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Causes of Hospital Admission among Patients Receiving Highly Active Antiretroviral Therapy

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Abstract: Highly active antiretroviral therapy has substantially improved the prognosis for HIV-infected patients globally. However, HIV infection remains a major cause of morbidity and mortality in many developing countries. The main objective of this study was to investigate the causes of hospital admission in patients receiving antiretroviral therapy in Lesotho. A 4 months cross-sectional study of HIV-infected, ART-treated adults admitted to the male and female medical wards at Queen Elizabeth II Referral Hospital in Maseru, Lesotho. A 96 patients enrolled, 62.5% were male and the median CD4 count on admission was 101 cells/μL (IQR 22-224). A 69.8% of the study participants had been receiving HAART for <6 months and 97.9% of all patients were on a first line NNRTI-based regimen. Patients were admitted for the management of opportunistic infections (71.9%), non-infectious HIV-related diseases (24.0%) and adverse drugs reactions (18.8%). The most frequent principal diagnoses were tuberculosis (45.8%), AZT-induced anaemia (11.5%), pneumonia (9.4%) and immune-inflammatory reconstitution syndrome (7.3%). In-hospital mortality among the study participants was 36.5%. HIV-related opportunistic infections are an important cause of hospital admission and mortality in the era of HAART. Efforts are needed to encourage patients to present early to HIV care. In addition, patient monitoring should be improved in order to facilitate early detection and management of treatment failure.

Key words: HIV, HAART, opportunistic infections, hospital admission, patient

INTRODUCTION

The introduction of Highly Active Antiretroviral Therapy (HAART) has improved the survival of persons infected with HIV (Palella *et al*., 1998; Mocroft *et al*., 2003). Global access to Antiretroviral Therapy (ART) has improved substantially in recent years however ART programmes in developing countries face several challenges that may hamper the successful implementation of HAART. Among the key challenges are inadequate laboratory support for diagnosis of HIV infection and monitoring of antiretroviral therapy; in addition delayed treatment-seeking behaviour among HIV-infected patients often means that antiretroviral therapy is initiated too late in the course of HIV infection to reduce morbidity and mortality (Jerene *et al*., 2006; Ojikutu, 2007; Ogoina *et al*., 2012).

In Lesotho, all HIV care services including HIV Testing and Counseling (HTC), laboratory investigations and antiretroviral drugs are provided free of charge in the public sector. Since, the launch of the national ART programme in 2004, HTC rates and ART coverage have increased steadily by the end of 2009, approximately 52% of the patients requiring antiretroviral therapy were receiving treatment (MHSW, 2010a). However, little is known about treatment outcomes in patients receiving ART in Lesotho where HIV/AIDS and HIV-related disease remain the major causes of morbidity and mortality in both hospitalised and clinic-based adult patients (MHSW, 2010b). The main objective of this study was to investigate causes of hospital admission in patients receiving antiretroviral therapy in Maseru, Lesotho.

MATERIALS AND METHODS

The study was conducted at Queen Elizabeth II Referral Hospital in Maseru, Lesotho between July 2010 and October 2010. For eligibility to participate in the study, patients had to be 16 years or older with a prior diagnosis of HIV infection, a known date of starting ART and a documented baseline CD4 count. All patients meeting the above criteria and who had been admitted for treatment of infectious and/or non-infectious HIV-related disorders and/or adverse drug reactions associated with the use of ARV drugs or drugs used for prophylaxis or treatment of opportunistic infections were invited to

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participate in the study in consecutive order. Prior to data collection, patients were asked to give their written informed consent. A predesigned form was used to collect patient demographic and medical data. Information obtained from the patient medical records included the following: date and diagnosis of HIV infection, date of initiation of ART, clinical and immunological staging on initiation of ART as well as the initial and current ART regimen. A complete clinical evaluation was performed for each patient prior to enrollment. Laboratory investigations included a complete blood count, differential count, tests of kidney function (serum creatinine, blood urea nitrogen) and tests of liver function (serum transaminases). Patient care was carried out according to current hospital protocols.

Data was analysed using SPSS 20.0 (Chicago, Il, USA). Descriptive statistical analyses were performed; demographic variables and laboratory parameters are presented as median with interquartile range and the frequency of other variables as percentages. Ethical approval was obtained from the Lesotho Ministry of Health and Social Welfare Ethics Committee.

