Chapter

Temporal and Spatial Distribution of Opportunistic Infections Associated with the Human Immunodeficiency Virus (HIV) in Uganda

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Abstract

The human immunodeficiency virus (HIV) remains one of the greatest challenges of the twenty-first century in the absence of an effective vaccine or cure. It is estimated globally that close to 38 million people are currently living with the HIV virus and more than 36 million have succumbed to this deadly virus from the time the first case was reported in early 1980s. The virus degrades the human body immunity and makes it more vulnerable to different kinds of opportunistic infections (OIs). However, with the introduction of highly active anti-retroviral therapy (HAART) in 2003, the pattern and frequency of OIs has been progressively changing though with variations in the different parts of the World. So this chapter discusses the temporal and spatial patterns of OIs in Uganda.

Keywords: HIV, opportunistic infections, temporal, spatial, distribution, Uganda

1. Introduction

Opportunistic infections (OIs) are the main cause of ill-health and mortality in persons living with HIV globally. OIs usually take advantage of a weakened immune system as found in persons infected with HIV to cause disease that may lead to death in the absence of effective treatment. Opportunistic infections can be viral, bacterial, fungal, or parasitic but their pattern of attack and frequency can vary in different individuals across the world [1–3]. Thus, while some HIV-infected individuals in developed countries rarely suffer from bacterial and protozoal infections, they are a major cause of morbidity and mortality in developing countries [2–4].

2. HIV and opportunistic infections

The human immunodeficiency virus (HIV) that causes acquired immunodeficiency syndrome (AIDS) remains one of the major global health challenges of the twenty-first century. According to the Joint United Nations Programme on HIV/AIDS (UNAIDS), 37.7 million people worldwide were estimated to be living with this deadly virus by the end of 2020 of which 25.3 million (67%) were in sub-Saharan Africa [5]. Since the outbreak of the HIV pandemic, an estimated 79.3 million cases have been recorded and 36. 3 million people worldwide have died and sub-Saharan Africa accounts for almost 70% of the total deaths [5].

HIV attacks and degrades the human body immune system rendering it defenseless against opportunistic infections normally checked by a competent immune system [6]. Opportunistic infections (OIs) remain the single main cause of ill-health and death among persons living with HIV. The natural history of HIV usually begins with an acute HIV syndromic phase, followed by an asymptomatic latency phase whose duration may vary from person to person (median duration ~10 years) to clinically apparent disease or symptomatic phase characterized by AIDS-defining opportunistic infections, and finally death from AIDS (**Figure 1**) [7].

During the asymptomatic phase, the T-cell-mediated immune system attempts to fight off the HIV infection but as the viral load increases, T-lymphocytes gets exhausted, CD4 cell count progressively falls down, and opportunistic infections start to appear in most cases when CD4 cell count has dropped below 200 cells/μl [7]. According to WHO, there are four clinical stages (WHO clinical stages) of HIV disease progression characterized by different opportunistic infections [8].

The first clinical stage is the asymptomatic phase in which the virus multiplies rapidly but is still hassling with the body immune system and no clinical signs are visible. The second clinical stage signals the end of the incubation period of the virus, and at this stage, its presumed viral load has significantly increased and CD4 cells significantly depleted allowing for the first opportunistic infections to appear, which may include herpes zoster, recurrent upper respiratory tract infections (bacterial sinusitis, tonsillitis, otitis media, and pharyngitis), fungal nail infections, recurrent oral or genital ulceration due to herpes simplex virus, extensive warts virus infection, or extensive molluscum

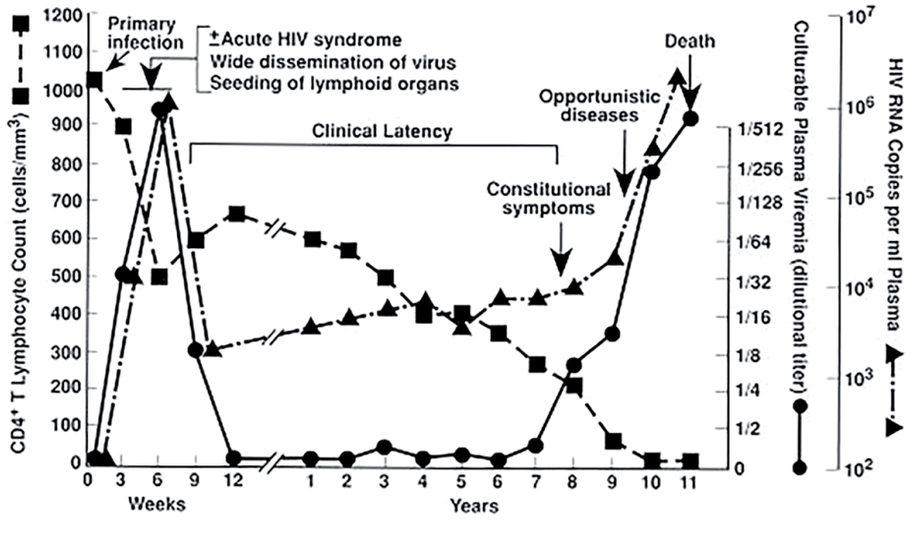

Figure 1.
The natural history of HIV infection (adopted from Pantaleo G, N Engl J Med 1993, 328:327–35).

contagiosum infection The third stage is the beginning of the AIDS (acquired immunodeficiency syndrome) stage in which the immune system is severely damaged and the persons becomes vulnerable to persistent diarrhea (>1 month), oral candidiasis, mycobacterium tuberculosis, oral hairy leukoplakia, and bacterial pneumonia.

