HHS Public Access

Author manuscript

*J Acquir Immune Defic Syndr*. Author manuscript; available in PMC 2016 April 08.

Published in final edited form as:

*J Acquir Immune Defic Syndr*. 2012 February 1; 59(2): 161–169. doi:10.1097/QAI.0b013e3182427029.

# Unresolved Antiretroviral Treatment Management Issues in HIV-Infected Children

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## Abstract

Antiretroviral therapy in children has expanded dramatically in low-income and middle-income countries. The World Health Organization revised its pediatric HIV guidelines to recommend initiation of antiretroviral therapy in all HIV-infected children younger than 2 years, regardless of CD4 count or clinical stage. The number of children starting life-long antiretroviral therapy should therefore expand dramatically over time. The early initiation of antiretroviral therapy has indisputable benefits for children, but there is a paucity of definitive information on the potential adverse effects. In this review, a comprehensive literature search was conducted to provide an overview of our knowledge about the complications of treating pediatric HIV.

Antiretroviral therapy in children, as in adults, is associated with enhanced survival, reduction in opportunistic infections, improved growth and neurocognitive function, and better quality of life. Despite antiretroviral therapy, HIV-infected children may continue to lag behind their uninfected peers in growth and development. In addition, epidemic concurrent conditions, such as tuberculosis, malaria, and malnutrition, can combine with HIV to yield more rapid disease progression and poor treatment outcomes.

Additional studies are required to evaluate the long-term effects of antiretroviral therapy in HIV-infected infants, children, and adolescents, particularly in resource-limited countries where concomitant infections and conditions may enhance the risk of adverse effects. There is an urgent

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L.M.M., C.V.H., and E.K. have no competing interests.

The conclusions and opinions expressed in this article are those of the authors and do not necessarily reflect those of their respective organizations, including the National Institutes of Health or the US Department of Health and Human Services.

Authors contributions—S.H., with the support of medical writer David Gilden, wrote the initial draft. C.H. provided expert advice and substantially revised the section on malaria. L.M. contributed substantially to the manuscript by providing extensive comments. All other authors contributed equally by providing expert comments. All authors have read and approved the final version.

need to evaluate drug–drug interactions in children to determine optimal treatment regimens for both HIV and coinfections.

### Keywords

antiretroviral; childhood growth and development; drug complications; HIV-infected infants; malaria; malnutrition; tuberculosis

## INTRODUCTION

The virologic and immunologi benefits of highly active antiretroviral therapy (HAART) in children in resource-rich countries have been confirmed by trial data in low-income and middle-resource countries.[1] Global treatment access for HIV-infected children is rapidly increasing; an estimated 356,400 children younger than 15 years received HAART in 2009 in resource-limited countries, a 29% increase since 2008.[2,3] The definition of who is in need of treatment is likewise expanding rapidly. Research has demonstrated that immediate HAART significantly reduces mortality and morbidity in HIV-infected infants,[4] and the World Health Organization has revised its guidelines to recommend HAART initiation in all HIV-infected children younger than two years.[5,6]

However, treatment in children is complicated by changing drug pharmacokinetics with age, caused by the continuing development and maturation of the organs involved in drug metabolism. Drug pharmacokinetics are further complicated by malnutrition and drugs required for treatment of coinfection with tuberculosis (TB) and malaria. Children initiate therapy during a period of rapid growth and development, and face a lifetime of drug exposure. HAART's potential adverse effects on metabolism are central to managing pediatric HIV, but research has been limited in children.

We describe some of the complications affecting pediatric HIV treatment for which further research is needed, including childhood neurologic and metabolic development, coinfection with TB or malaria, and malnutrition.

## RESULTS

This review includes pediatric HIV infection, antiretroviral therapy (ART), neurocognitive and bone development, metabolic disorders, TB or malaria coinfection, and malnutrition and attempted to differentiate treatment-related and HIV-related effects. Ninety-two articles formed the basis of this report (Table 1).