RESULTS

The study population was 62.5% male with a median age of 36 (IQR 32-42). Prior to ART initiation, most of the patients (84.4%) were in advanced clinical stage of HIV infection (WHO stage III/IV) and the baseline median CD4 count was 122 cells/μL (IQR 54-190). The majority of the patients (69.8%, n = 67) had been receiving HAART for <6 months. Nearly all patients (97.9%) were on a first line NNRTI-based ART regimen. The 7 patients (9.4%) had a history of drug substitution within the first line regimen; 6 due to adverse drug reactions and 1 as a result of TB co-infection; the 2 patients had been switched to second line regimen following ART failure. The 30 patients were concurrently receiving Antituberculosis Treatment (ATT) on admission. The median CD4 count on admission was 101 cells/μL (IQR 22-224) with 89% of the patients having CD4 counts below 350 cells/μL (Table 1).

Researchers investigated the causes of hospital admission and in-hospital mortality among patients who had received antiretroviral therapy for <6 months or longer. More than two thirds of all patients (71.9%, n = 68) presented with one or more opportunistic infections at admission; 18 patients (18.8%) were diagnosed with adverse drug reactions and 7 (7.3%) with immune reconstitution syndrome (Table 2). The most frequent principal diagnosis among both groups of patients was tuberculosis (45.8%) with the majority of the patients having pulmonary tuberculosis. The 30 patients were receiving antituberculosis therapy at the time of admission and 14 were diagnosed following hospital admission. The 15 patients (15.6%) were diagnosed with HIV wasting syndrome and 6 patients had central nervous symptoms (seizure n = 4; psychosis n = 2). The most common adverse drug reaction was AZT-induced anaemia (n = 11) followed by drug-induced hepatitis (n = 5), confusion secondary to efavirenz and lactic acidosis secondary to stavudine (n = 1, each). All the patients diagnosed with drug-induced hepatotoxicity were on efavirenz-based first line ART regimens with concurrent antituberculosis treatment. The overall all cause mortality

Table 1: Demographic and clinical characteristics of the study population at admission

Parameteres	Frequency (n (%))
Gender	
Male	60 (62.5)
Female	36 (37.5)
Median age, years (IQR)	36 (32-42)
Time on ART	
<6 months	67 (69.8)
≥6 months	29 (30.2)
Current ART regimen	
First line ART regimen	94 (97.9)
TDF/3TC/EFV	61 (63.5)
TDF/3TC/NVP	5 (5.2)
AZT/3TC/EFV	7 (7.3)
AZT/3TC/NVP	4 (4.2)
d4T/3TC/EFV	10 (10.4)
d4T/3TC/NVP	5 (5.2)
Second line ART regimen	2 (2.1)
Current TB treatment	30 (31.3)
Category I ATT	24 (25.0)
Category II ATT	6 (6.3)
Median CD4 count (cells/μL (IQR))	101 (22-224)

Table 2: Causes of hospital admission among the study population

Cause of hospital admission	Time on ART <6 months (n = 67)	Time on ART >6 months (n = 29)	n (percentage of participants) (Total = 96)
Opportunistic infections	50	18	680 (71.9)
Tuberculosis	35	9	44 (45.8)
Pulmonary TB	30	7	-
Extrapulmonary TB	5	2	-
Bacterial infections			
Pneumonia	6	3	9 (9.4)
Enteritis	4	3	7 (7.3)
Bacterial meningitis	2	3	5 (5.2)
Fungal infections			
Oral/Oesophageal candidiasis	12	4	16 (16.7)
Cryptococcal meningitis	1	2	3 (3.1)
Non-infectious HIV-related diseases	16	7	23 (24.0)
HIV wasting syndrome	11	4	15 (15.6)
CNS (unclassified)	4	2	6 (6.3)
Kaposi sarcoma	1	1	2 (2.1)
Adverse drug reactions	12	6	18 (18.8)
Anaemia	7	4	11 (11.5)
Hepatitis	4	1	5 (5.2)
Confusion	1	0	3 (3.1)
Lactic acidosis	0	1	1 (1.0)
IRIS	7	0	7 (7.3)

Table 3: Causes of death among the study population

Cause of death	Time on ART: <6 months (n = 28)	Time on ART: >6 months (n = 7)	n (percentage of deaths) (Total = 35)
Tuberculosis	12	5	17 (48.5)
Enteritis	4	1	5 (14.3)
Hepatotoxicity	3	0	3 (8.6)
IRIS	3	0	3 (8.6)
HIV wasting syndrome	3	0	3 (8.6)
Pneumonia	2	0	2 (5.7)
Anaemia (secondary to AZT)	1	0	1 (2.9)
CNS (unclassified)	0	1	1 (2.9)

rate was 36.5% (n = 35); TB was the leading cause of in-hospital death among the study population (Table 3).

