

A Spatiotemporal Analysis of HIV-Associated Mortality in Rural Western Kenya 2011–2015

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Background: Reliable data on the HIV epidemic is critical for the measurement of the impact of HIV response and for the implementation of further interventions.

Methods: We used mortality data from the Kombewa health and demographic surveillance systems (HDSS) from January 1, 2011 to December 31, 2015 to examine the space–time pattern of HIV-associated mortality. HIV mortality rate was calculated per 1000 persons living with HIV (for comparison with regional and national averages) and per 1000 person-years (p-y) for comparison with data from other HDSS sites. We used the Optimized Hot Spot Analysis to examine whether HIV-associated deaths would form statistically significant local aggregation in the 5-year period. *P*-value of <0.05 and <0.01 was considered significant.

Results: The HIV-associated mortality rate over the 5-year period was 9.8 per 1000 persons living with HIV (PLHIV). Mortality declined from 11.6 per 1000 PLHIV in 2011 to 7.3 per 1000 PLHIV by the end of 2015. The rates of HIV were highest among infants [hazard ratio (HR) = 2.39 (<0.001)]. Tuberculosis mortality rates were highest in the age group 5–14 years [HR = 2.29 (0.002)] and

the age group 50–64 years [HR = 1.18 (0.531)]. The overall trend in HIV-associated mortality showed a decline from 1.8 per 1000 p-y in 2011 to 1.3 per 1000 p-y by the end of 2015. The hotspot analysis showed that 20.0% of the study area (72 km²) was detected as hotspots ($Z = 2.382-3.143$, $P \leq 0.001$) and 4.2% of the study area as cold spots (15 km²).

Conclusions: HIV attributable death in the HDSS population is substantial, although it is lower than both the national and the regional estimates.

Key Words: HIV, mortality, HDSS, clustering, geographic differences, verbal autopsy

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INTRODUCTION

One of the global targets by the United Nations is to reduce the estimated number of HIV-associated deaths by 90% by the year 2030.¹ It is estimated that 1.5 million persons were living with HIV (PLHIV) in Kenya at the end of 2015, with 35,822 deaths attributable to HIV/AIDS.² The epidemic is geographically diverse, ranging from a prevalence of 26% in parts of Nyanza region in Western Kenya to a low of approximately 0.4% in the Northeastern region of the country.³ Available country level data show a steady decline in the number of HIV deaths at national level since the scale up of antiretroviral therapy (ART) in 2006.² Reliable data that show trends in HIV-associated mortality is therefore critical for the tracking and measurement of the impact of the HIV response and for the implementation of further interventions.

A major obstacle to the implementation of HIV-associated mortality surveillance, particularly in resource constrained countries, has been unreliable health data, likely secondary to weak or incomplete vital registration systems.⁴ One solution to address this is to collect prospective data from a population as is done in a health and demographic surveillance system (HDSS). A HDSS is a longitudinal, population-based health and vital event registry system that monitors demographic and health events in a geographically defined population. This continuous surveillance makes it possible to provide a cause-specific mortality and morbidity profile of residents living within the HDSS catchment area.⁵

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P.S. reviewed the literature, analyzed, and interpreted the data. P.S., W.O., B.O., and L.O. codesigned the study; S.O. helped with VA data coding, data management and provided local field supervision. J.C. helped with editing of the article. All authors (S.O., B.A., J. Oy., W.O., V.S., J. Ow., B.O., J. C., L.O.) commented on successive drafts, interpretation of results, and approved the final version.

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In such settings where vital registration systems are weak or nonexistent, few data regarding causes of death are available. One way of determining the magnitude of HIV-related mortality is by verbal autopsy (VA), which involves a structured interview with the caregiver or a close person to the deceased.⁶ The information contained in the VA interview is then used to assign the probable cause of death (COD). In the recent past, computerized models such as the InterVA-4 model are increasingly being relied upon to derive COD information, in an attempt to overcome limitations of alternative methods,^{7–10} such as physician coding.