### Neurocognitive Skills

Although ART clearly arrests many HIV pathogenic effects in children, these children do not seem to attain the developmental status of their peers. Neurocognitive developmental delays may be due to a direct effect of HIV, antiretroviral toxicity, or psychological and socioeconomic factors.[7]

An US observational study (PACTG 219/219C) found that HAART leads to a lower risk of HIV encephalopathy (n = 2272; adjusted HR: 0.50, 95% CI: 0.29 to 0.86).[8] There was a trend to a lower incidence of HIV encephalopathy in children receiving high compared with low central nervous system (CNS)–penetrating HAART regimens. Additionally, in those with HIV encephalopathy, high CNS-penetrating regimens had a substantial survival benefit (74% reduction in death) compared with low CNS-penetrating regimens.

The extent to which children's neurocognitive development is ultimately affected by long-term HAART requires further study. PACTG 219/219C included 1283 children aged 6–42 months exposed to HIV *in utero*.[9] In the pre-HAART era, mean cognitive and motor scores measured by the Bayley Scales of Infant Development were significantly lower in HIV-infected than HIV-exposed uninfected (HEU) children. Protease inhibitor (PI) therapy stabilized and slightly improved the HIV-infected children's neurocognitive deficits and slowed annual decline in Bayley Scales of Infant Development cognitive scores by 7.3 points; decline was −1.1 versus −8.4 points per year in children on PI-HAART compared with children in the pre-HAART era ($P = 0.02$). Decline in the HEU children's scores were also observed (−6.2 points per year). The overall gap between the HIV-infected and HIV-uninfected groups narrowed but neither caught up to accepted standards for their age. The decline in the HEU children could be due to poverty, possibly enhanced by *in utero* exposure to antiretrovirals.[10] These data demonstrate the importance of appropriate control group inclusion in pediatric studies. These observations are supported by a longitudinal study of infants born to mothers without HIV infection from disadvantaged socioeconomic areas in Cape Town who showed a decline in language and motor development between age 11 and 21 months.[11]

There are limited data from resource-limited countries; in an analysis of six publications in untreated African HIV-infected children, the magnitude of impairment of mental and motor development was similar to that reported in resource-rich countries.[12] A recent study assessed 295 Ugandan children, including 84 infected with HIV (53 on HAART).[13] The HIV-infected children had significant deficits in visual reception and language (but not motor) skills compared with children without HIV (maternal status unspecified). Children receiving HAART had improved neurologic outcomes (including motor skills) during the median 8 months' follow-up in this cohort. In Kinshasa, 35 HIV-infected children starting treatment (median age, 44.8 months) were studied prospectively with two control groups: 35 HEU children and 90 HIV-unexposed children.[14] At baseline, HIV-infected children had the lowest mean age-adjusted cognitive scores (65.8), children born to uninfected mothers had the highest (84.6), and HEU children had intermediate scores (74.8). After one year of care (including HAART when eligible), HIV-infected children achieved scores similar to HEU children (84.3 and 87.6, respectively) although scores for both groups were lower than in children of uninfected mothers (96.5). Motor skills followed a similar trend.

A similar study from Thailand included children aged 6–12 years[15]; 34 of 39 (85%) HIV-infected children were on HAART at baseline (median duration 35 weeks). Twenty-one percent had average or above average intelligence quotient scores compared with 49% of HEU and 76% of HIV-unexposed children ($P < 0.01$ for trend). Compared with baseline, verbal scores declined after 30 months in all groups, although performance scales did not

change; however, cognitive function was not improved by HAART. Biologic parents cared for only 28% of the HIV-infected children, compared with 78% in HEU and 92% in HIV-unexposed children. Education, age, and family income were significantly lower for HIV-infected parents. However, in a multivariate model, only HIV infection was a significant risk factor for delay. Further study is needed to address whether earlier initiation of therapy can preserve cognitive function.

