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# Impact of MDR-1 mutations on HIV viral load and gender-specific effects: Insights from Co-Infection with malaria parasites

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## ABSTRACT

**Objectives**: MDR-1 mutations in HIV patients cause a significant increase in viral load due to impaired function of the transporter protein responsible for eliminating drugs from cells. As a result, infected cells show reduced drug removal, leading to elevated viral replication and higher viral load levels in the bloodstream. This poses challenges in HIV treatment, potentially leading to treatment failure and the development of drug-resistant viral strains. Identifying MDR-1 mutations in HIV patients is crucial to optimise treatment approaches, potentially involving alternative medications or combination therapies to overcome drug resistance.

**Material and Methods:** The study utilised various laboratory techniques to analyse the collected blood samples, including HIV serology using rapid diagnostic kits, viral load estimation using the COBAS® Ampli Prep/COBAS® Taq Man® HIV-1 Test, microscopy for detecting malaria parasites and PCR for characterising Plasmodium species and studying resistance genes.

**Results**: There is a positive relationship with the viral load when comparing patients who tested negative for MDR-1 mutations to those who tested positive. The p-value for this relationship is stated as <0.001, which means it is less than 0.001. This indicates that the relationship is statistically significant ($p < 0.001$), and we can conclude that MDR-1 status has a significant impact on viral load. HIV patients with identified MDR-1 mutations have been shown to have a dramatic increase in their viral load than in the absence of the mutation.

**Conclusion**: In conclusion, this study sheds light on the impact of MDR-1 mutations on HIV viral load, gender-specific effects and their interactions with malaria co-infection. The findings emphasise the importance of personalised treatment strategies for HIV patients, considering genetic variations, gender-specific factors and co-infections to optimise management and improve health outcomes in regions with overlapping disease burdens.

**Keywords:** MDR-1, HIV, Mutations, Viral load, Plasmodium falciparum, Plasmodium vivax

## INTRODUCTION

Millions of people worldwide are affected by the Human Immunodeficiency Virus (HIV), which continues to pose a serious threat to global health.[1] Despite improvements in antiretroviral therapy (ART), medication resistance is on the rise, which can result in treatment failure and subpar therapeutic outcomes.[2] Multidrug Resistance-1 (MDR-1) mutations are one of the main mechanisms determining drug resistance in HIV patients.[3]

MDR-1, also known as P-glycoprotein or ATP-binding cassette sub-family B member 1 (ABCB1), is an essential transporter protein involved in the efflux of drugs and toxins from cells, including antiretroviral medications used to treat HIV.[4] When MDR-1 is mutated, its functionality may be

impaired, leading to reduced efficacy in removing HIV drugs from infected cells.[5] Consequently, this results in a reduction in drug concentrations within cells and an increase in viral replication, leading to elevated HIV viral load levels in the bloodstream.[6] MDR-1 mutations have been associated with treatment failure and the development of drug-resistant viral strains, posing significant challenges in the management of HIV infection.[7]

Interestingly, the impact of MDR-1 mutations on HIV viral load may not be uniform across all patient populations.[8] Several studies have reported gender-specific effects on disease progression and drug response in HIV patients with MDR-1 mutations.[9–10] Differences in hormonal regulation, immune responses, pharmacokinetics and adherence to medication between male and female patients could contribute to the observed disparities in viral load levels.[11]

Moreover, HIV is often associated with co-infections, and malaria, caused by Plasmodium vivax and Plasmodium falciparum, is among the most prevalent in regions where both diseases are endemic.[12] The interaction between HIV and malaria co-infection is complex, with potential implications for disease progression and treatment outcomes.[13] Malaria infections can influence HIV viral load through various mechanisms, including immune responses and inflammatory processes.[14]

Given the multifaceted nature of MDR-1 mutations, gender-specific effects and the potential impact of co-infection with malaria parasites on HIV viral load, there is a need for comprehensive research to better understand these relationships. This study aims to investigate the impact of MDR-1 mutations on HIV viral load and explore gender-specific effects in HIV patients. In addition, it will examine how co-infection with Plasmodium vivax and Plasmodium falciparum may modify the association between MDR-1 mutations and viral load levels.

