OPEN

All-cause mortality after antiretroviral therapy initiation in HIV-positive women from Europe, Sub-Saharan Africa and the Americas

The IeDEA and COHERE in EuroCoord Cohort Collaboration*

Background: Women account for over half of persons living with HIV/AIDS globally. We examined geographic variation in all-cause mortality after antiretroviral therapy (ART) for women living with HIV (WLWH) worldwide.

Methods: We pooled data from WLWH at least 18 years initiating ART 2000–2014 within COHERE (Europe) and IeDEA regions (East Africa, West Africa, South Africa, North America, Latin America/Caribbean). Mortality rates were calculated at 0–3, 3–6, 6–12, 12–24 and 24–48 months after ART, and mortality rate ratios were compared with European rates with piecewise exponential parametric survival models based on Poisson regression.

Findings: One hundred ninety thousand, one hundred and seventy-five WLWH (16% Europe, 47% East Africa, 13% West Africa, 19% South Africa, 1% South America, 3% North America and 2% Central America/Caribbean) were included. The highest death rates occurred 0–3 months after ART [1.51 (95% CI 1.25–1.82) per 100 person-years in Europe, 12.45 (11.30–13.73), 14.03 (13.12–15.02) and 9.44 (8.80–10.11) in East, West and South Africa, and 1.53 (0.97–2.43), 7.83 (5.44–11.27) and 17.02 (14.62–19.81) in North, South America and Central America/Caribbean, respectively] and declined thereafter. Mortality in Europe was the lowest, with regional differences greatest in the first 3 months and smaller at longer ART durations [adjusted rate ratios 24–48 months after ART: 3.63 (95% CI 3.04–4.33), 5.61 (4.84–6.51) and 3.47 (2.97–4.06) for East, West and South Africa; 2.86 (2.26–3.62), 2.42 (1.65–3.55) and 2.50 (1.92–3.26) for North, South America and Central America/Caribbean, respectively].

Conclusion: Global variations in short-term and long-term mortality among WLWH initiating ART may inform context-specific interventions.

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Introduction

The HIV pandemic continues to be a global health challenge; 36.9 million persons were estimated to be living with HIV in 2017 [1]. Women account for over half of the adults living with HIV worldwide and up to 60% of persons from low-income and middle-income settings, where health needs are the most pressing [1,2].

Access to healthcare and life-saving antiretroviral therapy (ART) varies greatly across regions and depends on structural and individual factors [1–3]. Access to HIV testing is a prerequisite to ART initiation, but delayed HIV diagnosis and linkage to care are major barriers to timely access to ART, and thus, its clinical benefits [3–6]. Largely a consequence of increases in the uptake of universal HIV screening during pregnancy to prevent mother-to-child HIV transmission over the last decade, women from most geographical regions are diagnosed with HIV earlier and have higher $CD4^+$ cell counts at diagnosis than heterosexually infected men [1,3–6]. These factors underlie some of the reported mortality differences

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between women and men favoring women [7–11]. However, no study has so far specifically compared early and late mortality differences among women living with HIV (WLWH) across different geographical regions worldwide.

Globally, WLWH differ in their age distribution, HIV transmission routes, socioeconomic status and viral and tuberculosis co-infection rates, and risk factors for non-HIV mortality [1,3–11]. Wide variations exist between countries and regions of the world in terms of access to HIV testing, ART regimens, and $CD4^+$ cell counts at ART initiation, along with HIV testing policies and guidelines for treatment. Many of these factors may be because of healthcare systems and resource availability for healthcare within the individual country. In turn, this may impact mortality rates for WLWH [1,2,12]. Finally, background mortality rates in different regions have striking variations that, together with the previously mentioned aspects, shape the mortality rates of WLWH [13]. Collaboration between large multiregional cohorts from different regions of the world provides an opportunity to describe geographic disparities in mortality. In this work, we estimate all-cause mortality after ART initiation, overall and by duration of ART use, among WLWH in Europe, the Americas and Sub-Saharan Africa up to 48 months after ART initiation, in order to help to understand key underlying drivers of mortality in women from different settings.

Methods

Setting and data sources

We merged databases from HIV cohorts in the International Epidemiology Databases to Evaluate AIDS (IeDEA) Collaboration and the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord (merger 2015). These collaborations have been described elsewhere [14–19].

IeDEA is an international research consortium that collects HIV/AIDS data through seven international regional centers, four in Africa and one each in the Asia-Pacific region; the Caribbean, Central and South America region; and North America. Five IeDEA regions contributed data to this study: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) [14], the Caribbean, Central and South America network for HIV epidemiology (CCASAnet) [15] and IeDEA East [16], Southern [16] and West Africa [16]. COHERE is a collaboration of HIV cohorts across Europe constituting 40 cohorts and cohort collaborations from 34 countries [17]. COHERE includes other collaborations, such as CASCADE [18] and EuroSIDA [19].

Institutional review boards approved the pooling of data and their use in collaborative analyses, and ethics permission was granted.

Study population and inclusion criteria

Eligible individuals were ART-naïve women, 18–80 years old at ART initiation, who started their first ART regimen between 1 January 2000 and 31 December 2014. North American participants were required to have a second visit within 12 months of enrollment, regardless of ART initiation status, so that anyone who died soon after enrollment would not have been included in NA-ACCORD. In Southern Africa, analyses were restricted to cohorts from the Republic of South Africa where patient records could be linked to the vital registry. We excluded individuals from the Asia-Pacific region [20] ($N = 849$) as the number of deaths was very low, those from Mexico because of having too few eligible participants ($N = 100$) and those from Argentina ($N = 545$) as mortality was reported to be under-ascertained and no further corrections could be applied.

