Epidemiology of HIV and selected blood-borne infections in East-Africa

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Introduction
Africa, more than any other continent, is still plagued with the burden of infectious disease. The human immunodeficiency virus (HIV), a newly emerging disease dramatically altered population health in sub-Saharan Africa in recent decades and changed the epidemiology of ancient infectious diseases such as human herpesvirus 8 (Kaposi's sarcoma associated herpesvirus), and tuberculosis. The separate emergence of two separate HIV species (HIV-1 and HIV-2) reflects the continued exposure of humans to pathogens emerging from Africa's forests.

Prevailing stigma, both old (tuberculosis) and new (HIV), as well as poor health care and health information systems are met by new and sophisticated prevention, treatment, and surveillance techniques. Surveillance is defined as the ongoing, systematic collection of data on the occurrence or distribution of diseases and other conditions or attributes in a population. HIV and related infectious disease surveillance – the monitoring or prompt reporting of every new case – is a key strategy in industrialised settings. In low resource settings, such as East-Africa, HIV and related infectious disease case surveillance is still in its infancy, reflecting the generally poor state of health information systems in the region. To fill the resulting information gaps, observational epidemiological research and surveys examine and estimate key aspects of HIV-related population health.

1.1 Epidemiology of HIV infection

1.1.1 Origin of the HIV epidemic

HIV, part of the lentivirus sub-family of retroviruses, consists of two major types, HIV-1 and HIV-2 [1]. HIV-1, comprising two main groups, M ("major") and O ("outlier"), is the predominant HIV type in Africa and the rest of the world, while HIV-2 is prevalent mostly in West-Africa [2]. Case reports and serological evidence suggests that the HIV-1 group M epidemic may have its origin in the area of Congo-Kinshasa (today’s Democratic Republic of Congo), Rwanda,
and Burundi [3]. The daily river-ferry from Kinshasa to Brazzaville may have been a route of spread to Congo-Brazzaville and the war between 1971-81 in Tanzania and Uganda may have facilitated its spread to these two countries, and on to other countries in East-Africa [3]. In East-Africa today, HIV-1 group M subtypes A and D predominate, apart from Ethiopia where subtype C is dominant.

1.1.2 HIV transmission

**Sexual HIV transmission**

Sexual transmission accounts for the bulk of new HIV infections in sub-Saharan Africa, including East-Africa. The transmission probability per sex act is mainly a function of HIV viral load (reflecting levels of HIV in the genital tract [4]), presence or absence of genital ulcers, and mode of sexual intercourse. Vaginal sex is estimated to carry a per act transmission probability of 0.0011 [5]. In the presence of sexually transmitted infections (STIs), this risk may increase eight-fold [6], whereas anal sex multiplies the base risk 2.6 fold [7]. HIV transmission through oro-genital contact likely is inefficient. Further, compared to the asymptomatic stage of HIV infection, which accounts for most of the infection’s duration, where HIV viral load is lowest, the primary HIV infection stage is estimated to be associated with an 9-40 fold increased HIV transmission probability [4, 8-11]. The transmission risk during the symptomatic HIV infection stage (lasting approximately 2 years prior to death) increases the asymptomatic stage base risk 7-fold [8]. Mathematical modelling suggests that although infectivity in the acute stage of HIV is very high and transmission probability is also increased during late-stage infection, no stage may be dominant in driving the HIV epidemic on a population level [12].

**Vertical HIV transmission**

Vertical HIV transmission from mother-to-child (MTCT) constitutes the second most frequent transmission mode in generalised epidemics. Without intervention, the MTCT risk is estimated at 20%
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perinatally [13]. HIV transmission continues during breastfeeding with an estimated monthly risk ranging from 0.75% (exclusive breastfeeding) to 1.5% (mixed breastfeeding) during the first 6 months, and a further monthly transmission risk of 0.75% after 6 months [14-16].

**Parenteral HIV transmission**

Parenteral HIV transmission includes the most efficient modes of transmission. Transfusion of HIV-positive blood carries an estimated transmission risk of 95%-100% [17], whereas the risk of infection through the use of a HIV contaminated syringe is estimated at 0.8% (median) [18].

