Care and Treatment of HIV-Infected Children in Africa

Issues and Challenges at the District Hospital Level

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Abstract: More than 90% of pediatric HIV infection occurs in sub-Saharan Africa and 75% of these children currently die before their fifth birthday. Most HIV-infected children in Africa rely on district hospitals for HIV treatment, but insufficient attention has been paid to improving HIV/AIDS care at this level. Considerable confusion exists about optimal use of combination antiretroviral treatment, prophylaxis for opportunistic infections and other rational healthcare interventions that can greatly improve the quality of life for these children. A simple and inexpensive infant HIV diagnostic assay and alternative laboratory markers of pediatric HIV disease progression would be highly beneficial. Routine anthropometric and neurodevelopmental assessments could help guide initiation and monitoring of antiretroviral therapy. Even in the absence of antiretroviral therapy, interventions such as immunizations, provision of micronutrients and nutrition counseling, prevention and treatment of opportunistic as well as endemic infections (such as helminths and malaria) can substantially reduce pediatric HIV-related morbidity and mortality. The need for pain relief, palliative care, counseling and emotional support is often underestimated. Surmounting the sense of hopelessness by providing district healthcare workers with training in basic pediatric HIV/AIDS care is an urgent priority.

Key Words: pediatric, HIV/AIDS, management, district hospitals, Africa

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Worldwide, approximately 3.2 million children live with HIV-1 infection. This number increases by an estimated 1500 new infections daily. More than 90% of HIV-infected children live in developing countries, especially in sub-Saharan Africa.[1,2] These are the locations with limited resources, staff, skills or technologies available to provide optimal care and treatment of HIV-infected patients. Fewer than 25% of the HIV-infected children born in Africa reach 5 years of age compared with greater than 75% of their counterparts in resource-rich settings.[3] At a pediatric referral hospital in Botswana, the percentage of childhood deaths attributable to HIV infection increased from 10% in 1990 to 78% by the end of the decade, coincident with a rise in HIV infection in the general population.[4] Pneumonia, diarrhea and malnutrition are the most common, but often preventable, causes of childhood death and more so in HIV-infected than in HIV-uninfected children.[5,6]

Even if programs for the prevention of mother-to-child transmission of HIV could be scaled up successfully, the need to improve HIV/AIDS care, treatment and counseling for infected children would remain critically important. Although the AIDS epidemic continues to exact a terrible toll in much of sub-Saharan Africa, industrialized and middeveloped countries such as Brazil and Thailand have successfully reduced HIV-related morbidity and mortality in children with widespread use of combination antiretroviral therapy (ART). In a pilot program of ART for children in Ivory Coast, starting ART caused a significant decrease in the incidence of pneumonia and acute diarrhea in children less than 6 years old. Provided treatment was started at a CD4-percent above 5, 98% of the children were still alive 24 months after initiation of highly active antiretroviral therapy.[7]

Currently, fewer than 5% of HIV-infected individuals living in Africa receive ART. The percentage of children among them is not well documented but is believed to be small.[2] In Uganda in 2002, only 2% (200) of all patients receiving ART were children and 60% of them were treated at one urban hospital. Multiple obstacles prevent children from receiving treatment: pediatric formulations are not optimal and widely available; lack of policies, protocols and knowledge; but also fear for needlestick injuries and feelings of fatalism and hopelessness toward treating HIV-infected children.[8]

Presently, most pediatric ART programs are concentrated in third-line health facilities in African capitals. Little attention has been given to the distinct role that each level of the healthcare system could fulfill. For the majority of Afri-

cans, the governmental healthcare system is the only accessible and affordable system. Although there are considerable variations in structure between and within African countries, it is usually organized around 3 levels of health care. First-line or primary healthcare centers are traditionally within walking distance, have a limited selection of medications available, may be able to perform basic laboratory tests (eg, rapid tests) and are run by nurses or, in resource-constrained settings, only a nurse aid. Patients with medical problems that cannot be managed at this level are referred to the second-line or district hospitals often by public transport at own expense. District hospitals (one per district) use more nurses and usually have one or more general practice physicians who may perform a limited set of surgical interventions (eg, cesarean sections). A wider array of medications is available. Radiology and more laboratory tests (eg, full blood count) can be performed. Complicated cases are referred to the third-line or tertiary health facilities (usually one per province) generally by ambulance. Tertiary hospitals use both general practice and specialist physicians. There is a greater variety of medications. More sophisticated laboratory tests (eg, CD4 count) can be performed. If more HIV-infected children are to be treated, healthcare teams led by general practitioners at district hospitals in collaboration with primary healthcare centers (including home-based and community health care) should take responsibility for general care, initiation of the first treatment regimen, follow up and toxicity monitoring for large numbers of children. Healthcare teams at tertiary hospitals led by pediatricians could then focus on complex issues, including toxicity management, subsequent ART regimens, sophisticated laboratory evaluations and drug resistance monitoring as well as serve as training centers.

This review article intends to strengthen the position of healthcare workers of district hospitals by summarizing the rationale of pediatric HIV care and treatment in this setting and identifying current gaps in knowledge.

DIAGNOSIS OF HIV/AIDS IN CHILDREN

Diagnosing HIV infection in children can be difficult and costly so efforts have been made to study the accuracy of several different clinical case definitions to identify HIV-infected children in the absence of HIV testing (Table 1). Diversity in study design, screening strategy and study characteristics limit direct comparison. Clinical case definitions can be useful to identify children at risk and are applied by the integrated management of childhood illnesses. However, especially for young infants, they fail to replace laboratory tests.[9] Treating children according to their "perceived" HIV status may cause mismanagement and neglect of medical problems or may defer interventions to when their biggest potential has already passed (Fig. 1). Operational research should determine whether a policy to integrate routine offering of a free HIV test at 6 to 14 weeks of age, integrated in the immunization schedule, would be feasible and acceptable to caregivers. A record on the growth chart, as recently introduced by the Zimbabwean government, could greatly facilitate integration of pediatric HIV care in general under 5 clinics and pediatric wards (Fig. 2).

Infant HIV Screening. Fewer than 10% of African women are currently believed to have access to a program for the prevention of HIV transmission from mother to child and few have access to ART for their own health.[2] Infant follow up and early determination of infant infection status should be an integral part of these programs. Early HIV testing could greatly improve pediatric HIV care at only marginal additional cost.[10]

At district hospitals, a rapid test could be performed on capillary blood from infants above 6 weeks old to identify HIV-affected children needing special follow up. In case of a positive rapid test, the remaining sample could be stored on filter paper and sent by postal mail or courier to a tertiary laboratory.[11] Depending on the capacity of this laboratory and the national guidelines, HIV DNA or RNA polymerase chain reaction or the ultrasensitive p24 antigen assay could be performed.[11–16] Results from CD4 measurements could be used for additional help. Operational research around the use of diagnostic assays is needed to allow timely inclusion in ART programs for many more children.

HIV Screening in Older Children. Rapid tests can be used reliably to diagnose HIV infection in older children once maternal antibody is no longer detectable and the child is no longer at risk for acquiring infection through breastfeeding. This could be favored by the substantially higher serum immunoglobulin concentration in African children than Western children.[17] Timing of seroreversion can vary by type of antibody test and population.[18] Seroconversion resulting from postnatal HIV infection can be expected up to 6 months but usually within 6 weeks after cessation of breastfeeding.[19]

At district hospitals, parallel enzyme immunoassays can be replaced by serial rapid tests performed on capillary blood stored in EDTA tubes. This reduces the cost of HIV screening and allows same-day receipt of test results. The use of Glucolets could simplify phlebotomy while reducing the risk of needlestick injuries and procedural pain. Unfortunately, there are still many missed opportunities for HIV testing in children more than 18 months old despite it being much easier and less costly than infant testing.[11,20]

MARKERS OF PEDIATRIC HIV DISEASE PROGRESSION

Considerable effort has been made to find markers identifying children at increased risk for accelerated progression to AIDS and death for initiation and monitoring of ART.

