opportunistic infections, such as tuberculosis and toxoplasmosis. A total of 45 subjects (56.2%) showed no detectable viral load and 55 subjects (68.8%) had a CD4 count of >200 cells/mm^3. Most of the subjects, namely 73 people (91.3%), had received treatment for ≥12 months and 46 subjects (57.5%) consumed EFV+FTC+TDF. Only 8 subjects (10.0%) had M184V and/ or K103N mutations (Table 1).

Risk factors of M184V and/or K103N mutations

Simple logistic regression was conducted to assess the association between demographic characteristics, treatment history, and the presence of M184V and/or K103N mutations. The results indicated a statistically significant association for male gender (p = 0.048), detectable viral load (p<0.01), and poor ART adherence (p<0.01). In contrast, other variables, including age, BMI, opportunistic infections, CD4 count, and treatment duration, showed no significant association (>0.05) (Table 2).

Based on the simple logistic regression, variables with a p-value of < 0.25 included gender, ART adherence, and viral load, which were selected for multivariate logistic regression. All three variables were included in the initial model (Table 3). Gender (p=0.047) and poor ART adherence (p=0.004) remained significantly associated with the risk of developing the M184V and/or K103N mutations, whereas viral load was found to be non-significantly associated (p = 0.996) as shown in Table 3. The results indicate that male individuals have a 10.03 times higher risk of developing these mutations compared to females (OR = 10.03, 95% CI: 1.03-97.350). Additionally, poor ART adherence was significantly associated with a decreased risk of mutation compared to good adherence (OR = 0.73, 95% CI: 0.012-0.427)

Table 2. **Association of risk factors with M184V and/or K103N mutations**

Variable	M184V and/ or K103N mutation		OR (95 % CI)	p-value
	Mutation	No mutation		
Age				
<35 years	5	39		
≥35 years	3	33	1.410 (0.31-5.93)	0.653
Gender				
Male	6	68		
Female	2	4	1.17 (0.13-10.79)	0.048
BMI				
Underweight	2	30		
Normal	5	32		
Overweight	1	6		
Obese	0	4	--*	0.661
Poor ART adherence				
Yes	5	10		
No	3	62	10.33 (2.13-50.14)	<0.010
Opportunistic infections				
Yes	3	26		
No	5	46	1.062 (0.24-4.80)	0.938
Viral Load				
Detectable	8	27		
Undetectable	0	45	Undefined	<0.010
CD4 Count (cells/mm^3)				
<200	4	22		
≥200	4	50	2.27 (0.52-9.93)	0.265
Duration of ART (months)				
<12	0	7		
≥12	8	65	Undefined	0.365

*OR is undefined for some variables because at least one cell in the 2x2 table contains zero, making the calculation unreliable

Table 3. Multivariate logistic regression for M184V and/or K103N mutations

Variable	p value	OR	95% CI
Gender	0.047	10.03	1.033 - 97.35
ART Adherence	0.004	0.73	0.012 - 0.427
Viral Load	0.996	Undefined	----

DISCUSSION

This study analyzed 80 patients diagnosed with HIV who were undergoing therapy with reverse transcriptase inhibitors at the VCT Clinic of Dr. M. Djamil Hospital, Padang. Among the 80 studied samples, 8 patients (10%) were found to have M184V and/or K103N mutations, while 72 patients (90%) did not exhibit these mutations. These findings are consistent with the study by Miti et al.[17] in Zambia, which reported that M184V was the most frequently detected mutation associated with resistance to lamivudine and emtricitabine, occurring in 81% of cases. Additionally, the K103N mutation was the most frequently observed NNRTI mutation (65.5%), conferring resistance to efavirenz and nevirapine. In their study, the ART regimens used included NRTIs, NNRTIs, and protease inhibitors (PIs).

In our study, the analysis of risk factors associated with M184V and K103N mutations in HIV patients receiving reverse transcriptase inhibitor therapy revealed that male gender, poor ART adherence, and detectable viral load were significantly correlated with the presence of these mutations. This study found a significant association between poor ART adherence and the presence of M184V and/or K103N mutations. However, since an OR <1 (OR:0.73; 95% CI: 0.012–0.427) indicates a decreased risk of mutation, this finding contradicts established medical knowledge, which recognizes poor ART adherence as a well-documented risk factor for the emergence of DRMs. A potential explanation for this unexpected result is the relatively small number of patients with DRMs (8 out of 80, or 10%), which may have led to instability in the logistic regression model and affected the reliability of the estimates.

The correlation of poor ART adherence with M184V and K103N mutation is consistent with a study by Metzner et al.[18] which demonstrated that minority K103N HIV-1 variants, which are associated with resistance to NNRTI, were found to re-emerge after poor ART adherence, even when they had previously become undetectable during treatment. Adherence to ART is emphasized as crucial, as poor adherence is strongly associated with suboptimal viral suppression and an increased risk of developing drug-resistant HIV strains.[19] The causes of poor adherence in HIV treatment are highly diverse, including patient-related challenges such as age, health literacy, psychosocial and neurocognitive issues, and substance abuse, among other factors.[19] This aligns with an umbrella review by Seyed-Alinaghi et al.[20] which analyzed 40 review studies and concluded that one of the primary factors contributing to HIV drug resistance and virological failure is poor adherence to ART, in addition to decreased CD4 count, elevated viral load, and certain treatment regimens.

