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Original Articles

Two-year treatment outcomes of patients enrolled in India's national first-line antiretroviral therapy programme

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ABSTRACT

Background. We aimed to analyse treatment outcomes of patients receiving first-line antiretroviral therapy (ART) through the national AIDS control programme of India.

Methods. Using routinely collected programme data, we analysed mortality, CD4 evolution and adherence outcomes over a 2-year period in 972 patients who received first-line ART between 1 October 2004 and 31 January 2005 at 3 government ART centres. Cox regression analysis was used to identify independent predictors of mortality.

Results. Of the 972 patients (median age 35 years, 66% men), 71% received the stavudine/lamivudine/nevirapine regimen. The median CD4 count of enrolled patients was 119 cells/cmm (interquartile range [IQR] 50–200 cells/cmm) at treatment initiation; 44% had baseline CD4 count < 100 cells/cmm. Of the 927 patients for whom treatment outcomes were available, 71% were alive after 2 years of treatment. The median increase in CD4 count was 142 cells/cmm (IQR 57–750 cells/cmm; $n=616$) at 6 months and 184 cells/cmm (IQR 102–299 cells/cmm; $n=582$) at 12 months after treatment. Over 2 years, 124 patients (13%) died; the majority of deaths (68%) occurred within the first 6 months of treatment. Those with baseline CD4 count < 50 cells/cmm were significantly more likely to die (adjusted hazard ratio 2.5, 95% confidence interval 1.3–3.2) compared with patients who had baseline CD4 count ≥ 50 cells/cmm. Over the 2-year period, 323 patients (35%) missed picking up their monthly drugs at least once and 147 patients (16%) were lost to follow up.

Conclusion. Survival rates of HIV-infected patients on first-line ART in India were comparable with those from other resource-limited countries. Most deaths occurred early and among patients who had advanced disease. Earlier initiation of HIV treatment and improving long term treatment adherence are key priorities for India's ART programme.

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INTRODUCTION

In recent years, numerous country-level antiretroviral therapy (ART) programme initiatives have been rolled out in developing countries to rapidly increase access to treatment for those who need it. While ART programmes in resource-limited countries such as Malawi,[1] Brazil,[2] Zambia,[3] Uganda[4,5] and Haiti,[6] have shown dramatic improvements in the survival of HIV-infected patients on ART, these programmes are facing several challenges of operational and clinical management including staff shortages,[7] infrastructural deficits and inequitable access to care in rural areas,[8] ART toxicity[9] and treatment failure.[10]

With an estimated 2.5 million people living with HIV (PLHIV), India has the third highest HIV burden in the world, after South Africa and Nigeria.[11] India launched its free national ART programme in April 2004 with financial support from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). From April 2004 to December 2009, the national ART programme scaled up from 8 to 230 public sector health facilities.[12] While several studies have assessed the safety, tolerability and immunological improvements among Indian patients receiving ART in the private and non-governmental sectors,[13–19] there are no published data on survival rates of patients being treated in the free national ART programme that is being scaled up using a public health approach. With 888 000 patients cumulatively enrolled in HIV care and 288 000 patients currently receiving ART at public sector health facilities by November 2009,

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India's free national ART programme is the largest in Asia.

We examined routinely collected ART programme data from 3 large public sector health facilities to determine treatment outcomes in terms of survival, adherence and improvement in clinical parameters.

METHODS

Programme description

Of the 35 states and union territories of India, 4 southern states (Andhra Pradesh, Karnataka, Maharashtra and Tamil Nadu) account for nearly 70% (1.5 of 2.5 million) of the total PLHIV burden. While all states now have at least 1 ART centre, the majority of ART centres and patients under treatment are in states with a high HIV burden. In the national ART programme, free treatment is offered to all clinically eligible PLHIV. Every person with a confirmed HIV infection is evaluated further by a counsellor and a physician, and subjected to baseline laboratory investigations including a CD4 test as per national treatment protocols.[20] If the patient is found clinically eligible (i.e. clinical stage 4 irrespective of CD4 count; or CD4 count <200 cells/cmm; or clinical stage 3 and CD4 count 200–350 cells/cmm) and agrees to adhere to treatment, then one of the following first-line regimens is started:

- Zidovudine (ZDV) (300 mg) + lamivudine (3TC) (150 mg) + nevirapine (NVP) (200 mg) or efavirenz (EFV) (600 mg)
- Stavudine (d4T) (30 mg) + 3TC (150 mg) + NVP (200 mg) or EFV (600 mg)

Patients are given drugs for 30 days and asked to return to the health centre after 4 weeks for a follow up evaluation and to collect drugs for the next 30 days.

