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Infectious Diseases of Poverty in Children: A Tale of Two Worlds

Caitlin Hansen, MD¹ and Elijah Paintsil, MD^{1,2}

¹Department of Pediatrics, Yale University School of Medicine, New Haven, CT, USA

²Departments of Pharmacology & Public Health, Yale University School of Medicine, New Haven, CT, USA

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INTRODUCTION

The phrase “Infectious diseases of poverty” (IDoP) is used to describe infectious diseases that are more prevalent among poor and vulnerable populations [1]. IDoP comprises (1) HIV/AIDS, Tuberculosis (TB), and Malaria - the “Big Three” (also referred to as “Unholy Trinity”); and (2) neglected tropical diseases (NTDs) [2]. Poverty has been inextricably linked with infectious diseases since antiquity. Poverty, acting through non-genetic heritable principles, has transformed infectious diseases into “inheritable” conditions. IDoP is seen in pockets of poverty in high-income countries (HIC) as well. IDoP perpetuates poverty by leading to adverse outcomes in pregnancy, child development, and workplace productivity [3]. Gross domestic product (GDP), an indicator of wealth of a country, is the most sensitive surrogate measure of burden of infectious diseases in a country. Figure 1 illustrates the positive correlation between poverty and infectious diseases. Substandard housing, lack of access to safe water and sanitation, and inadequate vector control contribute to the efficient transmission of these infections [4]. Other social determinants (e.g. gender inequality, unemployment, low educational status, poor nutrition) further compound the problem [5]. Strategies to prevent and control infectious diseases require tremendous resources. Therefore, infectious diseases have artificially divided the world into HIC and low and middle income countries (LMIC), with LMIC bearing the highest burden of IDoP. However, with globalization and increased interconnectedness of the world, IDoP can transcend this economic divide.

Corresponding Author: Elijah Paintsil, MD, Departments of Pediatrics, Pharmacology & Public Health, Yale University School of Medicine, 464 Congress Avenue, New Haven, CT 06520, elijah.paintsil@yale.edu.

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This article provides an overview of IDoP that affect children with a focus on epidemiology, clinical manifestations, diagnosis, management, and prevention. IDoP account for a significant disease burden and high disability-adjusted life years (DALY) (Table 1).

HIV

Epidemiology

Thirty-four years into the HIV epidemic, advances in prevention and treatment have been made. However, challenges remain regarding access to and management of antiretroviral therapy (ART), particularly in LMIC. Established modes of HIV transmission are: (1) sexual contact; (2) needle injuries; (3) mucous membrane exposure; (4) mother-to-child transmission (MTCT); and (5) transfusion with contaminated blood products. MTCT continues to fuel the pediatric HIV epidemic in LMIC [6]. The use of perinatal antiretroviral (ARV) drugs to prevent MTCT (PMTCT) of HIV has resulted in a dramatic decrease (to <2%) in the rate of vertical HIV transmission in the US [7].

Despite these successes, progress has not been uniform worldwide. At the end of December 2013, only 23% of the 3.2 million children estimated to be living with HIV were receiving ART and in 2013 alone, 240 000 were newly infected and 190 000 (170 000 – 220 000) died of HIV-related causes [8]. Poverty is inextricably related to the disparity in global coverage of ART, with LMIC reporting low coverage (Table 2). Sub-Saharan Africa, with the highest proportion of people living on <2 USD a day (Figure 1), is home to 91% of all children living with HIV [9].

Clinical Manifestations

The hallmark of HIV infection is progressive depletion of CD4 T-cells leading to development of opportunistic infections (OIs), AIDS, and death [7]. In acute simian immunodeficiency virus (SIV) infection, 30% to 60% of all gut-associated CD4 cells become infected leading to profound depletion within 4 days of infection [10]. Similar CD4 gastroenteropathy occurs with acute HIV infection, albeit, at a different pace. During primary infection, HIV infects gut-associated resting and activated memory CD4 cells leading to breach in the intestinal epithelial barrier with a loss of tight junctions, enterocyte apoptosis, local immune activation, and depletion of CD4 cells [11]. The breach in mucosal barrier facilitates translocation of pathogenic bacteria and microbial products from the gut lumen to the systemic circulation leading to chronic immune activation [12]. The time from acute infection to the development of AIDS is defined by a CD4 cell count of <200 cells/mm³ or the appearance of AIDS-defining OIs or cancers (Box 1) and ranges from 6 months to 25 years. However, in infants, disease progression is rapid: without treatment, 20% and 50% of perinatally infected infants will die by 3 and 24 months of age, respectively [13].

HIV infection in children results in a wide array of clinical manifestations (Box 1) and varied natural history. Early presentations of pediatric HIV infection include unexplained fevers, generalized lymphadenopathy, hepatomegaly, splenomegaly, failure to thrive, oral and diaper candidiasis, recurrent diarrhea, parotitis, hepatitis, CNS disease (e.g.,

hyperreflexia, hypertonia, floppiness, developmental delay), recurrent invasive bacterial infections, and other OIs (Box 1).

Diagnosis

HIV nucleic acid test (NAT) is used for diagnosis of HIV infection. NAT includes HIV DNA and RNA PCR assays, and related RNA qualitative or quantitative assays [14, 15]. HIV culture is not used for routine diagnostic testing [16]. Early HIV testing of all infants born to HIV-infected women is required. Infants born to women with HIV infection will be HIV antibody positive because of transplacental transfer of maternal antibodies. HIV RNA or DNA testing of an HIV-exposed infant should be performed at birth (for infants at high risk of HIV infection), at age 14–21 days, at 1–2 months, and at age 4–6 months. HIV infection can be excluded in a non-breastfed infant with two or more negative virologic tests (i.e., negative RNA or DNA), one at age 1 month and one at age 4 months, or two negative antibody tests from separate specimens obtained at age 6 months. The WHO recommends that all HIV-exposed infants have HIV virological testing at 4–6 weeks of age and HIV serological testing at 9 months to identify infants with persisting HIV antibody or who have seroreverted [17]. Furthermore, serological testing followed by virologic testing (if seroreverted) is recommended at least six weeks after breastfeeding cessation in children <18 months of age. For infants and children >18–24 months of age who present with symptoms consistent with HIV infection (Box 1) and unknown maternal HIV status, HIV diagnosis relies on antibody tests and a confirmatory PCR test.

Management

The goal of combination ART (cART) suppresses HIV viral replication and restores immune function. Current treatment strategies focus on timely initiation of cART regimens capable of maximally suppressing viral replication in order to prevent disease progression. There are emerging reports that very early cART is associated with very small proviral reservoirs and restricted HIV-specific immune responses in perinatal infection [18–20]. However, when to start (Box 2) and what ART regimen to start a patient on (Table 3) vary from country to country. The management of patients failing first-line regimens and treatment options for multiple drug resistant HIV is complicated and should involve an expert in HIV medicine.

The standard of care for monitoring treatment in HIV-infected children is routine laboratory monitoring of CD4 absolute count or percentage and HIV viral load [26]. The WHO recommends viral load surveillance as the preferred monitoring of HIV treatment; if not routinely available, CD4 count and clinical monitoring are used [17].

Prevention

HIV prevention in children can be categorized into (1) primary prevention, mainly by PMTCT; and (2) secondary prevention of morbidity and mortality of HIV. PMTCT rates as low as 1% has been achieved as a result of the use of the PACTG 076 regimen [21], cART, and appropriate management of labor and delivery. The birth of an infected child in a HIC is now rare and represents systems failure and missed opportunities during pregnancy, labor, and delivery [22]. The WHO recommends Option B+ as the main strategy to eliminate

MTCT: Option B+ proposes that all HIV-infected women receive lifelong ART beginning at their first pregnancy, regardless of CD4 count [2]. This strategy may improve maternal health through reduced morbidity and mortality, and reduce overall MTCT, especially in settings with high fertility rates [2]. The cost effectiveness of Option B+ has been reported by several studies [23–25].

