MEASURING
HIV INCIDENCE,
MORTALITY,
AND
THE CASCADE
OF HIV CARE
IN KENYA

Peter Wesley Young

Measuring HIV incidence, mortality, and the cascade of HIV care in Kenya

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Measuring HIV incidence, mortality, and the cascade of HIV care in Kenya

Het meten van hiv-incidentie, mortaliteit en de cascade van hiv-zorg in Kenia

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Chapter 1

General introduction and outline of the thesis

General introduction and outline of the thesis

The syndrome that would later be called acquired immunodeficiency syndrome (AIDS) was first described in 1981 among gay males (1). Thirty-nine years after AIDS was first identified, infection with human immunodeficiency virus (HIV) is found in every country on Earth, though the highest burden is found in eastern and southern Africa, which according to the Joint United Nations Programme on HIV/AIDS (UNAIDS) is where 54% of people living with HIV (PLHIV) resided in 2019 (2). According to UNAIDS estimates, new HIV infections peaked globally in 1998 at 2.8 million per year. UNAIDS estimates that 38 million people were living with HIV and 690 thousand died due to HIV in 2019 (2). In Kenya, an estimated 1.5 million people were living with HIV in 2019, of whom 74% were on antiretroviral treatment (ART). To date, no effective vaccines or cures for HIV infection have been identified, though research continues on new therapeutic options, vaccines, and functional cures. This introduction begins with a brief history of the identification of HIV and AIDS, followed by a summary of global efforts to control the HIV pandemic, then provides an overview of HIV epidemiology, biology and clinical presentation. It follows with a description of measurement issues related to the incidence of infection, disease progression, treatment, and death. Finally, it summarizes disease surveillance methods commonly applied to the HIV epidemic.

Early developments in the diagnosis and treatment of HIV

In 1983, a research group led by Françoise Barré-Sinoussi and Luc Montagnier in France identified the human immunodeficiency virus (3). The first commercially-available diagnostic test for HIV infection was based on the enzyme-linked immunosorbent assay (ELISA), which detects antibodies to HIV and was commercialized in 1985 (4). Given the silent nature of early HIV infection, low cost and accessible diagnostic tests meant blood donations could be screened and infections due to tainted blood products reduced or eliminated (5). Further, it allowed for the design of prevention campaigns based on getting tested and knowing one's HIV status (6).

In 1985, the nucleoside analog zidovudine (azidothymidine) was first tested in patients with AIDS and found to be effective at slowing the progression of HIV (7). However, used in isolation, it did not result in improved long-term outcomes for infected patients due to the rapid development of drug resistant virus leading to viral rebound and treatment failure (8). The introduction of combination therapy and the approval of the first protease inhibitors in 1996 drastically reduced HIV-associated morbidity and mortality (9–11), transforming HIV infection from a nearly universally fatal diagnosis to a chronic condition for those with access to

treatment (12). It would take years of concerted efforts by advocacy groups before antiretrovirals were readily accessible in developing countries, where most deaths due to HIV were occurring (13).

The global response to AIDS

In the midst of growing international recognition of the scope of the HIV epidemic, a dedicated AIDS program was first created within the World Health Organization (WHO) in 1986 (14). The Joint United Nations (UN) Programme on HIV and AIDS was created in 1994 to coordinate global action on HIV/AIDS (15). Launched by the UN in 2000, the Millennium Development Goals (MDG) included a commitment to universal access to antiretroviral treatment for all who needed it by 2010 (goal 6.B) and to halt and begin to reverse the spread of HIV by 2015 (goal 6.A). The Global Fund to fight HIV/AIDS, Tuberculosis and Malaria was launched in 2002. The following year, the US government announced the creation of the President's Emergency Plan for AIDS Relief (PEPFAR) and WHO launched the "3 by 5" initiative to put three million people, or half those in need under contemporary guidelines, on antiretroviral treatment by 2005 (16). The MDG HIV goals were not achieved: an estimated 25% of all people living with HIV were on treatment in 2010, and new infections still outstripped deaths among people living with HIV in 2019 (2), four years after the MDG deadline. Against this backdrop, world leaders endorsed the Sustainable Development Goals (SDG) in 2015, which included ending AIDS as a public health threat by 2030 (target 3.3) and ensuring access to universal health coverage (target 3.8). To operationalize these broad health imperatives, UNAIDS launched the Fast-Track approach in late 2014, which included the 90-90-90 targets to ensure 90% of people living with HIV are aware of their status, 90% of which are on HIV treatment, of which 90% were to be virally suppressed by 2020 (17), increasing to 95-95-95 by 2030. By meeting these goals, UNAIDS hoped to achieve an almost 90% reduction in new HIV infections in 2030 from 2010 to <280,000 per year, a nearly 80% reduction in deaths due to HIV and the elimination of HIV-related discrimination by 2030 (18). Although they garner less attention or funding, the 90-90-90 targets were accompanied by ambitious (non-treatment) prevention goals, and the impact modeling commissioned by UNAIDS assumed both the prevention and treatment targets would be met. Though performance is not as far off as for the 2015 universal treatment goal, the world does not appear to be on track to reach the 2020 diagnosis and treatment targets (19).

The Human Immunodeficiency Virus

The human immunodeficiency virus is a lentivirus of the retroviridae family. Lentiviruses are implicated in chronic conditions of the immune and central nervous systems (20). HIV has two types, HIV-1 and HIV-2; both are believed to

have resulted from separate crossover events to humans by different strains of the simian immunodeficiency virus (SIV). Based on genetic analyses, HIV-1 group M, the HIV sub-type responsible for the HIV pandemic, crossed over from SIVcpz in chimpanzees early in the 20th century, though the earliest blood specimen from which HIV has been retrospectively identified was taken in 1959 from a man living in present-day Kinshasa (21). The HIV-2 virus crossed over from SIVsmm, which infects the sooty mangabey (22). First described in 1986 (23), HIV-2 is most common in West Africa and Lusophone countries, is declining in prevalence, and is being replaced by HIV-1 (24). The HIV-1 virus is more virulent than HIV-2 and is responsible for most HIV infections around the world (25).

HIV targets the immune system by binding the CD4+ receptor of T-lymphocytes and macrophages (Figure 1) (26). After a series of subsequent steps, including co-receptor binding and membrane fusion, HIV infects the host cell by introducing viral genetic material and proteins, including reverse transcriptase, into the cytoplasm. The reverse transcriptase then transcribes the viral RNA into DNA, which after transport into the nucleus is incorporated by viral integrase into the host cell genome. The normal cell replication machinery then generates more viral RNA and protein components, which are released as mature infectious virus, allowing the cycle to repeat (27).

Figure 1. Model of the Human immunodeficiency Virus. Source: National Institute of Allergy and Infectious Diseases, National Institutes of Health, 2009.

During acute infection, viral copies can double more than once per day, reaching 10^5 – 10^6 copies per milliliter of blood within a couple of weeks (28). The intrinsic mutation rate of RNA viruses is 1–2 orders of magnitude higher than DNA viruses due to differences in transcriptional machinery (29), resulting in an error rate in HIV of about 1 in 10,000 nucleotides per copy (30), giving rise to a “quasispecies” of different viruses in each infected individual. This genetic diversity facilitates the rapid emergence of drug-resistant mutants when selective pressure is applied, such as continuous exposure to a single antiretroviral agent (31). When suppressed effectively through continuous combination antiretroviral treatment, HIV remains present in a latent state in viral reservoirs in different tissues, from which the virus can re-activate if treatment is suspended (32).

Clinical presentation

Acute HIV infection

Acute HIV infection is often sub-clinical or causes only mild symptoms that are non-specific and self-resolve. Among a cohort of HIV-negative female sex workers followed prospectively in Mombasa, Kenya, 24% presented no symptoms associated with primary HIV infection. Among those with symptoms, most were non-specific, such as fever, headache, fatigue, arthralgia, and vomiting (33). In a predominantly male European cohort, symptoms were also non-specific, with fever, fatigue, myalgia, skin rash, headache and pharyngitis all commonly reported (34). Both studies also showed that increasing severity of primary infection is associated with more rapid disease progression and mortality (33–35). HIV generally replicates silently for many years after the acute phase, slowly depleting the immune system until other opportunistic infections attack the body (36).

Advanced HIV disease

The WHO defines advanced HIV disease as having a CD4+ cell count of <200 cells/mm³ or a stage 3 or 4 event at presentation (37). A quarter to half of all patients present with a CD4+ count below this threshold, depending on region (38). Events such as cryptococcosis, *Pneumocystis jiroveci* pneumonia and *toxoplasmosis* are more frequent with decreasing CD4+ cell count (39). People living with HIV are also at increased risk of tuberculosis, even on long-term antiretroviral treatment or with high CD4+ cell counts (39,40), though the risk of tuberculosis (TB) infection increases exponentially with decreasing CD4+ cell count among those not on ART (41). Although many present with advanced disease due to missed opportunities for early diagnosis, up to 60% are ART-experienced in eastern and southern Africa (42,43). The occurrence of these and other conditions associated with HIV

infection is also used to stage HIV illness in the absence of or in conjunction with immunological markers, such as counts of CD4+ cells, the primary immune target of HIV infection (44).

Immune reconstitution disease, whereby the rapid restoration of immune function combined with the presence of antigen from opportunistic infection results in illness, commonly results in morbidity (16.1%) and more rarely in mortality (4.5%). It is most common in those starting treatment with low CD4+ cell counts (45).

An aging epidemic

As people living with HIV live longer due to increased access to effective treatment resulting in demographic shifts in the HIV-infected population, non-AIDS conditions associated with traditional risk factors are emerging as common causes of morbidity and mortality in this group (46). Treatment-associated toxicity along with increased immune activation and chronic inflammation due to HIV infection, even when infection is controlled by ART, increase disease and mortality risk (45).

Monitoring disease progression and treatment failure

Given HIV primarily targets CD4+ T-lymphocytes, measures of total CD4+ cells, and CD4+ percentage relative to other T cells are strong indicators for disease progression (47). Analyses of large population cohorts have shown the prognostic value of CD4+ cell counts, along with age and sex (48). Initially, CD4+ cell counts were used to determine when to initiate antiretroviral treatment as well as to assess treatment failure. Although the first WHO HIV treatment guidelines, targeted at resource-limited settings, did not mandate CD4 testing due to the complexity and limited availability, they did advocate for its expansion (49). Eventually, in 1996, the first viral load test based on the polymerase chain reaction was licensed for treatment monitoring. The monitoring of viral load is now recommended over CD4 testing alone for detecting treatment failure (50). Several platforms have been developed for measuring HIV viral load from whole blood, plasma and dried blood spots (DBS) (51). Many countries have adopted these platforms for routine monitoring of HIV treatment. World Health Organization guidelines were updated in 2013 to recommend viral load for monitoring patient response to treatment at 6 months and then every 12 months thereafter (52). Kenya adopted these guidelines in 2014, with additional testing for those with unsuppressed viremia (≥ 1000 copies per milliliter) to diagnose treatment failure (53). As of 2018, Kenya was estimated to have achieved 71% coverage of routine viral load among patients on treatment (54). Given its superiority for monitoring of treatment failure and that WHO

guidelines now recommend immediate initiation of treatment among all people diagnosed with HIV regardless of immune status (55), viral load testing has gained in importance relative to CD4 monitoring (56).

The cascade of HIV care

In the 1960s, tuberculosis and sexually-transmitted infection control programs usefully formulated the disease control process at the population level as a linear series, or cascade, of contingent events (57,58). Despite its clinical complexity and chronicity, HIV infection can also be reduced to a linear sequence of critical transitions, including infection, diagnosis, enrolment in care, initiation of antiretroviral treatment, and achievement of viral load suppression. Once a patient has been diagnosed and entered the health system, these transitions can be monitored to ensure a patient progresses from diagnosis to viral suppression as quickly as possible to minimize the risk of HIV-related morbidity and mortality and onward transmission of infection. Cohort analysis is an effective approach to monitoring how many patients are retained at each stage of the cascade, allowing for objective assessments of program quality and measurement of program outcomes (see first column in table 1).

Table 1. formulation of alternative versions of selected HIV testing and treatment indicators

Transition	Program			Cascade
	Cohort measures	Transition measures	Cross-sectional measures	Cross-sectional measures
Diagnosis (Dx)	N/A	Number of new Dx per unit time	Total number currently Dx* at end of period	Proportion of PLHIV ever Dx †
Treatment (Tx)	Proportion Dx that initiate Tx within time X, time from Dx to Tx initiation	Number of Tx initiations per unit time	Total number currently on Tx at end of period	Proportion of PLHIV that are on Tx
Viral load suppression (VLS)	Proportion of patients initiating Tx that achieve VLS within time X, time from Tx initiation to VLS	Number of patients newly VLS	Proportion of patients on Tx that are VLS	Proportion of PLHIV that are VLS

Notes: * difficult or impossible to measure in many settings due to lack of a comprehensive registry of ever-diagnosed patients. † often referred to as 'proportion of people living with HIV (PLHIV) that know their HIV-positive status.'

At an aggregate level, programs can track how many patients successfully enter, or are currently in, each of these states (depicted in the ‘transition’ and ‘cross-sectional’ measures under ‘program’ in table 1). In the absence of cohort analysis, various proxy measures can be defined, such as the number initiating treatment in a three-month period / the number diagnosed in the same period (a proxy for ‘linkage to care’ among those newly diagnosed). The proxy measures can be confounded by population mobility or delayed transition from one state to the next. They are not true proportions, as those starting treatment in this period may have been diagnosed in a previous period, and they can exceed 100% in some circumstances.

Figure 2. HIV testing and treatment cascade, eastern and southern Africa, 2019. Figures shown are coverage relative to the total population of people living with HIV. Figure source: UNAIDS, used with permission (59).

Cross-sectional measures benefit from not requiring an extended follow-up period, allowing for rapid action in response to poor performance. However, such cross-sectional measures of cascade indicators are an imperfect substitute for monitoring individual progression, since disengagement from (and re-engagement in) care can also happen anywhere along the cascade, potentially inflating the number of transitions to diagnosis, treatment, or viral load suppression. Even without re-engagement in care, patient choices about where to seek different services can skew cascade estimates at the facility or district level. In the absence of robust unique identifiers and centralized patient tracking, this results in inaccurate measures of program success.

The cross-sectional UNAIDS Fast-Track targets are appealing due to their simplicity: they reduce the complex series of events required to achieve successful HIV outcomes into just three indicators. However, they also present challenges

for estimation. The first 90 is not possible to measure entirely within a program as the denominator requires an estimate of the size of the catchment population of people living with HIV, which is rarely known with any precision at a local level. The numerator of the first 90 (and the denominator of the second 90) also requires a robust estimate of the number of people living with HIV ever diagnosed and still living, which is only available in jurisdictions with functioning case surveillance. The numerator of the second 90 (which is the denominator of the third 90) can be estimated from standardized, centrally-procured commodities, facilitating estimation. The numerator of the third 90 depends on an adequate coverage of routine viral load testing for estimation. When all three 90s are expressed as proportions of all people living with HIV, they form an HIV testing and treatment cascade (Figure 2)(60).

Given the limitations of routine data for estimating the HIV testing and treatment cascade, population-based surveys are also important tools for validating estimates in higher-prevalence populations. Each sentinel event in the cascade of care can present specific survey measurement challenges. Even HIV diagnosis or coverage of antiretroviral treatment can be challenging to measure with accuracy. A significant number of survey respondents who report not being aware of their HIV infection have antiretroviral drugs detected in their blood, indicating that they have been diagnosed and are on treatment (61). Though significant progress has been made, the world is not on track to meet the 2020 targets (Figure 2). The challenge of accurately modeling progress towards targets is explored in Chapter 3, while survey measurement issues are explored in depth in Chapters 4 & 5. As countries approach the 90-90-90 and then the 95-95-95 targets, measurement issues are likely to gain more attention, as small absolute differences in estimates can mean the difference between (apparent) success and failure.

Measures of HIV in the context of epidemic control

The SDGs strive to end AIDS as a public health threat by 2030. In order to better define what the 'end of AIDS' might look like, UNAIDS held consultations which led to four measures of epidemic control: relative reductions in incidence and mortality since 2010, crossing below absolute thresholds in incidence, achieving a ratio of new HIV infections to deaths among people living with HIV less than 1, and achieving an incidence to prevalence ratio less than a context-specific threshold (62,63). The UNAIDS Fast-Track targets are designed to measure successful rollout and uptake of HIV programs to diagnose patients and get them on treatment, rather than to assess progress towards epidemic control specifically. Although achieving the goals will be beneficial to those living with HIV, it appears that achievement will not be sufficient to control the HIV epidemic (64). The four large community trials

conducted in sub-Saharan African countries that aimed to measure the impact of universal test and treat (65–68) on HIV incidence exceeded targets for knowledge of status; three of the four also exceeded community ART coverage and viral load suppression targets. Nonetheless, the resulting HIV incidence reductions were only statistically significant in two out of four trials. They did not meet epidemic control targets of <1 new infection per 10,000 population per year, indicating that universal treatment is necessary but insufficient to eliminate HIV (69).

Measures of incidence

The impact of HIV prevention is measured through the incidence of new HIV infection. Infectious disease incidence is traditionally estimated through prospectively following an uninfected cohort of persons at risk. Given the relative infrequency of HIV transmission in most populations, large cohorts or long follow-up periods are needed to observe sufficient seroconversions to measure HIV incidence reliably. Trends in the prevalence of HIV infection in 15–19 year olds (male and female, or pregnant women) have been used as a proxy for monitoring incidence in a generalized epidemic, as this age group is likely to have been recently infected and not yet subject to significant HIV-related mortality. However, with expanded ART coverage among children leading to increased survival of HIV-infected children into adolescence, this assumption may no longer be valid (70). Alternative methods that can be applied in cross-sectional surveys or programmatic settings have also been developed, including biomarkers for recent infection, which estimate what proportion of infections are recent, i.e., within some window period that is assay- and population-dependent (71). These tests' specificity can be improved by screening out persons with evidence of antiretroviral treatment or viral suppression (72). Together with the number of uninfected in the sample and other assumptions, they can be used in a recent infection testing algorithm (RITA) to estimate incidence (73). Detection of recent infection before seroconversion using nucleic acid amplification testing (NAAT) to detect viral RNA in those who are antibody-negative is another approach (74); however, given the short window period between initial infection and seroconversion (approximately 14–28 days), use of this marker is most appropriate in large samples from high-incidence populations (75). A series of assays have been developed that use the differing concentrations of IgG and IgM antibodies over time to create tests for recent (<3–6 months) infection (76,77). The longer window period makes it possible to use these assays in moderate incidence populations, but still with large sample sizes (often >25,000 subjects). These assays do not provide accurate results in patients on treatment since treatment modifies the antibody response; hence questions on ART

status or additional biomarkers such as antiretroviral detection in blood and viral load suppression must be included in the RITA to rule out false-recent infections due to treatment exposure.

Other approaches to estimating incidence include mathematical models that use a combination of information about prevalence, treatment coverage, self-reported history of HIV testing, population structure, and expected mortality on and off treatment to estimate historical incidence (78,79). The Spectrum model developed by Avenir Health is one such model and has been adopted by UNAIDS as a standard approach recommended for estimating incidence and other HIV indicators for UN member states (80). According to the most recent estimates based on this model, HIV incidence peaked at 3,000,000 new infections per year among those aged 15 years and older in 1995 worldwide, falling to 1,600,000 new infections per year by 2017 (UNAIDS, 2018). In Kenya, in 2017, the official estimates were 45,000 new infections per year (corresponding to an incidence rate of 1.8 / 1000 susceptible in adults aged 15 years and older).

HIV mortality

The overall impact of HIV treatment (and indirectly, prevention) can be assessed by monitoring mortality due to HIV infection. Despite conceptual simplicity, measuring mortality at the population level, and attributing it to a specific cause, can be difficult in resource-constrained settings. Only 15% of the world's population is covered by vital statistics systems that produce high-quality data on the cause of death (81). Both deaths due to HIV and all deaths among those living with HIV are essential metrics. All-cause mortality among the HIV-infected is critical because, ultimately, the epidemic's course is determined by the relationship between new infections and deaths among those infected, as HIV is currently a lifelong infection. As illness and death due to HIV infection are almost entirely avoidable through effective antiretroviral treatment, HIV-associated mortality is an indicator of the quality of care and impact of treatment on quality and duration of life among those infected with HIV.

Ascertaining HIV as an underlying cause of death presents challenges due to the complexity of the disease. The International Statistical Classification of Diseases and Related Health Problems: 10th revision (ICD-10) provides rules for establishing the underlying cause from among a series of events leading to death (82), including for HIV (81). Many HIV-associated conditions are rare in immunocompetent individuals, hence their presence is highly indicative of underlying HIV infection. However, others such as tuberculosis are common causes of death in both HIV-infected and uninfected persons in many regions of the world, hence reliable

attribution of cause depends on knowing the HIV status of the individual. At the time of death HIV status may be unknown or unavailable to those certifying the cause of death, or there may be a reluctance to document HIV as a cause of death due to stigma. Deaths that occur in the community rather than in a health facility often do not have a reliable clinical history from which medical causes of death can be reliably deduced (83). While standardized methods for classifying causes for community deaths exist, their sensitivity and specificity for HIV are limited, particularly in children (84).

Mortality among people living with HIV can also be ascertained by monitoring patients enrolled in HIV care. As access to care and treatment expands, this group increasingly represents the entire HIV-infected population. However, many large HIV treatment programs manage thousands of patients and experience significant loss to follow-up among their patient population, making it difficult to determine if patients that are lost have disengaged from care, enrolled in care elsewhere without a formal transfer from their previous treatment site, or have died (85). Special studies in East Africa have shown that actual adult all-cause mortality among patients on ART can be threefold higher than that observed based on program data alone (86).

Figure 3. HIV disease monitoring and surveillance

HIV disease surveillance

Harold Jaffe and colleagues described the epidemiology of the first 1,000 cases of AIDS in the US reported to the CDC between June 1981 and February 1983 through a combination of active and passive surveillance measures (87); by 1989, 28 of 50 US states had implemented HIV case reporting in addition to AIDS case reporting (88). In the same year, the WHO Global Programme on AIDS first

advocated for countries to develop national HIV surveillance systems. Initial surveillance systems in sub-Saharan Africa were based on a combination of AIDS case reporting and cross-sectional, anonymous seroprevalence surveys in antenatal care services, as the uptake of facility-based antenatal care was high in many countries. Though limited to pregnant women, these surveys provided a snapshot of HIV prevalence in the general population and estimated trends in prevalence over time (89). In 2000, WHO issued guidelines for second-generation HIV surveillance, which recommended adapting surveillance to changing needs as epidemics matured and treatment availability increased, including through capture of risk behavior information to help monitor the effects of prevention efforts, and including key populations at greater risk for infection, such as men who have sex with men, sex workers, or injection drug users (90). National serosurveys were implemented in many countries either as add-ons to national health surveys such as the Demographic and Health Survey (DHS) program or as standalone surveys focused on HIV risk behaviors and infection prevalence in key populations or the general population. Over time, these surveys have evolved to focus more on the cascade of care and the impact of treatment programs, by requesting self-reported knowledge of HIV status and ART use and by testing for HIV, ART, viral load, and recent infection (91). In 2017, WHO introduced HIV case surveillance guidelines to bridge the gap between periodic national surveys, monitor outcomes including death, and provide more locally-actionable information about the HIV epidemic (Figure 3) (92).

In parallel with these efforts, large population cohorts have been used to monitor the impact of HIV and increasing treatment coverage on mortality in sub-Saharan Africa. Such population-based studies can attempt to ascertain HIV status, and its role in the cause of death, retrospectively once the death has occurred. Cross-sectional approaches are also possible; Mozambique conducted a nationally-representative post-census mortality survey in 2008/2009 based on verbal autopsy (93), and other countries have developed national sampling frames for longitudinal follow-up of mortality (94). Another approach is to ascertain HIV status post mortem as a public health intervention, which has been done sporadically, in Abidjan, Cote D'Ivoire in the 1990s (95), in the Democratic Republic of Congo in 2001 (96), in New York City from 2008–2012 (97), and Kenya in 2015 (98) and 2019. In an attempt to increase the availability and comparability of HIV-related mortality data, the WHO issued guidance on mortality measurement for HIV surveillance purposes in 2014 (81).

Thesis outline

This Ph.D. thesis aims to enhance our understanding of the epidemiology of HIV in Kenya, with a focus on measurement and estimation along the entire cascade of HIV care. Specifically, the thesis sets out to answer the following questions:

- What are the incidence and prevalence of HIV in Kenya?
- Has access to HIV treatment increased over time in Kenya, and have increases been equitably distributed?
- Has HIV incidence declined during the rapid scale-up of HIV prevention and treatment programs in the regions of Kenya most heavily impacted by the epidemic?
- Is excess mortality due to HIV still a significant public health problem in Kenya?
- Can measurement of the cascade of HIV care be further improved?

In chapter 2, data from a community-based HIV testing program nested in a health demographic surveillance site are used to assess recent changes in HIV incidence in western Kenya, a region that historically has had the highest HIV prevalence in Kenya. Testing results and demographic data from the surveillance site are used to construct an open cohort to measure trends in HIV incidence. This study's results are used to assess whether HIV incidence declined significantly from 2010 to 2016, concomitant with scale-up of voluntary medical male circumcision and antiretroviral treatment access.

Chapter 3 provides estimates of HIV prevalence and incidence in Kenya. It describes how the standard UNAIDS methodology for estimating HIV incidence, prevalence, mortality and other indicators are applied to Kenya and its 47 counties, as well as how these estimates have evolved from 2015–17 in response to changes in the methods endorsed by UNAIDS, and changing availability of data over time.

To determine whether the use of antiretroviral treatment has significantly increased, chapter 4 describes a two-country analysis looking at the equity of treatment coverage at the population level in Kenya and South Africa in 2007 and 2012. This chapter also describes using a biomarker to estimate quantities that traditionally had been self-reported by survey respondents.

Chapter 5 presents an analysis of an alternative biomarker-based adjustment approach to estimating knowledge of HIV-infected status, ART treatment coverage, and viral load suppression (the three indicators along the cascade of HIV care

included in the UNAIDS fast-track targets). The chapter presents a potentially improved method for estimating these indicators using a low-cost, widely available marker, namely HIV viral load.

Chapters 6 through 8 explore HIV-related mortality, using a relatively underutilized approach of mortuary-based HIV surveillance to measure rates of HIV-associated mortality and causes of death among those who were HIV-infected at the time of death in the capital city of Kenya. Chapter 6 presents the findings of a mortuary-based study undertaken in Nairobi in early 2015 at the two largest mortuaries in the city, which measured the prevalence of HIV among deaths as well as care-related indicators such as HIV diagnosis prior to death or hospitalization, treatment history, and viral load at the time of death. Chapter 7 applies the findings of this study, together with the mathematical model described in chapter 3, to estimate population indicators such as the fraction of deaths among adults in Nairobi attributable to HIV. Chapter 8 shares the results of a similar study conducted in a higher-HIV-prevalence region in western Kenya in 2019. Finally, the thesis is summarized in chapter 9 with a general discussion, a summary of findings and recommendations.

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Chapter 2

HIV incidence in western Kenya during scale up of antiretroviral therapy and voluntary medical male circumcision: a population-based cohort analysis

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Abstract

Background: In Kenya, coverage of antiretroviral therapy (ART) among people with HIV infection has increased from 7% in 2006, to 57% in 2016; and, in western Kenya, coverage of voluntary medical male circumcision (VMMC) increased from 45% in 2008, to 72% in 2014. We investigated trends in HIV prevalence and incidence in a high burden area in western Kenya in 2011–16.

Methods: In 2011, 2012, and 2016, population-based surveys were done via a health and demographic surveillance system and home-based counselling and testing in Gem, Siaya County, Kenya, including 28,688, 17,021, and 16,772 individuals aged 15–64 years. Data on demographic variables, self-reported HIV status, and risk factors were collected. Rapid HIV testing was offered to survey participants. Participants were tracked between surveys by use of health and demographic surveillance system identification numbers. HIV prevalence was calculated as a proportion, and HIV incidence was expressed as number of new infections per 1000 person-years of follow-up.

Results: HIV prevalence was stable in participants aged 15–64 years: 15% (4300/28,532) in 2011, 12% (2051/16,875) in 2012, and 15% (2312/15,626) in 2016. Crude prevalences in participants aged 15–34 years were 11% (1893/17,197) in 2011, 10% (1015/10,118) in 2012, and 9% (848/9125) in 2016; adjusted for age and sex these prevalences were 11%, 9%, and 8%. 12,606 (41%) of the 30,520 non-HIV-infected individuals enrolled were seen again in at least one more survey round, and were included in the analysis of HIV incidence. HIV incidence was 11.1 (95% CI 9.1–13.1) per 1000 person-years from 2011 to 2012, and 5.7 (4.6–6.9) per 1000 person-years from 2012 to 2016.

Interpretation: With increasing coverage of ART and VMMC, HIV incidence declined substantially in Siaya County between 2011 and 2016. VMMC, but not ART, was suggested to have a direct protective effect, presumably because ART tended to be given to individuals with advanced HIV infection. HIV incidence is still high and not close to the elimination target of one per 1000 person-years. The effect of further scale-up of ART and VMMC needs to be monitored.

Research in context

Evidence before the study

Scale-up of antiretroviral therapy (ART) and voluntary medical male circumcision (VMMC) is expected to lead to a reduction in HIV incidence in Siaya County, western Kenya, on the basis of their protective efficacy in clinical trials, supported by mathematical models and observational studies. Little information on the effect of ART and VMMC under programmatic conditions exists, and the coverage required to achieve HIV elimination is unknown. We searched PubMed with the terms “incidence”, “HIV”, “Kenya”, “sub-Saharan Africa”, “prevalence”, “risk factors”, “antiretroviral therapy”, and “voluntary medical male circumcision”, and searched publication lists from other sub-Saharan African institutions researching HIV. We restricted our search to English language articles published between 2006 and 2015.

Added value of this study

After programmatic real world scale-up of ART and VMMC in western Kenya, HIV incidence among individuals aged 15–64 years substantially decreased, as did HIV prevalence among those aged 15–34 years. However, HIV incidence remained well above the elimination target of 1 per 1000 person-years.

Implications of all the available evidence

Although scale-up of ART and VMMC under programmatic conditions had a substantial effect on HIV incidence, coverage probably has to be very high to achieve HIV elimination. Determination of the coverage required, through real-world experience, is a public health priority, essential for resource allocation and service delivery.

Introduction

UNAIDS estimated that HIV infection affected 36.7 million people globally in 2016, with 2.1 million new infections and 1.1 million AIDS-related deaths (1). The number of HIV-infected individuals receiving antiretroviral treatment increased from 7.5 million in 2010, to 17.0 million in 2015. Eastern and southern Africa account for more than half of the global HIV burden,¹ and, in this area, HIV/AIDS is among the leading causes of death (2). In Kenya, HIV prevalence in people aged 15–64 years was estimated at 5.6% in a national survey in 2012, compared with 7.2% in 2007 (3). The present study was done in western Kenya, where HIV prevalence was the highest nationally at 15.1% in 2012, and has shown no decline since 2007 (3).

Scale-up of antiretroviral therapy (ART) and voluntary medical male circumcision (VMMC) is expected to reduce HIV incidence. Use of ART by the HIV-infected partner of discordant couples reduced linked HIV transmission to the uninfected partner by 93% (4). VMMC reduced HIV transmission in clinical trials by more than 60% (5, 6, 7), which was sustained over time (8, 9). Modelling studies suggest ART has a substantial effect on HIV incidence (10, 11). Scale-up of ART in South Africa, and ART and VMMC in Uganda, were associated with a reduction of HIV incidence (12, 13).

In Kenya, ART coverage increased from 7% in 2006 to 57% in 2016 (14, 15). In Siaya County, the number of individuals on ART increased from 2096 in 2006, to 32,125 in 2011, to 70,261 in 2016 (14, 15). Before 2011, ART was prescribed to HIV-infected individuals with CD4 counts less than 200 cells per μL if the infection was classified as WHO stage 1 or 2, and to those with CD4 counts less than 350 cells per μL if the infection was classified as WHO stage 3 or 4. From 2011, eligibility for ART included people with CD4 counts less than 350 cells per μL and WHO stage 1 or 2 infection, and anyone with WHO stage 3 or 4 infection; from 2014, all HIV-infected people with CD4 counts less than 500 cells per μL were eligible for ART (16, 17); and from 2016, all HIV-infected people were eligible for ART regardless of CD4 cell counts (18).

A national VMMC programme was initiated in Kenya in 2008, and expanded to include male infants and boys aged 10–14 years in 2014 (19, 20). Kenya Demographic Health Surveys showed a substantial increase in the prevalence of circumcision among boys and men aged 15–49 years in western Kenya from 45% in 2008 to 72% in 2014 (21). Similar findings were reported by the Kenya AIDS Indicator Survey of 2012 (22).

In Siaya County, the Kenya Medical Research Institute (KEMRI) has operated a health and demographic surveillance system (HDSS) since 2001, covering close to 250,000 people (23). Gem is one of the three subareas of the HDSS in which home-based counselling and testing (HBCT) surveys have been done since 2011, to increase the coverage of HIV control interventions. This study is a secondary analysis of HBCT and HDSS data, aiming to determine the trends in HIV prevalence and incidence in Siaya County in 2011–16.

Study design and population

All households in the HDSS were visited two or three times per year to document births, deaths, and migration. The HDSS methods are described in detail elsewhere (23). Data collected in three HBCT surveys were available for analysis. Surveys

took place from October, 2010, to July, 2011 (referred to as HBCT 2011), January to May, 2012, and May to September, 2016. HBCT is a service delivery strategy to increase knowledge of HIV status and accelerate access to services for HIV-infected people. HBCT teams intended to cover as many households within Gem as possible, given time, funding, and test kit availability. The teams offered enrolment to all individuals aged 13 years or older. Individuals eligible to participate in the surveys were asked for written informed consent in Dholuo, English, or Kiswahili. For those aged 13–17 years, parental consent was sought as well as assent from the minor. HIV testing, HBCT data collection, and HDSS linkage were reviewed and approved by the KEMRI Scientific Ethics Review Unit (number 1801) and US Centers for Disease Control and Prevention (number 3308).

Procedures

Rapid HIV testing was done according to the national testing algorithm of the Kenyan Ministry of Health. In HBCT 2011, parallel testing was done with two HIV tests, followed by a third test in case of discrepant results between the first and second test. In the other surveys, the first test was used for screening, the second was for confirmation if the first test was positive, and the third as a referee test if the second test was negative. The first test was Determine (Alere, Orlando, FL, USA), the second was SD Bioline HIV-1/2 3.0 (Standard Diagnostics, Giheung-gu, Gyonggi-do, South Korea) in 2011 and 2012, and First Response (Premier Medical Corporation, Nadi Daman, India) in 2016, and the third was Uni-gold (Trinity Biotech, Bray, Wicklow, Ireland). All participants received risk reduction counselling. HIV-positive individuals were given a referral to services at the health facility of their choice. The HDSS resident identification number was recorded and used for linkage of the individual's HIV test results and data from questionnaires.

Statistical analysis

Survey responses to structured questionnaires and HIV test results were logged directly into portable netbook computers in the field. Data were transferred to a central server at the KEMRI Center for Global Health Research each day. Initial data management was done with STATA (version 14).

The HDSS identification numbers were replaced by anonymous study identification numbers, with the link table kept by the data managers of HDSS (DO) and HBCT (DK). The three datasets of the surveys in 2011, 2012, and 2016, were explored with frequency distributions, and then merged and further range and consistency checks done. Inconsistencies of age and sex between rounds were resolved by referring to the HDSS database. The HDSS database was also used to identify spouses of participants.

A previous study (24) in an adjacent area in Siaya County had reported HIV prevalence in the 15–34 years age group in 2003–04. We estimated HIV prevalence in the same age group in the three consecutive HBCT surveys to establish the trend in HIV prevalence among young adults over time. We also established the trend of HIV prevalence among all those aged 15–64 years. We compared HIV prevalence of repeat participants with that of single round participants to estimate the degree of self-selection bias in the serial prevalence estimates.

Participants aged 15–64 years who had enrolled in 2011 or 2012, were not HIV infected at enrolment and had participated in at least one further HBCT survey were eligible for the cohort analysis of HIV incidence. We defined HIV infection status on the basis of the HIV test results, and among people not tested we accepted self-reported HIV infection as evidence of infection. We did a sensitivity analysis to determine to what extent the inclusion of self-reported HIV-positive status and the exclusion of self-reported HIV-negative status influenced our main conclusions. We identified 51 individuals with apparent HIV seroreversion from HIV-positive to HIV-negative test results. This result was interpreted as a data entry problem of a key variable, and these individuals were excluded from all analyses.

HIV prevalence was calculated as a proportion and incidence was expressed as number of new infections per 1000 person-years of follow-up. Person-time in the denominator of the HIV incidence estimates started at their first participation in 2011 or 2012, and ended at their last survey participation if still HIV negative or after seroconversion. Seroconversions were assumed to have taken place at the midpoint between the last HIV-negative test result and first HIV-positive test result. Serial prevalence estimates and HIV incidence estimates were standardised for age and sex with the HDSS population as the standard population. The strength of association of risk factors for prevalent and incident HIV infection were calculated as odds ratios, derived from logistic regression in univariate and multivariate analysis. From the multivariate analysis, variables were excluded if their addition to the final multivariate model showed a p value of more than 0.1. For the analysis of risk factors for incident HIV, we ran an additional model with imputation of missing values. Imputed datasets were created in SPSS (version 24), followed by logistic regression.

Risk factors explored for incident HIV included age, sex, marital status, having had sex in the past 3 months, condom use with these partners, HIV status and ART use of the spouse, and self-reported circumcision status of men and of the main male

partner of women (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 24). Since many values for risk factor information were missing in 2011, we used information from 2012; if the individual had not participated in 2012, we used data from 2016.

Role of funding source

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Results

Gem had a population of 82,798 in 2012, according to the HDSS database, and the HBCT surveys included 28,688 individuals aged 15–64 years in 2011, 17,021 in 2012, and 16,772 in 2016. 464 (9%) of 4884 participants who reported being HIV positive had HIV tests. Of 464 adults who reported being HIV infected and were tested, six (1%) had a negative test result and were classified as non-HIV infected. Of 37,973 adults who reported not being HIV infected, 37,361 (98%) were tested and 1802 (5%) had a positive test result.

Among individuals aged 15–64 years, 4300 of 28,532 had HIV in 2011 (prevalence 15%), 2051 of 16,875 in 2012 (12%), and 2312 of 15,626 in 2016 (15%). 17,197, 10,118, and 9125 participants aged 15–34 years had known HIV status in 2011, 2012, and 2016. Crude prevalences were 11% (1893/17,197) in 2011, 10% (1015/10,118) in 2012, and 9% (848/9125) in 2016; adjusted for age and sex these prevalences were 11%, 9%, and 8%, compared with 20% in an earlier study in 2003–04, in an adjacent area (figure 1).

