CLINICAL STUDY OF MORBIDITY AND MORTALITY OF PEOPLE LIVING WITH HIV (PLHIV) ADMITTED TO A TERTIARY HEALTH CENTRE IN GUNTUR, ANDHRA PRADESH

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ABSTRACT

INTRODUCTION
Guntur district, which forms part of the AP state capital region, tops the list of HIV positive cases in the state. The district also had the dubious distinction of being the "HIV capital" in undivided Andhra Pradesh in the last two years. A proportion of the many patients who have advanced AIDS in Guntur diagnosed lately present for the first time requiring admission to hospital.

AIM
The aim of the study is to describe the clinical condition, inpatient case management and outcomes before discharge of people living with HIV admitted in Tertiary Health Centre in Guntur, Andhra Pradesh.

MATERIAL AND METHODS
This was an observational, analytic, prospective cohort study using a sample of all patients consecutively admitted in tertiary health centre from March 2015 to September 2015. Patients were divided into two groups, ART Group and non-ART Group. ART Group includes all the patients who were started immediately on Anti-retroviral Therapy (ART) before their discharge. Non-ART Group contains patients who did not received ART or who were terminally ill to start ART. Prevalence of opportunistic infections, morbidity and mortality outcomes of the two groups before discharge were determined.

RESULTS
Among the cohort of 203 PLHIV enrolled during the study period, only 85(42%) were initiated on ART immediately. In all patients, tuberculosis (67;35%) was the most common opportunistic infection followed by extra pulmonary tuberculosis (63; 31%) and Pneumocystis pneumonia (35;19%). The mean baseline CD4 cell count was 84 cells/uL for the non-ART group and 55 cells/uL for the ART group (p <0.01). The median duration from time of initial admission to ART initiation was 14 days. The median duration of stay from initial admission to discharge from hospital was 13 days in the NON ART group and 18 days in the ART group. The mortality before discharge among the non-ART group was 24% compared to 6% among the ART group (p =0.001). Immune reconstitution inflammatory syndrome was diagnosed in three patients (4%) among the admissions, but caused no deaths.

CONCLUSIONS
Average CD4 count is lower in patients admitted with AIDS defining illness. Tuberculosis co-infection contributes the largest burden of disease and was diagnosed in two thirds of all admissions. Starting ART as soon as it can be tolerated (within 2 weeks) after anti-tuberculosis therapy will be of great benefit in reducing mortality. Most patients stayed for a median of four days after the ART initiation. This was crucial to monitor and treat anticipated adverse events and drug toxicities from combined opportunistic infection treatment and ART.

KEYWORDS
People living with HIV (PLHIV), Human immunodeficiency virus (HIV), Acquired immunodeficiency syndrome (AIDS), Antiretroviral therapy (ART). Opportunistic infections (OI), Antituberculosis treatment (ATT).

INTRODUCTION: HIV/AIDS is a global pandemic. As of March 2015, there were 36.9 million (34.3 million–41.4 million) people living with HIV.[1] Despite the impressive roll-out of Antiretroviral Therapy (ART) programmes worldwide including in low and middle-income countries, 1.2 million.[1] (980 000–1.6 million) people died from AIDS-related causes worldwide. People who are diagnosed with HIV are linked to healthcare facilities able to provide ART and ideally ART

should be started before the development of opportunistic infections. However, the majority of patients enter into care late both in developed and developing countries.[2]

A high proportion of HIV patients in India continue to be diagnosed late (CD4 count<500 cells/mL) with increased risk of morbidity and mortality, high Healthcare costs, poorer response to Highly Active Antiretroviral Therapy (HAART) and also onward HIV transmission by patients unaware of their diagnosis.

One of the most important reasons for this late presentation is the poor linkage between healthcare centres performing HIV testing and ART centres. In ART centres, the measurement of the CD4 lymphocyte count is the first step of the assessment of HIV infected patients. Studies have shown that only 72% (95% confidence interval [CI], 60–84%) of patients diagnosed with HIV have a CD4 count measured and between one-third.[3,4] and two-thirds provide samples for CD4 counts within 2–3 months of the HIV positive test.[4,5] However, data from resource-limited settings are scarce.