In the era of expanded access to ART, millions of children with perinatally acquired HIV infection are now living longer. However, pediatric HIV faces new challenges related to adherence, drug resistance, reproductive health planning, transition to adult medical care, and the potential for long-term complications from HIV and the treatment thereof [26, 27].

TUBERCULOSIS (TB)

Epidemiology

TB is caused by the bacillus *Mycobacterium tuberculosis* and is the leading infectious cause of death worldwide. Childhood TB accounts for ~10–20% of the global burden of TB disease. In 2013, there were an estimated 9.0 million incident cases and 1.5 million deaths, [28] including 550 000 cases and 80 000 deaths among children. In the same year, TB case rates in the US continued to decline in all age groups except among children aged 14 years (0.8 cases per 100,000) [29]. Moreover, poor case ascertainment, absence of active case finding, and limited surveillance data in TB-endemic areas contribute to underestimation of global burden of pediatric TB disease [30]. Incidence of pediatric TB is an accurate measure of ongoing transmission of TB within a community.

The natural history of TB in children can be quite different from that of adults. Duration from TB exposure to infection to disease is much shorter due to several factors, by far the most important of which is poverty. Poverty increases a child's risk of TB exposure through cultural practices around child care [31], overcrowding in school and at home [32–36], poor housing with inadequate ventilation [37, 38], adults in household with comorbidities such as HIV [39], seasonal and environment-related exposure [40–42], and lack of public health infrastructure [43]. Following TB exposure, risk of a child developing infection is influenced by the acid fast bacilli (AFB) sputum positivity of the source case [33], duration and intensity of exposure [35, 44], infectiousness of the TB strain [45, 46], co-infections [47, 48], and the child's immune and genetic makeup [49, 50].

Clinical Manifestations

TB infection could be asymptomatic in children for several years. When disease occurs, signs and symptoms may be non-specific leading to diagnostic delay [51]. TB disease could manifest as pulmonary or extrapulmonary. Clinical manifestations of pulmonary TB in children include fever, weight loss, cough, and night sweats. Pulmonary TB is the most common manifestation of TB in children, accounting for 60%–80% of all cases [52]. Manifestations of extrapulmonary TB include lymphadenopathy (67%), CNS involvement (13%), miliary and/or disseminated disease (5%), and musculoskeletal (4%) [53]. TB can affect any organ and presentation may be non-specific or unusual, therefore, in TB-endemic areas physicians should have a high index of suspicion for TB [51]. In a TB-endemic area, the use of a symptom-based diagnostic approach provided a fairly accurate diagnosis of

pulmonary TB in HIV-uninfected children 3 years and older (sensitivity, 68.3%; specificity, 80.1%; and PPV, 82.1%) [54]. The symptom-based diagnostic approach comprised 3 well-defined symptoms at presentation: (1) persistent, non-remitting cough of >2 weeks' duration; (2) weight loss during the preceding 3 months; and (3) fatigue [54].

Diagnosis

Positive culture of *M tuberculosis* complex from gastric aspirates, sputum, bronchial lavage, pleural fluid, cerebrospinal fluid, urine, or other body fluid or tissue biopsy specimen establishes the diagnosis of TB. TB in children is usually paucibacillary, therefore, often AFB negative on microscopy (sputum smears are positive in <10–15% of children diagnosed with TB) [55, 56] and culture negative (confirmation by culture in only 30–40% of cases) [57, 58]. In non-TB endemic areas, in the absence of bacteriological confirmation, diagnosis of TB in children is based on a triad of (1) close contact with an infectious index patient, (2) positive tuberculin skin test (TST) result, and (3) abnormal chest x-ray findings [59]. The best specimen for diagnosis of pulmonary TB in a child with non-productive cough is an early morning gastric aspirate obtained before ambulation or feeding; 3 gastric aspirates on 3 consecutive mornings are required. There are innovative ways of obtaining swallowed respiratory samples for TB diagnosis in children who cannot produce sputum such as induction of sputum with aerosolized hypertonic saline [58] and the string test [60, 61]. Nucleic acid amplification tests (NAATs) for the detection of mycobacterial DNA or RNA are in clinical use. Their sensitivities are low in paucibacillary TB, which includes most cases of childhood TB and extrapulmonary TB [62].

The TST is the most common method for diagnosing latent TB Infection (LTBI) in asymptomatic patients. TST is an immune-based test driven by interferon gamma production by T lymphocytes. Ten to 15% of immunocompetent children with culture-proven TB may have negative TST initially [63]. Moreover, previous Bacille Calmette-Guérin (BCG) vaccination or infection with non-tuberculous mycobacteria may give false positive TST [64]. In most HIC countries with low TB incidence such as the United Kingdom, a TST is regarded as positive with induration of >5 mm in those without prior BCG vaccination and >15 mm for those with prior BCG vaccination [62]. In the US, TST results are interpreted based on an individual's risk of contracting TB and clinical factors: 5 mm (close contacts, TB disease, immunosuppression), 10 mm (increased risk of disseminated disease or increased exposure to TB disease), and 15 mm (children >4 years of age with no risk factors) [65]. WHO guidelines differ slightly with a positive TST being >5 mm for those with risk factors (e.g. HIV infection, malnutrition) and >10 mm for all others. [66]

Alternate tests to TST are the in vitro T-cell based interferon gamma release assays (IGRA). In these assays (e.g., QuantiFERON-TB Gold, T-SPOT.TB, and Gold In-Tube), interferon gamma is produced in response to stimulation of mononuclear cells or whole blood by specific *M. tuberculosis* antigens [62]. These antigens are present only in *M. tuberculosis* complex and absent from all strains of *Mycobacterium bovis* BCG and almost all environmental mycobacteria. They do not have significant advantages over the TST for the diagnosis of active TB disease but may be useful in excluding false-positive TST. In 2011, the WHO's Stop TB Department published new recommendations on the use of IGRAs and

TST to detect latent TB in LMIC: (1) IGRAs and TST cannot accurately predict the risk of infected individuals developing active TB disease; (2) Neither IGRAs nor TST should be used for the diagnosis of active TB disease; (3) IGRAs are more costly and technically complex than TST; and (4) Given comparable performance but increased cost, replacing the TST by IGRAs in resource-constrained settings is not recommended [67].

Management

LTBI can be effectively treated to prevent progression to active TB. The following regimens are recommended by WHO: 6 or 9 months isoniazid daily; 3-month rifapentine plus isoniazid weekly; 3- or 4-month isoniazid plus rifampicin daily; and 3- or 4-month rifampicin daily. Treatment of most forms of childhood TB disease (e.g., pulmonary and extrapulmonary) consists of a 6-month chemotherapy regimen with 4 drugs (isoniazid, rifampin, ethambutol, and pyrazinamide) in the initial intensive phase, followed by 2 drugs in the continuation phase (Figure 2). For miliary, meningeal, bone/joint, or disseminated TB, treatment is extended to 9–12 months. Directly observed therapy (DOT) is highly recommended.