Insights gained from this study may have significant clinical implications, guiding the development of personalised treatment strategies for HIV patients with MDR-1 mutations and co-infection with malaria parasites. Understanding the intricate interplay between genetic factors, gender-specific influences and co-infections is crucial for optimising HIV management and improving health outcomes, particularly in regions where both HIV and malaria are prevalent. Moreover, the findings may inform future research efforts aimed at mitigating drug resistance and enhancing the effectiveness of ART in HIV patients with diverse clinical backgrounds.

## MATERIAL AND METHODS

The study was conducted at the Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra state, South-East Nigeria, with five out-stations in Onitsha, Umunya, Ukpo, Awka, Neni and Oba. The hospital serves patients of high, middle and low socioeconomic status and is a principal referral centre in Anambra state and a major referral centre in South-East Nigeria.

The study design was a cross-sectional non-probability study aimed at analysing Plasmodium falciparum resistant genes to two anti-malaria drugs in HIV seropositive individuals co-infected with malaria parasites.

The study population consisted of 518 individuals, including 259 HIV-positive and 259 HIV-negative individuals, all of whom were 18 months and above. They were divided into three groups: Group A1 included HIV-positive patients on Highly Active Antiretroviral Treatment (HAART), Group A2 included HIV-positive patients not on HAART and Group B included HIV-negative individuals.

Ethical considerations were taken into account, and written consent was obtained from all participants. For minors, consent was obtained from their parents or guardians. A structured questionnaire was used to collect basic socio-demographic information from each participant.

The investigations performed on the collected blood specimens included:

(i) Assessment of malaria parasite using rapid diagnostic testing (RDT) for qualitative detection of malaria antigen Plasmodium falciparum.
(ii) Microscopy using the Giemsa-staining method.
(iii) Determination of the viral load for HIV sero-positive participants.
(iv) Characterisation of species of Plasmodium isolated using the polymerase chain reaction (PCR) technique.
(v) Subjection of Plasmodium falciparum to resistance studies using Pfmdr1 resistant genes-specific primers.

The minimum sample size for the study was calculated to be 260 individuals, and it included both HIV-positive and HIV-negative individuals aged 18 months and above. The study population was further categorised into different groups based on HIV status and treatment.

The study utilised various laboratory techniques to analyse the collected blood samples, including HIV serology using rapid diagnostic kits, viral load estimation using the COBAS® AmpliPrep/COBAS® TaqMan® HIV-1 Test, microscopy for detecting malaria parasites and PCR for characterising Plasmodium species and studying resistance genes.

## DATA ANALYSIS

The data collected from the socio-demographic and clinical characteristics of the participants was entered into Microsoft Excel version 2016 and analysed using R statistical package

## RESULTS

Table 1 summarises the results of a study that utilised linear regression to examine the association between the independent variables 'P. Falciparum', 'P. Vivax', and 'MDR-1' and the dependent variable 'viral load.' The statistical technique of linear regression[15] is used to characterise a dependent variable and one or more independent variables by fitting a linear equation to the observed data. The Beta values, which show how the dependent variable (viral load) changes when the relevant independent variable shifts by one unit while all other variables remain constant[16] serve as a representation of the regression coefficients. When comparing patients who tested negative for P. falciparum to those who tested positive, there is a negative relationship with viral load ($p < 0.3$). Therefore, the relationship is not statistically significant, and we cannot conclude that P. falciparum status has a significant impact on viral load. Also, there is a negative relationship with viral load when comparing patients who tested negative for P. vivax to those who tested positive ($p < 0.5$). Therefore, like P. falciparum, the relationship is not statistically significant, and we cannot conclude that P. vivax status has a significant impact on viral load. Furthermore, there is a positive relationship with viral load when comparing patients who tested negative for MDR-1 to those who tested positive ($p < 0.001$). This indicates that the relationship is statistically significant ($p < 0.001$), and we can conclude that MDR-1 status has a significant impact on viral load. The R-squared value ($R^2$) is a measure of the goodness of fit of the linear regression model.[17] It represents the proportion of the variance in the dependent variable (viral load) that is explained by the independent variables in the model. In this case, $R^2 = 0.701$, which means approximately 70.1% of the variance in viral load can be explained by the independent variables P. falciparum, P. vivax, and MDR-1 in the model. The remaining 29.9% may be attributed to other factors not included in this analysis.

