Early Retention in Care Neither Mediates Nor Modifies the Effect of Sex and Sexual Mode of HIV Acquisition on HIV Survival in the Americas

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Abstract

Early retention in care, sex, and sexual mode of HIV acquisition has been associated with mortality risk among persons living with HIV (PLWH). We assessed whether early retention in care mediates or modifies the association between mortality and sex and sexual mode of HIV acquisition among PLWH on antiretroviral therapy (ART) in the Americas. ART-naïve, adult PLWH (≥18 years) enrolling at Caribbean, Central and South America network for HIV epidemiology (CCASAnet) and Vanderbilt Comprehensive Care Clinic sites 2000–2015, starting ART, and with ≥1 visit after ART-start were included. Early retention in care was defined as ≥2 HIV care visits/labs ≥90 days apart in the first year of ART. Cox models assessed the association between early retention in care, sex, and sexual mode of HIV acquisition [i.e., women, heterosexual men and men who have sex with men (MSM)], and mortality. Associations were estimated separately by site and pooled. Among 11,721 included PLWH (median follow-up, 4.3 years; interquartile range, 2.0–7.6), 647 died (rate = 10.9/1000 person-years) and 1985 were lost to follow-up (rate = 33.6/1000 person-years). After adjustment for confounders, early retention in care was associated with lower mortality during subsequent years (pooled hazard ratio = 0.47; 95% confidence interval = 0.39–0.57). MSM had lower and heterosexual men had comparable mortality risk to women; risks were similar when adjusting for early retention in care. Additionally, no evidence of an interaction between early retention in care and sex and sexual mode of HIV acquisition on mortality was observed ($p > 0.05$). Early retention in care substantially reduced mortality but does not mediate or modify the association between sex and sexual mode of HIV acquisition and mortality in our population.

Keywords: retention in care, mortality, sex disparities, HIV, Americas

Introduction

STUDIES HAVE EXPLORED sex disparities in mortality in a multitude of populations living with HIV, with the magnitude of the mortality risk varying from study to study. Two meta-analyses addressed this topic, one including studies from varied income settings¹ and another focusing on low/middle-

income countries.² Both showed an overall increased risk of death for men compared to women. This increased risk for men has also been observed among individuals initiating antiretroviral therapy (ART) and achieving suppression within 6 months of treatment initiation,³ and it has been linked to more advanced HIV disease at presentation to care^{4,5} and increased prevalence of behavioral risk factors and co-morbidities.⁶

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An additional factor that may explain these sex disparities is retention in care. As the HIV cascade of care suggests, after HIV diagnosis and ART initiation, retention in care is needed to guarantee patient care and treatment success.⁷ Studies evaluating factors associated with retention have also shown it to be an important predictor of death.⁸ In a study of over 60,000 individuals from North America, women were less likely to have incomplete retention than men.⁹ However, in a more recent analysis of the same cohort, these differences were attenuated when accounting for covariates and probabilities of being lost to follow-up.¹⁰

Accordingly, it is possible that the observed relationship between groups defined by sex and sexual mode of HIV acquisition [i.e., women, heterosexual men and men who have sex with men (MSM)] and mortality might be mediated by retention in care. Said differently, these groups may be retained in care differently after enrollment, which may explain observed disparities in mortality. Alternatively, sex and sexual mode of HIV acquisition and retention in care might modify the effect of each other on mortality, such that their effects differ across strata of the other. In this study, we assessed whether early retention in care mediates or modifies the effect of sex and sexual mode of HIV acquisition on mortality among HIV-positive individuals using ART in the Americas. We restricted analysis to ART initiators to ensure equivalent access to care among study participants.

Methods

Study population

We combined data from sites in North, Central, and South America in a collaboration between the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) and the Vanderbilt Comprehensive Care Clinic (VCCC) cohorts. CCASAnet and VCCC cohorts have been previously described.^{11,12} Briefly, CCASAnet sites included in the present analysis are two sites in Argentina (Hospital Fernández and Centro Médico Huésped), one in Brazil (Instituto de Nacional de Infectologia Evandro Chagas, Fiocruz), one in Chile (Fundación Arriarán), two in Honduras (Instituto Hondureño de Seguridad Social and Hospital Escuela Universitario), one in Mexico (El Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán), and one in Peru (Instituto de Medicina Tropical Alexander von Humboldt). The two sites in Argentina and Honduras, respectively, were grouped together. The VCCC is a clinic in Nashville, Tennessee, providing primary and specialty care to HIV-positive individuals throughout the middle-Tennessee region.