With 2.1 million HIV infected people, India has the third largest burden of HIV worldwide.[6] and two thirds of the patients live in rural areas.[7] The total number of people living with HIV (PLHIV) in India is estimated at 21.17 lakhs (17.11 lakhs–26.49 lakhs) in 2015, Children (<15 years) account for 6.54%, while two fifth (40.5%) of total HIV infections are among females.[8] Undivided Andhra Pradesh and Telangana have the highest estimated number of PLHIV (3.95 lakhs) followed by Maharashtra (3.01 lakhs), Karnataka (1.99 lakhs), Gujarat (1.66 lakhs), Bihar (1.51 lakhs) and Uttar Pradesh (1.50 lakhs). These seven states together account for two-thirds (64.4%) of total estimated PLHIV (Figure 1). Rajasthan (1.03 lakhs), Tamilnadu (1.43 lakhs) and West Bengal (1.29 lakhs) are other states with estimated PLHIV numbers of 1 lakh or more.

Guntur had the highest number of HIV positive cases since 2013-14. Guntur district registered 5,195 (including 2,498 female) HIV positive cases during 2013-2014 and 6,027 cases (2,938 female) during the previous year. Hyderabad, which tops the HIV positive chart in Telangana state, reported 3,952 (2,525 female) cases during 2013-14.[8]
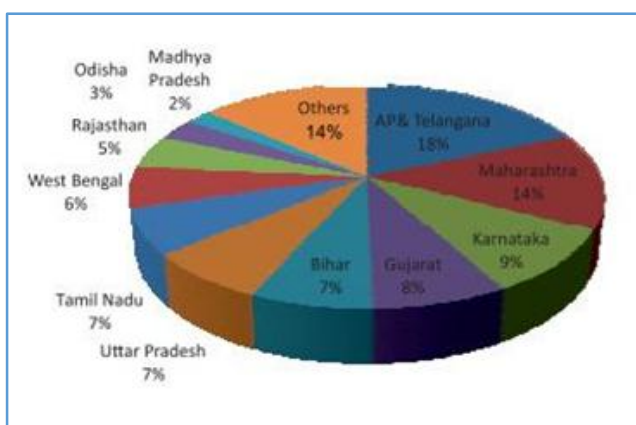
Figure 1

Factors associated with delayed entry into care were homelessness and illiteracy.[5,9] The incidence of opportunistic infections varied in different countries and many of previous studies did not include the opportunistic infections more commonly occurring in India.

The clinical course of Human Immunodeficiency Virus (HIV) disease and pattern of opportunistic infections (OI) varies from patient to patient and from country to country. The CDC developed a list of more than 20 OIs that are considered AIDS-defining conditions.[10] HIV patients having one or more of these OIs will be diagnosed with AIDS, no matter what your CD4 count happens to be:

- Candidiasis of bronchi, trachea, esophagus or lungs.
- Invasive cervical cancer.
- Coccidioidomycosis.
- Cryptococcosis.
- Cryptosporidiosis, chronic intestinal (Greater than 1 month's duration).
- Cytomegalovirus disease (Particularly CMV retinitis).
- Encephalopathy, HIV-related.
- Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis or esophagitis.
- Histoplasmosis.
- Isosporiasis, chronic intestinal (Greater than 1 month's duration).
- Kaposi's sarcoma.
- Lymphoma, multiple forms.
- Mycobacterium avium complex.
- Tuberculosis.
- Pneumocystis carinii pneumonia.
- Pneumonia, recurrent.
- Progressive multifocal leukoencephalopathy.
- Salmonella septicemia, recurrent.
- Toxoplasmosis of brain.
- Wasting syndrome due to HIV.

Andhra Pradesh assigned to category A with more than 1% ANC prevalence (Prevalence among pregnant women attending antenatal clinics) in district in any of the surveillance sites in the 3-year reference period. The following regimens are given to the patients in the study.