**1.1.3 Current epidemiology and burden of HIV disease in East-Africa**

**General population**

The HIV/acquired immunodeficiency syndrome (AIDS) epidemic in East-Africa likely is the second most severe worldwide after southern Africa. Uganda was among the first countries to declare its HIV epidemic in the mid-1980s [19-22] and reports followed about the likely heterosexual transmission of HIV in Uganda [23], in contrast to the western industrialised nations where men who have sex with men (MSM), intravenous drug use and blood transfusions accounted for the vast majority of HIV infections. Reports of HIV sero-positivity in various populations groups across East-Africa soon followed: a) 1984: in patients meeting the clinical AIDS definitions in Rwanda [24]; b) 1985: across different population groups, with wide variations, in Kenya, [25]; c) 1986: in healthy individuals and patients in Rwanda [26] d) 1987: in apparently healthy subjects and patients in Tanzania [27] and e) 1988: in pregnant women in Bujumbura, Burundi [28]. Since the late 1980s or early 1990s all eastern African countries experience generalised HIV epidemics, often exceeding 5% in prevalence. Although exact reasons remain unknown, low levels of male circumcision, high prevalence of genital
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herpes simplex virus type 2 (HSV-2), and partner concurrency (i.e., the presence of concurrent sexual relationships) are often cited as possible determinants [29]. The overall female-to-male HIV prevalence ratio is estimated at 1.33 in eastern Africa, a typical value for a generalised heterosexual epidemic, reflecting the higher biological and sociological vulnerability of women [30, 31]. The HIV dynamics seem to differ between eastern African countries, with for example a rapid initial expansion in Uganda [32], and a marked urban/rural divide in Ethiopia and Rwanda with lower rural prevalence [26, 33, 34], in contrast to regions in Tanzania [35]. By 2009, compared with 2001, HIV incidence had stabilised in Uganda and Kenya, defined by the Joint United Nations Programme on HIV/AIDS, (UNAIDS) as a relative change in HIV incidence of less than 25%, and decreased in Ethiopia, Eritrea, Rwanda and Tanzania, defined as a relative decrease in HIV incidence of >25% [30]. However, HIV remains among the leading causes of deaths among adults in this region. In Uganda, for example, approximately a quarter of all adults die of AIDS despite substantial anti-retroviral therapy (ART) coverage [36]. Table 1.1 shows select HIV-related indicators.

Table 1.1 HIV-related indicators in select eastern African countries

<table>
<thead>
<tr>
<th></th>
<th>Burundi</th>
<th>Ethiopia</th>
<th>Kenya</th>
<th>Rwanda</th>
<th>Tanzania</th>
<th>Uganda</th>
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<tbody>
<tr>
<td>HIV prevalence (%)*</td>
<td>3.3</td>
<td>N/A</td>
<td>6.3</td>
<td>2.9</td>
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<td>6.6</td>
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<tr>
<td>No. living with HIV (1000s)*</td>
<td>180</td>
<td>N/A</td>
<td>1,500</td>
<td>170</td>
<td>1,400</td>
<td>1,200</td>
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<tr>
<td>HIV incidence (%)*</td>
<td>0.2-0.3</td>
<td>N/A</td>
<td>0.53</td>
<td>0.18</td>
<td>0.45</td>
<td>0.74</td>
</tr>
<tr>
<td>No. new HIV infections (1000s)*</td>
<td>11-17</td>
<td>N/A</td>
<td>110</td>
<td>8.8</td>
<td>100</td>
<td>120</td>
</tr>
<tr>
<td>AIDS deaths (1000s)*</td>
<td>15</td>
<td>N/A</td>
<td>80</td>
<td>4.1</td>
<td>86</td>
<td>64</td>
</tr>
</tbody>
</table>

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High-risk populations

Within epidemics in Africa, there are population groups subject to markedly higher HIV infection risks. Such groups include female sex workers (FSWs) and their clients, MSM and injection drug users (IDUs).

In Kampala, Uganda, surveys among FSWs estimated an HIV prevalence of 33%, and among clients and partners of FSWs as 18% [40]. Given an estimated HIV prevalence of 10% among adult women in the general population in Kampala [37], and a self-reported median duration of sex work in Kampala of 3 years at the time of survey participation, this would suggest a substantial HIV incidence in FSW. UNAIDS-commissioned studies estimate that in Kenya 14% of incident HIV infections are due to commercial sex [38], whereas in Uganda, this proportion is estimated at 10% [39]. These proportions are likely higher if restricted to the urban populations of East-Africa.

MSM also show high levels of HIV infection due to the increased risk of HIV transmission by anal sex and severe stigma and criminalisation, leading to a lack of tailored prevention services. HIV prevalence among MSM in Kampala, Uganda, was estimated at 13.7% [40], similar to an estimate in Zanzibar (12.3%) [41], but substantially higher among “high-risk” MSM in Mombasa, Kenya, with an estimated 43% [42]. Estimates of the proportions of all new HIV infections in a given country that are due to MSM contacts vary between 0.9% in Uganda [39], and 15% in Kenya [38] and Rwanda [43]. However these proportions are very sensitive to the estimated national population sizes of MSM, which are difficult to estimate and politically delicate. MSM in East-Africa also demonstrate substantial sexual mixing. In Malawi for example, a third of MSM were married or cohabiting with a woman [44], whereas in Uganda 31% of Kampala MSM were ever married, and 78% ever had sex with a woman [40].
In contrast, there is a paucity of data on IDUs in East-Africa. In Nairobi, Kenya, HIV prevalence among IDUs was estimated at 36% [45], somewhat similar to an estimated 26% HIV prevalence among IDU in Zanzibar, Tanzania [46].

