Prevention of Mother-to-Child HIV Transmission in Resource-Poor Countries

Translating Research Into Policy and Practice

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Each year, an estimated 590 000 infants acquire human immunodeficiency virus type 1 (HIV) infection from their mothers, mostly in developing countries that are unable to implement interventions now standard in the industrialized world. In resource-poor settings, the HIV pandemic has eroded hard-won gains in infant and child survival. Recent clinical trial results from international settings suggest that short-course antiretroviral regimens could significantly reduce perinatal HIV transmission worldwide if research findings could be translated into practice. This article reviews current knowledge of mother-to-child HIV transmission in developing countries, summarizes key findings from the trials, outlines future research requirements, and describes public health challenges of implementing perinatal HIV prevention interventions in resource-poor settings. Public health efforts must also emphasize primary prevention strategies to reduce incident HIV infections among adolescents and women of childbearing age. Successful implementation of available perinatal HIV interventions could substantially improve global child survival.

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NUMEROUS INTERNATIONAL OBservational studies of mother-to-child transmission of human immunodeficiency virus type 1 (HIV) have been reported since the mid-1980s.[1,2] In 1994, results of Pediatric AIDS Clinical Trials Group study 076 (PACTG 076) showed a two-thirds reduction in perinatal transmission from HIV-infected women who received a complex regimen of zidovudine.[3] Impressive reduction in perinatal HIV transmission has been achieved in the developed world based on these clinical trial results.[4] In developing countries, trials of simplified zidovudine regimens in Southeast Asia and sub-Saharan Africa demonstrated reductions in transmission of one half to one third.[5-7] Recently, a trial in Uganda of a single-dose of nevirapine given to mother and neonate showed similar results.[8]

In this article, we review current knowledge about mother-to-child HIV transmission in developing countries, results of intervention studies, research requirements, and social and scientific implications of findings.

See also p 1167.

Magnitude of the Problem

The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that by the end of 1998 about 33.4 million people were living with HIV worldwide, including 22.5 million (67%) in sub-Saharan Africa.[9] In 1998, 590 000 new pediatric HIV infections occurred (10% of total new infections), almost all from mother-to-child transmission; 90% were in Africa. Of the 2.5 million acquired immunodeficiency syndrome (AIDS) deaths in 1998, about 510 000 (20%) occurred in children less than age 15 years. Infant and child mortality rates in east and southern Africa are now one third to two thirds higher than they would have been in the absence of AIDS, contributing to the progressive reduction in life expectancy in this region.[9,10]

The global epidemiology of pediatric HIV infection reflects the epidemiology of HIV in women. More than 80% of the 13.8 million women living with HIV by the end of 1998 were African. Available

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HIV prevalence studies in pregnant women offer the most objective data for comparing epidemics in different countries and indicate the magnitude of pediatric HIV and AIDS (FIGURE). In several urban centers in eastern and southern Africa, HIV infection rates in pregnant women now exceed 25%.[11]

In Africa and Asia, where heterosexual transmission of HIV is the dominant mode of spread, nearly 2 million children of HIV-infected parents are now orphaned annually (having lost mother or both parents).[10] Households headed by grandparents and children are the new reality in areas of high HIV prevalence. The physical and social welfare of AIDS orphans in developing countries are major and neglected problems.

