Research Article

Prevalence and risk factors for opportunistic infections in HIV patients who developed adverse drug reactions (ADRs) to antiretroviral therapy (ART) in a tertiary-care teaching hospital

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Abstract

Background: The introduction of highly active antiretroviral therapy (HAART) has led to decline in HIV-related opportunistic infections (OIs). Knowledge of the most common OI of that geographical area will help in implementing the preventive measures against that pathogen. We determined the prevalence and risk factors for OIs among patients who developed adverse drug reaction (ADR) to antiretroviral therapy (ART) in a tertiary-care teaching hospital. **Aims and Objective:** To collect demographic details of HIV-positive patients who were on ART and developed ADR to ART with OI and without OI; to determine the prevalence of OIs in HIV-positive patients who developed ADR to ART; and to investigate the sociodemographic and clinical risk factors associated with their occurrence. **Materials and Methods:** A cross-sectional study carried out between January and June 2012. The study population comprised HIV-infected patients, who were receiving ART at ART Center, KR Hospital of Mysore Medical College and Research Institute, Mysore, Karnataka, India, who developed ADRs to ART with or without OI. **Results:** The prevalence of OI was 50.63%. The sociodemographic variables that had significant positive association with the presence of OIs on univariate analysis includes employment [odds ratio (OR) = 4.96, 95% confidence interval (CI) = 2.52–9.75; $p = 0.00$). The risk of OIs did not significantly differ according to gender (OR = 0.77, 95% CI = 0.41–1.45; $p = 0.21$), age (OR = 1.658, 95% CI = 0.82–3.32; $p = 0.079$), residence (OR = 0.812, 95% CI = 0.43–1.52; $p = 0.26$), literacy (OR = 0.90, 95% CI = 0.48–1.70; $p = 0.38$), marital status (OR = 1.8, 95% CI = 0.70–4.61; $p = 0.11$), or weight (OR = 1.69, 95% CI = 0.84–3.42; $p = 0.07$). The univariate analysis of clinical risk factors for OIs had a significant positive association with WHO staging (OR = 24.04, 95% CI = 5.5–105.01; $p = 0.00$) and CD4 count (OR = 2.61, 95% CI = 1.32–5.16; $p = 0.00$). The risk of OIs did not significantly differ with adherence (OR = 0.37, 95% CI = 0.07–1.99; $p = 0.13$). **Conclusion:** OIs remain a challenge in patients receiving ART in resource-limited settings. There is a need to intensify the management of OIs despite ART use.

KEY WORDS: Adverse drug reactions; antiretroviral therapy; opportunistic infections; prevalence; risk factors

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Introduction

Acquired immunodeficiency syndrome (AIDS) is a global problem. It has now been reported from more than 190 countries around the world, and a pool of human immunodeficiency virus (HIV)-infected persons in Africa and Asia is large and expanding. India is estimated to have around 1.16 lakhs annual new HIV infections among adults and around 14,500

new HIV infections among children in 2011. The estimated number of person living with HIV/AIDS (PLHIV) in India maintains a steady declining trend from 23.2 lakhs in 2006 to 21 lakhs in 2011. The four high prevalence states of South India (Andhra Pradesh, Karnataka, Maharashtra, and Tamil Nadu) account for 53% of all HIV-infected population in the country. As on March 2013, there are around 18.13 lakhs PLHIV registered at the 400 ART centers functioning all around the country. Currently, nearly 6.5 lakhs are on first-line ART. Along with this, 840 link ART centers are primarily established for dispensing ARV drugs, monitoring side effects and treating minor OIs.[1]

Opportunistic infections (OIs) are defined as infections that are more frequent or more severe because of immune suppression in HIV-infected patients, and they are the major clinical manifestation of HIV patients.[2,3] OI cause significant morbidity and mortality in people with HIV infection.[4,5] The risk for the development of OI in HIV patients depends on exposure to potential pathogens, virulence of the pathogens, the degree of host immunity, and the use of antimicrobial prophylaxis.[6] Majority of these OI are associated with an increased hazard of death in HIV patients. Patients experiencing morbidity from opportunistic diseases may have interruptions in antiretroviral therapy (ART) causing more rapid progression of HIV disease. In addition, studies found that OIs cause an upregulation in HIV replication and higher viral load.[2,7–11]

