ORIGINAL ARTICLE

Factors Affecting Diagnostic Delay of Advance HIV Disease at Enrolment in the Indus Hospital, Karachi, Pakistan.

Jamil Muqtadir, Samreen Sarfaraz, Naseem Salahuddin

Department of Infectious Diseases, the Indus Hospital, Karachi, Pakistan.

Abstract

Background
Human immunodeficiency virus (HIV) infection is characterized by decreased CD4 cell count leading to opportunistic infections (OIs) and tumors. We have evaluated clinical profile, frequency and factors affecting the diagnostic delay of patients presenting with advanced HIV in Indus Hospital Karachi. There are limited studies in Pakistan which has evaluated risk factors for acquiring HIV infection therefore, this study was conducted.

Methods
A retrospective study was done at the Indus Hospital Karachi, from January to December 2017. All patients presenting with advanced HIV were included in the study. Clinical profile, frequency and factors affecting the diagnostic delay were evaluated.

Results
During study period 248, HIV patients were registered, of which 56(23%) had advanced HIV. Out of 56 patients, one was excluded due to Chronic Liver Disease. 45(82%) were male, 8(15%) were female and 2(4%) were transgender. Weight loss was the commonest symptom, followed by fever and loose stools. All patients had been visiting multiple health-care professionals before their final diagnosis was made. Among risk factors, exposure to female sex workers (34.9%) found to be commonest risk factor followed by injection drug use. Among the factors responsible for diagnostic delay, 94.5 % was missed diagnosis from health-care professionals, followed by lack of awareness from patients. Pallor was the commonest clinical examination finding, followed by oral thrush and lymphadenopathy. Hepatitis C was the most common coinfection, followed by syphilis and hepatitis B. Candidiasis was the most common opportunistic infection (27%), seven had oral candidiasis, seven had esophageal candidiasis and one had extensive gastrointestinal candidiasis. PCP (Pneumocystis carinii pneumonia) was the second most common opportunistic infection present in eleven 20%, followed by CMV (Cytomegalovirus) infection, MAC (Mycobacterium avium complex) colitis, cryptococcal meningitis and toxoplasmosis. Thirteen (23.2%) patients had other infections. 31 patients were followed, 12 were lost to follow-up, 8 died; 5 of PCP (Pneumocystis carinii pneumonia), 1 of cryptococcal meningitis, 2 of unknown cause while 4 were transferred to other facilities.

Conclusion
Advanced HIV represent about one third of all HIV patients. Weight loss was the commonest feature followed by fever and loose stools. Exposure to female sex workers was commonest risk factor for acquiring infection. Missed diagnosis was the commonest factor affecting the diagnostic delay.

Key words
Human immunodeficiency virus, opportunistic infections, Pneumocystis carinii pneumonia, Cytomegalovirus, Mycobacterium avium complex

Introduction

Human immunodeficiency virus (HIV) infection is characterized by decreased CD4 cell count and immunodeficiency, leading to opportunistic infections (OIs) and tumors.[1] According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 38 million people were infected with HIV globally in 2019.[2] According to UNAIDS, Pakistan is among the 11 countries in the Asia-Pacific which houses most of the people infected with HIV, and HIV prevalence in Pakistan by 2019 in adults and children is estimated to be 190000. According to a recent study, although there has been an increase in HIV prevalence in Pakistan, collective HIV infection rates in country are below 1% in general population (0.32%), increased prevalence is reported in IDUs (15.05%), sex workers (2.21%).[3] Persons living with HIV disease encounter intense and often unrelenting psychological and social stresses over the course of their illness. The stigmatizing nature of HIV and AIDS is a factor that affects delayed HIV testing by at-risk persons that leads to continuation behaviors, such as unprotected sex and needle sharing, and unknowingly transmitting HIV to others. Barriers to testing from the patient's perspective include delay in seeking medical care, fear of the financial burden brought by the disease, lack of education which diverts patients from taking medical care to hakims, faith healers and homeopaths, concerns about the impact of a positive result, fears around discrimination,

Corresponding Author: Jamil Muqtadir
HNo- A499/1, Ayesha Market near safora chorangi,
Gulistan-e-Johar, block-7,
Karachi, Pakistan.
Email: muqtdir169@yahoo.com

confidentiality, criminalization of risk behaviors, and limited knowledge about accessing testing or treatment on testing positive.[4] Reported concerns by clinicians include lack of knowledge about HIV and potential risk behaviors, lack of routine HIV screening even in the presence of associated symptoms, language barriers, and worry about informing individuals of a HIV-positive test result.[5]

To the best of our knowledge there is no study in Pakistan to see factors affecting the diagnostic delay of advanced HIV, therefore, we conducted study to evaluate the clinical profile, frequency and factors affecting the diagnostic delay of advanced HIV illness.

