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Mortality among people entering HIV care compared to the general US population: an observational study

Jessie K. Edwards, PhD,
Department of Epidemiology, University of North Carolina at Chapel Hill, NC

Stephen R. Cole, PhD,
Department of Epidemiology, University of North Carolina at Chapel Hill, NC

Tiffany L. Breger, PhD,
School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Jacqueline E. Rudolph, PhD,
Department of Epidemiology, Emory University, Atlanta, GA

Lindsey M. Filiatreau, MPH,
Department of Epidemiology, University of North Carolina at Chapel Hill, NC

Kate Buchacz, PhD,
Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA

Elizabeth Humes, MPH,
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Peter F. Rebeiro, PhD,
Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN

Gypsyamber D'Souza, PhD,
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

M. John Gill, MB ChB,
Department of Medicine, University of Calgary, Calgary, Alberta

Michael J. Silverberg, PhD,
Kaiser Permanente Northern California, Oakland, CA

W. Christopher Mathews, MD,
Department of Medicine, University of California San Diego, San Diego, CA

Michael A. Horberg, MD,

Correspondence: Jessie K. Edwards, Department of Epidemiology, University of North Carolina at Chapel Hill, 135 Dauer Dr., 2101 McGavran-Greenberg Hall CB7435, 919-966-8338, jessedwards@unc.edu.

Kaiser Permanent Mid-Atlantic Permanente Research Institute, Rockville, MD

Jennifer Thorne, MD,
School of Medicine, Johns Hopkins University, Baltimore, MD

H. Irene Hall, PhD,
Division of HIV/AIDS Prevention, Centers for Disease Control and Prevention, Atlanta, GA

Amy Justice, MD,
Yale School of Public Health, New Haven, CT and Veterans Affairs Connecticut Healthcare System, West Haven, CT

Vincent C. Marconi, MD,
School of Medicine, Emory University, Atlanta, GA and Rollins School of Public Health, Emory University, Atlanta, GA

Viviane D. Lima, PhD,
Faculty of Medicine, University of British Columbia, Vancouver, Canada

Ronald J. Bosch, PhD,
Harvard TH Chan School of Public Health, Boston, MA

Timothy R. Sterling, MD,
Department of Medicine, Vanderbilt University Medical Center, Nashville, TN

Keri N. Althoff, PhD,
Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD

Richard D. Moore, MD,
School of Medicine, Johns Hopkins University, Baltimore, MD

Michael Saag, MD,
Department of Medicine, University of Alabama at Birmingham, Birmingham, AL

Joseph J. Eron, MD
School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC

Abstract

Background: Understanding advances in the care and treatment of adults with HIV as well as remaining gaps requires comparing differences in mortality between people entering care for HIV and the general population.

Objective: To assess the extent to which mortality among people entering HIV care in the United States is elevated over mortality among matched individuals in the general US population and trends in this mortality difference over time.

Design: Observational cohort study

Setting: 13 US North American AIDS Cohort Collaboration on Research and Design sites

Participants: 82,766 adults entering HIV clinical care between 1999 and 2017 matched to a subset of the US population matched on calendar time, age, sex, race/ethnicity, and county using US mortality and population data compiled by the National Center for Health Statistics.

Measurements: 5-year all-cause mortality, estimated using the Kaplan-Meier estimator of the survival function.

Results: Overall 5-year mortality was 10.6%, while mortality among the matched US population was 2.9%, for a difference of 7.7 percentage points (95% confidence interval: 7.4, 7.9). This difference decreased over time, from 11.1 percentage points among those entering care between 1999 and 2004 to 2.7 percentage points among those entering care between 2011 and 2017.

Limitations: Matching on available covariates may have failed to account for differences in mortality due to sociodemographic factors rather than due to consequences of HIV infection and other modifiable factors.

Conclusion: Mortality among people entering HIV care decreased dramatically between 1999 and 2017, although those entering HIV care remained at modestly higher risk of death in the years after starting care than comparable individuals in the general US population.

