Mapping HIV in Kenya: Geospatial variability of HIV diagnoses, treatment, and impact

Implications for HIV epidemic control

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Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 28.06.2019

Year: 2019

Title: Mapping HIV in Kenya: Geospatial variability of HIV diagnoses, treatment, and impact

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DEDICATION

I dedicate this work to the many colleagues who contribute to reaching HIV epidemic control and to the HIV-infected and affected and those who live every day with the virus hoping for a cure.

ACKNOWLEDGEMENTS

SYNOPSIS

Background: Kenya is a country in sub-Saharan Africa (SSA) with an HIV prevalence in the adult population is around 5%, which is considered to be a generalized HIV epidemic. The generalized nature of the epidemic makes it difficult to target HIV services and interventions due to misalignment of geographic planning units and finer locations that may need extra resources. This thesis explored geospatial features and their associations with the HIV epidemic with a view of identifying gaps in prevention, care, and treatment. Using a variety of spatial statistics and analytics and mapping, we point out geographic areas that need focussed and intensified HIV interventions.

Methods: In Paper I, we conducted a spatial scan statistical analysis to identify hotspots with disproportionate HIV infections using cross-sectional household survey data. In Paper II, we identified disparate geographic regions with high numbers of newly diagnosed HIV infections using routine program data. In Paper III, we conducted spatial-temporal analyses to show impact of prevention of mother to child transmission of HIV (PMTCT) through reduced rates of HIV infections among infants. In Paper IV, we used spatial-temporal analyses and structural equation models to show the covariance relationship of antiretroviral therapy (ART) and viral load suppression (VLS) in reduced HIV positivity over time in Kenya.

Results: In Paper I, we have shown that HIV infection in Kenya exhibits localized geographic clustering associated with socio-demographic and behavioural factors, suggesting disproportionate exposure to higher HIV-risk. Identification of these clusters reveals the right places for targeting priority-tailored HIV interventions. The newly diagnosed HIV positives in Kenya are not necessarily, where the HIV burden is high. In Paper II, we identified wide-ranging spatial variation of new HIV diagnoses through cluster and hotspot identification analyses. High HIV-burden sub-National units (SNUs)/counties contain most high yielding sites but some sites are also in low-burden SNUs. Targeting HIV testing services for sites in low-burden regions needs a Geospatial approach. An outcome measure of the success of the PMTCT program through reduction of transmission is highlighted in Paper III. During this period – before universal treatment – the PMTCT program in this region had not reached the target rate

of ≤50 cases per 100,000 live births. Using spatial-temporal models with covariates provided better estimates of prevalence and explained the geographically distributed disease burden. In Paper IV we show that over a 3-years period, (2015-2017), improved viral load suppression rates had a direct effect on reduced HIV positivity rates during an era of scaled up ART coverage in Kenya. To assess the trends and impact of implementation of scaled-up care and treatment, spatial-temporal analyses help in identification of geographic areas that need focused interventions.

Conclusions: HIV prevalence in Kenya, though generalized, ought to be looked at more critically. Some efforts at epidemic control including ending mother to child transmission (e-MTCT) have born fruits though with geographical disparities. Given the present density of low-yield HTS sites in Kenya, geographic coverage and access to HTS may need better targeting at the spatial level to achieve knowledge of status for at least 90% of the population. Access to HTS is needed everywhere in Kenya, yet, targeting is difficult in low prevalence areas. Gains in reduced number of new HIV diagnoses have been demonstrated where viral load suppression rates are good. This study has demonstrated that geospatial analyses and mapping makes it easier to define refined geographic areas and hotspots in need of enhanced HIV prevention and treatment interventions. We have provided evidence that there are geographic disparities in HIV program impact in Kenya. Micro location-based planning is necessary for improved resource allocation. We recommend clustering analyses to identify areas with disproportionately high number of HIV-infected persons for re-allocation of resources within SNUs and continued use of geospatial analyses for advocacy and planning to help in achieving HIV epidemic control in Kenya.

LIST OF ORIGINAL PAPERS

This thesis is based on the papers listed below. Throughout the thesis, we have referred to them by their roman numerals.

Paper I

Waruru A, Achia TNO, Tobias JL, Ng'ang'a J, Mwangi M, Wamicwe J, Zielinski-Gutierrez E, Oluoch T, Muthama E, Tylleskär T. Finding Hidden HIV Clusters to Support Geographic-Oriented HIV Interventions in Kenya. **J Acquir Immune Defic Syndr 2018**.

Paper II

Anthony Waruru, Joyce Wamicwe, Jonathan Mwangi, Thomas N. O. Achia, Emily Zielinski-Gutierrez, Lucy Ng'ang'a, Fredrick Miruka, Peter Yegon, Davies Kimanga, James L. Tobias, Peter W. Young, Kevin M. De Cock, Thorkild Tylleskär. Where are the newly diagnosed HIV-infected persons in Kenya? Time to consider finer scale geo-spatially guided targeting to reach the "first 90" **Submitted for clearance**

Paper III

Waruru A, Achia TNO, Muttai H, Ng'ang'a L, Zielinski-Gutierrez E, Ochanda B, Katana A, Young PW, Tobias JL, Juma P, De Cock KM, Tylleskär T. Spatial–temporal trend for mother-to-child transmission of HIV up to infancy and during pre-Option B+ in western Kenya, 2007–13. **PeerJ 2018**;6:e4427. doi:10.7717/peerj.4427.

Paper IV

Anthony Waruru, Joyce Wamicwe, Maureen Kimani, Lucy Ng'ang'a, Kenneth Masamaro, Salome Okutoyi, Thomas N. O. Achia, Jacques Muthusi Kimeu, Emily Zielinski-Gutierrez, James L. Tobias, Stella Njuguna, Catherine Mbaire, Kevin M. De Cock, Thorkild Tylleskär. ART coverage and viral load suppression rates as correlates to new HIV diagnoses, in Kenya; Spatial-temporal analyses 2015-17. **Submitted for clearance**

GLOSSARY

Access	The physical presence of a facility offering that service within a given distance or catchment area of its potential clients [1].
Accessibility	The distance of travel time between the clients' location and the facility. This may also prevent an eligible individual from utilizing a service [1].
Catchment area	Geographic area from which a health facility attracts clients [1].
Catchment population	The population of a health facility's catchment area.
Centroid	The geographic centre point of a polygon (shape of a geographic region) [1].
Choropleth map	A thematic map in which administrative areas are coloured or shaded according to the range in which the aggregated statistic falls [1].
Clustering	A closely grouped series of events or cases of a disease or other health related phenomena with well-defined distribution patterns in relation to time or place or both [2]. It is an excess of cases above some background rate bounded in time and space [3].
Coverage	The proportion of persons that are eligible to receive an intervention or utilize a service that actually receive or utilize it [1].
Coverage gap	The proportion of people that are eligible to receive an intervention or utilize a service that do not receive or utilize it [1].
Disease mapping	Visual representations of disease distribution. The purpose of mapping in epidemiology is to describe the spatial variation in disease incidence for the formulation of etiological hypotheses; to identify areas of unusually high

	risk in order to take; preventive action; and to provide a reliable map of disease risk in a region to allow better resource allocation and risk assessment [4].
Eligible	The population that have the capacity or likely to benefit from an intervention or service [1].
Hotspot(s)	A place or collection of places within defined geographic boundaries that have a higher than average prevalence of a disease or phenomenon (such as more than usual number of female sex workers). In this proposal, hotspots refer to both.
Impact	The net improvement in population health status that can be attributed to an intervention or service.
Mapping	Visual representation of spatial data using cartographic methods
Spatial clustering	The process of grouping a set of objects into classes or clusters so that objects within a cluster have a high similarity in comparison to one another but are dissimilar to objects in other clusters
Spatial epidemiology	The description and analysis of geographically indexed health data with respect to demographic, environmental, behavioral, socioeconomic, genetic, and infectious risk factors [3]. It is a subfield of health geography focused on the study of the spatial distribution of health outcomes.
Spatial	Related to geographic space. This may be a visualized as a point on a map that has geo-reference of longitude and latitude or space that may have actual boarders such as administrative units.
Temporal clustering	An occurrence of a disease or disorder that has unusually high incidence occurring in close proximity in terms of time and geography.
Utilization	Actual use of a service by a person, client, eligible to use that service [1].

ACRONYMS AND ABBREVIATIONS

AIDS:	Acquired immunodeficiency syndrome
AIS:	AIDS indicator survey
ANC:	Antenatal clinic
ANN:	Average nearest neighbour
aOR:	Adjusted odds ratios
APR:	Annual progress report
ART:	Antiretroviral therapy
ARV:	Antiretroviral
CDC:	Centres for disease control and prevention
CI:	Confidence interval
DHIS2:	District health information system 2
DHS:	Demographic and health survey
DOD:	Department of defence
EID:	Early infant diagnosis (of HIV)
eMTCT:	(include definitions)elimination of mother to child transmission of HIV (eMTCT is achieved when <50 infections occur per 100,000 births)
EPP:	Estimation and projection package
ERC:	Ethical review committee
EWI:	Early warning indicators for HIV drug resistance
FSW:	Female sex workers
GIS:	Geographic information systems
HDI:	Human development index
HH:	High-rate clusters neighbouring other high-rate clusters
HIV:	Human immunodeficiency syndrome
HIVDR:	HIV drug resistance
HL:	High prevalence clusters neighbouring low prevalence clusters
HP:	High prevalence clusters
HTC:	HIV testing and counselling
HTS:	HIV testing services
HIVST	HIV self-testing
IDU:	Injecting drug users
ILRI:	International livestock research institute
INLA:	Integrated nested Laplace approximation
iPSL:	Integrated PEPFAR site list
IRB:	International review board
KAIS:	Kenya AIDS indicator survey
KDHS:	Kenya demographic health survey
KEMRI:	Kenya medical research institute
KEPH:	Kenya essential package for health
KII:	Key informant interviews
KNBS:	Kenya national bureau of statistics
KP:	Key populations including; female sex workers (FSW), men who have sex with men (MSM), injecting drug users (IDUs), and fisher folk
LFTU:	Lost to follow-up

LH: Low rate areas neighbouring high rate areas
LISA: Local indicators for spatial autocorrelation
LL: Low rate neighbouring low rate areas
LP: Low prevalence
MER: Monitoring evaluation and reporting
MFL: Master facilities list
MSM: Men who have sex with men
MTCT: Mother to child transmission (of HIV)
NACC: National AIDS control council
NASCOP: National AIDS and STI control programme
NNHC: Nearest neighbour hierarchical clustering
NPS: National population surveys
OR: Odds ratio
OSM: Open street map
PEPFAR: U.S. President's Emergency Plan for AIDS Relief
PII: Personally identifiable information
PLHIV: People living with HIV
PMTCT: Prevention of mother to child transmission of HIV
PNS: Partner notification service
QGIS: Quantum GIS
SAS: Statistical analysis system
SDG: Sustainable development goals
sdNVP   Single dose nevirapine
SIMS: Site improvement through monitoring systems
SNU: Sub-national unit
UHC: Universal health coverage
UNDP: United Nations Development Program
USAID: United states agency for international development
VCT: Voluntary counselling and testing
VL: Viral load
VLS: Viral load suppression
VMMC: Voluntary medical male circumcision
WHO: World Health Organization

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1.0 INTRODUCTION

Kenya

Location, population and culture

Kenya (figure 1) is located in the East Africa south of Sahara and is contiguous to 5 countries within the East Africa region and among about 50 sub-Saharan countries [5]. The country covers an area of 583,000 square kilometres, making it the 23rd largest state in Africa. The population per 2009 census was 40.6 million [6], and was estimated to be 51 million in 2018, ranking 29th in the world. The country borders the republic of Somali to the East, Ethiopia to the North East and South Sudan to the North West, Uganda to the West and Tanzania to the South West. The country is geographically and culturally diverse with 42 ethnographic communities. Kenya has a number of climatic regions; the counties to the East, North East and North are mostly arid or semi-arid with most of these having a low population density. Geographical and cultural diversity determine the kind of socio-economic activities in the country.

Infrastructure

Administratively, Kenya is subdivided into 47 counties also called constituencies or sub-national units (SNU). The main transport network starts from the port of Mombasa, through to Nairobi (the capital city) and forks towards Central, Eastern and Northern Kenya at Nairobi with the other main fork towards Western Kenya and to the border of Kenya and Uganda and Northern Tanzania.

Infrastructure can be described thus: a) **spatially universal infrastructure** includes services such as housing, water, sanitation, and other social services such as education and health; b) **economically productive infrastructure** includes energy, information communication technologies (ICT), irrigation, ports, and road and railway transport. Economically productive infrastructure complements the workforce in manufacturing and service industry and facilitates employment growth and rural-urban migration; c) **spatially connective infrastructure** includes transport modes that connect regions within a country, or that facilitate international trade across borders within a region or with global markets [7]. The impact of such connective infrastructure coupled with insecurity in the neighbouring Somalia (to the East) and South Sudan (to the North) has

resulted in an influx of refugees into Kenya over the past two decades (54.5% and 24.4% from Somalia and South Sudan, respectively) [8].

Kenya has three large cities (Nairobi, Mombasa, and Kisumu) each with a huge population of 2.75 million, 800,000, and 220,000, respectively. However, there are other towns with large populations including Nakuru, Eldoret, and Thika (each with over 200,000 residents) [9]. In 2017, it was estimated that over a quarter (26.6%) of Kenya's population live in urban areas and cities [10], meaning that a majority of Kenyans live in rural areas.
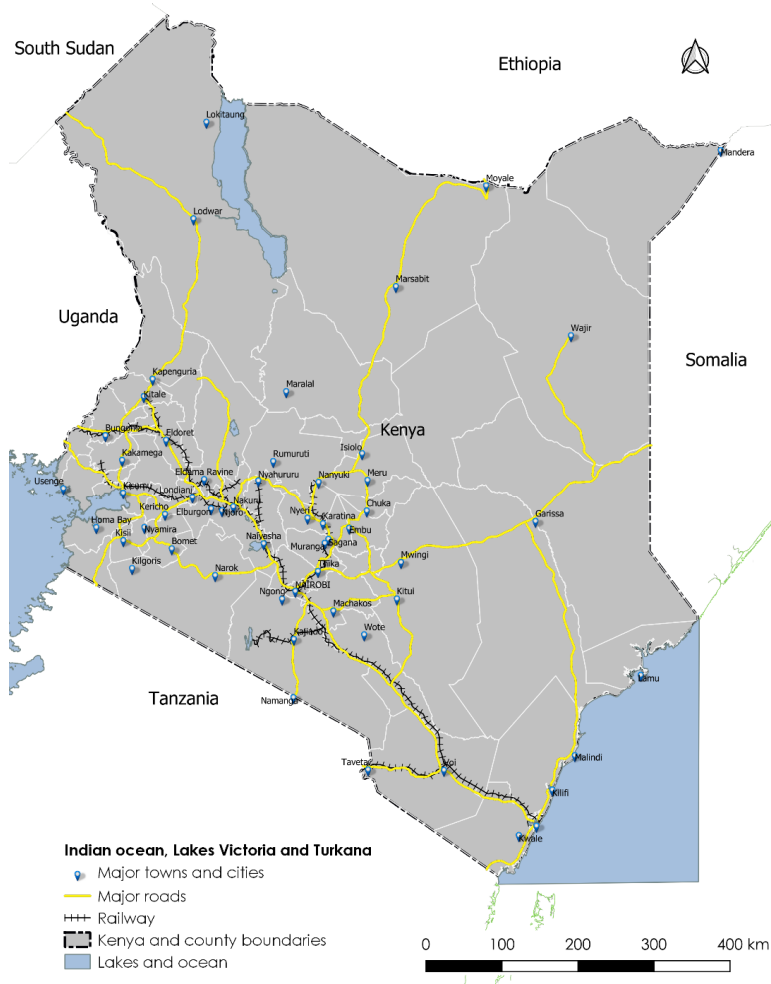
Figure 1: Map of Kenya, macro geospatial features, and neighbouring countries

Key demographic, geographical and health indicators

Key demographic and health indicators are presented in table 1. Kenya is ranked 143rd in terms of human development index (HDI) by United Nations Development Program (UNDP) [11]. With a HDI of 0.59, improved life expectancy of 67.3 years, at least 12

Table 1: Major population, geographical and health indicators in Kenya

Parameters	Estimate
Population and global health metrics	
Population (2017)a	45,800,000
Population under 15 years (proportion of total)	40.9
Population growth rate	0.029
Population density (by 2050)	831/square kilometer
Life expectancy at birth f/m (2017) a	61.1 males, 65.8 females
Neonatal mortality rate (per 1000 live births) b	39 (CI: 35 – 43) 20.9
Under five mortality rate (per 1000 live births) b	52 [48 – 57]
Maternal mortality ratio per 100,000 live births	510 [344-754]
Median duration of exclusive breastfeeding b	3.3 months
Geography, infrastructure and health systems	
Geography	
Total area (square kilometers)	582,646
Latitude	4.9 North, -4.9 South
Longitude	32.2 West, 42.0 East
Counties	47
Constituencies	290
Land use c	
Suitable land for rain-fed agriculture	17.0%
Forest reserves	2.4%
National parks, game reserves	7.5%
Transport and spatial infrastructure	
Classified roads d	63,575 km
Urban areas, cities and municipalities	3 cities, 66 urban centers
Health systems	
a. Number of health facilities (2018)	4868
b. Number of national referral hospitals (2018)	3
c. Physicians per 1000 population (2014)	0.204
d. Nursing/midwifery per 1000 population (2014)	1.582
e. Facility deliveries	61.2%

Sources:

a National council for population and development

b Stat compiler https://www.statcompiler.com/en/

c Land use in Kenya

d Kenya national highway authority http://www.kenha.co.ke/index.php/road-network

years of schooling, and gross national income per capita of over 2000 makes the country closer to attaining sustainable development goals (SDGs) 3, 4, and 8 placing the country among the countries with medium HDI.

Only under a fifth of Kenya's land is arable [12]. With population growth, this has led to high rates of rural-urban migration and possibly contributed to spread of HIV from urban to rural areas.

HIV epidemic in Kenya

Historical perspective

A historical perspective of the HIV epidemic and response in Kenya is presented in figure 2.

The 1980's

The first case of HIV/AIDS in Kenya was detected in 1984. In the early 80's very few cases of HIV/AIDS were reported in Kenya with some literature quoting as low as 26 cases between 1983 and 1985, [13]. The highest prevalence has consistently been among key populations (KP). Female sex workers have historically had the highest prevalence in Kenya and are described in literature as having been a major cause of infections in Nairobi city [14]. In 1985 HIV prevalence among female sex workers in Nairobi rose from 4% in 1981 to as high as 61% [15]. The rest of the details of the HIV epidemic in the mid to late '80s are scanty mostly due to lack of reliable data.

The 1990's

By the mid to late 1990's, over 10% of the adult general population was living with HIV, translating to about 2.1 million people. Among pregnant women, prevalence was between 15.3% in urban areas and 14% in other places. In some regions such as Kisumu, the prevalence among women age 15-19 was 23%, compared to 3.5% among men of the same age [15]. Around the same period, bed occupancy for patients admitted with AIDS-related conditions hit a high leading to detrimental health outcomes and reduced chances of recovery for patients with advanced disease [15]. One of the reasons why the disease spread so rapidly were low rates of condom use. For example, slightly over half of the young people believed that condoms protected them against infection. Reported condom use at last high-risk sex was only 42% among men and 16% among

women [15]. Reactions to the rise of the epidemic were first seen in the media and other informational and educative communication materials such as billboards. This. This led to accelerated HIV testing in the voluntary counselling and testing (VCT) strategy [16]. By the end of the 1990's, HIV was a serious epidemic having reached 14.1% by the end of 1999 [17]. Reacting to the rising epidemic, the Kenya government started publishing informative articles in the local dailies and initiated billboard campaigns. Most of the messages were on use of condoms and abstinence.

