HIV and schistosomiasis co-infection in African children

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HIV/AIDS and schistosomiasis both cause a substantial disease burden in sub-Saharan Africa and the two diseases often 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). 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. The prevalence of HIV and schistosomiasis might be even higher in data-deficient areas such as Madagascar or Mozambique.

As the HIV pandemic progresses, interventions against the increase in HIV-related disease have focused on universal access to antiretroviral therapy (ART). Many children in sub-Saharan Africa present for care late in their HIV disease progression, and there are nearly 1000 new cases of pediatric HIV infection every day—more than 2–5 million children younger than 15 years have HIV/AIDS. WHO guidance5 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.

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. 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 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). Praziquantel is a safe and affordable oral drug that is active against all forms of schistosomiasis and can be given by non-medical personnel. As new information emerges about schistosomiasis in early childhood, international policies and practices are beginning to respond to this unmet need.

Identification of disconnects in combined control

HIV control has only a short history, whereas schistosomiasis is an old disease 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 of control. 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 insufficient access to safe water, low socioeconomic status, and poor educational access. 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. 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.

To further complicate control, each disease agent has ecological and genetic diversity, with potential to adapt to new socioenvironmental settings. Therefore, there is limited 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. The first cases of HIV/AIDS in adults were described in 1981, and 5 years lapsed before evidence of routes other than sexual transmission emerged and paediatric HIV/AIDS was recognised. The importance of mother-to-child transmission of HIV has only slowly become a public...
Alongside this focus, and with much less political advocacy, the case for prevention of schistosomiasis in early childhood is only now beginning. Moreover, as the subtly disabling morbidities associated with chronic schistosomiasis in this age group are being better recognised, an imperative for early prevention and control is becoming much clearer.

Both diseases are difficult to diagnose in early childhood, and studies of HIV and schistosomiasis coinfection have been limited to adults. Paediatric studies (except for maternal–child health research) typically lag behind those in adults, and estimation of true burden of disease becomes a challenge because of an absence of paediatric diagnostics in resource-poor areas (appendix p 1).

**Reconnection of the importance of HIV and schistosomiasis co-infection**

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. Researchers doing experimental studies in animals are trying to understand the pathogenesis and immune responses when both infections are present. Investigators have carried out clinical studies of responses to antiparasitic and ART for HIV/AIDS disease progression. 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 experimental studies to develop a conceptual framework (figure 2) that identifies the transmission and later manifestations 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, but are not yet known in children born to women with both HIV and schistosomiasis. Risk for transmission from infected mothers to children ranges from 15–45%, depending on breastfeeding practices. Prepartum maternal helminth infections have been linked to increased mother-to-child transmission of HIV, but lesions from female genital schistosomiasis are possibly important also.

WHO advocates universal ART 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. The lack of consistent ART for pregnant women is one of the major hurdles to controlling HIV transmission. Alongside ART, antiparasitic treatment (with praziquantel, albendazole, or ivermectin) has the possible beneficial effect of lowering HIV viral load. However, the researchers who reported this benefit did not find consistent ART availability for participants and future studies should adopt full treatment of HIV and parasites as standard.

**Differences between children and adults**

Extrapolation of knowledge and recommendations from adult health interventions into paediatric settings often
has a so-called little adults approach. For HIV and schistosomiasis co-infection, this approach is especially flawed in research and policy. For example, children have a larger surface-to-volume ratio with higher metabolic rate, oxygen consumption, and caloric requirements than have adults, not only to maintain homeostasis, but also to grow and develop. Typically children need more food per kilogram of bodyweight than do adults. Consequently, children are particularly susceptible to any growth deficits caused by infections or reduced nutrient intake, and growth-faltering states are particularly associated with diseases such as HIV/AIDS and schistosomiasis. Moreover, these infections might have synergistic interactions that amplify their individual effects.

Drugs are often more widely distributed around children’s bodies than in adults and organ blood volumes in children are also higher. In schistosomiasis, this pattern could be highly relevant if blood flow to the liver is increased, because this difference 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 ART might change praziquantel efficacy after consideration that praziquantel’s antischistosomal activity is immune-dependent. 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). 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. 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. 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, confirming the important role of host immunity in drug action. Thus, if severely immune-suppressed people respond to treatment in the same way, particularly people with AIDS, then antischistosomal treatment probably has reduced effectiveness in co-infection. Although there are no studies of people to corroborate this finding, serial treatment 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. However, because of the scarcity of evidence, such generalised conjectures should be viewed with caution (appendix pp 2–3).

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. A fully competent T-cell population might be needed to augment schistosome-egg excretion, or perhaps worm fecundity, although reports of a cohort study in Zimbabwe provided evidence to the contrary.

