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# ASSESSMENT OF SWITCHING RATE OF ANTIRETROVIRAL THERAPY FROM FIRST-LINE TO SECOND LINE AMONG HIV INFECTED ADULTS IN NIGERIAN TERTIARY HOSPITAL, CAUSES AND DETERMINANT FACTORS

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## ABSTRACT

**Introduction: Over** the past decade there has been a concerted effort to provide access to antiretroviral therapy for HIV infected individuals in sub Saharan Africa. With increasing exposure to antiretroviral therapy (ART), the risk of resistance and subsequent treatment failure has become more important, and switching of patients to alternative second line regimens is increasingly needed. Switch from first to second line ART is recommended by WHO for patients with virologic failure. The reasons for such treatment failure may be associated mostly with resistance, side effects, toxicity / adverse effects, and pregnancy. **Objective**: This study was carried out to determine the rate of switching HIV infected patients on ART, from first line to second line regimen, time of switching, and determinants for the switch, in University of Port Harcourt Teaching Hospital. **Method:** Retrospective cohort study involving HIV infected patients in the University of Port Harcourt Teaching Hospital who are on first line antiretroviral treatment between 2006 and 2016 was carried out to determine the rate of switch of patients from first line to second line therapy. Sample size based on prevalence rate was determined. Ethical approval was obtained and data collection form was used to record relevant data from patients' folders. Information collected included demographic data of patients, date of initiation of therapy, initial ART combination, CD4 cell level, and viral load (where available), at initiation, date of switch to second line, CD4 cell level and viral load at switch, second line combination switched to, and reason/s for the switch. Collected data were analyzed using statistical package for social sciences (SPSS)

version 20. **Results**: Out of 239 patients assessed, 24(10.04%) switched from first line to second line ART at a rate of 22.9 per 100 person/years (95% CI = 13.3 – 32.5%). Of the patients that switched, 5(20.8%) were male and 19(79.2%) female. Most, 148 (62%), of the patients studied were within the ages of 30 -49 years, while 11(45.8%) that switched were within 40 – 49 years. The mean age of patients that switched was 41.8±10.6 years. The mean CD4 cell count of these patient at initiation of therapy was 212.3±118.91cells/$mm^3$ while at switch the mean CD4 cell count was 221.3 ±175.1 cells/$mm^3$. Of the patients that switched 15(62.5%) spent 2 – 4years, while 1(4.2%) spent 8 – 10years on their first line regimen prior to the switch. Reasons recorded for the switch included side effects 20.8%, toxicity/adverse effects (16.7%), pregnancy 8.3%, treatment failure 16.7% and 37.5% of the switched patients had no recorded reason given for the switch. **Conclusion:** This study identified a switch rate of 22.9 per 100 person years over a period of 10 years. The switching of patients was hardly based on virologic failure and in most of the switches no reason was documented for the action.

## INTRODUCTION

Over the past decade there has been a concerted effort to provide access to antiretroviral therapy (ART) for HIV –infected individuals in sub Saharan Africa, the region with the highest HIV burden.[1] The scaling up of ART also contributed significantly to the ongoing drop in annual new HIV infection around the world, children inclusive. According to the World Health Organization, expanding programs for PMTCT and the use of more effective ARV regimens helped prevent more than 800, 000 children from becoming newly infected between 2005 and end of 2012. In the 21 African priority countries in the Global Plan, which account for about 90% of all pregnant women living with HIV and new infections among children globally, mother- to –child transmission rate declined overall from an estimated 26% (24 -30%) in 2009 to 17% (15– 20%) in 2012.[2]

In many ways HIV is difficult to treat. This is because the virus reproduces very quickly and in large quantities, therefore if treatment is not effective enough or if dose of medications are missed, then the drug resistance can easily develop. Highly Active Antiretroviral Therapy works because there are usually at least 3 different drugs acting at different points in the virus life cycle. If the virus is resistant to one of the drugs the others might still suppress it. If patient misses doses or is not adherent to the HIV drugs, chances are that they may not be

effective at all or their efficacy may last only for few months. Once antiretroviral therapy is initiated, the patients generally remain on the medication indefinitely.

