The Changing Natural History of HIV Disease: Before and After the Introduction of Generic Antiretroviral Therapy in Southern India

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The number of individuals seeking treatment for infection with human immunodeficiency virus increased as the cost of highly active antiretroviral therapy (HAART) decreased 20-fold after the introduction of generic HAART in India in the year 2000. The incidence of tuberculosis and opportunistic infections decreased to <2 cases per 100 person-years. Death rates decreased from 25 to 5 deaths per 100 person-years between 1997 and 2003.

Until recently, HAART was not accessible to a vast majority of the estimated 5.13 million Indians living with HIV infection in India [1], primarily because of its high cost. However, production of antiretroviral medications by Indian generic manufacturers since the year 2000 has dramatically reduced the price of combination HAART to <$1 (in US dollars) per day and has significantly increased access to treatment in resource-limited regions [2].

The current study was conducted to investigate the impact of the introduction of generic HAART at a large HIV clinic providing treatment for HIV infection in southern India. Our hypothesis was that availability of cheaper, generic HAART would increase the number of individuals seeking treatment for HIV infection, attract patients earlier in the course of HIV disease, and alter the natural history of HIV disease by reducing the number of incident opportunistic infections and the mortality rate.

Participants and methods. The YRG Center for AIDS Research and Education (YRG CARE), one of the largest tertiary HIV care referral centers in Chennai, India, provides HIV clinical care services. Patients were followed up every 3 months, or more often if needed for clinical reasons. Specific opportunistic infections were diagnosed using the Centers for Disease Control and Prevention’s standard clinical definitions and laboratory procedures [3]. On the basis of the World Health Organization’s (WHO’s) guidelines [4], patients were advised to initiate antiretroviral therapy if the CD4 lymphocyte count was <200 cells/μL or if the patient developed an AIDS-defining illness.

All adult (age, ≥18 years), HIV-infected persons who registered for care at YRG CARE between 1996 and 2003 (n = 5711) were included in the analysis. Data were collected using a standardized collection form approved by YRG CARE’s standing institutional review board. After each patient visit, trained research nurses extracted demographic and clinical data from patients’ medical charts. Data collected included age, sex, demographic variables, mode of HIV transmission, date of HIV detection, presenting symptoms, opportunistic infections, laboratory results (of lymphocyte subsets and liver function tests), receipt of antiretroviral drug regimens, adverse events, reasons for modifying or discontinuing therapy, and causes and date of death.

Yearly population proportions were compared using a χ² test. Patients who had visited the clinic more than once and who had undergone at least 6 months of follow-up were included in the analyses of incidence calculations. The incidence of opportunistic infections was calculated by identifying previously uninfected persons who tested positive for tuberculosis or other relevant infections, using standard clinical definitions and comparison by calendar year. The primary endpoint in the survival analysis was death. Kaplan-Meier survival analyses were performed to determine the median duration of survival, in relation to receipt of HAART from the date of HIV detection, and log rank statistics were determined to test survival distributions. Statistical analyses were performed with SPSS software, version 10.05 (SPSS).

Results. Between 1996 and 2003, there were 5711 HIV-infected persons who registered for care at YRG CARE: 69% were men, 95% acquired HIV infection via heterosexual transmission, and the median age was 32 ± 8 years. In a time-trends analysis, none of these demographic variables changed significantly over the study period. The median CD4 cell count at baseline was 247 cells/μL (n = 1985). The most common HIV-associated infections at the first visit to the clinic were oral...
candidiasis (30.2%) and tuberculosis (26%–22% were pulmonary cases and 4% were extrapulmonary cases).

The cost of HAART decreased from $778 per month in 1996 to $100 per month in 2000—the year generic antiretrovirals were made available in India—to $33 per month in 2003 (figure 1). In 1996, only 13% of patients who qualified for HAART on the basis of the WHO guidelines were able to afford therapy. This number steadily increased, with 22% of patients who qualified for HAART accessing HAART in the year 2000, and 44% of patients who needed HAART receiving it in 2003 (P < .001) (figure 1). The median CD4 cell count prior to initiation of HAART was 101 cells/µL, with an increasing trend over the study period (P = .002).

The most common antiretroviral regimen was lamivudine, stavudine, and nevirapine (administered to 56% of patients receiving HAART) administered as a fixed-dose combination of 1 pill to be ingested twice daily, followed by zidovudine, lamivudine, and nevirapine (administered to 22% of patients receiving HAART), which is also usually administered as a fixed-dose combination. Overall, 81% of patients were receiving nevirapine-based HAART, 12% were receiving efavirenz-based HAART, and 2% were receiving protease inhibitor–based HAART.

