A pattern of Opportunistic Infections among HIV In patients on Antiretroviral Therapy in a Tertiary Care Hospital in Coastal Karnataka: A Retrospective Evaluation

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Abstract
Though the incidence of opportunistic infection (OI) is reducing with combination antiretroviral therapy. In this study we aimed to identify the pattern of the occurrence of opportunistic infections in HIV (Human Immunodeficiency Virus) patients. This was a retrospective, case-record based, time-bound study over a four year period (2013-2016) which included HIV positive in-patients aged >18 years of age, of either gender on Antiretroviral Therapy (ART). Demographic details, details of HIV infection including baseline and all available CD4 counts, details of the medications were recorded. Adverse drug reactions (ADR) were recorded by reviewing patient records. Among the files checked, 298 inpatients were on ART regimens recommended by the National AIDS Control Organization (NACO), and were included in the study. Among them, 70.8% of patients developed at least one OI, 29.8% developed two OIs, and 6.71% developed three OIs. The most common OI was pulmonary tuberculosis (48.3%). The most common ART regimen was a combination of Zidovudine + Lamivudine + Nevirapine. In our study, 70.8% of patients developed at least one OI, which suggests that despite availability of combination ART, OIs continue being a significant issue in patients with HIV in resource-limited settings.

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virtide and the recently introduced drugs like integrase inhibitors, maraviroc etc. (Flexner, 2011).

These drugs are always used in combination regimens according to the prescribed guidelines. In India, the National AIDS Control Organization (NACO) is the body that deals with various aspects regarding HIV, including regulatory aspects, publishing and updating guidelines on the management of HIV. Accordingly, as recommended by the NACO, various combinations of antiretrovirals (ARVs) are used to treat HIV patients. Initiation of ART is based on the clinical stage and CD 4 cell count. Nevertheless, the start of ART should never be deferred by the absence of a CD 4 cell count result. The CD4 count should only be used as a supplement to clinical assessment in matters of decision making (National AIDS Control Organisation, 2013; Kumara Sammy et al., 2011).

Opportunistic infection (OI) refers to an infection that is seen when the immune system in an individual is compromised. CD 4 count, which is one of the indicators of the severity of HIV infection (‘immunological response’), is also known to be correlated to the appearance of these opportunistic infections (OI). Presence of life-threatening OIs along with a CD 4 count of fewer than 200 cells/mm3 defines acquired immunodeficiency syndrome (AIDS). The Centers for Disease Control and Prevention (CDC) defines an OI as an infection that occurs more frequently and is more severe in individuals with weakened immune systems, including people with HIV. Commonly occurring OIs include those with Candida albicans, Pneumocystis jiroveci, Cytomegalovirus, etc. Infection with tuberculosis is now considered a co-infection, rather than an opportunistic infection (National AIDS Control Organisation, 2013, 2007).

Though the incidence of OIs has been reducing, in resource-limited settings, it continues to be a significant issue in the management of HIV disease progression. We conducted this study intending to identify the pattern of the occurrence of opportunistic infections in patients infected with HIV, along with the factors that affect their occurrence. We also aimed to study the switch over of treatment regimens, and the factors affecting them.

**METHODS**

This was a retrospective, case-record study based study conducted at a tertiary care hospital in Coastal Karnataka. The study population consisted of HIV positive subjects of either gender, aged more than 18 years, inpatients. This was a time-bound study over four years (2013-2016).

Patients whose CD4 counts were not available, those not compliant with ART, and patients with other known causes of immune deficiency were excluded from data collection.

Data was collected from the patient files from the medical records department. Demographic data collected included age, gender, and socio-economic status. CD4 cell count and HIV viral load were recorded as and when available. Other laboratory investigation reports collected include baseline haematology, liver function tests, renal function tests, blood sugar, fasting lipid profile (whichever available). Any clinically indicated additional investigations that had been done were also recorded.

Details regarding HIV infection were collected concerning the duration of illness, clinical signs and symptoms. Details on the presence of clinically diagnosed opportunistic infections, and the course of the disease, were collected. Details of treatment of opportunistic infections were collected, along with any preventive measures taken. Data regarding antiretroviral treatment was collected, and patients were grouped based on the regimen that was being followed. This included the treatment regimen that was first initiated and the patient’s response to the same. Data on the first switch over to other regimens, and subsequent switch overs if present and the reason(s)/drug(s) implicated for switch over was also collected.

The collected data was entered in MS-Excel, and analysis was done using SPSS (Statistical Package for the Social Sciences), version 11.5. Student-t-test was used to compare means. A p-value <0.05 was taken as statistically significant.

**Ethical considerations**

The study was conducted only after obtaining permission from the institutional ethics committee. Patients were assigned an identifier code, and personal information like name, address, contact details were not recorded.