However, certain clinical conditions may warrant informed judgment of switching from certain combination of first line ARV regimen to a second line combination. Switching may be prompted by both acute and chronic toxicities, concomitant clinical conditions, resistance and development of virologic failure. The WHO recommends switching from first line to second line ART for HIV patients with virologic failure[3] to avert drug resistance, advanced immune-suppressed increased morbidity and mortality, and to reduce risk of transmitting HIV to uninfected sex partner.[4-9] In order to promptly switch treatment and to ensure virolgic suppression, viral load (VL) monitoring to identify virologic failure is important. Although WHO recommended that viral load should be monitored routinely, access to viral load test is limited in many settings including sub Saharan Africa. Thus switching patient to second line ART is based on clinical and CD4 cell count criteria for treatment failure[3] however sensitivity and positive value of these criteria for virologic failure are poor.[10,11,12] Patients with suppressed viral replication may thus be unnecessarily switched to second line ART, whereas patients failing first line therapy may be switched late or not switched at all.[13,14,15] A decision for switch should also be made when there is no significant improvement in the patient's CD4 count after a long time on the regimen.

Substitution is different from switching because when there is substitution of a regimen the patient is still on that line of therapy (i.e. first line or second line) whereas switching involves moving to another line. Switching to second line involves introduction of a protease inhibitor to replace the non- nucleoside reverse transcriptase inhibitor.[16] Switching is most often associated with treatment failure, which can be categorized as virolgic failure, immunologic failure, clinical failure or some combination of the three.[17] Haas et al.,[16] defined switching to second line as a change from a non –nucleoside reverse transcriptase inhibitor (NNRTI) – based regimen to a protease inhibitor (PI) - based regimen with a change of one or more NRTI. The cardinal principle during switching is to maintain viral suppression, and this is achieved by reviewing the patient's full ART history including drugs adverse effects, virologic response as well as resistance profile, and by increasing the intensity of monitoring for 3 months to check for adherence, tolerability, viral suppression, using laboratory monitoring.[18] In an analysis of treatment programs in Africa, Asia, and Latin America, it was found that switching to second line regimens tended to occur earlier and at higher CD4

cell count in ART programs with VL monitoring compared with programs using CD4 monitoring.[19] In a study across 62 Medecins Sans Frontieres programs around the world, it was found that of 48,338 adult HIV patients followed up, 370 switched to second line regimen after a median time of 20 months at a switch rate of 4.8/1000 person years.[20] While a study across 17 HIV treatment programs from 14 countries in Africa, South America, Southern and Eastern Asia to determine the switching to second line ART in resources limited setting found overall switching rate of 2.4 per 100 person –year.[19] In sub Saharan Africa, Haas et al[16] found that 3.5% of overall 10,352 patient switched at a rate of 1.63 per 100 persons-year. A study in Uganda recorded a total of 66.1% of patients with virologic failure switched to second line ART at a rate of 49 per 100 persons year.[21]

This study thus aimed to assess the rate of switching HIV infected patients from first line to second line, and to determine the time of switch as well as factors associated with the switch.

## METHOD

### Study setting and design

A retrospective study was conducted among HIV- infected adult patients who are on ART between year 2006 and 2016 in University of Port Harcourt Teaching Hospital (UPTH), Rivers State. The UPTH is one of the Teaching hospitals in Nigeria, located in Choba community in Obio/Akpor local government area of River State, Nigeria. The hospital complexes are situated along East- West road about 20km North – West of Port Harcourt, an industrial and oil rich city in Niger Delta region of South –South geo-political zone of Nigeria.

The hospital records showed that a total of six thousand two hundred and fifty adult HIV infected patients are still receiving care in the hospital HIV clinic, as at the time of this study. The study included adult HIV patients aged 18 years and above, but excluded HIV patients who registered in UPTH but no longer receive their care in the hospital.

A sample size of 239 was obtained using sample size determination by Araoye 2004,[22] with HIV prevalence rate of 3.8%[23] for Rivers State.

Ethical approval was obtained from the UPTH research and Ethics committee, prior to conduction of the study.

Since 2002, UPTH with funding from Presidential Emergency Plan for AIDS Relief (PEPFAR) has been providing free ART to HIV patients. The first line regimen consists of two nucleoside/ nucleotide reverse transcriptase inhibitors (NRTIs: Zidovudine or Stavudine and lamivudine or Tenofovir) and one non –nucleoside reverse transcriptase inhibitor (NNRTs: Nevirapine or Efavirenz) while second line therapy consists of a protease inhibitor (ritonavir –boosted Lopinavir) with 2 NRTIs.

