

LONDON
SCHOOL of
HYGIENE
& TROPICAL
MEDICINE



Bustinduy, Amaya; King, Charles H.; Scott, Janet; Sousa-Figueiredo, Jose C; Betson, Martha; Stothard, J. Russell (2015) HIV and schistosomiasis coinfection in African children. Lancet Infect Dis. ISSN 1473-3099

Downloaded from: <http://researchonline.lshtm.ac.uk/2869512/>

DOI:

Usage Guidelines

Please refer to usage guidelines at <http://researchonline.lshtm.ac.uk/policies.html> or alternatively contact researchonline@lshtm.ac.uk.

Available under license: Copyright the author(s)

D-12-01177R1

S1473-3099(14)70001-5

Embargo: [add date when known]



HIV and schistosomiasis coinfection in African children

Amaya Bustinduy, Charles King, Janet Scott, Sarah Appleton, José Carlos Sousa-Figueiredo, Martha Betson, *J Russell Stothard

HIV/AIDS and schistosomiasis both cause a great disease burden in sub-Saharan Africa, and the two diseases share substantial overlap in their epidemiological characteristics. Although disease-specific control interventions are continuing, potential synergies in the control efforts for these two diseases have not been investigated. With a focus on children with schistosomiasis, we assess the risk for increased HIV transmission, HIV progression, and impaired response to drugs when given alongside HIV interventions. A new research agenda tailored to children is needed to better understand the interactions of these two diseases and the potential for combined responses.

Introduction

HIV and schistosomiasis are two of the most widespread infections worldwide; nonetheless, their combined effect has not been fully delineated, especially in sub-Saharan Africa. Although both diseases differ in their presentation, manifestations, and treatment, there is substantial geographical overlap in the poorest countries where endemicity is often high (figure 1).¹ For example, in Ethiopia, Nigeria, South Africa, Zambia, and Zimbabwe, adult HIV prevalence ranges from 15% to 28%, and the prevalence of schistosomiasis commonly exceeds 50% in high-risk rural communities.² The prevalence of HIV and schistosomiasis might be even higher in data-deficient areas such as Madagascar or Mozambique.³

As the HIV pandemic progresses, interventions against the increase in HIV-related disease have focused on universal access to highly active antiretroviral therapy (HAART). Many children in sub-Saharan Africa present for care late in their HIV disease progression,⁴ and there are nearly 1000 new cases of paediatric HIV infection every day—more than 2·5 million children younger than 15 years have HIV/AIDS.³ WHO guidance^{5,6} emphasises the importance of prompt diagnosis, treatment, and monitoring of HIV in children. Although there is a strong commitment from the international community to eliminate new childhood HIV infections by 2015, the HIV epidemic in sub-Saharan Africa shows little sign of abatement.⁷

Schistosomiasis, either urogenital or intestinal, is a chronic inflammatory disease caused by a water-borne parasitic blood fluke. In sub-Saharan Africa, 220 million people are infected with the parasite, and even more are at risk, mainly children.² Although congenital transmission does not occur, exposure and infection can take place very soon after birth, depending on an infant's environmental exposure to parasite-infested water. Until recently, the burden of disease from these early exposures was overlooked. However, infants and preschool-age children (aged 1–5 years) can have active disease^{8,9} and have poor access to deworming treatment because current measures are focused on preventive chemotherapy (ie, mass drug administration of praziquantel to school-age children aged 6–15 years).¹⁰ Praziquantel is a safe and affordable oral drug that is active against all forms of schistosomiasis and can be given by non-medical personnel.¹¹ As new information emerges about schistosomiasis in early

childhood, international policies and practices are beginning to respond to this unmet need [A: “inequity” has a specific meaning in the global health context, and I don't think the phrase is appropriate here, does “unmet need” work, or could you suggest an alternative phrase?].^{12,13}

Identification of disconnects in combined control

HIV control has only a short history, whereas schistosomiasis is an old disease,¹⁴ for which the inability to implement fully integrated preventive strategies because of shortfalls in water hygiene and sanitation has led to the dominance of preventive chemotherapy as the most cost-effective option. Locally applicable and integrated interventions tailored to the immediate epidemiological setting are desirable. Intricate understanding of the transmission biology, epidemiology, and social patterning (ie, HIV largely by sexual behaviour and schistosomiasis by water contact) of the diseases is needed.

Environmental risk factors for both infections include restricted access to safe water, low socioeconomic status, and poor educational access.¹⁵ HIV transmission risk is made up of complex individual behaviours, including commercial sex work, intravenous drug use, and various unsafe exposures to blood and other bodily fluids; in sub-Saharan Africa lack of autonomy for women and intolerance of male homosexuality are important factors.¹⁶ The social context of schistosomiasis is very different, but relates to unsafe exposures that are repeated often during domestic tasks or employment. Schistosomiasis is typically highly prevalent in fishing communities in which opportunities for HIV transmission can also be raised.^{15,17} To further complicate control, each disease agent has ecological and genetic diversity, with potential to adapt to control interventions.¹⁸

Although multidisease approaches are being promoted by WHO (eg, in management of HIV and malaria), related platforms for research and operational control of HIV and schistosomiasis simply do not exist.¹⁹ There is also little room for future optimism because the newly created Disease Reference Group of Helminthic Infections for the control and elimination of helminthiasis in people has not adopted a multiple-endemic-disease approach within their framework.¹⁸

The first cases of HIV/AIDS in adults were described in 1981,²⁰ and 5 years lapsed before evidence of routes other than sexual transmission emerged and paediatric HIV/

Parasitology Department, Liverpool School of Tropical Medicine, Liverpool, UK (A Bustinduy, J C Sousa-Figueiredo, Prof J R Stothard); Center for Global Health and Diseases, Case Western Reserve University, Cleveland, OH, USA (C King); [A: please provide affiliation for Janet Scott.] (J Scott); School of Clinical Medicine, University of Cambridge, Cambridge, UK (S Appleton); and Department of Production and Population Health, Royal Veterinary College, Hatfield, UK (M Betson)

Correspondence to: Prof J Russell Stothard, Parasitology Department, Liverpool School of Tropical Medicine, Liverpool L3 5QA, UK jrstoth@liverpool.ac.uk