**RESULTS**

Among the files that were deemed suitable to be included in the study and were checked from the medical records department, 298 inpatients were on ART and were compliant to therapy, and were included for data collection and analysis. These various ART regimens that the patients were on were those recommended by the NACO guidelines.

The baseline CD4 count and haematological investigations were noted. Besides, any other clinically warranted investigations explicitly required for any particular patient that had been done were also
Of the 298 patients, 177 were males (59.39%), and 121 females. A significant difference between male and female patients was observed concerning the patient's weight at baseline (p-value < 0.001). The most common ART regimen the patients were initially started on, was a three-drug combination of zidovudine, lamivudine, Nevirapine (44.4%), followed by various other regimens [Table 1].

Out of the 298 records studied, 211 patients (70.8%), developed at least one OI, 89 people (29.8%) developed two OIs, 20 patients (6.71%) developed three OIs, and six patients (2.01%) went on to develop four OIs. The most common OI was pulmonary tuberculosis. The other OIs included oral and oesophageal candidiasis, *Pneumocystis jiroveci* pneumonia, cerebral toxoplasmosis, herpes simplex infection, herpes zoster, CMV retinitis. One case of Kaposi sarcoma was also observed [Table 2].

**Adverse Drug Reaction & Switch-over of Regimen**

Of the 211 patients who developed at least one OI, 101 patients (47.86% of patients who developed an OI) also developed at least one ADR, and 32 patients (15.16% of patients who developed an OI) developed two ADRs. Zidovudine was the drug most commonly responsible for ADR. Anaemia was the most frequently observed ADR, followed by a rash, probably due to Nevirapine.

Out of 211 patients who developed OI, 69 patients (32.7% of patients who developed an OI) had the first switch of the regimen. The primary reason was the development of an ADR, followed by failure of therapy, and stopping anti-tubercular regimen. Seven patients (3.31% of patients who developed an OI) had the second switch of regimen, owing to the development of ADRs. Three patients switched for the third time (1.42% of patients who developed an OI), again due to an ADR.

An attempt was made to study the number of drugs other than those that are a part of antiretroviral therapy, administered to the patient during the period of stay in the hospital, and also when the patient was discharged from the hospital. The mean number of medications the patient received when in the hospital was 5, and the mean number of medications on discharge reduced to four. These included medications to treat the OI that had occurred, medications to prevent the occurrence of other OIs (prophylactic medications), and multivitamins. Also, patients who were co-infected with tuberculosis received anti-tubercular therapy as a part of DOTS therapy. Exact details of the treatment of the OIs concerning dose or duration were not available, as this was a retrospective case record-based study.

**DISCUSSION**

We conducted this study intending to identify the pattern of the occurrence of opportunistic infections in patients infected with HIV, along with the factors that affect their occurrence. We also aimed to study the switch over of treatment regimens, and the factors affecting them. The baseline characteristics of patients were not significantly different, except for weight, which was higher in male patients. In our study, there were a higher number of male patients than female patients, but the difference was not significant. This was in contrast to earlier studies, in which the number of female patients was predominant (67%) (Masenye et al., 2015; Dube et al., 2012). However, an earlier study conducted in India had more number of male patients than females, similar to our study. The gender difference could be because of higher treatment-seeking behaviour as among female patients compared to males. Also, in the said study, the mean age of patients was 37.68 years (Shet et al., 2014).

Out of 298 inpatients, 211 of them developed at least one OI which accounts for 70.8% of patients; 89 people developed two OIs (29.8%), 20 patients developed three OIs (6.71%), and six patients developed four OIs (2.01%). An earlier cross-sectional study conducted in Ethiopia to look at the prevalence of OI among HIV patients on ART concluded that the overall prevalence of OI was 42.8%, out of which, 61% of the patients had one OI, 34.8% had two OIs, 3.5% of the patients developed three OIs, and 0.7% of the patients developed four OIs (Moges, 2014).

Tuberculosis was the most commonly observed OI in our study at 68.2% of the total OIs seen (48.3% of the total number of patients). In a study conducted in Assam, tuberculosis was the most common OI at 65.43%, followed by dermatitis (39.50%), oral candidiasis (32.09%), and chronic diarrhoea (29.62%), and this is comparable with our study (Sonowal and Goswami, 2015). In another study conducted in Delhi region by the Delhi state AIDS control society, it was observed that tuberculosis accounted for 28.07% of OIs reported. Owing to the prevalence of tuberculosis in our country, this could be the reason for it being the most commonly observed OI. In our study, the second most commonly observed OI was lower respiratory tract infection including pneumonia at 34.59% of OIs (24.4% of a total number of patients); this excluded *Pneumocystis jiroveci* pneumonia which accounted for 16.58% of OIs (11.7%...
Table 1: Baseline characteristics of patients

| Parameter                  | Male             | Female           | p-value |
|----------------------------|------------------|------------------|---------|
| Age (years)                | 44.82 (10.377)   | 42.05 (10.229)   | .104    |
| CD4 count (cells/mm³)      | 268.54 (180.081) | 304.68 (207.086) | .253    |
| Weight (kg)                | 57.6593 (9.65197)| 51.1774 (10.26936)| .000    |

