Marked gender differences in mortality on ART in lower- and middle-income countries: a systematic review and meta-analysis

Sarah W Beckham,[a] Chris Beyrer,[a] Peter Luckow,[a] Meg Doherty,[b] Eyerusalem Negussie,[b] Stefan Baral[a]
[a] Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[b] HIV/AIDS, World Health Organization, Geneva, Switzerland

Introduction

Across all low- and middle-income countries (LMIC), men and women comprise similar proportions of people living with HIV who are eligible for antiretroviral therapy (ART). However, men are only 41% of those receiving ART.[1] There has been limited study of men's outcomes in ART programs, despite a number of studies suggesting that men have higher mortality rates than women.[2,3]

Objective

Conduct a systematic review (SR) and meta-analysis (MA) to assess differential mortality between men and women living with HIV and on ART in LMIC.

Methods

Systematic Review Protocol

Populations: Adults ≥15 years of age in low- and middle-income countries as defined by the World Bank. **Intervention:** HIV treatment. **Comparison:** Men versus women. **Outcomes:** All-cause mortality.

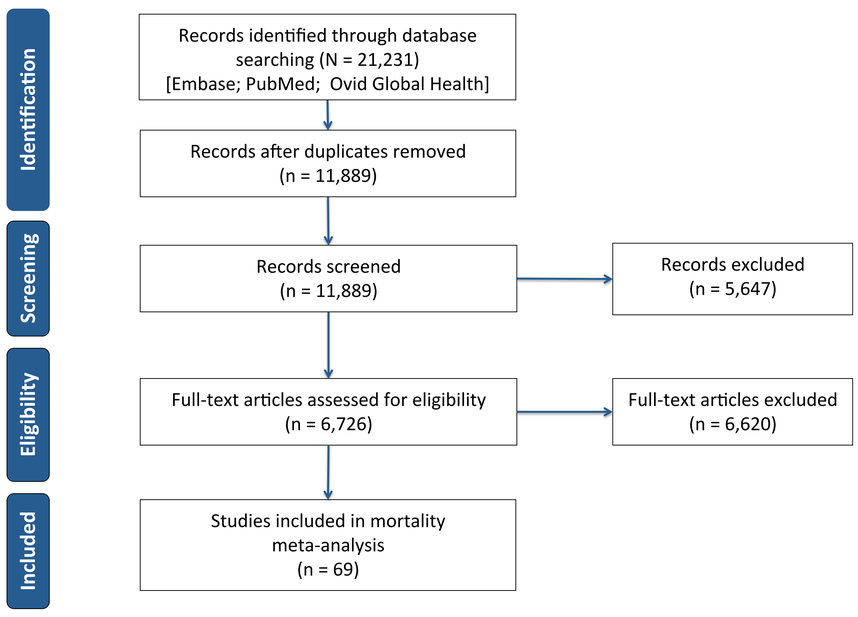
Databases: PubMed, EMBASE, Ovid Global Health.
Search Terms: Controlled vocabulary & keyword terms: HIV and AIDS, ART, LMIC, (not) children

Inclusion criteria: Observational studies (published 2008-2013) among people living with HIV and on ART before or at baseline, reporting hazard ratios of all-cause mortality for men and women, even if gender differences were not the main outcome. **Exclusion:** Included children < 15 years old; sample size <50 men or <50 women; systematic reviews; mathematical modeling; drug studies; co-infection studies other than opportunistic infections; studies explicitly only focused on one sex. **Review Process**: Screening and abstraction was conducted by two independent reviewers. Conflicts were resolved by a third reviewer. The screening process and search results are outlined below in **Figure 1**.

Meta-Analysis

Random-effects meta-analysis of hazard ratios (HRs) (men vs. women) for all-cause mortality using Stata 12.0 metan command (College Station, Texas). Heterogeneity analysis: I^2. Adjusted hazard ratios were used when available.

Figure 1. PRIMSA flow diagram of search results.



Results

The characteristics of included studies are listed in **Table 1**. The majority of the studies were conducted in sub-Saharan Africa, with a minority from Asian countries (including one study from Eastern Europe). Median follow-up time was 33 months.

Table 1. Characteristics of Included Studies

Region	n (studies)	n (HRs)
Africa	53	66
Asia	14	19
Latin America & Caribbean	1	1
Multi-regional	1	1
Total	**69**	**87**

Sample Sizes	M	F	Follow-up Time (months)
Minimum	97	57	3
Median	1737	2011	33
Maximum	29869	59006	144
Total	**249027**	**375067**	**2514**
Total (M+F)	**624,094**		

Pooled hazard ratios for all-cause mortality (men v. women), shown in **Table 2**, below, indicate men have a statistically significant 37% increased hazard for mortality while on ART.

37% increased hazard of death for men

Table 2. Increased Hazard for Mortality for Men on ART vs. Women

Region	n (male)	n (female)	n (HRs)	Pooled Hazard Ratio (95% CI)
All LMIC*	249,027	375,067	87	**1.37 (1.31-1.43)**
Africa	181,779	327,421	66	1.33 (1.26-1.39)
Asia	59,979	44,309	19	1.58 (1.42-1.75)

*Includes the study from Latin America & the Caribbean (Chile) and the multi-regional study.

