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Clinical Manifestations of HIV-Infection in the Era of Highly Active Antiretroviral Therapy

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1. Introduction

Today, more than 25 years after the description of the first AIDS cases in children, major advances have been made on the prevention and treatment of the infection caused by human immunodeficiency virus (VIH-1), mainly after the availability of highly active antiretroviral therapy (HAART). Despite improved access to antiretroviral treatment and prevention, the HIV-infection epidemic continues to expand. The progression of the disease is much faster in children than in adults as well as the risk of complications. Since most infections occur perinatally, the virus overcomes the capacity of the immature immune system to control the HIV replication and dissemination occurs to all organ systems including the central nervous system (CNS). As a consequence the clinical course is more accelerated in children than in adults, and the immunological dysfunction is greater. Without antiretroviral treatment, HIV-infection in children has a bimodal pattern: a rapidly progressive form (15-20%) characterized by the development of severe opportunistic infections (OI), encephalopathy and death in the first 3 years, and a second form less aggressive and more alike to the presentation seen in adults, that accounts for around 80% of cases. Furthermore as there are no accurate prognostic surrogate markers of disease progression at diagnosis, most children should be treated early. Nevertheless, there is a delay in the development and implementation of antiretroviral treatment in children and adolescents. In addition, the need for a lifelong medication, with complex schedules, frequent high pill burden and lack of suitable paediatric formulation with insufficient data for children makes more difficult to maintain a permanent adherence to medication. Currently, although most children are on a stable situation with high CD4 counts and complete control of viral replication, the long-term consequences of the disease and of the accumulated effects of HAART are unknown and of major concern.

2. Clinical manifestations of HIV-infection in the era of HAART

The mortality and morbidity in HIV-infected children has declined since 1996 with the introduction of HAART. The studies comparing pre-HAART and post-HAART era marked a significant difference with a reduction in rates of mortality and progression to AIDS (Brady et al., 2010, Sánchez Granados J, 2003). The hospitalization has markedly decreased in HIV-infected children who have access to HAART. Frequent causes of hospitalization like

bacterial infections and opportunistic infections have diminished after introduction of HAART (Puthanakit et al., 2007). Many children died of *Pneumocystis carinii* pneumonia whereas others succumbed to a variety of opportunistic infections, including disseminated cytomegalovirus, disseminated *Mycobacterium avium complex* (MAC) and recurrent, severe bacterial infections (Abrams, 2000). Opportunistic infections and other related infections are uncommon in children in the HAART era in developed countries (Gina et al., 2006). On the other hand, children with persistently low CD4 percentage are at risk for opportunistic illnesses (Ylitalo et al., 2006). Children who experienced opportunistic infections have higher mortality rates than do those who do not (Nesheim et al., 2007). The incidence of bacterial infections have decreased in the post-HAART era, as well as the time elapsed to the first bacteraemia episode has been prolonged, although children with a decline of CD4 T cells are still more likely to develop bacteraemia (Kapogiannis et al., 2008). Nevertheless, severe bacterial infectious still occurred at considerable high rates, even in the absence of a severe CD4 cell depletion (Chiappini et al., 2007). Antimicrobial prophylaxis has resulted in a successful prevention of several opportunistic infections in children with low CD4 cells. Since the advent of HAART has led to an increase the numbers of CD4 T cells and CD4 percentage to a level of lower risk in children, there is the possibility of safe discontinuation of prophylaxis for opportunistic infections once HIV-infected children demonstrate improvement in CD4 cell counts to levels at which such prophylaxis would not be initiated according to current guidelines (Nachman et al., 2005). Organ-specific diseases such as cardiomyopathy, nephropathy, encephalopathy, and others contribute substantially to the morbidity and mortality associated to with HIV infection. HAART results in a resolution of most of these organ-specific complications (Saulsbury, 2001). Other organ-specific diseases like, thrombocytopenia, wasting syndrome and lymphoid interstitial pneumonia, have dropped dramatically since the introduction of HAART (Guillén et al., 2010) and are also improved with effective antiretroviral therapy. As survival has been prolonged in perinatally HIV-infected children and adolescents in the HAART era and many of them are now reaching adulthood, an increase in the incidence rates over time in pregnancy-related conditions and gynaecological dysplasia is being observed in parallel with a decrease of the incidence of the other non infectious conditions. (Nachman et al., 2009).

Clinical	N Asymptomatic	A Mild symptoms	B Moderated symptoms	C Severe Symptoms
Immunological*				
- Not significant immunodeficiency[1]	N1	A1	B1	C1
- Moderate immunodeficiency[2]	N2	A2	B2	C2
- Severe immunodeficiency[3]	N3	A3	B3	C3

Table 1. Clinical and immunological stages (CDC 1993)

In 1994, the CDC proposed a classification of HIV-disease in children into 4 clinical categories (N, A, B, C) and 3 immunological categories (1, 2, 3), according to the degree of immunosuppression (CDC, 1994) (Table 1). In developing countries, WHO classification also considers 4 clinical categories according to severity and 3 immunological categories (WHO, 2007)(Table 2). There are a variety of OI and organ-specific diseases in different clinical classification and AIDS events. Since the CD4 absolute numbers decline physiologically from birth and the CD4 percentage is more preserved across ages, this parameter is preferred in children below 6 years of age, as it is a better predictor of disease progression. The absolute number of CD4 cells does not predict accurately the risk of complications like in adults, although the degree of immunosuppression influences the occurrence of an infection event or development of an organ-specific involvement.

*	**< 12 moths**	**1-5 years**	**6-12 years**
[1]CD4	> 1500/mm^3, > 25%	>1000/mm^3, > 25%	> 500/mm^3, >25%
[2]CD4	750-1499/mm^3, 15-24%	500-999/mm^3, 15-24%	200-499/mm^3, >15-24%
[3]CD4	< 750/mm^3, < 15%	<500/mm^3, < 15%	< 200/mm^3, < 15%

Table 1. Centers for Diseases Control. 1994 revised classification system for HIV infection in children less than 13 years of age. (CDC, 1994)

2.1 Impact of HAART on organ-specific diseases

In developed countries, HAART has dramatically changed the natural history of HIV infection in children. HAART has reduced the morbidity and mortality among HIV-infected children leading to substantial increase in CD4 T-lymphocyte count and a parallel decrease in HIV viral load. Perinatally-acquired HIV-infection has become a chronic disease, in which many infected children in developed countries are entering adolescence and adulthood.

There are a variety of organ-specific diseases in different clinical classification and AIDS events classified in the CDC and WHO classifications (Tables 1 and 2). The most frequent organ-specific diseases in pre HAART era in children were encephalopathy, cardiomyopathy, wasting syndrome, lymphoid interstitial pneumonia, thrombocytopenia and nephropathy. Most of them occur in advanced stages of immunosuppresion, although sometimes they may present as the initial manifestation of the disease, even with relatively preserved CD4 cell count or CD4 percentage. With successful HAART, the weight and height growth curves tend to normalize over time. In addition, the incidence of organ-specific diseases has dramatically decreased with the use of HAART. Most organ-specific diseases improve with HAART, and in many cases the organ-function is completely restored.

