High Rates of Regimen Change due to Drug Toxicity Among a Cohort of South Indian Adults with HIV Infection Initiated on Generic, First-Line Antiretroviral Treatment

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Abstract

Objectives: To determine the rates, reasons and predictors of treatment change of the initial antiretroviral treatment (ART) regimen in HIV-infected south Indian adults.

Methods: In this prospective cohort study, ART-naïve adults initiated on generic, fixed dose combination ART as per the National AIDS Control Organization guidelines were followed up at an academic medical center. Treatment change was defined as any event which necessitated a change in or discontinuation of the initial ART regimen.

Results: Two hundred and thirty persons with HIV infection (males 74.8% and median age 37 years) were followed up for median duration of 48 weeks. The majority (98.7%) had acquired HIV infection through the heterosexual route. Most (70.4%) had advanced HIV infection (WHO clinical stage 3 or 4) and 78% had CD4+ T-lymphocyte counts below 200 cells/µL. The initial ART regimens used were: Lamivudine (3TC) with Stavudine (d4T) (in 76%) or Azidothymidine (AZT) and Nevirapine (NVP) (in 86%) or Efavirenz (EFV). The cumulative incidence of treatment change was 39.6% (91 patients). Drug toxicity (WHO grade 3 or 4) was the reason for treatment change among 62 (27%) (incidence rate 35.9/100 person-years). The most common toxicities were attributable to the thymidine analogue nucleoside reverse transcriptase inhibitors (NRTIs), d4T and AZT [lactic acidosis (8.7%), anemia (7%) and peripheral neuropathy (5.2%)]. The other toxicities were rash (3.9%) and hepatitis (1.3%) due to NVP. The mortality (4.6/100 person-years) and disease progression rates (4.1/100 person-years) were low.

Conclusions: The ART regimens used in this study were effective in decreasing disease progression and death. However, they were associated with high rates of drug toxicities, particularly those attributable to thymidine analogue NRTI. As efforts are made to improve access to ART, treatment regimens chosen should not only be potent, but also safe.

Background

Highly active antiretroviral therapy (HAART) has dramatically reduced the morbidity and mortality associated with human immunodeficiency virus (HIV) infection, and has improved the prognosis for people living with HIV infection/AIDS (PLHA). About 33.2 million people worldwide are estimated to be living with HIV infection, the large majority of them in developing countries of Asia and Africa.¹ Since 2001, the World Health Organization (WHO) has advocated a “public health approach” to HAART to rapidly improve access to this life-saving intervention in resource-poor settings.² This approach focuses on maximizing survival at the population level through standardized sequencing of available antiretroviral drugs, delivered to individuals by means of simplified approaches to clinical decision making and basic laboratory monitoring.³

The free ART initiative was launched by the Government of India on 1 April, 2004 with a view to improve access to ART for the estimated 2.5 million PLHA in India. Currently, the National AIDS Control Organization (NACO) recommends the following drugs and drug combinations for first-line regimens:⁴

i. Stavudine (30 mg) + Lamivudine (150 mg)
ii. Azidothymidine (300 mg) + Lamivudine (150 mg)
iii. Stavudine (30 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
iv. Azidothymidine (300 mg) + Lamivudine (150 mg) + Nevirapine (200 mg)
v. Efavirenz (600 mg)
vi. Nevirapine (200 mg)

These drugs are chosen on the basis of their demonstrated efficacy in suppressing HIV replication and improving survival of PLHA,³ low cost and wide availability. However, concerns have emerged about the durability, safety and tolerability of these regimes. Lamivudine (3TC), Nevirapine (NVP) and Efavirenz (EFV) have a low genetic barrier for emergence of resistance,⁶ which can potentially jeopardize the durability of these regimes. The thymidine analogue nucleoside reverse transcriptase inhibitors (NRTI) [Stavudine (d4T) and Azidothymidine (AZT)]
and the non-nucleoside reverse transcriptase inhibitor (NNRTI) NVP are associated with several toxicities, which have led to the complete omission of d4T in treatment guidelines from industrialized countries. With the scaling up access to ART in our country, there is an opportunity to better understand the benefits and drawbacks of these regimens. Hence this study was conducted to determine the incidence and determinants of initial HAART regimen change in these patients.

Methods

This prospective cohort study was conducted at the Christian Medical College, Vellore, a 2200 bedded academic medical center in south India. Eligible subjects were recruited from the ‘Infectious Diseases Clinic’ (ID Clinic) which is a dedicated outpatient service for PLHA manned by staff from the departments of General Medicine and Infectious Diseases, Dermatology and Venereology, Child Health, Obstetrics and Gynecology, Psychiatry, medical social workers and a pharmacist. The ID Clinic provides generic, fixed-dose combination of anti-retroviral drugs at subsidized rates to patients.

