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**Short Communication** **Open Access**

# Evidence of virological failure in patients on second-line anti-retroviral therapy in Southwestern Nigeria: an indication for HIV drug resistance testing

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## Abstract:

**Background**: In sub-Saharan Africa where genotypic anti-retroviral (ARV) drug resistance testing is rarely performed and poor adherence is blamed for the inability to achieve viral suppression and treatment failure, programmatic approaches to preventing and handling these are essential. This study was aimed at assessing the virological outcomes among HIV patients receiving second-line anti-retroviral therapy (ART) in Southwestern Nigeria.
**Methodology**: This was a 5-year observational retrospective study of randomly selected people living with HIV (PLWHIV) who have been switched to second-line ART for at least six months before the commencement of the study in multiple comprehensive ART sites across the three levels of care, in Ondo and Ekiti States, Southwestern Nigeria, from January 2015 to December 2019. Quantitative viral load analysis was done using polymerase chain reaction (PCR) assay. Data were analyzed using the Statistical Package for Social Sciences (SPSS) version 24.0.
**Results**: A total of 249 (71 males and 178 females) subjects eligible for the study were recruited using simple random sampling technique. The mean age (± SD) of the subjects was 44.21 ± 11.45 years. The mean number of years the patients have been on ART regimen was 7.92 ± 2.68 years. The mean number of years the patients were on first line ART regimen before being switched to second line was 4.27 ± 2.63 years. Patients with viral load <1000 RNA copies/ml (suppressed viral load) were 216 (86.7%) out of which 113 (45.4%) had viral load <20 RNA copies/ml while 33 (13.3%) had viral load >1000 RNA copies/ml (unsuppressed viral load or virological failure).
**Conclusion**: About 13% of the patients on second line ART had unsuppressed viral load of more than 1000 RNA copies/ml indicating virological failure. Thus, critical factors such as poor adherence to ART and drug resistance chiefly contributing to virological failure have to be routinely checked.

**Keywords:** suppression, ART, resistance, virological, failure, Nigeria

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# Preuve d'échec virologique chez les patients sous traitement antirétroviral de deuxième intention dans le sud-ouest du Nigeria: une indication pour le test de résistance aux médicaments contre le VIH

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## Abstrait:

**Contexte:** En Afrique subsaharienne, où les tests génotypiques de résistance aux antirétroviraux (ARV) sont rarement effectués et où une mauvaise observance est imputée à l'incapacité d'obtenir la suppression virale et l'échec du traitement, des approches programmatiques pour les prévenir et les gérer sont essentielles. Cette étude visait à évaluer les résultats virologiques chez les patients VIH recevant un traitement antirétroviral (TAR) de deuxième intention dans le sud-ouest du Nigeria.
**Méthodologie:** Il s'agissait d'une étude rétrospective d'observation de 5 ans portant sur des personnes vivant

avec le VIH (PVVIH) sélectionnées au hasard et passées à un TAR de deuxième intention pendant au moins six mois avant le début de l'étude dans plusieurs sites de TAR complets aux trois niveaux. de soins, dans les États d'Ondo et d'Ekiti, dans le sud-ouest du Nigéria, de janvier 2015 à décembre 2019. L'analyse quantitative de la charge virale a été effectuée à l'aide d'un test de réaction en chaîne par polymérase (PCR). Les données ont été analysées à l'aide du logiciel Paquet statistique pour les sciences sociales (SPSS) version 24.0.
**Résultats:** Un total de 249 (71 hommes et 178 femmes) sujets éligibles à l'étude ont été recrutés à l'aide d'une technique d'échantillonnage aléatoire simple. L'âge moyen (± ET) des sujets était de 44,21±11,45 ans. Le nombre moyen d'années pendant lesquelles les patients ont été sous traitement antirétroviral était de 7,92±2,68 ans. Le nombre moyen d'années pendant lesquelles les patients étaient sous traitement antirétroviral de première ligne avant de passer en deuxième ligne était de 4,27 ± 2,63 ans. Les patients avec une charge virale <1000 copies d'ARN/ml (charge virale supprimée) étaient 216 (86,7%) dont 113 (45,4%) avaient une charge virale <20 copies d'ARN/ml tandis que 33 (13,3%) avaient une charge virale >1000 ARN copies/ml (charge virale non supprimée ou échec virologique).
**Conclusion:** Environ 13 % des patients sous TAR de deuxième ligne avaient une charge virale non supprimée de plus de 1000 copies d'ARN/ml indiquant un échec virologique. Ainsi, les facteurs critiques tels qu'une mauvaise adhésion au TARV et la résistance aux médicaments contribuant principalement à l'échec virologique doivent être systématiquement vérifiés.