The 2000's

The prevalence rates declined from 13.9% in 2001 to 10.2% in 2002 [18]. In 2001, an estimated 2.5 million adults and children were living within with HIV and prevalence was estimated at 15% among adults 15-49 years old. HIV prevalence began to decline from its peak of 13.4 %in 2000 and continued to decrease steadily to 6.9 percent in 2006. The decrease in prevalence coincided with the rapid expansion of preventative interventions since the year 2000, which resulted in a change in sexual behaviour and the increased use of condoms. The decline has also been attributed to the large number of people dying from AIDS in Kenya, which totalled 150,000 in 2003 alone [19]. The death toll affected all the sectors of the economy and had a detrimental effect on the workforce including the police force – with an estimated three quarters of all deaths attributed to AIDS [15]. Nearly 900,000 children were estimated to be orphaned by 2001. In the mid-2000, the AIDS response took a turn with the availability and provision of free ARVs in the public sector, which started in 2004. This may have led to improved survival and a stabilized prevalence to below 10% in subsequent years. In 2007, HIV prevalence among adults (15-49 years old) was 7.4% [20], and in a repeat population based survey in 2012, the prevalence was 5.6% among the same age group [21]. A repeat Kenya HIV Population HIV Impact Assessment is underway and results are expected mid-2019.

HIV/AIDS response

In 1999, the then Kenyan President Daniel Arap Moi declared the AIDS epidemic a national disaster. In the same year, he announced the formation of the National AIDS Control Council (NACC) as a state corporation [22]. This announcement was seen as

the first commitment to fighting HIV in the country. In 2005, the then president HE Mwai Kibaki declared total war against HIV/AIDS and established a cabinet committee on HIV/AIDS. This coincided with the launch of the second AIDS strategic plan whose goal was to "reduce the spread of HIV, improve the quality of life of those infected and affected and mitigate the socio-economic impact of the epidemic in Kenya" [23]. In subsequent years, other commitments have been made towards preventing new HIV infections among children through ending of mother to child transmission of HIV - "Beyond Zero" campaign, initiated in 2013 by H.E the first lady of Kenya, Margaret Kenyatta [24].

In Kenya and other countries, it has been over 10 years since the inception of the most resource-intense public health response to HIV pandemic – U.S. President's Emergency Plan for AIDS Relief (PEPFAR). Other initiatives such as the Global Fund to Fight AIDS, Tuberculosis, and Malaria, foundations such as the Clinton Foundation, Bill & Melinda Gates Foundation among others have also contributed to this fight.

Governance being a key pillar to epidemic control has been critical in the response. The national AIDS control council (NACC) takes the lead on coordination and evaluation of all activities against AIDS, while the Ministry of Health manages the mainly health-related interventions, implementation of guidelines and monitoring. To monitor the HIV/AIDS response in Kenya, various frameworks have been developed including the first ever Kenya National AIDS Strategic Plan (KNASP I), 1999/2000 – 2004. The second and third KNASPs were implemented during the years 2005/6 – 2009/10 and 2009/10 – 2012/13, [23,25]. After the third KASP, the Kenya AIDS Strategic Framework (KASF), [25] was launched. Covering the years 2014/15 – 18/19, the framework is different from the KASP approaches since it set precedence for implementation of HIV programs that focus on institutional capacity strengthening under a decentralised government including modalities for stakeholder engagement for a sustained HIV epidemic control. Under this plan, key proposals are to increase domestic financing of HIV to 50%, achieve integration of HIV activities in development plans by 80% of the counties and strengthening NACC's institutional capacity to

perform core mandates in a sustainable manner. The formation of Kenya National AIDS Authority in 2014 [26], overlapped with the establishment of the framework.

2014: Kenya AIDS strategic framework (KASF) – 2015-19. Kenya HIV prevention revolution road map.

2014: PEPFAR 3.0 Controlling the Epidemic: Delivering on the Promise of an AIDS-free Generation.*

2012: PEPFAR blueprint "Creating an AIDS-free generation".*

2017: PEPFAR Strategy for Accelerating HIV/AIDS Epidemic Control (2017-2020).*

2016: PEPFAR 3.0 aims to control and ultimately end the HIV/AIDS epidemic.*

2014: UNAIDS 90-90-90 and 95-95-95 treatment targets to help end the AIDS epidemic by 2030.*

2012: Kenya AIDS Indicator survey puts adult HIV prevalence at 5.6%.

2005: A five year HIV/AIDS strategic plan developed.

2003: The president's emergency plan for AIDS relief (PEPFAR) funds HIV program activities in Kenya.

2002: 'Total War on AIDS' declared in Kenya

2001: the Global Fund to Fight AIDS, TB and Malaria (Global Fund) is formed.*

1998: AIDS declared a national disaster in Kenya.

1997: UNAIDS (Joint United Nations Programme on HIV/AIDS) is formed.*

1995: Prevalence in Nairobi peaks at 17% and national prevalence is estimated at between 10 and 14%.

2000: Kenya develops a five year National AIDS Strategic Plan. AIDS education for all schools and colleges.

1997: The Kenyan Parliament approves a 15 year national AIDS policy and forms the National AIDS Control Council.

1996: Highly Active Anti-Retroviral Therapy (HAART) is developed.*

1990: Establishment of ANC sentinel surveillance

1988: Kenya's Ministry of Health issues guidelines stating that patients should be told their HIV status.

1984: the first case of HIV in Kenya is identified

1980: samples from female sex workers (FSW) program show zero HIV prevalence. Sexually transmitted infections (STI) program established.

1987: The WHO forms the Global Programme on AIDS.*

1985: the National AIDS Committee is established.

1981: retrospective HIV tests show a prevalence of 4% among FSWs.

Notes:

* International events

Figure 2: Historical perspective of the HIV epidemic and response in Kenya

Current status of the HIV epidemic

In the 30 years of HIV epidemic, there has been increased coverage and new modalities of HIV program implementation from HIV prevention, testing and counselling, linkage to care and treatment of HIV infected individuals including improved clinical and laboratory monitoring. However, HIV continues to be a major disease burden in Kenya. Jointly with Mozambique and Uganda, Kenya has the fourth largest HIV epidemic in the world [27]. This is not surprising since Eastern and Southern Africa region is the most affected by the HIV epidemic. It accounts for 45% of the world's HIV infections and over half (53%) of PLHIV globally [27]. A summary of key indicators is presented in table 2. In 2017, there were an estimated 1,493,000 people living with HIV in Kenya, including 105,200 children <15 years old. The adult (ages 15-49 years) prevalence was 4.9% and an estimated 52,800 new infections across all ages and 28,200 AIDS related deaths [28]. Over a tenth (12%) of the infections occurs among 15-24 year olds. The HIV program has had an improved coverage of ART, currently estimated at 75% among adults and 84% among children. Though heterosexual transmission is the most common mode of HIV transmission in Kenya, homosexual transmission among men who have sex with men also occurs. Heterosexual transmission mostly occurs between married or cohabiting couples, steady sexual and concurrent partnerships and transaction-based sexual encounters. Other sources of incident infections include injecting drug user and health facility related [29]. The drivers of the epidemic in Kenya are intergenerational sex, concurrent/multiple partnerships, and low prevalence of male circumcision in some communities [21,30]. According to the last population-based survey (Kenya AIDS Indicator Survey, 2012), the infection rates are highest among young women aged 15-19 years who are 3 times more likely to become infected with HIV than young men; women of 20-24 years are over 5.5 times more than their male peers [21].

Table 2: Key HIV indicators

Parameters	Estimate [lower, upper]
HIV and AIDS estimates	
Annual new HIV infections (all ages)	53,000 [31,000–86,000]
Annual new HIV infections (0–14)	8,000 [4,600–13,000]
Annual new HIV infections (women, 15+)	27,000 [16000–46,000]
Annual new HIV infections (men, 15+)	18,000 [9,800–31,000]
Adults and children living with HIV	1,500,000 [1,300,000 – 1,800,000]
People living with HIV (0–14)	110,000 [76,000–130,000]
People living with HIV (women, 15+)	860,000 [730,000–1,000,000]
People living with HIV (men, 15+)	520,000 [430,000–630,000]
AIDS-related deaths (all ages)	28000 [19,000–43,000]

Source: Kenya HIV estimates report 2018

Temporal variation in risk across geographic locations is a contributing factor for both the burden and the new HIV infections in Kenya. The five highest burden counties out of the country's 47 counties are Nairobi, Homabay, Siaya, Kisumu, and Migori – contributing over 40% of the burden in Kenya. Four out of these counties are in western Kenya. Using estimates and projections applied to county level population size, estimated HIV prevalence ranges from 0.1% in Wajir to 21.0% in Siaya. In absolute numbers, over half of all new HIV infections (52%) occur in eight (Nairobi, Homabay, Siaya, Kisumu, Migori, Kiambu and Kakamega) out of the 47 counties with nine counties contributing an incidence of ≥ 2.0 per 1000 population [28].

The impact of ART scale up has resulted in averting over half a million deaths and contributed to the reduction in incidence. Although over 2 million deaths have occurred cumulatively, ART coverage has had an impact: it is estimated that about 635,500 AIDS deaths have been averted between 2004 – 2017 and the incidence has reduced from 0.35% in 2010 to 0.19% in 2017. In the Kenyan PMTCT program, ART coverage is about 77% and over 130,000 child HIV infections have been averted since the scale up of ART in 2004 [28].

Health policy and guidelines in Kenya

Overall health governance

Kenya health sector strategic plans

Implementation of health services in Kenya has been guided by health sector strategic and investment plans. The first health sector strategic plan was developed for the years 1999-2004 in response to the need for health sector wide approach and engagement with stakeholders. At this time, HIV was becoming a major killer in Kenya and contributing substantively to the health burden in the country. In the second strategic plan (2005-2010), the main objective was to reduce health inequalities and to reverse the downward trends in health related outcome and impact indicators. Mid-term health sector plans have since been developed to conform with Kenya's "Vision 2030" of transforming Kenya into a globally competitive and prosperous country with a high quality of life by 2030. Subsequent plan was implemented in 2008-2012 with the most current plan covering the period 2013-2017. This third medium-term plan aims to achieve a level and distribution of health appropriate to a middle-income country. The underpinning of the plan is universal health coverage.

The universal health coverage

The universal health coverage (UHC) was launched in December 2018. This is the latest transformative policy that aims at bridging the poverty gap and improves access to healthcare. Although the programme is currently under pilot in four counties; Nyeri, Kisumu, Isiolo and Machakos, the aim is to expand UHC to all the 47 counties by 2022. HIV being a priority disease in Kenya is equally a priority in the UHC approach.

HIV guidelines and policy landscape

HIV testing

According to the last population-based AIDS indicator survey, about 70% of Kenyans aged 15 to 64 years old have ever been tested and among those, 56% had been tested in the previous year [21]. Among persons older than 18 months, HIV testing is mostly done using rapid antibody testing. The two approaches for HTS in Kenya are Client

Initiated Testing and Counseling (CITC) and Provider Initiated Testing and Counseling (PITC) [31]. The first guidelines for HIV testing in Kenya were published in 2001. Largely the focus was voluntary counselling and testing (VCT). Since then, these guidelines have been replaced by Guidelines for HIV Testing in Clinical Setting in 2004 and subsequently in 2008, 2010 and 2015 [31–33]. In the current 2015 guidelines, there is a shift from HIV testing and counseling (HTC) to HIV Testing Services (HTS) with an emphasis on the 5Cs of consent, confidentiality, counseling, correct results and connection (linkage to care). In the current algorithm, the screening test is Determine™ HIV-1/HIV-2 rapid test (Abbott Diagnostic Division, Hoofddorp, Netherlands) followed by First response™ (Premier Medical Corp. Lt, Daman, India), as the confirmatory test when the screening test produces reactive results. In the 2015 guidelines, the use of a tie-breaker in the HIV test algorithm sequence is no longer recommended. In early infant diagnosis (EID) settings, polymerase chain reaction (PCR) test is conducted at 6 weeks (corresponding to infant's first immunization) or at first contact after 6 weeks. To establish possible exposure status to maternal antibodies, infants aged 9- 18 months old can be tested using rapid HIV testing.

The general recommendation for HIV testing is annual for persons who have ongoing risk and more frequent after incidents of HIV exposure [32]. The HIV testing arena has evolved over the years with the 2015 guidelines including HIV self-testing (HIVST) using OraQuick® (OraSure Technologies Bethlehem, USA) to encourage testing. These developments set a stage for optimizing HIV testing and prompt start of ART in the current environment of test and start. Most of the persons tested in Kenya seek testing in health facilities and especially in the "opt-out" testing approach that is largely provider initiated. From only three sites offering client initiated counselling and testing services in Kenya in 1999, the services have increased to the current 6000 standalone (sites offering HTS services only) and integrated (sites within a health facility) sites. However, even with this rapid expansion, finding HIV infected persons has become a major focus due to diminishing yield even with increased testing. Recently, the introduction of index testing and partner notification services (PNS) has led to a major shift in the way clients seek HTS. HIV testing is free of charge in public facilities. The

development of HIV testing kits that are capable of detecting recent infections will additionally contribute to the number of approved HIV tests. Recency surveillance has been recently recommended in the country operational guidance as a routine activity to aid in monitoring HIV epidemic. This is particularly because finding the recently infected persons provides an opportunity to identify where the new infections are and target prevention.

HIV treatment

Kenya has had six guidelines for ARV treatment. The ART guidelines were first published 2001 and subsequently revised and updated in 2002, 2006, 2011, 2014, and 2016. These guidelines have largely been developed from adaptations of the WHO guidelines and take into account the local context including available treatment options. Due to a robust treatment program, Kenya has been at the forefront in adopting new technologies that translate research into program. For example, in 2016, Kenya became the second country in sub-Saharan Africa to issue full regulatory approval of PrEP after South Africa [34]. Whereas all these guidelines have led to earlier and more accurate diagnosis of HIV, better immunological classification, and patient management, their use has not always followed immediate release. The key component for these guidelines is the issue of when to initiate ART with the most current ART guidelines supporting HIV test and start.

Prevention of mother to child transmission

The goal for elimination of mother to child transmission e-MTCT for Kenya is matches that of the world health organization: 50 infections per 100,000 live births. For mothers in the PMTCT program, the guidelines are also included in the overall ART guidelines. However, there are specifics that relate to option B+ and its use in the country. Before 2013, use of long-life treatment for HIV-infected pregnant women instead of single dose Nevirapine was the norm. Kenya introduced life-long treatment for HIV-infected pregnant women (option B+) in 2013 this was only in the national referral hospitals which had facilities for monitoring the progress of the women. Option B+ was provided regardless of CD4 cell count (figure 3). Option B+ was rolled out to the rest of the

country in 2014 July and by October 2015 more than 90% of the sites were offering lifelong highly active antiretroviral therapy (HAART) to all the pregnant and breastfeeding women. In 2017, NASCOP launched the efficacious Dolutegravir as part of the first line regimen to be used with Tenofovir and Lopinavir as (TLD). However, due to the reports indicating the risk for neural tube defects in the unborn infants with use of Dolutegravir by pregnant women [35], the ministry of health issued a rapid communication to guide health care providers Kenya's regimen is combination of Tenofovir, Lopinavir and Efavirenz - (TLE) combination. The country is (in 2019) undertaking its own assessment of Dolutegravir use before making a firm statement on use during pregnancy.

	2001	2004	2006	2010	2013	2015
PMTCT	4 weeks AZT; AZT+ 3TC, or SD NVP	AZT from 28 wks + SD NVP	AZT from 28wks + sdNVP +AZT/3TC 7days	**Option A** (AZT +infant NVP) **Option B** (triple ARVs)	**Option B or B+** Moving to ART for all PW/BF	**Option B+** Lifelong ART for all PW/BF
ART	No recommendation	CD4 <200	CD4 <200	CD4 ≤350	CD4 ≤500	Regardless of CD4 count
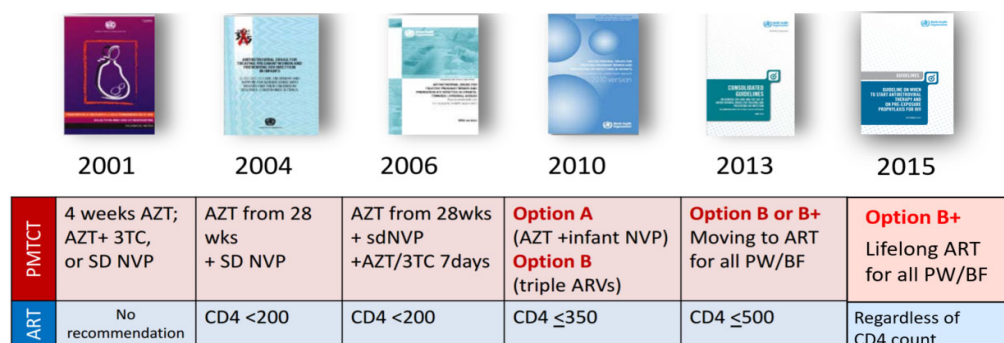
Adapted from Shaffer, WHO 2013
http://regist2.virology-education.com/2014/6thHIVped/21_McIntyre.pdf

Figure 3: Progression of treatment options in PMTCT program

HIV test and start

The precursor to HIV test and start was the 2014 guidelines launched in June 2014 when the Ministry of Health launched revised guidelines for ART that recommend early initiation start of ART in children, adolescents and adults including all HIV positive pregnant women [36]. In July 2016, Kenya launched the HIV test and start campaign dubbed "*anza sasa*" in Kiswahili meaning "start now" [37]. The aim of the campaign was to encourage PLHIV in care to start on ARV treatment regardless of their CD4 cell count. The 2016 guidelines provide the current standards for ARV treatment including

initiation [38]. The test and start strategy is unlike the previous year's guidance where PLHIV with CD4 count of >500 cells/ml were not eligible for ARV treatment.

HIV clinical monitoring

Guidelines relating to other HIV program supportive services include the monitoring and evaluation guidelines, guidelines for implementing electronic medical records systems, guidelines for differentiated service delivery models and others. Out of the six WHO strategies for monitoring HIV drug resistance (HIVDR). Kenya implements four: early warning indicators (EWI); surveillance of HIV drug resistance in populations prior to treatment initiation; cross-sectional surveys of HIV drug resistance in adults prior to ART initiation at representative ART clinics, and cross-sectional surveys of acquired HIV drug resistance in adults and children.

Monitoring HIV epidemic in Kenya

ANC sentinel surveillance

From 1990, Kenya conducted antenatal clinic sentinel-surveillance surveys in selected sentinel sites. These sites were selected to represent the urban and rural populations. These surveys led to high HIV estimates due to biases such as lack of representativeness and the assumption that the HIV prevalence among pregnant women was similar for both men and women.

