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Understanding the contribution of common childhood illnesses and opportunistic infections to morbidity and mortality in children living with HIV in resource-limited settings

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Abstract

Objective—Although antiretroviral treatment (ART) has reduced the incidence of HIV-related opportunistic infections among children living with HIV, access to ART remains limited for children, especially in resource-limited settings. This paper reviews current knowledge on the contribution of opportunistic infections and common childhood illnesses to morbidity and mortality in children living with HIV, highlights interventions known to improve the health of children, and identifies research gaps for further exploration.

Design and Methods—Literature review of peer-reviewed articles and abstracts combined with expert opinion and operational experience.

Results—Morbidity and mortality due to opportunistic infections has decreased in both developed and resource-limited countries. However, the burden of HIV-related infections remains high, especially in sub-Saharan Africa, where the majority of HIV-infected children live. Limitations in diagnostic capacity in resource-limited settings have resulted in a relative paucity of data on opportunistic infections in children. Additionally, the reliance on clinical diagnosis means that opportunistic infections are often confused with common childhood illnesses which also contribute to excess morbidity and mortality in these children. Although several preventive

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Disclaimers

The findings and conclusions in this article are those of the authors and do not necessarily represent the official position of the World Health Organization or the U.S. government including the U.S. Centers for Disease Control and Prevention and Agency for Toxic Substances Disease Registry and the United States Agency for International Development.

interventions have been shown to decrease opportunistic infection-related mortality, implementation of many of these interventions remains inconsistent.

Conclusions—In order to reduce opportunistic infection-related mortality, early ART must be expanded, training for front-line clinicians must be improved, and additional research is needed to improve screening and diagnostic algorithms.

Keywords

children; HIV; mortality; opportunistic infections

Introduction

Despite substantial global progress toward reducing new pediatric HIV infections, there were approximately 3.4 million children living with HIV and 230 000 AIDS-related deaths among children in 2011 [1]. More than 90% of HIV-infected children live in sub-Saharan Africa, meaning that this region is also disproportionately affected by pediatric HIV-related mortality [2]. Pooled analyses of data from sub-Saharan Africa show that more than half of HIV-infected infants die by age 2 years without antiretroviral treatment (ART), compared with 8% of HIV-exposed uninfected infants [3,4]. Even with ART, mortality rates in HIV-infected children are estimated to be at least 30 times higher than mortality rates among HIV-unexposed children, largely due to the impact of opportunistic infections and an increased susceptibility to common childhood illnesses such as diarrhea, pneumonia, malaria, and malnutrition [5–8]. Opportunistic infections are frequently the presenting symptom of HIV among children with undiagnosed infection or may be the determining factor for initiation of ART in known HIV-infected children who do not meet other criteria for treatment. As with adults, ART remains the single most effective intervention for reducing the incidence of opportunistic infections, decreasing opportunistic infection-related morbidity, and improving survival of HIV-infected patients [5,6,9,10]. Since the widespread introduction of ART in sub-Saharan Africa beginning in 2004, HIV-related mortality in children has decreased by more than 25% [1,6]. However, access to ART remains limited for children living with HIV. In the 22 high HIV burden countries identified as priorities in the ‘Global Plan Towards the Elimination of New HIV Infections among Children and Keeping their Mothers Alive’ only 34%of children in need of ART received treatment in 2012 compared with 63% of all people living with HIV (PLHIV), and HIV-infected children continue to suffer from disproportionately high rates of morbidity and mortality [11–13]. This paper reviews current knowledge on the contribution of opportunistic infections and common childhood illnesses to morbidity and mortality in children living with HIV, highlights interventions known to improve the health of children, and identifies research gaps for further exploration.

Opportunistic infection-related mortality among children living with HIV in the United States and Europe

The majority of data on the impact of opportunistic infections in children living with HIV come from cohort studies conducted as part of clinical trials in the United States and Europe.