India's National AIDS Control Organization (NACO; *www.nacoonline.org*) has developed standardized patient cards and registers for use at ART centres to track each patient's progress. For each patient registered for HIV care and treatment, a separate individual patient treatment record is filled in. This patient card is used to record the sociodemographic and baseline clinical characteristics and laboratory results, as well as the ART regimen prescribed. At each monthly follow up, this record is updated in terms of adherence, opportunistic infections (OIs), adverse effects and laboratory results. At the end of each month, the ART centre compiles an aggregated report of the monthly treatment activities and sends it to NACO, which maintains a centre-wise database in the national computerized management information system.

Study design

A retrospective cohort analysis was done for records of all patients enrolled for first-line ART at the selected government centres between October 2004 and January 2005.

Study centre selection

To ensure collection of the complete 2-year treatment data for each patient, ART centres were selected for this study using the following criteria:

1. Those that started functioning on or before 1 October 2004;
2. Those that enrolled at least 150 eligible patients in the first 6 months of operation. This was to ensure an adequate sample size at each centre, assuming a 10% mortality rate with a precision of 5%, 80% power, 95% confidence limits; and
3. Those maintaining good patient records.

Three ART centres that fulfilled the above criteria were chosen: Sir J.J. Hospital, Mumbai; General Hospital for Thoracic Medicine (GHTM) Tambaram, Chennai; and Osmania Medical College Hospital, Hyderabad.

Sampling methodology

All adult patients ≥15 years of age, who were enrolled consecutively and registered to receive ART at each of the selected centres between 1 October 2004 and 31 January 2005, were included in the study.

Data abstraction

Data sources included the ART patient register, patient treatment cards and additional records, if any, kept at each centre. Uniform data abstraction was conducted at each centre using a structured form. Key baseline demographic and clinical variables that were collected included age, sex, residence, weight, haemoglobin (Hb) and CD4 cell count. Monthly follow up data on primary end-point (mortality) and secondary outcomes of interest (such as side-effects of treatment, occurrence of OIs, and changes in CD4 cell count) were collected. No personal identification details were collected from patient records during data abstraction.

Treatment status for each month was abstracted from the patient record as: 'alive and on treatment', 'missed picking up drugs this month', 'stopped temporarily', 'lost to follow up' (if patients missed visits for 3 months consecutively) and 'died'. While data on side-effects and OIs were recorded at each monthly patient visit, CD4 cell count, Hb and weight were recorded every 6 months. At every patient visit, treatment adherence for the previous month was assessed and recorded, and patients were provided counselling and support.

Data management and analysis

Abstracted data were converted to an electronic format, entered and analysed using STATA software (version 9.0; Stata Corp., College Station, Texas, USA). Univariate and bivariate analyses of sociodemographic and clinical variables were done for primary end-point and secondary outcomes of interest. Changes in CD4 cell count, Hb level and weight were analysed in terms of the median change between baseline and follow up measures at 6, 12, 18 and 24 months. Kaplan–Meier curves were fitted to assess the probability of death stratified by CD4 cell count at initiation of treatment. The log rank test was used to examine statistical difference between the groups. Time was measured from the start of ART and ended at the earliest of: the date of death, the date of last follow up or at 24 months after start of treatment. Hazard ratio (HR) for the time-to-endpoint (mortality) was estimated using Cox proportional hazard regression model. Factors included in the model were age, weight and Hb as continuous variables; and sex, ART centre and baseline CD4 count as categorical variables. CD4 ≥50 cells/cmm was used as the reference category.