A study by Hutapea et al.[20] in Papua also demonstrated a significant association between viral load and the presence of M184V and K103N mutations. Their research found a strong correlation between HIV RNA levels and mutation occurrence, indicating that patients with an HIV RNA count of >1000 copies/mL were at a higher risk of developing mutations compared to those with lower HIV RNA levels (<1000 copies/mL).

A study by Barnabas et al.[22] reported that 52% of patients receiving ART in South Africa and Uganda were male. Additionally, a study by Derache et al.[23] involving 120 HIV patients found that 82% of the participants were male. A study by Metzner et al. [18] included 17 male subjects, of whom 6 had HIV-1 variants with K103N and/or M184V mutations before initiating ART. Similarly, a study by Luo et al.[24] involving 77 male participants found that 23 participants had the K103N mutation, but statistical analysis showed no significant association between gender and the presence of the K103N mutation. Another study by Zuo et al.[14] reported that 4.8% of male participants had HIV drug resistance, compared to 3.2% of female participants. However no statistically significant association was found between gender and the presence of drug resistance. In contrast, our study found a significant association between gender and the presence of M184V and/or K103N mutations, with male patients having a 10-fold increased risk of mutation. This difference in findings may be attributed to the unequal proportions of male and female participants in the present study, where male participants comprised 92.5% of the total sample.

The primary objective of ART is to suppress HIV viral replication. An undetectable viral load is defined as an HIV RNA count below 50 copies/mL (or 40–75 copies/mL, depending on the assay used).[11] Patients who adhere to ART consistently over time will maintain persistent low-level viremia (LLV), defined as a viral load between 50 and 1000 copies/mL for a prolonged period.[25]

The emergence of HIV mutations can lead to the development of drug-resistant viral strains, which may impact the effectiveness of ART. The presence of drug-resistant strains in individuals who have previously received ART or are ART-naïve can compromise the efficacy of ART regimens. When ART resistance occurs, the administered drugs fail to effectively control viral replication, leading to treatment failure. Therapeutic failure is suspected when there is no expected therapeutic response after at least six months of ART with high adherence.[7,11]

According to the World Health Organization, ART failure can be categorized into three types: clinical failure, immunological failure, and virological failure. **Clinical failure** is defined as the emergence of opportunistic infections classified as WHO stage 4 conditions after a minimum of six months of ART. Additionally, certain stage 3 conditions, such as pulmonary tuberculosis or severe bacterial infections, may also indicate clinical failure. **Immunological failure** occurs when ART is unable to achieve or maintain an adequate CD4 count despite viral suppression. It is characterized by a CD4 count of <250 cells/mm³ in the presence of clinical failure or a persistently low CD4 count of <100 cells/mm³. **Virological failure** is defined as a viral load exceeding 1000 copies/mL, confirmed by two consecutive measurements taken 3–6 months apart.[5, 26]

This study has several limitations. It did not consider other potential factors influencing mutation occurrence, such as genetic predisposition, disease stage, or HIV subtype. Additionally, the heterogeneity of the study sample and the occurrence of incomplete medical records may have affected the findings. Another limitation is the unequal proportions of male and female participants, as well as the small number of patients with DRMs (8 out of 80, or 10%), which may have influenced the observed association between gender and mutation occurrence. Future research should include a larger, more diverse population, and incorporate additional confounding variables to better understand the risk factors associated with HIV drug resistance mutations.

Moreover, this study highlights the critical role of ART adherence and routine viral load monitoring in preventing M184V and K103N mutations. Strengthening adherence strategies and implementing early interventions could help mitigate drug resistance and treatment failure. Notably, this study found a significant association of gender with M184V and K103N mutations, with male patients having a 10-fold increased risk of mutation. These results emphasize the need for targeted HIV treatment approaches, particularly for high-risk populations, to minimize the emergence of DRMs and improve long–term therapeutic outcomes. Further research should investigate additional risk factors, including genetic variations and viral subtypes, through larger multi-center studies. Additionally, identifying and addressing barriers to ART adherence could lead to more effective intervention strategies and enhance treatment success.

CONCLUSION

This study concludes that there are differences in risk factors between HIV patients with and without M184V and/or K103N mutations who received antiretroviral therapy. These mutations were significantly associated with poor ART adherence, detectable viral load, and male gender. Male gender had a higher risk of developing M184V and/or K103 mutations while poor ART adherence unexpectedly decreased the risk of mutation.

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Conflict of Interest

No relevant disclosure

Author Contributions

DE wrote the manuscript and designed the experiments; RN collected samples and clinical

information; SPR analyzed the data; DE and RM made manuscript revisions. All authors have read and approved the final manuscript.

Data Availability Statement

Requests for the original data presented in this study can be directed to the corresponding author.

Declaration the Use of AI in Scientific Writing

Nothing to declare

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