Population-based surveys

In 2003, Kenya included HIV testing in a population-based national survey - Kenya Demographic Health Survey (KDHS) [39]. This was the first population-based survey to include HIV testing. Subsequently, HIV-specific surveys (Kenya AIDS Indicator Survey (KAIS) were conducted in 2007 and 2012. Introduction of population-based surveys provided data on additional behavioural and risk factors that could not otherwise be collected using regular health facility data. Sampling strategies in these surveys ensure that the results are robust enough to be generalized at the national and sub-national level(s). Such measurements allow for spatial scaling of the data in secondary analyses (e.g. in figure 4).
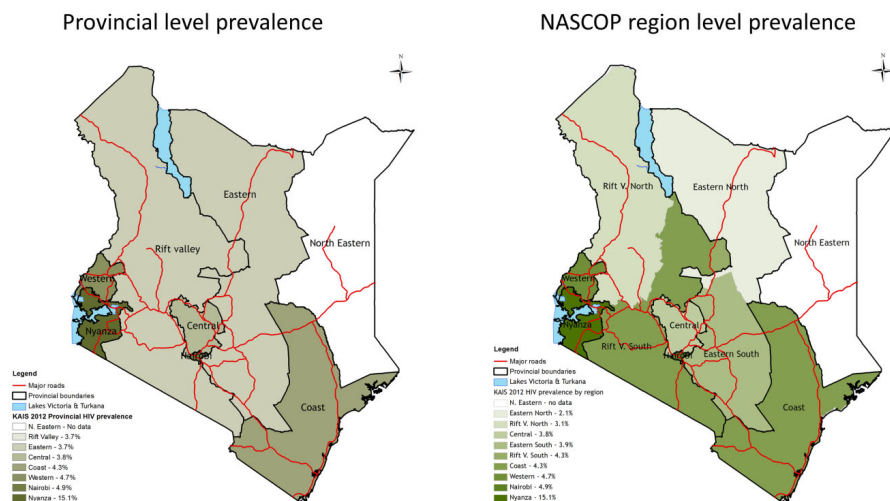
Figure 4: Regional HIV prevalence in Kenya, KAIS 2012

Due to limited resources, estimating HIV prevalence and other related indicators at granular health-planning units is not easy since the scales at which the epidemic is measured are often too broad and if more granular, expensive. Even with large population HIV impact assessments, it is not possible to analyse data to units that are granular to make programmatic planning sense and assist in more geographically focussed interventions. Recent translation of PHIA data to smaller geographic units is suggested where data are insufficient to answer questions [40].

The spatial epidemiology approach

Spatial heterogeneity and similarity

The HIV burden in Kenya is heterogeneous when measured at regional and planning unit levels, e.g. counties. Often, the geographic sub-national units are treated in isolation yet units that are contiguous are similar. Additionally, there may be pockets of disease within larger geographic confines. The spread of HIV is shaped by variations in individuals' behaviour within a specific population and public health response, which are themselves shaped by differences in social, cultural, economic, and political conditions. Regional differences in HIV incidence and burden in Kenya have been articulated in the Kenya HIV prevention roadmap [41]. The roadmap identifies high

burden counties using modelling and classifies the counties into high, medium and low incidence clusters. The Impact Action Agenda in the PEPFAR 3.0 strategy guidance outlines the three "rights": implementing HIV programs in the right way, in the right places at the right time [42].

HIV measurement in a spatial context

There is a need to measure efforts in HIV prevention and assess the coverage and impact of response to the HIV pandemic and equally important, answer the question whether these efforts are focussed in the right places (as illustrated in figure 5). Outputs from such spatial analyses can help in public health response and HIV program planning.
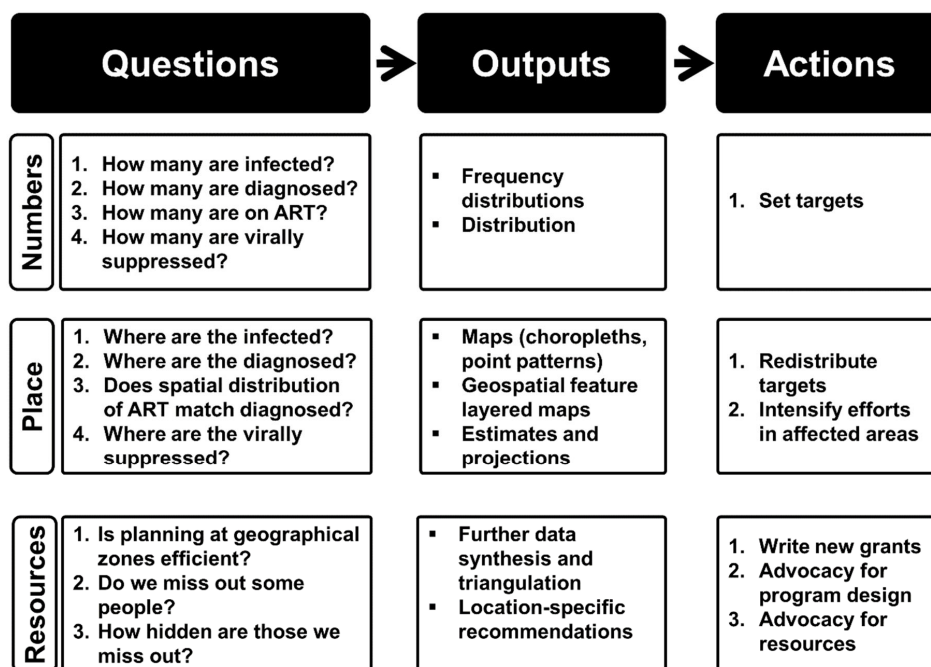
Figure 5: Geospatial public health approach for HIV epidemic control in Kenya

Person, place, time and HIV

The traditional focus of epidemiology three-way relationship "Person", "Place" and "Time" has been monumental in describing disease patterns such as HIV and their distribution. The historic example is from 1850's and John Snow's famous mapping of

a cholera outbreak in London [43]. Whereas this application to epidemiology continues to have its place, a fundamental question of disease patterns in the wider public health context is necessary. A consideration for public health approach includes detection of local disease patterns and their occurrence in global and local contexts including relationships with person-level risk factors.

In large population based surveys, it might be difficult to describe and map out HIV-infected persons. HIV-infected persons are therefore aggregated and efficiently described in the context of their demographic population profile, behavioural, and outcome characteristics of interest for example access to care [1]. Population size estimates derived from population census data adds weight to describe the magnitude of the health problem at hand.

The presentation of place and time provides an ecological setting for a population. In the recent past, evidence has been cited describing the relationship between HIV spread, small trading centres and roads that act as channels of communication [44]. Therefore, the description of social and physical environmental features of the population is important in understanding the dimensions of place and spread of HIV. In recent years, the analysis of "place" has focussed on detecting clusters with high (hotspots), or low prevalence (cold spots) by evaluating significant clusters. Use of Kulldorff's spatial scan statistic utilizes a Poisson model and is implemented in SaTScan™ software [45], and mapped using tool such as ArcGIS™, or Quantum GIS (QGIS). Spatial-temporal analysis provides insights into how the population related parameters change in both space and time.

Geographic scale

Spatial analyses of HIV prevalence by use of smaller regions and identification of hotspots can demonstrate intricate patterns and pinpoint gaps within the continuum of care. We utilized available programmatic (facility level data) and population-based data to explain variations in space and time and describe the elements within the continuum of HIV care. Aspects of analyses include trends of HIV treatment outcomes within

defined geographic confines such as sub-counties (formerly districts) and counties. We have also explored HIV clustering and areas with higher than overall prevalence of HIV (hotspots) and spatial patterns at national level.

It may be difficult to measure and understand disease at population level in the context of place and persons without conducting large population based surveys, intensive clinical trials, or analysis of large patient cohorts in HIV treatment cascade including HIV testing services (HTS), linkage to HIV care including impact of treatment. Other routine surveillance such as antenatal clinic (ANC) sentinel surveillance give additional data pillars which can be utilized to perform estimates and projections for treatment coverage and needs using modelling. The estimation and projection package (EPP) has been used for example to determine HIV incidence and triangulated with various methods [46]. However, survey and clinical data and estimates often need geographic context to add explanatory rigor. There is evidence of a relation between HIV disease clustering and its transmission [47]. For example, closeness to transmission routes including transport corridors has been found to impact on HIV prevalence in clusters close to roads [48].

The links between financial and human resource investments, HIV prevention and treatment outcomes are poorly described if not totally ignored. Geospatial mapping of HIV prevalence is commonly done at wider geographic region than smaller regions. To understand local epidemics, there is need to map HIV disease in smaller geographic regions, identify temporal trends and associate the disease with possible predisposing risk factors. For example, when HIV prevalence estimates are mapped at provincial level versus mapped at county level, localized patterns start emerging (Figure 2). Recently, there has been various studies mapping HIV prevalence clustering and incidence [48–51]. Additionally, there is recognition that identifying geographic areas with localized epidemics and populations most affected offers the opportunity to strengthen effectiveness of national HIV response after identifying pockets where services are inadequate [52].

HIV cascade and constructs for spatial epidemiology

Test, treat, and retain

Spatial factors associated with the cascade of care described by testing, treating and retention in care and treatment can be explored to demonstrate high yielding areas, linkages to care and retention in care. Retention in care in HIV treatment cohorts in sub-Saharan Africa is substantially higher than for patients in HIV care alone [53,54] and retention in care for patients not yet on ART is lower [55]. While understanding and spatially presenting where HIV testing happens can easily be done, it is important to present whether patients testing HIV-infected are successfully linked to HIV treatment programs and are accessing treatment. Among paediatric patients, early infant diagnosis (EID) can be used and as a means to improve retention [56]. Both adult and paediatric retention in care and treatment can be determined using proxy data that compares yield, prophylaxis and newly enrolled in ART within a given period and place. Geographical variations can be unravelled when such data are mapped to reveal where most gaps exist.

Viral load suppression (VLS)

Viral load suppression is an important biomarker when grouped geographically since it is a representation of the transmissibility of the virus within the groups [57]. Community viral load data can be used to predict reduction in HIV incidence [58], geographically map the burden of HIV infections [57], and hence demonstrate impact of HIV treatment as prevention and impact of treatment services. Community viral load has been described as 'an aggregate biological measure of viral load for a particular geographic location and for a particular group of people who share socio-demographic characteristics [58].

Treatment scale-up leads to reduced community viral load hence resulting in reduced HIV transmission. To demonstrate treatment impact, viral load data can be related to reduction on HIV incidence. ART data when mapped-out can be used to attribute impact

by associating lowered incidence with maturity of HIV programs in those areas since increased ART coverage may lead to decline in HTC positivity rates.

Other impact outcomes

An important milestone in the control of the HIV epidemic is when the number of annual new HIV infections is lower than the number of annual all-cause deaths among all PLHIV. This equilibrium is also referred to as the "tipping point". This measure has a strong epidemiological value and is relevant when treatment coverage is high [59]. Thus, HIV-related mortality has gained importance to help programs determine the tipping point and hence the progress towards epidemic control. However, mortality is not routinely analysed and can be misclassified as loss to follow-up in treatment programs [60]. Mapping out areas with highest reported mortality among HIV infected persons whether on treatment or not can provide insight into the impact of the HIV programmes. Using the tipping point outcome measure, Kenya's progress towards achieving epidemic control is presented in figure 6. In 2007, the number of new infections surpassed the deaths among PLHIV demonstrating the impact of ARV treatment, the rate of new infections notwithstanding.
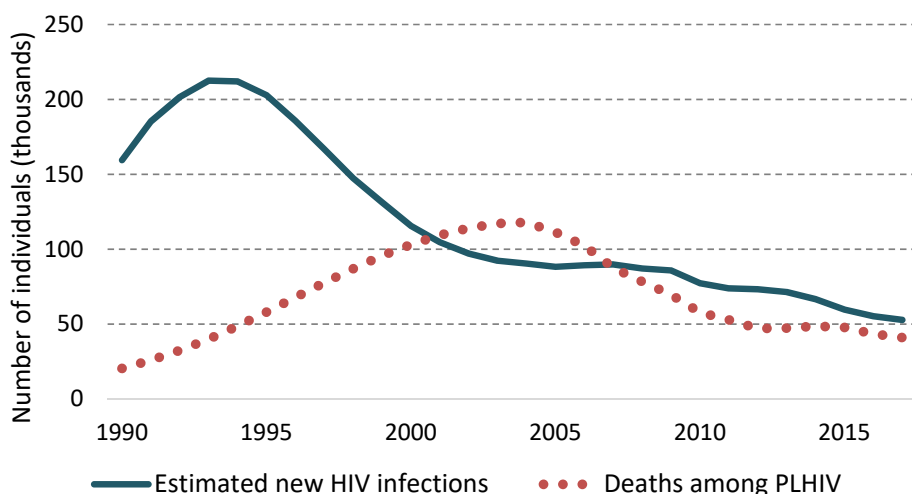
Source: Adapted using data sourced from AIDSInfo (http://aidsinfo.unaids.org/)
Figure 6: Kenya's progress towards HIV epidemic control

Mapping access and geographic coverage of HIV services

The existing use of HIV prevention, care, and treatment services to the target population can be described by access and yield. In Kenya, access to care has been found to be associated with ART status and low access attributed to shortage in supplies and prioritization of those in need [61]. There could be other reasons that have not been fully explored including distance to facilities where care is offered. These distance-based measures could be more useful in providing insight into coverage as measured by provider-patient ratios hence avoid some of the problems associated with provider-to-population ratios including overgeneralization of parameters [62]. Though distance to facility measures may suffer from attributing access to other attributes of health care providers and quality of service [63]. Though access can be described more broadly as availability, accessibility, accommodation, affordability and acceptability [62], the most spatially relevant aspect of access is accessibility as relates to geographical barriers that may include distance, transportation, travel time and cost. In our study, we explored Euclidean distances to geographic features of interest such as roads and closeness to towns and urban areas by overlying the analyses results on spatial features (Papers I and II).

The use of these parameters and associations across the continuum of care, applied to the specific population of interest, provides an important view of the resources allocated. This information can be triangulated with HIV acquisition determinants, risks and impact of HIV treatment as well as where i.e. "place". The utility of this is to map HIV prevention and treatment services to the community most at risk and in need hence optimizing resources. A 7-stepwise process has been proposed for consideration when using HIV program data [64], these steps though do not suggest outputs such as maps. Due to the nature of available program data in SSA, various purposes for its use have been suggested. These include use of maps to inform targeted HIV prevention and treatment services programming at appropriate geographical scale [65].

Rationale for this thesis

The purpose of this study is to explore spatial features as they relate to HIV behavioural risk factors, HIV testing, prevention, and describe HIV care access patterns, utilization, and treatment impact. Overall, the study seeks to answer the question whether HIV testing, prevention and treatment efforts have gone to the right places and measure their spatial temporal impact.

In our analyses, we explore factors associated with the spread of HIV, access and utilization of care and treatment services, and impact of treatment in relation to space, time, and persons. The purpose is to stimulate ways of looking at HIV prevention and treatment programming and sustainable resource allocation.

Findings from this study will add to the knowledge of health systems in Kenya and application of data and information for decision-making processes. This research will have implications on improved prevention efforts, targeting, patient care and management and overall health care programming.

Conceptual framework

HIV surveillance in the continuum of care

Surveillance can be described in relation to HIV disease stage (figure 7). At infection, surveillance system detects the cases and derives HIV incidence and associated behavioural and other risk factors. Over time, more persons are infected and those still alive and in treatment contribute to prevalence. Factors associated with retention in care and treatment including adherence and other behavioural factors can be related to this stage. Use of ART contributes to viral load suppression at the advanced HIV disease stage. Death is ultimately the end stage for an HIV-infected person.
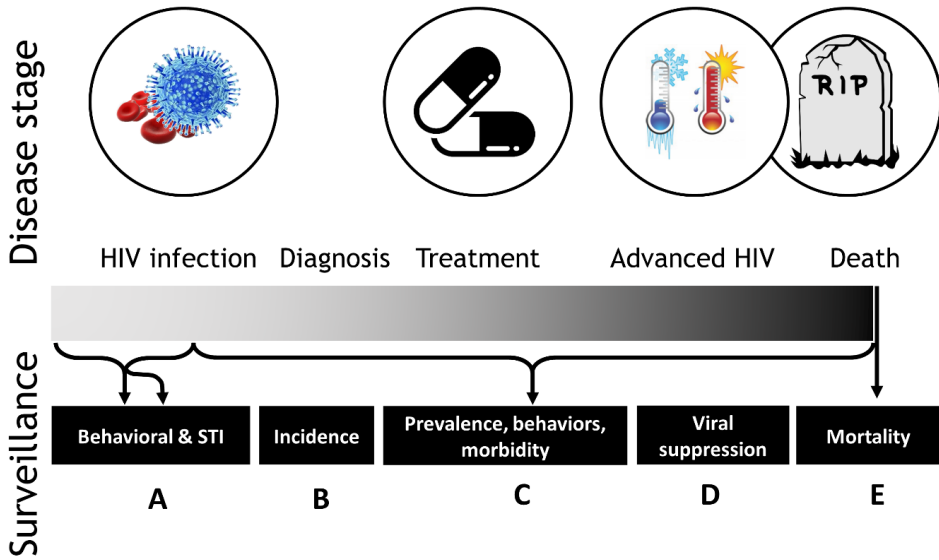
Figure 7: HIV disease stage, surveillance, and data points

The cascade of care and treatment

The cascade of HIV care and treatment [66] (figure 8), provides an analytical framework for this study. As is with epidemics, the population serves as the first reservoir for the disease of interest which when diagnosed in individuals, provides cases for eventual follow-up until cure or death.
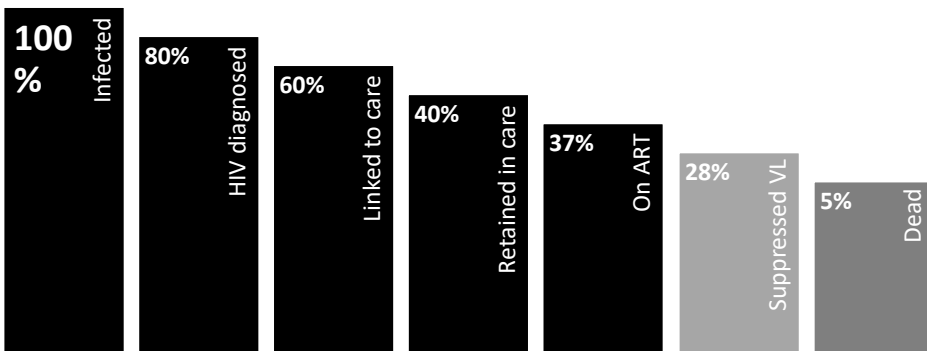
Figure 8: The cascade of HIV care and treatment (an example)

Spatial epidemiology in relation to the cascade of HIV care and treatment

Each of the surveillance stage can be described using spatial epidemiology. National population surveys (NPS) such as AIDS indicator surveys (AIS) and ANC sentinel surveillance will be useful in describing behavioural factors associated with prevalence, which can be in turn mapped out in relation to high-risk behaviour prevalence. In well-established and generalized epidemics and in absence of 4th generation test kits and incidence assays, early infant diagnosis (EID) can be used to describe transmission of HIV to infants and characterize incidence and prevalence in that population [67]. In advanced disease stage, ANC sentinel surveillance, population-based surveys with HIV testing, HIV drug resistance monitoring and ART cohort outcomes can used to describe the HIV disease. Mapping of routine viral load suppression rates can Geospatially demonstrate impact in the context of ART coverage. The last stage of HIV disease is more complex to spatially describe due to lack of available disease-specific related mortality data. However, trace-back methods have been used to characterise loss-to-follow-up (LTFU) data and determination of proportions dead of those truly LTFU [68].