RESULTS

Sociodemographic profile

In all, 972 adult patients were started on treatment between 1 October 2004 and 31 January 2005 at the 3 selected centres (178 at Osmania Medical College Hospital, Hyderabad; 520 at Sir J.J. Hospital, Mumbai; and 274 at GHTM, Chennai; Table I). Women accounted for 34% (331) of all patients; GHTM, Chennai had the highest proportion of women (45%).

The median age of patients registered for treatment was 35 years (range 15–75 years); 83% of patients were in the age

TABLE I. Sociodemographic and clinical profile of patients enrolled in the national antiretroviral therapy (ART) programme, 2004–05

Characteristic	*n*
Age (in years) (n=972)	
Median (range)	35 (15–75)
15–24	29 (3.0)
25–34	443 (45.6)
35–44	365 (37.6)
≥45	135 (13.9)
Sex (n=972)	
Men	638 (65.6)
Women	331 (34.1)
Transgender	3 (0.3)
Education (n=644)	
Illiterate	120 (18.6)
Primary school	227 (35.2)
Secondary school	221 (34.3)
College and above	76 (11.8)
Employment (n=762)	
Unemployed	240 (31.5)
Daily-wage employed	245 (32.2)
Regular employed	277 (36.4)
Marital status (n=672)	
Married	609 (90.6)
Unmarried	63 (9.4)
Among married, HIV status of the spouse (n=421)	
Positive	269 (63.9)
Negative	152 (36.1)
District of residence (n=897)	
In which ART centre located	331 (36.9)
Other than in which ART centre located	566 (63.1)
Previous history of ART (n=572)	
Received previously	90 (15.7)
Did not receive previously	482 (84.3)
Median duration of previous ART in months (range)	12 (0.5–48)
Diagnosis of tuberculosis during ART (n=794)	
Yes	205 (25.8)
No	589 (74.2)
Initial ART regimen (N=960)	
Stavudine, lamivudine and nevirapine	678 (70.6)
Stavudine, lamivudine and efavirenz	6 (0.6)
Zidovudine, lamivudine and nevirapine	273 (28.4
Zidovudine, lamivudine and efavirenz	3 (0.3)
CD4 count (cells/cmm) at baseline (n=927)	
Median (range)	119 (1–891)
<50	209 (22.5)
50–99	198 (21.4)
100–199	287 (31.0)
≥200	233 (25.1)
Haemoglobin (g/dl) at baseline (n=902)	
Median (range)	10.9 (1–17)
Men (*n*=589)	11.3 (1–17)
Women (*n*=313)	10.3 (4–16.1)
Weight (kg) at baseline	
Median (range)	48.0 (13.5–86)
<50	503 (55.3)
≥50	406 (44.7)

Value in parantheses are percentages unless otherwise stated

group of 25–44 years. Women registered for treatment were younger than men (32 years *v.* 35 years; p<0.01). Of the 69% patients (522/762) who were employed, nearly half (245/522) were daily wage earners. Ninety-one per cent of patients in the selected sample were married; of those married, 64% (269/421) reported having a spouse who was also HIV-positive. Sixty-three per cent of patients (566/897) were from districts other than the district in which the ART centre was located.

Clinical profile

Table I presents the demographic and clinical profile of patients enrolled on ART during the study period. The median baseline weight of patients was 48 kg (range 13.5–86 kg). Over half the patients on treatment weighed <50 kg at the start of ART. The mean Hb at baseline was 10.9 g/dl (range 1–17 g/dl); in 36% of patients, it was <10 g/dl, and in 6%, it was <8 g/dl.

Of the 572 patients in whom a past history of ART was recorded, 19% in Sir J.J. Hospital (77/395) and 7% in Tambaram Hospital (13/177) reported receiving antiretrovirals (ARVs) previously. Of those previously treated, the median duration of previous treatment was 12 months (range 15 days to 4 years). Nearly 75% of patients had severe immunodeficiency (CD4 count <200 cells/cmm) at the time of initiation of ART. Overall, the median CD4 count at baseline was 119 cells/cmm (interquartile range [IQR] 50–200 cells/cmm). Twenty-three per cent patients had a CD4 count of <50 cells/cmm; only 7 patients had a CD4 count >350 cells/cmm. The median CD4 count of patients at Osmania and Tambaram was less than that of patients at Sir J.J. Hospital. Women had a higher median CD4 cell count at baseline than men (111 *v.* 131, p=0.01). Men registered for HIV care were more likely to be eligible for and started on treatment than women (odds ratio [OR] 1.9; 95% confidence interval [CI] 1.8–1.9, p<0.001).