## Bone Development

Children may be especially vulnerable to antiretroviral-related effects on bone density due to higher bone turnover. The US studies of pediatric tenofovir-containing regimens found absolute bone mineral density (BMD) decreased in 30–40% of recipients after 6–12 months, particularly those younger than 12 years.[16,17]

One Italian study observed that bone mineral content (BMC) in 86 HIV-infected youth was lower than in 194 healthy HIV-unexposed controls.[18] The investigators found a significant difference in lumbar spine BMC between HIV-infected youth receiving PI-based therapy (N = 32) and the healthy controls (29.4g vs. 31.8g, respectively, $P = 0.013$). Whole body BMC also differed between these groups (1.65kg vs. 1.81kg, respectively, $P = 0.05$). Ritonavir and stavudine were associated with lower BMC. In a US study of 236 perinatally HIV-infected and 143 HIV-unexposed children (7–24 years), lopinavir/ritonavir was associated with lower BMC and total/spinal BMD, whereas nevirapine was associated with higher BMC and spinal BMD.[19] Although significant differences by HIV status were not seen for girls, perinatally infected boys had lower total/spinal BMD relative to HIV-unexposed boys, most pronounced with advancing puberty, suggesting a possible increased risk for bone disease during adulthood.

Another Italian study with 44 HIV-infected children (32 on HAART and 7 on dual therapy) and 1227 uninfected controls found significantly lower bone mineral quality (measured by the amplitude and speed of ultrasound propagation through bone) in the HIV-infected group.[20] Antiretroviral regimens were not specified. Bone mineral quality reductions correlated significantly with longer time on ART, older age, older skeletal maturity, and greater height.

Lack of data on calcium and vitamin D status in most studies complicates interpretation of HIV and HAART effects on BMC and BMD; even in developed countries, vitamin D deficiency in HIV-infected children has been observed.[21] Antiretrovirals may directly affect vitamin D levels.[22] A further problem in BMC/BMD measurement in children is age-related changes, differences in body size and composition, maturational timing and sex and racial differences, and increased variability in adolescence.[23] Thus, BMC and BMD must be evaluated as age-specific and sex-specific $z$ scores to account for expected developmental changes in bone.

## Metabolic Abnormalities

Data on HAART metabolic effects in children are limited. Possible metabolic perturbations include insulin resistance, dyslipidaemia, and hyperlactataemia. These abnormalities could translate into an increased lifetime risk for cardiovascular disease and diabetes. HAART

initiation and suppression of HIV replication are associated with declines in proinflammatory cytokines, most notably TNFα, which could be associated with improvements in metabolic perturbations secondary to HIV itself; in one study, reductions in TNFα were associated with improved total/HDL cholesterol ratio.[24]

A French observational study found high rates of metabolic dysfunction in HIV-infected children on HAART, with 42.7% exhibiting at least 1 abnormality.[25] Insulin resistance occurred in 13.2% of children on HAART (median age, 10 years). Lipodystrophy occurred in 24.6% and hypercholesterolemia in 15%. A London cohort following treated and untreated HIV-infected children for a median 4.5 years found that HAART, and PIs (nelfinavir and lopinavir) were associated with increasing total and non-HDL cholesterol levels[26]; 10% had LDL levels > 95$^{th}$ percentile.

In a US study of 240 HIV-infected and 146 uninfected children (median age 12.4 and 11.9 years respectively), HAART recipients lagged behind controls in height and weight, with a tendency toward lower total and limb fat.[27] The median treatment duration with nonnucleoside reverse transcriptase inhibitor (NNRTI)–containing and PI-containing regimens were 5 and 6 years, respectively. The children on PI-HAART had higher rates of hyperlipidaemia; 29% of children on PI regimens, and only 10% of controls, had total cholesterol > 200 mg/dL. In contrast, lipid levels in children on NNRTI were similar to the controls. Fasting insulin levels were highest in the NNRTI group, with the PI group slightly lower and controls substantially lower. In a Brazilian cohort of 94 HIV-infected children and 364 healthy controls, HIV-infected children had a higher risk of stunting, thinness, and higher waist-to-hip ratios.[28] PIs were associated with a 3.5-fold increased risk of thinness and lipoatrophy after adjustment for HIV and HAART type. A recent report implicated stavudine and efavirenz with lipoatrophy in HIV-infected African children.[29]

