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Gender-related differences in outcomes and attrition on antiretroviral treatment among an HIV-infected patient cohort in Zimbabwe: 2007–2010

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SUMMARY

Objectives: To determine (1) gender-related differences in antiretroviral therapy (ART) outcomes, and (2) gender-specific characteristics associated with attrition.
Methods: This was a retrospective patient record review of 3919 HIV-infected patients aged ≥15 years who initiated ART between 2007 and 2009 in 40 randomly selected ART facilities countrywide.
Results: Compared to females, males had more documented active tuberculosis (12% vs. 9%; $p < 0.02$) and a lower median CD4 cell count (117 cells/μl vs. 143 cells/μl; $p < 0.001$) at ART initiation. Males had a higher risk of attrition (adjusted hazard ratio (AHR) 1.28, 95% confidence interval (CI) 1.10–1.49) and mortality (AHR 1.56, 95% CI 1.10–2.20). Factors associated with attrition for both sexes were lower baseline weight (<45 kg and 45–60 kg vs. >60 kg), initiating ART at an urban health facility, and care at central/provincial or district/mission hospitals vs. primary healthcare facilities.
Conclusions: Our findings show that males presented late for ART initiation compared to females. Similar to other studies, males had higher patient attrition and mortality compared to females and this may be attributed in part to late presentation for HIV treatment and care. These observations highlight the need to encourage early HIV testing and enrolment into HIV treatment and care, and eventually patient retention on ART, particularly amongst men.

1. Introduction

With only 12% of the world's population, Sub-Saharan Africa has 68% of the world's burden of HIV/AIDS cases.[1] Zimbabwe, a country in southern Africa, is also badly affected by the HIV/AIDS epidemic, with recent statistics showing an HIV prevalence of 15% in the 15–49 years age group according to the 2010–2011 Zimbabwe Demographic and Health Survey.[2]

Since the national antiretroviral treatment (ART) programme was initiated in 2004, there has been a continuous increase in the cohort of HIV-infected individuals accessing this life-saving intervention in Zimbabwe. The number of health facilities offering ART services increased from 7 in 2004 to 960 by December 2012,[3] and those receiving ART increased from 24 500 people in 2005 to 531 136 by the end of 2012.[3] In terms of adult ART coverage, the country reached universal access levels of 85% in 2012, but with changing global guidelines, which recommended earlier ART initiation, the coverage dropped to 53% in December 2013.[4]

Despite this continued scale-up in numbers of HIV-infected patients receiving ART, a growing concern in most ART programmes is patient retention in care, which is critical for the success of such programmes. A meta-analysis of 32 ART programs in Africa, excluding Zimbabwe, showed that retention was 60%, with loss to follow-up being the major cause of attrition, followed by death.[5] Partly associated with attrition from HIV treatment and care is male gender,[6–11] and this has been attributed in part to

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advanced HIV disease at the time of ART initiation[7,12] and poor treatment adherence among males.[11,13] Despite knowing that attrition is higher among males, little is known about differences in the immunological response to ART between males and females in the routine ART programme setting. Furthermore, few studies have assessed the factors specific to males and females that influence attrition from ART. Identifying these gender-specific attrition-associated factors is critical for determining priority areas for improving patient retention for each sex.

In Zimbabwe, a review of the national ART programme revealed that patient retention rates at 36 months was 64.4% and that male gender increased the risk of attrition.[14] Using this dataset we conducted an extended data analysis aimed at determining: (1) gender-related differences in ART outcomes, primarily attrition from treatment, mortality, loss to follow-up, and immunological failure, and (2) gender-specific characteristics associated with attrition.

2. Methods

2.1. Study design

We conducted a retrospective cohort study using routinely collected ART programme data.

2.2. Setting: general and site-specific

2.2.1. Clinical procedures in the Zimbabwe National ART Programme

ART eligibility between 2007 and 2009 was based on national guidelines[15] adapted from the World Health Organization (WHO):[16] ART was initiated in patients with a documented HIV-positive test who were classified with WHO clinical stage 3 disease and a CD4+ cell count <350/μl, or WHO clinical stage 4 disease, or who had a CD4+ cell count <200/μl irrespective of the WHO staging. Although not mandatory, other recommended psychosocial criteria for evaluating ART eligibility, as they are considered a measure of patient reliability on treatment, were the following: (1) compliance with co-trimoxazole prophylaxis using pill counts or keeping appointments, as this will indicate the likelihood of adherence to ART; (2) completion of prescribed counselling session(s); (3) availability of a treatment partner and/or disclosure to that treatment partner; and (4) ease of follow-up of the patient. Co-trimoxazole was commenced at least 2 weeks before ART initiation among adult patients who were either in WHO clinical stage 2 or higher, or who had a CD4 cell count <200/μl; this would be continued indefinitely or until the CD4 count was >200/μl for >6 months.