During the 2-year treatment period, 26% of patients (205/794) in the sample were diagnosed with active tuberculosis (TB); this proportion varied from 53% at Tambaram Hospital to 12% at Sir J.J. Hospital.

Treatment substitution

Seventy-one per cent of patients were started on d4T+3TC+NVP (Table I). The second most common regimen was ZDV+3TC+NVP, which was prescribed to 28% of the patients. Only 9 patients (2%) were prescribed an EFV-based regimen.

Among 170 of the 972 patients, one of the drugs in the regimen had to be substituted during the 2-year treatment period. Half the substitutions were within the first 6 months of starting treatment. Of the 678 patients started on d4T+3TC+NVP, the regimen was changed to ZDV+3TC+NVP in 54 (8%) and to d4T+3TC+EFV in 48 (7%). Of the 273 patients started on ZDV+3TC+NVP, the regimen was changed to d4T+3TC+NVP in 29 (11%) and to d4T+3TC+EFV in 18 (7%).

Side-effects of treatment

During the 2-year treatment period, 22% of patients (214/972) reported one or more minor or major side-effects (data not shown). Of a total of 440 side-effects reported, the most frequent were diarrhoea and gastrointestinal adverse effects (31%), anaemia (10.9%) and skin rash (10.7%). Neurological side-effects were most commonly reported by patients started on a d4T-based regimen (68, 10%) and anaemia by those on a ZDV-based regimen (17, 6%). The occurrence of side-effects was not significantly associated with baseline weight, health facility or treatment outcomes.

Opportunistic infections

During the 2-year treatment period, 22% of patients (215/972) had one or more OIs. The frequency of OIs was highest in the initial months of treatment and declined sharply thereafter. The cumulative proportion of patients who reported an OI at 6, 12 and 18 months was 14.1%, 17.7% and 20.6%, respectively. Tuberculosis (TB) was the most common OI reported by 9.9% patients followed by candidiasis (9.1%). As expected, patients with a baseline CD4 count <200 cells/cmm were more likely to experience an OI than those with a CD4 count >200 cells/cmm (OR 2.4, 95% CI 1.6–3.8, p<0.001). However, the frequency of OIs did not differ significantly by health facility or by treatment outcomes.

Treatment outcomes

Patients improved clinically with regard to weight and Hb levels as well as CD4 count during the 2-year treatment period. The median increase in Hb was 2 g/dl (IQR 1–4 g/dl, *n*=201) and the median weight gain was 6 kg (IQR 2–10 kg, *n*=220). The median increase in CD4 count at 6 months after initiation of treatment was 142 (IQR 57–750; *n*=616) and at 1 year it was 184 cells/cmm (IQR 102–299; *n*=582). Among patients with baseline CD4 count <50 cells/cmm who survived for 6 months after initiation of treatment, there was an improvement in the median CD4 count from 23 cells/cmm to 202 cells/cmm.

Of the 972 adults started on treatment, treatment outcomes were available for 927 patients over 2 years; of these, 722 patients (78%; 95% CI 76%–81%) were alive after 1 year on first-line treatment and 656 patients (71%; 95% CI 68%–73%) were alive after 2 years of treatment. Overall, 124 (13%) of the 927 patients died during the 2 years. Sixty-eight per cent of deaths (80/124) occurred within the first 6 months of follow up; these 80 patients who died early had a median weight of 40 kg, median CD4 count of 52 cells/cmm and 73% were men. Compared with patients with a baseline CD4 count ≥50 cells/cmm, those with CD4 count <50 cells/cmm were more likely to die (adjusted hazard ratio [AHR] 2.5, 95% CI 1.3–3.2; Log rank p=0.001; Fig. 1).