The registered population of the Gem HDSS area aged 15–64 years in 2012 was 43,256; combined enrolment for the incidence cohort in 2011 and 2012 was 35,733 individuals with known HIV status (table 1; figure 2). Enrolment rates were higher for those aged younger than 25 years, than for older individuals (table 1). At enrolment, HIV prevalence was 5213 (15%) among 35,733. 4070 (15%) of 27,664 individuals who dropped out of the study were HIV infected (figure 1), suggesting that overall dropout was not associated with HIV status. 12,606 (41%) of the 30,520 non-HIV-infected individuals enrolled were seen again in at least one more survey

round and included in the analysis of HIV incidence (table 1). Participation in the HIV incidence analysis was lower for men and boys (35%) than women and girls (46%), and increased with age for both sexes (table 1).

Figure 1. HIV prevalence in men and boys, and women and girls aged 15–34 years in Siaya County, Kenya

Table 1. Age and sex distribution of HDSS population, participants enrolled in rounds 1 and 2, and those included in HIV incidence analysis

	HDSS general population	Enrolled in HBCT surveys 2011 or 2012		HIV negative at enrolment	HIV negative at enrolment and present at >1 survey	
	number	number	% of population		number	% of enrolled
Male						
15–24	8572	6998	82%	6884	1852	27%
25–34	4499	3030	67%	2520	807	32%
35–44	2845	1923	68%	1427	650	46%
45–54	2038	1491	73%	1144	576	50%
55–64	1836	1398	76%	1206	701	58%
subtotal	19790	14840	75%	13181	4586	35%
Female						
15–24	8266	7876	95%	7320	1934	26%
25–34	5507	4758	86%	3475	1686	49%
35–44	3758	3214	86%	2335	1524	65%
45–54	3327	2823	85%	2273	1580	70%
55–64	2608	2222	85%	1936	1296	67%
Subtotal	23466	20893	89%	17339	8020	46%
Total	43256	35733	83%	30520	12606	41%

Data are n or n (%). HDSS=health and demographic surveillance system. HBCT=home-based counselling and testing.

Figure 2. Study profile of home-based counselling and test surveys in 2011, 2012, and 2016, in Gem, Siaya County, Kenya

The proportion of HIV-infected individuals who were aware of their status increased over time, from 44% (1875/4300) in 2011, to 85% (1956/2312) in 2016. HIV prevalence at enrolment increased with age in both sexes up to age 35–44 years, after which it declined (table 2). Prevalence was lowest in people who were single (adjusted odds ratio 0.3, 95% CI 0.2–0.3), and increased in widowed (4.2, 3.7–4.7), widowed and remarried (5.0, 4.1–6.1), and separated (1.7, 1.5–2.0) individuals, compared with married individuals. Compared with individuals whose spouses were not HIV infected, those with an HIV-infected spouse not on ART had a much higher HIV prevalence (14.9, 12.7–17.5); prevalence was even higher if the spouse was on ART (26.8, 22.4–32.2). Circumcised men and boys had lower HIV prevalence (0.6, 0.5–0.8; table 2) than uncircumcised men and boys.

HIV incidence was 11.1 (95% CI 9.1–13.1) per 1000 person-years in 2011–12, and 5.7 (4.6–6.9) per 1000 person-years in 2012–16 (table 3). The age-standardised HIV incidence was slightly higher in women and girls (8.2 per 1000 person-years) than in men and boys (6.4 per 1000 person-years; table 3).

Table 2. Prevalence of HIV infection and risk factors at enrolment in 2011 or 2012, for the HIV incidence cohort

Men and boys									
Age, years	self-reported previous HIV- positive test result (n=2331)	HIV-positive test result at enrolment (n=2982)	Total HIV- positive at enrolment	Total enrolled (n=35,733)	% HIV +	Crude OR (95% CI)*	Adjusted OR (95% CI)†		
	628	1031	1659	14840	11%				
15-24	23	91	114	6998	2%	1	1		
25-34	164	346	510	3030	17%	12.2 (9.9-15.0)	5.3 (4.2-6.6)		
35-44	194	302	496	1923	26%	21.0 (17.0-25.9)	6.9 (5.4-8.7)		
45-54	163	184	347	1491	23%	18.3 (14.7-22.8)	5.6 (4.4-7.2)		
55-64	84	108	192	1398	14%	9.6 (7.6-12.2)	3.0 (2.3-3.9)		
Women and girls									
Age, years	1603	1951	3554	20893	17%				
15-24	148	408	556	7876	7%	4.6 (3.7-5.6)	2.6 (2.1-3.3)		
25-34	584	699	1283	4758	27%	22.3 (18.3-27.1)	6.6 (5.2-8.8)		
35-44	448	431	879	3214	27%	22.7 (18.6-27.8)	5.3 (4.2-6.7)		
45-54	282	268	550	2823	19%	14.6 (11.9-18.0)	2.7 (2.1-3.5)		
55-64	141	145	286	2222	13%	8.9 (7.1-11.1)	1.3 (1.0-1.7)		

Risk factors									
<u>Marital status</u>									
Single	87	286	373	12767	3%	0.1 (0.1–0.2)	0.3 (0.2–0.3)		
Married	1377	1916	3293	18744	18%	1	1		
Widowed	561	472	1033	2757	37%	2.8 (2.6–3.1)	4.2 (3.7–4.7)		
Widowed or remarried	112	135	247	508	49%	4.4 (3.7–5.3)	5.0 (4.1–6.1)		
Separated or divorced	93	170	263	923	28%	1.9 (1.6–2.2)	1.7 (1.5–2.0)		
Unknown	1	3	4	34	12%				
<u>HIV status spouse</u>									
not infected	255	449	704	8602	8%	1	1		
Infected, no ART	194	305	499	852	59%	15.9 (13.6–18.5)	14.9 (12.7–17.5)		
Infected, on ART	365	179	544	754	72%	29.1 (24.3–34.7)	26.8 (22.4–32.2)		
spouse not in survey	1417	2049	3466	25525	14%	1.8 (1.6–1.9)	2.5 (2.3–2.8)		
or no spouse									
<u>Male circumcision</u>									
No	273	437	710	5962	12%	1	1		
Yes	47	98	145	1891	8%	0.6 (0.5–0.7)	0.6 (0.5–0.8)		
Unknown	307	497	804	6987	12%	1.0 (0.9–1.1)	0.9 (0.8–1.1)		
Total	2231	2982	5213	35733	15%				

Data are n, N, %, crude OR (95% CI), or adjusted OR (95% CI). OR=odds ratio. ART=antiretroviral therapy. * In order to explore the interaction of the effects of age and sex, males aged 15–24 years are used as the reference category for both sexes. † Variables excluded from multivariate analysis if $p>0.10$.

Table 3. HIV incidence by age and sex and between rounds

	Incident HIV	Person-years of observation x 1000	crude rate per 1000 person-years	age and sex adjusted rate per 1000 person-years	95% CI*
Men and boys					
Age, years					
15–24	17	5.3	3.2		
25–34	27	2.5	10.7		
35–44	21	2.3	9.3		
45–54	13	2.1	6.3		
55–64	16	2.5	6.5		
All	94	14.6	6.5	6.4	(5.1–7.8)
Women and girls					
Age, years					
15–24	51	5.7	8.9		
25–34	56	5.8	9.6		
35–44	59	5.7	10.4		
45–54	40	5.9	6.8		
55–64	7	4.7	1.5		
All	213	27.7	7.7	8.2	(6.7–8.7)
Survey rounds					
2011–2012	118	10.7	11.1	11.4	(9.1–13.1)
2012–2016	95	16.6	5.7	5.5	(4.6–6.9)
2011–2016	94	15.1	6.2	6.6	(5.0–7.5)
All	307	42.3	7.3	7.4	(6.4–8.1)

* Using direct standardization, with the health and demographic surveillance system population as the standard population.

Age was a risk factor for incident HIV, with the highest incidence in those aged 25–44 years, for both sexes (table 4). Other risk factors included being widowed or divorced, reporting regular condom use with all partners, and having an HIV-infected spouse. Reported use of ART by the HIV-infected spouse was not associated with incident HIV infection, with CIs overlapping with those of HIV-infected spouses not on ART. Having a circumcised male partner was protective for women and girls, although the protective effect of circumcision was not significant among men and boys (table 4). 341 (6%) of the 5334 spouses surveyed had HIV infection; 16 (57%) of the 28 individuals reporting consistent condom use had a spouse who was HIV infected. The aforementioned risk factors for incident HIV

infection were all identified in univariate analysis, and, if significant in univariate analysis, remained significant in multivariate analysis and after unit imputation (table 4).

In a sensitivity analysis, if we accepted a self-reported status of not being HIV infected in the absence of test results for the individual concerned, HIV prevalence and incidence remained unchanged compared with the main analysis: at enrolment the estimated HIV prevalence changed from 14.6% (5213/35,733) to 14.4% (5151/35,824), and age-adjusted overall incidence remained at 7.4 per 1000 person-years. If we excluded self-reported HIV status, the results changed: HIV prevalence at enrolment was 9% (3204/33,723) instead of 14.6% (5213/35,733). Age-adjusted HIV incidence came down from 7.4 to 4.2 per 1000 person-years overall, from 11.1 to 9.6 per 1000 person-years for 2011–12, and from 5.5 to 2.4 per 1000 person-years for 2012–16. Ignoring self-reported HIV infection thus had the largest influence later in the study period, when a larger proportion of HIV-infected individuals reported their HIV status and thus would lead to a greater observed decline in HIV incidence.

Discussion

In the period in which ART and VMMC coverage increased most notably, we observed a decline of HIV incidence—by half—in those aged 15–64 years. Between 2011 and 2016, HIV prevalence declined by a third in participants aged 15–34 years, but not among those aged 15–64 years. In participants aged 15–34 years, HIV prevalence is probably primarily determined by HIV incidence in the past 5 to 10 years; whereas in participants aged 35–64 years, HIV prevalence is more likely to reflect HIV incidence over a longer period and the effect of declining excess mortality among HIV-infected individuals. In combination, we conclude that the data are consistent with a declining HIV incidence in 2011–16, in this area, possibly in combination with declining HIV-associated mortality resulting from the scale-up of ART. We plan to do further work to establish mortality trends. Given the decline of HIV incidence to 5.7 per 1000 person-years between 2012 and 2016, the incidence is not close to the elimination target of one per 1000 person-years (25).

The decline of HIV prevalence and incidence cannot be directly attributed to increasing ART and VMMC coverage. Other explanatory factors might include the natural history of the HIV epidemic in eastern Africa, which showed declines of HIV incidence even before the onset of large-scale ART use and expanding VMMC coverage (26). However, increased ART and VMMC coverage have probably been

Table 4. Risk factors for incident HIV infection

	Incident HIV	Remained HIV-negative	% converted	Crude OR (95% CI)	Adjusted OR (95% CI)*	Imputation missing values OR (95% CI)†
Men and boys						
15–24	12	1629	0.7%	1	1	1
25–34	26	874	2.9%	4.0 (2.0–8.0)	3.9 (1.4–10.9)	3.3 (1.6–7.1)
35–44	25	650	3.7%	5.2 (2.6–10.5)	7.1 (2.4–20.6)	4.2 (1.9–9.3)
45–64	31	1339	2.3%	3.1 (1.6–6.1)	3.9 (1.3–11.5)	2.6 (1.1–5.7)
All	94	4492	2.0%			
Women and girls‡						
15–24	34	1658	2.0%	2.8 (1.4–5.4)	4.2 (1.5–11.8)	2.2 (0.8–6.6)
25–34	63	1666	3.6%	5.1 (2.8–9.6)	8.8 (3.1–24.8)	3.0 (1.0–9.7)
35–44	61	1419	4.1%	5.8 (3.1–10.9)	7.3 (2.5–21.2)	3.0 (0.9–9.9)
45–64	55	3064	1.8%	2.4 (1.3–4.6)	2.2 (0.7–6.8)	1.1 (0.3–3.4)
All	213	7807	2.7%			
Risk factors						
Marital status						
Single	36	2864	1.2%	0.5 (0.3–0.7)	2.1 (1.1–4.2)	1.3 (0.8–2.2)
Married	197	7742	2.5%	1	1	1
Widowed	45	1143	3.8%	1.5 (1.1–2.2)	4.4 (2.3–8.4)	3.8 (1.7–8.2)
Widowed or remarried	17	178	8.7%	3.8 (2.2–6.3)	5.9 (1.2–28.9)	0.9 (0.3–2.9)
Separated or divorced	10	222	4.3%	1.8 (0.9–3.4)	3.4 (1.5–7.8)	0.4 (0.1–1.1)
Unknown	2	150	1.3%			
Sex past 3 months						
Yes	188	6877	2.7%	1.0 (0.8–1.3)		
No	109	3954	2.7%	1		
Unknown	10	1468	0.7%			
Total	307	12299	2.4%			

important determinants of declining HIV incidence, given their rapid scale-up in 2011–16 (14, 15, 21, 22) and known efficacy in the reduction of HIV transmission (4, 5, 6, 7, 8, 9).

The highest HIV prevalence and risk of incident HIV was found in participants of both sexes aged 25–44 years. The younger age at which women and girls acquire HIV infection was seen in the HIV prevalence results. This result was expected, and is attributed, at least in part, to common age differences in sexual partnerships (27). The risk according to marital status was also expected, with the particularly high prevalence among those widowed probably largely explained by death of the previous spouse because of HIV infection. Known HIV infection of a spouse remains a strong risk factor for incident HIV infection, suggesting room for improvement in the reduction of HIV transmission in discordant couples. ART use of the spouse was a risk factor for prevalent HIV, probably because ART was more likely to be prescribed to individuals with long-standing, advanced HIV infection (16, 17) and many of these individuals might have transmitted HIV before the onset of ART. In the present study, we suspect ART of the HIV-infected spouse was not associated with reduced risk of HIV infection for the same reasons: ART was more likely to be given to individuals with advanced HIV who were likely to have increased infectiousness. Moreover, the time between the surveys was long, and the onset of ART and degree of immunodeficiency was not well known, limiting our ability to show the protective efficacy of ART in discordant couples.

The protective effect of male circumcision was shown both for prevalent HIV infection in men and boys; however, it was not significant as a protective factor for incident HIV. Women and girls who reported having a circumcised male partner were less likely to acquire HIV infection, presumably because of the reduced HIV prevalence in their partners. This study adds to the evidence regarding the protective effect against HIV infection for female partners of circumcised men described in the meta-analysis (28) by Lei and colleagues. Condom use was not shown to be protective, presumably because condoms were more likely to be used in high-risk situations, such as with HIV-infected partners.

Although HIV incidence failed to reach elimination levels between 2012 and 2016, in this area, HIV incidence might have declined with the rollout of the test-and-start strategy since 2016. Further work is planned to assess progress towards the UNAIDS 90-90-90 targets. A study (29) published in 2017, suggests that linkage to care might be a challenge for the test and start strategy and would be important to monitor.

UNAIDS produces HIV prevalence and incidence estimates at a regional level in Kenya on the basis of the Spectrum model (30). These estimates are further broken down to county level through the use of additional county-specific data (eg, HIV prevalence among antenatal clinic attendees). The estimates are used to inform HIV testing and treatment targets. In 2016, HIV prevalence in the general population aged 15–49 years in Siaya County was estimated at 25% on the basis of the Spectrum model and at 17% among antenatal clinic attendees according to routine service delivery data. HIV prevalence in the HBCT survey 2016 in Gem among those aged 15–49 years was 14% (1796/12,772). These discrepancies suggest the need to review the HIV estimates at county level because they might be too high.

This study has various limitations. First, the surveys were done as service provision to identify HIV-infected individuals and link them to care, and were not intended primarily for cohort analysis. Survey participants were not randomly selected. However, given that the HBCT participants represented a large proportion of the eligible population, the prevalence estimates are probably robust. No specific measures were in place to reduce loss to follow-up. The loss to follow-up was high, though not associated with HIV prevalence. The differential participation by age and sex was resolved in the analysis by standardising for age and sex, which had little influence on the incidence estimates. Second, we excluded 51 apparent HIV seroreverters who changed from HIV-positive status to HIV-negative status, because reversion was attributed to data problems of a key variable. Because there were some misclassified reversions, some conversions might have been misclassified and HIV incidence might therefore have been somewhat overestimated. Third, we accepted self-reported HIV infection as evidence of infection in the absence of HIV test results. Excluding self-reported HIV infection would have led to substantially lower HIV prevalence and incidence estimates, in particular later in the study period. Given the positive predictive value of 98% of self-reported HIV infection, we believe including these people is likely to provide the best estimates of prevalence and incidence. The main finding, with respect to declining HIV incidence, did not depend on the HIV case definition. Fourth, we did not have data available on viral suppression in those receiving ART. Finally, risk factor variables had many missing values, in particular during the first survey, thus limiting our ability to determine their association with prevalent and incident HIV infection.

In conclusion, HIV prevalence in participants aged 15–34 years and the HIV incidence in all adults in this population has declined strongly during the scale-up of ART and VMMC. However, incidence is well above elimination level, and further scale-up of interventions is needed.

Contributors

MWB, DK, GO, LAM, EZ-G, and KMDC designed the study. DK, DO, GO, VK, FO, PO, LAM, MES, and EZ-G collected the data. MWB, DK, DO, GO, PO, JM, and RJ managed the data. MWB, DK, DO, GO, RJ, EZ-G, KMDC, and PWY analysed the data. MWB, DO, GO, RJ, MES, EZ-G, and KMDC drafted the Article. All authors were involved in critical revision of the Article and final approval for submission.

Declaration of interests

We declare no competing interests.

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Chapter 3

Evolution of sub-national HIV estimates for a high-HIV-burden region in Kenya

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Abstract

Introduction: According to official estimates, the Nyanza region of western Kenya comprising six high-HIV-burden counties accounted for 38% of prevalent HIV infections in Kenya in 2015. We iteratively revised epidemic models to obtain realistic HIV estimates for these counties, which is essential for program planning.

Methods: We revised annual estimates using the Spectrum model in 2016 and 2017, incorporating population-based survey estimates, routine antenatal (RANC) HIV prevalence from monthly facility reports from 2013–17 in the national health information system, and comparing with results from a longitudinal community-based HIV sero-surveillance activity in Gem sub-county, Siaya County. County-level official estimates were disaggregated from Spectrum using a workbook method and small-area estimation.

Results: Adult HIV prevalence estimates for the Nyanza region evolved from 16.1% (95% uncertainty interval [UI] 14.5–18.5) in 2015 to 13.3% (95% UI, 11.2–15.7) in 2017. Routine antenatal HIV prevalence was found to show similar trends to previous antenatal surveillance data and was incorporated in 2016, along with a new fitting algorithm in Spectrum. In Gem, community-based prevalence estimates were lower than RANC (ratio 0.82); both were significantly lower than the 2016 official estimate of 24.8% (95% uncertainty interval 20.0–29.5) for Siaya County. Population projections for Nyanza were adjusted to match official projections in 2017. The updates resulted in a 9% reduction in estimated adult PLHIV from 537,000 in 2015 to 486,000 in 2017. Revisions to the demographic model and inclusion of RANC accounted for 12% and 9% of the reduction in estimated PLHIV in Nyanza, respectively. After revisions, prior treatment targets for all six counties were above 2030 UNAIDS fast-track targets.

Conclusions: The revised official estimates for 2017 for Nyanza show that targets for knowledge of HIV status and antiretroviral treatment coverage based on the 2015 estimates may have been unreachable. Assessing models against high-quality epidemiological data is essential to ensure robust estimates. The inclusion of RANC in models may improve quality of HIV estimates and enable setting of more achievable program targets.

Introduction

Kenya is the fifth-highest HIV-burden country in the world, with an estimated 1.5 million people living with HIV (PLHIV) in 2017 (1,2). The Nyanza region of western Kenya, bordering Lake Victoria and comprising the six high-HIV-burden counties of Kisumu, Homabay, Siaya, Migori, Kisii and Nyamira, was the epicenter of the HIV epidemic with sustained HIV prevalence among adults aged 15–49 years of 14–16% from 2003–12 according to population-based surveys (3). Nyanza accounted for 38% of PLHIV, 37% of all patients on antiretroviral treatment (ART) and 39% of the estimated unmet need for ART in Kenya in 2015 (4).

Models are increasingly used to estimate the number of PLHIV to set national and sub-national testing, prevention and treatment targets focused on reaching a critical level of treatment coverage and viral suppression. Globally, national HIV estimates are developed through a country-led process coordinated by the United Nations Joint Programme on HIV/AIDS (UNAIDS) that relies on the Spectrum model (Avenir Health, Glastonbury, US) (5) to generate key HIV indicators, which are compiled and published by UNAIDS annually (6). A workbook method has been used in Kenya to generate official estimates for all 47 counties based on Spectrum files representing eight regions corresponding to former provinces, including Nyanza. As programs approach the UNAIDS Fast-Track targets of getting 90% of PLHIV diagnosed and 90% of diagnosed PLHIV on treatment by 2020 (7), consistent challenges in achieving these estimates-driven targets have led to questions about the accuracy of the official HIV estimates for these counties.

HIV prevalence in pregnant women from sentinel surveys in antenatal care (ANC) settings has long been used as a proxy for the prevalence of HIV in the adult population in the absence of population-based estimates; direct use of ANC sentinel surveillance (ANCSS) prevalence has been found to over-estimate true population HIV prevalence on average (8). In population-based surveys conducted in sub-Saharan Africa, the prevalence in pregnant women tends to be lower than in other women, though the prevalence was equal or greater in pregnant women than non-pregnant women in Kenyan surveys. These differences are not significant, though precision for estimating prevalence among pregnant women in population-based surveys is limited (9). Antenatal care sentinel surveillance and, starting in 2017, routine antenatal care (RANC) HIV prevalence are key inputs to Spectrum, and RANC data are readily available at high resolution and relatively high completeness for counties in Kenya, especially in the Nyanza region. Despite data quality concerns with RANC data (10,11) we evaluated whether recommended World Health Organization standards were fulfilled by conducting data and

administrative reviews of antenatal clinics that offered both routine testing and sentinel surveillance in 2010. Results The proportion of tests that were HIV-positive among women aged 15–49 years was 6.2 % (95 % confidence interval [CI] 4.6–7.7 %) in sentinel surveillance and 6.5 % (95 % CI 5.1–8.0 %, and as of yet limited direct evidence of the relationship between HIV prevalence in RANC and the general population, the use of RANC data as a proxy in Kenya is attractive because fertility (total fertility rate of 3.9), coverage of antenatal care (96% of pregnancies) and coverage of HIV testing in ANC (92% of women attending ANC) are high (12). Estimating HIV prevalence from a census of all women receiving RANC avoids some of the limitations of using ANCSS as a proxy for the general population, such as a bias towards larger facilities from predominantly urban areas, though other important biases remain, such as exclusion of men and non-sexually-active women.

Health and Demographic Surveillance Systems (HDSS) exist throughout Africa and provide robust data on relatively small yet well-characterized populations by enumerating their catchment population regularly and conducting active surveillance for demographic events such as births, deaths and in/out-migration. The Kenya Medical Research Institute (KEMRI), in collaboration with the U.S. Centers for Disease Control and Prevention (CDC) has operated an HDSS in Siaya County for nearly 20 years (13); KEMRI has conducted several HIV sero-surveillance activities since 2001 in the section of the HDSS located in Gem sub-county; a previous analysis showed declining HIV incidence in this population between 2001–6 (14). Comparing HIV prevalence from community-based surveillance activities within the HDSS with RANC prevalence for the same area could inform the representativeness of RANC prevalence in the region where the HDSS is located.

Given the key programmatic role played by HIV estimates, it is important to assess them thoroughly and compare them with all available data sources. To this end, we reviewed available epidemiological data for the Nyanza region, including RANC data, to update the estimates as part of the annual process led by the Kenya National AIDS Control Council (NACC) and National AIDS and STI Control Programme (NASCOP). As there is presently no “gold standard” external estimate for HIV prevalence for these counties, we first assessed consistency between RANC and ANCSS data, then representativeness of RANC in the region using the HDSS, which in turn required assessing the representativeness of the HDSS HIV prevalence data. After addressing these questions, we compared RANC HIV prevalence to official HIV prevalence estimates for the Nyanza region. We then developed revised estimates for the region, incorporating RANC and using RANC to distribute the regional estimates to the counties within the Nyanza region.

Methods

Study design

In this manuscript we describe the process used by the National HIV Estimates Task Team, convened by NACC and NASCOP, to revise national estimates annually. We have also conducted complementary retrospective analyses of existing data. In order to investigate what RANC HIV prevalence data can tell us about the estimates in the highest-burden counties, we assembled the following estimates and data: i) monthly RANC from facility reports from 2013–17 submitted to Kenya's national health information system (district health information system [dhis2] (15)) for all health facilities reporting in the six counties in the Nyanza region and ii) HIV prevalence from a community-based HIV sero-surveillance activity that screened persons aged 15–64 years in Gem sub-county of the KEMRI HDSS sub-county, Siaya County in four survey rounds between 2011 and 2016; iii) annual county-level HIV prevalence estimates for 2014–17 indirectly estimated from a mathematical model by the national HIV estimates task team. NACC publishes national estimates annually via the UNAIDS global reporting process, and county estimates every two years, most recently in 2018, through a national County Estimates report (4).

Given the community-based sero-surveillance activity in Gem HDSS provides a recent estimate of general adult HIV prevalence for a well-defined, if limited, geographic area, we first looked at its similarity with respect to the sub-county of Gem and Siaya County as a whole. We used data on current pregnancy among female DSS participants to assess the relationship between HIV prevalence and pregnancy status in this population. Then we used RANC data to compare HIV prevalence in pregnant women accessing ANC between the Gem HDSS, Gem sub-county and Siaya County. We then compared the RANC estimates to official county and regional estimates for Nyanza. We also compared the RANC to official Spectrum estimates for Nairobi County.

Data sources

Health and Demographic Surveillance System sero-surveillance activity:

The HDSS has operated continuously by KEMRI since 2002 (Figure 1), encompassing three areas within Siaya County (13). A population census is conducted twice annually, including births, deaths and migrations. We worked with data from Gem, one of the three HDSS areas, which in 2014, included 89,225 persons. To increase treatment coverage, KEMRI has conducted repeated rounds of door-to-door HIV sero-surveillance in 2011, 2012, 2014 and 2016 within the Gem catchment area. Each round attempted to cover as many households as possible, given available test

kits, time and funding. The activities targeted all residents aged 13 years and older, collected knowledge of status, and offered rapid HIV testing as per the national diagnostic algorithm. In 2011 and 2012, the national algorithm allowed for the use of two distinct parallel tests (Determine™ [Alere, Orlando, Florida, USA], and SD Bioline HIV-1/2 3.0 [Standard Diagnostics, Giheung-gu, Gyeonggi-do, Republic of Korea]) followed by a third tie-breaker in case of discrepant results (Uni-gold™ HIV [Trinity Biotech, Bray, Co Wicklow, Ireland]). During the 2013–14 round, a serial three-test procedure was used, including a screening test (Colloidal Gold [KHB Shanghai Kehua Bio-engineering, Ltd, Shanghai, China], replaced by Determine™ in 2015), a confirmatory test (First Response™ [Premier Medical Corporation, Nadi Daman, India]), and a tie-breaker for discrepant results (Uni-gold™ HIV) (16). In 2015, the national diagnostic algorithm was updated to a serial two-test procedure consisting of Determine™ followed by First Response™ as a confirmatory test, with repeat testing by a separate tester in the case of inconclusive (discrepant) results, and for confirming all positives before treatment initiation, and DNA PCR at a central lab to resolve repeatedly inconclusive results (17). Results were recorded and linked back to the resident's HDSS identifier. HIV status (either self-reported known-positive or HIV test result) was tabulated for participants aged 15–49 years independently for each round for this analysis. For female participants, we included current pregnancy status if they had participated in a biobehavioral survey within +/- 30 days of their HIV test in the 2016 round. Borgdorff *et al.* have previously described this dataset in more detail, including analyses conducted to establish the cohort's representativeness (14).

Figure 1. Location of the KEMRI health and demographic surveillance site (HDSS), Gem area in Gem sub-county, Siaya County, Kenya

Notes: HIV prevalence from official 2015 county estimates; shape files courtesy of <http://naturalearthdata.com> and KEMRI.

Routine ANC HIV prevalence:

Women attending antenatal care at public health facilities in Kenya are routinely offered free rapid HIV testing following the national HIV diagnostic rapid test algorithm, as described above. All public facilities and many larger private facilities report aggregate monthly indicators to dhis2, including the number of women seen at first ANC visit, the number of women tested in ANC, number of positive tests in ANC, and number of women with known HIV-positive status at first ANC. Routine ANC HIV indicators were cleaned by reviewing monthly reports from dhis2 for consistency and excluding monthly reports that showed clear signs of artifacts that would bias prevalence estimates (See Text S1, which provides a summary of the cleaning steps, their rationale, and the number of reports excluded during cleaning). After cleaning, we aggregated the RANC data by year and county, then for Nyanza as a whole, producing pooled estimates self-weighted by the number of pregnant women tested at each site. As routine ANC HIV testing is not reported by age bands, we did not restrict the analysis to women in a specific age group, though generally few women below age 15 or over age 49 years are seen in ANC settings in Kenya. We included results for 2014–17 in this analysis. We multiplied RANC HIV prevalence by the county-specific population projections used for the official Kenya HIV estimates to obtain hypothetical estimates of the population size of PLHIV aged 15 years and above. As this approach likely over-estimates HIV prevalence in older age groups by assuming the prevalence among those aged 50 years and older is the same as those aged 15–49 years, it produces a slight over-estimate of PLHIV, which is conservative for purposes of this analysis.

Official estimates:

Spectrum's Estimates and Projections Package (EPP) models the force of infection over time as a function of population, numbers of adults on ART based on reports from dhis2, HIV prevalence among pregnant women at sentinel sites, population-based sero-surveys, and more recently, HIV prevalence from routine testing in antenatal settings at either sentinel sites or all sites in a geographic area. The methods are described in detail elsewhere (5,18,19). The version of Spectrum used to generate the 2015 County estimates (5.441) did not yet allow the inclusion of RANC in the model, while the version used for 2016 (5.563) and 2017 estimates (5.63) does. Spectrum projections were developed annually for regions (former provinces of Kenya) such as Nyanza or Nairobi; we then used a bespoke structured Excel® workbook to assign weights to each county and disaggregate indicators such as HIV prevalence, PLHIV and need for prevention of mother-to-child transmission (PMTCT) to the county level. In the case of Nyanza starting in 2016, the weights were set using a small-area estimates model designed to predict HIV prevalence from the 2012 Kenya AIDS indicator survey (KAIS 2012) based on a multivariate

regression model incorporating RANC and percent of county population residing in rural areas. In prior years weights were distributed based on manual selection of a method based on an arithmetic average, linear regression, or other method based on recent Demographic and Health Surveys, AIDS Indicator Surveys, ANCSS or RANC data. These weights were then used to distribute PLHIV to the counties, ensuring the total PLHIV estimate (age 15+) equals the Spectrum estimate for the region. Spectrum also provides estimates of HIV infection among pregnant women generated from age-specific fertility rates, reductions in the same due to HIV infection, and age-specific HIV prevalence among women aged 15–49 years (5,20). County estimates for alternate years (2013, 2015, 2017) were validated through national and county-level consultations and published in an annual County HIV Estimates report (2,4,21).

To convey uncertainty in the model-based estimates, we used the Spectrum 95% uncertainty interval for Nyanza, which is generated by Monte Carlo simulation and reflects uncertainty in estimated HIV prevalence and other model parameters (18). Uncertainty intervals were calculated for official county estimates by computing a regional sample size and distributing it among the counties. The county estimates that result from this process are point estimates that are not meant to be interpreted as trends at the county level. We used the resulting annual county estimates of HIV prevalence for 15–49 year olds as well as PLHIV aged 15 years and above from the workbook from 2014–17, the most recent years for which county estimates were published, along with the Spectrum estimates for the entire region of Nyanza for the same years.

Program targets:

Regional program targets for the U.S. President’s Emergency Plan for AIDS Relief (PEPFAR) were extracted from publicly-available PEPFAR dashboards (www.pepfar.net) for fiscal year 2018 for total adults aged 15+ years currently on treatment by the end of period (i.e. September 30).

Population projections:

We analyzed the base demographic population used in Spectrum and compared with official population projections obtained from the Kenya National Bureau of Statistics to identify differences that could impact estimates.

Data analysis:

Official estimates, dhis2 data, and Spectrum uncertainty analyses were extracted, processed and visualized in the R program (22,23). To assess the impact of changes to the model and inputs on estimates, we incrementally backed-out updates to Spectrum and source data, tabulated resulting estimates and calculated incremental increases or decreases in estimates for each change.

Ethical considerations

The data used in this analysis were all collected for other purposes. The KEMRI HDSS HIV home-based counseling and testing program and longitudinal bio-behavioral surveillance were approved by the KEMRI and CDC ethics review boards. The 2012 KAIS survey was approved by the KEMRI Scientific and Ethics Review Unit and by the CDC Institutional Review Board (#6189), and the Committee on Human Research of the University of California, San Francisco. No personally identifiable data were accessed or used for this analysis.

Results

In August 2015, we conducted an assessment of the consistency between RANC HIV prevalence and ANCSS for Kenya based on the aggregated annual RANC HIV prevalence from the former ANC sentinel sites, which found that with some exceptions, the RANC prevalence appeared to behave consistently with recent ANC trends, with some outliers (Figure 2 panel A). Based on this assessment, the team began including county-level pooled RANC prevalence from 2012–14 onwards in data visualizations used for choosing weights to disaggregate Spectrum estimates to counties. In addition, annual RANC data, both for former ANCSS sites as well as pooled for the Spectrum regions from 2013 onwards, were subjected to additional data cleaning (see text S1) and included in EPP starting in 2017, after EPP was updated to allow their use in model fitting. These data were also used to set weights for distributing estimates for the Nyanza region starting in 2017 by applying a small-area estimates model.

Figure 2 panel B shows the comparison of KEMRI HDSS, Gem sub-county and Siaya County RANC HIV prevalence estimates. Gem sub-county RANC estimates are lower than those seen for Siaya County as a whole in 2015 (14.9% for the Gem HDSS area compared to 17.1% for Siaya County in 2015). The RANC prevalence for facilities within the Gem HDSS area is similar to the RANC prevalence in the

Figure 2. Routine antenatal care (RANC) HIV prevalence, and sero-surveillance HIV prevalence from the Gem area HDSS, Gem sub-county, and Siaya County, 2011–16

Notes: Panel A shows 2014 routine antenatal (RANC) HIV prevalence compared with ranges based on historical antenatal sentinel surveillance (ANC SS) observations, by site in decreasing order of prevalence. The ranges are computed as a minimum of 0.5 times the 2011 ANC SS value to either a maximum of 1.5 times the 2011 ANC SS value or the maximum ANC SS value ever observed, whichever is lower. Values outside the range are shown as hollow triangles. Panel B shows routine antenatal care (RANC) HIV prevalence estimates aggregated for the facilities within the HDSS catchment area, along with interquartile ranges across facilities, for all facilities in Gem sub-county, and Siaya County as a whole. HIV prevalence in pregnant women is broadly similar across these three overlapping areas. Panel C shows how HIV prevalence from the sero-surveillance activity among 15–49 year olds in Gem varies by pregnancy status from the longitudinal bio-behavioral survey. HIV prevalence in pregnant women is similar to non-pregnant women (and women without pregnancy data) and higher than the total prevalence in both 2013 and 2016 surveys.

entire sub-county of Gem (14.9% versus 15.4%), though it increases in 2016 to approximately equivalent with Siaya County overall, while the sub-county RANC prevalence remains stable between 2015 and 2016.

Examining HDSS HIV prevalence from four survey rounds, 28,532 adults aged 15–49 years participated in 2011, 16,875 participated in 2012, 21,197 participated in 2013, and 15,627 participated in the 2016 round of the sero-surveillance activity. In 2016, 1,734 women had matched pregnancy status from the longitudinal biobehavioral surveillance; HIV prevalence was not significantly different between pregnant women (15.6%) and non-pregnant women (17.8%, $\chi^2=0.120$, $df=1$, $p=0.729$) though both were higher than among men (8.7%) in 2016 ($\chi^2=106.2$, $df=2$, $p<0.0001$). Routine ANC prevalence for Gem was similar to that seen in the surveillance activity among women in both 2013 and 2016 (Figure 2, panels B & C). In sum, this provides evidence that RANC may be a reasonable estimate for HIV prevalence in adult women in this area, but an over-estimate for combined HIV prevalence in men and women.

Comparing the HIV prevalence in adults aged 15–64 years from the most recent national AIDS indicator survey for the Nyanza region, the HIV prevalence in adults aged 15–49 years in Nyanza was 15.7% (95% CI 12.0–19.5%) in 2012 versus 15.4% (95% UI 14.1–17.0%) in 2012 based on the Spectrum projection.

Figure 3. Comparison of HIV prevalence estimates for Nyanza region, Kenya, 2014–17

Notes: Official HIV prevalence estimates and HIV prevalence in pregnant women in routine ANC settings (RANC) are shown for the Nyanza region and counties for 2015–17. Uncertainty bounds are shown for official prevalence estimates. The center line represents equality between estimates, with points above/left of the line having greater estimates than RANC. Points are labeled with the ratio of estimates to RANC.

The ratio between adult HIV prevalence in the HDSS to the RANC prevalence in the HDSS catchment area was 0.82 (14.1% versus 17.2%) in 2016. Noting that recent RANC HIV prevalence over-estimates adult HIV prevalence in Gem, we proceeded to compare official county estimates derived from Spectrum and Nyanza region Spectrum estimates to RANC for those areas. The evolution of official prevalence estimates and RANC estimates for Nyanza as a whole and the corresponding counties from 2015 to 2017 are shown in Figure 3. All of the ratios are greater than one and range from 1.12 to 1.81 in 2015 and 1.04 to 1.29 in 2017. If we restrict the analysis to pregnant women in Spectrum rather than all adults, the ratio is 1.32 for Nyanza in 2015 and 1.12 in 2017. Thus Spectrum estimates were consistently higher by 12–81% for the highest HIV-prevalence counties and the highest HIV-prevalence region in Kenya in 2015, with the ratio reducing over time to 4–29% greater in 2017.

If we convert this analysis to look at absolute numbers of PLHIV instead of HIV prevalence, we see that Spectrum estimated there to be 537,000 PLHIV aged 15 years and above in Nyanza in 2015 (Figure 4). If we were to recalculate the burden of HIV using the RANC HIV prevalence instead of the Spectrum-based estimates, we would have a reduction of 108,000 PLHIV in this year in the region. The total reduction would be slightly larger after including children (<15 years). In the estimates for 2016, the first year in which Spectrum estimates include RANC as an input, the over-estimate declines to 105,000, and in 2017 it further declined to 16,000. Such an analysis assumes RANC is an unbiased estimate for adult HIV prevalence, whereas true HIV prevalence may be lower than RANC based on the evidence from the HDSS, which would result in a greater reduction.

Figure 4. Comparison of estimated adults living with HIV for Nyanza region, Kenya, 2015–17

Notes: The figure shows the impact of substituting HIV prevalence in pregnant women in routine ANC settings (RANC) for official estimates when calculating the estimated number of PLHIV aged 15 years and older by county for Nyanza for 2015–17. The total decrease for the six counties of Nyanza region is 108,000 (from 537,000 to 429,000) in 2015, 105,000 in 2016, and 16,000 in 2017. Error bars show Spectrum 95% uncertainty intervals for Nyanza, which are generated by Monte Carlo simulation and reflect uncertainty in Spectrum assumptions; intervals were calculated for official county estimates by computing a regional sample size and distributing to each county, which was then used to generate uncertainty intervals for the counties of Nyanza.