Limited data exist on prevalence and management of drug-resistant TB in children. Studies from South Africa report an increasing proportion of drug resistant TB isolates in children (7%–15%) [68, 69]. Drug-resistant TB is categorized into 2: (1) multidrug resistant (MDR) TB, defined as resistance to isoniazid and rifampin, the two most important first-line anti-TB drugs; and (2) extensively drug-resistant (XDR) TB, defined as MDR-TB with additional resistance to a fluoroquinolone and one of either amikacin, capreomycin, or kanamycin [70]. The management of drug-resistant TB is complicated and should involve an expert with experience in treating drug-resistant TB. Four or five anti-TB drugs that the child's resistant isolate or that of an adult contact's resistant isolate is susceptible to are used (Figure 3) [71]. These may include second-line anti-TB drugs that are usually expensive and cause more side effects that can affect compliance to treatment (Table 4).

Prevention

Prevention strategies of childhood TB include (1) immunization in high burden countries and improvement of housing and sanitation; (2) chemoprophylaxis of LTBI and efficient surveillance programs; and (3) discovery of more efficacious and tolerable anti-TB drugs to shorten treatment duration, improve compliance, and decrease community TB bacilli burden.

MALARIA

Epidemiology

Malaria, a mosquito-borne parasitic disease, is a leading cause of child mortality. Worldwide, an estimated 3.2 billion people are at risk for malaria; as an IDoP, the geographic distribution of endemic malaria closely mirrors that of the world's population residing in extreme poverty (Figure 1) [72, 73]. Progress has been made in malaria control and elimination. From 2000–2013, a 46% relative decrease in malaria infection prevalence occurred among children aged 2–10 years, and an estimated 4.3 million deaths were averted

worldwide [85]. Despite these gains, annually, there are 200 million cases of malaria and > 500,000 deaths, the majority of which occur in sub-Saharan Africa and in young children [74]. Mortality due to malaria disproportionately affects children aged <5 years, who comprise 78% of deaths [72].

Malaria is caused by the *Plasmodium* parasite transmitted by the bite of an infected female Anopheles mosquito. Five species of *Plasmodium* typically cause disease in humans: *P falciparum*, *P vivax*, *P ovale*, *P malariae*, and *P knowlesi*.

The *Plasmodium* life cycle includes stages in both mosquitoes and humans. When an infected mosquito bites a human, *Plasmodium* sporozoites are passed into the bloodstream and travel to the liver. There, sporozoites enter hepatocytes, where they replicate asexually and develop into schizonts. This stage, known as hepatic schizogeny, takes ~7–10 days for *P. falciparum* and *P. vivax* and ~2 weeks for *P. malariae*. Then infected hepatocytes rupture, subsequently releasing merozoites into the bloodstream to infect red blood cells. In the erythrocyte, merozoites either undergo a cycle of asexual reproduction and lysis, subsequently infecting other erythrocytes, or they differentiate into male and female gametocytes, which are ingested by biting mosquitoes to undergo sexual reproductive cycle in the mosquito's gut. In *P vivax* and *P ovale* malaria, a subset of infected hepatocytes develop into hypnozoites, which can remain dormant for weeks to years, causing relapse of disease upon reactivation.

Clinical Manifestations

Clinical presentation of malaria depends on the infecting species, parasite burden, and immune status of the patient. Acute malaria commonly presents with non-specific symptoms of fever, chills, headache, and myalgias. Gastrointestinal symptoms such as nausea, vomiting, and diarrhea, can also occur.

Severe malaria is generally due to infection with *P falciparum* and is characterized by one or more of the following: impaired consciousness, severe anemia, renal impairment, pulmonary edema, spontaneous bleeding, acidosis, hypoglycemia, jaundice, shock, or hyperparasitemia. Additional clinical and laboratory features of severe malaria can be found in Box 3. Manifestations of severe malaria vary by age, with severe anemia and hypoglycemia seen more commonly in children [74]. In endemic regions, recurrent infections in young children can lead to chronic anemia and splenomegaly [74].

Diagnosis

Diagnosis of malaria can be made by examination of Giemsa-stained thick and thin blood smears and rapid diagnostic tests (RDTs). Microscopic examination remains the gold standard of diagnosis. Examination of a thick smear allows for detection of parasites present in small numbers, while thin smears aid in species identification. Classic features of *P falciparum* on microscopy include ring forms in normal-sized erythrocytes (commonly multiply-infected) and extracellular crescent- or banana-shaped gametocytes. In *P vivax* and *P ovale* infections, erythrocytes are commonly enlarged with Schuffner's dots, or eosinophilic stippling, seen on the infected erythrocyte. RDTs detect various antigens or

enzymatic activities from malaria parasites and provide results in minutes. However, they may be less sensitive in non-falciparum malaria (depending on the type of test used) or low levels of parasitemia [75].

Management

Treatment depends on the *Plasmodium* species causing infection, as well as the geographic location where infection was acquired, due to varying antimalarial resistance. For uncomplicated malaria, WHO guidelines recommend artemisinin-based combination therapy (ACT) as the treatment of choice for *falciparum* malaria; ACT is effective in the treatment of all other human malarias as well [74, 76]. ACT consists of a rapidly-acting artemisinin component (artesunate, artemether or dihydroartemisinin) with a longer-acting antimalarial for 3 days; fixed-dose combination formulations are available [74]. For patients diagnosed within the U.S., CDC provides clinicians with guidance in selection of appropriate antimalarial therapy [77].

Individuals with *P vivax* or *P ovale* infections can be treated with ACT or chloroquine (if susceptible). Patients should also receive a 14-day course of primaquine to prevent relapse from the liver stage. Primaquine causes hemolysis in patients with G6PD deficiency, therefore, testing for G6PD deficiency is necessary prior to starting therapy.

Severe malaria is a medical emergency and patients with manifestations of severe disease (Box 3) require aggressive treatment with parenteral antimalarials and careful supportive care. Intravenous artesunate is the treatment of choice in severe disease as it has demonstrated reduction in mortality in children hospitalized with severe falciparum malaria as compared with IV quinine [74]. Following IV therapy, a course of ACT can be administered once oral tablets can be given. Supportive care for severe malaria may include infusion of dextrose to maintain euglycemia, blood transfusions for bleeding and severe anemia, hemodialysis in cases of acute renal failure, and treatment of seizures with benzodiazepines [74]. Unfortunately, the linkage between poverty and malaria extends to treatment access, with poorer groups more likely to self-treat than access trained health care providers [78].

Prevention

Vector control is of the utmost importance in the prevention of malaria. Strategies include use of insecticide-treated bed nets to prevent mosquito bites while sleeping, indoor residual spraying of long-lasting insecticide to kill mosquitoes, and treatment of water sources to kill mosquito larvae [73]. While these interventions are effective in interrupting the transmission of malaria, socioeconomic disparities exist in access to preventive measures [78].

Travelers to malaria endemic areas are at risk of infection, and chemoprophylaxis is recommended for travelers to these regions. Selection of appropriate prophylaxis depends upon local antimalarial susceptibility patterns (e.g. prevalence of chloroquine resistance), and prevalent malarial species (to determine the need for liver-stage prophylaxis in areas where *P vivax* and *P ovale* are the predominant malarial species). In addition, clinicians

should consider malaria on the differential diagnosis of any febrile illness in a traveler who has recently returned from an endemic region, even if chemoprophylaxis was given.

Insecticide and drug resistance remain major concerns to malaria control. A vaccine against malaria is not yet available. The most advanced vaccine candidate to date targets the pre-erythrocytic stage of *P falciparum*; data from ongoing phase 3 trials demonstrated 30–50% efficacy of the vaccine against clinical malaria in children, though efficacy waned over time [79–81].