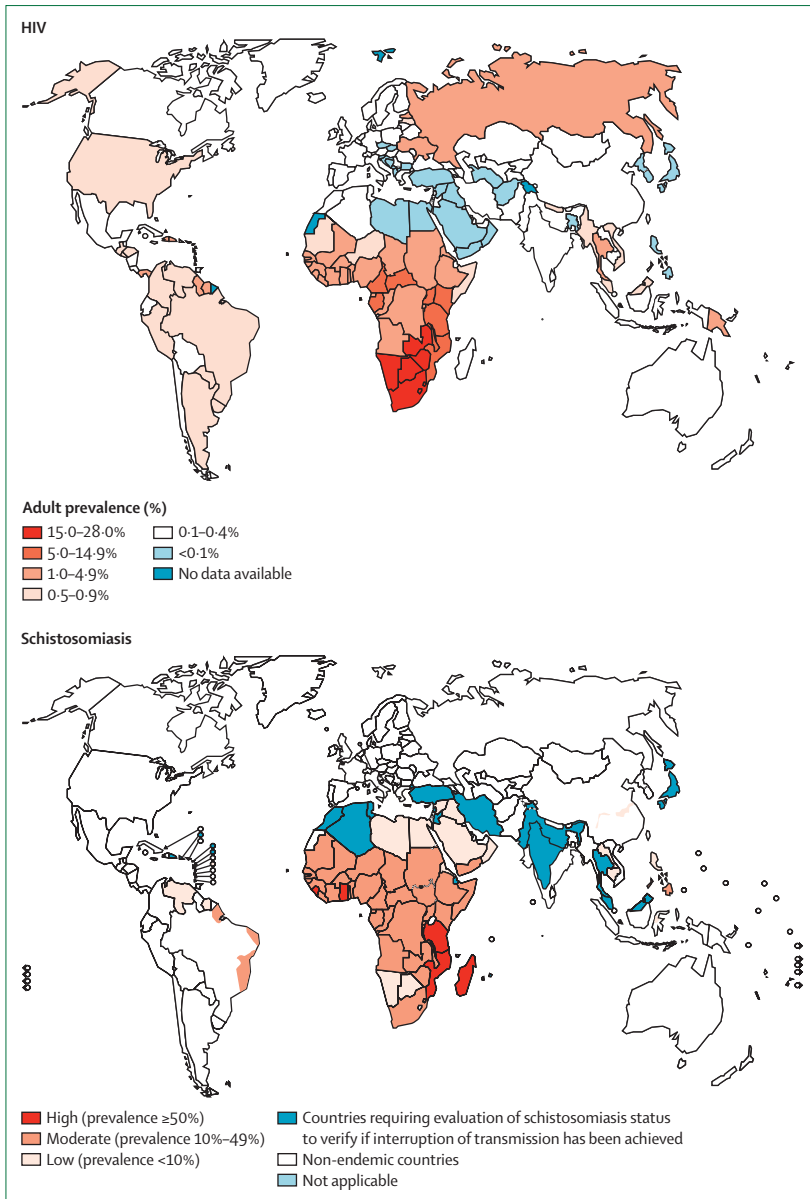


Figure 1: Global adult prevalence of HIV and schistosomiasis
 Different forms of schistosomiasis—urogenital and intestinal—are aggregated including adults and school-age children. Dual schistosome infections have not yet been fully estimated nor are prevalences of coinfections with HIV known. Data from WHO.

See Online for appendix

AIDS was recognised.²¹ The importance of mother-to-child transmission of HIV has only slowly become a public health priority.⁷ Alongside this focus, and with much less political advocacy, the case for prevention of schistosomiasis in early childhood is only now beginning.^{8,22–24} Moreover, as the subtly disabling morbidities associated with chronic schistosomiasis are being better recognised in this age group, an imperative for early prevention and control is becoming much clearer.^{25–29}

Both diseases are difficult to diagnose in early

1 childhood, and studies of HIV and schistosomiasis
 2 coinfection have been limited to adults.^{30,31} Paediatric
 3 studies (except for maternal–child health research)
 4 typically lag behind those in adults,³² and estimation of
 5 true burden of disease becomes a challenge because of
 6 an absence of paediatric diagnostics in resource-poor
 7 areas (appendix pp xxx [A: please add page numbers for
 8 table 1 in the appendix].³³

10 Reconnection of the importance of HIV and schistosomiasis coinfection

Given the potentially overwhelming burden of disease
 caused by dual infection, there are growing efforts to
 study the interactions between HIV and schistosomiasis,
 especially in areas where dual endemicity is most
 prevalent.^{34–37} Researchers doing experimental studies in
 animals are trying to understand the pathogenesis and
 immune responses when both infections are present.^{38,39}
 Investigators have done clinical studies of responses to
 antiparasitic and antiretroviral therapy for HIV/AIDS
 disease progression.^{40–43} However, all of these clinical
 studies exclusively targeted individuals older than
 18 years, and thereby overlooked interactions in
 childhood. Attempting to bridge this knowledge gap for
 childhood HIV and schistosomiasis co-infection, we
 reviewed the most relevant epidemiological and experi-
 mental studies to develop a conceptual framework
 (figure 2) that identifies the transmission and later mani-
 festations of disease in early life alongside current
 recommendations for treatment and integrated national
 control programmes.

Vertical HIV transmission

The close associations between mothers and their
 unborn children begin an intricate interplay of antigen
 exposure and immune-response modification that
 continues throughout childhood. This interplay might
 lead to increased susceptibility to certain diseases and
 decreased cognition; all of which are known downstream
 effects in children born to women with malaria or
 advanced HIV,^{26,44,45} but are not yet known in children
 born to women with both HIV and schistosomiasis. HIV
 transmission from infected mothers to children can
 occur through three different routes: intrauterine (5–10%
 [A: of transmissions, or of children with mothers with
 HIV? If transmissions, should the total percentages
 make up 100%?]), during delivery (15–30%), or through
 breastfeeding (5–30%).⁴⁶ Prepartum maternal helminth
 infections have been linked to increased mother-to-child
 transmission of HIV,⁴⁷ but lesions from female genital
 schistosomiasis are possibly also important.

WHO advocates universal HAART of all pregnant
 women with HIV, irrespective of their CD4 cell counts,
 but this target is far from a reality in resource-poor sub-
 Saharan Africa.⁷ The lack of consistent HAART for
 pregnant women is one of the major hurdles to
 controlling HIV-transmission. Alongside HAART

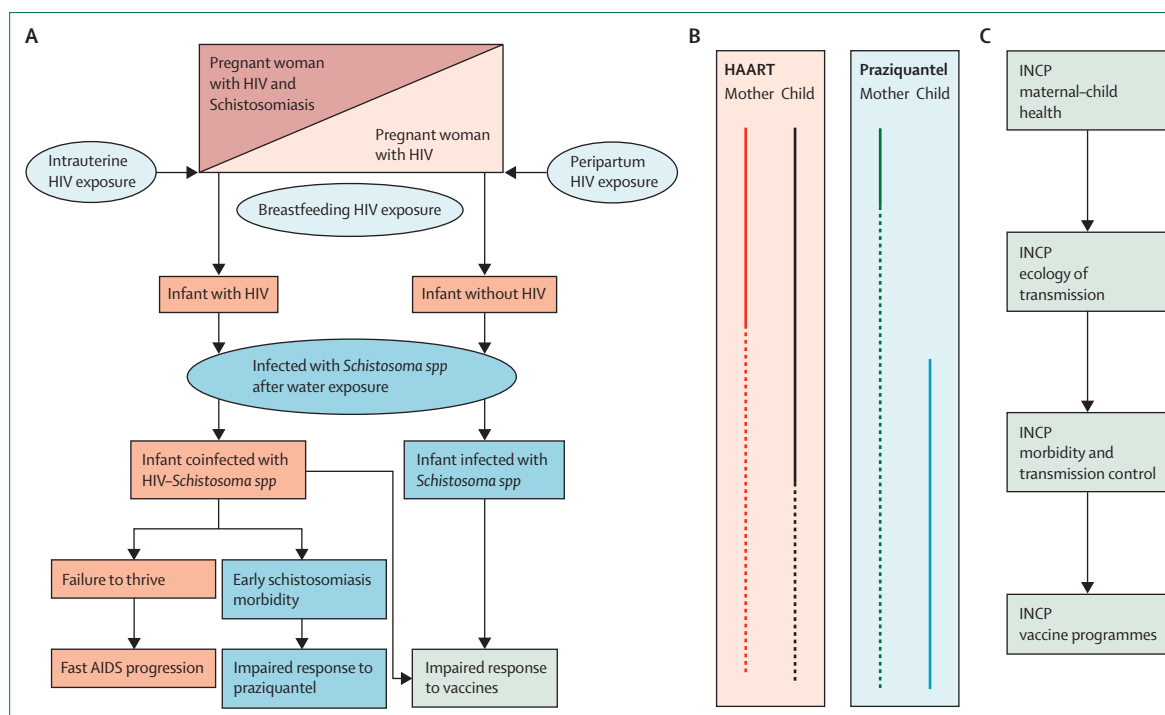


Figure 2: Conceptual framework of the epidemiology of HIV and schistosomiasis coinfection, dual treatment, and proposed control with national guidelines and interventions

(A) Proposed pathophysiological mechanism of mother-to-child transmission in pregnant women with one infection (HIV) or two infections (HIV and schistosomiasis). (B) Highly active antiretroviral therapy (HAART) and praziquantel treatment guidelines as recommended by WHO. Solid line indicates continued treatment. Dotted line indicates treatment based on CD4 cell count and clinical staging [A: ok?]. All pregnant women (M) are encouraged to start HAART (even if not indicated on the basis of CD4 cell counts) and to continue through children (Ch) born to women with HIV are to start HAART for 6 weeks, irrespective of their HIV status, since it is a difficult period to ascertain infection, particularly in resource-poor areas. (C) Integrated National Control Programmes should tailor their efforts on the basis of in-country prevalence. Programmes should use national health policies that include efforts to control HIV, schistosomiasis, other helminths and neglected transmitted diseases, and malaria. Different integrated programmes can include those for maternal-child health, transmission, and ecology of transmission that could target social and environmental determinants for all diseases (ie, water sanitation, sexual education and womens' capacity development, and vector control). PZQ=praziquantel. INCP=Integrated National Control Programmes.

antiparasitic treatment (with praziquantel, albendazole, or ivermectin) has the possible beneficial effect of lowering HIV viral load.⁴⁸ However, the researchers who reported this benefit did not find consistent HAART⁴⁰ effects. availability for participants, and future studies should adopt full treatment of HIV and parasite as standard.

