Coinfection with Helminths and HIV-1 in East Asia

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Abstract As geographic distributions of human immunodeficiency virus-1 (HIV-1) and helminth infections largely overlap in many regions of the world, including the East Asian region, HIV-1/helminth coinfection is a common finding. Both HIV-1 and helminth infections mutually interact on several levels, especially on the level of immunomodulation, which has potential effects on the risk of acquisition and the clinical course of the involved pathogens. In this chapter, we present the epidemiology of HIV-1/helminth coinfection in East Asia and summarize the current knowledge on mutual interaction and its effect on epidemiology, clinical course, and treatment of the respective pathogen.

Keywords HIV-1 · Helminth infection · Coinfection · East Asia

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J. Utzinger et al. (eds.), *Neglected Tropical Diseases - East Asia*, Neglected Tropical Diseases, https://doi.org/10.1007/978-3-030-12008-5_7

1 Introduction

The term coinfection refers to a concomitant infection with two or more pathogens in the same host. Different pathogens in the same host may interact in multifaceted ways, which may affect the epidemiology, course, and treatment of the associated diseases. In contrast, opportunistic infections are caused by pathogens that may produce invasive infections only under the precondition of a weakened immune system, e.g. acquired immune deficiency syndrome (AIDS) as a result of an advanced human immunodeficiency virus-1 (HIV-1) infection. Most AIDS patients die from a variety of opportunistic coinfections, including viruses (herpes viruses, JC virus, etc.), bacteria (*Mycobacteria*, *Bartonella*, etc.), fungi (*Cryptococcus* spp., *Histoplasma capsulatum*, *Penicillium marneffei*, *Pneumocystis jirovecii*, etc.), and parasites (*Toxoplasma gondii*, etc.) (Domingues and Waldman 2014).

HIV-1 coinfections with the hepatitis B and C viruses, *Mycobacterium tuberculosis*, and other opportunistic pathogens have been and continue to be the focus of international research efforts, whereas HIV-1/parasite coinfection received less attention. Reports originate mostly from Asia and Africa and mainly concern coinfections with *Plasmodium falciparum*, *Leishmania* spp., and intestinal parasites (*Cryptosporidium*, *Microsporidia*, *Cyclospora*, Entamoeba histolytica and Giardia intestinalis) (Tian et al. 2009). Even though there has been increasing interest in coinfection with HIV-1 and helminths during the past years, this research domain remains neglected.

Helminth infections affect more than a billion individuals, and more than 35 million persons are infected with HIV-1 globally. Both infections disproportionally concern people in low- and middle-income countries (LMICs), also in the Eastern Asian region, where especially in the Chinese provinces of Yunnan and Sichuan and in Southeast Asia, the burden of both diseases is high (Hotez and Ehrenberg 2010). Here, concomitant infections are common, and prevalence of helminth infection may reach above 20% in HIV-1-infected individuals.

Both HIV-1 and helminth infection have significant effects on multiple aspects of the host's immune system and may induce an inadequate immunological reaction to concomitant infections. Therefore, concerns have been raised that HIV-1 infection may increase the susceptibility to helminth infections and vice versa, negatively influencing their natural course and response to treatment.

In the following, we will cover the epidemiology of helminth/HIV-1 coinfections in East Asia and give an overview of HIV-1/helminth interaction on immunological and clinical level.

2 Epidemiology of Helminthiases in East Asia

Helminths are the most common infectious agents of humans in LMICs with over one billion people infected with one or more helminth species. Usually helminth infections are of chronic nature due to persistence of the parasite over years and

frequent reinfections in endemic areas (Hotez et al. 2008). All helminth infections have in common that their prevalence is closely linked to poor sanitation and hygiene and therefore to poverty and a lack of education (Hotez and Ehrenberg 2010). National control programmes for different helminth infections have been implemented in many countries with variable success. In the People's Democratic Republic of China, for example, overall helminth infection rates have dropped from 55% to 21% from 1990 to 2006. However, infection rates remain at high levels in the western part of the People's Republic of China, especially in rural areas (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005). This region remains the hot spot for helminth infections in the East Asian region, as helminth infection rates in other East Asian countries, such as Japan, South Korea, and Taiwan, have remained at relatively lower levels (Kim et al. 2009; Brooker et al. 2006).

2.1 Important Helminth Infections in East Asia

Soil-transmitted helminths (STHs: *Ascaris lumbricoides, Trichuris trichiura, and hookworm*) are the most common human pathogenic helminths worldwide (Lustigman et al. 2012). They are widely endemic in Southeast Asia and the People's Republic of China, especially in the southwestern provinces (Hotez and Ehrenberg 2010). In the People's Republic of China, it was estimated that around 129 million people were infected with STHs in 2005 (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005).

