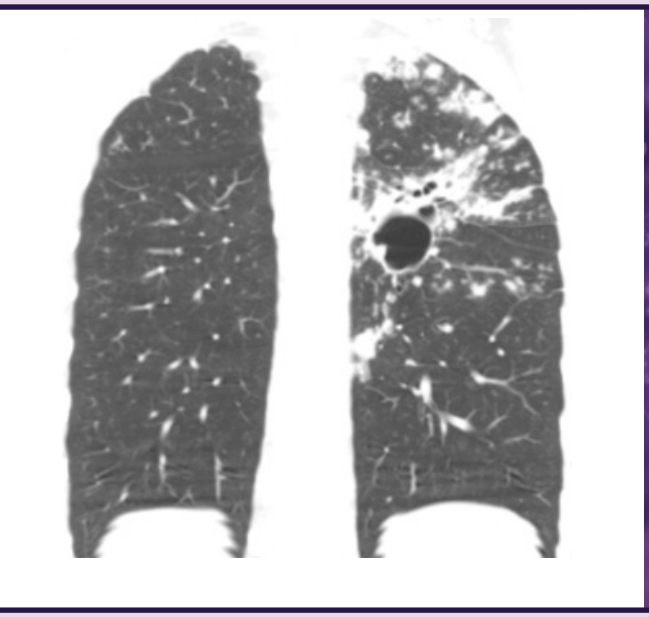
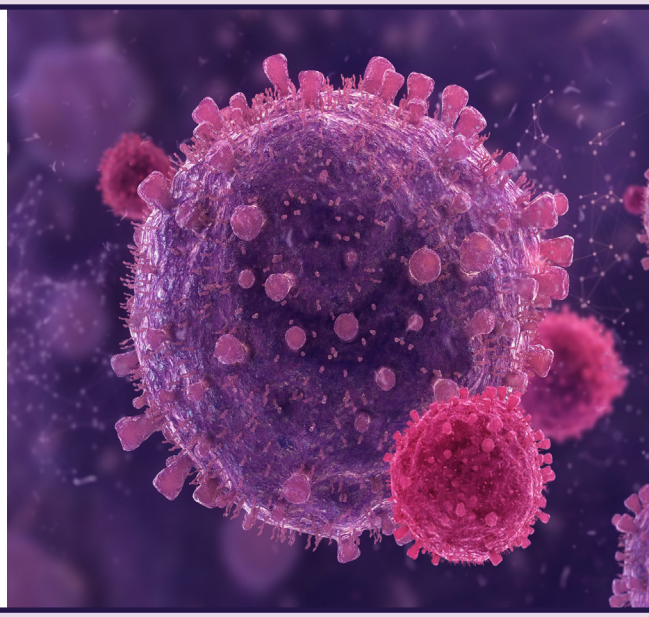
Incidence, risk factors and interventions addressing mortality associated with HIV and TB infections among children and adults in Kenya





Dickens Otieno Onyango

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Incidentie, risicofactoren en maatregelen om de mortaliteit in verband met HIV- en TB-infecties bij kinderen en volwassenen in Kenia aan te pakken
(met een samenvatting in het Nederlands**)**

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CHAPTER 1

General Introduction

Background

Tuberculosis (TB) and human immuno-deficiency virus (HIV) remain significant causes of morbidity and mortality in many low- and middle-income countries (LMIC) including Kenya. Before the COVID-19 pandemic, TB was the leading infectious cause of death worldwide followed by HIV (1). Globally, TB and HIV are estimated to cause 1.5 million and 863,000 deaths respectively every year (2, 3). While the HIV epidemic causes an increase in incident TB cases (4, 5), TB is a leading cause of hospitalization and death among people living with HIV (PLHIV) (6, 7). Because of their close association, the two infectious diseases can be considered as a syndemic which needs multidisciplinary approaches that consider them together rather than separately (4).

Kenya is a lower middle-income country located in East Africa covering an area of 582,000 km2 and lies between 5° N and 5°S latitudes and 34°E and 43°E longitudes. The country's Gross Domestic Product was 101.0 billion United States dollars in 2020 (8). Kenya's population was estimated at 47.6 million people, nearly half (46%) of whom live below the poverty line (9). A third of the country's population live in urban areas (9). Agriculture is the main economic activity providing livelihood to 32% of the population followed by wage employment (24%) (9). The country has a devolved health system, the national government is responsible for policy formulation and national referral hospitals, while county governments are responsible for provision of health services. Health services are provided by a mix of public (49%), private-for-profit (32%) and private-not-for-profit (16%) health facilities. Health service provision is categorized into levels ranging from community health services (Level 1), dispensaries (Level 2), health centers (3), county hospitals (Level 4), regional referral hospitals (Level 5) and national referral hospitals (Level 6).

Incidence and prevalence of TB and HIV in Kenya

A national TB prevalence survey conducted in 2016 reported TB prevalence in Kenya to be 558 per 100,000 population (10) (**Table 1**). Although TB incidence was estimated at 259 per 100,000 population translating to 139,000 incident cases in 2020 (2), only 72,943 (154 per 100,000) TB cases were notified suggesting that nearly half of TB cases were undiagnosed or not notified (11). According to the World Tuberculosis Report 2021, 33,000 people died from TB in 2020 in Kenya;

PLHIV accounted for 12,000 (36%) of these deaths (2). The National TB Control Program considers death and loss to follow up the biggest contributors to failures in achieving programmatic targets for successful treatment. Over 6% of TB patients die during treatment annually (11).

Kenya has a generalized HIV epidemic which has evolved over time. The Kenya Population-based HIV Impact Assessment (KENPHIA) survey conducted in 2019 reported HIV prevalence to be 700 per 100,000 children aged 0 to 14 years and 4,900 per 100,000 adults aged 15 to 64 years (12). HIV incidence in the country was estimated to be 140 per 100,000 people in 2019 translating to 40,825 new infections (12). According to estimates based on modelling using Spectrum version 5.52b3, there were 1.44 million PLHIV with 19,486 HIV-related deaths in 2020 (13). By the end of 2020, 79% of adult PLHIV in Kenya knew their status, 78.9% of those who knew their status were on antiretroviral therapy (ART) and 73.4% of those on ART were virally suppressed (14). Among children living with HIV (CLHIV), HIV status was known for 63.5%, 63.4% of those with known status were on ART and 54% of those on ART were virally suppressed (14).

Table 1: Incidence and prevalence of TB and HIV in Kenya in 2020

Indicator	Value	Source
Incident TB cases	139,000	Kenya Annual Tuberculosis Report 2020
TB incidence per 100,000 population	259	World Tuberculosis Report 2021
Tuberculosis case notification rate per 100,000 population	154	Kenya Annual Tuberculosis Report 2020
Number of deaths from TB	33,000	World Tuberculosis Report 2021
TB case fatality rate per 100,000 population	6300	Kenya Annual Tuberculosis Report 2020
TB prevalence per 100,000 population	558	Kenya TB prevalence survey 2016
HIV prevalence 15–64 years per 100,000 population	4900	Kenya Population-based HIV Impact Assessment 2018

HIV prevalence 0–14 years per 100,000 population	700	Kenya Population-based HIV Impact Assessment 2018
HIV incidence 15–64 years per 100,000 population	140	Kenya Population-based HIV Impact Assessment 2018
Number of PLHIV (all ages)	1,435,271	HIV estimates 2020
HIV-related deaths	19, 486	HIV estimates 2020
HIV testing among TB patients in 2020	98%	Kenya Annual Tuberculosis Report 2020
TB/HIV coinfection per 100,000 population	25%	Kenya Annual Tuberculosis Report 2020

Understanding TB and HIV mortality

Mortality can be used as an indicator of the health status of a population as well as to evaluate the impact of health interventions. According to global burden of disease estimates, PLHIV account for 16% of tuberculosis deaths globally (15). Mortality among patients on TB treatment is significantly higher among patients co-infected with HIV (16, 17); the case fatality ratio among co-infected patients is five times higher than among HIV un-infected TB patients (18). The increased mortality from TB and HIV co-infection can be attributed to several factors such as immunological and other biological interactions (19), including a delay in the diagnosis of either of the two diseases (19), delayed initiation of TB treatment or ART, the latter especially before implementation of the HIV test and treat policy (20). Prompt ART and antituberculosis treatment in HIV co-infected TB patients are effective in preventing TB-related mortality in PLHIV (21-23).

High income countries with low prevalence of TB and HIV have high quality data on causes of death including TB/HIV cause-specific mortality rates (24-26). However, such data is lacking from high prevalence LMIC settings due to poor quality of cause of death information captured by civil registration and vital statistics systems (27-29), the relatively few numbers of post mortems and inadequate diagnostic facilities (30, 31). Current data on causes of death from LMICs are based mainly on mathematical modeling of data from civil registration systems and verbal autopsies (32-34) whose accuracy is limited by incompleteness of data and lack of granularity on specific causes

of death (35). Furthermore, causes of death obtained from civil registration systems and verbal autopsy are non-specific and focus on underlying causes.

Data on causes of death in Kenya are available from a variety of sources including medical records of patients, civil registration and vital statistics and verbal autopsies conducted mostly within Health and Demographic Surveillance Systems (HDSS). Causes of death from medical records may be inaccurate due to inadequate diagnostic testing (30, 31) and may underestimate mortality as some patients who are counted as loss to follow up may actually be dead (36). Although civil registration data are a convenient source of mortality information, they may grossly underestimate mortality in sub-Saharan African countries including Kenya where the data is often incomplete and where less than 25% of deaths are notified (27, 37). Kenya has six active HDSSs platforms where mortality is measured and causes of death assessed through verbal autopsy (37, 38). Post mortem examination of tissues in combination with clinical information, remains the most reliable method for verifying causes of death (39). However, the proportion of deaths which are subjected to post mortem is low and has been falling (40-43). Minimally-invasive tissue sampling (MITS) autopsy is gaining prominence as a valid proxy for full post mortems (42-44) especially due to higher acceptability compared to full autopsies (45, 46). Additionally, surveillance for HIV-related mortality by testing decedents received by mortuaries has been successfully conducted in some sub-Saharan countries (47-50).

Public health policy makers need accurate data on TB and HIV cause-specific mortality rates and causes of death for monitoring trends in the population, evaluating the impact of disease control programs, and strategic planning (51). There is growing interest in generating more accurate data on causes of death due to the limitations of the existing data (52). Additionally, reducing TB and HIV cause-specific mortality is a key priority of global commitments such as the End TB Strategy (53) and Sustainable Development Goals (SDGs) (54) which target to end the two epidemics by 2030 (53, 54). Therefore, accurate data on mortality is needed to evaluate progress in achieving these global commitments. This thesis examines mortality due to TB and HIV infections using data from multiple sources to provide insight on TB and HIV related mortality in Kenya.

TB and HIV mortality preventive interventions

To reduce TB-related morbidity and mortality among PLHIV, the WHO recommends a three-pronged approach comprising intensified case finding, isoniazid prophylactic therapy (IPT), and tuberculosis infection control (55). Identifying people suffering from TB and prompt initiation of anti-tuberculosis treatment remains one of the most important interventions against TB-related mortality (55). Chest x-ray examination and microbiological confirmation through microscopy or Gene Xpert are the primary diagnostic tools for detecting active TB. TB diagnosis in PLHIV and children can be challenging due to non-specific clinical presentation, difficulties in obtaining sputum in children and reduced sensitivity of sputum microscopy in PLHIV (56, 57). These diagnostic challenges contribute to the limited knowledge on the epidemiology of pediatric TB, imprecise control targets and increased risk of TB-related mortality among children (56, 58). Several new tools have been developed to enhance TB diagnosis in PLHIV and children. These include sputum induction, testing alternative specimens (gastric aspirate and stool) using Gene Xpert, availability of more sensitive Xpert MTB/RIF Ultra (56) and urine lipoarabinomannan (LAM) (59). TB LAM improves the accuracy of TB diagnosis in PLHIV but has inconsistent accuracy in children (59).

TB preventive therapy (TPT) using IPT or other regimens is recommended for PLHIV aged at least 12 months in settings with high prevalence of latent TB (60) and effectively reduces mortality when combined with ART (61, 62). Implementing TPT is complex and comprises multiple steps (eligibility screening, initiation, follow up and completion) comprising a cascade (63). Drop-offs at any of these steps can undermine the effectiveness of TPT. Although TPT is a crucial intervention among children living with HIV (CLHIV) who are predisposed to severe or disseminated TB (64, 65), data is lacking on the performance of the TPT cascade among children living with HIV from high TB/HIV prevalence settings.

HIV-associated mortality can be reduced through interventions that prevent disease transmission (condom use, pre- and post-exposure prophylaxis, prevention of mother-to-child transmission [PMTCT], and ART), early diagnosis of HIV-infected people, timely ART initiation, and prevention or treatment of opportunistic infections. In 2014 UNAIDS proposed a framework for reducing HIV deaths and ending the HIV epidemic by 2030 which was dubbed 90–90–90 (66) and

later revised to 95–95–95 targets, which aimed to have identified 95% of HIV infected people, initiated ART for 95% of people diagnosed with HIV and achieved viral suppression among 95% of PLHIV on ART by 2030 (67). Kenya has made substantial progress in achieving the 95–95–95 targets. Timely ART initiation with subsequent viral suppression in PLHIV has been reported to increase their life expectancy by more than 20 years (68). Untreated PLHIV and those on ART but virally non-suppressed remain vulnerable to opportunistic infections which are common causes of mortality among those with advanced disease (69, 70). In the pre-ART era, opportunistic infections such as TB, pneumocystis pneumonia, toxoplasmosis and cryptococcal pneumonia were commonly associated with mortality among PLHIV (71). Additional data is needed to document the causes of death among PLHIV in the ART era.

Despite concerted efforts to meet the 95–95–95 targets, there remains a challenge in identifying undiagnosed CLHIV and adult PLHIV (72). By 2020, more than 10% of HIV-infected people in eastern and southern Africa still did not know their HIV status, which is necessary for entry into the HIV care cascade (67). Provider-initiated testing and counseling (PITC), which entails offering HIV testing to all people seeking care in health facilities (73) accounts for over 80% of all HIV tests in Kenya. Recently PITC yields have been dismal due to the high proportion of the population who already know their HIV status. For instance, 13 million HIV tests were conducted in Kenya between 2017 and 2018 yielded approximately 182,000 positives (1.4%); the yield in TB clinics was higher (9.6%) than other service delivery points in health facilities (1.2%) (72). Active case finding in high-risk groups such as TB symptomatic individuals and targeting health facilities with larger numbers of people with undiagnosed HIV infection are options for optimizing PITC yield.

HIV in children is mostly transmitted from their mothers (74); PMTCT is a strategy that entails HIV testing during pregnancy and childbirth, ART initiation among HIV-infected pregnant women and ART prophylaxis in HIV-exposed infants is crucial in reducing related mortality among children (75). HIV testing among HIV exposed infants coupled with early ART initiation is another important childhood intervention (76). Children who are missed by PMTCT and early infant diagnosis programs are particularly at risk of mortality due to late diagnosis (77).

Thesis objectives

Main Objective

This thesis sought to determine current TB and HIV cause-specific mortality, identify factors associated with TB and HIV mortality and assess the impact of interventions with the aim to reduce TB and HIV cause-specific mortality in Kenya.

Specific objectives

1. To estimate TB and HIV cause-specific mortality including the contribution of TB and HIV among causes of death in Kenya
2. To evaluate the risk factors for mortality including the effect of antiretroviral therapy among patients on TB treatment in Kenya
3. To assess the programmatic performance of interventions that indirectly contribute to reduction in HIV/TB-related mortality (HIV testing and IPT)

Outline of thesis

This thesis explores mortality associated with TB and HIV in Kenya in nine chapters (**Figure 1**). This first chapter is a general introduction which summarizes the epidemiology of TB and HIV and why mortality from the two diseases is a significant public health issue in Kenya. Mortality from TB and HIV was first assessed using mortality studies which are presented in chapter two, three and four. HIV prevalence among decedents, the fraction of mortality in the population attributable to HIV-infection, all-cause and cause-specific mortality rates and the 20 leading underlying causes death were assessed in a mortuary surveillance study that confirmed HIV infection among decedents received by two high-volume mortuaries in western Kenya from medical records or through post-mortem HIV testing. Causes of death among children aged under-five years stratified by HIV status were explored in a cross-sectional analysis of Child Health Mortality Prevention Surveillance (CHAMPS) data and presented in chapter four. CHAMPS conducts minimally invasive tissue sampling (MITS) autopsy to determine immediate, morbid (antecedent) and underlying causes of death in children aged under-five years in seven sites drawn from South Asia and sub-Saharan Africa (78). The effect of HIV-infection on mortality among children and adults on TB treatment presented in chapter five and six are based on retrospective analyses of nationally representative routine surveillance data obtained from the national TB control program. In chapter seven, health facility characteristics associated with new HIV

diagnoses were evaluated using data collected during an integrated TB and HIV case-finding intervention. During the intervention, all adults visiting participating health facilities were screened for TB symptoms, TB symptomatic individuals were tested for HIV using the national HIV testing algorithm. The isoniazid preventive therapy (IPT) cascade among children living with HIV (CLHIV) was evaluated using routine program data that was abstracted from the medical charts of CLHIV who were newly enrolled on HIV care over a three-year period and presented in chapter eight. The performance of the IPT cascade was assessed by calculating the proportions of eligible CLHIV who completed critical steps such as screening for IPT eligibility, IPT initiation and IPT completion. Survival analysis was used to establish TB incidence within 24 months of IPT eligibility screening stratified by IPT initiation and completion status. Finally, in the ninth chapter, a reflection is given on what the studies in this thesis have contributed towards the objectives and on possible next steps to reduced HIV and TB cause-specific mortality.

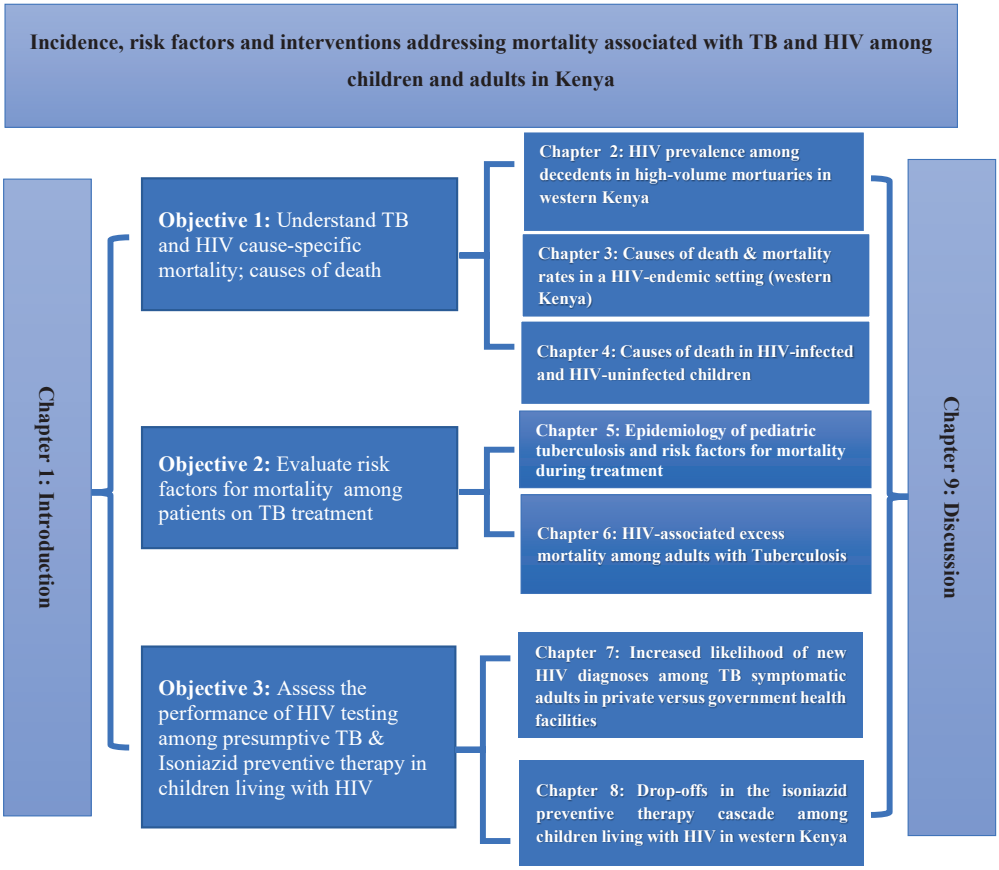

Figure 1: Overview of the various components of the thesis

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CHAPTER 2

High HIV prevalence among decedents received by two high-volume mortuaries in Kisumu, western Kenya, 2019

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Abstract

Background: Accurate data on HIV-related mortality are necessary to evaluate the impact of HIV interventions. In low- and middle-income countries (LMIC), mortality data obtained through civil registration are often of poor quality. Though not commonly conducted, mortuary surveillance is a potential complementary source of data on HIV-associated mortality.

Methods: During April-July 2019, we assessed HIV prevalence, the attributable fraction among the exposed, and the population attributable fraction among decedents received by two high-volume mortuaries in Kisumu County, Kenya, where HIV prevalence in the adult population was estimated at 18% in 2019 with high ART coverage (76%). Stillbirths were excluded. The two mortuaries receive 70% of deaths notified to the Kisumu East civil death registry; this registry captures 45% of deaths notified in Kisumu County. We conducted hospital chart reviews to determine the HIV status of decedents. Decedents without documented HIV status, including those dead-on arrival, were tested using HIV antibody tests or polymerase chain reaction (PCR) consistent with national HIV testing guidelines. Decedents aged less than 15 years were defined as children. We estimated annual county deaths by applying weights that incorporated the study period, coverage of deaths, and mortality rates observed in the study.

Results: The two mortuaries received a total of 1,004 decedents during the study period, of which 95.1% (955/1004) were available for study; 89.1% (851/955) of available decedents were enrolled of whom 99.4% (846/851) had their HIV status available from medical records and post-mortem testing. The overall population-based, age- and sex-adjusted mortality rate was 12.4 per 1,000 population. The unadjusted HIV prevalence among decedents was 28.5% (95% confidence interval (CI): 25.5–31.6). The age- and sex-adjusted mortality rate in the HIV-infected population (40.7/1000 population) was four times higher than in the HIV-uninfected population (10.2/1000 population). Overall, the attributable fraction among the HIV-exposed was 0.71 (95% CI: 0.66–0.76) while the HIV population attributable fraction was 0.17 (95% CI: 0.14–0.20). In children the attributable fraction among the exposed and population attributable fraction were 0.92 (95% CI: 0.89–0.94) and 0.11 (95% CI: 0.08–0.15), respectively.

Conclusions: Over one quarter (28.5%) of decedents received by high-volume mortuaries in western Kenya were HIV-positive; overall, HIV was considered the cause of death in 17% of the population (19% of adults and 11% of children). Despite substantial scale-up of HIV services, HIV disease remains a leading cause of death in western Kenya. Despite progress, increased efforts remain necessary to prevent and treat HIV infection and disease.

Introduction

Although estimated deaths from human immunodeficiency virus (HIV) disease have been declining globally since 2006 [1], HIV remains a serious public health problem, especially in low- and medium-income countries (LMIC) of Africa. In 2018, an estimated 770,000 deaths were attributed to HIV infection, including 310,000 in eastern and southern Africa, and specifically, 25,000 in Kenya [2]. In 2016, United Nations member states made a political commitment to reduce mortality from HIV by 75% between 2010 to 2020 [3]. By 2018, no country was on track to achieving the United Nations HIV mortality goal [4].

Estimates from the Kenya National AIDS and Sexually Transmitted Infections (STI) Control Program (NASCOP) indicated that HIV prevalence among adults aged 15–49 years reduced from 7.1% in 2007 [5] to 5.6% in 2012 [6], and to 4.9% in 2019 [7]. While the decline in prevalence has been attributed to reduced HIV transmission due to high antiretroviral therapy (ART) coverage [6], the role of mortality in reducing HIV prevalence is unclear. Accurate data on HIV-associated mortality can help evaluate the impact of HIV interventions and progress in HIV prevention and control [8]. However, data on HIV-associated mortality are not generally available in LMIC, including Kenya, where the quality of civil registration and vital statistics is low, and underreporting of deaths is substantial [9-11]. Furthermore, causes of death, even when established, are not systematically recorded by many routine death-reporting systems [12-15]. HIV testing of decedents received by mortuaries offers a way of gaining further insight into HIV-associated mortality.

The HIV epidemic in Kenya is heterogeneous across the country's 47 counties. HIV prevalence among people aged 15 years and above in Kisumu County (17.5%) is more than three times greater than the national prevalence [7]. In 2018, Kisumu County accounted for 6% of the estimated 28,200 HIV-associated deaths that were thought to have occurred in Kenya [16]. Kisumu was included among the nine of 47 counties that were responsible for 52% of Kenya's HIV-associated deaths, although these counties accounted for only 28% of the country's population [16].

Over the past three decades, studies in Cote d'Ivoire, the Democratic Republic of Congo, and Kenya have estimated HIV-associated mortality by testing adult decedents [17][18][19, 20]. The

feasibility of mortuary-based surveillance in Kenya was demonstrated in 2015 by a study of adolescent and adult decedents in the two largest mortuaries in Nairobi [21]. In that study, 19.5% of decedents were HIV-infected [19], and 65.7% of deaths among HIV-infected decedents were attributed to HIV [19]. Nairobi County has a substantially lower HIV prevalence (3.8%) than counties in western Kenya, where HIV prevalence is above 10% [7]. Systematically combining testing of decedents with unknown HIV status and abstraction of HIV status from medical records offers a way of assessing unexplored HIV-associated mortality. Given that the Nairobi study showed higher-than-expected mortality attributed to HIV, and poor coverage of diagnosis and treatment among HIV-infected persons dying, we undertook this investigation to estimate HIV-associated mortality in one of the highest HIV-burden regions of Kenya.

Methods

This study was approved by KEMRI's Science and Ethical Review Committee (#KEMRI/RES/7/3/1), Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) Ethics Review Committee (#ERC.IB/VOL.1/615), and the University of California, San Francisco's Committee on Human Research (#230355). Informed consent was waived by the ethical review committees. This project was reviewed under CDC human research protection procedures. The CDC investigators did not interact with living human subjects or have access to identifiable data or samples for research purposes. Results of HIV testing were not linked back to living family or next of kin of decedents.

Study Setting

Kisumu County, located in the Nyanza region of western Kenya, had an estimated population of 1,155,574 in 2019 [22]. The city of Kisumu has 15 mortuaries, including those at JOOTRH and Kisumu County Referral Hospital (KCRH). These two mortuaries ordinarily receive more than 70% of decedents notified to the Kisumu East civil registry [23], which accounted for 45% of all deaths notified in Kisumu County in 2019. Over two thirds (70%) of decedents in the two mortuaries died in the host hospitals, while approximately 30% died in the community or other health facilities. In 2018, the estimated HIV prevalence in Kisumu County was 17.5% [7], translating to over 122,000 (9,439 children and 112,561 adults) people living with HIV (PLHIV)

in the county, of whom 110,000 (90%) were diagnosed, and 105,000 (95% of the diagnosed) were on ART [24].

Study design

This was a cross-sectional study conducted in the two high-volume mortuaries attached to two referral hospitals in Kisumu County (JOOTRH and KCRH). Decedents admitted to the two mortuaries between April and July 2019 were consecutively enrolled. Data from the mortuaries were used to obtain medical records of decedents who died within the two hospitals. Chart reviews were done to establish if HIV infection was documented in medical records. Blood was collected by transthoracic cardiac puncture from decedents without documented HIV status in the medical records, including those dead-on arrival, or whose latest HIV-negative result was older than three months. Death was considered to be due to HIV/AIDS if HIV or AIDS was listed as the underlying cause of death.

Study Population and population projections

All decedents with intact bodies, including children (0–14 years), received by the two mortuaries between April through July 2019 were eligible for enrollment into this study. We excluded decedents from whom blood could not be collected due to deterioration, burns, or embalming, stillbirth, and those who had been dead for ≥48 hours.

The age and sex distribution of the county population was obtained from the 2019 Housing and Population Census Report [22]. The 2019 age and sex-specific HIV prevalence for Nyanza region were projected using Spectrum version 5.52b3 (Avenir Health, Glastonbury, Connecticut). These rates were then scaled to the County HIV prevalence estimate for Kisumu County for 2019 from the National AIDS Control Council [25] and used to project the number of people living with and without HIV by age and sex.

Variables

Demographic variables included age, sex, place of birth, date of birth, date of death, and place of death (died within JOOTRH or KRCH, died in the community or other facilities and transferred

to JOOTRH/KRCH after death). Clinical and laboratory variables collected for hospital deaths from paper-based medical records included date of admission, clinical diagnosis, date of diagnosis, time of death, cause of death (COD) based on postmortem results if available, sample collection date, HIV test results, and viral load (VL) (copies/milliliter [mL] of plasma).

HIV and viral load testing

For each decedent, a 6 mL non-clotted blood sample was collected and transferred into sterile ethylene diamine tetra-acetic acid (EDTA) sample tubes and transported in a cool box to the Kenya Medical Research Institute (KEMRI) HIV research laboratory in Kisumu within 4 hours of collection. HIV testing was conducted in compliance with the 2015 Kenya HIV Testing Services guidelines [26, 27]. Samples from children aged <18 months were tested using polymerase chain reaction (PCR). Samples from decedents aged 18 months and above were tested using Determine™ HIV-1/HIV-2® (Abbott Diagnostic Division, Hoofddorp, Netherlands) as the screening assay, and First Response® (Premier Medical Corp. Lt, Daman, India) as the confirmatory test. Samples that were reactive on Determine® and First Response® were considered positive. Samples that were reactive on Determine® and non-reactive on First Response® were considered discordant and retested by a different technician. After retesting, samples that remained discordant were tested using reverse transcriptase PCR (RT-PCR) to confirm the final HIV status. HIV-positive samples were further tested for viral load by RT-PCR using the Abbott™ system (Abbott Molecular, Inc., Des Plaines, IL). The use of rapid test kits in this study is supported by previous studies showing that HIV antibodies remain detectable in serum for up to 58 days after death [28, 29] and that performance of rapid HIV tests is comparable to that of standard enzyme immunoassay [28, 30-32].

Data analysis

Primary outcomes were the prevalence of HIV infection among decedents, attributable fraction among the HIV-exposed, and the population attributable fraction. We calculated the overall HIV prevalence among decedents stratified by age, sex, and place of death. HIV-associated mortality was defined as death in an HIV-infected person documented in the medical records or confirmed

through HIV testing. We adjusted the number of deaths observed over the study period (87 days) to estimate the number of county deaths expected over 365 days by multiplying them by 365/87 and adjusting for coverage (the proportion of expected county mortalities observed in the study). Mortality rates were calculated per 1000 people by dividing the annualized deaths by the 2019 population for Kisumu County by HIV status, age, and sex. Pooled HIV positivity and mortality rates were then computed weighted by the projected population size by age, sex and HIV status. The standardized mortality rate difference and standardized mortality rate ratio were calculated using Stata's epitab package (Stata Corporation, College Station, Texas, USA). The standardized mortality rate difference was calculated by subtracting mortality rates in the HIV-uninfected population from mortality in the HIV-infected population standardized to the HIV-infected population by age and sex. To obtain SMRR, we divided mortality rates for HIV-infected decedents by mortality rates of HIV-uninfected decedents standardized to the age and sex distribution of the HIV-infected population. Attributable fraction among the exposed (HIV-infected decedents) and population attributable fraction were calculated by dividing standardized mortality rate difference by mortality rates of HIV-infected decedents and mortality rates in the population, respectively [33]. We tested for interactions between age and sex using logit models. We conducted Monte Carlo simulations to assess the sensitivity of obtained risk ratios and attributable fractions to various epidemiological assumptions. All statistical tests were done at 5% level of significance.

