Long Term Outcome of Adult Patients on Antiretroviral Therapy (ART) in India

Abstract

We report the data analysis of 10 years (2005-2015) of follow up of an antiretroviral therapy (ART) centre in Mumbai (India) treating adult patients (age >18 years) working under corporation sector funded by national AIDS control organization (NACO). In the duration of study, total registered Human Immunodeficiency Virus (HIV) positive patients were 18554. Five thousand three hundred patients were lost to follow up and 1393 patients were transferred out to other ART centre. Thus only 11861 patients were evaluable. Male: female: transgender ratio was 1.92: 1: 0.015. HIV- 1 patients were 18474 and HIV- 2 patients were 80. ART was offered to the 6138 eligible patients. Out of these 4581 patients are alive and on ART. Total deaths were 942. One hundred and sixty patients required alternative ART while another 175 patients were put on second line ART.

At a median follow up of 5 years overall survival was 92% and adherence was 86%. The percentage of patients having documented opportunistic infections was as follows: candidiasis 35%, tuberculosis 23%, bacterial respiratory infections 15%, bacterial skin infections 14%, cryptosporidiosis 9%, Herpes simplex 7%, Herpes zoster 6%, pneumocystis jirovaci 5%, cryptococcal meningitis 2%, toxoplasmosis 2%, and micosporidiasis 1%, cytomegalovirus retinitis 0.5%. Most common dose limiting side effects of the ART were Zidovudin induced anemia (15%), Stavudine induced neuropathy and lip dystrophy (18% each) and efavirenz induced disorientation (8%) and they required substitution of drugs. Two percent patients were referred for second line ART (Switch regimen). The incidence of multidrug resistant kochs was 1.3%.

Keywords: Antiretroviral therapy; Medicine; AIDS; Hepatitis C; NACO; Medicine

Review Article

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Nivedita Moulick[1], Shreeniwas Raut[2], Rupal Malye[3], Amit Afre[4] and Nagappa Pujari[5]

[1]*Professor and Head of the department of medicine, LTMMC Sion, Mumbai*
[2]*Ex Senior Medical Officer of ART centre, Mumbai*
[3]*Associate Professor, Mumbai*
[4]*BSC Data Operator, Mumbai*
[5]*BAMSW Senior Counselor, Mumbai*

***Corresponding author:** Shreeniwas Raut, Senior Medical Officer of ART centre, Lokmanya Tilak Municipal Medical College and General Hospital, Mumbai, Tell: 9099407702; Email: shriniatbj@yahoo.co.in

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Abbreviations: ART: Antiretroviral Therapy; NACO: National AIDS Control Organization; LFU: Lost To Follow Up; ICTC: Integrated Counseling and Testing Centre; PLHIV: People Living with HIV

Introduction

Lokmanya Tilak municipal medical college and general hospital commonly known as Sion hospital has antiretroviral therapy centre running under National AIDS Control Organization (NACO) since 2005. We represent the adult ART centre connected to department of medicine. The whole ART therapy facility is governed by ministry of health and welfare. There is scarcity of long term data publications in India about ART centers. Some short term data evaluations of less than 800 patients are available online which lack many end points of evaluation. We hereby try to report a comprehensive analysis of follow up from 2005 to February 2015 (median follow up of 5 years).

Standard operating procedure (SOP) of ART Centre

Registration: All patients are registered here and receive booklet to record clinical visits.

Counselors: Counselors are mainly certified psychologists who can perform pre and post HIV test counseling. In ART centre they are mainly focused on pre and post ART counseling. The institute has separate integrated counseling and testing centre (ICTC), the SOP of which is not addressed here. ART centre receives patients mainly with seropositive results.

CD4 count: Every patient undergoes CD4 count and baseline blood and chemistry investigations.

Medical officers: They evaluate the patient clinically on every visit and prescribe treatment regimes.

Staff nurse: She manages the OPD based patient care and co-ordination.

Pharmacist: The patient will receive all the medicines for opportunistic infections as well as ART from pharmacist.