Figures expressed as mean (2SD); Student t-test: * = highly significant, p<0.001

Table 2: Commonly Observed Opportunistic infections among patients

| Opportunistic Infection Observed | Number of cases (%) [n=298] |
|----------------------------------|-----------------------------|
| Pulmonary Tuberculosis           | 144 (48.3)                  |
| Lower respiratory tract infection, including pneumonia | 73 (24.4)                  |
| Pneumocystis jiroveci pneumonia   | 35 (11.7)                   |
| Oral candidiasis                 | 31 (10.4)                   |
| Chronic Diarrhoea                | 31 (10.4)                   |
| Herpes Simplex infection         | 23 (7.71)                   |
| Cerebral Toxoplasmosis           | 21 (7.04)                   |
| Herpes zoster                    | 13 (4.36)                   |
| Cryptococcal infection           | 12 (4.02)                   |
| Cytomegalovirus infection        | 10 (3.35)                   |
| Oesophageal Candidiasis          | 8 (2.68)                    |
| Tubercular Meningitis            | 6 (2.01)                    |

of the total number of patients). The distinction between the two types of pneumonia was made because of the different aetiology and the treatment modalities. Oral and oesophageal candidiasis together accounted for 18.48% of OIs (13.08% of the total number of patients); 10.4% of the patients had chronic diarrhoea.

An earlier study conducted in Bhopal reported that bacterial infections accounted for the maximum number of OIs (44.14%), followed by fungal (32.43%), parasitic (16.21%) and viral infections (7.20%) (Agarwal, 2015). However, another study conducted in Ahmedabad found that the most common isolate was Candida (32.67%), followed by Mycobacterium tuberculosis (22.71%) and Cryptosporidium parvum (19.8%) (Patel et al., 2011). A study done earlier in Nepal had concluded that lower respiratory tract infections were more common in HIV infected individuals (Ojha et al., 2015).

If we were to consider the pathogen causing the disease and not the disease per se, Candida was the second most common pathogen observed in our study, which included cases of oral and oesophageal candidiasis. Infection with Candida is a widely recognised OI in patients with HIV according to earlier studies too (Dabla et al., 2015). Among viral infections, herpes simplex infections, including mouth ulcer, was seen. Herpes zoster was also seen to occur. Cytomegalovirus infection-causing retinitis was seen in ten patients. These viruses are known causative agents of OIs in HIV patients, though the incidence of each of these observed earlier is variable (Balkhair et al., 2012).

In prior studies, anaemia and rash had been observed to be the most frequent ADRs, while the most common clinical ADRs were gastrointestinal disturbances (Bhuvana and Hema, 2014; Lartey et al., 2014). Similar findings were observed in our study, too, with anaemia being the most common ADR. This could again be since a zidovudine-containing regimen was the most frequently used drug regimen. Other ADRs reported from earlier studies, and many of which were observed in our study as well, included generalised, fatigue, non-specific central nervous system disturbances such as headache, dizziness and insomnia, elevated liver enzymes, neutropenia, dyslipidemia, neuropathy, and cough. Peripheral neuropathy due to stavudine had been observed in prior studies and was observed in our study too (van Oosterhout et al., 2012).

**Switch-over of regimen**

In our study, out of 211 patients who developed OI, 69 patients had a first switch of the regimen. The primary reason was the development of an ADR, followed by ART Failure, and stopping the anti-
tubercular regimen. Seven patients had a second switch of regimen, owing to the development of ADRs. Three patients switched for the third time, again due to an ADR (Dube et al., 2012).

Having to take multiple medications in multiple doses is an issue that is less often addressed. Though the number of antiretroviral medications has decreased owing to them being dispensed as fixed-dose medications, the patients often get multiple other medications such as cotrimoxazole, multivitamins, other drugs to treat and protect against OIs. In our study, we attempted to study the number of medications that a patient got on discharge apart from ART and anti-tubercular therapy if indicated. The mean number of drugs each patient got on discharge was four. This observation was made earlier too (Krentz et al., 2012). A single-tablet regimen was seen earlier to be associated with more compliance than multiple pill-based regimens (Sutton et al., 2016; Nachega et al., 2014).

CONCLUSION

Of the inpatient records studied, 70.8% of patients developed at least one OI, 29.8% developed two OIs, and 6.71% developed three OIs. Pulmonary tuberculosis was the most commonly observed OI. Hence, this goes on to suggest that despite the availability of combination ART, OIs continue being a significant issue in patients with HIV in resource-limited settings, and this issue has to be tackled to make the best use of the available resources.

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Conflicts of Interest

The authors declare that they have no conflict of interest for this study.

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