Perspectives on paediatric HIV/AIDS: Prevention of mother to child transmission of HIV

Hoosen Mohamed Coovadia

Doris Duke Medical Research Institute, Nelson R. Madela School of Medicine, Niversity of KwaZulu-Natal, 719 Umbilo Road, Durban South Africa

Setting the scene: A personal perspective

IN today's highly reductionist world medicine has been streamlined into very narrow subspecialities. In developing countries professionals of my time rarely had an opportunity of obtaining formal education and training in these fields, instead they were dependent on experience and the guiding hand of skilled mentors. The research highlights I describe in this article belong to an infectious diseases specialist – but according to the current codes I am a dilettante in the subject. Accordingly, although my subject is paediatric HIV/AIDS, I feel impelled to provide some perspective to the paper by grounding it in a brief account of the succession of research, medical and social issues which led to my current preoccupation in preventing infectious diseases in general, and HIV transmission from mothers to their children in particular. I do this because it is not atypical of the circuitous and often rocky path through research among scientists in the third world; more to the point, the particular experience of dealing with health and disease of children in poor populations forges a state of mind and beliefs which moulds the future of research priorities. I have worked through my entire professional life among poor children living under extremely difficult conditions in South Africa. First, under the brutality and racial oppression of apartheid, and then, during the past 14 years of a democratically elected government, in a social and economic environment of a diminished yet unremitting deprivation and poverty, I studied the health and diseases of children which confronted me every day as a paediatrician in a 'black' hospital. The country at that time provided a stark contrast between the high standard of living of white South Africans and their offspring, and the abject living conditions of black South Africans and their children[1]. The differences between these two polarized groups were as much the disparities of class as they were of race. It was painfully obvious to me that the direct and visible roots of my patients' illnesses were the lack of land, job, income, education, housing, food, potable water, sanitation and electricity. But at a more fundamental level these hardships were the consequences of a lack of political, social and economic power; in a few words, democracy, freedom and human rights. It was always difficult for me to separate these two expressions of human health into the diseases of the body and the mind on the one hand, and the naked privations of context on the other. The 40 or so years of my career in medicine drew me into science as it inevitably plunged me into the struggle for liberty and equity; it was simultaneously a critical search for freedom for society as a whole as it was for the well-being of the individual infants and children in my care. It goes without saying that one does not work alone. Health research is complex requiring the contributions of people with a variety of skills and training; I have had many collaborators whose names can be obtained from my publications. The search for a balance in the types of research we did resulted in the following themes on the health and disease of children in developing countries. These themes are the road travelled to the work done on paediatric HIV/AIDS over the last 15 years.

Macronutrient and micronutrient (especially vitamin A, zinc) deficiencies were central to our group's early research focus. We published a paper on the immunodeficiency in malnutrition which accounted for frequent infections, and which I studied further in animal experiments and clinical situations[2]. Accurate clinical studies to show the value of vitamin A in measles[3], and the potential role of zinc in HIV-infected infants[4] were made. These, together with other papers influenced the management, and an appreciation of pathogenesis and contextual factors responsible for these disorders.

A paper on breastfeeding and HIV was published in the *Lancet*[5] and has influenced WHO policy and the global response of other institutions to this dilemma. My co-workers and I have championed a scientific approach to the options between breast- and formula-feeding among HIV-positive mothers, for the past eight years. A National Institutes of Health (NIH) study, in South Africa, Uganda and Zimbabwe, investigating the reduction of breastfeeding transmission of HIV through antiretrovirals given to the baby, is an attempt to find practical solutions to HIV transmission through breastfeeding. On balance, these studies are probably front-ranking scientific and public health publications which will result in prevention of infections and saving thousands, and maybe millions of infant lives.

e-mail: coovadiah@ukzn.ac.za

Severe infections such as measles[6], pneumonia[7], HIV[8], tuberculosis[9] and hepatitis B[10] accounted for much morbidity and deaths. I completed an evaluation of measles vaccine for young infants[11], and my MD (Ph D) was on genetic determinants and immunodeficiency as risk factors for severe disease in measles[12] (antedating the finding in HIV that lymphopenia reliably predicted prognosis). Investigations into the use of tests for accurate diagnosis of tuberculosis in children were carried out[13], a textbook on tuberculosis was published[14], the features and management of co-infection with HIV and TB[9] described; and management and aetiology of the major killer of children globally-pneumonia – was the subject of a recent study in the *Lancet*[7]. Hepatitis B was a prominent cause of renal disease in African children[15] (membranous nephropathy) before infant vaccination virtually eliminated it; my group has one of the largest published records of various facets of this disease. These publications have altered the approach to treatment of these disorders among children in developing countries.

The experiences during the past have encouraged me to develop a comprehensive and cohesive philosophy of the surface and deeper explanations for human disorders. Accordingly, in addition to elucidation of the direct agents and pathological processes responsible for these diseases, I have had to be centrally involved in alleviating the proximate causes and contexts of these problems. These convictions have led to participation in efforts aimed at ameliorating the broad social conditions of poverty, hunger and starvation in South Africa. These have instant application to the rest of Africa. In particular, I was able to gain insights into the relief of poverty and the implementation of relief and development programmes aimed at the 'poorest of the poor' during the transition from apartheid to independence in the early nineties through my involvement as a trustee on the broad-based Independent Development Trust. At one remove, but fundamental to the achievement of the basic human rights of black children to life, family, education, housing, liberty and the realization of their potential, I occupied important leadership positions in the national and global struggle against the apartheid regime. At independence, I participated in the initial planning of a democratic health system appropriate for mothers and children in the country. The task of attaining these goals for women and children, and indeed for all citizens, has not been diminished by the establishment of a democratic society; indeed the consolidation of peace and equity is even harder to attain. So it remains imperative to continue to raise issues of major importance for public health to this day. It is to this, which I turn to now.

The scale of the pandemic of HIV/AIDS

HIV/AIDS permeates every facet of society and penetrates to the deepest and most intimate reaches of individual identity; it is an agonizing journey through a series of personal, collective, institutional and societal disasters. In tracing the paths of the epidemic until recently, it was clear that the virus was moving relentlessly across Africa, to India, Eastern Europe, the Caribbean and China. Current data given below show signs of a decrease in the rate of spread and successes in controlling and managing this disease in some affected countries.

Throughout history epidemics of infectious diseases appear to have emerged, and often vanished, causing great distress and leaving in their wake huge swathes of death and destruction. The Black Death in fourteenth century Europe, which wiped out possibly a third of the population, and smallpox, tuberculosis and influenza, which have killed millions of humans until recently, are the clearest examples of such epidemics[16,17] and the spread of a range of 'emerging diseases', show that modern societies, interconnected through numerous global networks and communication channels, remain at risk and are not safe from spread of dangerous micro-organisms throughout the world. There are excellent accounts of many other global epidemics which have wreaked similar havoc among the world's peoples, and interesting speculations in the absence of evidence, on likely diseases of our earliest ancestors. There is much to learn about vulnerability, acquisition, biological and social impacts, and prevention of the worst consequences of disease from each of these epidemics. Research work on the fourteenth century plague of Europe continues to this day.

HIV/AIDS is unique in this array of catastrophic infectious diseases. Although HIV/AIDS has the destructive potential of many of the most severe of the historically documented epidemics, it is unique in the rapid and unrelenting genetic mutability of the virus, the immense damage inflicted on the precious cells of the immune system instrumental in protecting the host, the lethality of the disease in the absence of treatment, the labyrinthine pathways of metabolic and immunological derangements, the perplexing reactions of the immune system which currently defy identification of specific protective elements, the prolonged asymptomatic period during which a war is being fought between host and virus, and the puzzling combination of social and other risk factors which predispose to acquisition and progression of disease[18]. HIV/AIDS is pervasive in terms of its impact on multiple aspects of human society; political challenges, security, the economy, industry, commerce, military, demography, family life, social capital and disintegration, morality, human resources, etc. are all, to some extent, affected. While many of the other epidemics had one or a few of these negative features, none had so many and with such capacity for causing major social dislocation. The current numbers are staggering.

Every day 6800 persons become infected by HIV, and 5700 persons die from the extreme form of the disease – AIDS[19]. They die, mostly in poor populations, because of

a lack of infrastructure: health professionals and health facilities. They cannot reach clinics and hospitals, and because there is a severe shortage of health professionals to advise them on prevention measures and treat them with appropriate drugs[19]. By the final months of 2007 there were 33.2 million (range around the estimates 30.6–36.1 million) people living with HIV; of these, children (<15 years) comprised 2.5 million (2.2–2.6 million); further details on children are given in Tables l–3. Adults accounted for 30.8 million (28.2–33.6 million) and women 15.4 million (13.9–16.6 million). It is necessary to include the details of these estimates as there has been much controversy over the annual figures released by UN agencies[19]. Criticisms have been directed at the changing annual estimates, with the most recent figures (2007) revealing a massive decline in the global burden[19]. The main reason for this was a revision of the estimates of HIV in India, which had been much higher in the previous year. Figures from a few African countries also had to be revised. These estimates are derived from a number of sources and represent the best available information, and as methods of estimation improved, figures have been revised. It is an area of continuing research and improvement. A total of 2.5 million (1.8–4.1 million) became newly infected in 2007 adding to the burden of those still alive and living with HIV; adults made up 2.1 million (1.4–3.6 million) of these. At the other end, a total of 2.1 million (1.9–2.4 million) people died of AIDS in the same year; adults were 1.7 million (1.6–2.1 million) of these. The total of 33.2 million for 2007 represents a reduction of 16% compared to the figures obtained in 2006, for the reasons stated above; part of the decline in some countries is due to decrease in risky sexual behaviours resulting from implementation of effective prevention programmes and from the natural evolution of the epidemic. Tables 1–3 are based on UN data[19].

Sub-Saharan Africa is most severely affected: more than two-thirds (68%) of the global total of adults and about 90% of the children living with HIV are in this region. Africa is already reeling from just under two decades of unprecedented loss of its human and infrastructural capital. There are wide disparities in prevalence over the continent; the hardest hit is southern Africa, with prevalences much lower in west Africa. The reasons for these differences are not always clear. It is difficult to understand why the disease produces markedly dissimilar patterns of infection and morbidity; why there is explosive spread in one region, and slow gradual erosion in another. Indeed a key focus of research is the elucidation of the causes of these differences as the findings may provide essential clues to improving methods of prevention. It is possible that several factors – social, biological, behavioural, economic, historical and political – colliding and resonating among themselves generate a specific profile of the disease. The declines in the numbers living with HIV, new infections and AIDS deaths (Table 3) have paralleled the fall seen in other countries such as in South- and South-East Asia and in eastern Europe. A central feature of the disease in sub-Saharan Africa is that the proportion of HIV-infected women is higher (61%) than that in men. In other regions and countries there are more males than females infected by HIV. This epidemic often affects the most socially deprived and poorest communities worldwide, children, women and men who are at the margins of society, or groups subordinated to those who hold political, economic and social power: these include women and men in developing countries, women in all societies, gay men, intravenous drug users, alcohol abusers and children. This chapter is about one of these groups: children.