The Pediatric AIDS Clinical Trials Group (PACTG) and the Perinatal AIDS Collaborative Transmission Study (PACTS) have followed HIV-infected children in the United States since the mid-1980s [5,6,9,14–16]. Data from both PACTG and PACTS since 1997 show decreases in overall mortality and in opportunistic infection-related mortality for children following the introduction of ART. Overall mortality for children in both cohorts declined to 0.8 deaths per 100 person-years in the post-ART era from pre-ART rates of 7.2 and 18 deaths per 100 person-years in the PACTG and PACTS cohorts, respectively [5,9,16]. Similarly, data from a cohort of children in the United Kingdom and Ireland showed a decrease in overall mortality from 8.2 deaths per 100 person-years before 1997 to 0.6 per 100 person-years by 2006 [17]. The proportion of deaths due to opportunistic infections has decreased dramatically with the advent of ART, but these infections remain substantial contributors to mortality. In the PACTS cohort, 31.8% of deaths prior to 1991 when ART was not widely available were due to opportunistic infections, decreasing to 16.9% in years of monotherapy and dual therapy (1991–1996) and to 9.1% when combination therapy was available (1997–2004) [16]. Opportunistic infections accounted for 24% of all deaths in children in the PACTG cohort between 2001 and 2006 [5]. The most commonly occurring infections among HIV-infected children in the developed world include bacterial pneumonia, herpes zoster, dermatophyte infections, and oral candidiasis [6]. The opportunistic infections causing death have changed since the introduction of ART in the United States. The proportion of deaths due to *Mycobacterium avium* complex (MAC) and cryptosporidium have significantly decreased, whereas mortality due to other opportunistic infections such as *Pneumocystis jirovecii* pneumonia (PCP) and cytomegalovirus (CMV) remained relatively stable [5,18]. Data from other studies in the United States and other developed countries have largely corroborated the PACTG and PACTS data and have shown that opportunistic infection-related mortality has declined, but that HIV-related infections still remain an important cause of morbidity and mortality in children [14,15, 18–23].

Opportunistic infections among children living with HIV in resource-limited settings

There is a relative paucity of data on the burden of opportunistic infections in children living with HIV in resource-limited settings. There are few large published multicountry cohort studies specifically designed to measure the incidence of a broad range of opportunistic infections in HIV-infected children or determine specific causes of death in resource-limited settings where autopsies are not commonly performed. However, the data that are available suggest that ART has had a similar impact on decreasing opportunistic infection-related morbidity and mortality in resource-limited settings. Data from Thailand show that opportunistic infection-related mortality in children decreased from 27% of all causes of mortality in the pre-ART era (1989–2002) to 5.7% in the post-ART era (2003–2009). As seen in the United States and Europe, the types of opportunistic infections conferring higher morbidity (i.e., leading to hospitalization) have changed with the widespread availability of ART, although the specific trends were different in Thailand, where the incidence of PCP and recurrent salmonella septicemia decreased, whereas mycobacterial and systemic fungal infections increased [10]. A recent study demonstrated that the incidence of WHO stage 3 or

4 conditions among HIV-infected adults and children in resource-limited settings in Asia and Africa was approximately 14 times as high as among patients in a European cohort in the first 3 months after ART initiation, although overall incidence of these conditions decreased by more than 90% at the end of 12 months following ART initiation [24].

Even where ART is available, HIV-infected children in resource-limited settings continue to experience high levels of morbidity and mortality from opportunistic infections. A recent study from Latin America that compared a cohort of children with a similar length of follow-up, ART utilization, and CD4% at enrollment as the children in the PACTG study cohort showed a similar spectrum of opportunistic infections, but a much higher overall incidence of opportunistic infections than the children in the United States [25]. A systematic review of mortality in resource-limited settings in the ART era found that pediatric mortality remains significantly higher than developed countries despite more widespread ART availability, with 8 deaths per 100-child years compared with approximately 0.8–0.9 deaths per 100 child-years in developed countries [5,26]. This review also highlighted the delays in initiation of ART for children in resource-limited settings as evidenced by the relatively low $CD4^+$ cell count, low weight-for-age *z*-scores, and high viral loads compared with children in developed countries [26]. Routine program data on HIV-infected adults and children from 10 countries in Asia and Africa further indicate that the highest regional burden of opportunistic infections occurs in Africa, where the incidence of any WHO stage 3 condition was three times as high as in Asia, and with pulmonary tuberculosis (TB) being the most commonly reported condition [24].

Common childhood illnesses among children living with HIV

In addition to opportunistic infections, HIV-infected children also suffer from diseases common in HIV-unexposed children in these settings, including malaria, pneumonia, and diarrheal illnesses. A review of hospital admission data in Soweto, South Africa shows that pneumonia, diarrhea, and malnutrition were the most common causes of childhood hospitalization, especially in HIV-infected children prior to the availability of ART [27]. A more recent study from the Democratic Republic of Congo reported that the most common causes of death in children on ART included septic shock and diarrhea, which only cause 8% of deaths in HIV-infected children in the United States [6,28]. The higher incidence of diarrhea and diarrhea-related mortality among children living with HIV may be explained by an underlying immunocompromised state, comorbid infections, and/or malnutrition, which often result from delayed ART initiation [28–30]. Persistent diarrhea, in particular, is associated with a high risk of mortality in HIV-infected children. Restoration of immune function with ART is a critical component of prevention and treatment of diarrhea in children with HIV infection, yet access to ART remains limited, especially in sub-Saharan Africa [12,31].