In UPTH, the approach used for treatment of HIV was curled from Nigerian National Guideline for HIV/AIDS and care for adults and adolescents. There are several combinations of the drugs for first line and second line therapy and they differ among patients depending on patient's tolerability and allergic response.

After a patient initiates therapy the patient is seen weekly for the first month to monitor for any allergy and 2 monthly thereafter to monitor the CD4 level and refill medications. Access to viral load test is limited in the facility. In each visit, education on adherence and HIV risk reduction is given to the patients. Interventions to address immunologic failure included intensified adherence counseling and switching to second line ART. Decision about time to switch to second line were made based on case to case basis at clinician's discretion, and were based on the suspected cause of immunologic failure (poor adherence or suspected drug resistance). Resistance testing was also not immediately available in the facility.

**Data collection and Analysis**

Patients' folders were accessed and data were extracted from patients who were on HIV therapy between year 2006 and 2016. Information obtained included demographic data; clinical and laboratory data including CD4 level at initiation and at switch; viral load at initiation and at switch where available; treatment variables including ART regimen at treatment initiation and at switch; switch dates; reason/s for switch and the new regimen.

The data obtained were analyzed using SPSS version 20 software (IBM Corporation) for mean, standard deviation and p-values.

**RESULTS**

The demographic data of the studied population is shown in Table 1. A total of 239 patients with access to CD4 count monitoring were assessed. Viral load monitoring was not easily

accessible in the hospital so the switch to second line antiretroviral therapy was hardly based on viral load or virologic failure of the patient.

The result showed that 76(31.8%) of the patients were male and 163 (68.2%) were female. Most (62%) of the patients were between 30 – 49yrs with the mean age of the population being 40.4 ± 10.4 yrs. Of the total population studied, 24 (10.04%) switched from first line therapy to second line at various times within the study period (2006- 2016). More female 19(79.2%) switched from first line to second line than the male. Most of the patients that switched were within the age range of 40 – 49yrs.

The clinical characteristic of the studied population and the switched patients with length of duration on therapy are shown in Table 2.

**Table 1: Demographic data of the studied HIV infected patients.**

| **Overall Patients (N = 239)** | | **Switched Patients (N = 24)** |
|---|---|---|
| **Gender** | | **Gender** |
| Male | 76(31.8%) | 5(20.8%) |
| Female | 163(68.2%) | 19(79.2%) |
| Age (yrs) | | |
| <30 | 43(17.9%) | 5(20.8%) |
| 30 – 39 | 74 (31%) | 3(12.5%) |
| 40 – 49 | 74 (31%) | 11(45.8%) |
| 50 – 59 | 34(14.2%) | 3(12.5%) |
| ≥60 | 14(5.9%) | 2(8.4%) |

**Table 2: Clinical data of Patients who switched from first line to second line ART.**

| **S/No** | **Year of initiating of ART** | **Year of switching to second line ART** | **CD4 cells/mm$^3$ at initiation** | **CD4 cells/mm$^3$ at switch** | **Duration on first line ART (yrs)** |
|---|---|---|---|---|---|
| 1 | 2012 | 2016 | 96 | 65 | 4 |
| 2 | 2006 | 2016 | 144 | 39 | 10 |
| 3 | 2011 | 2015 | 254 | 225 | 4 |
| 4 | 2008 | 2014 | N/A | 318 | 6 |
| 5 | 2007 | 2012 | 130 | 638 | 5 |
| 6 | 2012 | 2015 | 112 | 198 | 3 |
| 7 | 2011 | 2014 | 275 | 301 | 3 |
| 8 | 2012 | 2015 | 94 | 90 | 3 |
| 9 | 2007 | 2014 | *N/A | 341 | 7 |
| 10 | 2011 | 2015 | 112 | 280 | 4 |
| 11 | 2008 | 2014 | 326 | 121 | 6 |
| 12 | 2007 | 2013 | 387 | 92 | 6 |
| 13 | 2010 | 2012 | 187 | 102 | 2 |
| 14 | 2012 | 2015 | 449 | 506 | 3 |

| | | | | | |
|---|---|---|---|---|---|
| 15 | 2007 | 2012 | 74 | 121 | 5 |
| 16 | 2011 | 2015 | 283 | 392 | 4 |
| 17 | 2009 | 2011 | 363 | 318 | 2 |
| 18 | 2010 | 2015 | 132 | 109 | 5 |
| 19 | 2008 | 2014 | 374 | 598 | 6 |
| 20 | 2009 | 2013 | 63 | 89 | 3 |
| 21 | 2010 | 2013 | 225 | 73 | 3 |
| 22 | 2009 | 2013 | 275 | 192 | 4 |
| 23 | 2013 | 2016 | 57 | 42 | 3 |
| 24 | 2012 | 2016 | 259 | 61 | 4 |
| | | | | | Total = 105 yrs |

