Factors associated with survival in adult people living with HIV/AIDS (PLHAs) in Mumbai, India (2004-2019): A retrospective cohort study

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ABSTRACT

Background: Knowledge of factors that affect survival in People living with HIV/AIDS (PLHAs) on anti-retroviral therapy (ART) will help us develop and implement interventions to improve the clinical outcomes and survival in these individuals. The aim of this study was to estimate the survival in PLHAs on ART in the government ART programme in Mumbai, and the factors associated with survival in these individuals. Methods: It is a retrospective survival analysis of 28,345 adult PLHAs from 18 government ART centres in Mumbai (registration period 2004–2019). We estimated the mortality rates and their 95% confidence intervals [CIs], plotted the Kaplan Meier Survival curves, estimated incidence rate ratios (IRR) and hazard ratios (HR). There were done for the whole cohort and according to various demographic and clinical characteristics. Results: The mortality in PLHAs on ART was 9.04 per 1000 person years. The HR was significantly for those aged 50 years and more at the time of registration (HR: 3.01, 95% CI: 2.37, 3.83; P < 0.001), in those with baseline CD4 count of less than 200 higher hazard (HR: 1.83, 95% CI: 1.47, 2.27; P < 0.001), those with an adherence of 80–95% (HR: 5.58, 95% CI: 4.61, 6.75; P < 0.001) and adherence of <80% (HR: 9.37, 95% CI: 7.74, 11.33; P < 0.001). Furthermore, the hazard was significantly higher in those with TB compared those without TB (HR: 3.28, 95% CI: 2.87, 3.75; P < 0.001). Time from diagnosis (per month increase) to initiation of ART was not significantly associated with mortality. Conclusions: Increasing awareness about HIV testing and early detection of HIV in those who have high-risk behaviours, prompt diagnosis and management of TB among those infected, and developing and implementing strategies (such as enhanced counselling, telephone-based applications, messages, or reminders) to ensure ART adherence of more than 95% in those on ART will potentially help improve survival in PLHAs in India.

Keywords: Adult PLHAs, antiretroviral therapy, hazard ratios, survival curves

Introduction

Globally, there are about 38 million people living with HIV/AIDS (PLHAs) as of 2019; of these 1.7 were new infections and 690,000 HIV-related deaths were reported in 2019.[i] India has reported a total of 2.1 million cases according to 2017 estimates.

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has also been reported that 19% of those infected need access to testing services.\(^9\)

Though ART services were available to those who could afford it in the initial years, the National AIDS Control Organisation introduced ART services in government centres free of cost in 2004.\(^{10,14}\) The guidelines for initiating ART therapy have changed from 2004 onwards, in accordance with the guidelines from the World Health Organization (based on CD4 counts, presence of co-infections, and stage of the disease).\(^{10} \) Since 2017, however, India has initiated ‘test and treat’ policy; thus, all individuals who are detected HIV positive are initiated on ART; the treatment options include first line, second line, and third line ART.\(^{16,16}\) In addition, viral loads have also been made available to monitor patients of ART. There has been gradual decline of about 71% in HIV-related deaths from 2005 through 2017; an estimated 69,110 deaths were ascribed to HIV-related illness.\(^7\) Over the period of 2005 through 2017, the cost of providing first line ART has also reduced; it has also been postulated that further scaling up ART services may help reduce the cost of ART.\(^8\)

Though, these are positive developments in HIV management, stigma related to HIV/AIDS still in an impediment in access to care.\(^9\) Thus, individuals may not get tested early; consequently, they may not be initiated on ART. Individuals who are detected later in the course of infection or with low CD4 counts may have a higher mortality.\(^{10,12}\) Besides this, place of residence and presence of opportunistic infections are associated with increased mortality.\(^{13,14}\) It has been more than 15 years since free ART was introduced in the government systems. Maharashtra has the highest number of HIV infected individuals in India.\(^2\) Mumbai, the capital of Maharashtra has been important in implementing the national HIV programme from the beginning. Thus, at this point it will be important to understand the factors that affect the survival in PLHAs who have been on the government ART programme. Knowledge of these factors will help us develop and implement interventions to improve the clinical outcomes and survival in these individuals.

With this background, we conducted the present study to estimate the survival in PLHAs on ART in the government ART programme in Mumbai, and the factors associated with survival in these individuals.

**Methods**

The present study is a retrospective survival analysis of 28,345 adult PLHAs.