Adult persons living with HIV (PLWH, aged ≥ 18 years at cohort enrollment) who enrolled after 2000, initiated their first ART regimen after enrollment or up to 30 days before enrollment, and with ≥ 1 visit after ART-start were included in the study. Individuals were categorized according to self-reported sex and sexual mode of HIV acquisition as women, heterosexual men, and MSM; and according to retention in care in the first year of ART. Early retention in care was defined as having ≥ 2 HIV clinic visits or CD4 or HIV-1 RNA viral load (VL) measurements ≥ 90 days apart during the first year after ART initiation. Individuals reporting nonsexual HIV transmission risk (i.e., perinatal, transfusion, occupational) were excluded; we controlled for injection drug use in the analysis. Male individuals with no information on sexual

HIV transmission risk were also excluded. Finally, only individuals known to be alive and not lost to follow-up 1 year after ART initiation (i.e., who had a clinical visit or CD4/VL measurement ≥ 1 year after ART initiation) were included in the primary analysis, so that all study participants would be uniformly eligible for early retention in care. In a secondary analysis, we assumed those with no visits and no evidence of death following the first year after ART initiation ($N = 1525$) were in fact not retained in the first year, that is, those lost to follow-up were classified as “not retained” but included in the study population while those who died during the first year ($N = 1975$) were still excluded from the analysis.

Outcome and follow-up

The primary outcome was mortality beyond the first year of ART initiation. Follow-up started 1 year after ART initiation date and ended at the date of death, last clinical/CD4/VL date or study closure, whichever occurred first. Study closure date was defined for each site individually, based on the 95th percentile of the most recent visit dates. Loss to follow-up (LTFU) was defined retrospectively as not having a clinical visit/CD4/VL in the last year before study closure date.¹³

Covariates and other risk factors

Additional covariates included in the analysis were as follows: age at ART initiation, year of ART initiation, injection drug use (yes/no), and pre-ART information including CD4 nadir, $\log_{10}$ VL, and AIDS-defining event.

Statistical analysis

Mortality and LTFU rates were calculated per 1000 person-years (PY). Adjusted Cox regression models assessed the effects of sex and sexual mode of HIV acquisition and early retention in care on mortality risk after 1 year of ART initiation for each site separately and results were pooled using a Mantel–Haenszel fixed effects model.

Multiple analyses were performed to evaluate mediation or effect modification of the association between sex and sexual mode of HIV acquisition and mortality risk by early retention. First, models for mortality were fit and adjusted hazard ratios (aHR) were pooled for sex and sexual mode of HIV acquisition, with and without adjustment for early retention in care, and point estimates were compared. Second, the interaction between early retention in care and sex and sexual mode of HIV acquisition on mortality after 1 year of ART initiation was evaluated using a likelihood ratio test from the Cox regression model (stratified by site). Third, separate models were constructed based on early retention in care status (retained/not retained), and the effect of sex and sexual mode of HIV acquisition on mortality after 1 year of ART initiation was tested using adjusted Cox regression models (stratified by site). Additional analyses included (i) Poisson regression models with robust standard errors (adjusted for site) to assess whether sex and sexual mode of HIV acquisition was associated with early retention. (ii) Adjusted Cox regression models for mortality at any time after ART initiation (including during the first year) by site; these models did not include early retention and the aHR for sex/sexual mode of HIV acquisition categories were pooled using a Mantel–Haenszel fixed effects model. The proportion of true

heterogeneity to total variance was calculated by the Higgins I^2 statistic.¹⁴ All models were adjusted for the covariates listed above. Age at enrollment and CD4 were included in the models as continuous variables using restricted cubic splines to relax linearity assumptions. Multiple imputation was performed for missing values of CD4 and $\log_{10}$ VL. Analyses were performed using R version 3.2.2, libraries “Survival,” “rms,” “MI.”

Results

A total of 11,721 PLWH were included in the analysis (Fig. 1), median follow-up time was 4.3 years (interquartile range, 2.0–7.6 years; Table 1), of which 647 subsequently died and 1985 were lost to follow-up, yielding, respectively, mortality and lost to follow-up rates of 10.9/1000 PY [95% confidence interval (CI) 10.1–11.8/1000 PY] and 33.6/1000 PY (95% CI 32.1–35.1/1000 PY) beyond the first year after ART initiation. Characteristics of the individuals included in the analysis (by site) are shown in Table 1.

