Gender-Based Differences in Treatment and Outcome among HIV Patients in South India

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Abstract

Objective: To describe gender-based differences in disease progression, treatment, and outcome among patients receiving highly active antiretroviral therapy (HAART) in South India.

Methods: Therapy-naïve patients initiating HAART between February 1996 and June 2006 at a tertiary HIV referral center in Chennai, South India, were analyzed using the YRG CARE HIV Observational Database. Patients with 1 year of follow-up after initiating HAART were examined to investigate immunological and clinical outcomes, including the development of adverse events to therapy and opportunistic infections.

Results: All previously therapy-naïve patients who initiated HAART with at least 1 year of follow-up ($n = 1972$) were analyzed. At enrollment into care, women had higher CD4 counts, lower hemoglobin, and higher body mass index (BMI) than their male counterparts ($p < 0.05$). At the time of initiating therapy, women had higher CD4 counts and lower hemoglobin ($p < 0.05$); women continued to have higher CD4 counts at 12 months ($p < 0.05$). After 1 year following HAART initiation, significantly more men developed tuberculosis and *Pneumocystis jiroveci* pneumonia ($p < 0.05$), more women experienced lactic acidosis and nausea, and more men developed immune reconstitution syndrome ($p < 0.05$).

Conclusions: Significant physiological, immunological, and clinical differences exist between men and women initiating HAART in a resource-limited setting in South India. Future studies should examine whether clinical management strategies should be different for men and women in resource-limited settings.

Introduction

TODAY, NEARLY HALF of the people living with HIV globally are women.¹ The rising number of women living with HIV requires greater clinical investigations examining gender-based differences in treatment and outcome in the era of antiretroviral therapy (ART),² particularly because generic medication has dramatically reduced the cost of treatment. Gender-based differences in pharmacokinetics, side effect profiles, and access to and efficacy of these medications may limit the generalizability of many clinical studies to women.² Observational studies conducted in the developed world have documented possible virological, immunological, and clinical differences between men and women receiving ART,^{3–5} which may be attributable to social and biological differences.^{2,6}

In our prior research as part of the natural history of HIV in South India, we found that female patients had higher median CD4 lymphocyte counts and greater survival rates than male patients, as many female patients were asymptomatic and were tested after their husbands had come for care.⁷ In a follow-up study, we found that the major reason for discontinuing or modifying ART was an adverse event (AE), such as rash, hepatotoxicity, and anemia,⁸ all of which may vary by gender. One of the major risk factors for the increasing prevalence in HIV infection among Indian women is being married and monogamous, suggesting high-risk activity among their spouses.⁹

The current study was developed to examine gender-based differences in treatment outcomes after initiation of ART in a resource-limited setting. These data will enable clinicians to develop more effective and better tolerated treat-

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Brown University's AIDS International Research and Training Program of the Fogarty International Center at the National Institutes of Health (grant D43TW00237) and an ACTG-ICTU/NIH-Chennai site grant supported this study.

ment strategies for HIV-infected women. In light of the increasing feminization of the HIV epidemic in the developing world, this study is timely in assessing gender-based differences in the era of highly active ART (HAART).

Materials and Methods

Setting

The YRG Centre for AIDS Research and Education (YRG CARE) in Chennai is a large HIV tertiary care center in India. Since 1996, it has provided comprehensive care for almost 10,000 HIV-infected individuals, with a strong couples counseling and testing program.¹⁰ All patients are treated according to the World Health Organization (WHO) treatment guidelines.¹¹ Patients are advised to initiate ART when CD4 counts reach <200 cells/ μ L or when the CD4 counts range between 200 and 350 cells/ μ L with an AIDS-defining illness. Nevirapine (NVP)-based regimens, which are the least expensive and most widely available, are generally used as first-line therapies. Patients are seen every 3 months or as clinically indicated. CD4 monitoring is done every 3–6 months. Plasma viral load monitoring was not the standard of care but was performed for patients who could afford virological testing or who were enrolled in clinical trials.

Subjects

Patients who were >18 years of age, attending the YRG CARE clinic between February 1996 and June 2006, and naïve to ART before initiation of HAART were included in the analysis ($n = 9110$, 31.5% female). Data were collected under the approval of YRG CARE's free-standing Institutional Review Board. Analyses used the YRG CARE HIV Observational Database.^{7,8} This database is updated daily by research

nurses who are trained to use a validated prospective data collection instrument, which includes demographics, clinical assessments, current treatment regimens, and AEs, as well as laboratory data, including hemoglobin, liver, and renal function tests, CD4 cell counts, plasma viral load (PVL), and genotypic testing, if available. This study is a retrospective analysis of the clinical data of patients with a minimum of 1-year follow-up after initiating HAART.

