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Epidemiological and Clinical Characteristics of HIV Infected Patients at a Tertiary Care Hospital in Oman

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ABSTRACT

Objectives: In 2015, the Joint United Nations Program on HIV/AIDS (UNAIDS) set a target that 90% of all people living with HIV will know their HIV status, 90% of those diagnosed will receive antiretroviral therapy, and 90% of those receiving antiretroviral therapy will have viral suppression by 2020. We sought to elucidate the epidemiological and clinical characteristics of HIV infected patients at the Infectious Diseases Clinic at Royal Hospital, Oman, with a focus on the UNAIDS 90-90-90 achieved rates. ***Methods***: We conducted a retrospective analysis of the medical records of 326 HIV infected patients from 1989 to 2016. Data collected included demographics, Word Health Organization (WHO) staging, laboratory analyses, and treatment outcomes. ***Results:*** The overall mean age of the cohort was 36.0±15.0 years, and 60.4% (n = 197) were males. The majority of patients acquired HIV through heterosexual transmission (58.9%; n = 192). At the time of the first clinic visit, 26.1% (n = 85) of patients had WHO stage 4 HIV infection. The rates of HIV/HBV and HIV/HCV coinfections were 2.7% and 5.8%, respectively. The baseline CD4+ cells count was < 200 cells/mm^3 in 38.0% (n = 124) of patients, 201–500 cells/mm^3 in 30.1% (n = 99) of patients, and > 500 cells/mm^3 in 27.0% (n = 88) of patients. The baseline HIV RNA titer was greater than 1000 copies/mL^3 in 74.5% (n = 243) of the cohort. A total of 96.3% (n = 314) of patients received antiretroviral therapy, most commonly non-nucleoside reverse transcriptase inhibitor-based regimens. HIV genotype resistance testing was performed in 165 patients (50.6%) either at baseline in treatment naïve patients or following treatment failure. Among the 326 patients included, 22 patients (6.7%) died, and 29 patients (8.9%) were lost to follow-up. ***Conclusions:*** Regarding the UNAIDs 90-90-90 target, over a quarter of the patients presented late with WHO stage 4 HIV disease, 96.3% of cohort patients received antiretroviral treatment, and 71.5% achieved virological suppression.

Human immunodeficiency virus (HIV) is increasingly recognized as an important health issue in the Middle East and North Africa (MENA) region.[1,2] In 2015, the World Health Organization (WHO) estimated that around 230 000 people were living with HIV in the MENA region with 21 000 new HIV infections and 12 000 acquired immune deficiency syndrome (AIDS)-related deaths.[3] This indicates a 35% rise in new HIV cases diagnosed and 66% rise in AIDS-related deaths.[4]

Routes of HIV transmission vary between countries in the region; some have higher prevalence among intravenous (IV) drug users, while in other countries, transmission is highest among sex workers.[5,6] HIV prevention in the MENA region is challenged by many cultural and social barriers, punitive laws, and political unrest, which exacerbate transmission and affect implementation of HIV care.[7] In addition, provision of HIV services requires identification of high-risk populations to stop transmission among the general population. This can be extremely difficult without a comprehensive understanding of HIV epidemiology.

In the MENA region, antiretroviral theraphy (ART) coverage remains the lowest; covering only

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17% of individuals.[7] In addition, access to HIV testing and counseling is still limited.[8]

Oman is classified as a low prevalence country for HIV/AIDS. This is probably due to religious and cultural practices discouraging premarital and extramarital relations and mandating male circumcision. Nevertheless, the HIV annual detection rate has been reported around 120 to 150 per year indicating a recent increase and reflecting a gap between religious values and believers practice.[9] Since 2010, the number of people receiving ART in Oman has increased dramatically and more recently all patients with CD4 lymphocyte count of < 500 cells/mm^3 are eligible for ART in concordance with the 2013 WHO guidelines.[10] By the end of 2014, 2506 HIV/AIDS cases were reported among Omani nationals, of which 908 were receiving ART.[9] In 2015, the Joint United Nations Program on HIV/AIDS (UNAIDS) set the ambitious 90-90-90 target. This global target states that by 2020, 90% of all people living with HIV will know their HIV status, 90% of those diagnosed will receive ART, and 90% of those receiving ART will have viral suppression.[11]