The introduction of highly active antiretroviral therapy (HAART) has led to a significant reduction in AIDS-related morbidity and mortality. Unfortunately, up to 25% of all patients discontinue their initial ART regimen because of treatment failure, toxic effects, or noncompliance within the first 8 months of therapy.[12] Since the introduction of ART, a significant decline in OIs and AIDS progression has been observed.[13–15] The relative frequencies of specific OIs may vary in different countries and even in different areas within the same country. Knowledge of the most common OI of that geographical area will help in implementing the preventive measures against that pathogen. There is insufficient knowledge about the burden and risk factors for OIs in HIV-infected populations receiving ART in Karnataka, India.

Hence, we conducted a study with the following objectives: to collect demographic details of HIV-positive patients who were on ART and developed adverse drug reaction (ADR) to ART with OI and without OI; to determine the prevalence of OIs in HIV-positive patients who developed ADR to ART; and to investigate the sociodemographic and clinical risk factors associated with their occurrence.

Materials and Methods

Study Design and Study Population

This was a cross-sectional study carried out between January and June 2012. The study population comprised HIV-infected patients, who were receiving ART at ART Center, KR Hospital of Mysore Medical College and Research Institute, Mysore, Karnataka, India, who developed ADRs to antiretroviral drug with or without OI. The study protocol along with the pro forma and informed consent in vernacular language were approved by the Institutional Ethical Committee before starting the study.

Inclusion criteria were HIV-infected patients, who were on ART and who developed ADR to the same, with or without OI during the 6-month study period, patients of either sex, and patients who gave written informed consent.

Exclusion criteria were patients with all other immune-compromised states such as malignancies, organ transplant, patients on steroids therapy or immunosuppressive therapy, and diabetes mellitus.

Data Collection

Pro forma contained patient identification data, personal history, family history, risk factor details, antiretroviral treatment history, and laboratory investigations. Essential laboratory investigations included hemoglobin, total leukocyte count, differential leukocyte count, erythrocyte sedimentation rate, serum creatinine, blood urea, serum bilirubin, SGOT, SGPT, blood sugar, VDRL, HBsAg, anti-HCV, and CD4 count. For each participant, detailed history and physical examination were carried out to identify features suggestive of ongoing OIs. Depending on the specific clinical diagnosis of OI made, appropriate investigations such as sputum acid fast bacilli (AFB); chest x-ray; stool microscopy; cerebrospinal fluid (CSF) analysis; blood, sputum, and urine cultures; and tissue histology were carried out to confirm the diagnosis where possible. Individuals diagnosed to have any OI were referred for appropriate treatment.

Opportunistic Infection Diagnostic Criteria

The diagnosis of OI was made according to standard guidelines and facilities, which were available in the institution. Where diagnosis was entirely based on clinical grounds, two independent physicians involved in HIV care and management were required to have the same assessment before such diagnosis was accepted.

Data Analysis

Data analysis was carried out using the SPSS software, version 17, and Epi Info, version 7.1.4 statistical software. Prevalence of HIV-related OIs was described in percentage. For univariate statistical analysis, the χ^2 test where appropriate was used to determine significance of association between OIs and various sociodemographic and clinical variables. *P*-values < 0.05 were considered statistically significant.

Results

Sociodemographic and Clinical Characteristics of the Study Participants

Of the 158 patients enrolled in the study, 80 subjects were HIV-infected patients who were on ART and developed ADR to ART with OI and 78 subjects were HIV-infected patients who were on ART and developed ADR to ART without OI. Details are shown in Table 1.