HAART-associated total cholesterol elevations represent a persistent management problem. The USPACTG 219C study, studied 240 perinatally infected children on HAART who developed hypercholesterolaemia.[30] Two years after detection of hyperlipidaemia, only 34% had achieved normal cholesterol levels (<200 mg/dL). Factors associated with normalization were as follows: virologic suppression (HIV RNA ≤400 copies/mL) (adjusted HR = 2.66); switching HAART regimen (adjusted HR = 2.37); and age >13 years (adjusted HR = 2.39). Only 15 children commenced statin therapy despite the potential future risk for cardiovascular disease. A South African study reported that children with viral suppression switched from a lopinavir/ritonavir-based to an efavirenz-based regimen experienced modest improvements in lipid profile and total body fat.[31] Mean total cholesterol was 161 mg/dL in 71 children who switched to efavirenz and 171 mg/dL in 85 remaining on lopinavir/ritonavir, $P = 0.05$ (follow-up time was not reported). It is possible that efavirenz use also promotes cholesterol elevations.[32]

## Treating HIV and TB Coinfection

Childhood TB comprises more than 20% of total TB in high-burden countries. A postmortem study of children dying of respiratory causes in Zambia documented TB in 18% of HIV-infected and 26% of uninfected children (n = 180 and 84, respectively).[33] In a South African survey between 2004 and 2006, HIV-infected infants had a 24-fold higher incidence

of culture-confirmed TB than infants without HIV.[34] HIV-infected children are prone both to relapse and reinfection by *Mycobacterium tuberculosis*.[35] In the CHER trial, early HAART reduced TB incidence by 50% compared with HAART initiated at a median of 7 months old.[4] Three retrospective paediatric studies showed a decline in TB incidence by 70%–80% after initiating HAART.[36–38]

TB treatment provides challenges for effective HAART. Another South African study of infants found that TB cotreatment when initiating PI-based therapy decreased virologic suppression (HIV RNA <400 copies/mL) by 46% (adjusted HR 0.54).[39] Starting TB treatment after initiating HAART reduced suppression still further (adjusted HR: 0.36). The poorer results were likely related to using ritonavir as a single PI in infants requiring rifampicin. Another retrospective study of 1029 South African children starting ART reported similar findings.[40] However, reduced treatment response was confined to children receiving a PI-based regimen [primarily standard ritonavir alone or boosted (lopinavir/ritonavir) at twice the normal dosage]. In children without TB, PI-based HAART resulted in a 78% virologic suppression rate after 6 months compared with only 63% in children cotreated for TB ($P = 0.003$).

Rifampicin, an essential anti-TB drug, has shortened the duration of TB treatment to 6 months. Unfortunately, rifampicin induces cytochrome P450 enzymes, glucuronidation and P-glycoprotein (P-gp) activity, resulting in increased metabolism and reduced concentrations of antiretrovirals.[41] Ritonavir inhibits cytochrome P450 3A, and P-gp, and at high doses, counteracts the rifampicin interaction with other drugs.[42] Even doubling the lopinavir/ritonavir (4:1) dosage gives inadequate lopinavir exposure in the presence of rifampicin.[43] Using a 4-fold higher dose of ritonavir (superboosting) is the most effective way to circumvent that effect.[44,45] Although lopinavir clearance is somewhat accelerated, children receiving “super-boosted” lopinavir with rifampicin achieved similar rates of HIV suppression up to 12 months compared with normal doses of lopinavir/ritonavir without rifampicin.[46] In children cotreated for TB, HIV RNA was <400 copies per milliliter at 6 months in 69.2% of super-boosted lopinavir/ritonavir recipients, 53.1% of double-dosed lopinavir/ritonavir recipients, and 49.3% in patients receiving ritonavir as a single PI. Drawbacks are the poor tolerability of ritonavir solution, the increased risk of adverse effects, and the short shelf life of ritonavir solution.[47] The increased risk of adverse effects, especially hepatotoxicity in adult studies of with high ritonavir doses,[47] was not seen in children.[46]

Data on the pharmacokinetic interactions between rifampicin and NNRTIs is very limited in children.[48] Substantial reductions in nevirapine concentration in young children were observed in 21 HIV/TB-infected children in Zambia cotreated with nevirapine-based HAART and rifampicin-based TB therapy.[49] Another study with 15 HIV/TB-coinfected children in Cape Town treated with efavirenz-based HAART and rifampicin showed no significant influence on mean efavirenz concentration.[50] However, over half had trough efavirenz concentrations below 1000 ng/mL during and after rifampicin administration, indicating suboptimal efavirenz dose irrespective of TB therapy.

