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# Impacts of HIV-1 and HIV-2 on the occurrence of opportunistic infections among HIV patients using HIV-1 anti-retroviral therapy in Njombe and Dar es Salaam, Tanzania: a retrospective cross sectional study

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## Abstract

**Introduction:** HIV-1 and HIV-2 are globally known human immunodeficiency virus (HIV) types with 55% genetic difference. Partly dominated HIV-2 type is shown to spread to other countries due to immigration and socio-economic interactions. This study aimed to determine sero-prevalence of HIV-1, HIV-2, and HIV-1/2 dual infection, and their impacts on the occurrence of opportunistic infections (OIs) among HIV-positive patients on antiretroviral therapy (ART) in Njombe and Dar es Salaam, Tanzania.

**Material and methods:** A retrospective cross-sectional study was conducted at eight health facilities. A total of 300 participants were recruited. Patients' history of OIs were obtained from patients' files and interviews. SPSS version 26.0 were used for analysis. Ethical clearance was sought from KNCHRE. All participants provided signed informed consent.

**Results:** The mean age of participants was 35 (SD ± 0.24) years. The general prevalence of HIV-1 was 69%, HIV-2 was 15%, and HIV 1/2 dual infection was 16%. Tuberculosis, *Pneumocystis* pneumonia, and esophageal candidiasis were common OIs in HIV-1/2 dual infection type ($p < 0.001$, $p = 0.02$, $p = 0.02$, respectively). HIV-2 and HIV-1/2 had two times higher risks of OIs (RR: 1.69, 95% CI: 1.39-2.07%, $p < 0.001$; and RR: 1.78, 95% CI: 1.51-2.10%, $p < 0.001$, respectively).

**Conclusions:** The study confirmed the presence of HIV-2 and HIV-1/2 dual infection in Tanzania. Additionally, it showed high-risk of OIs occurrence among HIV-2 and HIV-1/2 people living with HIV (PLHIV). Therefore, the initiation of HIV-2 ART regimen in Tanzania should be established to reduce poor treatment outcomes among HIV-2 and HIV-1/2 PLHIV.

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**Key words:** HIV-1, HIV-2, HIV-1/2 dual infection, opportunistic infections, anti-retrovirus.

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## Introduction

Human immunodeficiency virus (HIV) is a major public health concern, which causes high morbidity and mortality worldwide. Globally, it is estimated that 4 million individuals are living with HIV, of whom two-thirds are sub-Saharan African countries inhabitants [1]. Tanzania, with a 4.7% prevalence of HIV among adults aged between 15 and 49 years, is estimated to have 1.7 million people living with HIV (PLHIV) [2]. Despite the existence of various types of HIV and their strains, HIV-1 and HIV-2 are the most common types of HIV globally [3, 4]. HIV-1 is widely spread compared with HIV-2 type [5-7]. However, studies have shown the spread of HIV-2 in various parts of the world, including countries in Europe, Asia, the United States of America, and Western Africa [8]. Because of migrations, inter-marriage, and other social and economic factors, the HIV-2 type may continue to spread to other countries [8]. The Joint United Nations Programme of AIDS (UNAIDS) in 2017 reported that, among the 40 million people affected by HIV, 2 million are infected with HIV-2 type and HIV-1/2 dual infection [9-11].

Historically in Tanzania, a country in the eastern part of Africa, the prevalence of HIV-1 type is known to be higher than in other African countries [3, 4]. While the prevalence of HIV-2 infection is not clearly documented among PLHIV. As a part of the current study, a pre-survey was conducted on HIV voluntary counseling and testing (VCT) in Arusha, Dar es Salaam, and Kilimanjaro health facilities. The findings of this mini-study showed the occurrence of 5 to 10 new cases of HIV-2 and HIV-1/2 dual infection annually [12]. To reduce treatment failure, drug resistance, and other poor treatment outcomes, World Health Organization (WHO) recommends a proper antiretroviral therapy (ART) regimen for each type of HIV, i.e., HIV-1 and HIV-2. Despite WHO recommendations, ART regimen utilized in Tanzania does not differentiate between HIV types [16].