In this article, we present HIV-associated mortality rates as determined by computer-interpreted VA from the Kombewa HDSS in rural Western Kenya.¹¹ The Kombewa HDSS is located in a rural part of Kisumu County, Western Kenya, and covers an area of about 369 km² along the northeastern shores of Lake Victoria. A dynamic cohort of 141,956 individuals drawn from 34,718 households forms the HDSS surveillance population. Key demographic and health changes are monitored through biannual household surveys. The population residing in the HDSS area is largely rural and characterized by low economic status with high prevalence of infectious diseases, such as tuberculosis (TB), HIV, and malaria.^{12–14}

The HDSS area serves as the catchment population for both the United States President's Emergency Plan for AIDS Relief (PEPFAR) program within the US Army Medical Research Directorate-Kenya (USAMRD-K) and the clinical trials conducted at the Kombewa Clinical Research Center.¹⁵ The prevalence of HIV in the region encompassing the entire HDSS is nearly 4 times the nationally reported average with a general prevalence in Kisumu County of 20% as compared to the national prevalence of 5.9%.³ In 2012, the HDSS supported a door-to-door HIV counseling and testing initiative by the USAMRD-K PEPFAR program in a section of the HDSS area (Seme Subcounty). The exercise yielded a 3.5% HIV positivity among 40,976 individuals who agreed to counseling and testing (a service acceptance of 94%). The burden of TB disease in the region encompassing the entire HDSS that area is estimated at 500–600 cases per 100,000 population.¹² An analysis of 5196 registered deaths (among all ages) living in the area covered by the Kombewa HDSS from January 1, 2011 to December 31, 2015 reveals HIV as the leading COD, representing 12.6% of deaths for which a VA was available.¹⁶ Other top causes of death within the surveyed population include malaria (10.3%), pneumonia (10.1%), and TB (4.9%).

Information on subepidemics within the generalized epidemic area is important for program planning and focusing interventions for PLHIV within the HDSS population. Geospatial analytical methods provide a vital tool for understanding the nature of spatial variation in disease burden.¹⁷ Spatial analysis techniques have been successfully used elsewhere within the African continent^{18–21} and also globally^{22,23} to identify areas of high disease transmission, most-at-risk populations, access to health care services, and understanding the epidemiology of the disease. Despite increased application of such analyses, few studies in Kenya have analyzed the spatiotemporal variation and clustering of HIV with more granularity, even if such information can improve understanding and enhance effectiveness of inter-

ventions. In addition to the wasting syndromes typical of AIDS deaths, HIV has been shown to be an underlying CODs attributed to other diseases, most notably TB.^{24,25} In this article, deaths assigned to HIV are complemented with the corresponding rates for TB and pneumonia.

METHODS

Study Population and Location

Figure 1 shows the location of the Kombewa HDSS and the distribution of health facilities that provide HIV services. The Kombewa HDSS is located in a rural part of Kisumu County, Western Kenya, and covers the entire Seme Subcounty and parts of Kisumu West Subcounty within Kisumu County, western parts of Kenya. The Kombewa Clinical Research Centre, located at the heart of the HDSS area, is surrounded by 27 functioning health facilities, 24 of which are government and 3 are private or faith-based organizations. At the start of 2007, the USAMRD-K PEPFAR program was supporting only a few of HIV services both at the community and at the facility level. These services included HIV care and treatment in 10 sentinel facilities, prevention of mother-to-child transmission (PMTCT) in 22 sentinel facilities (including early infant diagnosis in 10 of these facilities), HIV testing and counseling in 22 sentinel facilities, and TB/HIV services (including nutrition counseling) in 10 sentinel facilities. By the end of 2017, the program had expanded these services to 24 sentinel facilities. In addition to the services previously provided, the program rolled out an orphans and vulnerable children program currently serving a total of 8681 OVCs (at the end of 2017). The program also initiated a HIV prevention strategy called Determined, Resilient, AIDS-free, Mentored, and Safe (DREAMS) at the community level. The DREAMS program seeks to reduce HIV infections among adolescent girls and young women through addressing the structural drivers that directly and indirectly increase girls' HIV risk, including poverty, gender inequality, sexual violence, and a lack of education.