Data from Botswana showed that the burden of respiratory disease among children living with HIV is particularly high, causing 83% of deaths among HIV-infected children compared to 27–42% in the United States [14,18,32]. Pneumonia was the most common serious bacterial illness among HIV-infected children admitted to a hospital in Cape Town, South Africa, with common causes including *Streptococcus pneumoniae*, *Staphylococcus*

aureus, and *Klebsiella pneumoniae* [33]. Similarly, a study in Thailand showed that the most frequent cause of hospital admission among children receiving ART was pneumonia and other bacterial infections, accounting for 62% of the admissions [34]. A systematic review of the causes of severe pneumonia in HIV-infected children in both resource-limited and developed countries found limited data, especially after the availability of ART. The available data suggest that PCP and CMV were the most common and second most common causes, respectively, of pneumonia in HIV-infected children; additionally, *Mycobacterium tuberculosis* was documented in 8% of children with acute pneumonia in South Africa [35]. The limited capacity to diagnose specific infections, such as PCP, CMV, and TB, among children in resource-limited settings means that these are often not differentiated from other common causes of respiratory disease in HIV-uninfected children [36,37]. Given these limitations, the true prevalence of these specific infections among HIV-infected children, stratified by ART exposure and CD4 cell count, remains unknown. A recent report showed that nearly 30% of the pneumonia burden in sub-Saharan Africa can be attributed to HIV-related immunosuppression (personal communication, WHO). Although common childhood illnesses contribute substantially to morbidity and mortality among children living with HIV, the relative burden of opportunistic infections may be underestimated in resource-limited settings due to limited diagnostic capacity and lack of routine surveillance for these illnesses.

Recommendations for prevention of opportunistic infections and common childhood illnesses among children living with HIV

Several medical interventions have been proven to reduce morbidity and mortality from opportunistic infections and are recommended as prophylactic therapy for children living with HIV. Cotrimoxazole has been shown to dramatically reduce the risk of opportunistic infections such as PCP and toxoplasmosis and to provide protection against common diseases such as malaria [38,39]. Since 2006, WHO has recommended cotrimoxazole preventive therapy for all HIV-exposed infants through the end of the breastfeeding period and for all HIV-infected infants and children under the age of 5 years [39]. To prevent TB-related morbidity and mortality in HIV-infected children, WHO recommends isoniazid preventive therapy (IPT) for all HIV-infected infants and children with a history of contact with a known TB case and for all HIV-infected children over age 12 months who are unlikely to have active TB or who have successfully completed treatment for TB disease [40–42]. WHO does not recommend the use of fluconazole for primary prophylaxis of cryptococcal infection in children and adolescents because available data suggest a lower incidence in these age groups [39].

Despite the known benefits and long-standing recommendations for cotrimoxazole and IPT, uptake of these interventions remains inconsistent. There are encouraging data from a recent national retrospective cohort study in Kenya, which show that 94% of HIV-infected children received cotrimoxazole prophylaxis at their last HIV clinic visit between 2004 and 2010 (unpublished data, CDC). However, data from a South African study showed that a third of HIV-exposed children attending a primary healthcare facility did not receive cotrimoxazole

[43]. No published global data are available on routine uptake of IPT among HIV-infected children.

Further research is needed on the optimal use and duration of opportunistic infection prophylaxis regimens for HIV-exposed and HIV-infected children. Recent data confirm the benefit of extended cotrimoxazole prophylaxis for HIV-infected children receiving ART in resource-limited settings, with ongoing reductions in hospitalizations for malaria and other infections beyond 96 weeks [44]. Cotrimoxazole has also been shown to moderately reduce malaria incidence in HIV-exposed uninfected infants through age 2 years [45]; however, there have been no randomized clinical trials assessing the long-term impact of cotrimoxazole in HIV-exposed uninfected infants. Data from South Africa suggest that there is little benefit of cotrimoxazole prophylaxis for lower respiratory tract infections and a trend toward an increased risk of diarrhea without a decreased risk of lower respiratory tract infections in HIV-exposed uninfected infants receiving cotrimoxazole prophylaxis for more than 2 months while breastfeeding, but these findings were not statistically significant [46,47]. As countries continue to scale up prevention of mother-to-child HIV transmission (PMTCT) programs to reach goals for global elimination of new pediatric HIV infections, the need for data on cotrimoxazole use, and other preventive therapies in HIV-exposed, uninfected infants increases.