Strongyloides stercoralis is endemic in several countries of East Asia (Schär et al. 2013). It has been estimated that worldwide, 30–100 million people are infected (Olsen et al. 2009). However, this number might be much higher as the infection is difficult to diagnose with current standard diagnostic methods (Steinmann et al. 2007). Exact prevalence data from eastern Asia is scarce, but a country-wide prevalence of as high as 14% for the People's Republic of China and 18.7% for Japan has been suggested (Schär et al. 2013).

Schistosoma japonicum, causing intestinal schistosomiasis, represents *Schistosoma* spp. in East Asia, where it is present in the People's Republic of China along the Yangtze River (Zhou et al. 2010). Its distribution is closely linked to water sites, which are habitat to the intermediate host snails. Due to successful control programmes, the number of people infected with *S. japonicum* in the People's Republic of China decreased dramatically in the last decades from 11.6 million in the mid-1950s to below 300,000 in 2011 (Yang et al. 2014).

Most cases of food-borne trematodiasis worldwide are found in the Southeastern and Eastern Asian region. The most important food-borne trematodes in this area are the liver flukes (*Clonorchis sinensis* and *Opisthorchis viverrini*) and lung flukes (*Paragonimus* spp.). These helminths are all transmitted via raw or undercooked freshwater fish, other aquatic products or water plants and lead to chronic inflammation of the liver, biliary tract, or lung tissue (Keiser and Utzinger 2009).

The global distribution of *C. sinensis* is restricted to this region, with an estimated 35 million people infected. The majority of cases (15 million) are found in the People's Republic of China, but the infection is also endemic in the Republic of Korea, Taiwan, and Vietnam (Lun et al. 2005). Global distribution of *O. viverrini* is limited to Southeast Asia, with an estimated ten million people infected, of which eight million are found in Thailand and two million in the Lao People's Democratic Republic (Keiser and Utzinger 2009). Fascioliasis and paragonimiasis are found both in Asia and on other continents. Global burden estimates for *Paragonimus* are 20 million and for fascioliasis 4–17 million infected individuals worldwide (Keiser and Utzinger 2009).

Lymphatic filariasis, leading to the clinical picture of elephantiasis, is no longer endemic in East Asia, especially due to successful control programmes, such as in Japan and the People's Republic of China (Yang et al. 2014). However, in several countries of Southeast Asia, the disease is still widely endemic with approximately 15 million people infected, representing a quarter of the global burden of lymphatic filariasis (Sudomo et al. 2010).

Echinococcosis is present in most countries of Eastern Asia. The vast majority of cases are caused by *Echinococcus granulosus*. However, it is estimated that the People's Republic of China contributes to 90% of the global burden of alveolar echinococcosis due to infections with *E. multilocularis* (World Health Organization et al. 2013; Torgerson et al. 2010). In the People's Republic of China, new cases of echinococcosis have been increasing continuously since 2004 (Zheng et al. 2013). During the 2006 national survey, 380,000 people in the People's Republic of China where infected with *Echinococcus* (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005) with 90% of infections caused by *E. granulosus* and 10% by *E. multilocularis* (Yang et al. 2014).

Cysticercosis, caused by the pork tapeworm *Taenia solium*, occurs in areas with inadequate sanitation and pork meat management. The exact prevalence in East Asia is unknown. In the People's Republic of China, the estimated number of cases of cysticercosis is currently three to six million (World Health Organization et al. 2013).

3 Epidemiology of HIV-1/AIDS in East Asia

Since the first HIV-1/AIDS patients were reported in the USA in 1981, the virus rapidly spread all over the world. Currently, HIV-1 is present in 210 countries, and around 75 million people have become infected with HIV-1, and about 35 million have died of AIDS worldwide. Thus HIV-1/AIDS has become one of the greatest pandemics in modern times with devastating socio-economic and demographic consequences (UNAIDS 2013; Piot and Quinn 2013). According to UNAIDS estimates, there were 35.3 million people worldwide living with HIV-1 infection in 2012, of whom 880,000 resided in East Asia (the People's Republic of China, Taiwan, North Korea, South Korea, and Japan). All countries, except for North

Korea, had reported HIV-1 and AIDS cases, with the People's Republic of China being the major contributor (Suguimoto et al. 2014).