NEGLECTED TROPICAL DISEASES (NTDs)

WHO defines NTDs as medically diverse infections that form a group because of their association with poverty [82]. NTDs comprise 17 parasitic, viral, and bacterial infections (Box 4) that affect 1 billion people worldwide [1]. In recognition of the association between neglected parasitic infections and child poverty in the US, [83] CDC has targeted five parasitic diseases – Chagas disease, cysticercosis, toxocariasis, toxoplasmosis, and trichomoniasis – for public health action [84]. A description of selected NTDs that may be encountered by pediatricians, even in HIC, follows; a summary of these selected NTDs is presented in Table 5.

CHAGAS DISEASE

Epidemiology

Chagas disease, caused by the parasite *Trypanosoma cruzi*, is found only in the Americas and often in rural areas of widespread poverty. Most infections are vector-borne and result from contact with an infected triatomine bug, however, transmission can occur from mother to child [85], blood transfusion, and organ transplantation [86]. Worldwide, an estimated 8 million people are infected with Chagas disease, including about 300,000 in the U.S. [86, 87]. Congenital Chagas disease occurs in ~1–10% of children born to infected mothers, with an estimated 63–315 infants congenitally infected in the U.S. each year [87].

Clinical Manifestations

Acute Chagas disease occurs immediately after infection, concurrent with parasitemia, lasting about 4–8 weeks. Often asymptomatic, mild non-specific symptoms such as fever, or, rarely, acute myocarditis or meningoencephalitis, may occur [86, 88]. In the absence of treatment, parasitemia declines after 8–12 weeks and lifelong chronic infection ensues. While most chronically infected individuals remain asymptomatic, 20–30% develop chronic Chagas disease [88] characterized by cardiac and gastrointestinal manifestations (Table 5).

Congenital Chagas disease often has no overt clinical manifestations; symptomatic newborns may present with low birth weight, low Apgars, organomegaly, anasarca, respiratory distress, hematologic abnormalities, or meningoencephalitis [85, 86]. While congenital Chagas disease can be potentially life-threatening, affected infants may go unrecognized due to nonspecific symptoms or because the diagnosis was not considered.

Diagnosis

In acute or congenital Chagas disease, parasites may be visualized on blood smear; PCR tests are also available. In chronic disease, serology is the mainstay of diagnosis [86]. Owing to limitations of serologic testing, at least two different tests based on different antigens or formats are required for accurate diagnosis [86].

Management/Prevention

Benznidazole and nifurtimox are available for treatment of Chagas disease. Both are effective in acute disease but less effective in chronic disease; benznidazole tends to be better tolerated [89]. Treatment is recommended in all cases of acute infection, congenitally infected infants, and chronic disease in children 18 years of age or younger [89].

In endemic areas, prevention has focused on reducing disease transmission from the triatomine vector by insecticide spraying and improved housing. Control efforts in the US center on preventing transmission through blood products (via donor screening since 2007), organ transplantation, and congenital infection [90, 91].

NEUROCYSTICERCOSIS

Epidemiology

Neurocysticercosis is a CNS infection with the larval form of the pork tapeworm, *Taenia solium*. Humans can become *T. solium* carriers by consuming undercooked pork. The adult *T. solium* worm produces infective eggs in the host intestine, which spread in the environment to humans via food contaminated with feces, or by autoinoculation. Ingested eggs invade the intestine and migrate to distant tissues, where they develop into cysticerci. In endemic regions of Central and South America, prevalence estimates of neurocysticercosis range from 15–38% [92]. In the U.S., population-level estimates of neurocysticercosis are incomplete, but regional data puts prevalence at 0.2–5.5 per 100,000 [93].

Clinical Manifestations

While many individuals infected with *T. solium* are asymptomatic, serious sequelae result when cysts localize to the brain, resulting in neurocysticercosis. Symptoms include seizures, headaches, hydrocephalus, or focal neurologic signs [93].

Diagnosis

Diagnosis is made with neuroimaging and serologic testing. The hallmark of neurocysticercosis on neuroimaging is cerebral calcifications; if the tapeworm scolex is visualized, this is diagnostic [93]. Enzyme-linked immunoelectrotransfer blot is the preferred serologic test for diagnosis of cysticercosis, though sensitivity is reduced in the presence of a single cyst or calcified cysts [93].

Treatment/Prevention

Treatment of neurocysticercosis is multifactorial, and as neurocysticercosis represents a spectrum of disease, treatment must often be individualized [94]. The initial goal of therapy

is to control symptoms. Antiparasitic therapy can be considered following symptom control, however, it may exacerbate symptoms due to the inflammatory response provoked by killing cysts. Therefore, steroids are often co-administered. Albendazole is the drug of choice, with praziquantel used as second-line therapy [94].

Hand hygiene is important in preventing cysticercosis. In addition, infected individuals and their close contacts should be screened for *T. solium* carriage, due to asymptomatic household tapeworm carriers being a common source of infective eggs [95]. Elimination of cysticercosis requires improvement in sanitary conditions worldwide [96].

TOXOCARIASIS

Epidemiology

Toxocariasis is caused by the roundworms *Toxocara canis* or *Toxocara cati* that are associated with dogs and cats, respectively. In the U.S., *Toxocara* seroprevalence is 13.9% among individuals aged ≥ 6 years [97].

Toxocara eggs are shed in the feces of the host dog or cat. Human infection occurs upon ingestion of infective eggs in contaminated soil. Infections typically occur in young children who may play in contaminated sandboxes or playgrounds. Following ingestion, *Toxocara* larvae hatch from eggs in the gastrointestinal tract, penetrate the intestinal wall, and hematogenously disseminate to distal organs.

Clinical Manifestations

Three major clinical syndromes of toxocariasis have been described: visceral, ocular, and covert toxocariasis. Most patients with *Toxocara* infection, however, are asymptomatic.

Visceral toxocariasis typically affects young children and occurs when larvae migrate to organs and tissues, most commonly the liver or lung, with resulting inflammatory response leading to location-specific symptoms (Table 5) [97].

Ocular toxocariasis results from larval migration to the eye. Inflammation and scarring can be severe and lead to blindness. A national survey of ophthalmologists, reported 68 cases of ocular toxocariasis, of whom 68% were reported to have experienced visual loss [97]. Each year, ~70 people (mostly children) are blinded from *Toxocara* infection [84].

In covert toxocariasis, symptoms are typically mild and nonspecific, and can include wheezing and eosinophilia, but not all signs and symptoms of visceral disease.

Diagnosis

Toxocara diagnosis is made by serology, the utility of which is limited because titers can remain elevated for years. Serology can be unreliable in cases of ocular toxocariasis. Other laboratory findings in acute infection may include eosinophilia, anemia, and hypergammaglobulinemia.

Management/Prevention

Albendazole or mebendazole is recommended for treatment of visceral and ocular toxocariasis. In ocular disease, steroids are beneficial in reducing inflammation to prevent scarring and vision loss. Prevention measures include regular deworming of dogs and cats, proper disposal of pet feces, and hand hygiene.

SCHISTOSOMIASIS

Epidemiology

Schistosomiasis is a common parasitic disease caused by *Schistosoma* worms spread by contact with infected freshwater snails. Five species infect humans; the three most common are *S. haematobium*, *S. mansoni*, and *S. japonicum*. Over 200 million people worldwide are affected; most infections occur in sub-Saharan Africa, with children carrying a substantial burden.

Clinical Manifestations

Schistosoma infection results from contact with cercariae, the free-swimming larval form of the worm, in contaminated fresh water. Cercariae penetrate skin; a maculopapular rash may occur following exposure. Over several weeks, parasites migrate through host tissues and develop into adult worms. Symptoms result from host response to egg deposition into tissues and may include fever, headache, myalgias, right upper quadrant abdominal pain, and diarrhea [98]. Tender hepatomegaly and splenomegaly may also be present. Chronic schistosomiasis results from granuloma formation at sites of maximal egg accumulation and leads to site-specific symptoms (Table 5): for *S. mansoni* and *S. japonicum* the intestine and liver are affected, whereas for *S. haematobium* genitourinary tract involvement is seen [98]. Chronic infections can result in impaired growth and development, chronic inflammation, anemia, and nutritional deficiencies [99]. Furthermore, infections acquired in childhood can progress to long-term consequences, including bladder cancer, liver damage, reproductive issues, and heightened HIV susceptibility, if treatment is delayed or not given [100].

