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Management of HIV-infected children

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HIV/AIDS is a major cause of infant and childhood mortality in Africa.¹ For the majority of children in Africa access to effective care and treatment is limited and most of the HIV-infected children in Africa will die from preventable, treatable childhood illnesses and opportunistic infections. In order to facilitate access to appropriate care for HIV-infected children, all health care workers looking after infants and young children must know how to identify HIV infection early, and then put in place a management plan for each individual child.

HIV/AIDS is incurable and must be managed like any chronic illness of childhood. Comprehensive care must include prevention, growth monitoring and nutrition support, immunisation, prevention of opportunistic infections, psychosocial support and timely treatment with antiretrovirals (ARV) where appropriate.

The care of an HIV-infected child will be discussed under the following headings:

- Early diagnosis of HIV infection in children
- Clinical manifestations of HIV disease in children
- Staging HIV infection and disease in children
- Medical management of HIV disease in children.

Early diagnosis of HIV infection in children

Perinatal transmission of HIV infection accounts for the majority of childhood HIV infections. The diagnosis of HIV begins with the identification and appropriate management of HIV-positive pregnant women. Awareness of the HIV

status of pregnant women allows for early identification of HIV-exposed babies and potential for early diagnosis of HIV-infected babies.

Early diagnosis in HIV-exposed infants remains difficult in most settings because of the presence of transplacentally acquired IgG antibodies, which may persist for up to 18 months. The diagnosis of HIV infection in infants relies exclusively on virological assays.

Timing of virological tests

The HIV DNA PCR is the most widely used virological test due to considerations of accuracy and performance times. However, this test is costly and assays require technical expertise which may not be universally available.

An HIV DNA PCR done at birth on HIV-exposed infants will identify only 30 - 50% of HIV-infected babies. In up to 70% of HIV-infected babies evidence of viral infection develops days to weeks after birth. In the absence of breastfeeding the sensitivity and specificity of the HIV DNA PCR approaches 100% by 6 weeks of age.² While the gold standard of diagnosing HIV infection in infants remains two concordant HIV DNA PCRs done at 6 weeks and 4 months of age, the South African Guidelines³ recommend one test in all HIV-exposed infants 6 weeks and older. The results of the one test must be interpreted in the context of the clinical picture of the child. If a child is breastfed, the HIV DNA PCR test must be repeated 6 weeks after cessation of breastfeeding. In infants and children above 18 months of age, HIV ELISA can be used to diagnose HIV infection accurately.

Clinical manifestation of HIV infection in children

Table I lists the clinical signs or conditions that may suggest HIV infection.

Staging HIV infection and disease in children

It is always important to examine and stage children with HIV infection. Clinical staging is a standardised method for:

- determining disease stage and/or progression

- strengthening clinical diagnosis when laboratory testing is not available
- the basis of treatment decisions.

The WHO⁴ has developed a four-stage system for paediatric HIV infection (revised in 2006), which is similar to the adult system (Table II). The other international staging system that is widely used is the US Centers for Disease Control and Prevention (CDC) clinical staging system.

The WHO paediatric staging of HIV/AIDS is given in Table II.

Immunological staging

The immunological staging system as developed by the CDC is based on CD4 counts by age and is also used mainly to make treatment decisions (Table III).

Medical management of children with HIV disease

It is important to note that however limited the resources are, there is always something that can be done for the individual child with HIV disease. Effective medical care of children with HIV disease minimises disease manifestations and maximises quality of life for each child. All children with suspected or confirmed HIV infection must have access to:

- monitoring of growth and development
- nutritional care and support
- prophylaxis and treatment of all opportunistic infections
- treatment of all incidental disease
- routine immunisations (EPI) and pneumococcal vaccine where available
- antiretroviral therapy when appropriate.