Table 1: Sociodemographic and clinical characteristics of the study participants

Characteristics	OI present, *n* = 80(%)	OI absent, *n* = 78(%)
Sociodemographic variables		
Age (years)		
<20	7 (8.75)	1 (1.3)
21-40	54 (67.5)	51 (65.3)
41-60	19 (23.75)	25 (32.1)
>60	0 (0)	1 (1.3)
Gender		
Female	37 (46.25)	41 (52.56)
Male	43 (53.75)	37 (47.44)
Residence		
Urban	39 (48.75)	34 (43.59)
Rural	41 (51.25)	44 (56.41)
Literacy		
Literates	46 (57.5)	43 (55.13)
College and above	4 (5)	8 (10.25)
Secondary school	25 (31.25)	22 (28.2)
Primary school	17 (21.25)	13 (16.6)
Illiterates	34 (42.5)	35 (44.87)
Employment		
Employed	54 (67.5)	23 (29.49)
Unemployed	26 (32.5)	55 (70.51)
Marital status		
Married	51 (63.75)	43 (55.13)
Divorcee	4 (5)	0 (0)
Widow	17 (21.25)	22 (28.2)
Single	8 (10)	13 (16.67)
Weight (kg)		
<40	27 (33.75)	18 (23.08)
>40	53 (66.25)	60 (76.92)
Clinical variables		
WHO clinical staging		
Stage 1	43 (53.8)	72 (92.3)
Stage 2	6 (7.4)	4 (5.1)
Stage 3	19 (23.8)	1 (1.3)
Stage 4	12 (15)	1 (1.3)
CD4 count (cells/μL)		
<250	61 (76.25)	43 (55.13)
>250	27 (33.75)	35 (44.87)
Adherence (%)		
<80	2 (2.5)	5 (6.41)
80–95	3 (3.75)	0 (0)
>95	75 (93.75)	73 (93.59)

Prevalence of Opportunistic Infections

The prevalence/frequency of opportunistic infections is shown in Table 2. Of the 158 patients, 80 patients developed OIs with a prevalence of 50.63%.

Risk Factors for Opportunistic Infections

As shown in Table 3, the sociodemographic variables that had significant positive association with the presence of OIs on univariate analysis includes employment [odds ratio (OR) = 4.96, 95% confidence interval (CI) = 2.52–9.75; p = 0.00]. The risk of OIs did not significantly differ according to gender (OR = 0.77, 95% CI = 0.41–1.45; p = 0.21), age (OR = 1.658, 95% CI = 0.82–3.32; p = 0.079), residence (OR = 0.812, 95% CI = 0.43–1.52; p = 0.26), literacy (OR = 0.90, 95% CI = 0.48–1.70; p = 0.38), marital status (OR = 1.8, 95% CI = 0.70–4.61; p = 0.11), or weight (OR = 1.69, 95% CI = 0.84–3.42; p = 0.07).

Table 2: Frequency of opportunistic infection

Opportunistic infection	Frequency (%)
Extrapulmonary tuberculosis	27 (33.9)
Pulmonary tuberculosis	18 (22.6)
Oral candidiasis	11 (13.8)
Herpes zoster	10 (12.5)
Upper respiratory tract infection	5 (6.35)
Herpes simplex	3 (3.75)
Diarrhea	3 (3.75)
Lower respiratory tract infection	2 (2.6)
Cryptococcal meningitis	1 (1.3)

The univariate analysis of clinical risk factors for OIs is also shown in Table 3. Occurrence of OIs had a significant positive association with WHO staging (OR = 24.04, 95% CI = 5.5–105.01; p = 0.00) and CD4 count (OR = 2.61, 95% CI = 1.32–5.16; p = 0.00). The risk of OIs did not significantly differ with adherence (OR = 0.97, 95% CI = 0.27–3.50; p = 0.96).

Discussion

This study determined the prevalence and risk factors for OIs in patients who developed ADR to ART at ART center, KR Hospital of Mysore Medical College and Research Institute, Mysore, Karnataka, India.