Table 1. HIV/AIDS in children

	2007
Number of children <15 years living with HIV	2.5 million (2.2–2.6 million)*
Children <15 years newly infected with HIV in 2007	420,000 (350,000–540,000)
Children <15 years: AIDS deaths in 2007	330 000 (310,000–380,001)

*Range around estimates.

The prime area of HIV/AIDS research of the group in Durban, South Africa, is prevention of infant and childhood infection. Children are nearly always infected from their mothers, across the placenta, during delivery and through breastfeeding; a minority, possibly under 5% are infected through nosocomial channels (e.g. use of unsterile needles in developing countries). There are three different routes of transmission of HIV[20]. The rate of transmission is 5–10% during pregnancy, 10–20% during labour and delivery, and varying rates according to the duration of breastfeeding, roughly 1% for each month of breastfeeding. In the developed countries, where breastfeeding is avoided by HIV-positive mothers, the main transmission is due to that which occurs during pregnancy, and in labour and through delivery. The risks and rates of breastfeeding transmission are discussed below.

The consequences of HIV infection in children are, broadly stated, biological mainly because of deterioration in immunity, psychological and social. Stigma and discrimination are a constant hazard for infected children. The figures in Tables 1 and 2 indicate the numerical dimensions of the disease in children, they do not convey the dreadful impact of the disease. The most dramatic effect is on survival[21]: it is a lethal disease without treatment, in general a quarter of HIV-infected babies in poor communities die by their first birthday, more than half by their second birthday, just under two-thirds by 5 years, and most by 8 years of age. There are various risk factors which account for the rate of mortality; these include the country background rate of child and infant mortality, access to care, age at diagnosis, immunodeficiency in the

Table 2. Trends in incidence and prevalence of HIV/AIDS in children

	2001	2007
Increase in number of children living with HIV	From 1.5 million (1.3–1.9 million)	To 2.5 million (2.2–2.6 million)
New infections among children declined	From 460,000 (420,000–510,000)	To 420,000 (390,000–470,000)
Deaths due to AIDS were unchanged, though they had risen and then fallen	From 330,000 (380,000–560,000)	To 330,000 (310,000–380,000)

Nearly 90% of all HIV-positive children live in sub-Saharan Africa.
There are an estimated 11.4 million (10.5–14.6 million) orphans due to AIDS in this region.

Table 3. Trends in incidence and prevalence HIV/AIDS in sub-Saharan Africa

	2001	2007
People newly infected with HIV	From 2.2 million (1.7–2.7 million)	To 1.7 million (1.4–2.4 million)
People living with HIV increased	From 20.9 million (19.7–23.6 million)	To 22.5 million (20.9–24.3 million)
Adult (15–49 years) HIV prevalence declined	From 5.8% (5.5%–6.6%)	To 5.0% (4.6%–5.5%)

Of the global total of 2.1 million (1.9–2.4 million) adult and child deaths due to AIDS in 2007, 1.6 million (1.5–2.0 million) occurred in sub-Saharan Africa.
More than two out of three (68%) adults infected with HIV live in this region, and more than three in four (76%) AIDS deaths in 2007 occurred there.

mother, and infant feeding of formula or breastmilk[22]. Disease and death are often due to progression of the HIV disease process itself, as it erodes and devitalizes tissues and organs. More often, morbidity and mortality in children are due to a relentless destruction of the immune system which opens the floodgates to multiple infections and malignancies. It follows that the types of infections which supervene are those which are latent and a range of disorders common to children in developing countries[23]. They die from Pneumocystis jiroveci during the immunologically vulnerable months of early infancy. Others include failure to thrive and malnutrition, acute bacterial infections (e.g. pneumonia, septicaemia), diarrhoeal diseases (e.g. cryptosporidium), viral infections (e.g. cytomegalovirus, herpes simplex), chronic diseases (e.g. tuberculosis) pneumonia, gastro-intestinal disorders, haematologic abnormalities, neurological dysfunction, cardiac abnormalities, renal disease and cancers. In the most affected countries, mortality from AIDS is contributing to a rise in infant and under five-year mortality rates. In the most seriously affected countries, such as Botswana and Zimbabwe HIV/AIDS mortality can account for more than 40% and 30% respectively of under five-year mortality[24]. Caring for the children who have been orphaned due to AIDS presents a great challenge in resource-poor communities. There are an estimated 11.4 million (10.5–14.6 million) orphans due to AIDS in sub-Saharan Africa who have lost either one or both parents to AIDS[19]. In most cases, the grandparents or extended family take on the responsibility for caring for orphans, which places a burden on this already stretched support system[25]. There are major social and economic consequences in the lives of children residing in communities affected by the AIDS epidemic. Income falls as illnesses in the family rise; increasing expenditure is caused by healthcare and funeral costs. In a household affected by AIDS, household income falls by up to 60%, whilst spending on healthcare increases four-fold[26]. Domestic chores, care-giving and income generation in the household often fall to children[27]. School attendance is disrupted with long term consequences for the development and earning capacity of the child[26]. Child abuse and child labour are exceedingly harmful to the well-being of children; exploitation and under-age employment require legal, moral, community and family pressures for prevention. HIV-affected households often have to cope with high incidences of crime, food insecurity, violence and single parent families[26]. In Africa about 40 million children experience some form of violence every year. For example in the Cameroon 16% of the secondary students were sexually abused, in Uganda the figure for girls is 31%, in Botswana 67% schoolgirls were sexually harassed by teachers, and in South Africa there were 32% child rapes by teachers[28]. In some settings, one of the most tragic outcomes is the death of a mother and/or father which leads to dissolution of the entire family, i.e. social structure to which individuals belong ceases to exist. In one South African rural area the chances of household dissolution were four-fold higher in households with AIDS deaths; similar findings are reported from other African countries[29]. Parental guidance, especially that by the mother, is lost. Providing adequate care and protection to children affected by HIV is a great challenge in developing countries[30]. What can be done to reduce the appalling impact of this disease in children? It is this to which I turn now.

The treatment of children who are already HIV infected will not be covered here in any detail as the subject deserves more attention than is within the scope of this

article. Comprehensive care of HIV-infected children has been highly successful in industrialized countries: with the use of antiretrovirals supplemented by intensified care growth and development are improved, morbidity and mortality are reduced, and in general the well-being of the child achieved. In poorer populations there are a number of barriers to overcome: diagnosis during infancy is costly because of the need for expensive molecular amplification techniques, best results with ARVs are in very young infants who need to be accessed and identified, health personnel may not have adequate training, health facilities are often unable to offer laboratory back-up, or optimum treatment, care and follow-up, drugs may be unavailable and supply may be available intermittently, opportunistic infections can be decreased but prophylaxis (INH for tuberculosis; cotrimoxazole for common infections) is frequently missed, and nutrition and psychosocial support lacking. Despite these difficulties, there are a number of highly successful child treatment programmes in developing countries, and the results are equivalent to those obtained in richer populations. Many of these programmes are run by health professionals fired by enthusiasm, dedication and passion. The critical next step is to promote, protect and nurture the development of such programmes to reach the majority of those in need.

Prevention of mother to child transmission of HIV

The main thrust of this article is an account of prevention of HIV transmission from mothers to infants. This has been the prime subject of our research from the early 1990s and therefore allows me the opportunity to record progression from a period when the virus was transmitted from HIV-positive mothers to their infants in about 25% of pregnancies in the industrialized world, to the present when transmission is down to about 1% or 2%. In some instances the transmission has been eliminated[31]. The most telling way to gauge this success is to note that UNAIDS estimates that there were 1600 new infections in children (<15 years) in North America in 2007, <1000 in western and central Europe, but 370,000 in sub-Saharan Africa in the same year[19]. This translates into about 1200 new HIV infections among children, overwhelmingly from Africa, every day in 2007. These figures should be appreciated in the context that transmission has now been reduced among populations in developing countries which have access to the appropriate health facilities. The fact is that only a minority of pregnant women in sub-Saharan Africa have access to HIV-prevention programmes. The reasons for this lack of access are similar to those for other programmes on HIV/AIDS in Africa and include the following: large demands because of an increasing population with HIV/AIDS, insufficient finances (indeed in many African countries much of the health budget is dependent on foreign aid), inequities in the health sector as in much of society as a whole, persistence of vertical programmes for individual diseases rather than integration of services, and an inability to co-ordinate funds from external donors. And even when pregnant women do have access to antenatal clinic services, there is a steep fall from those who are first seen in the clinic to the actual proportion receiving appropriate preventive therapy for themselves and their newborns. There are a number of reasons for this 'cascade of loss': stigma and discrimination deter women from either consenting to an HIV test after counselling or returning for the test results; inadequate counselling and unsympathetic health personnel; fear of disclosure of the test result to family and partners; transport and financial difficulties; illness in the families; and health services which are not free, poorly staffed, at distances from residences, and inconsistently functioning. In recent years there have been improvements in levelling the 'cascade': rapid HIV testing allows very quick results, abandoning the practice of taking elaborate and time-consuming individual consent for HIV testing, increase in number of counsellors and improved counselling, and some decrease in stigma and shame. The rate of HIV transmission was much higher, about 35%, in developing countries in the absence of antiretrovirals (ARVs) (Tables 4–6).

Prevention of mother-to-child transmission among non-breastfeeding populations

The reasons for success in the industrialized countries are not difficult to identify: strong support for research, convincing evidence in a stringently conducted trial, rapid transition from research into practice, available budget allocations, accessible health facilities, and trained personnel, on the supply side; and an informed population, on the demand side[32,33]. Prevention of mother-to-child transmission (MTCT) programmes have also succeeded in some middle-income countries like Thailand and Brazil, and in the Cape Province in South Africa, and in the Cameroon. As programmes are scaled-up in poorer populations, it is likely that many more countries and regions will achieve similar results. There are, however, many hurdles to overcome, and it will be necessary for progress on coverage and quality of these programmes to be regularly monitored, and the effectiveness of the more efficacious ARV regimens available to be evaluated by estimating the reduction in HIV transmission and increase in survival of infants. The demonstration that ARVs used during pregnancy, and in labour and through delivery, and for a short period after birth, among formula feeding infants, substantially decreased transmission of HIV, is the key finding which has revolutionized prevention of MTCT of HIV[34]. The application of this same principle to breastfeeding infants, with administration of ARVs to mothers or infants whilst breast-feeding continues, has recently

Table 4. Key antiretroviral trials to reduce mother-to-child transmission of HIV: non-breastfeeding women

