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ABSTRACT In Libya, little is known about HIV-related hospitalizations and in-hospital mortality. This was a retrospective analysis of HIV-related hospitalizations at Tripoli Medical Centre in 2013. Of 227 cases analysed, 82.4% were males who were significantly older (40.0 versus 36.5 years), reported injection drug use (58.3% versus 0%) and were hepatitis C virus co-infected (65.8% versus 0%) compared with females. Severe immunosuppression was prevalent (median CD4 count = 42 cell/µL). Candidiasis was the most common diagnosis (26.0%); Pneumocystis pneumonia was the most common respiratory disease (8.8%), while cerebral toxoplasmosis was diagnosed in 8.4% of patients. Current HAART use was independently associated with low

risk of in-hospital mortality (OR 0.33), while central nervous system symptoms (OR 4.12), sepsis (OR 6.98) and low total lymphocyte counts (OR 3.60) were associated with increased risk. In this study, late presentation with severe immunosuppression was common, and was associated with significant in-hospital mortality.

Profil clinique et facteurs associés à la mortalité chez des patients hospitalisés vivant avec le VIH/sida : analyse rétrospective du Centre médical de Tripoli (Libye), 2013

RÉSUMÉ En Libye, les connaissances sur les hospitalisations et la mortalité en milieu hospitalier liées au VIH sont rares. Nous avons procédé à une analyse rétrospective des hospitalisations liées au VIH au centre médical de Tripoli en 2013. Sur 227 cas analysés, 82,4 % étaient des hommes nettement plus âgés (40,0 contre 36,5 ans), qui déclaraient s'injecter des drogues (58,3 % contre 0 %) et qui étaient atteints d’une co-infection par le virus de l’hépatite C (65,8 % contre 0 %) comparativement aux femmes. L’immunosuppression sévère était prévalente (numération des lymphocytes T-CD4 = 42 cellules/µL). Le diagnostic le plus fréquent était la candidose (26,0 %) ; la pneumonie à Pneumocystis était la maladie respiratoire la plus fréquente (8,8 %), tandis que la toxoplasmose cérébrale était diagnostiquée chez 8,4 % des patients). Un traitement antirétroviral hautement actif en cours était indépendamment associé à un faible risque de mortalité en milieu hospitalier (OR 0,33), tandis que les symptômes du système nerveux central (OR 4,12), la septicémie (OR 6,98) et les faibles numérations lymphocytaires totales (OR 3,60) étaient associés à un risque accru. Dans cette étude, une présentation tardive accompagnée d'une immunosuppression sévère était fréquente, et était associée à une mortalité élevée en milieu hospitalier.

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Introduction

Human immunodeficiency virus (HIV) and its associated acquired immune deficiency syndrome (AIDS) continue to exact a significant deal of morbidity and mortality worldwide, with over 35 million people infected by the year 2013 (1). In developed countries, the wide availability of highly active antiretroviral therapy (HAART) since the mid-1990s has significantly reduced

AIDS-related hospitalizations and mortality, and improved the overall survival among affected individuals (2–5). It has also reduced rates of AIDS-defining caused by opportunistic infections, and changed the spectrum of HIV-related hospitalizations to become mostly due to chronic and non-AIDS-defining conditions, such as cardiovascular diseases and malignancy (6–8).

By contrast, AIDS is still the main reason for hospitalization in developing countries, with various opportunistic infections playing major roles in HIV-related morbidity and mortality (9–11). With such variations in the spectrum of HIV-related diseases, findings from developed countries might not be generalizable to our settings. In addition, although several studies have been conducted in other developing countries of Africa and Asia (12–17), the spectrum of diseases related to HIV/AIDS may have regional variations influenced by socioeconomic status, endemic infections, nutrition and availability of HAART and hepatitis coinfections. Knowledge regarding the spectrum of AIDS-defining illnesses and local prevalence of various opportunistic infections might be important for policy-makers and stakeholders to better manage limited screening, diagnostic and therapeutic resources and to plan actions to reduce morbidity and mortality. It might also be important in raising the awareness of physicians to most prevalent diagnoses and in taking decisions on empirical treatment and management plans.