HIV-associated opportunistic infections encompass numerous life-threatening diseases in patients with advanced stage of HIV, who are generally not on ART. These infections typically affect patients with low CD4+ counts and higher viral load [17]. Studies have demonstrated that HIV-infected individuals with CD4+ cell counts less than 200 cells per millimeter have a higher risk of developing opportunistic infections (OIs), and the number of subsequent deaths remains the highest [17]. These individuals are prone to a wide variety of bacterial, viral, fungal, and protozoal infections, including tuberculosis, *Toxoplasma gondii*, *Pneumocystis, jirovecii* (previously *Pneumocystis carinii*), *Cryptococcus neoformans*, *Mycobacterium avium*, *Mycobacterium tuberculosis*, *Cytomegalovirus*, and herpes simplex viruses [18, 19].

Moreover, studies have shown that 30% of PLHIV deaths were due to the existence of OIs, such as tuberculosis, Kaposi's sarcoma oral candidiasis, herpes zoster, cryptococcal meningitis, cerebral toxoplasmosis, and cytomegalovirus retinitis [20-22]. Research from HIV-2 endemic areas reported HIV-2 and HIV-1/2 dual infection to be among the leading factors contributing to high-rate of OIs incidence due to quick immunosuppression, which decreases CD4+ count [20, 23]. Tanzania is among the countries with the highest prevalence of OIs among PLHIV [2]. Despite the reported good adherence to ART among PLHIV, there are frequent incidences of OIs, such as tuberculosis, oral candidiasis, herpes zoster, and cryptococcal meningitis [2]. Whether OIs incidences among PLHIV in Tanzania are associated with HIV-2 type is not known. The present study aimed to determine the impacts of HIV-1 and HIV-2 types on the occurrence of opportunistic infections among HIV-positive patients using HIV-1 ART treatment in Njombe and Dar es Salaam, Tanzania.

## Material and methods

### Study area

A retrospective cross-sectional study was conducted from January to December 2021 in eight HIV Care and Treatment Centers (HCTC) in the Njombe region (southern highlands of Tanzania) and Dar es Salaam region (eastern part along the Indian Ocean Cost Belt), Tanzania. The Dar es Salaam region with 7,405,000 inhabitants [22] has HIV prevalence of 9% [24]. The region was selected because it is among the east African cities that attract local and international migrants coming to settle in, for business, or other economic activities [25]; hence, increasing the probability of HIV-2 spreading. Similarly, the Njombe region in the southern highlands of Tanzania has an estimated population of 889,946 [25]. The region was selected because of the highest HIV prevalence of 14.8%, which is mostly due to business activities carried out with nearby countries. The city of Njombe is a stop center for heavy truck drivers, who use the southern highway road from Dar es Salaam to other southern African countries. Therefore, the probability of HIV-2 infection spreading might be high.

### Study design and population

The study employed a descriptive quantitative cross-sectional study design. Initially, medical files of patients, who started ART treatment from 2017 to 2019 were used to select participants. PLHIV with at least 4 immunological laboratory test results (CD4+ count and viral load) were recruited. Also, the study excluded all PLHIV with age below 18 years and those referred from other healthcare HCTCs. Patients, who consented to participate, were required to sign informed consent form after a brief explanation of the study purpose. Confidentiality of participants' information was highly maintained by using identification numbers during interviews and extractions of data from patients' files.

### Sample size and sampling technique

A total sample of 300 PLHIV were enrolled in the study, with 150 participants from each region. A multi-stage sampling technique was used, while purposive sampling was

employed for the selection of districts. Simple random sampling was applied for the selection of eight health facilities and study participants.

