Effectiveness of highly active antiretroviral therapy using non-brand name drugs in Brazil

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Abstract

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In Brazil, HIV-infected individuals receive drugs (including non-brand name drugs which comprise locally produced generics and drugs that have not been tested in bioequivalence trials) free of charge from the government. The objective of the present study was to evaluate the effectiveness of highly active antiretroviral therapy (HAART) in Rio de Janeiro, Brazil, where non-brand drugs are widely used. For this purpose, we estimated the proportion of subjects with virologic failure (plasma HIV viral load greater than 400 copies/mL at 6 months after initiation of treatment). This was a retrospective cohort study of drug-naive HIV-infected subjects who initiated HAART. Subjects were included in the analysis if they were 18 years of age or older, were treatment naive, started HAART with a minimum of 3 drugs, and had available information on blood plasma HIV-1 viral load after 6 months on therapy. All subjects used antiretrovirals in dosing regimens recommended by the Brazilian National Advisory Committee for Antiretroviral Therapy. Chart reviews were conducted in three settings: at two public health outpatient units, at one clinical trial unit and at one private office. No comparisons of the effectiveness of non-brand name with the effectiveness of brand name drugs were made. We present results for 485 patients; of these, 354 (73%), 55 (11%), and 76 (16%) were seen at the public health outpatient units, private office, and clinical trial unit, respectively. Virologic failure was observed in 119 (25%) of the subjects. This study demonstrates the effectiveness of HAART in a setting where non-brand name drugs are widely used.

Introduction

Studies conducted in developed countries using brand name drugs have demonstrated that early virologic response after introduction of highly active antiretroviral therapy (HAART) is an important predictor of long-term treatment efficacy (1). Recently, the prospects for HAART in resource-poor settings have improved considerably with

the availability of non-brand name drugs, drastic price reductions of some brand name drugs, and some new initiatives of international agencies. In June 2005, the World Health Organization estimated that approximately one million individuals in developing countries were receiving HAART. This represents 15% of the estimated 6.5 million people in need of HAART in low- and middle-income countries (2-4). In Brazil, since 1996 virtually all HIV-infected individuals that are on treatment, including patients treated in private practice, receive their drugs free at public dispensaries. Drugs that are protected by patents are purchased exclusively from the patent holders. In addition, non-brand name drugs are also used. Non-brand name drugs include locally produced generic drugs (drugs that are bioequivalent to a brand name drug with respect to pharmacokinetic and pharmacodynamics properties as defined by Brazilian regulations) and locally produced drugs that have not been tested in bioequivalence trials. At present, the following antiretrovirals are bought exclusively from their patent holders: tenofovir, enteric-coated didanosine, efavirenz, nelfinavir, amprenavir, lopinavir/ritonavir, atazanavir, and enfurvitide. Abacavir has been licensed to a Brazilian manufacturer. Drugs that are not protected by applicable patent laws are purchased through public tenders. Thus, brand name and non-brand name zidovudine, lamivudine, didanosine, stavudine, nevirapine, saquinavir, indinavir, and ritonavir might be dispensed to patients, depending on the results of public bids by the suppliers.

Results of recent studies have suggested that virologic and immunological responses to HAART in developing countries are similar to those observed in high-income settings (5-11). Nonetheless, there is relatively little information on the effectiveness of antiretroviral therapy including non-brand name drugs (12). We designed the present study to investigate virologic response 6 months after the initiation of HAART in drug-naive subjects treated in three different settings in Rio de Janeiro, Brazil: in two public health outpatient units (PHU) and in one private office (PO), where patients use a mixture of non-brand name and brand name drugs (see above), and in a clinical trial unit (CTU), where only brand name drugs are used.

The objective of the present study was to evaluate the effectiveness of HAART in Rio de Janeiro, Brazil, where non-brand drugs are widely used. For this purpose we estimated the proportion of subjects with virologic failure (VF). In addition, we evaluated predictors of VF.

Patients and Methods

This was a retrospective cohort study of drug-naive HIV-infected subjects who started HAART between 1996 and 2004 in Rio de Janeiro, Brazil. The institutional review board of the Hospital Universitário Clementino Fraga Filho (HUCFF)/School of Medicine of the Universidade Federal do Rio de Janeiro approved the study.