Clinical definitions

Tuberculosis diagnosis was based on consistent history and physical examination and culture yielding *Mycobacterium tuberculosis* or positive sputum or aspirate tests for acid-fast bacilli, radiological features suggestive of TB, or clinical and radiological improvement in response to antituberculosis treatment. The most recent NIH definitions of AIDS-associated AEs were employed for diagnosis.¹² Lactic acidosis was diagnosed based on elevated serum lactate levels as per DAIDS NIH grading. Immune reconstitution inflammatory syndrome (IRS) was defined as a new lymph node enlargement and localized tenderness or fever with no other cause identified after a systemic clinical and laboratory evaluation.¹³

Statistical analysis

Descriptive statistics were calculated with mean and standard deviation (SD) for variables that were normally distributed, and the median and interquartile ranges (IQR) were calculated for variables influenced by extreme values. To compare proportions, chi-square statistics were used, and the Mann-Whitney *U* test was used to compare median durations. Statistical analyses were performed with SPSS soft-

TABLE 1. CLINICAL CHARACTERISTICS OF SOUTH INDIAN MEN AND WOMEN WHO INITIATED HAART AT ENROLLMENT TO CARE AND AT TREATMENT INITIATION ($N = 1972$)

	Male ($n = 1512$) Median (IQR), mean %	Female ($n = 460$) Median (IQR), mean %	p value ^a
Age (years)	35.5 $\pm$ 7.9	32.8 $\pm$ 8.6	<0.001
BMI (kg/m ²)	18.7 (16.7–21.4)	19.7 (16.7–22.3)	0.023
Total lymphocyte count	1500 (1000–2052)	1528 (1068–2137)	NS
Hemoglobin (g/dL)			
At enrollment	11.6 (9.7–13.1)	10.6 (9.0–11.6)	<0.001
At treatment initiation	11.4 (9.3–13.0)	10.4 (8.8–11.6)	<0.001
CD4 cell count (cells/ μ L)			
At enrollment	142 (62–242)	173 (80–280)	0.004
At treatment initiation	114 (55–179)	134 (62–191)	0.022
Opportunistic infections ^b			
at enrollment			
Toxoplasmosis	2.3%	0.9%	0.032
Tuberculosis	9.9%	5.4%	<0.001
Median time between enrollment and treatment initiation (months)	1 (0–11)	5 (0–23)	<0.001

^aChi-square test and Mann Whitney test performed as % detectable, % undetectable.

^bThe following opportunistic infections were not significantly different between men and women: *Pneumocystis jiroveci* pneumonia; cryptosporidial diarrhea; cytomegalovirus; progressive multifocal leukoencephalopathy; oral candidiasis.

ware (version 13.0; SPSS, Chicago, IL). A p value <0.05 was considered statistically significant.

Results

Within this clinic population, 1972 antiretroviral therapy-naïve patients initiated HAART with 1-year follow-up, and only these patients were used in subsequent analysis; 23.3% were female. The major mode of transmission was heterosexual for both men and women ($>90\%$). At enrollment into care, women had significantly higher body mass index (BMI) ($p = 0.023$) and lower hemoglobin than their male counterparts ($p < 0.001$). Women also had significantly higher CD4 counts than men (142 cells/ μ L for men vs. 173 cells/ μ L for women) ($p = 0.004$). Significantly more men had tuberculosis (9.9% of men and 5.4% of women, $p < 0.001$) and toxoplasmosis (2.3% of men and 0.9% of women, $p = 0.032$). Women initiated treatment after enrollment into care significantly later than men ($p < 0.001$) (Table 1).

Men and women tended to initiate therapy with similar regimens. The most common regimens for men and women were lamivudine (3TC) plus stavudine (d4T) plus NVP (56%

of men, 67.7% of women), 3TC plus d4T plus efavirenz (EFV) (17.7% of men, 16.5% of women), and zidovudine (AZT) plus 3TC plus NVP (17.1% of men, 7.3% of women). At the time of initiating first-line generic HAART, women had significantly higher CD4 counts ($p = 0.022$) and lower hemoglobin levels than men ($p < 0.001$). The median CD4 count at the time of initiating HAART was 114 cells/ μ L for men and 134 cells/ μ L for women; median hemoglobin was 11.4 g/dL for men and 10.4 g/dL for women.