Ascertainment of mortality

The primary outcome was death because of any cause in the 48 months after ART initiation. To address concerns regarding death under-ascertainment, a survey addressing ascertainment and matching with external mortality registries was distributed. Seventy-five percent of cohorts in Europe reported good or very good death ascertainment, but only 40% conducted cross-checks with mortality registries. Cumulative mortality in the European cohorts did not vary significantly according to self-assessment of mortality ascertainment (data not shown). Death ascertainment was reported to be poor in East and West Africa. To correct mortality estimates for East Africa, we used an inverse-probability-weighted estimator of the mortality rate where weights are constant and equal to the inverse ratio of the patients who could be traced out of all patients who were lost to follow-up [21]. For corrections of under-ascertainment in West Africa, we used a modification of the approach by Brinkhof *et al.* [22], which uses inflation factors to account for mortality under-reporting, under the assumption that mortality under-ascertainment was similar in the two regions [21]. Death rates based on observed data were estimated for different participant subgroups. These 'passive' mortality estimates were then multiplied by a group-specific inflation factor determined as the ratio of the lost-to-follow-up-adjusted death rates over the observed rates estimated within East African cohorts [21,22]. For the Republic of South Africa cohort, civil identification numbers, wherever available, were cross-checked with national population registers prior to data transfer to confirm dates of death. All sites in the Caribbean, Central and South America region, except for Argentina, reported ascertaining deaths with population-based mortality registries. North American cohorts link to a population-based death registry at least annually.

Statistical methods

Data-contributing regions were categorized as Europe; East Africa; West Africa; Southern Africa; South America; North America; and Central America and the Caribbean. The countries in each region are shown in Supplemental Table 1, http://links.lww.com/QAD/B551.

Participant characteristics at ART initiation by region were described using frequency tables for categorical variables and medians and interquartile ranges for continuous variables. Differences in sociodemographic and clinical characteristics by region were assessed with Kruskal–Wallis test for continuous variables and the chi-squared test for independence for categorical variables. We assumed that women from Haiti, Republic of South Africa, West Africa and East Africa with unknown transmission mode were infected through heterosexual contact [1].

Mortality rates were calculated by region for the intervals 0–3, 3–6, 6–12, 12–24 and 24–48 months after ART initiation. Mortality rate ratios, compared with Europe, were estimated at each interval using a piecewise exponential parametric survival model fit through Poisson regression. The use of a piecewise exponential parametric survival model fit through Poisson regression simplified the prediction of mortality rate ratios for each duration interval on ART, whereas the implicit assumption of constant hazards within each interval produced almost identical inter-regional comparative mortality rate ratio estimates when compared with a piecewise spline-based flexible parametric survival model [23,24]. Parametric survival models offer alternatives and may be more appropriate than semi-parametric techniques, such a Cox regression when the proportional hazards assumption is in question [25].

Multivariable models were adjusted for baseline age (<30, 30–44, 45–59, ≥60 years), $CD4^+$ cell counts within 6 months prior to ART initiation (0–24, 25–49, 50–99, 100–199, 200–349, ≥350 cells/μl, unknown) and period of ART initiation (2000–2003, 2004–2007, 2008–2011, 2012–2014). As the HIV epidemics in East, West and South Africa, the Caribbean, South and Central America are predominantly heterosexual epidemics, no adjustment for transmission category could be applied for comparisons between these regions and Europe or North America. Neither adjustment for HIV-RNA nor AIDS prior to ART initiation were included because of the high percentage of missing values in these regions. For comparisons between North America and Europe, multivariable models were additionally adjusted for transmission category, HIV-RNA, AIDS at ART initiation, and race/ethnicity in the subset of participants with available information for these variables.

A set of sensitivity analyses were undertaken. Analyses were repeated restricting to patients with documented or presumed heterosexual transmission, patients starting ART post2004, cohorts with more than 50% of data on $CD4^+$ cell counts at baseline and cohorts with 'very good' self-reported mortality ascertainment.

Statistical analyses were performed using Stata 14 (StataCorp, College Station, Texas, USA).

Results

A total of 190 175 women (16% Europe, 47% East Africa, 13% West Africa, 19% South Africa, 1% South America, 3% North America and 2% Central America/Caribbean) were included. Median age at ART initiation ranged from 33 years in South Africa to 40 years in North America. The proportion of persons who injected drugs was highest in North America (18%) and Europe (7%). Only 16% of the women in North America were of white race/ethnicity, whereas 63 and 17% were of black race and Hispanic ethnicity, respectively. Race/ethnicity data were available for 45% of European women, 26% of whom were black, largely migrants from sub-Saharan Africa. Of ART initiators, median $CD4^+$ cell counts at initiation were close to 250 cells/μl in Europe and North America, 141 cells/μl in South Africa and 170–190 cells/μl in other regions (Table 1).

In all regions except for North America, because of cohort inclusion criteria in that region, the highest death rates occurred during the first 3 months after starting ART and declined thereafter (Fig. 1). Women from Europe had the lowest death rates across the study period, whereas the highest were observed among women from Central America and the Caribbean between 0 and 3 months, in East Africa between 3 and 6 months and West Africa between 6 and 48 months from ART initiation.