The fourth and final stage is the climax of the AIDS stage characterized by multiple life-threatening opportunistic infections including pneumocystis jirovecii pneumonia, Kaposi's sarcoma, recurrent severe bacterial pneumonia, chronic herpes simplex viral infection, esophageal candidiasis, extra-pulmonary TB, cytomegalovirus infection, toxoplasmosis infection, cryptococcosis including meningitis, chronic cryptosporidiosis, chronic isosporiasis, extra-pulmonary histoplasmosis or coccidiomycosis, recurrent non-typhoid salmonella septicemia, and some may be hit by lymphomas (cerebral or B-cell non-Hodgkin).

3. The first opportunistic infection experience among HIV-positive individuals in Uganda

We conducted a study using clinical data obtained from the AIDS support organization database to assess the first opportunistic infection experience, and temporal and spatial distribution patterns of OIs in Uganda. TASO is one of the oldest and largest non-governmental organizations (NGO) providing HIV/AIDS care and treatment in Uganda and sub-Saharan Africa [9]. TASO was founded in 1987 and has 11 regional centers spread across Uganda which have been nationally recognized as centers of excellence (CoE) in HIV/AIDS care and treatment. Each center has four departments including administration, HIV counseling and psychosocial support, and medical (HIV clinic, pharmacy, medical laboratory, etc.) and data department. Additionally, TASO has 23 mini-TASO centers affiliated to public health facilities across the country. TASO serves predominantly HIV-positive patients of low socioeconomic status. All TASO centers offer free HIV testing and counseling, and comprehensive HIV treatment and care, including provision of free antiretroviral drugs and cotrimoxazole prophylaxis, home-based care, and psychosocial support [10].

National HAART rollout in Uganda started in 2004. Being one of the largest NGOs providing care and treatment to persons living with HIV, TASO has been instrumental in HAART rollout in Uganda. Initially, HAART access was based on the Ugandan Ministry of Health and WHO 2006 guidelines, that is, WHO stage 3 or 4 illness or a CD4 cell count <200 cells/μl for adults and adolescents and WHO stage III, advanced stage II or stage I with CD4 cell percentage less than 20% for those more than 18 months of age [11, 12]. However, following a policy review in HAART access, TASO adopted new HAART access guidelines in 2010 [13, 14] that raised the threshold for adults and adolescents to a CD4 cell count≤350 or WHO clinical stage 3 or 4 irrespective of CD4 cell count. In 2014, TASO started implementing the "test and treat" policy that recommends providing lifelong ART to all individuals who test HIV-positive irrespective of CD4 or WHO clinical stage. Initially, the target were HIV-positive pregnant or breast-feeding mothers, their children, HIV-positive individuals diagnosed with TB or hepatitis B co-infections, and HIV-positive individuals in sero-discordant relationships. Later in 2016, coverage was expanded to include everybody who test HIV positive to be eligible for HAART [15]. As part of comprehensive HIV care, TASO also implements universal cotrimoxazole prophylaxis as recommended by the Ministry of Health [16, 17].

The first opportunistic infection experience and the temporal and spatial distribution of each of the 17 selected OIs and Kaposi's sarcoma were assessed. Overall,

opportunistic infections (OIs) accounted for 99% of all opportunistic events compared with 1% due to opportunistic cancers (Kaposi's sarcoma, malignant melanomas, Burkitt's lymphoma, and other lymphomas). This is also additional evidence that opportunistic infections are the primary cause of morbidity and mortality among HIV-positive individuals in sub-Saharan Africa.

We assessed data pre-HAART (2001–2003), early HAART (2004–2006), mid-HAART (2007–9), and late-HAART (2010–2013). During pre-HAART period, 84.7% (n = 6549) of the participants had cough with fever, which was later confirmed to be pulmonary TB as their first opportunistic infection and 15.3% had others (diarrhea, candida, herpes zoster, etc.) (**Figure 2**). In early HAART period, 48.4% (n = 7539) had pulmonary TB as their first opportunistic infection, 18.5% had upper respiratory tract infection, 13.5% had persistent diarrhea, 9.6% had herpes zoster, and 10.1% had others (candida, malaria, genital ulcer, etc.) as their first opportunistic infection