At 1 year after initiating HAART, women continued to have higher CD4 counts than men (123 cells/ μ L for men vs. 145 cells/ μ L for women) ($p = 0.033$). Men and women modified their first-line regimens at similar rates in the first year after initiating HAART. Among the men and women who modified their treatment regimens, the main reasons for modification included avoiding risk of d4T toxicity (15% men, 18% women), developing AEs (10% of men, 10% of women), and experiencing immunological failure (10% of men, 8% of women) (Table 2).

More men (6.2%) than women (4.0%) died over the course of HAART ($p = 0.033$). More men developed tuberculosis (11.3% of men vs. 8.0% of women) ($p = 0.026$) and *Pneumo-*

TABLE 2. CLINICAL OUTCOMES OF PATIENTS 1 YEAR AFTER INITIATING HAART (N = 1972)

	Male (n = 1512) Median (IQR), mean %	Female (n = 460) Median (IQR), mean %	p value ^a
Median CD4 (cells/ μ L) at 12 months	123 (52–207)	145 (66–210)	0.033
CD4 (cells/ μ L) at 12 months			NS
<200	74%	71%	
201–350	19%	19%	
>350	8%	9%	
Incident opportunistic infections			
<i>Pneumocystis jiroveci</i> pneumonia	7.5%	5.2%	0.05
Tuberculosis	11.3%	8.0%	0.026
Cryptosporidial diarrhea	1.5%	1.3%	NS
Cytomegalovirus	1.5%	1.7%	NS
Progressive multifocal leukoencephalopathy	0.3%	0%	NS
Herpes simplex	13.1%	16.1%	NS
Toxoplasmosis	3.4%	3.0%	NS
Oral candidiasis	1.9%	2.6%	NS
Reported deaths	6.2%	4.0%	0.033
Percent modifying first-line regimen			NS
0	45%	48%	
1–2	45%	44%	
≥ 3	10%	8%	
Median follow-up time (months)	32 (6–124)	34 (6–116)	0.020
Adverse events			
Anemia	6%	7%	NS
Nausea	19%	27%	<0.001
Diarrhea	0.2%	0%	NS
Peripheral neuropathy	13%	10%	NS
Pancreatitis	1%	0.4%	NS
Hepatitis	4%	4%	NS
Rash	20%	19%	NS
Steven Johnson syndrome	1%	1%	NS
Lipodystrophy/lipoatrophy	4%	5%	NS
Immune reconstitution syndrome	6%	2%	<0.001
Lactic acidosis	0.7%	2.8%	<0.001

^aChi-square test and Mann Whitney test performed as % detectable, % undetectable.

cystis jiroveci pneumonia (7.5% of men vs. 5.2% of women) ($p < 0.05$). Significantly more men experienced IRS (6% of men vs. 2% of women) ($p < 0.001$), whereas significantly more women experienced nausea (27% of women vs. 19% of men) ($p < 0.001$) and lactic acidosis (2.8% of women vs. 0.7% of men) ($p < 0.001$) on HAART.

At the time of enrollment into care, PVL data were available for 6.0% of men (median, 95,442 copies/mL) and 5.9% of women (60,475 copies/mL), and at the time of initiating treatment, PVL data were available for 15.7% of men (100,000 copies/mL) and 5.0% of women (108,085 copies/mL), which did not differ significantly between men and women both at enrollment into care and at treatment initiation.

Discussion

This study demonstrated that Indian women who had access to care had significantly higher CD4 counts than their male counterparts at enrollment into care, treatment initiation, and 1 year after initiating HAART. Both men and women showed consistent yet modest gains in CD4 levels in the first year after initiating HAART. At the time of initiating HAART, as well as during the 12-month follow-up, the overwhelming majority of men and women evaluated reported CD4 levels < 200 cells/ μ L.