The Kombewa County Hospital located within the Kombewa HDSS serves as the main referral hospital (Fig. 1). Over the years, the site has been working in partnership with the Ministry of Health (MoH) by augmenting clinical staffing needs to support the health facilities operations through the HIV program and research activities. The support include pediatricians who provide consultation services, nurses, clinical officers, laboratory technologists, pharmacy, radiographers, HIV counselors, and community health workers. The site has also been involved in capacity building at the various health facilities, including the provision of laboratory equipment (hematology and chemistry machines), putting up an x-ray building and installation of state-of-the-art x-ray and ultrasound equipment, building of an ultramodern outpatient facility, provision of water and backup electricity, painting of the hospital, and advocating for the construction of a maternity ward and theatre, with support from a research partner and the government of Kenya; the construction work has begun. In addition, an

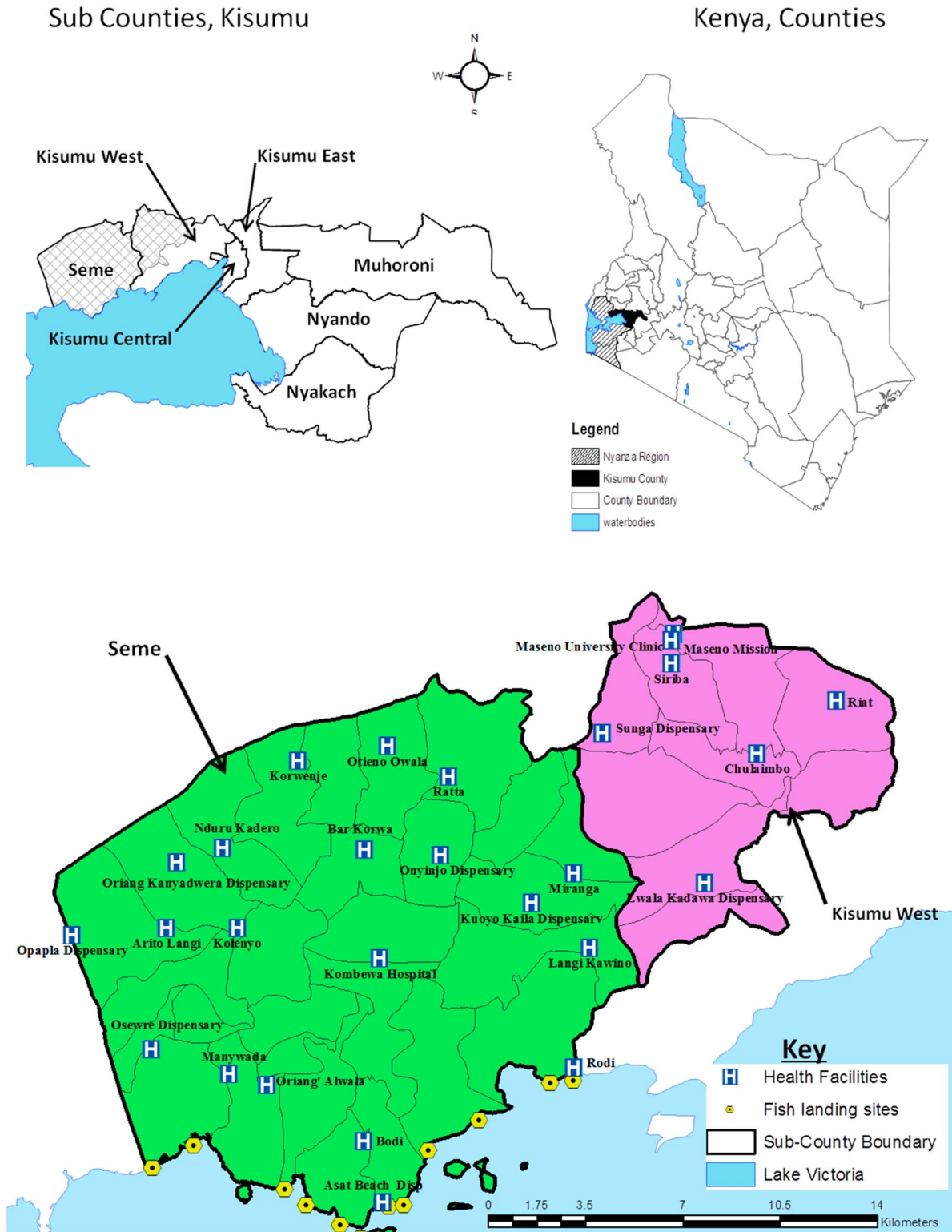


FIGURE 1. Map showing location of the Kombewa HDSS boundaries and location of sentinel health facilities.

upcoming project for a new pediatric research hospital, which is being funded by one of the USAMRD-K partners. The partnership with the MoH has resulted in improved services and patient care within facilities in the HDSS area.