The subjects were residents of southern Indian states (Tamil Nadu, Andhra Pradesh, Kerala and Karnataka). The diagnosis of HIV infection was confirmed by two serially reactive ELISA tests in symptomatic individuals and three tests in asymptomatic individuals. All subjects satisfied the medical eligibility for initiation of antiretroviral therapy [WHO clinical stage 3/4 or WHO clinical stage 1/2 with CD4+ T-lymphocyte (CD4 cell) counts less than 200 cells/µL]. The subjects were ART-naive (defined as having received less than 4 weeks of ART prior to enrolment). Patients who were pregnant, breast-feeding and younger than 13 years were not included.

All subjects had a detailed symptom-directed clinical evaluation to rule out any active opportunistic infections prior to initiation of HAART. Baseline anthropometric data including weight, height and body mass index (BMI), complete blood counts (CBC), biochemical tests (blood glucose, liver and renal function tests) and CD4 counts were obtained. All subjects had several (three to four) counseling sessions before initiation of HAART to assess treatment readiness and educate them regarding the need for life-long treatment, stringent adherence to therapy and potential side effects of the drugs.

All patients received a combination of two NRTI (either AZT 300 mg twice daily or d4T 30 mg twice daily with 3TC 150 mg twice daily) and an NNRTI (either NVP 200 mg once daily for 14 days followed by 200 mg twice daily or EFV 600 mg once daily at bed time). All the drugs were generic, fixed-dose combinations (AZT 300 mg + 3TC 150 mg, d4T 30 mg + 3TC 150 mg, AZT 300 mg + 3TC 150 mg + NVP 200 mg, d4T 30 mg + 3TC 150 mg + NVP 200 mg) procured from the same pharmaceutical manufacturing firm (CIPLA Ltd., Mumbai).

Follow up clinical assessments were done at two weeks, one month and subsequently once every 3 months after enrolment. Cohort surveillance was mainly passive. Patients had open access to the study clinic and were encouraged to attend whenever ill. Each episode of illness was investigated and managed according to established protocols. At each follow-up visit, the body weight was recorded, and each patient had a symptom-directed evaluation to assess any new events indicating treatment failure or drug toxicity. Follow-up CD4 cell count estimation was scheduled at 6 months after initiation of HAART, and every 6 to 12 months thereafter. Adherence was assessed by patient self report, and verified by pill count.

The primary outcome was the incidence of treatment change, defined as any event which necessitated a change or discontinuation of the initial HAART regimen, excluding dosage change or interruption of a drug for less than 14 days. The reasons for treatment change included:

1. Death (from any cause)
2. Treatment failure defined as a new or recurrent AIDS-defining illness diagnosed at least six months after the initiation of HAART
3. Non-adherence to therapy defined as ingestion of less than 90% of the prescribed doses of drugs. Patients who did not return for follow-up after initiation of HAART were also considered to be non-adherent.
4. Drug toxicity (WHO Grade 3 and 4) requiring substitution or immediate discontinuation of the offending drug

Statistical methods: Statistical Package for the Social Sciences (SPSS) software package (version 11.0) was used for data analysis. Rate of HAART regimen change was calculated as the number of events over the person-years follow-up. The time to change was estimated using Kaplan-Meier method. Determinants of treatment change were assessed by constructing univariate logistic regression models with “HAART regimen change” as the dependent variable. Odds ratio (OR) and confidence intervals (CI) were calculated and a two-sided ‘p’ value less than 0.05 was considered statistically significant. Baseline parameters considered as possible determinants of treatment change were age, sex, duration of HIV infection (from the time of diagnosis to initiation of HAART), WHO clinical stage, BMI, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) > 40 IU/ml, baseline CD4 cell counts, and HAART regimen used.

The study was approved by the institutional review board of Christian Medical College, Vellore, and written informed consent was obtained from all participants.

Results

Baseline characteristics (Table 1): Subjects were enrolled between March 2004 and May 2006. A total of 230 consecutive ART-naive patients were followed up for a median period of 48 weeks. The majority (74.8%) were males and the median age of the study population was 37 years [inter-quartile range (IQR), 34 to 44; mean (± S.D), 38.9 (± 8.4) years]. The route of acquisition of HIV infection was heterosexual contact in the majority (98.7%). Two patients had acquired the infection through blood transfusion, and one through homosexual contact. Majority (70.4%) of the patients had advanced stages of HIV infection (WHO clinical stage 3 or 4). The median CD4 cell count at baseline was 112.5 cells/µL (IQR: 57 to 190 cells/µL; mean (± S.D) 127.7 (± 81.06) cells/µL).