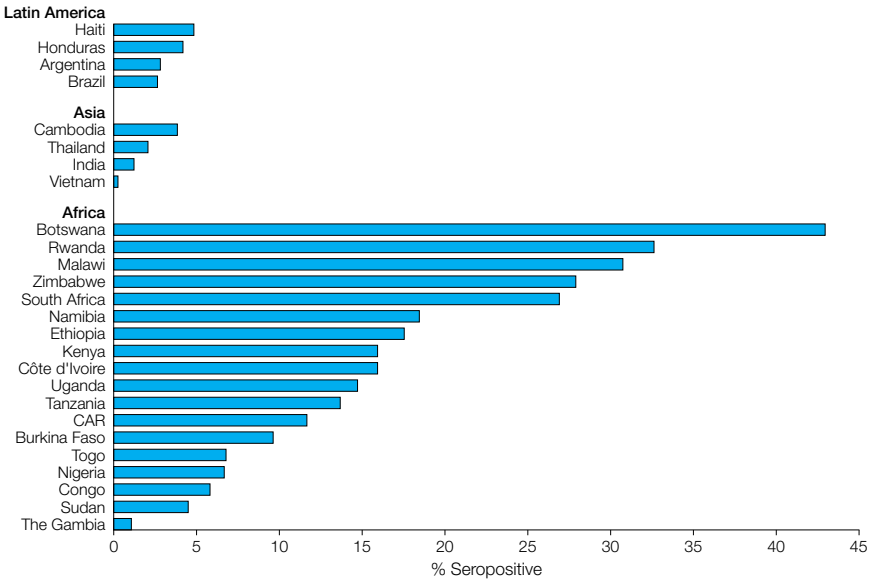
Timing and Rate of Mother-to-Child Transmission

Cumulative rates of mother-to-child HIV transmission reflect transmissions in the intrauterine or intrapartum periods, or postnatally through breast milk. These distinctions are important because of the different approaches required for prevention. Neonates with a positive HIV culture or genomic test (eg, DNA polymerase chain reaction) in the first 48 hours of life are considered to have acquired infection in utero.[12] However, current technologies cannot distinguish between late intrauterine, intrapartum, and early postpartum transmission. In the absence of breastfeeding, about 30% of infant HIV infections occur in utero and 70% during labor and delivery (TABLE 1).[13-15]

In industrialized countries, transmission rates in untreated nonbreastfeeding populations have ranged from 14% to 32% vs 25% to 48% among breastfeeding populations in resource-poor settings.[2] Reasons for higher rates in developing countries are multiple, but near-universal breastfeeding is probably most important. Risk factors for transmission, reviewed elsewhere,[1,2] include high maternal viral load,[23-25] advanced maternal immune deficiency,[26] and prolonged rupture of membranes.[27] Risk factors for breast milk transmission have been less studied, but transmission has been associated with both viral load and subclinical mastitis.[28] Recently, exclusive breastfeeding was associated with reduced risk of transmission compared with early mixed feeding in South Africa, a provocative finding that requires confirmation.[16]

Confusion has surrounded the risk of HIV transmission through breastfeeding. An early meta-analysis estimated a

Figure. Human Immunodeficiency Virus Type 1 Seroprevalence Among Pregnant Women



Based on the most recently available data (1996-1998) from the capital city or major urban centers of selected countries, as compiled by the US Bureau of the Census.[11] CAR indicates Central African Republic.

Table 1. Estimated Timing and Risk of Mother-to-Child Human Immunodeficiency Virus Type 1 (HIV) Transmission*

	No Breastfeeding, %		Breastfeeding Through 6 Months, %†		Breastfeeding Through 18 to 24 Months, %‡	
Timing	Relative Proportion	Absolute Rate	Relative Proportion	Absolute Rate	Relative Proportion	Absolute Rate
Intrauterine	25 to 35	5 to 10	20 to 25	5 to 10	20 to 25	5 to 10
Intrapartum	65 to 75	10 to 20	40 to 55	10 to 20	35 to 50	10 to 20
Postpartum breastfeeding						
Early (first 2 months)			20 to 25	5 to 10	20 to 25	5 to 10
Late (after 2 months)			5 to 10	1 to 5	20 to 25	5 to 10
Overall		15 to 30		25 to 35		30 to 45

*Rounded consensus estimates by the authors, based on a critical review of the relevant literature,[12-22] of the absolute transmission rates and proportion of transmission occurring at different time points in the absence of antiretroviral treatment.
†Postpartum transmission estimate at 6 months includes early breastfeeding transmission (first 2 months), which is difficult to distinguish from intrapartum transmission in published studies but likely accounts for more than half of breastfeeding transmission in the first 6 months.[22]
‡Data are cumulative totals; breastfeeding transmission estimates at 24 months include transmission occuring before 6 months.