1.1.4 HIV surveillance

General principles

The World Health Organisation (WHO), UNAIDS, and the US Centers for Disease Control and Prevention (CDC) issue key surveillance guidelines, such as those for 2nd Generation HIV Surveillance [47]. These guidelines prescribe an HIV surveillance approach depending on the epidemic setting (low-level, concentrated, generalised HIV epidemics). Countries where the HIV prevalence is estimated at below 1% in the general population and does not exceed 5% in “key populations” (high-risk groups) are defined as “low-level” epidemics. Concentrated epidemics are found where HIV prevalence exceeds 5% in at least one high-risk group (such as FSWs, MSM, or IDUs). Countries with generalised epidemics are defined as countries where the estimated HIV prevalence in pregnant women exceeds 1%. In generalised epidemics, as found throughout East-Africa, countries are supposed to regularly conduct surveys among ante-natal clinic (ANC) attendees.

The purported strengths of an ANC-based surveillance system, using “unlinked anonymous testing” (UAT) on left-over blood, were (and are) that pregnant women are healthy, that HIV testing may be done without informed consent (minimising selection bias), and that ANC attendees may be a proxy of the general adult population, including men and non-pregnant women. ANC-based HIV surveillance using UAT proved to be the cornerstone for the monitoring of all generalised HIV epidemics and to date provides the majority of African HIV surveillance data points used to estimate the burden of disease. Traditionally, the median ANC site HIV prevalences were reported and used for trend observations over time. Stratifications by urban/rural setting and
by age group provide additional important information about the broad distribution of HIV. In addition, HIV prevalence among 15-19 or 15-24 year-old ANC attendees may serve as a crude proxy for HIV incidence as the median duration of HIV infection in these young age groups presumably is low. In recent years the concept of UAT has come under criticism as the HIV test result cannot be returned to the patient hence theoretically impeding HIV treatment and control efforts [48]. At the same time, “Prevention of Mother To Child Transmission” (PMTCT) programs have undergone rapid expansion in most countries with generalised epidemics, and many more pregnant women are tested for HIV through PMTCT than in UAT-based surveillance rounds. Efforts are underway to evaluate the utility of PMTCT data for HIV surveillance and its potential to replace the UAT-based ANC surveillance systems [49, 50].

In addition, periodic national household-based surveys (e.g. AIDS Indicator Surveys or Demographic Household Surveys with HIV testing) are recommended. The great advantage of such surveys is the high precision of HIV estimates, the inclusion of both men and women (and at times children), and the often detailed HIV-related data collection. The key limitations of these surveys are their huge costs and the resulting donor dependency.

HIV surveillance in East-Africa

Reflecting the early start of the HIV epidemic in East-Africa, HIV surveillance started in the late 1980s. In Uganda, surveillance was first passive and based on a WHO recommended clinical case definition for AIDS in Africa [51]. Data collection began in 1987 and was primarily hospital-based. Serological HIV tests for surveillance were introduced shortly thereafter. Following WHO recommendations, surveillance was anchored among ANC attendees; the first data were reported in 1987 [52]. All countries in East-Africa comply with the WHO recommendations.
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HIV surveillance among high-risk populations

Household surveys among the general population suffer the potential of severe social desirability bias, leading to under-reporting of high-risk behaviours, such as drug use, multiple sex partners, anal sex, commercial sex, or even condom use. Many general population based surveys do not include data measures related to anal sex [53]. Further, unless very large sample sizes are achieved, general population surveys also likely cannot sample many enough high-risk individuals to warrant a meaningful analysis of such sub-groups, prompting the conduct of separate data collection activities aimed specifically at high-risk individuals. Such high-risk groups, also termed “hidden populations” due to their low social visibility, typically include FSWs, clients of FSWs, MSM, and IDUs. Non-commercial sex partners and spouses of these groups are also viewed at high-risk for HIV infection and serve as important bridging populations between these core groups and the lower risk general population. Other “high-risk groups”, defined on demographic, rather than behavioural, characteristics, can include long distance truck drivers, fishing communities, migrant workers, all of which are characterised by their mobility, or impoverished populations such as homeless populations or slum dwellers. However, generalising these demographic groups as “high-risk” can overestimate the number of persons at high-risk and divert resources otherwise available for behaviour-based high-risk populations. A separate high-risk group may be regarded as persons engaging in multiple concurrent partnerships (partner concurrency) [54]. In generalised epidemics, this sub-set of the general population may account for a significant proportion of incident and prevalent HIV-infections but is difficult to survey as demonstrated by the lack of specific survey data on such individuals.

Measuring and monitoring HIV disease in high-risk groups faces additional challenges and data requirements. Challenges include the identification of high-risk individuals and their
reluctance to participate in surveys. Additional data requirements include the geographic distribution of high-risk individuals and the population size of these groups.

Another challenge is that traditional sampling designs such as random or cluster sampling are usually infeasible as no complete sampling frame is generally available. Alternatives for sampling high-risk individuals include time-location sampling (TLS), and respondent driven sampling (RDS) [55]. TLS is a suitable sampling strategy when most members of a given high-risk group, such as FSWs in brothels, IDUs attending treatment centres, street children categorised by geographic location, or MSM frequenting bars or other social venues, are present at distinct venues at any one time [56-60]. RDS, a peer-referral sampling strategy, has been proposed recently [61-63] and represents an advanced form of snowball sampling [56, 64]. RDS surveys are increasingly being used worldwide, including in Africa [65], despite limitations [66].

