American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

POLICY STATEMENT

Increasing Antiretroviral Drug Access for Children With HIV Infection

Organizational Principles to Guide and Define the Child Health Care System and/or Improve the Health of All Children

Committee on Pediatric AIDS, Section on International Child Health

ABSTRACT

Although there have been great gains in the prevention of pediatric HIV infection and provision of antiretroviral therapy for children with HIV infection in resource-rich countries, many barriers remain to scaling up HIV prevention and treatment for children in resource-limited areas of the world. Appropriate testing technologies need to be made more widely available to identify HIV infection in infants. Training of practitioners in the skills required to care for children with HIV infection is required to increase the number of children receiving antiretroviral therapy. Lack of availability of appropriate antiretroviral drug formulations that are easily usable and inexpensive is a major impediment to optimal care for children with HIV. The time and energy spent trying to develop liquid antiretroviral formulations might be better used in the manufacture of smaller pill sizes or crushable tablets, which are easier to dispense, transport, store, and administer to children.

INTRODUCTION

Background

It is estimated that 540 000 (420 000–670 000) children younger than 15 years were infected with HIV in 2006, mostly through mother-to-child transmission during pregnancy, delivery, or breastfeeding. Effective prevention services, including prenatal HIV testing, perinatal antiretroviral (ARV) prophylaxis, and safe alternatives to breastfeeding, are offered to fewer than 10% of pregnant women worldwide. Because of this global failure in prevention of HIV in children, by the end of 2005 an estimated 2.3 million (1.7–3.5 million) children were living with HIV infection globally; of these children, 2.0 million reside in sub-Saharan Africa.[1]

In the absence of treatment, most infants and children younger than 5 years with perinatally acquired HIV infection experience rapid progression to severe symptomatic disease and death, particularly in resource-limited countries. In a study of almost 3500 children enrolled in 7 perinatal trials in Africa, 35% of infected children had died by 1 year of age, and 53% had died by 2 years of age.[2] In older African children with perinatally acquired HIV infection, most already suffer severe symptoms at the time of diagnosis, including profound growth retardation, and few live to reach adulthood.[3]

In sharp contrast, most children with perinatally acquired HIV infection in resource-rich countries are treated early with highly active ARV therapy (ART).[4,5] Such ART, consisting of a combination of 3 or more potent ARV drugs, has been shown to dramatically modify the course of HIV infection in children, reducing

www.pediatrics.org/cgi/doi/10.1542/peds.2007-0273

doi:10.1542/peds.2007-0273

Key Words
HIV, children, antiretroviral therapy, drug formulations

Abbreviations
ARV—antiretroviral
ART—antiretroviral therapy
PEPFAR—President's Emergency Plan for AIDS Relief
WHO—World Health Organization
FDA—Food and Drug Administration
FDC—fixed-dose combination

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

mortality by fivefold or more and resulting in high survival rates (>90%) into adulthood.[6–8]

There are now intensive efforts by governments as well as multilateral and nongovernmental organizations to increase the number of people being treated with ART in resource-limited parts of the world (eg, the Global Fund, the US government–sponsored President's Emergency Plan for AIDS Relief [PEPFAR], the World Health Organization [WHO]– and United Nations–led "3 by 5 Initiative" and Universal Access, the Clinton Foundation). It is estimated that children accounted for approximately 15% of the 5 million new HIV infections that occurred globally in 2005. The rapid progression to death disproportionately decreases the number of children living with HIV to approximately 6% of the total infected population. In 2005, it was estimated that at least 660 000 children were in need of ART.[1] Of those, 90% live in sub-Saharan Africa. However, fewer than 5% of those who receive ART through the WHO 3 by 5 Initiative are children,[1] and through March 2005 only an estimated 9500 children living in PEPFAR "focus countries" were treated under PEPFAR funding.