Material and Methods

This was a retrospective observational study conducted at The Indus Hospital Karachi, Pakistan, from January 2017 to December 2017. The Indus Hospital Karachi is tertiary care hospital that provides large number of in-patient and outpatient services in many specialties. The study included all patients with advanced HIV of either sex, aged 18-60years presenting in infectious diseases clinic, emergency room or inpatient and those with baseline CD4 <350/mm^3. Patients not meeting the criteria for advanced HIV, those stable on HIV and those having comorbid like Chronic Liver Disease and Chronic Kidney Disease were excluded from study. Data was collected using hospital management information system, data was collected on structured proforma. Detailed history and clinical examination of patients were done and labs were advised according to clinical suspicion of possible opportunistic infection for example lumber puncture for relevant investigations of cryptococcal meningitis/syphilis, brain imaging.

Statistical Analysis

Data entered and analyzed using SPSS version 24.0. Descriptive statistical analysis was performed. Mean (SD)/ Median (IQR) was computed as appropriate for all the quantitative variables like age, BMI, ESR, and CD4 count. Frequency along with percentage was computed for all the categorical variables like gender, physical examination, barriers in HIV diagnosis.

Definition

Advanced HIV Disease: Clinical stage IV or a CD4 cell count < 100 cells/µL at the time of HIV diagnosis.

Clinical Stage-IV: Patients diagnosed with Pneumocystis pneumonia, esophageal candidiasis and other features as explained by CDC.[6]

Delayed Diagnosis: A person diagnosed with HIV with a CD4 count below 350/mm^3 or an AIDS defining event, regardless of the CD4 count in the 6 months following HIV diagnosis.

Missed diagnosis: A person diagnosed with advanced HIV fulfilling the inclusion the criteria after visiting different health-care clinics for a period of >6months.

Results

248 patients were registered during that period, out of which 56 (22.6%) had advanced HIV. Out of 56, 1 patient was excluded due to Chronic Liver Disease Fig 1. 45(81.8%) were male, 8(14.5%) were female and 2(3.6%) were transgender. Demographic presentation and baseline biochemistry are shown in Tables 1 and 2. Weight loss was the commonest symptom, followed by fever and loose stools Fig 2. All patients had been visiting multiple health-care professionals before their final diagnosis was made. 12 patients denied history of any high-risk behavior. Among risk factors, exposure to female sex workers was found to be commonest risk factor followed by injection drug use. Four patients had history of blood transfusion, three had exposures to contaminated needles at health-care clinics and one had history of surgery Fig 3. Among the factors responsible for diagnostic delay, 94.5 % was missed diagnosis from health-care professionals, followed by lack of awareness from patients Fig 4. Eleven patients had anti tuberculosis therapy (ATT) in the past. Majority had taken ATT for presumed abdominal or pulmonary tuberculosis. Pallor was the commonest clinical examination finding, followed by oral thrush and lymphadenopathy. Three patients had positive Acid-fast bacilli (AFB) smear at the time of presentation, three had positive *Mycobacterium tuberculosis* (MTB) culture and four had positive Genexpert. Hepatitis C was the most common coinfection, followed by syphilis and hepatitis B. Candidiasis was the most common opportunistic infection (26.8%), seven had oral candidiasis, seven had esophageal candidiasis and one had extensive gastrointestinal candidiasis. PCP (Pneumocystis carinii pneumonia) was the second most common opportunistic infection present in eleven 19.6%, followed by CMV (Cytomegalovirus) infection, MAC (Mycobacterium avium