Though the national estimated prevalence of HIV-1 infection remains low at 0.037% (501,000/1367.82 million), the People's Republic of China is the most affected country in East Asia in terms of absolute numbers due to its big population (UNAIDS 2015a). After the detection of the first case of HIV-1/AIDS in 1985, the epidemic rapidly spread among injection drug users (IDUs) and female sex workers from rural regions in Yunnan province, an opium producing area, along major drug trafficking routes throughout the country (Suguimoto et al. 2014). In the twenty-first century, the pattern of the endemic is changing, and especially homosexual HIV-1 transmission in urban areas is becoming increasingly important; thus, HIV-1 prevalence among men

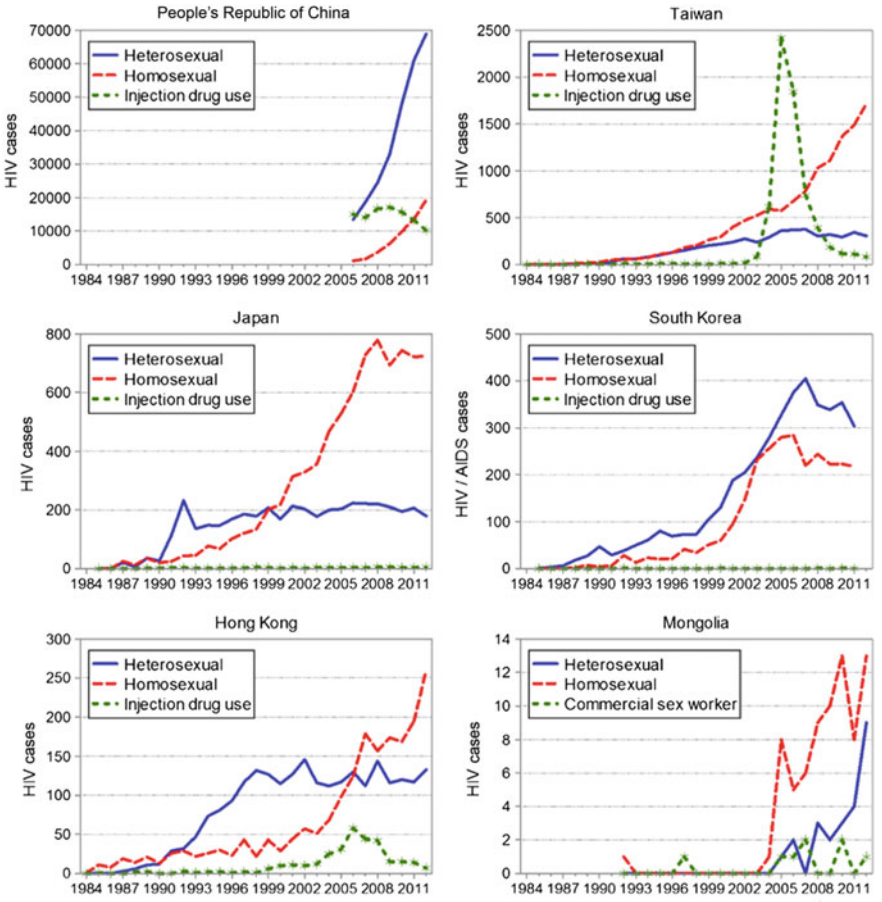

Fig. 1 Change in the trend of the annual number of HIV cases by main routes of transmission in the People's Republic of China, Taiwan, Japan, South Korea, Hong Kong, and Mongolia (1984–2012; People's Republic of China 2006–2012) (Reprinted by permission from Springer Nature: Springer, Current HIV/AIDS Reports, Changing patterns of HIV epidemic in 30 years in East Asia, Suguimoto et al. 2014)

having sex with men (MSM) is already higher than in IDUs and female sex workers in most of the provinces and reaches up to 10% in the southwestern part of the People's Republic of China, which remains the epicenter of the Chinese HIV-1/AIDS epidemic (Zhang et al. 2013).

Figure 1 shows temporal trends in the annual number of HIV cases. In Japan, South Korea, Taiwan, and Hong Kong, the prevalence of HIV-1 in the general population remains very low (e.g. in Japan 0.018% and in South Korea 0.014%) (Report to UNAIDS—HIV/AIDS Trends in Japan 2015; UNAIDS 2015b). In these countries, the HIV-1/AIDS epidemic is largely driven by MSM. In Japan the male-to-female ratio ranges between 16:1 and 12:1, and in Taiwan it is 30:1. In Japan and Taiwan, 74% and 84% of HIV-1-infections are attributed to homosexual transmission (Suguimoto et al. 2014; Centers of Disease Control, R.O.C. (Taiwan), Statistics of HIV 2015; Centers for Disease Control, R.O.C. (Taiwan)—Annual Report 2015). In South Korea, 92% of HIV-1 infections were diagnosed in men in the period between 1985 and 2011 (UNAIDS 2015b). In all these countries, the incidence of new HIV-1 infections is increasing. For example, in Japan, the number of newly reported HIV-1 infection in MSM increased steeply from 314 to 724 per year from 2001 to 2012, resulting in a prevalence of up to 6% among MSM in the large cities of the country (Report to UNAIDS—HIV/AIDS Trends in Japan 2015), and in Hong Kong, the number of cases is steadily increasing from about 400 in 2009 to 651 mainly male (84%) cases in 2014 (Prepared by Special Preventive Programme: FACTSHEET on HIV/AIDS Situation in Hong Kong 2014).