When assessing program targets against estimated PLHIV, we found that three out of six counties' targets for currently on treatment by Sep 30, 2018 were unachievable (i.e. > 100%) based on 2017 estimates of PLHIV aged 15+ years (Figure 5).

Figure 5. Coverage of PEPFAR antiretroviral treatment targets with estimated PLHIV aged 15+ years, 2015–17, Nyanza region

Coverage targets were computed by dividing PEPFAR fiscal year 2018 antiretroviral treatment (ART) targets by estimated PLHIV aged 15+ years for each County and Nyanza as a whole (confidence intervals are truncated at 150% coverage for display purposes). The UNAIDS Fast-Track targets for 2020 of 81% ART coverage, and for 2030 of 90% ART coverage of all PLHIV are shown for comparison purposes.

Sensitivity analysis

Our sensitivity analysis of the effects of data cleaning on estimated HIV prevalence in RANC showed that the cleaning steps had a modest impact on HIV prevalence, especially in more recent years (Table S1).

Influence of model inputs and attributes on outputs

To understand how and why the sub-national estimates evolved from the 2015 to 2017 versions, we incrementally removed model changes and assessed the incremental change in estimated adult PLHIV in Nyanza in 2015. Based on this analysis, matching the population to the Kenya National Bureau of Statistics projected population (12% reduction) and addition of RANC to the model (9%

reduction) were the most influential changes to the model. The model was also sensitive to changing assumptions about the ratio of incidence between pregnant women and all adults (Text S2, Table S3).

Discussion

Inclusion of routine HIV testing in ANC, HIV prevalence in the national and county estimation process, along with other model improvements introduced over time have led to reductions in estimated HIV prevalence and PLHIV in the highest-burden region of Kenya. Compared with RANC, estimated PLHIV were 29% greater overall for Nyanza, equivalent to 108,000 adults aged 15 or more years living with HIV. After the inclusion of RANC prevalence in the model-fitting procedure in Spectrum along with other updates to the model, 2017 official estimates were 2% greater than pooled RANC prevalence for Nyanza as a whole.

The Spectrum estimates in Nyanza for 2012 closely match the survey-based estimate, which is as expected given that EPP uses the survey estimates in the fitting process. Although population-based surveys are currently the gold standard for estimating population HIV prevalence in high-burden countries and areas, they suffer from limitations, including participation and response biases. As target-setting for HIV programs usually happens annually, survey-based estimates are often out of date before new estimates are available. Due to the expense and time required, survey estimates are often not available for all desired sub-national areas or sub-populations such as adolescents, needed for planning purposes. Thus reliance on model-based estimates is likely to continue as they provide a cost-effective, scalable and more easily updated program planning input.

It is crucial to ensure models are optimized, include all available relevant data, and are calibrated against other useful sources of information where available. Although the uncertainty interval from Spectrum includes the RANC HIV prevalence in some areas and years, uncertainty intervals are unfortunately often ignored in practice when setting program targets, with the point estimates taken as a fixed parameter rather than an estimated quantity measured with uncertainty. In the future, methods for incorporating uncertainty into workbook-based disaggregation of Spectrum estimates, such as those presented here, should be adopted and extended, though it is not clear how uncertainty could be built into program target-setting. The consistently lower prevalence in RANC versus among pregnant women in Spectrum indicates that while the model may fit historical survey estimates reasonably well, and appears considerably improved by the introduction of RANC data, it may not

yet be optimally fit to the current epidemic in the highest-burden region of Kenya, and that better data on fertility patterns among HIV-infected women may further improve estimates. In addition to supporting impact evaluation, longitudinal population surveillance data such as that provided by HDSS sites can be used to understand changes over time in the population's age and fertility structure, which can impact model assumptions.

Our analysis was subject to several limitations. The available data sources did not align perfectly by period, age group, or geographic area. We also chose to focus on the counties within the Nyanza region. Future analyses could extend this work to include other counties, though the Gem HDSS findings may not be generalizable to areas with different demographic structure or epidemiological patterns. Routine data from dhis2 are less than 100% complete; however, a sensitivity analysis did not find significant biases due to the exclusion of incomplete records. Differences in test algorithms between settings could partially explain differences in resulting prevalence estimates. However, although national HIV testing algorithms evolved over the period, both RANC and HDSS estimates were based on the same national algorithms, thus the algorithm is unlikely to lead to significant differences between these data sources.

Unoptimized estimates could bias assessments of program coverage and performance and lead to suboptimal allocation of resources between interventions and geographic areas. We believe that our results highlight the value of data comparison and calibration for assessing model-based estimates of HIV in the real world. Inclusion of available local-level data, such as Kenya's RANC and HDSS data, when understood in the context of available population-based survey data, can serve a critical role to supplement the estimates from global models. Our observations in Nyanza help ground discussions of appropriate service-delivery targets for these highest-burden counties.

Competing interests

The authors declare no conflicts of interest.

Collaborators

Kenya HIV estimates task team develops national HIV estimates and is convened by the National AIDS Control Council (NACC), chaired by NACC and the National HIV & STI Control Programme (NASCOP), and is comprised of representatives nominated from stakeholder organizations including Kenya Ministry of Health, Kenya National Bureau of Statistics, National CDC, USAID, UNAIDS, UNICEF, National Empowerment Network of People Living with HIV and AIDS in Kenya (NEPHAK).

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Authors' contributions

PWY, EZG and KDC drafted the manuscript, PWY designed and conducted the primary data analysis and prepared figures and tables, JW and JG assisted with interpretation of results and manuscript revision, KM and SM developed the method for generating confidence intervals for sub-national estimates, DK advised on interpretation and use of the KEMRI Gem DSS data, DK and MWB assisted with data management for the KEMRI Gem HDSS data. All authors read and approved the final manuscript.

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Supplemental materials

Text S1. Data cleaning steps and sensitivity analysis for routine antenatal care (RANC) HIV testing

Analysis of aggregate data requires careful data cleaning to ensure the validity of results. Routine ANC data were cleaned prior to analysis using the following rules, developed through trial and error, to identify and exclude invalid records or records that would bias prevalence estimates (justification for the exclusion are provided parenthetically):

- a) records that reported more positive tests results than tests performed were excluded (lack of face validity)
- b) records with only known positives but no tests performed (possible stock out)
- c) records where 100% of tests had positive results and more than three women were tested (lack of face validity)
- d) records from facilities with less than five tests performed per year (possible under-reporting)
- e) records where the number tested was greater than 1.1 times the number of first ANC visits (lack of face validity – high-volume sites)
- f) records where the number tested was greater than three more than the absolute number of ANC visits (lack of face validity – low-volume sites)

All rules except for (d) were applied at the level of individual monthly reports from a facility, thus if a given month was excluded the remaining months of available data were included. Rule (b) is important because test kit stockouts can significantly bias RANC results since previously-diagnosed women will continue to be reported in both the numerator and the denominator, but no women testing negative will be identified. Although technically the number of tests should always be less than or equal to the number of first ANC visits, some allowance was made for spillover of reporting of test results from one month to the next in rules (e) and (f).

The impact of the cleaning rules in terms of excluded records and HIV prevalence with and without exclusion of records is summarized for Siaya County, Gem Sub-County and the Gem HDSS catchment areas in Table S1. On average, the cleaning steps cause a slight reduction in HIV prevalence, with greater numbers of records excluded, and greater impact on HIV prevalence, in earlier compared with later years.

Table S1. Summary of the impact of data cleaning on routine ANC HIV prevalence, Siaya County, Kenya 2013–16

region	Year	Monthly reports		Results		Pooled prevalence of	
		evaluated	included	evaluated	included	all records	included records
Kisii	2013	1255	1255	26600	19980	5.635	5.265
Kisii	2014	1535	1534	31144	27035	4.698	4.583
Kisii	2015	1559	1559	32744	29182	4.230	4.212
Kisii	2016	1541	1538	30728	27770	3.908	3.900
Kisii	2017	1268	1271	27370	23616	3.877	3.773
Nyamira	2013	1055	1042	14319	10633	5.552	4.966
Nyamira	2014	1249	1247	17358	15366	3.566	3.599
Nyamira	2015	1328	1327	18962	17625	3.423	3.535
Nyamira	2016	1312	1315	16772	15194	3.404	3.436
Nyamira	2017	1053	1048	14390	12532	3.509	3.264
Migori	2013	1366	1363	33347	22992	13.872	14.074
Migori	2014	1572	1579	36805	31511	13.004	13.281
Migori	2015	1624	1623	39222	35190	11.833	11.930
Migori	2016	1662	1663	39406	33254	11.404	12.110
Migori	2017	1478	1475	33326	27813	11.820	11.922
Siaya	2013	1523	1514	29088	21647	19.771	19.162
Siaya	2014	1591	1582	27979	24479	17.320	17.109
Siaya	2015	1602	1602	26626	23755	16.796	17.079
Siaya	2016	1629	1629	26740	23515	17.498	17.147
Siaya	2017	1427	1424	25564	21987	17.681	17.274
Gem	2013	335	323	6068	4509	17.337	17.476
Gem	2014	347	345	5716	4976	14.538	14.891
Gem	2015	338	338	5058	4753	15.401	15.422
Gem	2016	342	342	5093	4305	15.708	15.540
Gem	2017	307	305	4712	4229	16.044	15.465
Gem-HDSS	2013	154	142	2932	2136	18.486	16.292
Gem-HDSS	2014	161	161	2850	2540	15.544	15.748
Gem-HDSS	2015	165	165	2413	2242	14.961	14.897
Gem-HDSS	2016	166	166	2387	2032	17.553	17.175
Gem-HDSS	2017	141	141	2174	1970	18.905	18.020
Kisumu	2013	1153	1152	36664	21586	17.979	17.308
Kisumu	2014	1373	1369	33930	27997	16.469	16.409
Kisumu	2015	1441	1440	33758	29336	15.570	15.592
Kisumu	2016	1484	1481	33193	29757	15.684	15.452

region	Year	Monthly reports		Results		Pooled prevalence of	
		evaluated	included	evaluated	included	all records	included records
Kisumu	2017	1408	1405	34678	31839	15.658	15.732
Homa Bay	2013	1619	1602	31446	20838	23.545	20.856
Homa Bay	2014	1968	1963	31711	26492	18.902	18.915
Homa Bay	2015	2147	2139	33496	30876	19.728	19.675
Homa Bay	2016	2222	2216	34084	31336	19.115	19.147
Homa Bay	2017	2207	2199	32811	30033	19.015	18.992

Notes: HDSS = KEMRI Gem health and demographic surveillance site.

Table S2. HIV prevalence estimates for Nyanza and Nairobi, 2014–17

region	source	2014			2015			2016			2017		
		HIV prevalence (95% UI)	Ratio to RANC		HIV prevalence (95% UI)	Ratio to RANC		HIV prevalence (95% UI)	Ratio to RANC		HIV prevalence (95% UI)	Ratio to RANC	
Kisii	RANC	4.6			4.2			3.9			3.8		
Kisii	Spectrum	7.9	1.72		4.7 (0.0–9.6)	1.12		5.4 (0.0–12.3)	1.39		4.4 (0.0–9.6)	1.17	
Nyamira	RANC	3.6			3.5			3.4			3.3		
Nyamira	Spectrum	5.9	1.64		6.4 (0.0–13.2)	1.81		5.1 (0.0–14.6)	1.49		4.2 (0.0–11.4)	1.29	
Migori	RANC	13.2			11.9			12.0			11.9		
Migori	Spectrum	13.5	1.02		14.3 (8.5–20.1)	1.20		16.2 (7.7–24.7)	1.34		13.3 (7.0–19.6)	1.12	
Siaya	RANC	17.1			17.1			17.1			17.3		
Siaya	Spectrum	22.4	1.31		24.8 (18.2–31.4)	1.45		25.6 (16.2–35.0)	1.49		21.0 (14.0–28.0)	1.22	
Gem-HDSS	HDSS							14.1	0.82				
Gem-HDSS	RANC							17.2					
Kisumu	RANC	16.4			15.6			15.5			15.7		
Kisumu	Spectrum	18.1	1.10		19.9 (14.6–25.2)	1.28		19.8 (11.8–27.8)	1.28		16.3 (10.3–22.3)	1.04	
Homa Bay	RANC	18.9			19.7			19.2			19.0		
Homa Bay	Spectrum	24.0	1.27		26.0 (19.9–32.1)	1.32		25.2 (16.4–34.0)	1.31		20.7 (14.2–27.2)	1.09	
Nyanza	RANC	12.9			12.5			12.6			12.9		
Nyanza	Spectrum	15.4 (13.8–17.2)	1.19		16.1 (14.5–18.5)	1.29		14.6 (12.0–17.5)	1.16		13.2 (11.2–15.6)	1.02	
Nyanza	Pregnant women	16.0 (13.8–18.4)	1.24		16.6 (14.8–18.7)	1.32		15.2 (12.0–18.4)	1.21		14.6 (9.0–24.3)	1.12	

Notes: † UI = uncertainty interval, RANC = routine HIV testing in antenatal care (ANC) settings, HDSS = KEMRI Gem health and demographic surveillance site.

Text S2. Assessment of influence of model inputs and attributes on outputs

To assess the impact of different changes to the estimates models over time, we incrementally removed changes to the models until the 2015 estimates (conducted in 2016) were recovered, summarizing incremental and cumulative changes. The projections used were reflective of projections tested during the annual estimates review process by the Kenya HIV estimates task team, in consultation with UNAIDS. Changes made can be summarized into three categories, Spectrum version utilized, epidemiological assumptions, demographic, epidemiological and program data inputs. Changes in Spectrum version reflect updates to the software which can include changes to the fitting process/algorithm or changes in epidemiological assumptions based on new scientific evidence (for example, changes in the mother-to-child transmission rate during breastfeeding) [1-4]. As we also changed some of these epidemiological assumptions independently of the Spectrum version, we also have included as a separate projection where they were found to have a notable impact on adult HIV prevalence. The particular change included here was the choice of pregnant women to adults incidence rate ratio (IRR) database. This database is updated every year and distributed with Spectrum and provides assumed IRRs between pregnant women and adults, by year, for a large number of countries and sub-national regions, including Nyanza region in Kenya. The third category includes changes to the demographic model of population growth for Nyanza to match the Kenya National Bureau of Statistics population projections [5], inclusion of or updates to HIV prevalence from routine antenatal care (RANC) data, and updated annual information on coverage of adult antiretroviral treatment, which affects mortality among people living with HIV as well as transmission risk.

This simple approach to summarizing the impact of model changes does have limitations. First, as we did not assess all possible permutations of model changes, we do not have a picture of interactions between changes, and it is possible if applied in a different order the incremental effects would vary. Furthermore, we did not evaluate the underlying causes of the changes but just summarized their impact on estimated adult PLHIV. Finally, we focused on one indicator relevant to the objectives of this analysis rather than looking at impact on other indicators (children living with HIV, incidence rates, mortality estimates, etc). However, this approach provides a simple assessment of the influence of model elements on the estimates and highlights the importance of carefully choosing model inputs.

Table S3. Influence of model inputs and attributes on outputs, Nyanza HIV estimates, 2015–17, Kenya

Projection †	Spectrum version ‡	People living with HIV aged 15+ years			Increase in estimate (2015)			
		(2015)	(2016)	(2017)	Incremental		Cumulative	
					absolute	percent	absolute	percent
2018 final	AIM 2018 \$	470,132	481,638	486,299				
2018-demog	AIM 2018 \$	527,144	532,978	537,592	57,012	12	57,012	12
2017 final	AIM 2017 \$	536,550	549,225		9,406	2	66,418	14
2017-r-spl/ASM	AIM 2017	528,088	542,440		-8,462	-2	57,956	12
2017-RANC	AIM 2017	577,715	601,935		49,627	9	107,583	23
2017-PW2A	AIM 2017	565,204	586,611		-12,511	-2	95,072	20
2016 final	AIM 2016	536,750			-28,454	-5	66,618	14

Notes: Years in parentheses indicate the calendar year of the estimate, whereas years in projection names refer to the year in which the projection was conducted. † Description of projections: 2018-demog = 2018 projection, before adjusting population to match Kenya National Bureau of Statistics official population projections; 2017-r-spl/ASM = 2017 projection, before switching to age-sex-specific r-spline model; 2017-RANC = 2017 projection, excluding routine HIV testing in antenatal care (RANC) results from r-spline fit; 2017-PW2A = 2017 projection, but using 2016 vs 2017 pregnant women to adult (PW2A) incidence rate ratio database. ‡ The official release name of the Spectrum version is provided, AIM 2018 is also known as Spectrum 5.63, AIM 2017 is also known as Spectrum 5.563, AIM 2016 is also known as Spectrum 5.441. § R-Spline ASM was not available in the respective Spectrum version in these years, therefore the R version of R-Spline ASM was run and the resulting incidence estimates were directly input into Spectrum. PLHIV = people living with HIV aged 15+ years.

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Chapter 4

Equity of antiretroviral treatment use in high HIV burden countries: Analyses of data from nationally-representative surveys in Kenya and South Africa

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Abstract

Objective: To assess changes and equity in antiretroviral therapy (ART) use in Kenya and South Africa.

Methods: We analysed national population-based household surveys conducted in Kenya and South Africa between 2007 and 2012 for factors associated with lack of ART use among people living with HIV (PLHIV) aged 15–64 years. We considered ART use to be inequitable if significant differences in use were found between groups of PLHIV (e.g. by sex).

Findings: ART use among PLHIV increased from 29.3% (95% confidence interval [CI]: 22.8–35.8) to 42.5% (95%CI: 37.4–47.7) from 2007 to 2012 in Kenya and 17.4% (95%CI: 14.2–20.9) to 30.3% (95%CI: 27.2–33.6) from 2008 to 2012 in South Africa. In 2012, factors independently associated with lack of ART use among adult Kenyan PLHIV were rural residency (adjusted odds ratio [aOR] 1.98, 95%CI: 1.23–3.18), younger age (15–24 years: aOR 4.25, 95%CI: 1.7–10.63, and 25–34 years: aOR 5.16, 95%CI: 2.73–9.74 versus 50–64 years), nondisclosure of HIV status to most recent sex partner (aOR 2.41, 95%CI: 1.27–4.57) and recent recreational drug use (aOR 2.50, 95%CI: 1.09–5.77). Among South African PLHIV in 2012, lack of ART use was significantly associated with younger age (15–24 years: aOR 4.23, 95%CI: 2.56–6.70, and 25–34 years: aOR 2.84, 95%CI: 1.73–4.67, versus 50–64 years), employment status (aOR 1.61, 95%CI: 1.16–2.23 in students versus unemployed), and recent recreational drug use (aOR 4.56, 95%CI: 1.79–11.57).

Conclusion: Although we found substantial increases in ART use in both countries over time, we identified areas needing improvement including among rural Kenyans, students in South Africa, and among young people and drug users in both countries.

Introduction

Significant progress has been made in recent years in scaling up the provision of anti-retroviral therapy (ART) to people living with HIV (PLHIV) in sub-Saharan Africa. As of December 2015, over 17 million people globally were accessing ART, reaching the target of the *Treatment 2015* agenda established in 2012 by the Joint United Nations Programme on HIV/AIDS (UNAIDS), the World Health Organization (WHO), and partners, ahead of schedule [1,2].

Modelling suggests that high levels of ART coverage are required to control the HIV epidemic [3]. Despite progress in scaling up ART, only about half of all PLHIV in the East and Southern African region were receiving treatment by the end of 2015 [4]. This is partly due to global and country-specific recommended treatment guidelines that were in place in the past that recommended ART initiation until after onset of illness or immune suppression [5]). However, low ART coverage could also be explained by other structural factors such as health system deficiencies, individual factors such as lack of awareness of HIV status, healthcare seeking behaviours and risk behaviours, and socio-demographic factors [6]. Access to ART has been found to be greater in females than males, lower among young compared with older people [7–9], and among those living in poverty [10]. Stigma and discrimination [11,12], as well as incorrect or incomplete information about HIV and treatment have also been associated with lower ART use [13].

Identifying and eliminating barriers to access will be important if countries are to achieve universal ART coverage. WHO recommends assessing treatment equity and addressing obstacles to equitable access in line with the 2015 “treatment for all” recommendations which makes identifying and addressing potential barriers to achieving universal treatment coverage even more urgent [14]. For this study, we defined inequitable ART use based on differences in the proportion of PLHIV on treatment between groups defined by socio-economic, demographic, and behavioural characteristics.

Both Kenya and South Africa have been severely affected by the HIV epidemic. In Kenya HIV prevalence was estimated at 5.6% in 2012 with 1.4 million adult PLHIV and 898,000 people on ART by end of 2015 [15]. South Africa has the greatest number of PLHIV worldwide, estimated at 7 million in 2015, a 12.1% prevalence in the general population in 2012, and the largest ART programme in the world with approximately 3.4 million people on ART by end of 2015 [2].

Kenya and South Africa have undertaken nationally-representative population-based surveys with financial and technical support from the U.S. Centers for Disease Control and Prevention (CDC) to track both the burden of the epidemic in the general population as well as the impact of prevention and treatment strategies over time. These surveys have included biomarkers to assess HIV prevalence, HIV incidence and ART usage. Biomarker measurement of ART use is particularly useful since it is conducted on all HIV-positive samples and is not subject to self-reporting biases. We used these surveys to investigate differences in ART use among groups to shed light on whether equitable distribution of treatment has been achieved and maintained over time.

Methods

Survey design

Two Kenya AIDS Indicator Surveys (KAIS), implemented in 2007 and 2012, were conducted to measure behaviours and biomarkers related to HIV infection, including HIV status, recency of HIV infection, CD4+ T-cell count, HIV-1 ribonucleic acid levels, and ART status among PLHIV aged 15–64 years in 2007 and 18 months–64 years in 2012. In South Africa, the Human Sciences Research Council (HSRC) has conducted four cross-sectional nationally-representative surveys to assess HIV prevalence, incidence and related behaviours in the general population since 2002. Data from the 2008 and 2012 surveys are presented here. The methods and results of all of the surveys have been described elsewhere [16,17]. In summary, the surveys were designed using multi-stage cluster sampling of households from a master sample to generate representative HIV prevalence estimates by sex, locality type, region, and national domains (and by age and race in South Africa). For Kenya, locality type is defined dichotomously as urban or rural, while for South Africa there are four defined locality types namely: urban formal, urban informal (informal settlements in urban areas characterized by shanty towns); rural formal (farming areas); and rural informal (informal settlements in rural areas also characterized by shanty towns). The 2007 Kenya survey included respondents aged 15–64 years, while the 2012 survey included respondents aged 18 months–64 years. The South African surveys both included respondents of all ages.

In both the Kenyan and South African surveys, written informed consent was sought from respondents prior to household and individual interviews and blood collection; assent was obtained from children aged less than 18 years in addition to consent from their caregiver or guardian. In the South African surveys, institutional review boards provided a waiver to allow use of verbal consent if a respondent

was not able to provide written consent. Venous whole blood was collected from participants and used to prepare dried blood spot (DBS) specimens in Kenya. During KAIS 2012, participants were also offered home-based counselling and testing with point-of-care CD4 testing offered to those who tested HIV-positive. In South Africa, DBS specimens were collected directly from capillary blood using a finger prick. In the 2007 Kenya and 2012 South African surveys, results of central HIV testing were made available for participant collection at a nearby health facility. Data from the questionnaires and the blood test results were linked using unique identifiers, which were anonymised prior to HIV and ART testing.

Laboratory methods

Survey HIV prevalence was based on centralized testing of plasma (KAIS 2007) or DBS specimens (KAIS 2012; South Africa 2008 and 2012) tested with validated enzyme-linked immunosorbent assays based on national HIV testing algorithms, as previously described [16–18]. In Kenya, CD4+ T-cell counts were measured with BD FACSCalibur flow cytometer (Becton Dickinson BioSciences, San Jose, CA). Remaining plasma and DBS specimens were stored at -80°C for future testing.

For all surveys, a qualitative antiretroviral (ARV) drug assay was applied to test for a panel of ARVs defined separately for each country by liquid chromatography-tandem mass spectrometry in all HIV-positive specimens [19]. Frozen stored DBS specimens from Kenya were tested in 2015 while DBS specimens for the South African surveys were tested within two months of specimen collection. Drug panels used for each country were designed to cover one or more drugs in all approved first- and second-line regimens in use at the time of each survey (also including salvage regimens in South Africa). Panels used were nevirapine (NVP), efavirenz (EFV), lamivudine (3TC), and lopinavir (LPV) in Kenya and azidothymidine (AZT), NVP, and EFV, LPV, atazanavir (ATV) and darunavir (DRV) in South Africa. The ARV drug assay's lower limit of detection was 0.02 µg/mL. Samples that fell above the lower limit of detection for any of the ARVs tested were classified as ARV positive.

Data analysis

Data from each survey were analysed separately. Previously-developed survey weights were applied in order to provide estimates representative of the population from which each survey was drawn. Analysis was limited to individuals aged 15–64 years testing HIV-positive in centralized laboratory testing. North Eastern Province was excluded from the 2012 Kenya survey due to insecurity at the time of the survey and thus the province was also excluded from the 2007 survey analysis for consistency. In cells where the denominator is less than 25 the proportion and confidence intervals were replaced with an asterisk.

Measures

The outcome measure of ART use was defined as having evidence of ART exposure in the survey blood specimen, i.e. a positive test for one or more ARVs among PLHIV. Note that treatment guidelines have evolved in both Kenya [20–22] and South Africa [23,24]. The guidelines in effect at the time of each survey are summarized in S1 Table.

A wealth index was created for each survey using measures related to household living standards including household characteristics (source of drinking water, access to electricity, main source of energy for cooking, type of toilet) and household ownership of assets (presence of a working refrigerator, radio, television, and in South Africa, mobile and landline phones) captured in the household questionnaire. The index was generated using factor analysis [25] and the resulting indices were grouped into quintiles from lowest (Quintile I) to highest (Quintile V) socioeconomic status (SES). As the indices were developed independently they are not directly comparable across countries.

Additional covariates were selected for inclusion in the analysis based on availability in the survey datasets and a structured literature review conducted prior to the survey that identified sex, age, disease stage, socio-economic status, employment, residency, cost, and decentralization of treatment as factors likely to predict ART use. Individual- and household-level factors identified in the review were included in the analysis.

For Kenya, employment status was defined as currently employed if the participant reported receiving payment or goods in exchange for work in the last seven days, otherwise they were unemployed. For South Africa, employment included self-employed as well as employment in the formal and informal sectors on a full-time or part-time basis. Students comprised those attending schools, including tertiary institutions.

Statistical methods

Logistic regression analysis was performed to assess associations between lack of ART (no evidence of ART exposure in the blood specimen) and selected demographic, socioeconomic and behavioural variables separately for each survey. Significance of covariates for purposes of model building was assessed using Wald tests. Variables were selected for inclusion in initial models based on significance of association with ART use in bivariate analyses ($p < 0.1$, presented in S3 and S4 Tables) or selected a priori in the case of sex, locality type, and household wealth. Models were then refined iteratively. Final regression models included covariates

that were significantly associated with the outcome in multiple regression analysis ($p < 0.05$) or that presented evidence of confounding as demonstrated by a 20% or greater change in coefficients of other significant covariates. Statistical significance for differences in prevalence of ART use between surveys was assessed by comparing confidence intervals (CI). For Kenya, separate models were developed including only women in order to further explore associations between pregnancy status and ART non-use.

To handle missing values, multiple imputation using chained equations was conducted with the Stata `mi` command on ART status, CD4 count, and disclosure of HIV status to last sex partner variables for each survey prior to regression analysis, to account for missing data for the Kenya surveys. The multiple imputation model assumes that data are missing at random. In South Africa, data were rarely missing and where this occurred the few cases affected were dropped at that stage of the analysis. A summary of the imputation modelling procedure is provided in S1 Text.

Analyses were conducted in SAS version 9.2 and Stata version 13 using commands designed to handle the complex survey design, except where otherwise noted.

Ethical approval

The South African surveys were approved by the HSRC Research Ethics Committee and by the U.S. Centers for Disease Control and Prevention (CDC) in Atlanta, USA. A waiver of written consent was granted for situations where respondents were unable to provide written consent but were able to provide verbal consent with signature of an impartial witness. The Kenyan surveys were approved by the Ethical Review Committee of the Kenya Medical Research Institute and the Institutional Review Board of the CDC. The 2012 KAIS was also approved by the Committee on Human Research of the University of California, San Francisco.

Results

In Kenya, 17,104 persons aged 15–64 years participated in KAIS 2007, of whom 88.3% provided a blood specimen and 1,097 tested HIV-positive in the survey (Fig 1). Of these, 575 (52.4%) had ART testing results available for complete case analysis; a total of 1,092 cases were available after imputing missing values. In 2012, 13,720 persons aged 15–64 years participated in the study of which 11,626 (84.7%) provided blood specimens and 648 tested positive in the survey. Of these, 559 (86.3%) had an ARV test result available for analysis, while after imputing missing values a total of 635 cases were available. Additional information about the multiple

imputation model is provided in S1 Text, including a table comparing the distribution of observed and completed values (S2 Table). In South Africa, 14,543 individuals participated in the 2008 survey, with 78.2% giving a blood specimen, and 1,284 testing HIV-positive (Fig 1). Corresponding figures for 2012 were 24,084 participants, 77.5% of whom gave a blood specimen, with 2,588 of these testing HIV-positive. Antiretroviral treatment results were available for almost all HIV-positive samples in South Africa (100% in 2008 [n=1,284], and 99.9% [n=2,586] in 2012) (Fig 1).

Fig 1. Study sample, HIV status and ART exposure testing, participants aged 15–64 years, Kenya and South Africa, 2007, 2008 and 2012

Notes: Data are unweighted. Percentages are calculated with respect to previous row, except interview response rates shown in first row which are calculated with respect to total eligible population (not shown). * For Kenya, 1092 cases have ART results available in 2007 and 635 have results available in 2012 after multiple imputation.

Kenya

The proportion of PLHIV on ART increased from 29.3% (95% confidence interval [CI]: 22.8–35.8) in 2007 to 42.5% (95% CI: 37.4–47.7) in 2012. For females, it increased from 31.2% (95% CI: 23.0–39.4) to 45.6% (95% CI: 40.5–50.7). The unadjusted proportion on treatment also increased significantly for the Rift Valley region, for those aged 35–49 years, for persons who were married or cohabitating, and for those who disclosed their status to their most recent sex partner.

The proportion of PLHIV on ART did not differ significantly by locality, province or sex, education or household wealth quintile in either Kenyan survey. However, the likelihood of being on ART differed by age and marital status in both surveys. ART coverage differed significantly by current CD4 count in 2007 ($p < 0.001$) but not in 2012. ART use varied by time since last HIV test in both surveys. In 2012, ART use varied by employment status ($p = 0.021$), disclosure to most recent partner ($p = 0.046$) and recreational drug use in the last 12 months ($p < 0.001$). Women who were pregnant in the last three years were less likely to be on ART in both surveys (Table 1).

Table 1. ARV exposure by selected characteristics of HIV-infected individuals aged 15–64 years old, Kenya 2007 and 2012

Variable	Kenya, 2007			Kenya, 2012		
	On ART			On ART		
	N	Weighted % (95% CI)	p-value	N	Weighted % (95% CI)	p-value
Locality type			0.875			0.240
Rural	389	29.7 (22.3-37.1)		317	39.9 (32.5-47.2)	
Urban	186	28.5 (15.5-41.4)		242	45.9 (38.9-52.9)	
Province			0.219			0.240
Nairobi	79	36 (14.3-57.7)		54	45.1 (32.4-57.8)	
Central	41	40.2 (25.3-55.2)		50	47.6 (34.2-61.0)	
Coast	78	15.4 (3.1-27.8)		55	41 (23.7-58.3)	
Eastern	47	28.9 (4.3-53.4)		66	59.3 (41.3-77.2)	
Nyanza	197	35.6 (22.2-49.0)		212	36.6 (29.1-44.0)	
Rift Valley	77	17.6 (8.9-26.3)		70	45.5 (29.4-61.6)	
Western	56	28.9 (10.5-47.3)		52	36.8 (22.7-50.8)	
Sex			0.259			0.120
Male	203	25.7 (18.5-32.9)		175	37.8 (28.6-46.9)	
Female	372	31.2 (23.0-39.4)		384	45.6 (40.5-50.7)	
Age (years)			<.001			<.001
15-24	100	18.2 (8.3-28.1)		59	21.6 (8.8-34.3)	
25-34	212	23 (15.0-31.0)		182	25.1 (18.1-32.2)	
35-49	208	38.3 (29.6-47.1)		229	55 (47.7-62.4)	
50-64	55	38.2 (24.2-52.3)		89	59.6 (48.6-70.6)	
Marital status			0.002			0.002
Single/never married	70	22.8 (10.1-35.6)		73	24.5 (12.8-36.2)	
Married/cohabitating	373	25.5 (19.3-31.7)		337	42 (35.4-48.7)	
Divorced/separated/ widowed	132	42 (30.6-53.3)		149	53.1 (44.7-61.5)	
Education			0.943			0.130
None	292	30 (20.7-39.3)		81	35.5 (24.0-46.9)	
Primary	181	27.4 (19.9-35.0)		298	39.5 (32.4-46.6)	
Secondary	77	29.5 (19.7-39.4)		28	45.7 (25.7-65.8)	
Higher	25	32.7 (9.8-55.6)		151	50.6 (40.8-60.4)	
Household wealth			0.507			0.900
Quintile I (lowest)	98	27.5 (14.7-40.2)		87	41 (28.0-54.1)	
Quintile II	102	20.7 (8.5-32.9)		133	40.6 (28.8-52.3)	
Quintile III	96	31.9 (19.3-44.5)		122	41.2 (30.9-51.4)	

Table 1. Continued

Variable	Kenya, 2007			Kenya, 2012		
	On ART			On ART		
	N	Weighted % (95% CI)	p-value	N	Weighted % (95% CI)	p-value
Employment			0.432			0.021
Unemployed	90	33.7 (19.4-48.1)		197	50 (41.1-58.8)	
Employed	485	28.5 (22.1-34.9)		361	39 (33.5-44.5)	
CD4 category (cells/ mm ³)			<.001			0.310
≤250	106	24.1 (15.4-32.8)		44	51.5 (37.0-65.9)	
250>-350	60	53.4 (38.1-68.8)		35	59.9 (42.5-77.4)	
350>-500	93	32.9 (22.2-43.7)		37	47.6 (27.9-67.4)	
>500	276	23.9 (15.6-32.2)		168	42.4 (32.9-51.9)	
Most recent HIV test†			<.001			<.001
<12 months ago	135	38.1 (27.5-48.7)		264	49.9 (42.1-57.6)	
1-2 years ago	69	47.1 (32.8-61.5)		100	32.9 (21.7-44.1)	
> 2 years ago	84	41.3 (25.4-57.2)		122	51.7 (42.1-61.3)	
Disclosed results to partner‡			0.572			0.046
Yes	193	35.3 (25.8-44.8)		174	69 (60.9-77.0)	
No	38	27.9 (5.3-50.4)		90	55 (43.1-66.9)	
Pregnancy and HIV testing§						
Pregnant	141	18.5 (10.3-26.7)	<.001	98	35.2 (24.6-45.8)	0.031
Not pregnant	231	38.1 (28.5-47.8)		286	49.1 (43.2-55.0)	
Antenatal care (ANC) visit	123	18.8 (10.1-27.5)	0.727	95	35.2 (24.5-45.9)	0.988
No ANC visit	18	*		3	*	
Ever tested for HIV in pregnancy	76	22.3 (11.7-32.9)	0.172	88	33.3 (22.0-44.6)	0.288
Never tested for HIV in pregnancy	47	13.4 (2.9-23.9)		7	*	
Recreational drug use§§						<.001
Yes	-			55	17.9 (6.5-29.4)	
No				504	45.3 (40.2-50.5)	
Total	575	29.3 (22.8-35.8)		559	42.5 (37.4-47.7)	

Notes: All numbers are unweighted except where otherwise specified. * Suppressed due to denominator <25 observations. † Applies to respondents who reported ever testing for HIV ‡ Applies to respondents who self-reported HIV-positive, partner refers to most recent sex partner. § Applies to pregnancy during last 3 years among female respondents only. §§ Drug use in last 12 months. ART = antiretroviral treatment, CI = confidence interval.

22 **Table 2:** Multiple regression analysis showing associations between selected characteristics of HIV-infected individuals with ART non-use among individuals aged 15–64 years, Kenya, 2007 and 2012

Variable	Kenya, 2007				Kenya, 2012					
	All PLHIV (n=1097)		Female PLHIV (n=729)		All PLHIV (n=648)		Female PLHIV (n=454)			
	aOR	95% CI	p-value	aOR	95% CI	p-value	aOR	95% CI	p-value	
Residence										
Rural					1.98	(1.23-3.18)	0.005			
Urban (ref)										
Age (years)										
15-24	3.69	(1.55-8.79)	0.004	3.30	(1.07-10.22)	0.039	0.002	9.21	(3.13-27.12)	<0.001
25-34	2.18	(0.96-4.95)	0.061	1.86	(0.66-5.28)	0.235	<0.001	5.30	(2.44-11.52)	<0.001
35-49	1.31	(0.68-2.51)	0.419	1.13	(0.47-2.70)	0.783	0.165	1.62	(0.78-3.34)	0.194
50-64 (ref)										
Marital status										
Single/never married (ref)										
Married/cohabitating								0.26	(0.12-0.58)	0.0011
Divorced/ separated/ widowed								0.32	(0.14-0.73)	0.0069
Education										
None (ref)										
Primary								0.79	(0.36-1.71)	0.5419
Secondary								1.00	(0.26-3.85)	0.9962
Higher								0.41	(0.19-0.89)	0.0250
Wealth quintile*								0.78	(0.64-0.95)	0.0122

Table 2: Continued

Variable	Kenya, 2007				Kenya, 2012				
	All PLHIV (n=1097)		Female PLHIV (n=729)		All PLHIV (n=648)		Female PLHIV (n=454)		
	aOR	95% CI	p-value	aOR	95% CI	p-value	aOR	95% CI	p-value
No (ref)									
Disclosed HIV status to most recent partner†									
Yes (ref)									
No					2.41	(1.27-4.57)	0.007		
Unaware of status					9.15	(5.19-16.13)	<0.001		
Recreational drug use in last 12 months									
No (ref)									
Yes					2.50	(1.09-5.77)	0.032		

Notes: Although current CD4 category was significantly associated with ART status in bivariate analysis, as a marker of current immune status it is likely to be confounded by duration of treatment, so it was not included in the regression analysis. * Odds of ART non-use was found to decrease linearly with wealth quintile among women in 2012 so it is included as a continuous term. † Applies to respondents who self-reported HIV-positive.

In bivariate analysis, in 2012, ART non-use was also greater among women aged 15–24 years (OR=5.6) and 25–44 years (OR=4.09) compared with those aged 50–64 years ($p<0.001$), and inversely with being married or cohabitating, or divorced, separated or widowed, compared to those who were single/never married ($p<0.001$), having last HIV test 1–2 years ago versus <1 year ago, not disclosing HIV status to their most recent sex partner ($p=0.011$), pregnancy in the last three years among women ($p=0.045$) and reporting having used recreational drugs in the last 12 months ($p=0.003$) (S3 Table).