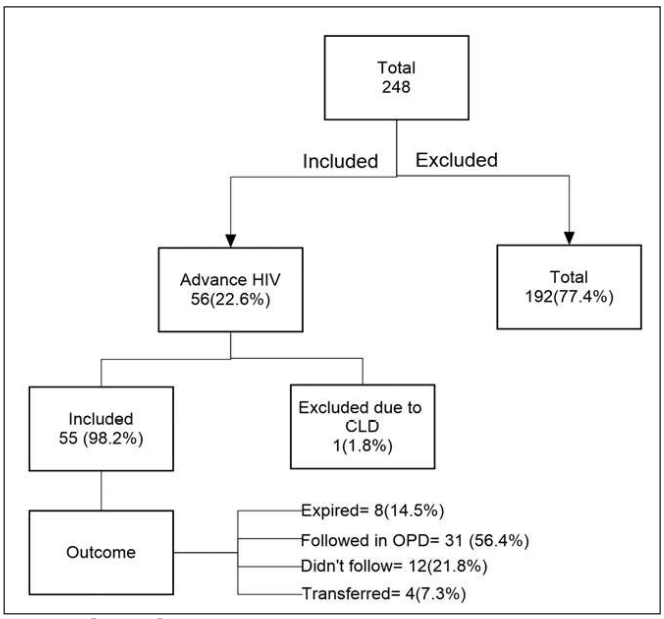

Fig 1. Flow Chart

HIV (human immunodeficiency virus), CLD (chronic liver disease), OPD (outpatient deparment)

Table 1: Demographic Information

Variables	n	%
Gender		
Female	8	14%
Male	45	82%
Transgender	2	4%
Place of Residence		
City	45	82%
Town	3	5%
Village	2	4%
Not recorded	5	9%
Religion		
Muslim	52	94%
Hindu	1	2%
Christian	2	4%
Marital status		
Married	33	60%
Un-married	19	34%
Divorced	2	4%
Not Recorded	1	2%
Number of children		
None	24	44%
1	5	9%
>1	18	33%
Not recorded	8	14%

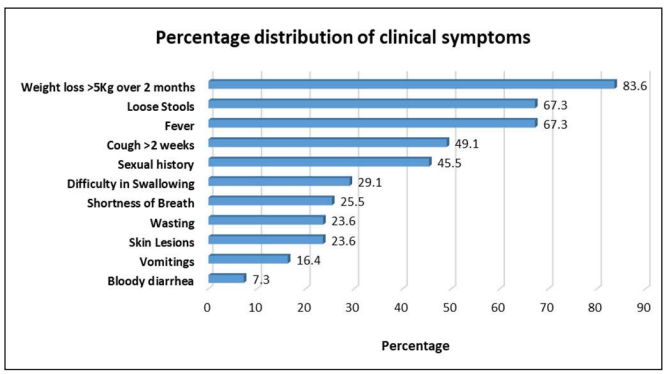

Fig 2. Frequency of symptoms

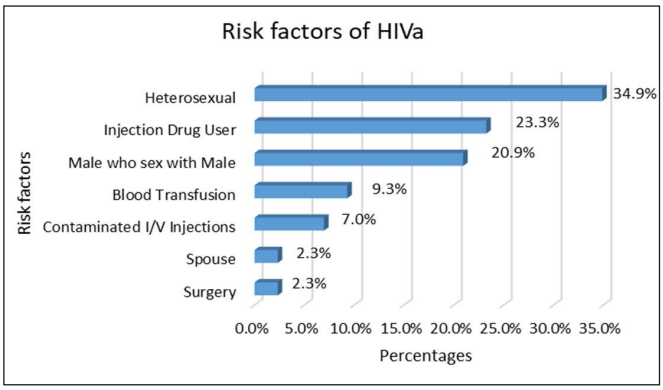

Fig 3. Risk factors for HIV

Table 2: Baseline Laboratory parameters

Age in Years	
Median (IQR)	31 (26 - 42)
Min-Max	18 – 67
BMI	
Median (IQR)	16.6 (14.4 - 18.8)
Min-Max	11 – 30
ESR	
Mean ± SD	67.52 ± 33.24
Min-Max	10 – 139
CD4 count	
Mean ± SD	91.6 ± 65.21
Min-Max	8 – 246
Hemoglobin	
Mean ± SD	10.48 ± 2.37
Min-Max	5.7 - 15.2
Total leucocyte count	
Median (IQR)	6220 (4622.5 - 8617.5)
Min-Max	1700 – 25040
Platelets	
Mean ± SD	268.74 ± 132.5
Min-Max	50 – 661
Creatinine	
Median (IQR)	0.7 (0.6 - 0.9)
Min-Max	0.4 - 1.5
Total Bilirubin	
Median (IQR)	0.4 (0.3 - 0.6)
Min-Max	0.2 - 1.1
Gama GT	
Median (IQR)	86 (43.5 - 195.5)
Min-Max	12 – 633
SGPT/ALT	
Median (IQR)	29 (18 - 51)
Min-Max	5 – 235
Alkaline phosphatase	
Median (IQR)	135 (89.5 - 300)
Min-Max	52 – 547
Lactate Dehydrogenase	
Mean ± SD	729.33 ± 423.95
Min-Max	301 – 1570