Diagnosis

Detection of *Schistosoma* eggs in urine or feces is diagnostic. Location of the spine – terminal (*S. haematobium*) or lateral (*S. mansoni*) – can aid in species identification. Serological testing aids in diagnosing patients who are infected, but not yet shedding eggs. Other supportive laboratory findings include eosinophilia, anemia, hypoalbuminemia, and elevated urea and creatinine [101].

Treatment/Prevention

Praziquantel is effective in achieving egg reduction rates and cures in 60–90% of patients [98, 100]. In endemic areas, regular school-based deworming is a common control measure; however, preschool-age children, who may have prevalence of disease similar to older children and adults, are often excluded from these programs [100]. Access to clean water and adequate sanitation are essential to prevention of schistosomiasis; travelers to endemic

areas should be advised to avoid swimming or bathing in fresh water and to drink water from a safe source. A vaccine against *Schistosoma* is not yet available.

DENGUE

Epidemiology

Dengue is caused by a flavivirus transmitted by *Aedes* mosquitoes. Four serotypes (DENV 1–4) exist. Dengue is endemic in greater than 100 countries in Africa, the Americas, the Mediterranean and Asia, with an estimated 390 million dengue infections annually, 96 million of which are clinically apparent [102–104]. The incidence of dengue is increasing, likely due to increased urbanization and ineffective vector control; dengue infection is closely associated with poor populations and urban crowding [96, 102]. The majority of dengue infections occur in children aged <15 years, who tend to suffer from greatest morbidity and mortality [83, 105].

Clinical Manifestations

Dengue may present with a wide range of symptoms from inapparent asymptomatic infection, to mild febrile illness, to life-threatening shock. Symptomatic illness begins with abrupt onset of fever accompanied by headache, arthralgia, myalgia, retro-orbital pain, and hemorrhagic manifestations [102]. Severe dengue, also known as dengue shock syndrome, is associated with rapid increase in (and reversal of) vascular permeability occurring towards the end of the febrile phase of illness that can lead to shock, severe bleeding, and organ failure [102, 105].

Diagnosis

Acute and convalescent serology is the mainstay of diagnosis. In primary infection, IgM antibody appears by day 3–5 of illness and IgG antibody is detectable by day 5 [105]. Infection is confirmed with seroconversion of IgM antibody or a four-fold rise in IgG titers. RT-PCR of blood or tissue can also be used; viremia typically correlates with fever, and lasts ~4–5 days after fever onset [103].

Management/Prevention

No specific antiviral therapy for dengue is available; treatment is supportive and consists of volume repletion, monitoring of hematologic parameters, and close observation for signs of severe disease [105]. Presently, the most effective method for prevention of dengue infection is vector control. Travelers to endemic areas should be counseled to avoid mosquito bites through the use of DEET-containing insect repellent, protective clothing, and bed nets. While no licensed vaccine is available, an investigational tetravalent vaccine demonstrated 61% efficacy against virologically confirmed dengue infection in Latin American children in a phase 3 trial [106].

CUTANEOUS LEISHMANIASIS

Epidemiology

Cutaneous leishmaniasis (CL) is the most common presentation of disease caused by infection with several species of *Leishmania*, a vector-borne parasite spread by the bite of the sandfly. CL is endemic in over 70 countries, with the majority of cases occurring in the Eastern Mediterranean region, Americas, and East Asia; globally, children have the highest burden of disease [107–109]. Infections, including those related to travel, are on the rise [108, 110].

Clinical Manifestations

CL is characterized by the development of skin lesions on exposed areas that develop weeks to months following a bite by an infected sandfly. Skin lesions typically evolve from firm papules to nodular lesions to large, nonpainful ulcers over the course of 2 weeks to 6 months [107].

Diagnosis

Parasitologic diagnosis, by visualization of *Leishmania* parasites in tissue biopsy or aspirate, is the gold standard. Culture of biopsy material can aid in species identification, but is time-consuming and may be of low yield. PCR is available to make species-level diagnosis, which helps guide therapy. CDC provides diagnostic testing and a guide to assist clinicians with specimen collection [111].

Treatment/Prevention

There is debate over the need for treatment of CL, which usually resolves spontaneously over several months. However, due to potential scarring, and to speed recovery, therapy is often given. Indications for treatment include (1) infection acquired in South or Central America (where *L. braziliensis* predominates, which can progress to potentially disfiguring mucosal disease); (2) lesion on the face, hands, feet or over the joints; (3) lesions present for >6 months; (4) multiple (>2–5) or large (>4–5cm) lesions; (5) evidence of local dissemination; or (6) immunocompromised host [107].

Several treatment options for CL exist (Table 5); the causative *Leishmania* species and strain, which is dependent on geography, likely affects drug efficacy. With any treatment, response can be slow, but reduction in lesion size and inflammation is generally seen after 4–6 weeks [107]. Prevention of CL focuses on avoiding sandfly bites in endemic areas and vector control through the use of insecticides and bednets. As a disease of poverty, there has been limited investment in a vaccine against *Leishmania* [109].

PREVENTION AND CONTROL OF IDoP in LMIC: Implementation Challenges and Future Research Priorities

Although progress has been made in tackling major IDoP worldwide, significant challenges remain to reach the WHO control and elimination targets set for 2020 (Table 5) [112]. Effective preventative or treatment interventions exist for a majority of IDoP in LMIC

[113]. Many neglected parasitic infections can be treated with a US\$0.50 treatment package [114]. Although evidence-based interventions exist to tackle various IDoP, coverage remains poor in many LMIC warranting development of innovative strategies. (Table 6) Integrated community-based interventions for prevention and control of IDoP is an area of active research [115]. Since transmission of IDoP is closely linked to social and economic inequalities, social science research may contribute to our understanding of implementation gaps and improve outcomes [116].

CONCLUSION

IDoP, including HIV/AIDS, TB, malaria, and NTDs, impact children worldwide. Clinicians must be familiar with the epidemiology and clinical manifestations of these infections to ensure prompt diagnosis and treatment.

Abbreviations

GDP	Gross domestic product
DALY	disability-adjusted life years
ART	antiretroviral therapy
MTCT	mother-to-child transmission
PMTCT	prevention of MTCT
AIDS	acquired immunodeficiency syndrome
SIV	simian immunodeficiency virus
AFB	acid fast bacilli
IDoP	infectious disease of poverty
IGRA	interferon gamma release assay
DOT	directly observed therapy
ACT	artemisinin-based combination therapy
CDC	Centers for Disease Control and Prevention
CL	cutaneous leishmaniasis
DEET	N,N-Diethyl-meta-toluamide
NTDs	neglected tropical disease
OI	opportunistic infection
PCR	polymerase chain reaction
RDT	rapid diagnostic test
WHO	World Health Organization
HIC	high income countries

LMIC low and middle income countries

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Key Points

- Poverty has been inextricably linked with infectious diseases since antiquity; where there is poverty, infectious diseases like human immunodeficiency virus (HIV) infection, tuberculosis (TB), malaria and Neglected Tropical Diseases (NTDs) thrive.
- Thirty four years into the HIV epidemic, several advances and significant milestones have been made, however, access to and management of antiretroviral therapy (ART) in children still lag behind that of adults.
- TB is the leading infectious cause of mortality worldwide; poverty and young age are significant determinants of progression from TB exposure to disease.
- Malaria remains a leading cause of child mortality; access to effective preventive measures and therapy must reach vulnerable populations.
- The needless death toll and the developmental consequences of these infections on children could be averted by improving housing, access to safe water and sanitation in resource-limited countries.
- Clinicians, both in endemic and non-endemic areas, must be familiar with the epidemiology and clinical manifestations of these infections to ensure prompt diagnosis and treatment.

