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Gender Differences in Mortality and CD4 Count Response Among Virally Suppressed HIV-Positive Patients

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Abstract

Background: Treatment outcomes for antiretroviral therapy (ART) patients may vary by gender, but estimates from current evidence may be confounded by disease stage and adherence. We investigated the gender differences in treatment response among HIV-positive patients virally suppressed within 6 months of treatment initiation.

Methods: We analyzed data from 7,354 patients initiating ART between April 2004 and April 2010 at Themba Lethu Clinic, a large urban public sector treatment facility in South Africa. We estimated the relations among gender, mortality, and mean CD4 response in HIV-infected adults virally suppressed within 6 months of treatment initiation and used inverse probability of treatment weights to correct estimates for loss to follow-up.

Results: Male patients had a 20% greater risk of death at both 24 months and 36 months of follow-up compared to females. Older patients and those with a low hemoglobin level or low body mass index (BMI) were at increased risk of mortality throughout follow-up. Men gained fewer CD4 cells after treatment initiation than did women. The mean differences in CD4 count gains made by women and men between baseline and 12, 24, and 36 months were 28.2 cells/mm^3 (95% confidence interval [CI] 22.2–34.3), 60.8 cells/mm^3 (95% CI 71.1-50.5 cells/mm^3), and 83.0 cells/mm^3 (95% CI 97.1-68.8 cells/mm^3), respectively. Additionally, patients with a current detectable viral load (>400 copies/mL) and older patients had a lower mean CD4 increase at the same time points.

Conclusions: In this initially virally suppressed population, women showed consistently better immune response to treatment than did men. Promoting earlier uptake of HIV treatment among men may improve their immunologic outcomes.

Introduction

The widespread use of highly active antiretroviral therapy (HAART) has caused significant reductions in HIV-related mortality worldwide.[1,2] Despite limited resources, HIV-infected individuals receiving antiretroviral therapy (ART) in resource-limited settings, including sub-Saharan Africa, have shown improvements in outcomes comparable to results from industrialized countries in terms of immunologic and virologic response.[3–9] Even among patients who are adherent to treatment and achieve viral suppression, lack of immunologic response to ART has been noted to be an important predictor of subsequent mortality.[10–12] As comprehensive HIV treatment involving ART is still relatively new in some resource-limited settings, however, gender differences in immunologic response to ART among those achieving viral suppression (<400 copies/mL) have not been well described. Differences by gender are critical to understand and address, particularly in a country like South Africa, which has the largest number of HIV-infected adults in the world and where >20% of women aged 20–24 years were estimated to be infected with HIV at the end of 2009.[13]

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Despite the limited information to date, there are reasons to think that men and women may differ with respect to immune recovery even if virally suppressed, as treatment outcomes among those receiving ART (i.e., both suppressed and non-suppressed patients) have shown differences. Although results from the developed world are conflicting,[14–19] results from South Africa[20] and India[21] showed that women had lower mortality and higher CD4 counts after 1 year on ART. It is not clear from these studies, however, how much of this association relates to differences in immunosuppression at ART initiation, differences in immune recovery over time on ART, biologic differences by sex, or simply different patterns of adherence. If women show increased immunologic responses to ART after achieving viral suppression, this could explain the reduced mortality women have shown in South Africa.[20] Additionally, high rates of loss to follow-up in some observational cohorts studied may introduce bias into the results presented.

Therefore, we set out to address the limitations of earlier studies by estimating the relations among gender, mortality, and mean difference in CD4 response at 12, 24, and 36 months on ART in the Themba Lethu Clinic, Johannesburg, South Africa, in a population with good mortality data through matching with the National Vital Registration system and by using inverse probability of censoring weights to correct estimates for loss to follow-up.

Materials and Methods

Cohort description

We conducted a cohort study of patients at the Themba Lethu Clinic. Themba Lethu is one of the largest ART clinics in South Africa, with nearly 32,000 patients enrolled in care since the clinic's inception in April 2004. Over 21,000 of these patients have been initiated on ART. Care was provided by clinic staff during the study period according to the 2004 South African National Department of Health guidelines.[22] Use of data for this analysis was approved by the Human Research Ethics Committee of the University of the Witwatersrand. Approval for analysis of de-identified data was granted by the Institutional Review Board of Boston University.