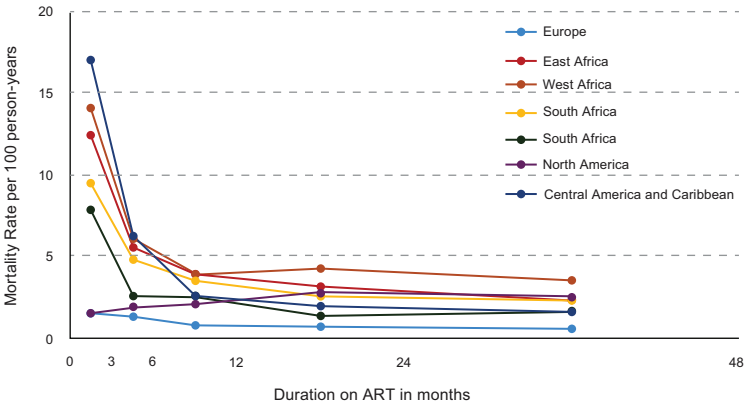
Mortality rates in women from Europe were significantly lower than rates in women from all other regions during the first 48 months after starting ART, except for North American women, whose rates were similar for the first 6 months and significantly higher thereafter (Table 2). The greatest differences were observed in the first 3 months and attenuated thereafter. Taking into account differences in baseline age, $CD4^+$ cell count and period of ART initiation, differences in mortality were attenuated although still of large magnitude and statistically significant. After additional adjustments for transmission category, HIV-RNA and AIDS prior to ART initiation for comparisons between North America and Europe, differences in mortality were reduced, but still present. Further adjustment for race/ethnicity in the subset of patients with available information for this variable contributed to reduction of differences between 6 and 48 months on ART.

Sensitivity analyses yielded results consistent with the main analyses (Supplemental Table 2, http://links.lww.com/QAD/B551).

Table 1. Characteristics of 190 175 women living with HIV in Europe, sub-Saharan Africa and the Americas who initiated ART 2000–2014.

	Europe	East Africa	West Africa	South Africa	South America	North America	Central America and Caribbean
Participants included [*n* (%)]	30 313 (15.9)	88 840 (46.7)	24920 (13.1)	35 612 (18.7)	1517 (0.8)	4801 (2.5)	4172 (2.2)
Age, years [median (IQR)]	35 (29–42)	34 (29–41)	34 (29–41)	33 (28–40)	35 (29–43)	40 (33–47)	36 (30–44)
<30	8795 (29.0)	27514 (31.0)	7178 (28.8)	12 038 (33.8)	437 (28.8)	844 (17.6)	1057 (25.3)
30–44	15 973 (52.7)	46 514 (52.4)	13 936 (55.9)	18 865 (53.0)	773 (51.0)	2433 (50.7)	2196 (52.6)
45–59	4666 (15.4)	13190 (14.8)	3454 (13.9)	4384 (12.3)	271 (17.9)	1384 (28.8)	816 (19.6)
≥60	879 (2.9)	1622 (1.8)	352 (1.4)	325 (0.9)	36 (2.4)	140 (2.9)	103 (2.5)
Mode of transmission [n (%)]							
Heterosexual	28 324 (93.4)	88 832 (99.99)	24 920 (100.0)	35 612 (100.0)	1510 (99.5)	3925 (81.7)	4171 (99.98)
IDU	1989 (6.6)	8 (0.01)	0	0	7 (0.5)	876 (18.3)	1 (0.02)
$CD4^+$ T-cell counts (cells/μl)							
Median (IQR)	248 (140–361)	172 (83–270)	168 (74–289)	141 (69–208)	191 (74–297)	246 (115–372)	168 (80–252)
0–24	1739 (5.7)	6478 (7.3)	691 (2.8)	2917 (8.2)	123 (8.1)	457 (9.5)	313 (7.5)
25–49	1134 (3.7)	5013 (5.6)	422 (1.7)	2611 (7.3)	106 (7.0)	193 (4.0)	295 (7.1)
50–99	2109 (7.0)	9730 (10.9)	780 (3.1)	5028 (14.1)	173 (11.4)	318 (6.6)	527 (12.6)
100–199	5314 (17.5)	21249 (23.9)	1589 (6.4)	11013 (30.9)	264 (17.4)	759 (15.8)	1159 (27.8)
200–349	9604 (31.7)	20811 (23.4)	1466 (5.9)	7121 (20.0)	426 (28.1)	1369 (28.5)	1242 (29.8)
≥350	7402 (24.4)	8904 (10.0)	1036 (4.2)	1121 (3.1)	189 (12.5)	1210 (25.2)	215 (5.1)
Unknown	3011 (9.9)	16 655 (18.7)	18936 (76.0)	5801 (16.3)	236 (15.6)	495 (10.3)	421 (10.1)
Year of ART initiation							
2000–2003	8043 (26.5)	907 (1.0)	1519 (6.1)	563 (1.6)	188 (12.4)	1440 (30.0)	502 (12.0)
2004–2007	9959 (32.8)	25 399 (28.6)	9165 (36.8)	11 859 (33.3)	440 (29.0)	1592 (33.2)	1306 (31.3)
2008–2011	9535 (31.5)	37 573 (42.3)	10 078 (40.0)	16 488 (46.3)	621 (40.9)	1749 (36.4)	2341 (56.1)
2012–2014	2776 (9.2)	24 961 (28.1)	4158 (16.7)	6702 (18.8)	268 (17.7)	20 (0.4)	23 (0.6)

ART, antiretroviral therapy; IDU, injection drug use.