The incidence of opportunistic infections among patients receiving HAART was significantly less than that among patients not receiving HAART: <2 cases per 100 person-years among patients receiving HAART and up to 10 cases per 100 person-years among patients who were not receiving HAART (figure 2). As the use of HAART increased, death rates decreased from 25 deaths per 100 person-years in 1998 to 5 deaths per 100 person-years in 2003 (figure 3). Patients who received HAART who had undergone a minimum of 6 months of follow-up (n = 558) had a median duration of survival of 36 months (95% CI, 19–54 months), compared with 20 months (95% CI, 17–23 months) for patients who should have initiated HAART but could not afford it (n = 1002; P = .00001).

The use of antiretroviral medications was associated with adverse events. The most common adverse event was rash (8%); however, Steven-Johnson syndrome occurred in only 0.4% of patients receiving generic HAART. Eighty-five percent of patients with rash were receiving regimens that included nevirapine. The next most prevalent symptoms were nausea (8%), diarrhea (6%), headache (6%), and peripheral neuropathy (4%). Anemia (defined as a hemoglobin level of <9 g/dL) was detected in 4% of patients and was largely (60%) caused by treatment with zidovudine. Lipodystrophy (defined as a clinical spectrum of peripheral fat loss in the face, limbs, or buttocks, with or without central fat accumulation in the abdomen, breasts, and over the dorsocervical spine, confirmed by anthropometric measurements) was identified in 2% of patients, 86% of whom were receiving HAART that included stavudine. Immune reconstitution syndrome was observed in 3% of the clinic cohort, of whom 86% were coinfected with *Mycobacterium tuberculosis* (P < .001).

**Discussion.** India has been a leader in the manufacture of generic antiretroviral drugs. Its pharmaceutical industry developed triple combination, easy-to-take, low-cost pills that made HAART accessible and affordable [2]. Cost has steadily decreased, and the introduction of generic nevirapine in 1999 to the India market allowed prices to reach $33 per month by the end of 2003 for a nonnucleoside-based HAART regimen.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Trends in antiretroviral prices (in US dollars), new patients seeking care, and the number of patients initiating HAART, 1996–2003. Reproduced with permission from [10].

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Currently, nevirapine-based HAART is available in India as a 1-pill, fixed-dose combination, a formulation unavailable in the developed world, because of patent protection laws.

Two concurrent trends were identified in this study. First, there was an increase in the use of HIV-care services from 1996 to 2003. Secondly, among persons who required therapy, we observed a 20% increase in the number of patients who could afford access to HAART. The increased use of care services may be attributable to the availability of affordable, convenient HAART and access to a continuum of care. Patients may be more likely to seek care if they believe that they will have access to more-affordable therapy.

We investigated the impact of HAART on the incidence of all major AIDS-associated infections and tuberculosis, the most common opportunistic infection in India [5, 6]. India has the highest burden of tuberculosis in the world, accounting for one-third of the world’s cases of tuberculosis and 2 million new cases per year [7]. We have continued to observe an increase in the incidence of tuberculosis and all other opportunistic infections among patients who did not have access to HAART, but as was observed in South Africa [8] and the United States [9], we observed a concurrent decrease in the incidence of tuberculosis among patients receiving HAART. Patients who received antiretroviral therapy also experienced longer durations of survival. The death rate was inversely proportional to the use of antiretroviral therapy, decreasing the most after the introduction of generic antiretrovirals into the country in the year 2000 [10].

Although the incidence of opportunistic infections and death decreased, patients experienced adverse effects resulting from
use of antiretroviral therapy. Rash and nausea were the most common adverse effects, although, as has been documented elsewhere, the pattern of adverse events with generic medicines was similar to patterns associated with proprietary medicines [11]. Immune reconstitution syndrome was observed primarily in patients with tuberculosis [12]. With a high burden of tuberculosis in the developing world, managing immune reconstitution syndrome may prove to be a challenge to physicians scaling up antiretroviral therapy in resource-limited regions. Lipodystrophy was observed primarily in patients receiving stavudine-based HAART. Stavudine-based HAART is currently the cheapest and most widely available triple-drug regimen in resource-limited regions, and the prevalence of lipodystrophy may rise as the use of antiretroviral therapy increases.

The introduction of generic antiretroviral therapy to India in 2000 has had a significant impact on the natural history of HIV infection in southern India. More people are seeking care, although it is unclear whether they are seeking care because of greater awareness of risk factors for infection or because of an increased number of lower-cost options for therapy. HAART has reduced both opportunistic infection morbidity and mortality in this cohort.

Increasing access to generic HAART could be an effective means of using limited resources to provide needed treatment in areas where the epidemic continues to rapidly expand. However, there are still many areas of concern. First, despite the decreasing cost, many patients are still unable to afford therapy. Second, the costs of laboratory evaluations of CD4 cell counts ($25) and viral loads ($104) remain high [13]. There is great need for low-cost methods to monitor therapy.

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