2.1.1 Category A organ-specific diseases

Hepatomegaly is a common clinical manifestation of paediatric HIV disease and is likely caused by the replication of HIV within the reticuloendothelial system. In HIV-infected children a variety of factors may be involved in hepatomegaly besides HIV itself, like concomitant hepatitis viruses, opportunistic infections, medications and malnutrition.

Generalized lymphadenopathy is another common clinical finding in HIV-infected children, but a differential diagnosis must be done with other viral infections, opportunistic and mycobacterial infections, and malignancy.

Clinical stage 1
Asymptomatic
Persistent generalized lymphadenoapathy
Clinical stage 2
Unexplained persistent hepatosplenomegaly
Papular pruritic eruptions
Fungal nail infections
Angular cheilitis
Lineal gingival erythema
Extensive wart virus infection
Unexplained persistent parotid enlargement
Extensive molluscum contagiosum
Recurrent oral ulceration
Unexplained persistent parotid enlargement
Herpes zoster
Recurrent of chronic upper respiratory tract infections (otitis media, otorrhoea, sinusitis, tonsillitis)
Clinical stage 3
Unexplained moderate malnutrition or wasting not adequately responding to standard therapy
Unexplained persistent diarrhoea (14 days or more)
Unexplained persistent fever (above 37.6^{o}C, intermittent or constant, for longer than one month)
Persistent oral candidiasis (after 6-8 weeks of life)
Oral hairy leukoplakia
Acute necrotizing ulcerative gingivitis or periodontitis
Lymph node tuberculosis
Pulmonary tuberculosis
Severe recurrent bacterial pneumonia
Symptomatic lymphoid interstitial pneumonitis
Chronic HIV-associated lung disease including bronchiectasis
Unexplained anaemia (<8.0g/dl), neutropaenia (<0.5x10^{9}/L^{3}) and or chronic thrombocytopenia (<50 x 10^{9}/L^{3})
Clinical stage 4
Unexplained severe wasting, stunting or severe malnutrition not responding to standard therapy
Pneumocystis pneumonia
Recurrent severe bacterial infections (e.g. empyema, pyomyositis, bone or joint infection, meningitis, but excluding pneumonia)
Chronic herpes simplex infection; (orolabial or cutaneous of more than one month's duration, or visceral at any site)
Extrapulmonary TB
Kaposi sarcoma
Oesophageal candidiasis (or candiadisis of trachea, bronchi or lungs)
Central nervous system toxoplasmosis (after the neonatal period)
HIV encephalopathy

Cytomegalovirus (CMV) infection; retinitis or CMV infection affecting another organ, with onset at age more than 1 month
Extrapulmonary cryptococcosis including meningitis
Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidioidomycosis, penicilliosis)
Chronic cryptosporidiosis (with diarrhoea)
Chronic isosporiasis
Disseminated non-tuberculous mycobacterial infection
Cerebral or B cell non-Hodgkin lymphoma
Progressive multifocal leukoencephalopathy
HIV-associated cardiomyopathy or nephropathy

Table 2. WHO clinical staging of HIV for infants and children with established HIV infection. (WHO, 2007)

Parotid swelling is thought to be caused by the HIV virus itself, although EBV may also play a role. Suppurative bacterial parotiditis is rare in HIV-infected children. Although very inusual, in progressive parotid swelling a malignancy must also be considered in the differential diagnosis.

Dermatitis in children can be secondary to infections or due to medications. The most common non-infectious diseases are atopic dermatitis and seborrheic dermatitis.

These manifestations are still common but less frequently observed since the introduction of HAART. In addition they all tend to improve or even disappear with the use of HAART

2.1.2 Category B organ-specific diseases

Hematologic disorders like anemia, neutropenia and thrombocytopenia more than 30 days of duration are category B manifestations. These manifestations can occur for many reasons like peripheral destruction, the most common cause of the HIV-associated thrombocytopenia, adverse effect of medications (zidovudine) or medications to treat opportunistic infections (ganciclovir), by HIV virus itself, nutritional status and changes in the bone marrow associated with chronic illness. Various studies have demonstrated a reduction in thrombocytopenia and other cytopenias when HAART is started.

Dilated cardiomyopathy has been described in 10%-20% of children with HIV infection. The mean age at diagnosis of cardiomyopathy in children is 18-24 months, but symptomatic cardiomyopathy may occur in children who are as young as 6 months age. Patients with dilated cardiomyopathy have been preceded by myocarditis, due to direct infection of myocardial cells by HIV. The resolution of this cardiomiopathy after introduction HAART has been described, with complete restoration of ventricular ejection fraction. Although cardiomyopathy appears to be rare nowadays in developed countries, it is not uncommon in children coming from high-prevalence areas with advances states of immunosuppression. In these patients a cardiac ultrasound is recommended as baseline evaluation.

Leiomyosarcoma is described in HIV-infected children, but the incidence is very low. The proportion of leiomyosarcoma or leiomyoma in HIV-infected children is 17% of all cancers in these children. Smooth-muscle tumors are reported in the gastrointestinal tract, liver, spleen and lung. In HIV-infected children these tumors are strongly associated to Epstein-Barr virus. In a study of malignancy in HIV-infected children no significant differences were found in the overall rates of soft tissue cancer between HIV-infected children and uninfected

children. Leiomyosarcoma was the only soft tissue cancer to occur in HIV-infected children whereas various different soft tissues sarcomas occurred in non-infected children. (Kest et al., 2005).

Lymphocitic interstitial pneumonia (LIP) is common in HIV–infected children non-treated with HAART. The etiology is unknown but it has been suggested that the coinfection with Epstein-Barr virus and HIV may result in a lymphoproliferative response. The patients are initially asymptomatic or have mild symptoms. They may include cough, mild tachypnea and in advanced stages hypoxemia. The course is usually complicated with recurrent episodes of acute lower respiratory tract infections frequently leading to bronchiectasis. The chest radiography usually shows a diffuse reticulonodular pattern more pronounced centrally. High resolution CT may improve the diagnostic accuracy; typical features include micronodules 1-3 mm in diameter, with a perylymphatic distribution, and subpleural nodules. Lung biopsy may show interstitial infiltrate of lymphocytes and lymphoid aggregates surrounding the airways. LIP has been associated with chronic liver disease and bilateral parotid enlargement. Treatment is symptomatic. Oral corticosteroids have been used. HAART has been described to improve the respiratory status in adults and has been reported to be associated with the resolution of radiographic abnormalities in children. LIP is a stage 3 of WHO AIDS defining illness it is an indication to start HAART in children who are not received antiretroviral treatment. (Zar, 2007).