4 Epidemiology of HIV-1/Helminth Coinfection in East Asia

The geographic distributions of HIV-1/AIDS and helminth infections considerably overlap in sub-Saharan Africa, South America, and Asia. In East Asia, the Chinese provinces of Guizhou, Guanxi, Sichuan, and Yunnan are of special concern, as they represent the regions with the highest burden of both HIV-1 and helminth infections in East Asia. This corresponds to the mostly rural and less developed areas in the People's Republic of China (Tian et al. 2012). In Yunnan province, which in 2014 was the province with the highest HIV-1 prevalence in the People's Republic of China, the helminth overall infection rate was as high as 22% in the last national survey (Coordinating Office of the National Survey on the Important Human Parasitic Diseases 2005). However, exact numbers of HIV-1/helminth coinfections in Asia are not available. Few studies have investigated the prevalence of helminth infection among HIV-1 patients and showed corresponding prevalence rates compared with non-HIV-1-patients (with the exception of lymphatic filariasis and *S. stercoralis*, which have been reported more frequently in HIV-1 infected patients) (Tian et al. 2012; Wiwanitkit 2001; Paboriboune et al. 2014).

5 Interaction of HIV-1 and Helminths in Coinfected Patients

Because of the largely overlapping geographic distribution of the HIV-1/AIDS epidemic and helminth infections, elevated HIV-1 transmission rates in sub-Saharan Africa compared with more industrialized countries, and a supposed harmful mutual interference on an immunological level, helminth infections have been postulated since the 1990s to affect the risk of acquiring and the course of HIV-1 infection (Lawn 2004; Borkow and Bentwich 2004; Bentwich et al. 1995).

5.1 Evidence for Interaction of HIV-1 and Helminths in Coinfected Patients Based on Immunological Findings

This chapter summarizes how helminth-induced immunological changes, including strong T-helper 2 (Th2) bias, chronic immune activation, and immune suppression, may affect the viral capacity of transmission and replication and lead to a faster disease progression of HIV-1 infection.

A pronounced type 2 immune response is the hallmark of a helminth infection and other large eukaryotic pathogens. A Th2 immune response is mediated by Th2 cells, secreting corresponding interleukins (IL-4, IL-5, IL-10, and IL-13), and characterized by the proliferation of B cells and immunoglobulin E (IgE) as well as eosinophil production (Brown et al. 2004). A Th1 immune response, in contrast, includes the secretion of interferon-γ (IFN-y) and interleukin (IL)–2 by Th1 lymphocytes, promoting the activation of macrophages and dendritic cells and thereby enhancing the ability to kill intracellular pathogens, which is essential for the control of viral infections (Brown et al. 2004). These two immune responses cross-regulate each other: cytokines produced by the Th1 subset suppress the secretion and/or the activity of cytokines of the Th2 subset and vice versa (Borkow and Bentwich 2004). Helminth-induced pressure towards a Th2-type immune response is so potent that bystander antigens become a target (Kullberg et al. 1992). It has been shown in humans and in animal models that an aberrant Th2 cell response to pathogens that are controlled by IFN-y and a Th1 cell response can result in progressive infection (Bretscher 2014). In HIV-1 infection, the Th1 cell response is associated with low viremia, slow disease progression, and better survival (Bretscher 2014; Clerici and Shearer 1993; Li et al. 2012). On the other hand, a switch to a Th2-induced cytokine profile may be related to progression to AIDS (Bretscher 2014; Clerici and Shearer 1993; Li et al. 2012). However, this point is still being debated (Zanussi et al. 1996). On the basis of this mechanism, helminth-induced Th2 immune response may affect the course of HIV-1 infection.

Chronic immune activation characterizes both helminth and HIV-1 infection, and levels of immune activation are higher in individuals coinfected with HIV-1 and helminths than in those with HIV-1 mono-infection (Mkhize-Kwitshana et al. 2011).

In HIV-1 infection, progression is marked by a continuous rise of the viral load accompanied by a progressive depletion of the total helper $CD4^+$ T-lymphocytes with a subsequent fatal immunodeficiency. It is widely accepted that during the acute phase of HIV-1 infection, the massive loss of $CCR5^+$ $CD4^+$ memory T cells located predominately in the mucosal surfaces of the intestinal, respiratory, and reproductive tract occurs in the first few weeks of infection due to the direct cytolytic effect of HIV-1. On the other hand, systemic chronic immune activation, which is considered a hallmark of the asymptomatic phase of infection, is the driving force of the progressive $CD4^+$ T-cell depletion over the years following initial infection (Borkow and Bentwich 2004; Douek et al. 2003; Sauce et al. 2011). High levels of immune activation in HIV-1-infected individuals without antiretroviral therapy (ART) are associated with increased levels of plasma viral load and accelerated disease progression (Lawn et al. 2001). High viral load is a major risk factor for sexual transmission and mother-to-child transmission of HIV-1. It is therefore conceivable that helminth-induced excess immune activation results in an increased risk of sexual and vertical HIV-1 transmission as well as in an accelerated disease progression (Lawn et al. 2001; Fang et al. 1995; Quinn et al. 2000).