Monitoring of growth and development

Growth failure or failure to thrive is a recognised common finding in children with HIV disease. Growth can also be used as a sensitive indicator of disease progression. The aetiology of this growth failure is multifactorial and includes the effects of underlying disease (TB, diarr-

Table I. Clinical signs or conditions that may suggest HIV infection

Specificity for HIV infection	Signs/conditions
Signs/conditions very specific to HIV infection	<ul style="list-style-type: none"> • Pneumocystic pneumonia • Oesophageal candidiasis • Extrapulmonary cryptococcosis • Invasive <i>Salmonella</i> infection • Lymphoid interstitial pneumonitis • Herpes zoster (shingles) with multi-dermatomal involvement • Kaposi's sarcoma • Lymphoma
Signs/conditions common in HIV-infected children and uncommon in uninfected children	<ul style="list-style-type: none"> • Progressive multifocal encephalopathy • Severe bacterial infections, particularly if recurrent • Persistent or recurrent oral thrush • Bilateral painless parotid enlargement • Generalised persistent non-inguinal lymphadenopathy • Hepatosplenomegaly (in non-malaria endemic areas) • Persistent and/or recurrent fever • Neurological dysfunction • Herpes zoster (shingles), single dermatome • Persistent generalised dermatitis unresponsive to treatment
Signs/conditions common in HIV-infected children but also common in ill uninfected children	<ul style="list-style-type: none"> • Chronic, recurrent otitis with ear discharge • Persistent or recurrent diarrhoea • Severe pneumonia • Tuberculosis • Bronchiectasis • Failure to thrive • Marasmus

Adapted from: Tindiyebwa D, *et al.*¹

hoes⁵), inadequate macronutrient (protein/calories) or micronutrient (vitamins/minerals) intake or a combination of factors.

At initial evaluation, the weight, height/length and head circumference of all children 2 years of age and younger must be carefully determined. The NCHS percentile charts must be used and updated regularly to monitor growth trends and to address growth failure. Developmental status must also be assessed and children with abnormalities must be referred for assessment by the appropriate specialists.

Nutritional care and support

The immunodeficiency of HIV infection can be exacerbated by malnutrition with

associated accelerated disease progression and mortality.⁵ Nutritional care and support must form an integral part of management of children with HIV disease. Nutritional care and support does not have to wait until signs of malnutrition develop and must include dietary instruction based on readily available foods, food supplements, micronutrient and mineral supplementation.

Primary co-trimoxazole prophylaxis

Pneumocystis carinii pneumonia (PCP) caused by *Pneumocystis jiroveci* (PJ) remains an important cause of death in children with HIV infection. The incidence of PCP peaks at 4 - 5 months of age and the risk of PCP in the first

year of life in HIV-infected children not receiving PCP prophylaxis is up to 20%. Co-trimoxazole prophylaxis significantly reduces both the incidence and severity of PCP. In a randomised clinical trial conducted in Zambia⁶ mortality declined by 43% and hospital admissions by 23% in the co-trimoxazole group when compared with the placebo group. This benefit of co-trimoxazole was demonstrated at all ages and all levels of CD4 percentage. Co-trimoxazole is administered once daily on every day of the week. The recommended approximate dosages are listed in Table IV.

In a child who cannot tolerate co-trimoxazole or where co-trimoxazole is contraindicated the alternative is to use dapsone 2 mg/kg once daily (up to a maximum of 100 mg/day).

Co-trimoxazole prophylaxis is recommended for:

- all HIV-exposed infants starting at 4 - 6 weeks of age and continued until HIV infection can be reliably excluded
- breastfed HIV-exposed children at any age until infection can be excluded 6 weeks after cessation of breastfeeding
- children above 1 year of age who are symptomatic (WHO stages II, III, IV) or with CD4% below 25%
- protection against invasive bacterial disease, *Streptococcus pneumoniae*, toxoplasmosis and non-typhoid *Salmonella*.

Co-trimoxazole prophylaxis must be seen as lifesaving and must form the basis of standard care in HIV-infected children.