Routine Anthropometry. Perinatally acquired HIV infection is associated with progressive growth retardation, possibly starting before birth.[21] Birth weight and growth curves for weight-for-age and height-for-age appear to be significantly different for HIV-infected and perinatally exposed HIV-uninfected children even after exclusion of rapid progressors.[22] The mean head circumference is more often below the third percentile for HIV-infected children (40% versus 22%).[23] Weight-for-age is the best indicator for disease progression and survival.[24–26]

Among adults in the United States, weight loss during the preceding 6 months is clearly correlated with disease progression and mortality.[27] For children, growth faltering

TABLE 1. Evaluation of World Health Organization (WHO) and Modified Clinical Case Definitions in African Children

Reference	Country and Timing of Research	Study Population	Age Group	n	HIV (%)	Standard Test	WHO Definition	
							Sensitivity (%)	Specificity (%)
Müller O, Musoke P, Sen G, et al[94]	Uganda, 1985–1989	Immune compromising conditions; chart review for outpatients	0–9 y	422	49	EIA	56	67
		Chart review for inpatients		89	51		49	64
Colebunders R, Greenberg A, Nguyen-Dinh P, et al[95]	RDCongo, 1986	Inpatients	1 m–12 y	163	13	EIA, WB	35	87
Msellati P, Lepage P, Dabis F, et al[96]	Rwanda, 1990	Inpatients	15 m–18 y	465	15	EIA, WB	34	94
Vetter KM, Djomand G, Zadi F, et al[97,98]	Ivory Coast, 1991–1992	Inpatients in one of the 3 university hospitals	28d–15 y	4443	8	EIA, WB	19	98
Jeena PM, Coovadia H, Chrystal V[99]	South Africa, 1993– 1994	Admissions to intensive care unit for pneumonia	1–18 m	159	23	EIA, p-24 Ag	77	84
Bakaki P, Kayita J, Moura Machado JE, et al[23]	Uganda, 1994– 1996	Admissions for sepsis and suspected HIV	3d–18 m	708	19	EIA, PCR	28	98
Yeung S, Wilkinson D, Escott S, et al[100]	South Africa, 1996– 1997	Inpatients	0–5 y	281	26	EIA, Ig3, PCR, p-24 Ag	22	96
Pediatric Studies Comparing WHO Clinical Case Definition Against a Modified Definition (M)							WHO/M Definition	
							Sensitivity (%)	Specificity (%)
Lepage P, van de Perre P, Dabis F, et al[101]	Rwanda, 1986	Inpatients	1 m–14 y	221	15	EIA, WB	41/47	92/95
Otieno FA, Mbori-Ngacha DA, Wafula EM, et al[102] (Nairobi definition)	Kenya, 1992	Inpatients not on immune- suppressing therapy	0–12 y	156	23	EIA, CD4/CD8 ratio	60/80	94/79
Chintu C, Malek A, Nyumbu M, et al[103]	Zambia, 1993	Inpatients	>6 m	134	22	Rapid tests, EIA, WB	69/79	64/91
van Gend CL, Haadsma ML, Sauer PJJ, et al[104]	South Africa, 2000	Inpatients in medical or intensive care unit	1m–13 y	222	31	EIA, p-24 Ag	14/63	97/96
Validation of this modified definition by Joubert G, Schoeman CJ, Bester CJ[105]	2002			202	43		/76	/73
Horwood C, Liebeschuetz S, Blaauw D, et al[106] (IMCI/ HIV algorithm)	South Africa, 2001	Pediatric outpatients of a district hospital	2–59 m	690	29	EIA, Vl	8/67	99/81

Excluding studies with a sample size of less than 100.[107,108]

EIA indicates enzyme immunoassay; WB, whole blood; PCR, polymerase chain reaction.

seems more important than manifest weight loss. In Ivory Coast, catchup growth after 18 months of ART was significantly improved for weight-for-age but not for height-for-age.[7] Whether growth retardation is an aggravating factor or rather a consequence (and thus possible marker) of pediatric HIV disease progression in African children needs further investigation.[25] Severe malnutrition indicates a category C (Centers for Disease Control and Prevention) or 4 (World Health Organization) that justifies initiation of ART. Once ART has been started, progressive growth retardation indicates treatment failure and this can easily be monitored at district hospital level.[1,22,28]

Routine Neurodevelopmental Assessments. Neurodevelopmental delay can be the first presenting symptom of HIV infection in young children. Verbal deficit, hyperactivity and irritability are other common findings, all resulting in poor school performance.

Even in seemingly asymptomatic children, HIV can affect portions of the central nervous system that are mediating motor and spatial memory development.[29] Between 15% and 40% (depending on age and clinical stage) of the neurologic examinations of HIV-infected children are abnormal compared with less than 5% in uninfected children.[30] By the age of 12 months, 30% of HIV-infected Ugandan children had motor abnormalities (compared with 11% for seroreverters and 5% for HIV-unexposed children) and 26% had cognitive abnormalities (compared with 6% for seroreverters or HIV-unexposed children).[29] Hypotonia is also more common in HIV-infected children.[23]

HIV encephalopathy, loss of developmental milestones and neurologic disease indicate a category C (Centers for Disease Control and Prevention) or 4 (World Health Organization) justifying initiation of ART. Progressive developmental delay and neurologic symptoms despite ART indicate treatment failure. More research is warranted to determine which selection of key questions about the development of the child and simplified neurologic tests for district hospital level would be the best choice to make a (differential)

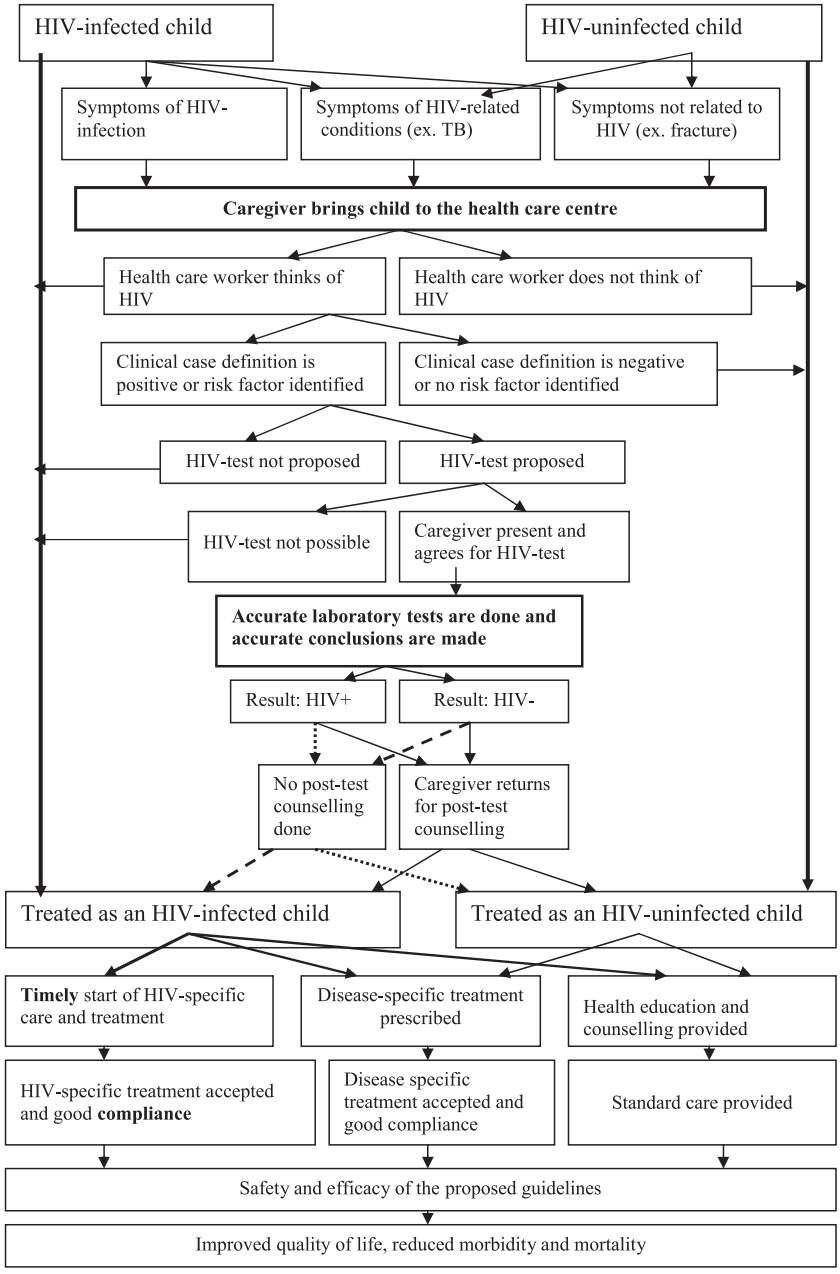

FIGURE 1. Model for operational analysis of routine pediatric care in relationship to HIV/AIDS care.