2.0 AIM AND OBJECTIVES

Aim

The purpose of this study is to explore spatial variability of HIV and explain HIV behavioural risk factors, prevention, HIV diagnoses, treatment, and impact in a spatial context. Overall, the study seeks to answer the question whether HIV diagnoses and treatment efforts have gone to the right places and measure their spatial and spatial-temporal impact.

The overarching research question is:

"Is there spatial variability of HIV in Kenya and do geospatial features, spatial, and spatial-temporal factors explain variability in relation to investments in HIV burden, programming, coverage, and impact in Kenya?"

Specific objectives

The specific objectives were to:

1. Describe spatial-epidemic clustering of HIV prevalence in Kenya other than the well-known subnational pattern [Paper I]

2. Explore relationships between HIV clustering, sociodemographic and behavioural risk indicators to geospatial features that facilitate risk for HIV infection [Papers I and II]

3. Explore geospatial factors associated with efficient HIV testing services that facilitate more new diagnoses in Kenya [Paper II]

4. Examine programmatic geographic coverage and associations with impact of HIV prevention and treatment in Kenya [Papers III & IV]

3.0 METHODS

Study settings

For Papers II and IV, the study was undertaken utilizing clinic-level data from HIV prevention care and treatment programs in the whole of Kenya. In Paper I, we used data from clusters selected from 44 counties leaving out three counties. These 44 counties cover most of the country. In Paper III, we used data from 12 districts (now referred to as sub-Counties) in the larger Nyanza region of western Kenya (figure 9).

For Paper III, the study location was the 12 districts in the Western part of Kenya - formerly known as Nyanza province, (figure 9).
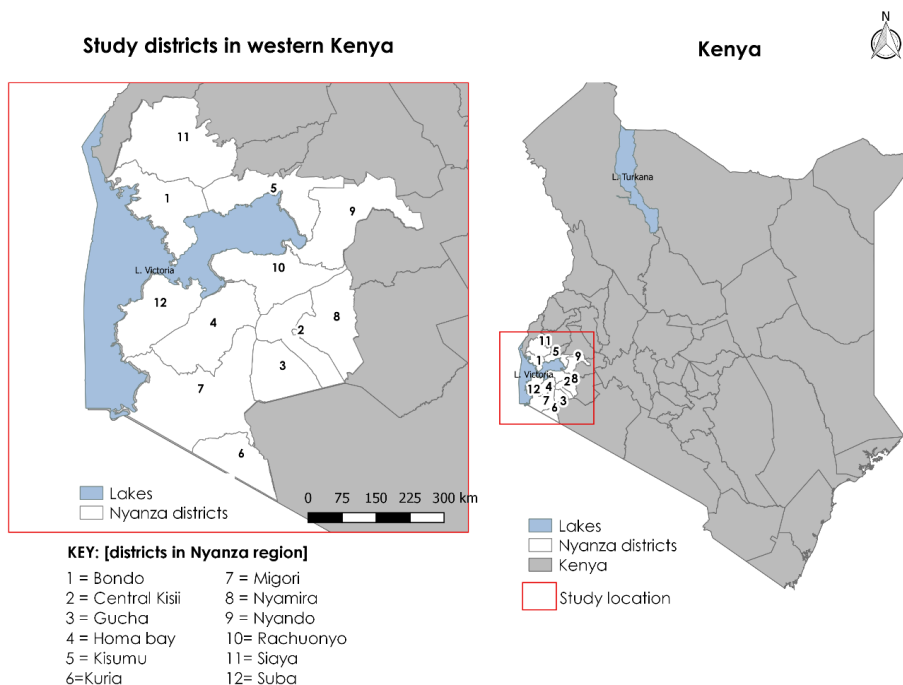

Figure 9: Study location (Paper III)

Health sector

Majority of Kenya's population receives healthcare services from the public sector and facilities operated by the ministry of health. After the 2010, constitution was promulgated leading to a decentralised system of government, health services were as well decentralised to the 47 constituencies. Kenya health facilities are classified

according the type of disease and conditions that they can handle as well as staffing and capacity under the Kenya Essential Package for Health (KEPH) [69]. The lowest level of health care provision in Kenya is the community health facilities. The health clinics are classified into dispensaries, health centres, sub-county hospitals, county referral hospitals, and three national referral hospitals (table 3). Kenya has both public and private sector hospitals estimated to be about 5000 in 2018. All the hospitals in Kenya are registered in the Master Facility List (MFL) maintained by the ministry of health. Most of the hospitals and health facilities are geocoded.

Table 3: Kenya Essential Package for Health (KEPH) facilities classification

Level	Type	Location
1	Community unit	Community
2	Dispensary	Village level
3	Health center	Locational level
4	Sub-county hospital	Sub-county headquarters
5	County referral hospital	County headquarters
6	National referral hospital	Nairobi (2) and Eldoret (1)

Study design, population, sample size and sampling

Summaries of study designs and sample sizes are presented for each Paper in table 4. The study design for Paper I is described in the full report and manuscript [70,71]. The population covered is derived from the population included in the original sample for large population based surveys such as the Kenya AIDS indicator survey (Paper I). Sample size determination are as per the original protocol for Paper I and not relevant in the other Papers since we have utilized routine program data.

Table 4: Summary of study designs and sample sizes

Paper	Design	Sample size and study entities	Data type
Paper I: Finding Hidden HIV Clusters to Support Geographic-Oriented HIV Interventions in Kenya. J Acquir Immune Defic Syndr 2018.	Cross-sectional two stage cluster randomized survey, purely spatial scanning	Individual level (n=15,333) data Household level survey, 9000 households in 378 clusters in	Secondary data
Paper II: Where are the newly diagnosed HIV-infected persons in Kenya? Time to consider finer scale geo-spatially guided targeting to reach the "first 90". Draft manuscript	Cross-sectional, observational, purely spatial scanning	HIV clinics offering HTS (n=), aggregation at constituency level (n=290)	Routine HIV clinic-level
Paper III: Spatial–temporal trend for mother-to-child transmission of HIV up to infancy and during pre-Option B+ in western Kenya, 2007–13. PeerJ 2018;6:e4427. doi:10.7717/peerj.4427.	Longitudinal, observational, spatial-temporal	HIV clinics offering early infant diagnosis (n=278), data aggregation at district level (n=12), individual infant records (n=100,000)	Routine HIV clinic-level
Paper IV: ART coverage and viral load suppression rates as correlates to new HIV diagnoses, in Kenya; Spatial-temporal analyses 2015-17. Draft manuscript	Longitudinal, observational, spatial-temporal	HIV clinics offering ART and viral load testing (n>3000 in 2018), aggregation at county level (n=47).	Routine HIV clinic-level

Data sources

Overall nature of the data

This thesis utilizes secondary data (Papers I and III) and routine aggregated data from clinics offering HIV services (Papers II and IV). In Paper I, we used data from a national two-stage cluster household-level survey (the Kenya AIDS Indicator Survey 2012). Population data were sourced from the Kenya National Bureau of Statistics (KNBS) projections based on Kenya population and housing census 1999. The census is conducted every 10 years but population projections can be made for the years between the censuses.

In all manuscripts, we have used secondary data that had not primarily been collected to address the specific objectives for each of the papers, nor were the data collected with Geospatial analyses as the objective. None of the manuscripts used data that had personally identifiable information (PIIs). Although at individual level, data for Papers I and III were is anonymized. The rest of the data (Papers II and IV) were aggregated at clinic level. During analyses, data were aggregated into units such as clusters, health facilities, and analytical categories. Where shape files are used, we have quoted appropriate referencing according to the creative commons licence agreements.

Copyright and permissions for shape files

Base shape files were obtained from International Livestock Research Institute (ILRI) website under the CC BY 4.0 license. For use of other open street maps (OSM), creative commons licenses apply. Regarding use of data for publication beyond the study dates, data used are for the period of the study covered by the protocol. Use of data for publishing beyond the expiry date is allowed under the local IRB standard operating procedures. The local IRB review procedures are articulated in the website and details are found here: https://www.kemri.org/index.php/seru-review-process. Descriptions relating to data use, approvals, and data access for each manuscript are provided as follows:

Details of data sources

Paper I

The data used came from the Kenya AIDS indicator survey (KAIS) that was conducted in 2012. A two-stage cluster randomized design was utilized during KAIS. Firstly, the clusters within a region were randomly selected. Then, 25 households within each cluster were randomly selected. Participants were interviewed using a standardized questionnaire regarding household and demographic characteristics, bio-behavioural factors, and use of HIV-related services such as HTS and VMMC. Data were collected using tablet computers and securely transmitted electronically to a central database in Nairobi. No personal identifiers were included and serial barcodes were used to link laboratory data to individual interview questionnaire data.

Paper II

The data used are aggregated at facilities reporting to the national level. These data are used with permission from the National AIDS and STI Control Program (NASCOP) who are the custodians. A protocol for HIV program aggregate data use was applied. The master facility list (MFL) that bears the geo-coordinates was obtained from the ministry of health. Data are available from https://www.datim.org/dhis-web-commons/security/login.action for authorized users. These data are also available from the district health information system 2 (DHIS 2) in the link https://hiskenya.org/dhis-web-commons/security/login.action. The data are also available at the following link: http://kmhfl.health.go.ke/.

Paper III

The data used comes from the pilot that was the precursor of the widespread implementation of early infant diagnosis (EID) in Kenya. The study was conducted in Western Kenya during the pre-option B+ period in Kenya. These minimal demographic and clinical data were abstracted from the patient charts using a standard tool. Serial numbers are used for purposes of linking the data to the laboratory data. No patient identifiers were collected. Other population counts data used in the Paper to supplement are based on the 2009 housing census available from the KNBS and projections calculated to match the study period.

Paper IV

The data used are aggregated at facilities reporting to the national level. These data are used with permission from the National AIDS and STI Control Program (NASCOP), United States Agency for International Development (USAID), and Department of Defence (DOD). A protocol for use of HIV program indicators [Monitoring, Evaluation, and Reporting (MER)] was applied. HIV testing data were obtained from https://www.datim.org/dhis-web-commons/security/login.action. These data are also available from the district health information system 2 (DHIS 2) in the link https://hiskenya.org/dhis-web-commons/security/login.action. Viral load data were obtained from the national viral load database <https://viralload.nascop.org/>. Shape polygons used in the manuscript are available from public repository hosted at <https://www.ilri.org/GIS> and are covered under the creative commons license CC BY 4.0 license.

Underlying analytical concepts

We have used both descriptive and explanatory research designs. We have used descriptive epidemiology approaches to explain the distribution of HIV and factors related to this distribution while the explanatory design will be used test of relationships and answer the question of place and time. The combination of the two designs enabled a description of relationships between variables. To detect global patterns, these methods are applied: i) Nearest neighbour analysis, ii) Global Moran's I [Paper II], iii) Getis-Ord and iv) Geary's C. To perform locational analyses, the methods applied are: i) Location, ii) Getis-Ord, iii) Anselin's LISA and iv) Kulldorff's scan-statistics [Papers I and II]. To check for predictive patterns, these methods are applied: i) Voronoi polygons, ii) Kriging, iii) Kernel density estimation and iv) Hierarchical spatial regression models [Papers III and IV]. Summaries of these concepts are presented in table 5.

Table 5: Spatial questions, nature of analyses and mapping

Spatial question	Spatial analysis approach	Mapping methods and interpretation
Show coverage over a geographical area	Spatial	Choropleths of contiguous geographic regions. Additional layers may be added such as highways, towns, and other geographical feature that impact on access to HIV services. At a more advanced level, topographical information may be useful.
To show trends over time and place	Spatial temporal	Map series by analysis periods (month/year).
Show clustering of small "hotspots" over a larger geographical area	Clustering	Clustering is best shown when representative data (e.g. from all facilities in a region) has been collected. Data are analyzed using specialized software e.g. SaTScan™ or ArcGIS or even QGIS and clusters highlighted.

Estimating rates, spatial autocorrelation and clustering

In identification of populations at higher risk, we used person data from national general population based surveys such as Kenya AIDS indicator survey available from National AIDS and STI Control program (NASCOP). To place these data in a spatial context, we used available spatial information, such as population statistics from the KNBS, Master facility codes with geo-locating information from the Kenya Ministry of Health, shape files with boundaries at various levels including county level other commercial spatial data including street network files. These geographies are appropriately and spatially associated with each other and additional statistics such as population estimates and prevalence using SaTScan™ software and mapped using ArcGIS™.

Mapping

Mapping has been done in ArcGIS™ as well as Quantum GIS (QGIS). Clusters were first identified using SaTScan™ and then mapped using either of the two softwares. We have included spatial layers to point out geographic features of interest such road networks, towns and economic activities. Other utilities of HIV mapping are used to describe HIV in terms of prevalence, burden, access, and utilization of services, and impact of prevention and treatment. Overall, spatial epidemiologic enquiry in this study relates to the HIV cascade and we have used mapping as point-patterns geographic autocorrelation, hotspots/clustering identification techniques and choropleths (table 6).

Table 6: HIV 90-90-90 cascade, geographic scale, and mapping techniques

Cascade element*	Spatial questions	Mapping scale and technique	Paper
First 90:	Where are the HIV infected?	National, point patterns and cluster maps	I, II
Second 90:	Where are the HIV newly diagnosed?	National and within SNU; point patterns and cluster maps	II
Third 90:	How is the impact of HIV treatment on: a) reduced HIV transmission to infants and b) viral load suppression distributed in space and time?	Sub-county in a high burden region and national; choropleths	III, IV

*According to the UNAIDS fast-track targets to end HIV [72]

Outcomes

In table 7, we define the variables used in the thesis. The main outcomes for this thesis were HIV prevalence, clusters of HIV-infected persons who were newly diagnosed, HIV mother to child transmission rates and viral load suppression rates. We calculated other outcome variables such as coverage, and positivity yield. Others were conceptual and derived from spatial analyses.

Table 7: Definition of outcome variables used in the thesis and their spatial scope

Outcome variables and concepts	Spatial scope	Definition/measurement	Papers
HIV prevalence rate	National	The proportion of a population that has a particular disease, injury, other health condition, or attribute at a specified point in time or during a specified period	I
Coverage	Sub-national	Coverage of ART: number of PLHIV on ART out of the estimated PLHIV	III and IV
Positivity	Facility level, Sub-national unit levels (county and constituency)	The proportion of HIV infected out of the population tested for HIV	II and III
Spatial autocorrelation and clusters	Facility level, national and sub-national unit levels (county and constituency)	Global: this is a measure of the overall clustering of the data at the aggregate spatial scope - measured using global Moran's I. Local: measured as local indicators of spatial association (LISA) to measure if one or more confined areas exhibit substantial deviation from spatial randomness compared to neighbouring areas [73] - measured using local Moran's I	I and II
HIV yield	Facility level, Sub-national	Number of newly diagnosed with HIV. A reduced number of HIV	II, III and IV

Outcome variables and concepts	Spatial scope	Definition/measurement	Papers
	unit levels (county and constituency)	infected over time was defined as an impact measure	
Spatially scanned rates of HIV infected	Defined windows of 100 km radius	Measured using Kulldorff spatial scan statistics within defined windows of 100 km radius	I and II
Hotspots	Occurrence within defined windows of 100 km radius	Local pockets of observed rates or numbers given the underlying population denominators	I and II
Elimination of Mother to Child Transmission of HIV (e-MTCT) impact target	Sub-counties within a high HIV burden geographical region	≤50 new paediatric HIV infections per 100,000 live births and a transmission rate of <5% in breastfeeding populations	III
Standardized MTCT rates	Within a high HIV-burden geographical region in western Kenya	[Absolute transmission (number infected) /women tested for HIV in 2013] x 100,000	III

Statistical analyses

Statistical methods used for each of the Paper are listed in table 8.

Spatial analyses

We fitted spatial-temporal semi-parametric Poisson regression models to estimate rates for MTCT and HIV positivity at district and county areal level (Papers III and IV, respectively) using R - Integrated Nested Laplace Approximation (INLA), appendix I. To detect clusters, we used Kulldorff spatial-scan Poisson models to scan for clusters with high rates (Papers I and IV, appendix II) implemented in SaTScan™ version 9.4. To assess for spatial autocorrelation, we used global and local Moran's I while measuring influential values using Moran's scatter plot and Cook's D_i (Paper IV, appendix III and IV). We implemented Moran's I in R statistical program and ArcGIS™ version 10.5.1.

Non-spatial analyses

We used Chi-square test for comparing proportions and Logistic regression to test for associations (Paper I) implemented in Statistical analysis system (SAS) version 9.3 (SAS Institute Inc., Cary, North Carolina, USA.). To test for association across categories we used Cochran-Mantel-Haenszel stratified test of association implanted in Stata version 14.1, (Stata Corp., College Station, TX, USA.) for (Paper III and IV). We used Kruskal-Wallis equality-of-populations nonparametric rank test to test for equality of medians for continuous variables implemented using Stata version 14.1, (Stata Corp, College Station, TX, USA.), (Paper IV). To detect direct effects between exogenous and endogenous variables, we used structural equation model (SEM) using Stata version 14.1, (Stata Corp, College Station, TX, USA.) (Paper IV).

Table 8: Statistical analyses methods used in the thesis

Statistical methods	Papers	Statistical software
Spatial-temporal semi-parametric Poisson regression models	Paper III, IV	R - Integrated Nested Laplace Approximation (INLA)
Cochran-Mantel-Haenszel stratified test of association	Paper III, IV	Stata version 14.1, (Stata Corp, College Station, TX, USA.)
Kruskal-Wallis equality-of-populations nonparametric rank test	Paper IV	Stata version 14.1, (Stata Corp, College Station, TX, USA.)
Chi-square test for comparing proportions	Paper I	Statistical analysis system (SAS) version 9.3 (SAS Institute Inc., Cary, North Carolina, USA.)
Logistic regression	Paper I	Statistical analysis system (SAS) version 9.3 (SAS Institute Inc., Cary, North Carolina, USA.)
Kulldorff spatial-scan Poisson model	Paper I, IV	SaTScan™ version 9.4
Mapping and data visualization	Paper I, II, III, IV	Quantum GIS (QGIS) version 2.16 and 3.2.2
Structural equation model (SEM)	Paper IV	Stata version 14.1, (Stata Corp, College Station, TX, USA.)

Ethical considerations

The thesis work was assessed by REK Vest, the Regional Committee for Medical and Health Research Ethics and it was considered to fall outside their mandate (REK Vest 2018/59). In Paper I, we used anonymized and de-identified data from the Kenya AIDS indicator survey (KAIS) conducted in 2012. Secondary and routinely collected HIV program data are used for Papers II and IV. In Paper III, we used de-identified patients data from the first pilot of early infant diagnosis in Western Kenya. Specific ethical considerations are listed for each Paper below:

Paper I: The Kenya Medical Research Institute's (KEMRI) Ethical Review Committee (ERC), the US Centres for Disease Control and Prevention's (CDC) Institutional Review Board (IRB), and the Committee on Human Research of the University of California, San Francisco (UCSF), approved this study. During data collection, at household level, the head of household consented to the household questionnaire; the heads of households were adults aged 18–64 years or emancipated individuals with no parent or guardian or not living with their parent/guardian. The field interviewer sought individual consent or assent for all eligible household members to participate in the individual questionnaires. In the case of participants aged 10–17 years, consent was obtained from a parent/guardian or other adult responsible for the child/youth health and welfare before the child/youth was asked for his/her assent. Oral informed consent for HIV testing was required for adults and emancipated minors. Verbal informed consent with a signature of the interviewer on the consent form served as documentation of the consenting. PII was not collected in the first place.

