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## Exploring the impact of therapeutic advances in HIV-related mortality in the United States

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### ABSTRACT

**Objectives:** Mortality from HIV has significantly declined with the introduction of highly active antiretroviral therapy (HAART). This study sought to examine the longitudinal trends in mortality from HIV-related diseases by race, sex, geographical region, and over time as HAART trends changed.

**Methods:** We queried the Centers for Disease Control and Prevention's Wide-Ranging Online Data for Epidemiologic Research database and performed serial cross-sectional analyses of national death certificate data for all-cause mortality with comorbid HIV from 1999 to 2020. HIV diseases (International Classification of Diseases, Tenth Revision codes B20-B24, O98.7, R75) were listed as the contributing cause of death. We calculated the age-adjusted mortality ratio (AAMR) per 1,000,000 individuals and determined mortality trends using the Joinpoint Regression Program. Subgroup analyses were performed by sex, race, region, and organ system. The study period was further stratified into three groups when specific drug regimens were more prevalent.

**Results:** In the 22-year study period, 251,759 all-cause mortalities with comorbid HIV were identified. The leading cause of death was infectious disease (84.0%, N = 211,438). Men recorded a higher AAMR than women (4.66 vs 1.65,  $P < 0.01$ ). African American individuals had the highest AAMR (13.46) compared to White, American Indian, and Asian individuals (1.70 vs 1.65 vs 0.47). The South region had the highest AAMR (4.32) and urban areas had a higher AAMR compared to rural areas (1.77 vs 0.88).

**Conclusions:** More than 80% of deaths occurred because of infectious disease over the last 2 decades with a decreasing trend over time when stratified by race, sex, and geographical region. Despite advances in HAART, mortality disparities persist which emphasizes the need for targeted interventions in these populations.

### Introduction

HIV has historically been associated with high morbidity and mortality but has seen a significant decline since the introduction of highly active antiretroviral therapy (HAART) [1]. Over the last 2 decades, antiretroviral therapy (ART) has evolved dramatically in the United States (U.S.) from taking a mix of pills during the day known as multi-tablet regimens (MTR) to a single dose known as single-tablet regimens (STR) and from non-nucleoside reverse transcriptase inhibitors and protease inhibitor-based regimens to integrase inhibitor (INI)-based ART [2]. Despite advances in the therapeutic approach to HIV, the real-world data on the impact of these changes on population mortality in the U.S. is not well-established. It is also important to dissect and identify persistent inequities that contribute to death in people with HIV which may help to inform interventions to improve health outcomes in the next decade [3].

Thus, we conducted this nationwide population-based study to determine the trends in all-cause mortality attributed to HIV disease by race, sex, geographic regions, and over time as HAART trends changed.

### Methods

#### Data source

The Centers for Disease Control and Prevention's (CDC) Wide-Ranging Online Data for Epidemiologic Research (WONDER) is a database available publicly online that contains public health data, including mortality data, demographic data, and encoded information on the underlying cause of death based on death certificates of United States (U.S.) residents from January 01, 1999, to December 31, 2020. The International Classification of Diseases, Tenth Revision (ICD-10) is