diagnosis for neurodevelopmental delay and to assess the recovery of mental functions after starting ART.[1,31]

Viral Loads. Viral loads, an age-dependent marker of viral progression, reach much higher values in African infants than in their Western counterparts.[32] The prognostic value of viral load appears to be weaker than CD4 in younger children (particularly infants) and viral load is probably unable to identify children less than 12 months old with the lowest risk of HIV disease progression.[33] It seems to be the most important predictor of growth failure and cognitive decline.[34] Inappropriate specimen storage and delays in specimen processing can lead to viral degradation. This limits access for remote district hospitals unless test performance on samples stored on filter paper can be made reliable.

CD4 Counts/CD4 Percents. CD4 counts differ by ethnic group, age, gender, exercise and comorbid medical conditions. There is also diurnal variation and effect of immunization.[32] Ideally, CD4 count and CD4% should be considered. CD4% has the strongest prognostic value for disease progression.[33,35] CD4% can be estimated by dividing the absolute CD4 count by the total lymphocyte count obtained from a full blood count, but in many African hospitals, even CD4 count is unavailable. Further scaling up of pediatric ART programs would greatly benefit from increased access to CD4 counts or the introduction of alternative markers.

Alternative Markers. Among HIV-infected children in industrialized countries, total lymphocyte count and serum albumin are independent predictors of mortality.[36] The use of

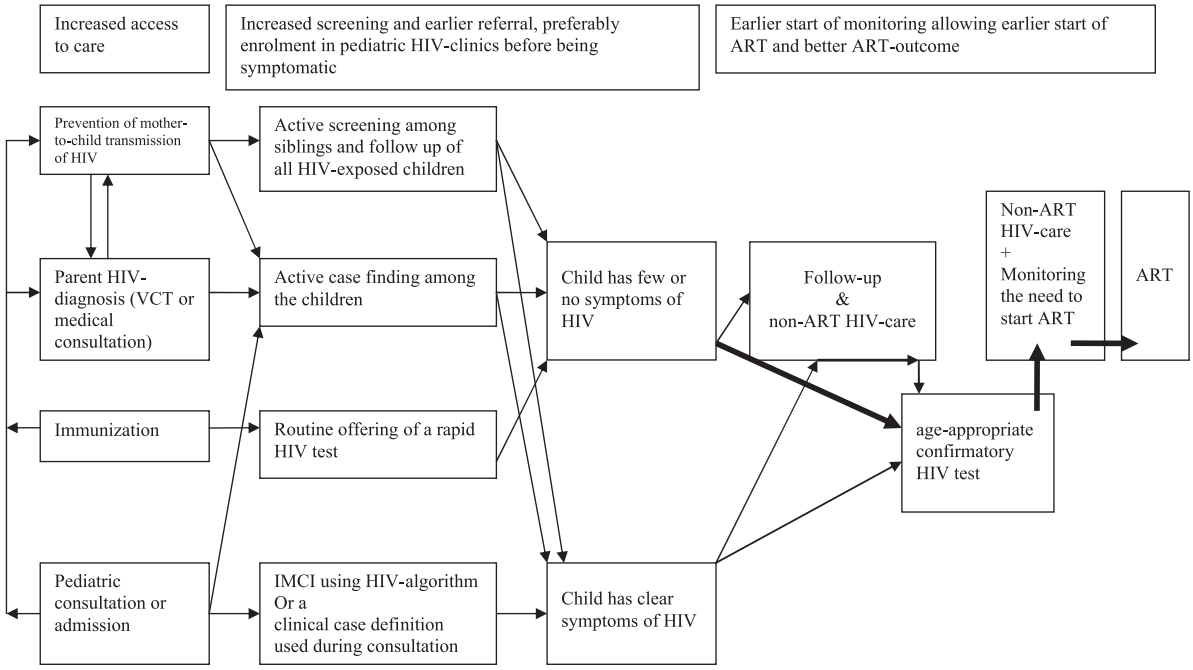

FIGURE 2. Proposed algorithm for increased access to pediatric HIV/AIDS care and ART.

these markers for initiation and monitoring of ART at the level of an African district hospital where malnutrition and coinfections are common confounders needs further research. Although the ultrasensitive p24 antigen assay seems to be a promising and inexpensive alternative for viral load tests, further validation is necessary.[37]

CRITICAL (NONANTIRETROVIRAL THERAPY) INTERVENTIONS FOR HIV-INFECTED CHILDREN

Immunizations

Children with asymptomatic HIV infection should receive all 6 vaccines of the Expanded Programme on Immunizations: Bacille Calmette-Guérin, polio, diphtheria, pertussis, tetanus and measles. HIV-infected children should receive an additional measles vaccine at 6 months of age. General recommendations advise deferring yellow fever vaccine and Bacille Calmette-Guérin in symptomatic children.[38]

The 9-valent pneumococcal conjugate vaccine is a promising candidate for expansion of Expanded Programme on Immunizations. Invasive pneumococcal disease is 40 times more common in South African HIV-infected children than in their uninfected counterparts (in the United States and Europe, this difference is only 5–10 times).[39] The vaccine prevents 65% of invasive pneumococcal disease in HIV-infected children in South Africa.[40] *Haemophilus influenzae* vaccine seems to have a lower efficacy in HIV-infected children (44%).[41] Boosting increased access to and possible expansion of Expanded Programme on Immunizations for the specific benefit of HIV-infected children, although benefiting also HIV-uninfected children, is justifiable.

Micronutrient Supplementation and Nutrition Counseling

Micronutrient deficiencies are common in HIV-infected children. For some of these nutrients (eg, albumin, vitamins E and B12), there appears to be a relationship between stage of HIV disease and the degree of deficiency.[42,43] Quarterly vitamin A supplements in Tanzanian HIV-infected children reduced all-cause mortality by 63% and diarrhea-related mortality by 92%.[44] This effect remained significant after adjustment for age and nutritional status. Similarly, a South African study of vitamin A supplementation reported a 31% reduction in overall morbidity and a greater reduction in the incidence of diarrhea among HIV-infected (49%) than in HIV-uninfected (29%) children.[45] Another clinical trial suggested a positive effect on linear growth and weight gain in HIV-infected infants and children with chronic diarrhea.[44] A broad consensus about the safety of providing vitamin A supplements to children has been reached. Continued availability of capsules of 50,000 IU and 100,000 IU would facilitate the promotion of more widespread implementation of this guideline.

Several studies point to a beneficial effect of other vitamin and mineral supplements, but there is not yet consensus about the preferred combination and amount of each essential nutrient. Whether zinc supplements are beneficial and iron supplements harmful for HIV-infected children remains under investigation.[46,47] Availability of a "combined" vitamin preparation or a fortified porridge would simplify treatment and reduce pill count.