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, 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 co-infection 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. 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. A drawback of the DALY is that the effect of comorbidities is overlooked, formally restricting 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 Africa and Zambìa identified female sex, young age (younger than 2 years), severe wasting, and anaemia as mortality risk factors for children with HIV. Although schistosomiasis was not included as a comorbidity in either study, it can contribute to wasting and anaemia and is present in both countries. 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. Whether co-infected 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. Research to assess the severity of schistosomiasis alongside HIV is needed.

### Is AIDS linked with schistosomiasis in co-endemic 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 cervico-vaginal biopsy samples. 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 interleukin 4 and interleukin 10 compared with that in individuals without HIV, and decreased cytolytic CD8 T-cell response to viral antigens when both HIV infection and schistosomiasis were present.
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. 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, with increased leukocytes and proinflammatory cytokines in semen. 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 helminth 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. 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 than the dose needed to infect controls without intestinal schistosomiasis. 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. Mice with schistosomiasis have raised concentrations of arginase-1 in macrophages; the arginase-1 in macrophages and neutrophils in individuals with HIV might worsen immune hyporesponsiveness, increasing opportunistic infections. The presence of increased HIV receptors on CD4 cells in patients with intestinal schistosomiasis creates further opportunity for HIV transmission and progression.

**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 system—parasitological cure in T-cell-depleted mice with intestinal schistosomiasis is decreased compared with infected controls. Initial action of praziquantel against adult worms is associated with tegumental disruption and later synergy with an effective antibody-mediated immune attack. 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 4–5). 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 of randomised trial data. When data for observational studies were included in the analysis, the apparent deworming effect was not as strong. 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, compared with those who were treated 3 months after diagnosis. Results of a double-blind, placebo-controlled, trial of multiple helminth co-infections 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 helminth infections, although the prevalence of intestinal schistosomiasis in this part of Uganda can be considered mild. A study in Ethiopia found evidence of a relation between deworming and decreased viral load. 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, 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.

**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. However, evidence from Uganda 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. 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. 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.

An era of community chemotherapy: drug-drug interactions

With the roll-out of ART and increasing use of praziquantel in early childhood, 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 ART drugs and antiparasitic drugs. The cytochrome P450 super-family of enzymes is central to drug metabolism and drug–drug interactions, particularly praziquantel. Praziquantel is rapidly absorbed and has more than 80% bioavailability after oral administration, with drug clearance predominantly occurring by first-pass metabolism of CYP1A2, CYP2C19, and CYP3A4, with a dominance of CYP3A. Based on knowledge of drug metabolism, the expected effects of clinicians giving both ART and praziquantel will probably differ dependent on which ART 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; 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, neither is likely 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 inductor of CYP450, particularly CYP2C19 and CYP3A4, and in theory, this action could reduce circulating praziquantel concentrations. Isoniazid and clarithromycin might increase praziquantel circulating concentrations. Clarithromycin is recommended for multidrug-resistant infections.

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 ART 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. Clinicians are reporting an increasing number of immune reconstitution disease cases in association with parasitic diseases, with flare-ups of reactivating schistosomiasis being noted as evidenced by raised eosinophilia, hepatosplenomegaly, and colitis with polyposis.

In Zimbabwe, results of a 2008 study show significant decreases in soluble tumour necrosis factor receptor 2 (a cytokine-associated marker linked with systemic inflammation) among patients with both HIV and schistosomiasis after they were given praziquantel. 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 ART. Because no studies have been carried out in patients given ART, this sphere remains to be explored in all age groups.

HIV and schistosomiasis co-infection and childhood vaccinations

After the expanded programme of vaccination, global vaccine coverage for children is increasing every year, 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, and children with HIV who do achieve protective antibody titres can have a more rapid waning of vaccine-induced immunity.

Children born to women who have parasitic diseases, including schistosomiasis, have a decreased response to certain childhood vaccinations (eg, BCG). 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; 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 immuneskewing 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.

Delineating a research agenda

As we have stated, there are several gaps in knowledge about HIV and schistosomiasis co-infection in children,
which is rather staggering. When planning future integrated health interventions, we firmly believe that there is a global duty to address 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 immunisation in children co-infected with HIV and schistosomiasis should be studied, with observation done 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.

In 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 ART and antituberculous drugs.

Investigators should more precisely measure the physical changes and psychological challenges to attainment of 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 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 also 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 co-infection.

Contributors
AB and JRS conceived the ideas for this Review, which were then developed in discussions with CK, JS, SA, JCS-F, and MB. SA and AB 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.

Declaration of interests
We declare that we have no competing interests.

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References


Review


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.


114 Sutcliffe CG, Moss WJ. Do children infected with HIV receiving HAART need to be revaccinated? Lancet Infect Dis 2010; 10: 630–42.