Study	Prophylaxis		Transmission rate or active vs placebo
	Mother	Infant	
PACTG 076[34]	Zidovudine (ZDV)	ZDV	8.3% vs 25.5%
Harvard University –Thai–PHPT–1[37]			
Arm LL	ZDV (from week 28)	ZDV (for 6 weeks)	@ 6 months: 6.5%
Arm LS	ZDV (from week 28)	ZDV (for 3 days)	4.7%
Arm SL	ZDV (from week 35)	ZDV (for 6 weeks)	8.6%
Arm SS	ZDV (from week 35)	ZDV (for 3 days)	10.5%
CDC Thai[36]	ZDV	–	9.4% vs 18.9% @ 6 months
Harvard University–Thai–PHPT–2[38]	ZDV + Nevirapine (NVP)	ZDV + NVP	1.1% vs 6.3% @ 6 months
Thailand[39]	ZDV + NVP	ZDV + NVP	4.6% @ 4 months
Thai ZDV & 3TC trial[126]	ZDV + Lamivudine (3TC)	ZDV (4 weeks)	2.8% @ 18 months
ANRS 075 study[127]	ZDV + 3TC	ZDV + 3TC (6 weeks)	1.6% @ 6 months

Table 5. Key antiretroviral trials to reduce mother-to-child transmission of HIV: breastfeeding women (1999–2003)

Study	Prophylaxis		Transmission rate: Active vs placebo
	Mother	Infant	
Ivory Coast[128]	ZDV		15.7% vs 24.9% @ 3 months
Ivory Coast			18.0% vs 27.5% @ 6 months
Burkina Faso[129,48]	ZDV		21.5% vs 30.6% @ 24 months
Petra Trial[49]	ZDV + 3TC	ZDV + 3TC (for 1 week)	5.7% vs 15.3% @ 6 weeks
			14.9% vs 22.2% @ 18 months
Arm A	ZDV + 3TC (intrapartum only)	ZDV + 3TC (for 1 week)	8.9% vs 15.3% @ 6 weeks
Arm B			18.1% vs 22.2% @ 18 months
HIVNET 012[46,47]	ZDV + NVP	ZDV + NVP	13.1% (NVP) vs 25.1% (ZDV) @ 14–16 weeks
			15.7% (NVP) vs 25.8% (ZDV) @ 18 months
SAINT[130]			
Arm 1	ZDV + 3TC	ZDV + 3TC	9.3% (ZDV) vs 12.3%(NVP)
Arm 2	NVP	NVP	

also been shown to be successful. The landmark study[34] PACT 076/ANRS 024, carried out in the USA and France, showed an efficacy of 68%. In this study the drug used was ZDV given at a dose of 100 mg orally from week 14–34 of pregnancy; 2 mg/kg intravenously at onset of labour and then at 1 mg/kg/h. The infant was prescribed 2 mg/kg orally four times a day for six weeks. At 18 months after birth, the transmission rate was 25.5% in the placebo group and 8.3% in the treated group. Although this study was crucial in establishing the principle of ARVs for reducing MTCT, it was deemed to be less than satisfactory for use in Africa and Asia. The price of the ARVs available at the time (1994) for use in such programmes was simply out of reach of poor countries; the health infrastructure for implementation, especially antenatal, delivery and postnatal follow-up services, were inadequate in developing countries, and avoidance of breastfeeding was neither feasible nor desirable in the third world[35]. Over the past 14 years the prices of ARVs have fallen steeply and some health services improved. Despite all this, it has been estimated that only about 10% of women who require these programmes actually receive them.

The need for regimens more appropriate for developing countries led to a number of studies in Thailand among non-breastfeeding populations, and in Africa among breastfeeding populations. The end result was that shorter regimens, using affordable drugs, and combination ARVs, became available. Among non breast-feeding women the short course CDC Thai regimen using ZDV from week 36 of pregnancy through labour and delivery, gave a 50.1% efficacy and transmission was reduced to 9.4% at six months[36]; other studies also using ZDV brought the MTCT rate to under 5%[37]. The best results were obtained by Lallemant *et al.* in Thailand[38]; they used ZDV from week 28 of pregnancy and combined this with NVP given

Table 6. Key antiretroviral trials to reduce mother-to-child transmission of HIV: breastfeeding women (2005)

Study	Prophylaxis		Transmission rate: Active vs placebo
	Mother	Infant	
Ditrame Plus 1.0[131]	ZDV + NVP	ZDV + NVP	6.5% vs 14.7% @ 6 weeks
Ditrame Plus 1.1[131]	ZDV + NVP + 3TC	ZDV + NVP + 3TC	4.7% @ 6 weeks
MASHI[132]	ZDV + NVP Placebo	ZDV (6 months in breastfed) + NVP Placebo	9.1% breastfed @ 7 months 5.6% formula fed @ 7 months 4.5% breastfed @ 1–7 months

to either the women during labour and delivery or to the newborn. The transmission rate at six months was as low as 1.1%. A French study by Mandelbrot *et al.*[39], using combination ARVs (ZDV + 3TC), reduced transmission to 1.6%[38]. Another similar regimen in Thailand, but beginning ZDV a little later (34–36 weeks) in pregnancy, was less successful – transmission was 4.6% at four months[39]. WHO recommendations now include the ZDV plus NVP regimen for developing countries[38].

Other ancillary measures have proven to be effective in reducing MTCT. A European randomized controlled trial of vaginal delivery versus caesarean section (CS) showed an 80% efficacy of CS in reducing transmission[40]. The MTCT rate among women allocated to vaginal delivery was 10.5% versus 1.8% in the elective CS group. A similar finding was obtained from a meta-analysis involving 15 American and European observational studies[41]. Caesarean sections have not been employed in developing countries to minimize MTCT, because sepsis rates of CS in developing countries are high and because of the inability of health services to cope with an increased burden of HIV-positive pregnant women. The availability of highly efficacious combination ARV regimens to reduce MTCT to under 2% has also rendered CS an unattractive option in developing countries. There is some evidence that safe deliveries with a minimum of instrument intervention are associated with a reduction in transmission of HIV[42].

Before moving onto breastfeeding issues and prevention trials in lactating women there is another public health matter of some importance. The discussion on measures to decrease MTCT so far have been on the use of ARVs and CS, and mention has been made of breastfeeding as a risk for transmission. However this is far too narrow an approach, a more holistic approach has been recommended by the WHO. The following are the elements of this comprehensive method: prevention of HIV in women as a prior step to preventing MTCT, reducing unintended pregnancies in HIV infected women, decreasing vertical transmission (as pointed out above through ARVs, etc.), and providing care, treatment and support to HIV-infected women, their infants and their families. This approach has been tested for its usefulness by a cost-effectiveness analysis of data on prevention of MTCT from eight African countries[43]. The analysis compared the effectiveness of a standard ARV intervention to prevent perinatal transmission of HIV with the outcome of the first two interventions suggested by WHO. Prevention of HIV in women by reducing HIV prevalence by 1.25% or lowering unintended pregnancies in HIV-infected women by 16%, yielded an equivalent decrease in HIV transmission from mother to infants to that obtained by use of an ARV for perinatal transmission. Therefore small reductions in either HIV prevalence among women of child-bearing age or in unintended pregnancies were similar in their effect as prevention of MTCT of HIV. There is an important general point to be made from this study: it is that health services which are combined at the point of delivery are more cost effective, better at utilizing health personnel and facilities, and are user-friendly for people[44].

Trials aimed at prevention of MTCT in breastfeeding populations have also been successful. These trials were all conducted in African countries where breastfeeding is the norm and where the practice has been preserved in most countries despite the spill-over effects from inconsistent application of policies for HIV-affected populations. The outcomes have not been as uniform as in non-breastfeeding women. WHO guidelines recommend the following: women not eligible for ARV treatment for their own condition should receive combination prophylaxis ARVs. These should preferably be ZDV from 28 weeks of gestation; ZDV, 3TC and a single dose of NVP (sdNVP) during delivery; and ZDV and 3TC for 7 days after delivery to reduce the development of NVP resistance. Newborn infants should receive a sdNVP and 1–4 weeks of ZDV, depending on the duration of the regimen received by the mother. Although steps are being taken to provide more effective regimens, the use of sdNVP alone should still be used in situations in which more effective regimens are not yet feasible or available[45].

Prevention of *perinatal* MTCT among breastfeeding populations

The HIVNET 012 trial in 1999 established the basis for one of the most widely used ARV regimens in developing countries: a single dose of 200 mg of oral NVP to the

mother at onset of labour, and a single 2 mg/kg dose of NVP within 72 h of birth to the infant (sdNVP), reduced HIV transmission from 25.1% to 13.1% at 14–16 weeks (47% relative efficacy). And maintained this effect at 18 months, 25.8% to 15.7% (42% relative efficacy)[46,47]. The simplicity, safety, affordability and effectiveness of this regimen made it acceptable through most of the affected countries in the third world. There were criticisms of the conduct of this study, and a number of audits, but the scientific foundations of the findings were never in serious doubt, and the problem appeared to be politically inspired. There have been large scale benefits of implementation of sdNVP, and these include the catalytic effect on implementation and extension of HIV services to infants, mothers and their families. Bottlenecks in health services delivery in developing countries have accounted for the failure of this regimen reaching more women who need the intervention. There have been a large number of other studies on breastfeeding women; these are given in the Table 5. The key issue facing health care providers is that high efficacy rates in early infancy, usually 6 months, are decreased with the transmission which occurs with continued breastfeeding. It follows that the prime indicator of an efficacious regimen is the transmission at the point of discontinuation of breastfeeding. The higher rates of efficacy during early infancy, 63% in PETRA and 47% in HIVNET 012, and a little later in the West African studies of 36% to 48%, had waned by 18–24 months to 41% in HIVNET 012, 33% in PETRA, and 23–28% in the West African studies[46–50].

Combination ARVs, tested after the above studies had been done, soon showed improved efficacies. The French group working in West Africa using a combination of ZDV from 36 weeks and sdNVP, obtained a transmission rate of 6.5% at 4–6 weeks, and 4.7% with the addition of 3TC from 36 weeks; historical data revealed a transmission of 14.7% at 4–6 weeks with ZDV alone[48,50]. In a recent comparison of the efficacy at six weeks of different regimens among breastfeeding African populations, the findings were: compared to placebo PETRA Arm A was the most effective, next was the short course antenatal ZDV, then the sdNVP; only the longest regimen of PETRA (Arm A) was significantly more effective than sdNVP[51]. In summary, although shorter courses of ARVs reduced *perinatal* MTCT and were therefore appropriate for developing countries, ARV prophylaxis which extended from the antepartum period, through labour and delivery, and into the postpartum period, were the most effective. Longer antepartum courses (from about 28 weeks) were better than shorter antepartum courses, and combination ARVs improved outcome over single ARVs. It must be stressed that the transmission solely due to breastfeeding was not specifically addressed in these trials and no effect of the interventions used could be assumed to achieve this. Trials aimed at tackling breastfeeding transmission are described in the next section.