Although TB is one the most common causes of mortality in PLHIV, the difficulty of confirming a diagnosis of active TB in children remains a barrier to increasing case finding and ruling out active disease prior to IPT. Many promising advances have been made for TB diagnosis among PLHIV in the past 5 years, including the introduction of rapid, near point-of-care diagnosis with the Xpert MTB/RIF assay [48]. Initial studies of Xpert MTB/RIF testing in children living with HIV show that diagnostic yield is up to a three times as high as smear microscopy of sputum, gastric aspirates, or nasopharyngeal aspirate specimens [48–53]. However, obtaining these specimens remains challenging in resource-limited settings, especially in the youngest children who are at highest risk of TB-related mortality. Novel approaches using stool and urine are being tested, but preliminary results have been mixed [49,54]. The difficulty of ruling out active TB in children with HIV in resource-limited settings further complicates scale-up of IPT provision. In a routine clinical setting offering IPT to HIV-infected children in Kenya, less than half of all children enrolled in HIV care between 2008 and 2011 received IPT; the median time to IPT initiation was 8 months due to the large burden of TB among HIV-infected children and the difficulty of excluding active TB disease in this setting [55]. Research on the impact of IPT on TB incidence and mortality has focused on adults; additional population-based studies in HIV-exposed and HIV-infected infants and children are needed to strengthen the evidence base for this intervention [56,57]. The optimal duration, safety, efficacy, and cost–effectiveness of IPT alone or in addition to ART have not specifically been evaluated among children living with HIV, particularly in routine program settings in resource-limited settings. Further research is recommended for improving the accuracy and feasibility of diagnosis of active TB and other opportunistic infections, such as PCP and CMV, in HIV-infected children in resource-limited settings.

Interventions to decrease the burden of common childhood illnesses will also help decrease morbidity and mortality among HIV-infected children. Increasing the coverage of routine childhood immunizations is one such essential intervention. Several studies have shown that the pneumococcal conjugate vaccine and the *Haemophilus influenza* conjugate vaccine may prevent a large proportion of HIV-associated and non-HIV-associated pneumonia in children [58–61]. In one study from South Africa, the overall reduction in invasive pneumococcal disease attributed to pneumococcal conjugate vaccination was 60 times higher in HIV-infected children compared with HIV-uninfected children [58,62]. Although limited data exist on the use of rotavirus vaccine in HIV-infected children, this vaccine has the potential to decrease the burden of acute gastroenteritis-related morbidity and mortality in high HIV prevalence regions [63–65].

Improving the health of families is also essential to improving outcomes for children. Data from multiple studies have shown that HIV-exposed and HIV-infected children are more likely to die when their mothers are ill or have died [66–68]. Importantly, data from South Africa show that mortality rates in children whose mothers received ART were not significantly different than HIV-unexposed children [68]. These data suggest that widespread implementation of universal ART for pregnant and breastfeeding women commonly referred to as (Option B+) may result in improved survival for children. Recognition and treatment of HIV infection and opportunistic infections in adults are also critical to the prevention of HIV infection and opportunistic infection-related morbidity in children, as these conditions tend to spread within families and households. HIV-infected women or HIV-infected family members who are co-infected with certain opportunistic pathogens are more likely to transmit these infections to their children, resulting in an increased likelihood of primary acquisition of such infections in the young child. For example, studies from Europe and Asia have shown that HIV-exposed infants have higher rates of congenital CMV infection than children born to mothers without HIV, and CMV is more common in HIV-infected infants than HIV-exposed uninfected infants [69,70]. Similarly, HIV-exposed infants are more likely to acquire hepatitis B and hepatitis C infection than HIV-unexposed infants [71–73]. Additional studies are needed to understand the prevalence and importance of perinatal transmission of CMV and hepatitis in sub-Saharan Africa. Infection with *Mycobacterium tuberculosis* among infants and children primarily reflects acquisition from family members with active TB disease. Furthermore, maternal TB infection is associated with not only an increased risk of TB in the infant, but also an increased risk of HIV transmission, making TB prevention and treatment among pregnant women a critical intervention for improving HIV-free survival for children [74,75].