**Table 1:** Linear regression report where the viral load is the dependent variable.

| Variable | Patient state | Beta | 95% CI | p-value |
|---|---|---|---|---|
| ***P. Falciparum*** | Negative | – | – | 0.3 |
| | Positive | −375 | −1,111, 360 | |
| ***P. Vivax*** | Negative | – | – | 0.5 |
| | Positive | −237 | −887, 413 | |
| **MDR-1** | Negative | – | – | <0.001 |
| | Positive | 2,647 | 1,899, 3,395 | |

$R^2 = 0.701$

HIV patients with identified MDR-1 mutations have been shown to have a dramatic increase in their viral load than in the absence of the mutation [Figure 1]. It was further revealed that the female gender diagnosed with HIV and also having MDR-1 mutations was found to have a higher viral load than the male gender.

Among patients with MDR-1 mutations, there was a notable increase in viral load even in the absence of Plasmodium

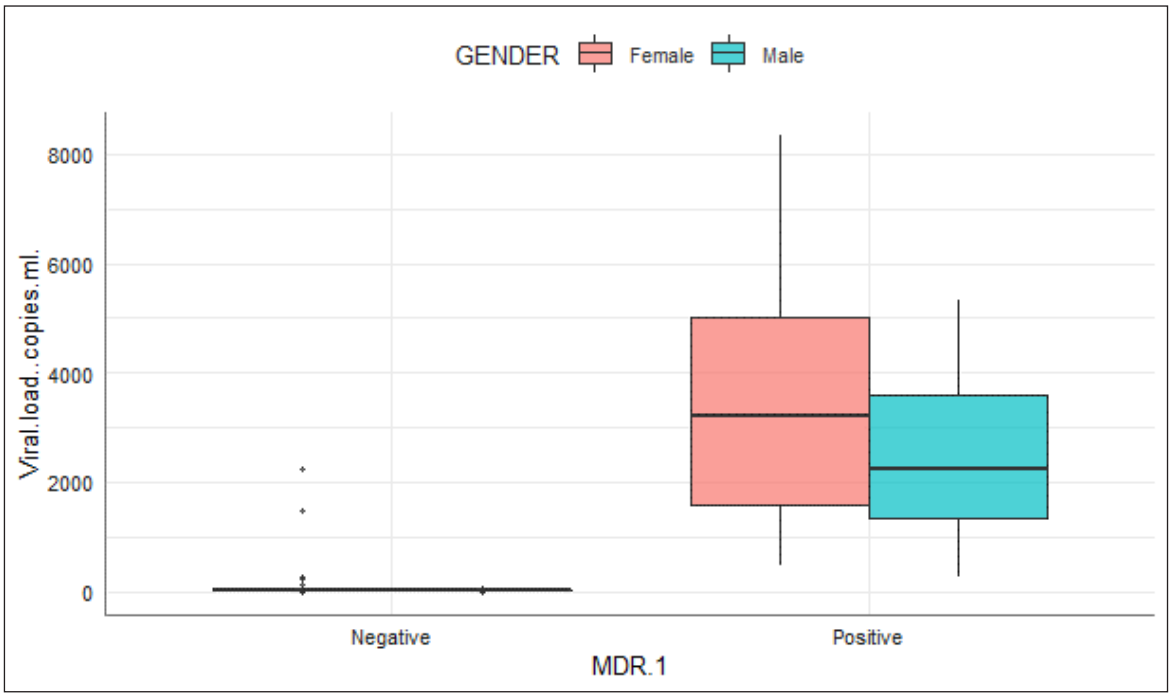


**Figure 1:** Viral load in the presence and absence of MDR-1 based on gender.

vivax infection [Figure 2]. This suggests that MDR-1 mutations alone are associated with elevated viral load levels, independent of the presence of Plasmodium vivax. The impaired function of MDR-1 in removing drugs from infected cells likely contributes to higher viral replication and, consequently, increased viral load in the bloodstream.[18]

When patients with MDR-1 mutations were co-infected with Plasmodium falciparum, there was a further rise in viral load levels [Figure 3]. This indicates that the co-occurrence of Plasmodium falciparum infection and MDR-1 mutations synergistically exacerbated viral replication, leading to an even higher viral load in the bloodstream.[19] The interaction