The infants of pregnant women, who had missed out on any ARVs during the antenatal, labour and delivery periods, can still be protected by the use of ARVs at birth and soon after. MTCT rates were 7.7% and 12.1%, at 6–8 weeks in a breastfeeding group given neonatal ZDV for 7 days with sdNVP at delivery, compared to sdNVP alone[52]. A randomized trial showed that sdNVP gave better results than six weeks neonatal ZDV; the MTCT rates were 8% and 13% respectively. This study was carried out in a breast and formula-feeding population[53]. A 2004 review of MTCT trials in developing countries by the Ghent Group concluded the following: the most frequently used ARVs were ZDV, ZDV + 3TC, and NVP; the MTCT rates over 24 months without ARVs were between 30 and 45%; the MTCT rates over 24 months with ARVs were between 16 and 23%[54].

Prevention of HIV transmission through *breastfeeding*

The HIV pandemic has caused confusion around infant feeding messages and has led to the erosion of breastfeeding practices. It is generally agreed that breastfeeding is the best form of nutrition for all infants everywhere, for a minimum of six months, and ideally to at least two years[55–59]. Infants to the age of six months should be 'exclusively breastfed', i.e. given breastmilk alone, without the addition of any other fluids such as water or nonhuman milks, or any other foods. Complementary foods and fluids are required beyond six months for optimum growth and development[59]. The multiple benefits of breastfeeding, both short- and long-term, have been extensively covered in the literature[55–57,60–63]. Improved survival in the first six months is the most important[64–67]. Avoidance is justified only under extreme conditions, such as maternal deaths or disabilities during massive social upheavals like conflicts and wars, rare metabolic disorders in infants, and very severe disease and use of potentially toxic drugs by the mother. In developing countries, replacement of breastfeeding with formula milks, other milks and foods, is attended by increased mortality, and poor growth and development[67,68]. The international campaign against the promotion of formula by large manufacturing companies led to the acceptance of an International Code of Ethics for the Marketing of Breastmilk Substitutes' by the WHO Assembly in 1981, and subsequently the ten-point 'Baby Friendly Hospital Initiative'[69]. Fostering, promoting and protecting breastfeeding is therefore an imperative for child health and a global good. But breastfeeding also transmits HIV (see below). Therefore the dilemma for HIV-infected women is to choose between breastfeeding, which protects against morbidity and mortality, and has other benefits, against exposing the infant to the risk of HIV transmission; formula has no risk of HIV transmission but

increases risks of morbidity and mortality in poor populations. Indeed, in recent trials among HIV-infected pregnant women the same lessons are being relearned. Evidence from a number of African countries shows that too early discontinuation of breastfeeding may be hazardous for the health of HIV-exposed infants. How do we balance the hazards of HIV transmission through breastfeeding, against the risks of mortality and heightened morbidity? It is possible to minimize the risks of transmission of HIV from breastmilk, which is the main burden of this article. We can also attempt to minimize the risks of mortality, and nutritional and infectious disorders from formula feeding. The latter has yet to be proven in underdeveloped regions already reeling from the HIV/AIDS epidemic among infants exposed to formula milks.

We have argued the ethical position of attempting to preserve breastfeeding through the HIV epidemic by making it safe (reducing the risk of HIV transmission) because there was much opposition to the idea and a case made for formula in Africa. The essence of our beliefs is guided by the three philosophical frameworks[70] on public health: (i) 'Utilitarianism' in which decisions are judged by outcomes, Jeremy Bentham's 'greatest good for the greatest number'; (ii) 'Liberalism,' which emphasizes rights and opportunities, especially individual rights, concentrates on where people start rather than where they finish; (iii) 'Communitarianism,' which pertains to individual and social virtue, and the creation of a good society. We believe that HIV and breastfeeding offers an illuminating ethical discourse highlighting the application of these principles; we have concluded that the ethical foundations of the breastfeeding studies and policies we suggest are just and fair[22].

The trials on reducing breastfeeding transmission of HIV followed those described above, which succeeded in decreasing transmission which occurred in the antenatal, peripartum and neonatal periods. As it is difficult to distinguish intrapartum transmission from breastfeeding transmission during the first 4–6 weeks after birth, for practical purposes most studies define breastfeeding transmission as that which occurs 4–6 weeks after birth. Much data has accumulated to demonstrate the feasibility of reducing breastfeeding transmission substantially. There has been some evidence that breastfeeding by HIV-infected mothers may in fact be harmful to their own health. These fears have not been substantiated by other studies[71–73] and an individual patient met-analysis[74] meta-analysis. Two Kenyan studies of formula versus breastfeeding suggested the following: a higher mortality among breastfeeding mothers in the first study[75] and in the second study[76] a more rapid decline in CD4 counts, and fall in Body Mass Index in the breastfeeding groups, but with no differences in viral counts and mortality between the two groups. There appeared to be no long-term effects of the fall in CD4 on viral levels or on mortality, therefore the implications of these findings on maternal health are not convincing.

Transmission rates due to duration of breastfeeding

Transmission occurs as long as breastfeeding continues[77–79]. In a Malawian study there was some evidence of a declining risk of transmission with increasing age of the infant[79]. The meta-analysis from sub-Saharan Africa, referred to above[77] showed children are at continued risk throughout breastfeeding.

We have recently summarized the pathogenesis of breastfeeding transmission[22] and will not repeat the details here except to add that the subject deals with the following: protective factors in breastmilk of HIV-infected women, integrity of the gastro-intestinal barrier, promotion of beneficial intestinal microflora, mammary epithelial permeability, breastmilk viral load in cell-free and cell associated forms, and miscellaneous factors.

Transmission rates due to mode of breastfeeding

The mode of breastfeeding ('exclusive' (EBF) or 'mixed' (MBF)) also affects transmission rates. Most early studies did not specify the pattern of breastfeeding[79–83]. As MBF is the form followed by the overwhelming majority of women throughout the world, despite EBF being the WHO recommended mode, it can be safely assumed that most of these previous studies reflected the results of MBF[84–86].

Ruth Nduati *et al.* in Nairobi, Kenya, randomized HIV positive pregnant women to formula or breast[81]. In the formula group there was 30% non-compliance and women mixed breastfed. At 24 months the excess transmission through breastfeeding was 16.2% (95% CI 6.5%–25.9%). The transmission rates at 24 months were 36.7% and 20.5% in the breast and formula feeding arms respectively. The mortality rates were similar: 24% in the breastfeeding arm, and 20% in the formula feeders, whilst a combined rate of HIV transmission and mortality was worse in the breastfeeding arm.

A Durban, South Africa study introduced for the first time the idea of differential rates according to type of breastfeeding[87,88]. HIV-positive women in EBF, MBF and formula groups were studied at 3 and 6 months. EBF was associated with similar rates of transmission at 6 months, as formula feeders (19.4% for each) which was significantly lower than that for MBF (26.1%). At 15 months, infants who had been mixed fed were more likely to be infected (36%) than those who had been exclusively breastfed (25%) or exclusively formula fed (19%). However this was a secondary analysis of a vitamin A intervention trial, therefore the data obtained required

confirmation through another study whose prime purpose was transmission according to breastfeeding pattern.

Other trials began to find similar results. In a large Zimbabwe trial, mixed breastfeeding was associated with a 4.03, 3.79 and 2.6 greater risk than exclusive breastfeeding of postnatal HIV transmission at 6, 12 and 18 months respectively[89]. Predominant breastfeeding was associated with a 2.63, 2.69 and 1.61 trend towards a greater risk of transmission during the same intervals compared to exclusive breastfeeding.

The Vertical Transmission Study from South Africa[5] included 2722 mothers and infants who were followed postnatally (1372 HIV-infected and 1345 uninfected women). WHO feeding definitions were used; with rigorous determination of cumulative exclusive breastfeeding rates using daily records of feeding practices based on a 6–9 day recall period; most previous studies of infant feeding practices were based on past 24 hours, 6 week or 3 month recall intervals. The risk of postnatal transmission to EBF infants between 6 weeks and 6 months of age was 4.04%. There was an almost 11-fold difference in postnatal transmission risk between EBF infants and infants who received breastmilk and solid foods, and a nearly two-fold difference between EBF infants and infants who received breastmilk and formula milk, during the first six months. Infants born to and breastfed (EBF or otherwise) by HIV-infected women with CD4 counts less than 200 cells/µl were almost four times more likely to become infected postnatally and/or die than infants born to mothers with CD4 counts more than 200 cells/µl.

The ZEBS study gave an identical 4% transmission risk with exclusive breastfeeding by about 4 months compared to a 10% risk with mixed feeding[90].

The Ditrame-Plus study by a French group working in Abidjan, Cote d'Ivoire, reported a 5.9% risk per child year for exclusive and 31.6% risk per child year for mixed breastfeeding[91].

An earlier report from Uganda showed a cumulative 11% transmission with exclusive breastfeeding compared to 17% with mixed breastfeeding at 6 weeks, and 16% and 20% respectively, at 6 months[92].

The Mashi Study in Botswana assessed the morbidity and mortality associated with infant feeding practices[93]. HIV-infected pregnant women were randomized to breastfeed while giving infant ZDV prophylaxis for 6 months, or to formula feed with one month of infant ZDV. There was little difference in the combined mortality and/or HIV infection. The mortality was higher and HIV transmission lower, in the formula fed group, whilst the mortality was lower and transmission higher in the breastfed group. Exclusive breastfeeding rates were low. Severe pneumonia (grades 3/4) rates were higher at 6 and 24 months among the formula fed compared to the breastfed infants and children. The ZDV given to breastfeeding infants did not appear to reduce postnatal transmission.

Breastfeeding for HIV-infected infants

The ZEBS study found that breastfeeding was of benefit to HIV-infected infants[94]. A small study of infants born to HIV-infected women in South Africa concluded that breastfeeding by HIV-infected women appeared to be beneficial to both HIV-infected and HIV-exposed, but uninfected infants[95].

Reducing breastfeeding transmission with antiretrovirals

A number of recent studies, some with methodological constraints, have reported gratifying results on interrupting the transmission of HIV through breastfeeding. Two studies provided ARVs to breastfeeding infants to prevent vertical transmission. Both employed NVP beyond sdNVP, extended for different periods whilst breastfeeding. The PEPI study in Malawi compared the standard sdNVP against NVP alone or with ZDV extended for 14 weeks after birth[96]. The HIV infection rate in the infants, the death rate and the HIV-free survival (which combines the HIV infection and mortality rates) were all improved in both extended dose NVP arms at 24 months compared to the standard dose NVP. The protective efficacy of both extended dose NVP arms was between 65 and 69% (with little difference between the two arms) up to about 14 weeks and then dropped thereafter. The SWEN study in India, Uganda and Ethiopia provided extended dose NVP for 6 weeks after birth and compared this to standard dose NVP[97]. The HIV transmission rate was significantly lower in the extended dose NVP at 6 weeks (2.5% vs 5.3%) and lower at 6 months (6.9% vs 9.0%), whilst the mortality was lower at 6 weeks (0.9% vs 1.6%) and significantly lower at 6 months (1.1% vs 3.6%). The combined index of HIV transmission and death was significantly lower at both times (3.7% vs 6.8% at 6 weeks; 8.1% vs 11.6% at 6 months).