Compared to women, MSM had lower mortality after 1 year of ART initiation (pooled aHR=0.75, 95% CI 0.61–0.92), while mortality risk for heterosexual men was not significantly different (pooled aHR=0.92, 95% CI 0.74–1.13). Across sites, the effect of sex/sexual mode of HIV acquisition differed in its direction and magnitude (Table 2). In contrast, retention in care during the first year after ART initiation was associated with a significant and substantial decreased risk of mortality 1 year after ART initiation across all sites; the pooled aHR was 0.47 (95% CI 0.39–0.57, Fig. 2). This point estimate and 95% CI correspond with e -values of 3.7 and 2.9, respectively, meaning that the strength of association on the risk ratio scale that an unmeasured confounder would need to have with both early retention and mortality, conditional on the measured covariates, to explain away the observed association would need to be at least 3.7 (for the

point estimate to be 1) or 2.9 (for the upper limit of the 95% CI to include 1)¹⁵; these are substantial, and suggest that early retention does in fact decrease the risk of mortality.

When including both sex/sexual mode of HIV acquisition and early retention in the adjusted Cox models, point estimates for the effect of sex/sexual mode of HIV acquisition on mortality remained nearly identical (Table 2). Compared to women, MSM had lower mortality after 1 year of ART initiation (pooled aHR=0.76, 95% CI 0.62–0.93), while mortality risk for heterosexual men was not significantly different (pooled aHR=0.91, 95% CI 0.74–1.12). Similarly, the protective effect of early retention in care also remained unchanged (Table 2 and Fig. 2). The greatest effect was observed in Mexico (aHR=0.35, 95% CI 0.13–0.93) and the smallest in the United States (aHR=0.63, 95% CI 0.38–1.03). These results suggest that early retention is not a mediator of the effect of sex/sexual mode of HIV acquisition on mortality.

Moreover, no interaction was found between sex/sexual mode of HIV acquisition and early retention (p -values for interaction term in models stratified by site were all >0.05). When restricting the analysis to those not retained ($N=2512$), sex/sexual mode of HIV acquisition was not significantly associated with mortality: compared to women, heterosexual men had a similar risk of death (aHR=1.07, 95% CI 0.75–1.52) and MSM had a nonsignificant lower risk of death (aHR=0.72, 95% CI 0.49–1.05). Restricting the analysis to those who were retained ($N=9209$), compared to women, the mortality after 1 year of ART initiation was similar to that reported above: nonsignificant for heterosexual men (aHR=0.91, 95% CI 0.74–1.12) and lower for MSM (aHR=0.76, 95% CI 0.62–0.93). These results again suggest that early retention is not an effect modifier of the association between sex/sexual mode of HIV acquisition and mortality.

Results from our secondary analysis assuming those lost to follow-up were in fact not retained were substantively similar to results from the primary analysis. Among 13,246 included

FIG. 1. Flow chart of study participants.