14% additional risk of postnatal transmission from breastfeeding for women with prevalent infections and a 29% risk for women with incident infections postpartum,[17] reflecting the reported increased infectiousness of primary HIV infection.[18] More recent data are available from Côte d'Ivoire,[19] a pooled international analysis,[20] and from Malawi.[21] Absolute transmission rates from breastfeeding were estimated at 3.2 to 9.2 per 100 years of breastfeeding among infants aged 1 to 6 months. Although unable to quantify very early transmission due to breastfeeding, Miotti et al[21] reported cumulative transmission risk from breastfeeding in Malawi to be 3.5% at 6 months, 7% at 12 months, and 10.3% at 24 months.

Results from a trial in Nairobi, Kenya, in which children born to HIV-infected women were randomized to breastfeeding or replacement feeding, show that more than 40% of infant HIV infections were acquired through breastfeeding and that most infections were acquired during the first few months of life.[22]

Table 1 summarizes our estimates, based on a critical review of the relevant data, for the relative proportions and absolute rates of mother-to-child transmission at various time points. The relative contribution of early postpartum breastfeeding transmission is least well defined. Available data suggest that a high proportion (one third to one half) of perinatal HIV infections in African settings is due to breastfeeding.[2,17,21,22] In addition, although difficult to quantify, substantial postnatal transmission from breastfeeding may occur among women who seroconvert during lactation.[17,18]

Antiretroviral and Other Interventions to Reduce Transmission

TABLE 2 summarizes data on different antiretroviral regimens shown to reduce mother-to-child transmission, stratified by breastfeeding practices. In the PACTG 076 trial, which defined the current US regimen, zidovudine was given to mothers beginning at 14 to 34 weeks of pregnancy, intravenously during labor, and for 6 weeks to infants, and resulted in a 68% reduction in transmission.[3] Shorter and simpler regimens were assessed in 5 randomized, controlled trials in Asia and Africa.[5-8,29]

A trial in Thailand[5] showed a 50% reduction in mother-to-child HIV transmission among nonbreastfeeding women who took an exclusively oral zidovudine regimen twice a day begin-

Table 2. Clinical Trials of Regimens to Reduce Perinatal Human Immunodeficiency Virus Type 1 (HIV) Transmission*

	Treatment				Transmission Rates, %			
			Postpartum					
Trial	Antepartum	Intrapartum	Mother	Infant	Active	Placebo	Reduction, %	*P* Value
No Breastfeeding								
Connor et al, 1994 (PACTG 076)[3]	100 mg 5/d starting at 14 to 34 wk	Intravenous 2 mg/kg loading, then 1 mg/kg per hour	None	2 mg/kg every 6 h for 6 wk	8.3	25.5	68	<.001
Mofenson et al, 1999 (PACTG 185)[24]	076 Regimen and HIV immunoglobin monthly	076 Regimen	None	076 Regimen	4.1	6.0†	33	.36
Shaffer et al, 1999 (THAI CDC)[5]	300 mg 2/d starting at 36 wk	300 mg every 3 h	None	None	9.4	18.9	50	.008
Breastfeeding								
Wiktor et al, 1999 (Abidjan CDC)[6]	300 mg 2/d starting at 36 wk	300 mg every 3 h	None	None	12.2 15.7	21.7 24.9	44 (at 1 mo) 37 (at 3 mo)	.05 .07
Dabis et al, 1999 (Abidjan ANRS)[7]	300 mg 2/d starting at 36 wk	600 mg at onset of labor	300 mg 2/d for 1 wk	None	16.8 18.0	25.1 27.5	37 (at 3 mo) 38 (at 6 mo)	.04 .03
Saba, 1999 (PETRA [zidovudine and lamivudine])[29]‡								
Arm A	2/d starting at 36 wk	Zidovudine every 3 h Lamivudine every 12 h	Every 12 h for 1 wk	Every 12 h for 1 wk	7.8	16.5	52 (at 6 wk)	.001
Arm B	None	Same	Same	Same	10.8	16.5	38 (at 6 wk)	.016
Arm C	None	Same	None	None	15.7	16.5	5 (at 6 wk)	.82
Guay et al, 1999 (Uganda HIVNET 012 [nevirapine])[8]	None	Single dose 200 mg of NVP at onset of labor	None	Single dose of NVP 2 mg/kg at 2 to 3 d	11.9 13.1	21.3§ 25.1§	44 (at 2 mo) 47 (at 4 mo)	.003 <.001