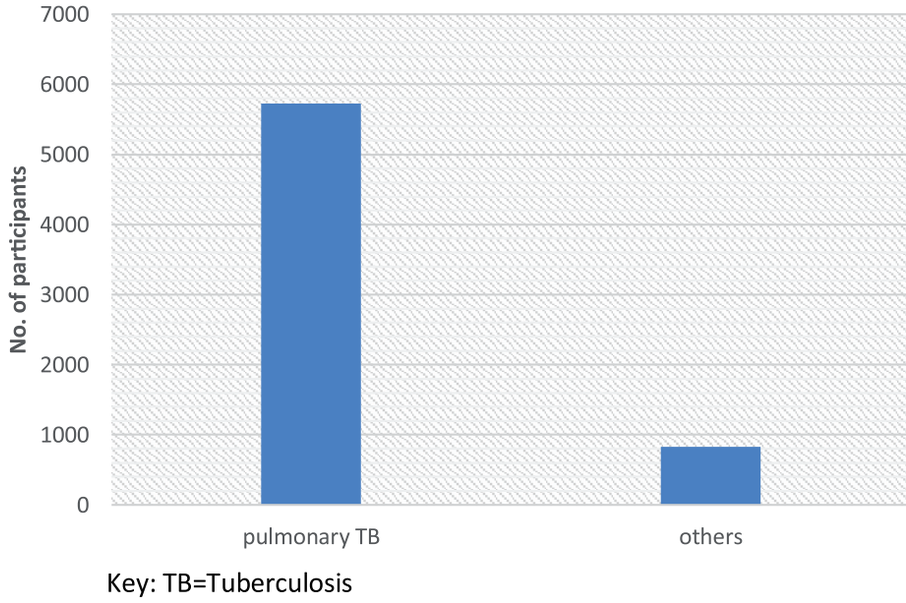

Figure 2.
First opportunistic infection to occur during pre-HAART (2001–2003). Key: TB = tuberculosis.

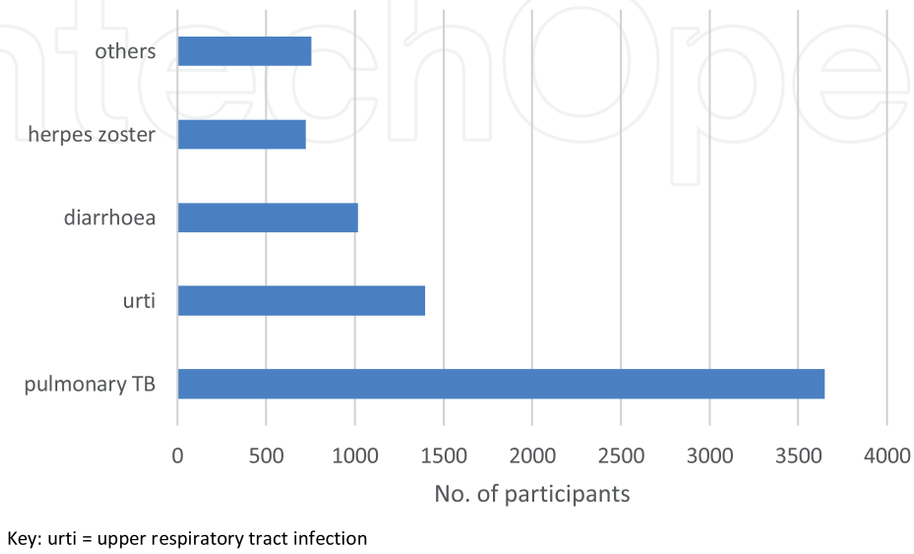

Figure 3.
First opportunistic infection to occur during early-HAART (2004–2006). Key: Urti = upper respiratory tract infection.

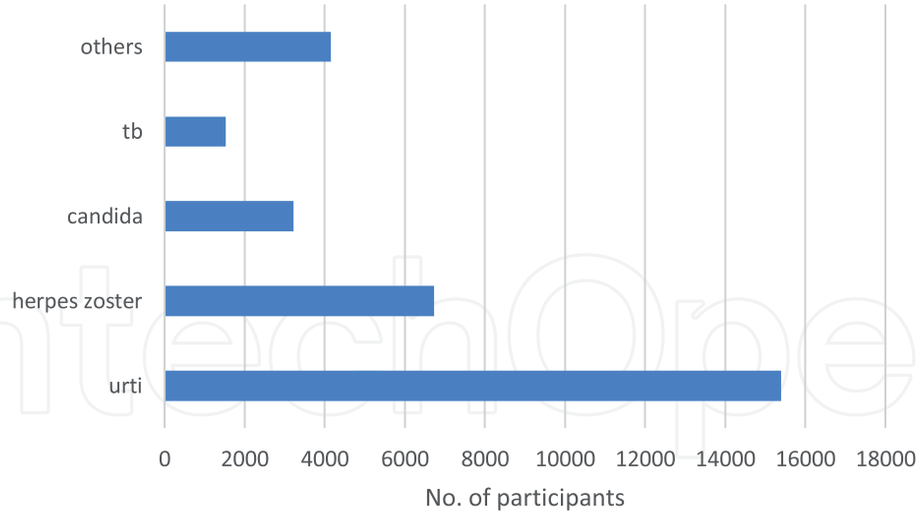

Figure 4.
First opportunistic infection to occur during mid-HAART (2007–2009).