Additionally, helminths and their excretory-secretory molecules manipulate the regulatory network of the innate and the adaptive immune system and reduce the ability of the host to generate a potent and protective immune response (Borkow and Bentwich 2004; Shapira-Nahor et al. 1998; Wammes et al. 2014; Schmiedel et al. 2015). In particular $FOXP3^+$ regulatory T (Treg) cells, which exert their function among others by the secretion of IL-10 and TGF-β, may be involved in the downregulation of both Th1 and Th2 cell responses (Schmiedel et al. 2015). The responsiveness is diminished to antigens from the infecting parasite but also to bystander antigen, to routine vaccinations, and even to allogenic tissue transplants (Maizels and Yazdanbakhsh 2003; Greene et al. 1983). While in helminth infection the modulation of the immune system serves to enhance the survival of the parasite and to reduce acute morbidity of the host due to immunopathologic complications, a downregulation of the Th1 immune response may be associated with an increased susceptibility to HIV-1 infection and diminished ability to control HIV-1 infection. However, Tregs interact with the immune system on several levels, which makes the impact of helminth-induced Treg expansion on HIV-1-related outcomes unpredictable (Chevalier and Weiss 2013). A study on HIV-1-exposed seronegative individuals in Kenya suggests that high Treg cell frequencies may protect from HIV-1 infection by reducing levels of immune activation and rendering $CD4^+$ T cells less susceptible to HIV-1 infection (Card et al. 2009).

It has been shown that deworming of helminth-infected patients results in a normalization of immunological parameters related to immune activation, Th2 immune response, and Treg-induced T-cell hypo-responsiveness (Borkow and Bentwich 2004; Schmiedel et al. 2015).

5.2 *Evidence for Interaction of HIV-1 and Helminths in Coinfected Patients Based on Epidemiological Findings*

With regard to the effect of helminthiases on the risk for HIV-1 transmission, the most consistent epidemiological evidence is available for female urogenital schistosomiasis (FUS) in sub-Saharan Africa (Downs et al. 2011, 2012). FUS results from the disposition of eggs of *S. haematobium* in the interconnected vascular network of the pelvic region and is characterized by a number of genital disorders, including pain, spontaneous and contact bleeding, vesicovaginal fistula, and infertility. FUS develops in 33–75% of women infected with *S. haematobium* and is associated with a three- to fourfold increased risk of HIV-1 infection (Downs et al. 2011; Kjetland et al. 2006; WHO 2009), which has been attributed not only to damage of the mucosal epithelial barrier but also to an increase of mucosal HIV-1 target cell populations (Kleppa et al. 2014). Gastrointestinal schistosomiasis, which is mostly prevalent in Asia, targets primarily the rectum and the distal colon, where migrating eggs harm the integrity of the mucosa. Therefore gastrointestinal schistosomiasis may represent a risk factor for HIV-1 transmission especially in individuals practicing active and passive anal sexual intercourse in analogy to other sexual-transmitted diseases and FUS. So far, no study analyzed the impact of gastrointestinal schistosomiasis on the risk of HIV-1 transmission in exposed target groups as MSM (Downs et al. 2011; Kjetland et al. 2006; WHO 2009; Craib et al. 1995). However, data from Tanzania suggest an association between gastrointestinal schistosomiasis and HIV infection even in women (Downs et al. 2012).

In primates, infection with *S. mansoni* leads to increased susceptibility for simian HIV (SHIV) virus without increasing parenteral susceptibility, which suggests higher mucosal susceptibility to HIV-1 also in gastrointestinal schistosomiasis (Chenine et al. 2008; Siddappa et al. 2011). However, other studies did not show an association of schistosomiasis or other helminths and HIV prevalence in epidemiological surveys (Nielsen et al. 2006; Sanya et al. 2015).

5.2.1 Impact of Helminth Infection on the Risk of HIV-1 Infection

Remarkable results have been reported from studies investigating the risk for HIV-1 infection in patients with lymphatic filariasis. An increased susceptibility to HIV-1 infection of peripheral blood mononuclear cells in vitro has been described in patients with filarial infections in the past (Gopinath et al. 2000). A recently published report raised the additional concern on the risk of HIV-1 transmission in the context of lymphatic filariasis. This prospective cohort study from Tanzania showed a significantly increased risk for HIV infection in patients with lymphatic filariasis (Kroidl et al. 2016). Even though lymphatic filariasis is no longer endemic in East Asia, these results have important implications for further research, also regarding other helminth infections.