Data manager: The daily, monthly and yearly data reports of patient visits, drug usage and other events are prepared by data manager and forwarded to authorities.

Community Co-coordinator: He/she work to establish a rapport with PLHIV to avoid any lack of communication.

Materials and Methods

This is a retrospective observational analysis.

Duration: 25 August 2005(date of start of ART centre) to 28 February 2015.

Inclusions: All the patients registered in ART centre at LTMMC, Sion during the study duration.

Exclusions: No exclusion criteria.

Results

The characteristics of the people living with HIV (PLHIV) are shown in Table 1. Total registrations were 18554, 1393 patients were transferred out to other ART centre chosen by patients for the convenience of the treatment and 5300 patients were lost to follow up. Thus total evaluable patients being 11861(18554-1393-5300=11861, this figure was taken as 100% for evaluation of ART centre). One hundred and twenty two patients died of advanced disease even before starting ART. At a median follow up of 5 years overall survival was 92%.

Pre-ART data: Pre-ART patients are those who are registered but not yet started on ART. They accounted 12294, out of these 4778 were lost to follow up and 1222 were transferred out, thus currently 6294 patients were on Pre –ART follow up.

On-ART data: On-ART patients mean those who were started on antiretroviral therapy. They comprised 6183, out of these 553 were lost to follow up, 140 were transferred out and 820 were dead ones. Thus 4581 patients were currently "On-ART". Forty four of these patients stopped ART due to some or other reasons (e.g. intolerance, side effects, lack of faith) and were started on alternative treatment.

Death: Total deaths occurred were 942, 122 being before starting ART and 820 On- ART. All these patients died of opportunistic infections (50% due to tuberculosis, 16% cryptococcal meningitis, 10% pneumocystis jirovaci pneumonia, 4% due to toxoplasmosis, 11 % due to bacterial infections, 1% due to malignancies and 8% due to other causes).

Special Conditions

HIV- 2: While majority of patients were infected with HIV-1 strain, 80 patients were recorded to have HIV-2 infection and only half of them were subjected to ART.

Alternative ART: Alternative ART is started to patients on first line ART when they have dose limiting side effects of first line agents making them intolerant to these agents and when there is yet no indication to start second line ART. One hundred and sixty patients required alternative ART.

Second line ART: One hundred and seventy five patients were referred for second line ART.

Antinatal seropositivity: Three hundred and sixty patients were recorded as seropositive pregnancies. Previously the guidelines suggested to follow up these patients and to start on ART only if they become eligible for ART due to other indications, but recently with new guidelines all pregnant seropositive patients were put on ART. All of these patients are currently "On- ART."

WHO stage wise distribution of all PLHIV on follows up while study evaluation is shown in Table 2. Thus 3175 patients were in stage 1, 3119 were in stage 2, 2339 were in stage 3, and 2289 were in stage 4. All stage 3 and 4 patients were on ART. Overall the decrease in CD4 count trend is in accordance with clinical deterioration.

At baseline CD4 documentation, only 20% patients were having CD4 count greater than 500 and only 34 % patients had CD4 count greater than 350 (Table 3). Thus the presentation of these PLHIV patients to ART centre is quite delayed and early detection rate is low.

Males represent 60.83% alive patients on ART; females being 38% while transgender being 1.11% (Table 4).

Year wise registrations are mentioned in Table 5, which states that in starting years of ART centre i.e. in 2005 and 2006 the registrations were very less and maximum registrations occurred in 2007 i.e., 3466. After that there is gradual decline in registrations, probably because of opening of multiple ART centers as well as reduction in incidence of HIV infection due to community awareness.

In accordance with other Indian data the predominant mode of infection in our institute is recorded to be heterosexual and homosexuals are less than 10% (Table 6). Intravenous drug abusers are 4% and it is less than 1% with blood transfusion. Worldwide reported high risk groups like migrants (10.21%) and truck drivers (5.2%) comprise a considerable percentage in our population also. Zidovudin + lamivudine+ Nevirapine (ZLN) based regimen which was previously treatment regimen of choice, is still predominant regimen in our setting (Table 7). Recently first line regimen of choice is changed to tenofovir + lamivudine+ efavirenz (TLE).