In our study, the prevalence of OIs was 50.63%. The higher prevalence of OI in our study could be because of inclusion of patients who developed ADR to ART; compliance to ART becomes a challenge; upon that initial period of ART, that is, within few days of initiation of ART, there is high risk of immune reconstitution inflammatory syndrome and OI; and ADRs to ART becomes even more risky for developing OI. All these together could have lead to increased prevalence.

The study done by Moges et al.[16] in North West Ethiopia showed overall prevalence of OIs to be 42.8% with repeated infection. Other similar studies revealed a prevalence of 47.6% both in Taiwan[17] and South Africa.[18] Conversely, Iroezindu et al.[19] showed only 22.4% of OI prevalence.

In our study, most common OIs were extrapulmonary tuberculosis (TB), 27 patients (33.9%); pulmonary TB, 18

Table 3: Risk factors for opportunistic infections in patients on ART who developed ADR to ART

	OI present, n = 80 (%)	OI absent, n = 78 (%)	Odds ratio (95% CI)	P
Age (years)				
<40	61 (76.25)	52 (66.67)	1.658 (0.82–3.32)	0.079
>40	19 (23.75)	26 (33.33)		
Gender				
Female	37 (46.25)	41 (52.56)	0.77 (0.41–1.45)	0.21
Male	43 (53.75)	37 (47.44)		
Residence				
Rural	41 (51.25)	44 (56.41)	0.812 (0.43–1.52)	0.26
Urban	39 (48.75)	34 (43.59)		
Literacy				
Illiterate	34 (42.5)	35 (44.87)	0.90 (0.48–1.70)	0.38
Literate	46 (57.5)	43 (55.13)		
Employment				
Employed	54 (67.5)	23 (29.49)	**4.96 (2.52–9.75)**	**0.00**
Unemployed	26 (32.5)	55 (70.51)		
Marital status				
Married	72 (90)	65 (83.33)	1.8 (0.70–4.61)	0.11
Single	8 (10)	13 (16.67)		
Weight (kg)				
<40	27 (33.75)	18 (23.08)	1.69 (0.84–3.42)	0.07
>40	53 (66.25)	60 (76.92)		
Clinical staging				
3 and 4	31 (38.75)	2 (2.56)	**24.04 (5.5–105.01)**	**0.00**
1 and 2	49 (61.25)	76 (97.44)		
CD4 count (cells/μL)				
<250	61 (76.25)	43 (55.13)	**2.61 (1.32–5.16)**	**0.00**
>250	19 (23.75)	35 (44.87)		
Adherence				
<95%	5 (6.25)	5 (6.41)	0.97 (0.27–3.50)	0.96
>95%	75 (93.75)	73 (93.59)		

(22.6%); oral candidiasis, 11 (13.8%); and herpes zoster, 10 (12.5%). Other OIs were upper respiratory tract infection in 5 patients (6.35%); herpes simplex and diarrhea, 3 (3.75%); lower respiratory tract infection, 2 (2.6%); and cryptococcal meningitis, 1 (1.3%).

The study by Damtie et al.[20] showed that TB followed by oral candidiasis and diarrhea were the major OIs encountered by HIV-infected patients. The study by Goud and Ramesh[21] also showed TB as the commonest OI. Moges et al.[16] in their study found that oral candidiasis, chronic diarrhea, and TB as common types of OI. The study by Ghate et al.[22] showed TB was the most common OI, followed by oral candidiasis, herpes zoster, and cryptococcal meningitis. In contrast, Gautam et al.[23] showed that herpes zoster was the most common OI, followed by TB, skin infection, and chronic diarrhea. Saha et al.[24] showed that the common co-infections/OIs were oral candidiasis followed by chronic diarrhea, HSV-2, TB, CMV, HBV, and HCV, while Elizabeth et al.[25] showed that the most common OIs were oropharyngeal candidiasis followed by TB. In the study by Shahapur et al.,[26] pulmonary TB was the most common OI, followed by candidiasis, cryptosporidial diarrhea, herpes zoster, cryptococcal meningitis, and pneumocystis pneumonia.