*All dosing regimens refer to oral zidovudine, except as indicated. The 076 regimen included intravenous zidovudine during labor, the Perinatal Transmission Study (PETRA) regimen used a combination oral dosage of zidovudine (300 mg) and lamivudine (150 mg), and the HIV Network, National Institute of Health (HIVNET) 012 regimen used a single dose of nevirapine (NVP) for the mother and child. PACTG indicates Pediatric AIDS Clinical Trials Group; THAI, Thailand; CDC, Centers for Disease Control and Prevention; and ANRS, Agence Nationale de Recherche Scientifique, Paris, France.
†Comparison group received 076 regimen and immunoglobulin intravenously (vs infants in active group who received HIV immunoglobin).
‡Preliminary results. This trial included women who breastfed and women who did not breastfeed their infants.
§Comparison regimen was intrapartum oral zidovudine and 1 week of zidovudine given to the neonate.

ning at 36 weeks' gestation and every 3 hours during labor; no treatment was given to the neonate. An identical regimen in a somewhat less adherent breastfeeding cohort in Côte d'Ivoire showed an efficacy of 37% at 3 months,[6] and a similar regimen (including 1 week of maternal postnatal treatment) showed a 38% reduction in transmission at 6 months.[7] A multicenter trial in Uganda, Tanzania, and South Africa evaluated combination zidovudine and lamivudine in 3 different regimens: prepartum from 36 weeks' gestation, intrapartum, and postpartum for 1 week for mother and child; intrapartum and postpartum; and intrapartum only.[29] Preliminary analysis of 6-week outcomes showed 52% efficacy for the full regimen, 38% efficacy for intrapartum and postpartum treatment, and no efficacy for the intrapartum-only regimen.

Trial results were recently reported for nevirapine, a nonnucleoside reverse transcriptase inhibitor with a prolonged half-life that rapidly crosses the placenta and crosses into breast milk.[8,30,31] Single-dose nevirapine treatment given to the mother at labor onset and then to the neonate was compared with zidovudine given to the mother during labor and to the neonate for 1 week.[8] At 4 months, the study showed a 47% reduction in transmission risk in the nevirapine group vs the ultrashort zidovudine group.

Among the major conclusions from these data are that several different short-course antiretroviral regimens are efficacious in reducing mother-to-child transmission; intrapartum zidovudine-lamivudine treatment alone[29] or ultrashort intrapartum-infant zidovudine[8] have little or no effect; and that efficacy at 3 to 6 months is lower in breastfed than in nonbreastfed infants.[5-7] While caution is required in comparing results across studies, zidovudine-lamivudine treatment starting at 36 weeks' gestation seems to offer little advantage over zidovudine alone.[5-7,29]

Furthermore, either a single dose of nevirapine given to mothers intrapartum and to the neonate or zidovudine-lamivudine given intrapartum followed by a week's dosing given to the mother and her infant provide similar reductions in transmission risk among those who breastfeed compared with giving 4 weeks of zidovudine treatment before and during delivery to the mother.[6-8,29] Among breastfeeding women, the addition of 1 week of maternal postnatal zidovudine treatment appears to provide no benefit over a short course of antenatal-intrapartum zidovudine treatment.[6,7]

In the absence of any maternal treatment, antiretroviral prophylaxis of the neonate also may be effective and relevant to resource-poor settings. Observational data from New York suggest that 6 weeks of infant zidovudine prophylaxis started within 48 hours after birth had an effect similar to that of maternal intrapartum and infant prophylaxis and reduced transmission from 26.6% to 9.3%.[32] Additional data are needed to confirm the efficacy of neonatal antiretroviral prophylaxis and the duration required in both nonbreastfeeding and breastfeeding settings.