***N/A= not available**

The total number of patents that switched from first line to second line ART was 24.

The mean CD4 cells/mm$^3$ of switched patients at initiation was 212.3±118.91 cells/mm$^3$ while the mean CD4 cells/mm$^3$ at switch was 221.3 ± 175.1 cells/mm$^3$.

To calculate the rate of switch from first line to second line ART per 100 person year.
Number of switched patients = 24
Total duration of all switches = 105 years
Rate of switch = 24/105 X I00 = 22.9 per 100 person year.

The length of time spent on first line regimen prior to switch to second line therapy is shown in Table 3.

**Table 3: Time Spent on First Line Therapy Prior To Switch To Second Line Therapy.**

| Duration on first line therapy | Number of switched patients | Percentage switched (%) | 95% Confidence Interval (95% CI) |
|---|---|---|---|
| 2 – 4 years | 15 | 62.5 | 56.8% - 68.2% |
| 5 – 7 years | 8 | 33.3 | 27.6% - 39% |
| 8 – 10 years | 1 | 4.2 | -1.5% - 9.9% |
| Total | 24 | 100 | |

The result further showed that more female 12(80%) spent 2 – 4 years on the first line antiretroviral therapy prior to switch to second line while one female spent 8 – 10 years on the first line therapy before switch to second line therapy.

The cumulative percentage of switch of patients made over the ten- year study is shown in Fig 1, while reasons for switch is shown in Fig. 2.

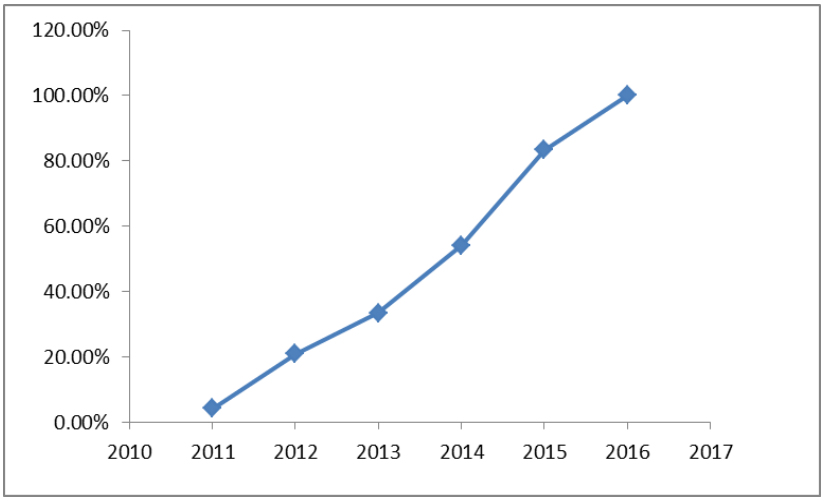
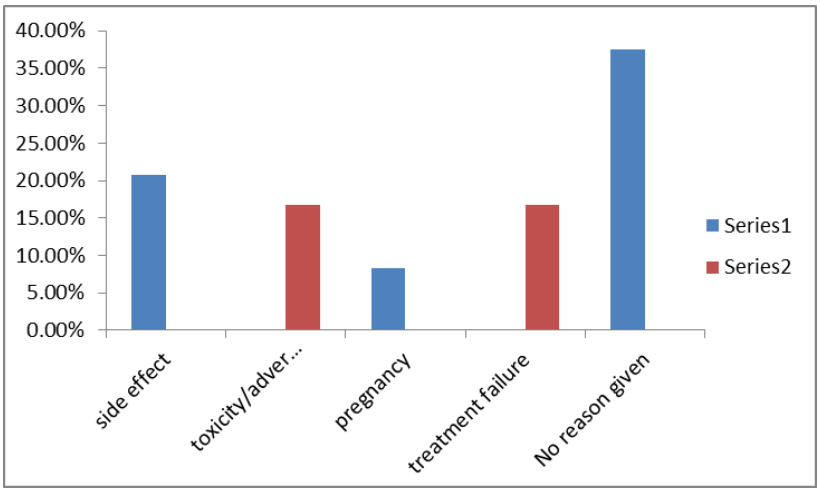