Initial WHO guidelines on ART in 2002 (updated in 2003) included only one chapter on ARV management for HIV-infected children.[9] These guidelines have been updated as a pediatric-dedicated guideline document,[10] driven by the recognition that children have lagged severely behind adults in receiving ART and that there are numerous barriers to delivery of ART to children in resource-limited settings.[1,11]

Providing all pregnant women with the most effective prevention services possible within local settings, including prenatal care, HIV diagnosis, ARV prophylaxis, and appropriate feeding options, is important for minimizing the risk of HIV infection for their child. For children infected with HIV, overcoming barriers that limit access to ART is critical, and the enormous scale of the problem makes this an issue of worldwide concern. These issues have been addressed by organizations that are actively involved in prevention of mother-to-child transmission of HIV, deliver ART to children worldwide, and train practitioners in the appropriate use of ART. These organizations include the WHO, the Baylor International Pediatric AIDS Initiative,[12] the Elizabeth Glaser Pediatric AIDS Foundation (see "What About Us" at www.pedaids.org/News/Publications/Other/Children_s%20Battle%20to%20Access%20AI.aspx), Medecins Sans Frontieres, the Children's HIV Association of UK and Ireland, the Forum for Collaborative HIV Research (www.hivforum.org/projects/Pediatric%20Formulations.htm), and the Clinton Foundation.

This statement lists these barriers and potential ways to overcome them and provides strong support for the critical and urgent need for provision of ART to HIV-infected children globally. Multiple pediatric organizations throughout the world have endorsed this statement (see "Organizations That Endorsed This Statement").

Barrier 1: HIV Diagnostic Testing

Barriers to testing infants and children for HIV infection lead to a delay in diagnosis, and many infants and young children die before HIV is diagnosed or therapy can be given. Most pediatric HIV infections worldwide are attributable to mother-to-child transmission, with transmission occurring during pregnancy, around the time of birth, or through breastfeeding. Special tests are needed to diagnose HIV infection in infants and young children.

For adults and children older than 18 months, diagnosis of HIV infection is made by identification of antibodies to HIV in serum. However, because of the passive transplacental transfer of maternal HIV antibodies to the infant, newborn infants and children younger than 18 months will often test positive for the presence of anti-HIV antibodies even in the absence of true infection. Therefore, definitive diagnosis of HIV infection among infants and children younger than 18 months often requires the use of HIV-specific RNA or DNA nucleic acid tests to detect the virus itself,[13] instead of the inexpensive and readily available serologic assays that can be used in adults and children older than 18 months. These HIV-specific RNA or DNA assays are more expensive and more complex to perform and are not available in many areas of the world in which the risk of HIV infection in infancy is highest. In such settings, HIV antibody testing may be used to exclude HIV infection in nonbreastfed infants older than 9 to 12 months, because loss of passively transmitted maternal HIV antibody (seroreversion) occurs by 12 months of age in 95% of HIV-exposed but uninfected infants.[14]

Appropriate use of these nucleic acid tests requires that exposure of the infant or young child to HIV be identified by determination of maternal HIV-infection status. Ideally, this would occur before or during pregnancy. However, communication of maternal HIV-infection status from the mother's health care professional to the child's health care professional often does not occur. The linking of infant exposure to maternal infection will require system changes to optimize infant testing. The lack of appropriate testing in the youngest age group with the highest risk of HIV-related death prevents ART from being used in the very infants and young children who could potentially benefit the most from treatment with ARV drugs. To allow for early identification of HIV-infected infants and young children younger than 18 months, appropriate virologic testing technologies must be made available in resource-limited settings.

Psychological barriers to testing infants also may lead to a delay in diagnosis. The social stigma of the diagnosis for mother and child[15] and lack of treatment availability[16] may keep women from testing themselves to learn their

own HIV status and testing their children for HIV. Community-wide fear of discussing HIV infection in children may compound the effect of this barrier.

Barrier 2: Clinicians to Provide Care for Children With HIV

Even where appropriate HIV diagnostic testing is available and drugs for treatment of HIV infection and prophylaxis for HIV-associated infections are accessible, lack of personnel trained in treatment of children with HIV severely limits access to treatment for large numbers of children. In many areas of the world, medical care is provided by physicians, nurses, and other clinicians with training and experience in the management of adult, but not pediatric, patients. Even the best programs for training health care professionals in the principles of HIV care for children offer little practical exposure to treating pediatric patients, which is time- and resource-intensive. Some programs send health care professionals from resource-rich areas of the world to resource-limited areas to train local practitioners (eg, Medecins Sans Frontieres, the Baylor Pediatric AIDS Corps, the Clinton Foundation, the Children's HIV Association of UK and Ireland, UK/Kwazulu-Natal, the South Africa Collaboration). Additional efforts are needed to expand the availability of clinicians who are skilled in pediatric HIV care in resource-limited areas of the world,[17] including integrating pediatric HIV care into existing comprehensive child health programs, expanding local networks of experienced health care professionals, and linking local clinicians with local, regional, and international experts.

