Chapter 15

Burden of Opportunistic Infections in HIV/AIDS Patients in the Highly Active Antiretroviral Therapy Era: A Regional Institute of Medical Sciences, Imphal Perspective

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INTRODUCTION

With the advent of highly active antiretroviral therapy (HAART) in 1996, there has been a decline in morbidity, mortality from opportunistic infections (OIs) in HIV patients globally. However, AIDS defining OIs continue to occur despite HAART. Bauer and associates studied hospitalization rates in HIV patients from 1993 to 1999 in San Diego. From 1993 to 1997, hospitalization rates fell, but from 1997 to 1999, they rose due to non-HIV-related events despite the fact that hospitalized individuals had higher CD4+ counts and lower viral load (VL). In an analysis of 1,670 deaths in the EuroSIDA cohort of HIV patients (1994–2000), Mocroft and colleagues found that the ratio of AIDS related to AIDS-unrelated deaths declined from 17 in 1996 to 5 during 1997–2000, suggesting that the causes of death were not the traditional AIDS defining OIs. When investigators assessed the causes of death, many deaths that occurred since 1997 were due to malignancies and Hepatitis B virus (HBV), hepatitis C virus (HCV)-related liver disease. Another potential change in morbidity and mortality pattern could be due to an uprisin in microvascular complications related to HIV and HAART toxicity.

When clinical deterioration occurs during immune recovery following HAART initiation and is associated with the host inflammatory response to pathogens, it has been described as immune reconstitution inflammatory syndrome (IRIS). Immune reconstitution inflammatory syndrome usually occur within a few weeks to months after the initiation of HAART and majority present with unusual manifestations of OIs, while the CD4+ cell count is increasing and the VL is decreasing. Diagnosis of IRIS requires the worsening of a recognized (paradoxical) or unrecognized (unmasking) pre-existing infection in the setting of improving immunologic function.

Studies have indicated IRIS ranges from 10% to 30% in patients who have been infected for several years. It is more common in patients with CD4+ cell counts above 100 cells/µL and in patients with a history of tuberculosis (TB) or hepatitis C virus (HCV)-related liver disease. IRIS can occur in the presence of HIV infection and HAART was 1,284 days and 1,228 days respectively.

People living with HIV/AIDS (PLWHA) are 6–50 times more likely to develop active TB than HIV-uninfected people. India has 5.2% prevalence of HIV/TB co-infection as per WHO in 2006. Southeast Asian region has the second highest burden of HIV/TB co-infection, with 13% of the global caseload as per WHO in 2008. Highly active antiretroviral therapy is a crucial component of case management of HIV/TB, reducing mortality risk by 64–95% and halving recurrence rates. HAART has an important role in the prevention of HIV/TB, reducing risk in treated cohorts by a mean of 67%.

With this study our objective was to describe the burden of OIs and OIs occurring in relation to IRIS and treatment failure in HIV patients in the HAART era.

MATERIALS AND METHODS

About 322 HIV/AIDS patients attending antiretroviral therapy (ART) center and in-patients in medicine ward in RIMS Hospital Imphal, with their informed written consent, were studied between June 2010 and June 2012. The study design was observational cross-sectional with retrospective chart review of natural course of HIV infection with treatment history of the study population. Age, sex, duration of HIV infection, HAART duration and regimen and adverse events were noted. Their records were studied for past OIs and simultaneous screening for present OIs with appropriate investigations was performed. CD4+ cell count was done using Fluorescent Activator Cell Sorter machine. All patients were screened for HBV and HCV coinfections.

Study population was divided into four time frames: ART naive (Frame 1), less than 3 months of HAART initiation (Frame 2), greater than 3 months: 1 year HAART (Frame 3) and greater than 1 year HAART initiation (Frame 4).

Antiretroviral therapy-associated TB, TB-IRIS (paradoxical and unmasking) was diagnosed according to International Network for the Study of HIV-associated IRIS criteria. Treatment failure was diagnosed according to National AIDS Control Organisation (NACO) 2008 guidelines.

Statistical analysis was performed using the SPSS version 16 software.

RESULTS AND OBSERVATIONS

There were 209 males and 113 females with male: female ratio of 1.84:1 and mean age was 39.37±7.3 years. Mean duration of HIV infection and HAART was 1,284 days and 1,228 days respectively. About 42.2%, 32.3%, 19.6% and 5.9% patients belonged to stages 1, 2, 3 and 4 in WHO clinical staging respectively. About 10.2% patients were HAART naive, 76.1% patients on first-line HAART (29.8% zidovudine based and 46.3% stavudine based), 3.7% patients on alternative first-line HAART and 9.3% patients on second-line HAART according to 2008 NACO guidelines. Mean baseline CD4 and peak CD4 cell count during therapy was 156.43±85.83 cells/mm³ and 401.11±273.3 cells/mm³ respectively.