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INTRODUCTION

Understanding progress and gaps in the care and treatment of adults with HIV requires monitoring differences in mortality between people with and without HIV infection. HIV-related mortality has been declining since the introduction of effective treatment in 1996 due to improving treatment options and evolving care guidelines(1-9), but the extent to which people entering HIV care in the United States have a higher risk of mortality over the following years compared to peers in the general population over the same time period remains unclear. Prior work to elucidate temporal trends in mortality among adults with HIV over the years after entering care has not made comparison to the general US population.

To understand differences in mortality between people entering HIV care and the general population, we estimated the cumulative risk of all-cause mortality over 5 years among 82,766 people entering such care between 1999 and 2017 at US clinical sites affiliated with the North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD). The NA-ACCORD pooling project is representative of people in care for HIV in the US and leverages data collection mechanisms that are well-integrated into clinical HIV care (10).

Because demographic groups with historically elevated mortality also have an elevated risk of HIV infection (11), we compared mortality among people entering HIV care to mortality among the subset of the US population matched to NA-ACCORD participants on key demographic variables constructed from data compiled by the National Center for Health Statistics (NCHS). We also assessed whether the mortality difference between people entering HIV care and their matched counterparts in the general US population varied by demographic characteristics and by calendar time.

METHODS

Data sources

Population and mortality data—We obtained data from the NCHS Detailed Mortality Files on the 47,812,945 deaths occurring in the United States for the years 1999 to 2017 (12). We aggregated the number of deaths for each year for strata defined by age, sex, race/ethnicity (non-Hispanic white, non-Hispanic Black, non-Hispanic American Indian, non-Hispanic Asian/Pacific Islander, or Hispanic), and county of residence. We merged the mortality data with census data provided by the NCHS describing the estimated population size in each of the strata defined above for all US counties over the relevant time period. These merged data, containing both the number of deaths and population size by year, age, sex, race/ethnicity, and county of residence, composed our "population and mortality" data.

HIV cohort data—Data on adults entering HIV care in the United States were obtained from NA-ACCORD, the largest consortium of HIV cohorts in the US and Canada (10). NA-ACCORD includes over 20 contributing single and multisite clinical and interval epidemiologic HIV cohorts. Contributing sites report individual, standardized, data on demographics, medications, diagnoses, laboratory values, and vital status to a central Data Management Core, where they are pooled, harmonized, and undergo quality control. NA-ACCORD has demonstrated that the demographic characteristics of its US participants are similar to that of newly diagnosed persons with HIV infection captured by the US Centers for Disease Control and Prevention's HIV surveillance system (13). Participants were enrolled in NA-ACCORD-contributing cohorts if written informed consent or a waiver of consent were obtained, and NA-ACCORD enrollment criteria include 2 HIV care visits within 12 months. For this analysis, we included data from the 13 US clinical cohorts that contribute data to NA-ACCORD. Human subjects research activities have been approved by each cohort's local Institutional Review Boards and the Johns Hopkins School of Medicine.

Among NA-ACCORD participants, date of death was obtained through participating cohorts' regular queries to the Social Security Death Index, the National Death Index, and state vital statistics registries. Age at entry into care, birth sex, race, ethnicity, transmission risk factor, and ZIP Code, CD4 cell count, and viral load at enrollment, were abstracted from clinical records. We harmonized covariate data between NA-ACCORD and the population and mortality file for the US population by collapsing race categories in NA-ACCORD to match those provided in the NCHS data. Moreover, in NA-ACCORD, place of residence was provided using 3- or 5-digit ZIP Codes rather than counties. To harmonize the population and mortality data for the general population described below, we mapped 5-digit ZIP Codes to counties using ZIP Code-to-county crosswalk tables provided by the US Department of Housing and Urban Development (14). When only 3-digit ZIP Codes were provided, we mapped the 3-digit ZIP Code to a list of possible counties using the same crosswalk tables.

We included 93,408 adults 18 years of age or older who newly enrolled in HIV care at a participating site in the United States during or after 1999. To identify patients newly enrolled in care at cohort entry, we selected those who enrolled after the cohort was established, did not have a recorded date of antiretroviral therapy (ART) initiation or AIDS

diagnosis ≥14 days prior to the cohort enrollment date, and did not have a suppressed viral load (<75 copies/mL) measured between 30 days prior and 7 days after cohort enrollment. We additionally excluded 3 intersex patients and 10,599 patients (11%) due to missing data, including race/ethnicity (n=4813), ZIP Code at entry into care (n=6142), and dates of death (n=40), for a final analytic sample of 82,766 patients.