Barrier 3: ARV-Drug Formulations

Assuming that appropriate HIV diagnostic testing is available and the necessary clinical personnel are available to provide care and treatment to HIV-infected children, appropriate formulations of ARV agents for children are also necessary. Lack of availability of appropriate ARV formulations that are inexpensive and easily usable is a major impediment to access to economical health care for children with HIV. As of September 2005, 21 ARV agents were approved by the US Food and Drug Administration (FDA) for use in HIV-infected adults and adolescents older than 16 to 18 years in the United States, but only 13 were approved for children and adolescents younger than 16 to 18 years, and only 11 have pediatric formulations available[4] (see www.aidsinfo.nih.gov/other/cbrochure/english/13_en.pdf for a complete listing of HIV medications available in oral [liquid, capsule, and tablet] and intravenous formulations).

Because of the lack of appropriate pediatric formulations for certain drugs, caregivers of pediatric HIV patients may break or crush tablets meant for an adult patient in an attempt to produce child-size doses. With tablets that are asymmetric or not scored, this may lead to administration of erratic and inappropriate doses. Even with symmetrical tablets scored in the middle, the large quantity of medication in pills meant for adult use could mean that accurately breaking a scored tablet in half might not allow administration of a dosage small enough for an infant or young child, nor will it allow the incremental increases in doses required as the child grows. This problem can be addressed by developing products that contain smaller drug amounts per tablet or tablets that are scored to allow division accurately into halves or quarters. For regulatory purposes, bioequivalence studies may need to be performed by using the divided pills. Drug companies that are currently developing such drug formulations are to be commended.

Even when liquid formulations are available, special requirements and characteristics of such formulations may preclude their widespread use. For example, liquid drug formulations often require special storage such as refrigeration. The large volume of liquid formulations dispensed to allow ART to continue uninterrupted between clinic visits may make use of such drugs difficult in settings where transportation and storage are a challenge. For example, a 10-kg child who is being treated with standard doses of stavudine, lamivudine, and nevirapine, for whom a 3-month supply of drugs is dispensed at a clinic visit, would require 18 bottles of liquid that weigh almost half as much as the child (4.3 kg). For a rural family who may have walked a long distance to reach the clinical center, this is a significant issue. One commonly used ARV agent (zidovudine) requires high volumes of liquid and storage in brown glass bottles, which adds difficulty to treatment efforts.

Another problem with liquid formulations is the taste. When liquid formulations are developed, the taste is often so unpleasant that they may be practically unusable. Bad-tasting drugs are a well-recognized factor in treatment failures in children and lead practitioners to try many approaches to improve palatability of ARV drugs for children. When these attempts fail, some practitioners in resource-rich countries sometimes resort to insertion of gastrostomy tubes for medication administration.[18–20]

Finally, liquid formulations may contain excipients (additives to maintain the drug in solution) that could be harmful to children. For example, the oral solution of amprenavir has a high content of propylene glycol and vitamin E and should not be used in children younger than 4 years; other liquid formulations may contain high amounts of alcohol. Liquid formulations may contain high concentrations of sugar, which can be detrimental to dental health—a particular problem for children with HIV, many of whom have severely decayed teeth.

Although pharmaceutical companies may spend time and resources attempting to formulate different ARV medications into liquid formulations, this approach may not enable widespread, global access to ART for children. Such time and resources might be better used in the development of formulations that are more acceptable to

children and families than some of the liquid formulations that are currently available. Specifically, in addition to production of appropriate liquid formulations, development of the following should be strongly considered: (1) smaller tablets; (2) tablets in which active drug is uniformly distributed and in shapes that can be easily and accurately divided into halves or quarters to administer smaller doses; (3) capsule sprinkle formulations that can be opened and mixed with food; or (4) tablets that can be crushed, dissolved in water, or chewed.