Mortality rates per 100 p-y	Duration on ART (months)				
	0 – 3	3 - 6	6 - 12	12 - 24	24 - 48
Europe	1.51 (1.25 – 1.82)	1.31 (1.07 – 1.60)	0.80 (0.66 – 0.96)	0.70 (0.61 – 0.82)	0.56 (0.49 – 0.64)
East Africa					
Non corrected	5.65 (5.34 – 5.98)	2.95 (2.71 – 3.20)	1.51 (1.38 – 1.65)	0.99 (0.91 – 1.08)	0.59 (0.54 – 0.64)
Corrected[1]	12.45 (11.30–13.73)	6.23 (5.38 – 7.20)	3.77 (3.28 – 4.32)	3.05 (2.72 – 3.43)	2.32 (2.07 – 2.59)
West Africa					
Non corrected	6.37 (5.76 – 7.04)	2.62 (2.23 – 3.08)	1.58 (1.35 – 1.83)	1.37 (1.22 – 1.55)	0.90 (0.80 – 1.01)
Corrected[2]	14.03 (13.12 – 15.02)	5.54 (4.96 – 6.19)	3.94 (3.58 – 4.33)	4.23 (3.95 – 4.53)	3.55 (3.34 – 3.76)
South Africa	9.44 (8.80 – 10.11)	4.75 (4.29 – 5.26)	3.48 (3.18 – 3.80)	2.52 (2.32 – 2.73)	2.35 (2.18 – 2.52)
South America	7.83 (5.44 – 11.27)	2.52 (1.31 – 4.85)	2.49 (1.55 – 4.01)	1.38 (0.86 – 2.22)	1.60 (1.12 – 2.29)
North America	1.53 (0.97 – 2.43)	1.91 (1.24 – 2.92)	2.13 (1.58 – 2.87)	2.78 (2.28 – 3.41)	2.45 (2.05 – 2.93)
Central America and Caribbean	17.02 (14.62-19.81)	6.03 (4.64 – 7.84)	2.61 (1.95 – 3.49)	1.92 (1.50 – 2.46)	1.63 (1.30 – 2.04)

[1]Mortality estimates for East Africa corrected by using an inverse-probability-weighted estimator of the rate where weights are constant and equal to the inverse ratio of the patients who could be traced out of all patients who were lost to follow-up

[2]Death rates based on observed data were estimated for different durations on ART (0-3, 3-6, 6-12, 12-24, 24-48 months) and then multiplied by inflation factor for each specific duration on ART determined as the ratio of the lost-to-follow-up-adjusted death rates over the observed rates estimated within East African cohorts

Fig. 1. Crude mortality rates per 100 person-years for women initiating antiretroviral theray by global region.

Table 2. Mortality rate ratios (95% confidence interval) compared with Europe by duration on antiretroviral therapy.

Mortality rate ratio	Duration on antiretroviral therapy (months)				
	0–3	3–6	6–12	12–24	24–48
East Africa					
Noncorrected	3.74 (3.08–4.54)	2.25 (1.81–2.81)	1.89 (1.54–2.33)	1.41 (1.18–1.67)	1.04 (0.89–1.22)
Corrected[a]	8.25 (6.69–10.17)	4.76 (3.71–6.11)	4.73 (3.74–5.98)	4.33 (3.58–5.24)	4.10 (3.45–4.88)
Corrected and adjusted for baseline patient characteristics[b]	7.25 (5.87–8.97)	4.24 (3.30–5.46)	4.24 (3.35–5.37)	3.89 (3.21 – 4.72)	3.63 (3.04–4.33)
West Africa					
Noncorrected	4.22 (3.42–5.21)	2.00 (1.55–2.60)	1.98 (1.55–2.52)	1.95 (1.61–2.36)	1.59 (1.33–1.90)
Corrected[c]	9.30 (7.63–11.32)	4.23 (3.36–5.34)	4.94 (4.00–6.11)	6.01 (5.09–7.09)	6.28 (5.43–7.26)
Corrected and adjusted by age at ART initiation	9.73 (7.99–11.85)	4.50 (3.57–5.67)	5.10 (4.12–6.31)	6.09 (5.16–7.19)	6.42 (5.55–7.43)
Corrected and adjusted by age and period of ART initiation	8.95 (7.34–10.91)	4.05 (3.21–5.11)	4.38 (3.54–5.43)	5.37 (4.54–6.35)	5.61 (4.84–6.51)
Corrected and adjusted by age, period of ART initiation and $CD4^+$ in patients with available $CD4^+$	3.42 (2.53–4.62)	1.44 (0.94–2.19)	2.07 (1.46–2.94)	2.42 (1.86–3.15)	2.49 (1.98–3.14)
South Africa					
Crude	6.25 (5.13–7.62)	3.63 (2.89–4.56)	4.37 (3.54–5.39)	3.57 (3.01–4.24)	4.16 (3.57–4.83)
Adjusted for baseline patient characteristics[b]	5.42 (4.43–6.64)	3.15 (2.50–3.97)	3.77 (3.05–4.67)	3.05 (2.56–3.63)	3.47 (2.97–4.06)
South America					
Crude	5.19 (3.45–7.81)	1.93 (0.98–3.83)	3.13 (1.88–5.22)	1.95 (1.19–3.22)	2.84 (1.93–4.16)
Adjusted for baseline patient characteristics[b]	4.47 (2.97–6.72)	1.67 (0.84–3.32)	2.70 (1.62–4.52)	1.69 (1.02–2.78)	2.42 (1.65–3.55)
North America					
Crude	1.02 (0.62–1.67)	1.46 (0.91–2.34)	2.67 (1.88–3.81)	3.95 (3.07–5.08)	4.34 (3.47–5.42)
Adjusted for baseline patient characteristics[b]	0.88 (0.53–1.44)	1.25 (0.78–2.02)	2.30 (1.61–3.27)	3.40 (2.64–4.37)	3.72 (2.97–4.65)
Additional adjustment for transmission category, HIV-RNA and AIDS prior to ART initiation	0.69 (0.42–1.14)	0.99 (0.62–1.60)	1.80 (1.25–2.58)	2.65 (2.03–3.44)	2.86 (2.26–3.62)
Additional adjustment for transmission category, HIV-RNA, AIDS prior to ART initiation and race/ethnicity in patients with available info on race/ethnicity	0.53 (0.31–0.89)	0.92 (0.55–1.55)	1.48 (0.99–2.22)	2.39 (1.77–3.24)	2.78 (2.11–3.66)
Central America and Caribbean					
Crude	11.27 (8.87–14.33)	4.61 (3.31–6.42)	3.28 (2.32–4.63)	2.73 (2.04–3.65)	2.88 (2.22–3.75)
Adjusted for baseline patient characteristics[b]	9.92 (7.79–12.63)	4.12 (2.95–5.74)	2.93 (2.07–4.15)	2.43 (1.82–3.26)	2.50 (1.92–3.26)