The MITRA-PLUS an open-label, randomized, prospective study from Tanzania, gave HAART to all HIV + pregnant women for 6 months[98,99]. The breastfeeding transmission at 24 weeks was 0.9%. The Dream study in Mozambique provided HAART for HIV-positive pregnant women from the antenatal period[100]; the postnatal transmission rate by 12 months was 1.3%, and the overall mortality was 48.3/1000 births compared to a national figure of 101/1000 births.

In the KIBS study in Kenya, HAART was given from 34 weeks gestation to 6 months postpartum. The postnatal transmission rate (after 6 weeks) was about 3.5% by 12 months and 2.6% by 6 months[101]. The WHO Kesho Boro Observational cohort compared the effects of HAART for pregnant women with CD4 counts <200 cells/µl and ZDV plus sdNVP for women with CD counts above 500 cells/µl. The transmission rate in those on HAART who 'ever

Table 7. Key antiretroviral trials to reduce breastfeeding transmission of HIV

Trial	Prophylaxis	Transmission effect
Antiretrovirals to mother whilst breastfeeding		
DREAM[98] (Mozambique)	Highly active antiretroviral treatment (HAART) for 6 months	Breastfed 0.8% @ 6 months Formula fed 1.8% @ 6 months Breastfed 1.3% @ 12 months
AMATA[103] (Rwanda)	HAART after 2nd trimester, continued for a month after cessation of breastfeeding	No transmissions
MITRA-PLUS[98] (Tanzania)	HAART for 6 months	0.9% @ 6 months
Kibs[101] (Kenya)	HAART from 34 weeks gestation to 6 months postpartum + NVP to infants	@ 6 months: @ 12 months: Overall 5.0% Overall 5.9% Postnatal 2.6% Postnatal 3.5%
Kesho-Boro[102] (multi-country)	HAART for mother	Breastfed babies 8% @ 12 months
Antiretrovirals to infant whilst breastfeeding		
MASHI[93] (Botswana)	ZDV for 6 months	No significant effect
SWEN[97] (Ethiopia, Uganda, India)	6 weeks extended NVP vs single dose NVP	2.5% vs 5.3% @ 6 weeks 6.9% vs 9.0% @ 6 months
PEPI (Malawi)[96]	14 weeks extended NVP vs single dose NVP	5.2% vs 10.6% @ 9 months

Table 8. Comparison of trials to reduce breastfeeding transmission: infant prophylaxis (PEPI, SWEN) and maternal prophylaxis (KIBS)

	PEPI[96]	SWEN[97]	KIBS[101]
	14 week Ext NVP	6 week Ext NVP	Maternal HAART
6 weeks	1.7%	2.5%	1.5%
6 months	4.0%	6.9%	2.6%
12 months	7.0%	–	5.9%
Increment	+3.0% (6–12 months)	+4.4% (6 weeks–6 months)	+3.3% (6–12 months)

breastfed' was 8% which was identical to those on ZDV plus sdNVP; in those who 'never breastfed' the transmission rate in those on HAART was 11% compared to 0% in women on ZDV/sdNVP[102].

The AMATA study from Rwanda showed similarities for HIV transmission rates, psychomotor development, morbidity and mortality between formula fed and breastfed children whose mothers had received HAART[103]. Results for 419 infants at six weeks, 236 at seven months are available; only six HIV were positive (1.4%) at birth. Breastfeeding transmission at 7 months was 0. No significant differences were detected between formula fed (FF) and breastfed (BF) for psychomotor development; morbidity (1.23 episodes in FF vs 1.21 in BF), mortality (2.9% in FF vs 1.3% in BF).

In the Dream study in Mozambique, referred to above, two cohorts of HIV-positive women, were given antenatal HAART from the 25th week of gestation regardless of severity of disease[100]. Women who chose formula were provided free milk, nutritional supplements and water filters for 6 months, and those who chose breastfeeding were given postnatal HAART for 6 months. The HIV transmission at 6 months was 0.8% in the breastfed group and 1.8% in the formula fed children ($p = 0.38$); infant mortality was 28.5 per 1000 person-years in the breastfed and 27 per 1000 person years in the formula fed. Underweight and anaemia incidences were also similar between the two feeding groups. Nonetheless, the authors conclude that the formula feeding plus water filters option was inferior to the breastfeeding plus HAART option as it was 'technically difficult and extremely expensive' and adherence to formula was poor as women mixed breastmilk with formula. Six months of formula was as costly as 6 months of HAART, 'presenting an insurmountable stumbling block for scaling up the intervention'

Changing womens' behaviour on breastfeeding practice; exclusive breastfeeding

Given the advantages of EBF even for HIV-positive women, is it possible to change women's behaviour away from MBF to EBF? Cross-sectional DHS surveys suggest that globally only 25% of all infants under six months are exclusively breastfed[86]. Researchers and policy makers question whether, indeed, exclusive breastfeeding is feasible.

A number of studies concentrating on hospital policies and practices, and on support in the community, have shown that it is possible to increase the rates of exclusive breastfeeding in the first six months. For example, the Baby-Friendly Hospital Initiative (BFHI), based on the

Ten Steps to Successful Breastfeeding[69,104], has shown significant impact on exclusive breastfeeding outcomes while mothers are still in hospital. A facility-based breastfeeding intervention trial (PROBIT) in Belarus, based on the BFHI, emphasizing health care worker assistance with initiating and maintaining breastfeeding and subsequent postnatal support for the mother, increased the duration and exclusivity of breastfeeding in the first year of life[61].

In a randomized trial in Brazil[105], 350 mothers giving birth at two hospitals where maternity staff were trained according to the BFHI, were assigned to ten postnatal home visits to promote and support breastfeeding ($n = 175$) or no home visits ($n = 175$). The hospital-based intervention achieved a high rate (70%) of exclusive breastfeeding in the hospitals, but the rate was not sustained at home, and at 10 days only 30% of infants were exclusively breastfed. The patterns of exclusive breastfeeding in the two trial groups for days 10–180 differed significantly ($p < 0.0001$) with a mean aggregated prevalence of 45% among the group assigned home visits compared with 13% for the group assigned none. It is clear that a combination of promotional systems (hospital and community) is needed. Studies from Mexico[106] and Bangladesh[107] showed that appropriate interventions can increase rates of EBF. In an alternative approach, a study assessed the feasibility, effectiveness and safety of an educational intervention to promote exclusive breastfeeding for the first six months of life in India[108]. Health and nutrition workers were trained to counsel mothers individually on exclusive breastfeeding at multiple opportunities through existing primary health care services. At three months the exclusive breastfeeding rates were 79% (381) in the intervention and 48% (197) in the control communities (OR 4.02, 95% CI 3.01–5.38, $p < 0.0001$). All these studies were conducted in areas of low HIV prevalence. It is unclear whether similar results can be obtained in areas of high HIV prevalence where infant formula is being promoted and, sometimes, provided freely as part of PMTCT programmes.

The first study to specifically address this was conducted amongst HIV-infected and HIV-uninfected women in South Africa[5]. Lay counsellors trained on the WHO/UNICEF breastfeeding counselling course[109] supported women who chose to breastfeed, both antenatally and postnatally at their homes. All HIV-negative women were encouraged to exclusively breastfeed for six completed months, with continued breastfeeding for two years. All HIV-positive women were counselled, individually, according to the UN guidelines, to help them find a feeding option most suited to their socio-economic situation for the first six months. All women choosing to breastfeed (HIV-positive or HIV-negative) were supported to exclusively breastfeed for six months at home by lay counsellors. The median duration of EBF during the first six months was 177 (R 1-180, IQR 150–180) and 175 days (R 1–180, IQR 137–180) in HIV-negative and positive women respectively. At five and a half months of age, over 60% of infants born to HIV-positive and HIV-negative women were still exclusively breastfeeding. Exclusive breastfeeding rates in HIV-negative women were high, demonstrating that with high quality counselling and support, 'spillover' of inappropriate feeding and erosion of EBF among HIV uninfected women did not occur[110].

What are the results of current trials on use of breastfeeding and formula feeding for HIV positive pregnant women?

The hazards of avoidance of breastfeeding will differ according to socio-economic conditions in individual households, and the level of community development. A good example of the use of formula is a cohort study from Cote d'Ivoire which followed infants over two years[91].

There was access to piped water and intensive nutritional counselling starting antenatally. There were no significant differences in morbidity (diarrhoea, respiratory infection, malnutrition) hospitalization and mortality between the breastfed and formula-fed children. No significant differences in mortality were observed between the data from this study when compared to historical long-term breastfeeding controls. This study's findings appeared contrary to others from Africa. Evidence from Botswana[93], Malawi[111], Nigeria[112], Mozambique[113] and Uganda[114] shows that too early discontinuation of breastfeeding may be hazardous for the health of HIV-exposed infants. These infants are more likely to suffer from pneumonia, diarrhoea, sepsis, malnutrition, growth faltering and higher rates of mortality than infants who are breastfed. How do we balance the hazards of HIV transmission through breastfeeding, against the risks of mortality and heightened morbidity? We set out to review the studies which could assist in making decisions on infant feeding for HIV-infected women in specific situations in Africa[115].

We were able to stratify studies according to whether the results showed that formula feeding was equivalent to breastfeeding[91,93,100,116], avoidance of breastfeeding was hazardous[117–120] and breastfeeding could be made safe, thereby reducing risks of vertical transmission[5,94,103,121,122]. We concluded that the evidence favours exclusive breastfeeding in developing countries[115]. We also noted that the pre-occupation with reducing HIV transmission had obscured an even larger goal: to improve survival of infants as we reduce transmission.

Resistance

The remarkable success of the large number of trials to reduce transmission of HIV from mothers to their infants has not been without its problems of toxicity and adverse

effects of drug usage. In general the hazards of treatment with ARVs and other drugs have been minimal, and this may be because the drugs are safe and the preventive intervention brief. The development of virus strains in mothers and HIV-infected-infants resistant to NVP was a rather surprising side effect, as the regimen entailed only a single dose of the drug to the mother and to the infant. As sdNVP has been one of the most practical regimens for use in developing countries, although the efficacy of other combination regimens is now known to be superior as detailed above, the impact of inducing drug-resistant strains in millions of women and their HIV-infected infants, was a daunting prospect. The dangers were that resistant strains may have spread to the adult population, and compromised the subsequent use of NVP-like drugs (non-nucleoside-reverse-transcriptase inhibitors) for prevention of transmission in further pregnancies or for treatment, rather than prevention, of HIV/AIDS in the mothers and their infected infants. In the event, the use of combination drugs and the natural fading over short periods of resistant strains from the circulation have diminished the threat of harm. This subject has been recently reviewed with extensive references[8,45,123–125].