With the paucity of published data on HIV/AIDS in Libya (18), the spectrum of AIDS-defining illnesses remains largely undetermined and little is known about the causes of HIV-related hospitalizations, clinical profiles and factors associated with mortality in hospitalized patients with HIV. In this study, we aimed to: define the spectrum of HIV-related causes of hospitalization; assess the profile of hospitalized HIV-positive adults; and examine the clinical and laboratory factors associated with in-hospital mortality among adults with HIV/AIDS admitted to Tripoli Medical Centre during the year 2013.

Methods

Study site

Tripoli Medical Centre is a university and tertiary referral hospital with a capacity of 1200 beds. It provides specialist medical services to patients from Tripoli and other cities in the western and central regions of Libya. The department of infectious diseases provides specialist HIV management as an ambulatory care as well as a 14-bed capacity dedicated for management of inpatients with HIV/AIDS.

Study design

This was a retrospective, observational analysis of HIV-related hospitalizations at the Centre from January to December 2013. As a routine screening, all admitted patients had their HIV, HBV and HCV status determined by 4th-generation enzyme-linked immunosorbent assay

testing. Patients who were 15 years of age or more at the time of hospitalization and with positive HIV test results were identified through the department's inpatient registry. Their case notes and discharge summaries were then reviewed and relevant data abstracted using a standard data collection form. Ethical approval was granted by the department of medicine and the scientific committee at Tripoli Medical Centre.

Data collection

The following variables were collected anonymously: demographics (age, sex, marital status) and HIV risk factors (HAART use; clinical signs and symptoms at the time of hospitalization); serological testing for hepatitis C (HCV) and hepatitis B virus (HBV) infections; haematological and biochemical laboratory results at the time of hospital admission and before rehydration, blood transfusion or administration of antibiotics; diagnosis during hospitalization; and status upon discharge (alive or dead).

In-hospital diagnosis

Although efforts were made to ascertain the diagnoses, the lack of some diagnostic facilities at the Centre and the presence of patients with advanced illness at the time of presentation might have prohibited invasive diagnostic procedures. In such instances, the following criteria were used to establish a diagnosis:

pulmonary tuberculosis (TB): a positive sputum smear or culture for acid-fast bacilli or a compatible clinical presentation with suggestive findings on chest X-ray or computerized tomography scan and a response to anti-TB treatment.

extrapulmonary TB: a histopathological diagnosis from an extrapulmonary site (e.g. lymph node; pleura) or a compatible clinical presentation with suggestive findings on imaging scans and a response to anti-TB treatment.

cerebral toxoplasmosis: a compatible clinical presentation with suggestive findings on brain magnetic resonance imaging and a response to anti-toxoplasmosis treatment.

progressive multifocal leucoencephalopathy: a compatible clinical presentation with suggestive findings on brain magnetic resonance imaging.

Pneumocystis jiroveci: a compatible clinical presentation with suggestive findings on chest X-ray/computerized tomography and a response to treatment (provided that TB was excluded).

cryptococcal meningitis: a compatible clinical presentation with the detection of cryptococcal antigen in cerebrospinal fluid or serum.

candidiasis: a compatible clinical presentation and/or findings on gastroscopy.

sepsis: systemic inflammatory response syndrome with an identified focus of infection. Systemic inflammatory response syndrome was defined as 2 or more of the following: fever > 38 °C or 90 beats per minute; respiratory rate > 20 breaths per minute or an arterial carbon dioxide tension 12 000 or

All individuals with central nervous system symptoms or signs were screened for cryptococcal infection using a cryptococcal antigen test. Patients with retinitis had cytomegalovirus DNA test (polymerase chain reaction assay), whereas for patients with oesophagitis, gastritis, enteritis or colitis and not responding to medications, endoscopy, biopsy and histopathological examination for cytomegalovirus were performed. Severe immunosuppression was defined as CD4 count **S tatistical analysis**

R, version 3.1.1, a language and environment for statistical computing (R Foundation for Statistical Computing, Austria,) was used to conduct planned analyses.

Quantitative variables were summarized using the median and interquartile range (IQR), and bivariate analysis was done using Mann–Whitney U-test. Categorical variables (grouped quantitative and qualitative variables) were summarized using frequency tables and percentages of total, while the bivariate analysis was performed using chi-squared or Fisher exact tests; they were presented graphically using bar charts.