Thus far, evaluations of several low-cost preventive measures other than antiretroviral drugs have been disappointing. A study in Malawi showed that vaginal cleansing with chlorhexidine hydrochloride showed no overall efficacy,[33] although a subanalysis suggested protection in women with ruptured membranes for more than 4 hours.[34] Likewise, maternal vitamin A supplementation trials have not shown benefit for reducing perinatal HIV transmission.[16,28]

Research Requirements

Primary Prevention of HIV Infection in Women. Because most pediatric HIV infections are acquired from the mothers, the most effective means of preventing pediatric infection is primary prevention of HIV in women. Particularly in developing countries, women constitute a vulnerable population who are at risk beginning at a young age. Research priority areas include assessment of microbicides, and female condoms and other female-controlled barrier methods, as well as educational, behavioral, and cultural interventions directed at protecting girls and young women via delay of initiation of sexual activity. Adolescents and adult women must be included in research on control of sexually transmitted diseases and evaluations of HIV vaccines.

Determining the Shortest Effective Drug Regimen. Because there are data suggesting postexposure treatment of the infant can prevent transmission,[8,29,32] more research is needed on neonatal treatment alone and comparisons of short-course antenatal regimens with or without neonatal prophylaxis (eg, antenatal short-course zidovudine plus single-dose intrapartum and neonatal nevirapine vs the nevirapine regimen alone) to assess additive effect. It is important to determine whether intrapartum nevirapine dosing is still effective if given late in labor, because in the Uganda trial,[8] nevirapine was taken by women at home at labor onset. Optimal timing for initiation and duration of neonatal prophylaxis needs defining, particularly in settings without safe alternatives to breastfeeding. These questions are especially relevant for women presenting late in pregnancy or in labor and in settings where diagnosis of HIV infection may only be feasible in the peripartum period

Identifying the Optimal Drug or Drug Combination. Data on viral load as a major transmission risk factor,[23,25] observational data on protease inhibitor-containing regimens,[35] and results from intervention trials[5,24] suggest that short antenatal regimens that maximally suppress viral load at delivery could reduce transmission below rates obtained with short-course zidovudine treatment.

In all settings, the goal should be maximal reduction of perinatal transmission. For middle-income countries, short-course combination antiretrovirals (and, possibly, elective cesarean delivery) merit evaluation; this approach (and replacement feeding) could make transmission levels of 5% or lower achievable. For resource-poor settings, nevirapine or other potent drugs with a long half-life given at labor onset and to the neonate appear most feasible but

require further evaluation of efficacy, safety, and resistance.

In areas where seroprevalence is high and where voluntary counseling and testing are not yet widely available, consideration might be given in the short term to providing nevirapine treatment to all mothers and infants.[8,36] Such a scenario would still urgently require HIV counseling and testing (including rapid diagnosis at delivery), so women and their families could make informed decisions about breastfeeding, reproductive health choices, and other HIV prevention interventions.

There have been reports of possible adverse pregnancy outcomes associated with antiretrovirals, including preterm delivery with protease inhibitor–containing regimens[37] and mitochondrial dysfunction in infants of women receiving nucleoside analogs.[38] Thus, monitoring for toxic effects is essential. To date, a 5-year follow-up shows that uninfected children exposed to perinatal zidovudine have normal growth and development and that there are no cases of neoplasm.[39] In the United States, a review of more than 2000 case records from perinatal cohorts showed no increase in rates of prematurity in infants exposed to combination therapy, and a review of cohort and surveillance data of 14 000 case records of uninfected children found no cases suggestive of mitochondrial dysfunction in the 33 uninfected children who died.[40] Safety data from about 700 mother-infant pairs to date indicate no significant adverse reactions with single-dose nevirapine.[8,30,31]

Prevention of Breastfeeding-Related HIV Transmission. Better understanding of the timing of breastfeeding-related HIV transmission is needed to assess potential interventions. Other issues include the relationship of HIV RNA levels in breast milk and plasma; the unit of infection (cell-free vs cell-associated virus); infectiousness of colostrum; immunologic properties possibly enhancing or reducing transmission; the role of mastitis, breast abscess, and other local factors; neonatal factors (eg, prematurity and gastric alkaline pH); breastfeeding duration; and effect of mixed feeding.