Patients

Study subjects came from 3 different settings: 2 PHU (HUCFF, a large teaching hospital of the Universidade Federal do Rio de Janeiro, and Centro Municipal de Saúde João Barros Barreto, a primary care facility run by the City of Rio de Janeiro Health Department), one CTU (Projeto Praça Onze, Universidade Federal do Rio de Janeiro), and the PO of one of the authors (MS). Subjects were included in the analysis if they were 18 years of age or older, were treatment naive and started HAART with a minimum of 3 drugs, and had available information on blood plasma HIV-1 viral load after 6 months on therapy. All subjects used antiretrovirals in dosing regimens recommended by the Brazilian National Advisory Committee for Antiretroviral thera-

py of the Ministry of Health, Brazil.

Study endpoint and exposure variables

The primary endpoint of this study was VF at 6 months on HAART, which was defined as a plasma HIV load greater than 400 copies/mL 6 months (range: 3 to 9 months) after initiation of treatment. When more than one measurement was available, the one closest in time to 6 months on therapy was utilized. Exposure variables were age, gender, year of HAART introduction, type of combination regimen prescribed, setting where care was provided, and baseline CD4 cell count, CD4 percentage and HIV-1 viral load. No comparisons of the effectiveness of non-brand name with the effectiveness of brand name drugs were made. An intent-to-continue-treatment approach, which ignored subsequent therapy changes or interruptions, was used. Data were abstracted from charts by trained research assistants and entered in the database using the Teleform 6.1® software.

Statistical analysis

The main analysis was an evaluation of the determinants of VF at 6 months on HAART. Univariate analyses identified variables associated with VF. Categorical data were analyzed using the chi-square test or Fischer's exact test when appropriate. Continuous variables were analyzed using t-tests, when appropriate. HIV load in blood plasma was not normally distributed and therefore the data were log-transformed (base 10). Odds ratios (OR) and 95% confidence intervals (95%CI) were calculated. Univariate analysis identified variables to be included in the logistic multivariate analysis. Two indicator (dummy) variables were created to accommodate the 3 modes of health delivery. All reported P values are two-sided. SPSS® for Windows 9.0 was used for data analysis.

Results

A total of 485 subjects were included in the analysis. The mean age at HAART initiation was 38 years and 308 (64%) were males. Three hundred and fifty-four subjects (73%) came from the PHU, 55 (11%) from the PO and 76 (16%) from the CTU. The median year of HAART introduction was 2001. Two hundred and eleven subjects (44%) initiated a protease inhibitor (PI) containing regimen and 258 (53%) initiated a non-nucleoside (NN) reverse transcriptase inhibitor-containing regimen (NNRTI), while 10 (2%) were prescribed a three-nucleoside regimen and 6 (1%) initiated a regimen containing both a PI and an NN. Median CD4 cell count and percentage at baseline were 174 cells/μL and 12%, respectively. Median baseline HIV-1 load was 82,550 copies/mL for the 260 subjects who had that measurement available. Table 1 shows the distribution of the selected variables by type of health delivery mode.

Mean baseline HIV-1 load was 4.19 $\log_{10}$ for subjects prescribed a PI-containing HAART and 4.32 $\log_{10}$ for those prescribed an NNRTI-containing HAART (P = 0.71, t-test). Subjects prescribed a PI-containing regimen had a slightly lower CD4 count at baseline (mean 201 cells/μL for the NNRTI group and 160 cells/μL for the PI group, P = 0.02, t-test).

Table 1. Distribution of selected variables among subjects seen in three health delivery settings.

	PHU (N = 354)	PO (N = 55)	CTU (N = 76)
Age in years (mean ± SD)	41 ± 11	46 ± 12	37 ± 10
Male (%)	59	80	72
Median year of HAART introduction	2000	2000	2001
PI containing HAART (%)	53	37	11
Median baseline HIV-1 load	71,000	128,709	75,466
Median baseline CD4 count (cells/μL)	179	206	199

HAART = highly active antiretroviral therapy; PI = protease inhibitor; PHU = public health unit; PO = private office; CTU = clinical trial unit.