Study population

Our analysis included nonpregnant, ART-naïve, HIV-positive patients >18 years of age, initiated onto standard public sector first-line ART regimens between April 2004 and April 2010. Pubic sector regimens include stavudine (d4T) or zidovudine (AZT) with lamivudine (3TC) and either efavirenz (EFV) or nevirapine (NVP). Patients with a baseline (within 6 months before ART initiation) CD4 count <350 cells/mm^3 who suppressed their HIV viral load by 6 months on treatment were included in the analysis. Pregnant women were excluded, as they are initiated on different ART regimens and have more variable CD4 counts than the general treated population because of the hemodilution effect of pregnancy.[23]

Study variables

Patient-level data at Themba Lethu are captured in an electronic patient management system (Therapy Edge-HIV^{TM}). The primary exposure was patient gender. Baseline characteristics were stratified by gender and summarized with descriptive statistics. The primary dependent variables were mortality and mean change in CD4 cell count from baseline to 12, 24, and 36 months of treatment. Deaths are ascertained by either hospital notification, families notifying clinic staff, counselors identifying deaths through active tracing, or linkage with the South African National Vital Registration Infrastructure Initiative.[24–26] Loss to follow-up was defined as having not attended a scheduled clinic visit within 4 months. For death, person-time accrued from ART initiation until the earliest of (1) death, (2) loss to follow-up, or (3) close of the dataset (March 31, 2011) was used. Transferred patients were censored at their last visit.

Statistical analysis

Clinical and demographic characteristics of the patients included in the analysis were summarized using simple proportions for categorical variables and medians with interquartile ranges (IQR) for continuous variables. We used a multivariate Cox proportional hazards model to calculate an adjusted association of gender with all-cause mortality. To calculate the association of gender with change in CD4 count from baseline to 12, 24, and 36 months, we used a multivariate linear generalized estimating equation (GEE) model. In both cases, we controlled for potential confounders, including age, time on ART, year of ART initiation, current tuberculosis infection, World Health Organization (WHO) stage, CD4 count, body mass index (BMI), and hemoglobin count.

In both models, we used inverse probability of censoring weights to adjust for selection bias due to loss to follow-up.[27–29] Inverse probability of censoring weights reweight individuals who do not become lost to represent those who become lost and, thus, create a weighted pseudopopulation that represents the overall population had there been no censoring, subject to the exchangeability assumption.[28] Stabilized weights were obtained by fitting two pooled logistic regression models for becoming lost, one controlling for baseline predictors of loss to follow-up (gender along with baseline same as the baseline covariates), and a second controlling for baseline covariates as well as time-updated and time-dependent predictors of becoming lost (current CD4 count, BMI, and hemoglobin). although similarly constructed weights (inverse probability of treatment weights) can be used to adjust for confounding,[27] we did not apply these to this analysis, as treatment in this case is gender, which is time-fixed at baseline, which means that controlling for time-updated covariates in treatment weights may bias our estimates, as these may be affected by gender and not *vice versa.*

To directly address the issue of whether any differences in immunologic response by gender are actually a reflection of differences in patterns of adherences, our primary analysis was performed on those with a suppressed HIV viral load (<400 copies/mL) within the first 6 months after initiating ART. We did this to determine the relationship between gender and mortality and immunologic response among a population of HIV-infected adults who we could reasonably assume were at least initially adherent to treatment—in other words, where the association between gender and the measured outcomes was not likely to be mediated through adherence. We then also performed a mediation analysis where we adjusted all models for updated viral load status (suppressed or unsuppressed) to determine if the association of

gender mediated through viral load (and, by proxy, adherence) differed from those in the main analysis.

Results

Of the 11,692 patients eligible for analysis, 8,119 (69%) had a viral load measurement at 6 months, and 7,354 (91%) of those achieved viral suppression and were included in our analysis. This included 63% ($n=4,621$) women and 37% ($n=2,733$) men. The majority of patients were on d4T/3TC/EFV (90.1%). Patients had a median CD4 count of 93 cells/mm^3 (IQR 36–159), a median age of 36.7 years (IQR 31.6–43.0), and a median follow-up time on ART of 35.4 months (IQR 20.3–54.7) (Table 1). At ART initiation, men were older (median 37.9 vs. 35.8 years) and had more risk factors for poorer treatment outcomes than women. Men sought treatment with a lower median CD4 cell count (81 vs. 100 cells/mm^3) and a lower median BMI (20.4 vs. 22.5 kg/m^2) and were more likely to be classified with a WHO clinical stage III/IV condition (46.3% vs. 40.5%) than women.