All first-line TB drugs are associated with hepatic dysfunction, as are the PIs and the NNRTIs, nevirapine, and efavirenz.[51] Other adverse effects common to TB and HIV drugs include the following: gastrointestinal dysfunction; peripheral neuropathy (stavudine, didanosine, isoniazid, and cycloserine); rash (efavirenz, nevirapine, abacavir, and all first-line anti-TB agents); CNS dysfunction (efavirenz, isoniazid and cycloserine); and anemia (zidovudine and rifampicin).[51]

Another concern in HIV/TB-coinfected patients is that initiating HAART may result in immune reconstitution inflammatory syndrome (IRIS), in which children with preexisting TB may experience a transient TB symptoms exacerbation within several months of starting HAART. There are few pediatric studies on IRIS. One study prospectively followed 169 South African HIV-infected infants initiating HAART (median age 8 months).[52] Of 34 (21%) who developed IRIS, 24 were due to Bacille Calmette Guérin (BCG), 6 (7.1%) due to TB, and 5 due to TB and BCG. A study in older Ugandan children (median age, 6 years) similarly showed that 38% of 160 participants experienced some form of IRIS,[53] most secondary to TB. In a study of IRIS-related BCG adenitis in infants in the CHER study, 32 (8.7%) of 369 developed BCG IRIS.[54] Incidence was 10.9 and 54.3 per 100 person-years among infants with CD4 counts ≥25% at enrollment receiving early (at median age 7.4 weeks) versus deferred (23.2 weeks) HAART, respectively (HR: 0.24, $P < 0.001$), again emphasizing a benefit from early HAART. Eight (25%) had concurrent BCG and TB IRIS.

New treatment guidelines for pediatric HIV-TB coinfection recommend initiating TB treatment immediately in any child with HIV and active TB.[51] HIV-infected children who meet criteria for ART initiation should commence HAART 2–8 weeks into TB therapy.

An observational study in India also demonstrated the importance of early HAART initiation HIV/TB-infected children.[55]

Children on HAART who develop active TB should initiate TB therapy with adjustment of their HAART regimens. Because of drug interactions, the recommended HAART regimen for children receiving rifampicin is a triple nucleoside reverse transcriptase inhibitor (NRTI) regimen[6,51]; after completion of rifampicin, children can switch to a standard HAART regimen, though there are no data on this approach in children.[56] Due to rifampicin interactions, standard HAART regimens for HIV-infected children without TB are viewed as alternatives in children on TB treatment. In children >3 years or >10 kg, the alternative regimen is two NRTIs plus efavirenz; if younger than 3, choices include two NRTIs plus either nevirapine or super-boosted lopinavir/ritonavir.

The new guidelines also recommend increased pediatric TB drug dosing and addition of ethambutol to the standard 3-drug anti-TB regimen for the first two months.[51] More data on safety and efficacy of these higher dose regimens are needed, and on pharmacokinetics of antiretroviral and anti-TB agents, alone and together.[51,57] Finally, data on optimal management of children with HIV/TB coinfection with malnutrition, extrapulmonary disease, multidrug-resistant TB and IRIS are limited.