Paper II: Ethical approval for the study was obtained from the United States Centres for Disease Control and Prevention (CDC). Further consent was not necessary since these data were routinely collected de-identified and aggregated from routine HIV clinic services. Non-HIV spatial related data are approved for use under the creative commons license (CC BY-SA 3.0) with attribution.

Paper III: Ethical approval for the study was obtained from the KEMRI and the United States Centres for Disease Control and Prevention. Further consent was not necessary since these data were routinely collected deidentified data from routine clinic services.

Paper IV: The Ministry of health, National AIDS and STI Control Programme, and President's Emergency Plan for AIDS Relief (PEPFAR) funding agencies provided concurrencies. Analyses are from aggregate data whose use for dissemination is covered under the monitoring evaluation and reporting (MER) protocol of the US Centres for Disease Control and Prevention.

4.0 SUMMARY OF RESULTS

Paper I

Finding hidden HIV clusters to support geographic-oriented HIV interventions in Kenya

In a spatially well-known and dispersed HIV epidemic, identifying geographic clusters with significantly higher HIV-prevalence is important for focusing interventions for people living with HIV (PLHIV).

We used Kulldorff spatial-scan Poisson model to identify clusters with high numbers of HIV-infected persons 15-64 years old. We classified PLHIV as belonging to either higher or lower prevalence (HP/LP) clusters, and then assessed distributions of socio-demographic and bio-behavioural HIV risk factors and associations with clustering.

About half of survey locations, 112/238 (47%) had high prevalences of HIV (HP clusters), with 1.1-4.6 times greater PLHIV adults observed than expected. Persons in the highest wealth index compared to respondents in lowest wealth index had higher odds of belonging to a HP cluster, adjusted odds ratio (aOR), 1.61 (95% CI: 1.13-2.3), aOR 1.66 (95% CI: 1.09-2.53), aOR 3.2 (95% CI: 1.82-5.65), aOR 2.28 (95% CI: 1.09-4.78) in second, middle, fourth and highest quintiles respectively. Respondents who perceived themselves to have greater HIV risk or were already HIV-infected had higher odds of belonging to a HP cluster, aOR 1.96 (95% CI: 1.13-3.4) and aOR 5.51 (95% CI: 2.42-12.55) respectively; compared to perceived low risk. Men who had ever been clients of FSW had higher odds of belonging to a HP cluster than those who had never been, aOR 1.47 (95% CI: 1.04-2.08); and uncircumcised men vs circumcised, aOR 3.2, (95% CI: 1.74-5.8).

HIV infection in Kenya exhibits localized geographic clustering associated with socio-demographic and behavioural factors, suggesting disproportionate exposure to higher HIV-risk. Identification of these clusters reveals the right places for targeting priority-tailored HIV interventions.

Paper II

Where are the newly diagnosed HIV-infected persons in Kenya? Time to consider finer scale geo-spatially guided targeting to reach the "first 90"

The bulk of HTS targeting in Kenya is in five high HIV-burden counties: Nairobi, Homabay, Kisumu, Siaya, and Migori, which account for over 40% of the estimated people living with HIV (PLHIV). Geographic analyses help us to unmask local patterns that go beyond the traditional data aggregation methods, and are useful in helping to focus and prioritize HTS strategies to reach the "first 90". We analyzed the year 2016 site-level HTS data in Kenya to assess the spatial distribution of HIV-infected and compared their distribution within counties [sub-national units (SNUs)]. We classified clustering of newly diagnosed HIV-infected persons using spatial autocorrelation: neighbours as hotspots neighbouring other hotspots (HH), hotspots neighbouring low-spots (HL), low-spots neighbouring hotspots (LH), and low-spots neighbouring low-spots (LL).

Out of 4,021 HTS sites, 3,969 (98.7%) had geo-coded data. Global Moran's I was 0.023, expected I was -0.00025, Z-score 33.9 and p<0.001. Most sites showed no clustering (3034, 76.4%); others were grouped as HH (438, 11.0%), HL (66, 1.7%), LH (275, 6.9%), and LL (156, 3.9%). Of the HH sites, 301 (68.7%) were in high HIV-burden SNUs distributed within each: Homabay with 78/184 (42.4%), Kisumu 57/137 (41.6%), Siaya 50/145 (34.5%), Migori 43/139 (30.9%), and Nairobi 73/239 (30.5%). HH sites in high burden counties were near water bodies (Homabay, Kisumu, Siaya, and Migori) or a large city (Nairobi) and in low HIV-burden areas near major roads. Out of 290 constituencies, 23(12%) had high HTS-yield values. We identified 123 clusters with high counts of newly diagnosed HIV-infected persons. Some of these clusters 73 (59.3%) were not in the five high HIV burden counties and would not be considered high priority for HTS services. We found that there is need to corroborate findings from different spatial statistical methods.

Paper III

Spatial-temporal trend for mother to child transmission of HIV up to infancy and during Pre-Option B+ in western Kenya, 2007-13

We aimed at understanding coverage and trends in elimination of mother-to-child transmission of HIV (eMTCT). This is one of the desirable outcomes of the prevention of mother to child transmission of HIV programming. In this paper, we present spatial-temporal analysis of 7-years of HIV early infant diagnosis data collected from 12 districts in western Kenya from January 2007 to November 2013, during pre-Option B+ use.

We included in the analysis infants up to one year old. We performed trend analysis and examined trends and associations of infant HIV status at first diagnosis with early diagnosis (<8 weeks after birth), age at breastfeeding, use of single dose nevirapine (sdNVP), and maternal antiretroviral therapy (ART) status. We also fitted spatial and spatial-temporal semi-parametric Poisson regression models to explain HIV-infection rates, calculated new infections per 100,000 live births, and mapped fitted MTCT estimates for each district in Nyanza region.

We found that unadjusted pooled positive rate was 11.8% in the 7-years period and declined from 19.7% in 2007 to 7.0% in 2013, p<0.01. Uptake of testing ≤8 weeks after birth was under 50% in 2007 and increased to 64.1% by 2013, p<0.01. By 2013, the overall standardized MTCT rate was 447 infections per 100,000 live births. The spatial-temporal model with maternal and infant covariates was best in explaining geographical variation in MTCT.

During this pre-Option B+ period, the PMTCT program in this region has not achieved e-MTCT target of ≤50 case rates per 100,000 live births. Co-joined analysis of time and covariates in a spatial context provides a robust approach for explaining differences in programmatic impact over time. Geographical disparities in program achievements may signify gaps in spatial distribution of e-MTCT efforts and could indicate areas needing further resources and interventions.

Paper IV: *ART coverage and viral load suppression rates as correlates to new HIV diagnoses, in Kenya; Spatial-temporal analyses 2015-17*

We hypothesized that good antiretroviral therapy (ART) coverage and high rates of viral load suppression (VLS) should reduce transmission of HIV, and ultimately, HIV incidence reflected as the number of new HIV diagnoses. We used 3 years (2015-2017) of HIV program data in Kenya to assess whether trends in HIV positivity were associated to ART coverage and VLS rates and spatial-temporally auto correlated at county-level [sub-National unit (SNU)].

ART coverage was defined as the proportion of persons on ART out of the estimated PLHIV and VLS (proportion of persons on ART with VL<1000 copies/mL) and HIV positivity rates were analysed as proportion of reported HIV infected out of the number tested for HIV in the reporting period within an SNU.

We found that a spatial-temporal model with covariates was better in explaining geographical variation in HIV positivity [deviance information criterion (DIC) 381.3], compared to either a non-temporal spatial model (DIC 444.3), or temporal model without covariates (DIC 449.2). Overall, the fitted HIV positivity decreased over 3 years from median of 2.9% in 2015, [interquartile range (IQR): 1.9-3.4] to 1.5% in 2017, IQR(1.3-2.0), p=0.037. VLS had a direct effect on HIV positivity rates p=0.004, but ART coverage did not, p=0.843.

From 2015-2017, there has been improved ART coverage and sustained VL coverage and suppression rates. We have observed a general decline of rates of new HIV diagnoses associated with VLS rates. To assess the trends and impact of implementation of scaled-up care and treatment, spatial-temporal analyses help to identify geographic areas that need focused interventions.

5.0 DISCUSSION

What do our findings show?

HIV new diagnoses hotspots in Kenya

HIV infection in Kenya exhibits localized geographic clustering that is associated with certain socio-demographic and behavioural factors revealing disproportionate exposure to higher HIV-risk. By using mapping techniques, we were able to identify clusters with higher numbers of HIV-infected persons (Papers II and I). We identified clusters with high numbers of infected persons that were either close to large agricultural commercial enterprises such as tea farms and others that were in informal urban settlements (Paper I). Higher numbers of new HIV diagnoses are still occurring in high burden regions but granular clustering analyses show that there are low burden areas that also exhibit disproportionate high numbers of newly diagnosed HIV-infected persons (Paper II). Others have recently demonstrated changing trends of increasing rurality (most of the PHIV living in areas considered to be rural) of HIV [74]. We concluded that HIV clustering analyses reveal unexpected locations in a generalized epidemic. Identification of these clusters spots the right places for targeting priority-tailored HIV interventions.

Geographical features and individual level risk factors associated to hotspots

Geographic factors associated with HIV explore and risk include closeness to transport corridors [75,76]. Using clustering analyses, we assessed distributions of hotspots in relation to geographic features and associations with socio-demographic and bio-behavioural HIV risk factors. Our findings show spatially aligned higher new HIV diagnoses occurring along the major transport corridors (Paper II). At individual level, risk factors that may explain spatial clustering shows that wealthier respondents, adults who reported that they had a higher perception of HIV risk, men who had ever been clients of female sex workers, and uncircumcised men were associated with HIV clustering (Paper I).

HIV program reach and impact

In Paper III and IV, we explored place and time factors and considered geographical coverage of HIV programming to end mother to child transmission in a high burden

region (Paper III). We also analysed national-level data within the 47 sub-national units in Kenya to assess the impact of ART coverage and improved viral load suppression rates on reduced HIV positivity (Paper IV). These papers are about programmatic geographic coverage and associations with impact of HIV prevention and treatment in Kenya. In Paper III, we show that significant progress had been made before 2013 in reducing MTCT of HIV-infection rates, which was commensurate with an increased uptake of testing of infants at ≤8 weeks of age. The PMTCT program had however not achieved e-MTCT target of ≤50 case rates per 100,000 live births. We also demonstrate that spatial-temporal models with covariates was the best in explaining MTCT trends in time and space and that identification of geographical areas that are lagging behind are achieved using spatial-temporal analyses bearing in mind inclusion of useful covariates in the model. In Paper IV, we demonstrate the spatial-temporal impact of viral load suppression rates and ART coverage as co-variates to explain reduced new HIV infections. The impact of scaled up treatment becomes apparent for demonstrating continued HIV program reach. Geographic areas that need continued programming are exposed.

Methodological considerations

The modifiable areal unit problem has been well-described [77,78]. Most of our data were at a fine geographical or individual level that allowed us to choose the level of areal aggregation that made most sense. For example, utilizing methods that have an underlying base of the population at risk is an important consideration allowing us to develop our spatial models in several dimensions.

Assumptions and limitations

Secondary data

Secondary data are collected beforehand for a purpose that may not have factored spatial analyses. When using secondary data, the researcher can no longer influence collection methodologies and the selection of variables. This may limit what is possible to study or what to control for and is an inherent limitation in secondary data use. However, the great advantage is that such data are readily available for use and may hence be a very economical way of advancing knowledge.

Use of routine program data

Little or lack of data on quality of services offered to HIV infected patients may mask the real relationship between access to HIV case and other geographical features. However, due to continued site improvement through monitoring systems (SIMS), HIV services are expected to be fairly standardized hence choice of facility may not be due to differences in actual services but personal preference. Overall, routine clinic data has been shown to have utility in accurately mapping HIV prevalence and in identifying areas where HIV burden is concentrated [79,80]. We similarly postulated that these data are a reflection of the status of the HIV epidemic in Kenya and/or nature of HIV programs implemented and services offered.

Sample size and sampling

Using secondary data had limitations of sample size to answer a secondary objective that was not accounted for when calculating the original sample size. In Paper I, we used data collected at household-level though our aggregation after identifying clusters were for the entire population. For Papers II to IV, we used the entire datasets available and hence sampling approaches including sample size determinations were not necessary.

Heterogeneity

Heterogeneity is assumed at the areal micro-geographical scale yet persons might vary in demographic and behavioural characteristics. Interpreting data at individual level based on areal aggregates should be avoided [81]. We avoided ecological fallacy by not making assumptions that aggregate areal data (Paper II, and IV) would apply to individuals. However, in papers III, and I we did additional non-spatial analyses that included individual level characteristics and covariates.

Timing of events

In temporal analysis, it is not always easy to describe when events of particular interest happened. For example, describing infection incidence may not be practical without determination of how recent HIV infections had occurred.

Mobility of persons

Persons are not confined in a geographical space and could acquire and or transmit infections elsewhere than in the geographical space where they are ascribed to belong. Without individual level data, it is difficult to analyse the impact that mobility has over risk for HIV acquisition or transmission. However, in a recent publication, risk was not influenced by mobility [82]. However, these data were from a confined demographic surveillance system setting. In our study, we were able to characterize patterns that may be impacted by spatially connective infrastructure including the impact of cross-geographic regions within Kenya e.g. counties, or that facilitate international trade across borders within East, Central and Southern regions and other global markets.

Distance measures

Distance measures may be unavailable, as one may not have access to full road network or transportation options for analysis. Geographic distance is a rough proxy for social distance/social network via which HIV is transmitted and also can influence access to HIV related services [83–86]. Therefore, distance and social networks is important for interpretation. Distance measures are hard to take into account in aggregated data so we assumed uniformity within areal units such as counties. In paper II, we have added a roads network layer to improve interpretation of our findings. However, we did not include distance measure due to the limitations above.

Information bias

In our setting, it had been demonstrated that data collected in face-to-face interviews are limited by socially desirable responses; for example in a PMTCT setting [87]. We did not have a way to control for such biases (Paper I) since reported HIV risk factors were collected in face-to-face household interviews. The programmatic data that we have used in Paper II, III and IV are reported through ministry of health channels and eventually to donors. We expect that these data are of high quality since rigorous data cleaning is done after submission and many data quality audits done at least annually.

Lack of contiguity among geographical units

In Paper II, we aggregated data at constituency level for some of the analyses. In four constituencies out of 290, there were no numbers reported. Autocorrelation for the neighbours of those constituencies may be affected by this lack of contiguity. We adjusted for this by choosing multiple corroborative analyses to strengthen our findings.

Cluster size definition

Poor definition of the scan window size while detecting clusters can affect sensitivity and specificity of the detection. This may lead to detection of small clusters that do not have programmatic and epidemiological impact if the scan window is too small and the proportion of the population at risk is too large (>50%) affecting sensitivity and specificity respectively. A balance of the two must be maintained and appropriate number of cases defined. A threshold of 5 cases or more has been suggested by Neutra [88]. In our study, we considered a minimum of 10 HIV-infected persons and corroborated scanned clusters with spatially auto-correlated values detected using local Moran's I.

Time and aetiology

Overlapping time scale to the observed phenomenon may be a problem where disease aetiology needs to be explained in the context of time. In the HIV program, the change of policies or clinical guidelines may affect outcomes and it is not always possible to measure the time lag between introduction and actual implementation and benefits to patients.

Denominator adjustments and standardization

Epidemiology is the science of denominators. Under- or over-estimation of the denominator may lead to under- or over-estimation of the actual rate. Whenever possible, adjustments and standardization gives a better comparative measure. We used weighted data whenever feasible (Paper I), standardized estimates such as for rates (Paper III) and fitted rates to account for population denominators.

6.0 IMPLICATIONS FOR HIV EPIDEMIC CONTROL

Approaches for HIV program interventions

Based on the papers in this thesis, we conclude along the following themes.

HIV in person, place and time

Characterising the infected, where they are at and putting this in the context of time is useful for HIV program interventions. We recommend Bayesian approaches to such analyses due to the limitations of routine HIV clinic-level data. Adding spatial components as well as temporal aspects strengthen the estimates of HIV program outcomes.

HIV program investments

We have demonstrated that HIV program investments in Kenya have largely born fruits and match a geographically diverse HIV burden. However, precision planning may be even more impactful with geospatial analyses. Since micro facility level, planning is not ideal, as the PEPFAR program in Kenya transitions to the government of Kenya, sustained resource allocation will become increasingly important at microscale.

Stemming new HIV infections

The recent developments of laboratory and rapid assays to test for recent HIV infections provides an opportunity for integrated data sources that can inform rapid response when mapped. Recent infections are those that have occurred up to a period of one year after HIV infection has been acquired [89]. Triangulating recent infection data with viral load suppression rates will demonstrates the role of expanded ART coverage in mobile populations and give an impetus to expand viral load monitoring in an HIV test and treat environment. Hotspot analyses and mapping are useful techniques to facilitate epidemic control decisions.

Sustainable HIV programming

Routine HIV program clinic-level data can efficiently provide timely information at a small geographical scale to inform targeted action. These data when embedded in a case-based surveillance system will provide finer disaggregation of other risk factors to

guide interventions. Developing and using spatial maps from routing HIV clinic-level data can inform the provision of targeted and to-scale prevention and treatment services.