### Data collection

An interview was performed by administering a set of questionnaires to obtain information on socio-demographic characteristics (age, marital status, level of education, employment, occupation) and history of OIs incidence. Patient register files were used to examine the history of emerging OIs from ART initiation till date. Opportunistic infections investigated included tuberculosis (TB), herpes zoster, cryptococcal meningitis, toxoplasmosis, *Pneumocystis* pneumonia (PCP), esophageal candidiasis, Kaposi's sarcoma, and skin infections. All extracted data on OIs from patients' files were filled out in a questionnaire. To obtain HIV-1 and HIV-2 sero-prevalence, a 20 µl of whole blood sample was drawn from patients, and retained in an EDT tube for determination of HIV types, current levels of CD4+ count, and viral load. A 1.5 µl of blood samples were pipetted and placed into SD Bioline (Alere Medical Company) as an initial HIV rapid test; the results were confirmed by Determine TM (Trinity Plc., Ireland) HIV rapid test for HIV types identification.

### Data analysis and interpretation

SPSS version 26.0 was used to enter, clean, and analyze the gathered data. Categorical variables were reported as counts and percentages, and $\chi^2$ was applied to compare these categorical variables. Logistic regression models were used to determine the association between the occurrence of OIs and CD4+ count, viral load, and social demographic measures. Odds ratios (OR), 95% confidence intervals (CIs), and *p*-values were utilized for testing the significance of variables. All tests with a $p$-value ≤ 0.001 were deemed statistically significant.

### Ethical considerations

The study sought ethical clearance from KNCHREC, and the permission to conduct the study was obtained from the Regional Medical Officers (RMO) of the Dar es Salaam and Njombe regions. Signed informed consent was acquired from all participants. In order to maintain confidentiality, a unique identification number was assigned to each participant's questionnaire.

## Results

### Social demographics of the participants

The study enrolled 300 PLHIV, of whom 140 (46.7%) were males and 160 (53.3%) were females. Among the recruited HIV-positive individuals, 207 had HIV-1 and 44 had HIV-2 types, and 49 had HIV-1/2 dual infections. The mean age of patients was 35 years (range, 15-90 years), with standard deviation of ±0.24. Eighty-three patients (40.1%) aged 41-55 years had HIV-1 type, while 16 (36.4%) aged 26-40 years had HIV-2 type. HIV-1/2 dual infection was detected in 19 (38.5%) participants aged 26-40 years. According to HIV types, female participants were more dominant in both HIV-1 and HIV-2 (110 cases, 53.6%), and HIV-1/2 dual infection was discovered in 25 females (50.6%). Regarding education level, HIV-1 (117, 56.5%), HIV-2 (20, 45.5%), and HIV-1/2 dual infection (26, 53.1%) patients had primary education. Also, the results showed that 68 (32.9%) of HIV-1 PLHIV were married, and 18 (40.9%) and 19 (38.5%) of HIV-2 and HIV-1/2 dual infection were single, respectively. Moreover, regarding economic status, HIV-1 (116, 56.0%), HIV-2 (25, 55.5%), and HIV-1/2 dual infection (168, 55.1%) participants had an income of < 10,000 Tzsh per month. With respect to occupation, 48 HIV-1 cases (23.2%) were not employed, 7 HIV-2 (15.9%) were employed, and 170 HIV-1/2 dual infection patients (56.7%) were self-employed. Table 1 summarizes the demographic results in association with the prevalence of HIV types.

### Trends of the occurrence of opportunistic infections among the participants by HIV types

The most frequent OI was tuberculosis (85 pts, 28.3%), followed by skin infections (69 pts, 23%), herpes zoster (47 pts, 15.7%), PCP (32 pts, 10.7%), and esophageal candidiasis (19 pts, 6.3%). When comparing opportunistic infections among HIV-1, HIV-2, and HIV-1/2 dual infection, tuberculosis, PCP, and esophageal candidiasis were most common among patients with HIV-1/2 ($p < 0.001$, $p = 0.02$, and $p = 0.02$, respectively). Skin infections, herpes zoster, and toxoplasmosis were frequently observed in HIV-2 patients ($p = 0.66$, $p = 0.02$, and $p = 0.32$, respectively). Figure 1 shows the trends in the occurrence of opportunistic infections among HIV-1, HIV-2, and HIV-1/2 dual infection patients.