There were 362 episodes of OI in 322 study population. About 223 episodes occurred in time frame 1, 38 in Frame 2, 8 in Frame 3 and 45 in Frame 4. P value for multivariate analysis of HAART with OIs for time frames 2, 3 and 4 were 0.047, 0.207 and 0.000 (< 0.05 significant) respectively (Figure 1).

Negative correlation co-efficient of 0.361 was found in Pearson’s correlation between baseline CD4 cell count and OI before HAART with significant p value of 0.01.
Figure 1: Composite bar chart showing distribution of opportunistic infections episodes in the 4 time frames

Most commonly encountered OI was TB with 92 episodes. In extrapulmonary TB (EPTB) there were 25 episodes of TB lymphadenitis, 10 pleural effusion, 9 abdominal TB, 3 tuberculous meningitis and two episodes each of tuberculoma brain, Pott’s spine and disseminated TB. Ten (27.78%) out of thirty-six episodes of pulmonary TB were sputum acid fast bacilli (AFB) positive and 8 (14.28%) out of 56 episodes of EPTB were AFB positive. Second most common OI found was candidal infection in 60 episodes (46 oral, 3 esophageal, 8 urinary, 4 respiratory, 1 vaginal and 1 episode of isolated gastric candidiasis), followed by *E. coli* infection in 30 episodes. Cryptococcosis was found in 29 episodes with 25 being cryptococcal meningitis (CM) including 3 caused by *C. albidas*, 1 cryptococcoma in the brain and 3 episodes of cryptococcosis isolated from lymph glands. *P. jirovecii* infection in 17 episodes and 26.41% were sputum positive.

Antiretroviral therapy-associated TB was found in 48 episodes among 287 patients on HAART. Around 31 (9.3%) patients had IRIS predominantly occurring in time frame 1 and the mean baseline CD4 cell count in them was 83.03 cells/mm$^3$. There was a negative Pearson correlation co-efficient of 0.306 between baseline CD4 cell count and IRIS with p value of 0.01. Tuberculosis was the common OI implicated in IRIS with 19 episodes (32.2%), followed by 10 episodes (16.94%) of CM IRIS and 9 episodes (15.2%) of *P. jirovecii*-IRIS. Tuberculosis-IRIS was pulmonary in six episodes and extrapulmonary in the other 13 (Figure 2).

Thirty-nine patients who had 45 episodes of OI in time frame 4 had HAART failure with TB (excluding TB pleural effusion and TB lymphadenitis) implicated in 25 episodes, gastrointestinal infection with oral candidiasis, *Cryptosporidium, Isospora* in 10 and three episodes of cryptococcosis and *P. jirovecii* each. Around 27 out of 39 HAART failure patients had confirmed virological failure with mean viral load (VL) of 28,084 copies/ml and remaining 12 patients had clinical and immunological failure only without evidence of virological failure. Seven patients with HAART failure had HCV coinfection.
Adverse events following HAART were seen in 148/287 patients with ≥4 having metabolic syndrome features and 21 having neurotoxic picture.4 Patients had co-existent malignancies (Ca cervix, Mantle Cell Lymphoma, Undifferentiated Small Cell Lymphoma, AML 1 each). Hepatitis B Virus coinfection was found in 10 patients, HCV coinfection in 43 patients and both HBV/HCV coinfections in five patients. Features of decompensated liver disease were found in 21 out of 58 hepatitis co-infected patients.

DISCUSSION

In the pre-HAART era, common OIs seen in America and Europe were Pneumocystis carinii pneumonia (PCP), cytomegalovirus and toxoplasmosis.21 Studies in HAART naive population in Africa and South Asia showed that TB topped the list.22,23 National AIDS Control Organisation34 analysis of various OIs reported from different parts of India in HAART naive population were TB (64%), candidiasis (58%), cryptosporidial diarrhea (35%), herpes zoster (11.8%), toxoplasmosis (7.4%), bacterial infections (7.6%), PCP (4%), CM (3%) and the prevalence of the same OIs in our present study were 25.41%, 16.57%, 3.31%, 3.4%, 24.86%, 4.6% and 6.9% respectively. The above statistic shows that HAART offers protection against most OIs and decreases their prevalence whereas prevalence of CM has not decreased despite HAART indicating that there is widespread reservoir of this agent in India as evidenced by an epidemiological study from the north.25,26 Histoplasmosis, blastomycosis, Mycobacterium avium-intracellulare were not seen in our study similar to other studies in our country.27,28