Nephropathy prevalence varies from 2% to 10% in HIV-infected children, and has been reported to be more common in African-American children than Hispanic or white HIV-infected children. The clinical presentation varies from asymptomatic proteinuria to symptomatic renal tubular acidosis, hematuria, proteinuria and acute renal failure. Nephropathy is associated with a higher degree of immunosupresion and a higher mortality. Biopsy diagnosis can reveal the typical histologic features of minimal change nephritic syndrome, mesangioproliferative glomerular lesions, and “lupus-like” renal lesions. Other patients show renal changes consistent with the diagnosis of HIVAN (HIV-associated nephropathy) or HIV-immune complex disease (HIVICK). The introduction of HAART has revolutionized the clinical management of HIV-associated renal disease. The use of HAART is associated with a marked improvement of HIVAN, resulting in slower progression to end-stage renal disease or even in recovery from dialysis-dependent renal failure provided the kidney damage is not too severe (Mc Culloch et al., 2008).

2.1.3 Category C organ-specific diseases

Encephalopathy has been reported between 13-35% of children with HIV infection and in 35-50% of children with AIDS. Studies have demonstrated that HIV enters the central nervous system (CNS) soon after the infection and may persist in this compartment over the entire course of HIV infection. Mechanisms of pediatric HIV neuropathogenesis and factors associated with neurodevelopmental abnormalities in perinatally infected children are not yet fully understood. Neurotropic HIV likely develops distinct genotypic characteristics in response to this unique environment. (Van Rie et al., 2007). Complementary studies are usually non-specific, in fact the isolation of HIV from cerebrospinal fluid does not correlate with clinical symptoms. Neuroimaging has provided the best evaluation showing cortical atrophy with abnormalities in the subcortical white matter and in basal ganglia regions. The use of HAART is highly effective in reducing the incidence of HIV encephalopathy among perinatally infected children. CNS-penetrating antiretroviral regimens are important in affecting survival after diagnosis of HIV encephalopathy (Patel el al., 2009).

Malignancy prevalence in HIV infected children is significantly higher than in the normal population, approximately 2% compared with 1%. The types of malignancy reported show the following proportions of malignancies: 65% non-Hodgkin´s lymphoma, 17% leiomyosarcoma or leiomyoma, 8% leukemia, 5% Kaposi´s sarcoma, 3% Hodgkin´s lymphoma and less than 2% vaginal carcinoma in situ and tracheal neuroendocrine carcinoma. Non-Hodgkin´s lymphoma occurred most commonly in the gastrointestinal tract (37%), followed by the CNS (17%), liver and spleen involvement were common sites too. Although the immunosupresion of HIV disease in cancer pathogenesis is recognized, the etiology of cancer in paediatric HIV infection is not well-understood. In one study, a high viral load of Epstein-Barr virus was associated with the development of malignancy, but only in children with CD4 T cells counts > 200/µl (Pollock et al., 2003). In other study, the incidence of cancer in HIV infected children was highest in patients who received HAART less than 2 years compared to children with more than 2 years of HAART. (Kest et al., 2005)
The wasting syndrome has been described in HIV infected children. The relationship between protein-energy malnutrition and adverse effects on the immune system result in immune deficiency states. Malnutrition may exacerbate the immunological effects. The causes of malnutrition in HIV children include decreased nutrient intake, gastrointestinal malabsorption, increased nutritional requirements or tissue catabolism and psychosocial factors, as well as medications and infections that may also cause malnutrition. HAART has decreased the incidence of wasting syndrome, but new side effects like lipodystrophy has been well defined in children (Miller, 2003). HIV-infected children have experienced significant improvement on growth since the introduction of HAART. An increase in the mean of weight z-scores to normal values was obtained by week 48 and an increase in mean height z-scores approached normal values by 96 week (Verweel et al., 2002; Guillén et al., 2007)

2.2 Impact of HAART on bacterial and opportunistic infections

Bacterial infections and OI infections still occur in the HAART era in children, mostly in those with persistently low CD4 T lymphocyte counts caused by failure of adherence to multiple drugs or drug resistance. By contrast, OI and serious bacterial infections, herpes zoster and tuberculosis (TB) continue to present in children who are not severely immunocompromised. The incidence of OI is higher in developing countries, where the use of HAART is less extended, the follow-up more difficult and the socioeconomic conditions worse.
In contrast with adults, OI in children usually reflect a primary infection by a pathogen, whereas in adults they are often secondary to reactivation from latent infections. Perinatal transmission of hepatitis C virus and cytomegalovirus are more frequent in HIV-infected women than in non-infected women. Children undiagnosed of HIV infection are at risk to suffer an OI because of the lack of HAART and primary prophylaxis. Besides, in children the diagnosis of OI in some situations is difficult. In the first moths of live it is not possible to distinguish between specific antibodies against common pathogens and antibodies belonging to the mother due to transplacental transfer. Furthermore, the diagnostic yield for many OI in children is usually lower than in adults and requires admission or invasive procedures. TB diagnosis requires obtaining smears of induced sputum or gastric lavage, with lower sensitivity than sputum smears in adults, and therefore the diagnosis often rely on an epidemiological history of an adult being diagnosed of TB.

The most frequent bacterial and OI in the pre HAART era in children were severe bacterial infections (bacteraemia and pneumonia), herpes zoster, *Pneumocystis jirovecii* pneumonia, esophageal candidiasis and disseminated *Mycobaterium avium complex* (MAC), less common were cryptosporidiasis, tuberculosis (TB), systemic fungal infections and toxoplasmosis.(Dankner et al., 2001). The widespread use of HAART has decreased the incidence of bacterial infections and OI in children. Some of the opportunistic infections complicating HIV are not curable with available treatments, effective HAART has resulted in improved immune status leading to control the infection. (Gona et al., 2006) Early diagnosis, primary prophylaxis and antiretroviral treatment in vertically infected children are of major importance. The recommendation to start HAART in children has shifted towards an earlier initiation, to include infants less than 2 years in WHO guidelines in developing countries and in less than one year old in American and European guidelines, independently of immunological stage (WHO, 2010; CDC, 2010; PENTA, 2009).

Primary and secondary prophylaxis is important to prevent OI in children. All children below 1 year old must to receive primary prophylaxis for PCP, children aged 1 to 4 years should receive it if they have a CD4 count below 20% of total lymphocyte count. Children aged 5 and above should receive such prophylaxis if they have a CD4 count below 200-250 cells/mm3 or less than 15%. There are few data for recommendations for prophylaxis of other OI. Secondary prophylaxis is used after the treatment of some opportunistic infections to prevent the reactivation or re-infection. Discontinuation of primary prophylaxis for *Pneumocystis jirovecci* and other OI is possible and safe when immune reconstitution is reached.

Vaccines are other important tool to prevent potential severe infections in HIV-infected children, including varicella and human papillomavirus vaccine. Recent evidence shows that children who were already HIV-infected when vaccinated with BCG at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease. This has changed the recommendations for not using this vaccine in countries with a high burden of TB, until a diagnosis of HIV-infection has been ruled out. Live attenuated vaccines are not recommended in children with severe immunosuppresion, those with CD4 cells percentage less than 15%.