### Effects of HIV types on the occurrence of opportunistic infections among PLHIVs with HIV-1, HIV-2, and HIV-1/2 dual infection

Among the 300 PLHIVs included in the study, 174 (58%) reported having at least one opportunistic infection during ART treatment. Interestingly, the relative risk of OI occurrence was two times higher in PLHIV with HIV-2 and HIV-1/2 compared with PLHIV with HIV-1 (RR: 1.69; 95% CI: 1.39–2.07%; $p < 0.001$), (RR: 1.78, 95% CI: 1.51-2.10%, $p < 0.001$). Comparing HIV-2 and HIV-1/2, high relative risks of 78% (RR: 1.78; 95% CI: 1.51-2.10%) were seen in HIV-1/2 dual infection PLHIV compared with relative risks of 69% (RR: 1.69; 95% CI: 1.39-22.07%) in HIV-2 PLHIV. Table 2 displays the effects of HIV types on

**Table 1.** Demographic characteristics of participants

| Variable | HIV-1 | HIV-2 | HIV-1/2 | Total |
|---|---|---|---|---|
| Age (years), *n* (%) | | | | |
| 11-25 | 43 (20.8) | 12 (27.3) | 10 (20.4) | 65 (21.7) |
| 26-40 | 62 (30.0) | 16 (36.4) | 19 (38.8) | 97 (32.3) |
| 41-55 | 83 (40.1) | 14 (31.8) | 17 (34.7) | 114 (38.0) |
| > 55 | 19 (9.2) | 2 (4.6) | 3 (6.1) | 24 (8.0) |
| Sex, *n* (%) | | | | |
| Male | 97 (46.9) | 19 (43.2) | 24 (49.0) | 140 (46.7) |
| Female | 110 (53.1) | 25 (56.8) | 25 (51.0) | 160 (53.3) |
| Education level, *n* (%) | | | | |
| None | 19 (9.2) | 2 (4.6) | 6 (12.2) | 27 (9.0) |
| Primary | 117 (56.5) | 20 (45.5) | 26 (53.1) | 163 (54.3) |
| Secondary | 61 (29.5) | 19 (43.2) | 15 (30.6) | 95 (31.7) |
| College | 10 (4.8) | 3 (6.8) | 2 (4.1) | 15 (5.0) |
| Marital status, *n* (%) | | | | |
| Single | 61 (29.5) | 18 (40.9) | 19 (38.8) | 98 (32.7) |
| Married | 68 (32.9) | 8 (18.2) | 16 (32.7) | 92 (30.7) |
| Widow | 29 (14.0) | 7 (15.9) | 6 (12.2) | 42 (14.0) |
| Co-habited | 5 (2.4) | 1 (2.3) | 0 (0) | 6 (2.0) |
| Divorced | 44 (21.3) | 10 (22.7) | 8 (16.3) | 62 (20.7) |
| Income (in Tzsh), *n* (%) | | | | |
| < 10,000 | 116 (56.0) | 25 (56.8) | 27 (55.1) | 168 (56.0) |
| 10,000-100,000 | 49 (23.7) | 10 (22.7) | 13 (26.5) | 72 (24.0) |
| 100,000-500,000 | 34 (16.4) | 9 (20.5) | 7 (14.3) | 50 (16.7) |
| > 500,000 | 8 (3.9) | 0 (0) | 2 (4.1) | 10 (3.3) |
| Occupation, *n* (%) | | | | |
| Employed | 36 (17.4) | 7 (15.9) | 9 (18.4) | 52 (17.3) |
| Self-employed | 123 (59.4) | 21 (47.7) | 26 (53.1) | 170 (56.7) |
| Unemployed | 48 (23.2) | 16 (36.4) | 14 (28.6) | 78 (26.0) |

