Patients’ demographic and clinical characteristics and level of care associated with lost to follow-up and mortality in adult patients on first-line ART in Nigerian hospitals

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Abstract

Introduction: Clinical outcome is an important determinant of programme success. This study aims to evaluate patients’ baseline characteristics as well as care associated with lost to follow-up (LTFU) and mortality of patients on antiretroviral treatment (ART).

Methods: Retrospective cohort study using routine service data of adult patients initiated on ART in 2007 in 10 selected hospitals in Nigeria. We captured data using an electronic medical record system and analyzed using Stata. Outcome measures were probability of being alive and retained in care at 12, 24 and 36 months on ART. Potential predictors associated with time to mortality and time to LTFU were assessed using competing risks regression models.

Results: After 12 months on therapy, 85% of patients were alive and on ART. Survival decreased to 81.2% and 76.1% at 24 and 36 months, respectively. Median CD4 count for patients at ART start, 12, 18 and 24 months were 152 (interquartile range, IQR: 75 to 242), 312 (IQR: 194 to 450), 344 (IQR: 227 to 501) and 372 (IQR: 246 to 517) cells/µl, respectively. Competing risk regression showed that patients’ baseline characteristics significantly associated with LTFU were male (adjusted sub-hazard ratio, shR = 1.24 [95% CI: 1.08 to 1.42]), ambulatory functional status (adjusted shR = 1.31 [95% CI: 1.08 to 1.59]) and care in a secondary site (adjusted shR = 0.76 [95% CI: 0.66 to 0.87]). Those associated with mortality include CD4 count < 50 cells/µl (adjusted shR = 2.84 [95% CI: 1.20 to 6.71]), WHO clinical Stage III (adjusted shR = 2.67 [95% CI: 1.26 to 5.65]) and Stage IV (adjusted shR = 5.04 [95% CI: 1.93 to 13.16]) and care in a secondary site (adjusted shR = 2.21 [95% CI: 1.30 to 3.77]).

Conclusions: Mortality was associated with advanced HIV disease and care in secondary facilities. Earlier initiation of therapy and strengthening systems in secondary level facilities may improve retention and ultimately contribute to better clinical outcomes.

Keywords: antiretroviral treatment; mortality; lost to follow-up; Nigeria.

Introduction

Antiretroviral therapy (ART) for the treatment of HIV infection has been shown to profoundly alter HIV disease progression, including incidence of opportunistic infections in people living with HIV (PLHIV) [1–3]. Nigeria, Africa’s most populous country, accounts for about 10% (3.3 million) of the estimated 33.3 million PLHIV globally [4,5]. The period between 2005 and 2010 coincided with increased availability of antiretroviral drugs and treatment for PLHIV in Nigeria mainly through donor funding [6]. The country rapidly scaled up ART enrolment and has steadily increased the number of PLHIV initiated on ART from 90,008 in 2006 [7] to an estimated 300,000 at the end of 2009 [8].

The measurement of plasma HIV RNA levels is commonly used as an indicator of treatment effectiveness in resource-rich settings [10]. For resource-limited settings, where there is limited laboratory support, World Health Organization (WHO) in 2006 recommended use of CD4 cell count measurements and clinical outcome measures for monitoring ART in the absence of viral load [11]. Many studies have therefore reported CD4 count increase as a measure of treatment outcome [13–15]. The challenges of delivering ART in low-resource settings have also been documented, most notably: shortages of healthcare staff; inadequate availability of drugs; weak health systems and laboratory capacity; and poor health data management systems [9,16,17]. Although there is evidence that ART reduces mortality and improves immunological, virological and clinical outcomes in HIV patients, most studies have considered patients’ characteristics as well as drug regimen [18–25] and attempted to explain the observed variability in treatment outcomes using these characteristics. Few studies have considered differences in the health...
delivery system on outcomes especially in resource-limited settings [26].