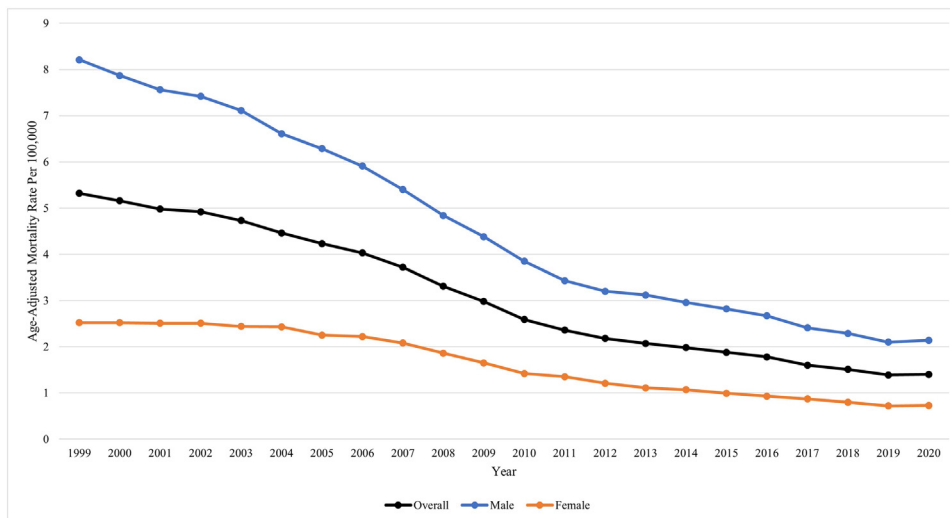
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**Figure 1.** Trends in age-adjusted mortality ratio of HIV-related mortality, stratified by gender groups, between 1999 and 2020.

used to classify the causes of death for 1999 and beyond. This study approach has been validated in similar research on other topics of interest [4,5]. Institutional review board approval was not required for our study as the population data is publicly available and anonymized.

We queried the CDC WONDER database from 1999-2020 and evaluated the demographics for all-cause mortality in the general population followed by overall HIV mortality. We performed serial cross-sectional analyses of national death certificate data for HIV-related mortality. We utilized HIV diseases (ICD-10 B20-B24, O98.7, R75) listed as the underlying cause of death to analyze the age-adjusted mortality ratio (AAMRs) standardized to 2000 U.S. census proportions as the unit of analysis. The underlying cause of death is defined by The World Health Organization as the disease or injury that initiated a train of events leading directly to death [6]. Demographic features were then used to stratify the study population based on race, sex, geographic consensus region, and urbanization. The study period was further divided into three groups when specific drug regimens were more prevalent: 1999-2007 (multi-tablet regimen prevalence [MTRp]), 2008-2014 (single-tablet regimen prevalence [STRp]), and 2015-2020 (integrase inhibitor prevalence [INIp]).

#### Participants

The study included individuals aged 15 years or older. Individuals aged <15 years or individuals with unknown age at the time of death on the death certificate were excluded from the data query.

#### Statistical analysis

We calculated the AAMR per 1,000,000 (1 million) individuals and determined the mortality trends over time by using the Joinpoint Regression Program. Subgroup analyses were performed by sex, race, consensus region, state, and urbanization level. Urban was defined as (small metro counties, medium metro, large fringe metro, and large central metro) and rural as (non-core, non-metro counties, and micropolitan non-metro) according to the 2013 U.S. Census Classifications [7]. Additional analyses were performed to categorize the underlying causes of death by organ systems in three different time periods (MTRp, STRp, and INIp).

## Results

#### Overall trend in all-cause mortality related to HIV

A total of 251,759 all-cause mortalities with comorbid HIV in the U.S. were identified between 1999 and 2020. The AAMR from HIV-

related mortality decreased significantly from 5.32 per 1,000,000 individuals in 1999 to 1.40 per 1,000,000 individuals in 2020 ( $P < 0.01$ ) (Figure 1).