The percentage of patients having documented opportunistic infections was as follows (Table 8): candidiasis 35%, tuberculosis 23%, bacterial respiratory infections 15%, bacterial skin infections 14%, cryptosporidiosis 9%, Herpes simplex 7%, Herpes zoster 6%, pneumocystis jirovaci 5%, cryptococcal meningitis 2%, toxoplasmosis 2%, and micosporidiasis 1%, cytomegalovirus retinitis 0.5%. HIV –Tuberculosis coinfection is a common scenario in India (Table 9). We documented only 14.25% sputum positive pulmonary kochs as compared to sputum negative (28.64%). Also extrapulonary Tuberculosis were 57.17% and multi-drug-resistant (MDR) tuberculosis was 1.3%.

We registered 102 cases of HIV with hepatitis B co-infection and the median survival of these cases was 41 months (Table 10). Similarly HIV – hepatitis C co-infection registered in 23 cases and the median survival of these patients was 16 months. Both these types were given lamivudine based ART regimens with avoiding Nevirapine.

HIV and pregnancy (Table 11): Majority of these patients had CD4 count>250. Previously these patients were put on ART only if they satisfied other indications but for preventing vertical transmission of HIV to newborn babies recent guidelines suggested ART for all pregnant patients. All the patients in this list are now on ART.

Twenty eight cases of malignancies were documented, out of which AIDS related malignancies were 15 (11Non-Hodgkin lymphoma and 4 primary CNS lymphoma) and other malignancies accounted 13 (Table 12).

Figure 1 show that means CD4 count of On-ART patients was increasing from 2005 to 2015 indicating effectiveness of ART.

Figure 2 shows overall survival of PLHIV increased from 2005(56%) to 2015(92%) as the adherence increased from 2005 (52%) to 2015(86%).

Table 1: Characteristics of PLHIV.

Indicator	Number (N)
Total registrations	18554
Transfer out	1393
Lost to follow up (LFU)	5300
Evaluable patients :(18554-1393-5300) =	11861 (taken as 100% for study evaluation)
Patients who died prior to starting ART	122
Alive and on follow up	10919(92%)
Pre Art Data	
N	12294
LFU	4778
Transfer outs	1222
Current pre ART	6294
On Art Data	
N	6138
LFU	553
Transfer outs	140
Death	820
Current on ART	4581
Stopped ART	44
Deaths	
Total deaths	942
Deaths before starting ART	122
Deaths on ART	820
Special Conditions	
HIV 2	N=80, on ART=40
Second line	175
Alternate ART	160
Total antenatal seropositive registrations	360

Table 2: Cross sectional WHO clinical Stage distribution of PLHIV in February 2015.

Cross Sectional who Clinical Stage Distribution of PLHIV in February 2015		Mean CD4 count
Stage 1	3175	625
Stage 2	3119	426
Stage 3	2339	253
Stage 4	2286	199
Total current alive and on follow up	10919	

Table 3: Baseline CD4 profile of all adult patients.

Baseline CD4 Profile of all Adult Patients	
<50	7%
51-100	8%
101-200	21%
201-250	9%
251-350	15%
351-500	14%
>500	20%
Total	100%

Citation: Moulick N, Raut S, Malye R, Afre A, Pujari N (2015) Long Term Outcome of Adult Patients on Antiretroviral Therapy (ART) in India. MOJ Immunol 2(4): 00056. DOI: 10.15406/moji.2015.02.00056

Table 4: Gender wise Data of PLHIV in February 2015.

Gender wise Data of PLHIV in February 2015			
Gender	**Males (M)**	**Females (F)**	**Transgender(TG)**
current follow up	7111	3701	107
Pre ART	4324	1958	56
alive On ART N=4581	2787(60.83%)	1743(38%)	51(1.11%)
deaths (N=942)	651	279	12

Table 5: Year wise Registration of PLHIV in our ART centre.