The levels of care in the public sector in Nigeria include primary centres, typically staffed by nurses, community health officers (CHOs), community health extension workers (CHEWs), junior CHEWs and environmental health officers; secondary hospitals, typically staffed by medical officers, nurses, midwives, laboratory scientists, pharmacists and CHO; and tertiary centres, typically staffed by medical specialists [27]. Initiation of PLHIV on ART in the country was initially restricted to tertiary centres due to weak health systems in other levels of care. In 2004, following the rapid scale up of ART services and infrastructural upgrade, secondary hospitals began providing ART services.

There are few studies from Nigeria evaluating the various aspects of the country’s HIV programme [28]. One study used pharmacy refill records to evaluate risk factors for lost to follow-up (LTFU) and non-adherence to ART [12]. Another reviewed impact of hepatitis B on ART programme [29]. Others reviewed either patient’s perception or performance on ART [30–35]. None of the studies reviewed described survival or LTFU on ART in relation to level of care. This study evaluated patients’ baseline characteristics as well as level of healthcare associated with clinical outcomes of patients on ART in hospitals supported by the Global HIV/AIDS initiative in Nigeria (GHAIN).

Methods

Study design

This was a retrospective study reviewing routinely collected patient level data between January 2007 and December 2010. Although data were reviewed retrospectively, the patient-level data were prospectively collected over the study period.

Study context/setting

States in Nigeria are grouped into six geopolitical regions; the northern part of the country has three regions: North West, North East and North Central, while the south is divided into: South West, South-South and South East regions [36]. The GHAIN is a United States Agency for International Development/US President’s Emergency Plan for AIDS Relief supported project that was launched in December 2004 [37]. The project assisted several hospitals in Nigeria to provide comprehensive HIV/AIDS care and treatment services in all six geopolitical regions of the country. In 2007, the project piloted the use of Lafiya Management Information System (LAMIS®), an open source electronic medical record (EMR) system, in 10 hospitals and later scaled up LAMIS to a total of 14 hospitals by October 2010 [38]. GHAIN-supported hospitals benefited from infrastructure upgrade and systems strengthening that included support for antiretroviral logistics and supply chain management.

Site selection criteria

The site selection criteria for this study were (1) ART sites using an EMR system; (2) hospitals providing comprehensive ART services to adults; and (3) hospitals starting ART services by January 2007. All 10 hospitals that piloted LAMIS met these criteria and were included in the study. Four of the hospitals were secondary and six were tertiary level facilities. There was at least one hospital from all six regions in the country. Figure 1 shows names of the 10 hospitals included in the study and their locations in the country.
Study population
The analysis included male and female patients aged ≥ 16 years initiated on first-line ART in all of the 10 study sites between January and December 2007. Study exclusion criteria included adult patients on second-line ART, patients <16 years old, HIV-positive patients who were not on ART, pregnant women, and patients initiated on ART outside the defined study period.

Clinical procedure
Patient monitoring and management in selected hospitals were based on Nigerian national ART guidelines, which were derived from the WHO guidelines [39]. The entry point in the HIV/AIDS care and treatment program in all the selected sites is usually from the HIV counselling and testing (HCT) unit of the hospital or through a referral from other hospitals where the patient had received HCT and has been identified as HIV positive and subsequently referred for ART services. At the ART sites, patients undergo clinical evaluation by a clinician followed by baseline laboratory investigations.

HIV-positive patients assessed as being in WHO clinical Stage III or IV, or with a CD4 count <200 cells/mm³ (irrespective of WHO staging) were considered eligible for ART [39]. The first-line ART regimen included a fixed-dose combination of zidovudine (ZDV), lamivudine (3TC) and nevirapine (NVP). In the case of ZDV- and NVP-related side effects or contraindications, the respective alternatives were stavudine (d4T) or tenofovir (TDF) and efavirenz (EFV) [39].