Differences between children and adults

Extrapolation of knowledge and recommendations from⁴⁵ adult health interventions into paediatric settings often has a so-called little adults approach. For HIV and schistosomiasis coinfection, this approach is especially flawed in research and policy. For example, children have a larger surface-to-volume ratio with higher metabolic⁵⁰ rate, oxygen consumption, and caloric requirements than adults, not only to maintain homeostasis, but also to grow and develop. Typically children need more food per kilogram of bodyweight than do adults.⁴⁹ Consequently, children are particularly susceptible to any⁵⁵ growth deficits caused by infections or reduced nutrient intake, and growth-faltering states are particularly

associated with diseases such as HIV/AIDS⁵⁰ and schistosomiasis;^{27,51} moreover, these infections might have synergistic interactions that amplify their individual

Drugs are often more widely distributed around children's bodies than in adults and organ blood volumes are also higher.⁵² In schistosomiasis, this pattern could be highly relevant if blood flow to the liver is increased, as this would lead to swift clearance of praziquantel and a strong pharmacodynamic argument to challenge dosing recommendations directly extrapolated from adults (ie, 40 mg/kg). Other unanswered questions include how HIV infection or continuing HAART might change praziquantel efficacy after consideration that praziquantel's antischistosomal activity is immune-dependent.⁵³ Thus, the context, timing, and progression of each infection is important.

HIV precedes schistosomiasis in children

HIV infection in infants and young children is nearly always vertically transmitted; thus HIV infection precedes

schistosomiasis (figure 2), whereas in adult-acquired infection the reverse is often true (table).⁵⁴ This distinction is very important because the parasitic infection (schistosomiasis) in adult-acquired HIV has intrinsically different immunopathological and immune-modulating effects, which probably shape the pattern of disease. To our knowledge, this concept has not been investigated clinically; however, investigators of two studies of animals have attempted to assess it for retroviral replication and worm reduction after praziquantel treatment.^{38,39} Rhesus macaques carrying a latent chronic simian-human immunodeficiency virus (SHIV) infection (in analogy with HIV) were infected with cercariae of *Schistosoma mansoni* and had an increase in SHIV replication and faster disease progression than had animals without intestinal schistosomiasis.³⁹ In the other study, T-cell-depleted mice infected with *S mansoni* and later treated with two antischistosomal drugs (praziquantel and oxamniquine) had little worm clearance compared with mice with a healthy immune system,³⁸ confirming the important role of host immunity in drug action. Thus, if severely immune-suppressed people respond to treatment in the same way, particularly those with AIDS, then antischistosomal treatment is likely to have reduced effectiveness. Although there are no studies of people to corroborate this finding, serial retreatment studies of adults with HIV who were at high risk of *S mansoni* suggest that adults with more years of parasite exposure in childhood (hence more potential for established antiparasite immune responses) have longer infection-free periods after praziquantel treatment.⁵⁵ However, because of the scarcity of evidence, such generalised conjectures should be viewed with caution (appendix pp xxx) [A: please add page numbers for table 2 in appendix].

Schistosomiasis precedes HIV in adults

In endemic areas, as part of daily water contact, individuals typically contract schistosomiasis during childhood, with subsequent activation of the immune system by antigen-specific and non-specific immunomodulation biasing towards a T-helper-cell 2 polarity, potentially increasing susceptibility to viral and mycobacterial infections. Later HIV infection might also change the host-parasite immune balance. Epidemiological studies of adults in the Democratic Republic of the Congo, Ethiopia, and Kenya show a decrease in schistosome-egg excretion for those who acquired HIV later in life.³⁴⁻³⁶ A fully competent T-cell population might be needed to augment schistosome-egg excretion, or perhaps worm fecundity, although reports of a cohort

	HIV	Schistosomiasis
Adult	Older than 14 years	Age 2-5 years
Child	Birth or infancy	Younger than 2 years

Table: Common age of primary infection of HIV and schistosomiasis

study in Zimbabwe provided evidence to the contrary.³⁷ Nonetheless children’s expected response to egg excretion in the presence of HIV is unknown. Results of targeted epidemiological surveys have shown a high percentage of the infants and preschool-age children assessed were shedding eggs,^{8,9,22,24,56} but studies have not investigated the HIV status of examined children. For example, children with lower or intermittent egg output might have a very light intensity infection or they might have compromised immune systems from HIV infection (or other immune deficiencies), which impairs efficient egg excretion and, for this reason alone, HIV infection should be considered as a possible contributing factor to rate of egg excretion.

Effect of coinfection on mortality and morbidity

HIV infection remains a major public health threat in sub-Saharan Africa with 1.3 million deaths attributed to AIDS every year;³ at least 5% of all disability-adjusted life-years (DALYs) lost in low-income and middle-income countries are believed to be due to HIV/AIDS.⁵⁷ A drawback of the DALY is that the effect of comorbidities is overlooked,⁵⁸ formally bottlenecking the scope of health research and intervention programmes. The real context of HIV in sub-Saharan Africa is one in which children have two or more concurrent parasites in addition to their chronic HIV infection. For example, results of two paediatric cohort studies in South Africa⁵⁹ and Zambia⁶⁰ identified female sex, young age (younger than 2 years), severe wasting, and anaemia as mortality risk factors for children with HIV.^{59,60} Although schistosomiasis was not included as a comorbidity in either study, it can contribute to wasting and anaemia^{51,61-64} and is present in both countries.^{65,66} The potential detrimental synergy between HIV and schistosomiasis will be most severe in early childhood due to metabolic insults during key periods of growth and development.

Several studies from schistosomiasis-endemic countries have shown severe morbidity with end-organ fibrosis in children, disorders that were previously thought to be clinically relevant only during adulthood.⁶⁷ Whether coinfecting children are more or less at risk of end-organ fibrosis caused by schistosomiasis is unknown, but we hypothesise that children with HIV have less ultrasound-detectable fibrosis but more liver cellular damage, putting them at greater risk of liver dysfunction and failure. This damage could be caused by T-cell dysregulation, fuelled by HIV infection, preceding the onset of schistosomiasis-related hepatosplenic disease. This progression is, of course, not the case in adults, because liver pathology caused by schistosomiasis is already underway when HIV infection is acquired.^{68,69} Research to assess the severity of schistosomiasis alongside HIV is clearly needed.

Is AIDS linked with schistosomiasis in coendemic areas?

There has been much discussion about whether schistosomiasis increases susceptibility to HIV; in Malawi where urogenital schistosomiasis is common, an increased susceptibility to HIV transmission among women has been suggested by the patterns of submucosal inflammation found around parasite eggs in cervicovaginal biopsy samples.^{70,71} Studies in Kenya and Uganda, where intestinal schistosomiasis is common, have shown immune-modulation of anti-HIV responses in patients with schistosomiasis, including decreased production of interleukins 4 and 10 compared with that in individuals without HIV⁷² and decreased cytolytic CD8 T-cell response to viral antigens when both HIV infection and schistosomiasis were present.⁷³

The risk of HIV transmission might be increased by inflammation in the female genital tract from urogenital schistosomiasis, women in Tanzania and Zimbabwe with female genital schistosomiasis have an increased age-adjusted rate of HIV infection compared with those without female genital schistosomiasis.^{74–76} The effect of maternal female genital schistosomiasis on HIV transmission, during parturition, for example, is not known. Additionally, men with urogenital schistosomiasis in Madagascar had substantial damage to their reproductive tracts,⁷⁷ with increased amounts of leucocyte and proinflammatory cytokine in semen.⁷⁸ As with other proinflammatory sexually transmitted infections, urogenital schistosomiasis in both sexes could increase HIV transmission as children enter puberty and become sexually active.

Babies of mothers who have both HIV and other common helminthic infections (lymphatic filariasis, urogenital schistosomiasis, and hookworm) during pregnancy are more likely to have HIV 1 year after birth than are babies born to mothers with HIV alone.⁴⁷ The risk of intrauterine, perinatal, or breast-feeding-related mother-to-child HIV transmission might be increased by substantial immune-modulation in utero during the development of a doubly exposed fetus, rendering the baby more susceptible to viral infections.