TABLE 1. CHARACTERISTICS OF THE STUDY POPULATION BY SITE

	ARG, N = 1896	BRA, N = 2539	CHL, N = 1567	HND, N = 595	MEX, N = 1001	PER, N = 2512	US, N = 1611	Total, N = 11721
FU in years, median (IQR)	4.4 (1.9–8.3)	4.2 (1.9–7)	4.9 (2.4–9.2)	5.2 (2.4–7.9)	4.6 (1.9–7.3)	3.8 (1.7–6.8)	4.5 (2.5–7.8)	4.3 (2–7.6)
Age at ART initiation in years								
Median (IQR)	36 (30.1–43.5)	35.5 (29–43.2)	35.4 (29.6–42.5)	35.3 (29.7–43)	34.2 (28.5–41.3)	33.8 (27.8–41.7)	37.4 (28.8–44.7)	35.3 (29–42.9)
<30	464 (24.5)	727 (28.6)	416 (26.5)	155 (26.1)	315 (31.5)	853 (34)	455 (28.2)	3385 (28.9)
30–39	763 (40.2)	912 (35.9)	637 (40.7)	249 (41.8)	395 (39.5)	919 (36.6)	491 (30.5)	4366 (37.2)
40–49	438 (23.1)	643 (25.3)	334 (21.3)	136 (22.9)	205 (20.5)	490 (19.5)	482 (29.9)	2728 (23.3)
50+	231 (12.2)	257 (10.1)	180 (11.5)	55 (9.2)	86 (8.6)	250 (10)	183 (11.4)	1242 (10.6)
Sex and sexual mode of HIV acquisition								
Women	719 (37.9)	787 (31)	159 (10.1)	364 (61.2)	108 (10.8)	729 (29)	411 (25.5)	3277 (28)
Heterosexual men	441 (23.3)	668 (26.3)	205 (13.1)	168 (28.2)	173 (17.3)	886 (35.3)	259 (16.1)	2800 (23.9)
MSM	736 (38.8)	1084 (42.7)	1203 (76.8)	63 (10.6)	720 (71.9)	897 (35.7)	941 (58.4)	5644 (48.2)
IDU								
No	1880 (99.2)	2535 (99.8)	1567 (100)	594 (99.8)	997 (99.6)	2512 (100)	1579 (98)	11664 (99.5)
Yes	16 (0.8)	4 (0.2)	0 (0)	1 (0.2)	4 (0.4)	0 (0)	32 (2)	57 (0.5)
Nadir CD4 (cells/mm ³)								
Median (IQR)	201 (85.5–292.5)	223 (89–326)	186 (74–274)	125 (65–200)	144 (47–262.5)	119 (47–237)	216 (90–334)	179 (66–286)
<51	284 (15)	393 (15.5)	259 (16.5)	95 (16)	246 (24.6)	644 (25.6)	288 (17.9)	2209 (18.8)
51–200	567 (29.9)	665 (26.2)	472 (30.1)	309 (51.9)	342 (34.2)	963 (38.3)	434 (26.9)	3752 (32)
201–350	569 (30)	815 (32.1)	512 (32.7)	107 (18)	236 (23.6)	566 (22.5)	507 (31.5)	3312 (28.3)
351+	283 (14.9)	479 (18.9)	128 (8.2)	22 (3.7)	115 (11.5)	180 (7.2)	348 (21.6)	1555 (13.3)
Missing	193 (10.2)	187 (7.4)	196 (12.5)	62 (10.4)	62 (6.2)	159 (6.3)	34 (2.1)	893 (7.6)
HIV RNA log ₁₀ (copies/mL) pre-ART								
Median (IQR)	4.8 (4.2–5.3)	4.9 (4.4–5.5)	4.9 (4.4–5.4)	5 (4.5–5.1)	5 (4.8–5.3)	5.2 (4.7–5.5)	4.8 (4.2–5.3)	4.9 (4.4–5.4)
Missing	420 (22.2)	384 (15.1)	155 (9.9)	476 (80)	78 (7.8)	568 (22.6)	52 (3.2)	2133 (18.2)
ADE pre-ART								
No	1416 (74.7)	1675 (66)	1039 (66.3)	248 (41.7)	439 (43.9)	1571 (62.5)	1354 (84)	7743 (66.1)
Yes	480 (25.3)	864 (34)	528 (33.7)	347 (58.3)	562 (56.1)	941 (37.5)	257 (16)	3979 (33.9)
Early retention								
No	633 (33.4)	348 (13.7)	398 (25.4)	362 (60.8)	52 (5.2)	569 (22.7)	150 (9.3)	2512 (21.4)
Yes	1263 (66.6)	2191 (86.3)	1169 (74.6)	233 (39.2)	949 (94.8)	1943 (77.3)	1461 (90.7)	9209 (78.6)
Deaths during FU	64 (3.4)	169 (6.7)	82 (5.2)	43 (7.2)	36 (3.6)	96 (3.8)	157 (9.7)	647 (5.5)
LTFU	671 (35.4)	152 (6)	193 (12.3)	229 (38.5)	116 (11.6)	198 (7.9)	426 (26.4)	1985 (16.9)

Values are represented in median (IQR) and *n* (%).

ADE, AIDS-defining event; ARG, Argentina; ART, antiretroviral therapy; BRA, Brazil; CHL, Chile; FU, follow-up; HND, Honduras; IDU, injection drug use; IQR, interquartile range; LTFU, loss to follow-up; MEX, Mexico; MSM, men who have sex with men; PER, Peru; US, United States.