All out-patients initiated on ART went through at least three sessions of adherence counselling before ART was initiated, and subsequently, they received ongoing adherence counselling at every contact with the facility. Patients requiring admissions or too sick to receive adherence counselling, usually patients with WHO Stage IV disease, received drugs at the specified interval by the nurse in the ward, so that their adherence could be monitored. ART patients who are stable on treatment have their follow-up appointments and investigations except otherwise indicated at six month intervals. Common indications that required an earlier appointment or investigations were unsatisfactory patient adherence level and suspected treatment failure.

Data collection
Clerks at the various points of service captured data for patients newly initiated on ART and on follow-up into the LAMIS. Patients already on ART before introduction of LAMIS had their data entered as backlog. Electronic processes were put in-place to ensure security of data during entry into LAMIS and during transmission and storage.

Definitions
Patients were classified as “defaulters” when they missed any clinical or drug pick-up appointment. Defaulting clients were classified as LTTF if they failed to return to the clinic after 90 days from their expected clinic appointment date and a tracking team had made efforts to contact patients but failed [40]. Patients were considered to have “stopped treatment” when they stopped ART for any reason, including medico-social reasons. Patients referred to as “transfer out” were those who formally requested to transfer care to another ART site for convenience or due to relocation [40]. Time on ART was calculated in months using the time interval between the date of ART initiation and (1) date of known death, (2) date of leaving the programme due to LTTF, default or stopping of treatment and (3) when 36 months of follow-up had accrued.

Data analysis
Data was exported from LAMIS to Stata version 12.0 (Stata Corporation, College Station, TX, USA) for statistical analysis. The main outcome measures were mortality and LTTF. The predictor variables analyzed were adult patients’ characteristics at ART initiation: demographic characteristics (age, sex); CD4 cell count; clinical staging (Stage I to IV); weight (kg); and functional status (working, ambulatory or bedridden). We used competing risk cumulative incidence curve to illustrate time to death and time to LTTF by WHO clinical staging and level of care. Potential predictors associated with time to mortality and time to LTTF were assessed using competing risks regression models described by Fine and Gray [41]. Competing risk for death were LTTF, treatment stop and default. Similarly, competing risk for LTTF were mortality, treatment stop and default. All statistical tests were two-sided at α = 0.05. We performed automated and manual consistency checks on the data. In instances where we observed data inconsistencies in the EMR, these were corrected using source documents. Cases that were missing at least one of the variables in the regression model were excluded from the analysis.

Ethical approval
The Nigerian National Health and Research Ethics Committee (NHREC) and FHI360’s Protection of Human Subjects Committee (PHSC) approved the study protocol. Both committees determined study as exempt from oversight.

Results
Patients’ baseline characteristics
A total of 4785 patients met the study criteria. Of these, 3325 (69.5%) patients were from secondary facilities and 1460 (30.5%) were from tertiary facilities. There were 2840 (59.4%) female patients. The total duration of follow-up was 12,448 person years. The median age and baseline weight at ART initiation were 34 years (interquartile range, IQR: 28 to 41) and 55 kg (IQR: 48 to 62), respectively. Median CD4 count was 152 cells/µl (IQR: 75 to 242). A substantial proportion of patients were in WHO Stage III (42.1%) and majority (90.6%) of the patients had a working functional status at baseline. Table 1 summarizes baseline characteristics of the study population.

CD4-cell count changes at follow-up
The CD4 cell count analysis was limited to patients who had been on ART and followed up for at least 24 months. The follow-up median CD4 count for patients on ART for at least 24 months showed a progressive rise. The median CD4 cell count increased by 14.6% from 152 (IQR: 75 to 242) at baseline to 181 (IQR: 95 to 289) at six months; this further increased to 312 (IQR: 194 to 450), 344 (IQR: 227 to 501) and
Treatment outcome and follow-up

The mean duration of follow-up for the 4840 patients was 28.05 months with 2513 patients alive and on ART at the censoring date of 30 November 2010. During 12,448 person years of follow-up, 362 (7.6%) had stopped treatment and 246 (5.1%) patients were transferred out of the hospitals. LTFU increased with follow-up from 4.3% between 0 and 12 months to 11.3% between 24 and 36 months. Table 2 shows details of treatment outcome by duration on ART.