In multiple regression, only younger age was associated with lack of ART use among PLHIV in 2007, with an adjusted odds ratio (aOR) of ART use of 3.69 (95% CI: 1.55–8.79) for PLHIV aged 15–24 versus 50–64 years of age. In 2012, when controlling for residency, age group, disclosure, and recreational drug use, ART non-use was more likely in respondents living in rural compared with urban areas (aOR 1.98, CI 1.23–3.18), and in younger respondents (aged 15–24 years, aOR 4.25, CI 1.70–10.63, aged 25–34, aOR 5.16, CI 2.73–9.74 compared with those aged 50–64 years). ART non-use was also more likely in those who reported they had not disclosed their status to their last sex partner (aOR 2.41, 95% CI: 1.27–4.57) and those who reported a recreational drug use in last 12 months (aOR 2.50, 95% CI: 1.09–5.77) (Table 2). In order to explore the association between recent pregnancy and ART non-use among women, separate multiple regression models were constructed for women in both 2007 and 2012. No significant association between lack of ART use among those recently pregnant was found in 2007 (aOR 1.30, 95% CI: 0.76–2.21) or 2012 (aOR 0.97, 95% CI: 0.54–1.74). However, the women-only model for 2012 did reveal associations with marital status, education, and wealth quintile not seen in the combined male-female model. Lack of ART was significantly less likely among married women compared with single women (aOR 0.26, 95% CI: 0.12–0.58), as among women who were divorced, separated or widowed (aOR 0.32, 95% CI: 0.14–0.73). Wealth quintile also showed a 22% increase in odds of ART use for each increase in wealth quintile (aOR of non-use: 0.78, 95% CI: 0.64–0.95). Unlike in the combined male-female model, disclosure of status and recreational drug use in last 12 months was not found to be associated with ART non-use in women (S5 Table).

South Africa

Overall the proportion of PLHIV on ART increased from 17.3% (95% CI: 14.2–20.9) in 2008, to 30.3% (95% CI: 27.2–33.6) in 2012. ART use increased more than four-fold among those living in rural informal areas from 7.7% (95% CI: 3.7–15.4) in 2008 to 34.3% (95% CI: 30.8–38.9) in 2012 (S1 Fig), and more than doubled among females from 16.8% (95% CI: 13.5–20.7) in 2008 to 43.2% (95% CI: 30.9–37.7) over the same period. Although ART use increased across all age groups, increases were

much greater among the older age groups with 14.9% (95% CI: 8.9–23.7) of those aged 50–64 years on ART in 2008 compared with 43.3% (95% CI: 36.1–50.7) in 2012. The proportion of PLHIV on ART differed significantly by marital status in both survey years ($p=0.031$ in 2008 and $p=0.002$ in 2012). In 2012 the proportion of PLHIV on ART also differed significantly by sex ($p=0.001$), by age ($p<0.001$), by employment status ($p<0.001$) and by recreational drug use ($p<0.0001$) (Table 3). On bivariate analysis, ART non-use was significantly associated with province, marital status, highest level of education, employment status and household wealth in 2008. In 2012 there was significantly greater ART non-use among males ($p=0.001$), those aged 15–24 (OR 4.57, $p<0.001$) and 25–34 years (OR 2.75, $p<0.001$) versus those aged 50–64 years, those who were employed ($p<0.001$) or students ($p<0.033$) versus unemployed, and those with recent recreational drug use ($p<0.001$), while those who were divorced/separated/widowed had lower non-use of ART compared with those who were single/never married/no stable partnership ($p<0.017$). Recency of testing showed no significant association with ART non-use in either survey year (S4 Table).

On multiple regression analysis, marital status was significantly associated ART non-use: being divorced, separated or widowed was associated with a lower likelihood of ART non-use when compared to being single or never married (aOR 0.45, 95% CI: 0.22–0.91, $p=0.027$). Significant associations were also observed by level of education (aOR 0.14, 95% CI: 0.03–0.68, $p=0.014$ for tertiary (higher) level of education versus no education), employment status (aOR 2.16, 95% CI: 1.26–3.71, $p=0.01$ for those who were employed versus the unemployed) and household wealth (aOR 0.43, 95% CI: 0.20–0.90, $p=0.03$ for Quintile III versus Quintile I) in 2008. In 2012, younger age was significantly associated with ART non-use (aOR 4.23, 95% CI: 2.56–6.70, $p<0.001$ and aOR 2.84, 95% CI: 1.73–4.67, $p<0.001$ for age groups 15–24 years and 25–34 years, respectively, compared to age group 50–64 years). Students were significantly more likely not to use ART (aOR 1.61, 95% CI: 1.16–2.23) compared to those who were unemployed. Recreational drug users were also more likely not to use ART (aOR 4.56, 95% CI: 1.79–11.57, $p=0.001$) when compared to non-drug users (Table 4).

Table 3: Antiretroviral exposure by selected characteristics of HIV-infected individuals aged 15–64 years old, South Africa, 2008 and 2012

Variable	South Africa, 2008			South Africa, 2012		
	ART		p-value	On ART		p-value
	N	Weighted % (95% CI)		N	Weighted % (95% CI)	
Locality type			0.211			0.068
Urban formal	481	15.9 (11.3-22.0)		888	27.1 (21.3-33.8)	
Urban informal	345	20.5 (14.1-29.0)		525	27.2 (22.7-32.3)	
Rural formal	117	19.4 (13.9-26.2)		335	27.5 (19.6-37.2)	
Rural informal	341	7.7 (3.7-15.4)		840	34.7 (30.8-38.9)	
Province			0.710			0.200
Western Cape	83	28.3 (16.1-44.7)		157	27.5 (18.6-38.6)	
Eastern Cape	146	19.1 (10.1-33.2)		324	31.2 (25.1-38.2)	
Northern Cape	70	18.9 (8.9-35.8)		131	13.6 (5.6-29.6)	
Free State	125	13.5 (8.1-21.6)		258	27.0 (20.2-35.1)	
KwaZulu Natal	288	15.4 (10.2-22.6)		726	32.8 (28.2-37.7)	
Northwest	114	21.5 (13.8-31.8)		211	39.6 (30.0-50.2)	
Gauteng	211	18.6 (10.7-30.4)		291	26.2 (18.0-36.5)	
Mpumalanga	141	16.4 (10.7-24.2)		291	35.9 (27.9-44.7)	
Limpopo	106	13.8 (7.3-24.7)		197	24.8 (15.6-37.1)	
Race			0.864			0.102
Black African	1205	17.3 (14.2-21.0)		2365	30.0 (26.8-33.4)	
Other race	79	16.2 (7.6-31.5)		223	40.8 (29.0-53.7)	
Sex			0.650			0.001
Male	352	18.5 (12.6-26.4)		801	24.1 (19.5-29.5)	
Female	932	16.8 (13.5-20.7)		1787	43.2 (30.9-37.7)	
Age (years)			0.350			<0.001
15-24	279	11.6 (4.9-25.2)		399	14.3 (10.0-20.0)	
25-34	441	17.7 (13.0-23.6)		926	21.7 (17.9-26.1)	
35-49	444	20.8 (15.9-26.8)		912	41.0 (35.5-46.7)	
50-64	120	14.9 (8.9-23.7)		349	43.3 (36.1-50.7)	
Education			0.177			0.661
None	73	6.5 (2.2-17.5)		-	-	
Primary	297	16.0 (10.7-23.3)		568	32.8 (27.4-38.8)	
Secondary	794	17.5 (13.6-22.3)		1544	30.4 (26.7-34.4)	
Higher education	43	31.1 (12.5-58.7)		84	26.5 (13.9-44.6)	
Missing/unknown*	77	-		392	-	

Table 3: Continued

Variable	South Africa, 2008			South Africa, 2012		
	ART		p-value	On ART		p-value
	N	Weighted % (95% CI)		N	Weighted % (95% CI)	
Marital status			0.031			0.002
Single	726	17.5 (13.2-23.0)		530	33.3 (26.0-41.6)	
Married	342	13.2 (9.3-18.4)		1784	27.7 (24.4-31.3)	
Divorced/ separated/ widowed	143	28.8 (19.3-40.5)		229	47.0 (38.8-55.3)	
Household wealth			0.118			0.738
Quintile I	375	15.1 (10.6-21.2)		759	31.4 (26.9-36.4)	
Quintile II	382	15.0 (10.9-20.4)		683	29.1 (24.1-34.6)	
Quintile III	243	24.5 (16.7-34.4)		652	31.1 (24.2-38.9)	
Quintile IV	197	13.1 (7.7-21.5)		315	27.0 (19.4-36.4)	
Quintile V	68	24.0 (9.8-47.8)		148	37.8 (24.2-53.6)	
Employment			0.186			<0.001
Unemployed	706	20.4 (16.2-25.5)		1489	33.9 (30.2-37.9)	
Employed	426	11.4 (8.1-15.7)		101	9.7 (4.2-20.9)	
Student	61	22.2 (5.2-59.6)		933	27.8 (23.2-32.8)	
Most recent HIV test			0.328			0.209
<12 months	365	21.8 (15.6-29.4)		1276	35.4 (31.3-39.7)	
1-2 years	192	17.3 (10.9-26.5)		266	33.4 (25.8-42.0)	
2-3 years	91	23.4 (13.2-37.9)		152	30.5 (21.8-40.9)	
3+ years	98	31.3 (19.5-46.0)		245	44.3 (33.6-55.6)	
Alcohol intake in last 12 months			0.491			0.066
Non-high-risk drinker	1083	16.6 (13.3-20.6)		2050	31.5 (27.9-35.3)	
High-risk drinker	113	20.8 (11.1-35.7)		249	21.2 (13.4-31.8)	
Recreational drug use†			0.871			<0.001
Non-drug user	10101	17.5 (14.0-21.5)		2345	32.1 (28.9-35.6)	
Drug user	45	15.8 (4.1-45.1)		122	9.0 (4.3-17.6)	
Total	1284	17.4 (14.2-20.9)		2586	30.3 (27.2-33.6)	

Notes: All numbers are unweighted except where otherwise specified. * Estimates not presented for missing/unknown categories. † Refers to last 3 months.

Table 4: Multiple regression analysis showing associations between selected characteristics of HIV-infected individuals with ART non-use among individuals aged 15 to 64 years, South Africa, 2008 and 2012

Variable	South Africa, 2008		South Africa, 2012	
	Multiple Regression Analysis n=1170		Multiple Regression Analysis n=2138	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Locality type				
Urban formal (ref)	Ref		ref	
Urban informal	0.49 (0.24-0.98)	0.04	1.20 (0.75-1.92)	0.441
Rural formal	1.20 (0.38-0.82)	0.75	0.85 (0.46-1.54)	0.583
Rural informal	0.52 (0.25-1.09)	0.084	0.78 (0.50-1.20)	0.259
Province				
KwaZulu-Natal (ref)	ref			
Western Cape	0.40 (0.13-1.20)	0.104		
Eastern Cape	0.86 (0.38-1.97)	0.727		
Northern Cape	0.60 (0.20-1.80)	0.358		
Free State	1.49 (0.63-3.54)	0.365		
Northwest	0.71 (0.30-1.68)	0.431		
Gauteng	0.70 (0.30-1.62)	0.402		
Mpumalanga	0.84 (0.38-1.83)	0.656		
Limpopo	1.50 (0.49-4.55)	0.477		
Sex				
Male (ref)			ref	
Female			0.73 (0.52-1.04)	0.084
Age (years)				
15-24	2.68 (0.813-8.808)	0.105	4.23 (2.56-6.70)	<0.001
25-34	0.67 (0.30-1.49)	0.326	2.84 (1.73-4.67)	<0.001
35-49	0.55 (0.27-1.14)	0.108	1.08 (0.50-1.20)	0.741
50-64 (ref)	ref		ref	
Marital status				
Single/Never married/no stable partnership (ref)	ref		ref	
Married/stable partnership	1.52 (0.85-2.72)	0.159	1.25 (0.86-1.82)	0.241
Divorced/Separated/ Widowed	0.45 (0.22-0.91)	0.027	0.99 (0.59-1.67)	0.977
Education				
None (ref)	ref			
Primary	0.34 (0.97-1.22)	0.099		
Secondary	0.29 (0.09-0.99)	0.048		
Higher education	0.14 (0.03-0.66)	0.014		

Table 4: Continued

Variable	South Africa, 2008		South Africa, 2012	
	Multiple Regression Analysis n=1170		Multiple Regression Analysis n=2138	
	aOR (95% CI)	p-value	aOR (95% CI)	p-value
Employment				
Unemployed (ref)	ref		ref	
Employed	2.16 (1.30-3.94)	0.004	2.53 (0.91-7.07)	0.075
Student	0.32 (0.06-1.76)	0.191	1.61 (1.16-2.23)	0.004
Household wealth quintile				
Quintile I (ref)	ref			
Quintile II	0.89 (0.47-1.69)	0.724		
Quintile III	0.443 (0.20-0.95)	0.037		
Quintile IV	0.82 (0.33-2.03)	0.673		
Quintile V	0.40 (0.13-1.26)	0.116		
Alcohol intake in past 12 months				
Non high-risk drinker (ref)			ref	
High-risk drinker			1.36 (0.72-2.55)	0.344
Recreational drug use in past 3 months				
No (ref)			ref	
Yes			4.56 (1.79-11.57)	0.001

Discussion

Use of ART increased significantly in both countries, consistent with ART program scale-up and evolving treatment guidelines in both Kenya and South Africa during the study period. The proportion of PLHIV on ART was higher in Kenya than in South Africa both in 2007/2008 and 2012. However South Africa had a larger number of PLHIV compared to Kenya in both surveys, and the proportion of PLHIV on ART in South Africa nearly doubled over this period. While in South Africa it appears disparities in ART use may have decreased over the period of analysis, in Kenya household wealth among women and rural residency among men and women combined were both significantly associated with ART non-use in 2012 but not in 2007.

The analyses showed both similarities and differences in ART use in Kenya and South Africa. In both countries, after controlling for other covariates, there were no significant disparities in ART use by province and sex. In Kenya in 2012 lack of ART use was higher in rural areas while no differences were observed by locality type in South Africa in either survey year. Differences by household wealth were only seen in 2012 in Kenya, among women only, and in 2008 in South Africa, where they were limited to one quintile.

Older age was associated with greater likelihood of ART use in both countries in both survey periods when controlling for other factors. This may partially reflect natural disease progression and ART eligibility criteria at the time, with older people more likely to have been infected for a longer period of time compared to younger people, thus reaching the thresholds for ART treatment required by contemporary treatment guidelines. Nonetheless this finding of age differences in non-use of ART among PLHIV suggests need for strengthening efforts to ensure that younger people know their status, start ART, and adhere to care and treatment. In the 2012 KAIS 82% of HIV-infected youth aged 15–24 years (50.6%) were unaware of their HIV status, compared with 58.9% of those aged 25–34 [26], while the 2012 South Africa survey found a significantly lower proportion of youth aged 15–24 years had been tested for HIV compared with those aged 25–49 years (78.2%) [18]. With the adoption of the test-and-treat policy in 2016 in both countries, decreasing disparities in ART use by age group are expected in the future. Nonetheless, high uptake of testing among young people combined with appropriate linkage to care will be a necessary precondition to achieving adequate ART coverage. Future studies may also find that reduced ART use among women with a recent pregnancy, as seen in both survey years in Kenya, may have since been mitigated by changed eligibility criteria which made all pregnant women eligible for life-long ART with the adoption of option B+ for PMTCT starting in 2014 regardless of CD4 count in Kenya [21]. In South Africa this policy was implemented in January 2015 [27].

Overall, household wealth and educational level were not associated with ART use in either country in 2012, which is perhaps a result of the large, government-sponsored ART programs in both Kenya and South Africa offering ART to all regardless of ability to pay. However, in a sub-group analysis among women in Kenya, ART use was associated with increasing household wealth among women. In both countries, recent illicit/recreational drug use was associated with lower ART use, though drug users make up a small proportion of PLHIV. This finding could reflect low treatment access, adherence and/or retention in care in this population group. In a separate analysis of KAIS 2012, Mukui *et al.* found a significant association between both younger age and recreational drug use and poor

adherence to treatment, and argue that increased identification and management of recreational drug use in this population is needed in order to mitigate its potential effects on adherence [28].

Kenya's epidemic is highly geographically heterogeneous, with highest prevalence in the Nyanza region and the greatest burden of PLHIV in Nyanza and Nairobi [15]. Point estimates for ART use increased across all regions except Nyanza, though only Rift Valley increased significantly. Given that over a third of PLHIV in Kenya live in Nyanza, additional efforts to achieve increases in ART use in this region are warranted. The appearance of reduced ART use in rural relative to urban areas in 2012, not seen in 2007, may reflect either reduced barriers to access in urban areas or challenges in accessing drugs in rural areas due to increased travel costs, fear of stigma, or other barriers, and is a cause for concern [29,30].

In South Africa, HIV prevalence also varied across provinces and geographic locations, being highest in both urban and rural informal settlements in 2012. While ART use was lowest in rural informal settlements in 2008, it increased dramatically in 2012 reaching the same levels of use observed in other locality types, suggesting success in increasing geographical equity in ART access in South Africa over time. This suggestion is further corroborated by the absence of significant associations between ART non-use and province in both survey years and by locality type in 2012.

The lower levels of ART use among employed PLHIV versus unemployed in South Africa in 2008 might be due to a healthy worker effect, given that treatment initiation guidelines in South Africa historically recommended ART initiation based on CD4 count. Comparatively lower ART use among South African students in 2012, even when controlling for age, is an interesting finding, and could also be a reflection of the healthy worker effect as well as the natural disease progression as discussed above.

In Kenya, non-disclosure of HIV status to partners was significantly associated with higher adjusted odds of lack of ART use among PLHIV, suggesting that stigma may impact an individual's decision regarding use of ART. The most recent stigma index survey conducted in Kenya in 2009-2010 found high levels of social exclusion (40%) and internalized stigma with 46% of PLHIV feeling guilty or ashamed for being HIV-positive [31]. In contrast, the stigma index survey conducted in South Africa in 2014 found low levels of social exclusion among PLHIV, however it

revealed high levels of internalised stigma with 29% of participants in the survey reporting that they felt ashamed, while 28% had feelings of guilt [32]. This suggests need for continued stigma reduction strategies among PLHIV in both countries.

This analysis was subject to several limitations. Antiretroviral treatment access from 2007–2012 in both countries was highly dependent on treatment guidelines implemented at the time that individual patients engaged in care, and these guidelines have evolved over time. Our analysis did not attempt to establish eligibility for treatment, nor would it be entirely possible in a cross-sectional study to account for eligibility prior to ART initiation, but rather included all PLHIV regardless of eligibility. Since we measured presence of trace quantities of ART metabolites in blood we are not able to distinguish between PLHIV who have never been on ART, those who have stopped taking ART (i.e. disengagement from care) or those that have not taken their drugs for several days or weeks (i.e. non-adherent). Data regarding distance to the nearest facility offering ART, which may have provided further insights about ART accessibility, were not available. We also did not consider self-reported HIV status when assessing ART use. Finally, sample size was limited for some domains, especially in Kenya, which could have limited our power to detect differences in some cases and prevented more detailed sex-specific analyses.

In spite of these limitations, measurement of ART use in nationally-representative surveys in two countries with large HIV treatment programs allowed for an objective assessment of trends in ART use among PLHIV in the era of treatment expansion and identification of potential barriers to ART access and uptake. Both countries demonstrated substantial increases in ART use over time with broadly equitable access to ART across geographic and socioeconomic status with some exceptions. Our analyses did find evidence of increasing disparities in access to ART by household wealth in women in Kenya, and lingering inequities in use by age and among those who use recreational drugs, indicating some populations may require increased adherence support or access to HIV testing. To the degree that lower use in youth may be due to eligibility criteria, the adoption of test-and-treat provides a new opportunity to increase access to ART among youth.

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Supporting Information

S1 Table. Treatment guidelines by survey year in Kenya and South Africa

Survey	Kenya	South Africa
2007-2008	CD4<200 cells/mm ³ , or WHO stage III or IV	CD4<200 cells/mm ³ , WHO stage IV
2012	CD4<350 cells/mm ³ , or WHO stage III or IV, or co-infected with TB	CD4<200 cells/mm ³ , or WHO stage IV, or CD4<350 cells/mm ³ and pregnant or co-infected with TB
Present	Test-and-treat from mid-2016	Test-and-treat from 1 st September 2016

S1 Text. Statistical Methods for addressing missing data

In order to address missing values for several key variables including ART use (the dependent variable) and CD4 count, we used multiple imputation. Potential targets for imputation were selected by first inspecting patterns of missing values using the Stata `mi misstable` command, resulting in the selection of ART use (the dependent variable), CD4 count, and disclosure of HIV status to sex partner as targets of imputation. We assumed that missing values were missing at random (MAR), in other words that the missingness can be completely explained by other observed covariates in the dataset. Given that missing ART status and CD4 count is generally due to laboratory transport or processing errors, or due to depletion of sample, all of which generally occur independently from factors likely to influence ART use, CD4 count or disclosure of HIV status, this assumption seemed plausible. We used multiple imputation with chained equations (MICE), implemented with the Stata `mi` command. This method was selected due to the ready availability of implementations in statistical software, as well as its flexibility and simplicity of specifying restrictions on imputed values (for example, allowing the exclusion of specific auxiliary variables in the model for specific imputation targets). Imputations were run separately on each survey. First, variables identified as likely to be associated with the outcome of interest were selected. Additional auxiliary variables were also selected. In the case of 2007, the following variables were selected as targets for multiple imputation based on the proportion of responses that were missing and their relevance to the primary analysis: CD4 category, ART status, and disclosure of HIV status to most recent sex partner. The following variables were selected as predictors of the response variables: cluster number, province, sex, wealth index quintile, employment status, educational level, age group, marital status, locality, history of HIV testing. Self-reported ART status was considered for inclusion but dropped due to collinearity with the dependent variable, as were household-level variables. The data were `svyset` before analysis

using the normalized KAIS blood weights. The following equation was used to create 20 imputed datasets for the 2007 KAIS for HIV-positive respondents using chained equations to allow multiple outcomes to be imputed sequentially.

The imputation was restricted to HIV-positive respondents, as only these respondents are included in the analysis of ART use. CD4 category is an ordinal variable so was imputed using an ordered logistic model, ART status is a Boolean variable so was imputed using a logistic model, while disclosure status was a categorical variable with three unordered levels and was imputed using multinomial logistic regression. The MICE method assumes a joint normal distribution of imputed values.

After imputation, 517 of 522 missing ART status had been imputed, 81 of 84 missing CD4 category had been imputed, and 61 of 61 missing disclosure had been imputed. Not all cases were successfully imputed due to missingness of the predictors.

For the 2012 KAIS, CD4 count was not included as a target for imputation as the proportion of missing values was low. Cluster number was omitted from the predictors due to colinearity with ART status. Self-reported ART status was also included as a predictor of disclosure, but omitted from predicting the ART biomarker again due to colinearity. Several household-level variables were also found to be predictive of the response and were included in the final equation: sex of head of household, whether head of household was known to be HIV-infected, HIV test result of head of household, and the household hunger scale index.

After imputation, of 648 HIV-positive respondents, 89 missing ART status had been imputed, while 20 missing disclosure status had been imputed (there were no cases where imputation was unsuccessful).

To assess imputation errors such as misspecification of the imputation model or convergence issues, trace plots were used to look for patterns in the imputations to assess possible trends in imputed values or variances. The Stata `mi xeq` command was used to inspect and compare distributions of imputed values for individual imputations. Supplemental Table S2 compares the distribution of values for the observed and complete datasets.

S2 Table. Comparison of observed and completed values for multiply-imputed variables, Kenya 2007 and 2012

Variable	Kenya, 2007				Kenya, 2012			
	observed data		completed data		observed data		completed data	
	Weighted %	95% CI	Weighted %	95% CI	Weighted %	95% CI	Weighted %	95% CI
ART status								
not on ART	70.7	(63.5-76.9)	72.5	(68-77)	57.5	(52.3-62.5)	58.5	(53.8-63.3)
on ART	29.3	(23.1-36.5)	27.5	(23-32)	42.5	(37.5-47.7)	41.5	(36.7-46.2)
Current CD4 category (cells/mm³)								
<250	18.8	(16.1-22)	19.0	(15.9-21.7)	16.2	(11.9-21.7)	16.2	(11.3-21.1)
250>-350	12.5	(10.3-15.1)	12.4	(10-14.8)	14.8	(10.4-20.6)	14.8	(9.7-19.9)
350>-500	16.9	(14.6-19.4)	17.0	(14.5-19.5)	14.7	(10.5-20)	14.7	(9.9-19.4)
>500	51.7	(47.9-55.5)	51.8	(48-55.6)	54.3	(47-61.4)	54.3	(47.1-61.6)
Disclosed results to most recent partner								
Yes	77.6	(75.9-79.2)	77.3	(75.6-79)	21.4	(18.2-25.1)	21.5	(18.1-24.9)
No	9.8	(8.6-11.1)	9.7	(8.5-11)	49.5	(44.6-54.4)	49.3	(44.4-54.1)
N/A	12.6	(11.4-14)	13.0	(11.6-14.3)	29.1	(25.1-33.5)	29.2	(25-33.5)

S3 Table. Bivariate regression analysis showing associations between selected characteristics of HIV-infected individuals with exposure to ART among individuals 15–64 years, Kenya 2007 and 2012

Variable	Kenya, 2007			Kenya, 2012		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
Residency type						0.232
Urban (ref)	ref			ref		
Rural	0.81	(0.45-1.46)	0.474	1.27	(0.86-1.89)	
Province			0.518			0.648
Central	0.67	(0.27-1.67)		0.83	(0.4-1.7)	
Coast	1.71	(0.63-4.68)		1.10	(0.47-2.59)	
Eastern	1.02	(0.36-2.88)		0.63	(0.27-1.49)	
Nairobi (ref)	ref			ref		
Nyanza	0.80	(0.34-1.87)		1.18	(0.65-2.14)	
Rift Valley	1.26	(0.48-3.31)		0.94	(0.42-2.09)	
Western	0.84	(0.33-2.16)		1.31	(0.61-2.82)	
Female sex	0.92	(0.61-1.38)	0.673	0.80	(0.54-1.2)	0.288
Age (years)			0.002			<0.001
15-24	3.69	(1.55-8.79)		5.60	(2.45-12.78)	
25-34	2.18	(0.96-4.95)		4.09	(2.4-6.96)	
35-49	1.31	(0.68-2.51)		1.22	(0.72-2.05)	
50-64 (ref)	ref			ref		
Marital status			0.069			<0.001
single/never married (ref)	ref			ref		
married/cohabitating	0.67	(0.33-1.38)		0.38	(0.21-0.71)	
divorced/separated/widowed	0.44	(0.2-1)		0.27	(0.14-0.53)	
Education			0.921			0.190
None (ref)	ref			ref		
Primary	1.04	(0.62-1.75)		0.88	(0.5-1.56)	
Secondary	0.87	(0.45-1.69)		0.76	(0.29-1.97)	
Higher	0.80	(0.28-2.28)		0.57	(0.32-1.04)	
Employment status						0.078
Employed	1.04	(0.59-1.84)	0.880	1.41	(0.96-2.07)	
Unemployed (ref)	ref			ref		
Household wealth quintile			0.736			0.934
Quintile I (ref)	ref			ref		
Quintile II	1.07	(0.54-2.11)		0.95	(0.46-1.95)	
Quintile II	0.74	(0.36-1.52)		0.93	(0.46-1.86)	
Quintile IV	0.75	(0.35-1.58)		0.88	(0.45-1.73)	
Quintile V	0.76	(0.38-1.52)		0.75	(0.36-1.55)	

Table S3. Continued

Variable	Kenya, 2007			Kenya, 2012		
	OR	(95% CI)	p-value	OR	(95% CI)	p-value
CD4 category (cells/mm³)			0.010			0.301
<250 (ref)	ref			ref		
250-349	0.40	(0.19-0.87)		0.63	(0.25-1.59)	
350-499	0.74	(0.37-1.47)		1.16	(0.45-3.02)	
500+	1.23	(0.7-2.17)		1.30	(0.65-2.59)	
Testing history			0.675	2.08		0.013
<1 year ago (ref)	ref			ref		
1-2 years ago	0.80	(0.42-1.51)		1.93	(1.16-3.22)	
>2 years ago	0.77	(0.41-1.45)		0.85	(0.52-1.37)	
Disclosure of HIV status to most recent partner*						0.011
No	1.60	(0.55-4.65)	0.381	2.08	(1.18-3.66)	
Yes (ref)	ref			ref		
Pregnant in last 3 years †	1.77	(1.05-2.97)	0.033	1.66	(1.01-2.73)	0.045
ANC visit last pregnancy †	0.78	(0.17-3.66)	0.752	1.02	(0.06-16.89)	0.991
Any HIV test during ANC last pregnancy †	0.63	(0.24-1.67)	0.350	2.08	(0.36-11.96)	0.405
Sex and pregnancy history			0.078			0.098
Male (ref)	ref			ref		
Female - not pregnant in last 3 years	0.76	(0.48-1.22)		0.71	(0.46-1.1)	
Female - pregnant in last 3 years	1.35	(0.82-2.22)		1.19	(0.71-1.99)	
Recreational drug use in last 12 months						0.003
No (ref)	ref			ref		
Yes	-	-	-	3.22	(1.51-6.87)	

Notes: * Applies to respondents who self-reported HIV-positive. † Applies to women only.

S1 Fig. Antiretroviral exposure by locality type among HIV-infected individuals aged 15–64 years old: South Africa, 2008 and 2012

S4 Table. Bivariate regression analysis showing associations between selected characteristics of PLHIV with non-use ART among individuals 15–64 years: South Africa 2008 and 2012

Variable	South Africa, 2008		South Africa, 2012	
	Bivariate Analysis		Bivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Locality type				
Urban formal (ref)	ref		ref	
Urban informal	0.73 (0.40-1.34)	0.313	0.99 (0.67-1.48)	0.972
Rural formal	0.79 (0.45-1.38)	0.405	0.98 (0.57-0.69)	0.935
Rural informal	2.25 (0.94-5.42)	0.069	0.70 (0.49-1.00)	0.053
Province				
KwaZulu-Natal (ref)	ref		ref	
Western Cape	2.16 (0.91-5.12)	0.079	1.29 (0.74-2.23)	0.372
Eastern Cape	1.67 (0.59-4.69)	0.333	1.20 (0.66-2.17)	0.549
Northern Cape	1.69 (0.55-5.21)	0.364	0.42 (0.138-1.25)	0.119
Free State	2.53(1.01-6.35)	0.048	0.98 (0.52-1.84)	0.938
Northwest	1.44 (0.59-3.52)	0.423	1.73 (0.89-3.36)	0.105
Gauteng	1.72 (0.65-4.53)	0.27	0.94 (0.47-1.88)	0.853
Mpumalanga	2.01 (0.84-4.80)	0.115	1.48 (0.79-2.76)	0.223
Limpopo	2.45 (0.89-6.77)	0.083	0.87 (0.40-1.88)	0.722
Race				
Other race (ref)	ref		ref	
Black African	0.93 (0.38-2.26)	0.864	1.61 (0.91-2.85)	0.102
Sex				
Male (ref)	ref		ref	
Female	1.13 (0.67-1.88))	0.65	0.61 (0.46-0.81)	0.001
Age (years)				
15-24	1.33 (0.44-4.02)	0.612	4.57 (2.70-7.22)	<0.001
25-34	0.81 (0.41-1.62)	0.556	2.75 (1.85-4.08)	<0.001
35-49	0.67 (0.34-1.29)	0.228	1.10 (0.75-1.60)	0.63
50-64 (ref)	ref		ref	
Marital status				
Single/Never married/no stable partnership (ref)	ref		ref	
Married/stable partnership	1.39 (0.83-2.34)	0.208	1.30 (0.90-1.89)	0.161
Divorced/Separated/Widowed	0.53 (0.28-1.00)	0.05	0.56 (0.35-0.91)	0.017
Education				
None (ref – 2008)	ref		n/a	n/a
Primary (ref – 2012)	0.36 (0.11-1.23)	0.103	ref	

Table S4. Continued

Variable	South Africa, 2008		South Africa, 2012	
	Bivariate Analysis		Bivariate Analysis	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Secondary	0.33 (0.10-1.04)	0.059	1.12 (0.84-1.48)	0.441
Higher education	0.15 (0.03-0.76)	0.021	1.36 (0.57-3.25)	0.493
Employment				
Unemployed (ref)	ref		ref	
Employed	2.00 (1.26-3.18)	0.003	4.79 (1.93-11.88)	0.001
Student	0.90 (0.17-4.75)	0.901	1.33 (1.02- 1.74)	0.033
Household wealth quintile				
Quintile I (ref)	ref		ref	
Quintile II	0.99 (0.57-1.74)	0.983	1.13 (0.82-1.55)	0.467
Quintile III	0.52 (0.27-0.98)	0.042	1.02 (0.68-1.53)	0.932
Quintile IV	1.23 (0.59-2.56)	0.555	1.26 (0.79-2.02)	0.334
Quintile V	0.58 (0.18-1.84)		0.76 (0.38-1.50)	0.426
Most recent HIV test				
<12 months (ref)	ref		ref	
1-2 years	1.32 (0.68-2.58)	0.406	0.09 (0.71-1.67)	0.69
2-3 years	0.91 (0.41-2.05)	0.822	1.24 (0.77-2.01)	0.365
3+ years	0.61 (0.29-1.29)	0.197	0.69 (0.44-1.08)	0.103
Alcohol intake in the last 12 month				
Non high-risk drinker (ref)	ref		ref	
High-risk drinker	0.75 (0.34-1.68)	0.492	1.71 (0.96-3.04)	0.069
Recreational drug use in the last 3 months				
No (ref)	ref		ref	
Yes			4.80 (2.20-10.47)	<0.001

S5 Table. ARV exposure by selected characteristics of HIV-infected women aged 15–64 years old, Kenya 2007 and 2012

Variable	Kenya, 2007			Kenya, 2012		
	On ART		p-value	On ART		p-value
	N	Weighted % (95% CI)		N	Weighted % (95% CI)	
Locality type			0.715			0.576
Rural	255	30.1 (21.0-39.3)		216	42.7 (35.6-49.8)	
Urban	117	33.7 (16.6-50.7)		168	49.3 (42.0-56.6)	
Province			0.271			0.721
Nairobi	46	40.2 (10.0-70.5)		37	49.7 (37.1-62.2)	
Central	23	*		40	51.4 (36.8-66.0)	
Coast	49	12.4 (1.5-23.2)		40	38.6 (20.8-56.3)	
Eastern	35	39.2 (10.5-67.9)		53	69.2 (50.3-88.0)	
Nyanza	135	35.5 (20.6-50.4)		132	40.7 (33.8-47.5)	
Rift Valley	48	18.3 (7.4-29.2)		45	40.8 (25.1-56.5)	
Western	36	37.1 (13.0-61.2)		37	40.5 (28.8-52.2)	
Age (years)			<.001			0.007
15-24	83	18.2 (6.9-29.5)		50	17.7 (7.4-28.0)	
25-34	136	24.3 (14.0-34.6)		123	29.6 (21.1-38.1)	
35-49	126	43.5 (32.2-54.9)		157	59.1 (51.2-67.0)	
50-64	27	38.9 (21.5-56.3)		54	67 (53.4-80.6)	
Marital status			<.001			0.822
Single/never married	42	25.8 (9.0-42.6)		51	19.4 (9.3-29.6)	
Married/cohabitating	220	23.7 (16.3-31.1)		201	46 (39.1-52.8)	
Divorced/separated/widowed	110	45.8 (33.6-58.0)		132	54.6 (45.7-63.6)	
Education			0.394			0.937
None	212	34.3 (23.1-45.5)		64	37.6 (22.7-52.5)	
Primary	111	24.7 (15.9-33.5)		187	40.1 (33.3-47.0)	
Secondary	36	32.3 (15.2-49.4)		18	*	
Higher	13	*		114	56.2 (46.8-65.6)	
Household wealth			0.815			0.886
Quintile I (lowest)	71	30.4 (16.2-44.6)		61	37.9 (23.5-52.2)	
Quintile II	72	24.4 (11.5-37.3)		89	42.4 (31.1-53.8)	
Quintile III	58	34.2 (18.7-49.7)		86	44.5 (32.2-56.8)	
Quintile IV	81	33.1 (17.3-48.9)		92	49.8 (38.5-61.1)	
Quintile V (highest)	90	34 (21.9-46.1)		56	54 (41.8-66.2)	

Table S5. Continued

Variable	Kenya, 2007			Kenya, 2012		
	On ART		p-value	On ART		p-value
	N	Weighted % (95% CI)		N	Weighted % (95% CI)	
Employment			0.646			0.019
Unemployed	81	33.8 (18.7-49.0)		165	47.8 (39.3-56.3)	
Employed	291	30.4 (22.3-38.5)		218	44.2 (37.7-50.7)	
CD4 category (cells/mm³)			<.001			0.086
≤250	58	20.5 (8.8-32.2)		29	46.7 (29.0-64.3)	
250>-350	45	58.5 (42.5-74.5)		25	60.3 (40.0-80.5)	
350>-500	56	34.2 (20.7-47.6)		24	*	
>500	184	27 (17.1-36.9)		120	48 (38.3-57.7)	
Most recent HIV test †			0.897			0.690
<12 months ago	92	40.7 (28.4-53.0)		188	51 (42.5-59.6)	
1-2 years ago	55	44.6 (28.0-61.1)		70	29.4 (18.3-40.5)	
> 2 years ago	56	41.6 (25.9-57.4)		89	55.9 (45.7-66.0)	
Disclosed results to most recent partner ‡			0.369			<0.001
Yes	135	31.2 (21.1-41.3)		78	61.9 (49.3-74.4)	
No	19	*		126	65.4 (56.9-73.9)	
Recreational drug use in last 12 months						0.002
Yes	-			7/19	*	
No				365	46.2 (40.9-51.4)	
Total	372	31.2 (23.0-39.4)		384	45.6 (40.5-50.7)	

Notes: All numbers are unweighted except where otherwise specified. * Suppressed due to denominator <25 observations. † Applies to respondents who reported ever testing for HIV ‡ Applies to respondents who self-reported HIV-positive. ART = antiretroviral treatment, CI = confidence interval.

Chapter 5

Use of viral load to improve survey estimates of known HIV-positive status and antiretroviral treatment coverage

5

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Abstract

Objective: To compare alternative methods of adjusting self-reported knowledge of HIV-positive status and antiretroviral (ARV) therapy use based on undetectable viral load (UVL) and ARV detection in blood.

Design: *Post hoc* analysis of nationally-representative household survey to compare alternative biomarker-based adjustments to population HIV indicators.

Methods: We reclassified HIV-positive participants aged 15–64 years in the 2012 Kenya AIDS Indicator Survey (KAIS) that were unaware of their HIV-positive status by self-report as aware and on antiretroviral treatment if either ARVs were detected or viral load was undetectable (<550 copies/mL) on dried blood spots. We compared self-report to adjustments for ARVs measurement, UVL, or both.

Results: Treatment coverage among all HIV-positive respondents increased from 31.8% for self-report to 42.5% [95% confidence interval (CI) 37.4–47.8] based on ARV detection alone, to 42.8% (95% CI 37.9–47.8) when ARV-adjusted, 46.2% (95% CI 41.3–51.1) when UVL-adjusted and 48.8% (95% CI 43.9–53.8) when adjusted for either ARV or UVL. Awareness of positive status increased from 46.9% for self-report to 56.2% (95% CI 50.7–61.6) when ARV-adjusted, 57.5% (95% CI 51.9–63.0) when UVL-adjusted, and 59.8% (95% CI 54.2–65.1) when adjusted for either ARV or UVL.