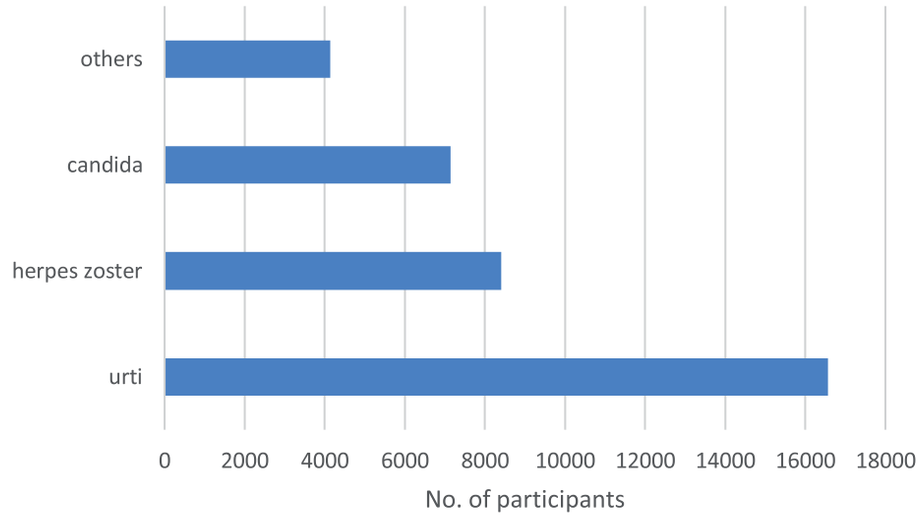

Figure 5.
First opportunistic infection to occur during late-HAART (2010–2013).

(**Figure 3**). In mid-HAART period, 49.6% (n = 31,032) had upper respiratory tract infection as their first opportunistic infection, 21.7% had herpes zoster, 10.4% had candida, 4.9% had pulmonary TB, 13.4% had others (diarrhea, toxoplasmosis, etc.) as their first opportunistic infection (**Figure 4**). In late-HAART period, 45.7% (n = 36,236) had recurrent upper respiratory tract infection as their first opportunistic infection, 23.2% had herpes zoster, 19.7% had candida, and 11.4% had others (pulmonary TB, diarrhea, etc.) as their first opportunistic infection (**Figure 5**).

4. Temporal and spatial distribution of opportunistic infections in Uganda

4.1 Fungal opportunistic infections

4.1.1 Candidiasis

Candidiasis caused by the fungus *Candida albicans* has been associated with HIV/AIDS from the very beginning of the HIV pandemic. Candidiasis can affect the

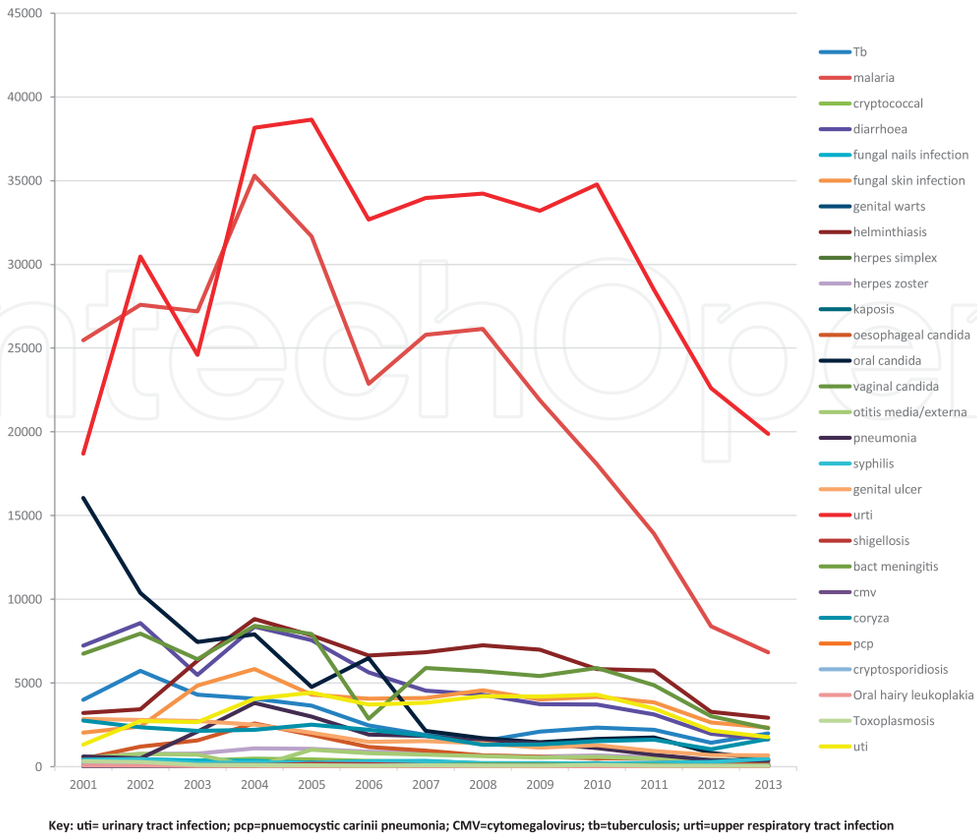

Figure 6.
Temporal distribution of OIs associated with HIV in Uganda.

skin, nails, and mucous membranes throughout the body. Most commonly associated with HIV are oral and esophageal candidiasis. Oral candidiasis is usually the first clinical manifestation of AIDS in most HIV-infected persons causing oral pain that can make eating of food very difficult resulting in malnutrition and HAART failure. Esophageal candidiasis appears later in advanced stages and can also cause a lot of pain in the chest making swallowing of food difficult and hence malnutrition and HAART failure. Studies in the developed countries show high prevalence of oral candidiasis (44.8%) and as high as 67% in sub-Saharan Africa before introduction of effective antiretroviral treatment [2] [18]. In Uganda, most studies before HAART reported high prevalence of both oral and esophageal candidiasis among HIV-infected persons [19–21].