Despite substantial recent progress in the management of HIV infection in Oman, studies that report epidemiology, clinical characteristics, and outcomes are limited. We sought to review the clinical epidemiology of a cohort of 326 patients presented at a tertiary care hospital in Oman with a focus on our achieved rates on two of the three UNAIDS targets: percentage of HIV patients on treatment, and percentage of patients with viral suppression.

METHODS

We conducted an observational review of patients infected with HIV from 1989 to 2016 at the Royal Hospital, Muscat, Oman. Over the 27-year period, 326 patients were identified, all of whom were Omani nationals. Participants included newly diagnosed HIV patients hospitalized at Royal Hospital or diagnosed during antenatal screening, and those referred from other hospitals with treatment failure. The information was obtained from hospital medical records and included demographic data such as geographic origin, age, gender, marital status, education level, mode of transmission, WHO staging, opportunistic infections, laboratory analyses, lymphocyte subset analysis, HIV RNA polymerase chain reaction (PCR), HIV mutations, and ART.

Serologic testing for HIV 1 and 2 was performed using a chemiluminescent microparticle enzyme immunoassay (MEIA, AxSYM HIV 1/2 gO, Abbott Laboratories, Abbott Park, USA). If serology was reactive, specimens were confirmed using the INNO-LIA HIV I/II score (INNOGENETICS NV, Technologiepark, Belgium); a line immunoassay for the confirmation and discrimination of antibodies to HIV-1, HIV group O, and HIV-2 in human serum and plasma. We used the WHO classification and staging of AIDS.[12] Lymphocyte subset analysis was obtained by standard flow cytometric methods.

Molecular testing included HIV PCR, which uses three sets of four primers from envelope, polymerase, reverse transcriptase, and core protein genes. Viral load was measured using the branched DNA method (VER SANT HIV-1 RNA 3.0 Assay, [bDNA], Bayer Diagnostics, Berkeley, CA, USA). Results were reported in a range from 20 to > 500 000 IU/mL. HIV genotype resistance testing was performed by PCR amplification and DNA sequencing (HIV-1 GenoSure PRIme, LabCrop, France).

Descriptive statistics were used to summarize the data. For categorical variables, frequencies and percentages were reported. Differences between groups were analyzed using Pearson's chi-square test. For continuous variables, mean and standard deviation were used to summarize the data. An a priori two-tailed level of significance was set at $p < 0.050$. Statistical analyses were conducted using SPSS Statistics (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp).

RESULTS

The overall mean age of the cohort was 36.0±15.0 years, and 60.4% (n = 197) were males. The route of transmission in females was predominately by heterosexual contact in 89 (68.9%) patients, prenatal or vertical transmission in 29 (22.5%), and blood transfusion in three (2.3%) patients. There was no data for eight patients (6.2%). In males, transmission was by several routes; 103 patients (52.3%) acquired HIV by heterosexual contact, 24 (12.2%) by prenatal transmission, 20 (10.2%) by homosexual contact, four (2.0%) by IV drug use, and one (0.5%) by blood transfusion. For 45 patients (22.8%), there

Table 1: Demographic and clinical characteristics of the cohort.