Year wise Registration of PLHIV in our ART centre	
Year	**Registrations of PLHIV**
2005	278
2006	578
2007	3466
2008	2978
2009	2117
2010	2441
2011	2217
2012	1805
2013	1295
2014	1130
2015 Till February end	249
Total registrations	18554

Table 6: Modes of transmission and high risk groups in total registered patients.

Modes of transmission and high risk groups in total registered patients	
Heterosexual	13002(70 %)
FSW	303(1.63%)
MSM	1777(9.57%)
IDU	750(4%)
Vertical Transmission	21(0.11%)
Blood transfusion	118(0.63%)
Migrants	1896(10.21%)
Truck Drivers	966(5.2%)

Table 7: Current status of ART regimens.

Current Status of ART Regimens	
ZLN	2958
TLE	901
ZLE	275
TLN	110
SLN	1
SLE	1
Second line	175
Alternative ART	160
Total	4581

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Table 8: Opportunistic infections in PLHIV.

Opportunistic Infections in PLHIV	
Opportunistic infections	**N**
Tuberculosis	2802(23%)
Candidiasis	4151(35%)
Cryptosporidiosis	1067(9%)
Microsporiosis	118(1%)
Pneumocystis jirovaci	593(5%)
Herpes simplex	830(7%)
Herpes zoster	711(6%)
Bacterial infections (respiratory)	1779(15%)
Cryptococcal Meningitis	237(2%)
Toxoplasmosis	237(2%)
Cmv retinitis	59(0.5%)
Mycobacterium avium complex	-
Bacterial skin infections	14%
Others	506
Total	13104

Table 9: HIV –Tuberculosis (HIV-TB) co-infection.

HIV –Tuberculosis (HIV-TB) co-infection	
Total RNTCP referrals	5604
Total tuberculosis	2802(100%)
Sputum positive TB	399(14.25%)
Sputum negative TB	802(28.64%)
Extra pulmonary TB	1601(57.17%)
MDR Tb	38(1.3%)

Table 10: HIV – Hepatitis B/C co- infection.

HIV – Hepatitis B/C co- infection			
Co-infection	**N**	**Treatment Regimen**	**Median Survival**
HIV- Hep. B	102	ZLE/SLE/TLE	41 months
HIV –Hep. C	23	ZLE/SLE/TLE	16 months

Table 11: Baseline CD4 counts of pregnant patients (N=360).

Baseline CD4 Counts of Pregnant Patients (N=360)	
<50	0
50-100	0
101-200	7%
201-250	2.5%
251-350	10%
351-500	33%
>500	47%

Table 12: Malignancies documented in PLHIV.

Malignancies Documented in PLHIV	
AIDS Related Malignancies (N=15)	
Non-Hodgkin lymphoma	11
Primary CNS lymphoma	4
Other Malignancies (N=13)	
Hodgkin lymphoma	2
Multiple Myeloma	1
Cervical cancer	5
Rectal cancer	1
Lung cancer	1
Head and Neck cancer	1
Liver cancer	1
Multiple Myeloma	1
Total	28

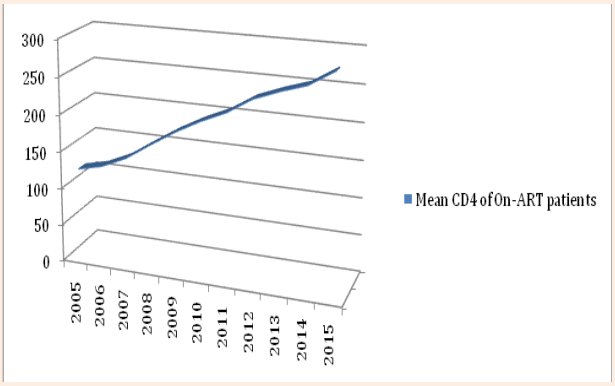

Figure 1: Shows that mean CD4 count of On-ART patients was increasing from 2005 to 2015 indicating effectiveness of ART.