Immunisation of children with HIV disease

Children with HIV disease are more vulnerable to severe, recurrent or unusual infections by vaccine-preventable pathogens. While it is recognised that in this group of patients responses to immunisation may be suboptimal, routine immunisation is considered to be both safe and beneficial.⁷ Immunisations should generally be offered early before the onset of HIV-induced immune attrition.

In areas where tuberculosis is endemic, the recommendation is that all newborn babies, irrespective of HIV exposure, must be routinely immunised with the Bacille Calmette-Guérin (BCG) vaccine. The risk for developing BCG-related complications exists,⁸ but giving BCG immediately after birth minimises this risk. Theoretical

Table II. WHO paediatric staging of HIV/AIDS⁴

Stage	Symptoms
Stage I	<ul style="list-style-type: none"> • Asymptomatic
Stage II	<ul style="list-style-type: none"> • Persistent generalised lymphadenopathy (PGL) • Unexplained persistent hepatosplenomegaly • Papular pruritic eruptions • Extensive wart virus infection • Extensive molluscum contagiosum • Fungal nail infections • Recurrent oral ulcerations • Unexplained persistent parotid enlargement • Lineal gingival erythema • Herpes zoster
Stage III	<ul style="list-style-type: none"> • Recurrent or chronic upper respiratory infections (otitis media, otorrhoea, sinusitis or tonsillitis) • Unexplained moderate malnutrition not adequately responding to standard therapy • Unexplained persistent diarrhoea (14 days or more) • Unexplained persistent fever (above 37.5° C intermittent or constant, for longer than 1 month) • Persistent oral candidiasis (after first 6 - 8 weeks of life) • Oral hairy leukoplakia • Acute necrotising ulcerative gingivitis/periodontitis • Lymph node tuberculosis • Pulmonary tuberculosis • Severe recurrent bacterial pneumonia • Symptomatic lymphoid interstitial pneumonitis • Chronic HIV-associated lung disease including bronchiectasis • Unexplained anaemia (< 8.g/dl), neutropenia (< 0.5 x 10⁹/l), and/or chronic thrombocytopenia (< 50 x 10⁹/l)
Stage IV	<ul style="list-style-type: none"> • 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 or meningitis but excluding pneumonia) • Chronic herpes simplex infection (orolabial or cutaneous of more than 1 month's duration or visceral at any site) • Extrapulmonary tuberculosis • Kaposi's sarcoma • Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) • Central nervous system toxoplasmosis (after 1 month of life) • HIV encephalopathy • Cytomegalovirus infection: retinitis or cytomegalovirus infection affecting another organ, with onset at age older than 1 month • Extrapulmonary cryptococcosis (including meningitis) • Disseminated endemic mycosis (extrapulmonary histoplasmosis, coccidiomycosis) • Chronic cryptosporidiosis • Chronic isosporiasis • Disseminated non-tuberculous mycobacterial infection • Cerebral or B-cell non-Hodgkin's lymphoma • Progressive multifocal leukoencephalopathy • Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

concerns that immunisations may accelerate the course of HIV infections are not supported by available data.⁹ The policy is that all children irrespective of HIV exposure or infection must be

immunised according to the national EPI guidelines. Pneumovax should be available, as a routine vaccine to all HIV-infected children because of the seriousness of pneumococcal infections.

Antiretroviral therapy in children with HIV disease

ART has only recently been available in public hospitals in South Africa, and health

Table III. Immunological classification based on total and % CD4 count

Immunological category	Age of child		
	< 12 months	1 - 5 years	6 - 12 years
	CD4/ μ l (%)	CD4/ μ l (%)	CD4/ μ l (%)
No evidence of suppression	$\geq 1\ 500$ (≥ 25)	$\geq 1\ 000$ (≥ 25)	≥ 500 (≥ 25)
Evidence of moderate suppression	750 - 1 499 (15 - 24)	500 - 999 (15 - 24)	200 - 499 (15 - 24)
Severe suppression	< 750 (< 15)	< 500 (< 15)	< 200 (< 15)