Characteristic, n (%) unless specified otherwise	All (N = 326)	Female (n = 129)	Male (n = 197)	*p*-value
Age, mean ± SD, years	36.0 ± 15.0	33.0 ± 15.0	38.0 ± 15.0	< 0.001
Mode of transmission				
MSM	20 (6.1)	0 (0.0)	20 (10.2)	< 0.001
Blood transfusion	4 (1.2)	3 (2.3)	1 (0.5)	
Heterosexual	192 (58.9)	89 (69.0)	103 (52.3)	
IV drug user	4 (1.2)	0 (0.0)	4 (2.0)	
Prenatal	53 (16.3)	29 (22.5)	24 (12.2)	
Unknown	53 (16.3)	8 (6.2)	45 (22.8)	
Reasons for HIV testing				
Unknown	15 (4.6)	4 (3.1)	11 (5.6)	< 0.001
Antenatal screen	28 (8.6)	27 (21)	1 (0.5)	
Postnatal screen	43 (13.2)	23 (17.8)	20 (10.2)	
Post transfusion screen	1 (0.3)	0 (0.0)	1 (0.5)	
HIV contact	60 (18.4)	29 (22.5)	31 (15.7)	
AIDS-related symptoms	169 (51.8)	44 (34.1)	125 (63.5)	
Needle stick injury	1 (0.3)	0 (0.0)	1 (0.5)	
Pre-employee screening	5 (1.5)	2 (1.6)	3 (1.5)	
Prisoner	3 (0.9)	0 (0.0)	3 (1.5)	
TB	1 (0.3)	0 (0.0)	1 (0.5)	
WHO stage 4				
No data	10 (3.1)	3 (2.3)	7 (3.6)	< 0.001
No	231 (70.9)	107 (82.9)	124 (62.9)	
Yes	85 (26.1)	19 (14.7)	66 (33.5)	
HBsAg				
Negative	295 (90.5)	117 (90.7)	178 (90.4)	0.658
Positive	9 (2.8)	2 (1.6)	7 (3.6)	
Not done	22 (6.7)	10 (7.8)	12 (6.1)	
HCV IgG				
Negative	276 (84.9)	112 (86.8)	164 (83.7)	0.364
Positive	19 (5.8)	4 (3.1)	15 (7.7)	
Not done	30 (9.2)	13 (10.1)	17 (8.7)	

SD: standard deviation; MSM: men who have sex with men; IV: intravenous; HIV: human immunodeficiency virus; AIDS: acquired immune deficiency syndrome; TB: tuberculosis; WHO: World Health Organization; HBsAg: surface antigen for hepatitis B; HCV IgG: test for hepatitis C. Percentages might not add up to 100% due to rounding off.

was no documented data available for transmission route [Table 1].

The WHO has established a four-stage classification system based on opportunistic infections and other HIV related outcomes. In our cohort, 169 patients (51.8%) presented with HIV related symptoms and 85 patients (26.1%) had WHO stage 4 HIV symptoms (i.e., AIDS). Our data also showed that the rates of HIV/HBV and HIV/HCV coinfections were 2.8% and 5.8%, respectively [Table 1].

At the time of first hospital visit, male patients presented with lower CD4 + cells (< 200 cells/mm^3) than females (46.2% vs. 25.6%; $p = 0.003$). However, there were no significant differences in HIV RNA titers (> 1000 copies/mL^3) between genders (76.1% vs. 72.1%; $p = 0.136$) [Table 2].

Low-level HIV viremia ranging from 21 to 1000 IU/mL was seen in 48 (14.7%) patients. Twenty-four (7.4%) patients had undetected HIV viral load on initial presentation (0–20 IU/mL). Those patients were transferred from other institutes for either treatment continuation with their partners or further antenatal care.

At the time of analysis, only 50 (15.3%) patients had CD4+ < 200 cells/mm^3 while 257 (78.8%) had

Table 2: Clinical outcome characteristics of the cohort.