Mortality on ART

A total of 136 deaths (2.8%) occurred over a 36-month follow-up period giving an overall mortality rate of 11 deaths per 1000 person years. One-third (45/136) of all deaths occurred in the first 3 months, whereas 89 of the deaths (65.4%) occurred in the first 12 months on ART. Majority (72.8%) of the patients who died over the 36-month follow-up period were in the age group of 25 to 45 years, 53.7% being males. After adjustment using competing risks regression model, patients’ baseline characteristics significantly associated with mortality were: low CD4 count and advanced WHO clinical stage. Patients with CD4 cell count below 50 cells/mm$^3$ had more than two-fold higher risk of mortality than those with CD4 count greater than 350 cells/mm$^3$ (adjusted sub-hazard ratio, sHR$^{2.84}$ (95% CI: 1.20 to 6.71)). It was evident that patients in WHO clinical Stage IV had the highest risk of mortality (adjusted sHR$^{5.04}$ (95% CI: 1.93 to 13.16)). Patients in secondary level facility (adjusted sHR$^{2.21}$ (95% CI: 1.30 to 3.77)) were at much higher risk of mortality than those in the tertiary facility. Table 3 provides details of the multivariate competing-risks model of baseline characteristics and level of care associated with deaths. Figure 2a,b show cumulative incidence curve of WHO clinical staging and level of care associated with mortality.

Table 2. Treatment outcome by duration on antiretroviral therapy ($N=4785$)

| Duration on antiretroviral therapy (months) | 0 to 12 (%) | 12 to 24 (%) | 24 to 36 (%) | 0 to 36 (%) |
|--------------------------------------------|-------------|--------------|-------------|-------------|
| Alive and on ART                           | 4065 (84.95)| 3299 (81.16) | 2513 (76.17)| 2513 (52.52)|
| Dead                                       | 89 (1.86)   | 33 (0.81)    | 14 (0.42)   | 136 (2.84)  |
| LTFU                                       | 210 (4.39)  | 404 (9.94)   | 371 (11.25) | 985 (20.59) |
| Default                                    | 132 (2.76)  | 110 (2.71)   | 301 (9.12)  | 543 (11.35) |
| Treatment stop                             | 176 (3.68)  | 157 (3.86)   | 29 (0.88)   | 362 (7.57)  |
| Transfer out                               | 113 (2.36)  | 62 (1.53)    | 71 (2.15)   | 246 (5.14)  |
The cumulative total number of patients lost to follow-up (LTFU) at 36 months was 985 (20.6%) giving an incidence of 79 per 1000 person years. Of these, 210 (21.3%), 404 (41.0%) and 371 (37.7%) were LTFU at 12, 24 and 36 months on ART, respectively. Review of baseline characteristics of the 985 patients LTFU showed that the majority (72.2%) were in the age group 25 to 45 years and 55.0% were females. Factors associated with LTFU were male gender, being ambulatory, WHO Stage II and level of care. Male patients (adjusted sHR = 1.24 [95% CI: 1.08 to 1.42]) were more likely to be LTFU than females. The hazard of being LTFU decreases with WHO clinical staging (Stage II (adjusted sHR = 1.31 [95% CI: 1.08 to 1.59]). Table 4 provides detail of the multivariate competing-risks model of baseline characteristics and level of care associated with LTFU.

**Discussion**

This study demonstrated baseline characteristics associated with mortality and LTFU of patients on ART in selected secondary and tertiary hospitals in Nigeria. We found that patients’ baseline characteristics associated with mortality on ART include CD4 count (< 50 cells/µl), WHO Stage III and IV. Our study also found an association between mortality on ART and level of patient care. We observed that being in care at secondary level hospitals was associated with higher mortality than at tertiary sites. The factors associated with LTFU were male, WHO Stage II and ambulatory status. However, being in care in a secondary site was associated with lower risk of LTFU than at tertiary sites.