## HIV and Malaria in Children

HIV and malaria overlap geographically, particularly in sub-Saharan Africa, where *P. falciparum* malaria is most prevalent. In areas of stable transmission intensity, patients develop semi-immunity to *P. falciparum* malaria: in individuals older than 5 years, infection occurs, but progression to clinical disease is uncommon (patients chronically exposed to *P. vivax*, which occurs in areas of lower transmission, may also develop some acquired immunity). Antimalarial treatment is more efficacious on a background of pre-existing host immunity.[58,59] Interactions of HIV with *P. falciparum* malaria are thought to be partially due to the interference of HIV on the development of malaria semi-immunity. At the same time, immune activation due to malaria antigen exposure makes CD4+ cells more susceptible to HIV.[60] Malaria treatment also reduces viral load increases that occur with acute malaria infection.[61]

In children, the interaction of HIV and malaria is complicated by the effect of HIV on immune function in early life because younger children have not yet acquired immunity to malaria and thus present a less obvious HIV effect. For example, the ability to clear drug-resistant malaria in HIV-infected young children does not seem to correlate with CD4 level.[62] However, some studies suggest that HIV/malaria-coinfected children have higher rates of parasitemia and parasite density than children infected with malaria only.[62,63] Studies show HIV/malaria-coinfected children are also more likely to suffer comorbidities than HIV-uninfected children. They may also be more likely to develop anemia[64,65] or cerebral malaria.[66] HIV, malnutrition, and invasive bacterial infections have been independently associated with severe malaria.[67] In HIV-infected children, some studies suggest that malaria may affect the occurrence of comorbidities, and HIV/malaria coinfection may worsen neurodevelopment delays.[68]

Malaria treatment and prevention guidelines for HIV-infected children parallel guidelines for uninfected children, with the caveat that physicians pay close attention to potential drug-drug interactions. World Health Organization recommends artemisinin-based combination therapy (ACT) for for uncomplicated *P. falciparum* malaria treatment.[69] Many antimalarial drugs, including the quinine, and the artemisinin derivatives and other ACT components, are metabolized by cytochrome p450 enzymes and have bi-directional potential interactions with antiretrovirals.[70]

In a Ugandan study, artesunate/amodiaquine was highly effective for malaria treatment in HIV-infected children, but associated with a high risk of neutropenia, especially in those on antiretrovirals.[71] Artemether/lumefantrine has proven efficacy in children, including those with HIV.[72,73] A study in healthy adults assessed the interaction between artemether/lumefantrine and lopinavir/ritonavir: lopinavir/ritonavir moderately reduced total exposure to artemether's active metabolite by almost half, although more than doubling lumefantrine exposure.[74] In another adult study, artemether/lumefantrine at therapeutic doses had no significant cardiac effects,[75] but some concern remains that increased lumefantrine levels may prolong QT interval. Thus, caution is recommended with coadministration until further safety data is available.[76]

NNRTIs may also have pharmacokinetic interactions with antimalarial drugs; an adult study evaluating amodiaquine and efavirenz pharmacokinetics was stopped after observing dramatic hepatic aminotransferase elevation, perhaps due inhibition of CYP2C8 leading to high concentrations of toxic quinoneimmines.[77,78] There are only limited pediatric studies on antiretroviral-antimalarial drug interactions.[79]

Cotrimoxazole has been shown to reduce malaria clinical episodes in adults and children on prophylaxis, although studies are ongoing to address cotrimoxazole prophylaxis impact on parasite antifolate drug resistance.[80–83] Moreover, use of cotrimoxazole may, if coadministered with regimens that could induce neutropenia (such as amodiaquine-containing ACT), depress neutrophil counts. This may be enhanced with HIV infection.

There is potential benefit to using PI-based HAART HIV-infected patients in malaria-endemic areas, as preclinical data show an antimalarial effect of PIs at clinically relevant concentrations, whereas NNRTIs have only a mild effect against blood stage *P. falciparum* in vitro at super-therapeutic concentrations.[84–87] Studies in adults and children are ongoing to determine clinical relevance.

## Protein–Energy Malnutrition and Recovery From HIV

Severely malnourished children enter a physiologic state known as reductive adaptation.[88] This energy-conserving process causes heart, kidney, and metabolic function to decline >25% from normal. Reductive adaptation and water retention, infections, loss of blood proteins, and other changes resulting from malnutrition can alter drug pharmacokinetics, which could lead to changes in efficacy and safety, but antiretroviral pharmacokinetic studies in children with malnutrition are limited.[89] A recent review noted that drug absorption and elimination decreases are common in the small number of antiretrovirals evaluated.[90] Decreases in absorption and elimination have opposing effects on drug levels, so ultimate impact is difficult to predict.