Characteristic, n (%) unless specified otherwise	All (N = 326)	Female (n = 129)	Male (n = 197)	*p*-value
Genotype resistance test				
No	161 (49.4)	56 (43.4)	105 (53.3)	0.081
Yes	165 (50.6)	73 (56.6)	92 (46.7)	
Baseline CD4 count, cells/mm^3				
< 200	124 (38.0)	33 (25.6)	91 (46.2)	0.003
201–500	99 (30)	46 (35.7)	53 (26.9)	
> 500	88 (27.0)	43 (33.3)	45 (22.8)	
No data*	15 (4.6)	7 (5.4)	8 (4.1)	
Latest CD4 count, cells/mm^3				
< 200	50 (15.3)	12 (9.3)	38 (19.3)	0.009
201–500	112 (34.4)	39 (30.2)	37.1)	
> 500	145 (44.5)	73 (56.6)	72 (36.5)	
No data*	19 (5.8)	5 (3.9)	14 (7.1)	
Baseline HIV viral load, IU/mL				
0–20	24 (7.4)	15 (11.6)	9 (4.6)	0.136
21–1000	48 (14.7)	18 (14.0)	30 (15.2)	
> 1000	243 (74.5)	93 (72.1)	150 (76.1)	
No data*	11 (3.4)	3 (2.3)	8 (4.1)	
Latest HIV viral load, IU/mL				
0–20	169 (51.8)	71 (55.0)	98 (49.7)	0.734
21–1000	64 (19.6)	24 (18.6)	40 (20.3)	
> 1000	81 (24.8)	31 (24.0)	50 (25.4)	
No data*	12 (3.7)	3 (2.3)	9 (4.6)	
On ART				
No	12 (3.7)	5 (3.9)	7 (3.6)	0.977
Yes	314 (96.3)	124 (96.1)	190 (96.4)	
Outcome				
Alive	275 (84.4)	116 (89.9)	159 (80.7)	0.051
Dead	22 (6.7)	4 (3.1)	18 (9.1)	
Lost to follow-up	29 (8.9)	9 (7.0)	20 (10.2)	

HIV: human immunodeficiency virus; ART: antiretroviral therapy. Percentages might not add up to 100% due to rounding off.

CD4+ values > 200 cells/mm^3, and no data was available for 19 (5.8%) patients indicating a good immunological response to ART. Complete HIV RNA viral suppression was seen in 169 (51.8%) patients. Sixty-four (19.6%) HIV infected patients had low-level viremia ranging from 21 to 1000 IU/mL, while complete virological failure was seen in 81 (24.8%) patients. HIV genotype resistance testing was performed in 165 (50.6%) patients. HIV resistance testing was mostly done in treatment failures and treatment naïve patients particularly pregnant females.

ART was given to 314 (96.3%) patients. Twelve patients (3.7%) either refused or deferred therapy. Among patients on ART, 35.0% (n = 110) of the patients received ART prior to 2009 while 65.0% (n = 204) received ART after the implementation of universal HIV treatment policy in 2010.

The most common ART regimen was non-nucleoside reverse transcriptase inhibitor-based therapy with nucleoside reverse transcriptase inhibitors backbone that included either combination of lamivudine/zidovudine or tenofovir disporoxil/emtricitabine. Tenofovir disoproxil based regimens were widely used after 2010. The most common protease inhibitors were lopinavir/ritonavir and atazanavir/ritonavir. Integrase inhibitors (INIs) have been used most recently as a second-line alternative for treatment failures.

Among a total of 326 HIV infected patients, 6.7% (n = 22) died and 8.9% (n = 29) were lost to follow-up. The annual mortality rate was 0.342 per 1000 per year for the last five years [Figure 1].