Severe immunodeficiency indicated by low CD4 count and advanced WHO clinical staging are well-documented factors associated with mortality of HIV-positive patients [42–46]. In our study population, patients with WHO Stage III disease accounted for 42.1% of patients initiated on ART. This finding was comparable with findings reported in South Africa [16,47]. The proportion of patients with Stage IV (2.9%) disease in our study was much lower than those reported in both studies [16,47]. Further studies are required to ascertain specific reasons for the low proportion of patients in WHO Stage IV in our study population. Though, a previous study in Nigeria suggested that severely immune-compromised patients may have been too sick to access care [48].

We also found that 33.1% and 65.4% of all deaths in our study population occurred in the first 3 and 12 months, respectively. Other studies from Zambia and Malawi reported mortalities of 71% and 77%, respectively, occurring within the first three months on ART [46,47]. The lower proportion of early deaths observed in our study could be attributed to the relatively low proportion of patients with Stage IV disease and adherence counselling processes in each site. Several studies have reported marked improvement in survival associated with ART in high- and middle-resource countries [3,10,49–54]. There is further evidence from these settings that with sustained high levels of treatment adherence, the risk of morbidity and mortality may diminish to levels observed in the general population [55].

The retention rates in our study of 85.0% at 12 months and 76.2% at 36 months on ART were comparable with findings.
from a systematic review of 39 cohorts in sub-Saharan Africa that reported 80.2% and 72.3% retention at 12 and 36 months, respectively [44]. Our retention rates were also comparable to rates reported by the national ART programme in Botswana of 82.7% and 79.3% at 12 and 36 months, respectively [42]. Patients LTFU accounted for the majority of attritions from care throughout the follow-up period. These finding were consistent with reports from other studies from several countries in sub-Saharan Africa [44, 56–58]. Although we did not investigate reasons for LTFU in our study population, one study suggested that patients LTFU may in fact have informally transferred to other sites [44], while some others reported that the majority of patients that were LTFU may have actually died [59–61].

We observed that being male was a risk factor for LTFU. This finding was consistent with those reported by a previous study in Nigeria and a study that reviewed 29 ART programs in 13 low-income countries [48, 62]. This supports the proposition of gender differences in health-seeking behaviour [48, 62, 63]. We did not investigate the reasons for the gender differences with LTFU; however, a previous study suggested that women are more likely than men to attend health services because of dedicated provisions of reproductive and child health services, whereas services addressing men’s health needs are largely under-developed [62]. We also observed that patients in WHO Stage II had a higher risk of LTFU compared to other stages. This finding may be due to patients who may have considered themselves well and need not return to continue ART.

Our findings also highlight the need to consider level of care and patients’ clinical outcomes. We found that care in a secondary facility was associated with a higher risk of mortality but lower risk of LTFU compared to tertiary sites. This finding corroborates results from a study in Malawi that observed better retention but higher mortality among patients on ART in rural health centres compared to hospitals [64]. However, one study in South Africa comparing nurse-monitored versus doctor-monitored ART care at primary healthcare centres found no difference in retention rates between nurse-monitored ART and doctor-monitored ART patients [65].

A study in Malawi suggested that better geographical access provided by lower level facilities and better personal knowledge of the patient by the providers at that level may
be reasons for lower LTFU in lower level facilities [64]. Another study in Nigeria, however, reported that patients may not necessarily utilize services at facilities close to their communities due to stigma [48]. These findings have implications for the current drive to decentralize ART services to primary health centres and suggest that lower level care requires systematic strengthening of their health system to ensure that the standards of patient care is comparable to what are available in tertiary facilities.