HIV/AIDS Mortality Data

Data on HIV-associated mortality is based on 5196 registered resident deaths (among all ages) in the Kombewa HDSS that occurred between January 1, 2011 and

December 31, 2015, as previously described elsewhere.¹⁶ In brief, the recorded deaths in the HDSS were evaluated using a standardized VA interview by specially trained lay interviewers to record events surrounding death. Assignment of COD was made using the InterVA-4 model version 4.02.⁷ For 3903 of these deaths (75.1%), VA interviews were successfully completed. Deaths assigned to HIV, TB, and pneumonia were extracted from the overall data set together with data on person-time exposed by year, age, and sex.

Statistical Analyses

HIV mortality rate was calculated as the number of HIV deaths per 1000 population (of PLHIV) for comparison with regional and national averages. The number of PLHIV was estimated using the prevalence of rates for each year (15.2% in 2011, 15.1% in 2012, 15.0% in 2013, 14.8% in 2014, and 14.6% in 2015). For comparison with available data from other HDSS sites, we also calculated HIV mortality rates as the number of cause-specific deaths per 1000 person-years (p-y). Cox regression model adjusted for sex was built to evaluate the influence of age on mortality. Annual mortality rates over the 5-year period were also calculated for the assessment of cause-specific mortality trends. *P*-values of <0.05 were considered significant. All analyses were performed using STATA version 12 (Stata Corporation, College Station, TX).

Spatial Interpolation and Spatiotemporal Trends

The mortality data for each case included location (latitude and longitude coordinates) of the households, allowing point interpolation mapping. Spatial analysis techniques within the ArcGIS 10 software V. 10.3.1 (Environmental Systems Research Institute, Redlands, CA) were used to generate continuous surface data from point data of HIV mortality for the study area. To produce smooth surfaces of HIV mortality for visualization, the *Kriging* spatial interpolation method was used for the years (2012, 2013, 2014, and 2015). Spatial interpolation methods apply mathematical models to estimate the value of attributes at sites not sampled within the area covered by existing observations. For unknown points, interpolation technique takes some form of weighted average of the values at surrounding points to predict the value at the point where the value is unknown.^{26,27} Interpolation is based on the assumption that spatially distributed objects are spatially correlated; in other words, things that are close together tend to have similar characteristics (Tobler's first law of Geography). This is the basic premise behind interpolation, and near points generally receive higher weights than far away points. Geo statistical interpolators including *Kriging* use weights combining distance with probabilistic statistical models of the spatial variation among measured points. The year 2011 (baseline year for the Kombewa HDSS) was excluded from the trend analysis to ensure trend continuity.

However, the data for 2011 were included in the aggregated mapping for 2011–2015.

Hotspot Analysis

We examined whether HIV-associated deaths would form statistically significant local aggregation of mortality over the 4-year period. We used the Optimized Hot Spot Analysis, a statistical method available in ArcGIS (Version 10.3.1). This method uses the Getis-Ord G_i^* statistic to generate *Z* scores (SD) and *P* values (statistical probabilities) to identify the location and degree of spatial clustering of HIV-associated deaths. The tool automatically aggregates incident data into weighted feature (which is a count of the number of points that occur within a short distance of each other). The data were aggregated using the aggregation scheme, COUNT_INCIDENTS_WITHIN_FISHNET_POLYGONS, which created a fishnet (grid) polygon mesh. The fishnet was positioned over each incident and points were counted within each polygon. This aggregation scheme was used because it is simple and appropriate for point feature data. The *z*-score, *P*-value outputs for each feature in the input feature class is accompanied by confidence level bin (Gi-Bin). The Gi-Bin field identifies statistically significant hot and cold spots, corrected for multiple testing and spatial dependence using the false discovery rate (FDR) correction method. Features in the ± 3 bins (features with a Gi-Bin value of either +3 or -3) are statistically significant at the 99% confidence level; features in the ± 2 bins reflect a 95% confidence level; features in the ± 1 bins reflect a 90% confidence level; and the clustering for features with 0 for the Gi-Bin field is not statistically significant. *P*-value of <0.05 and <0.01 was considered significant.

RESULTS

HIV Mortality Trends

For the 3903 deaths (75.1%) for which VA interviews were successfully completed, there were 491 deaths (12.6%) attributed to HIV, 394 (10.1%) attributed to pneumonia, and a further 193 (5.0%) to TB. The rates of HIV and pneumonia were highest among infants [hazard ratio (HR) = 2.39 (<0.001) and HR = 1.80 (0.001), respectively] (Table 1). Rates of deaths attributed to TB were highest in the group 5–14 years [HR = 2.29 (0.002)] and the age group 50–64 year [HR = 1.18 (0.531)]. The HRs for HIV, TB, pneumonia, and other top causes of mortality in the Kombewa HDSS are presented in Table 1.