Table IV. Co-trimoxazole prophylaxis

Age	Approximate weight	Co-trimoxazole daily dose
6 weeks - 2 months	5 kg	2.5 ml
2 - 12 months	5 - 9.9 kg	5 ml
12 - 24 months	10 - 14.9 kg	7.5 ml
24 - 60 months	15 - 21.9 kg	10 ml or 1 tablet
> 60 months	> 22 kg	15 ml or 1½ tablets

care providers are still gaining experience in the provision of this to children. Children who qualify for ART must be referred timeously for appropriate treatment. ART has been shown to improve morbidity and age-related mortality from HIV infection and must be offered to all HIV infected children who are eligible according to national guidelines.

Conclusion

HIV and AIDS in children presents a major threat to their well-being. Every HIV-infected child has the right to comprehensive care and treatment and all health care providers need to be vigilant in identifying HIV-infected children early and to offer each individual child optimal care, including antiretroviral therapy where indicated.

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Persistent diarrhoea

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Persistent diarrhoea (PD) is defined by the World Health Organization as episodes of diarrhoea that last for 14 or more days.¹ The epidemiology and impact on mortality has been well described.² PD poses challenges for investigation and management because of the close association with malnutrition and increased vulnerability to infections. This association often makes it difficult to define the initiating event. It is therefore imperative that the care of infants with PD is directed at nutritional support while further investigations and management follow. This review highlights the basic

approach to PD of presumed infectious origin and describes selected non-infectious conditions. The purpose of the latter is to illustrate the principles of investigation that may broadly be guided by knowledge of the epidemiology of common conditions, dietary evaluation, timing of onset, and presence of extra-intestinal manifestations.

The reader is referred to the World Health Organization (WHO) manual (2005) for physicians and other senior health workers on the treatment of diarrhoea that provides guidelines for the basic approach to and management of PD.¹ These include initial resuscitation and correction of fluid and electrolyte impairments, initiation of a nutritious diet that may necessitate temporary reductions in lactose intake, micronutrient/mineral supplementation and, where appropriate, use of antibiotics for intestinal and extra-intestinal infections.

The majority of infants and young children in developing countries will benefit from the above approach without requiring invasive gastrointestinal investigations. An important addition to these guidelines, and a gap that has been addressed in the current WHO guidelines for the integrated management of childhood illness,³ would be that in regions of high HIV prevalence testing for HIV infection is warranted early in the course of management. HIV testing and staging allows timely initiation of antiretroviral therapy. The high prevalence of symptomatic HIV in children hospitalised with diarrhoea in South Africa supports this approach.⁴ The HIV epidemic has changed the epidemiology of PD in childhood. *Salmonella* spp.² and *Cryptosporidium parvum*^{2,5} have assumed increasing importance, but are difficult to eradicate. The HIV-infected child with prolonged or recurrent dysentery requires referral for evaluation of possible cytomegalovirus disease and rarer conditions such as Kaposi's sarcoma. The long-term goal should be to initiate antiretroviral therapy before the child reaches this advanced stage of HIV disease.

The challenge for health workers in our environment is the child who fails to respond to the guidelines described above and in whom basic investigations fail to reveal an aetiology. In these situations a detailed re-evaluation is warranted. This includes obtaining a history of antibiotics and other medications that cause gastrointestinal upset. This is crucial in an era where maintenance therapy is increasingly used for chronic conditions in paediatric practice. The impact on nutrition and quality of life

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will often determine the extent to which modifications of such treatment regimens are required.

While infectious and post-infectious causes are responsible for the majority of cases of PD globally and locally, an awareness of non-infectious causes is necessary, especially in communities with wide socioeconomic heterogeneity. The proportion of PD attributable to non-infectious causes assumes greater relevance and deserves attention in the setting where the usual risk factors for infectious diarrhoea and malnutrition are not apparent. Non-infectious causes of PD include among others, cow/soy milk protein intolerance, coeliac disease (gluten-sensitive enteropathy) and cystic fibrosis (secondary to pancreatic impairment). The latter are more likely in children of Caucasian origin.