In East-Africa, HIV surveys among high-risk groups are usually anecdotal, often limited to national capitals or few major urban centres, and of varying quality, in particular with regard to the sampling design which often amounted to little more than convenience sampling. Surveys among FSWs and, less often, clients of FSWs are among the oldest high-risk group surveillance efforts. Surveys among IDUs are rare and limited to major coastal urban settings such as Dar es Salaam, Tanzania, or Mombasa, Kenya. Surveys among MSM are still the exception rather than the rule in East-Africa.

The reasons why high-risk group surveys are less prominent than surveillance efforts in the general population may be an inadvertent consequence of epidemic classification, as “generalised” epidemics may falsely suggest that everyone is at equal (high) risk for HIV infection or that surveillance and control of HIV in high-risk populations is less important. Other reasons for the relative negligence of high-risk group surveillance may be donor-driven, as organisations such as PEPFAR (the US President’s
Emergency Plan for AIDS Relief, the largest HIV-related donor in sub-Saharan Africa), the Global Fund for AIDS, TB, and Malaria, and UNAIDS are focused on numerical target settings such as the number of people in HIV care and treatment, or the number of HIV-positive pregnant women taking ARVs, to which the much smaller high-risk populations can “contribute” relatively little. Finally, prevailing stigma against high-risk behaviours (sex work, injection drug use, and especially homosexuality) is rampant in much of Africa which hinders access not only to HIV services but likely also contributes to reluctance to regularly collect survey and surveillance data in these groups.

A range of methods are available to estimate the population size of high-risk groups, including capture-recapture [67, 68] the multiplier method [69], census and enumeration, as well as network scale-up [70-72], all of which suffer from various limitations. Due to the low social visibility of high-risk groups, such as MSM, IDU and FSWs, methods that are implemented within the general population (such as network scale-up) may need to be adjusted for [73].

1.1.5 Modelling and projections

Surveys and surveillance usually report the burden of disease through proportions, rates, and ratios. For HIV control efforts though, donors, policy makers, and programme planners need to also consider the absolute burden of disease and the population sizes in need of interventions or services. Such indicators include the number of persons that need to be tested for HIV, or admitted to care or treatment. The absolute size of the HIV epidemic and number of persons accessing services determines the resources needed, including staff, infrastructure, and commodities. Countries with generalised epidemics, including eastern African countries, also often have significant population growth, which adds to the growing absolute burden of HIV disease even in stable epidemic scenarios.
For the general population, HIV-related size estimates are often obtained through modelling and projections, using tailored software packages such as Spectrum [74]. These techniques allow the estimation of new HIV infections, vertical infections and AIDS deaths, and facilitate projections into the immediate future years. ANC surveillance data play a key role as input data for such modelling and projections exercises [75] as their trend data allow to forecast the epidemic’s likely course into the future [74, 76]. In the absence of near-complete health information systems, such model and projection-based estimates provide critical information to describe the estimated burden of HIV disease.

1.1.6 HIV control efforts

General principles

HIV control efforts have undergone remarkable change both qualitatively and quantitatively. Early in the epidemic, in the 1980s, control efforts largely consisted of collecting anecdotal data on the scale of the epidemic, establishing nascent HIV monitoring systems, beginning of screening programmes for blood donors, and calls for a reduction in the number of sexual partners (“zero grazing” in Uganda) [21, 77]. In the 1990s, eastern African nations witnessed a continuation of substantial AIDS-related mortality without having the means to emulate the triple ARV-based treatment programmes industrialised countries began to establish. Hence, behaviour change programmes (ABC – Abstinence, Being faithful, Condoms) continued to be the only substantive tools available to Ministries of Health in the region [78, 79], supported by donor funds that often emphasized abstinence and “faithfulness”, de-emphasised the role of condoms, and provided funds to faith-based organisations. Only in the last decade, when massive donor funding began to pour into sub-Saharan Africa, began the era of substantial decline in mortality along with the rise of biomedical control programmes.
Biomedical interventions

Theoretical models suggest a potential to minimise or even eradicate HIV epidemics through a "Test & Treat" approach, i.e., identifying and placing all HIV-infected individuals on ART, either alone or in combination with other interventions [80, 81]. However, the global economic setting in recent years makes it unlikely that the necessary funding will be made available, and concerns about the ethics of such an approach as well as behavioural dis-inhibition and ARV resistance question the validity of this theoretical approach [82, 83]. Recent study findings suggest a large potential of select biomedical interventions to curb the HIV epidemics in Africa, including male medical circumcision (MMC), ART, PMTCT, including family planning, microbicides and ARV-based pre-exposure prophylaxis (PrEP).