**Table 2.** Performance of models

| HIV type | Number of individuals | Number of OIs | Crude RR (95% CI) | *p*-value | Adjusted (95% CI) | RR[a] *p*-value |
|---|---|---|---|---|---|---|
| HIV-1 | 207 | 104 (50.2) | Ref. | | | |
| HIV-2 | 44 | 32 (72.7) | 1.45 (1.15-1.81%) | 0.001 | 1.69 (1.39-2.07%) | < 0.001 |
| HIV-1+2 | 49 | 38 (77.6) | 1.54 (1.26-1.89%) | < 0.001 | 1.78 (1.51-2.10%) | < 0.001 |

*CI – confidence interval, RR – relative risk, OIs – opportunistic infections*
*[a]Adjusted for age, sex, education level, occupation, baseline CD4+ count, weight, viral load.*

the occurrence of opportunistic infections among HIV-1, HIV-2, and HIV-1/2 dual infection PLHIV.

## Discussion

The current findings demonstrate impacts of HIV-1, HIV-2, and HIV-1/2 dual infection on the occurrence of OIs among PLHIV on ART in Njombe and Dar es salaam regions. The risks of developing OIs differ from one type to another. With reference to PLHIVs with HIV-1, the high risks of the occurrence of the OIs occurred with PLHIVs with HIV-2 and HIV-1/2 dual infection. When HIV-2 and HIV-1/2 dual infection patients were adjusted with age, sex, education, CD4+ count, and viral load, the highest risks were

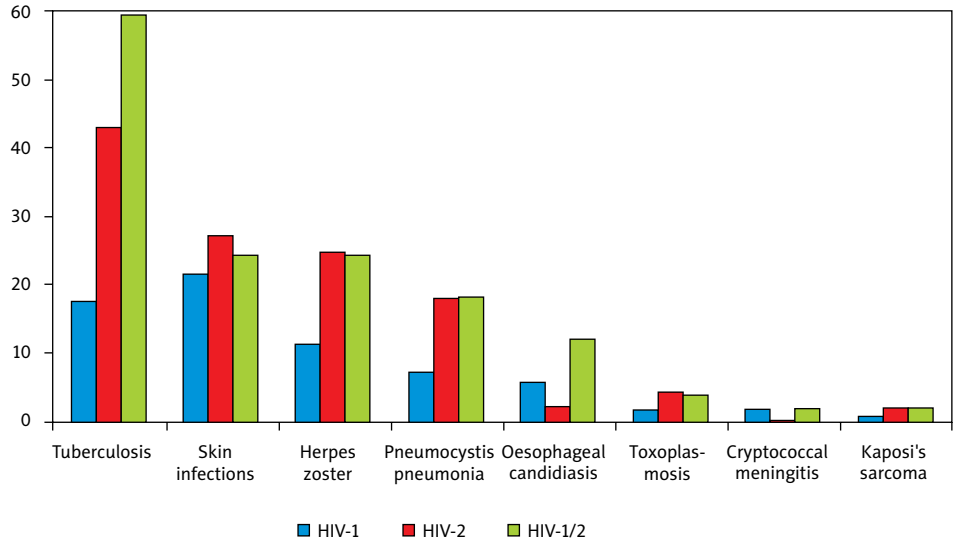


**Figure 1.** Trend of occurrence of opportunistic infections among HIV-1, HIV-2, and HIV-1/2 dual infection patients

observed for HIV-1/2 dual infection individuals, possibly due to a lower CD4+ count and a higher viral load. The results are consistent with a study conducted by Esbjörnsson *et al.* [9] in Gabon, which showed smaller risks of OI occurrence among PLHIV with HIV-2, who were using HIV-2 ART regimen [9]. Another cohort study conducted by Harries *et al.* [26] in Burkina Faso demonstrated a reduced risk of OIs occurrence in PLHIV if they adhered to HIV-2 ART regimen. Similar studies indicated good clinical impacts of 76% reduction of OIs when protease inhibitors (PI) were combined with HIV-1 ART regimen for treatment of either HIV-1, HIV-2, or HIV-1/2 dual infection [22, 23]. Therefore, from the current and previous studies, the implementation of ART regimen for HIV-2 and HIV-1/2 dual infection patients should be emphasized.