In our study, the risk of OIs did not significantly differ according to gender, age, residence, literacy, marital status, or weight. Moges et al.[16] in their study assessed the factors associated with occurrence of OIs among HIV-infected patients taking ART. Accordingly, younger age, advanced baseline WHO stage, khat use, ART adherence, recent hemoglobin status, and recent weight were found to be associated factors for OIs occurrence.

In this study, neither age nor gender had a significant relationship with occurrence of OIs. Palella et al.[27] also found no signification association between age and OIs in a cohort of US patients. In contrast Lawn et al.[28] demonstrated increased risk of TB in younger patients (<33 years), while Ghate et al. in a predominantly HAART-naive population in India reported that older age was a strong determinant of OIs. Contrarily, male gender was found to be strongly associated with the occurrence of OIs in other reports.[29,30] Large prospective cohort studies are needed to further investigate the relationship between sociodemographic variables and HIV-related OIs in developing countries.

In our study, occurrence of OIs had a significant positive association with WHO staging (OR = 24.04, 95% CI = 5.5–105.01; p = 0.00) and CD4 count (OR = 2.61, 95% CI = 1.32–5.16; p = 0.00), which was similar to the study conducted by Damtie et al.[20] and Iroezindu et al.[19] So, early initiation of ART could prevent OI.

In a study done by Moges et al.,[16] patients with advanced baseline WHO stages of III and IV were more likely to develop OIs, than those with a baseline WHO stages of I and II, which is similar to our study. Similar finding was also observed in a study conducted in Nigeria showing that advanced WHO clinical stage at baseline to be an independent clinical risk factors for the occurrence of OIs.[19] Similar findings were also observed in studies by Manosuthi et al.,[31] Ledergerber et al.,[13] Srirangaraj et al.,[32] Kaplan et al.,[33] and Lawn et al.[28] This could be because of lower immunity with higher WHO staging, which further predisposes for OIs.

Strengths of the STUDY

The study includes HIV patients who developed ADRs to ART, unlike other studies that have included ART-naive patients or ART-experienced patients only. To our knowledge, this is the first study.

Limitations of the Study

Because of the high cost of the plasma viral load determination, monitoring of HIV RNA levels and HIV drug resistance testing in HIV-infected patients on ART is still not offered as a standard of care test in resource-limited settings. So, the impact of HIV RNA levels and HIV drug resistance testing in the study subjects was not assessed.

Conclusion

Indian guidelines and Western country guidelines have certain differences; wherever possible, that gap should be bridged. Developed countries initiate ART at higher CD4 count. They may have more chance of developing resistance to first-line drugs and need for newer class of antiretroviral drugs. Patients in developed countries can afford for, unlike resource-limited countries such as India.

India is a low-income country, and only treatment and diagnostic options available in the country were included. The need to bridge the gap in the treatment recommendations between public and private sector programmes has been taken into account, considering that many patients transit between the two sectors for treatment. The guidelines are intended to reflect "best practice" while it is acknowledged that certain recommendations are inspirational for poorly resourced settings, the unavailability of diagnostic/monitoring tests should not be a barrier to providing ART to those in need.

Individuals who continue to have low CD4 cell count while on ART should be aggressively evaluated for OIs, and practical efforts to optimize their immunological recovery should be made. Prophylaxis for TB and fungal infections, especially candidiasis, should be widely implemented in the routine management of PLHIV after exclusion of active disease, irrespective of ART use. ART adherence counseling should be intensified in patients receiving ART.

Better accessibility to ART centers is needed. Optimal doctor patient ratio is necessary to deliver a quality service. Effective counseling regarding the disease, complications, treatment, and its reactions and awareness regarding opportunistic reactions, regular follow-up, and compliance to therapy are very essential.

Intervention programs and services especially to rural and remote areas rather than urban areas should be given. Special facilities should be given to needy people that would avoid late transfer of patients and late diagnosis. This would increase

survival rate and decrease morbidity and mortality of the disease. If possible, rehabilitation centers for the diseased people should be recognized and encouraged in the society.

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