Statistical methods—Participants in NA-ACCORD were followed from the date of entry into care until death or administrative censoring at 5 years after entry into care, cohort closure, or 31 December 2017 (whichever occurred first). We estimated mortality risk (15) over the 5-year period after entry into HIV care at participating sites using the Kaplan-Meier estimator (16) and standard errors using Greenwood's variance estimator,(17) implemented using the 'survival' package in R.

Our goal was to compare observed cumulative mortality for eligible people entering care at an NA-ACCORD site with their expected mortality had they had the same mortality risk as people of the same age in the same year and with the same demographics (sex, race/ethnicity, and county of residence) in the general population. To compute expected mortality, we created a synthetic cohort (18) of all people in the United States of the same age in the same year matched to each eligible participant starting care at an NA-ACCORD site on sex, race/ethnicity, and county of residence using the population and mortality data described above. We computed expected mortality in each synthetic cohort using the Kaplan-Meier estimator. The overall expected mortality was the average of the expected mortality risk estimated among the synthetic cohort matched to each individual in NA-ACCORD. Technical details are provided in the Supplementary Material.

We compared mortality 5 years after entry into HIV care for participants in NA-ACCORD to mortality over the same time period among the matched US population using risk differences and ratios. We also stratified participants by calendar period of study entry (1999 – 2004, 2005 – 2010, and 2011 – 2017) and compared mortality separately within each stratum. In addition, we stratified the 5-year mortality differences across demographic variables to examine differential trends in these differences over calendar years. Throughout, standard errors for the differences and ratios were estimated using the delta method (19).

To further examine temporal trends, we also stratified 1-, 2-, and 5-year mortality among people entering care in NA-ACCORD and the matched general population by year of entry into care.

All analyses were conducted using SAS 9.4 (Cary, NC) or R 3.6.1.

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RESULTS

Of the 82,766 eligible participants in NA-ACCORD, 84% were male, 46% were non-Hispanic Black, 16% were Hispanic, and the median age at entry into care was 42 years (interquartile range [IQR]: 33, 50) (Table 1). At entry into HIV care, eligible participants resided 324 counties across the US. All regions of the country were represented, with most participants seeking care in the Northeast/mid-Atlantic (35%) or South (34%). Until the last time period (2011 to 2017), the majority of those entering care were between the ages of 35 and 54, but the proportion of those under age 35 and ages 55 and older increased over time. Participants entered the study with a range of CD4 cell counts, and measured CD4 cell count at baseline increased over calendar years, from a median of 284×10^6 cells/L (IQR: 105, 479) among participants entering NA-ACCORD between 1999 and 2004 to 366×10^6 cells/L (IQR: 175, 558) among participants entering between 2011 and 2017.

Overall, 7796 deaths occurred within 5 years of entry into care among eligible participants in NA-ACCORD. The 5-year mortality among people entering HIV care was 10.6%, while mortality among the matched US population was 2.9%. (Figure 1A). Mortality over the first 5 years after entry into HIV care declined substantially over time, from 14.5% among those entering care between 1999 and 2004 to 5.0% among those entering care between 2011 and 2017. Over the same time period, mortality declined less in the matched US population, from 3.4% between 1999 and 2004 to 2.3% between 2011 and 2017. Kaplan-Meier curves for the mortality risk functions are presented in Supplemental Figures 1 and 2.

The difference in 5-year mortality between people entering HIV care and the matched US population was 7.7 percentage points (95% confidence interval [CI]: 7.4, 7.9) (Figure 1B) while the ratio was 3.60 (95% CI: 3.52, 3.69) (Supplemental Table 1). The dramatic decrease in 5-year mortality for those entering HIV care over calendar years coupled with the small decline in 5-year mortality over the same time period in the matched general population meant that the elevation in mortality for people with HIV fell over time. The mortality difference was largest among those entering care between 1999 and 2004 (difference = 11.1 percentage points; 95% CI: 10.7, 11.6) and fell to only 2.7 percentage points (95% CI: 2.2, 3.1) for those entering care between 2011 and 2017. For those entering care between 2011 and 2017, one and two year mortality continued to decline during this period, approaching the matched US population estimate by 2015 (Figure 3, Supplemental Figure 3).