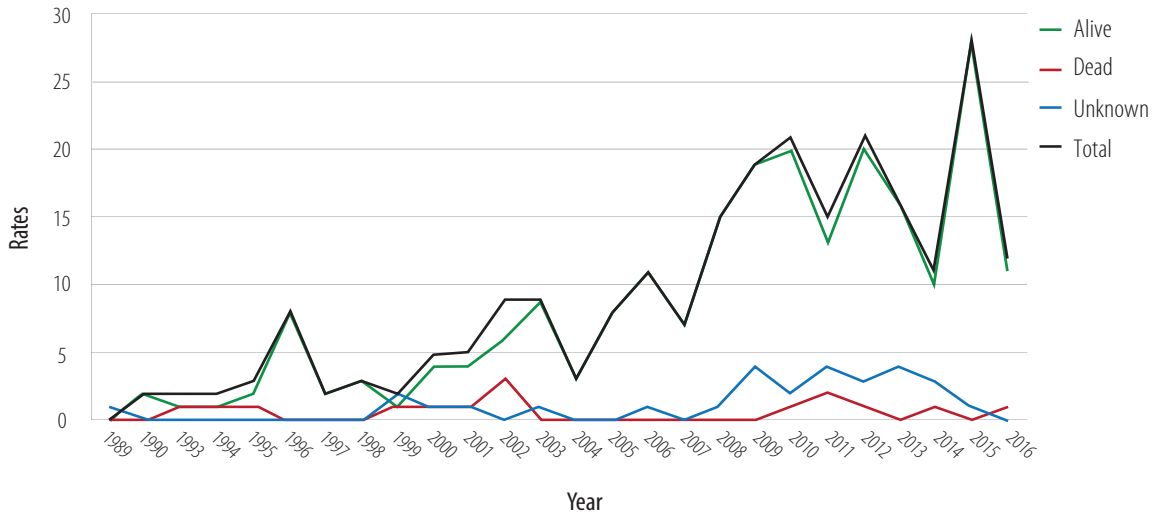

Figure 1: Survival and mortality rates of 326 HIV-1 patients over the last 27 years.

DISCUSSION

To our knowledge, this is the first study describing the epidemiology, clinical, and laboratory characteristics of a cohort of 326 HIV infected patients and their outcomes in Oman. The most common mode of transmission in both genders was heterosexual contact causing 58.9% of infections. Men who have sex with men (MSM) are among the groups affected by HIV in the region.[8,9] However, due to discrimination and social stigma, the true prevalence of HIV in MSM is unknown and probably underestimated with national data suggesting a prevalence of 13.9%, followed by mother-to-child (5.5%), IV drug use (4%), and blood transfusion (2.8%).[9] A recent report from the MENA had indicated an increase in HIV acquisition through IV drug users (IVDUs) in countries like Oman, Bahrain, Morocco, Egypt, and KSA.[5,13,14] This might be partly explained by the increase in HIV screening programs among IVDUs.

In our cohort, 45 (22.8%) male patients had an unknown mode of transmission, most likely the under-reporting is due to fear of discloser and stigma in particular among MSM population. In addition, a higher rate of mother-to-child transmission has been observed (around 16%) probably representing earlier transmissions when no antenatal screening was done, and management of HIV in pregnancy was suboptimal. Since 2009, a universal screening program for all pregnant females has been taking place in Oman with an acceptance rate of 99%.[9]

HIV coinfection affects the natural history and clinical outcomes of individuals infected with HBV or HCV virus, resulting in rapid progression to liver cirrhosis and hepatocellular carcinoma.[15–17] The prevalence of HBV and HCV coinfection with HIV is not well documented in the region. A systematic review and meta-analysis report on the prevalence of HIV, HBV, HCV, and HIV coinfections in different subpopulations conducted in Iran estimated the prevalence rates of HIV/HBV and HIV/HCV around 1.9% and 10.9%, respectively.[18] Similarly, a retrospective analysis of 142 HIV positive patients in Western Saudi Arabia estimated the prevalence of HIV/HBV and HIV/HCV coinfections at 2.8% and 8.5%, respectively.[19]

The prevalence of HIV/HBV and HIV/HCV coinfection seen was low at 2.8% and 5.8%, respectively. The low prevalence of HIV/HBV coinfection is probably due to the low to intermediate prevalence of HBV in the general population[20] and HBV vaccination since 1990. However, a more accurate estimate is required in other high-risk groups, such as IVDUs and prisoners.[21]

Several studies from the MENA region have reported a correlation of HIV, HBV, and HCV with age and gender.[22–25] HBsAg was more common among males in all age groups while anti-HCV was more prevalent among older females.[25–28] In contrast, in our study HIV/HCV coinfection was more prevalent in young patients and predominately in men with IVDU risk. HIV/HBV coinfection did not correlate with age or gender.