#### Causes of death among HIV-related mortality

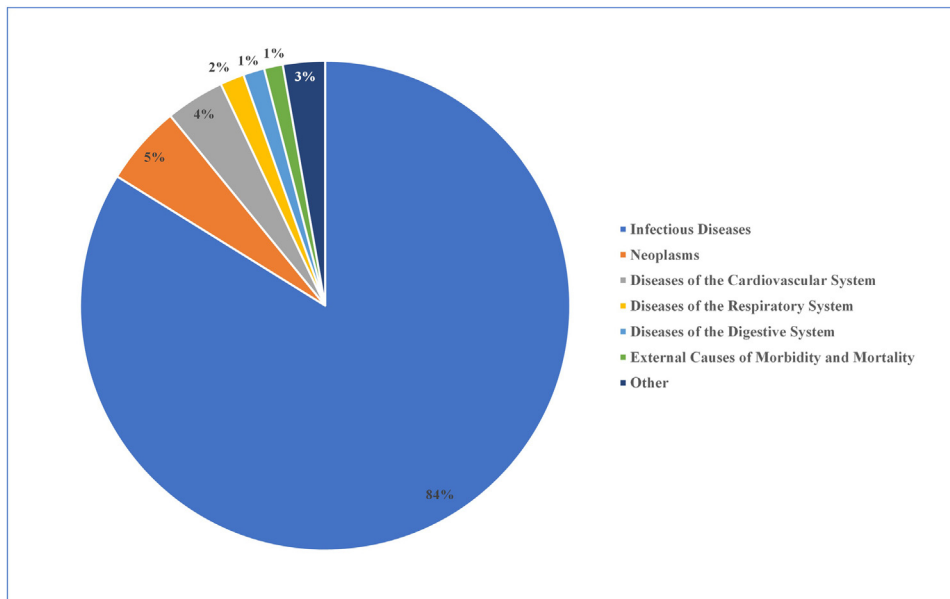
Among all reported HIV-related deaths, the most common cause of death was infectious diseases (84.0%,  $N = 211,438$ ), followed by neoplasms (5.3%,  $N = 13,264$ ) and diseases of the cardiovascular system (3.9%,  $N = 9797$ ) (Figure 2). The AAMR in HIV was also highest in infectious diseases at 3.12 per 1,000,000 individuals, followed by neoplasms (0.18 per 1,000,000 individuals), diseases of cardiovascular system (0.12 per 1,000,000 individuals), diseases of respiratory system (0.05 per 1,000,000 individuals) and diseases of gastrointestinal system (0.04 per 1,000,000 individuals). Further analysis of infectious-related causes showed significantly decreasing mortality trends from 89.6% during MTRp to 81.8% in STRp and 71.5% in INIp (Figure 3). On the contrary neoplasms and diseases of the cardiovascular system showed an increase from 3.3% and 2.5% (MTRp) to 6.7% 4.3% (STRp), and 8.7%, and 7.1% in INIp, respectively.

#### Racial and gender disparities

Overall, men recorded a higher AAMR compared to women (4.66 vs 1.65 per 1,000,000 individuals,  $P < 0.01$ ) (Figure 1). African American individuals had the highest AAMRs (13.46 per 1,000,000 individuals) compared to White, American Indian, and Asian individuals (1.70 vs [1.65 vs 0.47] per 1,000,000 individuals). Similar decreasing trends were seen in all racial groups: African American men from 36.12 to 8.11 per 1,000,000 individuals, African American women from 13.13 to 3.54 per 1,000,000 individuals, White men from 4.91 to 1.36 per 1,000,000 individuals, and White women from 1.00 to 0.27 per 1,000,000 individuals (Figure 4). Trends in groups with the highest mortality were further categorized. Men revealed a 53.72% decrease from MTRp to STRp and a 38.74% decrease from STRp to INIp. African American individuals also showed a decreasing course of 54.92% from MTRp to STRp and 43.38% from STRp to INIp.

#### Regional disparities

When stratified by consensus regions, the South region had the highest AAMR from HIV-related mortality (4.32 per 1,000,000 individuals), followed by the Northeast region (3.93 per 1,000,000 individuals), West region (2.06 per 1,000,000 individuals), and Midwest region (1.52 per



**Figure 2.** Causes of deaths among HIV-related mortality reported, stratified by organ system.

1,000,000 individuals) (Figure 5). Infectious and parasitic diseases, neoplasms, and diseases of the circulatory system were the three most common causes of mortality in all regions. These were followed by diseases of the respiratory and digestive system in all regions except in the South where external causes contributed to higher mortality rates. Across the states, Florida had the highest AAMR at 6.57 per 1,000,000 individuals, while North Dakota had the lowest AAMR at 0.4 per 1,000,000 individuals (Figure 5). When stratified by urbanization, urban areas had a higher AAMR from HIV-related mortality compared to rural areas (1.77 vs 0.88 per 1,000,000 individuals).