Mortality

By the end of the study follow-up, 333 (4.5%) patients had died; 1,382 (18.8%) were lost to follow-up, and 598 (8.1%) had transferred to another treatment facility. A higher proportion of men than women (5.2% vs. 4.1%, $p=0.026$) died during the follow-up period. Similarly, a larger percentage of males were lost than their female counterparts (21.1% vs. 17.4%, $p<0.001$). Although there was no difference in risk of death at 12 months on treatment, adjusted hazard ratios (HR) showed men had a 20% higher risk of death at both 24 months (HR 1.2, 95% confidence interval [CI] 0.9-1.6) and 36 months (HR 1.2, 95% CI 0.9-1.6) of follow-up compared to women (Table 2). Both these estimates, however, overlapped the null. Additionally, older age and anemia were predictive of death at 12, 24, and

Table 1. Baseline Characteristics and Outcomes of ART Patients at Themba Lethu Clinic Stratified by Gender (n=7,354)

	Gender		
Characteristic	*Male* (n=*2,733*)	*Female* (n=*4,621*)	*Total* (n=*7,354*)
Age, years			
18–24.9	49 (1.8%)	274 (5.9%)	323 (4.4%)
25–29.9	252 (9.2%)	747 (16.2%)	999 (13.6%)
30–39.9	1341 (49.1%)	2090 (45.2%)	3431 (46.7%)
40–49.9	780 (28.5%)	1129 (24.4%)	1909 (25.9%)
>50	311 (11.4%)	381 (8.3%)	692 (9.4%)
CD4 at ART Initiation (cells/mm^3)			
0–50	987 (36.1%)	1330 (28.8%)	2317 (31.5%)
51–100	586 (21.4%)	950 (20.6%)	1536 (20.9%)
101–200	887 (32.5%)	1792 (38.8%)	2679 (36.4%)
201–350	228 (8.3%)	480 (10.4%)	708 (9.6%)
Missing	45 (1.7%)	69 (1.4%)	114 (1.6%)
WHO stage at ART initiation			
I/II	1468 (53.7%)	2750 (59.5%)	4218 (57.4%)
III	1057 (38.7%)	1590 (34.4%)	2647 (36.0%)
IV	208 (7.6%)	281 (6.1%)	489 (6.6%)
First-line ART regimen			
d4T/3TC/EFV	2484 (90.9%)	4143 (89.6%)	6627 (90.1%)
d4T/3TC/NVP	156 (5.7%)	363 (7.9%)	519 (7.0%)
AZT/3TC/EFV	87 (3.2%)	102 (2.2%)	189 (2.6%)
AZT/3TC/NVP	6 (0.2%)	13 (0.3%)	19 (0.3%)
CD4 at ART Initiation (cells/mm^3)			
Median (IQR)	81 (29–151)	100 (41–163)	93 (36–159)
Time on ART (months)			
Median (IQR)	35.1 (19.5–53.9)	35.8 (21.0–55.2)	35.4 (20.3–54.7)
Hemoglobin at ART Initiation (μg/dL)			
Median (IQR)	12.5 (10.7–14.0)	11.2 (9.8–12.5)	11.7 (10.1–13.0)
BMI at ART Initiation			
Median (IQR)	20.4 (18.5–22.7)	22.5 (19.7–25.9)	21.6 (19.1–24.7)
Age at ART Initiation			
Median (IQR)	37.9 (33.3–43.9)	35.8 (30.6–42.3)	36.7 (31.6–43.0)
Outcomes			
Death, *n* (%)	143 (5.2)	190 (4.1)	333 (4.5)
Loss to follow-up, *n* (%)	576 (21.1)	806 (17.5)	1382 (18.8)
Transferred, *n* (%)	195 (7.1)	403 (8.7)	598 (8.1)
Alive and in care, *n* (%)	1819 (66.6)	3222 (69.7)	5041 (68.6)

ART, antiretroviral therapy; AZT, zidovudine; BMI, body mass index; d4T, stavudine; EFV, efavirenz; IQR, interquartile range; NVP, nevirapine; 3TC, lamivudine; WHO, World Health Organizations.