Regardless of the adherence to ART treatment, a study shows that at least one of OIs occurred in an HIV patients during their course of treatment. Moreover, the study observed a frequent occurrence of OIs in HIV-infected patients with HIV-2 and HIV-1/2 dual infection compared with those with HIV-1, due to low CD4+ count and high viral load. Furthermore, the study revealed that tuberculosis was the leading and most frequently occurring OI in patients with HIV-2 and HIV-1/2 dual infection as compared with those with HIV-1. This result is consistent with previous studies conducted by Prince *et al.* [28] in Senegal, who demonstrated a decrease in the prevalence of OIs among HIV-2 and HIV-1/2 dual infection patients, due to the use and adherence to HIV-2 ART regimen. Additionally, this study is in line with a clinical trial conducted by Smith [27] in San Francisco, USA, who aimed to understand the efficacy of NNRT HIV-2 ART regimen towards optimal ART for HIV-2 infection. The results reported a reduction of OIs, especially tuberculosis, by 64% in HIV-2 patients.

Research results indicate low effectiveness of HIV-1 ART treatment regimen for HIV-2 and HIV-1/2 dual infection patients, due to low CD4+ counts and high viral load. Hence, the initiation of HIV-2 regimen should be implemented to reduce OIs in HIV patients. Sex, age, marital status, and education in this study showed associations with the occurrence of OIs among HIV-infected patients with HIV-1, HIV-2, and HIV-1/2 dual infection. Young HIV patients were more infected with HIV-2 type and HIV-1/2 dual infection due to their higher risk of HIV infection, such as multiple sex partners and unprotected sex. Moreover, HIV patients with primary education, married, and self-employed were more likely to have HIV-2 and HIV-1/2 dual infection; thus, their risks for OIs emerging also increased due to dropping CD4+ counts and viral loads caused by HIV-2 and HIV-1/2 dual infection. The results of our study are similar to the study conducted by Prince *et al.* [28], which demonstrated that female and married participants with either HIV-2 or HIV-1/2 dual infection, were more likely to have OIs. The increased risk of emerging OIs explain the delay in health seeking, which causes a rapid reduction of CD4+ count and an increase in viral load, possibly due to the existence of HIV-2 and HIV-1/2 dual infection in PLHIV.

Despite the evidence of the existence of HIV-2 and HIV-1/2 dual infection in Tanzania, the national guideline for HIV/AIDS treatment does not recommend the use of HIV-2 and HIV-1/2 dual infection regimens. Regardless of HIV type, the patients can use only HIV-1 ART regimen. Therefore, PLHIV with either HIV-2 or HIV-1/2 infections maintain a high-risk of OIs occurrence. In order to reduce this risk, HIV-2 ART regimen should be implemented for HIV-2 and HIV-1/2 dual infection patients.

## Conclusions

The current study determined the impacts of HIV-2 and HIV-1/2 dual infection on the occurrence of opportunistic infections. In summary, the study documented HIV type

associated with a high-risk of OIs occurrence, while HIV patients with HIV-2 and HIV-1/2 have a higher risk of OIs occurrence compared with HIV-1 PLHIV. Percentage wise, the risk of the occurrence of OIs in HIV-2 individuals is 72.7%, HIV-1/2 dual infection is 77.6%, and HIV-1 is 50.2% only. Both HIV-2 and HIV-1/2 patients have a 2-fold higher risk of obtaining OIs compared with HIV-1 PLHIV. Low CD4+ count and high viral load are the factors contributing to the increased risk of OIs occurrence. Therefore, proper management of HIV-2 and HIV-1/2 dual infection in Tanzania should be highlighted and included in treatment guidelines to reduce the occurrence of OIs in HIV-infected patients.

## Disclosures

1. Institutional review board statement: The ethical clearance number KNCHREC 0010 was sought from Kibong'oto Infectious Diseases Hospital, Nelson Mandela African Institution of Sciences and Technology and Center for Education Development in Health Research Committee (KNCREC).
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4. Conflicts of interest: None.

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