Results

Overview of decedents' place of death and determination of HIV status

Of 1,004 decedents received by the two mortuaries during the study period, 95.1% (955/1,004) were potentially available (not transferred out and not dispatched for burial before enrolment) for the study, 89.1% (851/955) of whom were enrolled (**Figure 1**). Of 104 ineligible decedents, 66 (63.5%) were stillbirths. Of the 851 decedents enrolled, 555 (65.2%) had died in JOOTRH or KCRH, and 296 (34.8%) were dead on arrival. Of the 555 decedents who had died within JOOTRH or KCRH, 34.4% (191/555) had HIV status documented in the chart; 61.8% (118/191) were known to be HIV-positive. Of the 296 decedents who were dead on arrival, 1% (1/296) was known to be HIV-positive. Blood samples were drawn from the remaining 659 decedents with unknown HIV

status (364 who had died in JOOTRH or KCRH and 295 who were dead on arrival); <1% (5/659) had untestable blood specimens. Of the 654 samples tested, 18.7% (122/654) were HIV-positive. HIV positivity was 14.8% (54/364) among tested decedents who died in hospital and 23.4% (68/290) among tested decedents who were dead on arrival. Overall, 846 decedents had their HIV status determined, 192 through documentation, and 654 through post mortem HIV testing. Thus, 28.5% (241/846) overall were determined to be HIV infected (119 by medical records review and 122 by testing). The age and sex adjusted pooled HIV prevalence was 26.3% (95% CI: 23.4–29.4) (**Table 1**). The adjusted HIV prevalence was higher among females 29.0% (95% CI: 24.8–33.5) than males 24.1% (95% CI: 20.3–28.3) (p-value=0.05).

Table 1: Unadjusted and adjusted HIV prevalence among Kisumu decedents by age and sex (N=846)

Sex	Age group (Years)	Number of deaths	Unadjusted Positivity % (95% CI)	Age and Sex Adjusted Positivity* % (95% CI)
Male	0–14	76	13.16 (7.19–22.85)	-
	15–24	33	21.21 (10.33–36.62)	-
	25–44	145	37.93 (30.37–46.12)	-
	45+	182	21.98 (16.53–28.61)	-
	Total	436	25.69 (21.80–30.00)	24.06 (20.27–28.32)
Female	0–14	84	11.90 (6.50–20.81)	-
	15–24	25	40.00 (22.74–60.17)	-
	25–44	101	65.35 (55.52–74.02)	-
	45+	200	21. 50 (16.33–27.76)	-
	Total	410	31.46 (27.14–36.13)	28.98 (24.81–33.54)
	Grand total	846	28.49 (25.54–31.63)	26.28 (23.42–29.36)

* Positivity adjusted by expected age-sex distribution among decedents according to population projection

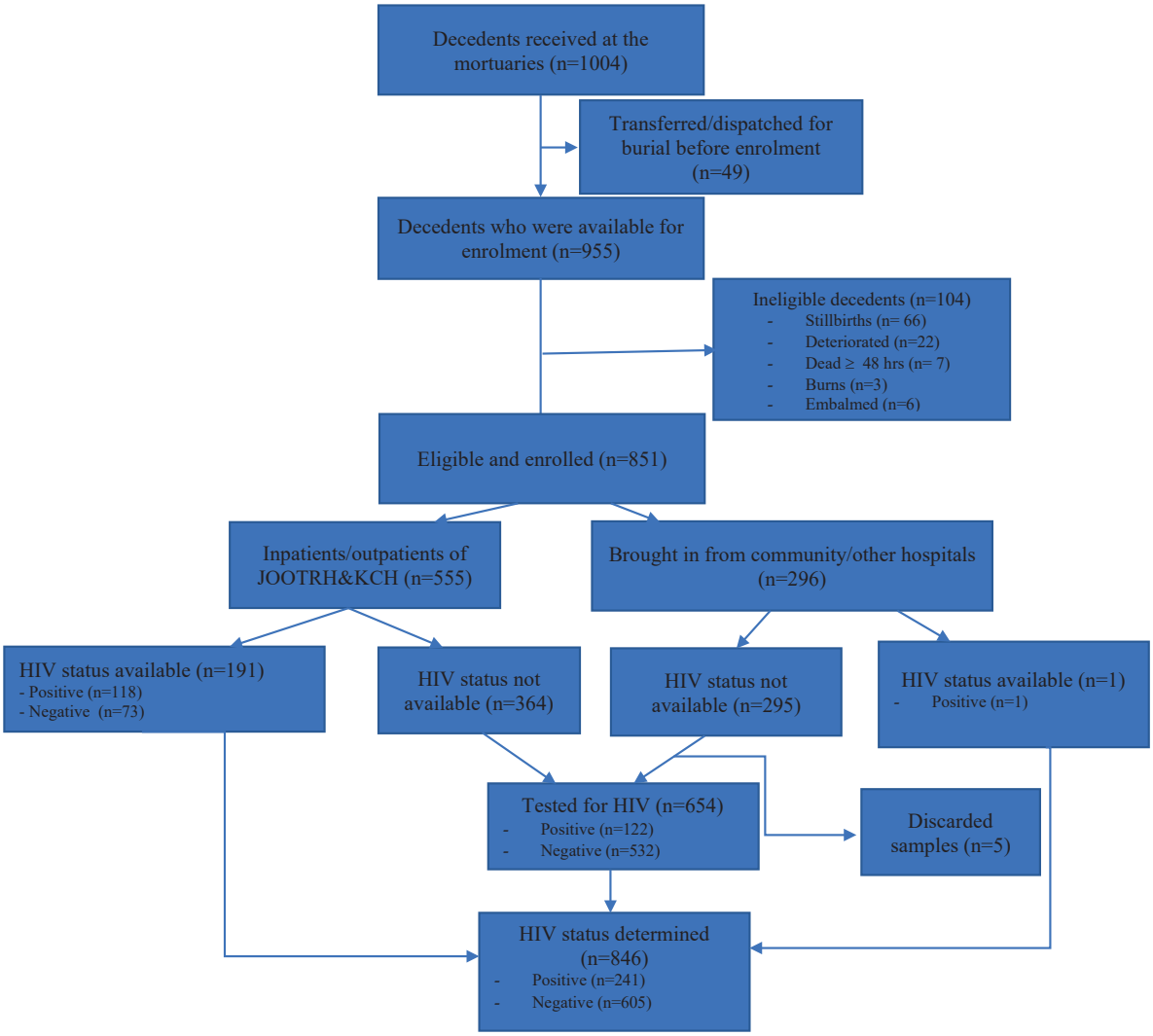

Figure 1: Flowchart depicting the source of decedents received by high-volume mortuaries, eligibility and source of their HIV status, Kisumu County, 2019

Demographic characteristics of enrolled decedents

Children accounted for 18.9% (161/851) of enrolled decedents. About half, 49.7% (80/161) of decedent children were under one-year-old, 28.0% (45/161) were aged one to four years, while the age groups five to nine and 10 to 14 years each accounted for 11.2% (18/161). Most decedent children, 82.0% (132/161), were inpatients in the two hospitals before death, 16.2% (26/161) were dead on arrival, and 1.2% (2/161) died in the outpatient departments. One decedent 0.6% (1/161) was brought in as a police case.

Adolescents and adults accounted for 81.1% (690/851) of enrolled decedents; 9.9% (58/690) of adolescent and adult decedents were aged 15 to 24 years, 19.0% (131/690) were aged 25 to 34 years, 17.0% (117/690) were 35 to 44 years old, and 55.7% (384/690) were aged 45 years and above. Males accounted for 52.5% (362/690) of decedent adolescents and adults. Most adolescent and adult decedents, 54.8% (378/690), were inpatients in the two hospitals, 33.0% (228/690), were dead on arrival, 6.2% (43/690) died within outpatient departments, and 5.9% (41/690) were police cases.

HIV prevalence, treatment, and viral suppression

Among the 119 decedents with documented HIV-infection, 58.8% (70/119) had medical records indicating they were on ART during the hospitalization preceding death, 16.0% (19/119) were not, and 25.2% (30/119) had no documented ART status (**Figure S1**). Among the 122 decedents who were HIV-positive through testing, viral load (VL) was available for 96.7% (118/122); one sample returned invalid results while four samples were insufficient. The median VL for the 117 decedents was 839 copies per milliliter (copies/mL) of plasma (interquartile range (IQR): 40–37,526); 49.6% (58/117) of decedents with VL results had copies above 1,000 copies/mL. The median viral load among decedent children was 322,911 copies/mL (IQR: 147,371–578,504 copies/mL); 100% (11/11) of children with VL had copies above 1,000 copies/mL.

HIV-related mortality rates and attributable fraction

According to the 2019 Kenya Housing and Population Census, the population of Kisumu County in 2019 was 1,155,574 [22]. Using Spectrum (Avenir Health, Glastonbury, Connecticut), we estimated 83,085 people were living with HIV. We projected those 14,352 deaths occurred in the county in 2019, giving an overall mortality rate of 12.4 per 1,000 population (**Table 2**). The overall mortality rate was higher in males (13.1 per 1,000 population) than females (11.8 per 1,000 population) (p-value<0.001). The mortality rate was four times higher in the HIV-infected (40.7 per 1000) than the HIV-uninfected population (10.2 per 1,000) (p-value<0.001). The mortality rate in the HIV-infected population was 14.2% higher in males (44.3 per 1,000 population) than females (38.0 per 1,000 population) (p-value<0.001). Male and female children (0–14 years) and adults aged 45 or older had higher death rates than persons aged 15–34 and 35–44. The overall unadjusted mortality rate ratio (HIV-infected versus HIV-uninfected) was 4.0; the mortality rate ratio was highest among male children (12.8), followed by female children (11.4).

Table 2: Mortality rates by age, sex and HIV status, Kisumu County, 2019

		HIV-uninfected			HIV-infected				Overall		
Sex	**Age group (Years)**	**Deaths**	**Pop.**	**Mortality Rate (Per 1,000 pop)**	**Deaths**	**Pop.**	**Mortality Rate (Per 1,000 pop)**	**Mortality Rate Ratio (HIV-infected/-uninfected)**	**Deaths**	**Pop.**	**Mortality Rate (Per 1,000 pop)**
Male	0 –14	2,497	223,104	11.2	378	2,645	142.9	12.8	2,875	225,749	12.7
	15–24	493	113,399	4.4	133	3,869	34.4	7.9	626	117,268	5.3
	25–44	788	130,210	6.1	481	17,057	28.2	4.7	1,269	147,267	8.6
	45+	2,024	58,979	35.3	570	11,666	48.9	1.4	2,594	70,646	36.7
	Total	**5,802**	**525,691**	**11.0**	**1,562**	**35,237**	**44.3**	**4.0**	**7,364**	**560,928**	**13.1**
Female	0–14	2,237	224,836	10.0	302	2,672	113.0	11.4	2,539	227,508	11.2
	15–24	345	123,028	2.8	230	7,648	30.1	10.7	575	130,676	4.4
	25–44	359	129,604	2.8	677	24,139	28.1	10.1	1,036	153,743	6.7
	45+	2,228	69,278	32.2	610	13,389	45.6	1.4	2,838	82,667	34.3
	Total	**5,169**	**546,746**	**9.5**	**1,819**	**47,848**	**38.0**	**4.0**	**6,988**	**594,594**	**11.8**
Grand Total		**10,971**	**1,072,437**	**10.2**	**3,381**	**83,085**	**40.7**	**4.0**	**14,352**	**1,155,522**	**12.4**

Adjusted for age and sex, the mortality rate among PLHIV was thrice higher than that among HIV-uninfected people (standardized mortality rate ratio=3.1; 95% CI: 2.60–3.64) (**Table 3**). The standardized mortality rate ratio was marginally higher in females (3.32; 95% CI: 2.63–4.20) than males (2.84; 95% CI: 2.23–3.61). Adjusted for age and sex, there were 28 additional deaths annually for every 1,000 people among PLHIV (standardized mortality rate difference= 0.028; 95% CI: 0.022–0.033), 29 for men and 27 for women. Overall, the attributable fraction among the exposed was 0.71 (95% CI: 0.66–0.76); the attributable fraction among the exposed was 1.4 times higher in children <15 years (0.92; 95% CI: 0.89–0.94) than in adolescents and adults (0.64; 95% CI: 0.56–0.69). The overall population attributable fraction was 0.17 (95% CI:0.14–0.20); the population attributable fraction was 1.7 times higher in adolescents and adults (0.19; 95% CI: 0.14–0.24) than in children (0.11; 95% CI: 0.08–0.15).

Table 3: Standardized mortality ratios, risk difference and attributable fractions, Kisumu County, 2019

	Sex		
Indicator	**Male**	**Female**	**Total**
Children (0–14)			
SMRR	12.53 (8.24–19.06)	11.53 (7.22–18.39)	12.06 (8.83–16.47)
SMRD	0.130 (0.075–0.184)	0.104 (0.054–0.154)	0.117 (0.080–0.154)
AFe	0.92 (0.88–0.95)	0.91 (0.86–0.95)	0.92 (0.89–0.94)
AFp	0.12 (0.07–0.17)	0.11 (0.06–0.16)	0.11 (0.08–0.15)
Adolescents & Adults (15+)			
SMRR	2.28 (1.74–3.00)	2.90 (2.25–3.74)	2.59 (2.15–3.12)
SMRD	0.020 (0.012–0.029)	0.022 (0.015–0.029)	0.021 (0.016–0.027)
AFe	0.58 (0.45–0.68)	0.67 (0.57–0.74)	0.64 (0.56–0.69)
AFp	0.15 (0.09–0.21)	0.22 (0.16–0.29)	0.19 (0.14–0.24)
Overall			
SMRR	2.84 (2.23–3.61)	3.32 (2.63–4.20)	3.08 (2.60–3.64)
SMRD	0.029 (0.020–0.038)	0.027 (0.020–0.034)	0.028 (0.022–0.033)
AFe	0.69 (0.61–0.76)	0.73 (0.66–0.78)	0.71 (0.66–0.76)
AFp	0.15 (0.10–0.19)	0.19 (0.14–0.23)	0.17 (0.14–0.20)

SMRR, standardized mortality rate ratio; SMRD, standardized mortality rate difference; AFe, attributable fraction in the exposed

Discussion

Data on mortality due to HIV can help evaluate the impact of ART programs and guide efforts to strengthen HIV care. Despite the high ART coverage among PLHIV documented through population-based surveys [7], we determined that nearly one-third of decedents in Kisumu were

HIV-infected. This analysis demonstrates that 17% of mortality in the western Kenya population could be prevented through early identification of PLHIV, prompt ART initiation, and strengthening adherence to ART. It is a cause for concern that only about one third of in-hospital decedents had their HIV status documented in their medical records; that about 15% of hospital decedents with undocumented HIV status were actually HIV-infected; and that about one quarter of those who were dead on arrival were HIV-positive. The high proportion of decedents who were virally non-suppressed together with a high median viral load (839 copies/mL) suggest that many may not have been on ART or had failed treatment. Clearly, increased effort is required to diagnose all persons with HIV and assure rapid initiation of ART, adherence to treatment, and appropriate laboratory monitoring [34]. Work is also required to understand apparent differences between the uptake of diagnostic testing and ART among decedents documented by this study, and results from HIV program evaluations which suggest 90% of admitted patients are tested for HIV.

The adjusted HIV positivity among decedents in this study was higher than observed in Nairobi [35] but lower than studies conducted during the pre-ART era in other high HIV prevalence settings such as the Democratic Republic of Congo [18] and Cote d'Ivoire [36]. The higher positivity in decedents in Kisumu compared to Nairobi could be explained by differences in overall population HIV prevalence. According to the Kenya Population Population-based HIV Impact Assessment (KENPHIA) 2018, HIV prevalence in the adult population was five times higher in Kisumu County (17.5%) than in Nairobi County (3.8%) [7]. HIV prevalence among decedents whose HIV status was obtained from medical records was several times higher than the population prevalence, likely because patients with serious HIV disease are concentrated in hospitals [36]; by contrast, the prevalence among those who were tested in the study was similar to the population prevalence. This is supported by evidence from other sub-Saharan countries where HIV has been reported to be a leading cause of hospitalization [37, 38] and inpatient mortality [39, 40].

In this study, the first of its kind to include children from a high HIV prevalence setting, children living with HIV were over ten times more likely to die than their HIV-uninfected counterparts. The attributable fraction among the exposed, above 90%, indicates that HIV was the cause of death in most of these children. Previous studies have documented a larger gap in HIV diagnosis, ART

initiation, and viral suppression in children than in adults [41-44]. Late HIV diagnosis [45] and high loss to follow-up after ART initiation [46] are important contributors to mortality in HIV-infected children. All the decedent children with viral load results were unsuppressed, indicating that they were possibly not on ART, had just recently initiated ART, were not adhering to ART, were on a sub-optimal regimen, or were experiencing treatment failure. We could not establish whether children under one year were being followed up for being HIV exposed. Over the last decade Kenya has accelerated efforts to control the pediatric HIV epidemic through intensified identification of HIV-infected children and ART initiation. In an evaluation of the United Nations Joint Program on HIV/AIDS (UNAIDS) 90–90–90 targets using KENPHIA data, 78.9% of HIV-infected children had been identified, 93.2% of whom were on ART, and 67.1% of whom were virally suppressed [7]. Just as for adults, the optimistic assessment of program quality from population-based surveys fails to capture mortality data and related insights into diagnosis and treatment. Greater effort is required to diagnose, treat, and ensure viral suppression among HIV-infected children.

The population attributable fraction for adolescents and adults observed in our study was similar to that reported by the Nairobi mortuary study (17% vs. 16%) [35]. The similarity in population attributable fraction despite large differences in HIV prevalence could be due to enhanced implementation of ART programs over the intervening years, especially in high prevalence counties. Global Burden of Disease data reported larger declines in HIV-specific mortality in counties with the highest burden of HIV [47]. Nonetheless, despite high ART coverage, estimated at 76% for all persons with HIV in the 2018 population-based survey [7], HIV remains a leading cause of mortality in this high HIV burden setting, with more than two-thirds of deaths in PLHIV attributed to HIV infection. Other studies have also reported higher mortality in HIV-infected people even in the era of ART [35], probably resulting from late ART initiation [48-52], pretreatment drug resistance, treatment failure arising from poor adherence, and treatment interruptions [53]. Early identification of PLHIV and ART initiation could substantially dent the impact of HIV on mortality in high prevalence settings [54, 55].

Unlike the Nairobi study, which tested all decedents, our study explored the abstraction of HIV status from medical records, a more convenient approach to HIV surveillance among decedents.

However, we noticed that documentation of HIV and ART status in medical records was poor. Although we successfully obtained HIV infection information for half of all HIV-infected decedents from medical records, critical information was missing. This may have been caused by the segmental nature of handling medical records in this setting. Often, HIV programs maintain electronic health records (EHR) within comprehensive care centers that are not readily available to other service delivery points such as inpatient departments. Expansion of EHRs to other service delivery points could increase the quality of HIV information available in the medical records and contribute to better patient outcomes.

Our study had several limitations. It was conducted exclusively in public-sector mortuaries. Not all deaths in the community are captured by mortuaries of any kind. Nonetheless, we believe our data are representative. Our two study hospitals receive 70% of decedents in Kisumu, with the other 30% shared by private and other public facilities. We used data from three months to estimate annual mortality. This approach may have introduced bias from seasonal differences in mortality. We utilized HIV status from medical records for hospital deaths when available as advised by the ethical review committee, but this precluded viral load testing for HIV-positive decedents thus identified. Abstracting ART status from medical records could have led to misclassification of decedents and testing of blood for ART metabolites was not possible. [56]. Obtaining HIV status from the medical records could have biased the estimates calculated in the study (HIV prevalence and attributable fractions). However, we minimized this by testing decedents whose documented HIV-negative status was older than three months.

Conclusions

Our study documented a higher-than-expected prevalence of HIV infection among decedents received by two high-volume mortuaries in western Kenya. The majority of HIV-infected decedents with viral load measurements were not virally suppressed. The fraction of mortality in the population attributable to HIV infection was high, 17% (17%). Preventing HIV-attributable mortality could substantially reduce overall mortality in this high-HIV-prevalence population.

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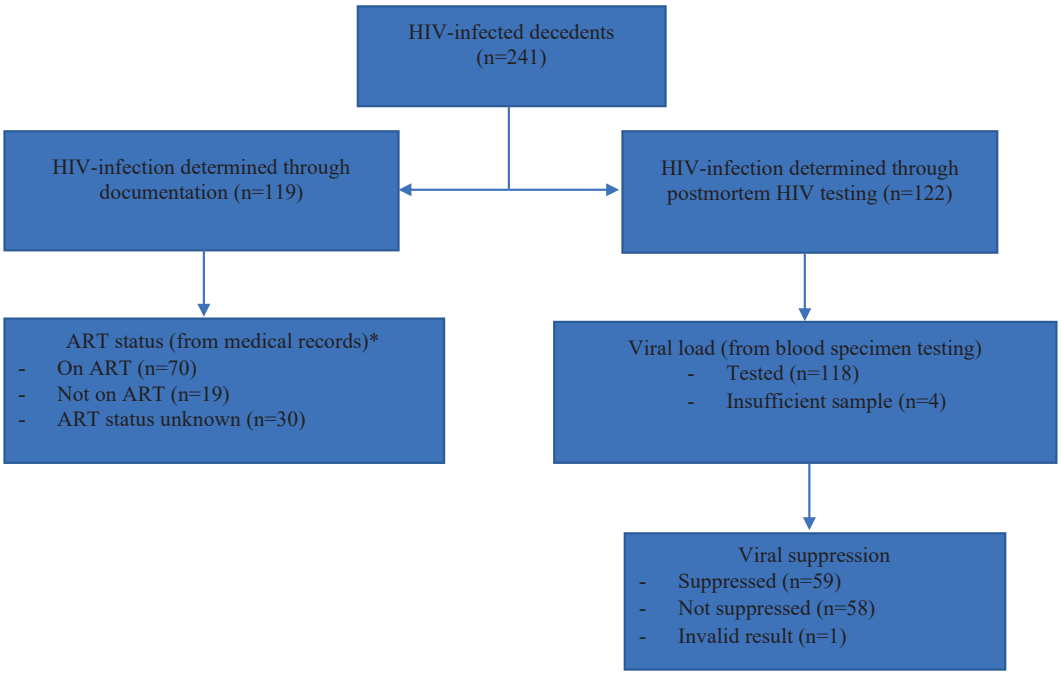

Figure S1: ART status and viral suppression among HIV-infected decedents enrolled in the HIV mortality surveillance study, Kisumu County, 2019

* Viral load were not abstracted from the inpatient/outpatient hospital records, they are usually recorded in comprehensive care center records that were not reviewed as part of this protocol

CHAPTER 3

Causes of death in HIV-infected and HIV-uninfected children in the Child Health and Mortality Prevention Surveillance study—Kenya

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Abstract

Objectives: Describe the causes of death among infants and children <5 years stratified by HIV status.

Design: Cross-sectional analysis of causes of death ascertained through minimally invasive tissue sampling (MITS) in the Kenya Child Health and Mortality Prevention Surveillance site.

Methods: We included decedents aged 28 days to <5 years, whose death was reported within 36 hours, underwent MITS, and had HIV test results and causes of death determined. MITS specimens were tested using Taqman Array Cards, culture, cytology, histopathology and immunohistochemistry and HIV polymerase chain reaction. A panel evaluated epidemiologic, clinical, verbal autopsy and laboratory data to assign causes of death using ICD10 guidelines. Causes of death and etiological agents were stratified by HIV status.

Results: Of 176 included decedents, 14% (n=25) were HIV-infected, median viral load was 112,205 copies per milliliter (interquartile range [IQR]= 9,349–2,670,143). HIV-disease (96%; n=24) and malnutrition (23%; n=34) were the leading underlying causes of death in HIV-infected and HIV-uninfected decedents, respectively. Malnutrition was more frequent in the causal chain of HIV-infected (56%; n=14) than HIV-uninfected decedents (31%; n=49) (p-value=0.03). Viral pneumonia was twice as common in HIV-infected (50%; n=9) than HIV-uninfected decedents (22%; n=7) (p-value=0.04).

Conclusion: Nearly all HIV-infected decedents' underlying cause of death was HIV disease which was associated with malnutrition. Our findings underscore the need for strengthening early identification and management of HIV-infected children. Prevention, early diagnosis and treatment of malnutrition could be instrumental in improving the survival of HIV-infected and HIV-uninfected children.

Key words: Cause of death, HIV, child mortality, infant mortality

Introduction

Sub-Saharan Africa has the highest child mortality rate in the world, with 1 in 13 children dying before their fifth birthday [1, 2]. Infectious diseases, including malaria, diarrhea, sepsis, Human Immunodeficiency Virus (HIV)/acquired immunodeficiency syndrome (AIDS) (HIV/AIDS) and pneumonia are leading drivers of high childhood morbidity and mortality in this region [3, 4]. In spite of near-universal access to antiretroviral therapy (ART), numerous studies have documented persistently high mortality rates among children living with HIV (CLHIV) [5-7], particularly among children co-infected with HIV and tuberculosis (TB) [8].

Between 1990 and 2015, under-five mortality in Kenya decreased from 102.3 to 49.4 per 1,000 live births, a substantial decline, which nevertheless fell short of the millennium development goal target of 34 deaths per 1,000 live births by 2015 [9]. There are marked regional disparities in under-five mortality rates in Kenya. In the area formerly known as the Nyanza region in western Kenya, under-5 mortality was 82 per 1000 births in 2014, nearly twice the national average [9]. Higher child mortality in western Kenya has largely been attributed to the high burden of infectious diseases, including malaria and HIV [10]. Kisumu and Siaya counties together accounted for less than 5% of all children <15 years of age in Kenya, but nearly 20% (18,940) of all children living with HIV [11, 12]. Despite aggressive scale-up of programs to prevent mother-to-child transmission (MTCT) of HIV [13] and to initiate children living with HIV on sustained ART [14], mathematical modeling and routine surveillance data point to persistent mother-to-child transmission of HIV and high mortality among CLHIV [11, 15] in this region.

Little is known about HIV prevalence or the immediate and underlying causes of death among children in western Kenya. Reliable data on causes of death in children under five are remarkably limited in low- and middle-income countries (LMIC), including Kenya, where cause of death information is often derived from modeling of data obtained from administrative sources and verbal autopsies, the accuracy of which has been challenged [16, 17]. Post-mortem validation of cause of death is necessary, particularly in LMICs where civil registration and vital statistics systems are weak [18]; however, determination of cause of death in low-resource settings is impaired by inadequate diagnostic facilities, multiple co-morbidities [19, 20], and the conduct of relatively few autopsies owing to low acceptability and inadequate pathology expertise [21-26].

Minimally-invasive tissue sampling (MITS) for determination of causes of death [27-29] has been shown to be sufficiently accurate in the pediatric population [30, 31] and more acceptable than full autopsies in the general population [32, 33]. The Child Health and Mortality Prevention Surveillance (CHAMPS) study uses MITS autopsy results, health records and other data sources to determine and track causes of under-five mortality in seven sites in south Asia and sub-Saharan Africa including Kenya [34]. We analyzed CHAMPS data collected in Kenya to estimate HIV cause-specific morality rates in children under 5 years of age, and to describe the causes of death among infants and children aged 28 days to under 5 years by HIV status.

Methods

Study setting: CHAMPS activities are conducted in Siaya and Kisumu Counties located in the former Nyanza region in western Kenya. Mortality surveillance is conducted within two health and demographic surveillance system (HDSS) sites which have a combined under-five population of 22,270: Karemo, a rural area in Siaya County and Manyatta, an urban informal settlement in Kisumu County [35]. In Kenya, deaths that occur in the community are notified through village chiefs who fill a death notification that is forwarded to the civil registration and vital statistics department [36, 37]. For hospital deaths, medical personnel fill out a death notification form, including a section on causes of death [36, 37]. Only 46.6% of routine causes of death data are correctly captured. Most death notifications have incomplete information or the mechanism of death is recorded as the cause of death (e.g respiratory failure is recorded as the cause of death instead of pneumonia) [37].

CHAMPS mortality surveillance is conducted through focal persons based in health facilities, community health volunteers, village reporters, religious leaders and other community resource persons [38]. When a potentially eligible death is detected, the CHAMPS surveillance team is notified through a phone call or text message. The surveillance team then screens the notified death for eligibility through an in-person interview with the next of kin. All stillbirths and deaths among HDSS residents less than 5 years of age are eligible for enrollment; deaths notified within 36 hours are eligible for MITS. Written informed consent are provided by parents, guardians or relatives of eligible decedents prior to enrollment.

Study design and procedures: CHAMPS mortality surveillance and MITS procedures are described in detail elsewhere [38, 39]. Briefly, verbal autopsies are conducted within four weeks of death, and clinical data are abstracted from the medical records. Maternal clinical records, containing maternal demographic characteristics, antenatal care visits, maternal TB, HIV and ART status, are abstracted for stillbirths, neonates (decedents aged less than 28 days) and infants (decedents aged 28 days to less than one year) but rarely for older children. MITS is conducted at Jaramogi Oginga Odinga Teaching and Referral Hospital in Kisumu; specimens collected are tested by real-time PCR using TaqMan Array Cards, bacterial culture, cytology and histopathology at the Kenya Medical Research Institute (KEMRI) histopathology laboratory; the CDC pathology laboratory in Atlanta, GA, USA reviews histopathology slides and performs immunohistochemistry to detect antigens of disease-causing microorganisms (etiological agents) in tissues. HIV polymerase chain reaction (PCR) tests and TB tests using Gene Xpert® (MTB/RI; Sunnyvale, CA) are performed at KEMRI laboratory in Kisumu, Kenya.

A determination of cause of death (DeCoDe) panel of experts evaluates all available information from linked maternal data, child clinical data, individual demographic and epidemiologic data, verbal autopsy and laboratory results [40]. Causes of death are assigned and coded according to the International Statistical Classification of Diseases tenth revision (ICD-10) rules [41]. If multiple diseases or conditions contributed to death, the conditions are arranged in a causal sequence from the "underlying", "morbid" and "immediate" causes of death resulting in a causal chain. Diseases or conditions that triggered the chain of events that directly led to death are listed as underlying causes of death; diseases or conditions that directly caused death are listed as immediate causes of death. If there is a condition by which the underlying cause brings about the immediate cause of death, then that is listed as a morbid cause of death. For instance, if a decedent has HIV, pneumonia and sepsis contributing to death, HIV disease is listed as the underlying cause because it caused immunosuppression which predisposed the child to pneumonia (morbid cause), the organism causing pneumonia then spread through blood to other tissues causing sepsis (immediate cause) which directly caused death. If only one disease or condition is identified as the cause of death, this condition is listed as both the underlying and immediate cause of death. HIV disease is considered the underlying condition in HIV-infected decedents who meet the clinical (diagnosis

of any WHO stage 3 or 4 conditions) or immunological criteria of advanced HIV [42]. When HIV disease is listed as the cause of death, a specific sub-diagnosis is assigned based on ICD-10 codes which are broadly classified into HIV-disease resulting in infectious and parasitic diseases, HIV disease resulting in malignant neoplasms, HIV disease resulting in other specified diseases, HIV disease resulting in other conditions and unspecified HIV disease [41]. For instance, HIV-infected decedents with features of malnutrition have HIV disease resulting in wasting syndrome (ICD-10 code B22.2) listed as the underlying cause of death.

Data analysis

Data were analyzed using Stata version 16. We calculated frequencies and proportions to describe the socio-demographic and clinical characteristics of decedents, stratified by HIV status. Decedents with a positive MITS HIV PCR result were considered HIV-infected, and decedents with a negative MITS HIV PCR result were considered HIV-uninfected. Decedents who did not have a MITS HIV PCR result were excluded from analysis. Viral load less than 1000 copies per milliliter were considered virally suppressed, consistent with Kenyan guidelines [13].

Immediate morbid, and underlying cause-specific mortality fractions were compared between HIV-infected and HIV-uninfected decedents. We used Pearson's chi square or Fisher's exact test if the expected value in 20% or more of the cells was less than 5 to compare categorical variables; a p-value <0.05 was considered statistically significant. Analysis of causes of death included decedents 28 days to <5 years of age enrolled in CHAMPS in May 2017 through September 2020 who had a MITS autopsy, documented DeCoDe determination, and HIV PCR test result. We calculated the all-cause and HIV cause-specific mortality rates per 1,000 live births, and per 1,000 children under 5 years in the CHAMPS study area for the period of January 1, 2018 to December 31, 2019. Overall mortality rates were calculated by dividing the total number of death notifications for children 0–59 months, irrespective of study eligibility, by the number of live births/number of children under 5 years at annual mid-point, respectively, in each of the study catchment areas during the 2 years. HIV cause-specific mortality rates were calculated by multiplying the overall rates by the proportion of deaths due to HIV among decedents 0–59 months enrolled in CHAMPS. The denominators were obtained from HDSS notifications.