As patients are living longer, other infections have assumed more importance in the prognosis, as has been well documented with viral hepatitis in co-infected adults. Improvement in the immune system after the introduction of HAART, even in the absence of complete viral suppression, may serve as prevention and therapy for many AIDS-defining OI, particularly those lacking effective therapy. With the immune boost achieved shortly after the initiation of HAART, a new immune reconstitution inflammatory syndrome (IRIS) has emerged. IRIS occurs shortly after the initiation of HAART due to an exaggerated inflammatory response. It is less well characterized in children than adults. The incidence is higher in children with low CD4 count and in developing countries. It is common in infants immunized with Bacille Calmette-Guerin (BCG) vaccine. Typically, IRIS occurs between 2 and 6 weeks after the introduction of HAART, but may occur up to 7 months later. This syndrome consists of an exacerbation of signs and symptoms associated with the underlying disease, of infectious and non-infectious etiology, resulting in an apparent clinical worsening. IRIS result from a rapid rebound in immune function that respond to a variety of clinically occult or latent infections that were present at the time of initiation of HAART, not previously recognized by a severely dysfunctional immune system. IRIS can complicate the management of these children.

It is important to distinguish between failure in HAART, failure in treatment of an OI and antimicrobial resistance or compliance. If an OI becomes apparent in the first 12 weeks of HAART initiation and there is a suspicion, HAART must be continued and treatment for the OI started. When an OI present after 12 weeks on HAART with virologic and immunological responses, it may be either IRIS or manifestations of the OI with partial immune reconstitution that have not controlled the infection. In the last situation HAART should be continued and treated accordingly. If an OI occurred in the setting of a virologic and immunological failure on HAART, this regimen must be revaluated while treatment for the OI given as early as possible.

The time of initiate HAART when an OI is present is unknown. The risk of complications associated with some antiretrovirals, the drug-drug interactions that make more difficult the management and the confusion with IRIS syndrome has led to suggest, in some circumstances, to wait some time before HAART initiation. Some OI improve with the early use of HAART. In other infections, like cryptococcal meningitis, it is recommended to wait a response to therapy to start HAART. In general, HAART should be initiated early after the OI has been diagnosed. Recently, a trial conducted in South Africa showed that the initiation of HAART simultaneously with TB treatment significantly improved survival.

In HIV infected children other difficulty is that the pharmacokinetics data of many commonly used drugs are incompletely known and the potential interactions between the different antiretrovirals and the drugs used to treat the OI may be significant, reducing the number of options available for treatment (CDC, 2009).

2.2.1 Impact of HAART on bacterial infections

During pre-HAART era, serious bacterial infections were the most commonly diagnosed infections in HIV-infected children. Pneumonia was the most common bacterial infection followed by bacteraemia and urinary tract infection. Other serious bacterial infectious including osteomyelitis, meningitis, abscess and septic arthritis occurred as well. HIV-infected children are at risk of serious bacterial infections during the early years of life, and in these patients the risk is magnified by the direct effects of HIV related with T and B cell dysfunction. The most common blood isolate organism among HIV-infected children is *Streptococcus pneumoniae*. A significant decrease in bacteraemia incidence and the time to first bacteraemia incident were seen in the post HAART era. In pre-HAART era children with a decline of CD4 T cells were more likely to develop bacteraemia, and children who experienced bacteraemia had an associated higher mortality (Kapogiannis et al., 2008). In era post-HAART the bacteraemia has decreased but the incidence remains substantially higher than in HIV-uninfected children. There are no data currently on whether initiation of HAART during acute sepsis reduces short-term morbidity or mortality. Paediatric HIV infection is not a homogeneous condition in the era of HAART. Susceptibility to sepsis differs according to stage of disease, access to HAART, and virologic and immunologic response to treatment. HIV-infected children have higher risk of developing pneumonia and of more severe disease than immunocompetent children. Pneumonia remains a major cause of death and hospitalization, particularly in developing countries. HAART has demonstrated to decrease the incidence of pneumonia. The vaccine, early HAART and antibiotic prophylaxis are preventive strategies to prevent pneumonia (Gray & Zar, 2010).

The prophylaxis with vaccination is important in these children and prophylaxis with Trimethoprim-sulphametoxazole (TMP-SMX) produce a benefit to reduce the incidence of

these infections. In developing countries where the access to HAART is limited, these children can benefit from prophylaxis with TMP-SMX to avoid bacterial infectious. The WHO recommends prolonged daily prophylaxis for HIV-infected infants and children. Intermittent prophylaxis was associated with more invasive bacterial disease than daily prophylaxis, but the survival was similar (Zar et al., 2010). Opportunistic infections prophylaxis can be withdrawn safely for HIV-infected patients who experience CD4 cell recovery while receiving stable antiretroviral therapy, no increase in the rate of serious bacterial infection was observed. (Nachman et al., 2005).

2.2.2 Impact of HAART on opportunistic infections

Oropharyngeal candidiasis continues to be one of the most frequent opportunistic infection in HIV-infected children and often present as an initial manifestation of the disease. Oesophageal or pulmonary candidiasis has decreased after introduction of HAART. In children who not respond to HAART, candida esophagitis can occur and be concomitant to another opportunistic infection. Disseminated candidiasis is rare among HIV-infected children. There are no data in children to make recommendations for treatment or prevention of oropharyngeal candidiasis. With the available data from adults no conclusion can be made about the effectiveness of what antifungal is better for prophylaxis, although fluconazole is better than placebo. Ketoconazole, fluconazole, itraconazole and clotrimazole improved the treatment outcomes (Pienaar et al., 2010).

Cytomegalovirus infection can be acquired during infancy, early childhood or adolescence. HIV-infected women with CMV infection have a higher rate of CMV shedding from the cervix than do women without HIV infection and the risk for mother to infant transmission of CMV may increased among infants born to women infected by both CMV and HIV. After being born, HIV-infected children have higher risk for CMV infection (Schleiss MR, 2009). In era pre HAART co-infection appear to have faster progression of HIV disease. CMV retinitis is a frequent manifestation in HIV infected children. Viral dissemination can affect multiple organs producing pneumonitis, gastrointestinal disease and involvement of the central nervous system. Disseminated disease and retinitis must be treated with induction therapy and after chronic suppressive therapy. The safety of discontinuation of secondary prophylaxis in children with retinitis has not been well studied, but if the child has completed 6 months of HAART and the CD4 count are >15% in children 1-5 years old or > 100 cells/mm^3 in older than 6 years, secondary prophylaxis is usually withdrawn safely.

HSV-1 (*Herpes simplex virus-1*) causes gingivostomatitis in HIV-infected children when they experiment the primary infection by contact with infected oral secretions. If the patient is severely immunocompromised the HSV-1 may produce severe local lesions or disseminated infection with visceral involvement like esophagus, CNS, lung, spleen, liver and kidney. HAART has decreased the rates of systemic HSV infection. The HIV infected children can also have recurrences of gingivostomatitis. Neonatal transmission occurs with the exposure to maternal genital fluids. Congenital HSV infection is rare but it has cutaneous, ocular and CNS involvement. Caesarean delivery must be considered in women with active genital HSV. HSV-2 is acquired in adolescents by contact with infected genital secretions and the risk of genital HSV reactivation increases with the immunosupresion. HSV infection can increase the risk for mother to child HIV transmission. The treatment is acyclovir orally or intravenously depending on the severity of the infection. Valacyclovir, a prodrug of acyclovir, can also be effective.