Health systems gaps

In order to improve access to pediatric HIV care and treatment in resource-limited settings, these services are increasingly being decentralized to district hospitals and primary healthcare settings. In these lower-level healthcare facilities, treatment options, human resources, and capacity for laboratory, radiologic, and pathologic diagnosis of opportunistic infections are more limited than at secondary or tertiary level health facilities [76]. Given these limitations, management decisions are often made on the basis of clinical presentation alone. However, clinical diagnoses are often incorrect, as highlighted by autopsy studies in

HIV-infected adults and children in sub-Saharan Africa, which show frequent discordance between clinical and postmortem diagnoses [36,77,78]. PCP and CMV pneumonia were identified as the main causes of mortality in autopsy studies of HIV-infected infants who died with presumptive bacterial pneumonia in Africa prior to the widespread availability of ART [77,79,80]. Additionally, these studies have identified lymphoid interstitial pneumonia (LIP) as one of the most common contributors to mortality [36]. LIP is commonly confused with TB, and the difficulty of confirming both of these diagnoses makes management difficult. Although corticosteroids are often available at a district hospital for children with LIP showing severe dyspnea, cyanosis, or hypoxia, this is often not the routine practice when the diagnosis is unclear or when clinicians are not experienced in managing clinical complications in children [81,82]. LIP has been shown to respond well to ART, but remains an important clinical consideration, especially in settings with low coverage of ART for HIV-infected children [83].

Identifying the various opportunistic infections in HIV-infected children requires a high index of suspicion from the healthcare worker, underscoring the need to ensure that clinical training emphasizes the importance of testing sick children for HIV and including opportunistic infections in the differential diagnosis of common childhood illnesses. Developing simplified algorithms for prevention, recognition, and treatment of opportunistic infections and other common illnesses in HIV-infected children will ensure that mid-level providers can deliver high quality pediatric HIV services. One proposed strategy involves including recommendations for diagnosis and management of opportunistic infections in Integrated Management of Childhood Illnesses (IMCI) guidelines along with treatment guidelines for common childhood illnesses such as diarrhea, pneumonia, and malaria and other interventions such as nutritional support, micronutrient supplementation, and deworming treatment [84,85]. However, data on the effectiveness of IMCI for early HIV diagnosis and for pediatric HIV management are limited; additional studies are needed to evaluate this approach [86,87].

Summary

There are clear regional differences in the incidence of HIV-associated opportunistic infections and opportunistic infection-associated mortality among children living with HIV globally. As PMTCT coverage increases, the number of annual pediatric HIV infections will continue to decrease, but continued expansion of HIV testing and treatment for children will remain critical for decreasing the impact of HIV until virtual elimination of mother-to-child HIV transmission becomes a global reality [12,88]. Implementation of family-centered and other innovative approaches to HIV testing and care is needed to help identify children living with HIV earlier and initiate ART earlier. Expanding coverage of ART for HIV-infected children in resource-limited settings is the most critical intervention to reduce the impact of opportunistic infections. If the recently published WHO guidelines recommending universal treatment of HIV-infected children younger than 5 years and treatment of older children with $CD4^+$ cell counts below 500 are adopted widely, treatment coverage for children living in resource-limited settings should dramatically increase.

Adopting a universal treatment policy for the youngest children is likely to have the most impact in resource-limited settings in which access to $CD4^+$ cell count testing or diagnostics for opportunistic infections are the most limited, in much the same way that Option B+ has expanded access to ART for pregnant women. However, even with ART, opportunistic infections and common childhood illnesses remain a major cause of morbidity and mortality for children with HIV. The limited attention to and capacity for diagnosis of pediatric opportunistic infections in resource-limited settings mean that the true burden of opportunistic infections in children living with HIV is unknown, especially in sub-Saharan Africa, where the majority of HIV-infected children live. These children are also more susceptible to common childhood illnesses, such as pneumonia and diarrhea, which are often more severe and fatal for HIV-infected children than uninfected children. Because many of these conditions have similar clinical presentations, healthcare workers relying on clinical symptoms alone may find it difficult to reliably distinguish opportunistic infections from common childhood illnesses.

Although guidelines for prevention, diagnosis, and management of opportunistic infections have been published in developed countries, these may not always be directly applicable to the management of disease in children living in resource-limited settings, highlighting the need to develop context-specific guidelines for opportunistic infection and healthcare worker training curricula. Further research is needed to identify the true burden of opportunistic infections, essential diagnostics, and treatment protocols for the routine package of care, especially in lower-level healthcare facilities in resource-limited settings. Ultimately, earlier diagnosis of HIV, earlier initiation of ART for all children, increased usage of evidence-based prophylactic regimens, and increased clinical suspicion for opportunistic infections are needed to improve the longterm health of children living with HIV.

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