ART, antiretroviral therapy.
[a]Mortality estimates corrected by using an inverse-probability-weighted estimator of the rate where weights are constant and equal to the inverse ratio of the patients who could be traced out of all patients who were lost to follow-up.
[b]Baseline patient characteristics are age (<30, 30–44, 45–59, ≥60 years), $CD4^+$ T-cell count (0–24, 25–49, 50–99, 100–199, 200–349, ≥350 cells/μl, unknown) and period of ART initiation (2000–2003, 2004–2007, 2008–2011, 2012–2014).
[c]Mortality estimates corrected by using a modification of the approach by Brinkhof and colleagues, which uses inflation factors to account for mortality under-reporting, under the assumption that mortality under-ascertainment in West Africa was similar to that in East Africa. Death rates based on observed data were estimated for different durations on ART (0–3, 3–6, 6–12, 12–24, 24–48 months) and then multiplied by inflation factor for each specific duration on ART determined as the ratio of the lost-to-follow-up-adjusted death rates over the observed rates estimated within East African cohorts.

Discussion

This large collaborative study found that there was significant variability in all-cause mortality among WLWH in Europe, the Americas and sub-Saharan Africa up to 48 months after ART initiation, with distinct geographical patterns for short-term, midterm and long-term mortality. The highest mortality was observed in WLWH in Central America and the Caribbean and sub-Saharan Africa, who also had the lowest $CD4^+$ cell counts at ART initiation. The lowest mortality was reported in women living in Europe, who had, together with women from North America, the highest $CD4^+$ cell counts; women living in South America had intermediate mortality. These differences were apparent after correcting for under-ascertainment in mortality in most of the African sites. Mortality was highest in the first 3 months after ART initiation in all evaluable regions, and

decreased from then onwards to reach stable rates from the first until the fourth year following ART, when inter-regional differences were attenuated.

The baseline differences of WLWH explained some of the relative differences encountered but did not fully explain the higher mortality observed in women from sub-Saharan African and American regions compared with the women on ART living in Europe. Indeed, women from sub-Saharan Africa and from Central America and the Caribbean had the lowest $CD4^+$ cell counts at ART initiation, a strong predictor of subsequent HIV-related, mortality [8–11,26]. Median $CD4^+$ cell counts at ART initiation were close to 250 cells/μl in women living in North America and Europe, but mortality rates differed substantially. The lower mortality of WLWH in Europe compared with women in North America has been previously reported [8,9] and attributed to the accessibility and equity of health services, to background mortality rates, to causes of death of populations affected by HIV in the different settings, and to near complete death ascertainment in North America [27]. Our findings build on these explanations expanding comparisons to East and West Africa, the Caribbean, Central and South and America.

Most of the European countries included in this study have universal healthcare systems, which grant free access to HIV testing, HIV care and ART medications, and this may account for some of the better HIV-related outcomes observed among women in European cohorts. However, not all countries in Europe provide free access to ART for undocumented migrants, a nonnegligible proportion of WLWH in Europe [28,29]. Even for documented migrant women, barriers to access care because of socioeconomic, gender, ethnic and cultural factors exist and may have a negative impact on survival [30]. Barriers to accessing adequate healthcare have been consistently reported in black and Latina women and First Nations/indigenous women in North America, irrespective of HIV status [10,30–33]. In addition, access to HIV testing and life-saving ART among women from low-income and middle-income settings is considerably lower than in Western Europe and North America [1,2,34]. These health inequities may lead to lower $CD4^+$ cell counts at ART initiation, which likely account for the exceedingly high early and overall mortality observed in the women in sub-Saharan Africa and Central and South America and the Caribbean.