## Discussion

### Overall trend and causes of death among HIV-related mortality

Our study provides insights into trends in HIV mortality over the last 20 years in the U.S. More than 80% of HIV-related deaths occurred because of infectious diseases. This is evident as research demonstrates how viral and host factors contribute to the pathogenesis of HIV rendering untreated individuals more susceptible to opportunistic infections [8]. The introduction of HAART significantly contributed to extended life expectancy of persons with HIV and a concomitant decline in major causes of HIV-related mortality [9]. Our study showed that from 1999-2020, a decreasing trend in infectious-related mortality was observed with cases declining from 134,726 (MTRp) to 69,450 (STRp) and 47,583 during INIp. Identifying prognostic factors for survival among people with HIV is crucial and there may be multiple explanations for this [9]. First, rates of medication adherence and viral load suppression were shown to be higher in patients with simpler medication regimens and lower pill burden [10,11]. Second, this may also be explained by improved tolerability and efficacy of HAART. Studies demonstrated improved efficacy and safety profiles of Integrase Strand Transfer regimens compared to other classes of HAART [12]. In addition to advances in HAART, better management of opportunistic infections, enhanced prevention measures, and improved access to healthcare also contribute to improved survival [9]. Apart from infectious diseases, other major causes of HIV-related mortality included neoplasms (5%) followed by diseases of the cardiovascular (4%) and respiratory system (2%) (Figure 2). In contrast to the declining rate of infectious diseases, our study demonstrated the increase mortality from other leading causes of death including neoplasms, and cardiovascular and respiratory diseases (Figure 3). This stimulates new questions to address reasons for the

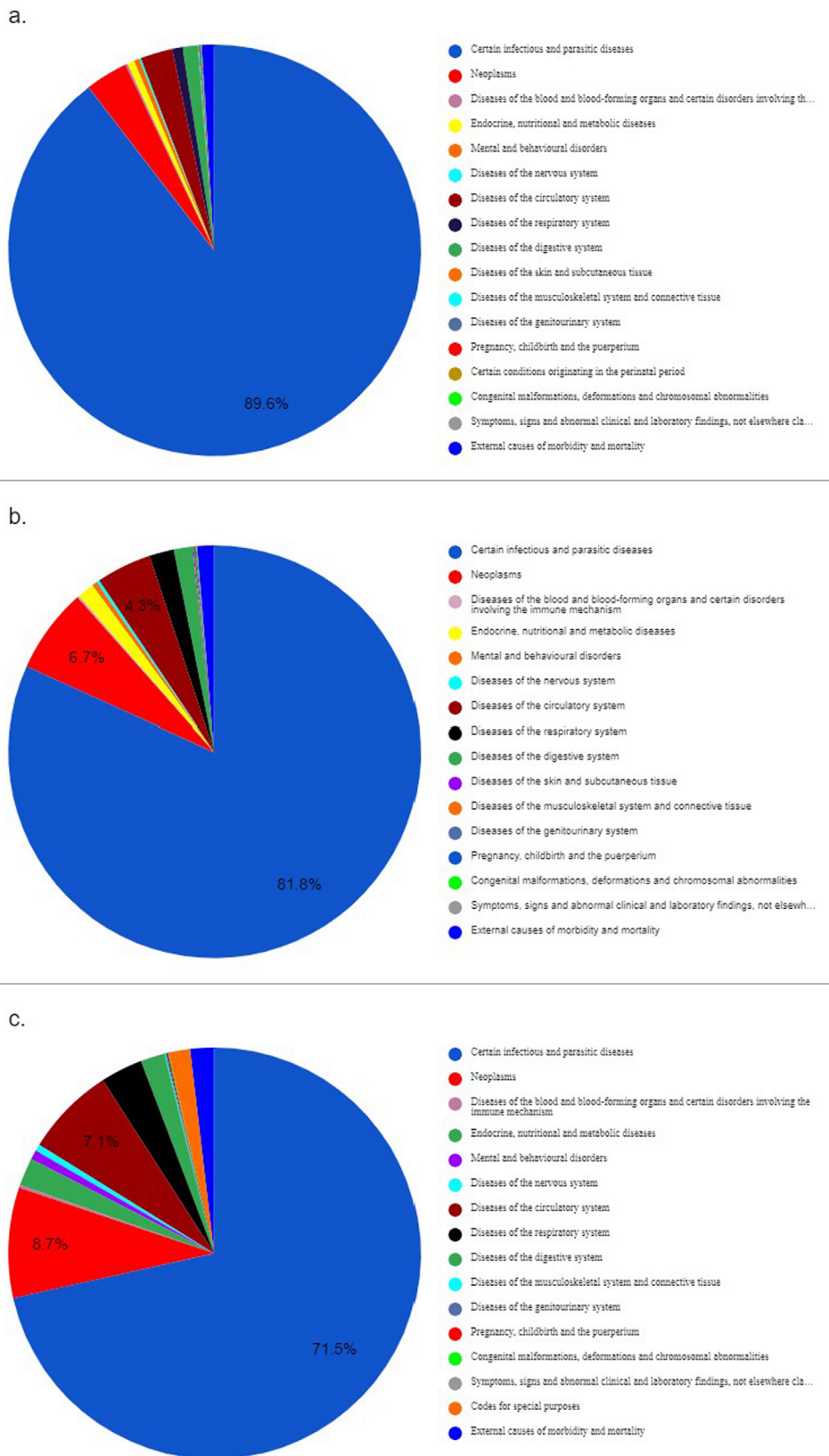
increase in the mortality from such causes in people with HIV. Hypotheses suggested a multitude of reasons including greater vulnerability to cardiovascular disease and neoplasms resulting from aging, chronic inflammation and immune dysregulation, greater accuracy of diagnostic and screening tests in the general population, and other risk factors such as smoking and alcohol consumption [13,14].