The virus *varicella zoster* (VZV) is associated with more severe disease in HIV infected children in pre-HAART era than in uninfected children. After HAART and vaccination the rates of varicella has decreased. In some cases, disseminated varicella can develop in children with severe immunocompromise, but not in children with higher CD4. Retinitis can be a complication of varicella. Herpes zoster after infection of varicella is described like a decline in specific cellular immunity to VZV and can involve various dermatomes. HIV-infected children before HAART with low CD4 percentage at the time of primary varicella were at higher risk to subsequent zoster. In HIV-1 infected children the incidence of herpes zoster was higher in advances stages of immunusuppression. It has been reported an increase of herpes zoster after the introduction of HAART, but the incidence is less than pre-HAART era, possible due to vaccination. (Levin et al., 2009) A VZV-associated IRIS has been described after 1-3 months after the introduction of HAART with mild cutaneous manifestations and with the distribution by dermatomes, responding to acyclovir (Puthanakit et al., 2006). The treatment of choice is acyclovir, other alternatives are valacyclovir or famciclovir. The prevention for varicella in a contact must be the vaccination or varicella zoster immunoglobulin, in some cases acyclovir can be used.

Congenital toxoplasmosis has been rarely reported in HIV-infected children. It may occur when a HIV-mother acquired the primary Toxoplasma infection during the pregnancy, although perinatal transmission has been described in women with chronic Toxoplasma infection because the reactivation of replication in women with severe immunosupresion. The symptoms in congenital infection are generalized lymphadenopathy, hepatosplenomegaly, jaundice, hematologic abnormalities and CNS disease. CNS disease in HIV-infected children acquired after the delivery is very rare, and this occur like in adults when the CD4 were less than 50 cells/mm^3, but in HIV-infected children with neurologic symptoms, it must be considered. Ocular toxoplasmosis often is associated with CNS infection. Mother with acute toxoplasmosis must be treated and empiric therapy in newborn initiated. The treatment in congenital toxoplasmosis is pyrimethamine combined with sulfadiazine with folinic acid with a recommended duration of 12 months. Cerebral toxoplasmosis should be treated during 6 weeks depending of the evolution. Corticosteroids and anticonvulsants may be necessary. Primary prophylaxis must be done with TMP-SMX in children with CD4<15% in children under 6 years old or CD4 < 100 cells/mm^3 or older than 6. Discontinued primary prophylaxis is possible when the immune restoration occurs. Secondary prophylaxis must be used until immune reconstitution with HAART is initiated, then discontinuation of secondary prophylaxis must be considered.

Cryptococcosis occurs less frequent in children than in adults. In era pre-HAART cryptococcosis cases were in older children and with severe immunosuppression. In the HAART era the rate of this infection has decreased, remaining uncommon. The clinical manifestations of this infection are meningoencephlalitis, pulmonary or disseminated infection. The treatment is therapy of induction during 2 weeks with amphotericin B or liposomal amphotericin B and flucytosine in CNS disease and after the consolidation therapy during 8 weeks with fluconazole. When CNS is not affected the flucytosine may not be used. Fluconazole is used to prevent recurrences. If a restoration of immune status is produced by HAART, fluconazole can be discontinued. In some cases IRIS may develop when HAART is initiated simultaneously and therefore it is recommended to delay HAART, but if the patient is on HAART previously, this must be continued.

Cryptosporidiosis/isosporidiosis have declined dramatically after HAART. Before HAART these infections occurred with advanced immunosupresion. Although the incidence of these

parasitic infections has declined with HAART, developing countries with less access to HAART have high incidence of these infections. Watery diarrhea is the most common manifestation of *crypstosporidium*, that can migrate into bile duct resulting in inflammation and slerosing cholangitis. Pancreatitis occurs rarely. Effective HAART is the main treatment for these infections. In crypstosporidiosis a 3-day course of nitazoxanide significantly improved the resolution of diarrhoea, parasitological eradication, and mortality in HIV seronegative, but not HIV seropositive, children (Amadi et al., 2002). IRIS has not been described with cryptosporidiosis treatment.

The incidence of tuberculosis depends on the site, and where the incidence of tuberculosis is high, it depends on the age and is increased in HIV co-infected children. So in sub-Saharan countries the incidence rate in HIV-children below 12 months of age is 1595/100.000 compared with 659/100.000 in HIV-uninfected. In older than 12 months-old the incidence rate is 5930/100.000 in HIV-infected children (Verhagen et al., 2010). The resistance of tuberculosis is increasing and it is an obstacle to control the TB worldwide. The diagnosis in children is more difficult than in adults due to the difficulty to obtain a smear of bronchial secretions for a bacteriologic diagnosis. The tuberculin skin test (TST) in HIV-infected children with tuberculosis disease can be negative. Recently, an IFN-γ release assay from lymphocytes after stimulation by highly specific synthetic *Mycobacterium tuberculosis* antigens has been developed, which sensitivity is higher than TST, but is commonly leads to indeterminate results in young and immunocompromised children. To obtain a specimen for microbiologic diagnosis is more combersome in children because of their difficulty in producing sputum, so there is a need to rely on gastric aspirates, although hypertone saline induced sputum induction has shown good results (Zar et al., 2005). The microbiological diagnosis relies on microscopic acid-fast bacilli staining, the isolation the mycobacteria in the culture, and recently nucleic acid amplification can improve the diagnostic yield. Drugs susceptibility testing is important due to increasing resistance. It is recommended a standardization of clinical and radiographic case definition to avoid confusion in the diagnosis. To prevent *M. tuberculosis* infection, BCG vaccine is not currently used due to the risk of disseminated disease in HIV-infected children (WHO, 2007). Treatment of latent tuberculosis infection is indicated in HIV infected children with isoniazide, if resistance to this drug is not suspected in the source case. There are insufficient data to guide isoniazide prophylaxis in HIV-infected children in high-prevalence countries in the absence of TB exposure (Gray et al., 2009). In HIV-infected children with TB disease, initiation of TB treatment is the priority although the optimal timing of HAART initiation is uncertain. Recently, a trial conducted in South Africa in adults showed that the initiation of HAART simultaneous with TB treatment significantly improve survival. (Abdool et al., 2010). Rifampin is a potent induction of the CPY3A that precludes treatment with all protease inhibitors (IP) but may allow the treatment with non-nucleoside reverse transcriptase inhibitors (NNRTIs). In many countries of Africa a PI-based antiretroviral regimen is indicated in HIV-infected children less than 36 months like first line regimen: in children older than 3 years IP can be replaced by efavirenz to avoid interactions with TB treatment; in younger than 3 years efavirenz can be replaced by nevirapine however there is a high percentage of resistance in children exposed to single dose nevirapine used for prevention of mother to child transmission (PMTCT). The management of TB resistance in cases of MDR and XDR TB must be guided by expert based on guidelines (WHO, 2008) (CDC, 2007).

IRIS has been described in children and must be suspected in children with advanced immunosupression who start HAART. TB therapy must not be discontinued and symptomatic treatment can be used including corticosteroids. BCG IRIS has been reported in children initiating HAART.