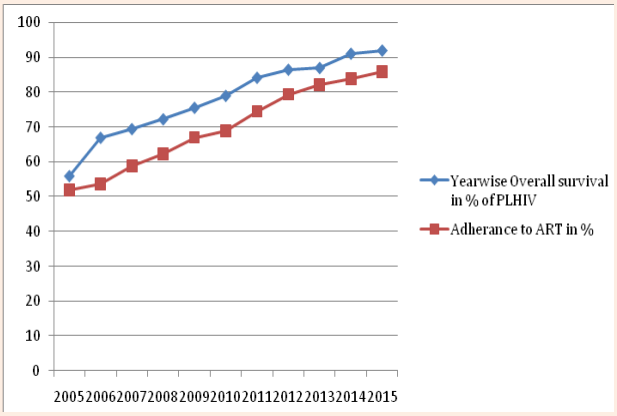

Figure 2: Shows overall survival of PLHIV increased from 2005 (56%) to 2015 (92%) as the adherence increased from 2005 (52%) to 2015 (86%).

Common dose limiting side effects of the ART were Zidovudin induced anemia in 15%, Stavudine induced lip dystrophy/ neuropathy 18%, efavirenz induced disorientation in 8%, lamivudine induced pancreatitis in 0.05%, Nevirapine induced rash/hepatitis 0.05 and tenofovir induced renal failure in 1% patients. All these patients required substitution of drugs. Commonly Zidovudin and Stavudine were substituted for each other in Zidovudin induced anemia and Stavudine induced neuropathy. Nevirapine and efavirenz were substituted with each other for Nevirapine induced hepatitis and efavirenz induced CNS dysfunction. When both Zidovudin and Stavudine could not be used, tenofovir was used as reserve drug. Also if both efavirenz and Nevirapine could not be used then protease inhibitors were used. Removal of lamivudine for side effect was a very rare event. Due to notable irreversible severe side effects of Stavudine, this drug is recently removed from the standard first line regimen. Now the first line regimen being TLE (Tenofovir +Lamivudine+ Efavirenz).

Discussion

HIV and ART related medicine in India was planned and maintained through NACO guidelines which is ultimate extrapolation of WHO guidelines [1,2]. In a resource poor country like India it is very difficult to maintain and publish long term data of any health care measure outcome. There are a very few publications related to this topic [3-8].

The most landmark decision in private sector was breakage of patents by local pharmaceutical companies; the rationale was making available the essential drugs to resource poor countries [8]. While there have been some attempts of publishing small scale data in India and modified suitable guidelines for India, there were no publications of ART outcomes of more than thousand patients followed up for five years or more [3-9].

Sample size in our population is sufficient to represent the statistics of PLHIV related event in entire India. Initial adherence rates to ART were poor and there is no need of other explanation than the stigma attached to this disorder. But the improving adherence has made ART more efficient and currently the overall survival is same as any other chronic manageable disease. It is also reflected through increasing mean CD4 counts of on-ART patients.

A considerable number of patients present in a late phase of AIDS and they are already infected with various disseminated opportunistic infections. Hence, they died even before starting ART. This was common in initial days but now such cases are decreasing.

A major problem in government set up is “lost to follow up” (LFU). Some things to know for such cases are

a. The stigma related to HIV is a major obstacle to patients to follow up in any government set up.

b. Patients may choose private doctors according to their affordability and convenience to follow up.

c. Patients may do the HIV testing in multiple set ups before believing they have the test positive.

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d. Patients may not have social support for continuation of treatment.

e. The social adjustment problems may be their initial priority rather than taking treatment.

f. Improving in temporal adherence and on-ART CD4 counts is a positive thing that suggests, the LFU problem is becoming manageable and less severe.

The outcomes of alternative ART and second line ART (switch regimens) are not delineated in this report as our centre had to refer for these treatments in centre of excellence. Also mother to child transmission prevention and documentation is handled by a different setup called prevention of parent to child transmission (PPTCT). All the opportunistic infections are treated with standard universal treatment protocols and malignancies are referred to regional cancer centre for management.

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