Therefore, for this paper I restrict the description to a brief but concise summary. The following, render the mother or infant more susceptible to development of NVP-resistant strains of HIV: long-half life of the drug, high maternal viral load and low CD4 counts, HIV subtype (Clade C > A > D), more maternal doses of NVP, shorter periods after administration of the drug, and body compartment (rate of NVP resistance mutations was higher in breastmilk than in blood). In the systematic review and meta-analysis of summarized data[123], the following were shown: '. . . NVP resistance prevalence was 35.7% (95% confidence interval (CI) 23.0–50.6) in women in 10 study arms using single-dose NVP +/– other antepartum antiretrovirals and 4.5% (CI 2.1–9.4) in three study arms providing also postpartum antiretrovirals (adjusted odds ratio 0.08; CI 0.04–0.16). The corresponding estimates in children were 52.6% (CI 37.7–67.0) in seven study arms using single-dose NVP only and 16.5% (CI 8.9–28.3) in eight study arms combining single-dose NVP with other antiretrovirals'.

A number of studies have shown that the maternal effects of resistant strains do not appear to be particularly harmful: NVP used for MTCT programmes do not appear to reduce the efficacy of the drug when used subsequently in further pregnancies for prevention of transmission or for initiation of Highly Active Antiretroviral Treatment (HAART) for progression of the disease. McConell *et al.*[125] have noted the viral load responses of women who began treatment for their own HIV disease progression after participating in MTCT programmes. In studies from Thailand, Botswana and South Africa, they found no significant differences in viral load responses among women who started treatment for their own condition six months after prior exposure to the drug in MTCT programmes. Two studies found worse responses when treatment was begun within six months of exposure to NVP in MTCT programmes. No differences were detected in MTCT rates after receipt of NVP in repeat pregnancies. They suggest that NVP still has a role in MTCT programmes in poor countries where complex regimens may be unavailable.

Although these findings are reassuring, more work needs to be done, especially for long term outcomes. The outcome in infants who become HIV infected despite participation in MTCT programmes in which NVP is used, is less secure: Lockman *et al.*[124] found that virologic failure at 6 months and 12 months after intiation of ARVs for disease treatment occurred more frequently in infants previously exposed to NVP in MTCT programmes than in infants who had not been exposed. However the numbers of infants were small: 15 in each of the placebo and ARV treatment groups.

Trials are under way currently in infants to determine outcome of treatment with NVP- and non-NVP containing HAART. Measures employed to minimize development of NVP resistance include the use of combination drugs and omission of either the maternal or the infant dose of NVP. Delaying treatment with HAART, if possible without compromising maternal or infant health, is an option but probably neither ethically sound nor feasible.

Conclusion

Achievements in minimizing transmission of HIV from mothers to their infants are one among the many great successes in the search for measures to ameliorate the disease and control the spread of the global epidemic. Interventions aimed at primary prevention of HIV infection among women of child-bearing age and termination of unintended pregnancies in those already HIV infected, are not only central to prevention of mother-to-child transmission of HIV but are also cost-effective and beneficial to infant, women, family, and community health and well-being. The perinatal transmission of HIV has been successfully reduced by ARVs and other ancillary measures in the industrialized world and in some middle-income countries; the transmission rates are as low as 1% from levels of about 25%. We now have the means to reduce mother to child transmission in all countries as there are promising regimens to decrease postnatal transmission in poor populations for whom avoidance of breastfeeding is often more dangerous for infant health and survival than the risk of vertical transmission of HIV through breastfeeding. It is imperative in Africa and other poor regions of the world to scale up the interventions which can remove the dangers of HIV transmission from mothers to their infants. Treatment of HIV-infected children with antiretrovirals and other drugs has been suc-

cessful in developing and developed countries although many challenges remain to improve coverage and quality. We should also prepare for a broader approach by investing in progressive social development policies which strengthen family life, enhance community programmes, and build safety-nets for those who are poor. There is a pressing need for governments and the global community to create societies which preserve, protect and sustain the lives of the poor amongst them. Scientific advances over the past quarter of a century together with a rising tide of global philanthropy have saved millions of childrens' lives. It would be a tragic irony to have saved children through prevention of vertical transmission of HIV, only to crush their hopes and blight their lives by a failure of social, economic and political policies to secure their futures.

1. Jinabhai, C. C., Coovadia, H. M. and Abdool-Karim, S. S., Socio-medical indicators of health in South Africa. *Int. J. Health Serv.*, 1986, **16**, 163–176.
2. Smythe, P. M. *et al.*, Thymolymphatic deficiency and depression of cell-mediated immunity in protein–calorie malnutrition. *Lancet*, 1971, **2**, 939–943.
3. Coutsoudis, A., Broughton, M. and Coovadia, H. M., Vitamin A supplementation reduces measles morbidity in young African children: a randomized, placebo-controlled, double-blind trial. *Am. J. Clin. Nutr.*, 1991, **54**, 890–895.
4. Bobat, R., Coovadia, H. M., Stephen, C., Naidoo, K., McKerrow, N., Black, R. and Moss, W., Safety and efficacy of zinc supplementation for children with HIV-1 infection in South Africa: a randomized double-blind placebo-controlled trial. *Lancet*, 2005, **366**, 1862–1867.
5. Coovadia, H. M. *et al.*, Mother-to-child transmission of HIV-1 infection during exclusive breastfeeding in the first 6 months of life: an intervention cohort study. *Lancet*, 2007, **369**, 1107–1116.
6. Coovadia, H. M., Wesley, A., Brain, P., Henderson, L. G., Hallett, A. F. and Vos, G. H., Immunoparesis and outcome in measles. *Lancet*, 1977, **1**, 619–621.
7. McNally, L. M. *et al.*, Effect of age, polymicrobial disease, and maternal HIV status on treatment response and cause of severe pneumonia in South African children: a prospective descriptive study. *Lancet*, 2007, **369**, 1440–1451.
8. Coovadia, H. M. and Archary, D., Prevention of transmission of HIV-1 from mothers to infants in Africa. In *Hot Topics in Infection and Immunity in Children III* (eds Pollard, A. J. and Finn, A.), Springer Science + Business Media, New York, 2006, pp. 201–216.
9. Jeena, P. M., Pillay, P., Pillay, T. and Coovadia, H. M., Impact of HIV-1 co-infection on presentation and hospital-related mortality in children with culture proven pulmonary tuberculosis in Durban, South Africa. *Int. J. Tuberc. Lung Dis.*, 2002, **6**, 672–678.
10. Bhimma, R., Coovadia, H. M. and Adhikari, M., Nephrotic syndrome in South African children: changing perspectives over 20 years. *Pediatr. Nephrol.*, 1997, **11**, 429–434.
11. Kiepiela P. *et al.*, Lack of efficacy of the standard potency Edmonston-Zagreb live, attenuated measles vaccine in African infants. *Bull. WHO*, 1991, **69**, 221–227.
12. Coovadia, H. M., Host allergic response variation in children with measles infection. MD Thesis, University of Natal, Durban, 1978.
13. Coovadia, Y. M., Dawood, A., Ellis, M. E., Coovadia, H. M. and Daniel, T. M., Evaluation of adenosine deaminase activity and antibody to *Mycobacterium tuberculosis* antigen 5 in cerebrospinal fluid and the radioactive bromide partition test for the early diagnosis of tuberculosis meningitis. *Arch. Dis. Child.*, 1986, **61**, 428–435.
14. Coovadia, H. M. and Benatar, S., *A Century of Tuberculosis – South Africa Perspectives*, Oxford University Press, Cape Town, 1991.
15. Bhimma, R., Coovadia, H. M., Adhikari, M. and Connolly, C. A., The impact of the hepatitis B virus vaccine on the incidence of hepatitis B virus-associated membranous nephropathy. *Arch. Pediatr. Adolesc. Med.*, 2003, **34**, 482–490.
16. McNeill, W. H., *Plagues and People*, Anchor Books, New York, 1976.
17. Hui, D. S., Chan, M. C., Wu, A. K. and Ng, P. C., Severe acute respiratory syndrome (SARS): epidemiology and clinical features. *Postgrad. Med. J.*, 2004, **80**, 373–381.
18. Levy, J. A., *HIV and the Pathogenesis of AIDS*, ASM Press, Washington DC, 1998, 2nd edn.
19. AIDS Epidemic Update, Joint United Nations Programme on HIV/AIDS, WHO, UNAIDS, Geneva, Switzerland, 2007.
20. De Cock, K. M. *et al.*, Prevention of mother to child HIV transmission in resource-poor countries: translating research into policy and practice. *JAMA*, 2000, **283**, 1175–1182.
21. Newell, M. L., Coovadia, H., Cortina-Borja, M., Rollins, N., Gaillard, P. and Dabis, F., Mortality of infected and uninfected infants born to HIV-infected mothers in Africa: a pooled analysis. *Lancet*, 2004, **364**, 1236–1243.
22. Coovadia, H. M. and Bland, R. M., Preserving breastfeeding practice through the HIV pandemic. *Trop. Med. Int. Health*, 2007, **12**, 1116–1133.
23. Coovadia, H. M. and Bobat, R., Human immunodeficiency virus. In *Paediatrics and Child Health. A Manual for Health Professionals in Developing Countries* (eds Coovadia, H. M. and Wittenberg, D. F.), Oxford University Press, Cape Town, 2004, 5th edn, pp. 343–356.
24. Walker, N., Schwartländer, B. and Bryce, J., Meeting international goals in child survival and HIV/AIDS. *Lancet Infect. Dis.*, 2002, **360**, 284–289.
25. *Africa's Orphaned Generations*, UNICEF, New York, 2003.
26. Case, A. and Ardington, C., The impact of parental death on school outcomes: Longitudinal evidence from South Africa. *Demography*, 2006, **43**, 401–420.
27. McNally, L., Hadingham, J., Archary, D., Moodley, R. and Coovadia, H. M., HIV-exposed but uninfected children: Why are they vulnerable? *Vulnerable Children Youth Studies*, 2006, **1**, 139–148.
28. Mugawe, D. and Powell, A., *African Child Policy Forum* (eds Southwood, L. and Taft, K.), 2006.
29. Hosegood, V., McGrath, N., Herbst, K. and Timaeus, I. M., The impact of adult mortality on household dissolution and migration in rural South Africa. *AIDS*, 2004, **18**, 1585–1590.
30. Ford, K. and Hosegood, V., AIDS mortality and the mobility of children in KwaZulu Natal, South Africa. *Demography*, 2005, **42**, 757–768.
31. Naver, L. *et al.*, Children born to HIV-1-infected women in Sweden in 1982–2003: trends in epidemiology and vertical transmission. *J. Acquir. Immune Defic. Syndr.*, 2006, **42**, 484–489.
32. Thorne, C. and Newell, M. L., *HIV. Sem. Fetal Neonatal Med.*, 2007, **12**, 174–181.
33. Webber, M. P., Chazotte, C., Fox, A. S., Moskaleva, G., Arnold, J. and Schoenbaum, E. E., Implementation of expedited human immunodeficiency virus testing of women delivering infants in a large New York city hospital. *Obstet. Gynecol.*, 2003, **101**, 982–986.
34. Connor, E. M. *et al.*, Reduction of maternal infant transmission of human immunodeficiency virus type 1 with ZDV treatment. *N. Engl. J. Med.*, 1994, **331**, 1173–1180
35. Coovadia, H. M., Prevention and treatment of perinatal HIV-1 infection in the developing world. *Curr. Opin. Infect. Dis.*, 2000, **13**, 247–251.