Figure 2 shows the HIV mortality rates per 1000 PLHIV in the HDSS over the 5-year period (2011–2015) against the national and regional estimates (from 2006 to 2016). The overall HIV mortality rate over the 4-year period was 9.8 per 1000 PLHIV. In general, the HIV mortality declined from 11.6 per 1000 PLHIV in 2011, to 7.3 per 1000 PLHIV in 2015. Over the same period, the national average declined from 29.6 per 1000 PLHIV in 2011 to 24.1 per 1000 population by the end of 2015. The regional rate (Nyanza)

TABLE 1. HRs for HIV/AIDS-Related Mortality and Other Top Causes of Death in the Kombewa HDSS

Cause of Death (ICD-10)	Neonate (n = 68)	Infant (n = 215)	1–4 yrs (n = 412)*	5–14 yrs (n = 207)	15–49 yrs (n = 1095)	50–64 yrs (n = 546)	65+ yrs (n = 1364)
HIV/AIDS	—	2.39 (<0.001)	1	0.75 (0.070)	0.73 (0.006)	0.61 (<0.001)	0.52 (<0.001)
Pneumonia	—	1.80 (0.001)	1	0.78 (0.267)	0.54 (<0.001)	0.62 (0.013)	0.41 (<0.001)
TB	—	—	1	2.29 (0.002)	0.94 (0.761)	1.18 (0.531)	0.76 (0.173)
Malaria	18.33 (<0.001)	2.80 (<0.001)	1	0.65 (0.002)	0.74 (0.029)	0.61 (0.017)	0.49 (<0.001)
Diabetes	—	—	1	2.78 (0.012)	2.01 (0.038)	1.70 (0.184)	1.04 (0.909)
Diarrhea	—	1.64 (0.008)	1	—	0.80 (0.662)	1.11 (0.632)	0.71 (0.161)
Indeterminate	33.63 (<0.001)	3.060 (<0.001)	1	1.12 (0.652)	0.72 (0.078)	0.59 (0.012)	0.61 (0.007)
All cause	38.54 (<0.001)	2.07 (<0.006)	1	0.79 (<0.001)	0.68 (<0.001)	0.65 (<0.001)	0.56 (<0.001)

*HR age 1–4 = 1 (reference age).

declined from 38.0 per 1000 PLHIV in 2011 to 26.9 per 1000 PLHIV in 2011.

Within the general HDSS population, the HIV-associated mortality rate was 1.66 per 1000 p-y. The rates declined steadily from 1.8 per 1000 p-y in 2011 to 1.3 per 1000 p-y in 2015. All the age groups, with the exception of 65+ age group, recorded a decline in HIV mortality from 2011 to 2015. Rates in the age group <1 year declined from 8.2 deaths per 1000 p-y in 2011 to 5.6 deaths per 1000 p-y in 2015. In the age group 1–4 years, the rate declined from 1.7 deaths per 1000 p-y in 2011 to 0.9 deaths per 1000 p-y by the end of 2015. In the age group 5–14 years, the HIV-associated mortality rate in 2011 was 2.3 deaths per 1000 p-y and 1.6 deaths per 1000 p-y by the end of 2015. In the age group 65+ years, however, there was a steady increase from the initial 4.6 deaths per 1000 p-y in 2011 to a high of 10.7 deaths per 1000 p-y in 2014. By the end of

2015, the rate had slightly declined to 9.1 deaths per 1000 p-y.

Spatiotemporal Trends in HIV Mortality

Raster image maps displaying the geographic distribution and variation of HIV-associated mortality are illustrated in Figure 3. These maps present the distribution of mortality across the study area, with the red color exhibiting regions with higher HIV-associated mortality rates and the blue color exhibiting regions with lower HIV mortality. The maps for each year portray what appears to be high occurrence of mortality in certain locations of the study area. The western region of the study area (Seme) consistently portrayed higher HIV mortality over the 5-year period (2012–2015). Conversely, the eastern part of the study area (Kisumu West) exhibited more areas with blue colors (denoting lower mortality).