Virologic failure at 6 months

VF was observed in 119 (25%) of the subjects. VF occurred in 104 (29%), 3 (6%) and 12 (15%) of the subjects treated at PHU, PO and CTU, respectively. In univariate analysis, VF was associated with a lower baseline CD4 count (mean: 138 cells/μL vs 201 cells/mm^3, P < 0.01), higher baseline viral load (mean 4.12 $\log_{10}$ vs 4.93 $\log_{10}$, P = 0.003), therapy started before 2000 (OR = 2.71; 95%CI = 1.75-4.2), and use of PI vs NNRTI (OR = 2.19; 95%CI = 1.43-3.37).

In the multivariate analysis, receiving care at the PO was associated with a significantly lower risk of VF (OR = 0.10; 95%CI = 0.02-0.45 for being treated at the PO) compared with treatment at PHU. The risk of VF was not significantly different between patients treated at the CTU and patients treated at the PHU (OR = 0.82; 95%CI = 0.39-1.70). VF was independently associated with a lower baseline CD4 cell count/mm^3 and with initiation of HAART before 2000. Table 2 shows the final multivariate logistic model. Baseline HIV-1 load was not included in the model because a significant proportion of subjects did not have this measurement available. Nevertheless, in a model that included baseline HIV-1 load, the re-

sults obtained were similar to those presented here (data not shown).

Discussion

The main finding of the present study is that the virologic effectiveness of HAART in a developing country where non-brand name drugs are widely used is comparable to that reported in developed countries using brand name drugs (13,14). Study participants started HAART with fairly low-baseline CD4 levels, a predictor of VF (1,14). Nonetheless, VF at 6 months on therapy was observed in 25% of the subjects, a result that compares favorably to what has been reported in developed countries (1,13). The main predictors of VF in our study were lower baseline CD4 counts, introduction of HAART before 2000, and treatment not provided in a private office. The finding that lower baseline CD4 was an independent predictor of failure is consistent with reports from other settings (1,14,15). Individuals who started HAART before 2000 had more than twice the chance of failing treatment than those who started treatment in more recent years, probably reflecting the introduction of efavirenz and the use of ritonavir-boosted regimens becoming much more common over time (7).

Being treated at a private office was associated with a lower risk of virologic failure. In Brazil, patients treated at private offices also receive their drugs free at public dispensaries. Thus, they receive the same mixture of non-brand name and brand name drugs as patients treated in PHU. The reasons that may explain the lower failure rate at the PO were not investigated in the present study. Data on co-morbidities prior to initiation of treatment were not available for all patients. Nonetheless, given their higher socio-economic status, the lower VF rate observed at the PO may reflect a lower prevalence of co-morbidities associated with poverty, particularly tuberculosis. Additionally,

Table 2. Multiple logistic regression analysis of determinants of virologic failure after 6 months on therapy.

Characteristic	OR (95%CI)	P value
Antiretroviral regimen		
NNRTI containing HAART	1	Reference
PI containing HAART	1.31 (0.73-2.37)	0.38
Year of HAART introduction		
≥2000	1	Reference
<2000	2.37 (1.28-4.41)	0.006
Baseline CD4 count (cells/μL)	0.996 (0.993-0.997)	0.016
Health delivery setting		
Public health units	1	Reference
Private clinic	0.10 (0.02-0.45)	0.03
Clinical trial unit	0.82 (0.39-1.70)	0.59

OR = odds ratio; 95%CI = confidence interval at 95%; NNRTI = non-nucleoside reverse transcriptase inhibitor; HAART = highly active antiretroviral therapy; PI = protease inhibitor.

patients at the PO are likely to have a higher educational level, more access to information and a closer doctor-patient relationship, factors that positively influence compliance with therapy (8). Further studies are necessary to confirm and investigate the reasons for the difference in effectiveness of HAART between patients treated at private offices and public clinics. These, in turn, may assist with the development of strategies to improve the effectiveness of HAART among lower income patients.

There are other limitations to the present study, including its retrospective design. A substantial proportion of patients from the PHU had to be excluded because of lack of viral load measurements. Finally, although it is highly likely that the vast majority of patients treated at the PHU and the PO received non-brand name drugs, we cannot be sure about this, since brand name and non-brand name drugs might be dispensed, depending on the results of public bids.

Acknowledgments

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