A more rapid progression of HIV infection with pre-existing schistosomiasis seems likely because a 17-times-lower viral inoculum of SHIV was sufficient to infect rhesus macaques with intestinal schistosomiasis via mucosal exposure, as compared with the dose needed to infect controls without intestinal schistosomiasis.⁷⁹ In mice, T-regulatory cell upregulation, which occurs in schistosomiasis, can inhibit the ability of CD8 cells to control viral replication and, if similar in human beings, could potentially increase HIV progression with concurrent schistosomiasis.⁸⁰ Mice with schistosomiasis have increased concentrations of arginase-1 in macrophages, and the arginase-1 in macrophages and neutrophils in individuals with HIV might worsen immune hyporesponsiveness, increasing opportunistic infections.^{81,82} The presence of increased HIV receptors on CD4 cells in patients with intestinal schistosomiasis

further raises opportunity for HIV transmission and progression.⁸³

Treatment with praziquantel

The effect of HIV

The effectiveness of praziquantel is dependent on adequate blood concentrations of the drug and on presence of an intact and robust immune system⁸⁴—parasitological cure in T-cell-depleted mice with intestinal schistosomiasis is decreased compared with infected controls.³⁸ Initial action of praziquantel against adult worms is associated with tegumental disruption and later synergy with an effective antibody-mediated immune attack.⁸⁴ By contrast, studies of adults with HIV suggest that early immune-suppression does not adversely affect antischistosomal treatment with praziquantel, with no difference noted in parasitological cure rates between patients with HIV and those without in Kenya, Zambia, and Zimbabwe (appendix pp xxx [A: please add page number for table 3 in the appendix. Please supply the appendix with table 3 included]).^{43,85,86} However, effects of antiparasitic treatment on HIV-related markers are not clear because a 2009 meta-analysis showed some benefit for deworming in the prevention of HIV progression after pooling randomised trial data.⁸⁷ When data for observational studies were included in the analysis, the apparent deworming effect was not as strong.⁸⁸ Most surprisingly perhaps, no study has yet investigated treatment of both HIV and schistosomiasis with antiretroviral drugs as part of the regimen. In Zimbabwe, an unblinded randomised controlled trial showed a decrease in viral load and an increase in CD4 cell counts among adults who received early praziquantel treatment, as compared with those who were treated 3 months after diagnosis.⁸⁹ Results of a double-blind, placebo-controlled, trial of multiple helminth coinfections in a cohort of pregnant women in Uganda showed no difference in viral load between women with HIV given praziquantel and those given placebo. However, investigators did report a benefit for patients treated with albendazole for other helminthic infections, although the prevalence of intestinal schistosomiasis in this part of Uganda can be considered mild.⁴⁸ A study in Ethiopia found evidence of a relation between deworming and decreased viral load.⁹⁰ Conversely, results from two Ugandan studies showed a transient increase in viral load and decreased CD4 cell counts after treatment, mainly in individuals with severe intestinal schistosomiasis,^{42,91} from a transient host immune activation after praziquantel treatment, yielding a situation that favours increased viral replication. Other results from Kenya, Malawi, Uganda, and Zambia have shown no effect of praziquantel on HIV viral markers.^{40,92,93}

Use of praziquantel in children

The dosage for praziquantel in children (ie, at 40 mg/kg) is a direct extrapolation from adults, and is probably flawed because no information about praziquantel

pharmacokinetics and pharmacodynamics in young children is available. Nonetheless, studies indicate efficacy and safety on-the-ground with use of a praziquantel dosing pole, which allocates treatment on the basis of children's height [A: OK?].^{9,12,94} However, evidence from Uganda⁹⁵ has raised questions about recommended dosing, which might be inadequate for the metabolism of pre-school-age children and about whether children's immune systems are sufficiently developed to provide potent parasite clearance. This effect on parasite clearance could be worsened by concurrent HIV infection or some other congenital or acquired immune deficiency.

Extrapolation of dose by weight from adults is particularly problematic because blood volumes, metabolic rates, and extracellular volumes are better correlated with body surface area. As a result, drug doses normalised to the weight of adults can result in lower doses in young children than when normalised to body surface area.⁹⁶ Developmental changes are also important; particularly pertinent to praziquantel is the maturation of drug metabolism because the fetal liver contains only 30–40% of the CYP450 detoxification system content of adults, which typically ascends to a peak by age 10 years.⁹⁷ These reduced enzyme concentrations might suggest slower drug clearance from the bloodstream in children, which is consistent with observations that drug concentrations are generally reported as higher in children than in adults.⁹⁸

An era of community chemotherapy: drug–drug interactions

With the roll-out of HAART and increasing use of praziquantel in early childhood,⁹⁹ there might be substantial benefit to treat both diseases simultaneously and as early as possible; however, some further consideration of drug interactions and side-effects would be advisable because of the many potential interactions between antiretroviral therapy and antiparasitic drugs. The cytochrome P450 super-family of enzymes is central to drug metabolism and drug–drug interactions, particularly praziquantel.¹⁰⁰ Praziquantel is rapidly absorbed and has more than 80% bioavailability after oral administration,¹⁰¹ with drug clearance predominantly occurring by first-pass metabolism of CYP1A2, CYP2C19, and CYP3A4, with a dominance of CYP3A.^{102,103} Based on knowledge of drug metabolism, the expected effects of clinicians giving both HAART and praziquantel will probably differ dependent on which antiretroviral therapy drugs are used. For example, decreased praziquantel concentrations could occur if given concurrently with non-nucleoside reverse transcriptase inhibitors nevirapine or efavirenz, so-called HIV backbone treatments. These drugs are CYP450 inducers. Coadministration of praziquantel with protease inhibitors, which tend to inhibit CYP450 metabolism, could lead to increased praziquantel concentrations;¹⁰⁴ thus, well designed studies of paediatric pharmacokinetics

are needed to ensure safe and effective dosing when drugs are given concurrently.

Other drugs commonly used in sub-Saharan Africa are artemisinin-combination drugs and quinine derivatives for malaria, but based on their liver enzyme metabolism,^{105,106} neither is unlikely to affect praziquantel metabolism when given concomitantly. Antituberculous treatments (rifampicin, isoniazid, and clarithromycin) might have an effect on circulating praziquantel concentrations. Rifampicin is a potent inducer of CYP450, particularly CYP2C19 and CYP3A4, and in theory, this action could reduce circulating praziquantel concentrations.¹⁰³ Isoniazid and clarithromycin might increase praziquantel circulating concentrations.^{107–109} Clarithromycin is recommended for multidrug-resistant infection ~~but if treatment with praziquantel was judged essential and, as an open conjecture, rifampicin could be stopped 4 weeks before praziquantel was given and then reinstated a day after the praziquantel regimen then praziquantel might be able to be given, although repercussions of this regimen are not known and ethically questionable [A: OK? JS's corrections were unclear here. Please clarify].~~¹⁰⁷

Immune reconstitution inflammatory syndrome

Immune reconstitution inflammatory syndrome, more recently referred to as immune reconstitution disease, is a well known disorder that can occur after initiation of HAART in some individuals. Immune reconstitution disease is a collection of inflammatory disorders associated with paradoxical worsening of existing infectious processes, particularly opportunistic infections of HIV/AIDS.¹¹⁰ Clinicians are reporting an increasing number of immune reconstitution disease cases in association with parasitic diseases, with flare-ups of reactivating schistosomiasis being noted—evidenced by raised eosinophilia, hepatosplenomegaly, and colitis with polyposis.⁴⁵

In Zimbabwe, results of a 2008 study show significant decreases in soluble tumour necrosis factor receptor II (a cytokine-associated marker linked with systemic inflammation) among patients with both HIV and schistosomiasis after they were given praziquantel.⁴¹ This finding suggests a reduction in inflammatory responses after praziquantel, which might lead to decreased HIV viral replication and even attenuate the risk of immune reconstitution disease after HAART. Because no studies have been done in patients given HAART, this sphere remains to be explored in all age groups.