Highly active ART improves immune function by suppressing HIV replication and increasing CD4+ T-cell counts.29 In our study, the proportion of IRIS was 9.3% (31/322), a finding consistent with studies done elsewhere showing 10–25% occurrence.30–32 In our study most of the IRIS cases occurred within the first 3 months of HAART initiation, which is consistent with prior reports.31 Of the 31 IRIS cases, 88% were unmasking IRIS, and 12% were paradoxical episodes, consistent with the South African study.33 Our finding of TB-IRIS in majority of the IRIS patients (32.2%) is in accordance with other studies.33,34 The IRIS patients in our study had significantly low baseline CD4+ count and higher proportion of EPTB. Previous studies also described both low baseline CD4+ count and EPTB as the possible risk factors for the occurrence of IRIS.34,35 Among 287 patients in our study who started HAART, 31 (10.8%) patients developed 48 episodes of ART-associated TB. An earlier study at the infectious disease institute clinic found that 9.6% of HAART naive patients developed ART-associated TB and most were diagnosed within 3 months of HAART.36 Multivariate analysis shows that a raised C-reactive protein (CRP) (≥5 mg/L) and low body mass index (BMI) (<18.5 kg/m²) were predictors of ART-associated TB in Worodria et al. 2011 study.37 An increment in the level of CRP is independent of the stage of HIV infection and thus is useful for supporting a diagnosis of OIs in HIV co-infected patients. C-reactive protein is also useful in monitoring TB treatment response.38 Low BMI is a marker for poor prognosis in patients with HIV and has also been associated with increased risk of TB and death.39,40 Early initiation of TB treatment in HIV-infected patients with wasting and increased CRP levels prior to initiating HAART may therefore alleviate the excess morbidity due to undiagnosed TB and ART-associated TB.

Several studies have demonstrated a survival benefit of early HAART in HIV/TB coinfection. In the Starting Antiretroviral Therapy at Three Points in Tuberculosis trial, a 56% reduction in mortality was observed in patients who started HAART during TB treatment compared to those who started after completion of TB treatment.41 CAMBodian Early versus Late Introduction of Antiretroviral Drugs trial showed that the initiation of HAART 2 weeks after starting TB treatment significantly enhanced survival in TB/HIV co-infected patients compared to starting HAART at 8 weeks.42 This further emphasizes the need to screen for TB prior to HAART and to ensure early treatment for both TB and HIV.

Patients with a HAART failure usually harbor a WHO stage 3 or stage 4 events with the exclusion of TB lymphadenitis and TB pleural effusion. This is evidenced by a 2009 Ugandan Study which showed that ART-associated TB was a risk factor for virological failure.43 There are studies in literature where oral candidiasis has been shown as indicator for HAART failure.44 Patients diagnosed with ART-associated TB are likely to fail therapy, because of drug interactions of antituberculous treatment and HAART, HAART adherence due to increased pill burden. In our study, seven patients with HAART failure had HCV coinfection; evidences also indicate that HCV is associated with impaired CD4+ T-cell recovery during HAART.45 However, there are contrasting facts in the WHO report for Europe region which states that HCV has little or no effect on the response to HAART or on immunological, virological or HIV-related clinical disease progression.46 A prospective study with mortality analysis with respect to OIs and IRIS would have improved the results of our study.

CONCLUSION

Though the incidence of OIs has decreased in the HAART era, they do occur in a sizeable number of patients. Opportunistic infections occur more in HAART naive compared to the HAART sensitized group and in the latter, OIs are common within 3 months of HAART initiation as a result of IRIS or after 1 year of HAART period where it can be indicator of treatment failure. Tuberculosis coinfection is a major problem across all spectrums of HIV/AIDS patients, viz. HAART naive, less than 3 months of HAART initiation manifesting as IRIS and greater than 1 year of HAART initiation as an indicator for HAART failure. Thus intensive screening for TB and other OIs, OI prophylaxis, early HAART initiation and comprehensive TB and other OI treatment before and during HAART alleviates morbidity, prolongs life span and improves quality of life in PLWHA. Further, co-morbidities resulting from adverse events of HAART, HBV/HCV coinfections which hamper the quality of life and increase morbidity in PLWHA, should be addressed with equal importance parallel to HAART.

REFERENCES

Human Immunodeficiency Virus