Several recent studies provide information on short-term outcomes of severe malnutrition in HIV-infected children, although long-term studies are limited.[91] One study followed 1207 Ugandan and Zimbabwean children initiating HAART at ages 3 months to 17 years (median, 6 years)[92]; 3.2% were hospitalized for severe malnutrition a median of 28 days after starting HAART. The proportion hospitalized for severe malnutrition was higher (11%) among low-weight children with advanced HIV (baseline weight-for-age and CD4-for-age $z$ score < −3). Six-month mortality among unhospitalized children initiating HAART was 1.7% but 32% for those hospitalized with kwashiorkor (edema) and 20% with marasmus (emaciation).

In a South African study, severely underweight children initiating HAART showed a nonsignificant trend for lower 2-year virologic suppression compared with normal or moderately underweight children.[93] The severely underweight group also had a higher 2-year mortality rate. A multivariate analysis from a Ugandan study found that stunted children were significantly overrepresented in HAART recipients with virologic suppression but inadequate CD4 cell gain after one year.[94] There was also a nonsignificant trend for severely underweight children with similar median age to exhibit poor virologic and/or immunologic response 1 year after initiating HAART. Both studies found children exhibited

robust height and weight gains on HAART regardless of pretreatment status. Previous studies observed that children who start treatment with less growth deficiency have a better chance of normalizing their height and weight.[95–98]

Optimal treatment strategies are required for malnourished children. In Lilongwe, Malawi, nutritional supplementation given to untreated HIV-infected children with severe acute malnutrition resulted in weight gains comparable with those in uninfected children.[99] However, before nutritional recovery, the mortality rate among the HIV-infected children was 3-fold higher than in children without HIV. A Zambian report observed that nutritional rehabilitation in HIV-infected treatment-naïve children did not retard their CD4 cell declines or need for starting HAART.[100]

## CONCLUSIONS

Although the effect of HAART in reducing morbidity and mortality in HIV-infected children is clear, it requires lifelong treatment starting at a very young age. Yet there is little definitive information on HAARTs potential adverse effects on growth and development. The relationship between pediatric HAART and interventions for malnutrition, TB and malaria is another critical area for further research (Table 2).

A coherent research strategy and new studies are required that include a range of age stratifications with long-term follow-up as children mature.[101] Finally, it is essential that these studies are also conducted in low-resource countries, where most HIV-infected children reside.

## Acknowledgments

This literature review is partly based on a mapping exercise and the consultation process initiated by the International AIDS Society-Industry Liaison Forum that resulted in the Environmental Scan, “Mapping HIV Research Priorities for Women and Children”, and the Consensus Statement, “Asking the Right Question: Advancing an HIV Research Agenda for Women and Children”, which were released by the IAS and partner organizations. These are: AVAC, Global Advocacy for HIV Prevention; Boehringer Ingelheim; Clinton Health Access Initiative; Coalition on Children Affected by AIDS; Elizabeth Glaser Pediatric AIDS Foundation; European AIDS Treatment Group; International Community of Women Living with HIV/AIDS; International Treatment Preparedness Coalition; Merck; Treatment Action Group; UNAIDS; UNICEF; ViiV Healthcare; and World Health Organization. The mapping exercise was financially supported by unrestricted educational grants from Abbott, Boehringer Ingelheim, Gilead, Merck, Pfizer, Tibotec and ViiV Healthcare, as well as the International AIDS Society. The authors are grateful for their support. The content of the mapping exercise and its literature review was guided and conducted by an Expert Reference Group of which the authors of this article were members. The Expert Reference Group included experts from United Nations agencies and public institutions. The authors would like to acknowledge the contribution of David Gilden, Rodney Kort, and Clemens Roll, independent consultants who provided support in the search and review of literature for the environmental scan. David Gilden also provided support in drafting and revising this article.

The mapping exercise was financially supported by unrestricted educational grants from Abbott, Boehringer Ingelheim, Gilead, Merck, Pfizer, Tibotec and ViiV Healthcare, and the International AIDS Society.