HAART regimens used (Figure 1): Sixty eight percent of the patients initiated treatment with a combination of d4T + 3TC + NVP. Stavudine was part of the NRTI backbone in 76% of the patients. Nevirapine was the NNRTI used in 86% of the patients. Twenty six (11.3%) patients received concomitant anti-tuberculous therapy. All patients also received trimethoprim-sulfamethoxazole (TMP-SMX) prophylaxis (except one who received dapsone due to TMP-SMX allergy).

Primary outcome (Figure 2): Total follow-up time was approximately 173 person-years, with a median duration of follow-up of 48 weeks (IQR, 16 to 52 weeks; mean (± S.D), 39 (±24.2) weeks). The cumulative incidence of treatment change of
the initial HAART regimen was 39.6% (91 patients). The median time to treatment regimen change was 12 weeks.

Reasons for initial HAART regimen change (Table 2):
1. Deaths: Eight (3.5%) subjects died during follow up. The mortality rate was 4.6/100 person-years. Five deaths were due to related causes; two patients died due to drug toxicities (one had toxic epidermal necrolysis and the other lactic acidosis), and three due to treatment failure.
2. Drug toxicity: WHO Grade 3 or 4 toxicities occurred in 62 patients (27%) and were the commonest reason for treatment change. The incidence rate for drug toxicity was 35.9/100 person-years.
3. Non-adherence: Nineteen patients (8.3%) were non-adherent (incidence rate 11/100 person-years).
4. Treatment failure: Seven patients (3%) developed new or recurrent AIDS-defining illnesses during the follow-up period, an incidence rate of 4.1/100 person years. The events were disseminated tuberculosis (seven patients) and cytomegalovirus retinitis (one patient). Four among these also had oropharyngeal candidiasis. Three patients eventually succumbed to these illnesses.

Drug toxicity (Table 3): The commonest drug toxicities we observed were lactic acidosis (LA), anemia and peripheral neuropathy. All of these were attributable to the thymidine analogue NRTI (d4T and AZT).
LA was diagnosed in 20 (8.7%) patients, an incidence rate of 11.6/100 person-years. All these patients were on d4T. The median time to diagnosis of LA was 42 weeks (range 24 to 67 weeks). The mean (±SD) venous bicarbonate and anion gap levels in these patients were 15 (±5.3) mmol/L and 22.5 (±6.4) mmol/L respectively. The mean level of venous lactate in these patients was 3.7 mmol/L. One patient died due to severe metabolic acidosis. Severe anemia (WHO Grade 3 or 4) was diagnosed in 16 (7.0%) patients (incidence rate 9.3/100 person-years). The median time to diagnosis of anemia was 8 weeks (range 3 to 36 weeks). Severe, symptomatic peripheral neuropathy was the reason for treatment change in 12 (5.2%) patients (incidence rate 7/100 person-years). The median time to development of peripheral neuropathy was 32 weeks (range 20 to 56 weeks). Severe rash [Stevens-Johnson syndrome or toxic epidermal necrolysis (TEN)] occurred in 9 (3.9%) patients, and one patient who had TEN died. The median time to treatment change due to drug rash was 2 (range 2 to 6) weeks.

Predictors of treatment change: A univariate logistic regression analysis showed the following factors to be significant predictors of treatment regimen change:

1. Advanced HIV infection (WHO clinical stage 3, 4) [OR, 1.59; 95% CI, 1.38 to 1.88].
2. Duration of HIV infection (from the time of diagnosis to initiation of HAART) more than 3 months [OR, 1.22; 95% CI, 1.04 to 1.44].
3. Current smoking [OR, 2.16; 95% CI, 1.52 to 3.06].
4. BMI > 25 kg/m² [OR, 1.56; 95% CI, 1.18 to 2.06].
5. AST levels > 40 U/L [OR, 2.26; 95% CI, 1.47 to 3.47].
6. ALT levels > 40 U/L [OR, 4.07; 95% CI, 2.36 to 6.99].

In the multivariate model, advanced HIV infection (OR, 1.39; 95% CI, 1.21 to 1.61; p <0.001), current smoking (OR, 1.51; 95% CI, 1.08 to 2.18; p <0.02), BMI more than 25 kg/m² (OR, 1.68; 95% CI, 1.29 to 2.18; p <0.001) and baseline elevated ALT (OR, 2.48; 95% CI, 1.60 to 3.49; p 0.001) remained predictors of treatment regimen change. Age, sex, route of HIV acquisition, CD4 cell counts and individual regimens were not associated with the HAART regimen change.