Practical applications in Kenya

The 90-90-90 context

According to the 2017 estimates for the HIV epidemic in Kenya, 88.7% of Kenyans living with HIV are virally suppressed hence meeting the UNAIDS target for the "third 90" (figure 10). The "first 90" is the poorest performing at 71.9%. Our findings demonstrate an approach that could help in meeting the first 90 through better targeting (Paper I and II). This approach is already being used in the HIV program planning for the country operational plan 2019 (personal communication). Once PLHIV are initiated on ARV treatment, regular monitoring of those in treatment is equally important. In Paper IV, we showed that improved viral load suppression results in reduced HIV positivity.
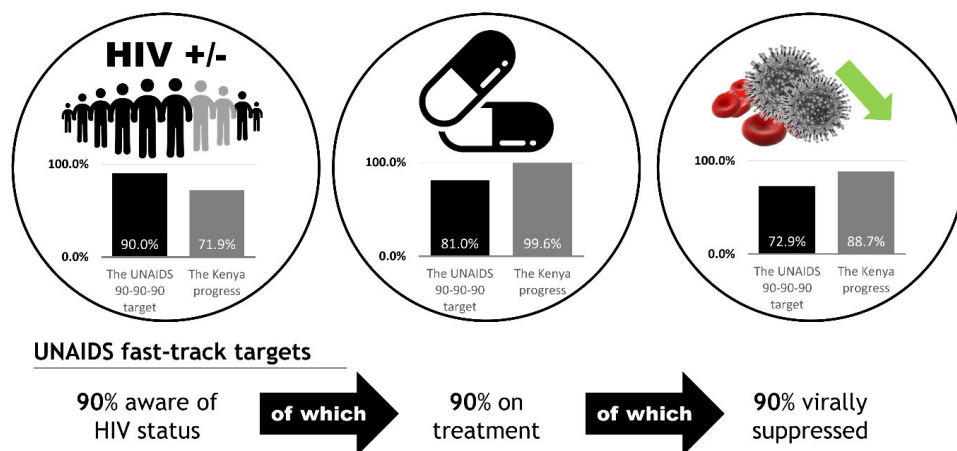
Source: Kenya HIV program data 2018

Figure 10: Kenya's progress towards UNAIDS 90-90-90 targets in 2017

Implications for resource allocation

The Kenya HIV program funding has levelled in the recent past (figure 11). This means that the HIV program in Kenya needs to be more efficient and take up domestic financing. With an aging population, thanks to lifelong ARV treatment, the prevalence

has stabilized to about 5% among adults aged 15 years and above. Furthermore, the country is facing an increasing burden of other non-communicable diseases. Our spatial and spatial temporal analyses presented in this thesis if interpreted in the context of HIV epidemic control and efficient resource allocation have potential. Example, analytics for the country operational plans have included mapping as a key component. Cluster identification was a key part of the country operational planning process in 2019.
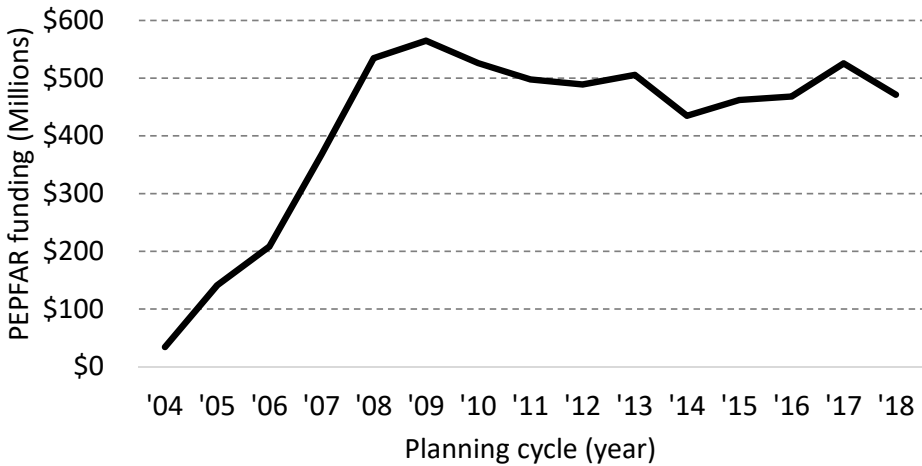
Source: Kenya HIV program budgeting data 2018

Figure 11: HIV investments in Kenya (2004 - 2018)

The current cost of HIV testing algorithms is $0.89 for Determine™ and $0.77 for First Response™ rapid test kits [90]. This could lead to an expenditure of about $10,680,000.00 per year spent on one type of test assay alone without taking into account personnel and logistics related costs. In an inefficient HTS program, most of the testing is not targeted to identify HIV infected persons. The harder work of finding the newly infected can be translated to cost savings through use of efficient methods that are geographically guided. For example, it is not necessary to equitably budget for high targets in locations that have lower yield regardless of number of HIV tests done. With accelerated case-finding and optimal linkage to treatment followed by increased rates of viral load suppression, the chain of HIV transmission can be broken. The economic benefit would be through efficient case identification instead of a wide, non-

specific case identification approach. By putting the newly diagnosed HIV infected persons on ARV treatment and enhancing viral load suppression, future cost savings can be achieved through averted new infections. In hotspot and cluster detection and hotspot-targeted approach for HIV, savings may be achieved by reducing the number of test kits needed to attain high number of HIV infected persons identified and linked to ARV treatment and other interventions. To make economic sense, the cost for program implementation should outweigh the costs of hotspot-detection. We propose a cluster detection process to improve efficiencies in HTS. There is still a gap of reaching the undiagnosed HIV infected persons. It is difficult to quantify the contribution of Geospatial analyses in identifying the remaining undiagnosed cases. However, geospatial analyses can contribute to better resource planning through focusing in identified high yielding clusters leading to better case detection. The impact of scaled up ARV treatment in Kenya can be best understood in the context of space and time. Our findings are applicable in monitoring the micro geographic areas that may need intensified efforts.

What is the value added from our analyses?

Cluster detection translated to efficient HIV testing

From cluster detection analyses (Paper II), we anticipate that the gap in diagnosis of newly infected persons can be closed faster if there is focus on clusters with statistically significant number of HIV-infected persons. Our analyses show that up to 57% or more HIV-infected persons are detected in clusters with high counts of infected persons. Identifying newly HIV infected persons is a critical gap in HIV epidemic control. From recent estimates, there has been a 32% decline in the number of new annual HIV infections from 2010 to 2017 [28]. We estimate that about 300,000 (1,500,000 PLHIV [28] minus 1,200,000 currently in HIV care – HIV program data) persons remain undiagnosed and initiated on treatment. If the Kenya program focusses on clusters with high numbers of HIV-infected persons yet to be diagnosed and put on treatment, the financial burden will be much less and efforts will be much more efficient in identifying these persons.

Spatial and spatial-temporal analyses

Spatial-temporal analyses add value through combination of the two aspects of time and space. We have presented HIV program impact in prevention of mother to child transmission of HIV (Paper III) and in reduced HIV positivity due to improved HIV treatment coverage (Paper IV). These analyses provide powerful advocacy tools to demonstrate impact over time but also point out geographic areas that still need focussed interventions.

Mixed methods to collaborate findings

Other than spatial analyses, in papers I, III and IV, we have additional methods to further help to explain spatial and spatial-temporal analyses results. We recommend use of mixed methods to provide robust evidence of HIV program impact.

7.0 FUTURE PERSPECTIVES

Geospatial data availability and use

There are more opportunities in geospatial analyses utilizing HIV program data and data from other diseases. Regardless of imperfections of such data, there are opportunities to consider ways to improve data quality and routinizing spatial analyses for program planning.

Program managers need skills in spatial epidemiology for improved HIV programming and resource allocation.

We recommend the following:

a. Data availability needs to be a priority of the Kenya Ministry of Health as well as for the donor agencies

b. There is need to build dynamic national and regional dashboards that incorporate geospatial analyses.

c. There is need to build spatial data analyses, interpretation and use capacity below the national level to allow for easy program planning.

d. The country has developed some individual data level repositories for the HIV program primarily for cohort analyses but with potential for HIV case-based surveillance. There is an opportunity to build in automated spatial analyses dashboards as extra modules.

e. Improving the master list of health facilities to have complete geocodes is critical for appropriate point-pattern analyses and mapping use cases.

f. People participation in mapping exercises for communicable disease detection and reporting additionally contributes to quality geospatial data.

HIV program planning considerations

It is clear from our findings that geospatial analyses are needed, now more than ever. Kenya has made good progress in the second and third "90". Future work lies in regular monitoring of HIV drug resistance. This arena could also benefit from geospatial analyses to identify pockets that may be experiencing higher community viral load and

or HIV drug resistance patterns. The next frontier in surveillance of HIV drug resistance patterns is inclusion of geospatial analyses and mapping techniques to trigger action for individual patient level monitoring of factors associated with HIV drug resistance. Monitoring of migration and movement of persons across borders as a geospatial analysis will help in aiding better estimates of persons in need of HIV services within a geographical confined and spatial planning unit.

Methodological perspectives

We have used mixed methods of analyses for all the papers. Currently, there are no convenient methods to combine spatial and spatial temporal models to include other interpretive post-analytics such as SEM and logistic regression. Expanding spatial and spatial temporal models to include other post-analytics currently carried out outside the spatial and spatial temporal models may add value. The scope of our thesis did not allow for exploration of how to integrate these analyses in one package.

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ERRATA

In the thesis version submitted on 11th April 2019, we noted a few errors and omissions that are listed below.

Acknowledgements

We have added three names erroneously omitted - Frank Basiye, Mary Mwangi, Maureen Kimani and Peter Juma.

The synopsis of the thesis

ART has been consistently defined as "*antiretroviral therapy*" only.

In the study setting section, we have corrected an erroneous reference to figure 10 to figure 9

Paper II

We have reorganized the order of co-authors as well as added one co-author erroneously omitted.

Paper IV

We have added Maureen Kimani as co-author erroneously omitted.

APPENDICES

Appendix I: Specifications for spatial-temporal models

Let Y_{it} denote the number of cases with outcome of interest in areal location i and time t out of N_{it} persons at risk, $i = 1, \dots, 12$ and $t = 1, \dots, 7$. We assumed that Y_{it} has a Poisson distribution with a risk of experiencing outcome of interest θ_{it}. That is, $Y_{it} \sim Poisson(E_{it} \exp(\theta_{it}))$, where E_{it} denotes the expected number of cases in areal location i and time t. We model the risk experiencing outcome of interest using Hierarchical spatial Poisson regression models that accounts for excess heterogeneity and similarity over space and time. A class models were fitted to the data to assess the effects of selected covariates on the outcome of interest. These were based on a variant of the Knorr-Held[1] formulation expressed as:

$$log(Y_{it}) = log(E_{it}) + \sum_{j=1}^{n_f} f^{(j)}(u_{ji}) + \sum_{k=1}^{n_\beta} \beta_k z_{ki} + v_i + v_i + \gamma_t + \phi_t$$

where $\{f^{(j)}(.)\}$'s are unknown functions of the covariates u, the $\{\beta_k\}$'s represent the linear effect of covariates z, v_i's are spatial unstructured components, which are independent and identically distributed with zero mean and unknown precision, τ_v; and v_i's is spatially structured component which is assumed to vary smoothly from region to region. To account for such smoothness v_i's are modelled as an intrinsic Gaussian Markov random field with unknown precision τ_s. In this formulation, ϕ_t represents temporally unstructured components which are independent and identically distributed with zero mean and unknown precision, τ_ϕ; and γ_t is the temporally structured effect, modelled dynamically using a random walk through the following structure:

$$\gamma_t | \boldsymbol{\gamma}_{t-1} \sim N(\gamma_{t+1}, \tau_\gamma) \text{ for } t = 1$$

$$\gamma_t | \boldsymbol{\gamma}_{t-1} \sim N\left(\frac{\gamma_{t-1} + \gamma_{t+1}}{2}, \frac{\tau_\gamma}{2}\right) \text{ for } t = 1$$

$$\gamma_t | \boldsymbol{\gamma}_{t-1} \sim N(\gamma_{t-1}, \tau_\gamma) \text{ for } t = 12 \ (Paper\ III) \ or \ t = 3 \ (Paper\ IV)$$

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[1] Knorr-Held, L., *Bayesian modelling of inseparable space-time variation in disease risk.* Statistics in medicine, 2000. **19**(17-18): p. 2555-2567

Estimation of parameters was carried out using the Integrated Nested Laplace approximation approach. The latent Gaussian field for the model was $\xi = \{f^{(j)}(.), \beta_k, \upsilon_i, \nu_i, \gamma_t, \phi_t\}$ with hyperparameter vector $\theta = \{\tau_\beta, \tau_\upsilon, \tau_\nu, \tau_\gamma, \tau_\phi, \}$. Vague independent Gamma priors are assigned to each of the elements in ϑ.

The model was also expanded to include an interaction between space and time as follows:

$$log(Y_{it}) = log(E_{it}) + \sum_{j=1}^{n_f} f^{(j)}(u_{ji}) + \sum_{k=1}^{n_\beta} \beta_k z_{ki} + \upsilon_i + \nu_i + \phi_t + \delta_{it},$$

Where $\delta_{it} \sim N(0, \tau_\delta)$.

Appendix II: Log-likelihood ratios, Kulldorff spatial-scan statistics

The likelihood-ratio test (LR statistical test) is used to compare the goodness of fit of two models. The Kulldorff spatial scan statistics utilize this approach to determine clusters.

We define a parameter space Θ and a null hypothesis H_0, with the parameter in a specified subset Θ_0 of Θ. The alternative hypothesis H_1, is thus that Θ is the complement of Θ_0. That is, in $\Theta \backslash \Theta_0$ denoted by Θ_0^c. Thus

H₀: cases occur purely at random within a defined geographical area, i.e.

$\theta \in \Theta_0$,

H₁: cases are clustered in a detectable pattern within a defined geographical area, i.e.

$\theta \in \Theta_0^c$.

The likelihood function is $\mathcal{L}(\theta|x) = f(x|\theta)$ (where f is the probability density function of a parameter θ, with x held fixed at the value observed (HIV diagnosed cases). The likelihood-ratio test is denoted by λ such that:

$$\lambda(x) = \frac{\sup\{\mathcal{L}(\theta|x) : \theta \in \Theta_0\}}{\sup\{\mathcal{L}(\theta|x) : \theta \in \Theta_0^c\}}$$

The likelihood-ratio test has a critical region of the form $\{x|\lambda \leq c\}$ where c is any number satisfying the condition $0 \leq c \leq 1$. The model was phrased as log-likelihood ratio that a specific geo-coded location (site) has more HIV-infected persons than expected. The numerator of this ratio is less than the denominator; so, the likelihood ratio is between 0 and 1. Low values of the likelihood ratio mean that the observed result was much less likely to occur under the null hypothesis as compared to the alternative. Hence, a cluster was considered statistically significant when its log likelihood ratio was greater than the critical value.

These tests were purely spatial and data were considered to be cross-sectional (non-temporal). We reported significant standard Monte Carlo p-values for all identified clusters after looping through a maximum of 999 iterations.

Appendix III: Moran's Index

Moran's Index (Moran's I) is a generalization of Pearson's correlation coefficient that measures the overall spatial autocorrelation of the data. The index has values ranging from -1 to +1; where -1 is perfect clustering of dissimilar values, 0 is no autocorrelation and +1 indicates perfect clustering of similar values.

Calculations for Moran's I are based on a weighted matrix, with units i and j. Similarities between units is calculated as the product of the differences between x_i and x_j with the overall mean.

The Moran's statistic is calculated as:

$$I = \frac{N}{W}\frac{\Sigma_i\Sigma_j w_{ij}(x_i - \bar{x})(x_j - \bar{x})}{\Sigma_i\Sigma_j(x_i - \bar{x})^2},$$

where N is the number of spatial units (sites, constituencies) indexed by i and j, x is the variable of interest (HIV positive cases); $\bar{x}$ is the mean of x; w_{ij} is a matrix of spatial weights with zeroes on the diagonal (i.e., $w_{ij} = 0$); and W is the sum of all w_{ij}.

The test allowed us to assess how similar or different HIV infected cases were spatially distributed in neighbouring constituencies instead of randomly distributed in the country (spatial autocorrelation).

Appendix IV: Cook's D$_i$

For our analyses, we used Cook's distance, (Cook's D$_i$) [91], to find influential outliers such that observations with a Cook's D$_i$ of more than 3 times the mean, μ, is a possible outlier and reported these using the Moran's scatter plot.

D$_i$ was defined according to Faraway [92]. The change in the linear fit $X^T(\hat{\beta} - \hat{\beta}_{(i)}) = (\hat{y} - \hat{y}_{(i)})$, where (i) indicates the fit without a case.

For each case, the value is reduced to:

$$D_i = \frac{(\hat{y} - \hat{y}_{(i)})^T(\hat{y} - \hat{y}_{(i)})}{p\hat{\sigma}^2},$$

$$= \frac{1}{p}r_i^2\frac{h_i}{1 - h_i}.$$

Thus, the residual term is r_i^2 compared to the second term. Combining the two leads to detection of influence. A plot of D$_i$ can be used to identify influential observations. For the Moran scatter plot, the x-axis contains the observations of interest (in our case the HIV positive cases) and the y-axis the spatially lagged values. The scatter plot is divided into 4 partitions (figure 12). Statistically influential values in each of the partitions are marked and observations outputted for further investigation and description.
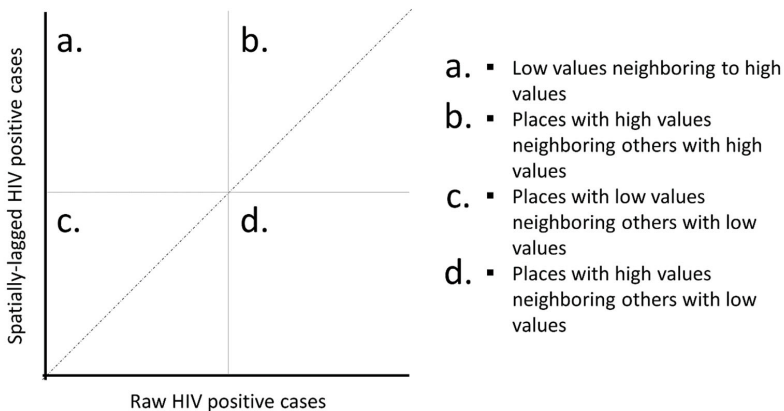
Figure 12: Four partitions and relationships between raw and spatially lagged values

ORIGINAL ARTICLES

Mapping HIV in Kenya: Geospatial variability of HIV diagnoses, treatment, and impact

Implications for epidemic control

Spatial–temporal trend for mother-to-child transmission of HIV up to infancy and during pre-Option B+ in western Kenya, 2007–13

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ABSTRACT

Introduction: Using spatial–temporal analyses to understand coverage and trends in elimination of mother-to-child transmission of HIV (e-MTCT) efforts may be helpful in ensuring timely services are delivered to the right place. We present spatial–temporal analysis of seven years of HIV early infant diagnosis (EID) data collected from 12 districts in western Kenya from January 2007 to November 2013, during pre-Option B+ use.

Methods: We included in the analysis infants up to one year old. We performed trend analysis using extended Cochran–Mantel–Haenszel stratified test and logistic regression models to examine trends and associations of infant HIV status at first diagnosis with: early diagnosis (<8 weeks after birth), age at specimen collection, infant ever having breastfed, use of single dose nevirapine, and maternal antiretroviral therapy status. We examined these covariates and fitted spatial and spatial–temporal semiparametric Poisson regression models to explain HIV-infection rates using R-integrated nested Laplace approximation package. We calculated new infections per 100,000 live births and used Quantum GIS to map fitted MTCT estimates for each district in Nyanza region.

Results: Median age was two months, interquartile range 1.5–5.8 months. Unadjusted pooled positive rate was 11.8% in the seven-years period and declined from 19.7% in 2007 to 7.0% in 2013, $p < 0.01$. Uptake of testing ≤8 weeks after birth was under 50% in 2007 and increased to 64.1% by 2013, $p < 0.01$. By 2013, the overall standardized MTCT rate was 447 infections per 100,000 live births. Based on Bayesian deviance information criterion comparisons, the spatial–temporal model with maternal and infant covariates was best in explaining geographical variation in MTCT.

Discussion: Improved EID uptake and reduced MTCT rates are indicators of progress towards e-MTCT. Cojoined analysis of time and covariates in a spatial

context provides a robust approach for explaining differences in programmatic impact over time.

Conclusion: During this pre-Option B+ period, the prevention of mother to child transmission program in this region has not achieved e-MTCT target of ≤50 infections per 100,000 live births. Geographical disparities in program achievements may signify gaps in spatial distribution of e-MTCT efforts and could indicate areas needing further resources and interventions.

INTRODUCTION

An estimated 2.6 million children were living with HIV in 2014, making mother to child transmission of HIV (MTCT) an important contributor to the overall global burden of HIV (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015b*). Between 2000 and 2014, new pediatric infections declined by up to 50% amidst some geographical variations (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2016b*). Worldwide, 220,000 children became newly infected with HIV in 2014, the vast majority (190,000) of whom were living in sub-Saharan Africa (SSA) (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015a*). Kenya was estimated to have 101,000 children living within HIV in 2012 (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2012*), with 13,000 new infections annually (*National AIDS and STI Control Programme (NASCOP), 2014*), and has the fifth highest HIV-incidence among children in SSA (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014a*). Effective implementation of prevention of mother to child transmission of HIV (PMTCT) programs are therefore critical to reduced HIV transmission and elimination of mother-to-child transmission of HIV (e-MTCT).