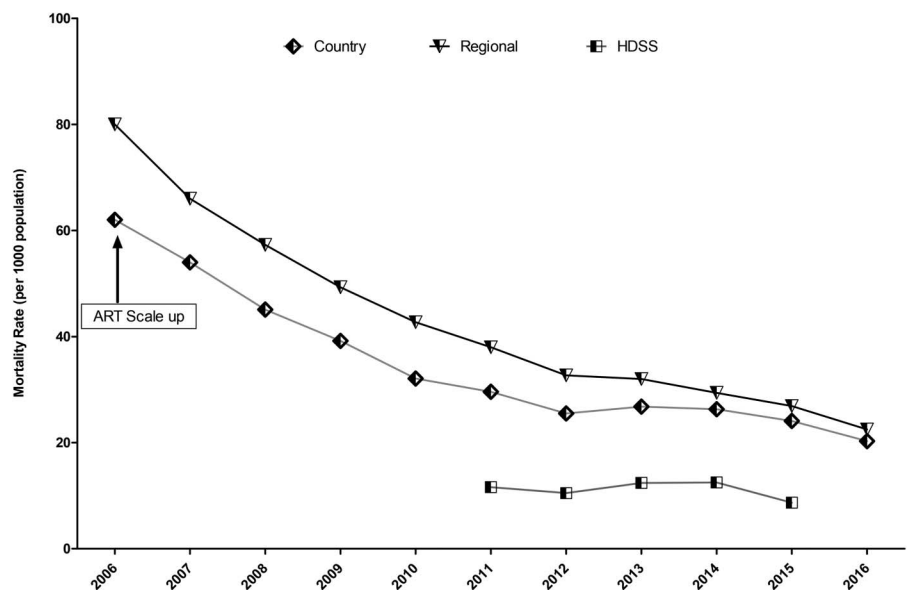


FIGURE 2. HIV mortality trends at national, regional, and HDSS level (Source: <http://aidsinfo.unaids.org/>).