Strategies to prevent transmission via breast milk that require evaluation include replacement feeding, exclusive breastfeeding followed by early weaning (vs the more common practice of mixed feeding), and postpartum infant and possibly maternal antiretroviral prophylaxis during breastfeeding. Evaluations of replacement feeding and early weaning must assess their impact on survival and disease in infants, especially diarrheal and respiratory disease as well as nutritional status,[41] and on local breastfeeding norms, birth spacing, and maternal health.

Perhaps the most feasible strategy for reducing breastfeeding-related transmission in resource-poor settings would be to combine several weeks to months of postnatal antiretroviral prophylaxis of HIV-exposed infants with weaning at about 6 months. Another important strategy will involve assessment of the efficacy of HIV vaccines, when available, for breastfed infants of HIV-infected mothers and for HIV-negative mothers post partum.

HIV Counseling and Testing. Innovative strategies are needed to expand uptake of voluntary HIV counseling and testing.[6,42] Assessment of the acceptability and performance of rapid HIV testing is required for women without regular antenatal care.[43] Also, the psychosocial and medical impact of increased testing of women needs assessment (eg, monitoring of domestic violence), as do ways to use maternal counseling and testing to extend general prevention and care efforts.

Implementation and Evaluation. In conjunction with local initiatives, international agencies, donor countries, and pharmaceutical companies are helping establish pilot perinatal HIV-prevention projects in Africa, Asia, and the Americas, which will include thousands of women. The current core strategy is based on short-course zidovudine, with breast milk substitutes at birth or early weaning. As more data become available, nevirapine will likely be an important option in resource-poor areas and for women in all settings without antenatal care. Operational research should be included in implementing and evaluating programs for perinatal HIV prevention. Cost-effectiveness analyses of different approaches, accounting for local context, may be useful for decisions on policy, and drug pricing and procurement.[36,44]

Basic indicators for use in monitoring pilot programs, some requiring follow-up and cohort analysis, are listed in TABLE 3. Evaluation of public health programs cannot be as detailed and may have to rely on analyses of clinic records for monitoring service delivery and utilization. The social and medical impact of programs (eg, effects of increased HIV testing of women, effect of replacement feeding on overall breastfeeding practices, infant health outcomes, and intervention costs) will need monitoring.

Ethical Aspects of Research on Mother-to-Child HIV Transmission

The placebo-controlled trials of short-course zidovudine in resource-poor countries stimulated an intense debate in the medical and lay press of developed countries. Critics' main arguments were that a placebo design was unjustified because a beneficial effect of short-course zidovudine was expected, even if it had not been evaluated in controlled trials, and, because the PACTG 076 regimen was the standard in industrialized countries, this should have been used as the comparison reference in all settings.[45] Proponents of the research argued that the PACTG 076 regimen was not applicable in developing countries due to inadequate medical infrastructure and cost, was inappropriate as the reference because it stood no realistic chance of being implemented, and would not help answer the critical question of whether feasible but unstudied regimens were better than no intervention.[46-48]

A recent discussion of research ethics, accounting for realities of international disparities in medical care, resulted in a consensus statement emphasizing several guiding principles, the most important of which is the con-

Table 3. Monitoring and Evaluation Indicators for Pilot Projects and Programs for Prevention of Mother-to-Child Human Immunodeficiency Virus Type 1 (HIV) Transmission*

Baseline information prior to initiation
Prevalence and quality of antenatal care
Prevalence of HIV infection in pregnant women
Accessibility or acceptability of HIV counseling and testing
Delivery in hospital
Duration of breastfeeding; alternatives to breastfeeding
Infant and child mortality (<2 years; <5 years)
Fertility and birth spacing
Accessibility and nature of routine child health services
Outcome and performance markers for pilot projects
Provision of antenatal care
Provision and uptake of HIV counseling and testing
Social consequences of voluntary counseling and testing for HIV-infected women
Adherence to zidovudine regimen
Infant feeding practices
Social impact of use of breast milk substitutes including uptake by noninfected women
Infection status of HIV-exposed children
Growth monitoring of HIV-exposed children
Birth spacing
Infant and child mortality
Outcome and performance markers for programs
Coverage and uptake (number of deliveries; proportion receiving HIV testing; number and proportion of women treated, etc)
Administration, logistics, supplies
Cost
Medical and social impact (HIV or acquired immunodeficiency syndrome in children, infant and child mortality, feeding practices, acceptance, community support, etc)