Regimen I (a): Tenofovir + Lamivudine + Nevirapine. First line regimen for patients with Hb<9 gm/dl and not on concomitant ATT.

Regimen II (a): Tenofovir + Lamivudine + Efavirenz. First line regimen for patients with Hb<9 gm/dl and on concomitant ATT.

MATERIALS AND METHODS: The study was performed in Guntur, a district situated in Andhra Pradesh, India. In Guntur, most of the population live in rural areas and there is a high prevalence of HIV infection. The HIV epidemic is largely driven by heterosexual transmission and is

characterized by poor socio-economic conditions and high levels of illiteracy in the HIV population. HIV testing is offered free of cost in any of the governmental integrated and counselling testing centres spread across the district, and it is also available in most of the private clinics. The study used an observational, descriptive and prospective study design and was conducted in 2014/2015 at Tertiary Health Centre, Guntur. The study involved the prospective analysis of data from a large number of inpatients who were divided into two groups, namely ART group and non-ART group based on initiation of ART.

**The objectives of the study are:**
1) To describe the demographic and disease profile of people living with HIV (PLHIV);
2) To measure the inpatient prevalence of AIDS-defining conditions in people living with HIV adults admitted; and
3) To compare clinical outcomes of the ART and NON ART group at the time of discharge of this cohort of PLHIV.

Sampling: The study sample was a convenience sample consisting of all patients admitted during 18-month period from March 2014 to September 2015.

Inclusion criteria include all patients older than 18 years of age who were living with HIV and AIDS. Those excluded from the study population were patients less than 18 years of age and who were pregnant.

RESULTS: The results of the data are summarized and analyzed using appropriate descriptive and analytic biostatistics. The baseline characteristics of the entire cohort are described. The outcomes in the ART and non-ART groups are compared. The timing of ART initiation and outcome of those initiated on ART is described. The risk factors associated with in patient mortality in the ART group are analyzed.

Baseline Characteristics of The Entire Cohort: Two hundred sixteen (216) patients were admitted with AIDS. From this group 14(6%) patients are already on ART, 203 (94%) were ART naive and thus evaluated for commencing inpatient ART. Only 85(42%) of these were initiated on ART soon after hospital admission (Figure 2). The rest 118(58%) were not considered for ART for a number of irreversible medical conditions and other reasons.
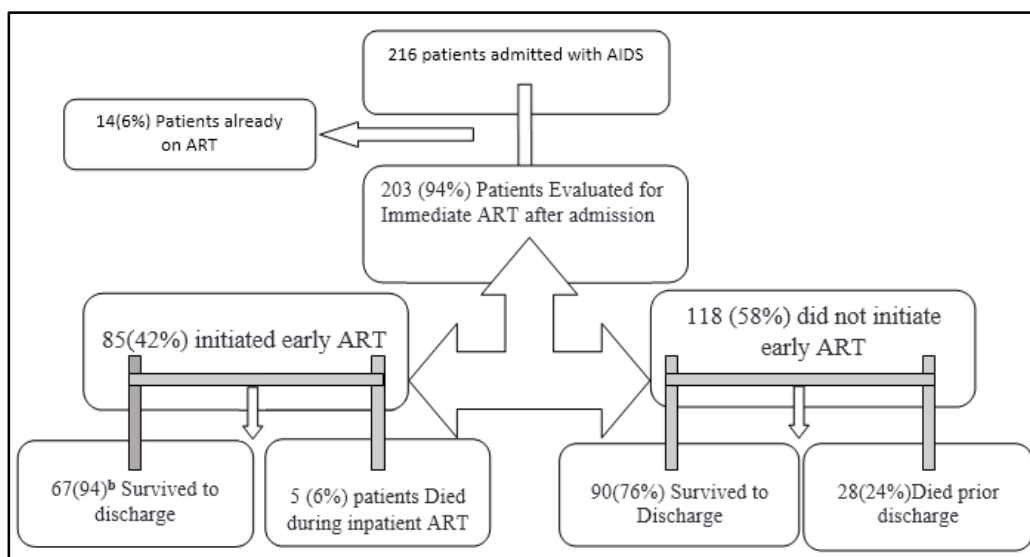
Figure 2: Flow chart of all patients admitted with AIDS