A stepwise logistic regression analyses was conducted to calculate adjusted odds ratios (OR). To maintain the assumption of independent observations in patients with two hospitalizations, only data available from the last admission were used.

Missing values were excluded during the analysis of continuous variables, but were included as a “missing” category during the grouped analysis. All analyses were 2-sided, and P-values of

Results

Our inpatient registry reported 340 hospitalizations in the year 2013; 227 were for individuals with positive HIV tests. During the study period, 211 HIV-positive patients were hospitalized; 16 of them had a re-hospitalization during the same year. The reason for re-hospitalization was different for all 16 patients (e.g. Pneumocystis jiroveci then skin Kaposi sarcoma 3 months after starting HAART).

Demographic characteristics

Table 1 summarizes the main demographic characteristics of the study group. The majority of patients were male (187, 82.4%) with a median age of 40 years (IQR 37.5–45 years) for males and 36.5 years (IQR 30–45 years) for females (P = 0.01). Most male patients were single (55.6%), reported injection drug use as a route of HIV transmission (58.3%) and tested positive on HCV serology test (65.8%). In contrast, most female patients were married (57.5%) or widowed (22.5%) and identified marital heterosexual contact as a route of HIV transmission (87.5%), while none of them tested positive on HCV or HBV serological tests.

Clinical symptoms and signs at admission

The clinical symptoms and signs at time of admission are summarized in Table 2 . Fever was the most common presenting symptom (42.3%) followed by oral thrush (29.1%). When analysed as groups of symptoms at time of admission, constitutional symptoms were the most common (59.9%), followed by gastrointestinal (48.5%) symptoms.

Although the majority of patients were known to have HIV infection before admission (85.9%), most hospitalized patients were not on HAART (141, 62.0%), of whom 103 (45.4%) had never received HAART before.

In-hospital diagnoses

The spectrum of diagnoses is presented in Figure 1 . Oral and oesophageal candidiasis was the most common diagnosis (26.0%) followed by extrapulmonary TB (9.3%) and sepsis (9.3%). Pneumocystis jiroveci was the most common respiratory disease (8.8%) whilst cerebral toxoplasmosis was the most commonly identified intracranial mass lesion (8.4%).

Laboratory test results at admission

Tables 3 and 4 summarize the laboratory test results at time of admission. Data on CD4 counts were available for 169 inpatients (74.4%). The median count was 42 cells/µL, with 150 patients (88.8% of available data) having CD4 counts **In-hospital mortality**

The median duration of hospital stay was 8 days and overall mortality was high (85 patients, 37.4%), with a significantly higher rate among males than females (40.6% versus 22.5%; P = 0.049) (Table 1). Just over one-third of patients (30, 35% of all deaths) died within 48 hours of hospital admission.

Factors associated with in-hospital mortality

A total of 184 (87.2%) patients with complete data were included in a stepwise logistic regression analysis, and results on independent risk factors are summarized in Table 5 . Current HAART use was independently associated with a low risk of in-hospital mortality (OR 0.33; 95% CI: 0.14–0.8; P = 0.015). Central nervous system symptoms (OR 4.12; 95% CI: 1.77–9.6; P = 0.001), sepsis (OR 6.98; 95% CI = 1.71–28.44; P = 0.007), hyponatraemia (OR 2.69; 95% CI: 1.12–6.44; P = 0.023) and low total lymphocyte counts (OR 3.6; 95% CI: 1.36–9.52; P = 0.01) were associated with increased risk.

Discussion

In 2013 at Tripoli Medical Centre, AIDS-defining opportunistic infections were the most common reasons for HIV-related hospitalizations. Inpatients were mostly middle-aged men who were known to be HIV-positive before admission; a finding similar to previous reports from both developed and developing countries (7,9). HIV-related hospitalizations were mostly among patients in their economically productive years, therefore increasing the socioeconomic burdens on the patients and their families.

Injection drug use was the most commonly identified HIV risk factor among males, with a concomitantly high prevalence of HCV coinfection. Although this is different to findings from developed (7) and other developing (19) countries where homosexual and heterosexual transmissions were the most common respectively, it was consistent with a previous report on the high prevalence of HIV/HCV coinfection among injection drug users in Libya (20). Nonetheless, a proportion of patients denied any HIV risk factors, and others presented at an advanced stage and died before verifying any HIV risk factor (reported as “unknown”). This might have led to under-representation of some HIV risk activities previously reported in Libya (21).