Patterns in mortality differences were similar across demographic groups defined by race, ethnicity, age, and sex (Figure 2; Supplemental Table 2). Notably, by the most recent calendar period, 5-year mortality among participants entering care between the ages of 18 and 34 was only modestly elevated compared to mortality among their peers in the matched US population (mortality difference: 0.9 percentage points; 95% CI: 0.4, 1.4). For older people entering HIV care (55+), the mortality difference also declined substantially over time but remained substantial in the most recent calendar period (6.3 percentage points; 95% CI 4.4, 8.2).

5-year mortality among non-Hispanic Black people entering care at participating sites fell considerably over the calendar periods from 16.5% in the earliest period (1999 and 2004) to 4.9% in the most recent period (2011 and 2017), while mortality among non-Hispanic white people entering HIV care fell less dramatically (from 13.8% to 6.0% over the same period) (Supplemental Figure 4). Notably, by the last calendar time period, 5-year mortality among people entering care at study sites was lower among Black people than white people. Mortality in the matched general US population fell among both groups, though remained higher for non-Hispanic Black people than non-Hispanic white people in all calendar periods, such that the disparity in mortality between people entering HIV care and the general population was smaller for non-Hispanic Black people than non-Hispanic white people in the most recent calendar period.

Among those entering care between 1999 and 2004, the largest mortality differences between those with and without HIV were seen in the South (difference: 13.5 percentage points; 95% CI: 12.6, 14.3) (Supplemental Table 2). However, the South also saw the greatest reduction in disparity over time such that the difference in mortality between 2011 and 2017 was only 2.8 percentage points (95% CI: 1.9, 3.7).

The trends in 5-year mortality differences over calendar periods were significantly ($p<0.05$) different from 0 for all subgroups except non-Hispanic American Indians, for whom the sample size was small (Supplemental Table 2). Ratios comparing mortality by subgroup are presented in Supplemental Table 3.

Patterns in mortality and mortality differences, both overall and stratified by age group, were similar when results were stratified by individual year of study entry rather than calendar period (Figure 3 and Supplemental Figures 4 and 5). Mortality differences were smaller when compared after the first year or 2 years in care than at 5 years. Mortality differences and trends over time were attenuated when analysis was limited to participants entering care with CD4 cell counts $>500 \times 10^6$ cells/L (n=13,673) (Supplemental Figure 6).

DISCUSSION

People entering HIV care in the United States had higher mortality over the subsequent years than people of similar demographics and geographic context in the general US population, but this disparity in mortality declined over calendar years between 1999 and 2017. By the latest calendar period examined (2011 – 2017), 5-year mortality for someone starting care for HIV was only 2.7 percentage points higher than 5-year mortality among people of the same age, sex, race/ethnicity, and county in the general population. In later years of the study, mortality risks for people in NA-ACCORD after 1 year in care were similar to 1-year mortality risks in the general population.

This decline in mortality among people with HIV likely reflects advances in HIV care and treatment (13,20), new guidelines indicating earlier treatment (21), greater engagement in care, higher levels of viral suppression (22), a trend towards linking people with HIV to care earlier in the course of infection (i.e., at higher CD4 cell counts) (23), and evolving patient characteristics in the cohort over time. These trends, specifically CD4 cell count at

entry into care, engagement in care, and time to viral suppression, have been shown to differ by population subgroup (24-27). The confluence of these factors limits our ability to assign causes to the observed patterns. For example, the dramatic decline in mortality among Black people entering HIV care may have been due to improvements in care or could reflect trends in the demographic and clinical features of Black people enrolled in participating sites over time (such as age or timing of presentation to care).