HIV and schistosomiasis coinfection and childhood vaccinations

After the expanded programme of vaccination, global vaccine coverage for children is increasing every year,¹⁹ whereas knowledge for the effects of coexisting childhood morbidities on response to vaccines is lagging behind, restricting vaccines' optimum effectiveness in on-the-

ground settings. Although safe, vaccination in children with HIV is less immunogenic than in children without HIV,^{111–113} and children with HIV who do achieve protective antibody titres can have a more rapid waning of vaccine-induced immunity.¹¹⁴

Children born to women who have parasitic diseases, including schistosomiasis, and have a decreased response to certain childhood vaccinations (eg, BCG^{115,116}). A 2011 randomised controlled trial in Uganda showed no association between single praziquantel or albendazole treatment of late-term pregnant women and the response of their infants to BCG;¹¹⁷ it is unlikely that one maternal dose of praziquantel can erase fetal immune sensitisation to schistosome antigens. However, the question remains as to whether maternal parasite infection, and then immune-skewing by HIV, modifies or exacerbates disease among children who then acquire schistosomiasis early in life, and whether HIV and schistosomiasis have combined effects on the efficacy of later childhood vaccinations—all of these events can also be set against pubertal hormonal production and its potential protection against schistosomiasis.^{118,119}

Delineating a research agenda

As we have stated, there are several gaps in [A: We would like to avoid use of our because of majestic plurals. OK?] knowledge about HIV and schistosomiasis coinfection in children, which is rather staggering. Within the planning context for future integrated health interventions, we firmly believe that there is a global duty to address promptly the disparity between paediatric and adult research and, as conceptual guidance, we suggest a timeline for future paediatric HIV and schistosomiasis research, delineated into key developmental periods of the child (figure 3).

Before birth, there should be better documentation of

the intricate relation between HIV and concurrent helminthiasis in mothers and unborn children, including efforts to develop non-invasive imagery methods or assays for detection of female genital schistosomiasis to clarify the at-risk population. Pregnant women with female genital schistosomiasis should receive praziquantel and rates of HIV transmission from treated mothers to children should be recorded. The effect of untreated vertically transmitted HIV in children who contract schistosomiasis at an early age should be investigated along with their rate of progression to AIDS. The response to immunisations in children coinfecting with HIV and schistosomiasis should be studied, with observation of children born to women with schistosomiasis. Researchers should investigate the extent of fetal immune priming and modulation during the antenatal period and how this priming affects risk of schistosomiasis disease and HIV progression later in life.

For children, the timing and successful occurrence of key stages as they progressively gain independence from their mothers is important. Interactions between HIV and schistosomiasis in causative mechanisms of anaemia, growth, retardation, decreased cognition, and decrease in overall quality of life need to be elucidated.

Pharmacokinetics and pharmacodynamics of praziquantel efficacy in children should be investigated in field settings, as should drug–drug interactions of antiparasitic drugs used in preventive chemotherapy alongside HAART and antituberculous drugs.

Investigators should more precisely measure the physical changes and psychological challenges to attain wellbeing for older children and adolescents with chronic diseases such as HIV and schistosomiasis by doing culturally sensitive studies of issues surrounding the

beginning of sexual activity and minimisation of further risks of HIV transmission. Non-invasive methods for

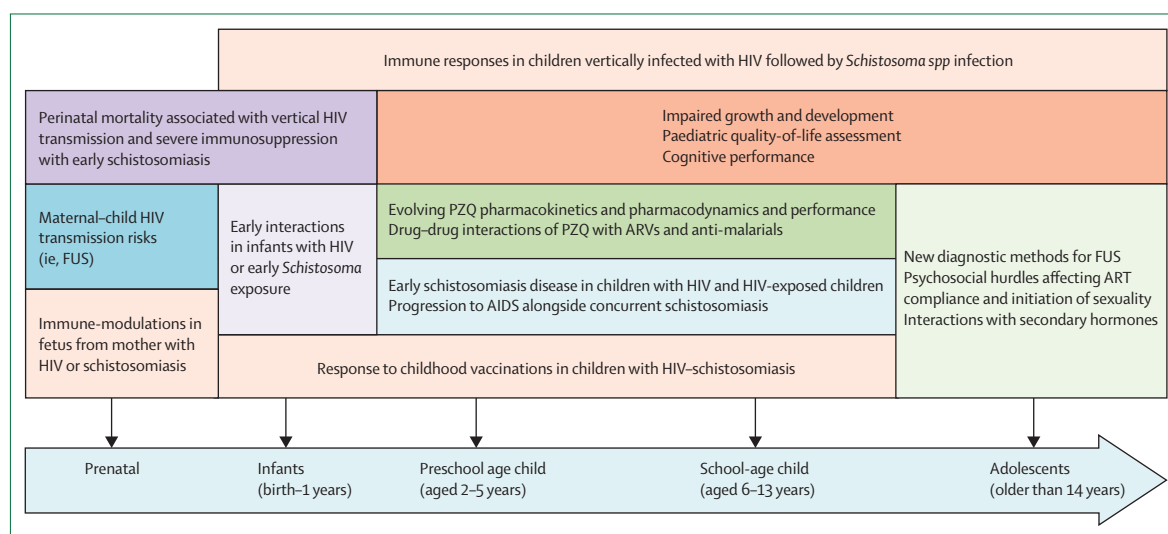


Figure 3: Suggested topics for research of paediatric HIV and schistosomiasis infection in dual endemic areas of sub-Saharan Africa

FUS=female genital schistosomiasis. PZQ=praziquantel. ARV=antiretrovirals.

Search strategy and selection criteria

We identified papers through searches of PubMed and Google Scholar for articles published from Jan 1, 1990, to July 30, 2013, with use of the terms "HIV", "AIDS", "schistosomiasis", "children", "paediatrics", "Africa", "morbidity", and "immunology". We applied additional terms and filters for "HIV-schistosomiasis co-infection". From the results of this search, we reviewed articles published in English, French, and Spanish.

detection of genital schistosomiasis in both sexes and clinical staging schedules for disease management are needed. Pubertal hormonal production and its potential protection against schistosomiasis progression and reinfection rates should be studied. Social determinants of health encompassing behavioural and psychosocial problems should be recorded to ensure the development and application of tailored interventions.

Conclusion

Provision of optimum public health care for paired management of HIV and schistosomiasis in sub-Saharan Africa might be more than a decade away. Failure to develop and implement a realistic research agenda for infected children will result in the neglect of the youngest children who might be at particular risk for increased HIV transmission, HIV progression, and impaired response to drugs. We hope that this review will stimulate a collective agenda to ensure that real progress will be made in the long-term management of paediatric HIV and schistosomiasis coinfection.

Contributors

ALB and JRS conceived the ideas for this Review, which were then developed in discussions with CK, JS, SA, JCS-F, and MB. SA and ALB assembled the bibliography and produced the table and figures, with assistance from JCS-F and MB. All authors contributed to the Review, with CK and JS particularly focusing on quality-of-life and pharmacology aspects, respectively.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

AB, JCS-F, MB, and JRS received support from the Wellcome Trust, UK.