DEMOGRAPHICS	
Median age (years)	38(32-45)
Men no. (%)	112(55%)
Women no. (%)	91(45%)
LAB DATA	
Median baseline CD4 count (cells/uL)	28(12-83)
Baseline CD4 cell count category (%) b	
0-49 cells/uL	62(66%)
50-99 cells/uL	17(10%)
100-199 cells/uL	24(15%)
200-349 cells/uL	15(09%)
Median baseline haemoglobin (g/dl)	9.7(7.6-11.3)
Median baseline albumin (g/l)	22(17-27)
Table 1	

The median age of those admitted was 38 years. There were more men (55%) than women (45%) in the cohort. The majority (76%) of patients had a CD4 count of less than 100 cells/uL. Only 9% of these PLHIV had a CD4 count >200 cells/uL. The median CD4 count for those who had this measure recorded was 28 cells/uL. (Table 1).

Comparison between the ART and Non-ART Groups: The ART group had a mean CD4 count of 55 cells/uL and the non-ART group (comprising 118 PLHIV) had a mean CD4 count of 84 cells/uL (p<0.01). Other baseline characteristics in both groups were similar.

The ART and non-ART groups had a similar proportion of opportunistic infections. The mortality before discharge from hospital was four times lower in the ART group (05/72,

6%) compared to the non-ART group (28/118, 24%) (p<0.05) (Table 2).

A significantly higher proportion of the patients who did not initiate ART during their inpatient stay died, compared to only the patients who initiated ART. This is despite the non-ART group having a higher mean CD4 count on admission. The median length of admission for patients who did not initiate ART was 13 days (mean 16 days).

Pulmonary tuberculosis was the leading cause of death (12 out of 28 deaths; 42%) in the non-ART group. Out of 37 patients with pulmonary tuberculosis in the non-ART group, 12(33%) died, whereas only three out of 30 patients (09%) with pulmonary tuberculosis in the ART group died (Table 2).

Morbidity and Mortality	Art Group 85(%)	Non-Art 118(%)	Total 203 (%)
Acute OI or Complication no (%)	N=72.[b]	N=118	N=191
Pulmonary tuberculosis	30(42%)	37(31%)	67(35%)
Extrapulmonary tuberculosis	14(19%)	49(38%)	63(31%)
Pneumocystis jiroveci pneumonia	12(16%)	23(19%)	35(19%)
Chronic diarrhoea (>14 days)	07(10%)	07(06%)	14(07%)
Cryptococcus meningitis	03(04%)	01(01%)	04(02%)
HIV associated nephropathy	03(02%)	01(01%)	04(02%)
Others.[c]	03(02%)		04(02%)
Outcomes at Discharge			
Early mortality prior to discharge no. (%)	05(06%)	28(24%) p<0.001	
Mortality from pulmonary tuberculosis	03/30(09%).[d]	12/37(33%).[d] p<0.001	
Discharged home no. (%)	67(94%)	90(76%)	
Table 2			

b: Baseline opportunistic infection not available in 13 patients. (So n is 85 - 13 = 72).
c: Other opportunistic infections were Candida oesophagitis, herpes zoster, lymphoma and Kaposi's sarcoma were listed.
d: 03/30 deaths (09%) in the ART group and 12/37 deaths (33%) were due to pulmonary tuberculosis.

Outcomes in the Art Group: In the ART group the median duration from time of initial admission for PLHIV to ART initiation was 14 days. The median duration of stay from initial admission to discharge from hospital was 18 days. Almost half (51%) of the patients were initiated on ART within two weeks from the time of their initial admission to the hospital. The time to initiate ART in only 14 patients (18%) was more than three weeks. Almost all the patients started either on regimen 1a or regimen 2a.