*Synopsis of indicators developed by the United Nations Children's Fund, World Health Organization, Joint United Nations Programme on HIV/AIDS (UNAIDS), and Centers for Disease Control and Prevention in preparation for initiating pilot programs.

cept and definition of a local standard of care where the research is conducted.[49] Researchers have an obligation to provide the best level of care that is practically attainable in the host country, not the level of care available in industrialized countries or available to the local elite. In many settings, short-course zidovudine (or nevirapine) would now be the standard against which to compare new regimens. The consensus statement emphasized that international researchers and host countries have an obligation to attempt to implement regimens proven successful in developing countries.

Implications for Policy and Programs

Perinatal HIV Prevention Is a Child Survival Issue. Prevention of mother-to-child HIV transmission should be considered in the context of child survival and reproductive health, not simply HIV and AIDS prevention. To give perinatal HIV prevention lower priority because children do not transmit HIV would fail to take into account the impact HIV and AIDS have on child health and health programs for mothers and children in heavily affected countries. The concern that perinatal HIV prevention will result in more orphans, a criticism that could apply equally to other health interventions, such as providing HIV-exposed children with routine vaccinations, should serve to strengthen HIV prevention and care for women, not weaken perinatal HIV prevention. Short-course perinatal antiretroviral regimens can be considered pharmacologic AIDS vaccines for infants.[50] Adequate family planning services for all women are an additional essential component of primary prevention of perinatal HIV transmission.

Program Components and Priorities. The critical policy decisions concern recommendations about HIV counseling and testing, choice of drug regimens, and infant feeding. Relevant decisions should be based on the best available scientific data, recognizing that heterogeneity in the epidemic and in infrastructure between and within countries precludes uniform recommendations. Because of rapid advances in knowledge, public health–related recommendations will need frequent updates.[51,52]

HIV Counseling and Testing. Policies and practices need review to ensure that pretest counseling requirements are not barriers to diagnosing HIV infection in women and preventing transmission to their children. In the United States, it has been recommended that offering women the opportunity to decline HIV testing ("informed right of refusal") while incorporating routine HIV counseling and testing into standard antenatal care reconciles the need for informed consent with that of expanding HIV testing and treatment access.[53] Similarly, in developing countries, prenatal counseling and testing must be simplified as much as possible and offered routinely while remaining voluntary, confidential, and supportive of HIV and AIDS prevention in women and their partners. Increased use of rapid testing may be especially helpful for women in resource-poor settings who access antenatal care sporadically or only access care at delivery.

Drug Regimens. Currently, settings where the full PACTG 076 regimen cannot be implemented would be best served by adopting either the short-course zidovudine regimen evaluated in Thailand and west Africa,[5-7,51,52] or the intrapartum and short-term neonatal regimens of nevirapine[8] or zidovudine-lamivudine,[29] recognizing that experience with nevirapine is limited to 1 study. Apart from availability of drugs and trained personnel, ensuring optimal benefit from short-course antiretroviral treatments requires a high level of antenatal care, HIV testing before the last month of pregnancy, safe and affordable alternatives to breastfeeding, and community support.

Where safe alternatives to breastfeeding are not widely available, women choosing to breastfeed should be offered one of the proven short-course regimens and be advised about likely advantages of exclusive breastfeeding followed by early weaning.[16,51] For HIV-infected women with late or no antenatal care, the current best options are intrapartum and postpartum infant treatment with nevirapine, zidovudine-

Table 4. Replacement Feeding Considerations for Infants of Human Immunodeficiency Virus Type 1 (HIV)–Infected Women in Resource-Poor Countries