TABLE 2. SEX AND SEXUAL MODE OF HIV ACQUISITION EFFECT ON MORTALITY BEYOND THE FIRST YEAR AFTER ANTIRETROVIRAL THERAPY (ART) INITIATION BY SITE AND POOLED ACROSS SITES (ADJUSTED HAZARD RATIOS AND MANTEL-HAENSZEL FIXED EFFECT)

	ARG	BRA	CHL	HND	MXC	PER	US	Pooled effects	I ² , %
N	1896	2539	1567	595	1001	2512	1611		
Deaths	64	169	82	43	36	96	157		
Models with sex/sexual mode of HIV acquisition ^a									
Sex/sexual mode of HIV acquisition									
Women	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Heterosexual	0.91 (0.49–1.70)	1.11 (0.77–1.61)	0.89 (0.43–1.84)	1.26 (0.59–2.70)	1.75 (0.56–5.43)	0.61 (0.38–1.01)	0.77 (0.48–1.23)	0.92 (0.74–1.13)	0.0
MSM	0.69 (0.38–1.22)	0.84 (0.57–1.24)	0.52 (0.27–0.99)	2.08 (0.79–5.48)	1.07 (0.35–3.30)	0.65 (0.39–1.07)	0.71 (0.48–1.03)	0.75 (0.61–0.92)	10.3
Models with sex/sexual mode of HIV acquisition and early retention ^a									
Sex/sexual mode of HIV acquisition									
Women	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Heterosexual	0.90 (0.48–1.67)	1.09 (0.75–1.58)	0.96 (0.46–2.00)	1.23 (0.57–2.63)	1.58 (0.50–4.94)	0.63 (0.39–1.03)	0.77 (0.48–1.23)	0.91 (0.74–1.12)	0.0
MSM	0.69 (0.38–1.25)	0.84 (0.57–1.24)	0.58 (0.30–1.10)	2.52 (0.86–7.39)	1.03 (0.34–3.14)	0.65 (0.40–1.08)	0.72 (0.49–1.05)	0.76 (0.62–0.93)	8.4
Retention	0.39 (0.23–0.64)	0.44 (0.31–0.64)	0.46 (0.29–0.72)	0.43 (0.19–0.98)	0.35 (0.13–0.93)	0.53 (0.34–0.82)	0.63 (0.38–1.03)	0.47 (0.39–0.57)	0.0

Bold indicate statistically significant results.

^aAdjusted for: Age (splines, 3DF); nadir CD4 pre-ART (splines, 3DF); AIDS-defining event pre-ART; pre-ART VL log₁₀; ART start year.

ART, antiretroviral therapy; I², Higgins I² statistic measuring the proportion of true heterogeneity to total variance; MSM, men who have sex with men; VL, viral load.

FIG. 2. Early retention in care effect on mortality in subsequent years by site and pooled across sites (hazard ratios and Mantel-Haenszel fixed effect).

individuals, MSMs mortality risk was lower (pooled aHR = 0.76, 95% CI 0.62–0.93) and heterosexual men had a similar mortality risk (pooled aHR = 0.91, 95% CI 0.74–1.13) compared to women; compared to those not retained, early retention in care led to a much lower mortality risk (pooled aHR = 0.47, 95% CI 0.39–0.57).

An additional analysis showed sex and sexual mode of HIV acquisition was associated with retention in the unadjusted but not in the adjusted analysis, again suggesting a lack of mediation (Table 3). Table 4 shows the estimated aHRs for mortality at any time after ART initiation (including during the first year). Compared to women, MSM had a lower mortality risk (pooled aHR = 0.77, 95% CI 0.65–0.90), while heterosexual men had a similar mortality risk (pooled aHR = 0.99, 95% CI 0.84–1.16).

Discussion

We sought to evaluate whether early retention in care mediates or modifies the association between sex and sexual mode of HIV acquisition and mortality risk among PLWH on ART in the Americas. Our hypotheses were that early retention might explain the observed sex and sexual mode of HIV acquisition disparities in mortality or that both early retention and sex and sexual mode of HIV acquisition might modify the effect of each other such that the effect of sex and sexual mode of HIV acquisition on mortality would differ if the individual was retained in care or not. Our results do not support either of these hypotheses.