The strength of our study was the large enough sample available for the analysis and the use of EMRs at the study sites. However, limitations include a limited number of observed variables that went into data analysis because data was collected using national data collection tools not primarily designed for research purposes. In addition, because we could not ascertain outcomes of patients LTFU, our mortality results might be an underestimation. Furthermore, findings from our study were drawn from 10 (purposively) selected sites; limiting the generalizability of our findings.

Conclusions
This study demonstrated that mortality and LTFU amongst first-line ART patients in selected Nigerian hospitals were comparable with those reported in other settings in sub-Saharan Africa. Mortality was associated with advanced HIV disease at baseline and being in care at secondary level facilities. LTFU was associated with male gender, ambulatory functional status and WHO Stage II. Study findings suggest that further evaluation of systems at secondary and tertiary levels will be needed to establish specific reasons for differences in risk for mortality and LTFU. Earlier initiation of ART with improved adherence counselling especially amongst males and interventions to strengthen systems at secondary level facilities may improve retention and ultimately contribute to better clinical outcomes.

Table 4. Multivariable competing-risks model of baseline characteristics associated with LTFU (adjusted for type of facility)

|           | Unadjusted sHR (95% CI) | p   | Adjusted sHR (95% CI) | p   |
|-----------|-------------------------|-----|-----------------------|-----|
| Gender    |                         |     |                       |     |
| Female    | 1.00                    |     | 1.00                  |     |
| Male      | 1.22 (1.07 to 1.38)     | 0.002| 1.24 (1.08 to 1.42)   | 0.002|
| Age (years) | 1.00 (0.99 to 1.01) | 0.735| 1.00 (0.99 to 1.00)   | 0.347|
| CD4 count (cells/μl) |     |     |                       |     |
| > 350     | 1.00                    |     | 1.00                  |     |
| 200 to 350| 0.98 (0.77 to 1.26)     | 0.889| 0.90 (0.70 to 1.17)   | 0.438|
| 50 to 199 | 0.89 (0.68 to 1.15)     | 0.366| 0.84 (0.65 to 1.10)   | 0.211|
| < 50      | 1.24 (0.94 to 1.63)     | 0.122| 1.16 (0.88 to 1.53)   | 0.302|
| WHO clinical staging |     |     |                       |     |
| Stage I   | 1.00                    |     | 1.00                  |     |
| Stage II  | 1.43 (1.18 to 1.73)     | <0.001| 1.31 (1.08 to 1.59)   | 0.005|
| Stage III | 1.17 (0.97 to 1.42)     | 0.099| 1.12 (0.92 to 1.37)   | 0.270|
| Stage IV  | 0.98 (0.63 to 1.51)     | 0.912| 0.84 (0.53 to 1.32)   | 0.452|
| Functional status |     |     |                       |     |
| Working   | 1.00                    |     | 1.00                  |     |
| Ambulatory| 1.33 (1.08 to 1.63)     | 0.006| 1.25 (1.01 to 1.54)   | 0.038|
| Bedridden | 1.41 (0.82 to 2.45)     | 0.218| 1.37 (0.78 to 2.41)   | 0.274|
| Type of facility |     |     |                       |     |
| Tertiary  | 1.00                    |     | 1.00                  |     |
| Secondary | 0.74 (0.65 to 0.84)     | <0.001| 0.76 (0.66 to 0.87)   | <0.001|

Abbreviations
ART, antiretroviral treatment; CHEWs, community health extension workers; CHOs, community health officers; d4T, stavudine; EFV, efavirenz; EMR, electronic medical record; GHAIN, Global HIV/AIDS initiative in Nigeria; HCT, HIV counselling and testing; IQR, interquartile range; LAMIS, Lafiya Management Information System; LTFU, lost to follow-up; NHREC, Nigerian National Health and Research Ethics Committee; NVP, nevirapine; PHSC, Protection of Human Subjects Committee; sHR, sub-hazard ratio; TDF, tenofovir; WHO, World Health Organization; ZDV, zidovudine; 3TC, lamivudine.
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