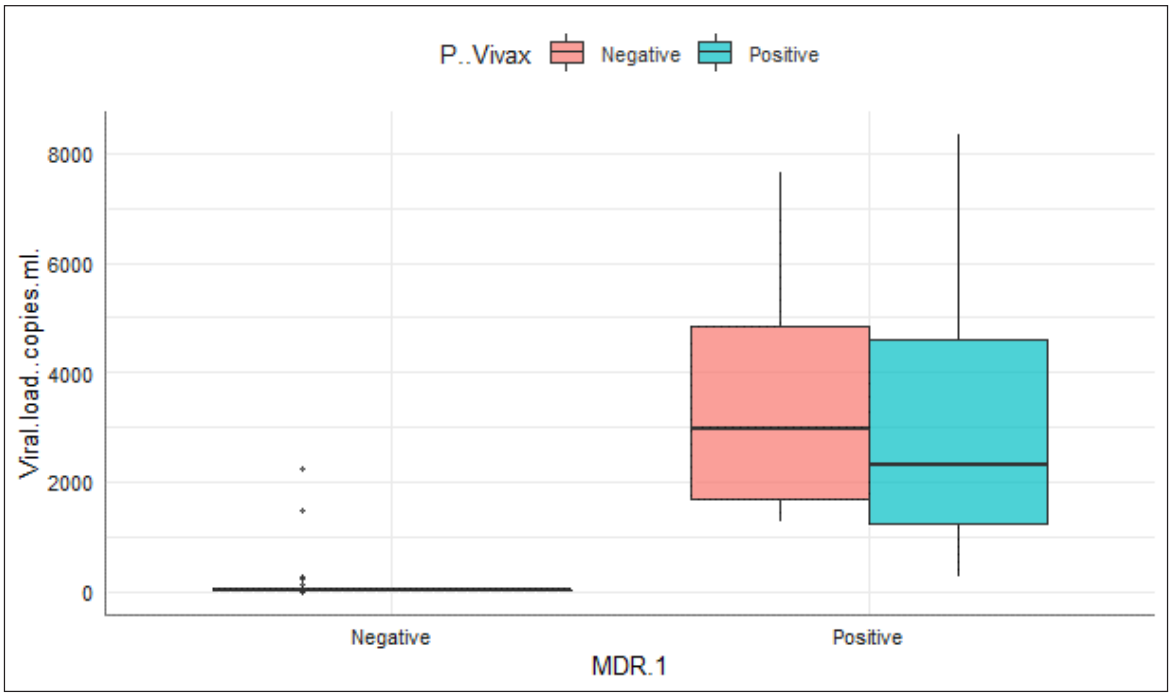


**Figure 2:** Viral load in the presence and absence of MDR-1 based on the presence of *P. vivax.*

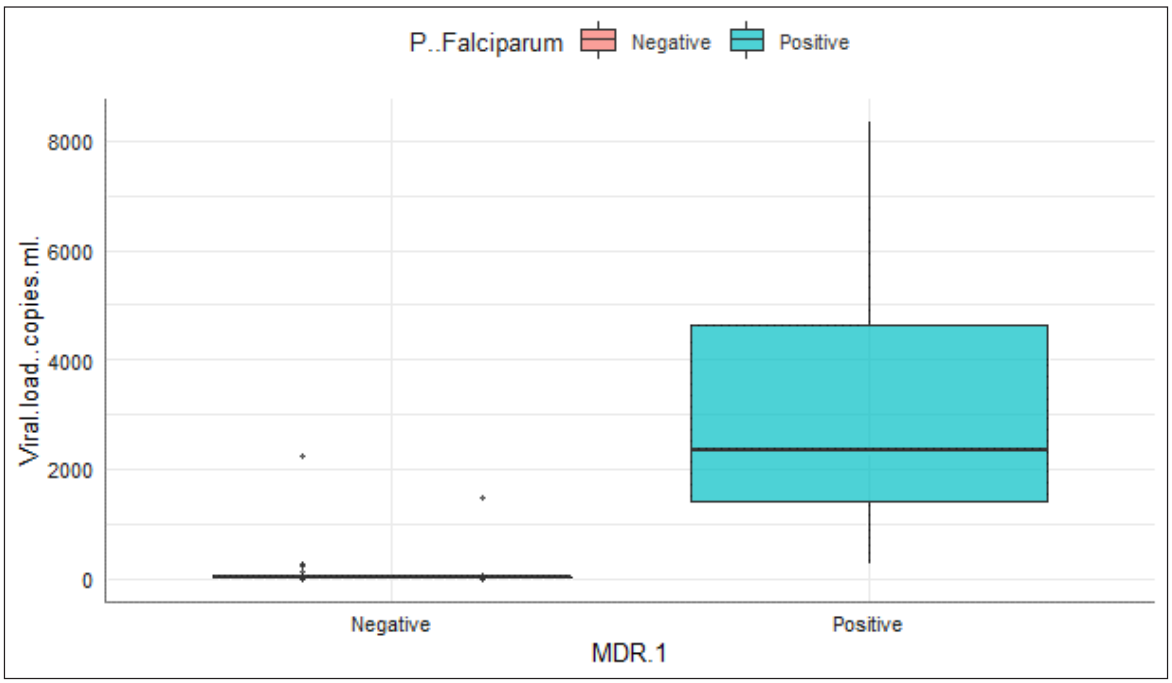


**Figure 3:** Viral load in the presence and absence of MDR-1 based on *P. falciparum* infection.

between MDR-1 mutations and Plasmodium falciparum infection likely plays a role in this observed effect, but the exact mechanisms require further investigation.

## DISCUSSION

The highly significant relationship between the MDR1 variable and viral load is of great importance. MDR1, as a transporter protein responsible for eliminating drugs, including antiretrovirals, from cells, appears to have a substantial impact on drug efficacy and viral suppression.[20] HIV patients with MDR1 mutations may experience treatment challenges due to reduced drug removal from infected cells, leading to increased viral replication and higher viral load levels.[21] This finding highlights the need to closely monitor MDR1 mutations in HIV patients and consider alternative treatment strategies or combination therapies to overcome drug resistance and improve treatment outcomes.

When compared to HIV patients without the mutations, MDR-1 mutations are significantly more likely to increase viral load. MDR-1, also known as P-glycoprotein or ABCB1, is a crucial transporter protein that expels a variety of toxins and pharmaceuticals from cells, including antiretroviral treatments used to treat HIV.[22] The ability of MDR-1 to remove HIV medicines from infected cells may be compromised by mutations that affect the protein's function.[23] The outcome is a rise in the levels of viral load in the bloodstream as the viral replication inside the cells is less inhibited.