Effect of biomedical interventions

- ART can reduce HIV transmission among HIV-infected people by 92% [84], to 96% [85]
- ARV-based PrEP can reduce HIV acquisition in uninfected individuals in HIV-discordant relationships by 62%-73% [86]
- ARV-based PrEP may reduce HIV acquisition in MSM by an estimated 44% [87]
- ARVs can reduce the risk of MTCT, to an estimated 11% for single dose nevirapine [88, 89], 4% using dual ARV regimens [90, 91], and 2% when using triple ARV regimens [13]
- MMC can reduce HIV acquisition risk by at least 60% [92-94]
- Latex condoms are estimated to have a 80% effectiveness in preventing HIV transmission [95, 96]
- Microbicides can reduce HIV acquisition depending on the level of adherence [97]
1.2 Epidemiology of selected blood-borne infections

HIV-related opportunistic infections (OIs) are defined as infections that occur more frequently or in more severe form in immunosuppressed HIV-infected individuals than in uninfected individuals. OIs comprise a wide spectrum of viruses, bacteria, protozoa, as well as fungal infections, and account for the bulk of the HIV-related morbidity and mortality. Despite large-scale ART programmes and the accompanying decline of OI-related morbidity and mortality [98, 99], OIs continue to occur mostly because of late HIV diagnosis, poor adherence to, or lack of ART uptake [100].

Several OIs are caused by blood-borne pathogens, including hepatitis B and C virus, plasmodia spp., and human herpes virus 8. The high prevalence of HIV in East-Africa is reflected by even higher HIV prevalences in hospitalised patients. At the same time, the need for blood transfusions in East-Africa is substantial, due in part to malarial anaemia, sickle cell anaemia, and obstetrical complications. Screening of donated blood for blood-borne pathogens has evolved dramatically in recent decades due to increased funding and assays suitable for mass screening. Prior to the recognition of the HIV pandemic, screening often was anecdotal or non-existent and donors usually were recruited among relatives of candidate transfusion recipients or were commercial donors – both of which are more likely to carry blood-borne pathogens than volunteer non-remunerated donors. Screening for syphilis and HIV (antibodies) were among the first routine measures employed in the 1980s, followed by testing for hepatitis B surface antigen. Recently, screening for hepatitis C is increasingly common such as at the Uganda Blood Transfusion Services. The short refrigeration time of donated blood due to high demand and the non-removal of the buffy coat may increase the transmissibility of (cell-associated) pathogens.
1.2.1 Human herpesvirus 8

**Human herpesvirus 8**

Human herpesvirus 8 (HHV-8), also known as Kaposi’s sarcoma (KS)-associated herpesvirus, (KSHV) is a novel human gamma herpes virus. HHV-8 was first identified in 1994 in KS lesions [101] and it is now accepted that HHV-8 is the causative agent for KS [102-104]. In KS specimens, HHV-8 DNA could be isolated in 83% to 100% of cases regardless of the patient’s HIV status, or type of KS [105-107]. It is also considered a candidate etiologic agent for B-cell lymphoma, multicentric Castleman’s disease and potentially for other tumours [108]. Although HHV-8 can be differentiated into several subtypes, the importance of subtypes for transmission or pathogenesis is unknown [109-111]. HHV-8 represents a classic OI in HIV-infected individuals [112, 113] and HHV-8 sero-prevalences in East-Africa are the highest in the world, with many estimates originating from Uganda [114-116]. The widely discrepant prevalence estimates within and across geographic regions likely also reflect the state of development of HHV-8 testing technologies and current lack of a gold standard.

**Kaposi’s sarcoma**

KS is a vascular neoplasm primarily affecting the skin, subcutaneous tissue, and occasionally internal organs. KS is classified in four epidemiological types [117-119]: Classical KS is seen mostly in elderly men of Mediterranean origin or of Jewish descent. Endemic KS was first described in Uganda and occurs mainly in eastern and Central Africa, affecting men, women, and children, and tending to have a more aggressive clinical course than classical KS. A third form is known as immunosuppression-associated KS, found among immunosuppressed patients such as organ transplant recipients. The fourth type, KS among AIDS patients, termed epidemic KS, is often the most frequent malignancy in patients with AIDS. Rates of (AIDS-associated) KS are very high where both HIV and HHV-8 prevalences reach high levels, such as in Uganda where in the early
1990s KS accounted for approximately half of all cancers reported to the National Cancer Registry [120]. The incidence of KS then declined along with the decrease in HIV prevalence and expansion of ART [120-123]. Similar trends have also been observed in other parts of Africa, such as Zimbabwe [124, 125] and Zambia [126].

**Seroprevalence of HHV-8 in East-Africa**

In Africa, HHV-8 is primarily or at least partially acquired during childhood, presumably by non-sexual routes [127-130]. In Uganda, one study’s finding suggested an HHV-8 incidence of approximately 4% among children less than ten years of age [131]. Another study found that seroprevalence reached high levels in young adults in Uganda (35.5% by age 21 years), with little increase thereafter [132]. This suggests that HHV-8 seroprevalence in East-Africa rises sharply during childhood and more slowly during adulthood [133]. HHV-8 testing of stored plasma samples from a nationally representative survey in Uganda estimated the HHV-8 seroprevalence among adults aged 51-59 years as 56.2% [136].