Definition
Feeding a child who is not receiving any breast milk from birth to 2 years with a diet that provides all the nutrients the child needs
First 6 Months
Breast-milk substitute is essential
Commercially prepared infant formula (needs clean water, accurate measurements of powder and water, and good hygiene and clean utensils); or
Home-prepared infant formula with micronutrient supplements (same clean water and hygiene requirements)
6 Months to 2 Years
Breast-milk substitute is preferable, plus nutrient-enriched family foods 3 times daily, including milk products (protein, calcium); meat or fish products (protein, iron, zinc, calcium); fruit and vegetables (vitamins A and C, folate); micronutrient supplements; or if suitable breast-milk substitute is not available, nutrient-enriched family foods 5 times daily

lamivudine (for 1 week), or zidovudine (for 6 weeks). Based on trial results, intrapartum zidovudine-lamivudine treatment alone or intrapartum and 1 week of neonatal zidovudine treatment alone is not recommended. Programs should establish an evaluation component prior to widespread implementation of interventions.[51,52]

Infant Feeding. Policy statements and guidelines on infant feeding and HIV have been published by international agencies.[52,54,55] Women with HIV infection should be assisted in choosing how to feed their infants by having complete and accurate information. Uninterrupted access to safely prepared, nutritionally adequate breast-milk substitutes would likely result in the lowest risk of disease and death. However, artificial feeding in unhygienic circumstances may be associated with increased risk of morbidity and mortality from infectious disease and malnutrition. Cup feeding instead of bottle feeding is recommended for women in developing countries to minimize contamination risk. It is impossible to give advice about these competing risks that is generalizable to all contexts.

Breastfeeding ordinarily provides infants with complete nutrition to age 4 to 6 months, about half of nutritional needs from age 6 to 12 months, and up to one third of needs from age 12 to 24 months. TABLE 4 lists the essentials of replacement feeding from birth to 2 years. For HIV-infected women who elect to breastfeed, early weaning following exclusive breastfeeding as soon as the infant can take adequate replacement food seems appropriate. In practice, this is usually when the infant is about age 6 months. Breastfeeding beyond this, assuming adequate nutrition can be provided, may be associated with greater risk than benefit.

In high-incidence areas, women of HIV-negative or unknown serostatus should be advised to use barrier contraception while breastfeeding to prevent incident infections in themselves and HIV transmission to their infants. Because women who do not breastfeed lose the contraceptive effect of lactational amenorrhea, which has implications for birth spacing, family planning services are needed. Monitoring is needed to assess the impact of replacement feeding on overall breastfeeding practice in the community and on infant and child morbidity and mortality.

Linkage to Other Health Care Interventions. Interventions to prevent mother-to-child HIV transmission highlight weaknesses of allied services in resource-poor settings but offer the challenge to strengthen them. Most obvious is the poor quality of maternal health care services in developing countries, illustrated by high rates of maternal mortality[56] and the general absence of treatment for HIV infection. Identifying HIV-infected women offers an opportunity to introduce rational simple HIV and AIDS care, including screening for tuberculosis and prophylaxis with isoniazid and co-trimoxazole.[57] Antenatal HIV counseling and testing can help to involve women and their male partners in HIV and AIDS prevention activities, HIV and AIDS care, and child health promotion.

CONCLUSIONS

The PACTG 076 regimen and the clinical impact of highly active antiretroviral therapy have resulted in 2 distinct epidemics. In industrialized countries, impressive reductions in HIV-related disease and death have occurred, so virtual elimination of new pediatric HIV infections is feasible. By contrast, developing countries face increasing levels of infection, disease, and death due to HIV. Perinatal HIV prevention offers a tenuous link to bridge this gap, to apply some of the recent biomedical advances in a rational manner in developing countries, and to regain some of the achievements in child survival that HIV and AIDS have erased.

Prevention of HIV infection in children requires HIV and AIDS to be addressed as a disease of the family and community and leads to consideration of other interventions, such as reproductive health care for women and support for children orphaned by the epidemic. Few other aspects of HIV research have demonstrated results as dramatic as the perinatal prevention trials. If international research is to serve any purpose, then the results of the short-course antiretroviral trials for preventing mother-to-child HIV transmission must lead to public health action now.

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