36. Shaffer, N. *et al.*, Short-course ZDV for perinatal HIV-1 transmission in Bangkok, Thailand: a randomised controlled trial. Bangkok collaborative perinatal HIV transmission study group. *Lancet*, 1999, **353**, 773–780.
37. Lallemant, M. *et al.*, A trial of shortened ZDV regimens to prevent mother-to-child transmission of human immunodeficiency virus type 1. Perinatal HIV prevention trial (Thailand) investigators. *N. Engl. J. Med.*, 2000, **343**, 982–991.
38. Lallemant, M. *et al.*, Single-dose perinatal NVP plus standard ZDV to prevent mother-to-child transmission of HIV-1 in Thailand. *N. Engl. J. Med.*, 2004, **351**, 217–228.
39. Chalermchokcharoenkit, A. *et al.*, Combination short-course ZDV plus 2-dose NVP for prevention of mother-to-child transmission: Safety, tolerance, transmission, and resistance results. Programme and abstracts of the 11th Conference of Retrovirus and Opportunistic Infections, San Francisco 8–11 February 2004; Abstract 96.
40. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. The European Mode of Delivery Collaboration. *Lancet*, 1999, **353**, 1035–1039.
41. The International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1 – a meta-analysis of 15 prospective cohort studies. *N. Engl. J. Med.*, 1999, **340**, 977–987.
42. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from 15 prospective cohort studies. *AIDS*, 2001, **15**, 357–368.
43. Sweat, M. D., O'Reilly, K. R., Schmid, G. P., Denison, J. and de Zoysa, I., Cost-effectiveness of NVP to prevent mother-to-child HIV transmission in eight African countries. *AIDS*, 2004, **18**, 1661–1671.
44. Duerr, A., Hurst, S., Kourtis, A. P., Rutenberg, N. and Jamieson, D. J., Integrating family planning and prevention of mother-to-child HIV transmission in resource-limited settings. *Lancet*, 2005, **366**, 261–263.
45. Dao, H. *et al.*, International recommendations on antiretroviral drugs for treatment of HIV-infected women and prevention of mother-to-child HIV transmission in resource-limited settings: 2006 update. *Am. J. Obstet. Gynecol.*, 2007, **197**, S42–55.
46. Guay, L. A. *et al.*, Intrapartum and neonatal single-dose NVP compared with ZDV for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*, 1999, **354**, 795–802.
47. Jackson, J. B. *et al.*, Intrapartum and neonatal single-dose NVP compared with ZDV for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet*, 2003, **362**, 859–868.
48. Leroy, V. *et al.*, Twenty-four month efficacy of a maternal short-course ZDV regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS*, 2002, **16**, 631–641.
49. Petra Study Team, The efficacy of three short course regimens of ZDV and 3TC in preventing early and late transmission of HIV-1 from mother to child in Tanzania, South Africa, and Uganda (Petra Study): a randomised, double blind placebo controlled trial. *Lancet Infect. Dis.*, 2002, **359**, 1178–1186.
50. Dabis, F. *et al.*, Improving child health: the role of research. *BMJ*, 2002, **324**, 1444–1447.
51. Leroy, V. *et al.*, Is there a difference in the efficacy of peripartum antiretroviral regimens in reducing mother-to-child transmission of HIV in Africa? *AIDS*, 2005, **19**, 1865–1875.
52. Taha, T. E. *et al.*, NVP and ZDV at birth to reduce perinatal transmission of HIV in an African setting: a randomized controlled trial. *JAMA*, 2004, **292**(2), 202–209.
53. Gray, G. E. *et al.*, A randomized trial of two postexposure prophylaxis regimens to reduce mother-to-child HIV-1 transmission in infants of untreated mothers. *AIDS*, 2005, **19**, 1289–1297.
54. Gaillard, P. *et al.*, Use of antiretroviral drugs to prevent HIV-1 transmission through breast-feeding: from animal studies to randomized clinical trials. *J. Acquir. Immune Defic. Syndr.*, 2004, **35**, 178–187.
55. Ashraf, R. N. *et al.*, Breast feeding and protection against neonatal sepsis in a high risk population. *Arch. Dis. Child.*, 1991, **66**, 488–490.
56. Cesar, J. A., Victora, C. G., Barros, F. C., Santos, I. S. and Flores, J. A., Impact of breast feeding on admission for pneumonia during postneonatal period in Brazil: nested case-control study. *BMJ*, 1999, **318**, 1316–1320.
57. Heinig, M. J. and Dewey, K. G., Health advantages of breastfeeding for infants: a critical review. *Nutr. Res. Rev.*, 1996, **9**, 89–110.
58. *Global Strategy for Infant and Young Child Feeding*, WHO, Geneva, 2003.
59. The optimal duration of exclusive breastfeeding. Report of an expert consultation. WHO, Geneva, 2001.
60. Klement, E., Cohen, R. V., Boxman, J., Joseph, A. and Reif, S., Breastfeeding and risk of inflammatory bowel disease: a systematic review with meta-analysis. *Am. J. Clin. Nutr.*, 2006, **80**, 1342–1352.
61. Kramer, M. S. *et al.*, Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. *JAMA*, 2001, **285**, 413–420.
62. Schack-Nielsen, L. and Michaelsen, K. F., Breast feeding and future health. *Curr. Opin. Clin. Nutr. Metab. Care*, 2006, **9**, 289–296.
63. Victora, C. G. *et al.*, Evidence for protection by breast-feeding against infant deaths from infectious diseases in Brazil. *Lancet*, 1987, **2**, 319–322.
64. WHO collaborative study team on the role of breastfeeding on the prevention of infant mortality. Effect of breastfeeding on infant and child mortality due to infectious diseases in less developed countries: a pooled analysis. *Lancet*, 2000, **355**, 451–455.
65. Bahl, R. *et al.*, Infant feeding patterns and risks of death and hospitalization in the first half of infancy: multicentre cohort study. *Bull. WHO*, 2005, **83**, 418–426.
66. Edmond, K. M., Zandoh, C., Quigley, M. A., Amenga-Etego, S., Owusu-Agyei, S. and Kirkwood, B. R., Delayed breastfeeding initiation increases risk of neonatal mortality. *Pediatrics*, 2006, **117**, e380–e386.
67. Jones, G., Steketee, R. W., Black, R. E., Bhutta, Z. A. and Morris, S. S., How many child deaths can we prevent this year? *Lancet*, 2003, **362**, 65–71.
68. Black, R. E., Morris, S. S. and Bryce, J., Where and why are 10 million children dying every year? *Lancet*, 2003, **361**, 2226–2234.
69. Protecting, promoting and supporting breastfeeding: the special role of maternity services. A joint WHO/UNICEF statement. *Int. J. Gynaecol. Obstet.*, 1990, **31** (Suppl 1), 171–183.
70. Roberts, M. J. and Reich, M. R., Ethical analysis in public health. *Lancet*, 2002, **359**, 1055–1059.
71. Coutsoudis, A., Coovadia, H., Pillay, K. and Kuhn, L., Are HIV-infected women who breastfeed at increased risk of mortality? *AIDS*, 2001, **15**, 653–655.
72. Kuhn, L. *et al.*, Prolonged breast-feeding and mortality up to two years post-partum among HIV-positive women in Zambia. *AIDS*, 2005, **19**, 1677–1681.
73. Sedgh, G., Spiegelman, D., Larsen, U., Msamanga, G. and Fawzi, W. W., Breastfeeding and maternal HIV-1 disease progression and mortality. *AIDS*, 2004, **18**, 1043–1049.
74. Breastfeeding and HIV international transmission study group. Mortality among HIV-1-infected women according to children's feeding modality: an individual patient data meta-analysis. *J. Acquir. Immune Defic. Syndr.*, 2005, **39**, 430–438.
75. Nduati, R. *et al.*, Effect of breastfeeding on mortality among HIV-1 infected women: a randomised trial. *Lancet*, 2001, **357**, 1651–1655.