**Fig. 1: Cumulative percentage patient-switch from first line ART to second line ART over the10-year study.**




**Reasons for switching patients from first line ART to second line ART**

In this study, no reason was documented for switching majority of the patients (37.5%) from first line to second line therapy. A further 20.8% was switched to second line therapy due to side effects of the drugs, while 16.7% of the switch was due to toxicity/adverse effect and treatment failure respectively. However, 2(8.3%) switched as a result of pregnancy.

## DISCUSSION

This retrospective study assessed the rate of switch of HIV infected patients from first line to second line therapy between 2006 to 2016 and found a switch rate of 22.9 per 100 persons/ year (95% CI, 13.3 – 32.5%). This result differed from similar study in Tanzania where the switch rate was 5.4 per 100 persons/ year.[4] The high switch rate in our study may be attributed the criteria employed to switch the patients to second line therapy. However, in a cohort study among HIV positive patients in 16 countries in sub Saharan Africa, Haas et

al.,[16] reported that about 1.6 in every 100 patients switched to second line antiretroviral therapy (ART) each year, and that overall 7.9% of patients were on second line ART after 5 years. They also identified that switching varied greatly between treatment programs and monitoring strategies. WHO[3] recommendations of when to switch HIV patients on first line to second line therapy include use of viral load test (where available) to confirm treatment failure. Where routinely available, to use viral load test every 6months to detect viral replication, and persistent viral load of > 5000 copies/ml confirms treatment failure. The Panel also recommended use of immunological criteria to confirm clinical failure, when viral load is not available. However, viral load measure is considered more sensitive indicator of treatment failure compared to clinical or immunological indicators.[25] In this study viral load test was not easily accessible, as such the switch was hardly based on virologic failure. Our result on the rate of switch, though lower than that reported in Uganda[21], does not compare directly to reported rate of switching in other various settings that range from 2.6 to 4.2/100 pys.[16,24,25] This may be attributed to criteria for analysis of switched patients and the reasons for their switching to second line therapy.

In this study it was identified that a good number (37%) of switched patients have no documented reason for their switch to second line therapy, while 20.8% was due to side effects of the drugs. Toxicity/adverse drug effect can affect patient's compliance /adherence to therapy. In this study 16.7% switched to second line therapy due to toxicity/adverse drug effect. Compared to similar studies in Addis Abba[26]; Southern Ethiopia[27]; and India[28], toxicity/adverse effect as predictor of switching to second line drug in these studies was higher. The lower incidence of switching to second line due to toxicity/adverse drug effect maybe associated to the use of less toxic first line drug such as Tenofovir.

Most (62.5%) of the patients in this study had been on the first line regimen for 2 – 4 years before switch. This time line is similar to other studies in other settings as in Bedelle[29], all patients stayed on ART for less than 3 years; in Addis Ababa (30) about 98% of patients stayed on ART for less than 1.4 years and in Dessie[31] only 6% of the patients stayed on ART for more than 2 years. This average range of time may be attributed to waning compliance /adherence or possible boredom to same drug over a period of time. Also the insignificant difference in the mean CD4 cells at initiation and at switch (212.3 ±118.91 and 221.3±175.1) may be a contributory factor. However, one female stayed for 10years on the first line ART before switching to second line therapy.

Evidence of growing number of ageing population among HIV patients may be reflected in our result that showed majority (45%) of the switched patients to be within 40 -49 years. Similar study in Uganda showed that majority of the switched patients were 40years and above.[32]

## CONCLUSION

This study identified the rate of switching antiretroviral therapy from first line to second line among HIV infected patients in University of Port Harcourt Teaching Hospital to be 22.9 per 100 person/year. The study also identified that a good number of switches to second line therapy had no documented reason for the switch. The difference between the mean CD4 cell count at initiation of therapy and at point of switch was also noted to be very minimal.

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