Conclusions: Undetectable viral load, which is routinely measured in surveys, may be a useful adjunct or alternative to ARV detection for adjusting survey estimates of knowledge of HIV status and antiretroviral treatment coverage.

Introduction

Since the 2007 Kenya AIDS Indicator Survey (KAIS), HIV seroprevalence surveys have often included questions on knowledge of HIV status and antiretroviral (ARV) use among HIV-infected respondents, as well as biomarkers such as viral load (VL) [1–3] and ARV testing. Self-reported knowledge of status and antiretroviral treatment (ART) status can be subject to either positive or negative social desirability bias in some respondents [4] due to the stigma associated with HIV [5,6]. Some respondents may also have inaccurate recall or understanding of detailed questions about their HIV testing and care histories [7].

Antiretroviral testing can be used to adjust self-reported HIV status by reclassifying respondents with ARVs detected in their blood as being previously diagnosed and on ART [8,9]. In the 2012 KAIS 46.9% of HIV-infected respondents self-reported that they were aware of their HIV-positive status, but ARVs were also detected in 21.0% of those not reporting prior HIV diagnosis and 19.3% of those reporting no previous HIV test. However, antiretroviral testing is relatively complex, expensive, and only available within a very limited number of specialized laboratories worldwide, necessitating international shipping, resulting in additional cost, administrative paperwork, and potential for delays.

Unlike ARV testing, which is added exclusively to correct self-reported HIV status and ART use, viral load testing is widely available and routinely included in surveys to estimate population viral suppression (defined as VL < 1000 copies/mL [10]). Undetectable viral load (UVL) is generally indicative of viral suppression due to treatment, hence it could serve as an alternative, indirect marker for treatment. Although the presence of elite controllers (EC) who have UVL in the absence of treatment could confound use of UVL as a proxy for ART use, in US and European cohorts EC are believed to represent only 0.15–1.5% of the HIV-infected population [11], while in East African settings similarly low prevalence of EC has been observed [12,13], limiting the potential impact of this confounding.

Given viral load testing is already conducted routinely in HIV surveys, we examined whether adjusting estimates of knowledge of HIV-positive status and ART coverage using a measure of viral load would achieve similar results to adjustments based on detection of ARVs in a national household survey conducted in Kenya in 2012.

Methods

The 2012 KAIS included behavioral questions including self-reported HIV and ART status as well as collection of venous blood from which DBS were prepared by field teams and plasma separated and shipped for HIV testing at a national laboratory [2]. After participating in other survey procedures, participants were offered rapid HIV testing by trained HIV counselors in their homes with immediate return of results based on national HIV testing guidelines [14]. Participants testing positive for HIV at the central laboratory were subsequently tested for viral load using the Abbott M2000 platform on DBS subsequently stored at -80°C for future testing. In 2015, DBS were shipped to the University of Cape Town for testing for presence of efavirenz, nevirapine, lopinavir or lamivudine by liquid chromatography tandem mass spectrometry (limit of detection 0.02 µg/mL) [15]. These ARVs were selected to cover first- and second-line regimens in use in Kenya at the time of specimen collection [16–18].

We retrospectively re-analyzed survey data to compare self-reported and biomarker-adjusted versions of knowledge of status and ART use among HIV-infected respondents aged 15–64 years.

Measures

We defined UVL as having a viral load <550 copies/mL on dried blood spots, the limit of detection for the assay used in the study [19]. To calculate UVL-adjusted status, we updated the status for those respondents categorized as ‘unaware’ or ‘aware, not on ART’ with undetectable viral load to ‘aware, on ART’. Similarly, ARV-adjusted status was calculated by updating the status for respondents with ARVs detected in blood to ‘aware, on ART’. For either case, the status for respondents with missing biomarker results was not updated.

We explored differences in self-reported, ARV-adjusted, and UVL-adjusted indicators by age, sex, marital status, educational attainment and mobility. Results were analyzed in R version 3.5.0 [20] using the survey package [21] to adjust and weight results to account for the complex survey design. Wald confidence intervals for survey indicators were calculated on the logarithmic scale and transformed to probability scale using the ‘logit’ method of the `svyprop` function in R; confidence intervals previously reported by Kim et al. [16] were calculated on the probability scale.

Ethical considerations

The 2012 KAIS was approved by the University of California, San Francisco, the U.S. Centers for Disease Control (CDC) in Atlanta, GA, USA and the Kenya Medical Research Institute. Prior to household and individual interviews and blood collection written consent was obtained; in the case of children aged less than 18 years assent was sought in addition to permission from their caregiver or guardian.

Results

Among 648 HIV-infected respondents, self-reported status was 'unaware' among 343 (53.1%), 'aware, not on ART' among 100 (15.1%), and 'aware, on ART' among 205 (31.8%) (Supplemental Table S1). Of those with UVL and unaware of their HIV-positive status by self-report, 40 also had ARVs detected in blood (Supplemental Table S2). Antiretroviral treatment coverage among all HIV-infected increased from 31.8% (95% CI 27.3–36.6) based on self-report to 42.8% (95% CI 37.9–47.8) when combining self-report and ARV detection, to 46.2% (95% CI 41.3–51.1) when combining self-report and UVL, and finally to 48.8% (95% CI 43.9–53.8) with self-report, UVL or ARVs combined (Table 1). Changes in ART coverage were consistent across demographic characteristics, although the 15–24 year age group saw greater increases when adjusted compared to other age groups (Supplemental Figure S1).

Knowledge of status increased from 46.9% (95% CI 41.4–52.4) based on self-report to 56.2% (95% CI 50.7–61.6) when adjusting with ARVs, to 57.5% (95% CI 51.9–63.0) when adjusting for UVL, and to 59.8% (95% CI 54.2–65.1) when adjusting for either ARV or UVL (Table 2). Similar to population ART coverage, ART among those with known HIV-positive status also increased from self-report to adjustment, with similar increases between adjustment methods. The youngest age group also saw the biggest impact of adjustment versus self-report for these indicators in both relative and absolute terms.

We repeated the analysis excluding the respondents for whom either the ARV or UVL biomarkers were not available; findings were similar (Supplemental Table S3).

Table 1. Self-reported and adjusted estimates of ART coverage among people living with HIV, KAIS 2012

Characteristic	Self-reported (N=648)			ARV only (N=559)			Self-report or ARV (N=648)			Self-report or UVL (N=648)			Self-reported, ARV or UVL (N=648)		
	n	%	se	n	%	se	n	%	se	n	%	se	n	%	se
Sex															
Male	51	27.0	3.7	64	37.8	4.7	74	39.9	4.5	78	41.9	4.4	84	44.3	4.5
Female	154	34.7	2.5	171	45.6	2.6	198	44.6	2.5	217	48.8	2.5	230	51.6	2.5
Age group															
15–24 yrs	6	7.1	2.7	11	21.6	6.4	14	20.7	5.8	19	28.8	6.2	20	29.9	6.2
25–34 yrs	48	21.1	3.1	50	25.1	3.6	65	29.3	3.5	65	28.2	3.3	76	33.9	3.6
35–49 yrs	104	41.1	3.9	121	55.0	3.8	133	52.9	3.6	147	58.2	3.4	152	59.5	3.3
50–64 yrs	47	48.0	5.4	53	59.6	5.6	60	60.6	5.3	64	64.0	5.0	66	65.5	5.0
Marital status															
Single/never married	16	16.7	4.0	18	24.5	5.9	22	23.8	5.1	29	32.5	5.6	31	33.9	5.7
Married/cohabitating	118	31.4	3.2	141	42.0	3.4	163	43.3	3.2	175	46.1	3.1	186	48.6	3.2
Divorced /sep / widowed	71	41.5	4.0	76	53.1	4.3	87	52.6	4.0	91	54.2	3.9	97	58.1	4.0
Highest educational attainment															
None	28	33.2	5.8	31	35.5	5.9	39	44.6	6.0	39	45.2	6.0	41	46.5	6.0
Primary	94	26.7	2.8	111	39.5	3.6	126	38.4	3.3	137	40.8	3.3	148	44.3	3.5
Secondary	10	31.4	10.2	14	45.7	10.1	15	43.7	9.8	16	50.7	9.3	18	54.9	9.6
Higher	73	40.8	4.3	78	50.6	5.0	91	50.2	4.4	102	55.8	4.2	106	57.2	4.1
Employment															
unemployed	82	36.2	4.3	91	50.0	4.6	106	47.6	4.3	114	50.6	4.3	118	52.2	4.2
employed	123	29.6	2.6	144	39.0	2.8	166	40.5	2.8	181	44.0	2.7	196	47.2	2.8
Mobility															
Not away for >1 month in last year	112	31.2	3.0	126	42.0	3.5	146	42.2	3.2	156	44.5	3.3	166	46.8	3.2
Away >1 month in last year	87	32.1	3.4	101	43.7	4.0	117	43.7	3.6	129	48.0	3.7	137	51.4	3.9
Total	205	31.8	2.4	235	42.5	2.6	272	42.8	2.5	295	46.2	2.5	314	48.8	2.5

Note: self-reported: self-report only, ARV-only: based on presence/absence of ARVs only, self-report or ARV: either self-reported known-positive on ART or ARVs detected, self-report or UVL: either self-reported known-positive/on ART or viral load was undetectable, self-report, ARV or UVL: either self-reported known-positive/on ART, ARVs detected, or UVL, N: unweighted denominator, n: unweighted numerator, se: standard error. Missing biomarker results were treated as biomarker not present. Percentages and standard errors are weighted and adjusted to account for the survey design.

Table 2. Self-reported and adjusted estimates of HIV care cascade, KAIS 2012

Characteristic		Self-report			Self-report or ARV			Self-report or UVL			Self-report, ARV or UVL		
Variable	Level	n	%	se	n	%	se	n	%	se	n	%	se
Awareness of HIV infection (1st 90)													
Gender	Male	73	38.0	4.3	92	49.5	4.9	95	50.7	4.9	99	52.6	5.0
	Female	232	52.2	2.8	268	60.4	2.6	275	61.7	2.5	286	64.2	2.5
Age group	15–24 yrs	16	18.0	5.0	24	31.7	6.5	27	37.7	7.0	28	38.8	7.0
	25–34 yrs	88	41.1	4.3	102	48.2	4.3	102	46.7	4.3	111	52.0	4.3
	35–49 yrs	144	55.9	3.8	167	65.7	3.4	172	67.6	3.3	176	68.5	3.3
	50–64 yrs	57	56.9	5.5	67	66.4	5.2	69	68.0	5.0	70	68.7	5.0
Total		305	46.9	2.8	360	56.2	2.8	370	57.5	2.8	385	59.8	2.8
ART coverage among previously-diagnosed (2nd 90)													
Gender	Male	51	71.0	5.8	74	80.7	4.5	78	82.5	4.0	84	84.2	3.9
	Female	154	66.4	3.3	198	73.9	3.0	217	79.1	2.7	230	80.4	2.6
Age group	15–24 yrs	6	39.3	10.4	14	65.5	10.0	19	76.3	7.3	20	77.0	7.1
	25–34 yrs	48	51.2	5.8	65	60.9	5.3	65	60.3	5.3	76	65.2	5.1
	35–49 yrs	104	73.6	4.4	133	80.5	3.7	147	86.2	2.7	152	86.8	2.6
	50–64 yrs	47	84.3	5.2	60	91.3	3.8	64	94.1	2.7	66	95.5	2.3
Total		205	67.9	3.2	272	76.2	2.8	295	80.2	2.3	314	81.7	2.3
Viral load < 1000 copies/mL among those on ART (3rd 90)													
Gender	Male	35	72.8	6.3	52	75.9	5.1	62	82.5	4.3	62	78.4	4.6
	Female	115	76.6	3.8	146	75.4	3.5	178	83.5	2.8	178	78.8	2.9
Age group	15–24 yrs	2	34.6	19.8	9	72.4	11.3	15	83.9	7.4	15	80.8	7.9
	25–34 yrs	29	57.3	8.2	35	50.0	7.3	46	68.4	6.7	46	57.0	6.6
	35–49 yrs	84	84.5	3.8	108	85.6	3.3	127	89.1	2.7	127	87.2	2.9
	50–64 yrs	35	74.9	6.6	46	77.5	5.7	52	81.2	5.2	52	79.2	5.3
Total		150	75.4	3.3	198	75.6	2.8	240	83.1	2.3	240	78.6	2.5

Note: self-reported: self-report only, self-report or ARV: either self-reported known-positive/on ART or ARV's detected, self-report or UVL: either self-reported known-positive/on ART or viral load was undetectable, self-report, ARV or UVL: either self-reported known-positive/on ART, ARV's detected, or UVL, n: unweighted numerator, se: standard error, viral suppression defined as <1000 copies/mL. Missing biomarker results were treated as biomarker not present. Percentages and standard errors are weighted and adjusted to account for the survey design. The unweighted denominators can vary due to adjustment for the 2nd and 3rd 90 and for each indicator/measure combination are as follows: 1st 90: 305 for all measures, 2nd 90: 360 for self-report or ARV, 370 for self-report or UVL, 385 for self-report, ARV or UVL, 3rd 90: 200 for self-reported, 266 for self-reported or ARV, 308 for self-report, ARV or UVL.

Discussion

In order to balance resources between finding undiagnosed HIV infections, linking patients to HIV treatment, and ensuring retention and adherence to care it is necessary to obtain the best possible estimates of knowledge of HIV-positive status and ART use. We set out to establish whether viral load, a routinely-available marker in HIV surveys, can be used to adjust self-reported estimates of knowledge of HIV-positive status and ART use. In KAIS 2012, UVL-adjusted point estimates were similar to, but slightly greater than ARV-adjusted estimates of knowledge of status and ART coverage, suggesting adjustment with UVL might have been sufficient. When measuring ART coverage, all of the adjusted estimates (ARV only, UVL only, and either ARV or UVL) had overlapping confidence intervals, but are notably higher than estimates based on self-report alone.

The change in estimates when adjusting by ARVs and UVL were similar across demographic groups, but 15–24 year olds did see a larger additional increase when adjusting by UVL. This may indicate poor recent adherence in this group leading to non-detection of the ARV biomarker but undetectable viral load (<550 copies/mL in this study). Li et al found that 37% of patients still had a viral load <200 copies/mL four weeks after interrupting ART [22]. Many ARVs reach undetectable levels in blood within several days of treatment interruption [8,15,23], thus in populations with poor adherence or high rates of treatment interruption, adjusting based on UVL may result in higher estimated ART coverage than measures incorporating ARV detection.

The performance of UVL for adjusting ART use will depend on the prevalence of UVL in the population on HIV treatment. In populations with effective ART programs with high rates of viral suppression in the treated population, it may be a relatively sensitive marker for ART use; however, in populations with poor treatment outcomes a larger proportion of patients on treatment would not have UVL.

The prevalence of elite controllers has not been established in Kenya, hence it is not possible to quantify their influence on the UVL-adjusted estimates, but given the similarity between UVL-adjusted and ARV-adjusted estimates, their potential impact was limited. Simultaneously adjusting for either UVL or presence of ARVs may in fact be closest to true population prevalence of the indicators of interest. Without better data on prevalence of elite controllers in this population it is more conservative to use one or the other marker rather than both combined. In settings with ample evidence of low prevalence of elite control, or where population high

ART coverage and immediate treatment initiation means even elite controllers are likely to be on treatment, using the combined indicator would likely represent the most sensitive approach to estimating population-based knowledge of status and ART coverage.

This analysis was subject to several limitations. While adjusting for biomarkers associated with ARV exposure from a single time-point can account for misreporting of status among those on ART, it cannot account for those who misreport their knowledge of HIV-positive status but are not currently on treatment, or those who may be on treatment but transiently non-adherent to medications. Other established methods for reducing bias in self-reported estimates, such as computer-assisted self-interview methods, may also be helpful [24]. This analysis was based on data from a single country with low ART coverage (43.5%) and viral suppression among those on treatment (73.9%) at the time of the survey compared with current program coverage; the UVL adjustment may perform differently in other populations. Simulation or replication of this analysis in a diverse set of populations, including the more recent population-based HIV impact assessments conducted in many countries, could help elucidate the performance of UVL adjustment in different settings. Finally, poor specimen quality could result in false-negative results for both biomarkers. In spite of these limitations, this analysis does strongly suggest that use of UVL to adjust self-reported HIV status and ART use should be considered, especially in surveys where the inclusion of the ARV biomarker may be cost-prohibitive or subject to delays.

Conclusion

Streamlining the estimation of key HIV program indicators should allow governments, donors and other stakeholders to assess program performance more quickly and affordably. Viral load, which is routinely measured in HIV surveys, may be a useful biomarker for adjusting self-reported indicators of HIV diagnosis and treatment in cross-sectional surveys in absence of, or in addition to, adjustment based on detected ARVs in blood.

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Competing interests

All authors declare no competing interests.

Authors' contributions

PWY, EZG and KDC conceived the study. PWY conducted the analyses. All authors contributed to drafting and critical review of the manuscript.

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Supplemental Material

Table S1. Self-reported HIV status and antiretroviral treatment (ART) use, KAIS 2012

Characteristic	Unaware n (%)	Aware, not on ART n (%)	Aware, on ART n (%)	N
Gender				
Male	120 (62.0)	22 (11.0)	51 (27.0)	193
Female	223 (47.8)	78 (17.5)	154 (34.7)	455
Age				
15-24 yrs	59 (82.0)	10 (10.9)	6 (7.1)	75
25-34 yrs	121 (58.9)	40 (20.0)	48 (21.1)	209
35-49 yrs	120 (44.1)	40 (14.8)	104 (41.1)	264
50-64 yrs	43 (43.1)	10 (8.9)	47 (48.0)	100
Marital status				
Single/never married	67 (73.5)	10 (9.8)	16 (16.7)	93
Married / cohabitating	210 (54.2)	57 (14.4)	118 (31.4)	385
Divorced / sep / widowed	66 (38.9)	33 (19.7)	71 (41.5)	170
Highest educational attainment				
None	49 (53.9)	12 (12.9)	28 (33.2)	89
Primary	192 (55.8)	60 (17.5)	94 (26.7)	346
Secondary	18 (57.4)	3 (11.2)	10 (31.4)	31
Higher	83 (47.4)	25 (11.9)	73 (40.8)	181
Employment				
Unemployed	124 (49.1)	33 (14.7)	82 (36.2)	239
Employed	218 (55.1)	67 (15.3)	123 (29.6)	408
Mobility				
Not away for >1 month in last year	196 (54.6)	52 (14.2)	112 (31.2)	360
Away >1 month in last year	131 (51.4)	45 (16.6)	87 (32.1)	263
ARV biomarker				
Present	55 (25.2)	12 (4.5)	168 (70.4)	235
Absent	233 (72.3)	73 (22.3)	18 (5.4)	324
UVL biomarker				
Present	65 (28.7)	25 (9.9)	145 (61.3)	235
Absent	253 (66.5)	74 (19.2)	55 (14.3)	382
Total	343 (53.1)	100 (15.1)	205 (31.8)	648

Note: ARV biomarker: test for presence of antiretrovirals in blood, UVL biomarker: present if respondent had undetectable viral load (<550 copies/mL) in blood. Missing values: one respondent was missing education and employment status, respectively, while 89 respondents were missing the ARV biomarker and 31 were missing viral load measure. Percentages are weighted to account for survey design.

Table S2. Comparison of antiretroviral (ARV) detection and undetectable viral load (UVL) by self-reported HIV status, KAIS 2012

Status	ARV biomarker	UVL biomarker			Total
		Present	Absent	Missing	
Unaware of HIV-positive status	present	40	15	0	55
	absent	14	209	10	233
	missing	11	29	15	55
	total	65	253	25	343
Aware of HIV-positive status, not on ART	present	8	3	1	12
	absent	12	61	0	73
	missing	5	10	0	15
	total	25	74	1	100
Aware of HIV-positive status, on ART	present	132	35	1	168
	absent	3	15	0	18
	missing	10	5	4	19
	total	145	55	5	205
Self-reported adherent last 30 days	present	116	3	9	128
	absent	27	11	4	42
	missing	1	0	14	15
	total	144	14	27	185
Self-reported non-adherent last 30 days	present	16	0	1	17
	absent	8	3	1	12
	missing	0	0	5	5
	total	24	3	7	34
N		235	382	31	648

Note: ARV biomarker is present if ARVs detected in blood, UVL biomarker present if viral load undetectable (<550 copies/mL). Self-reported adherence is based on response to question among those who self-reported aware of HIV-positive status and on ART: 'In the last 30 days, have you missed taking any of your ARV pills?' One respondent who reported 'don't know' to this question was excluded from the self-reported adherence analysis.

Figure S1. Absolute and relative changes in ART coverage and HIV cascade indicators due to adjustment, by covariates, KAIS 2012
Note: relative differences are shown on log (2) scale, all differences are shown versus self-report. Self-report: self-report only; self-report or ARV: either self-reported known-positive/on ART or ARVs detected; self-report or UVL: either self-reported known-positive/on ART or viral load was undetectable.

Table S3. Sensitivity analysis of self-reported and adjusted estimates of HIV care cascade restricted to participants with ARV and UVL biomarkers present, KAIS 2012

Characteristic	Self-report			Self-report or ARV			Self-report or UVL			Self-report, ARV or UVL		
Variable	level	n	%	se	n	%	se	n	%	n	%	se
Awareness of HIV infection (1st 90)												
Gender	Male	62	37.1	4.5	81	50.0	5.3	82	50.3	86	52.4	5.4
	Female	207	55.8	3.0	243	65.5	2.7	241	64.9	252	67.9	2.7
Age group	15–24 yrs	15	21.7	6.0	23	39.2	7.9	25	44.8	26	46.2	8.3
	25–34 yrs	76	42.0	4.6	90	50.3	4.7	86	46.9	95	53.0	4.7
	35–49 yrs	126	56.5	4.0	149	67.7	3.6	148	67.5	152	68.5	3.6
	50–64 yrs	52	58.5	5.8	62	69.4	5.5	64	71.2	65	72.0	5.3
Total		269	48.5	3.0	324	59.4	3.0	323	59.2	338	61.8	3.1
ART coverage among previously-diagnosed (2nd 90)												
Gender	Male	44	71.8	6.4	66	81.8	5.0	68	82.9	73	84.3	4.4
	Female	141	68.0	3.4	185	76.0	3.0	191	79.3	204	80.8	2.8
Age group	15–24 yrs	6	41.8	10.8	14	67.8	10.0	18	77.5	19	78.2	7.2
	25–34 yrs	42	51.8	6.4	58	61.8	5.7	55	60.5	65	65.5	5.6
	35–49 yrs	94	75.4	4.5	123	82.8	3.7	127	86.1	132	86.9	2.9
	50–64 yrs	43	84.9	5.4	56	92.4	3.7	59	93.6	61	95.0	2.6
Total		185	69.2	3.5	251	77.9	3.0	259	80.5	277	81.9	2.6
Viral suppression among those on ART (3rd 90)												
Gender	Male	32	75.5	6.4	49	78.0	5.1	56	84.3	56	79.6	4.8
	Female	108	76.5	4.0	139	75.3	3.6	158	82.7	158	77.6	3.3
Age group	15–24 yrs	2	34.6	19.8	9	72.4	11.3	14	82.9	14	79.7	8.4
	25–34 yrs	27	58.4	8.6	33	50.3	7.5	40	68.1	40	55.5	7.0
	35–49 yrs	77	83.3	4.2	101	84.8	3.6	110	87.8	110	85.7	3.3
	50–64 yrs	34	80.6	6.4	45	82.2	5.4	50	85.6	50	83.3	5.1
Total		140	76.2	3.4	188	76.2	3.0	214	83.2	214	78.2	2.7

Note: self-reported; self-report only, self-report or ARV: either self-reported known-positive/on ART or ARVs detected, self-report or UVL: either self-reported known-positive/on ART or viral load was undetectable, n: unweighted numerator, se: standard error, viral suppression defined as <1000 copies/mL. Percentages and standard errors are weighted and adjusted to account for the survey design.

Chapter 6

HIV-related deaths in Nairobi, Kenya: Results from a HIV mortuary surveillance study, 2015

6

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Abstract

Background: Death is an important but often unmeasured endpoint in public health HIV surveillance. We sought to describe HIV among deaths using a novel mortuary-based approach in Nairobi, Kenya.

Methods: Cadavers aged ≥ 15 years at death at Kenyatta National Hospital (KNH) and City Mortuaries were screened consecutively from January 29th to March 3rd 2015. Cause of death was abstracted from medical files and death notification forms. Cardiac blood was drawn and tested for HIV infection using the national HIV testing algorithm followed by viral load testing of HIV-positive samples.

Results: Of 807 eligible cadavers, 610 (75.6%) had an HIV test result available. Cadavers from KNH had significantly higher HIV positivity at 23.2% (95% CI 19.3–27.7) compared to City Mortuary at 12.6% (95% CI 8.8–17.8), $p < 0.001$. HIV prevalence was significantly higher among women than men at both City (33.3% versus 9.2%, $p = 0.008$) and KNH Mortuary (28.8% versus 19.0%, $p = 0.025$). Half (53.3%) of HIV infected cadavers had no diagnosis prior to death and an additional 22.2% were only diagnosed during hospitalization leading to death. Although not statistically significant, 61.9% of males had no prior diagnosis compared to 45.8% of females ($p = 0.144$). Half (52.3%) of 44 cadavers at KNH with HIV diagnosis prior to death were on treatment, and one in five (22.7%) with a prior diagnosis had achieved viral suppression.

Conclusions: HIV prevalence was high among deaths in Nairobi, especially among women, and prior diagnosis among cadavers was low. Establishing routine mortuary surveillance can contribute to monitoring HIV-associated deaths among cadavers sent to mortuaries.

Introduction

Globally, the number of people living with HIV (PLHIV) in 2015 was estimated at 36.7 million persons (1). Between 2010 and 2015, antiretroviral therapy (ART) use for HIV-infected persons increased by 126% in parallel with a 26% reduction in HIV-related deaths, from 1.5 million deaths in 2010 to 1.1 million deaths in 2015 (1,2). Sub-Saharan Africa bears the greatest burden of HIV. In 2015, there were 470,000 HIV-related deaths in East and Southern Africa representing 43% of global deaths due to HIV (1-3).

Kenya is estimated to have the fourth-largest HIV epidemic in the world, with 1.5 million PLHIV (4). The country reported an estimated 30% decline in HIV-related deaths between 2010 and 2015, from 52,314 to 35,822 respectively (5). This is attributed to the rapid increase of number of ART sites and increased ART coverage (6). However, HIV remains a serious public health challenge despite these achievements. Nairobi, the national capital, has the highest burden of HIV in the country with 171,510 residents estimated to be living with HIV and 2,500 HIV-related deaths occurring per year (5). Antiretroviral therapy coverage among PLHIV in Nairobi was estimated at 72% in 2014, nine percentage points below the treatment coverage target of 81% set in UNAIDS 90-90-90 fast-track targets for epidemic control by 2020 (6,7).

Although the impact of ART on mortality in African settings has been widely demonstrated (8-10) monitoring HIV-associated mortality is vital for tracking the success of the national ART program. Although standardized mathematical models based on indirect methods are used to estimate and project the number of people dying due to HIV (11), these models rely on assumptions that are subject to uncertainty, and can limit understanding of the true level of HIV-associated mortality. The national vital statistics system also tracks cause of death, but limited standardization of cause of death coding, lack of availability of HIV status at time of certification of cause of death, and the low estimated coverage of death reporting (<50%) limit the generalizability of these statistics (12,13). Early studies demonstrated the ability of enzyme-based assays to detect HIV in post mortem blood specimens (13-15). A mortuary-based surveillance system could help estimate the proportion of deaths that are HIV-associated, the proportion of deaths that are directly due to HIV, provide the actual age and sex distribution of HIV mortality, and relate HIV mortality to important factors such as viral suppression, ART use and HIV diagnosis, and hence to missed opportunities for epidemic control. We conducted a surveillance study in the two largest mortuaries in Nairobi. A prior publication from this study describes the fraction of deaths attributable to

HIV in the Nairobi population by comparing the observed sero-prevalence among deaths with that expected based on demographic models (16). In this manuscript, we map HIV deaths to the steps in the cascade of care including HIV diagnosis, treatment, and achieving viral suppression. We describe the prevalence of HIV among cadavers by age, sex and other factors, and the proportion of HIV-infected cadavers whose underlying cause of death was classified as due to HIV and other causes. We also explore important behavioral and biological covariates such as HIV test history and viral suppression among HIV-associated deaths in order to better define the gaps that, if addressed, may help prevent excess HIV-related mortality.

Materials and Methods

This study was conducted in the two largest mortuaries in Nairobi – Kenyatta National Hospital (KNH) Mortuary and City Mortuary covering 51% of all reported deaths in Nairobi county (18). The KNH Mortuary is attached to Kenyatta National Hospital which is a national public referral and teaching hospital, while City Mortuary is managed by the Nairobi County Health Services and receives cadavers from other facilities as well as medico-legal cases brought by the police. All cadavers admitted to both mortuaries were screened consecutively between January 29th and March 3rd 2015. Cadavers aged ≥ 15 years at time of death were eligible for the study. We abstracted cause of death and demographic variables from death notifications and pathology reports. For eligible deaths that occurred at KNH, additional variables regarding history of HIV diagnosis and ART were abstracted from patient files. Cadavers brought in by the police (which require autopsy to establish cause of death) are referred to as medico-legal cases and are generally taken to City Mortuary.

Cardiac blood samples were collected for this study using transthoracic aspiration; although cadavers were not excluded based on time from death to admission or collection, those from which HIV test results were not obtained were excluded from analysis. HIV testing was conducted using the national diagnostic algorithm (17): screening was done using Colloidal Gold assay (KHB Shangai Kehua Bio-Engineering Co, Ltd, Shanghai, China), confirmation of HIV-positive samples was done using First Response HIV 1-2-0 assay (PMC Medical India Pvt Ltd, Mumbai, India), and samples with discrepant results were tested using Unigold HIV assay (Trinity Biotech PLC, Bray, Ireland) as a tie breaker. HIV RNA testing was performed on HIV-positive samples using the Abbott m2000 real time RNA system (Abbott Molecular, Inc., Des Plaines, IL) to determine the HIV RNA concentration. Viral suppression was defined as HIV-1 RNA concentration < 1000 copies/milliliter.

Measures

Sex, age, and cause of death were abstracted from death certificates completed by the attending physician or, in case of autopsy, by the pathologist. Where age was not available from records it was estimated by mortuary technicians. Prior HIV diagnosis and ART use were ascertained from the clinical history documented in patient files for deaths occurring at KNH. HIV positivity was based on HIV serology performed during the study.

Data analysis

Data were analyzed in Stata 14 (StataCorp, Texas, USA). We conducted bivariate analysis to assess the relationship between HIV and select characteristics, and the chi-square test for independence and Fisher's exact test were used to assess statistical significance. The logit transformation was used to compute confidence interval limits. Multiple logistic regression was used to further explore associations between characteristics and outcome of HIV status. Predictive margins of HIV prevalence as a function of sex and age group were plotted to describe interaction between these variables when predicting HIV status of cadavers. In stratified analyses, the numerator, proportion and confidence intervals were replaced with an asterisk where the denominator was less than 20.

Ethics approvals

This public health surveillance study was approved by the US Centers for Disease Control and Prevention Center for Global Health Associate Director for Science as research that did not involve human subjects (because subjects were deceased). Kenyatta National Hospital/University of Nairobi Ethical Review Board also approved the study. Nairobi County Health Services and the Kenyatta National Hospital Research Office gave administrative approval.

Results

A total of 807 cadavers received at the mortuaries were found to be eligible and enrolled into the study (Figure 1). Specimens were not available for 167 (20.7%) cadavers due to various reasons including logistical/staffing (n=91), extensive burns or putrefaction (n=26), other/legal/discharge or transfer of cadaver (n=31), and failed collection attempt (n=19). Of the 640 (79.3%) with a blood specimen collected, 610 (95.3%) had sufficient quality for HIV testing, and 119 (19.5%) were HIV-positive. Of the 119 HIV-positive specimens, 90 (75.6%) were from cadavers at KNH mortuary for which medical records were abstracted. Of the 90 HIV-

positive specimens at KNH, 44 (48.9%) had a prior HIV diagnosis, 23 of whom had a documented history of ART use, while of these, 12 had viral load testing results available in the study.

Cadavers were more likely to be males at City (86.0%) versus KNH (67.2%, $p<0.001$). Cadavers also differed between mortuaries in terms of age: the median age was 33 years at City Mortuary (inter-quartile range [IQR] 28–42) and 44.5 years at KNH (IQR 33–59.5, $p<0.001$). Given the demographic differences between the deaths enrolled at City and KNH mortuaries, the remaining analyses are stratified by mortuary.

Figure 1: Data flow of eligible cadavers aged ≥ 15 years, HIV mortuary survey.

Notes: KNH = Kenyatta National Hospital, ART = antiretroviral treatment, VL = viral load, COD = cause of death

HIV prevalence differed by sex at both mortuaries: among 30 females at City Mortuary, HIV positivity was 33.2%, while among 184 males it was 9.2% ($p=0.008$); at KNH, HIV positivity was 28.8% among 170 females, compared with 19.0% among 226 males ($p=0.025$). Specimen availability was not associated with age, sex or mortuary but specimens were less likely to be available for medico-legal cases at City Mortuary ($p=0.004$) (Table S1). At City Mortuary, the HIV positivity was significantly higher among cadavers admitted as non-medico-legal cases at 30% (95% CI 18.9–44.1) compared to medico-legal cases at 7.3% (95% CI 4.2–12.5), $p=0.001$.

As medical chart abstraction was performed for deaths at KNH, additional HIV diagnosis and care information was available for HIV-infected deaths at this mortuary (Table 3). About one quarter (24.4%) of HIV-infected deaths had a diagnosis prior to the hospitalization just prior to their death, while an additional 22.2% were diagnosed while hospitalized. The remaining half (53.3%) did not have a diagnosis prior to death. Although 61.9% of males had no prior diagnosis compared to 45.8% of females, the difference was not significant ($p=0.144$). Two thirds (66.7%) of HIV infected cadavers aged 45 years and above did not have a prior HIV diagnosis, while under half (46.7%) of those aged between 15–44 years had no prior HIV diagnosis, again the difference was not significant ($p=0.079$). In contrast, the majority (84.1%) of the deaths where HIV was assigned as the underlying cause had a prior HIV diagnosis, compared to only 35.7% being diagnosed among those for which the underlying cause assigned was not HIV ($p=0.001$).

In a multiple logistic regression model including mortuary, age and sex as independent predictors, the adjusted odds of HIV infection were twice as high at KNH Mortuary compared with City Mortuary (adjusted odds ratio [aOR] 1.80, 95% CI 1.08–3.01), higher for women than men (aOR=6.39, 95% CI 1.47–27.68) among cadavers aged 15–24 years old, and significantly lower for cadavers aged 45+ years (aOR=0.18, 95% CI 1.64–18.67) versus 15–24 years among women (Table S2). There was a significant interaction between sex and age, consistent with higher prevalence among younger females and older males. When modeling finer-grained age groups, the peak risk of HIV infection for females was seen in the 35–44 years age group, while for males it was in the 45–54 years age group (Figure S1). No significant interaction was found between sex and mortuary.

Half (52.3%) of the 44 cadavers with HIV diagnosis prior to death were on treatment, although treatment status was missing for 10 cadavers, so the true prevalence of treatment may have been higher. Among those with a prior HIV diagnosis, 10 had

Table 1. Demographic characteristics of cadavers aged ≥ 15 years by mortuary, HIV mortuary surveillance study, Nairobi, Kenya 2015 (n=610)

	City Mortuary		KNH† Mortuary		Total		Significance*
Selected characteristics	n	(%)	n	(%)	n	(%)	χ ² (degrees of freedom), p-value
Sex							
Male	184	(86.0)	226	(57.1)	410	(67.2)	χ ² (1) = 52.7, p<0.001
Female	30	(14.0)	170	(42.9)	200	(32.8)	
Total	214		396		610		
Age in years							
15–24	36	(16.8)	26	(6.6)	62	(10.2)	χ ² (5) = 64.3, p<0.001
25–34	75	(35.0)	79	(19.9)	154	(25.2)	
35–44	57	(26.6)	93	(23.5)	150	(24.6)	
45–54	30	(14.0)	72	(18.2)	102	(16.7)	
55–74	12	(5.6)	89	(22.5)	101	(16.6)	
75+	4	(1.9)	37	(9.3)	41	(6.7)	
Total	214		396		610		
Median (IQR)‡	33.0	(28.0–42.0)	44.5	(33.0–59.5)	40.0	(33.0–53.0)	
Medico-legal cases							
Yes	164	(76.6)	n/a	n/a	164	(76.6)	n/a
No	50	(23.4)	n/a	n/a	50	(23.4)	
Total	214		n/a	n/a	214		

Notes: * chi-square test for independence between mortuary and sex or age. † KNH = Kenyatta National Hospital. ‡ IQR = Inter-quartile range.

achieved viral suppression (Table 4). Only two of the 23 with evidence of treatment were not virally suppressed at time of death, though an additional 11 cadavers did not have viral load available.

Table 2. HIV positivity rates among cadavers aged ≥ 15 years at KNH and City Mortuaries, Nairobi, Kenya 2015 (n=610)

Selected characteristics	City Mortuary			Significance†	KNH Mortuary			Significance†
	n	%	(95% CI)	F(df1,df2), p-value	n	%	(95% CI)	F(df1,df2), p-value
Sex								
Male	184	9.2	(5.8–14.4)	F(1,609) = 7.15, p=0.008‡	226	19.0	(14.4–24.7)	F(1,609) = 5.06, p=0.025‡
Female	30	33.3	(18.9–51.8)		170	28.8	(22.5–36.1)	
Male								
15-24	30	6.7	(1.7–23.2)	F(2,609) = 0.21, p=0.813§	17	11.8	(2.9–37.0)	F(2,609) = 0.69, p=0.502§
25-44	119	10.1	(5.8–17.0)		96	21.9	(14.7–31.3)	
45+	35	8.6	(2.8–23.5)		113	17.7	(11.7–25.9)	
Total	184	9.2	(5.8–14.4)		226	19.0	(14.4–24.7)	
Female								
15-24	6	50	(16.6–83.4)	F(2,609) = 3.19, p=0.042§	9	33.3	(11.0–66.9)	F(2,609) = 11.98, p<0.001§
25-44	13	46.2	(22.2–72.0)		76	46.1	(35.1–57.4)	
45+	11	9.1	(1.2–44.3)		85	12.9	(7.3–22.0)	
Total	30	33.3	(18.9–51.8)		170	28.8	(22.5–36.1)	
Age in years								
15-24	36	13.9	(5.9–29.4)	F(2,609) = 0.50, p=0.604	26	19.2	(8.2–38.8)	F(2,609) = 7.35, p<0.001
25-44	132	13.6	(8.8–20.6)		172	32.6	(26.0–39.9)	
45+	46	8.7	(3.3–21.0)		198	15.7	(11.2–21.4)	
Total	214	12.6	(8.8–17.8)		396	23.2	(19.3–27.7)	
Police case								
Yes	164	7.3	(4.2–12.5)	F(1,213)=10.94, p=0.001¶	n/a			F(1,213)=10.94, p=0.001¶
No	50	30.0	(18.9–44.1)		n/a			
Total	214	12.6	(8.8–17.8)		n/a			
Total	214	12.6	(8.8–17.8)	n/a	396	23.2	(19.3–27.7)	F(1,609)=11.63, p<0.001 π

Notes: * n/percentages not shown are based on <20 cases. † F-tests for differences in HIV prevalence by group as follows: ‡ by mortuary, sex; § by mortuary and sex, age; || by mortuary, age; ¶ by medico-legal status (at City mortuary only); π overall between mortuaries.