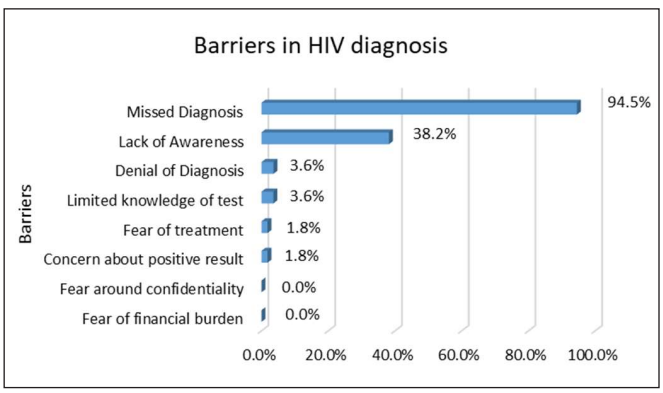

Fig 4. Diagnostic Barriers

complex) colitis, cryptococcal meningitis and toxoplasmosis.

Thirteen (23.2%) patients had other infections like lung abscess, infective endocarditis. 31 patients were followed, 12 were lost to follow-up, 8 died; 5 of PCP (Pneumocystis carinii pneumonia), 1 of cryptococcal meningitis, 2 of unknown cause while 4 were transferred to other facilities.

Discussion

The number of HIV/AIDS infections in Pakistan has been increasing at an alarming rate; from 2005 to 2015, the number of reported infections in Pakistan increased from 8, 360 to 45, 990 cases, the highest global average increase of 17.6% in history.[7] Joint United Nations Program on HIV/AIDS (UNAIDS) in 2017 reported that the prevalence of HIV in Pakistan between 15-49 years of age is 0.18% per 1000 population.

Delay in knowing the HIV positive status is challengeable in achieving the targets, results in the advancement of the disease that poses a less favorable clinical course, with reduced or incomplete treatment response, more rapid clinical progression, higher risk of mortality on the victims and burden to the healthcare system.

This study was conducted at large tertiary care hospital Karachi, Pakistan, is the first, to our knowledge, to quantify the delay in time from initial presentation to the health care system and ultimate diagnosis in patients with advanced HIV/AIDS. Xie J *et al*.[8] in Beijing, China also found that although a large proportion of patients had clues for immune compromise, yet they had not been offered HIV testing during previous medical visits. In Indonesia a cross sectional study Nugroho A *et al*,[9] consistent with our data that the length of diagnostic delay in among HIV positive was 6-12 months, Patient were hospitalized when severity of disease compelled them for an ADI (AIDS defining illness) and their CD4+T cell counts were below 250 cells/µL, as demonstrated by Lazar R *et al*[10] in New York 2103. On the other hand, limited knowledge of HIV, poverty, fear of positive results, denial of diagnosis was also responsible for delay in diagnosis. These barriers were also seen by Koirala S *et al*,[11] and Courtney LP *et al* in their study.[12]

Therefore, more research about clinician attitudes, behaviors and practices is essential. On the other hand, safe sex practices, awareness about HIV transmission are essential in order to identify feasible strategies to reduce barriers to testing in healthcare facilities.

About socio-demographics status Aniley *et al*[13] Choi BY *et al*[14] found that, mean age of patients with advanced HIV at the time of presentation was 26-41 years, prevalence was more common in females (64.1%) and majority of patients were living in urban areas (84%). Study done at 19 US cities by Wejnert C *et al*,[15] Out of total HIV-positive victim, 151 MSM (Male who have sex with males) (8%) and 184 PWID (People who inject drugs) (12%) were unaware of their infection. Similar risk factors with different ratio was found in the study done by and Uruena JMR *et al*.[16] HIV epidemic in Brazil remained with prevalence above 5% in specific populations, such as MSM, transgender women, female sex workers, heterosexual males and IDU reported by Benzaken AS *et al*.[17]

Persistent unexplained fever was most frequent presenting symptom among those advance HIV patients supported by Ansari JA *et al*.[18] In Gujrat, Pakistan HIV/AIDS out break and in Switzerland by Braun DL *et al*.[19] fever was the most common and genital ulcer were the least common clinical manifestation, whereas weight loss up to 5% and fever was second most common presenting illness in our patients. Loose stools, chronic cough, skin and oral lesion were other common findings.