Mycobacterium avium complex (MAC) disease is caused by multiple species of nontuberculous mycobacteria. The incidence has decreased after introduction of HAART. MAC produces lymphadenitis and a disseminated infection in children with advanced immunologic deterioration. The main treatment is to preserve the immune function with HAART. The specific treatment is combined therapy with a minimum of 2 drugs. IRIS may occur, so antimycobacterial therapy should be started 2 weeks before HAART to minimize the IRIS symptoms. The chronic suppressive therapy may be safely discontinued if immune reconstitution is reached.

Pneumocystis jirovecii pneumonia has decreased in HAART era. Around 80% of immunocompetent children have acquired antibodies for *Pneumocystis* by the age of 2-4 years, and the infection is usually asymptomatic or presenting with mild respiratory symptoms. However, in HIV-infected children the infection frequently is very severe associated with high mortality, being an AIDS event occurring in the first year of life between 3-6 moths. HAART and prophylaxis for *Pneumocystis* has decreased the incidence. *Pneumocystis* pneumonia depends of the grade of immunosupression of the child, so marked decrease in CD4 is a risk factor for this. *Pneumocystis* pneumonia is characterized by fever, tachypnea, cough with hypoxia low arterial oxygen pressure, lactic dehydrogenase is often increased and the radiography can indicate bilateral diffuse parenchymal infiltrates. The microbiologic diagnosis is based on the identification of *Pneumocystis* in respiratory secretions. Bronchoalveolar lavage is the procedure of choice with a high diagnostic yield in HIV-infected children. Coinfection by other microorganisms must be considered. Prophylaxis is recommended in all the children since 4-6 weeks of age during the first year of age independently of CD4 count, with TMP-SMX. Infants with indeterminate HIV infection must received prophylaxis until they are confirmed to be non-infected. In older children prophylaxis is indicated if the CD4 are less than 15%. TMP-SMX is also effective to prevent toxoplasmosis and bacterial infections. The treatment is with TMP-SMX intravenously during 21 days. IRIS is rare to occur with this infection. Adverse reactions are frequent with TMP-SMX so other drugs must be considered. In cases of severe infection corticosteroids must be considered starting in the first 72 hours of diagnosis.

2.2.3 Impact of HAART in other infections

Malaria and HIV infection are two infections with a similar distribution in most countries, mainly in sub-Saharan Africa. An increased susceptibility in HIV-infected patients has been described in adults due to impaired immune response to malaria through cellular immunosuppression resulting in a higher likelihood of increased parasitaemia and severe malarial infections. HIV infection increases the incidence of clinical malaria, inversely correlated with the degree of immunodepression. HIV infection is associated with an increase of cerebral malaria (Imani et al., 2011). The effect of malaria on HIV infection is not as well established. Malaria, when fever and parasitemia are high, may be associated with transient increases in HIV viral load. The effect of subclinical malaria on HIV viral load is uncertain.

TMP-SMX may be effective in the prevention of malaria but the development of resistance is of concern. Severe malaria is clinically similar to other severe febrile illnesses. However, in

endemic areas, parasitological confirmation of parasitaemia is often unavailable or unreliable and false positive malaria microscopy is common. The routine use of parenteral antibiotics among children with a positive malaria slide and life-threatening disease is warranted because invasive bacterial infections are likely to be overlooked and are associated with increased mortality. During pregnancy, placental malaria is associated with higher plasma and placental HIV viral loads, independently of the severity of immunodeficiency. Both infections have been associated with maternal and infant morbidity and mortality (Brentlinger et al., 2006)). HIV-1 exposure and HIV-1 infection are associated with increased prevalence of severe malarial anaemia during acute *P. falciparum* infection, independent of parasite density. HIV infection status does not affect the choice of therapy and no recommendations exist for alternative dosing of antimalarial drugs in HIV-infected persons. IRIS caused by malaria has been not reported.

HBV-HIV co-infection in children is less frequent nowadays in developed countries since the universal policy o HBV vaccination to newborns. Nevetheless, HBV is still a major problem in developing countries.

The clearance rates in HBV monoinfected children are 10% in newborns, 70% in children 1-5 years old, and 94% in >5 years. Chronic hepatitis is defined as persistence of HBsAg for more than 6 months. Children can acquire the infection perinatally, parenterally or through sexual transmission. Most children with chronic HBV infection are asymptomatic. They can develop cirrhosis and hepatocellular carcinoma over 2 or 3 decades. The diagnosis is made by detection of HBsAg. HBeAg seroconversion is defined as loss of HBeAg followed by the production of antibodies to HBeAg (anti-HBe) and is defined as an inactive carrier state. HBV DNA is a marker of replication of HBV. Biopsy determines the grade of hepatic inflammation and fibrosis by metavir classification. Percutaneous transient elastography (Fibroscan) is less aggressive than biopsy and useful to determine the grade of inflammation and fibrosis of the liver. The indications for treatment of chronic HBV in HIV co-infected children include evidence of HBV viral replication indicated by detectable serum HBV DNA, with or without HBeAg positivity, for >6 months, persistent elevation of serum transaminase levels or evidence of chronic hepatitis on liver biopsy. Treatment is not recommended for children with immunotolerant chronic HBV infection (i.e., normal serum transaminase levels despite detectable HBV DNA). After initiation of HAART, liver function may worsen due to immune reconstitution syndrome causing an increased immune response to HBV in the liver and subsequently a "flare" of hepatitis. HBV itself, however, has no detrimental effect on the course of the HIV infection.

HCV-HIV co-infection occurs approximately in 30% of adults. Vertical transmission of HCV is 3-5 fold higher in HIV-HCV co-infected mothers. HCV can be accelerate the progression of HIV infection increasing the viral replication, produce a worse immune reconstitution and there is an increase of hepatic toxicity. HIV influences in HCV infection increasing the progression of the liver disease. In HIV-HCV coinfection liver pathology develops more rapidly than in HCV mono-infection. The HCV is usually asymptomatic. Chronic HCV infection is defined as the presence of HCV RNA for > 6 months. In perinatally-acquired HCV-infected children, 20% had apparent clearance of infection, 50% had chronic asymptomatic infection and 30% had chronic active infection. During the infancy there might be an immunotolerance to this infection. The diagnosis is by serologic antibodies but these can be persistently negative in HIV-infected children. Therefore, HCV RNA qualitative or quantitative should be used for diagnosis of infection. HCV viral load does not correlate with the degree of liver damage. There are different genotypes of HCV, genotypes 2 and 3 are more likely than 1 or 4 to achieve sustained virologic response to treatment. The biopsy

or fibroscan are used to know the grade of inflammation or fibrosis of the liver. The indications for HCV treatment can be detectable HCV-RNA, persistent elevation of transaminases, evidence of chronic hepatitis on liver biopsy, children >3 years old and no decompensated liver disease. The treatment accepted in children is standard interferon-alfa-2b with ribavirin. Pegilated interferon-alfa administered for 24-48 weeks with ribavirin is recommended in adults. Although, the experience of HCV treatment in coinfected children is scarce, (Navarro et al., 2007) and there is a need of studies. HAART should be initiated. HAART should be initiated earlier than in non-HCV infected children

2.2.4 Immune Reconstitution Inflamatory Syndrome (IRIS)

Antiretroviral therapy improves immune function and CD4 cell count in HIV-infected children within the first few months after starting HAART producing an increase of CD4 cells and decrease in viral load. This changes are associated with an increase in the capacity to develop inflammatory reactions. Some patients develop a paradoxical inflammatory response by their reconstituted immune system to infectious or non-infectious antigens, resulting in apparent clinical worsening. There are two types of IRIS: ¨unmasking¨ IRIS and ¨paradoxical¨ IRIS. The unmasking IRIS is an occult and subclinical opportunistic infection, unmasked by immune recovery following the HAART initiation. Paradoxical IRIS is a clinical recrudescence of a successfully treated infection, symptomatic relapse despite initial clinical improvement and continued microbiologic treatment success; the antigen driving the immune activation often elicits a robust immune response in the setting of few or no detectable organism and the culture may be sterile due to effective opportunistic infection treatment.