Our findings need to be placed in the context of background mortality rates of women from the general population living in geographical regions with generalized HIV epidemics, together with mortality patterns of racial and ethnic minorities in North America and Europe, with concentrated HIV epidemics [1,35,36]. Globally, all-cause mortality in women living in sub-Saharan Africa, the Caribbean, and Central and South America is also higher than among the women from Europe and North America [13]. Within North America, African-American and Latina women have higher mortality rates than white women, both in general [35,36] and from HIV-infection [31], but patterns have been described to be complex and evolve over time [37]. Conversely, migrant women in Europe have lower all-cause mortality relative to general population women, consistent with healthy migrant selection bias [38].

For all regions analyzed, and with different magnitudes, mortality was highest in the initial 3 months following ART. The exception to this pattern was North America given NA-ACCORD's inclusion criteria, as anyone who died very soon after enrollment (including those who initiated ART) was excluded, thereby artificially reducing early mortality in North America. Higher mortality soon after ART has been well described and attributed to late ART initiation and is largely caused by AIDS-defining conditions preventable with ART [39–42]. Failures in earlier HIV testing and/or linkage to care to commence ART represent a clear opportunity for intervention. Unfortunately, cause of death was not available in our dataset for most settings, but studies that have analyzed causes of death patterns report that, for both AIDS and non-AIDS defining causes of death, rates are lower in WLWH in Europe than in North America [10].

These analyses have been performed in the largest and most globally representative sample assembled to date of WLWH. Data from 56 countries in seven multisite cohort collaborations have been harmonized to reach a final sample of nearly 200 000 women initiating ART and under follow-up. Inevitably, selection and information biases were likely to be present, and multiple strategies were used to minimize their effects. Stringent inclusion criteria were required leading to the exclusion of Asia Pacific cohort, Central Africa and some countries within Central and South America [14–19]. Under-ascertainment of mortality at clinical sites in East and West Africa were partially corrected by a modification of Brinkhof and colleagues' approach [21,22,43,44]. However, under-reporting is likely to be time-sensitive in sites in sub-Saharan Africa and is also likely to increase overtime.

Sensitivity analyses to account for potential selection biases derived from lack of cross-checks with mortality registries in some of the European cohorts, and of differential data availability to characterize losses to follow-up were also performed. Unfortunately, having missing data was inevitable in such an ambitious data collection and harmonization exercise. For example, information on $CD4^+$ cell count and HIV-RNA viral load was missing for a large proportion of the women from lower income settings and reveals the lack of availability of clinical monitoring tools in those regions. Type of ART regimen was not available from all sites, and

given that the study period started in 2000, we assumed all the women to be on at least three antiretroviral drugs. Although mortality of women living with HIV in Europe may be under-ascertained, this was assessed through sensitivity analyses that excluded cohorts that did not perform cross-checks with mortality registries and/or reported incomplete or poor death ascertainment, and the main findings did not significantly change. A recent publication highlights that European cohort participants were generally representative of the national HIV-diagnosed population reported by surveillance systems, but that PWID, migrants, persons with low $CD4^+$ cell counts and those over 55 years of age are generally under-represented in European cohorts [45]. Finally, as of today, national ART guidelines have expanded in most settings to 'Treat All' patients with HIV, regardless of $CD4^+$ cell count or clinical stage, as recommended by WHO in 2015. Although we have controlled for baseline AIDS status and $CD4^+$ cell count, it is possible that differences in ART guidelines between regions, which in part determine who initiates ART, could explain some of the differences observed.

The global health inequalities highlighted in this study pertain to women who have accessed health services and have started ART, so they are likely to underestimate overall gaps for women living with HIV, particularly those not yet diagnosed or linked to care. Voluntary antenatal HIV testing, widely implemented in most countries included in these analyses, has been a major step forward in increasing access to health services, but requires expansion and improvement. The data presented can support the development of context-specific interventions to help countries reach their 2020 targets and improve the life expectancies of HIV-positive women at the global level.

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Conflicts of interest

There are no conflicts of interest.