Baseline demographic were same is our patients similar to study conducted by Boniphace I *et al*.[20] their CD4+T cell count was below 250 and total leukocyte count b/w 1700-25040 cu/ml compared to Sinha S *et al*.[21] In our study 21.8% of patients with advanced HIV had history of diagnosed /labeled / presumed as a case of TB, 78.2% had given no h/o TB in past. Other known previous co morbid was diabetes mellitus (3.6%), chronic liver disease (1.8%).

At the time of presentation, pallor, oral thrush, enlarged lymph nodes were the common clinical findings while dehydration, ascites, palpable spleen, palpable liver, reduced breath sounds and abnormal fundoscopic findings were also seen.

Most of our patients were co-infected with hepatitis C similar to study Heijnen M *et al*.[22] and most specific ADI diagnoses were *Pneumocystis jirovecii* pneumonia 11 (20%), consistent with study conducted by Lazar R *et al*.[10] Our findings were not consistent with study done by Qi T *et al*.[23] and McCarthy GA *et al*.[24] where Cryptococcus neoformans (22.7 %) and systemic Kaposi's sarcoma or lymphoma was most common ADI were found.

Syphilis 14(25.5%), Cytomegalovirus infection 5 (9%) and hepatitis B 3(5.5%) were also common in our study.

In our patients, normal radiograph was found in 53(96.4%) patients. AFB stain and culture positive came in 3 (5.5%), these findings show inverse relation with study done by Olatunji AA *et al*.[25]

From all included advance HIV positive 31(56.4%) patients properly followed in OPD, 12 (21.8%) loosed follow up and 8 (14.5%) were expired.

Study Strengths and Limitations

Strength of our study was that despite many studies on HIV related problems, there was no study conducted on factors responsible for diagnostic delay in Pakistan before. Therefore,

this study would probably be the first on this specific issue. The main limitations of the present study include the cross-sectional design where cause cannot be attributed, a single-center experience, low female representation in the study cohort and nonrandomized study design. Hence, the figure does not reflect true frequency and severity of the disease. Secondly, there were some confounding factors in this study, such as age, race, diet, travel to endemic area, treatment of HIV and so on. All the study participants were also selected without specification that could increase the recall bias. Moreover, this study was conducted with small sample size and in urban environment, representing advanced cases of HIV therefore, cannot be applied to patients with asymptomatic or mild HIV infection therefore; the results might not be generalizable to larger populations.

Conclusion

Advanced HIV represent about one third of all HIV patients. Weight loss was the commonest feature followed by fever and loose stools. Exposure to female sex workers was commonest risk factor for acquiring infection. Missed diagnosis was the commonest factor affecting the diagnostic delay.