Ethical approval for this study was obtained from KEMRI scientific and ethics review unit (SERU) and Emory University (Atlanta, GA, USA).

Results

Overview of study participants

A total of 389 deaths in children aged 28 days to <5 years were reported in the CHAMPS catchment area during the study period; 71% (n=275/389) were enrolled (**Figure 1**). Of enrolled decedents, 75% (n=206/275) underwent MITS, of which 89% (n=183/206) had a documented DeCoDe

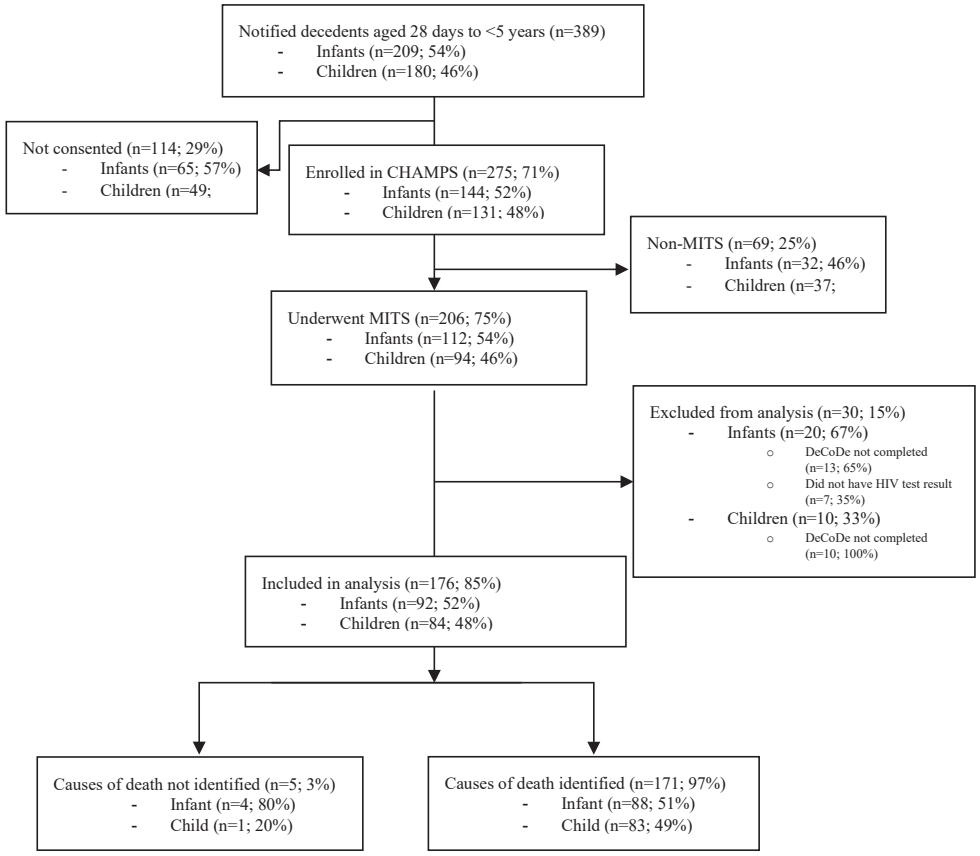

Figure 1: Summary of decedent notifications and MITS procedures of decedent infants and children aged one to four years enrolled in the Kenya CHAMPS site 2017 to 2020

review. Of the decedents that had both MITS and DeCoDe, 96% (176/183) had an HIV PCR test result and were included in this analysis.

Demographic and clinical characteristics

Overall, 52% (n=92/176) of decedents included in the analysis were infants (aged 28 days to 11 months), 57% (n=100/176) died in a health facility, and 14% (n=25/176) were HIV-infected (**Table 1**). All of the HIV-infected decedents with maternal information (100%, n=19/19) had mothers with primary school or less level of education compared to 71% (n=83) of the HIV-uninfected decedents' mothers (p=0.02). Children aged 12 months to <5 years accounted for 64% (n=16/25) of HIV-infected decedents and 45% (n=68/151) of HIV-uninfected decedents (p-value=0.08). Viral load testing was conducted for 92% (n=23/25) of HIV-infected decedents and nearly all (96%, n=22/23) decedents had a viral load >1,000 copies per milliliter (c/mL), only one decedent (4%) was virally suppressed. The median viral load was 112,205 c/mL (IQR: 9,349–2,670,143 c/mL).

Table 1: Demographic, clinical and maternal characteristics of HIV-infected and HIV-uninfected decedents aged 28 days to <5 years enrolled in the Kenya CHAMPS study, 2017–2020 (N=176)

Characteristics	HIV-uninfected	HIV-infected	Total	P -value
	N (col %)	N (col %)	N (col %)	
All	151	25	176	
Child age (N=176)				
Infant (28 days-11 months)	83 (55)	9 (36)	92 (52)	0.08
Child (1-4 years)	68 (45)	16 (64)	84 (48)	
Sex (N=176)				
Male	78 (52)	14 (56)	92 (52)	0.69
Female	73 (48)	11 (44)	84 (48)	
HDSS (N=176)				
Manyatta	79 (52)	15 (60)	94 (53)	0.52
Karemo	72 (48)	10 (40)	82 (47)	
Place of death (N=176)				
Community	65 (43)	11 (44)	76 (43)	0.93
Health facility	86 (57)	14 (56)	100 (57)	
Number of living siblings (N=81)				
0	25 (34)	1 (13)	26 (32)	
1-2	38 (52)	6 (74)	44 (54)	0.39
≥3	10 (14)	1 (13)	11 (14)	
Maternal age group (N=150)				
<25 years	38 (29)	2 (10)	40 (27)	
25 – 34 years	82 (64)	18 (86)	100 (67)	0.12
>34 years	9 (7)	1 (5)	10 (7)	
Maternal education (N=136)				
No Education	2 (2)	0 (0)	2 (1)	
Primary	83 (71)	19 (100)	102 (75)	0.02
Secondary and above	32 (27)	0 (0)	32 (24)	
Maternal marital status (N=156)				
Currently married	117 (88)	21 (91)	138 (88)	1.00
Unmarried	16 (12)	2 (9)	18 (12)	
Number of ANC visits (N=151)				
1 to 3	97 (74)	18 (90)	115 (76)	0.16
≥4	34 (26)	2 (10)	36 (24)	
Maternal HIV status (N=140)				
HIV positive	24 (20)	15 (79)	39 (28)	0.00
HIV negative or unknown	94 (80)	4 (21)	98 (72)	

Underlying causes of death

Causes of death were determined for the majority of included decedents (97%, n=171/176). Cause of death was undetermined for five decedents due to inadequate information. Pediatric HIV-disease was the underlying cause of death in 96% (n=24/25) of HIV-infected decedents (**Table 2**). By ICD-10 classification, seven distinct categories of pediatric HIV-disease were identified in HIV-infected decedents (**Table S1**); 60% (n=15/25) died of HIV-disease resulting in wasting. Leading underlying causes of death in HIV-uninfected children were malnutrition (23%; n=34/146), malaria (23%; n=33/146), pneumonia (10%; n=14/146) and gastroenteritis (7%; n=10/146), which together accounted for over 60% of deaths in this group (**Table 2**).

Table 2: Underlying* causes of death of HIV-infected and HIV-uninfected decedents aged 28 days to <5 years enrolled in the Kenya CHAMPS study, 2017–2020 (N=171)

Underlying	HIV-uninfected (n=146) n (%)	HIV-infected (n=25) n (%)	Total (n=171) n (%)
Malnutrition	34 (23)	0 (0)	34 (20)
Malaria	33 (23)	0 (0)	33 (19)
HIV disease	0 (0)	24 (96)	24 (14)
Pneumonia	14 (10)	0 (0)	14 (8)
Gastroenteritis	10 (7)	0 (0)	10 (6)
Prematurity	8 (5)	0 (0)	8 (5)
Aspiration pneumonia	6 (4)	1 (4)	7 (4)
Cerebral palsy	6 (4)	0 (0)	6 (4)
Congenital malformation	6 (4)	0 (0)	6 (4)
Sepsis	4 (3)	0 (0)	4 (2)
Other	4 (3)	0 (0)	4 (2)
Down's syndrome	3 (2)	0 (0)	3 (2)
Sickle cell disease	3 (2)	0 (0)	3 (2)
Child neglect	2 (1)	0 (0)	2 (1)
Congenital infections	2 (1)	0 (0)	2 (1)
Trauma	2 (1)	0 (0)	2 (1)
Diabetes mellitus	1 (1)	0 (0)	1 (1)
Failure to thrive	1 (1)	0 (0)	1 (1)
Foreign body in trachea	1 (1)	0 (0)	1 (1)
Intestinal obstruction	1 (1)	0 (0)	1 (1)
Leukemia unspecified	1 (1)	0 (0)	1 (1)
Myeloid leukaemia	1 (1)	0 (0)	1 (1)
Pertussis	1 (1)	0 (0)	1 (1)
Meningitis	1 (1)	0 (0)	1 (1)
Toxic effects of carbon monoxide	1 (1)	0 (0)	1 (1)

* Underlying cause of death: the disease or condition that triggers the chain of events that eventually cause death.

Immediate and morbid causes of death

The majority (92%, n=157/171) of decedents had immediate causes of death that were different from the underlying causes of death. Malaria was the immediate cause of death in 28% (n=41/146) of HIV-uninfected and 29% (n=7/25) HIV-infected decedents (p-value=0.91) (**Table 3**). Sepsis was the immediate cause of death in 23% (n=34/146) of HIV-uninfected and 17% (n=4/25) of HIV-infected decedents (p-value=0.47). Pneumonia, as an immediate cause of death, was twice as prevalent among HIV-infected (33%; n=8/25) as compared to HIV-uninfected decedents (16%; n=23/146) (p-value=0.05).

Table 3: Immediate and morbid causes of death of HIV-infected and HIV-uninfected decedents aged 28 days to <5 years enrolled in the Kenya CHAMPS study, 2017—2020 (N=171)

Causes of death	HIV-uninfected (n=146)	HIV-infected (n=25)	p-value
Immediate conditions			
Malaria	41 (28)	7 (29)	0.91
Sepsis	34 (23)	4 (17)	0.47
Pneumonia	23 (16)	8 (33)	0.05
Aspiration Pneumonia	14 (10)	2 (8)	1.00
Gastroenteritis	11 (8)	3 (13)	0.42
Bacteremia	3 (2)	0 (0)	1.00
Head injury	2 (1)	0 (0)	1.00
Pneumonitis	2 (1)	0 (0)	1.00
Other conditions	16 (11)	1 (4)	0.47
Morbid conditions			
Malnutrition	15 (10)	5 (21)	0.17
Pneumonia	15 (10)	1 (4)	0.70
Malaria	3 (2)	2 (8)	0.15
Gastroenteritis	3 (2)	1 (4)	0.46
Anaemia	1 (1)	1 (4)	0.26
Surgical complications	2 (1)	0 (0)	1.00
Other conditions	11 (8)	3 (13)	0.42

* Immediate cause of death – the disease or condition that directly leads to death

** Morbid cause of death – diseases or conditions by which an underlying condition leads to the immediate cause of death.

Forty four percent (n=11/25) of HIV-infected decedents had at least one morbid condition listed in the causal chain compared to 24% (n=35/146) of HIV-uninfected decedents (p=0.05). Malnutrition was the most common morbid condition overall and was more frequent in HIV-infected (21%; n=5/24) than HIV-uninfected (10%; n=15/146) decedents (p-value=0.18). The

prevalence of malnutrition in the entire causal chain (immediate, morbid and underlying causes of death) was significantly higher among HIV-infected (56%; n=14/25) than HIV-uninfected decedents (32%; n=49/151) (p-value=0.04) (data not shown).

Infectious pathogens

Etiological agents (disease causing microorganisms) were identified for 92% (n=36/39) of decedents with sepsis in the causal chain; 25% (n=9/36) of sepsis incidents with etiological agents were caused by multiple pathogens. Bacterial pathogens accounted for 89% (n=41/46) of sepsis pathogens among HIV-uninfected and 75% (n=3/4) among HIV-infected decedents (p-value=0.41) (**Table 4**). *Klebsiella pneumoniae* was isolated in 35% (n=16/46) of HIV-uninfected and none of HIV-infected decedents with sepsis pathogens (**Table S2**). Adenovirus was the most common viral cause of sepsis in both HIV-infected (25%, n=1/4) and HIV-uninfected (7%, n=3/46) decedents.

Table 4: Etiological agents of sepsis, pneumonia and gastroenteritis of HIV-infected and HIV-uninfected decedents aged 28 days to <5 years enrolled in the Kenya CHAMPS study, 2017—2020

Etiological agent	HIV-uninfected	HIV-infected	p-value
Sepsis (N=39)			
Bacterial pathogens	41 (89)	3 (75)	0.41
Viral pathogens	5 (11)	1 (25)	
Pneumonia (N=53)			
Bacterial pathogens	45 (76)	7 (39)	0.06
Fungal	1 (2)	2 (11)	
Viral pathogens	13 (22)	9 (50)	
Gastroenteritis (N=20)			
Bacterial pathogens	1 (14)	0 (0)	1.00
Viruses	6 (86)	1 (100)	

Etiological agents were identified in 79% (n=42/53) of decedents with pneumonia in the causal chain. The frequency of viral pneumonia was two-fold higher in HIV-infected decedents (50%; n=9/18) as compared to HIV-uninfected decedents (22%; n=13/59) (p-value=0.06). Cytomegalovirus was the most common cause of viral pneumonia in both HIV-infected (28%; n=5/18) and HIV-uninfected (8%; n=3/59) decedents. While Klebsiella pneumoniae was the most frequently identified bacterial cause of pneumonia in HIV-uninfected children (31%; n=18/59), Streptococcus pneumoniae was the most common bacterial cause of pneumonia in HIV-infected children (22%; n=4/18). Pneumocystis jiroveci caused pneumonia in two HIV-infected and one

HIV-uninfected decedent. Although five decedents (one HIV-uninfected and four HIV-infected) had been on TB treatment ante-mortem, Mycobacterium tuberculosis was not detected in this study.

All-cause and HIV cause-specific mortality rates

The overall under-five mortality rate was 63.4 per 1,000 live births and was marginally higher in the Karemo versus Manyatta HDSS (66.4 vs. 59.0 per 1,000 live births, respectively; p-value=0.23) (**Table S3**). There were 14.5 deaths per 1,000 under-five children overall, with significantly higher mortality in Karemo than in Manyatta (16.5 vs 12.1 deaths per 1,000 children, respectively, p-value<0.01). The HIV cause-specific mortality rate was 9.4 per 1,000 live births overall, and 8.9 versus 10.0 per 1,000 live births in the Karemo versus Manyatta HDSS, respectively (p-value=0.62).

Discussion

Over one tenth of decedent children in this study were HIV-infected. HIV positivity was higher in decedents aged one to four years than in post-neonatal infants (children aged 28 days to 11 months). The immediate causes of death in HIV-infected and HIV-uninfected decedent children were similar, with malaria, sepsis and pneumonia being predominant. The under-five mortality rates (63.4 per 1,000 live births) observed in this study period (2018–2019) demonstrate a marked decline in under-five mortality from the 2003 and 2014 estimates for the Nyanza region (206 and 82 per 1,000 live births, respectively) [9] and estimates in the Siaya HDSS in 2008 (202.8 per 1,000 live births; 47.5 per 1,000 children under 5 years) [43] but remain substantially (22%) above the national average (49.4 per 1,000 live births). Nearly all deaths were due to causes for which effective interventions are widely available in Kenya [44].

Although recent studies have reported a decline in HIV cause-specific mortality globally [45], and in Kenya [44] , our findings suggest that HIV cause-specific mortality in infants and children aged 28 days to less than 5 years remains relatively high in western Kenya. Despite earlier studies reporting high ART coverage among HIV-infected pregnant women [46, 47] and low mother-to-child transmission rate [48] in Kenya, the HIV cause-specific mortality rate observed in this study (9.4 per 1,000 live births) was relatively high compared to estimates based on verbal autopsy data

(7.54 and 5.18 per 1,000 person-years in children aged 1-11 months and 1 to 4 years, respectively) [49]. Our finding suggests that there continues to be children living with vertically-acquired HIV who have either not been identified, or have been diagnosed with HIV but not initiated on sustained ART in high-prevalence settings. Such children are at risk of dying from their HIV infection. Indeed, the 2018 Kenya Population-based HIV Impact Assessment (KENPHIA) reported that 79% of CLHIV had a known HIV status, 93% of whom were on ART, but viral suppression was only achieved for 67% [50]. In our analysis, while the knowledge of HIV and ART status could not be objectively assessed, nearly all HIV-infected decedents were virally non-suppressed indicating delayed diagnosis, delayed ART initiation, poor adherence, ART failure or drug resistance. This analysis speaks to the importance of strategies to strengthen efforts aimed at early identification of CLHIV, prompt ART initiation and focused interventions to improve the management of virally-unsuppressed children to further reduce HIV cause-specific mortality among children aged under 5 years.

Unlike the global burden of disease that is based on underlying causes of death alone [51], CHAMPS provides an opportunity to examine the contribution of conditions throughout the causal chain [34]. Malnutrition was the leading underlying cause of death among HIV-uninfected decedents but was more frequent in the causal chain of HIV-infected decedents as HIV-disease with wasting syndrome or as morbid conditions. This finding is in line with recent studies from Asia and Uganda that reported increased mortality among HIV-infected children who have severe acute malnutrition [52, 53]. The increased risk of death could be due to the synergistic immuno-suppressive effects of both diseases rendering the child vulnerable to fatal infections. Early identification and management of malnourished children, including HIV testing and counseling for children with unknown HIV status, and special focus on management of children with known HIV-infection could substantially reduce under-five mortality.

Malaria was the leading immediate cause of death among the HIV-uninfected children in this analysis, and the second leading cause of death among the HIV-infected children. Malaria blood slide positivity as high as 38% has been observed in endemic settings in western Kenya where malaria accounts for up to 27% of outpatient morbidity in children under five years [54]. Furthermore, malaria-related mortality in hyperendemic parts of western Kenya remains high (60.9

per 1, 000 under-five admissions) despite increasing coverage of preventive interventions and case management [54].

Pneumonia was the leading immediate cause of death in HIV-infected children, which is consistent with findings reported by a study that assessed health outcomes of children on ART in 4 hospitals in western Kenya [55] and an autopsy study conducted in Zambia [56]. In HIV-uninfected decedents, bacterial pathogens (*Klebsiella pneumoniae and Streptococcus pneumoniae)* were the most common causes of pneumonia, which is in contrast to previous studies that reported *S. pneumoniae,* and *Staphylococcus aureus* were the leading causes of severe pneumonia in children in India and Ethiopia [57, 58]. The high frequency of *K. pneumoniae* is unexpected. *K. pneumoniae* rarely causes community-acquired pneumonia and is difficult to treat [59], raising the possibility of nosocomial infections [60]. *K. pneumoniae* has been reported by some studies as a leading cause of nosocomial infections in Kenya [61, 62]. In a retrospective review of blood culture isolates over a ten-year period at Moi Teaching and Referral Hospital in western Kenya, *K. pneumoniae* accounted for 23% of isolates with high prevalence in the newborn unit and pediatric wards [63]. As expected, viruses and *Pneumocystis jiroveci* (atypical pathogens) were the predominant causes of pneumonia in HIV-infected children. Emerging evidence shows that pneumonia is frequently caused by co-infections with bacterial and viral pathogens, regardless of HIV status [64, 65]. Ante-mortem diagnosis of pneumonia largely relies on clinical presentation and radiological findings, whereby it is often impossible to distinguish viral from bacterial disease. In Kenya, antibiotics are recommended for empirical treatment of pneumonia in children aged under 5 years [66]. A study reported that 30% of HIV-infected children with pneumonia fail treatment in 48 hours, probably due to targeting the wrong organism [67]. Pneumonia treatment guidelines could be reviewed to incorporate the management of viral pneumonia, especially in HIV-infected children.

Mycobacterium tuberculosis, the primary etiological agent of TB, was not detected in any of the decedents in this population. However, at least four (16%) of the HIV-infected children had documentation of TB treatment; three of these children had HIV with wasting as the underlying COD. This is in contrast to a study conducted in Mozambique, which found TB in 6% of children undergoing complete diagnostic autopsy [68]. Although minimally invasive autopsies have been found to be effective for detecting TB using lung and other body fluids [69], the notable lack of TB

in our study could be explained by MITS having missed tuberculosis lesions in the lungs in some cases.

Sepsis is recognized as a leading cause of morbidity and mortality in children under-five years in sub-Saharan Africa [70]. In a South African study, the prevalence of sepsis among children admitted to a pediatric intensive care unit was 42.6% and was highest in infants (50.4%) [71]. Of the deaths in the pediatric intensive care unit, 14.2% were sepsis-related [71]. Globally bacterial pathogens, particularly *S. aureus*, *Pseudomonas* species and *E. coli* are responsible for a majority of sepsis cases [71-73]. In our study, viral pathogens were more common than previous studies, which estimated they account for less than 1% of sepsis cases [74, 75]. Among the bacterial causes, *K. pneumoniae* was leading in HIV-uninfected and *S. pneumoniae* in HIV-infected decedents. This could be because *K. pneumoniae* was more common in younger children (infants) most of whom were HIV-uninfected. In the South African study, *S. pneumoniae* was the most common gram-positive bacterium causing sepsis [71].

Our study had some limitations. Nearly 30% of notified deaths were not enrolled due to lack of informed consent. It is possible that factors related to the child's cause of death could have influenced the parents' decision to participate in the surveillance project, though we were unable to assess this possibility. Past medical history of decedents and their mothers relied on medical records, which may be incomplete or inaccurate regarding HIV and ART status of mothers or decedents. We could not examine maternal HIV testing and ART during pregnancy because the CHAMPS protocol specified maternal medical record abstractions only for stillbirths, neonates and infants. We were also unable to estimate HIV-free survival among children due to limitations in the study design. Due to the small sample size of HIV-infected children, multivariable analysis of factors associated with specific causes of death controlling for multiple confounders could not be completed. Nonetheless, despite these limitations, the detailed clinical and pathological data collected allow for a richer understanding of child mortality and the role of pediatric HIV infection in child mortality in this setting.

Conclusion

Conditions with effective and widely available interventions (malnutrition, HIV, malaria, pneumonia and gastroenteritis) were responsible for the majority of deaths among infants and children. Nearly all deaths among HIV-infected decedents were due to uncontrolled HIV infection as indicated by the high prevalence of wasting and high viral load. These findings underscore the need to strengthen identification of CLHIV, prompt ART initiation, aggressive treatment monitoring as well as screening and early management of malnutrition among CLHIV. With the exception of pneumonia, immediate causes of death were similar in HIV-infected and HIV-uninfected decedents. Differences in the etiology of pneumonia could inform clinical algorithms with emphasis on treatment of viral pneumonia in children.

Authors' contributions

DOO, VA, JAA, SW, AKI, DMB, EZG and BTB conception, design and execution of this study. DOO, MABVDS, JAW, PWY, RR, EAO, RHJ and CMY jointly conducted all quantitative analysis. DOO, JAW and CMY participated in preparing the first draft. VA, JAA, SW, AKI, EAO, DMB, EZG, MABVDS, PWY, RR, RHJ and BTB reviewed and critically revised the manuscript for intellectual content. All authors contributed substantially to review and revision of the manuscript and have read and approved the final manuscript.

Conflict of interest

There are not conflicts of interest

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Table S1: ICD-10 classification of underlying causes of death in HIV-infected decedents 28 days to < 5 years enrolled in the Kenya CHAMPS study, 2017—2020 (N=25)

ICD 10 code	Condition	n (%)
B22.2*	HIV disease resulting in wasting syndrome	15 (60)
B24	Unspecified HIV disease	3 (12)
B20.7	HIV disease resulting in multiple infections	2 (8)
B20.9	HIV disease resulting in unspecified infectious or parasitic disease	2 (8)
B20.6	HIV disease resulting in Pneumocystis jirovecii pneumonia	1 (4)
20.8	HIV disease resulting in other infectious and parasitic diseases	1 (4)
J69.0	Aspiration pneumonia	1 (4)

*Includes children with wasting, failure to thrive and slim disease

Table S2: Etiological agents of sepsis, pneumonia and gastroenteritis of HIV-infected and HIV-uninfected decedents aged 28 days to <5 years enrolled in the Kenya CHAMPS study, 2017—2020 (N=171)

Etiological agent	HIV-uninfected	HIV-infected	Total
Sepsis (N=39)			
Bacterial pathogens	***41 (89)***	***3 (75)***	***44 (88)***
Klebsiella pneumoniae	16 (35)	0 (0)	16 (32)
Streptococcus pneumoniae	9 (20)	1 (25)	10 (20)
Staphylococcus aureus	4 (9)	0 (0)	4 (8)
Streptococcus pyogenes	4 (9)	0 (0)	4 (8)
Escherichia coli	4 (9)	1 (25)	5 (10)
Acinetobacter baumanii	1 (2)	0 (0)	1 (2)
Haemophilus influenzae	1 (2)	0 (0)	1 (2)
Enterobacter cloacae	1 (2)	0 (0)	1 (2)
Streptococcus species	0 (0)	1 (25)	1 (2)
Enterococcus species	1 (2)	0 (0)	1 (2)
Viral pathogens	***5 (11)***	***1 (25)***	***6 (12)***
Adenovirus	3 (7)	1 (25)	4 (9)
Cytomegalovirus (CMV)	2 (4)	0 (0)	2 (4)
Pneumonia (N=53)			
Bacterial pathogens	***45 (75)***	***7 (38)***	***52 (66)***
Klebsiella pneumoniae	18 (31)	1 (6)	19 (25)
Streptococcus pneumoniae	14 (24)	4 (22)	18 (23)
Haemophilus influenzae	5 (8)	0 (0)	5 (6)
Staphylococcus aureus	5 (8)	0 (0)	5 (6)
Escherichia coli	2 (3)	0 (0)	2 (3)
Streptococcus species	0 (0)	2 (11)	2 (3)
Haemophilus parainfluenza	1 (2)	0 (0)	1 (1)
Fungal	***1 (2)***	***2 (11)***	***3 (4)***
Pneumocystis jiroveci	1 (2)	2 (29)	3 (6)
Viral pathogens	***13 (24)***	***9 (50)***	***22 (30)***
Cytomegalovirus (CMV)	5 (8)	5 (28)	10 (13)
Respiratory syncytial virus	1 (2)	2 (11)	3 (4)
Human metapneumovirus	0 (0)	1 (6)	1 (1)
Influenza A/B	4 (7)	0 (0)	4 (5)
Parainfluenza virus	1 (2)	1 (6)	2 (3)
Adenovirus	2 (0)	0 (0)	2 (3)
Gastroenteritis (N=20)			
Bacterial pathogens	***1 (14)***	***0 (0)***	***1 (12)***
Campylobacter jejuni	1 (20)	0 (0)	1 (1)
Viruses	***6 (86)***	***1 (100)***	***7 (88)***
Adenovirus	2 (29)	1 (100)	3 (38)
Rotavirus	2 (29)	0 (0)	2 (25)
Norovirus	2 (29)	0 (0)	2 (25)

Table S3: Under-five mortality rate and HIV cause-specific mortality rate per 1, 000 live births in the Kenya CHAMPS site, 2018-2019

Mortality indicator	Karemo	Manyatta	Total
Number of under-five deaths notified to HDSS (neonates included)	285	170	455
Estimated number of under-five deaths who were HIV-infected*	40	30	70
Estimated number of deaths caused by HIV**	38.4	28.8	67.2
Number of live births	4291	2883	7174
Under-five population	17293	14107	31400
Under-five mortality rate per 1,000 live births	66.4	59.0	63.4
HIV-cause specific rate per 1,000 live births	8.9	10.0	9.4
Under-five mortality per 1,000 children	16.5	12.1	14.5

CHAPTER 4

Leading causes of death and high mortality rates in an HIV endemic setting (Kisumu County, Kenya, 2019)

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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: Medical experts trained in COD certification examined medical charts and ascertained causes of death for 456 decedents 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 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 the independence of proportions using Pearson's chi-squared test.

Findings: 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 male decedents (42.1%; p=0.039). Conversely, more men/boys (8.6%) than women/girls (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%; κ=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. The epidemiologic transition suggests the need for increased focus on controlling noncommunicable conditions 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.

Keywords: Causes of death, mortality, global burden of disease (GBD), the epidemiologic transition, Kisumu, Kenya

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].

The overall crude mortality rate in Kenya is estimated to be 550/100,000 population [4]. Estimated all-cause mortality rates increased from 850/100,000 in 1990 to 902/100,000 in 2006 but subsequently decreased to 519/100,000 population by 2016 [5]. Infectious 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 infectious 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 had 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]. The number of deaths due to road-traffic accidents is 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. 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 men and 313 among women [14].

Although summarizing mortality rates using GBD classes is important, accurate and specific UCOD data are needed to guide and evaluate appropriate public health responses in preventive and curative services. The 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 a systematic assembly of health records, among other approaches [15]. Thus, to improve vital statistics, post-mortem examinations complemented by a hospital-based review 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 [17], and has a high HIV burden [18]. The two largest mortuaries in the county are located at Jaramogi Oginga Odinga Teaching and Referral Hospital (JOOTRH) 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 [19]. Deaths in Kisumu East civil registry for 3 years (2017–2019) contributed to a median of 74.8% of deaths registered in the entire county [20]. 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 a more extensive cross-sectional surveillance study to understand HIV-associated mortality in Kisumu County through determining prior HIV diagnosis, HIV-positivity, and viral load among cadavers; assessing the feasibility of using oral fluid obtained from cadavers for non-invasive rapid HIV antibody testing; and assessing the quality of the UCOD certification, HIV status documentation, and efficiency of death notification in Kisumu County.

Inclusion and exclusion criteria

Three categories of decedents from the two mortuaries were included in the larger study: hospital deaths (all deaths occurred in the hospital wards or outpatient department), dead on arrival (DOA; deaths occurred 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 larger study to establish the leading COD. They included all available medical files of the cadavers admitted to the two morgues during April 16–July 12, 2019, for hospital-based deaths of patients of any age. This analysis included decedents who died within the two hospitals whose medical records were available and excluded all decedents that were DOA, as they did not have medical history records at the hospitals. Decedents with unavailable death notification forms and medical charts were excluded.

Sample size

The sample size of 690 for the larger 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 also included to cover all decedents admitted to the mortuaries during the study period.

Ascertaining COD

For the purposes of 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 [21]. Afterward, the medical officers used a data entry form modified from the standard death notification form to abstract clinical information for hospital-based deaths from medical records. 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 accuracy and consistency and submitted to a central database.

Routinely notified versus panel-assigned COD

We abstracted immediate COD, antecedent COD, and UCOD as documented from notification forms for all deaths that occurred 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 was 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 larger study, as described elsewhere [22]. 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 as assigned based on ICD-10 coding rules.

Summary measures

Two parameters were used to calculate the summary rates. First, we considered the contribution of the two mortuaries to deaths in Kisumu East civil registry (42.0% in 2017) [19]. We then considered the contribution of the Kisumu East civil registry 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 reported during the study period multiplied by the estimated deaths attributed to specific causes based on the annualized number of deaths. These rates were 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 the Kenya health information system data to determine the number of deliveries in the two facilities during 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/) [23]. This tool provides a stepwise approach to a comprehensive analysis of ICD-10–coded data. We reviewed coded mortality data for errors and tabulated and presented the UCOD by age and sex in tables and charts using the tool. 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 larger 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 confirmed 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; **Fig. 1**). Therefore, 52% of decedents admitted to the mortuaries (442/851) during the study period could be included in our secondary analysis.