Four patients experienced adverse events as inpatients soon after commencing ART and one patient died of drug induced hepatitis. IRIS was diagnosed in 4% of patients (n =3) post ART but caused no deaths. IRIS was related to pulmonary tuberculosis (1), extrapulmonary tuberculosis (1) and pneumocystis pneumonia (1). Six percent (n=5) patients who initiated ART died during the inpatient stay. Among the 5 patients who died in the ART group, pulmonary tuberculosis was the cause of death in three, extra pulmonary tuberculosis in 1 and pneumocystis pneumonia in 1 of the deaths.

Days from initial ward admission to ART initiation	
No.	(%)
0-7 days	05(06%)
8-14 days	35(45%)
15-21 days	23(31%)
>21 days	14(18%)
Total	72.[d] patients
ART regimens initiated	No (%)
Regimen I (a)	35(48%)
Regimen II (a)	37(52%)
	72(100)
Table 3	

Regimen I (a): Tenofovir + Lamivudine + Nevirapine. First line Regimen for patients with Hb <9 gm/dl and not on concomitant ATT.

Regimen II (a): Tenofovir + Lamivudine + Efavirenz. First line Regimen for patients with Hb<9 gm/dl and on concomitant ATT.

d: In 5 patients, total length of stay not recorded.

Outcomes	Patients
Timing of ART initiation	
Median duration (days) of total admission	18(15-25)
Median days from initial ward admission to ART initiation	14(11-19)

Outcomes	Patients
Suspected IRIS	
Suspected IRIS events during in patient ART initiation, no (%)	3(4)
Underlying opportunistic infection among patients with IRIS	
Pulmonary tuberculosis	1/3
Extra pulmonary tuberculosis	1/3
Pneumocystis jiroveci pneumonia	1/3
Deaths among patients with suspected IRIS syndrome	0(0%)
Total deaths during inpatient ART initiation ~	
Deaths, no. (%)	5(6%)
Median days to death after ART initiation (n=5)	10
Adverse events during inpatient ART initiation	
Hepatitis. No. (%)	3
Renal insufficiency. No. (%)	1
Deaths among patients with suspected adverse event	1(1%)
Table 4: Outcome	

Opportunistic Infection	N	Time from admission to ART	Time from admission to discharge
All infections	69	14/16	18/21
Pulmonary tuberculosis	30	13/15	17/20
Extra pulmonary TB	14	12/15	17/19
P. jiroveci pneumonia	12	18/19	22/24
Chronic diarrhoea	07	16/16	19/21
Cryptococcus meningitis	03	16/16	19/20
Others	03	13/13	18/17
Table 5: Outcomes by opportunistic infection among PLHIV commenced on ART			

Time to Art Initiation after Diagnosis of Different:
Opportunistic Infections: Among the different opportunistic infections, the mean time to ART initiation from initial admission was 15 days for those with pulmonary TB and extrapulmonary TB. Patients with Pneumocystis pneumonia started ART after a mean of 19 days. Those with cryptococcal meningitis and chronic diarrhea commenced ART after 16 days. Longest for pneumocystis pneumonia.

The mean time from admission to ART initiation in all patients was 16 days. Time taken from admission to discharge from the hospital was 21 days.

DISCUSSION: Tuberculosis co-infection contributes the largest burden of disease and was diagnosed in two thirds of all admissions. Other common presenting infections were extra pulmonary tuberculosis, pneumocystis pneumonia are also common. Treating pulmonary tuberculosis and HIV/AIDS diseases simultaneously presents several challenges. Although there is increasing evidence from Sapit.[11] trial and Camalia.[12] study that earlier initiation of ART may lead to reduced morbidity and mortality, data from Indian studies are lacking. There are no studies to establish the survival benefit of starting ART within 2 weeks of ATT initiation.

In our study the initiation of ART occurred within two weeks for most opportunistic infections including TB when the patient is admitted to the Hospital. The results of our study demonstrate that early ART can be safely and efficiently initiated among patients with tuberculosis co-infection with less incidence of IRIS and drug reactions (less than 10%).