In our recent study, prevalence of oral candida substantially reduced from 34.6% before HAART to 7.2% after HAART (**Figure 6**) [22].

Our recent study also shows that the frequency of oral candida varied by geographical area. HIV-positive patients in western Uganda had higher prevalence of oral candida compared with HIV-positive patients in other geographical areas. Geographical variation in prevalence of oral candidiasis could be an issue of genetic susceptibility and probably level of endemicity. In Netherlands, it was reported that compared with patients from Western Europe, Australia and New Zealand, patients of sub-Saharan African origin had a significantly lower risk for pneumocystis jiroveci pneumonia (PJP) and the authors suggested that differences in genetic susceptibility could be the reason for the lower PJP incidence in the African patients [23]. However, further research is required to gain more insight into the cause of this geographical variation in distribution pattern of oral candida in Uganda.

4.1.2 Pneumocystis carinii pneumonia (PCP) renamed pneumocystis jiroveci pneumonia (PJP)

PCP/PJP caused by *Pneumocystis carinii/jiroveci* used to be one of the most frequent OIs associated with advanced AIDS in the developed countries [24]. Previous studies show that over 80% of the AIDS patients develop PCP when their CD4 cell count drops below 200cell/μl [25]. Before the advent of HAART, it was the most prevalent opportunistic infection in both adults and children in the USA [2] and Western Europe [26, 27].

However following the introduction of HAART, PCP has virtually disappeared among HIV-positive patients in the developed countries [28]. Previous studies also show that PCP/PJP was very rare in sub-Saharan Africa [29–31].

In our recent study, PCP/PJP was very rare reinforcing previous evidence that this OI is not endemic in sub-Saharan Africa.

4.1.3 Cryptococcal meningititis

Cryptococcal meningitis caused by *Cryptococcus neoformans* is one of the most fatal fungal opportunistic infections associated with HIV/AIDS [6]. The disease spectrum includes pneumonia, cutaneous lesions, and meningitis [24]. Cryptococcal meningitis is the most common cause of mortality in adults with HIV [32]. It is the main single cause of death for 20–30% of persons with AIDS in sub-Saharan Africa [6, 33]. Cryptococcal meningitis is often the cause of poor prognosis on HAART [33].

Review of published literature on HIV-associated cryptococcal meningitis shows that its prevalence varies widely both within and between countries [34–37]. In the developed countries, the incidence of cryptococcal disease appears to have generally decreased during the era of HAART [34, 36, 38]. A review of studies on HIV/AIDS-related opportunistic infections in sub-Saharan Africa found 25% prevalence of cryptococcal meningitis among AIDS patients in Ethiopia [39] and 12–50% in South Africa accounting for 44% of the deaths [40]. In Uganda, a study at Mulago National referral hospital found out that the rate of cryptococcal infection among HIV-infected patients was more than double that reported in HIV patients in North America (40.4/1000 person-years vs. 17–20/1000 person-years) prior to the introduction of HAART [41]. In three separate cohort studies in Uganda, cryptococcal meningitis was the leading cause of death (20–40%) [37, 41, 42].

In our recent study findings, the frequency of cryptococcal meningitis substantially declined attributed to increased availability of highly potent systemic antifungal drugs such as fluconazole and HAART (**Figure 5**). Similar findings were also obtained in studied conducted elsewhere [43, 44]. Our recent findings also show that the prevalence was lower in western Uganda compared with the rest of the geographical areas studied probably because of variation in the endemicity of the causative agent. This is consistent with previous studies that show the prevalence of cryptococcosis varied widely both within and between countries [34, 36, 45].

4.1.4 Histoplasmosis

Histoplasmosis is a fungal infection caused by *Histoplasma capsulatum* considered diagnostic of AIDS in an HIV-infected person [24]. In about two-thirds of AIDS patients with histoplasmosis, it is the initial OI and over 90% of the cases have occurred in patients with CD4+ cell count <100 [46]]. Though it is a major AIDS-defining illness in Central and South American countries [46], few studies about

it have been published in Africa. In Uganda, a recent study confirmed its absence among HIV-infected individuals [22].

4.2 Viral opportunistic infections

4.2.1 Cytomegalovirus (CMV)

This virus causes HIV-associated retinitis resulting in eventual blindness [6]. Prior to the introduction of HAART, cytomegalovirus was commonly reported among HIV-infected patients in many developed countries [2, 26, 27]. A cross-sectional review of AIDS patients' medical records in France [27] found 37% of the patients suffered from cytomegalovirus infection. Another retrospective review of medical records in Italy [26] found 25.6% of the AIDS patients had cytomegalovirus infection. Cytomegalovirus was predominantly common at very low CD4 levels, with the majority of cases of CMV retinitis occurring at CD4 counts below 50 cells/mm^3. However, with the advent of HAART, there has been tremendous decline in the incidence of CMV in the developed countries.

The few studies that have reported on cytomegalovirus in sub-Saharan Africa show that it is very rare among HIV-positive patients. One study in Burundi reported cytomegalovirus retinitis diagnosed in only 1% of the AIDS patients [47] and also in only 1% of the AIDS patients in Malawi [48]. In our recent study in Uganda, it was found to be very rare (<1%) (**Figure 6**).