Nutritional counseling alone can result in increased energy intake among patients with HIV/AIDS.[48] In the early stages of HIV infection, counseling should emphasize in-

creasing protein and energy intake (eg, by mixing oil, eggs or milk powder through the meal). In case the caregiver lacks the physical strength or means to prepare calorie-dense meals, nutritional supplements could be helpful.[47–49] Once HIV infection is more advanced, malabsorption becomes the determining factor and counseling should aim to enhance digestion and absorption.[47,50] Loss of developmental feeding skills, interference with effects of intercurrent illnesses, medication and psychosocial problems should be assessed routinely.[50] Nutritional interventions may be able to restore intestinal absorption and increase CD4 cell count (eg, fish oil supplements, fortified porridge).[51] Clinical trials to assess the potential efficacy and safety of nutritional supplements and nutritional counseling at the grassroots level for African HIV-infected children are necessary to reduce confusion and unnecessary investments. Even after introduction of ART, nutritional counseling remains an important part of the care plan.[52] Therefore, sufficient attention should be given to training in nutritional counseling of healthcare workers at the district hospital level.

Breastfeeding Counseling for HIV-Exposed Infants

Mixed feeding before 3 months of age is associated with a nearly double risk for HIV transmission than exclusive breastfeeding. Breastfeeding after 6 months of age is associated with a more than doubling in the risk of HIV transmission.[53,54] Initiatives to reduce the infectiousness of breast milk such as Pretoria Pasteurization are too impractical or culturally unacceptable for many resource-limited settings, whereas complete avoidance of breastfeeding through replacement feeding is often not affordable, feasible, acceptable, sustainable or safe.[55] Other maternal and/or infant biomedical interventions are currently under investigation.[56]

The gap between nutritional guidelines and actual practice is often quite wide. The potential cumulative positive impact on the child's health of every individualized infant feeding counseling session guided by what is possible for this particular mother, or material for information, education and communication provided by a district healthcare worker cannot be underestimated.[54,57]

Prevention and Treatment of Endemic Infections

Helminthic Infections. Some investigators have argued that the widespread prevalence of helminthic infections in Africa might offer an explanation for the higher viral loads and more rapid spread of HIV in Africa. In Ethiopian children, viral load correlated with egg burden and number of helminthic infections.[58,59] Quarterly treatment of worms made 70% of the children helminth-free and resulted in a significant decrease in viral load within 6 months. The latter effect of antiparasitic drugs appears to be species-dependent.[58] Regular antihelminthic treatment can be provided at the district hospital level and may decrease the incidence of diarrhea by 30% to 50% but is often neglected.[60]

Malaria. HIV infection is a major problem in many malaria-endemic areas in Africa. The median viral load can be as much as 7 times higher in HIV-infected adults with malaria and can be reduced with successful antimalarial therapy.[61] Lower CD4 counts are associated with higher malaria parasitemia and an increased frequency of clinical malaria. Whether malaria treatment or prophylaxis could slow pediatric HIV disease progression is unknown.[62]

Maternal placental malaria in HIV-infected patients is associated with a higher risk for infant death than the risk for infant death in case of placental malaria without HIV infection or when the mother is infected with HIV but does not have malaria.[63] Even after adjustment for maternal viral load, the risk for HIV transmission from mother to child in rural Uganda was substantially higher in the case of malaria coinfection, but a study from Kisumu, Kenya, failed to demonstrate a consistent increased risk of HIV transmission.[64,65] Further research will reveal how much district hospital staff can influence mother-to-child transmission of HIV, child mortality and morbidity by promoting the use of bed nets for mother and child (which can prevent up to 7% of global child mortality) and prescribing cotrimoxazole prophylaxis or intermittent malaria prophylaxis with sulfadoxine pyrimethamine during pregnancy.[5]

Prevention and Treatment of Opportunistic Infections

Many opportunistic infections are not easily diagnosed at the level of a rural district hospital such as *Mycobacterium avium intracellulare* and *Cytomegalovirus*, which have a lower prevalence among African children.[66] Others such as *Cryptococcus* can be diagnosed (by India ink staining of cerebrospinal fluid) but cannot necessarily be treated at the level of a district hospital.[67] Lymphoid interstitial pneumonia can be confused with tuberculosis and although 4 to 6 weeks of corticosteroids can be given at a district hospital in case of severe dyspnea, cyanosis or oxygen saturation below 90%, it is not yet common practice.[68] Availability of ART could greatly reduce the risk of opportunistic infections. In this article, only the 3 most common ones are discussed.

Pneumocystis jirovicii. The incidence of *Pneumocystis carinii* pneumonia (PCP, currently *P. jirovicii*), in African HIV-infected children is comparable to that in industrialized countries and much higher than among adults. The case-fatality rate (40–87%) and peak incidence (3–6 months of age) of PCP are comparable to those in industrialized countries.[4,69–73]

There is a consensus about the need to start PCP prophylaxis at 6 weeks of age, even in areas with high levels of bacterial resistance[74] (Table 2). Early infant testing and widespread administration of ART in the United States allowed earlier cessation of cotrimoxazole in HIV-affected children (usually around 4 months old) and HIV-infected children who have obtained immune restoration under ART.[73] At African district hospitals, increased attention for HIV testing could also allow earlier cessation of PCP prophylaxis in many HIV-affected children, but it is less clear whether PCP prophylaxis in HIV-infected children with immune restoration under ART could be discontinued safely.[75]

Widespread cotrimoxazole prophylaxis has the potential to increase antibiotic resistance of *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Enterobacteriaceae* and pos-

TABLE 2. Studies of the Prevalence of *Pneumocystis jirovecii* Pneumonia in Children in Africa

Reference	Country and Timing of Research	Study Population	Age	n	HIV (%)	Arguments in Favor of PCP Prophylaxis
Lucas SB, Peacock CS, Hounnou A, et al[4]	Ivory Coast, 1991–1992	Inhospital deaths	3 m–12 y	155	50	PCP found in 31% of HIV-infected versus 0% of HIV-uninfected children
Graham SM, Mtitimila EI, Kamanga HS, et al[72]	Malawi, 1996	Admissions for severe pneumonia	2 m–5 y	150	62	PCP found in 11% of HIV-infected versus 0% of HIV-uninfected children
Ansari NA, Kombe AH, Kenyon TA, et al[4]	Botswana, 1997–1998	Inhospital deaths	1 m–13 y	250	68	PCP only found in HIV-infected children (18%) and responsible for 48% of the mortality in this group
Zar HJ, Dechaboon A, Hanslo D, et al[70]	South Africa, 1998	Admissions to the intensive care unit for pneumonia with confirmed HIV	3–23 m	151	100	PCP found in 15% of children without, versus 2% of children on PCP prophylaxis. Forty-seven percent of children died in hospital as a result of PCP
Ruffini DD, Madhi SA[71]	South Africa, 1999	Admissions for severe pneumonia with confirmed HIV	2–24 m	105	100	*P. jirovecii* cysts found in 49% of the cases PCP in 20% of HIV-infected hospitalized children with severe pneumonia
Chintu C, Mudenda V, Lucas S, et al[69]	Zambia, 1997–2000	Inpatient deaths resulting from respiratory disease	1 m–16 y	264	68	HIV-infected children at 5 times higher chance of getting PCP (95% confidence interval: 2.12–15.68, $P = 0.0001$)

sibly *Plasmodium falciparum* (resistance to sulfadoxine/pyrimethamine).[76–79] Earlier cessation of PCP prophylaxis in HIV-exposed, uninfected children might reduce the risk for such resistance.[79]

Timely recognition of PCP is quite difficult in resource-limited settings. The long-term outcome of PCP, in the absence of ART, is poor.[80] District hospital staff may thus greatly influence early HIV-related mortality by improving adherence to PCP prophylaxis through health education of the mother and providing a more extensive care to HIV-exposed children.