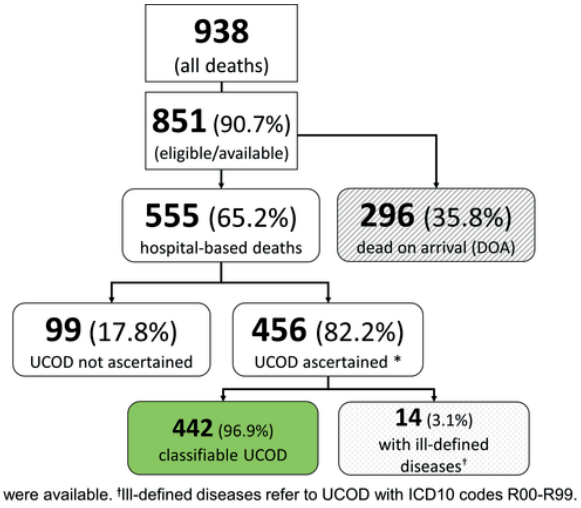

Fig 1: Deaths of hospitalized patients at two referral hospitals, Kisumu County, Kenya (2019).

Caption: The figure presents the data flow for the study and the analysis for this manuscript.

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 female (234) and male decedents (208) had their UCOD established and classified (**Table 1**).

Table 1. Distribution of ascertained causes of death by age and sex, and global burden of disease category from admissions at two large hospitals, Kisumu County, Kenya (2019)

		Group I[†]		Group II[‡]		Group III[§]	
	All	Male	Female	Male	Female	Male	Female
Age (years)	N (%*)	n (%)	n (%)	n (%)	n (%)	n (%)	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 chi-squared test show significance of differences in proportions for each GBD category by sex.

The prevalence of GBD group I causes was similar among men (49.0%) and women (45.7%; p=0.486). Significantly more women (52.1%) than men (42.3%) died due to GBD group II causes (p=0.039), and significantly more men (8.7%) than women (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 (**Fig. 2**). The largest age band for the population is 10–14 years. Children that were 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.

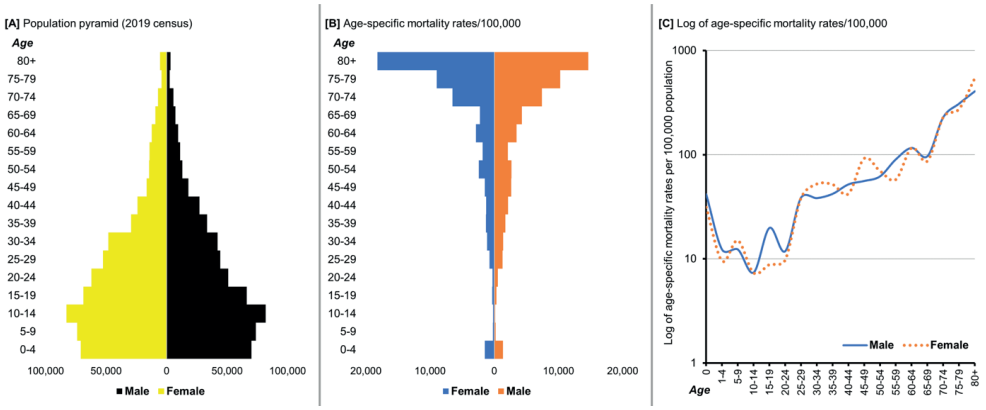

Figure 2: Population pyramid and estimated deaths per 100,000 by sex and age, Kisumu County, Kenya (2019).

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.

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 men had UCOD due to road traffic accidents, ranking sixth, but only three traffic accident-related deaths were reported among

women. Significantly more women (12.8%) than men (5.3%) died of hypertensive disease (p=0.006) and cancer (women, 6.8%; men, 1.9%; p=0.013).

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

	Total (n=442)	**UCOD by sex, rank, n (%)** [*]		
Causes of death	**Rank, n (%)**	***Male***	***Female***	**p-value**[†]
Leading causes	*n=341 (77.1)*	*n=149 (71.6)*	*n=192 (82.1)*	-
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
All other causes[¶]	*-, 101 (22.9)*	*-, 59 (28.4)*	*-, 42 (17.9)*	-
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/remained 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

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 County, Kenya (2019)

	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, reported 3,360 total

deliveries in the two facilities during April 1–July 31, 2019, and 81 (2.4%) stillbirths over 121 days [20]. 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 that were 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 were incorrectly ordered 10/167 [6.0%]), or incorrect 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]. Agreement between notified and ascertained UCOD was 29.2% (κ=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 the ascertained cause of death (COD) in Kisumu County, Kenya (2019)

		Type of errors, n (%)		
	N (%)	**Correct COD**	**Erroneous COD**	**p-value**
COD type				
Underlying	236 (100)	69 (29.2) *	167 (70.8) †	
Immediate	236 (100)	60 (25.4) ‡	176 (74.6)	
Sex				0.174§
Male	124 (52.5)	41 (33.1)	83 (66.9)	
Female	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%; κ=0.26); †Wrong assignment of COD (n=157 [94.0%]) and wrong sequence (n=10 [6.0%]); ‡Poor interrater agreement (25.4%; κ=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). Men (81,154/100,000 population) had a higher crude all-cause mortality rate compared to women (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, men had the highest rate (1,594/100,000 population; women, 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 359/100,000 population among all decedents. Women and girls of any age (274/100,000 population) had a slightly >20% higher mortality rate associated with HIV than boys and men (224/100,000 population), and deaths that were directly attributed to HIV/AIDS were nearly 40% higher among girls and women (413/100,000 population) than among boys and men (298/100,000 population). The rate of death due to HIV/AIDS was much greater among persons aged ≥15 years (388/100,000 population) compared to younger individuals (53/100,000 population) (**Table 5**).

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

	Mortality rate per 100,000 population								
Cause of death	**All**			**<15 years old**			**15+ years old**		
	M/F*	**M**	**F**	**M/F***	**M**	**F**	**M/F***	**M**	**F**
All-cause	***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
HIV									
HIV-associated[¶]	359	298	413	85	81	89	549	455	627
Due to HIV/AIDS[#]	251	224	274	53	40	67	388	362	410

*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 COD

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 [24] and double the rate found in a Nairobi mortality study (12.6%) [25]. 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. The prevalence of HIV infection was 23.7% among DOA compared to 31.0% among 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% [18], and our finding of high HIV-related mortality rates are 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 broad 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 the 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 men and women, which is below the proportions previously reported of 12.3%, [26], and 22.8%, [27], in informal urban settlements in Kenya. Cancer was the fourth leading COD and accounted for a greater proportion of deaths among women than men. 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, responsible for an estimated 9.6 million deaths in 2018 [29]. Additionally, our findings point to an epidemiologic transition underway in Kenyan adults in rural settings. This transition highlights the increasing importance of preventing noncommunicable diseases and reduce 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 infectious 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 (~10%), with similar mortality rates for both men and women [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 noncommunicable diseases among women and girls compared to men and boys.

Although exclusion of police cases and DOA likely disproportionately affected our estimates of violence-related deaths (relatively low overall even for men) and injury-related deaths, deaths due to injuries were still four times higher among men than among women, 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 men than for women. Deaths due to road traffic-related injuries could be decreased, especially among younger men, by training 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, we probably missed injury-related childhood deaths. However, in our study, hospital-based deaths had a proportionately higher number of decedents aged <5 years at the time of death than those DOA (**S1 Fig.**), whereas more decedents aged <70 years at the time of death were DOA than hospital-based deaths. Thus, the age distribution for DOA compared to hospital-based deaths was similar for most decedents aged 5–69 years (**S1.**). In our study, the proportions of deaths due to communicable diseases compared to noncommunicable diseases were approaching 1:1, similar to those previously reported through CRVS for Kisumu County [19]. 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 noncommunicable 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 partly due 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 pregnant and postpartum women the danger signs of complications during pregnancy and the peripartum period could trigger timely health-seeking behavior [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]. Still, it 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, 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. However, the rate we found was lower than that reported in a similar setting in neighboring Siaya County (1,446/100,000 population) [39] 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 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]. The 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 noncommunicable diseases 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.

Our study's very low agreement of ascertained UCOD compared to notified UCOD indicates that mortality statistics that depend wholly on death notifications may be grossly inaccurate. In addition, 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 [40]. 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 [41]. In 2015, Kenya scored 0 in each of these elements [40]. 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 [42].

Data contained in death notification forms in Kenya are 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 maximum acceptable 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 the time of certification in settings where HIV is a significant COD, and 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 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. We assumed that both mortality rates and reporting rates were similar in all calendar months for mortality rate estimates. The study was conducted in public health facilities, and we assumed that the cadavers admitted in JOOTRH and KCRH would represent the 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 estimating 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 to calculate mortality rates. These decedents were not selectively admitted to the morgues due to 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 noncommunicable disease related mortality rates, with HIV contributing to the highest proportion of communicable disease-related deaths. Men have higher rates of injury-related deaths than women, whereas women have higher rates of noncommunicable 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 noncommunicable disease-related deaths. Additionally, prevention and treatment of hypertension and increased screening and community awareness, including advocating for behavior changes such as cessation of smoking, could help decrease noncommunicable 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 [44]. 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 co-investigators and offered 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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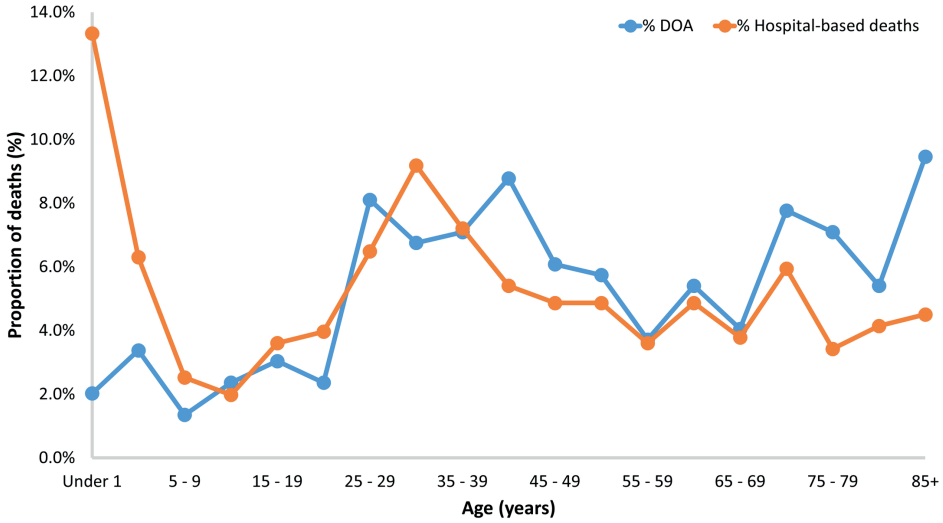
Supporting Information



S1 Fig. 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 compared to 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 5

Epidemiology of pediatric tuberculosis in Kenya and risk factors for mortality during treatment: a national retrospective cohort study

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Abstract

Objectives: To describe the epidemiology of childhood TB in Kenya, assess the magnitude of TB/HIV co-infection and identify risk factors for mortality during TB treatment.

Study design: We conducted a retrospective analysis of Kenya national tuberculosis program data of patients enrolled from 2013 through 2015. A total of 23,753 children aged less than 15years were included in the analysis. Survival analysis was performed with censorship at 9 months, mortality was the main outcome. We used Cox proportional hazards regression for assessing risk factors for mortality.

Results: Childhood TB accounted for 9% (n=24,216) of all TB patients; 98% (n=23,753) of the notified children were included in the analysis. TB/HIV co-infection was 28% (n=6,112). Most TB cases (71%; n=16,969) were detected through self-referral. Treatment was successful in 90% (n=19,088) while 4% (n=1,058) died. Independent risk factors for mortality included: being HIV-infected but not on ART (aHR=4.84; 95% CI-3.59-6.51); being HIV-infected and on ART (aHR=3.69; 95% CI-3.14-4.35); children aged less than five years (aHR=1.25; 95% CI-1.08-1.44) and being diagnosed with smear negative pulmonary disease (aHR=1.68; 95% CI-1.27-2.24).

Conclusions: Most childhood TB cases in Kenya were detected through passive case finding. TB/HIV co-infection is high among children on treatment for TB, and HIV is associated with increased risk of death. There is need to intensify active case finding among children. TB preventive interventions among HIV-infected children, early diagnosis of HIV and early ART initiation among children on TB treatment should be strengthened.

INTRODUCTION

According to the World Health Organization (WHO), TB is the leading infectious cause of death globally and is thought to be an important cause of mortality in children (1). The incidence and epidemiology of paediatric TB is poorly characterized globally; challenges in diagnosis mean that most cases are never detected or treated (2). TB control programs have historically ignored paediatric TB because it was believed to be of less public health importance than adult disease due to the low risk of transmission of TB by children. This neglect has contributed to a lack of focused global targets (3, 4). However, TB in children should be a priority area of focus for TB control programs, as infection with *Mycobacterium tuberculosis* progresses rapidly to disease in young children (5) and young children are predisposed to severe or disseminated forms of TB (6). Although the true burden of TB mortality in children is unknown, WHO estimates that 210,000 children died of TB globally in 2015(7); 17% of these deaths occurred among HIV-infected children (8). Risk factors for mortality among children on TB treatment in high-burden settings have not been well characterized.

Kenya is currently experiencing the twin epidemics of TB and HIV. The country is categorized among the WHO high TB and high TB/HIV burden countries (9). In spite of an overall decline in TB incidence, the incidence among those who are HIV-positive has remained persistently high (10). The TB epidemic among adults puts children at risk of acquiring the disease. While childhood TB remains a serious public health problem in Kenya, its epidemiology has been described for two provinces only (11). This analysis seeks to describe the epidemiology of childhood TB in Kenya at a national level, assess the magnitude of TB/HIV co-infection in children, and identify factors associated with mortality during TB treatment.

METHODS

Study design

We conducted a retrospective cohort analysis of routine programmatic data from 3837 health facilities reported to the Ministry of Health in Kenya. We included all patients <15 years old who started their TB treatment between 1st January 2013 and 31st December 2015.

Study setting

Kenya's population in 2016 was estimated to be 47 million, of whom children aged <15 years made up 41%. By age group, 7.25 million children were aged 0–4 years; 6.62 million of them were aged 5–9 years; and 5.81 million were aged 10–14 years (12). Childhood TB is managed according to the national treatment guidelines for management of TB in children adopted from WHO recommendations (13). The National TB Control Program (NTP) coordinates all aspects of TB management in the country. The diagnosis of pediatric TB is based on clinical evaluation in addition to laboratory investigations when possible. Tuberculin skin test, chest radiography, and sputum smear examination support clinical evaluation. The Xpert® MTB/RIF assay was introduced in 2011, and implementation was scaled up in 2014; its use is currently being scaled up for both adults and children. Treatment regimens and duration follow national guidelines (13). All children on TB treatment are offered HIV counseling and testing. Bacille Calmette-Guerin (BCG) vaccine is administered to all newborns at birth as part of the Kenya Expanded Program on Immunization.

Data sources

This study used data from the electronic TB surveillance system (TIBU) that was introduced in Kenya in 2012. All public, faith-based and private treatment centers in the country enter individual-level data for children and adults into this system. The system captures data from nearly 100% of all treated TB patients according to an assessment in one district conducted in 2013 (14). It includes information on demographic factors, diagnostic tests performed and treatment outcome. We obtained anonymized TIBU data from the National Tuberculosis Control Program.

Definitions

Children were classified as having either pulmonary TB alone or having any extra-pulmonary TB, which included children with both pulmonary and extrapulmonary TB. Children who completed treatment or achieved cure were considered to have successful outcomes while children who died during treatment, failed treatment or defaulted from treatment were considered to have poor outcomes. Cure was defined as at least two negative sputum tests in a patient who had a positive sputum smear or culture at treatment initiation. Patients with a positive sputum smear at month 5 were considered to have failed treatment. Patients missing more than two appointments during the intensive phase or missing for more than a month during continuation was considered as loss to follow up. Patients with negative or unavailable sputum smears at baseline who completed a full

course of anti-tuberculosis treatment were considered to have completed treatment. “Death” was considered to be mortality from any cause during treatment.

Data analysis

We excluded from analysis children with missing outcomes or missing outcome date, and children whose recorded treatment outcome date was earlier than the treatment start date. We calculated TB notification rates per 100,000 people by age groups (0 to 4 years, 5 to 9 years and 10 to 14 years); we divided notified cases by yearly populations projected from the 2009 Population and Housing Census (15). For survival analysis, time to death or censoring was defined as the time between treatment initiation and outcome date. We evaluated the proportional hazards assumptions by testing the significance of time-dependent interaction terms for each covariate. If the outcome was death, the outcome date was assumed to be the date of death. Patients who were lost to follow-up, or who had their treatment classified as transferred out, failure, success, or cure were censored at the outcome date. Patients with a follow-up time beyond 9 months were censored at 9 months regardless of the eventual outcome.

To determine risk factors for mortality, we conducted bivariate and multivariable analysis using Cox Proportional Hazards regression with death as the outcome of interest. Variables with p values of 0.2 or less on bivariate analysis were eligible for inclusion in a multivariable model, and the final model was constructed using a backward elimination approach. Robust standard errors that take into account the potential effect of clustering by health facility were calculated. Patients who transferred out were excluded from the risk factor analysis. Data was analyzed using R version 3.3.2 and Stata version 12.

Ethical Considerations

This analysis involved the use of de-identified data which was collected as part of routine program monitoring. Approval to use TIBU data was obtained from the National Tuberculosis Control Program. This analysis was approved by Jaramogi Oginga Odinga Teaching and Referral Hospital ethical review board.

RESULTS

Pediatric TB Notifications

From January 2013 through December 2015, Kenya notified 263,201 TB patients, 9% (n=24,216) of whom were children aged less than 15 years. Among children, the highest case notification rates were among children aged 0 to 4 years (**Table 1**).

Table 1: TB Case Notification Rate per 100, 000 Population in Kenya (N=23, 753)

Age Group	2013			2014			2015		
	Population (millions)	Notified TB Cases	Case Notification Rate per 100, 000 population	Population (millions)	Notified TB Cases	Case Notification Rate per 100, 000 population	Population (millions)	Notified TB Cases	Case Notification Rate per 100, 000 population
0-4 years	6.97	4,025	57	7.07	3,922	55	7.17	3,244	45
5-9 years	6.21	2,178	35	6.36	2,097	33	6.49	1,619	25
10-14 years	5.29	2,356	45	5.47	2,485	45	5.65	2,099	37
15+ years	25.21	82,036	325	25.96	81,575	314	26.75	75,380	282

In total, 98% percent (n=23,753) of the notified children were included in the analysis; 0% (n=11) were excluded from analysis because they had unknown outcomes, 1% (n=273) because they had missing outcome dates, and 1% (n=179) because the outcome date was before the treatment start date. A total of 8,554 children were notified in 2013, 8477 in 2014 and 6722 in 2015. Children aged zero to four years accounted for 47% (n=11,160) of the children treated for TB (**Table 2**). Most cases of childhood TB (67%; n=15,955) were detected through self-referral (i.e., presenting to the clinic with symptoms).

Table 2: Socio-demographic and clinical characteristics of children treated for TB in Kenya (N = 23,753)

Socio-demographic/clinical characteristics Indicator		Number	%
Age Category	0-4 years	11,160	47
	5-9 years	5,799	24
	10-14 years	6,788	29
Sex	Female	11,403	48
	Male	12,350	52
Year	2013	8,554	36
	2014	8,477	36
	2015	6,722	28
Ownership of health facility where child was registered	Public	18,432	78
	Private	4,769	20
	Prisons	143	<1
	Other Faith Based	409	2
Means of identification	Self-referral	15,955	67
	HIV Clinics	2,861	12
	Contact Investigation	2,374	10
	Other*	2,563	11

**Antenatal clinics, community health workers, chemists/pharmacies, voluntary counselling and testing centers, and private clinics that do not provide TB services*

TB/HIV Co-infection

Overall, 93% (n=22,081) of the children treated for TB were tested for HIV. Of those tested, 28% (n=6112) were HIV-infected. HIV positivity was highest among children tested in the 5–9-year-old age group (35%, n=2044). Among HIV-infected children, 92% (n=5,606) were on antiretroviral therapy (ART). Among children on ART, 42% (n=2,402) had a recorded date of ART initiation. Of these, ART was initiated before TB diagnosis in 65% (n=1,552) and after TB diagnosis in 35% (n=851). The probability of survival up to 9 months (270 days) during treatment was highest among HIV-negative patients (survival probability=0.97; 95% CI: 0.96–0.97) and

lowest among HIV-infected patients who were not on ART (survival probability=0.81; 95% CI: 0.65–0.90).

TB Diagnosis

In total, 12% (n=2, 877) of children had TB disease that was bacteriologically confirmed by smear, GeneXpert, or culture (**Table 3**). Overall, 32% (n=7,578) of the children had sputum smear examination performed; of these, 36% (n=2,755) tested positive for *Mycobacterium tuberculosis*. A quarter (n=5,874) of the children were diagnosed with extra-pulmonary TB majority of whom had lymphadenitis (45%; n= 2,641). GeneXpert was performed for 2% (n=454) of all children, 63% (n=285) of whom tested positive. Among 353 children who had both GeneXpert and sputum smear microscopy performed, 65% (n=231) had a positive Gene Xpert result while 52% (n=182) had a positive smear result.

Table 3: Diagnostic characteristics of children treated for TB in Kenya

Characteristic		**Age 0-4** (N=11,160) n (%)	**Age 5-9** (N =5,799) n (%)	**Age 10-14** (N=6,788) n (%)	**Total** (N=23,753) n (%)
Sputum Smear microscopy	Smear microscopy performed	1,103 (10)	2,128 (37)	4,347 (64)	7,578 (32)
	Smear positive, out of those with smear performed	181 (16)	512 (24)	2,062 (47)	2,755 (36)
Gene Xpert	GeneXpert performed	91 (1)	131 (2)	232 (3)	454 (2)
	Xpert positive, out of those with Xpert performed	57 (63)	71 (54)	157 (69)	285 (63)
Any microbiological confirmation	Yes	218 (2)	548 (9)	2,111 (31)	2,877 (12)
	No	10,942 (98)	5,251 (91)	4,677 (69)	20,870 (88)
Chest Xray	Xray performed	6,261 (56)	3,068 (53)	2,737 (40)	12,066 (51)
	Xray not performed	4,899 (44)	2,731 (47)	4,051 (60)	11,681 (49)
Type of TB	Pulmonary	8,764 (79)	4,101 (71)	5,008 (74)	17,873 (75)
	Lymphadenitis	1100(10)	807(14)	734(11)	2641(11)
	Pleural effusion	277(3)	266(5)	303(4)	846 (4)
	Miliary TB	194(2)	134(2)	140(2)	468 (2)
	TB Meningitis	101(1)	59(1)	72(1)	232(1)
	Abdominal	33(<1)	31(1)	56(1)	120(<1)
	Skeletal	85(1)	87(2)	132(2)	304(1)
	Others	606(5)	314(2)	243(4)	1263(5)
	Type not recorded				

Treatment Outcomes

Of the 23,753 children, 80% (n=19,088) completed treatment and 10% (n=2,405) were cured. Poor outcomes were reported for 8% (n=1,833) children, including 4% (n=1,058) who died, 3% (n=760) who were lost to follow-up, and 1% (n=15) who experienced treatment failure; 2% (n=427) transferred out of the facility where they initiated treatment, so their final treatment outcome is unknown. Among children with meningitis, military, skeletal, and abdominal TB, which are more serious forms, the case fatality was higher (5%; 171/3,233) than among children with lymphadenitis (3%; 81/2,641) or children with pulmonary TB (4%; 830/17,873).

Risk Factors for Mortality

Among children with known treatment outcomes, age, type of TB, type of health facility attended, the means of identification, HIV and ART status were significantly associated with mortality in bivariate analysis (**Table 4**). HIV-infected children who were not on ART had almost five times the likelihood of death (HR=4.80; 95% CI-3.59-6.43) as HIV-negative children. HIV-infected children on ART had greater than three times the likelihood of death (HR=3.51; 95% CI-3.04-4.05) as HIV-negative children. By age group, children aged less than 5 years had 12% higher risk of death (HR=1.12; 95% CI-0.98-1.27) than children aged more than 5 years. The likelihood of death was twice as high among children with sputum smear-negative TB (HR=2.21; 95% CI-1.67-2.94) compared to those with smear-positive disease. Children treated in public health facilities had 28% increased likelihood of death (HR=1.28; 95% CI-1.03-1.58) compared to children treated in private or faith-based facilities. Children who were identified through contact investigation had 24% (HR=0.76; 95% CI-0.59-0.97) lower risk of death than children identified through self-referral. Sex violated the proportional hazards assumption, but male sex was associated with decreased odds of death (odds ratio=0.86; 95% CI 0.77-0.99).

In a sex-stratified multivariable model, age, the type of TB, the type of facility attended, the means of identification, and the HIV and ART status were significant predictors of death (**Table 4**). The greatest increases in likelihood of death were observed for children who were HIV-infected but not on ART (aHR=4.84; 95% CI-3.59-6.51) and children who were HIV-infected and on ART (aHR=3.69; 95% CI- 3.14-4.35). Children aged less than five years had 25% higher likelihood of death (aHR=1.25; 95% CI-1.08-1.44) than children aged more than five years. The risk of death among children with smear-negative pulmonary disease was 68% higher (aHR=1.68; 95% CI-

1.27-2.24) than children with sputum smear-positive disease; children with extra-pulmonary disease had similar risk of death as those with smear-negative disease. The likelihood of dying was 39% (aHR=1.39; 95% CI-1.13-1.14-1.69) higher among children treated in public health facilities than those treated in private or faith-based facilities. Children who were identified through contact investigation had 25% (aHR=0.75; 95% CI-0.57-0.98) lower risk of death than children identified through self-referral.

Table 4: Bivariate and multivariable analysis of risk factors for mortality among children treated for TB in Kenya (N= 23, 654)

Characteristic		No of deaths/Total	Hazard Ratio (95% CI)	Adjusted Hazard Ratio (95% CI)
Sex*	Male	586/12105 (5)	1	
	Female	472/11221(4)	0.86 (0.77-0.99)	
Age Group (in years)	<5	514/10920(5)	1.12 (0.98-1.27)	1.25 (1.08-1.44)
	>=5	544/12406(4)	1	1
Type of TB	Smear positive	60/2722(2)	1	1
	Smear negative	221/4472(5)	2.21 (1.67-2.94)	1.68 (1.27-2.24)
	Smear not done	525/10351(5)	2.32 (1.78-3.03)	1.87 (1.41-2.47)
	Extra-pulmonary	252/5781(4)	1.94 (1.47-2.56)	1.65 (1.24-2.19)
HIV infection	Negative	415/15705(3)	1	1
	Positive on ART	513/5500(9)	3.51 (3.04-4.05)	3.69 (3.14-4.35)
	Positive not on ART	59/491(12)	4.80 (3.59-6.43)	4.84 (3.59-6.51)
	Unknown	71/1630(4)	1.64 (1.27-2.12)	1.57 (1.22-2.02)
Ownership of Health	Private or Faith Based	187/5069(4)	1	1
	Public	871/18257(5)	1.28 (1.03-1.58)	1.39 (1.14-1.69)
Means of identification	Contact investigation	69/2332(3)	0.76(0.59-0.97)	0.75(0.57-0.98)
	Self-referral	729/18184(4)	1	1
	HIV clinic	260/2810(9)	2.32(2.02-2.68)	1.00(0.98-1.19)

**Sex violated the proportional hazards assumptions so odds ratio is presented instead of hazard ratio. The multivariable model was therefore stratified by sex*

DISCUSSION

Our analysis of nationally representative data collected over three years reveals a high TB/HIV co-infection rate among children with TB. While treatment outcomes are good for children with TB, children with HIV are at elevated risk of death, especially if they are not receiving ART. As is to be expected, most TB diagnoses in children are not bacteriologically confirmed. GeneXpert testing coverage was low. Furthermore, most children are being diagnosed with TB through

passive case-finding rather than through active case-finding strategies such as contact investigation and screening of HIV-infected children.

The case notification rate for childhood TB declined from 2013 to 2015. This may be a result of gains made in controlling TB in Kenya, as adult case notification has also declined. In addition, early initiation of ART among HIV-infected children may have prevented new cases. However, active case-finding strategies are necessary to improve case detection and the timeliness of TB diagnoses. Contact investigation is a WHO-recommended intervention that involves health worker visits to homes of new TB cases especially sputum smear-positive patients, screening close contacts, and referral of high-risk contacts to health facilities for diagnostic tests (16, 17). The lower mortality among children identified through contact investigation that we observed in this study may reflect the benefit of early case detection. However, although Kenya has adopted contact investigation guidelines in line with current WHO recommendations, implementation is still weak. Another WHO-endorsed active case-finding recommendation is intensified TB case-finding among people living with HIV, which involves screening for TB symptoms at every clinic encounter (19). Intensified case finding is one of the key TB/HIV collaborative activities implemented in Kenya; HIV-infected children are routinely screened using a questionnaire at every clinic visit. However, our data suggests that the yield of the two-active case finding strategies may be suboptimal in children since the majority of children are still diagnosed through passive case-finding. There is a need to intensify the use of community health workers in contact investigation and improve the monitoring of these investigations through a case investigation register. Similarly, efforts at intensified case finding among HIV-infected children should be enhanced in order to improve the timeliness diagnosis of TB.

We found that over a quarter of children with TB in Kenya were HIV-infected, which is slightly lower than the 31% co-infection rate among adults with TB in Kenya and the 32% co-infection rate reported in a sample of Malawian children with TB (20, 21), but still substantial. Prevention of TB among HIV-infected children is a key priority in Kenya. Isoniazid preventive therapy, cotrimoxazole preventive therapy, and ART are known to prevent TB among HIV-infected children (23, 24). Although the coverage of cotrimoxazole preventive therapy and ART were commendably high among pediatric TB patients, one in three children had ART initiated after TB

diagnosis. Furthermore, since TIBU does not record information of isoniazid preventive therapy, the coverage of this intervention is unknown. TB/HIV collaborative activities should be enhanced to ensure early diagnosis of HIV, early initiation of ART, and use of cotrimoxazole and isoniazid preventive therapies to prevent TB in children.

Although treatment success rate was higher than the WHO target of 85%, nearly one tenth of children experienced poor outcomes, and death accounted for close to 60% of children with poor outcomes. The strongest predictor of death among children in our study was HIV infection. HIV-infected children experience faster disease progression and are predisposed to poor treatment response (25-28). The elevated risk of mortality among HIV infected children being treated for TB has been documented in other settings, with a study from South Africa, reporting that HIV-infected children with TB were almost seven times more likely to die than HIV negative children (29). However, unlike a study from Malawi, we did not find that children on ART at the time of starting TB treatment were more likely to die than children who initiated ART after being diagnosed with TB (21). The use of ART among TB/HIV co-infected children reduces morbidity and mortality (24, 30). Our observation that HIV-infected children on ART still had nearly 4 times the likelihood of death as HIV-negative children could be due to early mortality among children who were started on ART when their disease was already advanced, virological failure, Immune Reconstitution Syndrome (IRIS) or poor adherence to ART (31, 32). Improving the coverage of HIV interventions for children and the coordination between TB and HIV services is essential to reducing TB-associated mortality in children. A study from Malawi, a similarly high HIV burden country, reported a 13% reduction in TB-associated mortality as a result of improvement in HIV interventions (33).

The difference in the risk of mortality between children treated in public compared to private health facilities could be explained by the differences in health care seeking behavior of their respective clientele. Clients of public health facilities generally belong to a lower wealth quintile which often contributes to a delay in seeking healthcare for their respiratory symptoms. Our observation that children with pulmonary smear-negative disease had elevated risks of death compared to children with smear positive disease could be explained by the nature of this diagnosis. TB symptoms in children are non-specific, and diagnosing TB without bacteriologic confirmation may involve first

putting children on antibiotics to treat pneumonia and diagnosing TB only after other possible diagnoses are excluded. Thus, children with bacteriologically unconfirmed disease may experience delayed initiation of TB treatment (34). In addition, because the clinical diagnosis of TB is quite often a diagnosis of exclusion, it is possible that some of the observed mortality may result from misdiagnosis, as the true cause of illness was not treated. Timely diagnosis of TB in children can be promoted by training doctors in clinical diagnostic algorithms, expanding access to x-ray, and utilizing more sensitive bacteriological confirmation methods such as the GeneXpert (35) the use of which is currently being expanded in Kenya.