4.2.2 Herpes simplex virus types 1 and 2(HSV-1 and HSV-2)

Herpes infections are the most commonly diagnosed infections among HIV-positive patients both in developing and developed countries [49]. Both viruses cause severe and progressive rapture of the body mucus membranes. HSV-1 affects mainly the membranes of the nose and mouth leading to herpes-caused pneumonia, which can result into death in AIDS patients [49]. HSV-2 also affects the membranes of the anus and genitals causing severe peri-anal and genital ulcers, which can facilitate HIV transmission and is one of the most sexually transmitted co-infections with HIV [49–51]. Previous studies in Uganda found high prevalence of HSV-2 in HIV-positive patients with genital ulcer disease [52].

In our recent study, frequency of genital ulcers declined significantly attributed to increasing availability of HAART and effective treatment (**Figure 5**). Previous studies also showed that acyclovir significantly reduces both genital ulcers and HSV-2 shedding [53]. Though prevalence reduced, genital ulcer has not been completely eliminated implying that HSV-2 could be highly endemic and its sexual transmission is still ongoing in Uganda. It was more common in central and western Uganda compared with other geographical areas of Uganda.

4.2.3 Herpes zoster (Shingles)

Herpes zoster (Shingles) caused by *Varicella zoster* virus is usually a latent infection in immuno-competent persons [6]. However, the virus is quickly reactivated when the immune system is compromised and like Herpes simplex, it has the potential to cause a rapid onset of pneumonia in AIDS patients. Untreated Herpes zoster viral pneumonia can result into death and Herpes zoster is usually an early indicator that the patient is progressing to AIDS [54].

Most studies in the developed countries have reported on Herpes zoster as one of the most frequent AIDS-defining illnesses among HIV-infected persons [2, 27, 55]. In a cohort study in the USA, Herpes zoster accounted for 36% of the opportunistic diseases that appeared in the first 24 weeks of HAART treatment [56]. In developing countries, Herpes zoster is one of the most common opportunistic infections associated with HIV/AIDS [57, 58]. In a population-based cohort in south-western Uganda, the incidence of Herpes zoster was found to be 5.4 per 100 person years of observation [58].

In our recent study, frequency of herpes zoster reduced substantially attributed to increasing availability of HAART. The mean annual prevalence reduced from 1.3% in 2002 to 0.33% in 2013 [59]. These findings are consistent with findings from studies that reported significant reduction in incidence of Herpes zoster after HAART roll-out [60]. The prevalence was more in central and western regions of Uganda compared with other geographical areas. The variance in prevalence of herpes zoster by geographical area could partly be due to differences in the level of natural immunity or endemicity of the infectious agent or other unknown biological factors.

4.3 Bacterial opportunistic infections

4.3.1 Tuberculosis (TB)

Tuberculosis caused by *Mycobacterium tuberculosis* affects about one-third of the world's population and is the leading cause of morbidity and mortality among HIV/AIDS patients in the world [61]. However, it is most common in low- and middle-income countries in which it is responsible for over 75% of mortality among HIV-infected patients [62–65]. A meta-analysis of the published research in sub-Saharan Africa shows that the incidence of tuberculosis varied widely among cohorts of HIV-infected patients in different countries [3]. Studies in Cote d'Ivoire and Kenya found tuberculosis to be the primary cause of death in 32 and 47% of deaths, respectively [62, 66].

Uganda was listed among the 22 high-burden TB countries in the world [67] and studies conducted in eastern Uganda showed that over 80% of the HIV-related morbidity and 30% of the HIV related death were due to TB [68, 69].

In our recent study, the frequency of *M. tuberculosis* has substantially reduced over time consistent with studies elsewhere that reported significant decreasing trends in tuberculosis prevalence attributed to HAART [70–72]. These findings are in agreement with another study that assessed the effect of HAART on TB incidence in Uganda and showed TB reduced from 7.2% at baseline to 5.5% after 1.4 yrs. of follow-up [68]. Though TB had a significant declining trend in this study, it has not been completely eliminated even after introduction of HAART. This could probably be attributed to the fact that TB is endemic in the country and improvements in TB diagnosis with introduction of Gene-Xpert technology [73] that has improved TB detection rates in Uganda. In our recent study, it was also observed that TB was more frequent among HIV-positive patients in Northern and Eastern Uganda compared with other geographical areas probably because of the socioeconomic disparities in the regions.

4.3.2 Mycobacterium avium *complex (MAC)*

M. avium complex are benign in immuno-competent individuals but can cause severe, life-threatening diarrhea, and septicemia in HIV-infected individuals who are severely immune-compromised [56]. Unlike TB, MAC is only environmentally acquired (food, animals, water supplies, and soil) and not transmissible from person

to person. MAC accounts for 18–43% of illness in HIV-positive patients and has been implicated as the main cause of a non-specific wasting syndrome in USA [2, 74]. In sub-Saharan Africa, *M. avium* complex is very rare and was only reported in South Africa and Kenya [75, 76]. No information was available on its prevalence among HIV-positive individuals in Uganda.