### Racial and gender disparities

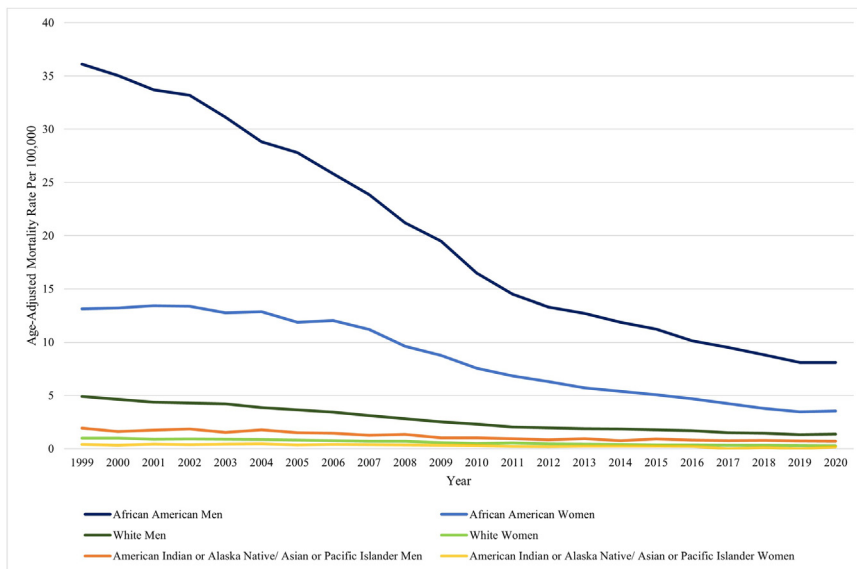
The overall AAMR from HIV-related mortality has also decreased significantly over the last 2 decades. Men and African American individuals had a higher AAMR from HIV-related mortality. In our study, men recorded a higher AAMR compared to women (4.66 vs 1.65 per 1,000,000 individuals,  $P < 0.01$ ). In 2018 alone, men accounted for 81% of the new HIV diagnoses in the U.S. [15]. Research has demonstrated that gender differences in mortality became more apparent after the introduction of HAART, even in areas where care access and gender equity were desirable, women showed more consistency with treatment adherence and follow-up with medical providers [16]. Our study also showed that African American individuals had the highest AAMRs (13.46 per 1,000,000 individuals) compared to White, American Indian, and Asian individuals (1.70 vs 1.65 vs 0.47 per 1,000,000 individuals). Nevertheless, decreasing mortality trends were seen in all racial groups highlighting the effectiveness of HAART. Despite the advances in HAART, significant racial and gender disparities persist. This could be attributed to poor adherence to treatment, late initiation of ART, inability to access healthcare, or social factors such as depression and lack of support [17]. HIV transmission rates may be influenced by undiagnosed infection within communities. One study demonstrated that approximately 15% of Black or African American patients were not aware of their HIV infection when compared to 12% of White patients [18]. Greater attention to this community may be required to improve survival and clinical outcomes.