References

- Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis* 2009; **3**: e412.
- Gryseels B, Polman K, Clerinx J, Kestens L. Human schistosomiasis. *Lancet* 2006; **368**: 1106–18.
- UNAIDS. Global report: UNAIDS report on the global AIDS epidemic 2010. Geneva: United Nations Programme on HIV/AIDS, 2010.
- Boender TS, Sigaloff KC, Kayiwa J, et al. Barriers to initiation of pediatric HIV treatment in Uganda: a mixed-method study. *Aids Res Treat* 2012; **2012**: 817506.
- WHO. WHO recommendations on the diagnosis of HIV infection in infants and children. Geneva: World Health Organization, 2010.
- WHO. Dept of HIV/AIDS. Antiretroviral therapy of HIV infection in infants and children: towards universal access: recommendations for a public health approach. Geneva: World Health Organization, 2007.
- UNAIDS. Progress report on the global plan towards the elimination of new HIV infections among children by 2015 and keeping their mothers alive. Geneva: United Nations Programme on HIV/AIDS, 2011.
- Garba A, Barkiré N, Djibo A, et al. Schistosomiasis in infants and preschool-aged children: infection in a single *Schistosoma haematobium* and a mixed *S haematobium*–*S mansoni* foci of Niger. *Acta Trop* 2010; **115**: 212–19.
- Sousa-Figueiredo JC, Pleasant J, Day M, et al. Treatment of intestinal schistosomiasis in Ugandan preschool children: best diagnosis, treatment efficacy and side-effects, and an extended praziquantel dosing pole. *Int Health* 2010; **2**: 103–13.
- Crompton DWT, WHO. Preventive chemotherapy in human helminthiasis: coordinated use of anthelmintic drugs in control interventions: a manual for health professionals and programme managers. Geneva: World Health Organization, 2006.
- Fenwick A, Webster JP, Bosque-Oliva E, et al. The Schistosomiasis Control Initiative (SCI): rationale, development and implementation from 2002–2008. *Parasitology* 2009; **136**: 1719–30.
- Stothard JR, Sousa-Figueiredo JC, Betson M, et al. Closing the praziquantel treatment gap: new steps in epidemiological monitoring and control of schistosomiasis in African infants and preschool-aged children. *Parasitology* 2011; **138**: 1593–606.
- WHO. Report of a meeting to review the results of studies on the treatment of schistosomiasis in preschool-aged children. Geneva: World Health Organization, 2011.
- Fairley J. Bilharzia. A history of imperial tropical medicine. Cambridge: Cambridge University Press, 1991.
- King CH. Parasites and poverty: the case of schistosomiasis. *Acta Trop* 2010; **113**: 95–104.
- Coates TJ, Richter L, Caceres C. Behavioural strategies to reduce HIV transmission: how to make them work better. *Lancet* 2008; **372**: 669–84.
- Bruun B, Aagaard-Hansen J, for the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases. The social context of schistosomiasis and its control: an introduction and annotated bibliography. Geneva: World Health Organization, 2008.
- Utzinger J. A research and development agenda for the control and elimination of human helminthiasis. *PLoS Negl Trop Dis* 2012; **6**: e1646.
- WHO. Malaria and HIV/AIDS interactions and implications: conclusions of a technical consultation convened by WHO, 23–25 June 2004. Geneva: World Health Organization, 2004.
- CDC. Pneumocystis pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep* 1981; **30**: 250–52.
- Quinn TC, Mann JM, Curran JW, Piot P. AIDS in Africa: an epidemiologic paradigm. *Science* 1986; **234**: 955–63.
- Odogwu SE, Ramamurthy NK, Kabaterine NB, et al. *Schistosoma mansoni* in infants (aged <3 years) along the Ugandan shoreline of Lake Victoria. *Ann Trop Med Parasitol* 2006; **100**: 315–26.
- Sousa-Figueiredo JC, Basáñez MG, Mgeni AF, Khamis IS, Rollinson D, Stothard JR. A parasitological survey, in rural Zanzibar, of pre-school children and their mothers for urinary schistosomiasis, soil-transmitted helminthiasis and malaria, with observations on the prevalence of anaemia. *Ann Trop Med Parasitol* 2008; **102**: 679–92.
- Verani JR, Abudho B, Montgomery SP, et al. Schistosomiasis among young children in Usoma, Kenya. *Am J Trop Med Hyg* 2011; **84**: 787–91.
- Bustinduy AL, Thomas CL, Fiutem JJ, et al. Measuring fitness of Kenyan children with polyparasitic infections using the 20-meter shuttle run test as a morbidity metric. *PLoS Negl Trop Dis* 2011; **5**: e1213.
- Ezeamama AE, Friedman JF, Acosta LP, et al. Helminth infection and cognitive impairment among Filipino children. *Am J Trop Med Hyg* 2005; **72**: 540–48.
- Stephenson LS, Latham MC, Adams EJ, Kinoti SN, Pertet A. Physical fitness, growth and appetite of Kenyan school boys with hookworm, *Trichuris trichiura* and *Ascaris lumbricoides* infections are improved four months after a single dose of albendazole. *J Nutr* 1993; **123**: 1036–46.
- King CH, Dangerfield-Cha M. The unacknowledged impact of