Even in the era of safe, simple, and effective ART, mortality in the years after entering care for HIV may remain higher than mortality among similar people in the general population for at least four reasons. First, though universal immediate treatment (regardless of CD4 cell count) has been recommended in the US since 2012 (28), not everyone entering care for HIV able to start treatment immediately (23,29,30). For example, a recent analyses have reported that, even in high income countries, the median CD4 cell count at ART initiation was below 400×10^6 cells/L for both men and women (26, 31). In the universal treatment era, delays in starting ART are typically due to delays in HIV diagnosis and linkage to care. Second, treatment alone is not a panacea. Although new treatments are vastly improved, they remain imperfect, are only effective when adhered to, and may increase the risk of adverse events with prolonged exposure. With the important exception of long lasting ART, the majority of antiretroviral drugs must be taken every day. Nonadherence, either fleeting or sustained, or treatment discontinuation due to disengagement from care, limits the ability of these drugs to curb mortality. Moreover, treatment itself may play a role in other disease processes (32-38). Third, even in the presence of effective ART, HIV may play a role in non-AIDS related comorbidities and mortality, particularly among people who enter care with advanced immune suppression or at older ages (39-42). Fourth, people with HIV may have higher prevalence of other risk factors for mortality, such as smoking(43-45), substance use(46,47), and comorbidities(48-50).

Previous studies have illustrated that life expectancy among people with HIV is approaching, yet remains below, that of the general population (5,7,8,51), and that heterogeneity in life expectancy between subgroups exists(6). These studies typically compared life expectancy at a specific age (e.g., age 20) between people with and without HIV. But people are diagnosed with HIV at all ages, and it is unclear what an elevation in life expectancy at age 20 means for someone diagnosed with HIV in their 30s, 40s, or beyond. Unlike prior work that compared life expectancy, here we directly compared mortality for people entering HIV care with mortality among their age- (and other covariate-) matched peers in the general US population.

Comparing mortality between people starting HIV care and people of the same age in the general population directs focus to the time after entry into care, when clinicians can intervene on factors that may reduce mortality. Thus, this comparison can be used to guide a set of actionable interventions and assess the effects of such interventions. For example, using the current results as a reference, we could assess how the disparity in mortality between people with HIV and the general population might narrow or widen under new treatments or new strategies to address comorbidities. With appropriate data, additional comparisons that examine mortality after HIV seroconversion (rather than entry into care)

could inform broader public health interventions, such as those aimed at accelerating diagnosis and linkage to care(52).

This study had limitations. Estimates of mortality among those entering care for HIV were limited to those entering care at participating NA-ACCORD sites, which may not be representative of all sites offering HIV clinical care in the United States(53). If people who inject drugs or other groups at higher risk for mortality are over represented in NA-ACCORD, our mortality estimates among people in NA-ACCORD may be higher than mortality among all people starting HIV care in the US. However, cohorts contributing to NA-ACCORD are diverse and representative of many HIV care settings(13). Moreover, we compared mortality after matching age, sex, race/ethnicity, and county to decrease differences in mortality associated with factors other than HIV(54), but both NA-ACCORD and data from NCHS lacked granular information on socioeconomic status and neighborhood. Moreover, we did not have information on smoking, substance use, or comorbidities, which may have been more prevalent in people with HIV(43,47,48) and likely varied over time. In addition, comparison of risks for some strata, such as NH American Indians, were based on small sample sizes in NA-ACCORD, leading to imprecise results.

Furthermore, while we matched on county of residence, counties are large and often diverse, meaning that county is likely to be an inadequate proxy for the attributes of “place” that affect mortality risk(55). This means that some of the difference in mortality between people entering HIV care and the matched general US population could be due to residual differences in geography not captured by the matching variables. Because HIV risk is likely to be spatially correlated with mortality within counties, but county is the most granular spatial unit available for this analysis, our reported mortality differences may overestimate the true difference in mortality between people entering HIV care and similar individuals in the general population. This issue may have been exacerbated when participants in NA-ACCORD had only 3-digit Zip Codes available. In these instances, participants were matched to residences of all counties intersecting the large area covered by the 3-digit Zip Code, which may have been heterogeneous with regard to mortality risk.