Table 2. Crude and Adjusted Hazard Ratios of Mortality (n = 7,020)

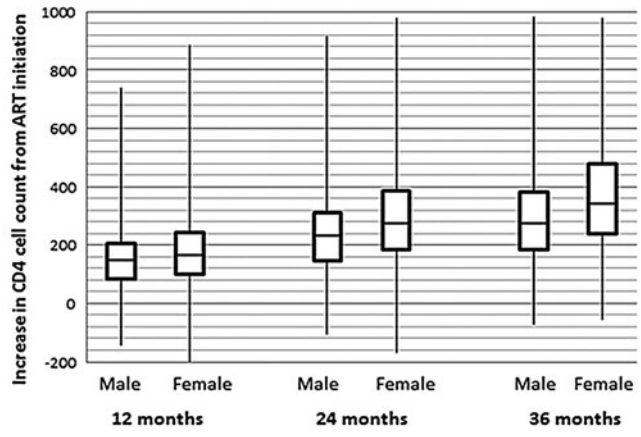
Variable		12 months		24 months		36 months	
		Crude (95% CI)	*Adjusted[a] (95% CI)*	*Crude (95% CI)*	*Adjusted[a] (95% CI)*	*Crude (95% CI)*	*Adjusted[a] (95% CI)*
Gender	Male vs. female	1.0 (0.7–1.5)	1.0 (0.7–1.5)	1.2 (0.9–1.6)	1.2 (0.9–1.6)	1.3 (1.0–1.6)	1.2 (0.9–1.6)
Age	≥40 vs. <40	1.3 (0.9–1.9)	1.4 (1.0–2.0)	1.4 (1.1–1.8)	1.5 (1.1–1.9)	1.3 (1.0–1.7)	1.4 (1.1–1.8)
Baseline CD4 count (cells/mm^3)	100–199 vs. 200–350	0.7 (0.4–1.4)	0.7 (0.4–1.2)	0.8 (0.5–1.3)	0.7 (0.4–1.1)	0.9 (0.5–1.4)	0.8 (0.5–1.3)
	50–99 vs. 200–350	1.1 (0.6–2.0)	0.9 (0.5–1.7)	1.1 (0.7–1.8)	0.9 (0.5–1.5)	1.3 (0.8–2.1)	1.1 (0.6–1.8)
	0–50 vs. 200–350	1.3 (0.7–2.4)	1.1 (0.6–2.0)	1.4 (0.9–2.2)	1.0 (0.6–1.7)	1.6 (1.0–2.5)	1.2 (0.8–2.0)
Baseline hemoglobin (μg/dL)	<10.0 vs. ≥10.0	1.6 (1.1–2.3)	1.5 (1.0–2.3)	1.6 (1.2–2.1)	1.5 (1.1–2.1)	1.6 (1.2–2.1)	1.5 (1.1–2.0)
Baseline BMI (kg/m^2)	<17.5 vs. ≥17.5	1.3 (0.8–2.1)	1.1 (0.7–1.9)	1.4 (1.0–2.1)	1.2 (0.8–1.8)	1.5 (1.0–2.1)	1.2 (0.8–1.7)

[a]Models were also adjusted for time on ART, baseline WHO stage, baseline hemoglobin, baseline BMI, tuberculosis status at ART initiation, and year initiated onto ART.

36months of follow-up. Estimates were also adjusted for time on ART, baseline WHO stage, baseline hemoglobin, baseline BMI, tuberculosis status at ART initiation, and year initiated onto ART.