In Oman, despite free access to healthcare and the significant programmatic improvement in management of HIV infection, patients still present at advanced stages due to the delay in screening and

detection of HIV. This was seen in our cohort, where 51.8% of HIV infected patients already presented with symptomatic infection and 26.1% were WHO stage 4 (AIDS) at the time of first hospital visit. It is well established that patients with CD4+ cell counts < 200 cells/mm^3 are at higher risk for opportunistic infections, cancers, and death.[29–33] The delay in diagnosis can be attributed to several factors such as a lack of HIV awareness among individuals and health care workers, a lack of surveillance of key populations (i.e., MSM or IVDU), a limited number of voluntary counseling and testing clinics, and no access to self HIV testing. In this study, male patients presented with significantly lower CD4 T lymphocytes than female patients (46.2% vs. 25.6%, respectively). This has been observed in several studies where females infected with HIV tend to be younger, have higher CD4 T lymphocyte counts and lower HIV viral loads at the time of initial HIV diagnosis.[34–37] However, correlation with transmission rates, clinical outcomes, rate of disease progression, and death has shown contradictory results. In a recent systematic review that included studies from both developed and developing countries, females starting ART had slightly better survival compared to males but showed no clear benefit in progression to either AIDS or to differences in HIV suppression and immunologic recovery.[38]

The difference in mortality was attributed to several explanations including a protective effect of female sex hormones and higher expression of IFN-stimulated genes in HIV-1-infected women.[39] In our setting, early detection in females could be partly attributed to the antenatal screening program that was adopted in the country from 2009.

HIV RNA viral suppression defined as viral load < 20 IU/mL was seen in 169 (51.8%) patients, while 64 (19.6%) patients had viral suppression per WHO criteria (i.e., viral load of < 1000 IU/mL). Complete virological failure was seen in 81 (24.8%) patients. The high virological failure rates can be attributed to de novo drug resistance or lack of adherence and compliance with HIV medications (which is more common in our setting). Nevertheless, as a result of implementing several interventions in our clinic (i.e., counseling on compliance and adherence by trained health care workers, detailed review by clinical pharmacists each visit, using clinical pathways, and HIV resistance testing), the number of patients achieving viral suppression has increased in the last few years, making the UNAIDS target of 90% of HIV patients on treatment virally suppressed feasible by 2020.

The current wide availability of ART and recent changes in international guidelines encouraging early initiation of ART regardless of CD4+ T lymphocytes has lowered morbidity and mortality among HIV infected individuals. The total number of deaths in Oman has decreased from 200 in 2003 to 100 in 2014 (UNAIDS published data 2018). However, the annual mortality rate in our cohort was 0.342 per 1000 person-years in the last five years; significantly higher than mortality rates reported from the developed countries (0.025 deaths per 1000 person-years).[40]

Among the greater ongoing challenges faced in Oman, are the rises in new HIV cases and AIDS-related mortality rates despite a strong national HIV program and the free access to ART. The increase HIV cases can be attributed to increased screening, better diagnostic modalities, and early detection; however, late presentation with advanced HIV infection and high mortality rates indicate a substantial gap in the cascade of HIV care. Thus, an urgent priority is to reach the UNAIDS target where 90% of all people living with HIV will know their HIV status. The national AIDS program should establish interventions that focus on early detection and preventive strategies. By outreaching key at-risk populations, the program can offer access to health services and engage infected people in a system that enables them to access HIV testing without fear.

One of the main limitations of our study is its cross-sectional design where some data are missing as some patients were lost to follow-up either due to death or transfer to other centers. In addition, despite a large number of patients in our cohort, the study data were collected from a single center, and this might not fully be representative of the country as a whole. Our results may only apply to Oman or countries with similar HIV prevalence rates and cultural background.

CONCLUSION

The majority of patients acquired HIV through heterosexual transmission. One-quarter of patients in our cohort were diagnosed late with symptoms of HIV related illness and AIDS, 96.3% of the patients were initiated on ART, and 71.5% achieved

virological suppression. Among the priorities in Oman are increasing HIV testing and early diagnoses in key at-risk populations, this will help in fast-tracking and linking infected individuals to appropriate services in order to reach the WHO 90-90-90 target by 2020.

Disclosure
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