County of residence was also subject to misclassification, particularly if participants relocated during the course of the study or did not have long-term permanent residences. Such misclassification could produce bias in the estimated mortality differences, though we expect the proportion of patients affected by this misclassification to be small. Finally, NA-ACCORD may have failed to capture all deaths among participants. Linkage to the National Death Index and state vital status registries likely mitigates this limitation, but any delays in linking to these registries could distort trends in mortality.

Understanding differences in mortality between people entering HIV care and the matched US population is critical to monitor opportunities to improve HIV care. While these differences have declined dramatically in the era of modern treatments, gaps remain. These gaps could reflect the effects of prolonged immune deficiency in those who present late to care or persistent immune activation and subsequent end-stage chronic diseases even among those successfully treated. Antiretroviral medications have adverse effects that may

contribute to mortality risk and the interplay between HIV and aging-related comorbidities and coinfections may accentuate differences in mortality, especially in older populations. (56-60) The uptake by clinicians and patients of standard preventative interventions, such as smoking cessation and lipid and cancer screening, may have lagged in people with HIV especially in earlier time periods and improved over time. Quantifying the elevation in mortality observed for people in care for HIV in the era of modern treatments will inform efforts to address both AIDS and non-AIDS related consequences of HIV infection and long-term ART.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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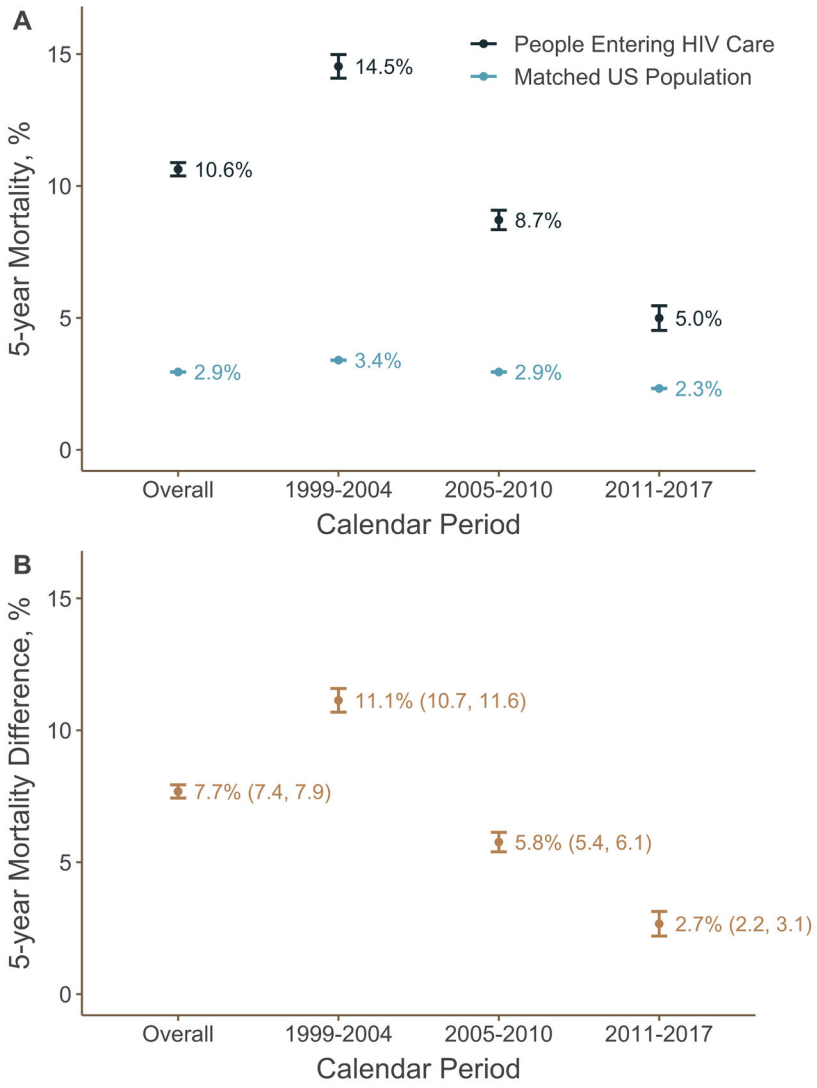

Figure 1.