Table 3. HIV testing history among HIV-infected cadavers at KNH Mortuary, Nairobi, 2015 (N=90)

Selected characteristics	Ever Diagnosed with HIV				No prior HIV diagnosis		Significance
	Prior to hospitalization		During hospitalization		Total		
	%	(95% CI)	%	(95% CI)	%	(95% CI)	
Fischer's exact test p-value†							
Sex							
Male	16.7	(8.0–31.4)	21.4	(11.4–36.6)	38.1	(24.6–53.7)	61.9 (46.3–75.4) 42
Female	31.3	(19.6–45.9)	22.9	(13.0–37.1)	54.2	(39.8–67.8)	45.8 (32.2–60.2) 48
Total	24.4	(16.5–34.6)	22.2	(14.7–32.2)	46.7	(36.5–57.2)	53.3 (42.8–63.5) 90
Age							
15–44	25	(15.5–37.7)	28.3	(18.2–41.2)	53.3	(40.5–65.7)	46.7 (34.3–59.5) 60
45+	23.3	(11.4–41.9)	10	(3.2–27.3)	33.3	(48.0–81.3)	66.7 (31.0–57.1) 30
Total	24.4	(16.5–34.6)	22.2	(14.7–32.2)	46.7	(42.8–63.5)	53.3 (48.0–81.3) 90
Underlying cause of death*							
Death due to HIV	43.2	(29.1–58.4)	40.9	(27.1–56.3)	84.1	(69.7–92.4)	15.9 (7.6–30.3) 44
Death due to any other cause	21.4	(6.8–50.4)	14.3	(3.4–43.8)	35.7	(15.3–63.2)	64.3 (36.8–84.7) 14
Total	37.9	(26.1–51.4)	34.5	(23.1–47.9)	72.4	(59.2–82.6)	27.6 (17.4–40.8) 58

Notes: * cause of death was only available for 58 HIV-positive cadavers with HIV testing history available. † test for difference between having prior HIV diagnosis or not and selected characteristic.

Table 4. HIV testing and ART history among cadavers diagnosed with HIV prior to death, KNH Mortuary, Nairobi, 2015 (N=44)

Indicator	n	%	(95% CI)
Total treated for HIV	23	52.3	(37.6–66.5)
Treated and virally suppressed	10	22.7	(12.6–37.4)
Treated and not suppressed	2	4.5	(1.1–16.6)
Treated and viral load unknown	11	25.0	(14.4–39.9)
Not treated	11	25.0	(14.4–39.9)
Treatment unknown	10	22.7	(12.6–37.4)

Notes: Includes two cases excluded from previous table where timing of HIV diagnosis was not known

Discussion

In this study we estimated HIV positivity in cadavers at the two largest mortuaries in Nairobi, HIV diagnosis prior to death, subsequent use of ART and viral suppression for hospital-based deaths. Females continue to bear the greatest burden of HIV infection. The percentage of female cadavers that were HIV-infected was greater than that for males at both mortuaries. While greater HIV-associated mortality in women than men was not surprising earlier in the epidemic, given the high ART coverage, especially among women, further research is warranted to confirm and interpret this finding.

We found that one in eight cadavers at City Mortuary and one in four cadavers at KNH Mortuary were HIV infected. The higher HIV positivity among cadavers at KNH compared to City Mortuary may be due to KNH's status as a referral hospital, the majority of whose patients are hospitalized prior to death and who might have sought care for HIV complications, while conversely City Mortuary primarily receives medico-legal deaths, which are likely to be due to external causes.

The last national survey conducted in 2012 estimated HIV prevalence among adults at 4.9% and that only 57.5% of adults living with HIV in Kenya had been previously diagnosed (18). We found that more than eight in ten hospitalized patients for whom the underlying cause of death assigned was HIV had been diagnosed prior to death, however only about half of these were known to have been diagnosed prior to admission. The remaining 15.9% of deaths due to HIV did not have a documented HIV diagnosis at time of death. These scenarios represent missed opportunities for diagnosis prior to life-threatening illness and death. Among those with prior HIV diagnosis, the approximately half of deaths with no evidence of treatment represent

additional missed opportunities to save lives. About one fifth of those with a prior HIV diagnosis were on treatment and virally suppressed at time of death. These deaths are difficult to explain in the absence of a detailed clinical history, including duration on treatment, and diagnosed comorbidities and opportunistic infections.

The study had important limitations. Medical history was only available for hospital-based deaths at KNH and in those cases, was limited to the inpatient records for their hospitalization just prior to death, representing only a third (199/610) of all deaths with HIV test results captured in this study, and 50% (199/396) of those captured at KNH Mortuary. This limited our ability to establish whether a detectable viral load was due to treatment failure, poor adherence, or lack of treatment. Cause of death was also missing for 38.5% (235/610) of sampled mortuary deaths. Our study relied on routinely recorded causes of death, and full autopsies were not performed specifically for this study, so the underlying cause of death may have been ascertained incorrectly. While we included the two largest mortuaries in Nairobi in the study, a demographic analysis reported elsewhere found coverage to be 51% of expected deaths in the city (16), hence our findings are not necessarily representative of all deaths in Nairobi. Although inclusion of City Mortuary may have led to over-representation of external causes among males, excluding City from the analysis did not have a significant impact on the association between sex and death due to HIV. Additionally, the fact that three-quarters of the deaths at City Mortuary were medico-legal cases may also explain why no deaths were assigned HIV as a cause of death at this mortuary.

In spite of these limitations, the implementation of a novel mortuary-based surveillance study in Kenya provided an estimate of the proportion of HIV-related deaths at the two largest mortuaries in Nairobi, as well as important ancillary information on ART use, viral load, and diagnosis of HIV prior to death. Although studies have documented a reduction in HIV associated mortality attributable to ART, the prevalence of HIV among deaths in Nairobi is still higher than in the general population (19–22). In assessing impact of HIV treatment programs, measurement of mortality is rarely undertaken. As national ART programs continue to scale-up in an effort to save lives and achieve epidemic control, it is critical that appropriate surveillance systems are implemented that can monitor reductions in mortality as well as the patterns of specific causes of death among PLHIV, including those that are not being reached by care and treatment programs. Although measuring the level of HIV infection among deaths can help interpret declining trends in HIV prevalence in Nairobi, increasing the representativeness of the catchment of mortuary surveillance and developing methods for generalizing to the population of all deaths in the community is key. Although strengthened

national vital statistics and HIV case-based surveillance would provide more robust and comprehensive data, establishment of routine mortality surveillance in sentinel sites could play an important role in monitoring outcomes among people living with HIV in Kenya. This study shows that routine testing of cadavers and linking results to clinical records is a feasible approach that can provide important insights into the levels of HIV-associated mortality in the era of widespread ART availability. The findings also highlight the need to determine why PLHIV continue to experience high mortality even as ART is believed to be widely accessible, so that appropriate actions can be taken.

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Table S1. Completeness of measures from HIV mortuary surveillance study among cadavers aged ≥ 15 years, Nairobi, Kenya 2015 (N=807)

N			n	(%)	χ ² (df)	p-value	n	(%)	χ ² (df)	p-value	n	(%)	χ ² (df)	p-value
Sex														
Male	535	411	76.8	χ ² (1)=1.31 p=0.252	χ ² (1)=0.28 p=0.593	243	59.3	40	66.7	42	70	χ ² (1)=2.08 p=0.149		
Female	272	199	73.2			114	57	41	69.5	48	81.4			
Total	807	610	75.6			357	58.5	81	68.1	90	75.6			
Age in years														
15–24	80	62	77.5	χ ² (2)=0.36 p=0.834	χ ² (2)=0.99 p=0.610	38	61.3	9	90	*	*	χ ² (2)=5.56 p=0.062		
25–44	400	304	76			182	59.9	49	66.2	55	74.3			
45+	327	244	74.6			137	56.1	23	65.7	30	85.7			
Total	807	610	75.6			357	58.5	81	68.1	90	75.6			
Mortuary														
City	281	214	76.2	χ ² (1)=0.075 p=0.784	χ ² (1)=6.89 p=0.009	110	51.4	16	59.3	n/a	n/a	n/a†		
KNH	526	396	75.3			247	62.4	65	70.7	90	97.8			
Total	807	610	75.6			357	58.5	81	68.1	90	75.6			
Medico-legal case														
Yes	226	164	72.6	χ ² (1)=8.20 p=0.004	χ ² (1)=29.14 p<0.001	101	61.6	*	*	χ ² (1)=0.77 p=0.381	n/a†			
No	55	50	90.9			*	*	*	*					
Total	281	214	76.2			110	51.4	16	59.3					

Notes: Analyses are unweighted. df = degrees of freedom. * Percentages not shown are based on <20 cases. † Medical histories not available for deaths from City Mortuary. ‡ Among HIV-positive specimens. § Among KNH cadavers.

Table S2. Interaction between sex and age on risk of HIV infection among cadavers aged ≥ 15 years, HIV mortuary surveillance study, Nairobi, Kenya 2015 (N=610)

Age group (years)	Males		Females	
	N infected / total	Odds Ratio (OR) (95% CI)	N infected / total	OR (95% CI)
15-24	4/47	1.0	6/15	6.39 (1.47-27.69) p=0.013
25-44	33/215	1.86 (0.62-5.56) p=0.265	41/89	7.09 (2.29-21.9) p=0.001
45+	23/148	1.58 (0.51-4.93) p=0.428	12/96	1.15 (0.34-3.89) p=0.818
Within-strata ORs (95% CI) p-value				
25-44				1.11 (0.36-3.44) p=0.856
45+				0.18 (0.05-0.61) p=0.006
Ratio of ratios of ORs (95% CI) p-value				
25-44				0.60 (0.12-2.87) p=0.518
45+				0.11 (0.02-0.59) p=0.010

Notes: all odds ratios adjusted for mortuary.

Figure S1. Predictive margins of HIV prevalence among cadavers for age when controlling for sex, HIV mortuary surveillance study, Nairobi, Kenya 201

Panel A shows larger age grouping used throughout analysis. Panel B shows finer-grained age grouping with peak marginal probability of HIV infection by sex peaking at 35–44 years among females and 45–54 years among males.

Chapter 7

HIV-associated mortality in the era of antiretroviral therapy scale-up – Nairobi, Kenya, 2015

7

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Abstract

Background: Declines in HIV prevalence and increases in antiretroviral treatment coverage have been documented in Kenya, but population-level mortality associated with HIV has not been directly measured. In urban areas where a majority of deaths pass through mortuaries, mortuary-based studies have the potential to contribute to our understanding of excess mortality among HIV-infected persons. We used results from a cross-sectional mortuary-based HIV surveillance study to estimate the association between HIV and mortality for Nairobi, the capital city of Kenya.

Methods and Findings: HIV seropositivity in cadavers measured at the two largest mortuaries in Nairobi was used to estimate HIV prevalence in adult deaths. Model-based estimates of the HIV-infected and uninfected population for Nairobi were used to calculate a standardized mortality ratio and population-attributable fraction for mortality among the infected versus uninfected population. Monte Carlo simulation was used to assess sensitivity to epidemiological assumptions. When standardized to the age and sex distribution of expected deaths, the estimated HIV positivity among adult deaths aged 15 years and above in Nairobi was 20.9% (95% CI 17.7-24.6%). The standardized mortality ratio of deaths among HIV-infected versus uninfected adults was 4.35 (95% CI 3.67-5.15), while the risk difference was 0.016 (95% CI 0.013-0.019). The HIV population attributable mortality fraction was 0.161 (95% CI 0.131-0.190). Sensitivity analyses demonstrated robustness of results.

Conclusions: Although 73.6% of adult PLHIV receive antiretrovirals in Nairobi, their risk of death is four-fold greater than in the uninfected, while 16.1% of all adult deaths in the city can be attributed to HIV infection. In order to further reduce HIV-associated mortality, high-burden countries may need to reach very high levels of diagnosis, treatment coverage, retention in care, and viral suppression.

Introduction

Access to antiretroviral treatment (ART) has increased from 1 million to 17 million people living with HIV (PLHIV) globally from 2003 to 2015 [1, 2]. High HIV burden countries have accounted for the majority of this scale-up, with the number of PLHIV on ART increasing from 4 million to over 10 million in the last 5 years in Eastern and Southern Africa [3]. In both high- and low-income countries ART substantially increases life expectancy, especially for patients who start ART early [4, 5]. Given the rapid increase in coverage of life-saving treatment, a commensurate decrease in mortality in HIV-infected populations in high-burden countries would be expected. While cohort studies have demonstrated reductions in mortality among patients accessing ART, high rates of loss to follow-up (LTFU) make it difficult to fully assess the impact of ART at the population level. Complementary surveillance systems that can systematically assess population impact of ART programs on all-cause mortality on an ongoing basis are needed.

Civil registration systems in developing countries are often incomplete and causes of death poorly characterized. While a large fraction of PLHIV may be enrolled in care, high levels of LTFU, undocumented transfers, and passive reporting of deaths mean that program data underestimate mortality in the population in care if not linked to vital statistics [6] or adjusted statistically with LTFU studies [7, 8]. Hospital-based surveillance can shed light on HIV mortality among hospitalized patients, when both testing and HIV surveillance are routinely conducted [9]. Disease case surveillance systems, which could link patient records across systems, are still in their infancy in these settings. Further, the population in care is likely to have reduced mortality compared with those not in care, due to having access to medical interventions.

In urban areas where a majority of cadavers pass through mortuaries, mortuary-based studies have the potential to contribute to our understanding of excess mortality among HIV-infected persons. Although the literature is sparse on use of HIV testing in mortuary settings for surveillance purposes, De Cock *et al.* conducted a mortuary-based study to estimate mortality rates due to HIV and AIDS in Abidjan, Cote D'Ivoire in the late 1980s, before effective treatment for HIV existed, demonstrating that HIV was the leading cause of death in the city at the time [10]. A similar study conducted in 2001 found that nearly half of adult deaths in Pointe-Noire, Republic of Congo could be attributed to HIV, while the City of New York has been routinely testing for HIV during autopsies since the early 1990's [11]. In Addis Ababa, Ethiopia, mortality surveillance at burial grounds demonstrated reductions in AIDS-related mortality following scale-up of ART [12].

Coverage of ART has rapidly expanded in Kenya, reaching 59% of all PLHIV by the end of 2014 [3], and is likely to be highest in the capital city of Nairobi. The high estimated coverage of death registration in Nairobi at 78% in 2014 [13], together with the fact that all registered deaths in Nairobi are notified by mortuaries, implies that mortuary-based surveillance could be representative of all deaths in the city. Relatively high ART coverage among PLHIV coupled with high levels of mortuary-based death registration and moderate HIV prevalence in adults, made Nairobi an attractive site for examining HIV-related adult mortality. We conducted a cross-sectional mortuary-based serological study to measure HIV prevalence among deaths in Nairobi. We used results from this study to estimate the population-level association between HIV and mortality for the city of Nairobi in the era of scale-up of ART towards universal access.

Materials and methods

Mortuary HIV surveillance

The two largest mortuaries in Nairobi in terms of admissions volume were selected for HIV mortuary surveillance. Kenyatta National Hospital (KNH) is a national teaching and referral hospital and its mortuary saw 9,272 admissions in 2014. In contrast, City Mortuary saw 5,253 admissions in 2014 and primarily receives cadavers brought by the police in addition to cases from smaller health facilities lacking a mortuary. All cadavers admitted to KNH and City Mortuary over a 33 day period from 29 January to 3 March 2015 were registered. Cadavers of persons aged 15 years and above at death were sampled using transthoracic aspiration of cardiac blood which was shipped within 6 hours to a central laboratory for processing. Plasma was tested using the national HIV diagnostic algorithm. Specimens were screened with Colloidal Gold assay (KHB Shanghai Kehua Bio-Engineering Co, LTD, Shanghai, China). Reactive results were confirmed using First Response HIV 1-2-0 assay (PMC Medical India Pvt Ltd, Mumbai, India). Specimens with discrepant results were tested with Uni-Gold *HIV* assay as a tie breaker (Trinity Biotech PLC, Bray, Ireland) and the result of the tie-breaker was taken as the final result for the specimen. Every seventh specimen that was non-reactive on the screening assay was confirmed as an internal quality assurance step.

Nairobi Civil Registration

To determine the proportion of annual deaths reported during the study period for City Mortuary, KNH, and city-wide, as well as the proportion of deaths reported by each mortuary and seasonal variation of reported deaths, we abstracted death notifications from the Vital Statistics office at Nairobi City Hall for adults aged 15

and above at time of death for all deaths reported in Nairobi in 2014. We extracted summary data of total deaths by age, sex and year for Nairobi from the 2014 annual vital statistics report for purposes of estimating the age/sex distribution of deaths in Nairobi. These data were used to assess the coverage of death reporting in Nairobi as well as the coverage of City and KNH mortuaries among all reported deaths.

Measures

Age and sex of cadavers in the mortuary study were based on the reported age and sex from the death notification, the sex, date of birth and age recorded in the patient medical records if the death occurred at Kenyatta National Hospital and medical records were available for abstraction, or the autopsy report completed by the pathologist. Age and sex of deaths reported to vital statistics were based on the age and sex recorded on the death notification.

Population Projections

Spectrum version 5.52b3 (Avenir Health, Glastonbury, Connecticut) was used to estimate ART program coverage, HIV-related mortality, as well as the age- and sex-specific HIV prevalence for Nairobi in 2015, based on official demographic statistics, HIV surveillance and program data and population-based survey data for Nairobi [14-17]. The age and sex distribution of HIV prevalence from Spectrum was applied to the sub-national population projection for Nairobi from the Kenya National Bureau of Statistics [18] to estimate the number of people living with and without HIV in Nairobi in 2015. A life table derived from the Spectrum projection for Nairobi was used to estimate age-specific mortality rates. The projection is summarized in S1 Table.

Analysis Methods

Data were logged into an Epi Info version 7.0.4 database (U.S. Centers for Disease Control and Prevention [CDC], Atlanta). Data cleaning, tabulation and statistical analyses were performed in Stata version 13 (Stata Corp., College Station, Texas). Coverage and representativeness of surveillance system deaths were assessed by plotting reported versus expected deaths by year and by age group and sex. Inverse probability weights were developed and used to adjust the observed deaths from the surveillance system to account for missing HIV status by age and sex, and mortuary population weights were developed to adjust for differences in age- and sex-specific coverage and annualize deaths with respect to expected deaths based on the KNBS population projection and the Spectrum life table. Mortality rates were calculated by dividing the weighted annualized deaths from the surveillance system by the estimated population size in Nairobi from the population projection, by age, sex and HIV status, then multiplying by 1000.

The standardized risk difference subtracts the mortality rate in the HIV-uninfected population from the corresponding rate in the HIV-infected population, by age and sex. It is an additive measure which describes the additional mortality burden in the HIV-infected population. The standardized mortality ratio (SMR) is a relative measure which divides the mortality rate in the infected population by the mortality rate in the uninfected population after standardizing to the age and sex distribution of the infected population. Both measures were calculated using Stata's `epitab` package.

The population attributable fraction (PAF) estimates the proportion of all deaths that would have been avoided if HIV were no longer a risk factor for mortality in the HIV-infected. Odds ratios were fit using logit models with population frequency rates normalized to the total observed deaths, and these were then used to calculate attributable fractions with Stata's `punaf` command [19]. We also used logit models to test for interaction between age group and sex.

Simulation Methods

Monte Carlo simulations were conducted to assess the sensitivity of risk ratio and attributable fraction estimates to epidemiological assumptions; additional details are provided in S1 Text.

Data Access

Data are available from the National AIDS & STI Control Programme (NASCOP), Ministry of Health, Kenya on request. Requests for access should be directed to head@nascop.or.ke.

Ethics Approvals

This public health surveillance activity was approved by the U.S. Centers for Disease Control Center for Global Health as research that did not involve human subjects (because subjects were deceased) and did not require institutional review board review for human experimentation [2014/062]. The Kenyatta National Hospital/University of Nairobi Ethical Review Committee also approved this study [P380/06/2014] and did not require consent from next of kin. All data on deceased subjects were de-identified prior to data analysis.

Results

We found a pooled, unadjusted HIV positivity rate of 19.5% (95% CI 16.5-22.9%) among deaths at KNH and City Mortuaries, the positivity differing significantly by sex (14.6% among men, 29.5% among women, $p<0.001$). After weighting to account for missing test results and the coverage of the included mortuaries with respect to expected deaths by age and sex, the estimated HIV positivity among adult deaths in Nairobi was 20.9% (95% CI 17.7-24.6%) (Table 1).

Table 1. Percent HIV positivity among cadavers at City and KNH mortuaries, Nairobi 2015

Sex	Age (years)	Unadjusted HIV-positivity (n=610)	(95% CI)	Adjusted HIV-positivity (n=807)*	(95% CI)
Male	15-24	8.5	(3.2,20.6)	8.9	(3.3,21.7)
	25-44	15.3	(11.1,20.8)	15.3	(11.1,20.8)
	≥45	15.5	(10.5,22.3)	15.8	(10.7,22.7)
	Total	14.6	(11.5,18.4)	14.8	(11.6,18.7)
Female	15-24	40.0	(19.1,65.4)	40.8	(19.6,66.1)
	25-44	46.1	(36.0,56.5)	46.1	(35.8,56.7)
	≥45	12.5	(7.2,20.8)	12.4	(7.2,20.7)
	Total	29.5	(23.5,36.2)	30.2	(24.0,37.3)
Grand-total		19.5	(16.5,22.9)	20.9	(17.7,24.6)

Notes: * Adjusted for missing HIV test results and coverage of selected mortuaries by age and sex, assuming HIV status missing at random.

A total of 807 deaths of persons aged 15 years and above (range 15-105 years, median 40 years) were reported during the 33 day period of data collection at the two mortuaries. These corresponded to 8,320 deaths when annualized and seasonally-adjusted. Based on a demographic projection, there were 16,173 deaths of persons aged 15 years and above for Nairobi City in 2015, indicating that after annualizing, the coverage of the sampled mortuaries was 65.0% of reported deaths, and 51.4% of expected deaths. Coverage versus expected deaths varied substantially by age and sex from 22.2% for women aged 15-24 years to 63.5% for men aged 25-44 years. Annualized deaths were then adjusted for this age- and sex-specific coverage to obtain the total adjusted deaths (Table 2).

An estimated 2.8 million adults aged 15 years and above were residents of Nairobi in 2015, corresponding to 160,386 HIV-infected and 2,649,060 HIV-uninfected adults based on an overall HIV prevalence of 5.6% for Nairobi (Table 3). Dividing the estimated deaths from the surveillance system by the total projected population, the

Table 2. Annualized and coverage-adjusted surveillance deaths, Nairobi 2015

Sex	Age (years)	Observed mortality deaths *	Annualized mortality deaths †	Registered deaths in Nairobi ‡	Estimated coverage of registered deaths	Expected deaths for Nairobi §	Estimated coverage of expected deaths	Adjusted mortality deaths ¶
Male	15-24	61	629	846	74.3%	1,059	59.4%	53
	25-44	277	2,856	3,124	91.4%	4,497	63.5%	225
	45+	197	2,031	3,552	57.2%	4,168	48.7%	209
	Total	535	5,515	7,522	73.3%	9,724	56.7%	486
Female	15-24	19	196	491	39.9%	881	22.2%	42
	25-44	123	1,268	2,076	61.1%	2,681	47.3%	134
	45+	130	1,340	2,707	49.5%	2,887	46.4%	144
	Total	272	2,804	5,274	53.2%	6,449	43.5%	321
Grand-total		807	8,320	12,796	65.0%	16,173	51.4%	807

Notes: Some totals do not match sum of rows due to rounding errors. * Deaths registered at KNH and City Mortuaries during the study period. † Deaths from study sites annualized based on seasonally-adjusted study period of 0.097 years. ‡ Deaths registered at Nairobi City Hall in calendar year 2014. § Expected deaths based on Kenya National Bureau of Statistics (KNBS) projection and Spectrum life table for Nairobi. ¶ Deaths annualized and adjusted for differential coverage by age and sex with respect to expected deaths for Nairobi.

crude mortality rate in Nairobi among persons aged 15 years and older was 5.76 / 1,000 persons. In women, age-specific mortality estimates ranged from 1.92 / 1,000 among those aged 15-24 to 16.70 / 1,000 among women aged 45 and above. In men, mortality ranged from 3.16 / 1,000 among men aged 15-24 to 17.41 among men aged 45 and above. Overall, the mortality rate among HIV-infected persons was 21.12 / 1,000 compared with 4.83 / 1,000 among HIV-uninfected persons aged 15 years and older. Among HIV-infected women the mortality rate was 20.59 / 1,000 compared with 21.89 / 1,000 among HIV-infected men (Table 3). The standardized mortality ratio was 4.35 (95% CI 3.67-5.15), indicating that risk of death was significantly higher among HIV-infected persons compared with HIV-uninfected persons, when controlling for age and sex. The standardized risk difference was 0.016 (95% CI 0.013-0.019), corresponding to 16 additional deaths per 1,000 population among the HIV-infected after adjusting for age and sex (Table 4). The interaction between age and sex was significant, so all estimates were calculated using models stratified by sex and age group.

Table 3. Estimated age- and sex-specific deaths, population, and mortality rates per 1000 population, Nairobi 2015

Sex	Age (Years)	HIV-negative	HIV-positive	Total
		deaths / pop (rate)	deaths / pop (rate)	deaths / pop (rate)
Male	15-24	967/330,458 (2.93)	95/6,011 (15.80)	1,062/336,469 (3.16)
	25-44	3,818/767,352 (4.98)	691/46,156 (14.97)	4,509/813,508 (5.54)
	45+	3,518/226,141 (15.56)	660/13,885 (47.53)	4,178/240,026 (17.41)
	Total	8,303/1,323,951 (6.27)	1446/66,052 (21.89)	9,749/1,390,003 (7.01)
Female	15-24	499/424,695 (1.17)	344/13,607 (25.28)	843/438,302 (1.92)
	25-44	1,449/737,582 (1.96)	1238/70,315 (17.61)	2,687/807,897 (3.33)
	45+	2534/162,832 (15.56)	360/10,412 (34.58)	2,894/173,244 (16.70)
	Total	4,482/1,325,109 (3.38)	1,942/94,334 (20.59)	6,424/1,419,443 (4.53)
Overall		12,785/2,649,060 (4.83)	3,388/160,386 (21.12)	16,173/2,809,446 (5.76)

Table 4. Risk difference (RD), standardized mortality rate (SMR) and population attributable fraction (PAF) due to HIV, Nairobi 2015

Statistic	Male		Female		Total	
	Estimate	(95% CI)	Estimate	(95% CI)	Estimate	(95% CI)
SMR	3.12	(2.43-3.99)	6.17	(4.86-7.83)	4.35	(3.67-5.15)
RD	0.015	(0.010-0.020)	0.017	(0.013-0.021)	0.016	(0.013-0.019)
PAF	0.101	(0.067-0.133)	0.254	(0.199-0.305)	0.161	(0.131-0.190)

Combining the risk estimates with the prevalence of HIV in the population, the population attributable fraction (PAF) was 0.161 (95% CI 0.131-0.190). The estimated PAF differed between men and women, with women having a higher PAF for HIV infection than men: the PAF for women was 0.254 and for men was 0.101 (Table 4).

There were 40,382 males and 77,640 females aged 15 years and above on ART in Nairobi by December 31, 2015 according to official HIV program statistics. The Spectrum ART coverage estimate for 2015 for all HIV-infected persons aged 15 or more years in Nairobi was 73.6%, 61.1% for males and 82.3% for females, and Spectrum predicted that 13.8% of male deaths and 8.3% of female deaths (11.4% combined) would have been HIV-infected in 2015 (S1 Table).

Our sensitivity analysis looked at several key parameters that were estimated for this analysis as presented in S2 Table. The outcomes were most sensitive to HIV prevalence in the mortuaries and in the population, as well as the ratio of observed to unobserved prevalence in the mortuaries. The uncertainty interval for the SMR obtained through the uncertainty analysis was 3.04–7.19, while for the PAF the uncertainty interval was 0.118–0.221 (S3 Table).

Discussion

We conducted an analysis to combine HIV prevalence in a sample of deaths in Nairobi with population estimates in order to assess the burden of mortality associated with HIV in adults. We believe this is the first African study of its kind in the era of ART scale-up and as such it provides important insights in to the association of mortality and HIV infection in a major urban center with generalized HIV prevalence and a public ART program that reaches the majority of adults living with HIV. People living with HIV are at risk from death from multiple competing causes, including HIV. By estimating measures such as the SMR, RD and PAF this study looks beyond disease prevalence and provides estimates of the continuing impact of HIV on the adult population of Nairobi. Despite 7 in 10 HIV-infected persons aged 15 years and above receiving ART, our study showed persons living with HIV had a four-fold increased risk of mortality compared with those not infected. The population attributable fraction of 0.161 shows that about one in six deaths would be avoided in Nairobi if the increased mortality associated with HIV infection were eliminated, and more deaths would potentially be avoided in women than in men.

Antiretroviral treatment has been shown to dramatically reduce premature mortality. A prior study in Central Africa conducted at the height of the HIV epidemic when HIV prevalence was similar to Nairobi, but before ART was widely available, found nearly half of adult deaths were HIV-infected, while an East African cohort study in the late 1990's found a 20-fold increased mortality risk among the HIV-infected before widespread access to ART. A national study in South Africa found consistent declines in population all-cause mortality associated with early expansion of ART access from 2005-2009. In our study, conducted after over a decade of ART scale-up, we found about 1 in 5 deaths was HIV-infected, yet people living with HIV continue to be at significantly increased risk of death with a greater than four-fold increased risk of mortality. This is especially true for women in Nairobi who have reached 82.3% ART coverage in 2015 – surpassing the UNAIDS fast-track target of 81% of all PLHIV on treatment.

This study had several limitations. The mortality data were collected in early 2015, but the distribution of deaths available for abstraction at the time of the study was for 2014. The coverage of the two participating mortuaries was moderate, but may not have been representative of all deaths in the city. The calculation of mortality rates assumes that measured deaths were from the resident population, however deaths in Nairobi are not necessarily drawn from the resident population of the city. Some Nairobi residents die outside the city limits, and some non-Nairobi residents die within the city. The latter group is likely to be over-represented at KNH since it is a national referral hospital and routinely receives patients transferred from other counties.

Although these two facilities do not include all deaths in the city, they do include a significant fraction of deaths that occur in Nairobi. Although there may be some seasonal factors that affect mortality, Nairobi does not generally suffer from seasonal malaria epidemics or other infectious disease outbreaks that are likely to be over- or under-represented during the study period. After seasonal and annual adjustments for total deaths, our study covered 51.4% of expected deaths based on demographic estimates, but covered 65.0% of reported deaths, but coverage varied substantially by age and sex. Our sensitivity analysis found that outcome measures were sensitive to assumptions about HIV prevalence and representativeness of sampled mortuaries, however our uncertainty analysis showed that overall conclusions were robust in the face of this uncertainty, lending confidence in the robustness of the findings that the risk of dying is greater in the HIV-infected population than in the HIV-uninfected population, and that a considerable fraction of deaths at the population level can be attributed to HIV in Nairobi.

Though a lower proportion of HIV-infected men access treatment, their lower HIV prevalence and competing causes of mortality result in HIV being a less frequent cause of death. A complete diagnosis, treatment and adherence history for all deaths could help elucidate to what extent undiagnosed infection, inadequate treatment access or late presentation, poor adherence, or treatment failure are responsible for the mortality differentials seen among PLHIV. Mathematical modeling has shown that the majority of deaths among PLHIV are likely to be among those not on treatment, even in high ART coverage settings, underscoring the need to reduce barriers to treatment initiation and improve retention on ART. Thus it was surprising to find a higher HIV-associated SMR among women than men, in spite of their greater access to ART. This may be due to over-representation of deaths due to external causes in our sample, which differentially affect men. If this is the case, our estimates of HIV mortality among men are conservative. Inclusion of additional mortuaries in future studies would help control this potential bias. Despite study limitations, it appears that mortality among PLHIV in Nairobi continues to be high in spite of high estimated ART treatment coverage. This high mortality among PLHIV may help explain why HIV prevalence has not increased in recent years in spite of continued new infections and a rapid expansion of public HIV care and treatment services [20].

Conclusion

Although sub-Saharan Africa has dramatically decreased mortality due to HIV through expansion of ART, in order to further reduce HIV-associated mortality, high-burden countries may need to reach very high levels of diagnosis, treatment coverage, retention in care, and viral suppression. Though hospitals are no longer overwhelmed with AIDS patients, Kenya has not yet achieved the goal of an AIDS-free generation.

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Supporting information

S1 Text. Simulation Methods

Monte Carlo simulations were conducted to assess the sensitivity of risk ratio and attributable fraction estimates to epidemiological assumptions (HIV prevalence in the mortuaries, in the population, coverage of the sampled mortuaries with respect to all actual deaths, and the impact of seasonality of overall death notifications at sampled mortuaries, the male/female population prevalence ratio, and the ratio of observed to unobserved HIV prevalence in mortuaries in Nairobi). Input parameters are summarized in S2 Table. Each input parameter was independently sampled 10,000 times in Stata from a normal (log-normal in the case of ratio measures) random distribution. The mean was set to the “best” value and the standard deviation chosen to cover alternative plausible values for the parameter. Through trial and error 10,000 runs were selected to ensure the Monte Carlo standard error, a measure of the accuracy of the simulation itself, was less than 2.5% as reported by Stata’s `simsum` command. R version 3.1.2 (R Development Core Team) was used to generate scatter plot matrices to visualize associations between input and output parameters. Non-parametric uncertainty bounds were generated for outcomes using the 2.5th and 97.5th centiles from the resulting distribution. Unlike traditional confidence intervals which describe uncertainty due to random sampling, the uncertainty bounds also reflect uncertainty about model assumptions. Results are summarized in S3 Table.

Figure S1. Scatter plot matrix showing pairwise correlation between statistics (PAF and SMR) and input parameters, Nairobi 2015

Definitions: PAF = population-attributable fraction, SMR = standardized mortality ratio, mratio = ratio of prevalence among all deaths vs sampled mortuaries, sp = study period, coverage = coverage of included mortuaries, mfratio = male/female HIV prevalence ratio in the population, hivp = population HIV prevalence, mhivp = mortuary HIV prevalence. The figure shows an inverse relationship between SMR and population HIV prevalence, and positive association between PAF and mortuary HIV prevalence and PAF and the ratio of prevalence among all deaths to sampled deaths. Other modeled inputs have less or no impact on estimated SMR and PAF.

Table S1. Summary of demographic and epidemic projection, population age 15 years and above, Nairobi 2015

Indicator	Total	Men	Women
Population*	2,809,448	1,390,003	1,419,445
PLHIV†	160,386	66,051	94,335
Number on ART (coverage)‡	118,022 (73.6%)	40,382 (61.1%)	77,640 (82.3%)
All deaths§	16,173	9,724	6,449
% deaths HIV-infected	11.4%	13.8%	8.3%
Standardized mortality ratio (SMR) due to HIV	3.84	6.64	1.91
Population-attributable fraction (PAF) due to HIV¶	0.081	0.117	0.035

Notes: * Total 2015 mid-year population and population age distribution from Kenya National Bureau of Statistics (KNBS) projections. † age-specific and total 2015 mid-year PLHIV from combining KNBS projected population with Spectrum age- and sex-specific HIV prevalence distribution. ‡ Number on ART from official country program statistics as reflected in Spectrum (numbers on ART and ART coverage reported for December 31). § Deaths obtained by applying mortality rates from Spectrum life table for Nairobi to KNBS projected population for 2015. || Standardized mortality ratio calculated by indirectly standardizing mortality rate in the HIV-negative population as estimated by Spectrum by 5-year age groups to the sex and age distribution among the HIV-infected, as estimated by Spectrum. ¶ Population-attributable fraction calculated by multiplying the proportion of deaths HIV-infected according to Spectrum by (SMR-1)/SMR.

Table S2. Parameters used for Monte Carlo simulation-based sensitivity and uncertainty analyses for standardized mortality ratio (SMR) and population attributable fraction (PAF), Nairobi 2015

Parameter	Mean	Sd
HIV prevalence	0.563	0.008445
Mortuary HIV prevalence	0.2133659	0.018062
Mortuary prevalence ratio	1.0	0.15
Male/female ratio	0.71501239	0.107
Sampling period	0.097	0.0093
Mortuary coverage	0.512	0.1

S3 Table. Simulation results for overall and sex-specific standardized mortality ratio (SMR) and population attributable fraction (PAF), Nairobi 2015

Statistic	Median	95% UI	MCSE
SMR	4.58	(3.04-7.19)	1.051%
SMR (male)	3.52	(2.31-5.60)	0.830%
SMR (female)	6.53	(4.31-10.37)	1.534%
PAF	0.167	(0.118-0.221)	0.019%
PAF (male)	0.120	(0.075-0.160)	0.016%
PAF (female)	0.268	(0.205-0.337)	0.024%

Notes: The Monte Carlo sampling error (MCSE) is a measure of the precision of the simulation and is a function of number of repetitions and variability in the simulated statistic. The number of repetitions was selected to ensure an MCSE less than 2.5% for each statistic for each sub-group (male, female or combined). The 95% uncertainty interval (2.5th to 97.5th centiles) summarizes the variability in the estimate that is due to the uncertainty in the input parameters as provided in S1 Table. The SMR fell between 3.04–7.19, and the PAF fell within 0.0118–0.221 in 95% of simulations, lending support to the robustness of the finding of increased mortality among PLHIV aged 15 years and older in Nairobi.

Chapter 8

Leading causes of death and high mortality rates in a HIV-endemic setting, Kisumu County, Kenya, 2019

8

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Abstract

Background: In resource-limited settings, underlying causes of death (UCOD) often are not ascertained systematically, leading to unreliable mortality statistics. We reviewed medical charts to establish UCOD for decedents at two high-volume mortuaries in Kisumu County, Kenya and compared ascertained UCOD to those notified to the civil registry.

Methods and Findings: Medical experts trained in COD certification examined medical charts and ascertained causes of death for 456 decedents who had been admitted to the mortuaries from April 16 through July 12, 2019. Decedents with unknown HIV status or who had tested HIV-negative >90 days before the date of death were tested for HIV. We calculated annualized all-cause and cause-specific mortality rates grouped according to the global burden of disease (GBD) categories and separately for deaths due to HIV/AIDS and expressed estimated deaths per 100,000 population. We compared notified to ascertained UCOD using Cohen's Kappa (κ) and assessed for independence of proportions using Pearson's chi-squared test.