In this study, a substantial proportion of children treated for TB were not subjected to any diagnostic test. This may be attributed to difficulty in obtaining sputum specimen for testing in children and limited availability of X-ray services. Consequently, these children were clinically diagnosed. Clinical diagnosis of TB relies on scoring systems and acumen of clinicians which is not standardized (36). This is a potential cause of bias, as children on treatment for clinically diagnosed TB may actually have other diseases which could drive mortality, or they could have simpler non-fatal conditions that could cause underestimation of TB case fatality ratios.

Our study was subject to several limitations. This study used routine data, which suffers from limitations of missing information and occasionally inconsistent data. Consequently, a small fraction of patients had to be excluded from the analysis. ART initiation dates were missing for most of the patients hence the timing of ART initiation could not be used in the mortality analysis. There was no variable indicating the basis of TB diagnosis, and X-ray findings were not captured, limiting our capacity to comprehensively assess diagnostic practices. The role of malnutrition as a potential confounder could not be assessed since data on nutritional status is not captured in Kenyan TB registers. Finally, because we only evaluated notified cases, we are limited in the conclusions we can make about the true epidemiology of childhood TB in Kenya, including undiagnosed patients.

In conclusion, most childhood TB cases in Kenya are being detected through passive case-finding. TB/HIV co-infection is high among children on treatment for TB, and HIV is associated with increased risk of death. There is need to intensify active case finding among children. TB/HIV

collaborative activities should be strengthened by implementing TB preventive interventions among HIV-infected children, ensuring early diagnosis of HIV and early ART initiation among children on TB treatment.

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Table S1: Distribution of Included and Excluded Patients by Characteristics

Characteristic	Included		Excluded		Total
	N	*Row %*	*n*	*Row %*	
All	23,753	98	463	2	24,216
Sex					
Female	11,403	98	216	2	11,619
Male	12,350	98	247	2	12,597
Age Group					
<5	11,160	98	203	2	11,363
>=5	12,593	98	260	2	12,853
HIV and ART					
Negative	15,969	98	304	2	16,273
Positive on ART	5,606	98	110	2	5,716
Positive not on ART	506	98	12	2	518
Unknown	1,672	98	37	2	1,709
Year					
2013	8,554	99	83	1	8,637
2014	8,477	99	71	1	8,548
2015	6,722	96	309	4	7,031
Sector					
Public	18,432	98	343	2	18,775
Private	4,769	98	102	2	4,871
Faith based	409	96	16	4	425
Prison	143	99	2	1	145
Treatment outcome					
Death	1,058	97	28	3	1,086
Cure	2,405	100	2	0	2,407
Treatment completed	19,088	99	121	1	19,209
Not completed	0	0	270	0	270
Loss to follow up	760	97	24	3	784
Transferred out	427	96	16	4	443
Failure	15	88	2	12	17
Type of Patient					
New	22,836	98	447	2	23,283
Retreatment/relapse	739	98	13	2	752

CHAPTER 6

Reduction of HIV-associated excess mortality by antiretroviral treatment among tuberculosis patients in Kenya

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Abstract

Background: Mortality from TB continues to be a global public health challenge. TB ranks alongside Human Immunodeficiency Virus (HIV) as the leading infectious causes of death globally. HIV is a major driver of TB related morbidity and mortality while TB is the leading cause of mortality among people living with HIV/AIDS. We sought to determine excess mortality associated with HIV and the effect of antiretroviral therapy on reducing mortality among tuberculosis patients in Kenya.

Methods: We conducted a retrospective analysis of Kenya national tuberculosis program data of patients enrolled from 2013 through 2014.We used direct standardization to obtain standardized mortality ratios for tuberculosis patients compared with the general population. We calculated the population attributable fraction of tuberculosis deaths due to HIV based on the standardized mortality ratio for deaths among TB patients with HIV compared to TB patients without HIV. We used Cox proportional hazards regression for assessing risk factors for mortality.

Results: Of 162,014 patients included in the analysis, 6% died. Mortality was 10.6 (95% CI: 10.4–10.8) times higher among TB patients than the general population; 42% of deaths were attributable to HIV infection. Patients with HIV who were not receiving ART had an over four-fold risk of death compared to patients without HIV (aHR=4.2, 95% CI 3.9-4.6). In contrast, patients with HIV who were receiving ART had only 2.6 times the risk of death (aHR=2.6, 95% CI 2.5-2.7).

Conclusion: HIV was a significant contributor to TB-associated deaths in Kenya. Mortality among HIV-infected individuals was higher among those not on ART than those on ART. Early initiation of ART among HIV infected people (a “test and treat” approach) should further reduce TB-associated deaths.

Introduction

Tuberculosis (TB) is an infectious disease caused by infection with Mycobacterium tuberculosis. Mortality from TB continues to be a global public health challenge. TB ranks alongside Human Immunodeficiency Virus (HIV) as the leading infectious causes of death globally [1]. In 2015, of the 10.4 million people who developed TB, 1.8 million died, of whom 0.4 million were persons infected with HIV [2]. The African region has the highest rates of TB incidence and mortality, while Kenya is one of the 22 countries with the highest TB burdens [3]. TB notifications in the country increased more than sixfold from 1990 (50 cases per 100,000) to a peak of 319 per 100,000 in 2006, largely due to the HIV epidemic; TB notifications declined from 2007 onwards but have remained persistently high TB among HIV-positive individuals (over 1,800 cases/100,000 population) [4, 5]. HIV prevalence among adults aged 15 to 64 years in the country was 5.6% in 2012 [6].

The high HIV prevalence in Kenya could be expected to lead to high mortality among TB patients who are co-infected with HIV. HIV is a major driver of TB related mortality while TB is the leading cause of mortality among people living with HIV/AIDS [7, 8]. Major factors associated with mortality among TB/HIV co-infected people include delay in diagnosis of either disease [9] and delay in initiating antiretroviral therapy (ART)[10]. Early initiation of ART in TB patients has been proven to improve survival of those who are co-infected [11-13].

Other risk factors for mortality have been described by numerous studies, which have consistently identified incomplete treatment due to default, drug resistance, male gender, and immunosuppression as predictors of mortality [14-19]. However, other risk factors have been identified only in certain settings, including having TB due to recent transmission [17] or having less than six years of formal education [17]. There have been conflicting reports on which age group is associated with mortality: some studies have reported higher risk among younger age groups [15, 16] while others have reported higher risk among older age groups [19, 20]. A study from western Kenya reported having unknown HIV status and not being on ART during TB treatment as risk factors [21].

Knowledge is lacking on the impact of HIV on mortality among TB patients in Kenya and the impact that ART has had on TB/HIV-associated mortality in a programmatic setting. This study sought to determine HIV-associated excess mortality, estimate the current impact of ART and the potential effect of further ART expansion on HIV-associated mortality in TB patients, and identify risk factors for mortality during TB treatment in Kenya, a middle-income country with high burdens of both TB and HIV.

Methods

Setting

In Kenya, TB is diagnosed and treated according to the national treatment guidelines adopted from World Health Organization recommendations [22, 23]. Tuberculin skin test, chest radiography and sputum smear examination are done to support clinical evaluation. More recently, the Gene Xpert MTB/Rif Assay has been introduced, and its use is being scaled up. New TB patients go through a four-drug (rifampicin, isoniazid, pyrazinamide and ethambutol) intensive phase of treatment for two months and a continuation phase of four months (isoniazid and rifampicin). Patients who have previously been treated for TB (i.e., retreatment patients) are put on an intensive phase of three months (rifampicin, isoniazid, pyrazinamide and ethambutol) and five months continuation (isoniazid and rifampicin). Patients with certain types of extra-pulmonary disease specifically tuberculous meningitis or bone and joint disease are treated for 12 months; two months of intensive phase and ten months continuation.

Data source

This study used data from the electronic TB surveillance system, Tuberculosis Information from Basic Unit (TIBU), which was introduced in Kenya in 2012. All public, faith-based, and private treatment centers in the country enter individual-level data into this centrally located system. Data used in this analysis were drawn from 3511 health facilities. An assessment conducted in one district and clinic reported that nearly 100% of all treated TB patients were captured in the TIBU system [24]. TIBU variables included in the risk factor analysis were treatment outcome, age, sex, region, HIV status, ART use, smear results, disease type, whether or not Directly Observed Therapy (DOT) was done, the person administering DOT, HIV status, ART status of HIV-infected patients, and previous TB treatment history.

Statistical analysis

We included all patients in the electronic register who had started their treatment during 1st January 2013 through 31st December 2014. Children aged less than 15 years were excluded from this analysis due to the uncertainty of a TB diagnosis in children and under-reporting of cases [21, 25, 26]. Before starting the analysis, we performed range and consistency checks.

Excess mortality by age and sex was determined by comparing the expected number of deaths (calculated using age- and sex-specific mortality rates published by the Kenya National Bureau of Statistics [27]) with the observed number of deaths in this treatment cohort. We calculated the population attributable fraction (PAF) of mortality among TB patients attributable to HIV by calculating a standardized mortality ratio (SMR) for HIV-infected compared with HIV-non-infected TB patients. PAF (%) was calculated as: (SMR-1)/SMR*100.

To determine risk factors for mortality, we conducted bivariate and multivariable analysis using Cox Proportional Hazards regression with death as the outcome of interest. Time to death or censoring was defined as the time between treatment initiation and outcome date. If the outcome was death, the outcome date was assumed to be the date of death. Patients who were lost to follow-up, or who had their treatment classified as failure, success, or cure were censored at the outcome date. Patients with a follow-up time beyond 9 months were censored at 9 months regardless of the eventual outcome.

A composite variable was created to describe disease type as smear positive pulmonary TB, smear negative pulmonary TB, pulmonary TB without a smear result, and extra-pulmonary TB. To describe HIV and ART status, we evaluated two composite variables. The first classified patients as HIV-negative, HIV-positive and receiving ART, HIV-positive and not receiving ART, and HIV status unknown. The second further categorized patients who were HIV-positive and receiving ART based on the time of ART initiation relative to TB treatment; patients could either have initiated ART before initiating TB treatment, after TB treatment, or at an unknown date.

We evaluated the proportional hazards assumption by testing the significance of time-dependent interaction terms. We included in a multivariable model all variables with evidence of bivariate

association (*P* value less than 0.2) and used backward elimination to construct the final model. During multivariable analysis, variables with *P* values greater than 0.05 were eliminated from the model. We used robust standard errors to take into account the potential effect of clustering by health facility. We assessed both a main effects multivariable model and a model including significant two-way interaction terms between covariates. Data was analyzed using Stata version 12.0 and SAS version 9.3.

Ethical considerations

This analysis involved the use of de-identified secondary data that was collected as part of routine program monitoring. Approval to use TIBU data was obtained from the National TB Control Program. This study was subjected to Human Research Protection review at the U.S. Centers for Disease Control and Prevention, which determined it not to constitute human subjects research.

Results

Patient population

During 2013–2014, health facilities in Kenya registered 163,618 TB patients aged 15 years and above. Of these, 1,604 (1.0%) were excluded from the analysis because of out-of-range values (age more than 100 years), missing key information (outcome or date of outcome), or inconsistencies (date of treatment outcome before start date), and 162,014 were included in the analysis. Included and excluded patients had similar distribution by sex, HIV status, ART status and year of registration; excluded records had more patients aged ≥75 years and from faith-based facilities (data not shown).

Of included patients, 57,408 (35.4%) were HIV-infected, with 50,616 (88.2%) of these reporting ART use. A total of 97,019 (59.9%) patients were HIV negative, 7,052 (4.4%) were not tested, and 535 (0.3%) declined HIV testing. Of the HIV-infected patients on ART, 22,318 (44.1%) had a known date of ART initiation; of these, 10,024 (44.9%) had started their ART before TB diagnosis, and 12,294 (55.1%) after TB diagnosis.

Mortality among TB patients

Of the 162,014 patients included in the analysis, 9,907(6.1 %) are known to have died; of these, 5,430 (53.6%) died within two months of TB treatment initiation. The case fatality rate was highest among persons with HIV who were not on ART (13.1%) followed by HIV-positive patients on

ART (9.9%) and HIV-unknown patients (5.9%), and lowest among HIV-negative patients (3.7%). The crude mortality rate was 12.7 (95% confidence interval [CI]:12.5–13.0) per 100 person-years of observation. The probability of survival up to 9 months during treatment was highest among HIV-negative patients (survival probability=0.95; 95% CI: 0.94–0.95) and lowest among HIV-positive patients who were not on ART (survival probability=0.83; 95% CI: 0.82–0.85) (**Figure 1**). The PAF of deaths in TB patients attributable to HIV was 42%.

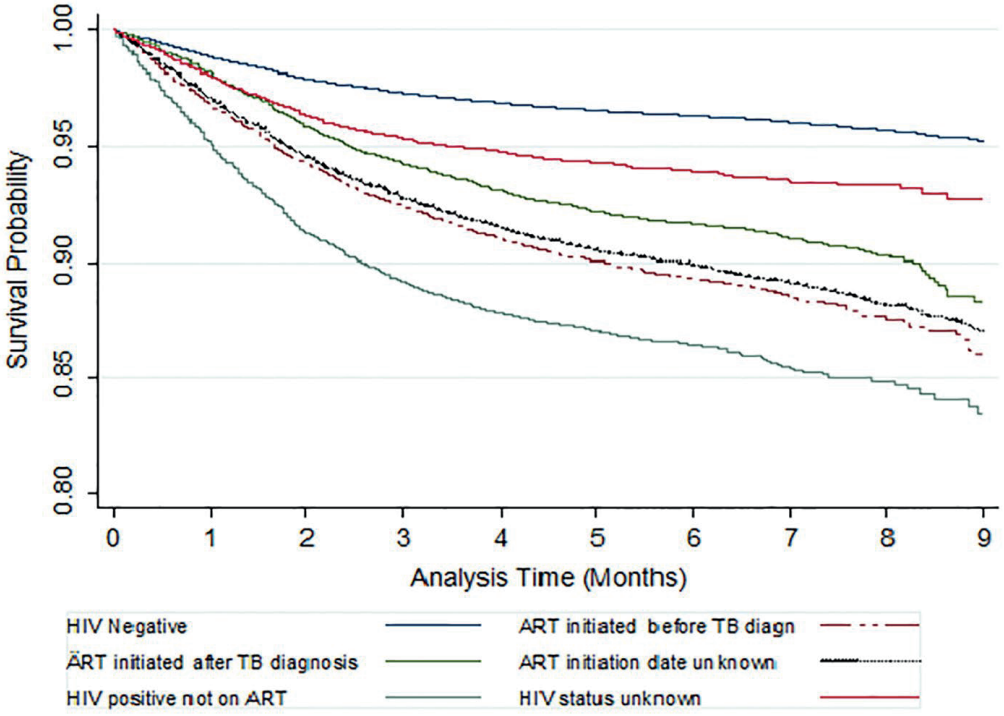

Figure 1: Survival of patients on tuberculosis treatment by their HIV and ART status

Compared to the general Kenyan population, TB patients were 10.6 (95% CI: 10.4–10.8) times more likely to die, and the excess mortality rate was 11.5/100 person-years (95% CI: 11.3–11.7) (**Table 1**). The SMR was similar among men and women and declined with age. Excess mortality was also similar among men and women and somewhat increased with age.

Table 1: Excess mortality among TB patients diagnosed in Kenya, 2013 to 2014, by age and sex

Sex (age group, in years)	Standardized Mortality Rate (95% confidence interval)	Observed mortality rate/100 person-years	Expected mortality rate/100 person-years	Excess mortality/100-person years (95% confidence interval)
Female (15–24)	25.1 (22.9–27.5)	6.6	0.3	6.3 (5.7–6.9)
Female (25–34)	14.9 (14.0–15.7)	11.8	0.8	11.0 (10.4–11.7)
Female (35–44)	12.0 (11.3–12.8)	15.2	1.3	13.9 (13.1–14.8)
Female (45–54)	16.2 (14.8–17.6)	15.7	1.0	14.7 (13.6–16.0)
Female (55–64)	14.1 (12.6–15.8)	17.3	1.3	16.0 (14.4–17.8)
Female (65\–74)	7.6 (6.7–8.6)	23.4	3.0	20.4(17.9–22.9)
Female (≥75)	2.2 (1.9–2.6)	32.7	14.9	17.8 (14.6–21.6)
Female (All)	11.6 (11.2–11.9)	12.8	1.1	11.7 (11.4–12.9)
Male (15–24)	14.3 (12.9–15.9)	4.3	0.3	4.0 (3.6–4.4)
Male (25–34)	15.2 (14.4–16.0)	9.1	0.6	8.5 (8.0–8.9)
Male (35–44)	10.1 (9.6–10.6)	13.2	1.3	11.9 (11.3–12.4)
Male (45–54)	12.7 (12.0–13.5)	17.8	1.4	16.4 (15.5–17.3)
Male (55–64)	13.1 (12.2–14.2)	22.3	1.7	20.6(19.2–22.1)
Male (65–74)	7.9 (7.2–8.6)	30.0	3.8	26.2 (24.1–28.4)
Male (≥75)	2.5 (2.2–2.7)	41.4	16.9	24.5 (21.6–27.7)
Male (All)	9.7 (9.5–9.9)	12.6	1.3	11.3 (11.0–11.6)
Total	**10.6 (10.4–10.8)**	**12.7**	**1.2**	**11.5 (11.3–11.7)**

Risk factors for death among TB patients

In bivariate analysis, age, TB treatment history, disease type, HIV and ART status, and geographic region were significantly associated with death (**Table 2**). Patients who were HIV positive but not on ART were almost four times likely to die than HIV negative patients (HR=3.9, 95% CI: 3.6–4.3). The risk of dying increased with increasing age; those aged ≥75 years were seven times more likely to die than those aged 15 to 24 years (HR=7.0, 95% CI-6.3–7.9).

Table 2: Bivariate and multivariable associations between patient characteristics and death among TB patients in Kenya

Characteristic	Deaths / Registered cases	Percent who died	Crude Hazard Ratio (95% CI)	Adjusted Hazard Ratio from main effects model (95% CI)
HIV and ART status				
HIV-negative	3,577 / 97,019	3.7	Reference	Reference
HIV-positive, on ART	4,993 / 50,616	9.9	2.75 (2.61–2.89)	2.60 (2.46–2.74)
ART before TB treatment	1,081 / 10,024	10.8	3.01 (2.78–3.25)	
ART after TB treatment	1,039 / 12,294	8.5	2.33 (2.14–2.53)	
ART date unknown	2,873 / 28,298	10.2	2.84 (2.68–3.01)	
HIV-positive, not on ART	891 / 6,792	13.1	3.93 (3.60–4.30)	4.23 (3.87–4.62)
Unknown HIV status	446 / 7,587	5.9	1.67 (1.48–1.87)	1.65 (1.48–1.85)
Sex*				
Female	3,932 / 63,331	6.2	Reference	
Male	5,975 / 98,682	6.1	0.97 (0.93-1.01)	
Age group				
15-24	810 / 31,328	2.6	Reference	Reference
25-34	2,585 / 52,371	4.9	1.93 (1.79–2.08)	1.44 (1.34–1.55)
35-44	2,591 / 38,574	6.7	2.62 (2.42–2.84)	1.68 (1.55–1.82)
45-54	1,703 / 20,766	8.2	3.22 (2.96–3.51)	2.12 (1.94–2.31)
55-64	994 / 10,245	9.7	3.84 (3.49–4.23)	2.89 (2.62–3.18)
65-74	733 / 5,800	12.6	5.12 (4.61–5.68)	4.51 (4.07–5.00)
>=75	491 / 2,930	16.8	7.02 (6.26–7.88)	6.57 (5.85–7.37)
Calendar year of enrollment				
2013	4,843 / 81,194	6.0	Reference	
2014	5,064 / 80,820	6.3	1.04 (1.00–1.09)	
Disease type				
Pulmonary, smear-positive	2831 / 76,426	3.7	Reference	Reference
Pulmonary, smear-negative	4186 / 52,301	8.0	2.24 (2.12–2.37)	1.57 (1.48–1.66)
Pulmonary, smear unknown	640 / 6,219	10.3	3.00 (2.71–3.33)	2.29 (2.07–2.53)
Extra-pulmonary	2250 / 27,068	8.3	2.31 (2.16–2.47)	1.88 (1.76–2.00)
TB treatment history[†]				
Retreatment/relapse	1,342 / 16,392	8.2	1.31 (1.23–1.39)	1.24 (1.16–1.32)
New	8,499 / 143,990	5.9	Reference	Reference
Type of health facility				
Faith based	114 / 2,509	4.5	0.73 (0.50–1.07)	
Private	1,755 / 30,552	5.7	0.92 (0.83–1.03)	
Public	8,038 / 128,953	6.2	Reference	
Region				
Central	1,263 / 17,970	7.0	1.73 (1.50–2.00)	1.87 (1.62–2.16)
Coast	902 / 16,894	5.3	1.29 (1.07–1.56)	1.45 (1.22–1.72)
Eastern	1,263 / 24,109	5.2	1.27 (1.09–1.47)	1.54 (1.33–1.79)
Nairobi	1,072 / 26,140	4.1	Reference	Reference
North Eastern	148 / 4190	3.5	0.86 (0.70–1.06)	1.24 (1.01–1.53)
Nyanza	2,391 / 25,462	9.4	2.32 (2.01–2.68)	1.98 (1.72–2.28)
Rift Valley	1,863 / 35,119	5.3	1.30 (1.12–1.52)	1.39 (1.19–1.62)
Western	1,005 / 12,130	8.3	1.99 (1.70–2.33)	1.83 (1.56–2.14)
Directly observed therapy				
Observed by household member	8,430 / 139,992	6.0	Reference	
Observed by community volunteer	122 / 1,712	7.1	1.19 (0.95–1.48)	
Observed by healthcare worker	1,347 / 20,168	6.7	1.06 (0.98–1.14)	
Not done	8 / 142	5.6	1.01 (0.50–2.04)	

* Sex violated the proportional hazards assumption, so crude odds ratios are presented. Multivariable analysis is stratified by sex.
[†]1,632 transfer-in patients excluded from analysis
CI= Confidence interval

In multivariable analysis, HIV status, age, disease type, treatment history, HIV, and geographic region were independently associated with death (**Table 2**). In an initial main effects model, compared to patients without HIV, the risk of death among patients with HIV who were receiving ART did not differ substantially for patients who initiated ART before TB treatment (aHR=2.8, 95% CI: 2.6–3.0) compared to patients who initiated ART after TB treatment (aHR=2.3, 95% CI: 2.1–2.5). Therefore, for ease of interpretation, we present the multivariable model including the simpler composite variable that included only whether or not the person received ART at any time.

In a main effects model, patients with HIV who were not receiving ART had an over four-fold risk of death compared to patients without HIV (aHR=4.2, 95% CI: 3.9-4.6). In contrast, patients with HIV who were receiving ART had only 2.6 times the risk of death (aHR=2.6, 95% CI: 2.5–2.7). Compared to patients without a history of prior treatment, retreatment patients (relapses, returnees after default, and treatment failures) had an increased likelihood of death (aHR=1.2, 95% CI: 1.2–1.3). In addition, patients from all other regions of Kenya had higher risks of death than patients in Nairobi, with patients from the former Nyanza province having a doubled risk (aHR=2.0 95% CI: 1.7–2.3).

Significant interactions were observed between HIV status and age, and between HIV status and disease type. A model including these pairwise interaction terms showed that the increased risk of death associated with HIV was more pronounced among younger patients than older patients (**Table 3**). For HIV-negative patients, the risk of death increased steadily with age, but for patients with HIV, this difference was much less pronounced (**Table S1**). Patients who were HIV-positive had elevated mortality regardless of disease type, but the increased risk of death associated with HIV was greater for patients with pulmonary smear-positive disease than other disease types (**Table S2**). Patients with all other disease types were more likely to die than patients with pulmonary smear-positive disease, regardless of HIV status (**Table S3**). Inclusion of interaction terms in the multivariable model did not affect the association between death and other covariates (data not shown).

Table 3: Adjusted hazard ratios for the association between HIV/ART status and death, stratified by age group, among patients with smear-positive pulmonary disease

HIV Status	Age Group in Years						
	15-24	**25-34**	**35-44**	**45-54**	**55-64**	**65-74**	**≥75**
HIV-negative	reference	reference	reference	reference	reference	reference	reference
HIV-positive, on ART	7.85 (6.65–9.27)	5.12 (4.56–5.76)	3.39 (3.00–3.82)	2.74 (2.41–3.12)	2.24 (1.89–2.65)	2.30 (1.86–2.86)	1.47 (0.97–2.23)
HIV-positive not on ART	10.25 (7.54–13.92)	8.22 (6.90–9.81)	6.20 (5.13–7.49)	4.79 (3.86–5.95)	3.83 (2.80–5.23)	4.52 (2.87–7.13)	3.08 (1.32–7.19)
HIV status unknown	1.97 (1.35–2.89)	2.34 (1.8–3.05)	1.97 (1.5–2.59)	1.55 (1.12–2.14)	2.04 (1.49–2.80)	1.89 (1.35–2.65)	1.64 (1.11–2.40)

Hazard ratios adjusted for TB treatment history and region, and analysis stratified by sex

Discussion

In this study TB patients experienced a tenfold increase in mortality rates compared with the general population, with 42% of these deaths attributable to HIV. HIV increased the risk of death among TB patients, especially for co-infected patients not receiving ART.

This SMR of 10 that we report is high compared with those reported in previous studies: 8 in Western Kenya [21], 8 in the Netherlands [28], 6 in Spain [29], 4 to 6 in India [15, 16], and 5 in China [30]. The major explanation for this observation may be Kenya's high HIV prevalence since the burden of TB/HIV co-infected patients is high, and these patients are at a particularly high risk for death. In Kenya, the re-emergence of TB has been linked to the HIV epidemic, and a third of TB cases have been attributed to HIV [5]. The Nyanza region in Western Kenya, which had the highest risk of death among TB patients, also has the highest HIV prevalence.

Excess mortality among TB patients with HIV was expected, even among those on ART [31, 32]. However, mortality was substantially lower among patients on ART compared to those who were HIV-infected but not on ART. The fact that 42% of the deaths in TB patients were attributed to HIV even though 88% of TB/HIV patients received ART suggests that without such high ART coverage, the HIV-associated mortality among TB patients would likely have been higher. Our observation that mortality was similar among those who initiated ART before TB diagnosis and those initiated ART after TB diagnosis could be due to selection bias in ART use. Previously, only HIV-infected people with advanced (based on clinical criteria or low CD4 count) disease were started on ART. The protective effect of ART that was started before diagnosis of TB was probably underestimated because these patients already had an increased likelihood of death due to their advanced immunodeficiency.

Together, these results suggest that TB is associated with a substantial burden of mortality in Kenya, that HIV contributes greatly to this risk, and that while ART is protective against death, its protective effect is far from complete. Thus, averting deaths caused by TB will require reducing overall TB risk by improving TB control, reducing risk among people living with HIV and reducing mortality by early initiation of ART among people living with HIV. Overall TB

prevention involves broad interventions like intensified case finding, treating all cases (especially smear positive cases), and treatment of latent TB infection. Furthermore, isoniazid preventive therapy (IPT) is effective in preventing TB in the immunocompromised, especially those infected with HIV [33, 34]. Although ART does not eliminate the occurrence of TB in HIV infected people, it reduces the risk of TB by 80% to 92% [35-38].

In addition to preventing TB, ART and IPT have both been proven to reduce mortality. A meta-analysis that included 21 studies (20 routine surveillance data and 1 clinical trial) reported a 44–71% reduction in mortality among TB/HIV co-infected individuals as a result of ART [39]. An econometric analysis of 41 high TB/HIV countries estimated that a 1% increase in ART coverage can result in 27% less TB deaths in the population [40], while a study in USA reported that immediate initiation of ART would reduce mortality by 17% [41]. Additionally, a combination of IPT and ART for persons living with HIV has been shown to reduce the risk of death by at least 60% [42, 43]. Prior to 2016 ART initiation in Kenya followed WHO guidelines which recommended treatment of those with advanced HIV. In 2015, WHO revised ART guidelines to recommend immediate initiation of ART upon HIV diagnosis, commonly referred to as "test and start" [44]. Kenya adopted this guideline in mid 2016 and is currently rolling out the strategy. Our results suggest that rolling out the "test and start" strategy may not only improve general survival and reduce TB incidence, but may also further reduce mortality in HIV-infected TB patients.

We found that retreatment patients had a higher risk of death than new patients. A similar finding has been reported by other studies [14, 15], but contradicts some earlier studies which reported new cases to be at increased risk [20, 45]. One reason why being on a retreatment regimen may be associated with increased mortality is that retreatment patients are more likely to have drug-resistant TB [46, 47]. A study done in Nairobi reported that 17.6% of retreatment cases had resistance to isoniazid and 6.6% had multi drug resistance compared to none among new patients [48]. In Kenya, there is a policy to subject retreatment cases to drug sensitivity testing. In this dataset, however, there was very limited information on drug resistance patterns, so we could not determine the contribution of drug resistance to mortality.

The observation that patients with pulmonary smear-negative disease and extra-pulmonary disease had elevated risks of death could be explained by the nature of these diagnoses. The diagnosis of both smear-negative and extra-pulmonary disease is clinical. Quite often, smear-negative disease is a diagnosis of exclusion. It is therefore possible that increased mortality among smear-negative and extra-pulmonary cases may result from a misdiagnosis, with the result that the true cause of illness such as lung cancer or lymphoma was not treated. For patients who genuinely have TB that is sputum smear-negative, there is a possibility of delayed initiation of anti-TB treatment occasioned by difficulties in making a timely diagnosis [49], especially among HIV infected individuals. The accuracy of clinical examination and diagnostic tests like radiology and sputum smear is lower among HIV infected people due to atypical disease presentation [50]. Timely diagnosis of sputum smear-negative disease can be promoted through utilization of bacteriological confirmation methods such as the Gene Xpert MTB Rif Assay [51], the use of which is currently being expanded in Kenya.

Mortality did not differ by the type of health facility or by the method of Directly Observed Therapy (DOT). Our findings suggest that TB patients in Kenya get similar standard of care regardless of the type of health facility attended. This is reasonable given that all TB treatment in Kenya is overseen by the national TB program, even when it occurs in private facilities. The finding that the method of observing therapy is not associated with mortality suggests that all of the methods currently used to ensure observation in Kenya are equally effective. Almost all TB patients in Kenya get some form of DOT. TB patients are first registered and counseled at the health facility, then given a choice of having DOT is to be administered at the facility, or at home by a household member or a community health volunteer.

The excess mortality among patients on treatment for TB observed in this study indicates that TB disease increases a person's risk of mortality regardless of their HIV or ART status. Our data demonstrate that we are still far from achieving the "End TB Strategy" target to end TB deaths globally by 2035 [53]. Consequently, there is an urgent need to redouble efforts to prevent TB by implementing the following strategies which are recommended by WHO: intensified case finding, isoniazid preventive therapy (IPT), infection control and early ART initiation [54]. Aggressive

implementation of the above strategies is likely to contribute to reduced TB associated mortality in Kenya.

This study used routine data, which suffers from limitations of missing information and occasionally inconsistent data. Consequently, a small fraction of patients had to be excluded from the analysis. However, it is important to note that the excluded observations were similar to included ones in key variables. Importantly, the national-level data used in this analysis has been validated by other evaluations and determined to be adequate in completeness and accuracy.

In conclusion, mortality among TB patients could be at least ten times higher than in the general population. HIV is a significant contributor to TB-associated mortality, especially among HIV-infected patients who are not on ART. There is urgent need to redouble efforts to prevent TB especially among high-risk populations. Early initiation of ART among HIV infected people (test and treat approach) should further reduce TB-associated deaths by preventing TB and reducing mortality among those with TB. Intensified TB case finding among HIV infected people will ensure timely identification of TB/HIV co-infected and timely initiation of TB treatment could further reduce mortality.