**Data sources**

Administrative and clinical data of PLHAs from 18 ART centres (registered from 2004 onwards) in Mumbai were included for the present study. All these data are electronically recorded in a datasheet in Mumbai. The following variables were extracted from the electronic records: (1) name of the ART centre; (2) date of HIV test; (3) date of ART registration; (4) date of ART initiation; (5) age at the time of registration in the ART centre; (6) gender; (7) marital status; (8) potential route of infection; (9) baseline CD4 counts; (10) treatment regimen (according to the NACO guidelines) (11) adherence to the ART medications; (12) presence of tuberculosis (TB) co-infection; (13) Date of last visit; (14) date of death (if person had died). The main outcome for the present analysis was death of the individual. The last data point was till October 2019. We only included individuals who were more than 18 years of age at the time of registration. We did not include individuals who were transferred to other ART centres (considered as transferred out) in the present analysis.

**Statistical analysis**

(a) Descriptive statistics: We estimated the means and standard deviations (SDs) and median and interquartile range (IQR) for continuous variables. The means across groups was compared using the analysis of variance (ANOVA). We compared the proportions using the Chi square test or Fisher’s exact test for low expected cell counts.

(b) Mortality and Survival statistics: We then estimated the mortality rates (per 1000 person-years) and their 95% confidence intervals [CIs] for the whole population and according to various demographic and clinical characteristics. We then plotted the Kaplan Meier Survival curves to estimate the survival. The equality of the survivor function was assessed using the log-rank test. We also estimated the survival (and their 95% CIs) at one, five, and 10 years. The time factor in our survival analysis was ‘years after initiation of ART’ and the main outcome event was death.

(c) Models: The next step in analysis was building of hazard models. We initially estimated the incidence rate ratios (IRR) for mortality and compared the mortality rates across various categories of clinical and demographic characteristics. Finally, we estimated the hazard ratios (HR) for mortality in this cohort. Initially, we used the Cox Proportional hazard models; however, the proportional assumptions were not met. Hence, we used other models for estimating the hazard ratio. The model that fit the best was chosen based on the Akaike Information Criteria, Bayesian Information Criteria, and Cox-Snell Residuals. Based on these criteria, we chose the Weibull model for the present analysis.\(^{15}\) The following variables were included in the models: age at the time of registration, gender, baseline CD4 count, adherence, TB co-infection, treatment regime, and time from ART diagnosis to initiation of ART. Data were entered in Ms Excel (© Microsoft, USA) and analysed using Stata Version 15.1 (© StataCorp, College Station, USA).

The study was approved by the Institutional Ethics Committee of the Mumbai Districts AIDS Control Society for secondary data analysis (Reference Number: 006/2019).

**Results**

The mean (SD) age at the time of registration 39.2 (9.9) years; it was significantly higher in the males compared with females or male-to-female transgendered people (TGH) 40.5 [9.9] vs
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37.5 [9.7] vs 35.2 [9.6]; P < 0.001). The proportion of males in the cohort was 56%, females was 43% and 0.65% were TGH. The potential routes of transmission were: heterosexual (91%), homosexual (2%), infected blood/unsafe injection (1%), and unknown (3%). Majority of them were married (64%) and 20% were widowed. The median (IQR) time of initiation of ART after HIV test was 1.4 (0.5, 22.1) months. The median (IQR) CD4 values at baseline was 264 (150, 436). About 4.5% of PLHAs had died and 7.9% were recorded as lost-to-follow-up. The total follow-up time (years after initiation of ART) in our study was 1,40,260 years. The mean survival of PLHAs after initiation of ART was 14.73 (95% CI: 14.67, 14.79) years. The maximum follow-up time was 15.67 years and the total follow-up time 1,40,260 years. In our study cohort, about 14% had TB.