Studies indicate that asymptomatic Indian women may be tested for HIV earlier, after their spouses are diagnosed at a more advanced stage of HIV and seek clinical care for an opportunistic infection.^{9,14–16} One of the major reasons why women appeared to come earlier in the course of their HIV infection was that many women were identified as HIV infected after their husbands developed advanced disease. Because the women had earlier access to treatment and clinical care, fewer women than men died in the first year after initiating therapy. Additionally, because of the increasing availability of antenatal testing as part of ongoing expansion in voluntary counseling and testing,^{15,17} Indian women who learned their serostatus at the time of pregnancy may have then reported to clinical care earlier than men. However, many Indian women at risk for HIV may not be seeking testing or may not seek continued clinical care after a positive HIV test because of concerns about confidentiality and fear of negative reactions from husbands, parents, and community.¹⁸

It appears that certain HIV-associated opportunistic infections disproportionately affect either men or women regardless of treatment status, which may reflect underlying biological differences between men and women. During the first year after initiating HAART, men experienced a significantly higher incidence of tuberculosis. In a prior study at YRG CARE, a high incidence of IRS was reported in the male population with a high background rate of tuberculosis.¹³ A study from South Africa found that although incident tuberculosis rates did not differ by gender, incident tuberculosis rates after initiating HAART were associated with a pretreatment CD4 count of < 100 cell/ μ L and advanced immunodeficiency.¹⁹ In this study, men had lower CD4 counts and more advanced disease than women at treatment initiation, which may have led to an increased incidence of tuberculosis and IRS. It is also possible that male occupations could have led to greater tuberculosis exposure.

Studies have shown that women have more severe AEs to

nucleoside therapy than men, including a higher incidence of neuropathy and toxicity-driven regimen alterations, which can lead to increased rates of discontinuation of therapy among women.²⁰ In the current study, men and women changed their first-line regimens at similar rates; however, women reported higher rates of lactic acidosis and nausea than men. Programs that make HAART available to women will need to anticipate having an expanded formulary to provide alternate medications.

Although other studies have noted differences in plasma viral set points between men and women,²¹ no significant difference was seen at enrollment into care and at treatment initiation in this study. Less than a tenth of the cohort had virological monitoring, however, because of the high cost, so inferences about this parameter are not feasible with this dataset. Many patients came late to care, with low CD4 cell counts, and then switched treatment regimens in this study, underscoring the desirability of low-cost virological monitoring in order to more carefully assess the efficacy of generic HAART regimens.

Possible limitations of the present study include the retrospective nature of the analysis and the lack of adequate background information on individuals who did not seek care. Additionally, differences between women and men at baseline were not accounted for in the analysis. However, this study demonstrated that significant physiological, immunological, and clinical differences exist between men and women initiating HAART in a resource-limited setting.

The present study found that when women were able to seek HIV treatment, they had a better immunological status than their male counterparts and continued to do better clinically over the course of the next year. In many parts of the world, women may experience diminished clinical outcomes in comparison to their male counterparts because of socioeconomic disenfranchisement and consequent late entry into HIV care.^{22,23} In light of the expansion of nationalized subsidized generic ART, the fact that most women acquired HIV from their husbands, active partner testing at this center, and increased antenatal screening, Indian women in the current study appear to be seeking care at an earlier course of the disease and do well in the short term. Although Indian women have a different spectrum of AEs and opportunistic infections compared with their male counterparts, women who are able to seek clinical care at an early stage and who are given access to drugs can achieve comparable results with men. Differential use of antiretrovirals for purely social reasons may lead to survival disadvantages for women.³ Based on the current study, programs should aggressively test the spouses of HIV-infected men, and wider antenatal screening programs may help to minimize the devastation of the widening and increasingly feminized AIDS epidemic in resource-limited settings.

Acknowledgments

We are grateful to the research nurses and all the clinical staff at the YRG Centre for AIDS Research and Education, VHS, Chennai, India, for their facilitation of the study.

Disclosure Statement

The authors have no conflicts of interest.