Females, on the other hand, were mostly infected with HIV through marital heterosexual transmission, and were more likely to be unaware of their positive HIV disease status before admission. This finding implicates marriage as a potential HIV risk factor, and highlights the importance of pre-marriage counselling and HIV testing for monogamous couples. It also highlights a potential role for public education on the risk of HIV transmission and available protective tools to reduce such risk among serodiscordant couples (22,23). Furthermore, unawareness of HIV status among women in their reproductive years poses a significant risk of mother-to-child-transmission (24), and adds another challenge to national prevention programmes.

In this study, the majority of patients were hospitalized with AIDS-defining illnesses, of which opportunistic infections were the most common. Pneumocystis jiroveci was the most common respiratory disease, especially among females, while cerebral toxoplasmosis was the most commonly identified intracranial mass lesion. Extrapulmonary TB was more common than pulmonary TB, as previously reported in patients with very low CD4 counts (25). However, findings of such a low prevalence should be interpreted with caution. It is possible that some cases with TB were missed or misclassified as sepsis syndromes, as the only available diagnostic modalities were chest X-ray and sputum for acid-fast bacillus stain; both of which are known to have poor sensitivity in HIV cases, especially at very low CD4 counts (26,27). As reported in previous studies from Africa, implementing new diagnostic modalities such as GeneXpert MTB/RIF (28) and TB-LAM (29) has the potential to diagnose TB among seriously ill patients with severe immunosuppression and may improve their overall prognosis (30,31).

Although the spectrum of opportunistic infections might be comparable across developing countries, the prevalence of the most common opportunistic infections shows wide regional variations. For instance, pulmonary TB was most commonly reported in India (32,33), Islamic Republic of Iran (14), most countries of Africa (9, 10,17,19), Bangladesh (34) and China (13), with very small contributions from Pneumocystis jiroveci (10,14) and toxoplasmosis (17,35). In contrast, the most commonly reported opportunistic infections were Pneumocystis jiroveci in Oman (12), toxoplasmosis in Lebanon (15) and cryptococcal meningitis in Thailand (16).

Knowledge regarding the prevalence of various opportunistic infections among HIV patients in developing countries with limited resources may aid in developing screening protocols, establishing appropriate prevention programmes, and guiding decisions on empirical treatment. It may also allow for better allocation of and prioritization of scarce diagnostic resources.

The risk of and mortality due to sepsis are reported to be higher in HIV-positive compared with HIV-negative patients (36–38). The aetiology of sepsis could also be different, with fungal and mycobacterial infections playing important causative roles (37,39). In our study, the aetiological causes of sepsis could not be ascertained because many inpatients had received various antibiotics before admission, resulting in negative blood culture results. Also special diagnostic techniques for TB, fungi and other atypical organisms known to cause sepsis among HIV patients were not available due to resource constraints. Consequently, our results might not be sufficient to clearly describe the spectrum of TB, atypical organisms and disseminated fungal infections among HIV inpatients.

Despite several years availability of HAART in Libya, late presentation and poor HAART uptake by patients were common; a finding similar to previous reports (40–42). Late presentation is known to be associated with poor response to HAART (43), increased mortality (especially shortly after commencing HAART) (11,40–42,44–46), and high cumulative risk of HIV transmission (47).

Furthermore, the finding that the majority of patients were known to be HIV-positive and yet were not on HAART highlights another significant gap in access to and retention of HIV care services. Previous studies have identified several factors as potentially contributing to late presentation, poor HAART uptake and low retention in HIV care. These factors include stigma, fear of status disclosure, complexity of treatment regimens and lack of psychosocial support (48); lack of confidentiality and fear of discrimination at health facilities, workplace and community (49); poor staff–patient relationships and underestimation of the need for HAART (50); and active drug use (43,46).

Stigma and fear of disclosure are particularly important among females living in a conservative society. Previous studies from other Arab countries have reported a high prevalence of stigma against HIV-positive patients and poor knowledge about the disease, especially among females (51–53).