The four leading UCOD were HIV/AIDS (102/442 [23.1%]), hypertensive disease (41/442 [9.3%]), other cardiovascular diseases (23/442 [5.2%]), and cancer (20/442 [4.5%]). The all-cause mortality rate was 1,086/100,000 population. The highest cause-specific mortality was in GBD category II (noncommunicable diseases; 516/100,000), followed by GBD I (communicable, perinatal, maternal, and nutritional; 513/100,000), and III (injuries; 56/100,000). The HIV/AIDS mortality rate was 251/100,000 population. The proportion of deaths due to GBD II causes was higher among females (51.9%) than males (42.1%; $p=0.039$). Conversely, more males (8.6%) than females (2.1%) died of GBD III causes ($p=0.002$). Most of the records with available recorded and ascertained UCOD ($n=236$), 167 (70.8%) had incorrectly recorded UCOD, and agreement between notified and ascertained UCOD was poor (29.2%; $\kappa=0.26$).

Conclusions: Mortality from infectious diseases, especially HIV/AIDS, is high in Kisumu County, but there is a shift toward higher mortality from noncommunicable diseases, possibly reflecting an epidemiologic transition and improving HIV outcomes. An increased focus on controlling noncommunicable conditions is needed despite the high communicable disease burden. The weak agreement between notified and ascertained UCOD could lead to substantial inaccuracies in mortality statistics, which wholly depend on death notifications.

Introduction

The World Health Organization (WHO) classifies health problems into three broad categories: Group I includes communicable diseases (including HIV/AIDS) as well as perinatal, maternal, and nutritional diseases; Group II includes noncommunicable diseases; and Group III includes injuries [1,2]. These classifications are used to calculate the global burden of disease (GBD) causes of death (COD) reports and to provide broad groupings of COD for comparing mortality rates between countries [3].

In Kenya, the overall crude mortality rate is currently estimated to be 550/100,000 population [4]. Estimated all-cause mortality rates increased from 850/100,000 population in 1990 to 902/100,000 in 2006 but subsequently decreased to 519/100,000 by 2016 [5]. Communicable diseases were the biggest contributor to mortality rates before the mid-2000s, driven largely by the impact of HIV. However, from 2006 to 2016, deaths due to communicable diseases, especially HIV/AIDS, have decreased; noncommunicable diseases and injuries account for an increasing fraction of deaths [5–7]. Among noncommunicable diseases, cancer is a major underlying cause of death (UCOD) even in rural settings [6], and approximately 100,000 Kenyans die of hypertension-related complications every year [8]. Hypertension further contributes to 50% of hospital admissions and over 40% of deaths in Kenya [9]. This epidemiological transition may be due to changes in population dynamics and other individual and environmental factors. The leading recertified UCOD in Kenya (estimated in 2016) were; HIV (11.0%), lower respiratory infections (9.1%), malaria (5.7%), non-HIV related tuberculosis (4.0%), diarrheal diseases (3.9%), prematurity and low birth weight (3.7%), digestive diseases (3.5%) and anemia (3.3%) [9]. Pneumonia, malaria, and cancer were leading COD in 2017 and were leading causes of morbidity. In 2017, deaths due to HIV/AIDS ranked fifth (8,800) but declined by 55% between 2010 and 2018 [10]. In 2017, of other communicable diseases, deaths due to tuberculosis ranked fourth; among deaths due to injuries, road traffic accidents were the ninth overall leading COD [11]. Deaths due to road traffic accidents are estimated to have increased by 8% from 2,907 in 2014 to 3,153 in 2018 [12].

In Kenya, mortality rates for children aged <5 years were 46.37 deaths per 1000 live births in 2018, a gradual decrease from 164.34 deaths per 1000 live births in 1969 [13]. However, 26/47 (55.3%) counties have not met the World Summit for Children target to reduce mortality rates to 70 deaths per 1000 live births by the year 2000, and only nine counties were on course to meet the millennium development goal to reduce mortality rates in children aged <5 years by two-thirds between 1990 and

2015 [13]. In 2009, the adult mortality rate (probability of dying between ages 15 and 60 years per 1000 population) was 348 among males and 313 among females [14].

Although summarizing mortality rates using GBD classes is useful, accurate and specific UCOD data are needed to guide and evaluate appropriate public health responses in preventive and curative services. Accuracy of mortality statistics can be improved by ascertaining the most probable COD and ensuring that death records include the correct UCOD. However, in resource-limited countries, UCODs recorded in civil registration and vital statistics (CRVS) systems are commonly determined by individual administrators or health providers, depending on the place of death, rather than on a systematic review of evidence in medical charts or autopsy. Often this is due to lack of medical attention at the time of death, a situation that could be remedied by the systematic assembly of health records, among other approaches [15]. Thus, to improve vital statistics, post-mortem examinations complemented by hospital-based reviews of clinical charts can help determine the UCOD. Methodologies for mortuary-based surveillance do not have to be invasive or logistically challenging. For example, minimally invasive autopsy techniques, such as oral swabs, have been used to improve vital statistics in outbreak investigations for diseases such as Ebola [16]. Such methods have utility in public health surveillance, and when combined with available medical history data, the most likely UCOD can be deduced. We ascertained UCOD, antecedent COD, and immediate COD for hospital-based deaths that occurred in two high-volume referral hospitals in Kisumu County, Kenya, compared them to those notified to the civil registry and estimated mortality rates.

Methods

Setting

Kisumu County had an estimated population of 1,155,574 in 2019 and has a high HIV burden [17]. The two largest mortuaries in the county are located at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOTRH) and Kisumu County Referral Hospital (KCRH), with the capacity to hold 99 and 46 bodies, respectively. There are three civil registries in the county (Kisumu East, Kisumu West, and Nyando). Kisumu East civil registry receives death notifications from Kisumu city and the surrounding areas. In 2019, notifications from the two mortuary facilities accounted for 42.0% of all reported deaths registered in the Kisumu East civil registry [18]. Deaths in Kisumu East civil registry over three years (2017–2019)

contributed to a median of 74.8% of deaths registered in the entire county [19]. Cause of death data from the two hospitals were used to estimate the number of deaths at the county level with the estimated county population as a denominator.

Study design and population

This study was part of an overarching cross-sectional surveillance study designed to: understand HIV-associated mortality in Kisumu County through determining prior HIV diagnosis, HIV-positivity, and viral load among cadavers; assess the feasibility of using oral fluid obtained from cadavers for non-invasive rapid HIV antibody testing; and assess the quality of the UCOD certification, HIV status documentation, and efficiency of death notification in Kisumu County.

Three categories of decedents from the two mortuaries were included in the overarching study: hospital deaths (all deaths occurring in the hospital wards or outpatient department), dead on arrival (DOA; deaths occurring elsewhere, either outside of hospitals or in other hospitals with subsequent transfer), and police cases (DOA cases or hospital deaths that required a post-mortem examination for legal reasons). Data for this manuscript were drawn from the overarching study to establish the leading COD and included all hospital-based deaths admitted to the two morgues from April 16–July 12, 2019, irrespective of age. This analysis included decedents who died within the two hospitals whose medical records were available. Dead on arrival cases were excluded as they did not have medical history records at the hospitals.

Sample size

The sample size of 690 for the overarching study was powered to measure HIV prevalence of 5% among deaths of individuals aged ≥ 15 years and was adjusted to account for the loss of specimens and ineligibility. All children aged < 15 years who died and were admitted to one of the two mortuaries during the study period were included to cover all decedents admitted to the mortuaries during the study period.

Ascertaining cause of death

For our study, a panel of six medical officers and two health records information officers were trained by master certification and coding trainers on International Classification of Diseases and Health Conditions, version 10 (ICD10) certification and coding rules [20]. Afterward, the medical officers used a data entry form modified from the standard death notification form to abstract clinical information from the medical records for hospital-based deaths. The following details were abstracted: signs and symptoms of illnesses preceding death, clinical diagnoses, and results of investigations, including HIV status and HIV treatment status.

Individual panel members used the abstracted information to assign immediate COD, antecedent COD, and UCOD and recorded them in a tool. Whenever UCOD was unclear, a panel discussion was held to determine and assign the most probable UCOD. The health records information officers then assigned the actual ICD10 code. These data were directly entered into an open data kit tool with logic checks for data accuracy and consistency and were submitted to a central database.

Routinely notified versus panel-assigned cause of death

We abstracted immediate COD, antecedent COD, and UCOD, as documented from notification forms for all deaths in the two hospitals. In Kenya, death notification forms are divided into two parts and are completed by trained medical officers in triplicate. The first part contains the burial permit, and the second part records the UCOD, antecedent COD, immediate COD, and other significant COD. The second part is submitted to the CRVS department for further analysis, reporting, and archiving in the permanent vital statistics within Kenya. In our study, a panel of trained medical experts revised the COD using the procedures described. As with the UCOD assigned by the medical expert panel, the deaths documented in the death notification forms were entered into the open data kit tool and were submitted to a central database. HIV status ascertained during the study, and UCOD assigned and coded by the medical experts' panel, were used for surveillance purposes and were not used to update CRVS information or decedents' medical records.

Outcomes

For decedents with unavailable HIV status, HIV status was ascertained using post-mortem testing in the overarching study, as described elsewhere [21]. HIV-associated mortality was defined as any death with a documented HIV-positive status, either in the medical files or post-mortem testing results. HIV/AIDS cause-specific mortality was considered for all decedents who had HIV assigned as their UCOD (ICD-10 codes B20-B24), per ICD-10 guidelines. Other COD were assigned based on ICD-10 coding rules.

Summary measures: Two parameters were used to calculate the summary rates. First, we considered the two mortuaries' contribution to deaths in Kisumu East civil registry (42.0% in 2017) [18]. We then considered Kisumu East civil registry's contribution to deaths in the entire county for 2017–2019 (median, 74.8%). Based on this coverage, we calculated the crude all-cause mortality rate for Kisumu County as the total number of deaths attributed to all causes reported during the study period (n=938), projected to 100% and annualized for 12 months. Rates were expressed per 100,000 of the mid-year population of Kisumu County [17], as shown in the formula:

$$CMR = \left(\frac{d}{p} \right) \times 100,000$$

Where d is the annualized deaths in Kisumu County (i.e., deaths reported during the study period calculated for 12 months), and p is the mid-year population for Kisumu County.

To calculate the cause-specific mortality rate, we used the proportion of deaths attributable to specific causes as reported during the study period multiplied by the estimated deaths attributed to specific causes based on the annualized number of all deaths, projected to 100% for the entire county and finally expressed per 100,000 population as shown in the formula:

$$CSMR = c \times \left(\frac{d}{p} \right) \times 100,000$$

Where c is the proportion of deaths reported during the study period attributed to a specific cause; d is the annualized deaths in Kisumu County (i.e., deaths reported during the study period calculated for 12 months); and p is the mid-year population for Kisumu County.

We summarized age-specific mortality rates by sex per 100,000 population and plotted these log-transformed rates for graphical interpretation.

Stillbirths: Stillbirths were not subjected to UCOD ascertainment by the panel, but we documented and quantified the occurrence of stillbirths at the two hospitals during the study period. We used data from the Kenya health information system to determine the number of deliveries in the two facilities from April 1–July 31, 2019 and calculated the stillbirth rate per 1,000 deliveries.

Statistical analysis

COD were summarized using the free Microsoft Excel-based tool *Analysing Mortality Levels and Causes-of-Death* (ANACoD V2.0), developed by WHO in collaboration with the University of Queensland and Health Metrics Network (<https://www.who.int/healthinfo/anacod/en/>) [22]. This tool provides a stepwise approach to a comprehensive analysis of ICD-10-coded data. Using the tool, we reviewed coded mortality data for errors and tabulated and presented the UCOD by age and sex in tables and charts. The tool also classifies UCOD using the GBD categorization and compares findings with those from other countries. To measure the interrater agreement of notified compared to ascertained COD, we used Cohen's

kappa (κ) statistic. We used the Pearson chi-squared test to compare proportions, and when the n-values were <5 , we used the Fisher exact test. P-values <0.05 were considered statistically significant.

Ethical considerations

No individual, personally identifiable information was included in the study database. Results of HIV tests conducted on decedents were not linked back to living individuals. This study was approved by the Kenya Medical Research Institute's Science and Ethical Review Unit; the JOOTRH ethics review committee; U.S. Centers for Disease Control and Prevention (CDC), Center for Global Health, Associate Director for Science, as research involving data and specimens from deceased persons; and University of California San Francisco Committee on Human Research.

Results

Overview of included deaths

Of the 938 deaths enrolled in the overarching study, 851 (90.7%) cadavers were eligible, and 555/851 (65.2%) died within the two hospitals. The rest (296/851; 35.8%) were either police cases or other DOA cadavers. We retrieved available medical charts and ascertained the probable UCOD for 456 decedents, representing 82.2% of the hospital-based deaths during the study period. The UCOD was not ascertained for 99/555 (17.8%) of the cadavers due to missing hospital records. Of the decedents with available records ($n=456$), 442 had UCOD that were classified, and 14/456 (3.1%) deaths could not be classified due to ill-defined diseases (ICD10 codes R00-R99; Figure 1). Therefore, 52% of decedents admitted to the mortuaries (442/851) during the study period could be included in our secondary analysis.

Of the 442 decedents whose UCOD were ascertained and classified, 51 (11.6%) were children aged <1 year, and 42 (9.5%) were aged >80 years. Children aged 10–14 years and young people aged 20–24 years accounted for the lowest proportions of decedents whose UCOD were ascertained and classified (2.7% each). Overall, a similar number of females (234), and males (208), had their UCOD ascertained and classified (Table 1).

The prevalence of GBD group I causes was similar among males (49.0%), and females (45.7%; $p=0.486$). Significantly more females (52.1%) than males (42.3%) died due to GBD group II causes ($p=0.039$), and significantly more males (8.7%) than females (2.1%) died due to GBD group III causes ($p=0.002$).

The estimated age-specific number of deaths pyramid was inverted compared to the population pyramid from the 2019 census (Figure 2). The largest age-band for the population is 10–14 years. Children aged <5 years and adults aged ≥70 years had the highest numbers of deaths/100,000 population. Higher mortality rates were reported for male decedents aged <1 year, 15–19 years, and 55–59 years, whereas female decedents aged 30–34 years, 45–49 years, and ≥80 years had higher mortality rates.

Figure 1. Deaths of hospitalized patients at two referral hospitals, Kisumu 2019

* Hospital records were available. † Ill-defined diseases refer to UCOD with ICD10 codes R00-R99.

Table 1. Distribution of ascertained causes of death by age and sex, and the global burden of disease category from admissions at two large hospitals, Kisumu 2019.**Caption:** The table presents deaths by 5-year age-bands among 208 males, and 234 females.

Age (years)	N (%*)	Group I†		Group II‡		Group III§	
		Males n (%)	Females n (%)	Males n (%)	Females n (%)	Males n (%)	Females n (%)
0	51 (11.5)	26 (25.5)	19 (17.8)	3 (3.4)	3 (2.5)	0 (0)	0 (0)
1-4	16 (3.6)	8 (7.8)	5 (4.7)	1 (1.1)	2 (1.6)	0 (0)	0 (0)
5-9	20 (4.5)	5 (4.9)	5 (4.7)	4 (4.5)	6 (4.9)	0 (0)	0 (0)
10-14	12 (2.7)	3 (2.9)	4 (3.7)	2 (2.3)	3 (2.5)	0 (0)	0 (0)
15-19	19 (4.3)	5 (4.9)	2 (1.9)	6 (6.8)	4 (3.3)	2 (11.1)	0 (0)
20-24	12 (2.7)	3 (2.9)	3 (2.8)	2 (2.3)	3 (2.5)	1 (5.6)	0 (0)
25-29	37 (8.4)	2 (2)	13 (12.1)	10 (11.4)	5 (4.1)	6 (33.3)	1 (20)
30-34	41 (9.3)	10 (9.8)	17 (15.9)	6 (6.8)	8 (6.6)	0 (0)	0 (0)
35-39	26 (5.9)	9 (8.8)	11 (10.3)	0 (0)	3 (2.5)	3 (16.7)	0 (0)
40-44	24 (5.4)	6 (5.9)	7 (6.5)	7 (8)	3 (2.5)	1 (5.6)	0 (0)
45-49	23 (5.2)	3 (2.9)	6 (5.6)	5 (5.7)	8 (6.6)	1 (5.6)	0 (0)
50-54	18 (4.1)	3 (2.9)	2 (1.9)	3 (3.4)	8 (6.6)	2 (11.1)	0 (0)
55-59	18 (4.1)	4 (3.9)	2 (1.9)	6 (6.8)	6 (4.9)	0 (0)	0 (0)
60-64	21 (4.8)	5 (4.9)	4 (3.7)	4 (4.5)	6 (4.9)	1 (5.6)	1 (20)
65-69	14 (3.2)	1 (1)	1 (0.9)	5 (5.7)	7 (5.7)	0 (0)	0 (0)
70-74	29 (6.6)	1 (1)	3 (2.8)	11 (12.5)	13 (10.7)	1 (5.6)	0 (0)
75-79	19 (4.3)	4 (3.9)	1 (0.9)	4 (4.5)	9 (7.4)	0 (0)	1 (20)
80+	42 (9.5)	4 (3.9)	2 (1.9)	9 (10.2)	25 (20.5)	0 (0)	2 (40)
Total	442	102	107	88	122	18	5
p-values¶	-	0.486		0.039		0.002	

* Column percentage; † Group I – Communicable, perinatal, maternal, and nutritional including HIV; ‡ Group II – Noncommunicable diseases; § Group III – Injuries; ¶ P-values calculated using a chi-squared test show the significance of differences in proportions for each GBD category by sex.

Figure 2. Kisumu County population pyramid and estimated deaths per 100,000 by sex and age, 2019.

Caption: A) Source of population data is 2019 census, B) Estimated deaths/100,000 calculated using the population denominator, C) Log-transformed age-specific mortality rates/100,000 population.

Table 2. Ascertained leading causes of death at two large hospitals and among all persons and by sex, Kisumu, 2019

Causes of death	Total (n=442)	UCOD by sex, rank, n (%) [*]		p-value [†]
	Rank, n (%)	Males	Females	
<i>Leading causes</i>	<i>n=341 (77.1)</i>	<i>n=149 (71.6)</i>	<i>n=192 (82.1)</i>	-
HIV/AIDS	1 , 102 (23.1)	1 , 43 (20.7)	1 , 59 (25.2)	0.258
Hypertensive disease	2 , 41 (9.3)	2 , 11 (5.3)	2 , 30 (12.8)	0.006
Other cardiovascular diseases	3 , 23 (5.2)	4 , 10 (4.8)	4 , 13 (5.6)	0.724
Cancer [‡]	4 , 20 (4.5)	11 , 4 (1.9)	3 , 16 (6.8)	0.013
Endocrine disorders	5 , 18 (4.1)	5 , 9 (4.3)	5 , 9 (3.8)	0.799
Lower respiratory infections	6 , 16 (3.6)	2 , 11 (5.3)	12 , 5 (2.1)	0.077
Perinatal conditions	7 , 16 (3.6)	6 , 8 (3.8)	6 , 8 (3.4)	0.810
Other digestive diseases	8 , 13 (2.9)	9 , 6 (2.9)	8 , 7 (3)	0.947
Malaria	9 , 12 (2.7)	8 , 7 (3.4)	11 , 5 (2.1)	0.428
Cerebrovascular disease	10 , 12 (2.7)	11 , 5 (2.4)	7 , 7 (3)	0.704
Prematurity & low birth weight	11 , 11 (2.5)	9 , 6 (2.9)	13 , 5 (2.1)	0.614
Road traffic accidents	12 , 11 (2.5)	6 , 8 (3.8)	- [§] , 3	0.125
Diabetes mellitus	13 , 10 (2.3)	16 , 4 (1.9)	10 , 6 (2.6)	0.755
Diarrheal diseases	14 , 9 (2)	11 , 5 (2.4)	15 , 4 (1.7)	0.740
Infectious diseases (other)	15 , 9 (2)	20 , 3 (1.4)	9 , 6 (2.6)	0.510
Birth asphyxia and birth trauma	16 , 6 (1.4)	11 , 5 (2.4)	- [§] , 1	0.104
Protein-energy malnutrition	17 , 6 (1.4)	- [§] , 3	18 , 3 (1.3)	1.000
Skin diseases	18 , 6 (1.4)	- [§] , 1	14 , 5 (2.1)	0.220
<i>All other causes[¶]</i>	<i>-, 101 (22.9)</i>	<i>-, 59 (28.4)</i>	<i>-, 42 (17.9)</i>	-
Total (N)	442	208	234	

^{*}UCOD: underlying causes of death. Causes of death exclude ill-defined diseases (ICD10 R00-R99). Three percent of underlying causes of death were/remaining ill-defined. Results within columns presented as rank, N (%). Rank is boldfaced.; [†]p-values show significance of differences in proportions for each UCOD by sex; [‡] Cancers include UCOD defined as: “Esophageal cancer”, “Cervix uteri cancer” and “Trachea, bronchus and lung cancers”, “Other neoplasms”, “Other malignant neoplasms”, – hence combined cancers reduce the number of leading causes to 18; [§] Not among 20 overall leading UCOD within the sex category, hence percentages and ranking not included; [¶] Includes all other mutually exclusive causes of death, percentages are out of the total number of deaths

Twenty leading causes of death

The 20 leading COD accounted for over three-quarters (77.1%, 341/442) of the ascertained deaths (Table 2). The four leading UCOD were HIV/AIDS (102/442 [23.1%]), hypertensive disease (41/442 [9.3%]), other cardiovascular diseases (23/442 [5.2%]), and cancer (20/442 [4.5%]). Lower respiratory infections were

important UCOD among male decedents (5.3% of deaths) but were ranked twelfth among female decedents (2.1% of deaths). More males had UCOD due to road traffic accidents, ranking sixth, but only three traffic accident-related deaths were reported among females. Significantly more females (12.8%) than males (5.3%) died of hypertensive disease ($p=0.006$) and cancer (females, 6.8%; males, 1.9%; $p=0.013$).

Among children aged <5 years, conditions arising during the perinatal period ($n=12$ [18.8%]), followed by prematurity and low birth weight ($n=11$ [17.2%]), were the first and second leading COD among 64 children. HIV/AIDS was the third leading COD among children aged <5 years (Table 3).

Table 3. Ascertained leading causes of death at two large hospitals and among children aged 0–4 years in Kisumu, 2019

Caption: Leading underlying causes of death among children aged 0–4 years ranked by frequency.

Causes of death*		n (%)†
Rank	Leading causes	n=64
1	Other conditions arising during the perinatal period	12(18.8)
2	Prematurity and low birth weight	11(17.2)
3	HIV/AIDS	6(9.4)
3	Birth asphyxia and birth trauma	6(9.4)
4	Diarrhoeal diseases	5(7.8)
4	Protein-energy malnutrition	5(7.8)
5	Lower respiratory infections	4(6.3)
6	Malaria	3(4.7)
7	Lymphomas and multiple myeloma	2(3.1)
7	Endocrine disorders	2(3.1)
8	Meningitis	1(1.6)
8	Other infectious diseases	1(1.6)
8	Other nutritional disorders	1(1.6)
8	Other malignant neoplasms	1(1.6)
8	Other digestive diseases	1(1.6)
8	Abdominal wall defect	1(1.6)
8	Other Congenital anomalies	1(1.6)
-	All other causes‡	4
Total		N=67

*Data for children overlap with data presented in Table 2; † Column percentages; ‡ Not ranked or included in the percentage.

Stillbirths

In both hospitals, there were 66 documented stillbirths during the study period. From health services program data reported through the Kenya health information system, there were 3,360 total deliveries in the two facilities from April 1–July 31, 2019, and 81 (2.4%) stillbirths over 121 days [19]. Using this denominator, we calculated approximately 2,416 deliveries in the 87 days of the study period and a stillbirth rate of 2.7% (66/2,416) or 27/1,000 deliveries.

Comparison of notified versus ascertained underlying causes of death

We abstracted data from available death notification forms for 236 records matched with UCOD records ascertained by the expert panel. Overall, over two-thirds (167/236 [70.8%]) of the decedents had incorrectly assigned UCOD in the death notification form (Table 4). The errors were attributed to either wrong sequencing, i.e., the chain of events leading to death was incorrectly ordered 10/167 [6.0%], or wrong assignment (157/167 [94.0%]) of UCOD among decedents. The proportion of incorrectly assigned UCOD was not significantly different by sex ($p=0.174$). Where underlying UCOD was HIV/AIDS, the concordance between panel-ascertained and notified deaths was higher (27/60 [45.0%]) compared to other UCOD (42/176 [23.9%]; $p=0.002$). The agreement between notified and ascertained UCOD was 29.2% ($\kappa=0.259$). The discrepancy was higher for immediate COD (176/236 [74.6%]) than for UCOD (167/236 [70.8%]).

Table 4. Comparison of notified versus ascertained cause of death (COD), Kisumu 2019

Caption: Comparison of notified versus ascertained COD and by selected variables.

	Type of errors, n (%)			p-value
	N (%)	Correct COD	Erroneous COD	
COD type				
Underlying	236 (100)	69 (29.2)*	167 (70.8) [†]	
Immediate	236 (100)	60 (25.4) [‡]	176 (74.6)	
Sex				0.174 [§]
Males	124 (52.5)	41 (33.1)	83 (66.9)	
Females	112 (47.5)	28 (25.0)	84 (75.0)	
Underlying COD				0.002 [§]
HIV/AIDS	60 (25.4)	27 (45.0)	33 (55.0)	
Other	176 (74.6)	42 (23.9)	134 (76.1)	

*Poor interrater agreement (29.2%; $\kappa=0.26$); [†] Wrong assignment of COD ($n=157$ [94.0%]) and wrong sequence ($n=10$ [6.0%]); [‡] Poor interrater agreement (25.4%; $\kappa=0.24$); [§] p-values show significance of differences in proportions for erroneously assigned COD.

Summary mortality rates

The all-cause mortality rate among all decedents was 1,086/100,000 population. Noncommunicable diseases contributed to the highest cause-specific mortality (516/100,000 population), followed by GBD I (513/100,000 population) and III (56/100,000 population). Males (81,154/100,000 population) had a higher crude all-cause mortality rate compared to females (1,021/100,000 population). Among decedents aged <15 years at death, the crude all-cause mortality rate was 524/100,000 population, and most deaths were attributed to communicable diseases (397/100,000 population compared to noncommunicable diseases [127/100,000 population]). Among decedents aged ≥15 years at death, males had the highest rate (1,594/100,000 population; females, 1,315/100,000 population), and GBD category II diseases were the leading COD (785/100,000 population compared to GBD I [566/100,000 population] and GBD III [97/100,000 population]). The HIV-associated mortality rate was 312/100,000 population among all decedents. Females of any age (274/100,000 population) had a 20% higher mortality rate than males (224/100,000 population), and deaths that were directly attributed to HIV/AIDS were nearly 40% higher among females (413/100,000 population) than among males (298/100,000 population). The death rate due to HIV/AIDS was greater among persons aged ≥15 years compared to younger individuals (Table 5).

Table 5. Estimated all-cause and cause-specific mortality rates by GBD and HIV disease classifications in Kisumu County, Kenya (2019)

Caption: The table shows mortality rates calculated for all causes of death and due to specific disease conditions per 100,000 population using the estimated mid-year population in Kisumu County, Kenya.

Cause of death	Mortality rate per 100,000 population								
	All			<15 years old			15+ years old		
	M/F*	M	F	M/F*	M	F	M/F*	M	F
<i>All-cause</i>	1,086	1,154	1,021	524	552	495	1,448	1,594	1,315
Group I [†]	513	566	467	397	446	348	566	613	521
Group II [‡]	516	488	532	127	106	148	785	797	760
Group III [§]	56	100	22	0	0	0	97	184	35
<i>HIV</i>									
HIV-associated [¶]	312	224	274	53	40	67	388	362	410
Due to HIV/AIDS [#]	251	298	413	85	81	89	549	455	627

*Male or female; † Group I – Communicable, perinatal, maternal and nutritional conditions including HIV; ‡ Group II – Noncommunicable diseases; § Group III – Injuries; ¶ HIV was listed as a significant cause of death; # UCOD was ascertained as HIV/AIDS.

Discussion

Leading causes of death

In Kisumu County, we found that the HIV/AIDS-related mortality rate is nearly 25%, which is similar to that observed in Abidjan by De Cock et al during the late 1980's [23] and double the rate found in a Nairobi mortality study (12.6%) [24]. In our study, the proportion of deaths attributed to HIV/AIDS was twice the proportion that is regularly reported through CRVS. However, the proportion is likely overestimated in our study because we did not include the DOA group. Prevalence of HIV infection was 23.7% among DOA compared to 31.0% among the hospital-based deaths. Among the 47 counties in Kenya, Kisumu County reported the greatest number of HIV/AIDS-related deaths (14.4% of all HIV/AIDS deaths nationally in 2017) [9], compared to only 2.4% of the current national population [17]. Kisumu County is ranked second in adult HIV prevalence at 17.5% [25], and our finding of high HIV-related mortality rates is consistent with the national HIV prevalence. Though our finding of a high proportion of HIV/AIDS-related deaths likely reflects the complexity of cases in the two referral hospitals, our sample did have wide geographic coverage, including decedents from all over the county. However, the difference in our findings compared to CRVS data could be explained by the extra step of ascertaining UCOD in our study; thus, we had higher sensitivity in identifying HIV/AIDS-attributable mortality. We also tested the cadavers for HIV, and availability of these test results helped us distinguish HIV-related from non-HIV-related deaths with similar clinical presentation.

The proportion of deaths with hypertension as an underlying cause was (9.3%) and greatest among persons aged ≥ 40 years (36/41; 87.8%) for both sexes, which is below the proportions previously reported of 12.3%, [26], and 22.8%, [27], in urban informal settlements in Kenya. Cancer was the fourth leading COD and accounted for a greater proportion of deaths among both sexes. Our findings are consistent with the reports that showed cancer as the third leading COD in Kenya, after infectious diseases and cardiovascular diseases [28], and the second leading COD globally, causing an estimated 9.6 million deaths in 2018 [29]. Additionally, our findings point to an epidemiologic transition underway in Kenyan adults in rural settings, highlighting the increasing importance of preventing non-communicable diseases to decrease adult mortality rates [6,7]. Nonetheless, infectious diseases still contribute to significant mortality in this population and, not surprisingly, most of the deaths among younger decedents were due to communicable diseases [30].

More than a fifth of certified deaths were among infants and among adults aged ≥ 80 years. Mortality rates among the geriatric population were similar to those previously reported in Kenya ($\sim 10\%$), with similar mortality rates for both males and females [9]. Although high mortality rates are expected among the geriatric population, the high proportion of deaths among infants reflects the persistent high infant mortality rates in the Nyanza region, estimated to be 72 deaths/1,000 live births [31]. Possible contributors to this high infant mortality rate are malaria and child and maternal nutrition risk factors [5]. We also observed a higher proportion of deaths attributed to non-communicable diseases among females compared to males.

Although exclusion of police cases and DOA likely disproportionately affected our estimates of violence-related deaths (relatively low overall even for males) and injury-related deaths, deaths due to injuries were still four times higher among males than among females, probably due to greater exposure to poor road safety precautions and/or occupational hazards. The cause-specific mortality rate for deaths caused by injuries (mostly road traffic related) was higher for males than for females. Deaths due to road traffic-related injuries could be decreased, especially among younger men, by training of passengers, drivers, and other road users on safety precautions.

Surprisingly, we did not find injury-related deaths among children. This is in contrast to studies for other resource-limited countries, which have reported high rates of injury-related deaths among children and younger persons [32,33]. Injuries are often reported as UCOD for DOA cadavers. Since we did not capture UCOD for DOA cadavers, it is possible that we missed injury-related childhood deaths. However, in our study, hospital-based deaths had proportionately higher number of decedents aged < 5 years at time of death compared to those DOA (Supplemental Figure), whereas more decedents aged < 70 years at time of death were DOA than hospital-based deaths. Thus, age distribution for DOA compared to hospital-based deaths was similar for most of the decedents aged 5–69 years (Supplemental Figure). In our study, the proportions of deaths due to communicable compared to non-communicable diseases were approaching 1:1, and similar to those previously reported through CRVS for Kisumu County [18]. However, this ratio is different compared to other similar resource-limited settings in which for every two deaths attributed to communicable diseases, there are three attributed to non-communicable diseases [34], indicating that HIV still contributes substantially to the burden of communicable diseases in Kisumu. Other infectious diseases contributed to more deaths among children than among adults.

Stillbirths

We reported a high rate of stillbirths as well as deaths due to perinatal conditions. The high incidence in this setting may be due in part to these referral hospitals attending to complicated pregnancies. These deaths may be related to lack of access to emergency care, during pregnancy, late presentation at health care facilities, and complications during childbirth. In Kenya, only about 18% of pregnant women have at least four ANC visits, and women with one visit within the first 3 months of pregnancy have better pregnancy outcomes than those with only one antenatal clinic visit [35]. Teaching expectant and postpartum women the danger signs of complications during pregnancy and the peripartum period could trigger timely health seeking behavior among women [43] and reduce maternal mortality and perinatal deaths [42]. Though our study lasted for only a few months, our estimated stillbirth rate (2.7%) is higher than the national average (1.3%) among women reporting a pregnancy in the 5 years before the 2014 demographic and health survey [34] but is similar to the 2015 estimate for sub-Saharan Africa (2.9% or 29/1000 live births) [44].

Annualized mortality rates

We found an all-cause mortality rate of 1,086/100,000 in Kisumu that was about twice the national crude death rate average of 551.8/100,000 population for 2015–2020 [4]. Mortality rates have been higher in western Kenya including Kisumu County [5], which is mostly attributed to communicable diseases, especially HIV/AIDS. The rate we found was lower than that reported in a similar setting in neighboring Siaya County (1,446/100,000 population) [40] and is also lower than the 2009 population census estimates of 1,370 deaths/100,000 population [14].

Notified versus ascertained underlying causes of death

Almost three-quarters of notified deaths at JOOTRH and KCRH had an incorrect UCOD in the death notification forms, which were submitted to the CRVS system. The errors were due to either wrong sequencing or wrong assignment, as noted in previous Ministry of Health reports [9]. Incorrect assignment was higher among male decedents compared to female decedents. Better assignment of underlying UCOD was observed for deaths due to HIV/AIDS, and the proportion with errors was higher for immediate compared to underlying COD. We could not determine whether the higher error rate for immediate COD was due to symptomatic presentation, availability of HIV diagnosis, or treatment records in patient charts. Among persons who died of HIV/AIDS, approximately 50% had one or more non-communicable disease documented along the causal pathway as an immediate or intermediate COD. Assignment of the wrong UCOD could be due to various factors. First, the clinician who certified the death may not have seen the patient during

hospitalization and thus may not be familiar with the patient's clinical history. Second, medical records may be unavailable or not reviewed by the certifier due to time constraints imposed by the urgency of completing administrative procedures related to the death.

The very low agreement of ascertained UCOD compared to notified UCOD in our study indicates that mortality statistics that depend wholly on death notifications may be grossly inaccurate. Certification of deaths by personnel who are not trained for that purpose may further compromise the quality of mortality data, which is also compounded by poor documentation. This was reflected in a previous study that found a low vital statistics performance index in Kenya [41]. This index is a composite metric that ranges from 0 to 1 for assessing the quality of data on mortality and COD containing six dimensions: quality of COD reporting, quality of reporting of age and sex of decedents, internal consistency, completeness, level of cause-specific detail, and data availability or timeliness [42]. In 2015, Kenya scored 0 in each of these elements [41]. Completeness, correctness, and order of COD statements among decedents have been noted to be poor in Kenya, with incomplete information and citing mechanisms of death as the most frequent errors [43].

Data contained in death notification forms in Kenya have been found to be of poor quality, with 18.4% containing ill-defined causes (such as those with incomplete descriptions of the cause or with vague descriptions), which is above the acceptable maximum threshold of 10% for all ages, and about a third of death notification forms were either incomplete or submitted without any COD listed [9]. Certification of deaths by clinicians trained on ICD procedures, availability of HIV status at time of certification in settings where HIV is a significant COD, and a thorough scrutiny of medical records before death certification could substantially improve the quality of UCOD information reported to CRVS.

Limitations and assumptions

Our study had several limitations. We used available medical records and post-mortem HIV testing to assign COD; no diagnostic autopsies were performed specifically for this study. Group I communicable diseases include perinatal, maternal and nutrition diseases. However, without post-mortem, there may be no proper differentiation of deaths related to maternal and child health versus communicable diseases for younger decedents. For mortality rate estimates, we assumed that both mortality rates and reporting rates were similar in all calendar months. The study was conducted in public health facilities, and we assumed that the cadavers admitted in JOOTRH and KCRH would be representative of Kisumu County population. Data abstracted from the Kisumu East Civil Registry indicate

that over 75% of deaths occur within health facilities, and about 42% of facility-based deaths are admitted to these two mortuaries. Thus, though facility-based COD statistics may not accurately represent the COD throughout the community, the benefits of an estimation of COD based on facility-based reported deaths outweigh this bias. To mitigate this limitation, we confirmed that the decedents in our study came from all geographical areas of Kisumu County. Since we did not have medical charts for the DOA (one-third of all decedents during our study period), we assumed the distribution of UCOD for those who were DOA was similar to those who died in the hospitals for purposes of calculating mortality rates. These decedents were not selectively admitted to the morgues as a result of death from any specific GBD category. Regardless, homicides and other violent deaths are underrepresented as COD in our study since we did not include the DOA group in our analysis. This bias may be around 3% of total mortality, since the estimated contribution of deaths caused by GBD III category in Kenya is about 8% [46], compared to the 3.8% we found in our analysis.

Conclusions

Kisumu County had similar communicable and non-communicable disease related mortality rates, with HIV contributing to the highest proportion of communicable disease-related deaths. Males have higher rates of injury-related deaths than females, whereas females have higher rates of non-communicable disease-related deaths. Although most deaths are preventable, our findings suggest that a holistic approach rather than focusing on one GBD category could help prevent deaths in Kisumu County. HIV prevention, improved viral load suppression among HIV-positive persons, and improved uptake of vaccines could help decrease communicable and non-communicable disease-related deaths, and prevention and treatment of hypertension and increased screening and community awareness, including advocating for behavior changes such as cessation of smoking, could help decrease non-communicable disease-related deaths.

Vital statistics reporting for hospital-based deaths could be improved by training medical officers on correct death certification, including proper sequencing using ICD10 rules. For deaths that occur within the community, training the chiefs and sub-chiefs who are responsible for collecting verbal autopsy data could help improve mortality surveillance, as recently reported in Uganda [45]. Routine review of patient charts and data quality reviews by trained medical experts before notification of death could improve the quality of COD reported to CRVS and

enhance the utility of such reports for planning. Regular mortality case review meetings may offer a forum to share experiences and ensure that UCOD are documented appropriately.

Our study demonstrates the feasibility of determining probable COD and providing more precise cause-specific mortality rates without using expensive post-mortem procedures. Our approach can be used in other limited-resource settings, particularly regions with high HIV burden, to help evaluate the impact of HIV care and treatment programs and to distinguish deaths caused by HIV/AIDS from other disparate causes and identify epidemiologic transitions.