Sub-group analyses were also run, calculating pooled hazard ratios by time on ART (≤12 months and >12 months) and by sub-region in Africa. See **Table 3**. All pooled HRs were statistically significantly worse for men, and were stronger after the initial 12 months on ART.

Table 3. Pooled HRs for Mortality, M vs. F, by Sub-region & Time (≤12 & >12 months)

Region	n (male)	n (female)	n (HRs)	Pooled Hazard Ratio (95% CI)	
				≤12 months on ART	>12 months on ART
All Africa*	181,779	327,421	66	1.33 (1.26-1.39)	1.42 (1.34-1.50)
East	67,356	126,410	20	1.19 (1.09-1.29)	1.38 (1.21-1.58)
Southern	93,664	162,040	31	1.26 (1.15-1.37)	1.31 (1.21-1.41)
West/Central	7,386	14,897	10	No pooled data	1.57 (1.28-1.92)
Asia	59,979	44,309	19	1.43 (1.13-1.80)	1.64 (1.45-1.86)

*Includes studies across multiple African regions.

Men's hazard of death persists across all regions

Men's hazard of death *increases* after initial year on ART

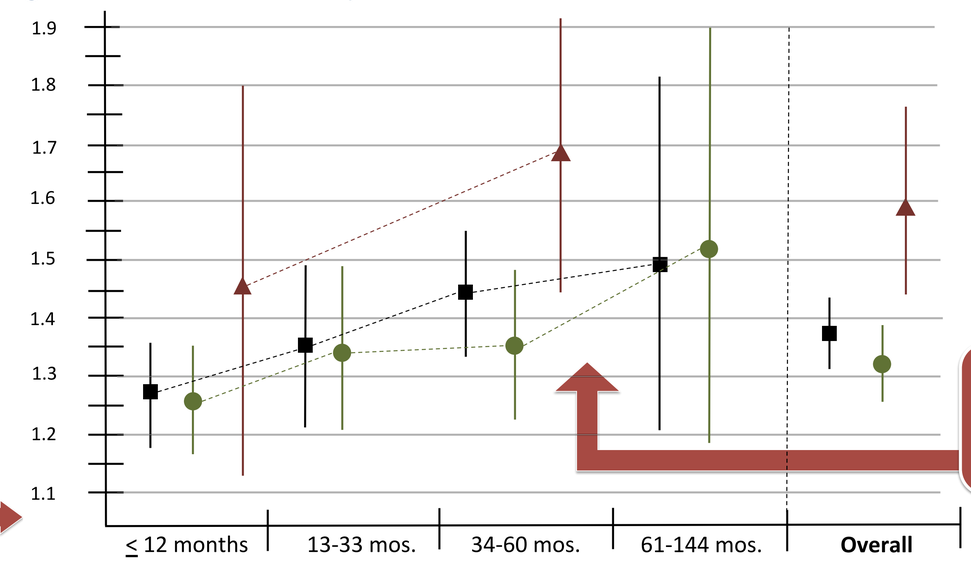
Some studies from Asia reported 20-60% of their participants were people who use drugs (PWUD). Subgroup analysis shows differences between studies with and without reported PWUD, show in **Table 4**.

Table 4. Pooled HRs for Mortality, M vs. F, by Drug Use & Time (≤12 & >12 months)

Asia	n (male)	n (female)	n (HRs)	Pooled Hazard Ratio (95% CI)	
				≤12 months on ART	>12 months on ART
No PWUD	8.413	9,984	12	1.37 (0.95-1.97)	1.84 (1.48-2.28)
Some PWUD	51,566	34,325	7	1.50 (1.08-2.08)	1.44 (1.34-1.55)

Pooled HRs were calculated by quartiles of time for each region. The trend for increased hazard of death for men persisted across all quartiles of time up to 12 years of follow-up (p-value 0.055).

Figure 2. Hazard of Mortality for Men Intensifies over Time on ART



	≤ 12 months	13-33 mos.	34-60 mos.	61-144 mos.	Overall
LMIC ■	1.27 (1.18-1.36)	1.35 (1.22-1.49)	1.44 (1.33-1.56)	1.49 (1.22-1.82)	1.37 (1.31-1.43)
Africa ●	1.25 (1.16-1.35)	1.34 (1.21-1.49)	1.35 (1.23-1.48)	1.50 (1.18-1.90)	1.33 (1.26-1.39)
Asia ▲	1.43 (1.13-1.80)	No pooled data	1.66 (1.44-1.91)	No pooled data	1.58 (1.42-1.75)

All HRs increase over time on ART*

All HRs show worse mortality for men (HR > 1)

*p=0.055, meta-regression, time as continuous variable predicting HR

Conclusions

- Men living with HIV had significantly greater hazards of mortality compared to women while on ART in LMIC.
- This effect persisted and increased over time on treatment.
- Clinical and prevention benefits of ART will only be realized if programs can improve male engagement, diagnosis, and support better long-term retention and adherence.

Literature cited

1. World Health Organization. (2013) *Global Update on HIV Treatment 2013: Results, impact, and opportunities: WHO report in partnership with UNICEF and UNAIDS*. WHO: Geneva.
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