Synopsis

The phrase “infectious diseases of poverty” (IDoP) is used to describe infectious diseases that are more prevalent among poor and vulnerable populations. Where there is poverty, infectious diseases like human immunodeficiency virus (HIV) infection, tuberculosis (TB), malaria and Neglected Tropical Diseases (NTDs) thrive. These infectious diseases do not only occur in regions of poverty, but also perpetuate poverty by leading to adverse outcomes on pregnancy, child development, and workplace productivity. In 2013, 190 000 (170 000 – 220 000) children died of HIV-related causes. In the same year, there were 550 000 and 80 000 TB cases and deaths in children, respectively. Children under 5 years of age account for 78% of malaria deaths per year. NTDs remain a major public health challenge in low-and middle-income countries. This article provides an overview of the major IDoP that affect children. Clinicians must be familiar with the epidemiology and clinical manifestations of these infections to ensure prompt diagnosis and treatment.

Box. 1 Common HIV-related manifestation in HIV-infected children

Mild HIV-Related Symptoms

Children with two or more of the conditions listed but none of the conditions listed in Moderate Symptoms category

- Lymphadenopathy (≥ 0.5 cm at more than 2 sites; bilateral at 1 site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory tract infection, sinusitis, or otitis media

Moderate HIV-Related Symptoms

- Anemia (hemoglobin <8 g/dL [<80 g/L]), neutropenia (white blood cell count $<1,000/\mu\text{L}$ [$<1.0 \times 10^9/\text{L}$]), and/or thrombocytopenia (platelet count $<100 \times 10^3/\mu\text{L}$ [$<100 \times 10^9/\text{L}$]) persisting for ≥ 30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush), persisting (>2 months) in children older than age 6 months
- Cardiomyopathy
- Cytomegalovirus infection, with onset before 1 month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus stomatitis, recurrent (>2 episodes within 1 year)
- Herpes simplex virus bronchitis, pneumonitis, or esophagitis with onset before 1 month
- Herpes zoster (shingles) involving at least 2 distinct episodes or more than 1 dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Persistent fever (lasting >1 month)
- Toxoplasmosis, onset before 1 month
- Varicella, disseminated (complicated chickenpox)

Stage-3-Defining Opportunistic Illnesses in HIV Infection

- Bacterial infections, multiple or recurrent
- Candidiasis of bronchi, trachea, or lungs
- Candidiasis of esophagus
- Cervical cancer, invasive
- Coccidioidomycosis, disseminated or extrapulmonary
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis, chronic intestinal (>1 month duration)
- Cytomegalovirus disease (other than liver, spleen, or nodes), onset at age >1 month
- Cytomegalovirus retinitis (with loss of vision)
- Encephalopathy attributed to HIV
- HSV: chronic ulcers (>1 month duration) or bronchitis, pneumonitis, or esophagitis (onset at age >1 month)
- Histoplasmosis, disseminated or extrapulmonary
- Isosporiasis, chronic intestinal (>1 month duration)
- Kaposi sarcoma
- Lymphoma, Burkitt (or equivalent term)
- Lymphoma, immunoblastic (or equivalent term)
- Lymphoma, primary, of brain
- Mycobacterium avium complex or Mycobacterium kansasii, disseminated or extrapulmonary
- Mycobacterium tuberculosis of any site, pulmonary†, disseminated, or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated or extrapulmonary
- Pneumocystis jirovecii (previously known as Pneumocystis carinii) pneumonia
- Pneumonia, recurrentb
- Progressive multifocal leukoencephalopathy
- Salmonella septicemia, recurrent
- Toxoplasmosis of brain, onset at age >1 month
- Wasting syndrome attributed to HIV

Adapted and modified from: Centers for Disease Control and Prevention: Revised Surveillance Case Definition for HIV Infection—United States, 2014. MMWR. 2014;63(No. RR-3):1–10; with permission. Abbreviations: HIV, human immunodeficiency virus; HSV, herpes simplex virus;

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Box 2. When to start ART in children

WHO Guidelines on when to start ART in children

- ART should be initiated in all children infected with HIV below five years of age, regardless of WHO clinical stage or CD4 cell count.
- ART should be initiated in all children infected with HIV five years of age and older with CD4 cell count ≥ 500 cells/mm³, regardless of WHO clinical stage.
- ART should be initiated in all children infected with HIV with severe or advanced symptomatic disease (WHO clinical stage 3 or 4) regardless of age and CD4 cell count
- ART should be initiated in any child younger than 18 months of age who has been given a presumptive clinical diagnosis of HIV infection

US Department of Health and Human Services (HHS) Guidelines on when to start ART in children

Combination Antiretroviral Therapy (cART) should be initiated urgently in all HIV-infected children with any of the following:

- Age <12 Months
- Age 1 year (with CDC Stage 3-defining opportunistic illnesses or CDC Stage 3 immunodeficiency)
- Aged 1 to <6 years, CD4 <500 cells/mm³
- Aged ≥ 6 years, CD4 <200 cells/mm³

cART should be initiated in HIV-Infected children aged ≥ 1 Year with any of the following:

- Moderate HIV-related symptoms (see Box 1)
- Plasma HIV RNA >100,000 copies/mL
- CDC Stage 2: (Age 1 to <6 years, CD4 count 500–999 cells/mm³; Age ≥ 6 years, CD4 count 200–499 cells/mm³; if CD4 count <350 cells/mm³; if CD4 count 350–499 cells/mm³)

cART should be considered for HIV-Infected children aged ≥ 1 year with:

- Mild HIV-related symptoms (see Box 1) or asymptomatic and CDC Stage 1: (Ages 1 to <6 years, CD4 count ≥ 1000 cells/mm³; Age ≥ 6 years, CD4 count ≥ 500 cells/mm³)

Paediatric European Network for Treatment of AIDS (PENTA) guidelines for ART initiation

ART is recommended:

- in all children under 1 year of age;

- in all children with significant disease [WHO stage 3 or 4 or CDC stage B or C];
- in asymptomatic children over 1 year of age based on age-specific CD4 count
- in those with hepatitis C virus (HCV) or active TB coinfection

ART should be considered:

- in asymptomatic children over 5 years of age at CD4 counts of 350–500 cells/mm³,
- in children with high VL (> 100 000 copies/ml);
- in asymptomatic children aged 1–3 years irrespective of immune status and VL;
- in sexually active adolescents, to minimize the risk of onward transmission;
- in the presence of any significant HIV-related clinical symptoms;
- in hepatitis B virus (HBV) coinfection irrespective of immune status.

Adapted and modified from the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (2013); US Department of Health and Human Services (HHS) Guidelines on Antiretroviral Agents in Pediatric HIV Infection (2013, revised in 2015); and Paediatric European Network for Treatment of AIDS (PENTA) guidelines for ART initiation (2015).

ART, antiretroviral therapy; CDC, Centers for Disease Control and Prevention; WHO, World Health Organization

From WHO. 2012. Management of severe malaria. Available at: http://apps.who.int/iris/bitstream/10665/79317/1/9789241548526_eng.pdf. Accessed 2 June 2015; with permission.