Tuberculosis. In South Africa, tuberculosis (TB) is 10 times more common in HIV-infected than in HIV-uninfected pregnant women and causes as much as 15% of maternal mortality. As a result, the incidence of TB in neonates and infants more than doubled in recent years.[81] Screening pregnant women for TB symptoms can be performed routinely at the district hospital level as an integral part of programs for the prevention of mother-to-child transmission of HIV.[82]

Approximately 80% of children in close contact with a patient with TB become infected with TB and 25% to 40% of them develop active TB. This causes a higher mortality in HIV-infected children (eg, 24% versus 4% in Ivory Coast), especially if the CD4% is below 10. In the absence of a simple, noninvasive and affordable assay to exclude pediatric TB, routine TB prophylaxis using isoniazid only cannot yet be recommended in HIV-infected children.[81,83,84] Coinfections may seriously complicate TB diagnosis and treatment as a result of drug interactions between TB treatment and ART. However, active case finding and inclusion of pediatric TB in Directly Observed Treatment programs can be done by district hospital staff.

Candida albicans. Alertness for *Candida* infection by district hospital staff and prompt treatment is necessary to alleviate the consequences of these lesions (odynophagia, decreased food intake and halitosis).[85] The benefit of using regular, possibly homemade mouthwashes (eg, 1 teaspoon vinegar or salt in 1 L water) and the prevention and timely treatment of dental caries in HIV-infected children has not been fully appreciated.[86]

Prophylactic Use of an Antibiotic

Cotrimoxazole is a highly effective prophylaxis against *P. jirovicii* and *Toxoplasma gondii* with also some activity against bacteria (such as *Streptococcus pneumonia*, *Salmonella* and *Nocardia*), malaria and other parasites (including *Isospora belli*).[87] Results of a randomized trial in Zambia comparing daily cotrimoxazole with placebo in HIV-infected children aged 1 to 14 years showed a 43% reduction in overall mortality (hazard ratio = 0.57; 95% confidence interval = 0.43–0.77) independent of baseline age group and CD4 count.[74] These results strengthen advocacy for prolonged use of cotrimoxazole for HIV-infected children.

Emotional Support, Pain Relief and Palliative Care

Chronic, severe pain is common in HIV-infected children, especially in those with low CD4 counts. In the United States, pain reporting by HIV-infected children is independently associated with a higher mortality within the next 3 years. It is hypothesized that pain may be a unique manifestation of HIV.[88] Because palliative care aims to relieve suffering, it should accompany all other care and not merely be applied toward the end stage of life. In one African study, half of the children with terminal AIDS received no analgesia and only 44% had a comfort care plan. Although an order "not to resuscitate" was found in 84% of the patient files, "lack of improvement despite the best available treatment" appeared to be the main justification. Among the most common causes of distress during the last 48 hours of life are

TABLE 3. Web Sites of Interest for Pediatric HIV/AIDS Care

Type of Information	Source	URL/E-Mail Address
Guidelines for ART, HIV/AIDS care and IMCI for developing countries	World Health Organization	www.who.int/3by5 www.who.int/vaccines-diseases www.who.int/child-adolescent-health
	Baylor International Pediatric AIDS Initiative	http://bayloraids.org/africa
Guidelines for ART and HIV/AIDS care (not necessarily specific developing world oriented)	Hopkins University	www.hopkins-aids.edu
	Women, Children and HIV	www.womenchildrenhiv.org
	U.S. Department of Health and Human Services (The Working Group on Antiretroviral Therapy and Medical Management of HIV-infected Children)	www.aidsinfo.nih.gov
	National Paediatric AIDS Network	www.npan.org
	European Network for Treatment of AIDS (PENTA)	www.ctu.mrc.ac.uk/penta
	University of Bordeaux (Intelligence report)	www.isped.u-bordeaux2.fr
	Columbia University (ICAP)	www.columbia-icap.org
	AIDS Education Global Information System	www.aegis.com
	The Body	www.thebody.com
	Medscape HIV/AIDS	www.medscape.com/hiv-aidshome
	University of California	http://hivinsite.ucsf.edu
Alternative tests for HIV diagnosis and monitoring	Forum for Collaborative HIV-research	www.hivforum.org
Drug interactions	Liverpool HIV Pharmacology Group	www.hiv-druginteractions.org
Memory books	Memory Book Project	www.memorybookproject.org/pages/597869/index.htm
Pain management	Texas Children's Cancer Centre	www.childcancerpain.org
Information about nutrition and fortified porridge	Quality Assurance Project	www.qaproject.org.
	Africafoods	www.africafoods.co.za
	Nutrition Society	www.nutritionsociety
Information about resistance	The International AIDS Society	www.iasusa.org
Assistance in resolving clinical problems concerning pediatric HIV care (especially ART) in African context through a a list serve	The Southern African HIV Clinicians Society Paediatric Discussion Group	Join for free by sending an e-mail to: sahivsoc@gomail.co.za or access: www.mylistmanager.co.za/cgi-bin/uls/uls.cgi?ulspop=1476

Retrieved February 3, 2006.

respiratory distress (49%), oral and esophageal candidiasis (37%) and painful skin conditions (32%).[89] Uganda is the first and only African country where palliative home-based care (including provision of free morphine) is part of the national health program.[90]

There has been little research into psychosocial support for African HIV-infected children and their families. Play therapy, memory boxes or memory books could be useful for the emotional well-being of these children. Simple tools like a mobile hung above a hospital bed and colored pictures on the walls increase stimulation, but none of these tools can replace the necessary human interactions and one-to-one contact with a loving, responsible caretaker.

For the majority of caregivers and health professionals, caring for HIV-infected patients has a great impact on their personal life and is associated with an increased risk for exhaustion, dropout from school, abuse, depression and social isolation.[91] There is growing awareness of the need for psychosocial support and training in palliative care for caregivers as well as district healthcare workers.[92]

ANTIRETROVIRAL TREATMENT

The impact of ART on the course of HIV infection in children has been demonstrated in resource-rich settings where many children with perinatal infection are becoming adolescents. It is anticipated that similar triumphs can be accomplished in low-resource settings, but there are several critical issues that need to be addressed to ensure successful treatment of children at the district hospital level.

Currently, there are significant limitations to ART formulations for children. For example, zidovudine liquid dosing requires large volumes of medication frequently causing nausea and vomiting. Few ART medications are available in small pill or capsule sizes. Dosing must be improvised if adult formulations are used. This can result in underdosing with development of ART resistance or overdosing with increased risk of toxicity. The feasibility of storing temperature-sensitive medications in a pit covered with a wet cloth, opening capsules and dissolving contents in water and cutting adult tablets in halves or quarters needs to be studied for a possible facilitation of pediatric ART. Also, availability of pediatric fixed-dose combinations for babies of 5 and 10 Kg would be very helpful.

Unlike adults, for whom most medications are administered in standard dosage, pediatric dosing is guided by weight or body surface area and must be recalculated as the child grows. Dosage guidelines using broad weight categories for each medication have been developed and can be used at district hospitals.[1,93]

Adherence to ART for a child is in most instances dependent on the commitment of the caretaker, the develop-

mental needs of the child and the potentially complex psychologic and social issues of the family. Adherence counseling in the group setting can be an effective way to support individual patients, maximize staff efforts and enable children and families to draw support from each other. Tangible support for families may be essential to ensure strict adherence, including accommodating problems with transportation to the hospital, dispensing extra doses of liquid or pills to account for wasted doses (spills, vomiting) and ongoing education and counseling for all caretakers.

The district hospital plays a critical role in the successful inclusion of HIV-infected children in the treatment paradigm. Care provided at the district level has the advantage of coming from healthcare workers within the community. They are uniquely prepared to address the variety of social and psychologic issues confronting children and families living with HIV and can, therefore, provide culturally sensitive support. Poor transportation in remote areas and the absence of the necessary financial means for the majority of the affected families make it impractical and unethical to continue limiting care and treatment of pediatric HIV to the tertiary hospital level.