**Mots clés:** suppression, TAR, résistance, virologique, échec, Nigeria

## Introduction:

In many countries of the sub-Saharan Africa, hundreds of thousands of people living with HIV (PLHIV) have initiated antiretroviral therapy (ART), which has led to a reduction in the death toll related to HIV. While a majority of these patients have achieved treatment success on first-line therapy, the number of those requiring second-line protease inhibitor-based drugs is increasing due to failure of the first-line therapy (1,2). The challenge with patients on second-line ART in resource-limited settings, where genotypic drug resistance testing is rarely performed in programs for patients before start of treatment (3), has been in the event of treatment failure, due to limited availability and financial implication of third-line therapy (4,5).

In Nigeria, the government in partnership with international collaborators, has since responded to the epidemic scourge of the HIV infection through different intervention programs, including the establishment and scale-up of national ART (6,7) as well as domesticated policy documents that are in line with international best standards. Although the "National Guidelines for HIV Prevention Treatment and Care" of 2016 has provided a guide on management of patients failing the second-line ART, the challenge of unavailability of drug sensitivity testing has also been highlighted (8).

Available studies assessing virological failure among patients on second-line ART in resource-limited settings have had different definitions for virological failure (4). In the Nigerian ART program, viral load of <1000 RNA copies/ml is regarded as evidence of viral suppression while a persistently detectable viral load of ≥ 1000 copies/ml on two consecutive viral load measurements within a 3-month interval, with Enhance Adherence Counselling (EAC) between measurements, after at least six months on ART, is considered virological failure (8). To reap maximum benefits from the second-line ART as well as plan for better management of patients requiring this line of ART, including drug sensitivity testing, there is need for extensive study of patients on this therapy, which appears to be limited in the Nigerian context.

During a median follow up period of 29 months of PLHIV in Southern Vietnam, 18.4% of the patients experienced treatment failure with four WHO stage IV AIDS events and 13.5% death recorded during the period (9). In Myanmar, where long-term outcomes of second-line ART of 824 patients was followed up, it was reported that of 52 patients who received viral load testing, 19 had virological failure and at the end of a seven year follow up, 88 (11%) patients died with 680 (83%) still under care (10).

The objective of this study is to assess the virological outcomes among HIV patients receiving second-line ART in Southwestern Nigeria, with the hypothesis that opportunistic infection and ARV adherence level do not have significant impact on viral load outcome.

## Materials and method:

#### Study setting and design

This was a 5-year retrospective study of paediatric, adolescent and adult HIV-infected patients who have been switched to second-line ART for at least six months as at the commencement of the study in multiple comprehensive ART sites across the three levels of care in Ondo and Ekiti States, Southwestern Nigeria, from January 2015 to December 2019.

#### Sample size and method of sampling

The sample size for the study was calculated using the formula, $n = Z^2PQ/d^2$ for population more than 10,000 (11) at 95% confidence interval (Z=1.96), 0.05 precision, and prevalence rate of Nigerians currently living with HIV/AIDS in Southwestern Nigeria of 1.2% (12). A total of 249 eligible HIV-

infected patients were selected by simple random sampling technique.

The inclusion criteria were patients living with HIV of all age groups and gender who have been on second-line anti-retroviral therapy (ART) at least six months as at the time of the study, and have at least one documented viral load result after the commencement of second-line ART.

**Data collection**

Relevant demographic ad clinical data such as age, gender, functional status, WHO clinical staging, ART regimen (at start and current) and ART adherence level were obtained from the patients' electronic medical record (EMR) with triangulation from patients' case folders. Confidentiality was strictly maintained throughout the study period in a computerized form through adequate security provision regarding data storage on the computer system.

**Statistical analysis**

The data analysis was done using the Statistical Package for the Social Sciences (SPSS) for windows version 24.0 software (SPSS Inc; Chicago, IL, USA). Frequency counts was generated for all variables and statistical test of significance for categorical data was performed with Chi-square test. Other data were expressed as mean ± standard deviation and analysed using the analysis of variance (ANOVA) with multiple comparisons done by Post Hoc Bonferroni test. Statistical significance was fixed at $p < 0.05$ and highly significance at $p < 0.01$.