Difference in CD4 count response

As expected, this population of initially virally suppressed patients showed good immune responses to treatment. Women demonstrated better median CD4 count increases from baseline than men across all time periods after ART initiation (Fig. 1): an increase of 166 cells/mm^3 (IQR 99–245) vs. 139 cells/mm^3 (IQR 82–204) by 12-months, 277 cells/mm^3 (IQR 183–384) vs. 218 cells/mm^3 (IQR 148–309) by 24 months, and 343 cells/mm^3 (IQR 240–481) vs. 272 cells/mm^3 (IQR 184–381) by 36 months on treatment. Estimates from adjusted models also demonstrated disadvantages in immunologic response for men at all time periods, and the differences, although small in the first 12 months on ART, increased with increasing time on treatment (Table 3). The mean differences in CD4 count gains made by women and men between baseline and 12, 24, and 36 months were 28.2 cells/mm^3 (95% CI 22.2–34.3), 60.8 cells/mm^3 (95% CI 71.1-50.5 cells/mm^3), and 83.0 cells/mm^3 (95% CI 97.1-68.8 cells/mm^3), respectively. Additionally, patients with lower CD4 cell count at ART initiation and more advanced age (>40 vs. <40 years) demonstrated a poorer CD4 cell count increase from baseline to 12, 24, and 36 months of follow-up.



	Median CD4 count over time on ART				Increase in CD4 from baseline on ART		
	0 months	12 months	24 months	36 months	By 12 months	By 24 months	By 36 months
Female	100	266	377	443	166	277	343
Male	81	220	299	353	139	218	272
Crude difference in increase by gender					27	59	71

FIG. 1. Median increase in CD4 cell count at 12, 24, and 36 months of antiretroviral therapy (ART), stratified by gender ($n = 7,354$).

Our results demonstrate similar findings to those from previous studies despite accounting for selection bias due to loss to follow-up. This, however, could be because loss to follow-up is, in fact, a mixture of various outcomes, including death,[26] so the usefulness of CD4 count in predicting loss to follow-up may be limited. In a sensitivity analysis, we included a second set of weights to adjust for death. These weights were constructed similarly to the censoring weights and made no qualitative difference to our results.

Mediation analysis

We performed mediation analyses estimating the relationships among gender and mortality and increase in CD4 cell count mediated through adherence by adjusting models for current HIV viral load status (suppressed to <400 copies/mL or not). The risk of death for men compared to women was unchanged at 12 months on treatment (HR 1.0, 95% CI 0.9-1.6), and men again had a 20% higher risk of death at both 24 (HR 1.2, 95% CI 0.9-1.6) and 36 months (HR 1.2, 95% CI 1.0-1.6) of follow-up compared to women. The estimates of difference in CD4 count increase also showed very similar results to the primary analysis: men had disadvantages in immunologic response for all time periods, and the differences again increased with increasing time on treatment. The difference in CD4 count gains made by women compared to men between baseline and 12 months was 28.2 cells/mm^3 (95% CI 22.0-34.3) greater for women. By 24 months, the difference was 60.8 cells/mm^3 (95% CI 71.1-50.5), and by 36 months, this had increased to 83.0 cells/mm^3 (95% CI 97.1-68.8) favoring women.

We performed further analyses restricted to those with suppressed viral loads at each time point considered. The proportion missing viral load data was similar at the time

TABLE 3. CRUDE AND ADJUSTED DIFFERENCE IN MEAN CD4 COUNT AT 12, 24, AND 36 MONTHS OF FOLLOW-UP FROM BASELINE (N = 7,020)

		12 months		24 months		36 months	
Variable		*Crude (95% CI)*	*Adjusted*[a] *(95% CI)*	*Crude (95% CI)*	*Adjusted*[a] *(95% CI)*	*Crude (95% CI)*	*Adjusted*[a] *(95% CI)*
Gender	Female vs. male	29.5 (23.2–35.8)	28.4 (22.2–34.3)	56.2 (46.2–66.2)	60.5 (50.2–70.8)	76.2 (62.2–90.2)	83.2 (69.0–97.4)
Baseline CD4 count (cells/mm^3)	100–199 vs. 200–350	13.3 (1.2–25.4)	8.7 (−3.5–20.9)	13.5 (−5.8–32.8)	11.4 (−7.8–30.5)	26.5 (−2.2–55.2)	25.0 (−2.3–52.4)
	50–99 vs. 200–350	19.2 (6.7–31.7)	12.5 (−0.1–25.2)	26.9 (6.2–47.5)	23.6 (2.9–44.2)	53.4 (22.4–84.4)	49.1 (19.3–78.8)
	0–50 vs. 200–350	29.2 (17.4–40.9)	20.7 (8.6–32.9)	57.0 (37.8–76.1)	53.4 (34.0–72.8)	89.6 (60.7–118.6)	88.2 (60.0–116.5)
Age	< 40 vs. ≥ 40	30.3 (24.0–36.6)	25.5 (19.3–31.7)	40.4 (29.8–50.9)	32.9 (22.4–43.4)	41.6 (27.0–56.3)	31.9 (17.4–46.3)