DISCUSSION

Researchers studied the causes of hospitalisation and in-hospital mortality among HIV-infected, ART-treated patients admitted to a tertiary level hospital in Maseru, Lesotho. The study population was made up of patients who had been admitted via the emergency department (n = 65, 67.7%) and referrals from lower levels of care including ART clinics and district hospitals (n = 31, 32.3%). The low percentage of patients who had been receiving ART for 6 months or longer in this study (30.2%) may reflect reduced HIV-associated morbidity following long term antiretroviral therapy among HIV-infected patients in general. However, it may also be indicative of a lower proportion of patients remaining on ART over the long term; a 2009 multi-center study conducted in Lesotho revealed that the loss to follow-up 12 months after initiating ART was as high as 65% (MHSW, 2010b). National population-based surveys consistently show roughly equal HIV prevalence among males and females with a slightly higher burden of infection in females (LDHS, 2009), however little is known about gender differences in ART uptake and treatment outcomes in Lesotho. In the study, 62.5% of the patients were male; a higher proportion of all males than all females had been on ART for <3 months (68.3 vs. 50.0%) and the in-hospital mortality was higher among males than females (41.7% of all males vs. 27.7% for females). Several researchers have reported that HIV-infected men are more likely than women to present late to HIV care (Muula *et al*., 2007; Skovdal *et al*., 2011; Vives *et al*., 2012). The delay in initiating antiretroviral therapy is associated with a higher risk of clinical deterioration and mortality early in therapy (Jerene *et al*., 2006; Cornell *et al*., 2012). The most common cause of hospitalisation was treatment for opportunistic infections. The spectrum of HIV-related infections was similar between patients who had been on antiretroviral therapy for <6 months and those with a longer duration of ART. This observation may be explained by the fact that the majority of the patients were profoundly immunosuppressed; around two thirds of patients from both groups had CD4 counts <200 cells/μL at the time of hospitalisation. Low CD4 counts are associated with a higher incidence of opportunistic infections (Deuffic-Burban *et al*., 2007). Researchers investigated CD4 count changes in patients who had been on ART for >6 months (n = 29); 75.9% of these patients had experienced immunological failure prior to hospitalisation. Currently there is no consensus on when and how to treat immunological failure. Lesotho has adopted the WHO guidelines on switching ARVs due to failure of the first line regimen: where viral load testing is not available, patients experiencing immunological failure are monitored for development of clinical signs and symptoms and switching to second line ARV regimen is recommended in patients presenting with WHO stage 4 clinical events (MHSW, 2010a, b).

The 18 patients (18.8%) were admitted for the treatment of adverse drug reactions. The reported incidence of adverse drug reactions in patients receiving HAART ranges from as low as 3% to over 70% in several cohort studies (Subbaraman *et al*., 2007; Eluwa *et al*., 2012). Drug-related toxicities are a major cause of hospital admission in HIV-infected patients and may be due to ARVs and/or other drugs used to treat HIV-associated diseases (Nunez *et al*., 2006; Mehta *et al*., 2008; Ogoina *et al*., 2012). In this study, the most common ADR in both the short and long-term was AZT-induced anaemia, however the frequency of other adverse effects may be higher than reported. In general, haemoglobin measurements were routinely recorded in patient medical files; in contrast baseline kidney and liver function laboratory data were missing for the majority of the study participants. The 30.2% of all patients had serum creatinine levels indicative of renal dysfunction (serum creatinine >130 μmol L^{-1}). The use of tenofovir (68.8% in the study) and advanced HIV-infection have been associated with the development of abnormal renal function (Szczech, 2008). Although, only 5 patients were diagnosed with clinical hepatitis, ALT elevations >2.5×ULN were observed in 17.7% of the study participants. The risk of developing hepatitis is higher in HIV-infected patients receiving concomitant ARV and anti-TB therapy (Subbaraman *et al*., 2007).

CONCLUSION

Opportunistic infections were the leading cause of hospital admission among this population of HIV-infected

patients receiving antiretroviral treatment in Maseru, Lesotho. The findings highlight the need for strategies aimed at increasing early diagnosis of HIV infection in order to facilitate adequate prophylaxis or treatment of HIV-related opportunistic infections and initiation of ART. In addition, improving ART response monitoring at the lower levels of the health care system could enable early detection of ARV-related toxicities and treatment failure.

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