Table 1: Table showing the mortality rates (per 1000 person-years) and incidence rate ratios in 28,345 PLHAs, Mumbai, India

| Characteristics       | Estimate (95% CI) | Incidence Rate Ratios | P      |
|-----------------------|-------------------|-----------------------|--------|
|                       | Mortality rate (per 1000 PY) |                       |        |
| Total                 | 9.04 (8.56, 9.55)  | Reference             |        |
| Age groups            |                   |                       |        |
| 19-29                 | 6.69 (5.59, 7.99)  | Reference             |        |
| 30-39                 | 6.47 (5.82, 7.18)  | 0.97 (0.79, 1.19)     | 0.75   |
| 40-49                 | 9.25 (8.44, 10.13) | 1.38 (1.13, 1.69)     | 0.002  |
| >=50                  | 18.10 (16.28, 20.13) | 2.71 (2.20, 3.33)   | <0.001 |
| Gender                |                   |                       |        |
| Male                  | 9.13 (8.49, 9.82)  | Reference             |        |
| Female                | 8.91 (8.19, 9.70)  | 0.98 (0.87, 1.09)     | 0.67   |
| TGH                   | 9.73 (8.64, 20.41) | 1.61 (0.51, 2.24)     | 0.87   |
| Baseline CD4 counts   |                   |                       |        |
| 0-200                 | 11.95 (11.10, 12.86) | Reference        | <0.001 |
| 201-350               | 5.87 (5.19, 6.64)  | 0.49 (0.43, 0.57)     | <0.001 |
| 351-500               | 7.17 (6.05, 8.49)  | 0.60 (0.50, 0.72)     | <0.001 |
| >=500                 | 6.44 (5.39, 7.69)  | 0.54 (0.44, 0.65)     | <0.001 |
| Adherence             |                   |                       |        |
| Good >95%             | 5.75 (5.36, 6.17)  | Reference             |        |
| Average 80-95%        | 36.74 (30.89, 43.69)| 6.39 (5.30, 7.71)  | <0.001 |
| Poor <80%             | 67.60 (57.04, 80.12)| 11.76 (9.79, 14.14) | <0.001 |
| TB                    |                   |                       |        |
| No                    | 7.02 (6.57, 7.51)  | Reference             |        |
| Yes                   | 24.44 (22.15, 26.97)| 3.48 (3.09, 3.92)  | <0.001 |

In the multivariate models, we found that HR was significantly high for those aged 50 years and more at the time of registration (HR: 3.01, 95% CI: 2.37, 3.83; P < 0.001) compared with those who were less than 30 years old. PLHAs with a baseline CD4 count of less than 200 had a significantly higher hazard (HR: 1.83, 95% CI: 1.47, 2.27; P < 0.001) compared with those who had a baseline CD4 count of greater than 500. However, there were no significant differences in other groups of CD4. The HR was significantly higher in those who reported an adherence of 80-95% (HR; 5.58, 95% CI: 4.61, 6.75; P < 0.001) and adherence of <80% (HR: 9.37, 95% CI: 7.74, 11.33; P < 0.001). Time from diagnosis (per month increase) to initiation of ART was not significantly associated with an increased hazard of mortality. Details of HRs and their 95% confidence intervals are presented in [Table 3].
Thus, we found that the overall mortality in PLHAs after initiation of ART was 9.04 per 1000 PY and the estimated mean survival time was 14.73 (95% CI: 14.67, 14.79) years. Poor adherence, presence of TB co-infection, low CD 4 counts at baseline (<200), and old age were significantly associated with low survival and increased hazard of mortality in our cohort.

Adherence to ART medications was the most important factor associated with increased hazard of mortality in these individuals. It has been shown that good adherence is associated with an increase in CD4 counts, appropriate virologic response, and...
Table 3: Table showing the hazard ratio estimates (and 95% confidence intervals) from univariate and multivariate models, Mumbai, India

| Age groups | Univariate Models | P | Multivariate models* | P |
|------------|-------------------|---|----------------------|---|
| 19-29      | Reference         |   | Reference            |   |
| 30-39      | 1.17 (0.93, 1.48) | 0.19 | 1.16 (0.91, 1.47) | 0.22 |
| 40-49      | 1.61 (1.29, 2.03) | <0.001 | 1.58 (1.25, 1.99) | <0.001 |
| >=50       | 3.03 (2.40, 3.83) | <0.001 | 3.01 (2.37, 3.83) | <0.001 |
| Gender     |                   |   |                      |   |
| Male       | Reference         |   | Reference            |   |
| Female     | 0.83 (0.73, 0.94) | 0.003 | 1.03 (0.90, 1.17) | 0.66 |
| TGH        | 1.09 (0.52, 2.29) | 0.83 | 1.59 (0.75, 3.35) | 0.23 |
| Baseline CD4 counts | | | | |
| >=500      | Reference         |   | Reference            |   |
| 351-500    | 1.20 (0.95, 1.55) | 0.13 | 1.14 (0.87, 1.48) | 0.33 |
| 201-350    | 1.15 (0.93, 1.43) | 0.20 | 0.95 (0.75, 1.21) | 0.69 |
| < 200      | 2.48 (2.05, 3.01) | <0.001 | 1.83 (1.47, 2.27) | <0.001 |
| Adherence  |                   |   |                      |   |
| Good >95%  | Reference         |   | Reference            |   |
| Average 80-95% | 5.58 (4.63, 6.73) | <0.001 | 5.58 (4.61, 6.75) | <0.001 |
| Poor <80%  | 9.58 (7.97, 11.52) | <0.001 | 9.37 (7.74, 11.33) | <0.001 |
| Tuberculosis |                  |   |                      |   |
| No         | Reference         |   | Reference            |   |
| Yes        | 3.57 (3.14, 4.06) | <0.001 | 3.28 (2.87, 3.75) | <0.001 |