References

1. Bongiovanni M, Adorni F, Casana M, Tordato F, Tincati C, Cicconi P, *et al*. Subclinical hypothyroidism in HIV-infected subjects. *J Antimicrob Chem* 2006;58(5):1086-9.
2. http://www.unaids.org/sites/default/files/media_asset/UNAIDS_FactSheet_en.pdf.
3. Ali M, Nadeem M, Numan M, Khalil A, Maqbool K, Yousaf M, *et al*. Thirty years of HIV in Pakistan: A systematic review of prevalence and current scenario. Fut Virol. 2017;12.
4. Deblonde J, De Koker P, Hamers FF, Fontaine J, Luchters S, Temmerman M. Barriers to HIV testing in Europe: a systematic review. *Eur J Pub Hea* 2010;20(4):422-32.
5. Yazdanpanah Y, Lange J, Gerstoft J, Cairns G. Earlier testing for HIV-how do we prevent late presentation? Antivir Ther. 2010;15 Suppl 1:17-24.
6. World Health O. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. Geneva: World Health Organization; 2007.
7. Hussain A, Hussain S, Ali S, Ali E, Mehmood A, Ali F. HIV/AIDS-A Growing Epidemic in Pakistan. *J Evol Med Dent Sci* 2018;7.
8. Xie J, Hsieh E, Sun MQ, Wang HL, Lv W, Fan HW, *et al*. Delays in HIV diagnosis and associated factors among patients presenting with advanced disease at a tertiary care hospital in Beijing, China. *PloS one* 2017;12(8):e0182335.
9. Nugroho A, Erasmus V, Coulter RWS, Koirala S, Nampaisan O, Pamungkas W, et al. Driving factors of retention in care among HIV-positive MSM and transwomen in Indonesia: A cross-sectional study. *PloS one* 2018;13(1):e0191255.
10. Lazar R, Kersanske L, Xia Q, Daskalakis D, Braunstein SL. Hospitalization Rates Among People With HIV/AIDS in New York City, 2013. *Clin Infect Dis* 2017;65(3):469-76.
11. Koirala S, Deuba K, Nampaisan O, Marrone G, Ekström AM. Facilitators and barriers for retention in HIV care between testing and treatment in Asia-A study in Bangladesh, Indonesia, Lao, Nepal, Pakistan, Philippines and Vietnam. *PloS one* 2017;12(5):e0176914.
12. Courtney LP, Goco N, Woja J, Farris T, Cummiskey C, Smith E, *et al*. HIV prevalence and behavioral risk factors in the Sudan People's Liberation Army: Data from South Sudan. PloS one. 2017;12(11):e0187689.
13. Aniley AB, Ayele TA, Zeleke EG, Kassa AA. Factors associated with late Human Immunodeficiency Virus (HIV) diagnosis among peoples living with it, Northwest Ethiopia: hospital based unmatched case-control study. *BMC Pub Hea* 2016;16(1):1076.
14. Choi BY, Choi JY, Han SH, Kim SI, Kee MK, Kim MJ, *et al*. Korea HIV/AIDS Cohort Study: study design and baseline characteristics. *Epidemiol Hea* 2018;40:e2018023.
15. Wejnert C, Prejean J, Hoots B, Hall HI, McCray E, Mermin J. Prevalence of Missed Opportunities for HIV Testing Among Persons Unaware of Their Infection. *JAMA* 2018;319(24):2555-7.
16. Reyes-Urueña JM, Campbell CNJ, Vives N, Esteve A, Ambrosioni J, Tural C, *et al*. Estimating the HIV undiagnosed population in Catalonia, Spain: descriptive and comparative data analysis to identify differences in MSM stratified by migrant and Spanish-born population. *BMJ open* 2018;8(2):e018533.
17. Benzaken AS, Oliveira MCP, Pereira GFM, Giozza SP, Souza FMA, Cunha A, *et al*. Presenting national HIV/AIDS and sexually transmitted disease research in Brazil. *Medicine* 2018;97(1S Suppl 1):S1-s2.
18. Ansari JA, Salman M, Safdar RM, Ikram N, Mahmood T, Zaheer HA, *et al*. HIV/AIDS outbreak investigation in Jalalpur Jattan (JPJ), Gujrat, Pakistan. *J Epidemiol Glob Hea* 2013;3(4):261-8.
19. Braun DL, Kouyos RD, Balmer B, Grube C, Weber R, Günthard HF. Frequency and Spectrum of Unexpected Clinical Manifestations of Primary HIV-1 Infection. *Clin Infec Dis* 2015;61(6):1013-21.
20. Boniphace I, Omari M, Susan Fred R, Ferdinand M, Marcel T. HIV/AIDS Clinical Manifestations and their Implication for Patient Clinical Staging in Resource Limited Settings in Tanzania. *The open AIDS J* 2011;5:9-16.
21. Sinha S, Gupta K, Khan NH, Mandal D, Kohli M, Das BK, *et al*. Higher Frequency of HIV-1 Drug Resistance and Increased Nucleoside Reverse Transcriptase Inhibitor Mutations among the HIV-1 Positive Antiretroviral Therapy-Naïve patients Coinfected With Mycobacterium tuberculosis Compared With Only HIV Infection in India. *Infect Dis* 2018;11:1178633718788870.
22. Heijnen M, Mumtaz GR, Abu-Raddad LJ. Status of HIV and hepatitis C virus infections among prisoners in the Middle East and North Africa: review and synthesis. *J Int AIDS Soc* 2016;19(1):20873.
23. Qi T, Zhang R, Shen Y, Liu L, Lowrie D, Song W, *et al*. Etiology and clinical features of 229 cases of bloodstream infection among Chinese HIV/AIDS patients: a retrospective cross-sectional study. *Eur J Clin Microbiol & Infect Dis* 2016;35(11):1767-70.
24. McCarthy GA, Mercey D. The changing clinical features of HIV-1 infection in the United Kingdom. Communicable disease report CDR review. 1994;4(5):R53-8.
25. Olatunji AA, Olatunji PO, Salako AA. Radiographic chest findings and immunological status in HIV-positive patients with tuberculosis coinfection in a sub-urban Nigerian tertiary hospital. *Ind J tubercul* 2016;63(2):74-8.