Barrier 4: Appropriate Dosing of ARV Drugs in Children

Even when appropriate formulations of ARV agents are available for children, pharmacokinetic data may be insufficient to appropriately guide drug dosing, especially in the youngest children, who metabolize these drugs differently,[21] but also in adolescents, who may need higher than the "maximum adult dose" for adequate drug exposure.[22] For many available drugs, dosage recommendations made by European or US guideline-writing groups on the basis of pharmacokinetic and clinical studies in children may differ from doses approved by the FDA and European Medicines Agency.[4,5] The variability of drug exposure achieved by administration of "standard doses" of ARV drugs to children results in wide differences in plasma concentrations for many drugs, and some suggest the need for monitoring drug plasma concentrations in children to improve therapeutic outcomes[23]; this is clearly not practical in resource-limited settings.

Completion of the appropriate studies of new ARV agents for use in children younger than 13 years lags behind those in adults. Although it may be appropriate to perform initial phase 1 or 2 studies in adults for initial determination of drug safety, pharmacokinetic studies in children need to follow along quickly to ensure that when the drugs are approved and available for use in adults, information is already available to define appropriate use in children. When new formulations are developed to allow once-daily dosing in adults, these formulations need to be appropriately tested in children, and regulatory approval needs to be gained through the FDA or European Medicines Agency to ensure that the advantages of once-daily dosing become more widely available to children and younger adolescents 13 to 18 years of age. This is particularly critical for life-threatening diseases such as HIV. Government regulations need to be tightened to enforce this approach to pediatric drug development and approval. International cooperation is crucial for successful completion of pharmacokinetic studies of ARV medications in children.

Earlier evaluation of ARV-drug safety and pharmacokinetics in children is needed so that when new ARV formulations are approved for use in adults, there are also preparations available for children; enough information about drug pharmacokinetics in children is available to allow rational dosing recommendations.

Appropriate dosing of drugs in pediatric patients requires measurement of weight and height and the complex calculation of body surface area. The requirement for different doses according to age, weight, and body surface area may put accurate prescribing and safe dispensing of ART and other drugs to pediatric patients beyond the reach of many of the front-line health care professionals who manage children with HIV. Dosing by weight band (recommending a specific dose for an all-inclusive range of weights, so that complex dosing calculations are not needed) has been recommended (see http://bayloraids.org/resources/DosingGuide.pdf), and studies of this approach have shown safety and efficacy for patients as well as acceptability to practitioners.[24,25] Additional work on this approach is needed, including educating practitioners in its safety and effectiveness. Simplified dosing guides have been developed by the WHO and are readily available to clinicians who care for children and adolescents with HIV infection in resource-limited settings (see www.who.int/hiv/paediatric/en/index.html). These guides will increase the accuracy of dosing and dispensing ARV medications to these patients.

Barrier 5: Other Issues Related to ARV Drugs for Infants, Children, and Adolescents With HIV Infection

Many drugs are now being coformulated into tablets that contain 2 or 3 different ARV agents. These fixed-dose combinations (FDCs)[26–28] are easier to prescribe and dispense, which minimizes errors. A lower pill burden may enhance patient adherence to therapy. Many FDCs have been developed as generic drugs and are offered in resource-constrained settings at reduced prices, thus improving availability of ARV medications for adults in many areas of the world.

FDCs for adults cannot just be cut or directly scaled down for children without appropriate pharmacokinetic studies,[29] because the component medications may be required in different proportions for children than adults. Moreover, if the tablets are not formulated in equal layers, breaking the tablet may result in unequal doses being administered. FDCs are not currently available for children. Developing FDCs that are appropriately formulated for children should be a high priority for pharmaceutical companies.[11] In addition, development of pediatric FDCs as generic drugs, which are more affordable, will enhance availability of FDCs for use in children as it has in adults. However, with generic formulations being manufactured in many countries, formulations need to be standardized to minimize prescribing errors that might occur if pills are supplied in nonstandard sizes.

Drug administration to children is more complex than it is to adults. Finding the best way to get liquids out of a bottle and measured appropriately while avoiding spillage and fully using all of the medication in a bottle is not necessarily straightforward. Syringes enhance dos-

ing accuracy, but without the use of special bottle tops, there may be wastage of liquid left in the bottom of a bottle or spillage when trying to get to the liquid at the bottom. Dividing or crushing tablets takes time and may diminish adherence if it is too difficult. These issues of ease and accuracy of drug administration need to be considered in the effort to increase access to ART for children.