[24] Due to decreased therapeutic efficacy in HIV patients with MDR-1 mutations, treatment may fail, which may result in the emergence of viral strains that are resistant to drugs.[25] This poses significant challenges in managing HIV infection as it limits the available treatment options and can compromise the success of ART.[26] The identification of MDR-1 mutations in HIV patients is crucial for optimising treatment strategies, potentially involving alternative medications or combination therapies to overcome drug resistance.

The observed gender difference in viral load among HIV patients with MDR-1 mutations suggests a potential influence of gender-specific factors on disease progression and drug response. Various factors could contribute to this disparity, such as differences in hormonal regulation, immune responses, pharmacokinetics (how drugs are processed in the body), and adherence to medication.[27] In addition, social and behavioural factors, such as healthcare access, treatment compliance, and stigma, may also play a role in shaping outcomes.[28] Understanding the reasons behind the gender differences in viral load among HIV patients with MDR-1 mutations requires further investigation through well-designed studies and clinical trials. This information can be critical for tailoring treatment approaches and improving health outcomes in male and female HIV patients with MDR-1 mutations.

This study also considered the impact of MDR-1 mutations on viral load in patients infected with two different species of malaria parasites, Plasmodium vivax and Plasmodium falciparum. We observed that patients who tested positive for MDR-1 mutations showed an increased viral load. This suggests that MDR-1 mutations may have a direct or indirect influence on viral replication or the effectiveness of antiviral responses, leading to higher viral loads.