**Transmission of HHV-8**

The modes of HHV-8 transmission are not yet fully understood. In the U.S. and Europe, HIV-infected MSM are at the highest risk of developing KS [103, 134, 135], significantly higher compared to AIDS patients who acquired HIV by contaminated blood products, IDU or through heterosexual contact [134]. KS has also been observed in HIV-negative MSM and heterosexual men and women [136-138]. Evidence is accumulating that HHV-8 may also be transmitted via organ transplantation, such as in kidney transplant recipients [139-141]. Serological evidence indicates that HHV-8 may be vertically transmitted [142, 143], although disputed by other studies [130]. A history of IDU was found to be a risk factor for HHV-8 infection, raising concern that HHV-8 may be transmitted parentally, although an examination of a historical cohort of US transfusion recipients found no evidence of transfusion-related HHV-8 transmission.
Studies have documented that horizontal, and perhaps sexual transmission, are likely to be the primary modes of HHV-8 transmission in Africa [145].

**HHV-8 transmission by transfusion**

The question of blood-borne transmission of HHV-8 and mass screening of donated blood for HHV-8 continues to be a research issue awaiting further clarification [146, 147]. Although evidence of HHV-8 infection has been found both among blood donors [146] and transfusion recipients [115], to date, laboratory and epidemiological studies have shown that risk of HHV-8 transmission by blood products either does not occur, or at most, occurs infrequently [146-150]. According to epidemiologic studies, persons with haemophilia in the United States who were infected with HIV by blood products rarely develop KS and have a similar prevalence of HHV-8 antibodies as the general population [148, 151]. Similarly, persons with AIDS who acquired HIV infection through receipt of contaminated blood products have a low incidence of KS [134, 138]. In a retrospective cross-sectional study among Ugandan sickle-cell anaemia patients, a history of blood transfusion was associated with small HHV-8 infection risk [152].

Several factors may have contributed to the fact that no studies to date have been able to document HHV-8 transmission by blood transfusion:
- Blood donors at risk for HHV-8 infection in the U.S. and Europe, such as MSM, IDU, or persons infected with HIV or hepatitis C, are routinely deferred from donating blood.
- HHV-8 transmission by blood may require a certain level of viraemia that is generally not present in antibody-positive individuals.
- The viability of HHV-8 in stored blood is unknown, but may be diminished after refrigeration and storage.
- Routine virus inactivation and sterilisation procedures for plasma derivatives may inactivate HHV-8.
In sub-Saharan Africa, the risk of HHV-8 transmission by blood transfusion has barely been evaluated. Two major conditions are different in the African setting. First, blood transfusions are often given as whole blood units. As HHV-8 is a cell-associated virus and can be detected in peripheral blood mononuclear cells (PBMC), the risk for HHV-8 transmission is possibly higher if whole blood is transfused. Second, HHV-8 seroprevalence, as well as rates of endemic and AIDS-associated KS are much higher in Africa than in North-America or Europe, suggesting an amplified risk of transfusion-associated HHV-8 transmission in unscreened blood. The risk of HHV-8 transmission by blood transfusion may further be higher in countries like Uganda than in industrialised countries as the refrigerated storage time of blood units after donation tends to be short due to high demand.

### 1.2.2 Plasmodium falciparum and other Plasmodia spp.

Human malaria is caused by four species of plasmodia, sporozoan parasites: *Plasmodium falciparum, Plasmodium vivax, Plasmodium ovale,* and *Plasmodium malariae.* Humans are the only reservoir for these Plasmodia spp, all of which are transmitted by *Anopheles* mosquitoes. Transmission of *Plasmodium* is infrequent in areas where the altitude exceeds 2000 meters.

The burden of malarial disease in East-Africa is substantial. The number of deaths per 100,000 population/year varies from 10 (Ethiopia), to 12 (Kenya), 15 (Rwanda), 87 (Tanzania), to 103 (Uganda). The vast majority of malaria-related deaths are caused by *P. falciparum*; deaths mostly occur due to severe anaemia or cerebral malaria. In highly endemic countries such as Tanzania and Uganda, malaria is often the most frequent reason for blood transfusions, mostly in children under five years of age.

HIV-infected persons appear to be at greater risk to develop clinical malaria and are more likely to experience treatment failure. Although the magnitude of these interactions are modest on the individual level, the large numbers of persons infected with...
HIV and *Plasmodia* spp. in Africa suggests that even small levels of such interactions may have a substantial impact on population health [158], although contested by others for countries with low HIV prevalence [159].

### 1.2.3 Hepatitis C virus

With the expansion of HIV treatment programmes in East-Africa, patients' life expectancies increased and the effects of hepatitis B and C virus (HBV, HCV) co-infections become increasingly apparent [160].