The criteria for diagnosis of paediatric IRIS are: a) evidence of clinical response to ART with a virologic response with > 1 $\log_{10}$ copies/ml, decrease in HIV RNA; b) clinical deterioration from an infectious or inflammatory condition temporally related to the initiation of ART (unmasking or paradoxical); c) symptoms cannot be explained by an alternative infection or neoplasm, treatment failure of the opportunistic infection, adverse drug reaction or complete non-compliance to ART or TB treatment.

The commonest causes are mostly mycobacterial, including tuberculosis, atypical mycobacteria and BCG-related and herpes zoster.

The incidence of IRIS is between 10-20% in developing countries. IRIS often occurs in older children who start HAART with an advanced stage of immunosupresion, although in young infants it may also occur. Risk factors for IRIS include a high pathogen load and very low CD4 cell count when HAART is initiated. Many children have a marked mortality within the first 90 days of HAART.

The treatment of ¨unmasking¨ IRIS is the treatment of the underlying opportunistic infection, in some cases also anti-inflammatory therapy and rarely discontinuation of HAART. Screening of occult infections before starting HAART can reduce IRIS. The treatment of ¨paradoxical¨ IRIS is observation in mild cases, non-steroidal anti-inflamatory drugs in moderate reactions, and corticosteroids in severe cases, considering the temporary cessation of HAART and surgical debulking (Boulware et al., 2008).

When a child starts HAART, is difficult to distinguish between HAART toxicity, from toxicity due to treatment to the opportunistic infection and IRIS. Opportunistic infections can occur in HIV-infected children experiencing virologic and immunologic failure on HAART. If symptoms appeared within the 12 weeks after initiation HAART, it may indicate ¨unmasking IRIS¨, so HAART must be continued and opportunistic infection treatment

initiated. If symptoms occurred after 12 weeks and there is immunologic and virologic response, it may be due to ¨paradoxical IRIS¨ or incomplete immune reconstitution allowing a new opportunistic infection. In both cases HAART must be continued and if the microbiologic evaluation demonstrates a microorganism, it should be treated.

2.2.5 Prophylaxis and vaccines

2.2.5.1 Prophylaxis

TMP-SMX prophylaxis is indicated in HIV-infected children since 4-6 weeks of age until the first year of life and in older children with CD4 less than 15%. TMP-SMX prophylaxis is indicated to prevent *Pneumocystis jirovecci* pneumonia but it has activity against a wide range of pathogens including *Pneumococcus, non-typhoidal Salmonella, Isospora, Cyclospora, Nocardia, Plasmodium falciparum and Toxoplasma gondii.* In developing countries, the CHAP study, a randomized study placebo-controlled trial of cotrimoxazole in Zambia, showed the impact of TMP-SMX on reducing mortality in HIV infected children from 6 months to 14 years (Chintu et al., 2004). WHO guidelines on co-trimoxazole prophylaxis published in 2006, recommend prophylaxis in infants less than 1 year until infection can be excluded or until 6 weeks after the cessation of breastfeeding (WHO, 2006). TMP-SMX prophylaxis has potential risk of resistance and side effects. Currently the number of HIV-infants children infected is decreasing due to the interventions to prevent mother to child transmission and WHO now recommend that breastfeeding women receive HAART or the infants receive nevirapine prophylaxis. Thus, a lower number of children are expected to become HIV-infected and to receive prophylaxis. Breastfeeding decreased the risk of infections such diarrhoea and pneumonia due to the immune protection. These preventive options and the molecular tests are more accessible in these countries, allows limiting the prophylaxis for the uninfected infants (Coutsoudis et al., 2010). WHO guidelines for HIV-infected children of 1-4 years recommend prophylaxis if they are symptomatic or have less than 25%. Similarly, the infants who start prophylaxis before the age of one and who subsequently are asymptomatic and/or have CD4> 25% should remain on co-trimoxazole prophylaxis until they reach five years old. In older than 5 years the recommendations are similar than adults. A randomized controlled trial has compared daily versus intermittent prophylaxis in South Africa, finding that the intermittent prophylaxis was associated with more invasive bacterial disease than daily prophylaxis, but survival was similar (Zar et al., 2010).

TMP-SMX has a range of side effects like skin rashes, gastrointestinal disturbances and marrow suppression which lead to neutropenia and anaemia, in rare cases Stevens-Johnson syndrome may occur. In adults has been studied when there is a hypersensitivity to co-trimoxazole, the management of these adverse reactions has included continuing the drug (treating-through) and reintroducing the drug at a later date, either using dose-escalation (desensitization), or rechallenge at full dose. It observed that cotrimoxazole desensitization resulted in better outcome. Data in children are required (Lin et al., 2007).

Discontinuation of primary and secondary prophylaxis with TMP-SMX in children is possible if a restoration of immune system has occurred (Urchel et al., 2005). Studies have studied the incidence of serious bacterial infections after the withdrawal of prophylaxis (Nachman et al., 2005).

2.2.5.2 Vaccines

HIV-infected children are at increased risk of infections, particularly invasive bacterial infections due to encapsulated bacteria. Cotrimoxazole prophylaxis and associated HAART

have shown improvements in morbidity and mortality in HIV-infected children. (Walker et al, 2007). However, even in the ART era, HIV infected children have increased susceptibility to vaccine preventable diseases.

Routine immunizations are generally well tolerated by HIV-infected children but vaccine safety remains an important issue. There have been concerns that vaccination itself could result in immunologic deterioration. Although plasma viral loads could be temporally increased after vaccination, no evidence of HIV disease progression has been observed. Recent evidence shows that children who were already HIV-infected when vaccinated with bacille Calmette-Guérin (BCG) at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease. Among HIV-infected infants, the benefits of potentially preventing severe tuberculosis therefore appear to be outweighed by the risks associated with the use of BCG vaccine. In 2007, HIV infection in infants was considered a full contraindication to BCG vaccination in the new revised World Health Organization guidelines (WHO, 2007). Live viral vaccines (eg. varicella, mumps, measles and rubella) are generally not contraindicated in children who have stable CD4 status and not have severe immune suppression.