Besides horizontal HIV-1 transmission, concerns have been raised regarding an increased risk of vertical HIV-1 transmission in coinfected mothers. Helminths' intravascularly secreted molecules can cross the placenta and induce immunological changes in the fetus similar to those observed in adults (Malhotra et al. 1997). By such an alteration of the fetal defense, the parental helminth infection may increase the risk for mother-to-child transmission (PMTCT) of HIV-1, which may occur in utero, peri-, and post-partum (by breast feeding). A retrospective study suggests an elevated risk for PMTCT by showing a positive association between an active helminth infection of the mother with high Th2-type cytokine response in the cord blood cells and the risk of HIV-1 infection of the fetus (Gallagher et al. 2005), whereas a randomized controlled trial did not find a benefit of deworming during pregnancy for vertical transmission of HIV-1 (Webb et al. 2011).

5.2.2 Impact of Helminth Infection on the Course of HIV-1 Infection

On the basis of the aforementioned alterations of the immune system, helminths may theoretically promote HIV-1 disease progression. Early, smaller studies suggested a faster disease progression in HIV-1-infected individuals living in sub-Saharan Africa and other developing countries compared with populations in the western hemisphere (Morgan et al. 1997; Deschamps et al. 2000; Hira et al. 2003). These discrepancies were attributed to differences in the virulence of the pathogen and disparities in access to healthcare but also to higher levels of immune activation generally seen in African subjects due to high prevalence of chronic coinfections (Bentwich et al. 1995; Lawn 2004), though a more recent study of nearly 2000 men working in South African gold mines with known date of seroconversion did find similar survival patterns compared with western populations (Glynn et al. 2007).

A large cross-sectional study enrolling more than 1500 HIV-1-seropositive individuals in Kenya found significantly higher $CD4^+$ T-cell counts in HIV-1 patients with helminth coinfection compared with HIV-1 mono-infected patients (Walson et al. 2010), which was confirmed by another trial in Uganda (Brown et al. 2004; Elliott et al. 2003). One of these trials additionally found similar viral loads and a similar CD4 cell decline over 12 months in co- and mono-infected individuals (Brown et al. 2004). A more recent study in a South African helminth-HIV-1 coinfected population classified the participants into four helminth infection phenotypes, according to the presence of eggs in the stool and to IgE concentration in the serum. High levels of immune activation and viral load and low CD4 cell counts could be demonstrated in individuals with Th2 bias as indicated by high egg count and IgE response, whereas patients with high egg counts and low IgE responses displayed low viral loads and higher CD4 cell counts (Mkhize-Kwitshana et al. 2011). This study demonstrates that individuals do not react in a uniform manner to parasite infections. Indeed only 38% of HIV-1-infected patients with a proven *A. lumbricoides* infection had elevated levels of *Ascaris*-specific IgE as a surrogate marker for Th2 immune response.

Several studies have explored the effect of anthelminthic treatment on the natural course of HIV-1 infection in helminth coinfected individuals and are summarized in two recent systematic reviews. The first review concluded that five of six included studies showed a statistically significant decrease in viral load after anthelminthic treatment (Modjarrad and Vermund 2010). The second systematic review presented meta-analyses separately by helminth species: a nonsignificant trend towards lower plasma viral load after treatment of *S. mansoni* coinfections was reported, but no effects in the case of other worm species (Sangaré et al. 2011). A recently published Cochrane review including 8 trials that enrolled 1612 participants concluded that on the basis of low-quality evidence, treating confirmed helminth coinfections may have small, short-term favourable effects on markers of HIV-1 disease progression (Means et al. 2016).

Nearly all studies addressing the issue of the effect of helminthiasis on HIV infection were limited to antiretroviral therapy (ART)-naïve patients. Only few studies so far have investigated the response to ART in individuals coinfected with HIV-1. Efraim et al. (2013) showed that in coinfected patients, the odds for immunologic treatment failure was four times higher and that $CD4^+$ T-cell count increases were significantly lower compared to HIV-seropositive patients without schistosomiasis (Efraim et al. 2013). Interestingly, Muok et al. (2013) observed that increase of CD4 counts 1 month after initiation of ART was significantly higher in HIV-1-infected patients with intestinal schistosomiasis than in non-coinfected patients (Muok et al. 2013). In the era of massive roll out of ART in resource-limited settings with high rates of helminth-HIV-1 coinfection, research on the effect of helminth coinfection on response to ART should get more attention by the scientific community and funding institutions.