WHO estimates that some 170 million people are chronic carriers of HCV [161]—far more than the number of HIV-infected persons globally. Africa appears to have the highest HCV prevalence, estimated at approximately 5% [162], but with significant variation: highest in Central Africa (6%) and lowest in East-Africa (1.6%). Many of the estimates do not stem from nationally representative samples hence the true picture of HCV infection in sub-Saharan Africa remains unclear. Within East-Africa, estimates range from 0.9% in Kenya to 6.6% in Uganda [162]. HCV prevalence among hospitalised patients in Uganda was estimated to be 2.3% with no difference between HIV-positive and HIV-negative patients and no association with IDU [163]. Transmission of HCV centres towards exposure to infected blood and blood products, including unscreened transfused blood, IDU, and medical, dental, or cosmetic procedures that involve exposure to HCV-infected blood products [164]. Exposure to HCV among IDUs may be high, reaching 51.4% in Kenya, and 22.2% in Tanzania [165]. Transmission from mother to child or by sexual intercourse appears to be far less frequent as is exposure to HCV-infected household items, such as shaving razors or toothbrushes [164]. The lack of a good understanding of the predominant mode of HCV transmission in Africa is of particular significance as no effective HCV vaccine is available and treatment is difficult to access.
Data on HIV/HCV co-infection in Africa are scarce but generally assumed to be low [160]. In Cameroon, the rate of HIV/HCV co-infection in pregnant women was estimated at 0.001% [166]. Among HIV-infected individuals, the prevalence of HCV infection varies widely by population group and setting: in Kenya, 3.7% among HIV-infected in-patients [167] and 0.7% among HIV-infected blood donors [168]. No signs of HCV infection were detected in Tanzanian blood donors [169, 170]. IDUs in Tanzania however do show increased risk for HCV and HIV/HCV co-infection [171]. A study in southern Ethiopia observed an anti-HCV positivity rate of 10.5% among HIV-infected voluntary counselling and testing (VCT) clients [172]. Taken together, these data contrast industrialised settings where rates of HIV/HCV co-infections generally are much higher, which in turn suggests different transmission routes for HCV and/or HIV in Africa.

Similar to HBV, HIV and HCV co-infected persons experience less often a spontaneous clearance of their HCV infection [173] and carry a higher risk of developing cirrhosis than HCV mono-infected persons [174, 175], leading to a higher risk of decompensated liver disease and related death [176]. Little is known about the effect of HCV infection on HIV disease progression, and the few available studies provide inconsistent observations [177-179].

HCV prevention

While almost all prevention programmes focus on preventing HIV infection, the similarities in transmission may be of benefit for the prevention of HCV. Efforts to prevent HCV infection include screening of blood products, steps to reduce nosocomial transmission through needles and syringes, making ARVs more widely available, and condom promotion. These prevention efforts will become increasingly important as the expansion of HIV-related ART programmes likely will lead to more frequent in liver disease in HIV and HCV co-infected persons. Few programmes in East-Africa...
target IDUs for HIV/HCV prevention, reflecting the facts that most HIV transmission occurs sexually, the paucity of data on IDU, and the low social visibility of IDUs.

1.3. Demographic profile of East-Africa

1.3.1 East-Africa: definition and boundaries

East-Africa (Figure 1.1) may be defined in several ways resulting in the inclusion of different groups of countries and varying geopolitical boundaries. Politically, the East-African Community (EAC) comprises Uganda, Kenya, United Republic of Tanzania, Rwanda, and Burundi [180]. The United Nations (UN) defines the Eastern African Region as including a total of 19 nations (comprising the EAC members as well as Comoros, Djibouti, Eritrea,
Ethiopia, Madagascar, Malawi, Mauritius, Mayotte, Mozambique, Réunion, Seychelles, Somalia, Zambia, and Zimbabwe [181]). Ethiopia, Eritrea, Djibouti, and Somalia are also often referred to as the “Horn of Africa”. Geographically, the Rift Valley constitutes the defining characteristic of East-Africa, extending from Ethiopia’s Afar depression to central Mozambique [182]. For the purpose of this thesis, the description of East-Africa shall focus on the East-African Community and the Horn of Africa, with special attention to Uganda, Kenya, and Ethiopia.

1.3.2 Climate

East-Africa’s climate is surprisingly cool and/or dry given its latitude [182]. Because large areas are of high altitude, temperatures remain moderate despite East-Africa’s location in the tropical belt straddling the equator. Further, substantial areas are dry or extremely dry, partly due to mountain ranges such as the Rwenzori and Ethiopian highlands which create a “rain shadow” of the westerly monsoon winds [183].