- chronic schistosomiasis. *Chronic Illn* 2008; **4**: 65–79.
- 29 King CH, Dickman K, Tisich DJ. Reassessment of the cost of chronic helminthic infection: a meta-analysis of disability-related outcomes in endemic schistosomiasis. *Lancet* 2005; **365**: 1561–69.
- 30 Webb EL, Ekii AO, Pala P. Epidemiology and immunology of helminth–HIV interactions. *Curr Opin HIV AIDS* 2012; **7**: 245–53.
- 31 Secor WE, Sundstrom JB. Below the belt: new insights into potential complications of HIV-1/schistosome coinfections. *Curr Opin Infect Dis* 2007; **20**: 519–23.
- 32 Stothard JR, Chiadini P, Booth M. Progress in paediatric parasitology: a preface to a topic focusing on ever younger subjects. *Parasitology* 2011; **138**: 1453–58.
- 33 Hesseling AC, Schaaf HS, Gie RP, Starke JR, Beyers N. A critical review of diagnostic approaches used in the diagnosis of childhood tuberculosis. *Int J Tuberc Lung Dis* 2002; **6**: 1038–45.
- 34 Karanja DM, Colley DG, Nahlen BL, Ouma JH, Secor WE. Studies on schistosomiasis in western Kenya: I. Evidence for immune-facilitated excretion of schistosome eggs from patients with *Schistosoma mansoni* and human immunodeficiency virus coinfections. *Am J Trop Med Hyg* 1997; **56**: 515–21.
- 35 Fontanet AL, Woldemichael T, Sahlu T, et al. Epidemiology of HIV and *Schistosoma mansoni* infections among sugar-estate residents in Ethiopia. *Ann Trop Med Parasitol* 2000; **94**: 145–55.
- 36 N'Zoukoudi-N'Doundou MY, Dirat I, Akouala JJ, Penchenier L, Makuwa M, Rey JL. [Bilharziasis and human immunodeficiency virus infection in Congo]. *Med Trop (Mars)* 1995; **55**: 249–51.
- 37 Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: implications of coinfection for excretion of eggs. *J Infect Dis* 2005; **191**: 1311–20.
- 38 Sabah AA, Fletcher C, Webbe G, Doenhoff MJ. *Schistosoma mansoni*: reduced efficacy of chemotherapy in infected T-cell-depleted mice. *Exp Parasitol* 1985; **60**: 348–54.
- 39 Ayash-Rashkovsky M, Chenine AL, Steele LN, et al. Coinfection with *Schistosoma mansoni* reactivates viremia in rhesus macaques with chronic simian-human immunodeficiency virus clade C infection. *Infect Immun* 2007; **75**: 1751–56.
- 40 Hosseinipour MC, Napravnik S, Joaki G, et al. HIV and parasitic infection and the effect of treatment among adult outpatients in Malawi. *J Infect Dis* 2007; **195**: 1278–82.
- 41 Erikstrup C, Kallestrup P, Zinyama-Gutsire RB, et al. Schistosomiasis and infection with human immunodeficiency virus 1 in rural Zimbabwe: systemic inflammation during co-infection and after treatment for schistosomiasis. *Am J Trop Med Hyg* 2008; **79**: 331–37.
- 42 Brown M, Mawa PA, Joseph S, et al. Treatment of *Schistosoma mansoni* infection increases helminth-specific type 2 cytokine responses and HIV-1 loads in coinfecting Ugandan adults. *J Infect Dis* 2005; **191**: 1648–57.
- 43 Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV in rural Zimbabwe: efficacy of treatment of schistosomiasis in individuals with HIV coinfection. *Clin Infect Dis* 2006; **42**: 1781–89.
- 44 Bangirana P, Musisi S, Boivin MJ, et al. Malaria with neurological involvement in Ugandan children: effect on cognitive ability, academic achievement and behaviour. *Malar J* 2011; **10**: 334.
- 45 Smith R, Malee K, Leighty R, et al, for the Women and Infants Transmission Study Group. Effects of perinatal HIV infection and associated risk factors on cognitive development among young children. *Pediatrics* 2006; **117**: 851–62.
- 46 De Cock KM, Fowler MG, Mercier E, et al. Prevention of mother-to-child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA* 2000; **283**: 1175–82.
- 47 Gallagher M, Malhotra I, Mungai PL, et al. The effects of maternal helminth and malaria infections on mother-to-child HIV transmission. *AIDS* 2005; **19**: 1849–55.
- 48 Webb EL, Kyosiimire-Lugemwa J, Kizito D, et al. The effect of anthelmintic treatment during pregnancy on HIV plasma viral load: results from a randomized, double-blind, placebo-controlled trial in Uganda. *J Acquir Immune Defic Syndr* 2012; **60**: 307–13.
- 49 Bearer CF. How are children different from adults? *Environ Health Perspect* 1995; **103**: 7–12.
- 50 Arpadi SM, Cuff PA, Kotler DP, et al. Growth velocity, fat-free mass and energy intake are inversely related to viral load in HIV-infected children. *J Nutr* 2000; **130**: 2498–502.
- 51 Friedman JF, Kanzaria HK, Acosta LP, et al. Relationship between *Schistosoma japonicum* and nutritional status among children and young adults in Leyte, the Philippines. *Am J Trop Med Hyg* 2005; **72**: 527–33.
- 52 Routledge PA. Pharmacokinetics in children. *J Antimicrob Chemother* 1994; **34** (suppl): 19–24.
- 53 Doenhoff MJ, Cioli D, Utzinger J. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. *Curr Opin Infect Dis* 2008; **21**: 659–67.
- 54 Secor WE. Interactions between schistosomiasis and infection with HIV-1. *Parasite Immunol* 2006; **28**: 597–603.
- 55 Black CL, Mwinzi PN, Muok EM, et al. Influence of exposure history on the immunology and development of resistance to human *Schistosoma mansoni*. *PLoS Negl Trop Dis* 2010; **4**: e637.
- 56 Mott KE, Dixon H, Osei-Tutu E, England EC. Relation between intensity of *Schistosoma haematobium* infection and clinical haematuria and proteinuria. *Lancet* 1983; **1**: 1005–08.
- 57 Jamison DT, Mosley WH. Disease control priorities in developing countries: health policy responses to epidemiological change. *Am J Public Health* 1991; **81**: 15–22.
- 58 King CH, Bertino AM. Asymmetries of poverty: why global burden of disease valuations underestimate the burden of neglected tropical diseases. *PLoS Negl Trop Dis* 2008; **2**: e209.
- 59 Zanoni BC, Phungula T, Zanoni HM, France H, Feeney ME. Risk factors associated with increased mortality among HIV infected children initiating antiretroviral therapy (ART) in South Africa. *PLoS ONE* 2011; **6**: e22706.
- 60 Sutcliffe CG, van Dijk JH, Munsanje B, et al. Risk factors for pre-treatment mortality among HIV-infected children in rural Zambia: a cohort study. *PLoS ONE* 2011; **6**: e29294.
- 61 Friedman JF, Kanzaria HK, McGarvey ST. Human schistosomiasis and anaemia: the relationship and potential mechanisms. *Trends Parasitol* 2005; **21**: 386–92.
- 62 Stephenson LS, Latham MC, Kurz KM, Kinoti SN, Oduori ML, Crompton DW. Relationships of *Schistosoma haematobium*, hookworm and malarial infections and metrifonate treatment to hemoglobin level in Kenyan school children. *Am J Trop Med Hyg* 1985; **34**: 519–28.
- 63 Mufasoni D, Karibushi B, Koukounari A, et al. Polyparasite helminth infections and their association to anaemia and undernutrition in Northern Rwanda. *PLoS Negl Trop Dis* 2009; **3**: e517.
- 64 Koukounari A, Estambale BB, Njagi JK, et al. Relationships between anaemia and parasitic infections in Kenyan schoolchildren: a Bayesian hierarchical modelling approach. *Int J Parasitol* 2008; **38**: 1663–71.
- 65 Simoonga C, Kazembe LN, Kristensen TK, et al. The epidemiology and small-scale spatial heterogeneity of urinary schistosomiasis in Lusaka province, Zambia. *Geospat Health* 2008; **3**: 57–67.
- 66 Saathoff E, Olsen A, Magnussen P, Kvalsvig JD, Becker W, Appleton CC. Patterns of *Schistosoma haematobium* infection, impact of praziquantel treatment and re-infection after treatment in a cohort of schoolchildren from rural KwaZulu-Natal/South Africa. *BMC Infect Dis* 2004; **4**: 40.
- 67 King CH. Long-term outcomes of school-based treatment for control of urinary schistosomiasis: a review of experience in Coast Province, Kenya. *Mem Inst Oswaldo Cruz* 2006; **101** (suppl): 299–306.
- 68 Secor WE, Karanja DM, Colley DG. Interactions between schistosomiasis and human immunodeficiency virus in Western Kenya. *Mem Inst Oswaldo Cruz* 2004; **99** (suppl): 93–95.
- 69 Mwinzi PN, Karanja DM, Kareko I, et al. Short report: evaluation of hepatic fibrosis in persons co-infected with *Schistosoma mansoni* and human immunodeficiency virus 1. *Am J Trop Med Hyg* 2004; **71**: 783–86.
- 70 Jourdan PM, Holmen SD, Gundersen SG, Roald B, Kjetland EF. HIV target cells in *Schistosoma haematobium*-infected female genital mucosa. *Am J Trop Med Hyg* 2011; **85**: 1060–64.
- 71 Jourdan PM, Roald B, Poggensee G, Gundersen SG, Kjetland EF. Increased vascularity in cervicovaginal mucosa with *Schistosoma haematobium* infection. *PLoS Negl Trop Dis* 2011; **5**: e1170.
- 72 Mwinzi PN, Karanja DM, Colley DG, Orago AS, Secor WE. Cellular immune responses of schistosomiasis patients are altered by human immunodeficiency virus type 1 coinfection. *J Infect Dis* 2001; **184**: 488–96.
- 73 McElroy MD, Elrefaei M, Jones N, et al. Coinfection with *Schistosoma mansoni* is associated with decreased HIV-specific cytotoxicity and increased IL-10 production. *J Immunol* 2005; **174**: 5119–23.