4.3.3 Bacterial pneumonia

Bacterial pneumonia caused by *Streptococcus pneumonia* is one of the commonest respiratory diseases in HIV-infected patients [6]. Though preventable, the disease is quite common among HIV-positive patients in sub-Saharan Africa [77–79]. Previous studies showed that the risk of bacterial pneumonia were higher among HIV-infected individuals compared with the general population [80, 81].

Though a conjugate pneumococcal vaccine is available [82], it has not been widely accessed by HIV-positive patients. HAART and cotrimoxazole prophylaxis have also been shown to be associated with a significant reduction in the risk of bacterial pneumonia [80, 83].

In our recent study, the frequency of bacterial pneumonia substantially reduced over time. This could probably be attributed to a combination of universal cotrimoxazole prophylaxis introduced in 2003 and HAART in 2004. Prevalence of bacterial pneumonia also varied by geographical area with the highest prevalence observed in Northern and Eastern Uganda. The geographical difference could be due to the socio-economic regional disparities with Northern and Eastern Uganda being more prone to OIs due to poorer living conditions compared with other areas [84].

4.4 Protozoal opportunistic infections

4.4.1 Toxoplasmosis

Toxoplasmosis caused by *Toxoplasma gondii* is a common opportunistic infection in advanced AIDS [6]. A study in Italy reported 15.2% prevalence of cerebral toxoplasmosis among AIDS patients [26], while another study in France reported a 37% prevalence among AIDS patients [27].

However, in sub-Saharan Africa, few studies have been published on this opportunistic infection and perhaps could be under-reported due to lack of surveillance capabilities. A study in Cote d'Ivoire showed only 4% prevalence of cerebral toxoplasmosis of which 60% died [85]. In our recent study, the prevalence of toxoplasmosis was very low (< 1%) (**Figure 6**).

4.4.2 Cryptosporidiosis

Cryptosporidiosis caused by *Cryptosporidium parvum* is usually associated with chronic diarrhea (>1 month) in HIV-positive individuals [24]. Diarrhea has for long been reported to be one of the commonest complication in HIV-positive individuals associated with high mortality rate [86]. Previous studies show up to 60% of people living with HIV experience diarrhea, which negatively affects their quality of life and adherence to HAART [87].

However, diarrhea among HIV-positive individuals may be due to multiple causes including infectious causes (bacterial, viral, protozoal, heliminthic, etc.) or

non-infectious causes (ARV drug effects, e.g., ritonavir-boosted protease inhibitors such as lopinavir/ritonavir or nelfinavir) [87–91]. The commonest infectious causes of diarrhea were reported to be helminthic infections (29.5%), bacterial infections (19.2%), and protozoal infections (9.2%) [92]. Enteric viruses have also been reported associated with diarrhea [86]. Prevalence was significantly higher among HIV-positive people when compared with matched controls [87]. Acute diarrhea (<1 month) in adults has been associated with bacterial infections (non-typhoid salmonella), while chronic diarrhea (>1 month) was reported to be associated with cryptosporidial or helminthic infections [93–96]. In Uganda, data on diarrhea disease burden among HIV-positive individuals in different geographical areas and trends were scarce.

Cryptosporidiosis occurs in HIV-positive individuals whose immunity is severely suppressed [6]. It is rare in developed countries probably because of the high hygienic standards [2]. It is associated with communities living in unhygienic conditions with high risk of exposure to the infectious agent [29, 97].

Previous studies in sub-Saharan Africa have reported prevalence of *Cryptosporidium* chronic diarrhea among HIV-infected patients as high as 17% in Kenya [97], 25–32% in Zambia [98], and 28% among HIV patients at Mulago in Kampala, Uganda [99]. Our recent findings show diarrhea mean annual prevalence reduced by 83% (12–2%) between 2002 and 2013 most likely because of HAART [100]. Prevalence was higher in Northern and Eastern Uganda compared with Central and Western Uganda probably because of the socioeconomic disparities between these regions with the latter being relatively more developed compared with the former [84]. However, more studies are required to give more insight on diarrhea causes among HIV-positive patients on HAART in different geographical areas.

4.4.3 Malaria

Although malaria is not diagnostic of AIDS [93], several studies show that malaria tends to occur with increased frequency and severity in HIV-infected adults compared with the general population [3, 101–106]. Previous studies show that HIV increases vulnerability to malaria infection and malaria could enhance the progression of HIV infection to clinical AIDS in the absence of effective treatment [107].

A review of studies on HIV-related opportunistic infections in sub-Saharan Africa showed a relatively higher prevalence of malaria parasitemia among HIV-infected women in Malawi on their first prenatal visit (32–54%) compared with HIV-negative women (19–42%) [3]. A study conducted in Uganda [104] found that most HIV patients seeking treatment for malaria had unexpectedly high levels of HIV infection and more than 30% of adults presenting at district health centers with uncomplicated falciparum malaria were co-infected with HIV. Another study conducted by researchers from Rome's Istituto Superiore di Sanità, University of Milan in Northern Uganda [105] examined the association between HIV and malaria and found high HIV prevalence among patients admitted for malaria at Lacor Hospital (48.8%) compared with that estimated for the general population living in the hospital's catchment's area (17.8%), suggesting an association between HIV and malaria. Other previous studies in Uganda also showed that the risk of clinically diagnosed malaria was significantly higher in HIV-infected individuals compared with HIV-negative controls [101, 106].