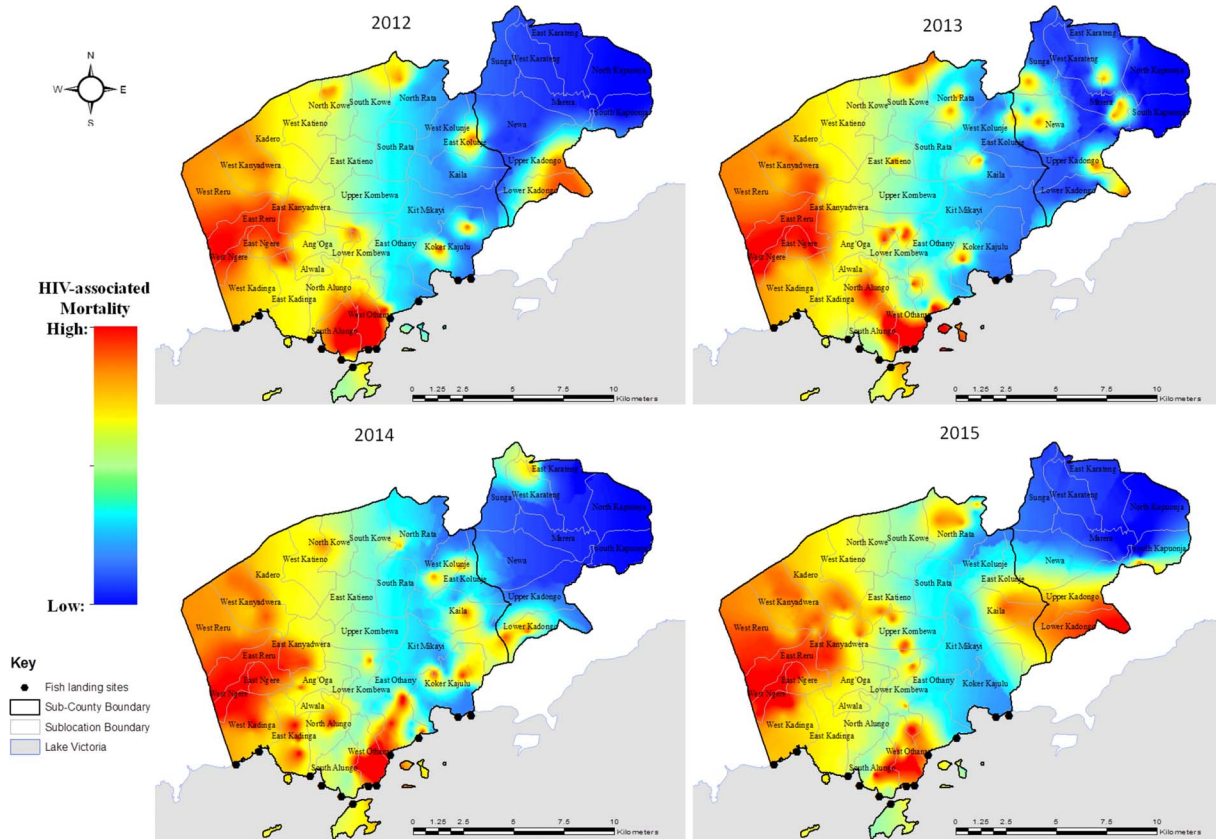


FIGURE 3. Interpolated spatiotemporal trends of the HIV-related deaths in Kombewa HDSS, 2012–2015. Continuous images produced by interpolating (Kriging).

HIV Mortality Hotspots

In the hotspot analysis (Fig. 4), red shading indicates areas with statistically significant clustering of positive HIV-associated mortality (90%, 95%, and 99% CIs) compared with neighboring areas. The dark blue areas show areas where HIV mortality is statistically less likely to occur (Fig. 4).

The hotspot analysis showed that 20.0% of the study area (an area of about 72 km²) was detected as hotspots and 4.2% as cold spots (15 km²). The hotspot areas were centrally located in Seme Subcounty, whereas the coldspot areas were largely concentrated in Kisumu West Subcounty.

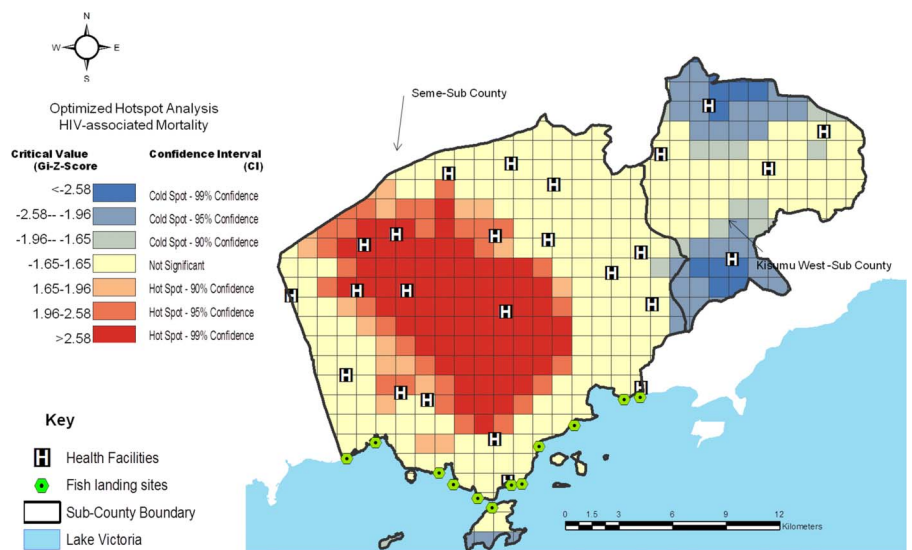


FIGURE 4. HIV-associated mortality in the Kombewa HDSS area 2011–2015; Getis-ord Gi* statistic (optimized hot spot analysis).

DISCUSSION

The overall trend in HIV mortality showed a decline during the period 2011–2015. The observed decline in mortality is consistent with national and regional level data that have also shown a decline over the years. The declining mortality in the surveyed population is a likely positive indicator of HIV prevention and treatment programs, such as ART and PMTCT within the HDSS area. For example, HIV program data for the HDSS area show an increase in ART uptake from 39.9% in 2007 to 99.9% by the end of 2017. ART uptake percentage represents individuals reached by HIV testing services and subsequently linked to ART clinics (9792 cases linked to ART of 9800 HIV-positive test). It is, however, important to note that current World Health Organization guidelines require treatment for all regardless of World Health Organization staging and CD4 count as was previously the case.²⁸ The percentage of ART patients with a suppressed viral load (<1000 copies/mL) stands at 88% (7556/8522) for test conducted between October 2016 to September 2017. Another area of success has been the PMTCT program, where 3046 of the 3093 pregnant women visiting health facilities had their HIV status known through program support, a service uptake of 98.5%. Final outcomes among HIV-exposed infants registered in the birth cohort (between 0 and 18 months of age) show that up to 81.4% were HIV negative and 3.9% were HIV infected and subsequently linked to ART services, 10.2% had an unknown HIV status (lost to follow-ups or transfer out), and 4.3% died during the review period.