### Regional disparities

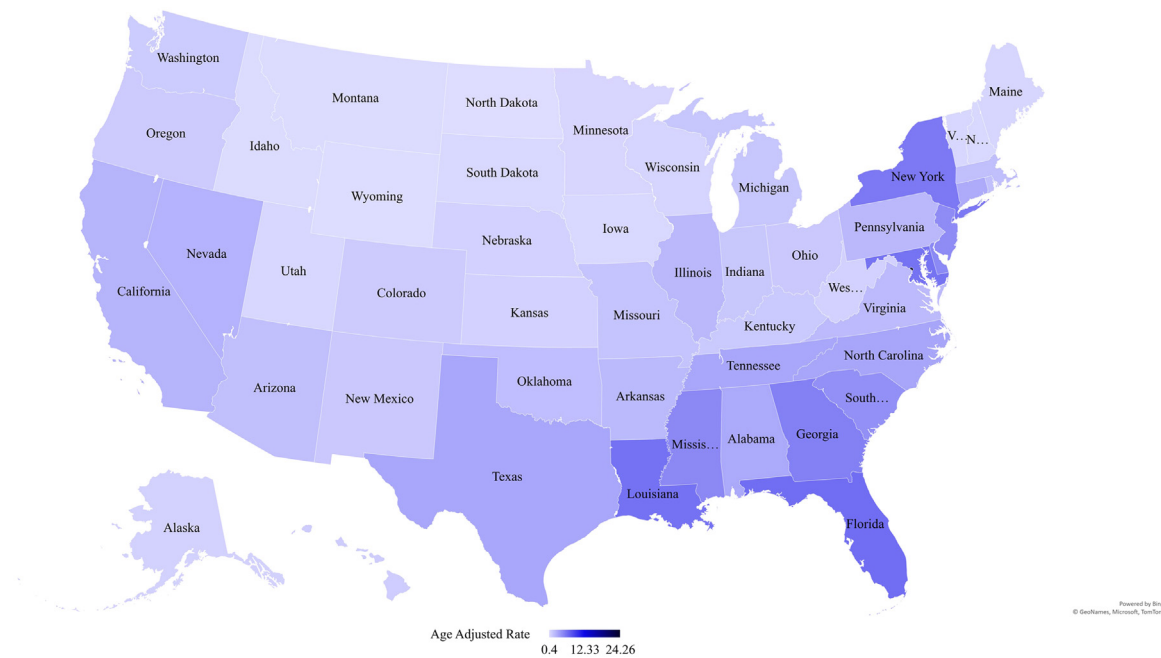
In the 22-year study period, 210 921 HIV-related mortality cases in the U.S. were identified. Only the top three causes of morbidity and mortality patterns remained consistent in all regions and the South region had the highest AAMR from HIV-related mortality. Southern states have been shown to have higher rates of new sexually transmitted disease diagnosis and lowest survival rates, despite lower population den-



**Figure 3.** Causes of deaths among HIV-related mortality reported, stratified by organ system, between multi-tablet regimens prevalence (a) single tablet regimens prevalence (b) and integrase inhibitor prevalence (c).