Prior research suggested that men were at higher risk of death and the plausible explanations were more advanced HIV disease at presentation to care and increased prevalence of risk factors for mortality and of comorbidities.^{2,6} Indeed, in prior research from a cohort in Brazil, we showed that adjustment for correlates of advanced HIV disease did mitigate but not nullify heterosexual men's increased mortality risk,⁵ and prior analysis from the CCASAnet cohort collaboration found sex differences in mortality that became nonsignificant after adjustment for confounders.¹⁶ In searching for an explanation for differences in mortality rates by sex/sexual mode of HIV acquisition, retention in care appeared to be a plausible mechanism. Repeated analysis had found that retention was a strong predictor of mortality.⁸ Moreover, again, in one of the cohorts included in this analysis retention was found to be the strongest predictor of mortality,¹⁷ and, in the present analysis, sex and sexual mode of HIV acquisition was associated with retention in unadjusted analysis (Table 3).

TABLE 3. STUDY POPULATION STRATIFIED BY EARLY RETENTION AND PREDICTORS OF EARLY RETENTION, POISSON MODIFIED REGRESSION MODEL WITH RETENTION = YES AS THE OUTCOME

	Retained, N = 9209	Not retained, N = 2512	Total, N = 11721	cRR (95% CI)	aRR (95% CI) ^a
Age ^b at ART initiation in years, median (IQR)	35.7 (29.2–43.4)	34 (28.4–41.6)	35.3 (29–42.9)	1.00 (0.95–1.05)	1.04 (0.99–1.09)
Sex and sexual mode of HIV acquisition, n (%)					
Women	2429 (26.4)	848 (33.8)	3277 (28)	Ref.	Ref.
Heterosexual men	2169 (23.6)	631 (25.1)	2800 (23.9)	1.05 (1.02–1.08)	0.99 (0.96–1.01)
MSM	4611 (50.1)	1033 (41.1)	5644 (48.2)	1.10 (1.08–1.13)	1.02 (0.99–1.04)
IDU, n (%)					
No	9168 (99.6)	2496 (99.4)	11664 (99.5)	Ref.	Ref.
Yes	41 (0.4)	16 (0.6)	57 (0.5)	0.92 (0.78–1.08)	0.88 (0.75–1.03)
Nadir CD4 ^b (cells/mm ³), median (IQR)	177 (64–283)	187 (78–294)	179 (66–286)	0.98 (0.94–1.02)	1.01 (0.96–1.05)
HIV RNA log ^b (copies/mL), median (IQR)	5 (4.5–5.4)	4.9 (4.3–5.4)	4.9 (4.4–5.4)	1.01 (0.99–1.04)	1.00 (0.98–1.023)
ADI diagnosis pre-ART, n (%)					
No	6077 (66)	1665 (66.3)	7742 (66.1)	Ref.	Ref.
Yes	3132 (34)	847 (33.7)	3979 (33.9)	1.00 (0.98–1.02)	1.00 (0.98–1.02)

Bold indicate statistically significant results.

^aAdjusted for site and year of ART initiation.

^bSplines with four knots.

ADI, AIDS defining illness; aRR, adjusted relative risk; ART, antiretroviral therapy; CI, confidence interval; cRR, crude relative risk; IDU, injection drug use; IQR, interquartile range; MSM, men who have sex with men.

However, we found no evidence of either mediation or effect modification. A first plausible explanation for the disparate findings is the study population's characteristics. We focused the present analysis on ART initiators, thus suggesting equivalent access to care. By doing so, we immediately excluded individuals at highest risk of death who reached care too late to start treatment, and who, as multiple analyses have indicated, are more likely to be men.^{18,19} Though studies have also shown that men are at increased risk of being lost to follow-up,²⁰ potentially contributing to a selection bias in our primary analysis wherein individuals lost to follow-up within the first year after ART initiation were excluded, our secondary analysis including those lost to follow-up during the first year corroborated the primary results.