Box 3. Features of Severe Malaria**Features of severe malaria**

Clinical	Impaired consciousness (including coma)
	Prostration (inability to sit, stand, or walk without assistance)
	Multiple convulsions (> 2 episodes in 24 hours)
	Deep breathing and respiratory distress (acidotic breathing)
	Acute pulmonary edema and acute respiratory distress syndrome
	Circulatory collapse or shock (systolic blood pressure <50mm Hg in children)
	Acute kidney injury
	Jaundice
Laboratory	Abnormal bleeding
	Hypoglycemia (<40mg/dl)
	Metabolic acidosis (plasma bicarbonate <15mmol/l)
	Severe normocytic anemia (<5 mg/dl in children)
	Hemoglobinuria
	Hyperlactatemia (lactate > 5mmol/l)
	Renal impairment (serum creatinine > 265 μ mol/l)
	Pulmonary edema (radiographic)

Box 4. Neglected Tropical Diseases

Neglected Tropical Diseases Prioritized by WHO, by Causative Pathogen

Protozoa	Chagas disease
	Human African trypanosomiasis (sleeping sickness)
	Leishmaniasis
Bacteria	Buruli ulcer
	Leprosy (Hansen disease)
	Trachoma
	Yaws
Helminth	Cysticercosis/Taeniasis
	Dracunculiasis (guinea worm disease)
	Echinococcosis
	Foodborne trematodiasis
	Lymphatic filariasis
	Onchocerciasis (river blindness)
	Schistosomiasis
Virus	Soil-transmitted helminths (Ascaris, hookworm, whipworm)
	Dengue
	Rabies

From WHO. Neglected Tropical Diseases.

http://www.who.int/neglected_diseases/diseases/en/. Accessed 6 June 2015; with permission.

Figure 1.

Global poverty and infectious diseases burden. Data from Population living on <2 USD per day (World Bank: <http://data.worldbank.org/indicator/SI.POV.2DAY/countries>); Adults and children estimated to be living with HIV (WHO: <http://www.who.int/hiv/data/en/>); Estimated TB cases per year (WHO: http://www.who.int/tdr/publications/global_report/en/); Confirmed malaria cases in 2013 (WHO: http://www.who.int/malaria/publications/world_malaria_report_2013/en/); Number of neglected tropical diseases (CDC: <http://www.cdc.gov/globalhealth/ntd/diseases/ntd-worldmap-table.html>).

Figure 2.

Treatment of TB disease in children. Treatment duration comprises of intensive and continuation phase. For most forms of pulmonary TB and extrapulmonary TB a 6-month course of chemotherapy regimen with 4 drugs (isoniazid (INH), rifampin (RMP), ethambutol (EMB), and pyrazinamide (PZA)) in the 2-month intensive phase, followed by 2 drugs (INH and RMP) in the 4-month continuation phase. For TB meningitis, the continuation phase is extend to a least 10 months using same drugs above. Recommended treatment duration of multidrug resistant (MDR)-TB is at least 20 months with four second-line drugs likely to be effective plus PZA.

Table 1

Estimated DALYs of Malaria, HIV/AIDS, Tuberculosis and NTDs, 2010.

Disease	DALYs (in thousands, 95% CI)
HIV/AIDS	81,547 (75,003–88,367)
Tuberculosis	49,396 (40,065–56,071)
Malaria	82,685 (63,426–109,836)
NTDs	
Leishmaniasis	3,317 (2,180–4,890)
Schistosomiasis	3,309 (1,705–6,260)
Dengue	825 (344–1,412)
Chagas disease	546 (271–1,054)
Cysticercosis	503 (379–663)
Other NTDs	4,724 (3,525–6,351)

Adapted from Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (dalys) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380(9859):2197–223; with permission.

DALY, Disability-adjusted life-years (cumulative number of years of life lost from ill health, disability, or premature death)

NTD, neglected tropical disease; CI = confidence interval

Table 2

Antiretroviral therapy coverage among HIV-infected children in low- and middle-income countries and by WHO region, December 2013.

WHO Region	Number on ART	Percent coverage (range)
Africa Region	630 300	22 (20–24)
Region of the Americas	26 400	51 (38–62)
South-East Asia Region	13 900	>95 (94–>95)
Eastern Mediterranean Region	1 100	7 (5–9)
Western Pacific Region	13 200	61 (56–67)
Total	684 900	47.2 (7–>95%)

Adapted from Global AIDS Response Progress Reporting (WHO/UNICEF/UNAIDS), 2014 (<http://www.who.int/hiv/data/pedartmap2014.png?ua=1>); with permission.

Table 3

Overview of Current Pediatric First-Line HIV Treatment Regimens

Organization (Source)	Age (years)	Preferred Regimen	Alternate Regimen
WHO (2013)	Children < 3 years	LPV/r + ABC + 3TC or LPV/r + AZT + 3TC	NVP* + ABC + 3TC or NVP* + AZT + 3TC (ABC + 3TC + AZT) [†]
	3 – 10 years (< 35 kg)	EFV + ABC + 3TC Or EFV + AZT (or TDF) + 3TC (or FTC)	NVP + ABC + 3TC Or NVP + AZT (or TDF) + 3TC (or FTC)
	10 – 19 years (< 35 kg)	EFV + TDF + 3TC (or FTC) Or EFV + AZT + 3TC EFV + ABC + 3TC	NVP + TDF + 3TC (or FTC) Or NVP + AZT + 3TC NVP + ABC + 3TC
US HHS (2015)	Children aged 14 days to < 3 years	2 NRTIs + LPV/r	2 NRTIs + NVP
	Children aged 3 to 6 years	2 NRTIs + EFV (or LPV/r)	–2 NRTIs + ATV/r (3 months to < 6 years) –2NRTIs + RAL (2 years) –2NRTIs + DRV/r (3 to < 12 years)
	Children aged 6	2 NRTIs + ATV/r or EFV or LPV/r	–2 NRTIs + DRV/r (12 years) –2 NRTIs + DTG (12 years and weighing 40 kg)
PENTA (2015)	Children < 1 year	ABC [‡] + 3TC + LPV/r Or (ABC + 3TC + AZT + NVP) ^δ	NNRTI backbone: AZT + 3TC
	Children 1 – 3 years	ABC + 3TC + LPV/r Or (ABC + 3TC + AZT + NVP) [#]	NRTI backbone: AZT + 3TC
	Children 3 – 6 years	ABC + 3TC + LPV/r or EFV	AZT + 3TC + NVP or DRV/r Or TDF + 3TC (FTC) + NVP or DRV/r
	Children 6 – 12 years	ABC + 3TC + ATV/r Or ABC + 3TC + EFV	AZT + 3TC + NVP (or LPV/r or DRV/r) Or TDF + 3TC (FTC) + NVP or LPV/r or DRV/r
	Children > 12 years	TDF + FTC + ATV/r or DRV/r or EFV Or ABC + 3TC + ATV/r or DRV/r or EFV	ABC + 3TC + NVP or LPV/r or RAL ^ψ or DTG

Data from the WHO consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach (2013); US Department of Health and Human Services (HHS) Guidelines on Antiretroviral Agents in Pediatric HIV Infection (2013, revised in 2015); and Paediatric European Network for Treatment of AIDS (PENTA) guidelines for ART initiation (2015).