In our recent study findings, malaria prevalence among HIV-positive individuals reduced in the period between 2001 and 2003 (80%) and leveled off in the

subsequent years. The reduction in malaria prevalence started in the period before HAART and could partly be attributed to universal cotrimoxazole prophylaxis [108, 109]. The study findings reinforce the existing evidence that malaria prevalence has significantly reduced among HIV-positive individuals due to the combined effect of cotrimoxazole prophylaxis and HAART [110–114].

However, the decline in malaria prevalence over time may not be attributed to HAART and cotrimoxazole prophylaxis alone but could also have been caused by the other malaria interventions in Uganda including massive distribution of insecticide-treated mosquito bed nets and introduction of indoor residual spraying especially in Northern Uganda [114, 115]. Though malaria prevalence among HIV-positive patients reduced in the era of HAART, it has not been completely eliminated. In view of the fact that malaria is highly endemic in Uganda and HIV-positive patients are highly vulnerable, malaria prevention/control should therefore remain an integral part of comprehensive HIV/AIDS care in Uganda. Prevalence was highest in Central Uganda, followed by Northern and Eastern regions. Geographical variation in prevalence of malaria could be influenced by malaria endemicity in the different geographical areas.

4.5 Helminthic opportunistic infections

The most common helminthic infections of public health importance are *Ascaris lumbricodes*, *Trichuris trichura*, *Necator americanus*, and *Ancylostoma duodenale*. Globally, it is estimated that about two billion people are infected with intestinal helminthic infections mainly in developing countries [116]. In HIV-positive patients, co-infection with intestinal helminthic infections was associated with dysregulation of the immune response causing inability of the HIV-positive patient to mount an effective immune response [116]. High prevalence of geohelminths can lead to increased prevalence of anemia thereby worsening the health conditions of persons living with HIV/AIDS [117].

In HIV-positive individuals, these parasites compete for food nutrients and cause mal-absorption of certain food nutrients and some of them suck blood (Hook worms) further weakening the body and causing faster progression of HIV disease [118]. The negative effects associated with these helminthic infections have been in terms of diminished physical fitness of the affected individuals who easily succumb to other opportunistic infections in addition to responding poorly to treatment [119].

In our recent study, geohelminths were the most frequent non-AIDS defining opportunistic infections before and after HAART. The study also found out that Northern and Eastern Uganda had the highest burden of the intestinal helminthic infections compared with other regions. The geographical difference could be due to the socioeconomic regional disparities with Northern and Eastern Uganda being relatively poorer compared with other areas [84]. Previous studies showed that poor socioeconomic status was associated with higher risk of geohelminths [120–122].

The high burden of geohelminths even after HAART shows that in high endemic settings, the effect of HAART on these worms is relatively insignificant and alternative or supplementary control efforts are therefore required. A Cochrane review of published literature on testing and treating HIV-positive patients for intestinal helminthic infections showed that regular deworming with a single dose of albendazole is feasible in developing countries and would potentially improve survival and the quality of life of persons living with HIV/AIDs [116]. It is therefore recommended that regular deworming becomes an integral part of comprehensive HIV/AIDS care in Uganda.

4.6 Upper respiratory tract infections (URTI)

Upper respiratory tract infections (URTIs) are contagious infections that affect mainly the nasal sinuses and the throat caused by a variety of bacteria and viruses such as influenza virus, streptococcus bacteria. The most frequent respiratory infections in HIV-infected patients are upper respiratory tract infections presenting as common cold (cough, fever, runny nose), epiglottitis, laryngitis, pharyngitis (sore throat), and sinusitis [123]. In this study, URTIs were the most frequent infections pre-HAART and have remained the most frequent infections even after HAART (**Figure 6**). Previous studies also show that upper respiratory tract infections are more common in HIV-infected persons compared with the general population attributed to the reduced immunity [124].

4.7 HIV-associated opportunistic cancers

Kaposi's sarcoma (KS) is the most reported opportunistic cancer associated with HIV/AIDS and with an infectious cause [24, 125, 126]. In fact, previous studies show that KS is caused by the human herpes virus type 8 (HHV8) [127, 128], and in Uganda, HHV8 has been identified in over 85% of KS tissue specimens [129, 130]. Sero-prevalence studies in Uganda also suggest that HHV8 is endemic in the general population [131, 132]. In our recent study, Kaposi's sarcoma was found rare among study participants. These findings are consistent with other studies elsewhere, which reported lower prevalence of KS in comparison with other OIs among HIV-positive individuals [133–135]. Prevalence was higher in central compared with other regions in Uganda. However, more studies giving insight on the role of HAART on HHV8 disease burden and determinants of its geographical distribution are required.

5. Conclusion

Today, most OIs are less common in people with HIV because of increasing availability of effective antiretroviral treatment. However, there are certain OIs such as intestinal helminthic infections and upper respiratory tract infections whose prevalence has persistently remained high despite increasing access to HAART. Most OIs have not been completely eliminated mainly because some people are not aware that they have HIV and so wait until they experience an OI. Some may delay to access treat due to late diagnosis or may be on treatment but develop resistance to available drugs.

By end of 2020, around 28million people were accessing effective antiretroviral therapy. Though the global strategy to eliminate HIV by 2020 failed, there is still hope that with sustained global HIV/AIDS eradication efforts, HIV could be eliminated by 2030.

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