SUMMARY AND RECOMMENDATIONS

To increase the availability and appropriateness of the use of ARV medications for children, the following are suggested ways of overcoming the aforementioned barriers.

Barrier 1: HIV Diagnostic Testing

- Enhance early identification of infants with HIV infection by making appropriate virologic testing technologies available throughout the world.
- Support political, religious, and other community leaders in their endorsement of the value of HIV testing linked to treatment and prevention. Cultural leaders need to demonstrate acceptance and community support of HIV-infected individuals.

Barrier 2: Clinicians to Provide Care for Children With HIV Infection

- Work to expand education of practitioners in the care of children with HIV and expand the number of such practitioners in resource-limited areas of the world.
- Integrate pediatric HIV care into comprehensive child health programs.
- Facilitate collaboration among experts to build capacity and expand expertise in areas of need.

Barrier 3: ARV-Drug Formulations

- Produce pill formulations in smaller milligram amounts and smaller pill sizes.
- Configure tablets so they can be divided easily. This requires that thought be given to production of scored tablets of symmetrical shape with uniform dispersal of active drugs within the tablet, which can be divided accurately and then easily crushed or dissolved.
- In addition to production of liquid formulations, consider production of other formulations for pediatric use, including tablets for dispersal, chewable tablets, or sprinkle formulations.
- Consider best-possible attributes of liquid formulations, including taste, color, consistency, and the highest concentration possible, but recognize that the extra time and expense needed to develop a liquid formulation may be at too high of a cost if it delays availability of medications that are appropriately formulated for infants and children.
- Expedite the availability of new drugs for use in children by requiring that pediatric formulations (liquids and/or appropriate tablet dosage forms and sizes) be available at the time of country approval of the use of the drug in adults unless there is a biological imperative not to develop the drug for use in children.
- Develop formulations and perform necessary studies to allow once-daily dosing in children at the same time as planned for adults.

Barrier 4: Appropriate Dosing of ARV Drugs in Children

- Require studies of drug pharmacokinetics in infants, children, and adolescents at the time that phase 2 and 3 studies are being conducted in adults so that when drugs are approved for use in adults, there is adequate information to allow their appropriate dosing in each of those specific age groups.
- Provide dosing tables for pediatric formulations, preferably weight-band–based tables, to increase the accuracy of dosing and dispensing ART to children.

Barrier 5: Other Issues Related to ARV Agents for HIV-Infected Infants, Children, and Adolescents

- Increase the availability of FDCs for pediatric use.
- Make pediatric formulations affordable in the manner that adult formulations have been made more affordable in many countries.
- Provide drug-administration devices and tools with medications (eg, syringes, bottle tops for use with syringes, medicine spoons, tablet cutters, tablet crushers) and devices to aid adherence, including pill boxes that can accommodate a month's worth of pills or calendars with medications attached.

COMMITTEE ON PEDIATRIC AIDS, 2005–2006

*Peter L. Havens, MD, Chairperson
Robert J. Boyle, MD
Patricia J. Emmanuel, MD
Patricia M. Flynn, MD
Lisa M. Henry-Reid, MD
Laura G. Hoyt, MD
Jennifer S. Read, MD
Katherine A. Tulenko, MD

LIAISONS

Mike Brady, MD
Committee on Infectious Diseases
CDR Kenneth L. Dominguez, MD
Centers for Disease Control and Prevention
Lynne M. Mofenson, MD
National Institute of Child Health and Human Development

Mary Glenn Fowler, MD
Past Liaison, Centers for Disease Control and Prevention

CONSULTANTS

*Diana M. Gibb, MD (Great Britain)
Joseph Mbuthia, MD (Kenya)
Ruth Nduati, MD (Kenya)
Dorothy Mbori-Ngacha, MD (Kenya)

STAFF

Anjie Emanuel, MPH
Jeanne Lindros, MPH

SECTION ON INTERNATIONAL CHILD HEALTH, 2005–2006

Donna M. Staton, MD, Chairperson
Ann T. Behrmann, MD
June P. Brady, MD
Caroline K. Dueger, MD
Elizabeth Hillman, MD
Anna M. Mandalakas, MD
Cliff M. O'Callahan, MD
Karen M. Olness, MD