Over the 2-year period, 35% of patients failed to collect their scheduled monthly drugs on at least 1 occasion. The frequency of missing an appointment for drug pick-up increased significantly after the first year on treatment.

The cumulative loss to follow up at 1 and 2 years after ART initiation was 11% (101/927) and 16% (147/927), respectively. While men were more likely to have died or been lost to follow up (32%) than women (24%), this was not statistically significant. Treatment outcomes (mortality and default) did not differ significantly by age, gender, history of previous ART or diagnosis of TB during ART treatment (data not shown).

DISCUSSION

This analysis of routinely collected data of the ART programme of India indicates that first-line treatment is feasible and effective as in other resource-constrained settings. The 12- and 24-month survival rates of patients in our study, 78% and 71% respectively, are similar to the survival rates reported from other developing countries.[1,3,21] Surviving patients in this study showed a median CD4 gain of 184 cells/cmm at 1 year after initiating treatment, which is comparable with other Indian studies.[13,16,19]

Consistent with the published literature, we found that mortality was significantly higher among those with advanced disease.[1,3,21-24] Moreover, a majority of the deaths (68%) occurred within the first 6 months after initiation of treatment. Some of the early mortality may be attributable to undiagnosed OIs; however, we were unable to assess this in our study. Twenty-three per cent of patients had CD4 <100 cells/cmm and 44% had CD4 <100 cells/cmm at initiation of treatment, indicating that they presented late for HIV care. The reasons for delays in care-seeking have not been systematically studied in India and can be due to a delay in HIV diagnosis or lack of access and availability of HIV care and treatment after HIV testing. According to the Third National Health and Family Survey (2005–06) (NFHS-3), only 3% women and 4% men reported having ever been tested for HIV and knowing their status; even among the HIV-positive population, only 7% of women and 13% of men reported having ever being tested.[25]

NACO has expanded HIV counselling and testing services to more than 5000 sites at the district-level in all the northern states and at the sub-district level in the high-burden southern and north-eastern states.[26] Despite this, ART centres are fewer in number and mostly located at district headquarter hospitals; thus each ART centre caters to a large population (average district population 2 million) spanning huge geographical areas. At the time of the study, institutional linkages between HIV testing centres and ART centres were not well defined. It is possible that individuals diagnosed at HIV testing centres at the sub-district level do not reach the HIV and ART service centres located at the district headquarters. Decentralization of HIV care services by integration into the primary healthcare system may facilitate early diagnoses and improve survival. In Lusikisiki, a rural area of South Africa, where HIV services were decentralized to the primary healthcare level, patients were enrolled earlier (at a higher immune status),[27] and had better treatment outcomes than those enrolled at the hospital. In India, it may take some time to decentralize ART services to primary healthcare facilities as trained healthcare providers and laboratory facilities are unavailable at the primary healthcare level. Meanwhile, to decrease patient travel costs, NACO has linked the large ART centres to smaller facilities at the sub-district hospital by establishing 230 LINK ART centres.

One of the major shortcomings of India's ART programme seems to be poor adherence to treatment reflected by a significant proportion of patients who were lost to follow up (16% over

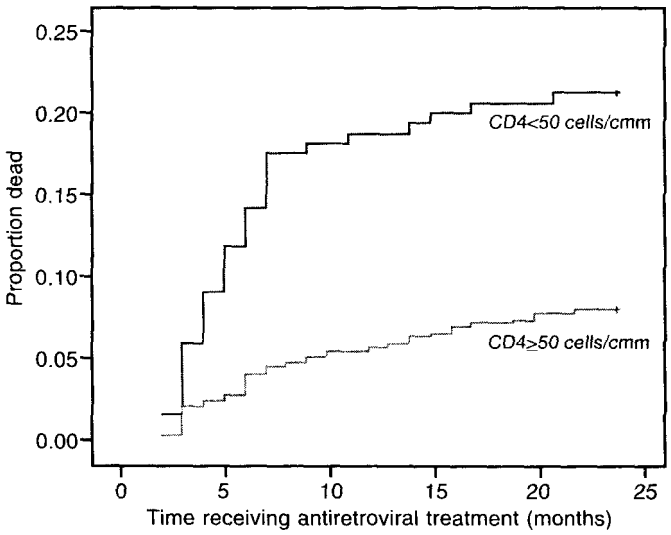

FIG 1. Kaplan–Meier curves of mortality among patients starting antiretroviral therapy, by CD4 cell count at treatment initiation, 2004–07