Cow's milk or formula protein intolerance presents within the first 6 months of life, usually with persistent and/or blood-tinged stools and anaemia. A temporal association should be sought with introduction of formula. This entity may be under-recognised in environments where dietary iron deficiency is common. Infants with anaemia and PD should have stools assessed for occult blood to screen for this condition prior to dietary manipulation or biopsy. It is worth noting that the RAST test may be negative in these infants.⁶

In older children coeliac disease should be considered after a careful search for other associated systemic manifestations such as anaemia and dermatitis herpetiformis.⁷ Besides serological tests small-intestinal biopsy is warranted for this condition, with assessment of response to dietary manipulation. Extensive dietary restrictions without any investigations must be avoided. Other conditions that warrant endoscopic biopsies include the congenital causes, autoimmune enteropathy and inflammatory bowel disease.

In conditions such as coeliac disease, cystic fibrosis, inflammatory bowel disease and primary immunodeficiency, other systemic manifestations provide clues to the necessity for referral and diagnostic investigations.⁷ Unlike the syndromic management of PD these conditions warrant detailed investigations in tertiary centres before definitive treatment is instituted.

Imaging studies are rarely indicated in the investigation of PD. However, in young infants with recurrent unexplained episodes despite appropriate basic management one should consider rare anatomical causes such as intestinal

malrotation or chronic small-intestinal obstruction or pseudo-obstruction. Upper gastrointestinal contrast studies with small-bowel follow-through are best conducted in centres with expertise in interpretation of these investigations.

The entity of toddler's diarrhoea is frequently considered in ambulatory care of infants. It should be stressed that this entity should only be considered in the infant who is not having any complications from diarrhoea, that is, there is no evidence of growth failure or fluid and electrolyte imbalance. The stools are not voluminous and may contain undigested food particles but never any blood.

In summary, the contribution of infectious causes, HIV and socioeconomic risk factors to PD makes most cases amenable to existing management guidelines. The child who fails to respond or has symptoms at an age outside of the peak prevalence period or without any of the usual risk factors should be referred for further evaluation.

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Disability – South Africa's forgotten children

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In 1995 South Africa adopted the Convention of the Rights of the Child. Article 23 of the Convention states: 'A mentally or physically disabled child should enjoy a full and decent life, in conditions that ensure dignity, promote self reliance and facilitate the child's active participation in the community.'

Based on research done here in South Africa, I hope to illustrate not only the burden of disease of children with disabilities (in especially) rural communities, but also how much still needs to be done to achieve the objects of the Conventions of the Right of the (disabled) child. Until recently the main issues increasing paediatric mortality and morbidity included infections and malnutrition. Even though these are still prevalent today, issues regarding disabilities (especially intellectual disability) have begun to emerge and demand due consideration.

Prevalence of disability

The prevalence of childhood disability varies, according to local definition of disability and the various environmental factors, from 5% to 17% of the population. According to the last census, there are about 200 000 disabled children in South Africa under the age of 10, and another 300 000 between 10 and 20 years of age, representing between 2% and 3% of the population in these age groups (Census 2001). More than likely this represents an underestimation of the magnitude of the burden of disability. In these age groups physical, intellectual and hearing disabilities are the most prevalent.

In an epidemiological study of 6 692 children aged 2 - 9 years in the Bushbuckridge district a minimum prevalence of 35.6 per 1 000 of the childhood population was observed.¹ The majority had mild intellectual disability (GIQ 56 - 80) and the ratio of mild to severe was 4.5:1. Epilepsy (15.5%) and cerebral palsy (8.4%) were the most commonly associated disabilities.² The prevalence in this study was similar to that found in another South African study in the Western Cape.²

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In a study in KwaZulu-Natal, using a similar epidemiological approach, the prevalence of disabilities was found to be 60 per 1 000 children overall, 28 per 1 000 for motor disability, 20 per 1 000 for hearing disability, 9 per 1 000 for seizure disorders and 2 per 1 000 had visual deficits.³ The higher prevalence of disability may be due to the inclusion of perceptual disabilities.