LIAISONS

Kevin R. Clarke, MD
Section on Residents
Donald Hillman, MD
Canadian Paediatric Society
Jane G. Schaller, MD
International Pediatric Association

STAFF

Anne McGhiey
Spencer Li, MPA

*Lead authors

ORGANIZATIONS THAT ENDORSED THIS STATEMENT

African Network for the Care of Children Affected by AIDS (ANECCA)
Baylor International Pediatric AIDS Initiative
British HIV Pharmacy Association (HIVPA)
British Pediatric Allergy, Immunity and Infection Group (United Kingdom)
Canadian Paediatric Society
Children's HIV Association of the UK and Ireland (CHIVA)
Elizabeth Glaser Pediatric AIDS Foundation
Pediatric European Network for Treatment of AIDS (PENTA)
Pediatric Infectious Diseases Society
Indian Academy of Pediatrics
International Pediatric Association
Latin American Pediatric Association (ALAPE)
Pediatric Association of Jamaica
Pediatric Society of Thailand
Royal College of Pediatrics and Child Health (United Kingdom)
South African Pediatric Association (SAPA)
Southern African HIV Clinicians Society
Union of National African Pediatric Societies and Associations (UNAPSA)
World Health Organization (WHO)

APPENDIX 1: INTERNET ADDRESSES OF ORGANIZATIONS REFERRED TO IN THIS POLICY STATEMENT

African Network for the Care of Children Affected by AIDS (ANECCA)
www.anecca.org
Baylor International Pediatric AIDS Initiative
http://bayloraids.org
Children's HIV Association of the UK and Ireland (CHIVA)
www.bhiva.org/chiva
Clinton Foundation
www.clintonfoundation.org/cf-pgm-hs-ai-home.htm
Elizabeth Glaser Pediatric AIDS Foundation
www.pedaids.org
Forum for Collaborative HIV Research
www.hivforum.org
Global Fund to Fight AIDS, Tuberculosis and Malaria
www.theglobalfund.org/en
Medecins Sans Frontieres (MSF)
www.msf.org
Pediatric European Network for Treatment of AIDS
www.pentatrials.org
President's Emergency Plan for AIDS Relief (PEPFAR)
www.usaid.gov/our_work/global_health/aids/pepfarfact.html
United Nations: Joint United Nations Program on HIV/AIDS (UNAIDS)
www.unaids.org/en
http://data.unaids.org/pub/GlobalReport/2006
World Health Organization (WHO)
www.who.int/en

APPENDIX 2: INTERNATIONAL COLLABORATORS

The following people were instrumental in arranging to have their respective organizations sign on in support of this document. The American Academy of Pediatrics appreciates their help with this endeavor and especially appreciates their ongoing efforts in care of children with HIV.

Dorothy Mbori-Ngacha
African Network for the Care of Children Affected by AIDS (ANECCA)
dngacha@ke.cdc.gov
Mark Kline
Baylor International Pediatric AIDS Initiative
mkline@texaschildrenshospital.org

Jennifer Swan
British HIV Pharmacy Association (HIVPA)
jennifer.swan@newhamhealth.nhs.uk
Hermione Lyall
Children's HIV Association (CHIVA, United Kingdom) and British Pediatric Allergy, Immunity and Infection Group (United Kingdom)
hermione.lyall@st-marys.nhs.uk
Elizabeth Moreau
Canadian Paediatric Society
elizabethm@cps.ca
Catherine Wilfert
Elizabeth Glaser Pediatric AIDS Foundation
wilfert@mindspring.com
Nitin Shah
Indian Academy of Pediatrics
drnitinshah@hotmail.com
Adenike Grange
International Pediatric Association
nikegrange@yahoo.com
Alberto Bissot
Latin American Pediatric Association (ALAPE)
abissot@cwpanama.net
Carlo Giaquinto
Pediatric European Network for Treatment of AIDS (PENTA)
carlog@pediatria.unipd.it
Celia D. C. Christie
Pediatric Association of Jamaica
celia.christiesamuels@uwimona.edu.jm
Christene Phillips
Pediatric Infectious Diseases Society
cphillips@idsociety.org
Usa Thisyakorn
Pediatric Society of Thailand
fmeduty@md.chula.ac.th
Mark Lallemant
Pediatric Society of Thailand
marc@phpt.org
Mike Sharland
Royal College of Pediatrics and Child Health
mike.sharland@stgeorges.nhs.uk
Raziya Bobat
South African Pediatric Association (SAPA)
bobat@ukzn.ac.za
Mark Cotton
South African Pediatric Association (SAPA) and Southern African HIV Clinicians Society
mcot@sun.ac.za
Francois Venter
Southern African HIV Clinicians Society
f.venter@rhrujhb.co.za
Peter Cooper
Union of National African Pediatric Societies and Associations (UNAPSA)
cooperpa@medicine.wits.ac.za
Siobhan Crowley
World Health Organization (WHO)
crowleys@who.int