Health system strategies and HIV service delivery interventions such as counselling, brief case management discussion with patients, simplified treatment regimens, screening and management of depression, and co-location with drug rehabilitation services could potentially improve access to and retention in HIV care, reduce late presentation and increase HAART uptake (54,55).

The fact that some patients were not aware of their HIV disease status until the development of opportunistic infections might also reflect low education and lack of awareness about the risk of HIV transmission. This could potentially be ameliorated through education programmes and HIV awareness campaigns targeting the general population, accompanied by screening high-risk groups such as injection drug users and sexually active youth. Once diagnosed, patients should then be promptly referred to specialist HIV care.

Anaemia was identified in the majority of our inpatients and was severe enough in 17% of them to require blood transfusion. Anaemia has previously been reported in many developed and developing countries (13,19,56) and has been linked with HIV-disease progression and poor outcomes (57–59). In the context of advanced medical illnesses such as AIDS, anaemia could be due to poor nutrition, infections such as candidiasis and TB, or the advanced stage of HIV disease itself (60,61).

We reported a high rate of in-hospital mortality of 37.4%, which was broadly similar to other developing countries where AIDS is still the main cause for hospitalization (9,17,19,32,62). By contrast, in developed countries during the era of HAART, in-hospital mortality is very low and it is mostly related to non-AIDS illnesses such as malignancy and cardiovascular diseases (4,6,7,63).

In this study, HAART use was associated with a reduced risk of mortality, a finding consistent with previous reports on improved survival among HIV patients receiving HAART (3,64–66). In addition, a presentation with central nervous system symptoms, development of hyponatraemia or a diagnosis of sepsis were independently associated with increased risk of mortality, generally reflecting the severity of underlying diseases (67,68). The lack of appropriate diagnostic tools (brain biopsy, GeneXpert MTB/RIF, TB LAM, special culture media for atypical pathogens) could have led to a delay in establishing diagnoses and late initiation of aetiology-specific treatments, which could have negatively affected patients' overall prognosis. In addition, a low total lymphocyte count, which serves as a valid surrogate indicator of immunosuppression in resource-limited settings (69–71), was also associated with increased mortality, emphasizing the impact of severe immunosuppression on HIV-related mortality (4,7,9,19). Patient's sex, HCV coinfection and anaemia were not predictive of mortality in this study. This could be due to the small number of females included, and the high prevalence of both HCV and anaemia among the study participants.

Our study has some limitations that should be acknowledged. The study was conducted retrospectively and some data on clinical and laboratory variables were missing. This study was of patients admitted to a tertiary health-care centre and its results may not be generalizable, as

such settings tend to receive seriously ill cases who need specialized care and management. In some instances, a definitive diagnosis could not be reached. This might have been due to the serious and advanced condition of patients at presentation, which prevented further invasive diagnostics, or due to inadequate diagnostic facilities (e.g. culture media for atypical organisms); unavailability of diagnostic facilities (e.g. brain biopsy and histopathological diagnosis of cerebral toxoplasmosis, central nervous system TB and progressive multifocal leukoencephalopathy) and other resource constrains. Additionally, cause of death could not be confirmed due to lack of permissions for post-mortem studies, raising a possibility that other diagnoses (which might have been missed ante-mortem) might have also influenced patient outcomes (72–74).

Despite the limitations, our study has important strengths. To our knowledge, this is the first study to describe clinical, immunological and biochemical profiles and examine factors associated with mortality among hospitalized adults with HIV/AIDS in Libya. Our study also had a high-level representation on HIV-related hospital admissions, as Tripoli Medical Centre is one of the only 2 centres offering HIV care in western Libya.

Conclusion

The issue of late presentation and AIDS-related mortality is challenging and requires coordinated approaches and collaboration among various stakeholders. More efforts should be placed on improving access to HIV care, especially for females and marginalized risk groups such as injection drug use and homosexual men, successful linkage to care after diagnosis, prompt initiation of HAART, and retention on treatment and in care. There should also be strategies to integrate HIV treatment centres with mental health and drug rehabilitation services. Additionally, increasing HIV awareness and education in the community, screening high-risk populations, and improving the diagnostic capacity of referral laboratories might help in changing the current situation of HIV wards in Libya.

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