References

1. UNAIDS DATA 2018. Available at: http://www.unaids.org/en/topic/data [Accessed January 2018]
2. Dutta A, Barker C, Kallarakal A. **The HIV treatment gap: estimates of the financial resources needed versus available for scale-up of antiretroviral therapy in 97 countries from 2015 to 2020.** *PLoS Med* 2015; **12**:e1001907.
3. Duda SN, Farr AM, Lindegren ML, Blevins M, Wester CW, Wools-Kaloustian K, *et al*., International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. **Characteristics and comprehensiveness of adult HIV care and treatment programmes in Asia-Pacific, sub-Saharan Africa and the Americas: results of a site assessment conducted by the International epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration.** *J Int AIDS Soc* 2014; **17**:19045.
4. IeDEA and ART Cohort Collaborations. Avila D, Althoff KN S Mugglin##C, Wools-Kaloustian K, Koller M, *et al*. **Immunodeficiency at the start of combination antiretroviral therapy in low-, middle-, and high-income countries.** *J Acquir Immune Defic Syndr* 2014; **65**:e8–e16.
5. IeDEA and COHERE Cohort Collaborations. **Global trends in CD4 cell count at the start of antiretroviral therapy: collaborative study of treatment programs.** *Clin Infect Dis* 2018; **66**:893–903.
6. Late presenters working group in COHERE in EuroCoord. Mocroft A, Lundgren J, Antinori A, Monforte Ad, Brännström J, *et al*. **Late presentation for HIV care across Europe: update from the Collaboration of Observational HIVEpidemiological Research Europe (COHERE) study, 2010 to 2013.** *Euro Surveill* 2015; **20**:47.30070.
7. Johnson LF, Keiser O, Fox MP, Tanser F, Cornell M, Hoffmann CJ, *et al*., International Epidemiologic Databases to Evaluate AIDS Southern Africa (IeDEA-SA) Collaboration. **Life expectancy trends in adults on antiretroviral treatment in South Africa.** *AIDS* 2016; **30**:2545–2550.
8. Jarrin I, Geskus R, Bhaskaran K, Prins M, Perez-Hoyos S, Muga R, *et al*., CASCADE Collaboration. **Gender differences in HIV progression to AIDS and death in industrialized countries: slower disease progression following HIV seroconversion in women.** *Am J Epidemiol* 2008; **168**:532–540.
9. Boulle A, Schomaker M, May MT, Hogg RS, Shepherd BE, Monge S, *et al*. **Mortality in patients with HIV-1 infection starting antiretroviral therapy in South Africa, Europe, or North America: a collaborative analysis of prospective studies.** *PLoS Med* 2014; **11**:e1001718.
10. Antiretroviral Therapy Cohort Collaboration (ART-CC). **Sex differences in overall and cause-specific mortality among HIV-infected adults on antiretroviral therapy in Europe, Canada and the US.** *Antivir Ther* 2015; **20**:21–28.
11. Cornell M, Schomaker M, Garone DB, Giddy J, Hoffmann CJ, Lessells R, *et al*., International Epidemiologic Databases to Evaluate AIDS Southern Africa Collaboration. **Gender differences in survival among adult patients starting antiretroviral therapy in South Africa: a multicentre cohort study.** *PLoS Med* 2012; **9**:e1001304.
12. Nelson LJ, Beusenberg M, Habiyambere V, Shaffer N, Vitoria MA, Montero RG, *et al*. **Adoption of national recommendations related to use of antiretroviral therapy before and shortly following the launch of the 2013 WHO consolidated guidelines.** *AIDS* 2014; **28 (Suppl 2)**:S217–S224.
13. GBD 2016 Causes of Death Collaborators. **Global, regional, and national age-sex specific mortality for 264 causes of death, 1980–2016: a systematic analysis for the Global Burden of Disease Study 2016.** *Lancet* 2017; **390**:1151–1210.
14. Gange SJ, Kitahata MM, Saag MS, Bangsberg DR, Bosch RJ, Brooks JT, *et al*. **Cohort profile: the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD).** *Int J Epidemiol* 2007; **36**:294–301.
15. McGowan CC, Cahn P, Gotuzzo E, Padgett D, Pape JW, Wolff M, *et al*. **Cohort profile: Caribbean, Central and South America Network for HIV research (CCASAnet) collaboration within the International Epidemiologic Databases to Evaluate AIDS (IeDEA) programme.** *Int J Epidemiol* 2007; **36**:969–976.
16. Egger M, Ekouevi DK, Williams C, Lyamuya RE, Mukumbi H, Braitstein P. **Cohort Profile: the international epidemiological databases to evaluate AIDS (IeDEA) in sub-Saharan Africa.** *Int J Epidemiol* 2012; **41**:1256–1264.
17. Chêne G, Phillips A, Costagliola D, Sterne JAC, Furrer H, Del Amo J, *et al*. **Cohort profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.** *Int J Epidemiol* 2017; **46**:797–1797.
18. Touloumi G, Pantazis N, Babiker, Walker SA, Katsarou O, Karafoulidou A, CASCADE Collaboration. **Differences in HIV RNA levels before the initiation of antiretroviral therapy among 1864 individuals with known HIV-1 seroconversion dates.** *AIDS* 2004; **18**:1697–1705.
19. Mocroft A, Kirk O, Aldins P, Chies A, Blaxhult A, Chentsova N, *et al*., EuroSIDA study group. **Loss to follow-up in an international, multicentre observational study.** *HIV Med* 2008; **9**:261–269.
20. Lee MP, Zhou J, Messerschmidt L, Honda M, Ditangco R, Sirisanthana T. **Impact of gender on long-term treatment outcomes of highly active antiretroviral therapy (HAART) in the TREAT Asia HIV Observational Database.** *AIDS Patient Care STDS* 2015; **29**:229–233.
21. Yiannoutsos CT, Johnson LF, Boulle A, Musick BS, Gsponer T, Balestre E, *et al*., International Epidemiologic Databases to Evaluate AIDS (IeDEA) Collaboration. **Estimated mortality of adult HIV-infected patients starting treatment with combination antiretroviral therapy.** *Sex Transm Infect* 2012; **88 (Suppl 2)**:i33–i43.
22. Brinkhof MW, Boulle A, Weigel R, Messou E, Mathers C, Orrell C, *et al*. **Mortality of HIV-infected patients starting antiretroviral therapy in sub-Saharan Africa: comparison with HIV-unrelated mortality.** *PLoS Med* 2009; **6**:e1000066.
23. Royston P, Parmar MK. **Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects.** *Stat Med* 2002; **21**:2175–2197.
24. Lambert PC, Royston P. **Further development of flexible parametric models for survival analysis.** *The Stata Journal* 2009; **9**:265–290.
25. Lee ET, Go OT. **Survival analysis in public health research.** *Annu Rev Public Health* 1997; **18**:105–134.
26. May MT, Vehreschild JJ, Trickey A, Obel N, Reiss P, Bonnet F, *et al*. **Mortality according to CD4 count at start of combination antiretroviral therapy among HIV-infected patients followed for up to 15 years after start of treatment: collaborative cohort study.** *Clin Infect Dis* 2016; **62**:1571–1577.
27. May MT, Hogg RS, Justice AC, Shepherd BE, Costagliola D, Ledergerber B, Antiretroviral Therapy Cohort Collaboration (ART-CC). **Heterogeneity in outcomes of treated HIV-positive patients in Europe and North America: relation with patient and cohort characteristics.** *Int J Epidemiol* 2012; **41**:1807–1820.
28. Deblonde J, Sasse A, Del Amo J, Burns F, Delpech V, Cowan S, *et al*. **Restricted access to antiretroviral treatment for undocumented migrants: a bottle neck to control the HIV epidemic in the EU/EEA.** *BMC Public Health* 2015; **15**:1228.
29. European Centre for Disease Prevention and Control. HIV and migrants. Monitoring implementation of the Dublin Declaration on Partnership to Fight HIV/AIDS in Europe and Central Asia: 2017 progress report Stockholm: ECDC; 2017
30. Migrants Working Group on behalf of COHERE in EuroCoord. **Mortality in migrants living with HIV in western Europe (1997–2013): a collaborative cohort study.** *Lancet HIV* 2015; **2**:e540–e549.
31. Murphy K, Hoover DR, Shi Q, Cohen M, Gandhi M, Golub ET. **Association of self-reported race with AIDS death in continuous HAART users in a cohort of HIV-infected women in the United States.** *AIDS* 2013; **27**:2413–2423.
32. McFall AM, Dowdy DW, Zelaya CE, Murphy K, Wilson TE, Young MA, *et al*., Women's Interagency HIV Study. **Understanding the disparity: predictors of virologic failure in women using highly active antiretroviral therapy vary by race and/or ethnicity.** *J Acquir Immune Defic Syndr* 2013; **64**:289–298.
33. Ludema C, Cole SR, Eron JJ Jr, Holmes GM, Anastos K, Cocohoba J, *et al*. **Health insurance type and control of hypertension among US women living with and without HIV infection in the Women's Interagency HIV Study.** *Am J Hypertens* 2017; **30**:594–601.
34. Jamieson D, Kellerman SE. **The 90 90 90 strategy to end the HIV Pandemic by 2030: Can the supply chain handle it?** *J Int AIDS Soc* 2016; **19**:20917.