Among the five (06%) patients initiated on ART who died during the inpatient stay tuberculosis (3%), extrapulmonary tuberculosis (1%) and pneumocystis pneumonia (1%) were reported the leading cause of death. This reflected the high prevalence of these opportunistic infections in PLHIV who present in an advanced stage of illness. IRIS was diagnosed in 4% of patients post-ART commencement, but was not a cause of mortality. These results demonstrate that the early ART mortality due to IRIS is low and should not preclude any patient from qualifying for expedited ART initiation. The majority of patients presented in our study have critically low CD4 counts (two-thirds below 50 cells/uL). Earlier initiation of ART showed survival benefit when compared to NON ART group. The median total duration of stay in our study in the ART group was 18 days (mean stay of 21 days). Most patients stayed for a median of 4 days after the ART initiation. This was crucial to monitor and treat anticipated adverse events and drug toxicities from combined opportunistic infection treatment and ART. The variable time to initiate ART after initial admission for different clinical conditions emphasizes

the need for an individualized approach to determine the optimal time to initiate ART. Different conditions and clinical presentations require different durations of treatment for the presenting opportunistic infection. Those patients that have associated physical and psychosocial co-morbidities require a longer time of ART readiness preparation.

Age, independent of CD4 cell count and other baseline factors, may be an important risk factor for very early (inpatient) mortality after ART initiation. Age increased likelihood of death through several mechanisms including presence of co-morbid disease, greater frequency of adverse drug. It is important to note that older patients still clearly benefited from early ART initiation.

A 58% of patients discharged from the hospital did not initiate ART during their admission; 76% of this non-ART group were discharged home or for follow-up; 24% of the patients who did not initiate ART died during their inpatient stay. They died soon after admission due to terminal medical conditions as they presented in an advanced stage of illness. The causes of death in these patients were mainly due to tuberculosis and extrapulmonary tuberculosis and reflect the high prevalence of these conditions in Guntur. The mortality before discharge was five times lower in the ART group (6%) compared to the non-ART group (24%) and this was statistically significant. There appears to be an early inpatient survival benefit for patients starting ART within two weeks of being admitted with an opportunistic infection (OI). Patients in the non-ART group were not initiated on ART because of many clinical reasons and personal reasons. Those patients who were terminally ill were unable to take oral medications and had lower CD counts. Even though other patients in this group had relatively higher CD4 counts and were eligible for ART were not yet willing to start ART. These factors would have contributed to a higher mortality (despite the higher mean CD4 count) in the non-ART group. Extrapulmonary tuberculosis (38%) was the leading cause of morbidity in the entire non-ART group when compared to ART group; 42 percent (12/28) patients with pulmonary tuberculosis died in the non-ART group. This disease seems to benefit significantly from early ART initiation as soon as diagnosis is made.

CONCLUSION: In our study average, CD4 count is lower in patients admitted with AIDS defining illness. There is a wide range of opportunistic infections that are common. Tuberculosis, extrapulmonary tuberculosis and pneumocystis pneumonia are common in patients with low CD4 counts. One important challenge linked with providing an optimal service for patients are the unique needs that each patient brings to the therapeutic encounter and the need for individualised attention. Tuberculosis co-infection contributes the largest burden of disease and was diagnosed in two-thirds of all admissions.

Starting ART as soon as it can be tolerated (within 2 weeks) after anti-tuberculosis therapy will be of great benefit in reducing mortality and mortality.

The median total duration of stay for all patients in the ART group was 18 days (mean stay of 21 days). The variable

time to initiate ART after initial admission for different clinical conditions emphasizes the need for an individualized approach to determine the optimal time to initiate ART. Most patients stayed for a median of four days after the ART initiation. This was crucial to monitor and treat anticipated adverse events and drug toxicities from combined opportunistic infection treatment and ART.

This study was the first attempt to assess the contribution of different cofactors that could be associated with the survival of Indians infected with HIV.

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