5.2.3 Impact of HIV-1 Infection on the Risk for Helminth Infections

The impaired cellular immunity in HIV-1-infected patients makes them more susceptible for several intestinal parasitic infections, including *Cryptosporidium*, *Isospora belli*, and *Microsporidia* (Wiwanitkit 2001). This raises the question whether the risk of acquiring intestinal and extraintestinal helminth infections might be higher in HIV-1-infected individuals living in endemic regions.

Few studies have compared the prevalence of helminth infections between HIV-1-infected and HIV-1-uninfected individuals. During a large survey in the People's Republic of China, no difference in prevalence of helminth infections between these two groups was found (Tian et al. 2012). Equally, a large study in Tanzania did not find a significant difference in *S. mansoni* infection prevalence and infection intensity between HIV-1-infected and HIV-1-uninfected individuals (Mazigo et al. 2014). Another survey in Brazil did not find a difference in the prevalence for STH or schistosomiasis, while reporting on a higher prevalence for *S. stercoralis* in HIV-1-infected patients (Feitosa et al. 2001). A recent meta-analysis identified 16 case-control studies comparing HIV-1-seropositive individuals with seronegative controls of which 12 showed a higher and 3 studies a statistically significant higher

S. stercoralis infection risk for HIV-1-infected individuals and resulted in a pooled odds ratio (OR) of 2.17 [95% Bayesian confidence interval (BCI): 1.18–4.01] for HIV-1-infected individuals compared to the HIV-1-seronegative controls. This suggests an opportunistic component in infection with *S. stercoralis* (Schär et al. 2013).

Data on coinfection with food-borne trematodiasis and HIV-1 is mainly limited to the observation that coinfections exist (Tian et al. 2012; Paboriboune et al. 2014). A study from Lao People's Democratic Republic showed a significant association between low CD4 counts and infection with *O. viverrini* (Paboriboune et al. 2014), whereas in another survey in the People's Republic of China, no difference was found in prevalence of *C. sinensis* between HIV-1-infected and HIV-1-uninfected individuals (Tian et al. 2012).

An association between lymphatic filariasis and HIV-1 infection has been found in different studies. It has been debated whether this is due to the suspected increased susceptibility for HIV-1 infection in people with lymphatic filariasis or vice versa (Nielsen et al. 2006; Gopinath et al. 2000; Kroidl et al. 2016; Gallagher et al. 2005). For another filarial infection, onchocerciasis, which is not present in East Asia, an impaired antibody response to filarial antigens has been described in HIV-1-positive patients (Tawill et al. 1996). However, as no epidemiological associations between HIV-1 and filarial infections have been found in other surveys, this topic is still debated (Fischer et al. 1995; Nielsen et al. 2007; Tafatatha et al. 2015).

Overall, data on risk of helminth infection in HIV-1-infected patients are scarce, and further research is needed to address this subject.

5.2.4 Impact of HIV-1 Infection on the Course of Helminth Infections and the Efficacy of Anthelminthic Treatment in Coinfected Patients

It has been suspected that the course of a helminth infection might be negatively influenced by HIV-1 infection in the coinfected host. However, data on this subject are scarce, and there is no clear evidence that HIV-1 infection has a significant impact on the course of disease for most of STHs and food-borne trematodes (Karp and Auwaerter 2007).

In schistosomiasis, epidemiological surveys and experimental studies in mice suggested that egg excretion and maturation of parasites may depend on the host's immune response and that $CD4^+$ T-cell depletion in HIV-1-infected individuals may be linked to a decreased luminal migration of schistosome eggs and an arrest of worm development (Karanja et al. 1997; Fontanet et al. 2000; Mwanakasale et al. 2003; Doenhoff et al. 1981; Davies et al. 2001; Kallestrup et al. 2005; Dunne et al. 1983). An impaired excretion of schistosome eggs in HIV-1-coinfected individuals would reduce the sensitivity of *Schistosoma* diagnostics in endemic countries and preclude schistosome treatment which may be beneficial for the course of HIV-1 infection. However, as no difference in infection intensities and egg output was found in two large survey in Zimbabwe and South Africa, the effect of HIV-1

infection on egg output in schistosomiasis remains unclear (Kallestrup et al. 2005; Kleppa et al. 2015).

Praziquantel is a safe, cost-effective, and easily applicable treatment of all species of schistosomes (Panic et al. 2014). The effect of praziquantel is immune dependent and leads to exposure of antigens of the worm to its surface, making it more susceptible to antibody-induced immune response. In mouse models, praziquantel was found to kill fewer schistosomes in both T-cell- and B-cell-deprived mice. Concerns have been raised whether praziquantel is an efficacious drug for treatment of immunocompromised patients, in particular people living with HIV/AIDS (Sabah et al. 1985; Doenhoff et al. 2008; Brindley and Sher 1987).