REFERENCES

1. World Health Organization. Progress on global access to HIV antiretroviral therapy: a report on "3 by 5" and beyond. March 2006. Available at: www.who.int/hiv/fullreport_en_highres.pdf. Accessed February 16, 2007 [see also www.who.int/hiv/mediacentre/2006_EpiUpdate_en.pdf. Accessed February 16, 2007]
2. Newell ML, Coovadia H, Cortina-Borja M, et al. Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet.* 2004;364:1236–1243
3. Marston M, Zaba B, Salomon JA, Brahmbhatt H, Bagenda D. Estimating the net effect of HIV on child mortality in African populations affected by generalized HIV epidemics. *J Acquir Immune Defic Syndr.* 2005;38:219–227
4. US Department of Health and Human Services. Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection. 2005. Available at: www.aidsinfo.nih.gov/contentfiles/PediatricGuidelines.pdf. Accessed June 14, 2006
5. Sharland M, Blanche S, Castelli G, Ramos J, Gibb DM; PENTA Steering Committee. PENTA guidelines for the use of antiretroviral therapy, 2004. *HIV Med.* 2004;5(suppl 2):61–86
6. McConnell MS, Byers RH, Frederick T, et al. Trends in antiretroviral therapy use and survival rates for a large cohort of HIV-infected children and adolescents in the United States, 1989–2001. *J Acquir Immune Defic Syndr.* 2005;38:488–494
7. Gibb DM, Duong T, Tookey PA, et al. Decline in mortality, AIDS, and hospital admissions in perinatally HIV-1 infected children in the United Kingdom and Ireland [published correction appears in *BMJ.* 2004;328(7441):686]. *BMJ.* 2003;327:1019
8. Matida LH, Marcopito LF, Succi RC, et al. Improving survival among Brazilian children with perinatally-acquired AIDS. *Braz J Infect Dis.* 2004;8:419–423
9. World Health Organization. Scaling up antiretroviral therapy in resource-limited settings: treatment guidelines for a public health approach, 2003 revision. Available at: www.who.int/hiv/pub/prev_care/en/arvrevision2003en.pdf. Accessed June 14, 2006
10. World Health Organization. Antiretroviral therapy of HIV infection in infants and children: towards universal access—recommendations for a public health approach. 2006. Available at: www.who.int/hiv/pub/guidelines/WHOpaediatric.pdf. Accessed February 16, 2007 [for a complete list of WHO guidelines, see www.who.int/hiv/pub/guidelines/en/index.html]
11. United Nations Children's Fund/World Health Organization. UNICEF/WHO technical consultation: improving access to appropriate paediatric ARV formulations—November 3–4, 2004. Available at: www.who.int/3by5/en/finalreport.pdf. Accessed June 14, 2006
12. Anabwani GM, Woldetsadik EA, Kline MW. Treatment of human immunodeficiency virus (HIV) in children using antiretroviral drugs. *Semin Pediatr Infect Dis.* 2005;16:116–124
13. King SM; American Academy of Pediatrics, Committee on Pediatric AIDS; American Academy of Pediatrics, Infectious Diseases and Immunization Committee. Evaluation and treatment of the human immunodeficiency virus-1–exposed infant. *Pediatrics.* 2004;114:497–505
14. Moodley D, Bobat RA, Coutsoudis A, Coovadia HM. Predicting perinatal human immunodeficiency virus infection by antibody patterns. *Pediatr Infect Dis J.* 1995;14:850–852
15. Varga CA, Sherman GG, Maphosa J, Jones SA. Psychosocial consequences of early diagnosis of HIV status in vertically