Great strides have been made in e-MTCT, for example, new HIV infections have been reduced by nearly half among children in the 21 priority countries with the highest HIV-burden in SSA (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015c*). This has been realized by implementing the United Nations four-pronged strategy for PMTCT: preventing new HIV infections among women of childbearing age; preventing unintended pregnancies among women living with HIV; preventing HIV transmission from a woman living with HIV to her baby; and providing appropriate treatment, care and support to mothers living with HIV, their children and families (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015b*). The same four-pronged strategy is adopted in the Kenya PMTCT guidelines (*National AIDS and STI Control Programme (NASCOP), 2012*). In Kenya, the burden of HIV among pregnant women is high. In 2013 alone, Kenya was ranked sixth among 21 countries in terms of HIV-positive women delivering in health facilities with an estimated 79,000 HIV-positive women giving birth (or pregnant) (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015d*). More recent estimate indicates that 79,500 (95% CI [70,100–91,200]) women are in need of PMTCT and overall MTCT rate as 8.3% (*National AIDS and STI Control Programme Ministry of Health,*

National AIDS Control Council (NACC), 2015). It is therefore critical to prevent HIV transmission from women to infants and children.

In the period 2010–2016, Kenya has been ranked 10th in Eastern and southern Africa in progress towards reduction of HIV incidence among 0–14 year olds (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2017*). Between 2010 and 2015, final MTCT rate reduced by half from 17% in 2010 to 8% in *National AIDS and STI Control Programme Ministry of Health, National AIDS Control Council (NACC) (2015)*. The UNAIDS 2016–2021 second e-MTCT strategy outlines the objectives to work towards zero new HIV infections among children, and improved mother survival by 2020 (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015e*). The impact target for e-MTCT has been set as ≤50 new pediatric HIV infections per 100,000 live births and a transmission rate of <5% in breastfeeding populations and <2% in nonbreastfeeding populations (*World Health Organization, 2014*). However, this transmission rate should be calculated as "final" infection status in breastfeeding populations. Measuring MTCT rates is therefore an essential indicator of PMTCT program success.

The UNAIDS fast-track 90–90–90 strategy (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2014b*) requires a location–population approach so as to refocus efforts in containing the HIV epidemic (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2015a*), hence the emphasis on "where," to identify pockets needing focused interventions. Program data are often reported at country-level and rarely in more refined subnational geographical areas. Ignoring the influence of interactions across neighboring subnational units such as districts and excluding temporal variables and covariates in analyses may not sufficiently explain access and coverage. Taking these considerations into account is important to improve assessment of gains towards e-MTCT through measuring MTCT and early infant diagnosis (EID) coverage over space, time and at a more granular level.

In Kenya, the EID program has expanded since initiation in 2004 and has been accompanied by accreditation of seven laboratories nationally with capacity to conduct polymerase chain reaction (PCR) testing of HIV. The expansion of EID was also commensurate with the recommendation for use of lifelong ART (Option B+) for all pregnant and breastfeeding women in Kenya (*National AIDS and STI Control Programme (NASCOP), 2012*), which fully came into effect in 2014. Although dried-blood-spot (DBS) PCR testing was available since 2005, there are minimal data available about the program scale-up, and the characteristics of children tested and identified as HIV-infected prior to 2007. The national EID database is useful for decision making at the national level but documenting regional variations has not been feasible with limited availability of programmatic, spatial, and spatial–temporal data. Various tools have been developed and applied in spatial–temporal analysis of diseases (*Rushton, 2003*; *Auchincloss et al., 2012*). In this analysis, we have used spatial–temporal analysis methods to present seven years of EID data collected from pre-Option B+ period of January 2007–November 2013 and to demonstrate usefulness of spatial–temporal trend analysis in identifying areas that may need further programmatic efforts.

METHODS

Study area

Nyanza region in western Kenya is approximately 2,549 km^2 with a population density of 440/km^2 (*Kenya National Bureau of Statistics (KNBS), 2010b*), and the highest adult HIV prevalence in Kenya (*National AIDS and STI Control Programme (NASCOP), 2014*). In 2004, when the President's Emergency Plan for AIDS Relief started in Kenya, and prior to 2007, the region was divided into 12 districts to facilitate geographical PMTCT programmatic planning. The 12 districts were: Bondo, Kisii, Gucha, Homa Bay, Kisumu, Kuria, Migori, Nyamira, Nyando, Rachuonyo, Siaya, and Suba. We have aggregated data at district level from 924 facilities from where EID samples were collected. These data represented nearly 90% (924/1,072) of the health facilities implementing the PMTCT program in Nyanza region by 2013.

Population and live births estimates

Parents or guardians of infants known or suspected of being perinatally HIV-exposed infants were asked for consent to diagnostic virologic testing of their children as part of routine HIV care. The population of infants and children tested included those whose mothers were diagnosed with HIV infection before or during pregnancy, at delivery, and up to the time the mothers brought their children for the first HIV test (usually at six weeks for first routine vaccinations). We estimated the number of live births based on the 2009 census (*Kenya National Bureau of Statistics (KNBS), 2010a*), using an estimated annual growth rate of 4.1%, 2012–2030 (*United Nations Children's Fund (UNICEF), 2016*), which gives a crude birth rate of 41 births per 1,000 population. We used this projection to validate the number of women tested as proxy for pregnant women presenting in the clinics in 2013 as basis for the calculation of standardized MTCT rates per 100,000 live births.

EID pilot program procedures in Nyanza

Use of the EID patient data collection tool was first implemented in health facilities requesting the Kenya Medical Research Institute (KEMRI) Kisumu laboratory to perform EID testing in 2006. As part of routine service delivery, this form was completed by clinicians at facilities requesting DBS PCR HIV testing and accompanied each specimen to the laboratory. Subsequently, the national EID form was developed by the National AIDS and STI Control Program and these forms were used by clinicians and accompanied specimens for HIV testing. EID results were added to the form once laboratory testing was completed. One copy of the form was sent back to the health facility for patient management and the second copy scanned into an electronic, password-protected database. The data presented in this analysis are for infants undergoing first EID PCR test.

Laboratory procedures

Between January 2007 and November 2013, blood samples were collected from infants presenting at health facilities in Nyanza region as part of a study: "Evaluation of HIV EID testing in Kenya," and transported to the Kisumu HIV laboratory for HIV diagnosis.

Testing was done using PCR on either COBAS Ampliprep/COBAS TaqMan HIV-1 assay (TaqMan; Roche Diagnostics, Mannheim, Germany) or Abbot (Abbott RT; Abbott Diagnostics, Wiesbaden, Germany) platforms. These results were returned to the submitting facility for clinical action and notification of the parent/guardian.

Measures

Mother to child transmission rates

The transmission rates calculated reflect MTCT up to infancy since we used the first PCR testing and included infants who were up to 12 months old at HIV diagnosis. To calculate MTCT rate, the main outcome variable, the number of infants with PCR-positive HIV-test results was taken as the numerator and divided by the total number of HEI tested during the study period to determine rates applicable within the geographic regions. Adjusted rates were further calculated using R version 3.2.3 (*R Core Team, 2015*) implemented in RStudio version 0.99.903 (*RStudio, 2016*). Standardized MTCT rates per 100,000 live births were calculated as: (absolute transmission (number infected)/ women tested for HIV in 2013) × 100,000.

Covariates selection

The following infant and maternal factors were included in the spatial–temporal model as covariates: early diagnosis (<8 weeks after birth), age of the child at specimen collection, infant ever having breastfed, use of single dose nevirapine (sdNVP), and maternal antiretroviral treatment (ART) status. In the descriptive outputs and logistic models, maternal regimen was categorized as: (a) sdNVP, (b) ART for prophylaxis = AZT that started at 14 weeks, intrapartum sdNVP and first dose of AZT+3TC and during postpartum period, daily AZT+3TC for seven days. This is also referred to as *short course* when ARVs starting at 14 weeks gestation and continued through the intrapartum and childbirth if not breast feeding or until one week after cessation of all breastfeeding, and (c) ART for treatment = Triple ARVs for women who had CD4 cell counts of ≤350 cells/mm^3 starting as soon as diagnosed and continued for life (*National AIDS and STI Control Programme (NASCOP), 2012*; *World Health Organization (WHO), 2012*). This was the precursor of Option B+ which did not start in Kenya until June 2014.

Analytical approaches

Statistical analyses

To explore associations of maternal and infant related factors to HIV acquisition, we conducted bivariate and multivariable logistic regression analyses using Stata 14.2 (Stata Corporation, College Station, TX, USA). Variables that were significant in the bivariate model were included in the multivariable model. Extended Cochran–Mantel–Haenszel test of trend for proportions was used to assess trend for both outcome and explanatory variables. These analyses informed variables to include in the spatial and spatial–temporal analyses.

Spatial and spatial–temporal model fitting in R-INLA

We performed spatial and spatial–temporal analyses in R version 3.2.3 (*R Core Team, 2015*) implemented in RStudio© version 0.99.903 (*RStudio, 2016*) using integrated nested

Laplace approximation (R-INLA) package (*Blangiardo et al., 2013*), to explore covariates to explain observed spatial–temporal trends using semiparametric Poisson regression.

We fitted five Poisson regression models as follows:

(1) To assess general associations of covariates with the outcome variable, we fitted a nonspatial generalized linear model.

To assess spatial relationships, we fitted semiparametric Poisson regression models as follows:

(2) a spatial model without covariates,
(3) a spatial–temporal model without covariates,
(4) a spatial–nontemporal model with covariates,
(5) and finally, a spatial–temporal model with covariates according to Blangiardo, Cameletti, and Rue (*Blangiardo et al., 2013*). This final model allows for an interaction of space, time, and covariates, which would explain differences in the time trend of MTCT rates for districts in Nyanza region.

For each of these spatial models (2–5), we used Bayesian deviance information criterion (DIC) according to *Spiegelhalter et al. (2002)* and *Spiegelhalter, Best & Carlin (1998)* to evaluate the strength of the fits combined with examination of posteriors generated through plotting. Bayesian analytic approach is conditional on the appropriateness of an assumed probability model. Hence, DIC is a useful tool to satisfy that our assumptions are reasonable approximation to reality. For the best fitting model, we conducted sensitivity analyses to assess the robustness of the priors (assumed probability distribution) selected. Full derived models are presented in Appendix 1.

Mapping

Each of the samples had at a minimum locator information which contained the name of the facility and district. Using spatial join technique, both the outcome and covariates data were aggregated at district (currently called subcounty) level to provide rates for spatial, and spatial–temporal analysis and mapping. For the final maps, we selected the best fitting model and extracted fitted estimates from R-INLA and mapped these rates as shaded choropleth maps to show the 12 districts by year of HIV-diagnosis (with color intensity depicting higher rates) using Quantum GIS version 2.14.1 (*QGIS Development Team, 2016*).

Ethical clearance and informed consent

Ethical approval for the study was obtained from the KEMRI and the United States Centers for Disease Control and Prevention. Further consent was not necessary since these data were routinely collected deidentified data from routine clinic services.

RESULTS

Trends in programmatic uptake and MTCT rates

These results represent data from 95,215 infants and equally distributed by sex. These were ~93.2% of all infants and children at HIV diagnosis (Fig. 1).
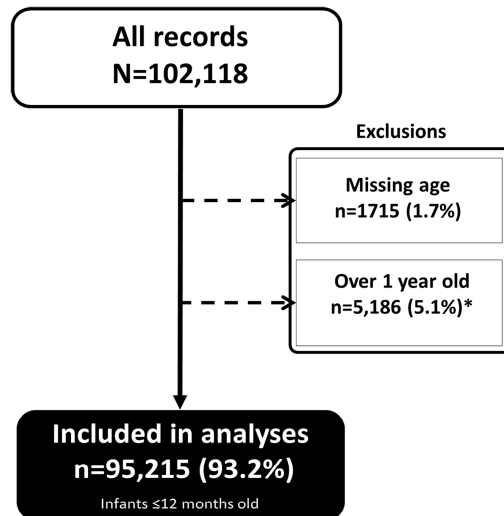
Figure 1 Infants included in the analyses. A total of 95,215 infants ~93.2% of all infants and children at HIV diagnosis were included in the analyses. Full-size ☑ DOI: 10.7717/peerj.4427/fig-1

Most of the infants were tested in 2011 and 2012. Median age at HIV testing was two months, interquartile range 1.5–5.8 months (Table 1). About three quarters (75.1%) of the infants were under six months old at the point of testing and the majority (60.0%) were tested at the maternity/postnatal ward. Median age at HIV testing decreased from approximately three months in 2007–2009 to under two months by 2013, $p < 0.01$.

The proportion of infants tested at maternity or postnatal ward increased from 44.9% to 74.1% by year 2013, $p < 0.01$. The proportion of infants reported to have been breastfed increased over the years from 65.3% in 2007 to 88.0% in 2012, $p < 0.01$. The proportion of mothers receiving ART for treatment (during pregnancy or breastfeeding period) increased from 52.8% in 2007 to 100% in 2013, $p < 0.001$; the proportion of mothers alive at the time of infant testing over the same period increased from 85.7% in 2007 to 98.9% by 2013, $p < 0.001$. Use of ART for treatment increased over the seven-year period from to 61.1% by 2013, $p < 0.001$. Overall, early testing (at <8 weeks after birth) was 55.5% and increased from 44.8% in 2007 to 64.1% in 2013, $p < 0.01$ (Fig. 2).

The unadjusted HIV-infection rates decreased from 17.0% in 2007 to 7.2% in 2013, $p < 0.01$.

Association of infants and maternal factors with HIV infection

In multivariable analysis; infants tested in 2009–2012 compared to those tested in 2013, late diagnosis (beyond eight weeks after birth), and use of sdNVP, ART for prophylaxis compared to ART for treatment were associated with MTCT (Table 2).

Table 1 Characteristics of infants and mothers for HEI tested for HIV and trends in Western Kenya, 2007–2013.

Characteristics	Total	2007	2008	2009	2010	2011	2012	2013	p-Value
Total tested each year	95,215	5,090	6,628	10,437	13,236	21,981	20,714	17,129	–
Sex									0.249
Male	47,733 (50.1%)	2,507 (49.3%)	3,293 (49.7%)	5,138 (49.2%)	6,696 (50.6%)	11,201 (51%)	10,328 (49.9%)	8,570 (50%)	
Female	47,482 (49.9%)	2,583 (50.7%)	3,335 (50.3%)	5,299 (50.8%)	6,540 (49.4%)	10,780 (49%)	10,386 (50.1%)	8,559 (50%)	
Age (median, IQR)	2.0 (1.5, 5.8)	2.8 (1.8, 6.0)	3.0 (1.5, 6.0)	3.0 (1.5, 6.0)	2.0 (1.5, 6.0)	2.0 (1.5, 5.0)	1.8 (1.5, 4.0)	1.8 (1.5, 4.0)	<0.001
Age (months)									<0.001
Under six months	71,486 (75.1%)	3,677 (72.2%)	4,626 (69.8%)	6,946 (66.6%)	9,458 (71.5%)	16,800 (76.4%)	16,334 (78.9%)	13,645 (79.7%)	
6–12 months	23,729 (24.9%)	1,413 (27.8%)	2,002 (30.2%)	3,491 (33.4%)	3,778 (28.5%)	5,181 (23.6%)	4,380 (21.1%)	3,484 (20.3%)	
Entry point[*]									<0.001
OPD	1,089 (1.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	278 (1.3%)	454 (2.2%)	357 (2.1%)	
Pediatric ward	239 (0.3%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	98 (0.4%)	89 (0.4%)	52 (0.3%)	
Maternity	57,171 (60.0%)	2,285 (44.9%)	2,997 (45.2%)	5,269 (50.5%)	7,034 (53.1%)	12,727 (57.9%)	14,174 (68.4%)	12,685 (74.1%)	
HBTC	363 (0.4%)	1 (0%)	3 (0%)	15 (0.1%)	35 (0.3%)	264 (1.2%)	24 (0.1%)	21 (0.1%)	
DTC/PITC	841 (0.9%)	369 (7.2%)	265 (4%)	181 (1.7%)	19 (0.1%)	2 (0%)	4 (0%)	1 (0%)	
VCT (Site/Mobile)	123 (0.1%)	31 (0.6%)	63 (1%)	18 (0.2%)	6 (0%)	0 (0%)	3 (0%)	2 (0%)	
Other	3,975 (4.2%)	792 (15.6%)	732 (11%)	364 (3.5%)	689 (5.2%)	890 (4%)	284 (1.4%)	224 (1.3%)	
Unknown	6,331 (6.6%)	154 (3%)	330 (5%)	752 (7.2%)	1,078 (8.1%)	2,037 (9.3%)	1,265 (6.1%)	715 (4.2%)	
Infant breastfed									<0.001
Yes	75,643 (79.4%)	3,324 (65.3%)	4,568 (68.9%)	7,271 (69.7%)	9,952 (75.2%)	17,678 (80.4%)	17,785 (85.9%)	15,065 (88%)	
No	2,126 (2.2%)	973 (19.1%)	985 (14.9%)	140 (1.3%)	8 (0.1%)	19 (0.1%)	1 (0%)	0 (0%)	
Unknown	3,600 (3.8%)	729 (14.3%)	614 (9.3%)	631 (6%)	432 (3.3%)	732 (3.3%)	278 (1.3%)	184 (1.1%)	
Did mother receive ARV?									<0.001
Yes	45,865 (92.8%)	1,598 (52.8%)	3,128 (64.4%)	4,314 (94.6%)	5,362 (99.5%)	9,999 (99%)	11,084 (100%)	10,380 (100%)	
No	3,182 (6.4%)	1,279 (42.2%)	1,568 (32.3%)	222 (4.9%)	23 (0.4%)	90 (0.9%)	0 (0%)	0 (0%)	
Unknown	352 (0.7%)	152 (5%)	162 (3.3%)	26 (0.6%)	5 (0.1%)	7 (0.1%)	0 (0%)	0 (0%)	
Mother alive/dead[†]									<0.001
Alive	91,610 (96.2%)	4,361 (85.7%)	6,014 (90.7%)	9,806 (94%)	12,800 (96.7%)	21,248 (96.7%)	20,436 (98.7%)	16,945 (98.9%)	
Dead	5 (0%)	0 (0%)	0 (0%)	0 (0%)	4 (0%)	1 (0%)	0 (0%)	0 (0%)	
Unknown	3,600 (3.8%)	729 (14.3%)	614 (9.3%)	631 (6%)	432 (3.3%)	732 (3.3%)	278 (1.3%)	184 (1.1%)	

Table 1 (continued).