Few studies have assessed the efficacy of praziquantel in HIV-1-schistosome coinfected patients demonstrating equal cure rates based on egg output for HIV-1-infected and HIV-1-uninfected patients, both for infections with *S. haematobium* and *S. mansoni* (Mwanakasale et al. 2003; Kallestrup et al. 2005; Karanja et al. 1998). However, in one study, antigen levels of *Schistosoma* spp. after praziquantel treatment were found to be significantly higher in HIV-1-infected versus HIV-1-uninfected individuals, even though cure rates based on egg output were not significantly different. This has led to the conclusion that the effect of praziquantel is limited to affecting the fecundity of adult schistosomes in the immunocompromised host, thus reducing egg excretion while leaving schistosomes metabolically active (Kallestrup et al. 2005).

This finding raises the concern that anthelminthic treatment regimens for HIV-1-infected patients might have to be adapted in order to achieve worm clearance and suggest that treatment control in immunocompromised patients might need to be based on antigen detection, since microscopic methods might give false negative results.

S. stercoralis is known to cause severe hyperinfection syndrome under different forms of immunosuppression, i.e. corticosteroid therapy or HTLV-1 virus infections. However, HIV-1 infection is not considered as a risk factor for hyperinfection syndrome as compared with the expected high numbers of HIV-1-*S. stercoralis* coinfections worldwide, only few reports of hyperinfection syndrome in HIV-1 patients are available, and most of them received concomitant corticosteroid therapy (Karp and Auwaerter 2007). The virtual absence of hyperinfection syndrome in HIV-1 infection may be explained by the finding that lower CD4 T-cell counts impede the development of infectious larvae which are necessary for autoinfection and therefore might protect from disseminated disease (Viney et al. 2004). Under this aspect, anecdotal reports of dissemination of *S. stercoralis* after initiation of ART might be considered as an immune reconstitution inflammatory syndrome (IRIS) in strongyloidiasis (Lanzafame et al. 2005; Brown et al. 2006).

Data on the course of cestode infections in HIV-1 patients is limited to single case reports. For echinococcosis, a case series from the People's Republic of China reports unusual growth rates and sizes of cysts in hepatic cystic echinococcosis among HIV-1-seropositive patients (Ran et al. 2015). A case of rapid progressive hepatic alveolar echinococcosis has been described in a patients infected with HIV-1 (Sailer et al. 1997).

Several cases on unusual manifestations of infections with *Taenia crassiceps* have been reported. This cestode is prevalent in the northern hemisphere with dogs and foxes as definite host. Unusual skin manifestations have been reported in HIV-1 patients. *T. crassiceps* is therefore discussed as an opportunistic infection (Klinker et al. 1992; Flammer Anikpeh et al. 2014; François et al. 1998; Chermette et al. 1995). Data on the cause of neurocysticercosis caused by *T. solium* in HIV-1-seropositive patients are scarce. It has been suggested that the frequency of giant cysts and racemose forms is higher in patients with HIV-1 (Delobel et al. 2004). Furthermore an IRIS in neurocysticercosis after starting ART has been suspected (Serpa et al. 2007).

6 Implications for Public Health

Coinfections of HIV-1 and helminths appear to be highly prevalent globally. Even though interaction of these infections is of growing interest in public health research, there is still a lack of data regarding this issue, the majority of studies originating from sub-Saharan Africa. However, more data from the Asian continent on this issue are needed, especially on helminth species that are specific to this region, such as *S. japonicum* or *C. sinensis*.

Several studies have suggested a negative impact of helminth infection on the risk of acquisition and the course of HIV-1 infection. Most helminth infections can be treated with a single and cost-effective treatment. Helminth control might therefore be an easy and efficient tool for HIV-1 management strategies.

Rural regions in the southwestern part of the People's Republic of China are the hot spots of HIV-1/AIDS endemic and helminth infections in East Asia. Therefore, the issue of HIV-1-helminth coinfection could be of particular relevance in these areas. Local control programmes for helminth infections may consider developing a special focus on HIV-exposed and HIV-infected populations as anthelmintic treatment may potentially reduce the risk for HIV-1 infection and slow down disease progression.

With regard to helminth infections in HIV-infected individuals, it needs to be noted that of selected helminth infections, the frequency (e.g. *T. crassiceps* and *S. stercoralis*) and the natural course of disease (e.g. *Echinococcus*, *T. crassiceps*, *and S. stercoralis*) might be altered by HIV-1 infection and associated therapies. Therefore campaigns and trainings to raise awareness and form local physicians in the field of HIV care may be discussed.

Additionally, HIV infections may complicate routine diagnostics of helminths infections, such as microscopy for the diagnosis of schistosome infection in HIV-1-seropositive individuals. Thus an alternative diagnostic work up, e.g. by measuring schistosome antigen in urine and/or serum, could be considered.

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