[a]Models were also adjusted for time on ART, baseline WHO stage, baseline hemoglobin, baseline BMI, tuberculosis status at ART initiation, and year initiated onto ART.

points considered (18% at 12 months, 17% at 24 months, and 17% at 36 months), and the proportion missing was similar for women and men (17% vs. 18% at 12 months, 18% vs. 17% at 24 months, and 16% vs. 19% at 36 months). Results were almost identical to the primary analysis for mortality. The estimates of difference in CD4 count increase still demonstrated disadvantages for men for all time periods, although the differences were somewhat smaller than those in the primary analysis. The difference in CD4 count gains made by women compared to men was 23.3 cells/mm^3 (95% CI 18.5-28.2) greater for women between baseline and 12 months, 35.5 cells/mm^3 (95% CI 30.0-41.1) by 24 months, and 44.5 cells/mm^3 (95% CI 35.5-53.9) by 36 months, favoring women.

Discussion

In this analysis of adults initiating treatment at a public sector clinic in Johannesburg, South Africa, we demonstrate gender differences in immunologic response to ART. Controlling for baseline clinical factors (WHO stage and CD4 count) and age at ART initiation, we showed that women demonstrated a small but consistently higher increase in CD4 cell count over 36 months of follow-up than men. Our results are in agreement with previous studies of treatment outcomes in the region, which have shown greater CD4 count increases among women in addition to possible advantages for women in terms of virologic outcomes.[5,18,30,31]

Gender disparate outcomes are of particular concern in South Africa, which has the largest number of HIV-infected adults in the world and an estimated 20% of all those receiving ART globally.[13] Estimates of gender differences in rates of HIV progression and virologic and immunologic responses to ART have varied.[32,33] Early studies suggested that clinical disease progression was more rapid in women than men.[34–36] These differences were attributed to women being less likely to initiate ART[17] or receive treatment for opportunistic infections, more likely to experience violence and discrimination, gynecologic morbidity,[37] and pregnancy,[38–40] and also more likely to be anemic and younger at the time of ART initiation.[41] Conversely, more recent studies have shown that women have a lower risk of morbidity and mortality[42] and better virologic and immunologic outcomes than men.[5,18,30,43]

Although the actual differences in immunologic response to ART in our study were relatively small early after initiating treatment, these differences tended to increase with increasing time on treatment. This result alone may have important public health implications because in sharp contrast to most European and North American cohorts, proportionally more women than men receive ART in Southern African cohorts.[41,44] In our own cohort, for example, >60% of those receiving ART were women. Thus, even modest differences in absolute risk may have profound implications for a public health approach to the administration of mass ART in South and sub-Saharan Africa.

Previous studies have shown that baseline CD4 cell count strongly predicts immunologic recovery.[12] In our study, men started treatment at lower median CD4 counts, which could account for part of the persistent difference in CD4 gain shown over time. We adjusted for baseline CD4 cell count in all models in an attempt to account for these differences. However, if disproportionately more men than women failed treatment over time, this may further explain any difference in

immunologic response. Previous studies that have shown gender differences in clinical and immunologic outcomes have postulated that that is owing to delayed presentation and access to HIV care and also poor adherence once on treatment, and women in this study presented at an earlier disease stage than men. Findings were similar in both sub-Saharan Africa[5,41] and the United States,[45] where women had higher baseline CD4 counts and were less likely to have an AIDS diagnosis at the time of starting ART. Studies from other African countries suggest that women may seek medical help earlier than men.[44,46] If men seek care with more advanced disease and with lower CD4 counts, they are likely to suffer poorer outcomes, even after ART initiation.[3,12] Financial constraints have been cited as obstacles to accessing and remaining in care[7–9,12,47,48]; if this is the case, however, we would expect to see fewer women accessing care, as they have traditionally been overrepresented among the poorest groups in society. In fact, Braitstein et al.[41] showed that women in resource limited settings were equally or more likely to access HIV care and initiate ART than men. Somewhat paradoxically, employment may present more difficulties than financial constraints for those attempting to access treatment. As more men (50.5%) were employed than women (40.1%) in this cohort, problems getting time away from work for regular clinic visits or loss of income due to days of work missed may impact men more than women in a setting where clinic visits often involve a significant part of the day spent in queues.