CONCLUSIONS

The number of African children living with HIV/AIDS continues to escalate despite advances in the prevention of mother-to-child HIV transmission. Regardless of access to ART, much more can be done by district healthcare workers to reduce morbidity and mortality among HIV-infected children than is currently achieved. Pediatric HIV/AIDS care is often dichotomized into providing either cotrimoxazole or ART. Several other rational, inexpensive and already available interventions with proven efficacy could be promoted to maintain the best possible quality of life for the child for as long as possible. Coordination among care providers is crucial.

District health workers caring for African HIV-infected children can strengthen advocacy for availability of ART and improve HIV/AIDS care through increased knowledge and testimonies of "successes." Simplified guidelines for the use of antiretroviral drug regimens (adapted to difficult field conditions), simplified administrative requirements and availability of reliable tests for HIV screening and monitoring of disease progression in African children could greatly improve pediatric HIV/AIDS care at the district hospital level. Even when additional resources for care and treatment of HIV-infected children have been identified, it is increasingly important to provide care also for the affected caregivers and district healthcare workers (ie, adequate training, provision of sufficient resources to perform their job, prevention of burnout, adequate salary support, provision of ART) in populations that are bearing the brunt of the HIV epidemic. Their knowledge and commitment to the provision of quality HIV/AIDS care can bring hope to many thousands of children and their families.

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REFERENCES

1. World Health Organization. Antiretroviral therapy of HIV infection in infants and children in resource-limited settings, towards universal access: recommendations for a public health approach (2006 revision). Geneva, Switzerland. Available at: www.who.int/hiv/pub/guidelines/art/en/index.html. Accessed August 2006.
2. Dabis F, Ekpini ER. HIV-1/AIDS and maternal and child health in Africa. *Lancet*. 2002;359:2097–2104.
3. Spira R, Lepage P, Msellati P, et al. Mother-to-Child HIV-1 Transmission Study Group. Natural history of human immunodeficiency virus type 1 infection in children: A five-year prospective study in Rwanda. *Pediatrics*. 1999;104:e1–e9. Available at: www.pediatrics.org/content/full/104/5/e56. Accessed April 2004.
4. Ansari NA, Kombe AH, Kenyon TA, et al. Pathology and causes of death in a series of human immunodeficiency virus-positive and -negative pediatric referral hospital admissions in Botswana. *Pediatr Infect Dis J*. 2003;22:43–47.
5. Jones G, Steketee RW, Black RE, et al. Bellagio Child Survival Study Group. How many child deaths can we prevent this year? *Lancet*. 2003;362:65–71.
6. Meyers TM, Pettifor JM, Gray GE, et al. Pediatric admissions with human immunodeficiency virus infection at a regional hospital in Soweto, South Africa. *J Trop Pediatr*. 2000;46:224–230.
7. Fassinou P, Elenga N, Rouet F, et al. Highly active antiretroviral therapies among HIV-1-infected children in Abidjan, Côte d'Ivoire. *AIDS*. 2004;18:1905–1913.
8. Fransman D, McCulloch M, Lavies D, et al. Doctors' attitudes to the care of children with HIV in South Africa. *AIDS Care*. 2000;12:89–96.
9. Gilks CF. What use is a clinical case definition for AIDS in Africa? *BMJ*. 1991;303:1189–1190.
10. Sherman GG, Matsebula TC, Jones SA. Is early HIV testing in infants in poorly resourced prevention of mother to child transmission programmes unaffordable? *Trop Med Int Health*. 2005;10:1108–1113.
11. De Baets AJ, Edidi BS, Kasali MJ, et al. Pediatric human immunodeficiency virus screening in an African district hospital. *CDLI*. 2005;12:86–92.
12. Lyamuya E, Bredberg-Radén U, Massawe A, et al. Performance of a modified HIV-1 p24 antigen assay for early diagnosis of HIV-1 infection in infants and prediction of mother-to-infant transmission of HIV-1 in Dar Es Salaam, Tanzania. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1996;12:421–426.
13. Sherman GG, Stevens G, Stevens WS. Affordable diagnosis of human immunodeficiency virus infection in infants by p24 antigen detection. *Pediatr Infect Dis J*. 2004;23:173–175.
14. the Working Group on Antiretroviral Therapy, the National Pediatric and Family HIV Resource Center, the Health Resources and Services Administration, the National Institutes of Health. *Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection.* US Department of Health and Human Resources; 2004;1–55.
15. Young NL, Shaffer N, Chaowanachan T, et al. Early diagnosis of HIV-1-infected infants in Thailand using RNA and DNA PCR assays sensitive to non-B subtypes. *J Acquir Immune Defic Syndr*. 2000;24:401–407.
16. Schüpbach J, Böni J, Tomasik Z, et al. Sensitive detection and early prognostic significance of p24 antigen in heat-denatured plasma of human immunodeficiency virus type 1-infected infants. *J Infect Dis*. 1994;170:318–324.
17. Moodley D, Bobat RA, Coutsoudis A, et al. Predicting perinatal human immunodeficiency virus infection by antibody patterns. 1995;14:850–852.
18. Chantry CJ, Cooper ER, Pelton SI, et al. Seroreversion in human immunodeficiency virus-exposed but uninfected infants. *Pediatr Infect Dis J*. 1995;14:382–387.
19. Ciesielski CA, Metler RP. Duration of time between exposure and seroconversion in healthcare workers with occupationally acquired infection with human immunodeficiency virus. *Am J Med*. 1997;102:115–116.