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Author contributions

DOO analyzed data and drafted the manuscript. CMY assisted with data analysis. MWB provided oversight during protocol development and data analysis. All authors contributed to and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

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Table S1: Adjusted hazard ratios for the association between age group and death, stratified by HIV/ART status

Age group	HIV status			
	HIV-negative	**HIV-positive, on ART**	**HIV-positive, not on ART**	**HIV status unknown**
15-24	Reference	Reference	Reference	Reference
25-34	1.60 (1.40–1.82)	1.04 (0.94–1.16)	1.28 (0.97–1.69)	1.90 (1.30–2.77)
35-44	2.46 (2.14–2.82)	1.06 (0.95–1.18)	1.49 (1.12–1.98)	2.46 (1.66–3.63)
45-54	3.60 (3.13–4.14)	1.26 (1.12–1.41)	1.68 (1.23–2.29)	2.83 (1.84–4.36)
55-64	5.02 (4.36–5.79)	1.43 (1.24–1.66)	1.88 (1.30–2.72)	5.20 (3.48–7.78)
65-74	6.90 (5.97–7.99)	2.03 (1.65–2.48)	3.05 (1.84–5.05)	6.62 (4.35–10.07)
≥75	9.85 (8.48–11.45)	1.85 (1.24–2.77)	2.96 (1.23–7.12)	8.18 (5.24–12.76)

Hazard ratios adjusted for TB treatment history and region, and analysis stratified by sex.

Table S2: Adjusted hazard ratios for the association between HIV/ART status and death, stratified by age group and disease type

HIV Status		Type of TB			
	Age group	Pulmonary, smear-positive	Pulmonary, smear-negative	Pulmonary, smear unknown	Extra-pulmonary
HIV-positive on ART, compared to HIV-negative	15-24	7.85 (6.65–9.27)	5.14 (4.36–6.06)	5.53 (4.33–7.05)	4.51 (3.80–5.35)
	25-34	5.12 (4.56–5.76)	3.35 (2.99–3.76)	3.61 (2.93–4.45)	2.94 (2.61–3.32)
	35-44	3.39 (3.00–3.82)	2.22 (1.98–2.49)	2.39 (1.94–2.93)	1.95 (1.71–2.22)
	45-54	2.74 (2.41–3.12)	1.79 (1.59–2.03)	1.93 (1.56–2.40)	1.57 (1.38–1.8)
	55-64	2.24 (1.89–2.65)	1.47 (1.26–1.71)	1.58 (1.25–1.99)	1.29 (1.09–1.52)
	65-74	2.30 (1.86–2.86)	1.51 (1.23–1.84)	1.62 (1.24–2.13)	1.32 (1.07–1.64)
	≥75	1.47 (0.97–2.23)	0.96 (0.64–1.45)	1.04 (0.67–1.61)	0.85 (0.56–1.28)
HIV-positive not on ART, compared to HIV-negative	15-24	10.25 (7.54–13.92)	6.49 (4.78–8.79)	6.52 (4.47–9.52)	4.98 (3.58–6.94)
	25-34	8.22 (6.90–9.81)	5.20 (4.34–6.24)	5.24 (3.88–7.06)	4.00 (3.23–4.95)
	35-44	6.2 0(5.13–7.49)	3.92 (3.27–4.70)	3.95 (2.95–5.28)	3.01 (2.44–3.72)
	45-54	4.79 (3.86–5.95)	3.03 (2.46–3.73)	3.05 (2.24–4.15)	2.33 (1.84–2.95)
	55-64	3.83 (2.80–5.23)	2.42 (1.78–3.30)	2.44 (1.66–3.58)	1.86 (1.35–2.56)
	65-74	4.52 (2.87–7.13)	2.86 (1.85–4.43)	2.88 (1.79–4.62)	2.20 (1.37–3.51)
	≥75	3.08 (1.32–7.19)	1.95 (0.82–4.60)	1.96 (0.81–4.75)	1.50 (0.65–3.45)
HIV status unknown, compared to HIV-negative	15-24	1.97 (1.35–2.89)	1.65 (1.13–2.43)	1.46 (0.91–2.32)	1.46 (0.99–2.17)
	25-34	2.34 (1.80–3.05)	1.97 (1.49–2.60)	1.73 (1.18–2.54)	1.74 (1.30–2.33)
	35-44	1.97 (1.50–2.59)	1.65 (1.25–2.20)	1.46 (0.97–2.17)	1.46 (1.09–1.96)
	45-54	1.55 (1.12–2.14)	1.30 (0.95–1.77)	1.14 (0.75–1.74)	1.15 (0.84–1.58)
	55-64	2.04 (1.49–2.80)	1.71 (1.28–2.29)	1.51 (1.01–2.26)	1.52 (1.12–2.05)
	65-74	1.89 (1.35–2.65)	1.59 (1.19–2.12)	1.40 (0.92–2.11)	1.40 (1.02–1.93)
	≥75	1.64 (1.11–2.40)	1.37 (0.98–1.92)	1.21 (0.77–1.89)	1.21 (0.84–1.75)

Hazard ratios adjusted for TB treatment history and region, and analysis stratified by sex

Table S3: Adjusted hazard ratios for the association between disease type and death, stratified by HIV/ART status

Type of TB	HIV status			
	HIV-negative	**HIV-positive, on ART**	**HIV-positive, not on ART**	**HIV status unknown**
Pulmonary, smear-positive	Reference	Reference	Reference	Reference
Pulmonary, smear-negative	1.99 (1.81–2.19)	1.30 (1.21–1.4)	1.26 (1.06–1.49)	1.67 (1.30–2.14)
Pulmonary, smear result unknown	2.84 (2.41–3.35)	2.00 (1.74–2.29)	1.81 (1.37–2.37)	2.10 (1.50–2.94)
Extra-pulmonary	2.62 (2.37–2.88)	1.50 (1.38–1.63)	1.27 (1.04–1.55)	1.94 (1.49–2.54)

Hazard ratios adjusted for TB treatment history and region, and stratified by sex

CHAPTER 7

Reaching 95-95-95 targets: the role of private sector health facilities in closing the HIV detection gap – Kisumu Kenya, 2018

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Abstract

Background: HIV testing efficiency could be improved by focusing on high yield populations and identifying types of health facilities where people with undiagnosed HIV infection are more likely to attend.

Methods: A retrospective cohort analysis of data collected during an integrated TB/HIV active case-finding intervention in Western Kenya. Data were analyzed from health facilities' registers on individuals who reported TB-suggestive symptoms between 1 July to 31 December 2018 and who had an HIV test result within one month following symptom screening. We used logistic regression with general estimating equations adjusting for sub-county level data to identify health facility-level predictors of new HIV diagnoses.

Results: Of 11,376 adults with presumptive TB identified in 143 health facilities, 1038 (9%) tested HIV positive. The median HIV positivity per health facility was 6% (IQR = 2–15%). Patients with TB symptoms were over three times as likely to have a new HIV diagnosis in private not-for-profit facilities compared to those in government facilities (adjusted odds ratio (aOR) 3.40; 95%CI 1.96–5.90). Patients tested in hospitals were over two times as likely to have a new HIV diagnosis as those tested in smaller facilities (i.e., health centers and dispensaries) (aOR 2.26; 95%CI 1.60–3.21).

Conclusion: Individuals with presumptive TB who attended larger health facilities and private not-for-profit facilities had a higher likelihood of being newly diagnosed with HIV. Strengthening HIV services at these facilities and outreach to populations that use them could help to close the HIV diagnosis gap.

Key words: Positivity, HIV Antibody; Testing, HIV; Hospitals, Private; Health Facilities

BACKGROUND

Finding new HIV cases is important for the achievement of the WHO 95-95-95 targets by 2030 [1]. The first of the targets, indicating that 95% of people living with HIV/AIDS (PLWHA) should know their status, is crucial as it is a prerequisite for entry into the HIV care cascade. However, by the end of 2019, over 10% of PLWHA in southern and eastern Africa did not know their status [2].

An established strategy for increasing detection of HIV is provider-initiated testing and counseling (PITC), whereby all people seeking care in health facilities are offered testing regardless of their reason for seeking care [3]. While this strategy has contributed to the closure of the HIV detection gap, testing yields in health facilities has been falling as more PLWHA are aware of their status, thus decreasing the HIV prevalence in those remaining with unknown status [4]. PITC efficiency could be improved by focusing on high yield populations such as TB symptomatic adults [5] and by identifying types of health facilities where people with undiagnosed HIV infection are more likely to attend. This may help identify facilities that could best contribute to improved HIV detection through augmented PITC programs or outreach services to the populations served by those facilities. To identify such health facilities, we analyzed data generated from an integrated TB/HIV active case-finding (ACF) intervention in western Kenya.

METHODS

Study design: We conducted a retrospective cohort analysis of HIV testing data collected programmatically during an active TB/HIV case-finding intervention among adults in health facilities in Kisumu County.

Study setting and intervention: Kisumu County in western Kenya has an estimated adult HIV prevalence of 17.5% [6], and an estimated 20% of adult PLWHA have not been diagnosed [7]. The annual TB case notification rate is 243 per 100,000 population [8]. The county has 230 health facilities across seven sub-counties.

The ACF intervention was initiated in two sub-counties in June 2016 and progressively expanded to cover the entire county by 2018. At each health facility, a Community Health Volunteer (CHV)

actively screened all adults (≥15 years old) who visited the health facility for symptoms that could be consistent with TB (i.e., presence of cough, fever, weight loss, night sweats, or difficulty breathing in the past four weeks). Individuals reporting any TB-related symptom were asked to provide sputum and were evaluated for TB. Per national guidelines, they were referred for HIV testing if they did not know their status or had a negative result older than three months. Healthcare workers and CHVs ensured that people were registered in the paper "TB-symptomatic adults" registers when they reported any symptom, and that the results of subsequent HIV and TB evaluation procedures were recorded in the registers as they became available.

Study population: Individuals who were registered in the TB-symptomatic adults registers of health facilities receiving the ACF intervention, who were screened for TB symptoms during 1 July through 31 December, 2018, and who had a new HIV test result were eligible for inclusion in our analysis. We defined a new HIV test result as one whose date was within 1 month after the TB symptom screening date. We excluded individuals who reported that they were living with HIV (and hence were not re-tested), individuals who were not tested because they reported a recent negative test, individuals who refused testing, and individuals for whom the date of testing could not be determined. We limited our analysis to health facilities with at least one new HIV test recorded in the TB symptomatic register during the analytic period. Our analysis did not have a pre-determined sample size; we extracted data from all health facilities that received the intervention for an analytic period that was feasible given available resources.

Data collection: HIV test results were abstracted from paper-based facility TB-symptomatic adults registers and stored in an electronic database (RedCap). Data quality assurance measures such as compulsory fields, range checks and branching logic were in-built into the RedCap database. During abstraction data quality assessments, which entailed verification of RedCap data with hard copy TB symptomatic registers, were conducted to ensure completeness and accuracy. Characteristics of health facilities were obtained from the Ministry of Health.

Variables: The outcome of interest was new positive HIV test results. Predictor variables were characteristics of health facilities. Health facility level was categorized into Tier 2 (dispensaries

and health centers) and Tier 3 (hospitals). Health facility ownership was categorized as public if the facility was owned by the government, private if it was owned by a private company and operating for profit, or private-not-for-profit if it was operating as a non-profit but not owned by the government. In Kenya, 70% of facilities in the private-not-for-profit category, including almost all of those offering HIV services, are operated by faith-based organizations [9]. The location of a health facility was considered urban if it was located within a municipality or a town, and rural if not. Facilities were also categorized by number of annual outpatient department visits; low-volume facilities have fewer than 7,500 outpatient visits, medium-volume facilities have 7,501–15,000 visits, and high-volume facilities have more than 15,000 visits. Finally, facilities were categorized based on the TB (TB diagnostic testing by GeneXpert MTB/RIF or smear microscopy) and HIV (antiretroviral therapy [ART]) services offered.

Data analysis: Logistic regression was performed with HIV test result as the outcome. Generalized estimating equations were used to account for clustering by health facility; all predictors were thus assessed at the cluster level since only health facility characteristics were considered as predictors. Odds ratios (OR) with robust standard errors were calculated. Bivariate analysis was performed, and predictors with a *p* value of 0.2 or less on bivariate analysis were included in a multivariate analysis. Backwards elimination was used to produce the final multivariable model, except that sub-county was forced into the model to account for possible geographic differences in HIV prevalence. Data were analyzed using Stata Version 14.

Ethical considerations: Ethical approval was obtained from the Kenya Medical Research Institute ethical review committee and the Centers for Disease Control and Prevention Institutional Review Board. A waiver of written informed consent was obtained because procedures were conducted as part of routine clinical care.

RESULTS

Kisumu County has 230 health facilities, of which 78% (n = 181) participated in the TB/HIV active case-finding program (**Figure 1**). Participation in the active case-finding program was higher in

public (98%; n=122/125) than private not-for-profit facilities (81%; n=26/32) (p-value=0.01) and private for-profit facilities (45%; n=33/73) (p-value <0.001).

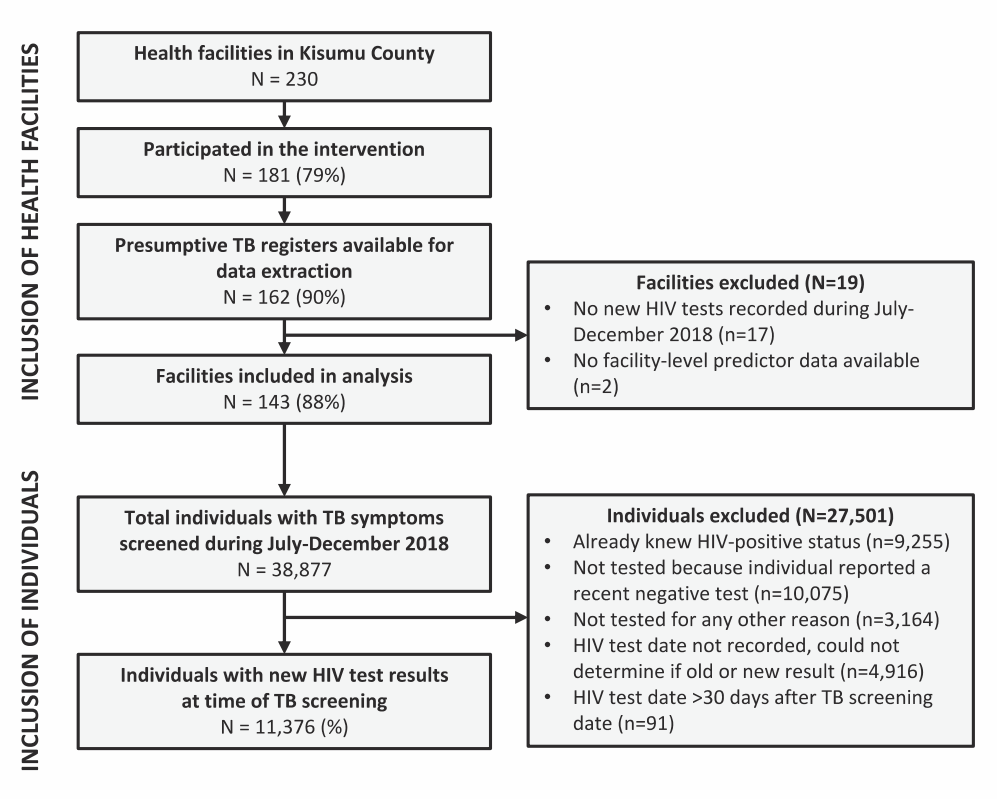

Figure 1: Inclusion of health facilities and individuals in analysis

This analysis included 143 participating health facilities that recorded at least one new HIV test administered to a patient recorded in the TB-symptomatic adults' register during the analysis period (**Table 1**). A total of 38,877 individuals with TB-consistent symptoms were identified in these facilities during July-December 2018 (**Figure 1**). Of these, 9,255 (24%) were not tested because they reported already knowing that they were living with HIV, and 10,075 (26%) were not tested because they reported a recent negative HIV test result. We included in the analysis 11,376 individuals with a documented new HIV test result, 1,038 (9%) of whom had a positive

HIV test. The median number of patients tested per health facility was 117 (interquartile range [IQR] = 72–194) with a median new HIV positivity rate of 6% (IQR = 2–15 %).

Table 1: Characteristics of health facilities implementing active case-finding for TB in western Kenya and median HIV test positivity among TB-symptomatic adults, 2018 (n=143)

Characteristic	Number of facilities	(%)	Number of TB-symptomatic adults	Median (IQR*) number of TB-symptomatic adults tested	Median (IQR*) number with positive results	Median (IQR*) % HIV test positivity
Ownership						
Government	102	(71)	9266	120 (77-206)	3(1-8)	5 (2-10)
Private not-for-profit	23	(16)	1327	98 (65-171)	5(2-11)	17 (5-39)
Private for-profit	18	(13)	783	77 (51-87)	4 (1-6)	10 (2-25)
Health facility level						
Tier 2**	117	(82)	7968	108 (65-154)	3(1-6)	5 (2-10)
Tier 3***	26	(18)	3408	446 (104-881)	12 (4-23)	16 (11-24)
TB Diagnostic site						
Yes	94	(66)	8417	120 (77-206)	5(2-11)	9 (5-19)
No	49	(34)	2959	102 (49-171)	1(1-3)	3 (1-5)
ART site						
Yes	132	(92)	10962	119 (76-194)	4(2-8)	7 (2-17)
No	11	(8)	414	47 (33-65)	1(0-3)	3 (0-5)
Facility setting						
Rural	97	(68)	7177	110 (66-163)	3(1-6)	5 (2-9)
Urban	46	(32)	4199	154 (85-474)	5(2-15)	12 (4-25)
Facility volume						
High (>15000 OPD cases/year)	22	(15)	2615	446 (85-881)	11(4-27)	16 (8–22)
Medium (7501 to 15000 cases/year)	45	(32)	4551	124 (102-200)	5(2-8)	5(2-12)
Low (<=7500 OPD cases/year)	76	(53)	4210	83 (49-124)	2(1-5)	5 (2–12)
Total	143	(100)	11376	117 (72-194)	4(1-8)	6 (2-15)

* Interquartile range **Dispensaries/ Health centers ***Hospitals

In bivariate analysis, likelihood of new HIV diagnoses was higher in private-not-for-profit facilities and private for profit than government-owned facilities (**Table 2**). Tier 3 facilities (hospitals), TB diagnostic sites, ART sites, facilities located in urban areas and Kisumu Central subcounty were also more likely to have new HIV diagnoses. Patients in Tier 3 facilities accounted for 30% of the HIV tests, but represented 49% of positive HIV test results in this population. Patients in private for-profit, private not-for-profit, and public facilities accounted for 7%, 12% and 81% of the HIV tests and represented 11%, 17% and 72% of positive HIV results, respectively.

Table 2: Bivariate and multivariate analysis of health facility characteristics associated with the yield of new HIV diagnoses (N= 11,376)

Facility characteristic	Positive/tested (% HIV-positive out of tested) (%)	OR (95% Confidence interval)	Adjusted OR (95% Confidence interval)
Ownership			
Government	746/9266 (8)	1	1
Private not-for-profit	179/1327 (14)	3.19 (1.76–5.78)	3.40 (1.96–5.90)
Private for- profit	113/783 (14)	1.98 (1.13–3.47)	1.56 (0.96–2.53)
Facility level			
Tier 2 (Dispensaries/ Health centers)	526/7968 (7)	1	1
Tier 3 (Hospitals)	512/3408 (15)	2.25 (1.48–3.40)	2.26 (1.60–3.21)
TB Diagnostic site			
No	106/2959 (4)	1	1
Yes	932/8417 (11)	3.24 (1.99–5.28)	1.22 (0.68-1.85)
ART site			
No	20/414 (5)	1	1
Yes	1018/10962 (9)	2.23 (1.03–4.83)	5.24 (2.54–10.81)
Facility setting			
Rural	428/7177 (6)	1	1
Urban	610/4199 (15)	2.71 (1.79–4.10)	1.56 (0.96-2.52)
Facility volume			
Medium (7,501-15,000 OPD cases/year)	288/4551 (6)	1	1
High OPD (>15,000 cases/year)	441/2615 (17)	2.56 (1.59-4.10)	0.85 (0.47-1.53)
Low (<=7,500 OPD cases/year)	309/4210 (7)	1.22 (0.73-2.04)	0.78 (0.52-1.17)
Sub county			
Muhoroni	99/1705 (6)	1	1
Kisumu Central	377/2212 (17)	3.06 (1.51–6.20)	3.16 (1.68–5.91)
Kisumu East	76/637 (12)	1.73 (0.89–3.36)	1.91 (1.06–3.42)
Kisumu West	130/1027 (13)	1.97 (1.01–3.83)	2.13 (1.23–3.68)
Seme	51/1048 (5)	0.71 (0.37–1.36)	0.84 (0.45–1.54)
Nyando	157/2686 (6)	0.99 (0.47–2.11)	1.08 (0.54–2.16)
Nyakach	148/2061 (7)	1.31 (0.64–2.68)	1.25 (0.64–2.43)

In multivariate analysis, patients tested in private not-for-profit facilities were over three times as likely to have a new HIV diagnosis compared to those tested in government facilities (adjusted OR [aOR] = 3.40; 95% CI=1.96–5.90). Moreover, the likelihood of new HIV diagnoses remained around twice as high among patients tested in Tier 3 facilities compared to Tier 2 facilities (aOR = 2.26; 95% CI = 1.60–3.21).

DISCUSSION

In our study, new HIV diagnoses were recorded for almost 1 out of every 10 people with TB-consistent symptoms and new HIV test results, but there was substantial variation among health facilities. Patients attending private not-for-profit facilities – a category dominated by facilities

operated by faith-based organizations – were three times more likely to test positive than those in government-owned facilities. This finding is consistent with a previous study from Kenya showing that patients diagnosed with TB in the private sector were more likely to have a positive HIV test.[10] Independently of facility ownership, patients in hospitals were twice more likely to test positive than those in health centers and dispensaries. This is consistent with findings from previous studies [11-13] probably because such facilities attend to sicker clientele. Together, these findings suggest that through strengthening HIV testing services in large hospitals and private not-for-profit facilities, along with strengthening targeted outreach to hard-to-reach or underserved populations, more PLWHA can be reached and linked to care who do not yet know their status.

Our findings underscore the importance of better partnership between government HIV programs and private not-for-profit facilities. The healthcare marketplace of many African countries comprises a mix of public and private facilities, with private not-for-profit facilities providing a substantial share of health care services [14]. Clients choose where they seek care based on different preferences, not necessarily attending the health facility closest to their home [15]. Private not-for-profit facilities may be attracting different clientele than government facilities, such as more educated clients or poorer clients [10,16]. In many countries, they are perceived as having greater accessibility, shorter wait times, and fewer problems with medication stock-outs [15,17-18]. Yet, basic services that are typically provided free of charge by government programs, such as vaccinations, may be less readily available [18].

Usage of the private sector for HIV testing is common in many sub-Saharan African countries including Kenya, generally correlating with usage of the private sector for other health conditions [16]. However, there are challenges to ensuring high HIV testing coverage in the private sector. Inconsistent access to government-subsidized ART medications and charging patients for HIV tests have been highlighted as barriers leading to lower coverage of HIV testing among patients diagnosed with TB in the private sector compared to the public sector [19]. Moreover, as donor funding for HIV services decreases, there is emerging evidence that private sector facilities may be more likely to discontinue or reduce HIV services than public sector facilities [20]. Together, these factors underscore the importance of national HIV programs having engagement strategies

to ensure that the substantial number of clients using private facilities are continue to be well reached with HIV services as donor support declines.

Our analysis was subject to several limitations. A substantial number (n=40) of private for-profit health facilities declined to participate in the intervention, so our results regarding HIV testing yields in this sector may have been affected by selection bias, which we are unable to address. Our analysis was also restricted to HIV testing in a target population of people with TB-consistent symptoms; therefore, our results do not tell us whether the general patient population of hospitals and private non-profit health facilities are more likely to have undiagnosed HIV, as facilities may differ in the proportions of patients with TB-consistent symptoms, and patients may choose to go to different types of facilities based on their symptomology. Finally, identification of people eligible for HIV testing followed the national algorithm that relies on self-report of HIV testing history, so response bias could have influenced the estimates of the absolute yield of HIV testing in this population. However, it is unlikely to have affected the associations observed between facility type and new HIV diagnoses since this response bias would likely not differ systematically based on health facility characteristics. Finally, routine data sources are prone to data errors and missing data, and while we attempted to ensure accurate abstraction of the information in the paper registers, we were unable to correct errors in the source data.

CONCLUSIONS

In conclusion, if the 95-95-95 targets are to be met by 2030, strengthening the partnership between government HIV testing programs and the private not-for-profit health sector could help to diagnose more people with HIV. Models exist for partnerships between government programs and private-not-for-profit facilities that preserve the autonomy of private-not-for-profit but ensure availability of basic services at all health facilities [10]. Leveraging these partnerships can help to substantially reduce HIV incidence and mortality by improving HIV testing yield and identifying PLWHA in a high yield subpopulation, and potentially improving linkage to care for those who do not yet know their status.

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CHAPTER 8

Drop-offs in the isoniazid preventive therapy cascade among children living with HIV in western Kenya, 2015-2019

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Abstract

Introduction: Isoniazid preventive therapy (IPT) can reduce the risk of tuberculosis (TB) in children living with HIV (CLHIV), but data on the outcomes of the IPT cascade in CLHIV are limited.

Methods: We evaluated the IPT cascade among CLHIV aged <15 years and newly enrolled in HIV care in eight HIV clinics in western Kenya. Medical record data were abstracted from September 2015 through July 2019. We assessed the proportion of CLHIV completing TB symptom screening, IPT eligibility assessment, IPT initiation, and completion. TB incidence rate was calculated stratified by IPT initiation and completion status. Risk factors for IPT non-initiation and non-completion were assessed using Poisson regression with generalized linear models.

Results: Overall, 856 CLHIV were newly enrolled in HIV care, of whom 98% ([95%CI 97-99]; n=841) underwent screening for TB symptoms and IPT eligibility. Of these, 13 (2%; 95%CI 1-3) were ineligible due to active TB and 828 (98%; 95%CI 97-99) were eligible. Five hundred and fifty-nine (68%; 95%CI 64-71) of eligible CLHIV initiated IPT; median time to IPT initiation was 3.6 months (interquartile range [IQR] 0.5-10.2). Overall, 434 (78%; 95% CI 74-81) IPT initiators completed. Attending high-volume HIV clinics (aRR=2.82; 95%CI1.20-6.62) was independently associated with IPT non-initiation. IPT non-initiation had a trend of being higher among those enrolled in the period 2017-2019 vs. 2015-2016 (aRR=1.91; 0.98-3.73) and those who were HIV virally non-suppressed (aRR=1.90; 95%CI 0.98-3.71). Being enrolled in 2017-2019 vs. 2015-2016 (aRR=1.40; 1.01-1.96) was independently associated with IPT non-completion. By 24 months after IPT screening, TB incidence was four-fold higher among eligible CLHIV who never initiated (8.1 per 1,000 person years [PY]) compared to CLHIV who completed IPT (2.1 per 1,000 PY; [rate ratio (RR) =3.85; 95%CI 1.08-17.15), with a similar trend among CLHIV who initiated but did not complete IPT (8.2/1,000 PY; RR=4.39; 95% CI 0.82-23.56).

Conclusions: Despite high screening for eligibility, timely IPT initiation and completion were suboptimal among eligible CLHIV in this programmatic cohort. Targeted programmatic interventions are needed to address these drop-offs from the IPT cascade by ensuring timely IPT initiation after ruling out active TB and enhancing completion of the six-month course to reduce TB in CLHIV.

INTRODUCTION

Tuberculosis (TB) is a leading cause of death among people living with HIV [1, 2] and a significant cause of morbidity and mortality in children living with HIV (CLHIV) [3, 4]. TB prevalence in Kenya was estimated to be 558 per 100,000 population in 2016 [5]. Childhood TB accounts for 9% of all TB notifications in Kenya, and nearly a third of children on TB treatment are co-infected with HIV [6].

A 6-month course of isoniazid preventive therapy (IPT) has been shown to reduce the risk of developing TB by up to 60% in children [7]. The implementation of IPT in CLHIV involves multiple steps, constituting a care cascade. These steps entail identifying eligible children, evaluation to rule out active TB, initiating them on IPT, and completion of six months of IPT [8]. Barriers at any step of the IPT cascade leads to drop-offs, thus reducing the potential benefit of IPT programs to reduce TB [8].

Although the Kenya Ministry of Health introduced IPT among CLHIV in 2014, rates of initiation remained low until September 2015 when a massive rollout began [9]. Data are limited on the programmatic performance of the IPT cascade among CLHIV including longer-term TB incidence in high TB burden countries. Most studies from high burden settings evaluated the IPT cascade among under-five children who are contacts of people with TB and reported IPT initiation rates ranging from 2.3% to 100% and completion rates ranging from 0% to 95% [10]. Previous studies that evaluated the IPT cascade in Kenya focused primarily on adults with HIV [9, 11, 12].

We conducted this analysis among CLHIV who were newly enrolled in high- and moderate-volume HIV clinics in Kisumu County, western Kenya to 1) determine the proportion of CLHIV completing key steps of the IPT cascade; 2) identify risk factors for IPT non-initiation and non-completion; and 3) compare the risk of TB among CLHIV who completed IPT versus those who did not.

METHODS

Study setting

The annual TB case notification rate in Kisumu County was 209 per 100,000 population in 2019; 52% of the notified cases were co-infected with HIV [13]. HIV prevalence among adults in Kisumu County was estimated to be 17.5% in 2018, over thrice the national prevalence of 4.9%, while the prevalence among children aged <15 years was 0.7% [14]. HIV services in the County are offered within HIV clinics that are mainly based in high-volume hospitals and follow national guidelines regarding TB screening and prevention [15]. CLHIV are enrolled in HIV clinics where they are initiated on ART and followed up monthly. Screening for TB symptoms is conducted at baseline and during monthly HIV clinic follow-up visits using an intensive case finding (ICF) questionnaire. CLHIV with cough of any duration, fever, night sweats, or noticeable weight loss are evaluated for active TB. All CLHIV aged 12 months and over without TB symptoms and those with TB symptoms ones in whom active TB is ruled out upon further evaluation are eligible for IPT [16]. CLHIV who are initiated on IPT are followed up at regular intervals as determined by respective clinics, which are usually synchronized with ART follow-up visits until they finish the six-month course. IPT follow-up information among children who initiated IPT including IPT completion outcomes at 6 months (completed IPT, lost to follow up, discontinued IPT, dead or transferred out) and TB status at 12, 18, and 24 months are recorded in a paper-based IPT register. For purposes of this analysis, transfer out was considered 'non-completion' due to a lack of further information. Other clinical information is recorded in electronic medical records that capture HIV treatment information including viral load, opportunistic infections, and the child's current care status (whether active, transferred out, or lost to follow-up). The medical charts are usually completed by nurses or attending clinicians. For this study, data was collected from eight HIV clinics in Kisumu County (Jaramogi Oginga Odinga Teaching and Referral Hospital, Kisumu County Hospital, Lumumba Sub- County Hospital, Migosi Sub- County Hospital, Rabuor Sub-County Hospital, St. Monica Clinic, Ahero County Hospital, and Chulaimbo County Hospital).

Study design

This was a retrospective cohort study based on a review of routinely collected data were abstracted from the paper-based registers and electronic medical records of CLHIV aged 12 months to <15

years who were newly enrolled in HIV care at the participating health facilities (including those who were transferred in from other facilities) from September 2015 through July 2019. Data abstraction occurred from November 2019 through November 2020. The data abstraction tool captured the following information: baseline demographic and clinical characteristics (date of HIV diagnosis, date of enrollment to HIV care, date of ART initiation, history of opportunistic infections, viral load at IPT initiation (within 6 months) or the most recent for non-initiators (within 6 months of the most recent IPT eligibility evaluation), screening for TB symptoms, IPT initiation, monthly IPT follow-up for six months, IPT outcome at six months, and TB status at 12, 18 and 24 months after IPT initiation. IPT initiation and completion statuses were assessed based on documentation by attending clinicians in the medical records and IPT cards.