5-year mortality (Panel A) and mortality differences in percentage points (Panel B) comparing mortality among 82,766 people entering care for HIV at a US NA-ACCORD clinical site between 1999 and 2004 (n = 32,588), 2005 and 2010 (n = 27,104), and 2011 and 2017 (n = 23,074) and a matched subset of the general US population. Bars represent 95% confidence intervals.

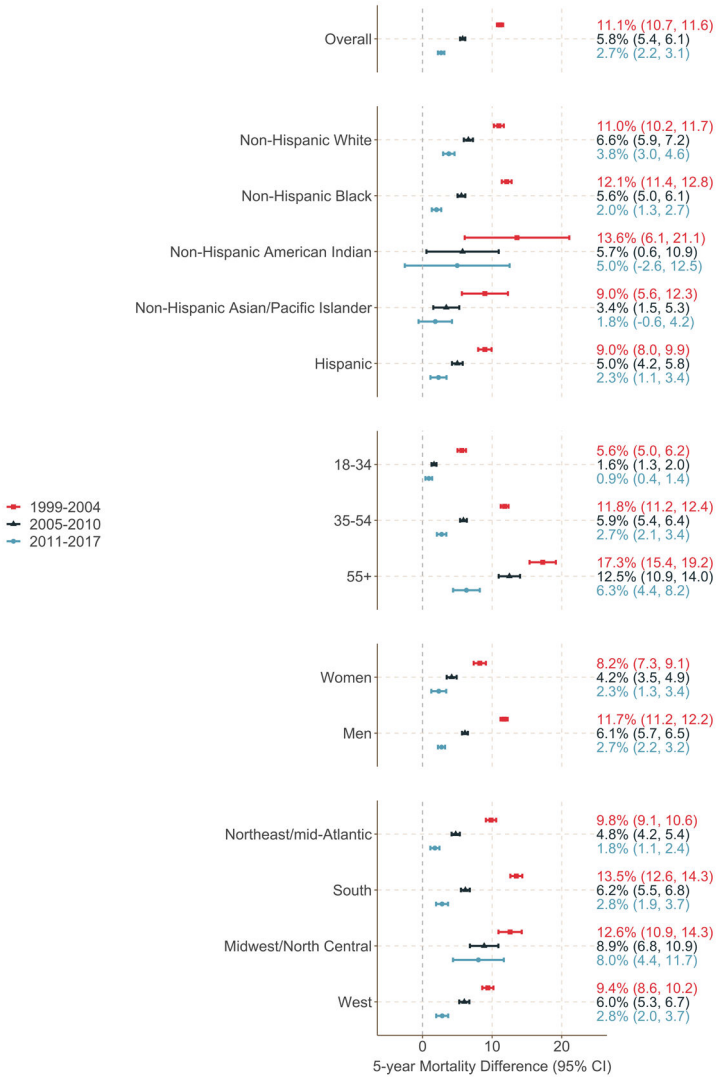

Figure 2.

Percentage point differences in 5-year mortality among 82,766 people entering care for HIV at a US NA-ACCORD clinical site between 1999 and 2004 (n = 32,588; red squares and bars), 2005 and 2010 (n = 27,104; black triangles and bars), and 2011 and 2017 (n = 23,074; blue circles and bars) and a matched subset of the general US population, overall and stratified by race/ethnicity, age, sex, and region.

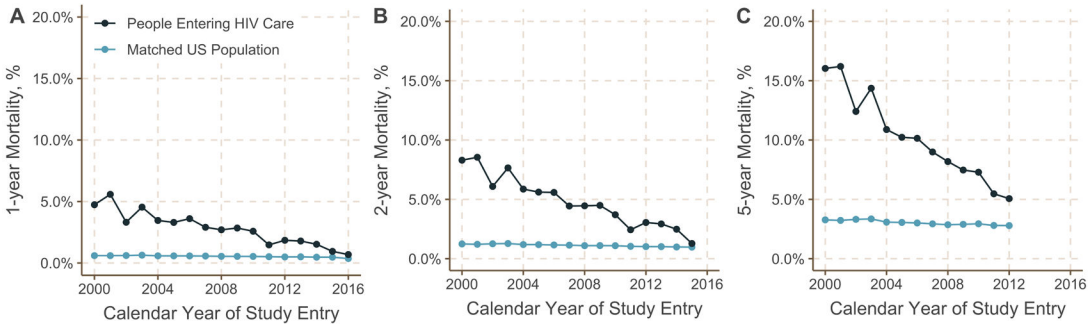

Figure 3.