*Models were also adjusted for regime and time from test to initiation of ART (in months)

Reduced mortality.[16-19] Indeed a randomised trial conducted by Kiwuwa-Muyingo and colleagues[20] found that about 16% to 33% of deaths could be potentially avoided by monitoring and improving adherence in PLHAs. In our study, adherence to medications was an important factor associated with mortality; the mortality increased with reducing adherence. Though, we did not assess the reasons for poor adherence in the population, previous literature has highlighted the role of access to care, mental health issues, stigma, social support, and alcohol use as potential barriers to adherence.[21-24] Indeed, the WHO has advocated an Enhanced Adherence Counselling programme; it involves education, counselling, assessment of individual requirement, and follow-up sessions.[25] Thus, one of the most important interventions for improving survival in PLHAs on ART will be to develop methods and techniques to ensure >95% adherence; this may include setting-up of telephone based applications, messages, or reminders for ART intake. However, these messages should not reveal the status of the individual; thus, these could be general messages that talk about health, prevention, and care. If individuals have disclosed their status to family members, spouses, partners, or friends, then they should be involved in improving the adherence of PLHAs. Primary care physicians and family physicians can help to monitor and improve adherence among their patients who are HIV infected and are currently on ART.

The other important factor associated with mortality was co-infection with TB, a finding that also been reported by other authors.[26,27] TB is one of the most common co-infections in PLHAs. Indeed, studies have shown that the prevalence of TB was as high as 34% and incidence was about 10% in PLHAs in India.[28] Thus, it is important to identify TB infection early and initiate prompt treatment in PLHAs. The introduction of Cartridge Based Nucleic Acid Amplification Tests (CBNAAT) has helped improve the diagnosis of TB even in extra-pulmonary cases.[29,31] It has also been shown that survival in HIV-TB co-infected can be improved by initiating ART at an appropriate time after starting of TB treatment.[32] Furthermore, treating physicians should use clinical judgement while starting ART to avoid mortality due Immune Reconstitution Syndrome.[33] Baseline CD4 counts at the time of diagnosis was another factor associated with mortality in our study population. Early diagnosis of HIV (> 200 CD4 cell count at baseline) will be useful to initiate ART early in the infection; this will reduce opportunistic infections and mortality in these patients.[34,35] Since, India already has the ‘test and treat’ policy, it will be important to improve testing[36] and increase awareness about early testing in those who have high-risk behaviours (such as multiple partners and unprotected sex). Family physicians can discuss high-risk behaviours and suggest testing for HIV and other sexually transmitted infections; thus, they can help in early detection of HIV.

The study was not without limitations. Since, we used clinical and demographic data from administrative records, we did not have detailed clinical information for entire duration of follow-up. Thus, we were not able to account for all the possible events in these analyses. Furthermore, though we used the baseline CD4 in the model, we did not account for later CD4 counts. Nonetheless, we have used a large database of PLHAs over a period of 15 years. Furthermore, we did account for demographic, clinical, and baseline CD4 counts in the model.
These analyses provide useful information on the factors associated with mortality in PLHAs. We found that adherence to ART, TB co-infection, and low baseline CD4 counts were significantly associated with mortality in PLHAs. Increasing awareness about HIV testing and early detection of HIV in those who have high-risk behaviours, prompt diagnosis and management of TB among those infected, and developing and implementing strategies (such as enhanced counselling, telephone based applications, messages, or reminders) to ensure ART adherence of more than 95% in those on ART will potentially help improve survival in PLHAs in India.

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Conflicts of interest

There are no conflicts of interest.

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