35. Hahn RA, Chang MH, Parrish RG, Teutsch SM, Jones WK. **Trends in mortality among females in the United States, 1900–2010: progress and challenges.** *Prev Chronic Dis* 2018; **8**:E30.
36. Harper S, Lynch J, Burris S, Davey Smith G. **Trends in the black-white life expectancy gap in the United States, 1983–2003.** *JAMA* 2007; **297**:1224–1232.
37. Borrell LN, Lancet EA. **Race/ethnicity and all-cause mortality in US adults: revisiting the Hispanic paradox.** *Am J Public Health* 2012; **102**:836–843.
38. Ikram UZ, Mackenbach JP, Harding S, Rey G, Bhopal RS, Regidor E, *et al*. **All-cause and cause-specific mortality of different migrant populations in Europe.** *Eur J Epidemiol* 2016; **31**:655–665.
39. Fenelon A, Chinn JJ, Anderson RN. **A comprehensive analysis of the mortality experience of hispanic subgroups in the United States: variation by age, country of origin, and nativity.** *SSM Popul Health* 2017; **3**:245–254.
40. Hessamfar-Bonarek M, Morlat P, Salmon D, Cacoub P, May T, Bonnet F. **Causes of death in HIV-infected women: persistent role of AIDS. The 'Mortalité 2000 & 2005' Surveys (ANRS EN19).** *Int J Epidemiol* 2010; **39**:135–146.
41. Ingle SM, May MT, Gill MJ, Mugavero MJ, Lewden C, Abgrall S, *et al*. **Impact of risk factors for specific causes of death in the first and subsequent years of antiretroviral therapy among HIV-infected patients.** *Clin Infect Dis* 2014; **59**:287–297.
42. Sobrino-Vegas P, Moreno S, Rubio R, Viciana P, Bernardino JI, Blanco JR, *et al*., Cohorte de la Red de Investigación en Sida, Spain. **Impact of late presentation of HIV infection on short-, mid- and long-term mortality and causes of death in a multicenter national cohort: 2004–2013.** *J Infect* 2016; **72**:587–596.
43. Geng EH, Emenyonu N, Bwana MB, Glidden DV, Martin JN. **Sampling-based approach to determining outcomes of patients lost to follow-up in antiretroviral therapy scale-up programs in Africa.** *JAMA* 2008; **300**:506–507.
44. An MW, Frangakis CE, Musick BS, Yiannoutsos CT. **The need for double-sampling designs in survival studies: an application to monitor PEPFAR.** *Biometrics* 2009; **65**:301–306.
45. Vourli G, Pharris A, Cazein F, Costagliola D, Dabis F, Del Amo J, *et al*. **Are European HIV cohort data within EuroCoord representative of the diagnosed HIV population?** *AIDS* 2019; **33**:133–214.