Mortality at 1 year (Panel A), 2 years (Panel B), and 5 years (Panel C) after entering HIV care among 82,766 people entering care for HIV at a US NA-ACCORD clinical site between 1999 and 2017 compared to mortality among a matched subset of the general US population, stratified by year of entry into care. The gap in 1-year mortality appears to close by the later years examined (panel A), but 5-year mortality remains elevated over the entire calendar period (panel C), suggesting that there may be factors that influence the effectiveness of care (e.g., treatment discontinuation, disengagement from care) and, therefore, increase mortality among those with HIV after the first year.

Table 1.

Characteristics of 82,766 eligible people entering care for HIV at a US NA-ACCORD clinical site between 1999 and 2017, stratified by calendar period at entry into care.

	Overall (*n* = 82,766)		Entered care between 1999 and 2004 (*n* = 32,588)		Entered care between 2005 and 2010 (*n* = 27,104)		Entered care between 2011 and 2017 (*n* = 23,074)	
Characteristic	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Race/Ethnicity								
NH White	29084	35.1	11994	36.8	9099	33.6	7991	34.6
NH Black	38263	46.2	15133	46.4	12854	47.4	10276	44.5
NH American Indian	350	0.4	131	0.4	118	0.4	101	0.4
NH Asian/Pacific Islander	1463	1.8	379	1.2	468	1.7	616	2.7
Hispanic	13606	16.4	4951	15.2	4565	16.8	4090	17.7
Age at study entry								
18-34	23169	28.0	7219	22.2	7564	27.9	8386	36.3
35-54	47067	56.9	21261	65.2	15221	56.2	10585	45.9
55+	12530	15.1	4108	12.6	4319	15.9	4103	17.8
Sex								
Female	13448	16.2	5412	16.6	4674	17.2	3362	14.6
Male	69318	83.8	27176	83.4	22430	82.8	19712	85.4
US Region of residence[a]								
Northeast and mid-Atlantic	29016	35.1	11018	33.8	9458	34.9	8540	37.0
South	27909	33.7	10591	32.5	9540	35.2	7778	33.7
Midwest and North Central	5332	6.4	2844	8.7	1471	5.4	1017	4.4
West	20509	24.8	8135	25.0	6635	24.5	5739	24.9
CD4 cell count at entry into care[b]								
750+	4483	5.4	1396	4.3	1463	5.4	1624	7.0
500-749	9250	11.2	2941	9.0	3171	11.7	3138	13.6
350-499	10047	12.1	3296	10.1	3601	13.3	3150	13.7
200-349	11083	13.4	4030	12.4	4020	14.8	3033	13.1
<200	17552	21.2	7139	21.9	6242	23.0	4171	18.1
Missing	30351	36.7	13786	42.3	8607	31.8	7958	34.5
Transmission risk factor[c]								
MSM	28782	34.8	8573	26.3	9599	35.4	10610	46.0
IDU	14746	17.8	8279	25.4	4218	15.6	2249	9.7

NH: Non-Hispanic; MSM: Men who have sex with men; IDU: injection drug use

[a]Region of residence was categorized by the first digit of the ZIP Code such that those beginning with 0, 1, or 2 were labeled “Northeast or mid-Atlantic,” those beginning with 3 or 7 were labeled “South”, those beginning with 4, 5, or 6 were labeled “Midwest and North Central”, and those beginning with 8 or 9 were labeled “West”

[b]Baseline CD4 cell count (in cells/mm^3) was defined as the last CD4 cell count measured between 30 days prior and 14 days after a participant’s enrollment date

[c] Transmission risk factors were not mutually exclusive (i.e., some participants appear in both “MSM” and “IDU” rows)