## Results:

**Socio-demographic and clinical data**

A total of 249 subjects (71 males and 178 females) eligible for the study were recruited. Majority of the subjects (54.7%) are in the age range 35-49 years with mean age (± SD) of 44.21 ± 11.45 years (Table 1). The mean number of years the patients have been on ART regimen is 7.92±2.68 years. The mean number of years the patients were on first line ART regimen before being switched to second line is 4.27±2.63 years. All the subjects were active on antiretroviral treatment.

Using the WHO strategy, those with viral load <1000 RNA copies/ml (suppressed viral load) were 216 (86.7%), out of which 113 (45.4%) had viral load <20 RNA copies/ml, while 33 (13.3%) had viral load >1000 RNA copies/ml (unsuppressed viral load). At the commencement of ART, 151 (60.6%) patients were on zidovudine, lamivudine and nevirapine regimen, 91 (36.5%) on tenofovir, lamivudine and efavirenz, while 7 (2.8%) were on zidovudine, lamivudine and efavirenz.

## Discussion:

This study outcome shows that 86.7% of the patients had suppressed viral load based on the viral load outcome using the WHO strategy for surveillance and monitoring of HIV drug resistance in low-and-middle-income-countries (LMICs), which indicated that viral load of <1000 RNA copies/ml should be taken as evidence of viral suppression (13). This outcome differs from that of Myanmar study which reported 36.5% virological failure among HIV patients on second line ART (10) as against 13.3% in our study. This finding implies generally that more patients in our study demonstrated treatment improvement with impressive suppression rate (86.7%) that can be alluded to the use of the protease inhibitors, and better drug adherence with 91.2% having good adherence (≥ 95%) than when they were on first line regimen where the adherence level was 82.3% and suppression rate was 83.1%. Our finding from monthly dose assessment carried out revealed that missed doses in patients on ARV drugs taken twice daily was ≤ 3 in a month while missed doses for ARV drugs taken once daily was only once a month. This finding may be due to reported general minimal side effects of the protease inhibitors in the combination, especially atazanavir/ritonavir (14).

The Chi-square analysis and odd ratio (OR) showed that the presence of opportunistic infections did not have significant impact on viral load outcome in our study [$\chi^2$ =1.15, OR: 1.05 (95% CI: 0.11 –1.76), $p$= 0.283], which may be occasioned by the fact that only about 5% of the patients had reported mild cases of opportunistic infections. Generally, opportunistic infections are caused by non-pathogenic micro-organisms which become pathogenic when the immune system is impaired by an unrelated disease. Their prevention or effective treatment when detected has always formed a core part of the HIV treatment and management program, with the use of antibiotics and antifungal medications in order to significantly reduce morbidity and mortality thus prolonging the lives of the patients (15).

However, antiretroviral (ARV) adherence level significantly affected the viral load outcome of the patients, as patients on second line ART having 91.2% good adherence (> 95% adherence) had suppressed viral load of 86.7% compared to patients on first line ART having 82.3% good adherence with suppressed viral load of 83.1% ($\chi^2$=16.03, OR: 2.15 (95% CI 0.37-7.31), $p$<0.001]. This indicates that patients on second-line ART tend to miss fewer doses, which may be due to the reported general minimal side effects of the

Table 1: Socio-demographic and clinical data of patients living with HIV on second line anti-retroviral therapy in Ondo and Ekiti States, Nigeria