- 74 Downs JA, Mguta C, Kaatano GM, et al. Urogenital schistosomiasis in women of reproductive age in Tanzania's Lake Victoria region. *Am J Trop Med Hyg* 2011; **84**: 364–69.
- 75 Kjetland EF, Ndhlovu PD, Gomo E, et al. Association between genital schistosomiasis and HIV in rural Zimbabwean women. *AIDS* 2006; **20**: 593–600.
- 76 Ndhlovu PD, Mduluzi T, Kjetland EF, et al. Prevalence of urinary schistosomiasis and HIV in females living in a rural community of Zimbabwe: does age matter? *Trans R Soc Trop Med Hyg* 2007; **101**: 433–38.
- 77 Leutscher P, Ramarokoto CE, Reimert C, Feldmeier H, Esterre P, Vennervald BJ. Community-based study of genital schistosomiasis in men from Madagascar. *Lancet* 2000; **355**: 117–18.
- 78 Leutscher PD, Pedersen M, Raharisolo C, et al. Increased prevalence of leukocytes and elevated cytokine levels in semen from *Schistosoma haematobium*-infected individuals. *J Infect Dis* 2005; **191**: 1639–47.
- 79 Chenine AL, Shai-Kobiler E, Steele LN, et al. Acute *Schistosoma mansoni* infection increases susceptibility to systemic SHIV clade C infection in rhesus macaques after mucosal virus exposure. *PLoS Negl Trop Dis* 2008; **2**: e265.
- 80 Dietze KK, Zelinsky G, Gibbert K, et al. Transient depletion of regulatory T cells in transgenic mice reactivates virus-specific CD8+ T cells and reduces chronic retroviral set points. *Proc Natl Acad Sci USA* 2011; **108**: 2420–25.
- 81 Pesce JT, Ramalingam TR, Mentink-Kane MM, et al. Arginase-1-expressing macrophages suppress Th2 cytokine-driven inflammation and fibrosis. *PLoS Pathog* 2009; **5**: e1000371.
- 82 Cloke TE, Garvey L, Choi BS, et al. Increased level of arginase activity correlates with disease severity in HIV-seropositive patients. *J Infect Dis* 2010; **202**: 374–85.
- 83 Secor WE, Shah A, Mwinzi PM, Ndenga BA, Watta CO, Karanja DM. Increased density of human immunodeficiency virus type 1 coreceptors CCR5 and CXCR4 on the surfaces of CD4(+) T cells and monocytes of patients with *Schistosoma mansoni* infection. *Infect Immun* 2003; **71**: 6668–71.
- 84 Brindley PJ, Sher A. The chemotherapeutic effect of praziquantel against *Schistosoma mansoni* is dependent on host antibody response. *J Immunol* 1987; **139**: 215–20.
- 85 Karanja DM, Boyer AE, Strand M, et al. Studies on schistosomiasis in western Kenya: II. Efficacy of praziquantel for treatment of schistosomiasis in persons coinfecting with human immunodeficiency virus-1. *Am J Trop Med Hyg* 1998; **59**: 307–11.
- 86 Mwanakasale V, Vounatsou P, Sukwa TY, Ziba M, Ernest A, Tanner M. Interactions between *Schistosoma haematobium* and human immunodeficiency virus type 1: the effects of coinfection on treatment outcomes in rural Zambia. *Am J Trop Med Hyg* 2003; **69**: 420–28.
- 87 Walson JL, Herrin BR, John-Stewart G. Deworming helminth co-infected individuals for delaying HIV disease progression. *Cochrane Database Syst Rev* 2009; **3**: CD006419.
- 88 Sangaré LR, Herrin BR, John-Stewart G, Walson JL. Species-specific treatment effects of helminth/HIV-1 co-infection: a systematic review and meta-analysis. *Parasitology* 2011; **138**: 1546–58.
- 89 Kallestrup P, Zinyama R, Gomo E, et al. Schistosomiasis and HIV-1 infection in rural Zimbabwe: effect of treatment of schistosomiasis on CD4 cell count and plasma HIV-1 RNA load. *J Infect Dis* 2005; **192**: 1956–61.
- 90 Wolday D, Mayaan S, Mariam ZG, et al. Treatment of intestinal worms is associated with decreased HIV plasma viral load. *J Acquir Immune Defic Syndr* 2002; **31**: 56–62.
- 91 Elliott AM, Mawa PA, Joseph S, et al. Associations between helminth infection and CD4+ T cell count, viral load and cytokine responses in HIV-1-infected Ugandan adults. *Trans R Soc Trop Med Hyg* 2003; **97**: 103–08.
- 92 Lawn SD, Karanja DM, Mwinzia P, et al. The effect of treatment of schistosomiasis on blood plasma HIV-1 RNA concentration in coinfecting individuals. *AIDS* 2000; **14**: 2437–43.
- 93 Modjarrad K, Zulu I, Redden DT, et al. Treatment of intestinal helminths does not reduce plasma concentrations of HIV-1 RNA in coinfecting Zambian adults. *J Infect Dis* 2005; **192**: 1277–83.
- 94 Mutapi F, Rujeni N, Bourke C, et al. *Schistosoma haematobium* treatment in 1–5 year old children: safety and efficacy of the antihelminthic drug praziquantel. *PLoS Negl Trop Dis* 2011; **5**: e1143.
- 95 Sousa-Figueiredo JC, Betson M, Atuhaire A, et al. Performance and safety of praziquantel for treatment of intestinal schistosomiasis in infants and preschool children. *PLoS Negl Trop Dis* 2012; **6**: e1864.
- 96 Fox EBF. Drug Therapy in Neonates and Pediatric Patients. In: Abernethy DR, Daniels CE, Dedrick RL, Markey SP, eds. Principles of Clinical Pharmacology, 2nd edn. Amsterdam: Elsevier, 2007.
- 97 Shimada T, Yamazaki H, Mimura M, et al. Characterization of microsomal cytochrome P450 enzymes involved in the oxidation of xenobiotic chemicals in human fetal liver and adult lungs. *Drug Metab Dispos* 1996; **24**: 515–22.
- 98 Hines RN, McCarver DG. The ontogeny of human drug-metabolizing enzymes: phase I oxidative enzymes. *J Pharmacol Exp Ther* 2002; **300**: 355–60.
- 99 Coutinho HM, Acosta LP, McGarvey ST, et al. Nutritional status improves after treatment of *Schistosoma japonicum*-infected children and adolescents. *J Nutr* 2006; **136**: 183–88.
- 100 Gonzalez FJ. Overview of experimental approaches for study of drug metabolism and drug-drug interactions. In: Li AP, ed. Drug–drug interactions: scientific and regulatory perspectives. Waltham: Academic Press, 1997: 255–269.
- 101 Patzschke K, Pütter J, Wegner LA, Horster FA, Diekmann HW. Serum concentrations and renal excretion in humans after oral administration of praziquantel—results of three determination methods. *Eur J Drug Metab Pharmacokin* 1979; **4**: 149–56.
- 102 Li XQ, Björkman A, Andersson TB, Gustafsson LL, Masimirembwa CM. Identification of human cytochrome P(450)s that metabolise anti-parasitic drugs and predictions of in vivo drug hepatic clearance from in vitro data. *Eur J Clin Pharmacol* 2003; **59**: 429–42.
- 103 Ridditid W, Wongnawa M, Mahatthanatrakul W, Punyo J, Sunbhanich M. Rifampin markedly decreases plasma concentrations of praziquantel in healthy volunteers. *Clin Pharmacol Ther* 2002; **72**: 505–13.
- 104 Dooley KE, Flexner C, Andrade AS. Drug interactions involving combination antiretroviral therapy and other anti-infective agents: repercussions for resource-limited countries. *J Infect Dis* 2008; **198**: 948–61.
- 105 Bapiro TE, Egnell AC, Hasler JA, Masimirembwa CM. Application of higher throughput screening (HTS) inhibition assays to evaluate the interaction of antiparasitic drugs with cytochrome P450s. *Drug Metab Dispos* 2001; **29**: 30–35.
- 106 Bapiro TE, Sayi J, Hasler JA, et al. Artemisinin and thiabendazole are potent inhibitors of cytochrome P450 1A2 (CYP1A2) activity in humans. *Eur J Clin Pharmacol* 2005; **61**: 755–61.
- 107 Sweetman SC. Martindale: The Complete Drug Reference, 37th ed. London: Pharmaceutical Press, 2012.
- 108 Nishimura Y, Kurata N, Sakurai E, Yasuhara H. Inhibitory effect of antituberculosis drugs on human cytochrome P450-mediated activities. *J Pharmacol Sci* 2004; **96**: 293–300.
- 109 Sandoz. Clarithromycin S. Camberley: Sandoz, 2012.
- 110 French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with highly active antiretroviral therapy. *HIV Med* 2000; **1**: 107–15.
- 111 Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N, for the Vaccine Trialists Group. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med* 2003; **349**: 1341–48.
- 112 Bertolini DV, Costa LS, van der Heijden IM, Sato HK, Marques HH. Immunogenicity of a meningococcal serogroup C conjugate vaccine in HIV-infected children, adolescents, and young adults. *Vaccine* 2012; **30**: 5482–86.
- 113 Scott P, Moss WJ, Gilani Z, Low N. Measles vaccination in HIV-infected children: systematic review and meta-analysis of safety and immunogenicity. *J Infect Dis* 2011; **204** (suppl): S164–78.
- 114 Sutcliffe CG, Moss WJ. Do children infected with HIV receiving HAART need to be revaccinated? *Lancet Infect Dis* 2010; **10**: 630–42.
- 115 Labeaud AD, Malhotra I, King MJ, King CL, King CH. Do antenatal parasite infections devalue childhood vaccination? *PLoS Negl Trop Dis* 2009; **3**: e442.
- 116 Malhotra I, Mungai P, Wamachi A, et al. Helminth- and *Bacillus Calmette-Guérin*-induced immunity in children sensitized in utero to filariasis and schistosomiasis. *J Immunol* 1999; **162**: 6843–48.

-
- 117 Webb EL, Mawa PA, Ndibazza J, et al. Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. *Lancet* 2011; **377**: 52–62. 1
- 118 Brown M, Kizza M, Watera C, et al. Helminth infection is not associated with faster progression of HIV disease in coinfecting adults in Uganda. *J Infect Dis* 2004; **190**: 1869–79. 5
- 119 Kurtis JD, Friedman JF, Leenstra T, et al. Pubertal development predicts resistance to infection and reinfection with *Schistosoma japonicum*. *Clin Infect Dis* 2006; **42**: 1692–98. 10
- 15
- 20
- 25
- 30
- 35
- 40
- 45
- 50
- 55