Data analysis

We assessed the cascade estimating proportions completing eligibility screening out of identified CLHIV, IPT initiation out of those who were eligible, and IPT completion out of those who initiated IPT with 95% confidence intervals. For this analysis CLHIV with a negative TB symptom screen, or if symptomatic, had active TB ruled out after further evaluation were considered to be eligible for IPT. Bivariate and multivariable analysis was conducted to determine risk factors for IPT non-initiation among eligible children and non-completion among those who initiated using a modified Poisson regression. We considered both patient-level and facility-level risk factors. Factors with a p-value of <0.10 on bivariate analysis were included in multivariate analysis. The most recent viral load results before IPT initiation (within six months) were included in the analysis. For IPT non-initiators, viral load results obtained within six months of the most recent IPT eligibility evaluation were used. CLHIV with a viral load of less than 1000 copies per milliliter was considered virally suppressed. HIV clinics were categorized into moderate-volume (<5000 active clients) and high-volume (≥5000 active clients). Factors with a p-value less than 0.05 were considered statistically significant in the multivariable analysis.

We compared TB incidence rates among three groups of CLHIV: (a) those who were eligible but never initiated IPT (IPT non-initiators), (b) those who initiated but never completed IPT (IPT non-completers), and (c) those who completed the six-month IPT course (IPT completers) as the

reference group. TB incidence rates were calculated as the sum of new cases divided by the person-years at risk while in care. Person-years at risk was calculated as the interval from the last date of IPT eligibility screening to the date of TB diagnosis or the date of the last clinic visit or the date they transferred care to another facility and rate ratios were calculated with 95% confidence intervals. Data were analyzed using Stata version 16 (StataCorp, College Station, Texas, USA).

Ethical considerations

Ethical clearance was obtained from the University of Washington Institutional Review Board, Kenyatta National Hospital/University of Nairobi Ethics Review Committee, and Jaramogi Oginga Odinga Teaching and Referral Hospital Ethics Review Committee. Informed consent was waived since this study only involved abstraction and analysis of data that was collected as part of routine clinical care.

RESULTS

Demographic and clinical characteristics of participants

Overall, 856 CLHIV between the ages of 12 months and 14 years were newly enrolled in HIV care from September 2015 through July 2019. At enrollment, the median age was 5 years (interquartile range [IQR] 1.9–9.2) and 54% (n=465) were female (**Table 1**). Seventy-eight percent (n=667) of the CLHIV were WHO stage 1 or 2, 14% (n=119) were WHO stage 3 or 4, while 8% (n=70) were missing information on WHO stage. Ninety-nine percent (n=844) of CLHIV had a date of ART initiation. Of these, 78% (n=657) were initiated on ART at enrolment. Among those who initiated ART post-enrollment, the median time to ART initiation was 0.5 months (IQR=0.2–2.3). Viral load was available for 58% (n=497) of CLHIV. The median viral load at IPT initiation was 60 copies per milliliter (IQR=0–1154); 71% (n=373) were virally suppressed. Among non-initiators, the median viral load within 6 months of the most recent IPT eligibility evaluation was 229.5 copies per milliliter (IQR=70- 8989.5); 56% (n=18) were virally suppressed.

Table 1: Baseline demographic and clinical characteristics

Characteristic	Number	Percent (%)
Age at enrollment		
Median age in years (interquartile range)	5.0	1.9-9.2
12 months to 4 years	425	50
5-9 years	239	28
10-14 years	187	22
Sex		
Male	391	46
Female	465	54
Facility volume		
High-volume (≥5000 active clients)	570	67
Moderate-volume (<5000 active clients)	286	33
Year of enrolment		
2015-2016	500	58
2017-2019	356	42
WHO stage		
Stage 1/2	667	79
Stage 3/4	119	14
Unknown	61	7
Timing of ART initiation (N=844)		
At enrolment	652	77
Post enrolment	192	33
Median months to ART post enrolment (interquartile range)	0.5	0.2-2.3

TB screening and IPT eligibility evaluation

Nearly all (98% [95% CI 97-99]; n=841) of the enrolled CLHIV were screened for IPT eligibility using the ICF tool (**Figure 1**); 2% (95% CI 1–3; n=13) of those screened were diagnosed with active TB. Thus, 98% (95% CI 97–99; n=828) of the CLHIV who underwent screening were eligible for IPT initiation.

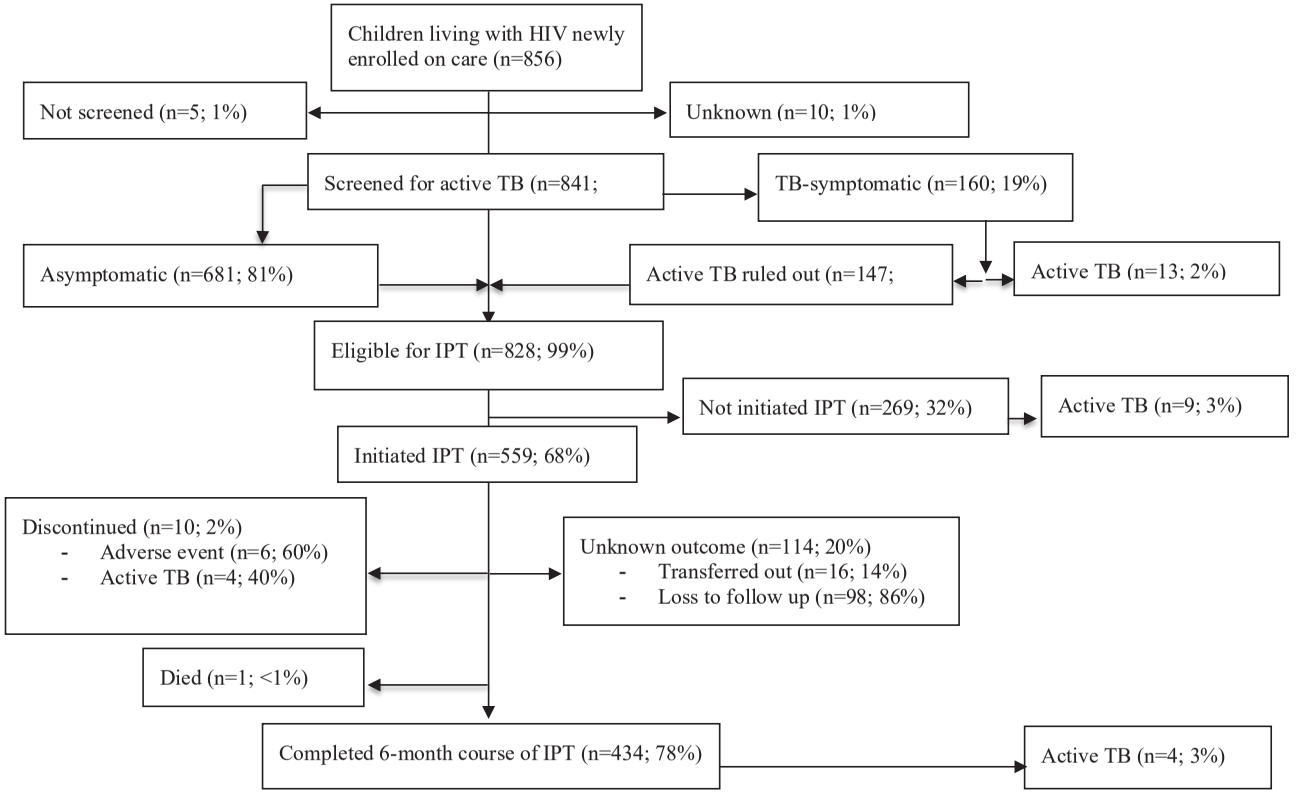

Figure 1: IPT cascade among CLHIV enrolled on HIV care, Kisumu County, western Kenya, 2015-2019

IPT initiation

IPT was initiated in 68% (95% CI 64–71; n=559) of eligible CLHIV (**Figure 2**). Of these children, 63% (95% CI 58–67; n=350) started within six months of enrolment into HIV care, 15% (95% CI 12-18; n=84) within 7 to 12 months and 19% (95% CI 16–23; n=108) after 12 months. The date of IPT initiation was unknown for 3% (n=17) of CLHIV who initiated IPT. Almost all (99%; n=554) were on ART at IPT initiation; one participant was not on ART when IPT was initiated while the ART status at IPT initiation of four participants was unknown.

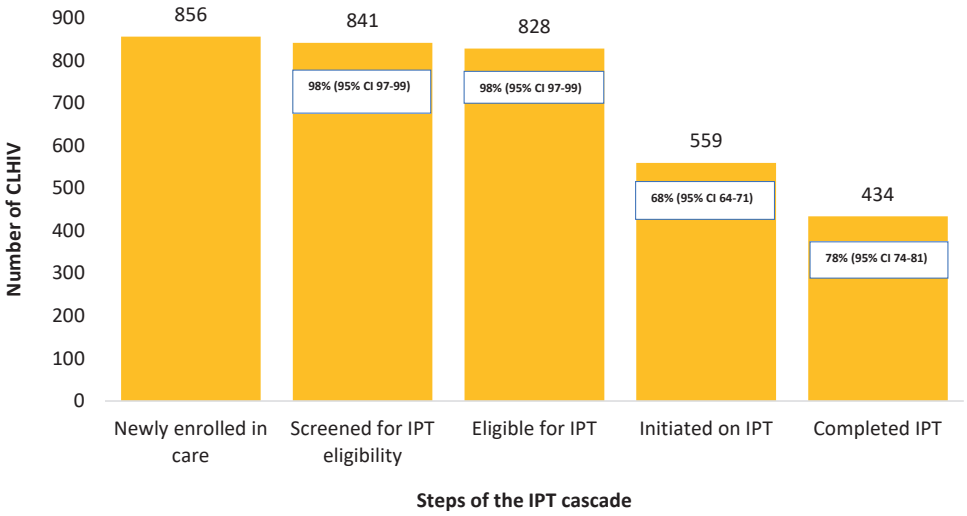

Figure 2: Children living with HIV completing steps of the isoniazid preventive therapy cascade, Kisumu County, western Kenya, 2015-2019
*Percentages reflect the proportion of participants from the previous step completing the step

IPT completion

Of 559 CLHIV who initiated IPT, 78% (95% CI 74–81; n=434) completed the six-month course. IPT was discontinued in 2% (n=10); six had adverse events while four were diagnosed with active TB. One child died of an unknown cause within 2 months of IPT initiation. IPT outcomes were unknown in 20% (n=114) of CLHIV who initiated; of these, 86% (n=98) were lost to follow-up while 14% (n=16) were transferred out to other health facilities. The median number of months on

IPT was 1.5 (IQR 1.0–2.8) among those who discontinued, 3.2 (IQR 2.9–6.2) among those who were lost to follow-up, and 2.1 (IQR 1.0–4.9) among those who transferred out.

Risk factors for IPT non-initiation and non-completion

In bivariate analysis, younger age, later year of enrolment, viral load non-suppression, and higher HIV clinic volume were associated with non-initiation of IPT among eligible CLHIV at a p-value <0.10 level and thus included in the multivariable model (**Table 2**). In multivariable analysis adjusting for factors with a p-value of <0.1 in bivariate analysis, IPT non-initiation was nearly twice higher among those enrolled between 2017 to 2019 than those enrolled between 2015 to 2016 (aRR=1.91; 95% CI 0.98–3.73), had a trend to be 90% higher among virally non-suppressed CLHIV than virally suppressed (aRR=1.90; 95% CI 0.98–3.71) and almost thrice as high among CLHIV attending high-volume HIV clinics than among those attending lower volume clinics (aRR=2.82; 95% CI 1.20–6.62).

Among CLHIV who initiated IPT, year of enrolment and HIV clinic volume were associated with non-completion of IPT in bivariate analysis at a p-value <0.10 level and thus included in the multivariable model. In multivariable analysis, IPT non-completion was 40% higher among those enrolled between 2017 to 2019 than those enrolled between 2015 to 2016 (aRR=1.40; 95% CI 1.01–1.96).

Table 2: Factors associated with non-initiation and non-completion of IPT in newly enrolled CLHIV in western Kenya

Characteristic	IPT initiation among eligible CLHIV n=828					IPT completion among initiators n=559				
	Initiated N (Row %) (N=559)	Not initiated N (Row %) (N=269)	RR (95% CI)	Adjusted** RR (95% CI)	P-value	Completed N (Row %) (N=434)	Never completed N (Row %) (N=109)	RR (95% CI)	Adjusted** RR (95% CI)	p-value
Age at enrollment										
1-4 years	254 (62)	153 (38)	1.36 (1.12-1.66)	1.32 (0.68-2.57)	0.39	199 (81)	46 (19)	0.88 (0.63-1.24)	-	
5-14 years	302 (72)	115 (28)	Ref			232 (79)	63 (24)	Ref		
Sex										
Male	255 (68)	118 (32)	Ref			199 (81)	47 (19)	Ref		
Female	304 (67)	151 (33)	1.05 (0.86-1.28)	-		235 (79)	62 (21)	1.09 (0.78-1.53)	-	
HIV clinic volume§										
High-volume	337 (61)	214 (39)	1.96 (1.51-2.53)	2.82 (1.20-6.62)	0.02	268 (82)	58 (18)	0.76 (0.54-1.06)	0.77 (0.55-1.08)	0.14
Moderate volume	222 (80)	55 (20)	Ref	Ref		166 (76)	51 (24)	Ref	Ref	
Year of enrolment										
2015-2016	350 (72)	134 (28)	Ref	Ref		285 (83)	60 (17)	Ref	Ref	
2017-2019	209 (61)	135 (39)	1.42 (1.17-1.72)	1.91 (0.98-3.73)	0.06	149 (75)	49 (25)	1.42 (1.02-1.99)	1.40 (1.01-1.95)	0.05
WHO stage at enrolment										
Stage 1/2	473 (72)	180 (28)	1.02 (0.73-1.42)	-		367 (80)	93 (20)	1.31 (0.76-2.28)	-	
Stage 3/4	81 (73)	30 (27)	Ref			66 (85)	12 (15)	Ref		
Unknown	4 (7)	55 (93)	3.44 (2.52-4.72)	-		1 (25)	3 (75)	4.88 (2.26-10.52)	-	
Viral load at IPT initiation*										

Suppressed	330 (95)	18 (5)	Ref	Ref		290 (88)	38 (12)	Ref	Ref	
Non-suppressed	132 (90)	14 (10)	1.85 (0.95-3.63)	1.90 (0.98-3.71)	0.06	108 (83)	22 (27)	1.46(0.90-2.37)	-	
Opportunistic infections										
Yes	27 (59)	19 (41)	1.29 (0.90-1.85)			20 (74)	7 (26)	1.32 (0.68-2.56)	-	-
No	530 (68)	249 (32)	Ref			413 (80)	101 (20)	Ref		
Had respiratory symptoms during screening										
Yes	106 (72)	41 (28)	0.84 (0.64-1.12)	-		79 (79)	21 (21)	1.06 (0.69-1.62)		-
No	448 (67)	221 (33)	Ref			351 (80)	87 (20)	Ref		
Time to IPT initiation										
<3 months						177 (77)	53 (23)	Ref		
3-6 months						69 (79)	18 (21)	1.11 (0.69-1.79)		
>6 months						173 (83)	36 (17)	0.83 (0.50-1.38)		

§ Low volume - <5000 active clients; high-volume - ≥ 5000 active clients
* Viral load suppression - less than 1000 copies per milliliter
** Adjusted for factors that with a p-value <0.1 during bivariate analysis

TB incidence by 24 months after enrolment in HIV care

Overall, 30 CLHIV were diagnosed with active TB, including 13 with prevalent TB who were diagnosed at screening for IPT eligibility. Seventeen new cases were diagnosed after enrolment with an incidence of 4.9/1000 person-years (**Table 3**); 53% (n=9) occurred among CLHIV who were eligible but never initiated IPT, 24% (n=4) among those who initiated IPT but did not complete the six-month course, and 24% (n=4) occurred among those who completed the six-month course. By 24 months after IPT screening, TB incidence was four-fold higher among eligible CLHIV who never initiated (8.1 per 1,000 person-years [PY]) compared to CLHIV who completed IPT (2.1 per 1,000 PY; [rate ratio =3.85; 95% CI 1.08–17.15), with a similar trend among CLHIV who initiated but did not complete IPT (8.2/1,000 PY; rate ratio =4.39 95% CI 0.82–23.56).

Table 3: Cumulative TB incidence per 1, 000 child years by 24 months after IPT eligibility evaluation

IPT initiation/completion status	TB-diagnosis	Person-time (years)	TB Rate/1,000 child years (95% CI)	Rate ratio (95% CI)
IPT eligible but never initiated	9	1108.8	8.1 (4.2-15.6)	3.85 (1.08-17.15)
Initiated but never completed IPT	4	433.3	9.2 (3.5-24.6)	4.39 (0.82-23.56)
Completed IPT	4	1901.5	2.1 (0.8-5.6)	Ref
Total	17	3443.6	4.9 (3.0-7.8)	

DISCUSSION

In this retrospective review of medical records of CLHIV in large HIV care programs following intensive scale-up of IPT in Kenya, we found high levels of screening for IPT eligibility, but suboptimal levels of IPT initiation and completion. IPT non-initiation among eligible CLHIV was associated with attending large referral hospitals for HIV care. There was a trend among those enrolled between 2017–2019 compared to earlier periods and those with HIV viral non-suppression. IPT non-completion was associated with being enrolled between 2017-2019 compared to earlier periods.

Although TB preventive therapy (TPT) is critical to reducing morbidity and mortality associated with TB in people living with HIV, it remains underutilized, especially in high TB/HIV burden

settings including sub-Saharan Africa (SSA) [17]. Our results add to the scant evidence on the programmatic performance of the TPT cascade in CLHIV from SSA. Barriers that have been identified to contribute to losses in the TPT cascade [18] could be similar across several SSA countries. Thus, our programmatic evaluation data of the TPT cascade could inform programmatic interventions in other countries that seek to improve the uptake and completion of this life-saving intervention in CLHIV.

Our findings, based on a large cohort of CLHIV aged 1 to 14 years from western Kenya (a region known for its high TB/HIV prevalence), contributes to the limited literature on IPT initiation and completion among CLHIV from high TB/HIV burden countries. The uptake of IPT among CLHIV in Kenya still falls short of the global target of >90% [19] and could be lagging behind that in adults living with HIV as reported by studies from other high TB prevalence countries [20, 21]. These findings strengthen the evidence from previous Kenyan studies that reported suboptimal IPT initiation among CLHIV, although those studies were conducted in regions of the country with lower TB/HIV prevalence, were based on small sample sizes, and did not include all age groups [12, 22, 23].

Additionally, in this study, a substantial proportion of IPT initiators (40%) were initiated after being on HIV care for over six months. Suboptimal or delayed IPT initiation in this study could be due to health system barriers, which have been documented in previous studies, including difficulties in ruling out active TB especially in CLHIV with respiratory symptoms [24], the fear of adverse reactions to INH (22), poor health provider adherence to IPT guidelines [25], frequent INH stock-outs, and concerns about inducing resistance to INH [26]. Our finding that CLHIV in high-volume referral hospitals were almost three times less likely to initiate IPT is similar to a finding by Karanja *et al.* that PLHIV in level 4 and 5 hospitals were less likely to complete IPT compared to lower-level facilities [11]. Such high-volume hospitals have more complex service delivery models that challenge the integration of TB/HIV services [27]. The lower IPT initiation between the period 2017 to 2019 compared to 2015 to 2016 was probably due to a greater programmatic focus during the rapid scale-up phase (2015-2016). Additionally, rapid scale-up occasioned intermittent stockouts of 100 milligrams INH pills (pediatric formulation) from 2017 onwards thus slowing down uptake. In this study, there was a trend of virally non-suppressed

CLHIV being less likely to initiate IPT suggesting that they could have been sicker at enrolment, thus their providers may not have felt confident in ruling out active TB. The impact of caregiver barriers, such as the cost of travel for IPT services and the perception of minimal risk in asymptomatic children [28], may have also contributed.

There are limited data on outcomes of IPT among CLHIV in other high HIV/TB settings in SSA. In a prospective cohort study that enrolled 66 CLHIV from a pediatric clinic in Tanzania, 74% completed IPT within 10 months [29]. A study that evaluated programmatic data among people living with HIV attending two clinics in Kinshasa, the Democratic Republic of Congo included 546 CLHIV on IPT, 87% of whom were reported to have completed the six-month course [30]. IPT completion in this study (78%) was similar to a study conducted at Kenyatta National Hospital (82%) in Kenya [22]. Together, these findings suggest that a substantial proportion of CLHIV do not complete the six-month course of IPT and thus continue to be at risk of developing TB. However, IPT completion in our study could have been higher than reported given that 14% of CLHIV transferred out to other facilities where they may have completed. IPT completion in CLHIV may be improved when IPT refills are synchronized with ART follow-up visits [31, 32]. In our study, HIV viral non-suppression showed a trend for association with non-initiation and non-completion of IPT and is perhaps due to these CLHIV and their caretakers already having difficulty adhering to ART [33]. Virally non-suppressed CLHIV may require additional support to initiate and complete IPT. IPT completion could also be improved by introducing shorter TB preventive therapy regimens [34, 35]. The Kenya Ministry of Health has recommended shorter regimens for under-five childhood contacts of bacteriologically confirmed TB. A similar switch to a shorter regimen, if effective and safe, should be assessed for CLHIV.

There are limited data on the effectiveness of IPT on TB incidence in CLHIV. Randomized trials have established the protective effect of IPT for both HIV-negative children [7] and adults living with HIV [36]. However, a 2018 systematic review of randomized trials of IPT for CLHIV identified only three trials comprising 977 total patients, [37] and while point estimates for the effect of IPT all fell on the side of protection, they failed to achieve statistical significance in two of the trials. Studies that evaluated programmatic data have reported protective effects of >80% for six months of IPT among CLHIV [31, 32]. In this study TB incidence among CLHIV who

completed a full six-month IPT course was four-fold lower compared to those who never initiated or those who initiated but never completed. These findings thus help to bolster the limited evidence from clinical trials and suggest a protective effect of IPT for CLHIV in programmatic settings.

Our study used routine data collected over several years from eight HIV clinics located within the largest hospitals in the County and was therefore suitable for evaluating the outcomes of programmatic IPT in CLHIV in a high burden region in Kenya. Routine data sources are prone to limitations such as incomplete data, which we minimized by abstracting data from multiple sources including IPT registers and HIV treatment records. However, we still had several instances of missing data elements on WHO staging (8%), HIV viral load (14%), and IPT initiation dates (3%). Secondly, these routine data sources did not capture some variables that could explain non-initiation or non-completion of IPT such as socio-economic status, caregiver characteristics (educational status, HIV status, viral load suppression status, and TB status), distance from the clinic, INH stock-outs and attitudes of providers and caregivers. There are efforts to evaluate these factors in a prospective study. Other than TB status, we did not abstract data on clinical outcomes such as mortality and loss to follow-up among IPT non-initiators thus these outcomes were not assessed during analysis. TB status was only captured in the medical charts if there was a TB diagnosis but the absence of TB or uncertainty in diagnosis was not outrightly documented in the medical charts.

CONCLUSIONS

In this study, we observed that while screening for IPT eligibility was high for CLHIV, there were substantial delays and drop-offs at initiation and completion of IPT. Targeted programmatic interventions are needed to address these drop-offs from the IPT cascade by ensuring timely IPT initiation after ruling out active TB and enhancing completion of the six-month course, especially in high-volume hospitals. While shorter course TB prevention regimens are becoming more available, they will likely increase completion but potentially not timely initiation. Virally non-suppressed CLHIV need additional support to initiate and complete IPT and to achieve viral suppression.

COMPETING OF INTERESTS: The authors have no competing interests to declare.

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CHAPTER 9

General Discussion

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* which can affect all organs in the body except the enamel of teeth. Human immunodeficiency virus (HIV) is a virus that attacks the immune system making the body vulnerable to opportunistic disease. TB and HIV have caused significant morbidity and mortality in low- and middle-income countries (LMIC), especially in sub-Saharan African countries which have a disproportionate burden of the two diseases. In such high prevalence settings, the two diseases are key drivers of mortality in the population. TB/HIV co-infection, particularly increases the risk of mortality several folds. This is clearly illustrated by recent data from Kenya. The United Nations sustainable development goals (SDGs) target to end the global TB and HIV epidemics by 2030. To reduce the burden of TB and HIV, two of the main infectious disease epidemics of the 21st century, improved insight is needed on the incidence and drivers of HIV- and TB related deaths in countries with high prevalence of both infections.

HIV-associated mortality in the population

Despite widespread antiretroviral therapy (ART) availability and use, the risk of death among PLHIV is still fourfold higher than among HIV-uninfected people (1), especially if they are not virally suppressed (2). Although the Kenya Population-based HIV Impact Assessment (KENPHIA) reported high ART coverage (76%) in 2018 (3), mortality studies documented high HIV prevalence among decedents and high HIV cause-specific mortality rates (4, 5). Recent mortality studies conducted in Nairobi (6) and western Kenya (4, 5) documented much higher HIV prevalence among decedents than the estimated HIV prevalence in the population. Majority decedents included in these studies had been inpatients in high-volume referral hospitals, where HIV-related complications are the leading indication for hospitalizations (7-9). Notably, HIV prevalence among decedents in the Kenyan studies (4-6) was much lower than similar studies from Cote d'Ivoire (41%) (10) and the Democratic Republic of Congo (45%) (11) that were conducted during the pre-ART era. This reflects the effect of widescale availability of ART on mortality. Kenya is among the countries where the number of HIV deaths is estimated to have reduced by more than 50% between 1990 and 2013 following the expansion of ART programs (12). Nevertheless, mortality studies suggest that HIV cause-specific mortality remains relatively high and that HIV remains a leading underlying cause of death in Kenya (4, 13, 14).

HIV cause-specific mortality in the post-ART era could be occurring among ART naïve PLHIV who do not know their status, PLHIV who have been on ART for a short duration or PLHIV who were failing ART treatment (15-20). The high prevalence of viral non-suppression among HIV-infected decedents in the Kenyan studies (4-6) suggests that these deaths were caused by uncontrolled HIV disease (4, 13). Viral non-suppression could be due to delayed diagnosis or delayed ART initiation (15-19), pretreatment resistance to ART, poor adherence, or treatment interruptions (20). In Kenya, undiagnosed HIV infection could be contributing substantially to viral non-suppression and mortality among PLHIV. KENPHIA reported much higher viral suppression among participants who knew their status and were on ART (children 67.1% and adults 90.6%) than among all HIV-infected participants (children 48.3% and adults 71.6%) (3). To further reduce HIV deaths, substantial effort is needed to identify all people living with HIV, and ensure prompt ART initiation and treatment monitoring to ensure viral suppression (21, 22). HIV case finding strategies that optimize testing yield should be prioritized to ensure timely HIV diagnosis and treatment initiation. Viral suppression could be achieved by optimizing ART with safer and more efficacious regimens especially in children, peer-led interventions and stigma reduction through engagement with stakeholders (23).

Kenyan studies that assessed the accuracy of cause of death data submitted to the civil registration documented a number of gaps (13, 24). Firstly, the HIV cause-specific mortality fraction estimate from civil registration data was two times lower than that ascertained by an expert panel (13). Secondly, the concordance between routinely assigned causes of death with expert panel-assigned ones was dismal (29%) (13). The types of errors leading to this discordance included recording the mechanism of death rather than the cause of death, incompleteness of underlying causes of death, and incorrect sequencing (13, 24). These findings confirm previous concerns about the accuracy of cause of death information from civil registration systems in LMICs (25-28). Civil registrations systems in LMICs are hampered by low coverage of actual deaths and inaccurate recording of causes of death (25, 26). Together, these findings highlight the need for strengthening civil registration systems in LMICs including Kenya. Options for strengthening civil registration systems in LMICs include using health facilities as an entry point for civil registration (29), verification of causes of death before submission to civil registration and health sector utilization of civil registration data (30).

TB-associated mortality in the population

There was a surprisingly low presence of TB in recent Kenya mortality studies, (4, 13) despite routine surveillance data showing that over 5% of patients on TB treatment die every year (31-33). While the low prevalence of TB in these mortality studies could be assumed to reflect programmatic success in TB control, these studies may have under-estimated mortality from the disease. Given that the prevalence of TB in the population is less than 1%, even if the absolute number of deaths from TB is high, this corresponds to a small percentage of the population which requires larger mortality surveillance studies for more accurate estimation of TB mortality. WHO estimates that 30% of TB cases are not detected and reported by routine surveillance systems (34) while the Kenya TB prevalence survey reported that disease prevalence was 2.5 times higher than the case notification rate for 2016 (35). Many of the undiagnosed TB cases die from the disease and could be detected by postmortem studies.

Autopsy studies are useful in identifying TB that was missed antemortem especially groups such as people with smear-negative or extrapulmonary disease, children and PLHIV (36). TB disease is often localized in the lungs or other tissues and can be missed by minimally invasive autopsy techniques such as blind MITS (37). Complete diagnostic autopsy studies have documented substantial TB prevalence in decedents from several LMICs (36, 38, 39). In a meta-analysis, 40% HIV-infected decedents had postmortem evidence of TB infection, half of these prevalent cases were not diagnosed before death (39). These findings reinforce the fact that TB remains an important cause of death in LMIC and the need to develop tools that can assist in estimating mortality from TB. While minimally invasive approaches such as MITS are becoming more popular due to higher acceptability, their role in estimating TB in decedents remain uncertain due to low concordance with complete diagnostic autopsies (37). There is need to explore strategies that can optimize the accuracy of MITS such as the use of ultrasound to localize tuberculous lesions during tissue sampling (40, 41). Furthermore, the high prevalence of TB in complete diagnostic autopsies suggest the need to strengthen TB prevention and control measures including case-finding, treatment and TB preventive therapy.

Mortality associated with TB/HIV co-infection

HIV is recognized as a major driver of mortality from TB (42, 43) especially when the diagnosis of either disease is delayed (44), or ART initiation is delayed (45). Prompt ART initiation has been associated with improved survival among TB/HIV co-infected people (46-48). Relying on guidance from WHO, the Ministry of Health in Kenya updated ART guidelines to allow for immediate ART initiation regardless of clinical or immunological status ("test and treat") in 2016 (49). Data is beginning to emerge on the reduction in mortality from TB among PLHIV in high prevalence settings resulting from "test and treat" implementation. Two studies from Uganda and Ethiopia have reported substantial reduction in all-cause mortality among PLHIV on ART post-"test and treat" (50, 51). It is unclear whether similar gains have been made in Kenya. The reduction in TB mortality among PLHIV can only be sustained over time if retention on ART is high.

According to routine surveillance data, Kenya's case fatality ratio among patients on TB treatment was 6.3% in 2020, falling short of the global target of 5% or less (31). The TB case fatality ratio is similar to that reported among patients who initiated TB treatment between 2013 and 2014 (32) despite significant reduction in TB/HIV co-infection over the same period (35% in 2014 (32) to 25% in 2020 (31)). Interventions such as expanded HIV testing among TB patients, early ART initiation, intensive TB case finding in PLHIV and TB preventive therapy among eligible PLHIV were expected to reduce mortality from TB by up to 80% (52-56). The persistently high case fatality among patients on TB treatment despite implementation of these interventions could be due to delay in diagnosing TB in people with respiratory symptoms, delayed diagnosis of HIV-infection among TB patients or failure to adhere to medications. Additionally, the COVID-19 pandemic could have contributed to the relatively high case fatality ratio in 2020. Globally, the pandemic disrupted TB diagnostic and treatment services as well as TB preventive therapy culminating in additional 100, 000 deaths compared to 2019 (34). According to modeling studies, the impact of COVID-19 on mortality from TB will be even worse in 2021 and 2022 (34).

TB/HIV mortality among children aged under-five years

Reducing under-five mortality is one of the major targets of the Sustainable Development Goal on health. In many LMIC countries including Kenya, high under-five mortality is responsible for the low life expectancy at birth. Despite a substantial reduction in the under-five mortality rate

between 1990 and 2015 (102.3 to 49.4 per 1, 000 live births), Kenya still failed to meet the millennium development goal target (34 deaths per 1,000 live births) (57). Under-five mortality is higher in western Kenya, a region with a disproportionately higher prevalence of infectious diseases including TB and HIV (58). The child health and mortality prevention surveillance (CHAMPS), which is conducting MITS autopsy for under-five decedents in western Kenya (4), provides a unique opportunity to examine the role of TB, HIV and other infections in driving under-five mortality.