exposed infants in Johannesburg, South Africa. *Health Care Women Int.* 2005;26:387–397
16. Levy NC, Miksad RA, Fein OT. From treatment to prevention: the interplay between HIV/AIDS treatment availability and HIV/AIDS prevention programming in Khayelitsha, South Africa. *J Urban Health.* 2005;82:498–509
17. Kline MW. Perspectives on the pediatric HIV/AIDS pandemic: catalyzing access of children to care and treatment. *Pediatrics.* 2006;117:1388–1393
18. Shingadia D, Viani RM, Yogev R, et al. Gastrostomy tube insertion for improvement of adherence to highly active antiretroviral therapy in pediatric patients with human immunodeficiency virus. *Pediatrics.* 2000;105(6). Available at: www.pediatrics.org/cgi/content/full/105/6/e80
19. Temple ME, Koranyi KI, Nahata MC. Gastrostomy tube placement in nonadherent HIV-infected children. *Ann Pharmacother.* 2001;35:414–418
20. King JR, Yogev R, Aldrovandi G, Chadwick E, Acosta EP. Pharmacokinetics of antiretrovirals administered to HIV-infected children via gastrostomy tube. *HIV Clin Trials.* 2004;5:288–293
21. Fraaij PL, van Kampen JJ, Burger DM, de Groot R. Pharmacokinetics of antiretroviral therapy in HIV-1-infected children. *Clin Pharmacokinet.* 2005;44:935–956
22. Grub S, Delora P, Ludin E, et al. Pharmacokinetics and pharmacodynamics of saquinavir in pediatric patients with human immunodeficiency virus infection. *Clin Pharmacol Ther.* 2002;71:122–130
23. Fraaij PL, Rakhmanina N, Burger DM, de Groot R. Therapeutic drug monitoring in children with HIV/AIDS. *Ther Drug Monit.* 2004;26:122–126
24. Ponnet M, Frederix K, Petdachai W, Wilson D, Eksaengsri A, Zachariah R. A drug dosage table is a useful tool to facilitate prescriptions of antiretroviral drugs for children in Thailand. *Int J STD AIDS.* 2005;16:420–426
25. Weidle PJ, Abrams, EJ, Gvetadze R, Rivadeneira E, Kline MW. A simplified weight-based method for pediatric drug dosing for zidovudine and didanosine in resource-limited settings. *Pediatr Infect Dis J.* 2006;25:59–64 [see also www.who.int/hiv/paediatric/en/index.html (WHO weight-band dosing guides) and www.columbia-icap.org/Resources/pdf/PedsDosingGuidesec.pdf (dosing guide in color)]
26. Pujari SN, Patel AK, Naik E, et al. Effectiveness of generic fixed-dose combinations of highly active antiretroviral therapy for treatment of HIV infection in India. *J Acquir Immune Defic Syndr.* 2004;37:1566–1569
27. Anekthananon T, Ratanasuwan W, Techasathit W, Sonjai A, Suwanagool S. Safety and efficacy of a simplified fixed-dose combination of stavudine, lamivudine and nevirapine (GPO-VIR) for the treatment of advanced HIV-infected patients: a 24-week study. *J Med Assoc Thai.* 2004;87:760–767
28. Valenti WM. Expanding role of conformulations in the treatment of HIV infection: impact of fixed-dose combinations. *AIDS Read.* 2004;14:541–550
29. Chokephaibulkit K, Plipat N, Cressey TR, et al. Pharmacokinetics of nevirapine in HIV-infected children receiving an adult fixed-dose combination of stavudine, lamivudine, and nevirapine. *AIDS.* 2005;19:1495–1499

Increasing Antiretroviral Drug Access for Children With HIV Infection

Committee on Pediatric AIDS, Section on International Child Health

Pediatrics 2007;119;838
DOI: 10.1542/peds.2007-0273

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Increasing Antiretroviral Drug Access for Children With HIV Infection

Committee on Pediatric AIDS, Section on International Child Health

Pediatrics 2007;119;838
DOI: 10.1542/peds.2007-0273