2 years) or did not keep their scheduled monthly appointments to collect their drugs (35% in our study). It has been previously shown that irregularities in keeping appointments in the initial months of treatment is a predictor of subsequent drop out.[28] Suboptimal adherence is an important factor in predicting viral suppression and clinical outcomes.[29,30] While there is much published literature on ART adherence globally,[31] few Indian studies have analysed factors associated with treatment default. A study of patients treated in the private sector in western India found that 27% of patients reported <95% adherence to treatment and that social support from family and friends (including reminders to take medication) were associated with optimal adherence.[32] Another qualitative study from southern India found social support to be an important factor for good adherence to ART.[33] The poor treatment adherence noted in our study may be because of poor access to treatment centres as all the selected ART centres were located in urban tertiary care hospitals (i.e. large hospitals), and most patients (63.1%) were from outside the treatment districts. Moreover, patients collect their drugs every month, at limited outpatient clinics during working hours. For lifelong treatment and to ensure good compliance, ARVs should be delivered as close as possible to where people live.

Our study has some limitations. First, the patient records were often incomplete, particularly with regard to recording of side-effects and OIs, and follow up measurements of clinical and immunological parameters. Thus, the frequency of side-effects and OIs reported may be underestimated and the reported clinical and immunological improvements may be biased towards a higher value. Second, treatment outcomes were not available for 45 of the 972 patients. Of those 45 patients for whom records were not available, 23 had no outcomes recorded for the entire 2-year treatment period; however, these patients did not differ with regard to age, sex, baseline weight and baseline CD4 cell count compared with those for whom treatment outcomes were available. For the remaining 22 patients treatment outcomes could not be ascertained as they had been transferred out and could not be tracked despite 3 follow up calls to the ART centres where they were transferred. It is unlikely that the mortality among these transferred patients was higher than the rest of the cohort as (i) all of them were transferred after 1 year when the mortality rate was likely to be lower; and (ii) of the 15 transferred patients for whom treatment outcomes could be tracked, only 1 had died. The third limitation is that, possibly, some treatment outcomes recorded as 'lost to follow up' may actually be 'deaths', thereby underestimating mortality in this study. In northern Malawi, 50% of patients recorded as lost to follow up were actually dead; the remaining had either stopped coming for treatment (15%), were untraced due to an incorrect address (27%) or were receiving treatment at another clinic (8%).[34] Lastly, as the results of this study are based only on 3 large urban ART centres, generalization of the results to the national level would need to be substantiated through further analyses. Since almost all the other ART centres are also located in large, urban hospitals, with similar facilities, staffing patterns and use of standard operating procedures as per the national guidelines,[35] the results of this analyses based on 3 centres is likely to be similar to the results from other centres.

Earlier HIV diagnosis, timely treatment and long term treatment adherence are key priorities for the ART programme in India. In addition to continued expansion of HIV counselling and testing services, there is a need to characterize delays in HIV diagnoses and care-seeking, and identify factors associated with these delays. Operations research to identify risk factors for loss to follow up can help in guiding interventions to keep potential defaulters on treatment. It is important to study risk factors for early mortality among patients enrolled on ART; this can help to guide appropriate clinical screening procedures to rule out certain infections and/or initiate prophylactic therapy among at-risk patients, and thereby contribute to reducing mortality.

In conclusion, rapid scale-up of the ART programme in India has been feasible with favourable patient outcomes in a large and diverse country with limited resources. The Government of India has introduced second-line ART at 10 large tertiary care centres (2 of which were included in this analysis). There are plans to scale up first-line ART to 375 centres and 1200 LINK ART centres by 2016, and second-line ART to 20 selected centres. In such a continually and rapidly expanding national treatment programme, it is vital to improve and maintain the quality of the first-line treatment while bringing services closer to the patients.

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