20. Respess RA, Rayfield MA, Dondero TJ. Laboratory testing and rapid HIV assays: Applications for HIV surveillance in hard-to-reach populations. *AIDS*. 2001;15:S49–S59.
21. Weng S, Bulterys M, Chao A, et al. Perinatal human immunodeficiency virus-1 transmission and intrauterine growth: A cohort study in Butare, Rwanda. *Pediatrics*. 1998;102:e1–e9. Available at: www.pediatrics.org/cgi/content/full/102/2/e24. Accessed March 2004.
22. Berhane R, Bagenda D, Marum L, et al. Growth failure as a prognostic indicator of mortality in pediatric HIV infection. *Pediatrics*. 1997;100:e1–e4. Available at: www.pediatrics.org/cgi/content/full/100/1/e7. Accessed April 2004.
23. Bakaki P, Kayita J, Moura Machado JE, et al. Epidemiologic and clinical features of HIV-infected and HIV-uninfected Ugandan children younger than 18 months. *J Acquir Immune Defic Syndr*. 2001;28:35–42.
24. Fontana M, Zuin G, Plebani A, et al. Body composition in HIV-infected children: Relations with disease progression and survival. *Am J Clin Nutr*. 1999;69:1282–1286.
25. van Kooten Niekerk NKM, Knies MM, Howard J, et al. The first 5 years of the family clinic for HIV at Tygerberg Hospital: Family demographics, survival of children and early impact of antiretroviral therapy. *J Trop Pediatr*. 2006;52:3–11.
26. Bobat R, Coovadia H, Moodley D, et al. Growth in early childhood in a cohort of children born to HIV-1- infected women from Durban, South Africa. *Ann Trop Paediatr*. 2001;21:203–210.
27. Tang AM, Forrester J, Spiegelman D, et al. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2002;31:230–236.
28. Rivera S, Briggs W, Qian D, et al. Levels of HIV RNA are quantitatively related to prior weight loss in HIV-associated wasting. *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998;17:411–418.
29. Drotar D, Olness K, Wiznitzer M, et al. Neurodevelopmental outcomes of Ugandan infants with human immunodeficiency virus type 1 infection. *Pediatrics*. 1997;100:e1–e7. Available at: www.pediatrics.org/cgi/content/full/100/1/e5. Accessed February 2004.
30. Msellati P, Lepage P, Hitimana DG, et al. Neurodevelopmental testing of children born to human immunodeficiency virus type 1 seropositive and seronegative mothers: A prospective cohort study in Kigali, Rwanda. *Pediatrics*. 1993;92:843–848.
31. Shanbhag MC, Rutstein RM, Zaoutis T, et al. Neurocognitive functioning in pediatric human immunodeficiency virus infection. *Arch Pediatr Adolesc Med*. 2005;159:651–656.
32. Taha TE, Graham SM, Kumwenda NI, et al. Morbidity among human immunodeficiency virus-1-infected and -uninfected African children. *Pediatrics*. 2000;106:1–8. Available at: www.pediatrics.org/cgi/content/full/106/6/e77. Accessed March 2003.
33. HIV Paediatric Prognostic Markers Collaborative Study Group. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: A meta-analysis. *Lancet*. 2003;362:1605–1611.
34. Lindsey JC, Hughes MD, McKinnney RE, et al. Treatment-mediated changes in human immunodeficiency virus (HIV) Type 1 RNA and CD4 cell counts as predictors of weight growth failure, cognitive decline, and survival in HIV-infected children. *J Infect Dis*. 2000;182:1385–1393.
35. Denny T, Yogev R, Gelman R, et al. Lymphocyte subsets in healthy children during the first 5 years of life. *JAMA*. 1992;267:1484–1488.
36. Mofenson LM, Harris DR, Moye J, et al. Alternatives to HIV-1 RNA concentration and CD4 count to predict mortality in HIV-1-infected children in resource-poor settings. *Lancet*. 2003;362:1625–1627.
37. Respess RA, Cachafeiro A, Withum D, et al. Evaluation of an ultrasensitive p24 antigen assay as a potential alternative to human immunodeficiency virus type 1 RNA viral load assay in resource-limited settings. *J Clin Microbiol*. 2005;43:506–508.
38. Moss WJ, Clements CJ, Halsey NA. Immunization of children at risk of infection with human immunodeficiency virus. *Bull World Health Organ*. 2003;81:61–70.
39. Madhi SA, Petersen K, Madhi A, et al. Impact of human immunodeficiency virus type 1 on the disease spectrum of *Streptococcus pneumoniae* in South African children. *Pediatr Infect Dis J*. 2000;19:1141–1147.
40. Klugman KP, Madhi SA, Huebner RE, et al. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV-infection. *N Engl J Med*. 2003;349:1341–1348.
41. Spoulou VI, Tsoumas DL, Papaevangelou VG, et al. *Haemophilus influenzae* type b conjugate vaccine-induced immunological memory in symptomatic HIV-1-infected children. *AIDS*. 2003;17:1396–1398.
42. Tang AM, Graham NM, Semba RD, et al. Association between serum vitamin A and E levels and HIV-1 disease progression. *AIDS*. 1997;11:613–620.
43. Tang AM, Graham NM, Chandra RK, et al. Low serum vitamin B-12 concentrations are associated with faster human immunodeficiency virus type 1 (HIV-1) disease progression. *J Nutr*. 1997;127:345–351.
44. Villamor E, Mbise R, Spiegelman D, et al. Vitamin A supplements ameliorate the adverse effect of HIV-1 malaria, and diarrheal infections on child growth. *Pediatrics*. 2002;109:e1–e10. Available at: www.pediatrics.org/cgi/content/full/109/1/e6. Accessed March 2003.
45. Coutsoudis A, Bobat RA, Coovadia HM, et al. The effects of vitamin A supplementation on the morbidity of children born to HIV-infected women. *Am J Public Health*. 1995;85:1076–1081.
46. Siberry GK, Ruff AJ, Black R. Zinc and human immunodeficiency virus infection. *Nutr Res*. 2002;22:527–538.
47. Piwoz EG, Preble EA. *HIV/AIDS and Nutrition. A Review of the Literature and Recommendations for Nutritional Care and Support in Sub-Saharan Africa.* Washington: SARA Project. Academy for Educational Development; 2000;1–54.
48. Rabeneck L, Palmer A, Knowles JB, et al. A randomized controlled trial evaluating nutrition counseling with or without oral supplementation in malnourished HIV-infected patients. *J Am Diet Assoc*. 1998;98:434–438.
49. Schwenk A, Steuck H, Kremer G. Oral supplements as adjunctive treatment to nutritional counseling in malnourished HIV-infected patients: Randomized controlled trial. *Clin Nutr*. 1999;18:371–374.
50. Leung J. An approach to feeding HIV-infected infants and toddlers. *Topics in Clinical Nutrition*. 1989;4:27–37.
51. Gibert CL, Wheeler DA, Collins G, et al. Community Programs for Clinical Research on AIDS. Randomized, controlled trial of caloric supplements in HIV infection. *J Acquir Immune Defic Syndr*. 1999;22:253–259.
52. Nerad J, Romeyn M, Silverman E, et al. General nutrition management in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 2003;36:S52–S62.
53. Coutsoudis A, Pillay K, Spooner E, et al. Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: A prospective cohort study. *Lancet*. 1999;354:471–476.
54. Iliff PJ, Piwoz EG, Tavengwa NV, et al. Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS*. 2005;19:699–708.
55. Jeffery BS, Mercer KG. Pretoria Pasteurization: A potential method for the reduction of postnatal mother to child transmission of the human immunodeficiency virus. *J Trop Pediatr*. 2000;46:219–223.
56. Gaillard P, Fowler MG, Dabis F, et al. Use of antiretroviral drugs to prevent HIV-1 transmission through breastfeeding: From animal studies to randomized clinical trials. *J Acquir Immune Defic Syndr*. 2004;35:178–187.
57. Flores M, Filteau S. Effect of lactation counselling on subclinical mastitis among Bangladeshi women. *Ann Trop Paediatr*. 2004;22:85–88.
58. Wolday D, Mayaan S, Mariam ZG, et al. Treatment of intestinal worms is associated with decreased HIV plasma viral load. *J Acquir Immune Defic Syndr*. 2002;31:56–62.
59. Bentwich Z, Kalinkovich A, Weisman Z, et al. Can eradication of helminthic infections change the face of AIDS and tuberculosis? *Immunol Today*. 1999;20:485–487.
60. Kelly P, Musonda R, Kafwembe E, et al. Micronutrient supplementation in the AIDS diarrhoea-wasting syndrome in Zambia: A randomized controlled trial. *AIDS*. 1999;13:495–500.
61. Hoffman IF, Jere CS, Taylor TE, et al. The effect of *Plasmodium falciparum* malaria on HIV-1 RNA blood plasma concentration. *AIDS*. 1999;13:487–494.
62. Whitworth J, Morgan D, Quigley M, et al. Effect of HIV-1 and increasing immunosuppression on malaria parasitaemia and clinical