76. Otieno, P. A. *et al.*, HIV-1 disease progression in breast-feeding and formula-feeding mothers: a prospective 2-year comparison of T cell subsets, HIV-1 RNA levels, and mortality. *J. Infect. Dis.*, 2007, **195**, 220–229.
77. Coutsoudis, A. *et al.*, Late postnatal transmission of HIV-1 in breast-fed children: an individual patient data meta-analysis. *J. Infect. Dis.*, 2004, **189**, 2154–2166.
78. Leroy, V. *et al.*, International multicentre pooled analysis of late postnatal mother-to-child transmission of HIV-1 infection. Ghent international working group on mother-to-child transmission of HIV. *Lancet*, 1998, **352**, 597–600.
79. Miotti, P. G. *et al.*, HIV transmission through breastfeeding: a study in Malawi. *JAMA*, 1999, **282**, 744–749.
80. Bobat, R., Moodley, D., Coutsoudis, A. and Coovadia, H., Breastfeeding by HIV-1-infected women and outcome in their infants: a cohort study from Durban, South Africa. *AIDS*, 1997, **11**, 1627–1633.
81. Nduati, R. *et al.*, Effect of breastfeeding and formula feeding on transmission of HIV-1: a randomized clinical trial. *JAMA*, 2000, **283**, 1167–1174.
82. Ryder, R. W. *et al.* Evidence from Zaire that breast-feeding by HIV-1-seropositive mothers is not a major route for perinatal HIV-1 transmission but does decrease morbidity. *AIDS*, 1991, **5**, 709–714.
83. Tess, B. H., Rodrigues, L. C., Newell, M. L., Dunn, D. T. and Lago, T. D., Infant feeding and risk of mother-to-child transmission of HIV-1 in Sao Paulo State, Brazil. Sao Paulo collaborative study for vertical transmission of HIV-1. *J. Acquir. Immune Defic, Syndr. Hum. Retrovirol.*, 1998, **19**, 189–194.
84. Perez-Escamilla, R., Breastfeeding in Africa and the Latin American and Caribbean region: the potential role of urbanization. *J. Trop. Pediatr.*, 1994, **40**, 137–143.
85. Trussell, J., Grummer-Strawn, L., Rodriguez, G. and Vanlandingham, M., Trends and differentials in breastfeeding behaviour: Evidence from the WFS and DHS. *Popul. Stud.*, 1992, **46**, 285–307
86. *Global Databank on Breastfeeding and Complementary Feeding*, WHO, Geneva, 2003.
87. Coutsoudis, A., Pillay, K., Kuhn, L., Spooner, E., Tsai, W. Y. and Coovadia, H. M., Method of feeding and transmission of HIV-1 from mothers to children by 15 months of age: prospective cohort study from Durban, South Africa. *AIDS*, 2001, **15**, 379–387.
88. Coutsoudis, A., Pillay, K., Spooner, E., Kuhn, L. and Coovadia, H. M., Influence of infant-feeding patterns on early mother-to-child transmission of HIV-1 in Durban, South Africa: a prospective cohort study. South African Vitamin A Study Group. *Lancet*, 1999, **354**, 471–476.
89. Iliff, P. J. *et al.*, Early exclusive breastfeeding reduces the risk of postnatal HIV-1 transmission and increases HIV-free survival. *AIDS*, 2005, **19**, 699–708.
90. Kuhn, L. *et al.*, High uptake of exclusive breastfeeding and reduced post-natal HIV transmission: prospective results from the Zambia exclusive breastfeeding study. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007.
91. Becquet, R. *et al.*, Two-year morbidity–mortality and alternatives to prolonged breast-feeding among children born to HIV-infected mothers in Cote d'Ivoire. *PLoS Med.*, 2007, **4**, e17.
92. Magoni, M. *et al.*, Mode of infant feeding and HIV infection in children in a program for prevention of mother-to-child transmission in Uganda. *AIDS*, 2005, **19**, 433–437.
93. Thior, I. *et al.*, Breastfeeding plus infant ZDV prophylaxis for 6 months vs formula feeding plus infant ZDV for 1 month to reduce mother-to-child HIV transmission in Botswana: a randomized trial: the Mashi study. *JAMA*, 2006, **296**, 794–805.
94. Kuhn, L. *et al.*, High uptake of exclusive breastfeeding and reduced early post-natal HIV transmission. *PLoS ONE*, 2007, **2**, e1363.
95. Coutsoudis, A., Pillay, K., Spooner, E., Coovadia, H. M., Pembrey, L. and Newell, M. L., Morbidity in children born to women infected with human immunodeficiency virus in South Africa: does mode of feeding matter? *Acta Paediatr.*, 2003, **92**, 890–895.
96. Taha, T. E. *et al.*, Extended infant post-exposure prophylaxis with antiretroviral drugs significantly reduces postnatal HIV transmission: The PEPI-Malawi study. 15th Conference on Retroviruses and Opportunistic Infections, Hymes Convention Center, Boston, Massachusetts, 2008; Abstract 42LB.
97. Sastry, J., The six week extended dose NVP (SWEN) study team. Extended-dose NVP to 6 weeks of age for infants in Ethiopia, India, and Uganda: A randomized trial for prevention of HIV transmission through breastfeeding. 15th Conference on Retroviruses and Opportunistic Infections, Hymes Convention Center, Boston, Massachusetts, 2008; Abstract 43.
98. Kilewo, C. *et al.*, Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania – the MITRA PLUS study. 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007; Abstract TUAX 101.
99. Karlsson, K. *et al.*, Prevention of mother-to-child transmission of HIV-1 through breastfeeding by treating the mothers prophylactically with triple antiretroviral therapy in Dar es Salaam, Tanzania: the MITRA PLUS study. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007; Abstract TUAX101.
100. Palombi, L., Marazzi, M. C., Voetberg, A. and Magid, N. A., Treatment acceleration program and the experience of the DREAM program in prevention of mother-to-child transmission of HIV. *AIDS*, 2007, **21** Suppl 4, S65–S71.
101. Thomas, T. *et al.*, Prevention of mother-to-child transmission of HIV-1 among breastfeeding mothers using HAART: The Kisumu breastfeeding study, Kisumu, Kenya, 2003–2007. 15th Conference on Retroviruses and Opportunistic Infections, Hymes Convention Center, Boston, Massachusetts, 2008; Abstract 45aLB.
102. Vincenzi, I., The Kesho Bora study group. HIV-free survival at 12 months among children born to HIV-infected women receiving antiretrovirals from 34 to 36 weeks of pregnancy. 15th Conference on Retroviruses and Opportunistic Infections, Hymes Convention Center, Boston, Massachusetts, 2008; Abstract 638.
103. Arendt, V. *et al.*, AMATA study: effectiveness of antiretroviral therapy in breastfeeding mothers to prevent post-natal vertical transmission in Rwanda. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007; TUAX102.
104. *Evidence for the ten steps to successful breastfeeding*, WHO, Geneva, WHO/CHD/98.9.
105. Coutinho, S. B., de Lira, P. I., de Carvalho Lima, M. and Ashworth, A., Comparison of the effect of two systems for the promotion of exclusive breastfeeding. *Lancet*, 2005, **366**, 1094–1100.
106. Morrow, A. L. *et al.*, Efficacy of home-based peer counselling to promote exclusive breastfeeding: a randomised controlled trial. *Lancet*, 1999, **353**, 1226–1231.
107. Haider, R., Ashworth, A., Kabir, I. and Huttly, S. R., Effect of community-based peer counsellors on exclusive breastfeeding practices in Dhaka, Bangladesh: a randomised controlled trial (see comments). *Lancet*, 2000, **356**, 1643–1647.
108. Bhandari, N., Bahl, R., Mazumdar, S., Martines, J., Black, R. E. and Bhan, M. K., Effect of community-based promotion of exclusive breastfeeding on diarrhoeal illness and growth: a cluster randomised controlled trial. *Lancet*, 2003, **361**, 1418–1423.
109. Breastfeeding counselling: a training course, WHO, UNICEF, Geneva, 1993.
110. Bland, R. M., Newell, M. L., Rollins, N. C., Coutsoudis, A. and Coovadia, H. M., WHO and UNICEF infant feeding policy for

HIV-positive women – how feasible is it? XVI International AIDS Conference, Toronto, 2006; Abstract TUPE0342.
111. Taha, T. E. *et al.*, The impact of breastfeeding on the health of HIV-positive mothers and their children in sub-Saharan Africa. *Bull. WHO*, 2006, **84**, 546–554.
112. Adejuyigbe, E., The influence of infant feeding choice on morbidity and mortality in HIV exposed infants in southwestern Nigeria. XVI International AIDS Conference, Toronto, 2006; Abstract MOPE02372006.
113. Johnson, W. *et al.*, The challenges of providing adequate infant nutrition following early breastfeeding cessation by HIV-positive, food insecure, Mozambican Mothers. XVI International AIDS Conference, Toronto, 2006; Abstract WEADO105.
114. Homsy, J. *et al.*, Mother-to child HIV transmission and infant mortality among women receiving highly active antiretroviral therapy (HAART) in rural Uganda. XVI International AIDS Conference, Toronto, 2006; Abstract TuPE0354.
115. Coovadia, H. and Kindra, G., Breastfeeding, HIV transmission, and infant survival: balancing pros and cons. *Curr. Opin. Infect. Dis.*, 2008, **21**, 11–15.
116. Mugo, P., Rumunyu, M. and Nzioka, G., Safety and efficacy of a replacement feeding program in prevention of mother to child transmission (PMTCT) of HIV in resource limited setting: the experience of Maragua district, Central province, Kenya. Program and abstracts of the 4th International AIDS Society Conference on HIV Pathogenesis, Treatment and Prevention, Sydney, Australia, 2007; TUPEB107.
117. Coutsoudis, A., Coovadia, H. M. and Wilfert, C. M., HIV, infant feeding and more perils for poor people: new WHO guidelines encourage review of formula milk policies. *Bull. WHO*, 2008, **86**, 210–214.
118. Creek, T., *et al.*, Role of infant feeding and HIV in a severe outbreak of diarrhea and malnutrition among young children, Botswana, 2006. Program and abstracts of the 14th Conference of Retroviruses and Opportunistic Infections, Los Angeles, USA, 2007; Abstract 770.
119. Noel, F. *et al.*, Contribution of bacterial sepsis to morbidity in infants born to HIV-infected Haitian mothers. *J. Acquir. Immune Defic. Syndr.*, 2006, **43**, 313–319.
120. WHO HIV and Infant Feeding Technical Consultation Held on behalf of the Inter-agency Task Team (IATT) on Prevention of HIV Infections in Pregnant Women, Mothers and their Infants, WHO, Geneva, 2006.
121. Sinkala, M. *et al.*, No benefit of early cessation of breast feeding at 4 months on HIV-free survival of infants born to HIV-infected mothers in Zambia: The Zambia exclusive breastfeeding study. Program and abstracts of the 14th Conference of Retroviruses and Opportunistic Infections, Los Angeles, USA, 2007; Abstract 74.
122. Wilfert, C. M. and Fowler, M. G., Balancing maternal and infant benefits and the consequences of breast-feeding in the developing world during the era of HIV infection. *J. Infect. Dis.*, 2007, **195**, 165–167.
123. Arrive, E. *et al.*, Prevalence of resistance to NVP in mothers and children after single-dose exposure to prevent vertical transmission of HIV-1: a meta-analysis. *Int. J. Epidemiol.*, 2007, **36**, 1009–1021.
124. Lockman, S. *et al.*, Response to antiretroviral therapy after a single, peripartum dose of NVP. *N. Engl. J. Med.*, 2007, **356**, 135–147.
125. McConnell, M. S., Stringer, J. S., Kourtis, A. P., Weidle, P. J. and Eshleman, S. H., Use of single-dose NVP for the prevention of mother-to-child transmission of HIV-1: does development of resistance matter? *Am. J. Obstet. Gynecol.*, 2007, **197**, S56–S63.
126. Chaisilwattana, P. *et al.*, Short-course therapy with ZDV plus 3TC for prevention of mother-to-child transmission of human immunodeficiency virus type 1 in Thailand. *Clin. Infect. Dis.*, 2002, **35**, 1405–1413.
127. Mandelbrot, L. *et al.*, 3TC-ZDV combination for prevention of maternal-infant transmission of HIV-1. *JAMA*, 2001, **285**, 2083–2093.
128. Wiktor, S. Z. *et al.*, Short-course oral ZDV for prevention of mother-to-child transmission of HIV-1 in Abidjan, Cote d'Ivoire: a randomised trial. *Lancet*, 1999, **353**, 781–785.
129. Dabis, F. *et al.*, 6-month efficacy, tolerance, and acceptability of a short regimen of oral ZDV to reduce vertical transmission of HIV in breastfed children in Cote d'Ivoire and Burkina Faso: a double-blind placebo-controlled multicentre trial. DITRAME study group. DIminution de la Transmission Mere-Enfant. *Lancet*, 1999, **353**, 786–792.
130. Moodley, D. *et al.*, A multicenter randomized controlled trial of NVP versus a combination of ZDV and 3TC to reduce intrapartum and early postpartum mother-to-child transmission of human immunodeficiency virus type 1. *J. Infect. Dis.*, 2003, **187**, 725–735.
131. Dabis, F. *et al.*, Field efficacy of ZDV, 3TC and single-dose NVP to prevent peripartum HIV transmission. *AIDS*, 2005, **19**, 309–318.
132. Shapiro, R. *et al.*, Maternal single-dose NVP may not be needed to reduce mother-to-child HIV transmission in the setting of maternal and infant zidocudine and infant single-dose NVP: results of a randomised clinical trial in Botswana. Program and abstracts of the 12th Conference on Retrovirus and Opportunistic Infections, Boston, 22–25 February 2005; Abstract 74LB.