Nonetheless, we did find that among patients still in care 1 year after ART initiation, MSM had lower mortality beyond the first year. Our findings highlight the different mortality rates between MSM and heterosexually infected men, and the need to stratify men by sexual HIV transmission risk in analyses. Had we run our main analysis with the variable sex at birth, we would have found that women were at higher risk of death than men (aHR of death for women was 1.22, 95% CI 1.02–1.45), largely driven by the decreased mortality risk among MSM. As such, our findings contrast with those from a South African cohort of over 11,000 individuals that showed that, even among those on treatment who achieved suppression within 6 months, men still had an increased risk of death.³ Similar to our analysis, this study also employed specific statistical techniques to account for those lost to follow-up and did adjust for many confounding factors. The authors argued that these discrepancies could in part be explained by poorer immunological gains for men compared to women. Their results, though initially contrasting ours, cannot be fully compared, however, given that men were not stratified by sexual mode of HIV acquisition.

The strong association between early retention in care and subsequent survival highlights the importance of patient engagement during the first year of treatment. Indeed, the large effect of early retention on subsequent mortality is quite remarkable and it suggests that efforts to improve retention in the first year of ART can have pronounced effects for the subsequent years. These results corroborate those reported by others^{7,17,21–23} and highlight that, as treatment is now recommended for all HIV-positive individuals, interventions to improve early retention in Latin America (and elsewhere) are warranted. A review of US studies addressing interventions to improve retention showed that the most efficient interventions used multiple strategies, including helping patients navigate increasingly complex healthcare systems, accompanying patients to medical appointments, and providing transportation or co-location services, among others.²⁴ Similarly, a recent study conducted in the Dominican Republic showed how an enhanced program that included adherence counseling in addition to an outreach program can result in improvements in viral suppression.²⁵ Future studies should address if these same interventions are feasible and efficient in other settings.

Our study did have several limitations. The high rates of LTFU in our cohort may have influenced mortality estimates, particularly if mortality ascertainment was incomplete and LTFU was informative (both of which are likely).¹⁶ That said, the results of the secondary analysis, considering those LTFU in the first year as not retained, suggests that high rates of LTFU in the first year did not influence the results of this particular analysis. The high mortality rate in the first year after ART initiation could lead to survival bias and thus influence our findings. Despite these limitations, our approach guaranteed a fair assessment of the impact of early retention by addressing it among those with equal chance of being or not being retained. Other limitations of this study were the lack of

TABLE 4. ADJUSTED HAZARD RATIOS (95% CONFIDENCE INTERVALS) PER SITE AND POOLED FIXED EFFECTS FOR OVERALL MORTALITY, COX REGRESSION MODELS

	ARG	BRA	CHL	HND	MXC	PER	US	Pooled effects	I ² , %
N	2259	2887	1688	738	1148	3195	1781		
Deaths	100	284	135	106	56	226	190		
Sex and sexual mode of HIV acquisition									
Women	Ref	Ref	Ref	Ref	Ref	Ref	Ref	Ref	
Heterosexual	0.95 (0.57–1.58)	1.16 (0.87–1.54)	0.83 (0.46–1.47)	1.15 (0.71–1.87)	1.68 (0.66–4.31)	0.90 (0.65–1.24)	0.74 (0.48–1.12)	0.99 (0.84–1.16)	0.0
men									
MSM	0.81 (0.50–1.30)	0.91 (0.67–1.23)	0.55 (0.33–0.91)	1.19 (0.49–2.88)	1.20 (0.47–3.02)	0.70 (0.50–1.01)	0.67 (0.48–0.95)	0.77 (0.65–0.90)	0.0

Bold indicate statistically significant results.

Adjusted for: age at enrollment (splines, 3DF); self-report IDU; nadir CD4 (splines, 3DF); AIDS defining illness pre-ART; pre-ART VL log; ART start year. ART, antiretroviral therapy; MSM, men who have sex with men; VL, viral load.

data to further stratify deaths by major causes (i.e., AIDS and non-AIDS related), or to stratify women by pregnancy status as, during the study period, ART use was not always continued after delivery, which could lead to higher risk of LTFU or death. Additionally, further research is needed to explore the role of social determinants of death, as studies have suggested that disparities in HIV outcomes likely reflect broader socioeconomic disparities of segments of society.^{10,26,27} In this regard, with the disparities evidenced in the heterogeneity among different sites, the use of a meta-analytic approach to combine effects across cohorts is an under-utilized technique²⁸ and a major strength of our study.

In sum, we found that early retention in care significantly decreased mortality risk after 1 year on ART. We found no evidence of retention in care mediating or modifying the association between sex and sexual mode of HIV acquisition meaning that other unmeasured factors might explain the lower mortality risk observed in MSM after 1 year of ART.

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