| Variables | Frequency (%) |
|---|---|
| **Age group (years)** | |
| 15 – 19 | 5 (2.0) |
| 20 - 24 | 4 (1.6) |
| 25 – 29 | 6 (2.4) |
| 30 – 34 | 25 (10.0) |
| 35 – 39 | 47 (18.9) |
| 40 – 44 | 52 (20.9) |
| 45 – 49 | 37 (14.9) |
| 50 – 54 | 31 (12.4) |
| 55 – 60 | 20 (8.0) |
| ≥ 60 | 22 (8.8) |
| **Gender** | |
| Male | 71 (28.5) |
| Female | 178 (71.5) |
| **Current WHO clinical staging** | |
| Stage I | 179 (71.9) |
| Stage II | 37 (14.9) |
| Stage III | 31 (12.4) |
| Stage IV | 2 (0.8) |
| **First line antiretroviral therapy (ART)** | |
| Tenofovir, Lamivudine & Efavirenz | 91 (36.5) |
| Zidovudine, Lamivudine & Efavirenz | 7 (2.8) |
| Zidovudine, Lamivudine & Nevirapine | 151 (60.6) |
| **Second line antiretroviral therapy (ART)** | |
| Zidovudine, Lamivudine & Lopinavir/Ritonavir | 18 (7.2) |
| Abacavir, Lamivudine & Atazanavir/Ritonavir | 4 (1.6) |
| Abacavir, Lamivudine & Lopinavir/Ritonavir | 2 (0.8) |
| Tenofovir, Lamivudine & Atazanavir/Ritonavir | 104 (41.8) |
| Tenofovir, Lamivudine & Lopinavir/Ritonavir | 121 (48.6) |
| **Total number of years active on ART** | |
| 3 | 20 (8.0) |
| 4 | 6 (2.4) |
| 5 | 12 (4.8) |
| 6 | 35 (14.1) |
| 7 | 49 (19.7) |
| 8 | 28 (11.2) |
| 9 | 30 (12.0) |
| 10 | 20 (8.0) |
| 11 | 25 (10.0) |
| 12 | 14 (5.6) |
| 13 | 5 (2.0) |
| 14 | 3 (1.2) |
| 15 | 2 (0.8) |
| **Number of years on first line ART regimen before switching** | |
| 1 | 44 (17.7) |
| 2 | 27 (10.8) |
| 3 | 47 (18.9) |
| 4 | 27 (10.8) |
| 5 | 29 (11.6) |
| 6 | 23 (9.2) |
| 7 | 15 (6.0) |
| 8 | 14 (5.6) |
| 9 | 17 (6.8) |
| 10 | 4 (1.6) |
| 11 | 0 (0.0) |
| 12 | 2 (0.8) |
| **Adherence on first line ART** | |
| Good (≥ 95%) | 205 (82.3) |
| Fair (85 – 94%) | 31 (12.5) |
| Poor (< 85%) | 13 (5.2) |
| **Adherence on second line ART** | |
| Good (≥ 95%) | 227 (91.2) |
| Fair (85 – 94%) | 16 (6.4) |
| Poor (< 85%) | 6 (2.4) |
| **Viral load outcome on first line ART** | |
| Suppressed viral load | 207 (83.1) |
| Unsuppressed viral load | 42 (16.9) |
| **Viral load outcome on second line ART** | |
| Suppressed viral load | 216 (86.7) |
| Unsuppressed viral load | 33 (13.3) |
| **Current tuberculosis status** | |
| No signs of tuberculosis | 230 (92.4) |
| Presumptive tuberculosis with signs | 19 (7.6) |
| **Opportunistic infections (OIs)** | |
| Present | 13 (5.2) |
| Absent | 236 (94.8) |

Table 2: Impact of opportunistic infections and anti-retroviral therapy adherence on viral load outcome

| Variables | $X^{2*}$ | OR | 95% CI | *p* value |
|---|---|---|---|---|
| Impact of opportunistic infection on viral load outcome | 1.15 | 1.05 | 0.11-1.76 | 0.283 |
| Impact of ARV drugs adherence level on viral load outcome | 16.03 | 2.15 | 0.37-7.31 | <0.001 |

*Null hypothesis is rejected when the test statistic ($\chi^2$) is greater than the critical value of 3.84; $X^2$ = Chi square; OR = Odd ratio; CI = Confidence interval

protease inhibitors in the combination, especially atazanavir/ritonavir (14), resulting in higher compliance and therefore higher suppression rates. Good adherence (> 95%) has always been associated with the beliefs regarding the positive impact of the medications on the patient's quality of life.

## Conclusion:

This study shows that about 13% of the HIV-infected patients on second line ART had unsuppressed viral load of more than 1,000 RNA copies/ml, indicating virological failure. With critical factors such as poor adherence to ART and drug resistance chiefly contributing to virological failure, routine adherence and viral load monitoring as well as the availability of HIV drug resistance testing to determine the resistance pattern of a specific HIV strain to ARV drugs in use will ensure that more patients comply with their regimen.

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