Discussion

We analyzed the outcome of generic, fixed-dose combination ART regimens recommended by NACO in 230 ART-naïve adult PLHA followed up at a tertiary care teaching hospital in south India. The majority of patients had advanced HIV infection (WHO clinical stage 3 or 4 and CD4 cell count less than 200 cells/µL). The cumulative incidence of treatment regimen change in this cohort was 39.6%. The incidence of mortality (4.6 per 100 person-years) and disease progression (4.1 per 100 person-years) was low and drug toxicity was the most important reason (35.9 per 100 person-years) for treatment change. This rate of treatment change is significantly higher than hitherto reported from India. Kumarasamy et al reported that 20% of their patients had modified their first-line HAART regimen, most often due to adverse events. In the TREAT Asia HIV Observational Database, the overall rate of treatment change among patients starting first-line triple combination antiretroviral treatment was 29 per 100 person-years, adverse events again being the commonest reason. Possible reasons for our finding include the advanced stage of immunosuppression of our patients and intensive monitoring for adverse drug reactions.

The initial choice of HAART regimen offers the best chance to control HIV replication. Potency of the regimen is the first line of defense against the development of resistance. Other factors that affect resistance development include tolerability, potential for optimum adherence, and genetic and pharmacologic barriers to development of resistance. The cumulative rate of treatment failure among adults in a large government funded ART programme at the largest HIV care center in India was 3.9% (95% CI, 2.9 to 4.9%). This finding, very similar to ours, is an indication of the potency of the first-line HAART regimens recommended by WHO and NACO. However, we observed that tolerability was poor. Forty percent of our patients had to change their regimen by 48 weeks. This could adversely impact adherence and lead to emergence of resistance and eventually treatment failure.

The most common drug toxicities we observed (lactic acidosis, anemia and peripheral neuropathy) were all caused by the thymidine-analogue NRTI, stavudine and azidothymidine. Lactic acidosis is due to the inhibition of mitochondrial DNA polymerase by the NRTI. Among the NRTI, stavudine and didanosine are much more likely to cause this complication than tenofovir or abacavir. Risk factors for this potentially life-threatening condition include simultaneous use of stavudine and didanosine, long duration of NRTI use, female gender and high baseline BMI. The clinical manifestations of this disorder (which occurs several months after starting HAART) are quite non-specific, and the diagnosis is confirmed by demonstration of metabolic acidosis with elevated anion gap, and elevated venous lactate levels. Any delay in diagnosis due to a lack of awareness of the manifestations or laboratory infrastructure may lead to avoidable mortality due to severe metabolic acidosis. Significant anemia, which occurs most commonly 4 to 6 weeks after starting treatment, is due to inhibition of erythropoiesis by AZT. Therefore, routine monitoring of hemoglobin is recommended during the initial 4 weeks after starting AZT-based regimen.

Drug toxicity may be life-threatening, disfiguring or distressing, thus adversely affecting quality of life and potential for optimum adherence. Lack of adherence ultimately leads emergence of resistance to antiretroviral drugs and treatment failure. Serious toxicities occurred as early as 2 weeks (drug rash) or as late as 42 weeks (lactic acidosis) in our cohort, emphasizing the need for continued vigilance for months after initiation of HAART. There is also a need for intense laboratory monitoring to diagnose drug toxicity early (anemia while on AZT and hepatitis while on NVP). This is bound to put an enormous strain on the healthcare infrastructure providing HAART to large number of PLHA. Therefore, there is an urgent need to provide drug regimes which are potent, efficacious, safe and tolerable and require only a minimum of laboratory monitoring.

Patients with advanced HIV infection were more likely to change the initial HAART regimen. This finding underscores the need for improved case finding, routine monitoring of CD4 cell counts and treatment initiation before patients develop severe immunodeficiency.

Our study has several possible limitations. Cohort surveillance was not active. Plasma viral load testing was not performed at follow-up visits. Therefore we may have underestimated the proportion of subjects with treatment failure. Our patients might not be completely representative of HIV-infected patients in India. We studied patients who were followed-up at a medical college. Therefore, care should be taken in extrapolating these results.
In conclusion, the currently recommended first-line HAART regimens have achieved their primary objective of reducing HIV related morbidity and mortality. They are however, poorly tolerated due to several short-term and long-term toxicities. There is an urgent need to introduce HAART regimens which are potent, safe, well tolerated and convenient.

References