In the Bushbuckridge study at least 291 children in this small isolated rural community in South Africa had at least 1 or more of the 5 researched disabilities. It is most likely that these data broadly represent the prevalence and plight of children with disabilities in most rural areas in South Africa.

The majority of these children were receiving no, inadequate or inappropriate intervention. These children's disabilities would therefore result in unnecessary life-long handicap.

The case for early detection and intervention

The importance of primary prevention of disability is universally accepted, even in the absence of an identified aetiology. Secondary prevention implies early identification of disability and intervention. Both the need for early diagnosis of abnormal development and the effectiveness of early intervention for actual or potential developmental disorders are treated with skepticism by many professionals. Some have a relatively hopeless or fatalistic attitude toward major disabilities (such as significant mental retardation). Relatively uninformed rural communities have even less insight into strategies that should be available to help

their children with special needs, and therefore they would be less inclined to lobby for or even demand services and relevant interventions for their disabled children.

Another misguided notion is that children with milder developmental delay (such as early language defects) will 'outgrow' their problems. Both of these attitudes delay the treatment of young children and may diminish the eventual outcome of the intervention programmes.

It is widely accepted that early experience influences all areas of development. There may be critical periods for the achievement of certain skills (usually before the age of 4 years) and an inability to achieve these may lead to permanent deficits. Failure to provide early stimulation may not only lead to a discontinuation of normal development, but may cause actual atrophy of sensory ability (e.g. amblyopia associated with strabismus). Furthermore, failure to remediate one disability may multiply its effects in other developmental areas, and may produce secondary emotional handicaps. Parents also need a great deal of support, encouragement and knowledge to manage their children with disabilities. The prognosis for the child is often directly linked to the parents' support, commitment and enthusiasm.

Identification of children with developmental disorders

A comprehensive paper is already published on this topic,⁴ but a simple approach is to consider 5 questions when a child is evaluated within the health system:

1. Can the child see?
2. Can the child hear?
3. Is language development adequate for age?
4. Could the child have motor delay?
5. Could the child have cognitive delay?

Some of these milestones have already been incorporated into the Road-to-Health charts. This is a step in the right direction. It behoves all health workers who come into contact with children to be alert regarding developmental issues. Perhaps developmental milestones should be included in the Integrated Management of Childhood Illnesses (IMCI) also.

Unfortunately it is not only the identification of these children that is a problem, but also the services available for support, intervention and rehabilitation. It is ethically questionable to screen for developmental delay and disabilities if there is no recourse to any intervention. It is in this area particularly that our children are poorly served. Services for children, beyond diagnosis, are obviously inadequate.

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single suture

Treatments for COPD do not appear to prolong survival

Treatments for chronic obstructive pulmonary disease (COPD) give symptomatic relief, but it's hard to show that they actually save lives. Even more data are needed from even larger trials before frustrated specialists can tell if treatment is prolonging lives. The latest, supposedly definitive, trial recently ran into problems. The trial was large ($N = 6\ 112$) and compared 4 treatments (a long-acting beta-agonist, an inhaled corticosteroid, both of these combined, and neither of these) for 3 years in patients with COPD. Four out of 10 patients dropped out of the trial, so the findings were borderline and difficult to interpret. Combination therapy saved more lives than the placebo, but only just, and the difference was not significant in the strict statistical sense. Neither of the treatments alone reduced mortality compared with placebo.

So where do these results leave patients? Until there is better evidence, combined treatment with an inhaled steroid and a long-acting beta-agonist should probably be reserved for people with severe disease. Others should stick with a long-acting beta-agonist alone. Combined treatment reduced exacerbations, improved symptoms, and protected lung function in this trial. But patients given an inhaled steroid (alone or in combination) had a significantly increased risk of pneumonia.

N Engl J Med 2007; 356: 775-789.