**Figure 4.** Trends in age-adjusted mortality ratio of HIV-related mortality, stratified by racial groups, between 1999 and 2020.



**Figure 5.** The age-adjusted mortality ratio of HIV-related mortality, stratified by states.

sity compared to other U.S. regions [19]. In 2010, approximately half (49%) of individuals living with HIV in the U.S. were diagnosed in this region [20]. Several factors likely contribute to this pattern including inferior health conditions, elevated poverty rates, widespread HIV-related stigma, less health education, and limited accessibility to healthcare providers because of the presence of healthcare deserts [19–21]. Effective HIV prevention strategies are imperative in these regions to mitigate the risk of HIV-related death; thus, it is crucial to urgently address the unique challenges that southern states face. When we examined data across various states, Florida exhibited the highest AAMR at 6.57 per 1,000,000 individuals, while North Dakota had the lowest AAMR at 0.4 per 1,000,000 individuals (Figure 5). Stratifying the data by urbanization revealed that urban areas had a higher AAMR from HIV-related mortality compared to rural areas (1.77 vs 0.88 per 1,000,000 individuals). Mortality disparities in urban areas are of significant concern and a sustained focus on areas with a high HIV burden is imperative for achieving success in the battle against HIV mortality. This underscores the

need for additional research to assess the fundamental reasons that contribute to pervasive racial, gender, and urbanization disparities in HIV mortality which may aid in informing targeted interventions to bridge the disparities noted in our study.

*Limitations*

Our study is subject to several limitations. By design, the CDC WONDER database utilizes death certificates and is subject to human reporting errors, which include but are not limited to inaccurate assessment of the cause of death, compilation errors, misclassifying demographics, or data loss. Secondly, people living with HIV in rural areas may have migrated to urban areas for advanced treatment which may have overestimated the mortality rates in urban locations. Another limitation relates to the use of ICD-10 codes as filter criteria where clinical data including infectious etiologies are deficient in determining etiology and severity making it difficult to further characterize the population’s clinical status.

The transition between the 9th and 10th revisions of the ICD codes that occurred during the study period could also contribute to biased results if states introduced changes in their reporting policies. However, this is not likely given the consistency of death certificate reporting [22]. Finally, this population study excluded information at the individual level including previous intervention, comorbidity burden, disease duration, or medical treatment which are important confounders for mortality. Nevertheless, our study adequately demonstrates the demographic and temporal relationship in HIV mortality over time and provides valuable insights into the need for urgent implementation of interventions to further decrease mortality in high-risk groups.

## Conclusion

Our study highlights a decreasing trend in overall HIV-related mortality over the past 2 decades with significant differences observed when stratified by regional subpopulations, urbanization level, gender, and racial background. These findings reflect the improved tolerability and efficacy of HAART, yet it highlights the persistent disparities that exist in HIV mortality. This affirms the need for targeted strategies that focus on the social drivers of health; particularly economic status, health access, and health care quality to decrease mortality disparities in the next decade. This may be done in the form of interventions to induce behavioral change and improve resource distribution to underserved populations across different regions. Additional emphasis should be placed on screening protocols for causes of mortality that have increased incidence in people living with HIV to improve survival in this population.

## Declarations of competing interest

The authors have no competing interests to declare.

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## Author contributions

The authors confirm their contribution to the paper as follows: study conception and design: Prince, MA, Tan, MC.; data collection: Tan MX; analysis and interpretation of results: Tan MX, Tan MC, Prince MA; draft manuscript preparation: Prince MA, George H, Tan MC, Prince EO, Nicholas RM, Slim J, Shaaban H; Study advisor: Slim, J. All authors reviewed the results and approved the final version of the manuscript. The data that support the findings of this study are openly available at CDC WONDER at <https://wonder.cdc.gov/mcd.html>.

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