References

1. UNAIDS. UNAIDS/WHO AIDS epidemic update. Available at www.unaids.org/epidemic-update/ Accessed August 9, 2007.
2. Gandhi M, Aweeka F, Greenblatt RM, Blasche TF. Sex differences in pharmacokinetics and pharmacodynamics. *Ann Rev Pharmacol Toxicol*. 2004;44:499–523.
3. Gandhi M, Bacchetti P, Miotti P, Quinn TC, Veronese F, Greenblatt RM. Does patient sex affect human immunodeficiency virus levels? *Clin Infect Dis* 2002;35:313–322.
4. Mocroft A, Gill MJ, Davidson W, Phillips AN. Are there gender differences in starting protease inhibitors, HAART, and disease progression despite equal access to care? *J Acquir Immune Defic Syndr* 2000;24:475–482.
5. Sterling T, Vlahov D, Astemborski J, Hoover DR, Margolick J, Quinn TC. Initial plasma HIV-1 RNA levels and progression to AIDS in women and men. *N Engl J Med* 2001;344:720–725.
6. Moore A, Kirk O, Johnson AM, et al. Virologic, immunologic, and clinical response to highly active antiretroviral therapy: The ender issues revisited. *J Acquir Immune Defic Syndr* 2003;32:452–461.
7. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of human immunodeficiency virus disease in southern India. *Clin Infect Dis* 2003;36:79–85.
8. Kumarasamy N, Solomon S, Chaguturu, SK et al. The changing natural history of HIV disease: Before and after the introduction of generic antiretroviral therapy in southern India. *Clin Infect Dis* 2005;41:1525–1528.
9. Newmann S, Sarin P, Kumarasamy N, et al. Marriage, monogamy and HIV: A profile of HIV-infected women in south India. *Int J STD AIDS* 2000;11:250–253.
10. Rogers M, Gopalakrishnan G, Kumarasamy N, et al. HIV in couples in South India: Implications for prevention. *Int J STD AIDS* 2005;16:442–445.
11. WHO. Scaling up antiretroviral therapy in resource-limited settings: Treatment guidelines for a public health approach—2003 revision. Available at www.who.int/hiv/pub/prev_care/en/arvrevision_2003en.pdf Accessed August 2, 2007.
12. Benson C, Kaplan JE, Masur H, Pau A, Holmes KK. Treating opportunistic infections among HIV-infected adults and adolescents: Recommendations from CDC, the National Institutes of Health, and the HIV Medicine Association/Infectious Diseases Society of America: University of Colorado Health Sciences Center, Centers for Disease Control, National Institutes of Health, University of Washington; 2005. *MMWR Recommendations and Reports*. 2004;53(RR-15): 1–112.
13. Kumarasamy N, Chagututu S, Mayer KH, et al. Incidence of immune reconstitution syndrome in HIV/tuberculosis-coinfected patients after initiation of generic antiretroviral therapy in India. *J Acquir Immune Defic Syndr* 2004;37:1574–1576.
14. Gangakhedkar R, Bentley ME, Divekar AD, et al. Spread of HIV infection in married monogamous women in India. *JAMA* 1997;278:2090–2092.
15. Bharucha K, Sastry J, Shrotri A, et al. Feasibility of voluntary counselling and testing services for HIV among pregnant women presenting in labour in Pune, India. *Int J STD AIDS* 2005;16:553–555.
16. Solomon S, Kouyoumdjian FG, Cecelia AJ, James R, James L, Kumarasamy N. Why are people getting tested? Self-reported reasons for seeking voluntary counseling and testing at a clinic in Chennai, India. *AIDS Behav* 2006;10:415–420.
17. WHO. Summary country profile for HIV/AIDS treatment scale-up: India, July 24, 2007. Available at www.who.int/hiv/HIVCP_IND.pdf
18. Rogers A, Meundi A, Amma A, et al. HIV-related knowledge, attitudes, perceived benefits, and risks of HIV testing among pregnant women in rural southern India. *AIDS Patient Care STDs* 2006;20:803–811.
19. Lawn S, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: Long-term incidence and risk factors in a South African cohort. *AIDS* 2005;19:2109–2116.
20. Currier J, Spino C, Grimes J, et al. Differences between women and men in adverse events and CD4⁺ responses to nucleoside analogue therapy for HIV infection. *J Acquir Immune Defic Syndr* 2000;24:316–324.
21. Farzadegan H, Hoover DR, Astemborski J, et al. Sex differences in HIV-1 viral load and progression to AIDS. *Lancet* 1998;352:1510–1514.
22. Eisenman D, Bogart LM, Bird CE, et al. Differential diffusion of HIV technologies by gender: The case of highly active antiretroviral therapy. *AIDS Patient Care STDs* 2007; 21:390–399.
23. Gardner L, Holmberg SD, Moore J, et al., for the HIV Epidemiology Research Study Group. Use of highly active antiretroviral therapy in HIV-infected women: Impact of HIV specialist care. *J Acquir Immune Defic Syndr* 2002;29:69–75.

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