HIV-infected children in the pre-HAART era had poorer responses to vaccines and more rapid waning of immunity. Lower CD4 cell counts, higher viral load, age or advanced HIV stage at vaccination, have been associated with the immunity response, although these risk factors have not been consistent across the studies. HAART is effective in HIV-infected children by suppressing viral replication and restoring immune function. However, HAART is unlikely to restore memory T cells for vaccine antigens to which children were exposed before treatment. Previously vaccinated children showed low levels of immunity after being started on HAART. No epidemiological, virological or immunological factors consistently predicted immunity after starting HAART in these children. There is increasing evidence of improved immunization responses following effective HAART (Sutcliffe & Moss, 2010).

Once children are commenced on ART, it is generally recommended to initiate vaccination or revaccination 6 months after CD4 cells recovery to the normal range of age. This recommendation is based on the progressive but not immediate immune recovery of HIV-infected children starting HAART (Weinberg, 2008). Nowadays, it is recommended in children who were vaccinated before starting on HAART to measure the immune response to previous vaccines to guide the need for further doses. If non protective antibody levels are demonstrated; booster doses or revaccination should be considered, based on the response after one booster dose. Some benefit may be gained from vaccination even when severe immunosupression, so this should be especially considered for high risk patients. Complete revaccination after immune reconstitution is recommended. Although most children on HAART respond to vaccination, immune reconstitution is not sufficient to ensure long-term immunity for some children. These suggest that children on HAART would benefit from revaccination.

Age of the patient when started on HAART might be important in enhancing vaccine responses. Early administration of HAART preserved the memory B-cell compartment. Children who were started on HAART in infancy, less than 12 months of age, had greater protective immunity that did children who were started on HAART later in childhood, and had similar levels of immunity compared with uninfected children of the same age (Pensieroso, 2009). These findings support recommendations for early administration of HAART among infants.

It is currently recommended to start vaccination of HIV-infected children in infancy with some modifications of the routine immunization schedule:

- Hepatitis B virus (HBV) immunization in a four-dose-schedule starting soon after birth is recommended. Standard doses are advised as the infant should not be immunocompromised at this age. Testing for adequate seroconversion at or after the time of the fourth dose is important. Booster dose o revaccination is recommended accordingly to anti-HBs titre for protection. Newborns of HBV-coinfected mothers also require one dose of anti-HBV immunoglobulin with the first dose of HBV vaccine.
- Diphteria, tetanus and acellular pertussis vaccine (DTPa) is recommended in a five-dose-schedule as in routine vaccination programs. One dose of dTpa adult vaccine (low dose diphtheria and pertussis) is recommended for adolescents who have completed the series of DTPa in childhood. Revaccination with dTpa is recommended every 10 years for adults.
- Four doses of parenteral polio vaccine (IPV) and Haemophilus influenzae type b (Hib) are recommended as in routine immunization programs. Hib vaccine could be considered in HIV-infected children more than 5 years old who did not receive the vaccine before.
- Meningococcal C vaccine is recommended in a three dose scheme in first year of life. It is also advised to vaccinate older HIV infected children with two doses, especially adolescents who have not been vaccinated before.
- A 3 dose primary immunization schedule of conjugate 13-valent pneumococcal vaccine (PCV13) in the first year of life is recommended, with a re-enforcing dose during the second year. The first dose of polysaccharide 23-valent pneumococcal vaccine (PPV23) is recommended after 24 moths old and at least 2 months after the final dose of PCV13. Revaccination with PPV23 every 5 years thereafter should be considered. For children aged 24 months or more, who have not been vaccinated against pneumococcal disease, 2 doses of PCV13 administered at least 2 months apart, and later PPV23 immunization schedule is recommended.
- Hepatitis A virus (HAV) vaccine could be considered in a two dose scheme for all hepatitis A seronegative HIV-infected children over 12 months of age, especially focussing on adolescents or populations with high endemic or epidemic diseases.
- Measles, mumps and rubella (MMR) vaccine is recommended in a two dose schedule unless there is evidence of severe immunocompromise (CD4 cell percentage < 15%).
- Varicella vaccine is indicated in two dose schedule in HIV-infected children more than 12 moths of age, in CDC clinical class N, A or B with CD4 threshold as stated for MMR vaccination and without evidence of varicella immunity.
- Live-attenuated human rotavirus vaccine have been studied in HIV infected infants, in clinical stages I and II according to WHO classification, in a three dose schedule starting on 6 to 10 weeks of age. The vaccine was safe and a satisfactory immune response was mounted without aggravating their immunologic or HIV condition (Steele, 2011). Although the data are limited, this vaccine could be considered in HIV infected infants within the routine age range recommended in HIV healthy infants.
- Human papillomavirus (HPV) vaccine. Data of quadrivalent human papillomavirus vaccine (QHPV) in HIV-infected children (60% female) aged from 7 to 12 years, with a CD4% ≥15 and on stable antiretroviral therapy showed that the vaccine is safe and immunogenic for the 4 antigens (Levin, 2010). Although the data are limited, this

vaccine is recommended for girls from 12 years of age (minimum age 9, maximum age 26 years), irrespective of CD4 count in a 3 dose schedule.

- Trivalent inactivated influenza vaccine is recommended yearly from 6 months of age. Vaccination schedule and doses are similar to those recommended for healthy children and adolescents.

3. Conclusion

HAART has dramatically decreased the incidence of opportunistic infections in children and organ-specific diseases in developed countries. Opportunistic infections may complicate the treatment of HIV due to the disease itself, toxicity of the drugs and immune reconstitution inflammatory syndrome. HAART, prophylaxis, vaccines help to reduce the incidence of opportunistic infections. However in developing countries where there is a greater number of new diagnosis of HIV-infected children, less access to antiretroviral drugs and higher prevalence of opportunistic infections like tuberculosis, the prevention and the treatment must to be a priority.

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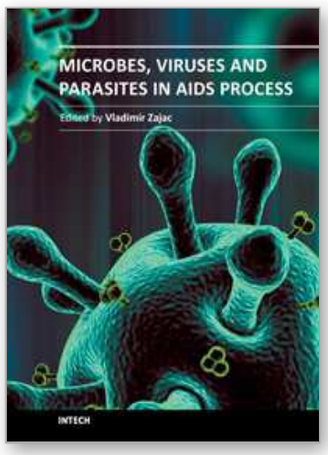

Microbes, Viruses and Parasites in AIDS Process
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The main goal in compiling this book was to highlight the situation in Africa in terms of AIDS and opportunistic diseases.Â Several chapters reveal great poverty, an apocalyptic situation in many parts of Africa.Â Global migration of people resulted in their exposure to pathogens from all over the world. This fact has to be acknowledged and accepted as African reality. New, unconventional hypotheses, not determined by established dogmas, have been incorporated into the book, although they have not yet been sufficiently validated experimentally.Â It still applies that any dogma in any area of science, and medicine in particular, has and always will hinder progress. According to some biologists, in the future, AIDS is very likely to occur in a number of variations, as a direct result of the ongoing processes in the global human society. Thus, we urgently need a comprehensive solution for AIDS, in order to be ready to fight other, much more dangerous intruders.

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