1.3.3 History

Home of modern humans [184], agriculture in the (Ethiopian) highlands dates back to 7000 B.C., but spread to the lowlands only considerably later [185]. The most widely spoken languages in East-Africa are the Oromo and Amharic dialects in Ethiopia, Somali (Somalia), Swahili (Tanzania) and Arabic spoken in some of East-Africa’s coastal regions, and furthermore numerous other dialects. The Portuguese were the first Europeans to establish a presence in East-Africa, dating back to 1505 [186]. Their control was later replaced by Omani Arabs, thus regaining control of the Indian Ocean trade, including slaves and spices. In the 19th century, the British Empire took a foothold in today’s Uganda, Kenya and coastal Somalia, part of Europe’s “Scramble for Africa” that saw Germany establishing German East-Africa (in today’s Tanzania), Portugal’s control of Mozambique, and France’s seizure of island territories in the Indian Ocean. Independence for East-African nations came
in the late 20th century, starting with Somalia (1960) and Tanzania (1961 in then Tanganyika), followed by Rwanda, Burundi, Uganda (1962), Kenya (1963), Djibouti (1977), and lastly Eritrea (1993). Ethiopia is an independent nation since the 4th century BC [187].

1.3.4 Demography

East-Africa experiences rapid population growth despite a decline in women’s total fertility rate (TFR) over the last decades (Table 1.2). Uganda’s TFR of 6.4 [188] suggests that this nation is growing at East-Africa’s fastest rate leading to a population doubling time of approximately 21 years. The HIV epidemic in this region has noticeably slowed (but not halted) both the rise in life expectancy as well as population growth [189].

Table 1.2 Demographic characteristics for select East-African countries

<table>
<thead>
<tr>
<th></th>
<th>Burundi</th>
<th>Ethiopia</th>
<th>Kenya</th>
<th>Rwanda</th>
<th>Uganda</th>
<th>East-Africa***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population growth rate (%)*</td>
<td>2.88</td>
<td>2.59</td>
<td>2.64</td>
<td>2.67</td>
<td>3.27</td>
<td>2.59</td>
</tr>
<tr>
<td>Total fertility*</td>
<td>4.66</td>
<td>5.38</td>
<td>4.96</td>
<td>5.43</td>
<td>6.38</td>
<td>5.3</td>
</tr>
<tr>
<td>Life expectancy at birth (years)*</td>
<td>50.3</td>
<td>55</td>
<td>54.2</td>
<td>49.9</td>
<td>52.4</td>
<td>53.2</td>
</tr>
<tr>
<td>Under-five mortality by sex*</td>
<td>166</td>
<td>131</td>
<td>104</td>
<td>155</td>
<td>122</td>
<td>124</td>
</tr>
<tr>
<td>Population (thousands)**</td>
<td>8,519</td>
<td>84,976</td>
<td>40,863</td>
<td>10,277</td>
<td>33,796</td>
<td>327,186</td>
</tr>
</tbody>
</table>

* 2005-2010
*** Includes additional countries in East-Africa not shown here
Chapter 1

1.4 Outline of this thesis

In Part 1 Chapter 2 examines the burden of HIV disease in Uganda and the potential effects of selected HIV/AIDS control programmes to mitigate it. Chapter 3 reports on the burden of and risk factors for HIV disease among men who have sex with men in Kampala, Uganda. Chapter 4 assessed the accessibility and quality of Prevention of Mother-To-Child HIV Transmission (PMTCT) programme data, as well as the utility for HIV surveillance, in Kenya. Chapter 5 compares the effects of antiretroviral prophylaxis for the prevention of PMTCT to that of existing family planning use and estimates the burden of paediatric HIV disease due to unwanted fertility in Uganda. In Chapter 6 we estimated the effect of CD4+ levels and antiretroviral treatment on the specificity of a widely used HIV recency assay, the BED enzyme immune assay, and evaluated a HIV avidity assay to detect BED-based false-recent results.

Part 2 focuses on HIV-related opportunistic infections and blood transfusion. In Chapter 7 we evaluated the risk of human herpesvirus 8 (HHV-8) transmission by blood transfusion in Uganda where HHV-8 is endemic, through a prospective observational cohort study of HHV-8-seronegative transfusion recipients receiving HHV-8-seropositive or seronegative blood. HHV-8 is etiologically linked to Kaposi’s sarcoma, representing up to half of all reported cancers in Uganda. In Chapter 8 we assessed HHV-8 seroprevalence, risk factors for infection, and HHV-8 serologic assays in a cross-sectional study of candidate Ugandan blood donors. In Chapter 9 we evaluated the risk of mortality associated with transfusion of HHV-8-antibody positive blood among transfusion recipients in Kampala, Uganda. In Chapter 10 we examine the prevalence of hepatitis C virus in candidate Ugandan blood donors and associated screening costs. In Chapter 11 we assessed the effect of HIV infection on morbidity and mortality in children receiving
blood transfusions due to severe malarial anaemia in Kampala, Uganda. In the General Discussion in Chapter 12 the main findings of this thesis are discussed. A summary is provided as well.

References


Chapter 1


Introduction


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50. Personal communication with Jesus Maria Garcia Calleja, WHO, Geneva, February 2012.


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187. Uganda Bureau of Statistics (UBOS) and Macro International Inc. 2007. Uganda Demographic and Health Survey 2006. Calverton, Maryland, USA; UBOS and Macro International Inc.