MDR-1 plays a critical role in the pharmacokinetics of many medications.[29] When MDR-1 is mutated, its function may be altered, affecting the distribution and clearance of drugs, including antiretroviral drugs used to treat HIV. This could result in reduced drug efficacy, leading to incomplete viral suppression and increased viral replication.[30] Plasmodium vivax and Plasmodium falciparum are two major species of malaria parasites that cause distinct types of malaria infections.[31] The co-infection of malaria and HIV is a complex scenario with potential interactions between the two diseases. The presence of malaria infection can impact HIV viral load due to factors such as immune responses and inflammatory processes.[32] Patients with MDR-1 mutations demonstrated increased viral load even in the absence of Plasmodium vivax infection. This suggests that MDR-1 mutations alone can contribute to elevated viral loads in the absence of the additional burden of Plasmodium vivax infection. Patients with MDR-1 mutations exhibited increased viral load when co-infected with Plasmodium falciparum. This suggests that the presence of Plasmodium falciparum infection, in combination with MDR-1 mutations, may further exacerbate viral replication, possibly due to interactions between the immune responses against both infections. It is important to note that the exact mechanisms underlying the observed relationships between MDR-1 mutations, HIV viral load, and Plasmodium infections require further investigation. Additional studies, including in vitro and in vivo experiments, are needed to elucidate the biological and immunological processes driving these observations.

## CONCLUSION

In conclusion, our work highlights the necessity of individualised treatment plans that take genetic variants, gender-specific characteristics, and co-infections into account and highlights the significance of MDR-1 mutations in determining viral load in HIV patients. In areas with overlapping disease burdens, these insights might help to improve patient outcomes and maximise HIV and malaria management. In order to expand our knowledge of the

intricate relationships between HIV, malaria, and genetic variables and to improve health outcomes generally, more research in this field is absolutely necessary.

### Ethical approval

Ethical approval was obtained from the Ethics and Research Committee of the Nnamdi Azikiwe University Teaching Hospital with a reference number of NAUTH/CS/66/VOL.12/199/2019/055.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

### Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

## REFERENCES

1. UNAIDS. Global HIV and AIDS statistics — 2021 fact sheet. 2021. Available from: https://www.unaids.org/en/resources/fact-sheet. [accessed 2023 August 12]
2. Hammer SM, Eron JJ. Re-emerging HIV epidemics. Lancet 2013;381:811–3.
3. Marcelin AG, Calvez V. Drug resistance in HIV. Curr Opin HIV AIDS 2010;5:1–9.
4. Gottesman MM, Ling V. The molecular basis of multidrug resistance in cancer: The early years of P-glycoprotein research. FEBS Lett 2006;580:998–1009.
5. Vanhove GF, Schapiro JM, Winters MA, Merigan TC, Blaschke TF. Patient-to-patient transmission of P-glycoprotein substrates/inhibitors between two individuals with multidrug-resistant human immunodeficiency virus infection. Clin Infect Dis 2001;33:710–2.
6. Schinkel AH, Jonker JW. Mammalian drug efflux transporters of the ATP binding cassette (ABC) family: An overview. Adv Drug Deliv Rev 2003;55:3–29.
7. Marcelin AG, Calvez V. Drug resistance in HIV. Curr Opin HIV AIDS 2010;5:1–9.
8. Huitema AD, van den Bergh J, Schellens JH. Drug insights: Influence of dosing schedule on drug-drug interactions with oral anticancer drugs. Nat Rev Clin Oncol 2010;7:473–84.
9. Moltó J, Valle M, Domingo P, Blanco A, Santos JR, Miranda C, *et al*. Estradiol and progesterone strongly inhibit the response to darunavir in PBMCs. AIDS Res Hum Retroviruses 2005;21:335–43.
10. Antinori A, Perno CF, Gianotti N, Forbici F, D'Arrigo R, Ippolito G, *et al*. Female sex and the use of anti-human immunodeficiency virus drugs: Lack of association with outcome in patients treated with protease inhibitors. Clin Infect Dis 2002;35:313–22.
11. French AL, Gawel SH, Hershow R, Benning L, Hessol NA, Levine AM, *et al*. Trends in mortality and causes of death among women with HIV in the United States: A 10-year study. J Acquir Immune Defic Syndr 2009;51:399–406.
12. Oladipo HJ, Tajudeen YA, Oladunjoye IO, Yusuff SI, Yusuf RO, Oluwaseyi EM, *et al*. Increasing challenges of malaria control in sub-Saharan Africa: Priorities for public health research and policymakers. Ann Med Surg (Lond) 2022;81. doi: 10.1016/j.amsu.2022.104366.
13. Chimombe T, Mudenda S, Bwalya S, N'gona T, Hikaambo CN, Mufwambi W, *et al*. Availability of Antimalarial Medicines in Community Pharmacies of Lusaka District, Zambia: Implications on Compliance to Malaria Treatment Guidelines. Pharmacol Pharm 2023;14:85–97.
14. Kamya MR, Gasasira AF, Yeka A, Bakyaita N, Nsobya SL, Francis D, *et al*. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: A population-based study. J Infect Dis 2006;193:9–15.
15. Hanpithakpong W, Kamanikom B, Dondorp AM, Singhasivanon P, White NJ, Day NP. A simplified strategy for antimalarial pharmacokinetic sampling. Antimicrob Agents Chemother 2008;52:4331–33.
16. Montgomery DC, Peck EA, Vining GG. Introduction to linear regression analysis. 5th ed. Wiley; 2012.
17. Field A, Miles J, Field Z. Discovering statistics using R. SAGE Publications; 2012.
18. Kutner MH, Nachtsheim CJ, Neter J, Li W. Applied linear statistical models. 5th ed. McGraw-Hill; 2004.
19. Lepist EI, Zhang X, Hao J, Huang J, Kosaka A, Birkus G, *et al*. Contribution of ABC (ATP-binding cassette) and solute carrier transporters to the pharmacokinetics of darunavir in HIV-infected and uninfected humans. J Clin Pharmacol 2012;52:633–42.
20. Zhang Z, Rosenbaum S. Role of P-glycoprotein in pharmacokinetics: Clinical implications. Springer Nature; 2019.
21. Marcelin AG, Calvez V. Drug resistance in HIV. Curr Opin HIV AIDS 2010;5:1–9.
22. Hogg RS, Bangsberg DR. Introduction: The state of the global HIV epidemic. Top HIV Med 2012;20:1–3.
23. Moltó J, Valle M, Domingo P, Blanco A, Santos JR, Miranda C, *et al*. Estradiol and progesterone strongly inhibit the response to darunavir in PBMCs. AIDS Res Hum Retroviruses 2005;21:335–43.
24. French AL, Gawel SH, Hershow R, Benning L, Hessol NA, Levine AM, *et al*. Trends in mortality and causes of death among women with HIV in the United States: A 10-year study. J Acquir Immune Defic Syndr 2009;51:399–406.
25. Polli JW, Wring SA, Humphreys JE, Huang L, Morgan JB, Webster LO, *et al*. Rational use of in vitro P-glycoprotein assays in drug discovery. J Pharmacol Exp Ther 2001;299:620–8.

26. Kute P, Kute V, Vanikar AV, Shah PR. Increased risk of tuberculosis in transplantation patients: A single center experience. Ren Fail 2011;33:53–8.
27. Hosseinpoor AR, Bergen N, Kirkby K, Schlotheuber A, Fuertes CV, Mac Feely S, *et al.* Monitoring inequalities is a key part of the efforts to end AIDS, tuberculosis, and malaria. Lancet 2022; 26;399:1208–10.
28. Naono A. "Going 'the Last Mile'to Eliminate Malaria" in Myanmar. Centaurus 2022;64:119–32.
29. Narain K, Rackimuthu S, Nawaz FA, Okonji OC, Ashworth H, Du Plessis SS, *et al*. Strategies for malaria vaccination during the COVID-19 pandemic in African countries. Bull World Health Organ 2022;100:582–582A.
30. Kamya MR, Gasasira AF, Yeka A, Bakyaita N, Nsobya SL, Francis D, *et al*. Effect of HIV-1 infection on antimalarial treatment outcomes in Uganda: A population-based study. J Infect Dis 2006;193:9–15.
31. Van Geertruyden JP. Interactions between malaria and human immunodeficiency virus anno 2014. Clin Microbiol Infect 2014;20:278–85.
32. Alemu A, Shiferaw Y, Addis Z, Mathewos B, Birhan W. Effect of malaria on HIV/AIDS transmission and progression. Parasit Vectors 2013;6:1–8.

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