In general, the HIV mortality for the HDSS over the 4-year period remains consistently lower than the national and regional estimates (Fig. 2). This is despite the area covered by the HDSS having an estimated prevalence that is nearly 4 times the national average.³ This is not unexpected given that the current standard of care within the MoH facilities has been greatly improved by the services provided by the USAMRD-K HIV PEPFAR program and other partners working in the HDSS area. The declining mortality pattern was replicable across all age groups with the exception of the age group 65+ years in which the mortality rate almost doubled from 4.6 deaths per 1000 p-y in 2011 to 9.1 deaths per 1000 p-y by the end of 2015. It is probable that with more HIV-positive individuals being linked to care, they are experiencing longer lives and thus able to transition from the lower age brackets to 65+ years. It is also possible that in the older age groups, COD could be because of other unreported conditions associated with ageing. However, in the absence of an autopsy to confirm COD, it is difficult to distinguish these scenarios given the current study design.

When compared against locally available HIV mortality estimates from HDSS sites in Kenya, the rate in this study population was slightly lower than that in neighboring Siaya County (data from the KEMRI/CDC HDSS), which reported an overall 3.1 deaths per 1000 p-y (16.7% of all deaths).²⁹ It is important to note that the reporting period for the KEMRI/CDC data was from 2001 (which predates the national ART scale-up in 2006). There is, therefore, a possibility that the effects of the scale-up were not manifest in the population

until much later. When compared to other sites within the country, the rate was expectedly higher than that in Nairobi (data from the Nairobi urban HDSS) and Kilifi (data from the Kenya Medical Research Institute (KEMRI)/Wellcome-Trust HDSS) at 1.00 per 1000 p-y (Nairobi) and 0.65 per 1000 p-y (Kilifi).²⁹

Geographically, we identified what seemed to be subepidemics within Seme Subcounty unlike Kisumu West Subcounty that largely had areas of lower HIV mortality burden. The 2 regions are demographically diverse in that the Seme Subcounty predominantly comprised the Luo ethnic community, whereas Kisumu West Subcounty has a mixture of Luhya and Luo ethnicities.¹¹ It is likely that cultural factors, such as male circumcision (commonly practiced among the Luhya community than among the Luo community) coupled with other cultural practice differences, play a role in the observed differences in disease burden as shown elsewhere.^{30,31} For instance, household data from the Kombewa HDSS show that only 33.3% and 43.4% of male adults from Seme Subcounty and from Kisumu West Subcounty, respectively, are circumcised (2015 data). The rates are, however, varied, with areas bordering predominantly Luhya populus to the North, like Sunga and East Karateng, reporting higher circumcision rates of up to 71.7% and 73.8%, respectively.

Hot spot analysis provided valuable visual information about the clustering of HIV mortality within the Kombewa HDSS. This finding suggests that HIV-associated mortality occurs in clusters and not spread uniformly or randomly throughout the study area. Understanding the stability of hotspots over time is crucial for guiding disease control strategies. Given limited resources, clustering of HIV risk in specific areas can decrease the average effectiveness of population-based prevention approaches. In contrast, targeted interventions are likely to lead to better prevention results for given resources, where the epidemic clusters geographically.³²

CONCLUSIONS

HIV attributable death in the Kombewa HDSS is substantial, although lower than the national and regional estimates. The identification of concentrated epidemics within generalized epidemic settings presents an opportunity for targeted interventions, to supplement measures aimed at the general population in such settings.

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This work is published with the permission of the Director, Kenya Medical Research Institute. Material has been reviewed by the Walter Reed Army Institute of Research. There is no objection to its presentation and/or publication. The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting true views of the Department of the Army or the Department of Defense.

Ethics and Consent: The Kombewa HDSS protocol and consent procedures are approved by KEMRI and WRAIR Institutional Review Boards annually. Data on deaths and causes of deaths are routinely collected under the HDSS protocol. Following cultural customs, household heads provide written consent for all household members to participate in the HDSS activities. Participation is voluntary and any individual can refuse to participate at any time.

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