Characteristics	Total	2007	2008	2009	2010	2011	2012	2013	p-Value
Maternal regimen[‡]									<0.001
sdNVP only	2,763 (6.7%)	0 (0%)	101 (16.7%)	498 (12.5%)	471 (8.8%)	680 (6.8%)	583 (5.3%)	430 (4.1%)	
ART for prophylaxis	16,185 (39.2%)	2 (66.7%)	191 (31.6%)	1,505 (37.8%)	1,611 (30.1%)	3,912 (39.4%)	4,558 (41.1%)	4,406 (42.5%)	
ART for treatment	22,389 (54.1%)	1 (33.3%)	313 (51.7%)	1,974 (49.7%)	3,272 (61.1%)	5,344 (53.8%)	5,941 (53.6%)	5,544 (53.4%)	
Testing facility									<0.001
Community/VCT	388 (0.4%)	0 (0%)	0 (0%)	12 (0.1%)	40 (0.3%)	291 (1.3%)	33 (0.2%)	12 (0.1%)	
Dispensaries/HC/Clinics/NH	53,390 (56.1%)	1,792 (35.2%)	2,523 (38.1%)	4,354 (41.7%)	6,849 (51.7%)	13,006 (59.2%)	13,474 (65%)	11,392 (66.5%)	
Subdistrict hospitals	9,255 (9.7%)	385 (7.6%)	704 (10.6%)	1,368 (13.1%)	1,372 (10.4%)	2,155 (9.8%)	1,831 (8.8%)	1,440 (8.4%)	
District hospitals	21,267 (22.3%)	1,939 (38.1%)	2,207 (33.3%)	3,188 (30.5%)	3,305 (25%)	4,503 (20.5%)	3,500 (16.9%)	2,625 (15.3%)	
Level 5 hospitals	5,313 (5.6%)	714 (14%)	697 (10.5%)	597 (5.7%)	804 (6.1%)	900 (4.1%)	826 (4%)	775 (4.5%)	
FBO	5,602 (5.9%)	260 (5.1%)	497 (7.5%)	918 (8.8%)	866 (6.5%)	1,126 (5.1%)	1,050 (5.1%)	885 (5.2%)	

Notes:
[*] Definitions: OPD, outpatient department; HBTC, home based testing and counseling; VCT, voluntary counseling and testing; SdNVP, single dose Nevirapine; ART, antiretroviral therapy; AZT, Zidovudine; 3TC, Lamivudine; HC, health center; NH, nursing home; FBO, faith-based organization.
[†] At time of sample collection.
[‡] ART for prophylaxis.
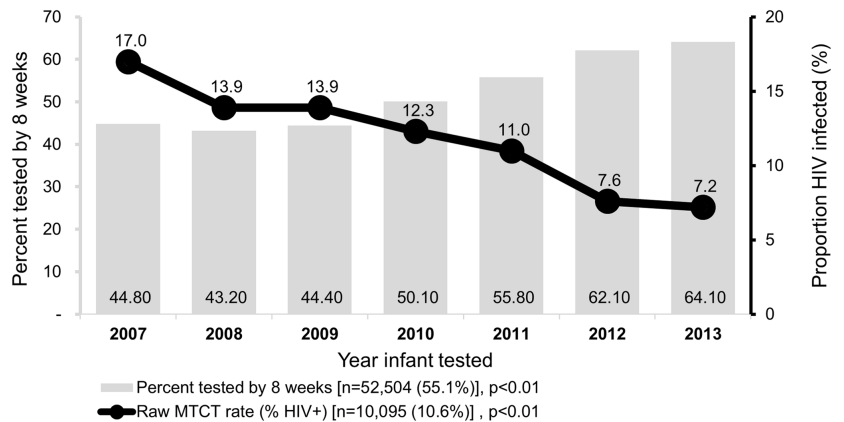
Spatial and spatial–temporal models

The spatial–temporal model that included time element (year of HIV diagnosis), spatial layer with contiguous districts and covariates produced the lowest DIC (305) compared to a spatial model without covariates (DIC 1319), a generalized linear model that had only the outcome with covariates (DIC 1153), spatial–nontemporal model with covariates (DIC 325), and spatial–temporal model (DIC 306) (Table 3).

Figure 3 contains choropleth maps for fitted MTCT rates for the seven-year period. Darker shades indicate higher HIV-infection rates. Infection rates gradually decreased from 2007 and by 2013, only two districts (Siaya and Suba) had rates higher than 8.0%.

Comparison of raw and fitted MTCT rates

Spatial–temporal and covariate-adjusted MTCT rates showed a gradual reduction from 19.8% in 2007 to 7.2% in 2013 compared to nonadjusted rates which reduced from 19.7% in 2007 to 7.0% in the seven-year period (Table 4). The overall reduction in MTCT rates over time was by 63.6%. However, this average trend compares at aggregate level but not over space and time. Both unadjusted and adjusted revealed that the reduction was more evident in some districts than others. We demonstrated similar reduction in standardized MTCT rates by using the number of infected infants for each district out of estimated live births (Table 5).

Standardized HIV MTCT rates per 100,000 live births

By 2013, the program had achieved an estimated 447 HIV standardized MTCT rates per 100,000 live births (Table 5). Nyamira, Gucha, and Kisii districts had the lowest HIV MTCT rates in 2013 while the highest MTCT rates were in Suba, Bondo, and Rachuonyo districts.

Table 2 Factors associated with mother to child transmission of HIV (MTCT) among infants in western Kenya, 2007–2013.

Characteristic	Total (*n*)	Positive, *n* (%)	Unadjusted		Adjusted	
			OR*	[95% CI]	aOR†	[95% CI]
Total	95,215	10,095				
Year						
2007	5,090	867 (17%)	2.7	(2.4, 2.9)	(Omitted)	(Omitted)
2008	6,628	923 (13.9%)	2.1	(1.9, 2.3)	1.8	(1.3, 2.4)
2009	10,437	1,454 (13.9%)	2.1	(1.9, 2.3)	1.5	(1.3, 1.8)
2010	13,236	1,632 (12.3%)	1.8	(1.7, 2.0)	1.6	(1.4, 1.8)
2011	21,981	2,414 (11%)	1.6	(1.5, 1.7)	1.4	(1.3, 1.6)
2012	20,714	1,574 (7.6%)	1.1	(1.0, 1.2)	1.0	(0.9, 1.1)
2013	17,129	1,231 (7.2%)	ref.‡		ref.	
Sex						
Male	47,733	4,811 (10.1%)	ref.		ref.	
Female	47,482	5,284 (11.1%)	1.1	(1.1, 1.2)	1.2	(1.1, 1.3)
Age (months)					¶	
Under six months	71,486	5,964 (8.3%)	ref.			
6–12 months	23,729	4,131 (17.4%)	2.3	(2.2, 2.4)		
Age at diagnosis						
Under/= eight weeks	52,504	3,307 (6.3%)	ref.		ref.	
Over eight weeks	42,711	6,788 (15.9%)	2.8	(2.7, 3.0)	2.5	(2.3, 2.7)
Maternal regimen						
sdNVP only	2,763	279 (10.1%)	2.0	(1.8, 2.3)	1.7	(1.5, 2)
ART for prophylaxis	11,634	1,199 (7.4%)	1.5	(1.3, 1.6)	1.5	(1.3, 1.6)
ART for treatment	4,551	1,171 (5.2%)	ref.		ref.	
Infant breastfed					¶	
Yes	75,643	7,703 (10.2%)	ref.			
No	2,126	327 (15.4%)	1.6	(1.4, 1.8)		
Unknown	17,446	2,065 (11.8%)	n.i§			
Mother received ARV					¶	
Yes	45,865	3,225 (7%)	ref.			
No	3,182	632 (19.9%)	3.3	(3.0, 3.6)		
Unknown	352	72 (20.5%)	n.i§			

Notes:
* OR, odds ratio.
† aOR, adjusted odds ratio.
‡ ref., referent category.
§ n.i, category not included in the analysis.
¶ Variable not included in the multivariable model due to collinearity.

DISCUSSION

We identified geographical variations and a significant decline in MTCT rates in the seven-year period. The fastest progress occurred in more recent years from 2011 to 2013. We estimated a reduction by 51.0% in overall fitted MTCT rates between the years 2009 and 2013. This reduced transmission at the later period for our analysis is comparable to

Table 3 Model comparison using deviance information criterion (DIC) to identify best fitting model.

Model type	DIC	Effective parameters	Model choice
Model 1—A generalized linear model (nonspatial)	1,153	4.0	Fourth
Model 2—Spatial model without covariates	1,319	11.8	Fifth
Model 3—Spatial–temporal model without covariates	306	59.7	Second
Model 4—Spatial–nontemporal model with covariates	325	62.3	Third
Model 5—Spatial–temporal model with covariates	305	58.8	First*

Note:
* Best fitting model with lowest DIC (>10) from the next model of a different nature (model 4).

55% reported in Kenya over the period 2009–2015 (*Joint United Nations Programme on HIV/AIDS (UNAIDS), 2016a*). While the overall MTCT rate up to infancy for the Nyanza region was ~7% in 2013, our results show great progress towards e-MTCT. PMTCT through widespread use of ART can reduce the rate of vertical transmission to <5% in breastfeeding populations (*World Health Organization (WHO), 2010*). Our study showed increased use of ART for life which is one of the factors that could have led to reduced MTCT. However, using percentage rates may not appropriately measure the progress since it does not take into account the underlying population. We additionally used standardized MTCT rates per 100,000 live births. Out of 12 districts, none had attained e-MTCT impact target of ≤50 pediatric infections per 100,000 live births. By 2013, of the 12 districts, only Kuria, Kisumu, and Migori were close to attaining e-MTCT goal of <5% MTCT rate. Standardized MTCT rate was still high at 447 per 100,000 live births and above the target of 50 new infections per 100,000 live births. This rate is moderate and comparable to estimated 384 infants per 100,000 live births in South Africa (*Goga et al., 2016*). The differences at district level for fitted MTCT rates and standardized MTCT rates per 100,000 live births may due to the differences with which the methods are applied with the latter taking into account estimated live births.

Our challenge then is to understand the drivers of these varied results despite uniform policy and little variation in resource availability. In understanding disparities in PMTCT progress, ecological studies such as ours have previously been proposed (*Hampanda, 2013*). In our setting, for example, one such study has identified social barriers which may slow progress towards e-MTCT. These include individual level factors such as mothers' competing priorities including work affecting service utilization and medication adherence; family-related factors such as lack of support by male spouses and partners; community-related such as fear and stigma; and institutional factors such as negative attitudes by health workers (*Onono et al., 2015*), and accessibility of facilities due to distance (*Gourlay et al., 2013*). These issues have been identified and described in other low-income settings (*Turan & Nyblade, 2013*). Challenges in implementation of Option B+ in western Kenya have been described despite successful implementation. These have to do with health system readiness, e.g., same-day initiation into treatment, staffing, training, and resource constraints; service-centered challenges such as scolding of nonadherent patients and inconvenient operation hours (*Helova et al., 2017*).
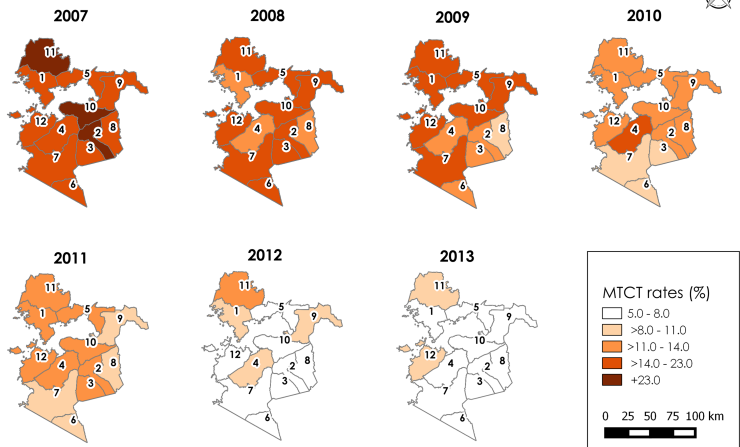
Figure 3 Study location and spatial–temporal trend of fitted MTCT rates in Western Kenya, 2007–2013.
(A) Figure shows the study location in relation to the rest of Kenya. (B) Shows spatial–temporal trend of fitted MTCT rates. Full-size ⊡ DOI: 10.7717/peerj.4427/fig-3

Table 4 Comparison of raw and fitted MTCT by district and year among infants in western Kenya, 2007 and 2013.

District	Raw MTCT rates (%)				Adjusted MTCT rates (%)			
	2007	2013	Reduction	Rank[*]	2007	2013	Reduction	Rank[*]
Total	19.7	7.0	64.3%	–	19.7	7.2	63.6%	–
Bondo	21.3	6.7	68.5%	4	17.6	7.8	55.8%	10
Kisii	17.9	6.6	63.1%	7	23.5	6.3	73.2%	3
Gucha	17.6	6.8	61.4%	8	17.1	7.2	57.6%	8
Homa bay	18.0	8.3	53.9%	11	20.6	7.9	61.7%	6
Kisumu	19.1	6.8	64.4%	6	21.4	5.5	74.3%	1
Kuria	33.3	7.4	77.8%	1	15.1	5.4	64.4%	5
Migori	17.6	7.4	58.0%	9	22.1	5.8	73.6%	2
Nyamira	18.5	4.9	73.5%	2	17.3	7.1	58.9%	7
Nyando	22.6	7.9	65.0%	5	16.2	7.4	54.6%	11
Rachuonyo	19.7	8.3	57.9%	10	23.2	6.7	71.2%	4
Siaya	10.1	7.2	28.7%	12	23.7	10.9	54.1%	12
Suba	20.2	6.0	70.3%	3	19.2	8.3	57.0%	9

Note:
[*] Rank = highest to lowest MTCT reduction rates (2013 minus 2007 rate).

Table 5 Absolute transmissions and transmission rates per 100,000 live births by district among infants in western Kenya, 2013.

District	Estimated live births in 2013[*]	Women tested for HIV in 2013[†]	HIV+ women in 2013	Infants tested in 2013	Absolute transmission (number infected)	Transmission rates per 100,000 live births[‡]	Rank[§]
All	275,169	203,069	15,136	17,129	1,231	447	–
Bondo	13,262	9,925	1,372	1,739	116	875	11
Kisii	36,841	25,143	622	701	46	125	3
Gucha	17,231	17,316	375	293	20	116	2
Homa bay	43,423	13,159	1,257	1,968	163	375	5
Kisumu	24,931	29,599	2,882	2,469	167	670	9
Kuria	11,696	13,774	214	473	35	299	4
Migori	30,193	26,391	2,503	2,582	190	629	7
Nyamira	26,640	15,827	354	445	22	83	1
Nyando	19,063	10,307	1,208	1,286	102	535	6
Rachuonyo	17,243	12,658	1,451	1,457	121	702	10
Siaya	24,984	21,589	1,998	2,276	163	652	8
Suba	9,662	7,381	900	1,440	86	890	12

Notes:
[*] Kenya population estimates 2010–2018.
[†] PEPFAR annual progress report (APR 2013) data.
[‡] Transmission rate per 100,000 live births $= \frac{\text{Absolute transmission in 2013}}{\text{Estimated live births in 2013}} \times 100,000$.
[§] Ranked from lowest to highest case rates.

Higher infection rates among infants tested after eight weeks after birth indicate high postnatal transmission during the breastfeeding period. In the more recent years where use of lifelong ART during pregnancy and after birth (Option B+) is common, transmission rates are expected to be lower than in previous years. The estimates and projections package has estimated that generally 50% or more of transmission is expected

to happen after six weeks of delivery in pre-Option B+ population for the Nyanza region. Early testing for HEI is recommended for timely intervention. According to the final stock-taking report on e-MTCT, by 2015, only four countries in East and Southern Africa were meeting targets of early testing to over 50% of HEI (*Claessens et al., 2014*). In our study, reduction in MTCT corresponded to a reduction in use of sdNVP use over time and adoption of more efficacious regimens. Our analyses covers a pre-Option B+ phase hence better progress would be expected during full implementation of Option B+. This progress towards use of efficacious regimens was in response to recommendations for use of universal ART (*World Health Organization (WHO), 2010*; *DeCock et al., 2000*). In this regard, Kenya has identified PMTCT goals for e-MTCT including implementing guidelines and improving EID and pediatric ART (*Claessens et al., 2014*).

Our best fitting model was a spatial–temporal model with covariates and had the least DIC (by over 10 points) from the next model of a different nature (spatial–nontemporal model). Therefore, this model was better in explaining geographical variation in MTCT rates over time. The fit observed for the spatial–temporal model with covariates can be explained by the way the PMTCT program has been implemented within the 12 districts. Initial PMTCT program implementation started in former southern Nyanza districts namely; Homa Bay, Suba, Migori, Gucha, Kisii, Nyamira, and Kuria districts. The spike in rates in Homa Bay district in 2010 may have been the result of intensified efforts in EID leading to diagnosis of more HIV-infected infants who may have been missed previously. After 2010, the trend shows a gradual reduction of MTCT rates for most districts up to the end of 2013. However, there was a spike for Gucha district in 2011 after a gradual decline up to 2010. By 2013 though, the decline to the 5–8% MTCT rate category was observed for most (10/12) districts. The highest rates by 2013 were in Siaya and Suba districts. Despite substantive program investments in these districts, the impact could be less due to rural nature of the district. Lower rates were observed in contiguous districts that were further away from Lake Victoria.

We acknowledge that our data have limitations. Routine program data may lack high-level quality due to missing values, although by focusing on a specific laboratory request form we had more complete results than routine patient records. In our data, we used the first infant PCR test and not the final one at 18 months. Our data does not describe final transmission rate, but lets us examine important factors in e-MTCT including early diagnosis. The variables included in the models are not exhaustive in explaining reducing MTCT rates including health seeking behaviors and other structural factors such as distance to health facility. We did not also include infant ART variable due to lack of sufficient data. However, we did include the variables that have been shown to be most important in impact on reducing MTCT rates in published literature such as level of facility (*Lerebo et al., 2014*), however, due to lack of data, we did not consider structural factors (*Aarons et al., 2016*), nor retention associated factors (*Obai, Mubeezi & Makumbi, 2017*) and other maternal related factors (*Lerebo et al., 2014*). We also acknowledge that DIC only measures the goodness of fit and cannot be used singly to conclusively indicate that the spatial–temporal model with covariates was best. We however tested for sensitivity with resulting similarity in final fitted rates.

CONCLUSION

To the best of our knowledge, there is no comparable geospatial–temporal analysis for MTCT in SSA countries. We have revealed geographic disparities in progress attained in reductions of MTCT in this high-burden, low-resource setting. Rigorous country-wide analyses of this nature will be a useful addition to unveiling progress towards e-MTCT. Taking into account adoption and use of national PMTCT program guidelines, the spatial disparities revealed in our study imply the need to consider location-specific challenges.

ACKNOWLEDGEMENTS

ADDITIONAL INFORMATION AND DECLARATIONS

Funding

Grant Disclosures

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

- Anthony Waruru conceived and designed the experiments, analyzed the data, contributed reagents/materials/analysis tools, prepared figures and/or tables, authored or reviewed drafts of the paper.
- Thomas N.O. Achia analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper, trained the lead author in analytical methods.
- Hellen Muttai conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the paper.
- Lucy Ng'ang'a conceived and designed the experiments, authored or reviewed drafts of the paper.

- Emily Zielinski-Gutierrez authored or reviewed drafts of the paper.
- Boniface Ochanda conceived and designed the experiments, performed the experiments, authored or reviewed drafts of the paper.
- Abraham Katana conceived and designed the experiments, authored or reviewed drafts of the paper.
- Peter W. Young authored or reviewed drafts of the paper.
- James L. Tobias analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper.
- Peter Juma analyzed the data, contributed reagents/materials/analysis tools, authored or reviewed drafts of the paper.
- Kevin M. De Cock authored or reviewed drafts of the paper.
- Thorkild Tylleskär authored or reviewed drafts of the paper, supervised the writing of the manuscript.

Human Ethics

The following information was supplied relating to ethical approvals (i.e., approving body and any reference numbers):

Ethical approval for the study was obtained from the Kenya Medical Research Institute (KEMRI) and the United States Centers for Disease Control and Prevention (CDC).

Data Availability

The following information was supplied regarding data availability:

Figshare: https://figshare.com/s/909012b948a0e9920955.

Supplemental Information

Supplemental information for this article can be found online at http://dx.doi.org/10.7717/peerj.4427#supplemental-information.

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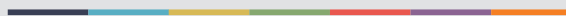
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