The authors S.H. is an employee of the International AIDS Society, and her salary is provided partly by unrestricted educational grants from the following pharmaceutical companies: Abbott, Boehringer Ingelheim, Gilead, Merck, Pfizer, Tibotec and ViiV Healthcare. M.F.C. is an investigator on GSK and Boehringer Ingelheim trials and has received honoraria from Abbott and GSK within the past 6 months. R.M. has served as an advisor to the BMS Foundation and the Merck Company Foundation.

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**TABLE 1**

Search Strategy

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|---|
| The Medline/PubMed database was searched using several key word Boolean strings listed below: |
| HIV AND (initiation OR initiating) AND antiretroviral AND (pediatric[title] OR child[title] OR children[title] OR infant[title] OR infants[title]) AND (progression OR outcome OR outcomes OR mortality OR survival) NOT (transmission[title] OR pregnancy[title] OR pregnant[title] OR PMTCT[title]) |
| HIV AND antiretroviral AND (pediatric[title] OR child[title] OR children[title] OR infant[title] OR infants[title]) AND (cognitive OR neurologic OR motor OR mental OR psychologic OR psychiatric OR psychosocial OR growth OR height OR weight OR bone OR body composition) |
| HIV AND antiretroviral AND (pediatric[title] OR child[title] OR children[title] OR infant[title] OR infants[title]) AND (mitochondrial OR lipodystrophy OR lipidemia OR cholesterol OR glucose OR insulin OR vascular OR cardio OR cardiac OR diabetes OR metabolic OR renal OR kidney OR hepatic OR liver) |
| HIV AND antiretroviral AND (pediatric OR child OR infant) AND (tuberculosis OR malaria) |
| HIV AND antiretroviral AND (pediatric OR child OR infant) AND malnutrition |

Additional literature was located through the PubMed “related articles” function and by articles’ reference lists. Abstracts from the International AIDS Conferences, and Conferences on HIV Pathogenesis, Treatment and Prevention (2008–2011), the Conferences on Retroviruses and Opportunistic Infections and the International Workshop on HIV Pediatrics (2009–2011) were searched separately. Published results were favored over conference presentations.

## TABLE 2

Summary of the Clinical Management Concerns When Treating HIV-Infected Children

| Area | Management Issues Requiring Research |
|---|---|
| Neurocognitive development | Children with HIV accelerate their neurologic development after starting HAART, but they do not catch up with other children |
| | Neurocognitive development in HIV-exposed but uninfected children is also below normal and needs further study |
| | The socioeconomic and medical reasons for residual developmental delay in HAART-treated children remains to be delineated |
| Bone growth | HAART in general, as well as specific antiretroviral agents, has been associated with subnormal bone mineral content |
| | Children may be especially vulnerable to these effects |
| | A major confounding factor is the worldwide deficiencies in calcium and vitamin D |
| Metabolic abnormalities | HAART initiation is associated with decreases in inflammatory cytokines |
| | Children on HAART nevertheless experience high rates of fat wasting, insulin resistance, dyslipidaemia and hyperlactataemia |
| | High cholesterol levels may lead to cardiovascular disease, but aggressive lipid management is lacking in children |
| HIV/TB coinfection | Concurrent HAART improves the response to TB therapy, but TB therapy can have negative effects on HAART effectiveness and toxicity |
| | Drug-drug interactions and overlapping toxicities pose challenges to concurrent treatment of HIV and TB |
| | Pharmacokinetic data on the drug-drug interactions are sparse in children |
| | Data on management of TB and malnutrition, extrapulmonary disease, drug resistance and IRIS in children are very limited |
| HIV/Malaria coinfection | HIV's effect on childhood malaria is unclear |
| | There is only limited paediatric data on PK and toxicity interactions between antiretroviral and antimalarial agents |
| | Some HAART components may be active against malaria, but this requires further study |
| Malnutrition | Malnutrition may interfere with absorption of HAART drugs |
| | Malnourished children have relatively poor outcomes after initiating HAART, but there are no long-term data in this area |
| | Researchers have not developed optimal antiretroviral/nutritional strategies for malnourished children |