CHAMPS identified malnutrition, malaria and HIV as the top three causes of under-five mortality in western Kenya (4). Malnutrition in combination with TB or HIV predispose children to conditions such as bacteremia and septicemia which often result in mortality (4, 59, 60). This is compounded by a failure to diagnose malnutrition during health facility encounters (61). Mortality associated with malnutrition could be reduced through timely diagnosis and management of malnutrition. Anthropometric assessments by community health workers is one of the approaches that has been shown to improve the timeliness of diagnosing malnutrition in some low resource settings (62). Additional data is needed to show if such relatively low-cost interventions can be scaled up and implemented programmatically. Consumption of a balanced diet with introduction of foods that are appropriate for age is pivotal in preventing malnutrition. Promoting exclusive breastfeeding during the first six months coupled with optimal complementary feeding practices during weaning, could substantially reduce the burden of malnutrition in the first year of life. Additionally, there is need to improve the availability of nutritious foods at household level through nutrition-sensitive agricultural practices.

Apart from HIV and TB, malaria is the other major cause of morbidity among under-fives in western Kenya and contributes substantially to under-five mortality (63). HIV and malaria co-infection is known to be a as dangerous as TB/HIV co-infection, the two diseases interact bidirectionally to worsen the outcomes of either disease (64). Between 2003 and 2015, the Ministry of Health rapidly expanded access to malaria interventions including long lasting insecticide treated nets (LLITNs) which is now available to over 80% of under-fives in malaria endemic areas, coupled with diagnosis and treatment with artemisinin combined therapy (65). Consequently, all cause-mortality among under-fives declined substantially as the coverage of these interventions

increased (65). However, data from CHAMPS and a study which estimated in-patient malaria case fatality ratio among under-fives demonstrate that mortality from malaria remains substantially high in western Kenya (4, 63). To further reduce mortality from malaria among under-five children, a new vaccine against malaria has been introduced as part of the routine immunization program. While the malaria vaccine is expected to reduce morbidity and mortality among under-fives, its impact is yet to be demonstrated.

Preventable and treatable infections, for which medications or preventive measures are widely available in Kenya, remain the leading causes of under-five mortality in the country (4). Mortalities arising from HIV, malaria and malnutrition suggests the need to improve the delivery of the existing interventions against such diseases (58). Programmatic evaluation is needed to identify the reasons why children continue to die of preventable and treatable conditions. A detailed examination of interventions such as prevention of mother-to-child transmission of HIV (PMTCT), HIV testing services and HIV care and treatment may reveal leakages that contribute to HIV-associated mortality. Assessment of insecticide treated net ownership and use, health care seeking behavior of caregivers of under-fives with febrile illnesses, and the management of children with malaria in health facilities could provide insight on causes of the substantial malaria mortality burden in under-fives. Strategies that could be used to improve the coverage of existing interventions against the most common infectious diseases include raising awareness among caretakers, strengthening the linkage between community-based and facility-based interventions and identifying children with missed opportunities through schools (66)

Interventions to reduce TB and HIV mortality

Many interventions are known to be effective for reducing mortality from TB and HIV. The impact of these interventions is not fully realized due to challenges experienced during implementation, such as stigma associated with the two diseases, challenges in accessing hard-to-reach populations and poor quality of health services, that culminate in inadequate coverage. Mortality from TB can be reduced through vaccination, early diagnosis and treatment of those with active disease, and preventive therapy in high risk groups including PLHIV (67). HIV-related mortality can be controlled through interventions that prevent transmission such as prevention of mother-to-child

transmission, condoms, medical male circumcision, pre-/post-exposure prophylaxis and treatment with ART; identification of PLHIV, prompt ART initiation, adherence support and viral suppression; and preventive therapy against opportunistic infections including TB (68).

TB preventive therapy is known to reduce TB incidence and mortality from TB in PLHIV by up to 60% especially if combined with ART (69, 70). Despite a 75 fold increase in the uptake of isoniazid preventive therapy (IPT) between 2015 and 2018 (71), PLHIV still account for a quarter of TB patients in Kenya (31). A number of barriers in the IPT cascade could be responsible for the substantial contribution of PLHIV among incident TB cases which increases the risk of mortality. Screening for IPT eligibility, the first step in the cascade, is riddled with several missed opportunities despite high uptake (72). Suboptimal initiation of IPT is another important barrier that has been documented by recent studies (66, 71, 73). However, most evaluation of IPT programs for PLHIV have focused on adults; our work attempted to fill the knowledge gap around IPT for children living with HIV (CLHIV). IPT initiation was suboptimal, particularly in virally non-suppressed CLHIV probably due to the difficulties that providers encounter in ruling out active TB among patients with advanced disease (74). There is evidence of decreasing momentum in IPT initiation after the rapid scale-up following the national launch in 2015 (71, 74). Additional programmatic efforts, especially continuous sensitization of health providers on the benefits of IPT, are needed to sustain the initial momentum in getting PLHIV to initiate TB preventive therapy.

Non-completion of the six-month course of IPT limits the effectiveness of TB preventive therapy. Evaluations of the IPT cascade conducted among adults reported that over 10% of PLHIV who initiated IPT did not complete the six-month course (66, 74, 75). In our evaluation, 22% of CLHIV who initiated IPT did not complete the six-month course. IPT non-completion had a trend of being higher in virally non-suppressed CLHIV who probably also had challenges adhering to ART. The high levels of IPT non-completion have been attributed to its long duration (six months) and the need for daily dosing (10). Newer short-course TB preventive therapy regimens, such as 3 months of isoniazid plus rifapentine (3HP) and 3 months of rifampicin plus isoniazid (3RH), have been shown to have higher adherence and completion rates than IPT (12, 13). Because these new regimens are based on rifampicin and rifapentine, which are well known for inducing the

metabolism of other drugs including antiretrovirals, there have been concerns about their use in PLHIV who are on ART. Unfortunately, 3RH requires ART dosage adjustment in CLHIV on lopinavir-ritonavir, nevirapine and dolutegravir based regimens hence it is only recommended for HIV-uninfected children (76). While recent studies have found that 3HP can be safely co-administered in adults on efavirenz and dolutegravir based regimens (77, 78), the implementation of 3HP in children is limited by the lack of child friendly formulations (76). Thus, the six-month IPT, despite its challenges, remains the preferred regimen in CLHIV(76). Short-course regimens that can safely be taken by CLHIV with the most common ART regimens are still needed.

Identifying undiagnosed PLHIV is critical as it acts as the entry to the care cascade. At the beginning of the HIV epidemic, voluntary counselling and testing was the primary strategy. In 2007 a new approach to HIV testing, the provider initiated testing and counselling (PITC), which entailed offering all patients attending a health facility an opportunity to be tested, was introduced (79). PITC became the main HIV testing strategy in Kenya accounting for over 70% of all HIV tests conducted annually (79). Over the years, the yield of new HIV diagnoses among people tested through PITC has been declining because most people already know their status (79). PITC yields could be increased by targeting health facilities whose catchment population have ongoing localized epidemics or that serve a population with high numbers of people who do not yet know their status (80).

In an evaluation of an active TB/HIV case finding intervention, the HIV testing yield among TB-symptomatic individuals was higher in private-for-profit and private-not-for-profit health facilities than public health facilities (81). Routine surveillance data has also shown higher HIV testing yields among TB patients in private facilities (82) . In many LMICs, private facilities provide health services to populations that are underserved by public health sector facilities (83). Patients who prefer such facilities may be attracted by several factors including availability of medication, accessibility and shorter waiting times. However, such patients maybe underserved by public health interventions that are usually offered at no cost in government facilities (84). The private-for-profit and private-not for-profit sectors account for a significant proportion of people accessing HIV testing in several LMIC countries (85). However, the utilization of such facilities for HIV testing still lags behind public facilities (85), due to fees charged on HIV tests and challenges in

accessing subsidized ART (86). These types of facilities are more likely to discontinue HIV services including HIV testing when donor support stops (87). Because of their ability to reach hard-to-reach populations, a closer collaboration with private-for-profit and private-not-for-profit sector facilities could substantially contribute to closing the HIV detection gap.

Strengths and Limitations of studies on TB and HIV mortality in LMICs

A variety of data sources and analytic approaches have consistently shown that mortality from TB and HIV remain major public health challenges in LMICs including Kenya. Many of these studies used routine data which is more cost-effective despite its limitations on documenting causes of death. Innovative methods, such as HIV testing of decedents and MITS, are increasingly being used by studies to overcome some of the challenges in attributing causes of death using routine data. Although childhood mortality contributes substantially to overall mortality in the population, data on definitive causes of mortality in this age group have been limited. CHAMPS, by focusing primarily on under-five mortality using cutting edge techniques, provides comprehensive information on causes of death including etiological agents. Such information could potentially inform public health policy and practice and may lead to the development of new tools for preventing child mortality.

Some of the innovations used in the mortality studies, such as MITS, are relatively expensive to set up and thus are currently only being applied in limited geographical areas. Because these mortality studies were mostly conducted in high TB and HIV prevalence settings, some of the estimates such as post-mortem HIV prevalence are not generalizable to all regions of Kenya. Nonetheless, they still provide estimates that can be extrapolated to other high prevalence settings or serve as sentinels for longitudinal assessment of mortality from TB and HIV. A number of studies abstracted mortality data from medical charts or routine surveillance data. Such routine data sources are prone to data quality challenges including missing information and inaccurate entries, although the impact of these limitations was minimized by triangulating several source documents. Estimates of causes of death from health and demographic surveillance systems (HDSS) are based on verbal autopsies that focus primarily on underlying causes of death thereby

excluding comorbidities that are also of public health importance. Furthermore, the ability of verbal autopsy to identify precise causes of death at individual level is limited.

Conclusions

TB and HIV remain leading causes of death in Kenya, especially in western Kenya which has a high prevalence of the two diseases, despite the availability of effective interventions. Nearly 20% of deaths in the population could be prevented if mortality from HIV were eliminated. Immediate causes of death among HIV-infected and HIV-uninfected children aged under-five years were similar and comprised of preventable and treatable conditions. The case fatality ratio among patients on TB treatment remains higher than the programmatic target of <5% despite the implementation of early ART initiation ("test and treat") that was expected to substantially dent HIV mortality in TB patients. Strategies for implementing existing interventions against infectious diseases including TB and HIV should be regularly evaluated to identify loopholes that continue to contribute to excess mortality.

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Summary

Tuberculosis (TB) and infection with human immuno-deficiency virus (HIV) are leading infectious causes of morbidity and mortality particularly in sub-Saharan Africa, which is disproportionately affected by the two epidemics. Kenya is listed by the World Health Organization (WHO) among the 30 countries with the highest HIV and TB burden in the world. In 2019 Kenya's HIV prevalence was estimated to be 4,900 per 100,000; TB prevalence was 558 per 100,000 population in a 2016 survey. Previous estimates of mortality from TB and HIV were based on modeling of civil registration and vital statistics (CRVS) data. CRVS systems in low- and middle-income countries are recognized to experience data quality challenges including under reporting, poor documentation of causes of death and lack of a mechanism for verifying causes of death. In this thesis, we provide updated estimates of TB and HIV mortality using a variety of data sources including routine surveillance, post mortem surveillance for HIV infection and minimally invasive autopsy. We thus present estimates of TB and HIV cause-specific mortality rates, case fatality and risk factors for mortality during TB treatment and the cause of death in under-fives stratified by HIV status. Additionally, we provide insights on the programmatic performance of selected interventions against the two diseases. While two chapters in this thesis used nationally representative data the other five chapters present the outcomes of studies that were conducted in western Kenya (Kisumu County and Siaya County) where HIV and TB prevalence is disproportionately higher than the national average.

Chapter one of this thesis provides a general overview on the epidemiology of TB and HIV in Kenya and presents a summary of the available interventions to control these diseases.

In **chapter two** HIV prevalence and population attributable fraction were estimated in a mortuary-based study. HIV status was assessed in 846/1004 decedents received by two high-volume mortuaries in Kisumu County through medical chart review and HIV antibody testing using the national HIV testing algorithm. Our findings pointed to a higher-than-expected HIV prevalence (28.5%) among decedents, with a high population attributable fraction (17%). The high level of viral non-suppression (50% had viral loads ≥1,000 copies/milliliter) suggests that uncontrolled HIV disease contributed substantially to these deaths. We further estimated that crude mortality among PLHIV was four times higher than among HIV-uninfected people.

Causes of death of 456 decedents, drawn from the mortuary study conducted in Kisumu County, who had been hospitalized immediately prior to death were determined by an expert panel from the medical records and are presented in c**hapter three.** HIV/AIDS was the leading underlying cause of death in these decedents (HIV cause-specific mortality rate: 251/100,000 population). While TB was not among the 20 leading causes of death, it was ranked 12th among the leading immediate causes of death. The estimated all-cause mortality rate for Kisumu County (1,086/100,000 population) was twice as high as the national all-cause mortality rate (551.8/100,000 population) probably due to its high infectious diseases' cause-specific mortality rate (513/100,000 population).

In **chapter four** we present data from the Child Health and Mortality Prevention Surveillance (CHAMPS), a global initiative that aims to identify definitive causes of under-five mortality determined through minimally invasive tissue sampling (MITS) several sites in sub-Saharan Africa (Kenya, Ethiopia, Mali, Mozambique, Sierra Leone and South Africa) and South Asia (Bangladesh). In Kenya, CHAMPS activities are conducted in two health and demographic surveillance systems (HDSS) located in Kisumu County (Manyatta HDSS) and Siaya County (Karemo HDSS). Among 176 decedents whose causes of death were determined by an expert panel, malnutrition, malaria, and HIV were the top three underlying causes of death. Among immediate causes of death, malaria, sepsis and pneumonia were leading and occurred in similar proportions among HIV-infected and HIV-uninfected decedents. HIV prevalence among decedents aged under-five years (14%) twenty times higher than the estimated prevalence among children in the population (0.7%); HIV was the underlying cause of death in nearly all (96%) of the HIV-infected decedents. Almost all decedents whose underlying cause of death was HIV/AIDS were virally non-suppressed indicating possible gaps in their HIV treatment or ART treatment failure. While *Mycobacterium tuberculosis* deaths were not detected in this study, five decedents (four HIV-infected) had been on TB treatment antemortem.

Epidemiological analysis of routine TB surveillance data, drawn from over 5,000 health facilities in Kenya, is presented in **chapter five** and **chapter six**. In **chapter five**, nearly a third (28%) of pediatric (aged <14 years) cases were co-infected with TB. The case fatality ratio among children

on TB treatment was 4%. The risk of death was five-fold higher among HIV-infected children who were not on ART and nearly fourfold higher among HIV-infected children on ART compared to HIV-uninfected children. In **chapter six,** the case fatality ratio among adults (≥15 years) on TB treatment was 6%; 42% of the deaths were attributed to HIV-infection. The risk of death was fourfold higher among HIV-infected adults who were not on ART and 2.6 times higher among HIV-infected adults on ART compared to their HIV-uninfected counterparts.

Over the years, Kenya has been implementing several interventions aimed at reducing morbidity and mortality from TB and HIV. This thesis evaluated two of such interventions**.** In **chapter seven**, we present a retrospective analysis of data from individuals with TB-suggestive symptoms from an integrated TB/HIV active case-finding intervention conducted in Kisumu County. Logistic regression with general estimating equations were used to model health facility characteristics associated with new HIV diagnoses**.** The odds of new HIV diagnoses among TB-symptomatic adults attending private not-for-profit facilities were thrice as high as those attending government facilities. This analysis thus provided insights on the potential role of private sector health facilities in closing the HIV detection gap and fast track the achievement of the United Nations Program on HIV/AIDS (UNAIDS) 95-95-95 targets.

TB preventive therapy is one of the high impact interventions aimed at reducing morbidity and mortality among HIV-infected children. Very little is known about the performance of the TB preventive therapy among HIV-infected children from high HIV/TB prevalence settings such as Kenya. We evaluated the programmatic performance of the isoniazid preventive therapy (IPT) among HIV-infected children enrolled in HIV care in selected health facilities in Kisumu County over a four-year period (September 2015 through July 2019) which is presented in **chapter eight**. This evaluation revealed that certain steps in the TB preventive therapy cascade (initiation and completion) account for majority of drop-offs. Of 856 HIV-infected children who were newly enrolled in HIV care, 98% were screened for IPT eligibility, 98% of whom were eligible for IPT. Of those who were eligible, only 68% initiated IPT; the median time to IPT initiation was 3.6 months. Overall, 78% IPT initiators completed. IPT non-initiation was associated with attending high-volume HIV clinics and HIV viral non-suppression.

Our reflections on TB/HIV associated mortality in low- and middle-income countries are summarized in **chapter nine**. Although mortality from TB and HIV has declined remarkably over the last decade, recent estimates indicate that the two diseases continue to cause substantial mortality especially in high prevalence counties located in western Kenya. Mortality from these diseases persists among people who suffer from either disease but remain undiagnosed, people who are inadequately treated due to poor adherence or drug resistance and people who are not reached with preventive interventions. This assertion is supported by mortality studies which have consistently shown that deaths among PLHIV predominantly occur among virally non-suppressed individuals. Additionally, these virally non-suppressed individuals are also unlikely to initiate and complete TB preventive therapy thereby elevating their risk of mortality.

In conclusion, this thesis demonstrates that TB and HIV remain leading causes of death in Kenya despite the availability of effective interventions. Preventing mortality from these diseases would substantially contribute to a reduction in overall mortality in populations which are affected by the twin epidemics. Existing interventions against the two diseases should be evaluated to identify gaps that continue to contribute to excess mortality from TB and HIV.

Samenvatting

Tuberculose (tbc) EN humaan immunodeficiëntievirus (hiv) infecties zijn belangrijke infectieziekte oorzaken van morbiditeit en mortaliteit, vooral in Afrika bezuiden de Sahara, dat onevenredig zwaar getroffen wordt door deze twee epidemieën. Kenia wordt door de Wereldgezondheidsorganisatie (WHO) gerekend tot de 30 landen met de hoogste hiv en tbc last ter wereld. In 2019 werd Kenia's hiv-prevalentie geschat op 4.900 per 100.000; de tbc-prevalentie was 558 PER 100.000 INWONERS in een onderzoek uit 2016. Schattingen van het sterftecijfer door tbc en hiv waren tot nu toe gebaseerd op modellering van gegevens uit de burgerlijke stand en de vitale statistieken (CRVS). CRVS-systemen in lage- en middeninkomenslanden worden gekenmerkt door problemen met de kwaliteit van de gegevens, waaronder onderrapportage, slechte documentatie van doodsoorzaken en het ontbreken van een mechanisme om doodsoorzaken te verifiëren. In dit proefschrift berekenen we actuele schattingen van de tbc en hiv-sterfte met een verscheidenheid aan gegevnsbronnen, waaronder data uit routinesurveillance, post-mortem surveillance voor HIV-infectie en minimaal invasieve autopsies. We presenteren op basis daarvan tbc en hiv specifieke sterftecijfers en case fatality ratios, risicofactoren voor sterfte tijdens tbc behandeling en schattingen van doodsoorzaken bij kinderen jonger dan vijf jaar, gestratificeerd naar hiv-status. Daarnaast geven we inzicht in de resultaten van specifieke interventies tegen deze twee infectieziekten. Terwijl twee hoofdstukken in dit proefschrift gebruik maakten van nationaal representatieve gegevens, presenteren de andere vijf hoofdstukken de uitkomsten van studies die zijn uitgevoerd in West-Kenia (Kisumu County en Siaya County), waar de hiv en tbc prevalentie onevenredig hoger is dan het nationale Keniaanse gemiddelde.

IN HET **eerste hoofdstuk** van dit proefschrift wordt een algemeen overzicht gegeven van de epidemiologie van tbc en hiv in Kenia en wordt een overzicht gegeven van de beschikbare maatregelen om deze ziekten onder controle te krijgen.

In **hoofdstuk twee** WORDEN de hiv-prevalentie en de populatie toerekenbare fractie geschat op basis van data uit een mortuariumstudie. Deze studie kon de hiv-status vaststellen van 846/1009 overledenen die bij twee grote mortuaria in Kisumu County binnenkwamen, door medische dossiers door te nemen en hiv-antilichaamtesten uit te voeren volgens het nationale hiv-

testalgoritme. Onze resultaten wezen op een hoger dan verwachte hiv-prevalentie (28,5%) in deze populatie, met een hoge populatie toerekenbare fractie (17%). Het hoge aantal patiënten waarbij hiv virus niet onderdrukt was (50% had ≥1.000 hiv kopieën/milliliter) suggereert dat ongecontroleerde hiv infectie aanzienlijk heeft bijgedragen aan deze sterfgevallen. We schatten verder dat de ruwe mortaliteit onder mensen met hiv vier keer hoger was dan onder mensen zonder hiv.

De doodsoorzaken van 456 overledenen, afkomstig uit het mortuariumonderzoek in Kisumu County, die onmiddellijk voor hun dood in het ziekenhuis waren opgenomen, werden door een panel van deskundigen vastgesteld aan de hand van de medische dossiers en worden in **hoofdstuk drie** GEPRESENTEERD. Hiv/AIDS was de belangrijkste onderliggende doodsoorzaak bij deze overledenen (hiv-specifiek sterftecijfer: 251/100.000 inwoners). Hoewel tbc niet tot de 20 belangrijkste doodsoorzaken behoorde, stond het op plaats 12 van de belangrijkste onderliggende doodsoorzaken. Het geschatte sterftecijfer door alle oorzaken voor Kisumu County (1.086/100.000 inwoners) was twee keer zo hoog als nationaal (551,8/100.000 inwoners), waarschijnlijk als gevolg van de hoge sterfte door infectieziekten (513/100.000 inwoners).

In **hoofdstuk vier** presenteren wij gegevens van de Child Health and Mortality Prevention Surveillance (CHAMPS), een wereldwijd initiatief dat tot doel heeft de oorzaken van sterfte bij kinderen onder de vijf jaar vast te stellen met behulp van minimaal invasieve autopsie (MITS). CHAMPS wordt op verschillende plaatsen in Afrika ten zuiden van de Sahara (Kenia, Ethiopië, Mali, Mozambique, Sierra Leone en Zuid-Afrika) en in Zuid-Azië (Bangladesh) geïmplementeerd, in Kenia in twee gezondheids- en demografische surveillancesystemen (HDSS) in Kisumu County (Manyatta HDSS) en Siaya County (Karemo HDSS). Bij de 176 overleden Kisumu kinderen waarvan de doodsoorzaken door een CHAMPS panel van deskundigen werden vastgesteld, waren ondervoeding, malaria en hiv de drie belangrijkste onderliggende doodsoorzaken. Van de directe doodsoorzaken waren malaria, sepsis en longontsteking het meest frequent; deze kwamen ze in vergelijkbare proporties voor bij overleden kinderen met en zonder hiv. De hiv-prevalentie onder de overleden kinderen (14%) was twintig keer hoger dan de geschatte prevalentie onder alle kinderen van deze leeftijd (0,7%); hiv was de onderliggende doodsoorzaak in bijna alle (96%) van de hiv-geïnfecteerde overledenen. Bij bijna alle overledenen van wie de onderliggende

doodsoorzaak hiv/AIDS was, was het hiv virus niet onderdrukt, wat wijst op mogelijke lacunes in hun hiv-behandeling (ART) en/of het falen van ART-behandeling. Hoewel tbcsterfgevallen niet werden gedetecteerd in deze studie, waren vijf overledenen (vier van hen hiv-geïnfecteerd) voor hun overlijden onder tbc behandeling.

Epidemiologische analyses van routine tbc-surveillancegegevens, afkomstig van meer dan 5.000 gezondheidszorginstellingen in Kenia, worden gepresenteerd in **hoofdstuk vijf** en **hoofdstuk zes**. In **hoofdstuk vijf** bleek dat bijna een derde (28%) van de gevallen bij kinderen (jonger dan 14 jaar) een co-infectie met hiv had. De case fatality ratio onder kinderen die een tbc-behandeling ontvingen was 4%. Het risico op overlijden was vijf keer hoger onder hiv-geïnfecteerde kinderen die geen ART kregen en bijna vier keer hoger onder hiv-geïnfecteerde kinderen die wel ART kregen in vergelijking met kinderen zonder hiv. In **hoofdstuk zes** constateerden WE dat het sterftecijfer onder volwassenen (≥15 jaar) die een tbc-behandeling ondergingen 6% was; 42% van deze sterfte werd toegeschreven aan een hiv-infectie. Het risico op overlijden was vier keer hoger onder hiv-geïnfecteerde volwassenen die geen ART kregen en 2,6 keer hoger onder hiv-geïnfecteerde volwassenen die ART kregen, in vergelijking met volwassenen zonder hiv.

In de loop der jaren heeft Kenia verschillende interventies ingevoerd om ziekte en sterfte als gevolg van tbc en hiv te verminderen. In dit proefschrift zijn twee van deze interventies geëvalueerd**.** In **hoofdstuk zeven** presenteren we een retrospectieve analyse van gegevens van mensen met tbc symptomen geïdentificeerd tijdens een geïntegreerde actieve opsporing van mensen met tbc en/of hiv infectie, een interventie uitgevoerd in Kisumu County. Logistische regressie met general estimating equations werd gebruikt om de kenmerken van de gezondheidszorg te identificeren die samenhingen met nieuwe hiv diagnoses in deze groep mensen met tbc symptomen**.** De kans op nieuwe nog niet gediagnosticeerde hiv-diagnoses bij deze groep was drie keer zo groot in particuliere not-for-profit klinieken als in overheidsklinieken. Deze analyse verschafte daarmee inzicht in de potentiële rol van particuliere gezondheidsinstellingen bij het verkleinen van de hiv-detectiekloof en het bereiken van de 95-95-95 doelstellingen van het Programma van de Verenigde Naties voor hiv/AIDS (UNAIDS).

Preventieve tbc-therapie met isoniazide (IPT) is een van de meest effectieve interventies om de morbiditeit en mortaliteit onder hiv-geïnfecteerde kinderen te verminderen. Er is echter weinig bekend over de resultaten van een tbc preventietherapie bij hiv-geïnfecteerde kinderen in een omgeving met een hoge hiv/tbc prevalentie, zoals in Kenia. Wij evalueerden de resultaten van IPT bij hiv-geïnfecteerde kinderen die ingeschreven waren in hiv-zorg in geselecteerde gezondheidsinstellingen in Kisumu County over een periode van vier jaar (september 2015 tot juli 2019). De resultaten hiervan worden gepresenteerd in **hoofdstuk acht**. Uit onze evaluatie bleek dat bepaalde stappen in de cascade van preventieve tbc-therapie (met name initiëring en voltooiing) verantwoordelijk zijn voor het grootste deel van de drop-offs. Van de 856 hiv-geïnfecteerde kinderen die nieuw in de hiv-zorg werden ingeschreven, werd 98% gescreend of zij in aanmerking kwamen voor IPT. Van degenen die in aanmerking kwamen, startte slechts 68% met IPT; de mediane tijd tot IPT-initiatie was 3,6 maanden. Over het geheel genomen voltooide 78% van de IPT-initiatiefnemers de behandeling. Het niet starten met IPT bij hiv geïnfecteerde kinderen was geassocieerd met het geregistreerd zijn bij een grote HIV-kliniek en met de aanwezigheid van hiv.

In **hoofdstuk negen** bediscussieren we onze bevindingen over tbc en hiv gerelateerde sterfte in lage- en midden-inkomenslanden en in het bijzonder Kenia. Hoewel de sterfte als gevolg van tbc en hiv de laatste tien jaar flink is gedaald, blijkt uit onze analyses dat deze twee infectieziekten nog steeds tot aanzienlijke sterfte leiden, vooral in gebieden met een hoge prevalentie zoals in het westen van Kenia. Het sterftecijfer als gevolg van deze ziekten blijft met name hoog onder mensen die geïnfecteerd zijn, maar niet gediagnosticeerd worden, mensen die onvoldoende behandeld worden als gevolg van slechte therapietrouw of resistentie tegen geneesmiddelen en mensen die niet bereikt worden met preventieve interventies. Deze observaties worden ondersteund door mortaliteitsstudies die consequent aangetonen dat sterfte onder mensen met hiv voornamelijk voorkomen bij mensen waarbij het virus niet onderdrukt is. Ook is het minder waarschijnlijk dat deze mensen een preventieve tbc-therapie starten en voltooien, waardoor hun risico op sterfte verder toeneemt.

Concluderend toont deze dissertatie aan dat tbc en hiv nog steeds belangrijke doodsoorzaken zijn in Kenia, ondanks de beschikbaarheid van effectieve interventies. Het verminderen van sterfte

gerelateerd aan deze infectieziekten zou aanzienlijk bijdragen aan een vermindering van de algehele sterfte in populaties die getroffen zijn door de dubbele epidemie. Beschikbare interventies moeten worden geëvalueerd om te identificeren hoe de persisterende oversterfte gerelateerd aan tbc en hiv beter kan worden bestreden.

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the inspiration that I needed to surmount challenges that came my way. I wish to thank my mother for understanding my absence, my friends for the social support even when I was pre-occupied.

Curriculum vitae

Dickens Onyango was born in Homabay County, Western Kenya in 1979. He earned a Bachelor of Medicine and Bachelor of Surgery (MBChB) from the University of Nairobi in 2005. Thereafter, he worked as a medical officer intern at Moi Teaching and Referral hospital and as medical officer at Iten District Hospital, a rural setting, in Rift Valley part of Kenya. Dr. Dickens Onyango became the District Medical Officer of Health, in 2007, a role that introduced him to public health which he is palpably passionate about. In 2010, Dickens joined the Kenya Field Epidemiology and Laboratory Management Training Program (FELTP), a program implemented through collaboration between the Ministry of Health and the United States Centers for Disease Control and Prevention (CDC), which provided a competency-based training in applied epidemiology. He simultaneously enrolled for a Master of Science in Epidemiology at Jomo Kenyatta University of Agriculture and Technology (JKUAT) graduating in 2013. While at the Kenya FELTP, Dickens spent one year at the National Tuberculosis (TB) and Lung Diseases Program (NTP) to gain practical experience in TB control. The insights he gained at the NTP inspired some of the work that fed into his doctoral thesis.

Upon completion of his FELTP training, Dickens was deployed to the then Nyanza province in western Kenya to serve as the provincial epidemiologist. Nyanza province was known for a high prevalence of infectious diseases including human immuno-deficiency virus (HIV) and TB. Kenya enacted a new constitution in 2010, which provided for county governments thus abolishing provinces and devolving health care delivery to counties after the 2013 general elections. In 2014, Dickens transitioned to Kisumu County government where he served in various capacities including County Epidemiologist and County Director of Health. These roles exposed Dickens to programmatic challenges in controlling TB and HIV, especially the excess mortality attributed to these diseases.

While working in Kisumu, Dickens developed a close working relationship with CDC and became a co-investigator of many CDC-led studies including the Child Health Mortality Prevention Surveillance (CHAMPS) project. Due to his passion in controlling TB and HIV and reducing mortality associated with these diseases, he decided to pursue a Doctor of Philosophy (PhD) degree focusing on mortality. With support from Prof. Martien Borgdorf, the then CDC director for

western Kenya, and Dr. Courtney Yuen from Harvard Medical School, Dickens started to work towards a PhD. However, Prof. Borgdorf retired in 2017 and could not continue to work closely with Dickens. He then introduced Dickens to Prof. Marianne van der Sande who was primarily based at the Institute of Tropical Medicine, Antwerp Belgium, who introduced him to Prof. Diederick Grobbee based at the Julius Center, Utrecht University. Prof. van der Sande together with Prof. Diederick Grobbee enthusiastically took up the role of promoters and assisted Dickens to successfully register at Utrecht University in July 2019 and obtain a University Utrecht Global Health Scholarship to support the PhD completion. In July 2019 Dickens was also awarded a Fogarty Global Health Fellowship with the Northern Pacific Global Health Consortium through the University of Washington, which contributed to the studies reported in chapter 8. He was also awarded a grant from the Kraanendonk Fund of the NVTG which partially contributed to chapter 8.

Currently Dickens lives with his wife and children in Kisumu City, the third largest city in Kenya. He works as a senior public health specialist in Kisumu County where his public health expertise enormously contributes to TB and HIV control. He also continues to support research on TB, minimally invasive tissue sampling to determine causes of death in children and adults, and maternal health.

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