Women were checked for pregnancy prior to ART initiation as it was deemed preferable to commence ART after the first trimester so as to minimize the risk of teratogenesis.[16] The recommended first-line ART regimen included two nucleoside reverse transcriptase inhibitors (NRTIs), namely stavudine and lamivudine, and one non-nucleoside reverse transcriptase inhibitor (NNRTI), namely nevirapine. Zidovudine could replace stavudine in the event of drug toxicity, while efavirenz could replace nevirapine in the event of an adverse reaction, during pregnancy, or if a patient was commenced on tuberculosis (TB) treatment.

2.2.2. Follow-up in the Zimbabwe National ART Programme

Patients are seen every 2 weeks during the first month of ART initiation, then every month for the following 3 months, and are reviewed every 3 months after the first 4 months. Patients can also visit the clinic immediately if they experience any side effects. Recommended clinical and laboratory monitoring indices include the patient's weight, WHO clinical stage, development of opportunistic infections (OIs), complete blood count (CBC), serum alanine transaminase (ALT), serum creatinine, and when available CD4+ cell counts. (Note: CD4 testing was not widely available between 2007 and 2009. By end of 2009, 68 CD4 machines were in 59 facilities located in 47 out of the country's 62 districts.[17]) Routine clinical monitoring is recommended every 3 months, CBC and CD4 cell counts should be conducted every 6 months, and ALT and creatinine should be measured every 12 months. Patient demographic, clinical, and laboratory information and visit dates are recorded in the Ministry of Health and Child Care (MOHCC) medical records maintained at the health facility.

2.2.3. Treatment outcome measures

ART outcomes during data abstraction were categorized as alive and retained on therapy, died, stopped treatment, transferred out, defaulted, loss-to-follow-up (LTFU), and other. LTFU was defined as patient absenteeism from a healthcare facility for >90 days after the last scheduled appointment with the healthcare provider or pharmacy, whilst defaulters were those who had not come back to the clinic for <90 days from the last scheduled appointment. The LTFU date was recorded as the date of the most recent visit or one day after ART initiation if patients only attended the initiation visit. In this analysis, our primary outcomes of interest were clinical ART outcomes and immunological failure. Clinical outcomes comprised all-cause mortality, LTFU, and attrition. Attrition referred to patients who were documented as having stopped ART, died, or who were LTFU. Immunological failure was defined in line with WHO 2006[16] and the Zimbabwe National ART guidelines[15] as (1) a decline in CD4+ cell count after ≥6 months on therapy, (2) a fall to pre-therapy CD4 count/percentage, or (3) a CD4 count ≤100 cells/μl after at least 6 months on therapy. Overall immunological failure was then determined as having been classified with immunological failure by any of the three criteria stated above.

2.2.4. Study sites

The study was conducted in 40 of 70 health facilities that were providing ART services to ≥50 HIV-infected patients for ≥6 months by May 31, 2008, for the purposes of logistical and financial feasibility. All provinces countrywide were represented in the sample whereby sites were selected randomly with the probability of selection being proportional to the number of adult patients who had received ART at each site, by May 31, 2008.

2.3. Study participants

Patients were included in the study if they were HIV-infected and ≥15 years old and had initiated ART between January 1, 2007 and December 31, 2009. Transfer-in patients were excluded from the sampling frame in order to avoid double-counting, as they may have been abstracted as transfer-out at another selected study site. A minimum of 3842 patients were required for the study, assuming a design effect of 2, 50% of adult patients were retained on ART at 12 months after ART initiation, a 95% confidence interval of ±2.5%, and 20% of charts were missing. Patient charts were selected randomly at each site using an R program.

2.4. Data variables, source of data, and data collection

Data variables included demographic data such as sex and age at enrolment into HIV care. Clinical information abstracted included WHO stage, weight, co-trimoxazole use, and CD4 count prior to ART initiation. Follow-up visit information included weight, haemoglobin, CD4 count, clinical stage, co-trimoxazole prescription, ART regimen, and the final patient outcome. Selected patient files were retrieved by ART clinic staff who were responsible for retrieving selected patient files, whilst missing ones were replaced by the next eligible patient record on the randomly ordered list. Trained health