3TC, lamivudine; ABC, abacavir; ARV, antiretroviral; ATV, atazanavir; d4T, stavudine; DRV, darunavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LPV/r, fixed dose formulation lopinavir/r; ATV/r, atazanavir plus ritonavir; DRV/r, darunavir plus ritonavir; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor; RAL, raltegravir; RTV, ritonavir; TDF, tenofovir; AZT, zidovudine

* NVP-based regimen if LPV/r is not feasible

[†] As an option for children who develop TB while on ART regimen containing NVP or LPV/r. Once TB therapy is completed, a switch to initial regimen is recommended

[‡] Prior to starting abacavir (ABC), test for human leucocyte antigen (HLA) B*5701. If positive, then ABC should not be prescribed

^δ In children < 3 years, consider adding AZT to NVP-based regimens if there is a very high viral load (VL) or central nervous system (CNS) involvement until VL has been suppressed for at least 3 months.

[#] Four-drug induction for infants on NVP-based therapy may be considered until VL has been suppressed for at least 3 months, followed by three-drug maintenance therapy

^ψ In rare instances (e.g. transmitted resistance or toxicity), raltegravir (RAL) may be used as first-line therapy in children < 12 years of age.

Table 4

Dosages and side effects of antituberculous drugs

Drug	Total Dose (mg/kg/day)	Routes of administration	Side effects
Isoniazid	5–10	PO/IV/IM	Hepatotoxicity, peripheral neuropathy, myelosuppression
Rifampin	10–20	PO/IV	Hepatotoxicity, myelosuppression, rash
Pyrazinamide	30–40	PO	Hepatotoxicity, arthralgia, rash
Ethambutol	15–25	PO	Optic neuritis
Amikacin	12–30	IV/IM	Nephrotoxicity, ototoxicity, hypokalemia
Kanamycin	15–20	IV/IM	Nephrotoxicity, ototoxicity, rash
Capreomycin	15–30	IV/IM	Nephrotoxicity, ototoxicity
Ofloxacin	15–20	PO/IV	Gastrointestinal disturbance, arthralgia, insomnia
Levofloxacin	7.5–10	PO/IV	Gastrointestinal disturbance, arthralgia, insomnia
Moxifloxacin	7.5–10	PO/IV	Gastrointestinal disturbance, arthralgia, insomnia
Ethionamide	15–20	PO	Gastrointestinal disturbance, hepatotoxicity, hypothyroidism
Prothionamide	15–20	PO	Gastrointestinal disturbance, hepatotoxicity, hypothyroidism
Cycloserine	15–20	PO	Psychosis, convulsions
Terizidone	15–20	PO	Psychosis, convulsions
Para-aminosalicylic acid	150–200	PO	Anorexia, diarrhea, hypothyroidism
Thioacetazone	150	PO	Severe skin rash, myelosuppression
Clofazimine	300	PO	Reversible discoloration of skin, hair, etc.
Linezolid	15–20	PO/IV	Myelosuppression, lactic acidosis, peripheral neuropathy, pancreatitis
Imipenem + cilastatin	40–80	IV/IM	Gastrointestinal disturbance, phlebitis, convulsion, encephalopathy

IM, intramuscularly; IV, intravenously; PO, by mouth.

Table 5

Key Points on Selected Neglected Tropical Diseases Affecting Children

Disease	Transmission	Diagnosis	Clinical Manifestations	Interventions	Key WHO 2020 Targets
Chagas disease	Vector-borne (triatomine bug), congenital, via blood transfusion or organ transplantation	Acute/congenital infection: blood smear examination for parasites, PCR Chronic infection: serology (at least two positive tests required for diagnosis)	Cardiomyopathy, megacolon, megaesophagus	Case detection and management, nifurtimox, benznidazole, vector control, screening of blood donors	Elimination of peridomestic infestation in Latin America by 2020
Toxocarasis	Ingestion of <i>Toxocara</i> eggs in contaminated soil	Serologic testing; stool examination not useful (eggs are not excreted by humans)	Visceral infection: Abdominal pain, fever, hepatomegaly, cough, wheezing, meningoencephalitis Ocular infection: strabismus, unilateral vision loss	Albendazole, mebendazole, ophthalmology referral ± steroids for ocular disease	Reach 75% of all school-age children for deworming by 2020
Cysticercosis	Ingestion of eggs excreted in the feces of tapeworm carrier	Neurocysticercosis: serologic testing, neuroimaging	Neurocysticercosis: seizures, headaches, increased intracranial pressure	Hand hygiene, symptom control, consider antihelminths/steroids Screening of close contacts for tapeworm infection	Validated strategy for control and elimination of <i>T.solium</i> taeniasis/cysticercosis available by 2015 Interventions for control and elimination scaled up in selected countries in Asia, Africa, and Latin America by 2020
Dengue	Vector-borne (<i>Aedes</i> mosquito)	Serologic testing; RT-PCR	Fever, headache, arthralgia, myalgia, retro-orbital pain, hemorrhagic manifestations, vascular permeability, shock	Supportive care, fluid repletion, vector control	Reduction of rates of morbidity by at least 25% and of mortality by 50% by 2020 by using an integrated vector management approach
Leishmaniasis	Vector-borne (sandfly)	Biopsy (visualization of parasites in tissue or aspirate material gold standard); culture, PCR	Cutaneous: skin papules → nodules → large, painless ulcers Mucosal: nasal stuffiness or bleeding, ulcerative destruction of nasopharyngeal mucosa Visceral: Fever, weight loss, hepatosplenomegaly	Case detection and management, antimonials, amphotericin B, miltefosine, azoles, vector control	Detection of at least 70% of all cases of cutaneous leishmaniasis and treatment of at least 90% of all detected cases in the Eastern Mediterranean Region by 2015, 100% case detection and treatment of visceral leishmaniasis on the Indian sub-continent by 2020
Schistosomiasis	<i>Schistosoma</i> worms spread by infected snails in contaminated fresh water;	Detection of <i>Schistosoma</i> eggs in urine or feces, serologic testing	Hematuria, genitourinary tract disease, intestinal and liver fibrosis, growth and cognitive delays	Praziquantel, clean water and sanitation	Elimination as a public health problem in multiple countries in Africa by 2020, and globally by 2025

PCR: polymerase chain reaction; RT-PCR: reverse transcription polymerase chain reaction; WHO: World Health Organization

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Adapted and modified from the following references:

- Murray CJ, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C et al. Disability-adjusted life years (daly's) for 291 diseases and injuries in 21 regions, 1990–2010: A systematic analysis for the global burden of disease study 2010. *Lancet* 2012;380(9859):2197–223.
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Table 6**Implementation Challenges and Future Research Needs for Prevention and Control of IDoP in LMIC**

Disease	Examples of Current Interventions	Implementation Challenges/Future Research Needs
Helminthic NTDs	School-based platforms	Evaluation of large-scale integrated programs in resourcelimited settings
Non-helminthic NTDs	Insecticide-treated bednets, community education and cleanliness campaigns, mass drug administration, treatment	Evaluation of effectiveness of various community delivery models Simultaneous improvements in water and sanitation are needed
Malaria	Insecticide treated bednets, indoor residual spraying	Integration of interventions with existing antenatal care and immunization campaigns to lower cost Prevention of drug resistance
HIV/AIDS	Community-based awareness and risk reduction interventions	Evaluation of effectiveness of community delivery platforms for PMTCT and models of care for improving morbidity and mortality
Tuberculosis	Treatment delivery through community health workers (coupled with DOT)	Comparative evaluation of various community-based delivery models for relative effectiveness

NTD: neglected tropical disease; HIV: human immunodeficiency virus; AIDS: acquired immune deficiency syndrome; TB: tuberculosis; PMTCT: prevention of mother to child transmission; DOT: directly observed therapy

Data from Bhutta ZA, Salam RA, Das JK and Lassi ZS. Tackling the existing burden of infectious diseases in the developing world: Existing gaps and the way forward. *Infectious Diseases of Poverty* 2014;3(28).