We also considered the effect of gender on mortality and found no difference at 12 months on treatment, but point estimates suggested an increased hazard of death for men at 24 and 36 months on treatment; however, neither of these estimates achieved statistical significance. This may be because of the low event rate at these time points, and longer follow-up may be required to determine if this represents a true effect. Rates of ART adherence have been shown to differ by gender.[49,50] It is, therefore, reasonable to suspect that ART adherence may mediate the relationship between gender and ART outcomes. Our analysis attempted to control for adherence by restricting the sample to those who achieved virologic suppression. Although it has been shown that adherence and virologic suppression are closely associated,[51] there may be a more subtle level of adherence that is not detected by a dichotomous virologic proxy variable. As we do not collect data directly on patient adherence it is possible that residual confounding is present in the analysis. Despite this, results from our mediation analysis were almost identical to those in the primary analysis. This suggests that different patterns of adherence do not fully explain the differences in CD4 gain by gender and that other explanations should be considered.

Biologic differences between the genders, such as the influence of sex hormones on immunity,[52] have been considered as explanations, but recent work among female children demonstrating lower viral loads and higher CD4 counts[53] makes this an unlikely explanation of all the effects seen. Differences in the normal range of CD4 counts between men and women are also possible explanations for differences in the rate of CD4 count reconstitution demonstrated in this and other work. Previous research has shown that women have higher CD4 counts than their male counterparts among HIV-uninfected individuals as well as for up to 5 years after HIV infection[54,55] but that these differences have little to no impact on rate of disease progression[18] in the absence of ART. It is, thus, plausible that the advantages for women in terms of immunologic response are related to the fact that women have a higher normal range to return to after effective treatment is implemented.

Our findings should be considered in light of the limitations of this study. As this is an observational study, we could not fully rule out confounding bias due to systematic differences between the men and women in our study in terms of health-seeking behavior (suggested by the greater proportion of women accessing treatment and the earlier stage at which women present) or other factors. However, we controlled for important predictors of our main outcome, minimizing the potential bias of our main results. Moreover, as gender cannot be randomized, carefully conducted observational studies are the only way to isolate gender-specific effects.

As with any study, results can be significantly biased by high rates of loss to follow-up. This is of particular concern if those who are lost to follow-up are significantly different from those who remain in the study in terms of the exposure or outcome of interest. The rates of loss to follow-up were 4-fold higher among men than women in this cohort, and, thus, the group of men who remained in care were likely to be at less risk of poor treatment outcomes and death than the women who remained in care. We used inverse probability of censoring weights to correct for this effect; but if correction was incomplete, residual bias from differential loss to follow-up may remain. A related issue is that of missing data, of which loss to follow-up is a special case. Here, we were missing viral loads throughout follow-up period. If those viral loads were associated with the true value of the missing viral loads (e.g., if unsuppressed viral loads were more likely to be missing than suppressed viral loads), analysis of the effect of gender on CD4 count or mortality might be biased. Sensitivity analysis among only those with suppressed viral load, however, suggests that any such effect is likely to be small.

Conclusions

Despite the limitations, our results are valuable in understanding the role of gender in response to ART in a resource-limited setting. We used several methodologic techniques in a large cohort of HIV-infected individuals to add to the debate about gender effects. We account for differences in adherence by restricting analysis to initially virally suppressed individuals and corrected for bias as a result of differing rates of loss to follow-up, a problem that can plague cohort analyses. Currently, men are accessing this treatment program with lower CD4 counts and at a later stage in disease progression compared to women. To improve this situation, it is important that counseling and testing programs target men in their publicity campaigns. The establishment of male-friendly clinic practices may facilitate earlier counseling and testing as well as access to treatment among men. This could include after-hours access, weekend clinics, workplace facilities for HIV counseling and testing, and alternative locations for obtaining treatment, such as post office medication collection points. Consideration of interventions such as these may begin to address gender differences due to late presentation. Once access to care is equal, the true biologic differences between genders may become clearer.

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Disclosure Statement

The authors declare no other conflicts of interest.

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