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Author contributions

AW was a co-investigator, developed the protocol, conducted study training and field supervision, reviewed the literature, conceived of the paper, analyzed and interpreted the data, and drafted the manuscript. DO was the principal investigator, both he and LN (a co-investigator) developed the protocol, provided field supervision, monitored the study, and helped with interpreting the results. AS and PKM provided data management and analysis support. WW, SS, EO, EN, SWM, JK, and TM collaborated in the study and provided supervision. KDC and PWY helped to conceptualize the Nairobi HIV-associated mortality surveillance study that provided the backbone on which the Kisumu study was designed. EAR and PWY were coinvestigators and provided additional technical input during the writing of the manuscript. MABS and KDC edited the manuscript. All authors reviewed and commented on successive drafts and approved the final version of the manuscript.

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Supplemental figure

Supplemental figure. Age distribution of deaths by type of cadavers admitted to the two morgues at two referral hospitals in Kisumu County, 2019

Caption: The hospital-based deaths had a higher proportion of children aged <5 years than dead on arrival (DOA) cadavers. Age distribution was similar for the rest of the cadavers, except for the DOA group, which had proportionately more cadavers aged ≥70 years than the hospital-based group.

Chapter 9

General discussion

General discussion

This thesis presents an overview of the changing epidemiology of human immunodeficiency virus (HIV) in Kenya, with a focus on issues with measurement and modeling of epidemic and program outcomes. HIV presents various challenges to effective measurement and control, which help explain its persistence as a public health threat 39 years after the discovery of what would later be referred to as acquired immune deficiency syndrome (AIDS). These include the frequently asymptomatic or nonspecific nature of initial HIV infection, slow disease progression that can take years before clinical manifestation, and chronic, life-long infection, as well as the stigma associated with an incurable sexually-transmitted infection. After providing background on HIV epidemiology and surveillance in the introduction, this thesis describes the epidemiology of HIV in Kenya through a series of studies that together span the cascade of HIV care from infection to death.

In this final chapter, I discuss what was already known alongside what these studies add to the knowledge of HIV disease surveillance and control. Finally, I discuss implications on future research and control efforts for HIV in Kenya, East Africa and globally.

Chapter 2. HIV incidence in western Kenya during scale-up of antiretroviral therapy and voluntary medical male circumcision: a population-based cohort analysis

What was known

Based on HIV Prevention Trials Network (HPTN) 052, the clinical trial which found a minimum 96% reduction in transmission of HIV infection in serodiscordant couples due to antiretroviral treatment (ART) use (1), the scale-up of early ART was expected to lead to reduced HIV incidence by suppressing viral load in patients on treatment and reducing the risk of onward transmission. Furthermore, prior studies had demonstrated that voluntary medical male circumcision (VMMC) could reduce the risk of HIV acquisition in males by approximately 60% (2–4). Models of these two interventions' scale-up led to predictions that their widespread implementation in sub-Saharan Africa would lead to significant reductions in population-level incidence (5,6).

From 2007 onwards, VMMC had been scaled up in traditionally non-circumcising ethnic groups throughout sub-Saharan Africa, including in Kenya. In Kenya, over 1.4 million circumcisions were conducted from 2009–16 (7), and estimates of coverage reached 100% in some age bands in priority counties in western Kenya (8).

Antiretroviral treatment coverage had also been widely scaled up, reaching 424,000 patients in the six counties of the former Nyanza province in western Kenya by the end of 2017 (9). While national surveys indicated there might have been a modest decrease in HIV incidence among adults at the national level from 2007 to 2012, these studies could not provide reliable sub-national incidence estimates (10).

What this thesis adds

The health demographic and surveillance system located in Gem sub-county, Siaya County, western Kenya, provides a platform for assessing trends in HIV incidence and coverage of HIV interventions. Although the system does not include HIV testing or behavioral questions as part of the underlying demographic census, a nested home-based counseling and testing program linked to the demographic platform at the individual level allows for longitudinally constructing participant profiles including change in HIV serostatus over time, which in turn allows for estimation of HIV incidence within the population.

This study found that HIV incidence had fallen significantly from 2010 to 2016. It also found that prevalence among 15–24 year olds had fallen, consistent with a reduction in incidence. Nonetheless, the incidence at the end of the period was still well above elimination targets, indicating that very high levels of both VMMC and ART may be required to reach incidence targets in the absence of other major changes in HIV prevention behaviors. The study demonstrated the value of direct HIV incidence estimation in high burden populations that are disproportionately affected by HIV and will thus have a disproportionate influence on the control of the epidemic at the national level. Such studies can also help relate changes in incidence with scale-up of prevention interventions that may not be apparent in national incidence surveillance.

Chapter 3. Evolution of sub-national HIV estimates for a high-HIV-burden region in Kenya

What was known

Global health initiatives are increasingly evaluated based on modeled estimates of disease burden (11,12). HIV program targets have been refined to greater and greater levels of specificity over the years. The President's Emergency Plan for AIDS Relief (PEPFAR) country operations plan guidance for fiscal year 2019 (13) required dividing targets into five-year age groups by sex, resulting in 24 age-sex bands and setting targets for each of these bands per health facility. In Kenya, PEPFAR reported supporting 2,865 health facilities with patients currently receiving ART in September 2019, suggesting at least 68,760 targets were set just

for this indicator in this year in Kenya alone. In 2020, PEPFAR's guidance relaxed this targeting requirement to require just setting the 24 age-sex band targets at the sub-national level, resulting in up to 960 separate targets for patients receiving ART across the 40 Kenyan counties that PEPFAR will support in 2021, but the age/sex/site reporting requirement remains.

While modeling approaches are continuously refined, the primary data used to develop the models that inform these increasingly precise targets are relatively stable over time, consisting of national seroprevalence surveys every five years, data on numbers of beneficiaries, and prevalence in defined populations such as pregnant women attending antenatal care (ANC). Hence, in addition to identifying new sources of information to refine estimates, continually improving the models themselves and reconciling them with other information sources is of utmost importance.

According to official HIV estimates for Kenya based on the Spectrum model, an estimated 1.5 million people were living with HIV in 2017 (9). The Nyanza region in western Kenya, which borders Lake Victoria, accounted for 38% of prevalent HIV infections and a similar proportion of national unmet need for treatment in 2015. However, other program data were consistent with much higher treatment coverage. For example, the yield of new positives in HIV testing programs in the region was relatively low (about 1%), whereas adult HIV prevalence was estimated at 16–21% throughout the region (14). This gap between testing yield and HIV prevalence suggests that most HIV-infected persons may have already been identified.

What this thesis adds

The Spectrum suite of mathematical models is updated regularly to respond to changing requirements and knowledge about HIV transmission dynamics (15). This study summarizes the model's application to Kenya with a focus on sub-national estimation and how these estimates evolved through three cycles of models from 2015–17. The paper shows that improving the fit of the model to available demographic data in Nyanza, where out-migration of working-age adults is high, and inclusion of routine ANC seroprevalence data in the model led to more plausible fits. The paper also compared the trends in routine ANC to a small-area population-based cohort within the region of interest.

The paper highlights the sensitivity of model-based estimates to how the models are applied and adjusted, and thus the importance of triangulating their output to local data sources, where available. It also showed that rather than having moderate to low

performance against the treatment cascade compared to the rest of the country, the performance was likely to be above average over the period of study. The 2018 Kenya Population-based HIV Impact Assessment (KENPHIA), released after this study, found ART coverage estimates in this region that validated these findings (16).

Chapter 4. Equity of antiretroviral treatment use in high HIV burden countries: Analyses of data from nationally-representative surveys in Kenya and South Africa

What was known

The Fast-Track 90-90-90 targets, announced by the Joint United Nations Programme on HIV/AIDS (UNAIDS) on World AIDS Day 2014, refocused global efforts on rapidly achieving a level of program coverage that could lead to epidemic control, reducing new infections while also preventing deaths among people living with HIV (17). UNAIDS projected that annual HIV infections and AIDS-related deaths would fall by 90% by 2030, and 21 million AIDS-related deaths and 28 million new infections would be averted by 2030 through rapid scale-up of treatment versus maintaining 2013 coverage levels of 38% among adults and 24% among children. However, there were large disparities in ART access within and across regions, and it was not known how easily disadvantaged populations could be reached with treatment. While global initiatives held promise to remove supply-side barriers to antiretrovirals, questions remained about supply-side issues that could block efforts to expand ART rapidly to reach high coverage levels. Surveys in Kenya and South Africa had included questions on ART status and testing for antiretroviral (ARV) exposure, which allowed for estimation of ART coverage by demographic and other factors in these countries and exploration of equity in ART access and the evolving picture of ARV access in two higher-burden countries in sub-Saharan Africa.

What this thesis adds

The study estimated both changes in ART use over five years of national program expansion and looked at patterns of ART use by sociodemographic factors to assess equity of access. The study found significant increases in ART use from 2007–12 and 2008–12 in Kenya and South Africa, respectively. In Kenya, ART coverage among all HIV-infected persons increased from 29.3% to 42.5% from 2007 to 2012, while in South Africa, it increased from 17.3% to 30.3% from 2008 to 2012. Although in South Africa it seemed disparities in ART access had decreased over the period, there was evidence of increasing disparities by residency and household wealth in Kenya. Younger age was strongly associated with ART non-use in both countries, as was illicit drug use, reaffirming the need to ensure young people and key populations have access to testing and treatment.

Chapter 5. Use of viral load to improve survey estimates of known HIV-positive status and antiretroviral treatment coverage

What was known

Estimating program coverage in terms of the proportion of people living with HIV who are infected and accessing treatment relies on population-based survey estimates in high HIV-burden countries due to the feasibility of obtaining nationally-representative population samples and the lack of robust case reporting systems in these countries. However, like other self-reported information on sensitive health topics, self-reported indicators of HIV status are likely subject to social desirability and recall biases (18). Blood-based tests for the presence of antiretroviral drugs are highly specific and sensitive for recent ARV drug exposure (19), thus testing blood for the presence of ARVs during surveys can improve estimates, though it imposes increased costs, complexity and time from collection to results.

While those on ART should generally have suppressed viral loads, it is not clear to what degree undetectable viral load (UVL) could be used as a proxy for ART use to adjust estimates of ART coverage and knowledge of status. Furthermore, as countries approach the 90-90-90 and 95-95-95 targets, quickly obtaining precise estimates becomes critical; hence leveraging additional biomarkers to increase precision, reduce cost or turnaround time is worth exploration.

What this thesis adds

This study used data collected in the 2012 Kenya AIDS Indicator Survey to analyze the impact of adjustments to self-reported HIV status using biomarkers for ARV exposure and viral load suppression separately and in combination. The study showed that upward adjustments of approximately 10 percentage points with ARV or 15 percentage points with UVL (17 points with both) versus self-report alone were seen in this survey. The UVL adjustments were generally higher than ARV adjustments. Adjustments were similar across demographic bands except for young people who saw greater adjustments for both ARV and UVL versus self-report.

The use of UVL is subject to limitations. Elite controllers would also have suppressed viral load in the absence of treatment and thus would result in biased estimates when UVL is used to adjust HIV status; however, the practical importance of this is limited by the rarity of elite control. Undetectable viral load may also capture some individuals who are ‘on ART’ from a program perspective but did not have detectable ARV exposure, for example, if they are on a less common regimen

not tested for in the survey ARV panel, or if their poor adherence leads to drug levels falling below the level of detection. Thus, a combined method using both biomarkers may be the most promising approach, where the inclusion of ARV testing is feasible.

Chapters 6-8. HIV-associated mortality

What was known

Before the advent of effective treatment, HIV was responsible for significant mortality in countries with a high prevalence of HIV infection, leading to observable demographic changes and readily apparent increases in hospitalization and death due to AIDS. The widespread availability of ARVs has changed that, but most people living with HIV are neither followed through prospective surveillance nor covered by population registries, which would ensure their cause of death is linked to their HIV status. Improved vital registration, unique identification, and individual case-based HIV surveillance systems should eventually allow for a more comprehensive assessment of death among people living with HIV. In the meantime, mortuary-based HIV surveillance can provide useful information about avoidable causes of death among people living with HIV. Also, HIV prevalence among deaths can help improve model-based epidemic estimates. Studies in Botswana, Côte d'Ivoire, Mozambique and the United States have all assessed HIV in mortuaries, though focusing on different research questions, populations and utilizing different methods (20–23).

What this thesis adds

Given the relatively high estimated adult ART coverage at the time of the Nairobi survey (74% in 2015), the Spectrum mathematical model predicted that 11.4% of deaths among adults aged 15+ would be HIV-positive. The adjusted HIV positivity for adult deaths in Nairobi from the study was 20.9% (Chapter 6). The HIV prevalence differed significantly between the two study mortuaries; 12.6% at the city mortuary, which serves smaller health facilities and receives the majority of 'police cases,' and 23.2% at Kenyatta National Hospital, which is a national referral hospital seeing many complex medical cases. Documentation of HIV status was poor among the HIV-infected deceased, with over half lacking evidence of diagnosis, and half of those with a known HIV-positive status being diagnosed during the hospitalization preceding death. Evidence of ART use was also limited—of those with known HIV status at time of death, approximately one in four had unknown treatment status, and one in four were not on treatment. This likely reflects both the increased risk of mortality among those who are not accessing HIV diagnosis and treatment services as well as the challenges of integrating demographic and health information across a

fragmented health system. Despite ART restoring near-normal life expectancy, and the relatively high ART coverage, the standardized mortality ratio (SMR) among the HIV infected versus the HIV uninfected was about four, with a population attributable fraction of 0.16, suggesting significant avoidable adult mortality in Nairobi (Chapter 7).

The Kisumu study, conducted in a higher-HIV-prevalence setting, extended the Nairobi study in several important ways: 1) all ages were included rather than just adults and adolescents aged 15 years and older, 2) oral fluid testing was piloted, and 3) where available, existing HIV status information was utilized. The study found that nearly a quarter (23.1%) of deaths of all ages were due to HIV/AIDS. The HIV mortality rate was 251 per 100,000 population. The study also found high overall rates of mortality due to non-communicable disease (516 per 100,000) and communicable, perinatal, maternal and nutritional causes (513 per 100,000 population), providing evidence that western Kenya may be experiencing a 'stalled' epidemiological transition from infectious to non-infectious causes of death. There were significant discrepancies between the underlying cause of death notified by the health system and that established using study procedures (Chapter 8).

Implications of this thesis for measurement and control of HIV

Modeling studies (24) followed by clinical trials which showed a large and significant impact of biomedical prevention (1,25) resulted in a large push to expand treatment and VMMC in high HIV-prevalence countries. Subsequent large community trials have shown that it is possible to obtain high levels of HIV diagnosis and ART coverage with concomitant reductions in the HIV incidence of between 20–30% over three years (26). In Kenya, the 2018 KENPHIA found 72% adult population viral suppression, indistinguishable from the UNAIDS target of 73%, yet adult HIV incidence was 0.14%, more than an order of magnitude greater than the elimination target of 1 per 10,000. While the further expansion of diagnosis and treatment of people living with HIV should further reduce HIV transmission, other complementary approaches to prevention are still required. Treating HIV as a traditional sexually transmitted infection, with case reporting and contact tracing are also necessary but have only recently begun to be scaled up (27). Applying research methods such as testing for recent HIV infection and phylogenetic analysis to identify clusters of transmission for disease control may also be beneficial (28,29) and need to be evaluated in different epidemic settings. Population mobility and traceability are other challenges in many high-prevalence settings, including in Kenya. Fragmented health and development programs in

the absence of unique identifiers that have difficulty linking interventions to individuals across space and time pose severe challenges to measuring outcomes and providing comprehensive services (30).

Population-based surveys will continue to be essential tools for HIV surveillance for the foreseeable future. Better use of available biomarkers should increase the precision of estimates of knowledge of HIV status and ART use. Interpretation of viral load-adjusted estimates would benefit from better characterization of the prevalence of elite control in countries with generalized epidemics and with different mixes of circulating HIV subtypes. While the validity of survey laboratory measures has been an ongoing topic of research (31–33), less attention has been paid to ensuring the validity of self-reported questionnaire data, for example, by following guidelines on question development (34). AIDS indicator survey questions are often derived from expert opinion, historical use or international norms rather than behavioral research into their validity. There is ample evidence that researchers' and respondents' understanding of questions often differs, to the detriment of the interpretation of results (35). Additional effort to ensure the validity of key self-reported measures such as knowledge of HIV-positive status and time since diagnosis is needed. Despite the large investments in population-based surveys to measure knowledge of HIV status among people living with HIV, UNAIDS relies on the indirect estimation of this indicator (36), a tacit acknowledgment of this reality.

While population-based surveys continue to be critical for monitoring progress in HIV control, in countries such as Kenya with decreasing HIV prevalence and incidence recorded over time, it will be increasingly difficult to obtain precise measures of HIV cascade indicators with national population surveys, more so for subnational or subgroup estimates needed to target interventions. Furthermore, surveys are based on probabilistic sampling; hence they do not identify a significant number of individuals in need of intervention due to recent infection, unknown HIV status, ART non-use or unsuppressed viral load. Strengthening unique identifiers and integrated health information systems that can support longitudinal HIV case surveillance (30), on which recent infection surveillance and other approaches can be layered, will be increasingly important.

In order to know whether ART programs are working as designed, more routine measurement of mortality among people living with HIV is needed. Progress on this front must proceed along two complementary avenues, a) ensuring the HIV status and cause of all deaths is determined and reported, and b) ensuring the ability to detect and report death among all people living with HIV. Furthermore,

surveillance studies can and should be used to assess the burden of HIV mortality and gaps in diagnosis and treatment among deaths admitted to mortuaries. Novel minimally-invasive approaches, such as oral fluid sampling for HIV testing of decedents, may have a role to play as well.

Recommendations

While universal test and treat (UTT) trials demonstrated that universal testing and treatment of those diagnosed are both possible in high-HIV-burden settings, the relatively modest decreases in 3-year HIV incidence suggest that a UTT strategy will not be enough to rapidly achieve fewer new infections per year than deaths among those who are HIV-infected. Moreover, concerns about the cost of universal testing have limited its use in practice. Thus, novel (and traditional) prevention strategies beyond UTT tailored to the population are still needed.

The rapid scaling of traditional public health approaches such as contact tracing and partner notification shows promise, with the proportion of contacts that are newly positive in these programs generally greater than that seen with other testing modalities (37). These approaches should be expanded for HIV control, and their effectiveness should be evaluated comprehensively to see if their introduction results in more timely diagnosis of infection and prevention of onward transmission. In addition to the scale-up of case identification techniques, testing for recent infection and phylogenetic analysis of viral specimens from those newly diagnosed may also be useful tools for identifying clusters and controlling onward transmission.

Knowledge of status is ascertained in population-based surveys through self-report. More work can be done to ensure the validity of this measure. In addition, viral load is now routinely measured in population-based HIV surveys. This marker can improve estimates of knowledge of status and ART use by adjusting for those who do not report their known HIV status but are likely to know their status due to their suppressed viral load.

To monitor the true impact of treatment on mortality, mortality should be added to HIV surveillance systems. In addition to standardized reporting of mortality among patient cohorts, novel, minimally invasive methods such as oral fluid testing should be further assessed and potentially introduced in HIV mortality surveillance systems to help determine HIV status among decedents of unknown HIV status at the time of death.

Population-based surveys are useful tools but will never replace case surveillance in terms of timeliness, precision, and direct applicability to programs. Surveillance systems must be developed to identify and control HIV transmission and manage the quality of the cascade of care in the future. For these systems to work well, we must continue to develop and strengthen unique identifiers and methods for coping with the lack of robust universal national identifiers.

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Appendices

Summary

Human immunodeficiency virus (HIV) presents various challenges to effective measurement and control, which help explain its persistence as a public health threat nearly 40 years after the discovery of what would later be referred to as acquired immune deficiency syndrome (AIDS). These include the frequently asymptomatic or nonspecific nature of initial HIV infection, slow disease progression that can take years before clinical manifestation, and chronic, life-long infection, as well as the stigma associated with an incurable sexually transmitted infection. CD4+ T-cell counts have been used to stage HIV disease progression; later, viral load testing based on the polymerase chain reaction became the preferred way to monitor treatment failure. This thesis presents an overview of the epidemiology of HIV in Kenya, with a focus on issues with measurement and modeling of incidence, mortality and indicators of program achievement.

Chapter 1 provides an overview of virological, clinical and surveillance aspects of HIV as well as a historical summary of global attempts to monitor and control the epidemic. A lentivirus of the *retroviridae* family, HIV has expanded worldwide over nearly 40 years since its discovery, with 38 million people infected in 2019. New HIV infections peaked globally in 1998 at 2.8 million per year; In 2019, 38 million people were living with HIV, with over half of those infected residing in East and southern Africa. In the same year, there were an estimated 690 thousand deaths due to HIV. In 2014, the Joint United Nations Programme on HIV/AIDS (UNAIDS) launched the Fast-Track approach to ensure 90% of those who are HIV infected know their status, 90% of those who know their HIV-positive status are on antiretroviral treatment, and 90% of those on treatment are virally suppressed by 2020, increasing to 95-95-95 by 2030 as part of the Sustainable Development Goal to end HIV as a public health threat by 2030.

HIV can be monitored through a testing and treatment cascade that starts with diagnosis, followed by antiretroviral treatment (ART) initiation, and finally, viral suppression. These three stages are embodied in the UNAIDS 90-90-90 targets. Cohort analyses can monitor the proportion of patients that make it to subsequent stages, hence providing an indicator of program success. However, these indicators can also be monitored cross-sectionally, which provides a more rapid assessment subject to limitations. Longer-term measures of program impact, and hence epidemic control, include HIV incidence and mortality, both of which present unique challenges. In addition to the traditional cohort-based approaches to

measuring incidence, various modeling approaches and biomarker approaches have been developed. Estimating HIV mortality requires either following HIV-infected persons until death or ascertaining HIV status at the time of death, combined with determining the underlying cause of death. All of these tasks present challenges such as loss to follow-up of patients on treatment and lack of training of clinicians on death certification, and lack of standardization of cause of death data. Ultimately one hopes to achieve a state of epidemic control, which has been defined multiply in terms of reductions in incidence and mortality or reductions in the ratio of new infections to deaths or new infections to prevalent infections.

Tracking the AIDS epidemic has evolved from disease-focused AIDS case reporting to sentinel antenatal clinic (ANC) HIV surveillance, followed by population-based behavioral and serological surveys, to HIV case surveillance. These surveys have evolved from identifying incident disease and prevalent infection to measuring the cascade of care among the HIV-infected population, as treatment has become a greater focus for preventing mortality and onward transmission.

Chapter 2 presented trends in HIV incidence in western Kenya, a high HIV prevalence region, during a period of rapid expansion of HIV treatment and voluntary medical male circumcision, the two most effective biomedical forms of HIV prevention. The study demonstrated the value of estimating HIV incidence in high-burden populations that are both disproportionately affected by HIV and will thus have a disproportionate influence on the control of the epidemic at the national level. Chapter 3 summarized the Spectrum HIV epidemic model's application to Kenya, with a focus on sub-national estimation using ancillary tools, and how these estimates evolved through three cycles of models from 2015–17. The paper showed that improving the fit of the model to available demographic data in Nyanza, where out-migration of working-age adults is high, and the inclusion of routine ANC seroprevalence data in the model, led to more plausible fits. The paper also compared the trends in routine ANC to a small-area population-based cohort within the region of interest. Chapter 4 investigated trends in ART use in Kenya and South Africa between 2007 and 2012. The study found significant increases in ART use from 2007–12 and 2008–12 in Kenya and South Africa, respectively. While in South Africa it seemed disparities in ART access had decreased over the period, in Kenya there was evidence of increasing disparities by residency and household wealth. Younger age was strongly associated with ART non-use in both countries, as was drug use, reaffirming the need to ensure young people and key populations have access to testing and treatment. Chapter 5 used data collected in the 2012 Kenya AIDS Indicator Survey to analyze the impact of

adjustments to self-reported HIV status using biomarkers for ARV exposure and viral load suppression, separately and in combination. The study showed that in this survey, adjustments of approximately 10 percentage points with antiretrovirals or 15 percentage points with undetectable viral load (17 points with both) versus self-report alone were seen. The undetectable viral load adjustments were generally higher than antiretroviral adjustments. The study described in Chapters 6 and 7 was conducted in mortuaries in Nairobi, Kenya, in early 2015. The adjusted HIV positivity for adult deaths in Nairobi from the study was 20.9%, higher than predicted from models. Documentation of HIV status was poor among the HIV-infected deceased, with over half lacking evidence of diagnosis. Half of those with known HIV-positive status were diagnosed during hospitalization preceding death. Evidence of ART use was also limited—among those diagnosed prior to death, approximately one in four had unknown treatment status, and one in four were not on treatment. In the higher HIV-prevalence region of Kisumu, 23.1% of deaths of all ages were due to HIV/AIDS, with an HIV mortality rate of 251 per 100,000 population. There were significant discrepancies between the underlying cause of death notified by the health system and the underlying cause established using study procedures.

Key recommendations for HIV epidemic monitoring and control

1. Given that universal test and treat will not be enough to rapidly suppress incidence to a point where epidemic control is reached, a new focus on a diversity of prevention strategies is needed to more rapidly reduce the number of new infections below the number of deaths to people living with HIV
2. Traditional public health approaches such as contact tracing and partner notification should be expanded for HIV control, and their effectiveness should be evaluated
3. The usefulness of recency testing and phylogenetic analysis for routine surveillance programs to quickly identify and control clusters of new infection should be assessed
4. More research into the accurate ascertainment of self-reported knowledge of HIV-positive status is needed given its importance as the first step in the testing and treatment cascade
5. Viral load measures should be used as an adjunct biomarker to improve (or simplify) survey estimates of ART coverage
6. Routine mortality surveillance should be implemented in order to monitor the real impact of treatment on morbidity and mortality
7. Novel, minimally invasive methods such as oral fluid testing should be further assessed and potentially introduced in HIV mortality surveillance systems
8. Surveys will never replace the need for HIV case surveillance. Surveillance systems should be developed to identify and control HIV transmission and manage the quality of care along the cascade.
9. Continued development and strengthening of unique identifiers and methods for coping with the lack of robust unique identifiers to support case surveillance are required

Dutch summary

Het meten van hiv-incidentie, mortaliteit en de cascade van hiv-zorg in Kenia

Het humaan immunodeficiëntievirus (HIV) zorgt voor verschillende uitdagingen ten opzichte van een effectieve meting en beheersing; dit verklaart de hardnekkigheid de bedreiging die het na bijna 40 jaar sinds de ontdekking voor de volksgezondheid is en wat later als het Acquired Immune Deficiency Syndrome (AIDS) bekend zou worden. Dit zijn onder meer de regelmatig a-symptomatische of niet-specifieke aard van de eerst HIV-infectie, de langzame voortgang van de ziekte die jaren kan duren voordat er zich een klinische manifestatie voordoet, en chronische levenslange infectie en ook het stigma geassocieerd met een ongeneeslijk seksueel overdraagbare infectie. Er werden tellingen van CD4+ T-cel gebruikt om de voortgang van de HIV-ziekte te ensceneren; later kreeg het testen van de virale belasting gebaseerd op de polymerase-kettingreactie de voorkeur om het mislukken van behandelingen te monitoren. Deze thesis bevat een overzicht van de epidemiologie van HIV in Kenia, gefocust op de problemen met meten en het modelleren van incidentie, mortaliteit en indicatoren van de prestaties van het programma.

Hoofdstuk 1 bevat een overzicht van de virologische, klinische en surveillance aspecten van HIV en ook een historische samenvatting van wereldwijde pogingen om de epidemie te monitoren en te beheersen. Als lentivirus van de retroviridae-familie, heeft HIV zich de afgelopen 40 jaar sinds haar ontdekking wereldwijd verspreidt, en heeft het 38 miljoen mensen geïnfecteerd in 2019. Nieuw HIV-infecties bereikte wereldwijd een piek in 1998 met 2,8 miljoen per jaar; in 2019 waren er 38 miljoen mensen met HIV, waarvan meer dan de helft van de geïnfecteerden in Oost- en Zuidelijk Afrika leven. In dat jaar zijn er naar schatting 690 duizend mensen overleden aan HIV. In 2014 lanceerde de Joint United Nations Programme on HIV/AIDS (UNAIDS) de Fast-Track benadering om ervoor te zorgen dat 90% van hen die met HIV zijn geïnfecteerd hun status te weten zouden komen, en dat 90% van hen die weten van hun HIV-positieve status een antiretrovirale behandeling krijgen, en dat 90% van hen die deze behandeling krijgen viraal onderdrukt zijn tegen 2020, toenemend tot 95-95-95 tegen 2030 als onderdeel van het Sustainable Development Goal om HIV tegen 2030 als bedreiging voor de volksgezondheid te elimineren.

HIV kan worden gemonitord door middel van een cascade van testen en behandelingen die begint met een diagnose gevolgd door een antiretrovirale behandeling (ART), en uiteindelijk, virale onderdrukking. Deze drie fasen worden belichaamd in de UNAIDS 90-90-90 doelen. Analyse in cohort kan het aandeel patiënten die de volgende fasen halen monitoren, en derhalve een indicatie geven van het succes van het programma. Deze indicatoren kunnen echter ook in meerdere secties worden gemonitord waardoor er een snellere schatting onderhevig aan beperkingen wordt gegenereerd. Metingen op de langere termijn van de impact van het programma, en dus de beheersing van de epidemie zijn inclusief HIV-incidentie en mortaliteit, waarvan beide unieke uitdagingen bieden. Naast de traditionele op groepsonderzoeken gebaseerde benaderingen om incidenties te meten, zijn er verschillende benaderingen qua modellering en benaderingen qua biomarkers ontwikkeld. Voor het schatten van de HIV-mortaliteit is het volgen van met HIV geïnfecteerde personen tot overlijden of het vaststellen van de HIV-status bij het overlijden nodig, gecombineerd met het vaststellen van de onderliggende doodsoorzaak. Al deze taken brengen hun eigen moeilijkheden met zich mee zoals het verlies van follow-up patiënten die een behandeling ondergaan en een gebrek aan training van artsen op het gebied van het maken van overlijdensverklaringen, en een gebrekkig standaardisatie van de data van de doodsoorzaak. Uiteindelijk hoopt men een toestand te bereiken waarin de epidemie onder controle is gebracht en welke in meerdere reducties in incidentie en mortaliteit is gedefinieerd of in reducties in de ratio van nieuwe infecties ten opzichte van overlijdens of nieuwe infecties ten opzichte van heersende infecties.

Het volgen van de AIDS-epidemie heeft zich ontwikkeld van op ziekte gefocuste AIDS casusmeldingen tot volledige antenatale zorg (ANC) HIV-surveillance, gevolgd door op de bevolking gebaseerd gedrag en serologische onderzoeken tot HIV-casus-surveillance. Deze onderzoeken hebben zich ontwikkeld van het identificeren van incidentziekte en heersende infectie tot het meten van de cascade aan zorg onder de door HIV geïnfecteerde bevolking, aangezien er meer gefocust wordt op behandeling ter voorkoming van mortaliteit en verdere transmissie.

In hoofdstuk 2 worden trends in HIV-incidentie in westelijk Kenia, een regio waar HIV erg heerst, beschreven gedurende een periode van snelle uitbreiding van de HIV-behandeling en vrijwillige medische besnijden van mannen, de twee meest effectieve biomedische vormen voor het voorkomen van HIV. Het onderzoek toonde de waarde van het schatten van HIV-incidentie in zwaar getroffen bevolkingen aan die buitenproportioneel getroffen zijn door HIV en dus een buitenproportionele invloed hebben op het onder controle brengen van de epidemie op nationaal niveau.

Hoofdstuk 3 bevat een samenvatting van het toepassen van het model van de Spectrum HIV-epidemie in Kenia, en is daarbij gefocust op subnationale schatting met behulp van aanvullende middelen en hoe deze schattingen zich ontwikkelden door de drie modelcycli in de periode van 2015-17. Het onderzoek toonde aan dat het verbeteren van de aansluiting van het model op de beschikbare demografische data in Nyanza, waar de emigratie van volwassenen in de werkzame leeftijd hoog is, en het meenemen van routine ANC seroprevalentie data in het model, tot geloofwaardigere aansluitingen leidden. Het onderzoek vergeleek ook trends in routine ANC met bevolkingsonderzoek in een klein gebied binnen de regio die werd onderzocht. In hoofdstuk 4 worden trends in het gebruik van ART in Kenia en Zuid-Afrika tussen 2007 en 2012 onderzocht. Het onderzoek ontdekte significante toenames in het gebruik van ART tussen 2007-12 en 2008-12 in respectievelijk Kenia en Zuid-Afrika. Hoewel het erop leek dat de discrepanties in het gebruik van ART gedurende de periode in Zuid-Afrika was afgenomen, was er bewijs van een toenemende discrepantie per residentie en huishoudelijke welvaart in Kenia. In beide landen werd de jongere leeftijd sterk geassocieerd met ART niet-gebruik, net als het gebruik van drugs, waardoor de noodzaak werd bevestigd om jonge mensen en belangrijke bevolkingsgroepen toegang te laten hebben tot testen en behandeling. In hoofdstuk 5 staat data die werd verzameld tijdens de Kenya AIDS Indicator Survey uit 2012 om de impact van aanpassingen bij zelfgerapporteerde HIV-status te analyseren met behulp van biomarkers voor blootstelling aan ARV en onderdrukking van virale belasting, zowel apart als in combinatie. Het onderzoek toonde aan dat in dit onderzoek aanpassingen van ongeveer 10 procentpunten met antiretroviralen of 15 procentpunten met niet vast te stellen virale belasting (17 punten bij beide) versus zelfrapportage werden waargenomen. De aanpassingen van de niet vast te stellen virale belastingen waren in het algemeen hoger dan de antiretrovirale aanpassingen. Het onderzoek dat wordt beschreven in hoofdstukken 6 en 7 werd begin 2015 uitgevoerd in mortuaria in Nairobi, Kenia. Uit het onderzoek bleek dat de aangepaste HIV-positiviteit voor overleden volwassenen in Nairobi 20,9% hoger was dan werd voorspeld uit de modellen. Documentatie over de HIV-status was gebrekkig onder de met HIV geïnfecteerde overledenen, waarbij bij meer dan de helft bewijs ontbrak van een diagnose. Bij de helft van hen waarvan men wist dat ze HIV-positief waren werd de diagnose vastgesteld tijdens het verblijf in het ziekenhuis voor het overlijden. Bewijs van het gebruik van ART was eveneens beperkt - bij ongeveer 1 op 4 was de status van de behandeling onbekend, en 1 op 4 onderging geen behandeling. In de regio Kisumu met een hogere HIV-gehalte, was 23,1% van alle overledenen van alle leeftijden het gevolg van HIV/AIDS, met een HIV-mortaliteitverhouding van 251 per 100.000 inwoners. Er waren significante discrepanties tussen de onderliggende doodsoorzaak gemeld door het zorgsysteem en de onderliggende oorzaak vastgesteld door onderzoeksprocedures.

Belangrijke aanbevelingen voor het monitoren en beheersen van een HIV-epidemie.

1. Gezien het feit dat universeel testen en behandelen niet voldoende zullen zijn om incidentie snel te onderdrukken tot een punt waar beheersing van de epidemie wordt bereikt, is een nieuwe focus op verschillende preventiestrategieën nodig om sneller het aantal nieuwe infecties onder het aantal overlijdens ten opzichte van mensen die met HIV leven te reduceren.
2. Traditionele benaderingen met betrekking tot de volksgezondheid zoals het volgen van contacten en het inlichten van de partner dienen eveneens controle over HIV te omvatten en hun effectiviteit dient te worden geëvalueerd.
3. Het nut van recent testen en fylogenetische analyse voor routine surveillanceprogramma's om snel clusters van nieuwe infecties te identificeren en beheersen dienen te worden geëvalueerd.
4. Meer onderzoek naar het accuraat vaststellen van zelfgerapporteerde kennis van HIV-positieve status is nodig gezien het belang ervan als de eerste stap in de cascade van het testen en behandelen.
5. Metingen van virale belasting dienen te worden gebruik als adjunct biomarkering om de schattingen van onderzoeken naar de dekking van ART te verbeteren (of te vereenvoudigen).
6. Surveillance met betrekking tot de routine mortaliteit dient te worden geïmplementeerd om de daadwerkelijke impact van de behandeling op morbiditeit en mortaliteit te monitoren.
7. Nieuwe minimaal invasieve methoden zoals het oraal testen van vloeistof dienen verder te worden geëvalueerd en mogelijk te worden geïntroduceerd in HIV-mortaliteit surveillancesystemen.
8. Onderzoeken zullen nooit de noodzaak voor HIV-casus-surveillance vervangen. Er dienen surveillancesystemen te worden ontwikkelt om HIV-transmissie te identificeren en te beheersen, en om de kwaliteit van zorg langs de cascade te beheren.
9. Doorgaande ontwikkeling en het versterken van unieke identificatiemiddelen en -methoden om the kunnen omgaan met het gebrek aan robuuste unieke identificatiemiddelen ter ondersteuning van casus-surveillance zijn vereist.

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I also must acknowledge the contributions of my many colleagues at the US Centers for Disease Control and Prevention in Nairobi who supported me in so many ways. Emily Zielinski-Gutierrez, who taught me how to laugh at some of the more absurd challenges we faced, Anthony Waruru for leading by example and finishing his doctorate before me, Prof Thomas Achia for your passion for teaching and for learning, Samuel Mwalili, and Jacques Muthusi, Clara Mutungu, Andrea Kim, Rachael Joseph, Marc Bulterys for the many ways you supported my efforts. Thank you to Daniel Kwaro, Joshua Gitonga, Kennedy Muttai and Lilly Nyagah for the close collaboration, and to Mary Mahy, John Stover and Jeff Eaton—my participation in the UNAIDS reference group under your leadership was always an intellectual stimulation and reminder that what one chooses to do, especially if done well and at the right time, can make a difference.

Finally, I would like to dedicate this thesis to Inocencia, thank you for supporting my pursuit of this dream; and to Nala, may this journey be a small inspiration to someday pursue your dreams, wherever they lead.

Curriculum Vitae

Peter Young was born on July 20, 1973, in Rochester, New York, United States. After completing his secondary education at Newton South High School in Massachusetts in 1991, he studied computer science and Spanish language at Hampshire College in Amherst, Massachusetts, from 1991–96, including six months teaching computer science courses at the National Autonomous University of Nicaragua (UNAN), in Managua. After graduation, he worked from 1996–98 at the Massachusetts Institute of Technology's Whitehead Institute, where he supported the Human Genome Project as a bioinformatician. In the Fall of 1998, Peter rode a bicycle 1600 kilometers along the Atlantic coast from Boston to eastern North Carolina, then spent a year working in Mexico City for several different non-governmental organizations. He returned to the Whitehead Institute, staying for two more years before moving to New York City in 2000 to join a startup company developing software to secure genetic information collected in clinical trials. In 2004, Peter enrolled in the Master of Public Health program at Columbia University, where he developed an interest in international public health. This led him to Mozambique, where he was accepted to a two-year fellowship at the U.S. Centers for Disease Control and Prevention (CDC) in 2006. This was followed by full-time employment at CDC in Maputo, and from 2014, in Nairobi, Kenya, where he worked as epidemiology team lead, then chief of the surveillance and epidemiology branch for the HIV program. While in Nairobi, he started a thesis focusing on HIV incidence, mortality, and the cascade of HIV care in Kenya with Prof Mirjam Kretzschmar as promotor and Dr Kevin De Cock as co-promotor, and he enrolled as an external Ph.D. candidate at Utrecht University in late 2017. In mid-2020, Peter returned to Maputo and CDC-Mozambique as the Associate Director for Science.

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