episodes in adults in rural Uganda: A cohort study. *Lancet*. 2000;356: 1051–1056.
63. Ticconi C, Mapfumo M, Dorrucci M, et al. Effect of maternal HIV and malaria infection on pregnancy and perinatal outcome in Zimbabwe. *J Acquir Immune Defic Syndr*. 2003;34:289–294.
64. Brahmbhatt H, Kigozi G, Wabwire-Mangen F, et al. The effects of placental malaria on mother-to-child HIV transmission in Rakai, Uganda. *AIDS*. 2003;17:2539–2541.
65. Ayisi JG, Van Eijk AM, Newman RD, et al. Maternal malaria and perinatal HIV transmission, Western Kenya. *Emerg Infect Dis*. 2004; 10:643–652.
66. Goulder P Jr, Jeena P, Tudor-Williams G, et al. Paediatric HIV infection: Correlates of protective immunity and global perspectives in prevention and management. *Br Med Bull*. 2001;58:89–108.
67. Gumbo T, Kadzirange G, Mielke J, et al. *Cryptococcus neoformans* meningoencephalitis in African children with acquired immunodeficiency syndrome. *Pediatr Infect Dis J*. 2002;21:54–56.
68. Graham SM, Gibb DM. HIV disease and respiratory infection in children. *Br Med Bull*. 2002;61:133–150.
69. Chintu C, Mudenda V, Lucas S, et al. Lung diseases at necropsy in African children dying from respiratory illnesses: A descriptive necropsy study. *Lancet*. 2002;360:985–990.
70. Zar HJ, Dechaboon A, Hanslo D, et al. *Pneumocystis carinii* pneumonia in South African children infected with human immunodeficiency virus. *Pediatr Infect Dis J*. 2000;19:603–607.
71. Ruffini DD, Madhi SA. The high burden of *Pneumocystis carinii* pneumonia in African HIV-1- infected children hospitalized for severe pneumonia. *AIDS*. 2002;16:105–112.
72. Graham SM, Mtitimila EI, Kamanga HS, et al. Clinical presentation and outcome of *Pneumocystis carinii* pneumonia in Malawian children. *Lancet*. 2000;355:369–373.
73. Simonds RJ, Oxtoby MJ, Caldwell MB, et al. *Pneumocystis carinii* pneumonia among US children with perinatally acquired HIV infection. *JAMA*. 1993;270:470–473.
74. Chintu C, Bhat GJ, Walker AS, et al. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): A double-blind randomised placebo-controlled trial. *Lancet*. 2004;364:1865–1871.
75. World Health Organization. Guidelines for cotrimoxazole prophylaxis for HIV-related infections in children, adolescents and adults in resource limited setting. 2006. Available at: www.who.int/hiv/pub/guidelines/ctx/en/index.html. Accessed August 2006.
76. Iyer JK, Milhous WK, Cortese JF, et al. *Plasmodium falciparum* cross-resistance between trimethoprim and pyrimethamine. *Lancet*. 2001;358:1066–1067.
77. Abdel-Haq N, Abuhammour W, Asmar B, et al. Nasopharyngeal colonization with *Streptococcus pneumoniae* in children receiving trimethoprim–sulfamethoxazole prophylaxis. *Pediatr Infect Dis J*. 1999;18:647–649.
78. Grimwade K, Gilks C. Cotrimoxazole prophylaxis in adults infected with HIV in low-income countries. *Curr Opin Infect Dis*. 2001;14:507–512.
79. Graham SM. Prophylaxis against *Pneumocystis carinii* pneumonia for HIV-exposed infants in Africa. *Lancet*. 2002;360:1966–1968.
80. Centers for Disease Control and Prevention, National Pediatric and Family HIV Resource Center, Working Group on PCP Prophylaxis for Children. 1995 revised guidelines for prophylaxis against *Pneumocystis carinii* pneumonia for children infected with or perinatally exposed to human immunodeficiency virus. *MMWR Morb Mortal Wkly Rep*. 1995;44:1–11.
81. Pillay T, Khan M, Moodley J, et al. Perinatal tuberculosis and HIV-1: Considerations for resource-limited settings. *Lancet Infect Dis*. 2004; 4:165.
82. Nachega J, Coetzee J, Adendorff T, et al. Tuberculosis active case-finding in a mother-to-child HIV transmission prevention programme in Soweto, South Africa. *AIDS*. 2003;17:1398–1400.
83. Zachariah R, Spielmann MP, Harries AD, et al. Passive versus active tuberculosis case finding and isoniazid preventive therapy among household contacts in a rural district in Malawi. *Int J Tuberc Lung Dis*. 2003;7:1033–1039.
84. Mukadi YD, Wiktor SZ, Coulibaly IM, et al. Impact of HIV infection on the development, clinical presentation, and outcome of tuberculosis among children in Abidjan, Côte d'Ivoire. *AIDS*. 1997;11:1151–1158.
85. Rachanis CC. Looking into the mouth—Oral manifestations of HIV infection. *Southern African Journal of HIV Medicine*. 2001;27–31.
86. Norval D. *Manual of Palliative Care in AIDS*. Houghton, South Africa: Centre for Palliative Learning, Hospice Association of the Witwatersrand; 2003.
87. Chokephaibulkit K, Wanachiwanawin D, Chearskul S, et al. *Pneumocystis carinii* severe pneumonia among human immunodeficiency virus-infected children in Thailand: The effect of a primary prophylaxis strategy. *Pediatr Infect Dis J*. 1999;18:147–152.
88. Gaughan DM, Hughes MD, Seage GRI, et al. The prevalence of pain in pediatric human immunodeficiency virus/acquired immunodeficiency syndrome as reported by participants in the Pediatric Late Outcomes Study (PACTG 219). *Pediatrics*. 2002;109:1144–1152.
89. Henley LD. End of life care in HIV-infected children who died in hospital. *Developing World Bioethics*. 2002;2:38–54.
90. Ramsay S. Leading the way in African home-based palliative care. *Lancet*. 2003;362:1812–1813.
91. Brouwer CN, Lok CL, Wolffers I, et al. Psychosocial and economic aspects of HIV/AIDS and counselling of caretakers of HIV-infected children in Uganda. *AIDS Care*. 2000;12:535–540.
92. The untapped potential of palliative care for AIDS. *Lancet*. 2003;362: 1773.
93. Weidle PJ, Abrams EJ, Gvetadze R, et al. A simplified weight-based method for paediatric drug dosing for zidovudine and didanosine in resource-limited settings. *Pediatr Infect Dis J*. 2006;25:59–64.
94. Müller O, Musoke P, Sen G, et al. Pediatric HIV-1 disease in a Kampala Hospital. *J Trop Pediatr*. 1990;36:283–286.
95. Colebunders R, Greenberg A, Nguyen-Dinh P, et al. Evaluation of a clinical case definition of AIDS in African children. *AIDS*. 1987;1:151–153.
96. Msellati P, Lepage P, Dabis F, et al. Evaluation of the WHO clinical definition of pediatric AIDS in Kigali, Rwanda. 7th International Conference on AIDS; June 2–16, 1999; Florence, Italy.
97. Vetter KM, Djomand G, Zadi F, et al. Clinical spectrum of human immunodeficiency virus disease in children in a west African city. *Pediatr Infect Dis J*. 1996;15:438–442.
98. Bélec L, Brogan T, Mbopi Kéou FX, et al. Surveillance of acquired immunodeficiency syndrome in Africa. An analysis of evaluations of the World Health Organization and other clinical definitions. *Epidemiol Rev*. 1994;16:403–417.
99. Jeena PM, Coovadia HM, Chrystal V. *Pneumocystis carinii* and cytomegalovirus infections in severely ill, HIV-infected African infants. *Ann Trop Paediatr*. 1996;16:361–368.
100. Yeung S, Wilkinson D, Escott S, et al. Paediatric HIV infection in a rural South African district hospital. *J Trop Pediatr*. 2000;46:107–110.
101. Lepage P, Dabis F, Commenges D, et al. Evaluation and simplification of the World Health Organization clinical case definition for paediatric AIDS. *AIDS*. 1989;3:221–225.
102. Otieno FA, Mbori-Ngacha DA, Wafula EM, et al. Evaluation of a proposed clinical case definition of paediatric acquired immune deficiency syndrome. *East Afr Med J*. 2002;79:111–114.
103. Chintu C, Malek A, Nyumbu M, et al. Case definitions for paediatric AIDS: The Zambian experience. *Int J STD AIDS*. 1993; 4:83–85.
104. van Gend CL, Haadsma ML, Sauer PJJ, et al. Evaluation of the WHO clinical case definition for pediatric HIV infection in Bloemfontein, South Africa. *J Trop Pediatr*. 2003;49:143–147.
105. Joubert G, Schoeman CJ, Bester CJ. Validation of a new clinical case definition for pediatric HIV infection, Bloemfontein, South Africa. *J Trop Pediatr*. 2006;51:387.
106. Horwood C, Liebescheutz S, Blaauw D, et al. Diagnosis of paediatric HIV infection in a primary health care setting with a clinical algorithm. *Bull World Health Organ*. 2003;81:856–864.
107. Jonckheer T, Levy J, Ninane J, et al. AIDS case definitions for African children. *Lancet*. 1988;2:690.
108. Atakouma DY, Agbèré AD, Tsolenyanu E, et al. Sida pédiatrique au CHU-Tokoin (Lomé): place de la malnutrition protéino-énergétique et essai d'élaboration d'un score de diagnostic clinique. *Cahiers Santé*. 1997;7:397–404.