Chapter 20
Pendulum Swings in HIV-1 and Infant Feeding Policies: Now Halfway Back

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Introduction: The Pre-HIV Era

As one of the defining characteristics of mammalian reproduction, it should come as no surprise that breastfeeding is the norm, the healthiest practice for both mothers and infants regardless of where they live [1]. Benefits of breastfeeding have been noticed by health practitioners since the middle ages with poignant records of the outcomes of foundlings given human milk compared to those fed with artificial feeds [2]. By the mid-twentieth century, the industry producing and selling infant formula was so confident that their product was equivalent to mother nature's "product" that a vast population-level experiment was conducted with tragic results. Infant formula began to be actively promoted in sub-Saharan Africa leading to the well-publicized increases in infant death [3].

Years of Denial

The first case of HIV transmission through breastfeeding was described in 1985, not long after the disease that would become a global pandemic was first noticed among gay men. Almost immediately, guidelines for HIV-infected women in the USA recommended artificial feeding [4]. However, the magnitude of the HIV epidemic among women in sub-Saharan Africa was not fully appreciated and the complexities of balancing the risks and benefits of replacement feeding among HIV-infected women in developing countries are so complex that initial international recommendations were vague [5]. Furthermore, at this time the epidemiology of breast milk HIV transmission largely relied on a methodologically flawed meta-analysis [6] that would, nevertheless, turn out to be remarkably accurate in its estimates of the risks of HIV transmission. This resulted in some uncertainty as to whether the magnitude

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of postnatal transmission was substantial enough to require changes in policy [5]. Through at least 1992, WHO recommended that HIV-infected women in the *developing* world continue to breastfeed [7].

Focus in the HIV research community turned to quantifying the risk of HIV transmission through breastfeeding. This quantification was most elegantly accomplished in a randomized trial conducted in Nairobi, Kenya [8]. Comparing women randomized to no breastfeeding vs. those randomized to some breastfeeding (median duration 17 months), the risk of postnatal HIV transmission through breastfeeding was reported to be 16% (95% CI 7–26%) consistent with the meta-analysis estimate:14% (95% CI 7–21) [6, 8]. This all-or-nothing approach to breastfeeding dominated thinking in the field for several years but is problematic for a number of reasons. Primarily, it is unhelpful as it polarizes decisions around two suboptimal alternatives. It also glosses over the duration of breastfeeding and the quality of breastfeeding (exclusive vs. nonexclusive)—parameters with considerable influence on the absolute magnitude of postnatal HIV transmission.

Recognizing the competing risks involved in avoiding breastfeeding, the Nairobi study group selected HIV-free survival as their primary study endpoint. This approach combines two adverse endpoints, namely HIV infection and death of uninfected children. This approach tempers enthusiasm for support of artificial feeding by reminding us that shifts away from breastfeeding carry a cost in terms of the lives of HIV-uninfected infants. However, only an HIV-uninfected child death is considered sufficiently severe to be counted as equivalent to an HIV infection. Thereby, the spectrum of other benefits of breastfeeding for maternal and child health is discounted. Using this endpoint, the Nairobi study reported a net benefit of formula feeding over breastfeeding [8] providing the impetus for a major pendulum swing in international infant feeding policy.

The Pendulum Swings Away from Breastfeeding

Trapped between a rock and a hard place, it was now incumbent on the WHO to provide guidance in the public health minefield of infant feeding policies for HIV-infected women. WHO policy shifted towards support of formula feeding with a big IF. Formula feeding was supported for HIV-infected women if it was Affordable, Feasible, Acceptable, Sustainable and Safe (AFASS) [9, 10]. This cumbersome acronym allowed some policy makers and implementers to be deluded into thinking that there were no real dangers of artificial feeding that could not simply be overcome with AFASS-enhancing programs.

In part, the growing disregard of the dangers of shifts away from breastfeeding was supported by the results of the Nairobi study [8]. It remains unclear why this study reported so few adverse outcomes of formula feeding. No study to date has been able to replicate such good outcomes with formula. All studies in subsequent years, many of them considerably larger and some of them randomized and with at least equivalent methodological rigor, have reported, at best, no benefit with shifts away from breastfeeding [11, 12] or, in program settings, worse HIV-free survival [13, 14] (Table 20.1). We speculate that strict selection of study participants from atypically good socioeconomic circumstances and extensive monitoring and support during the trial limited its generalizability. Lack of any type of antiretroviral intervention and low rates of exclusive breastfeeding undoubtedly also led to the high rates of HIV transmission observed. The small sample size was vulnerable to chance fluctuations and may have contributed to the lack of balance between the groups in important confounders that some have pointed out [15].

AFASS Takes Hold

With AFASS policies in place, the population experiment of the effects of withholding breast milk on child survival could once again be repeated. Because of, or in spite of, information being given to HIV-infected women, the past 10 years have seen major changes in how women in sub-Saharan Africa

Table 20.1 Studies reporting the effects on HIV-free survival when breastfeeding is curtailed

	Study design	Comparisons	HIV-free survival
Nairobi, Kenya [8]	Randomized trial ($n=401$)	Formula from birth vs. breastfeeding (median 17 months)	Net benefit of formula
Botswana (MASHI) [11]	Randomized trial ($n=1,200$)	Formula from birth vs. breastfeeding for 6 months	Equivalent outcomes
Lusaka, Zambia (ZEBS) [29, 87, 88]	Randomized trial ($n=958$)	Early weaning at 4 months vs. breastfeeding (median 16 months)	Equivalent outcomes (in intent to treat analysis)
South Africa [13]	Program evaluation	Formula from birth vs. some breastfeeding	Worse outcomes with formula if poor socioeconomic status
Cote d'Ivoire [12]	Epidemiologic study of self-selected feeding choices ($n=557$)	Formula from birth vs. breastfeeding to 4 months	Equivalent outcomes
Rakai, Uganda [14]	Program evaluation ($n=182$)	Formula from birth vs. breastfeeding	Worse outcomes with formula
Rwanda [18]	Epidemiologic study ($n=532$)	Formula from birth vs. breastfeeding for 6 months	Equivalent outcomes
Western Kenya [19]	Program evaluation ($n=2,477$ but high drop-out)	Formula from birth vs. breastfeeding to 4 months	Equivalent outcomes

feed their infants and little support for exclusive breastfeeding. In some settings, there has been almost complete avoidance of breastfeeding and in others, much shorter durations of breastfeeding than usual in these communities. In circumstances where adequate data before and after these changes were collected at least the adverse consequences of these changes could be scrutinized. One group who initially theorized that shifts away from breastfeeding simply to avoid HIV would *not* result in adverse health outcomes [16], observed in their own program, substantial elevations in mortality among women who elected not to breastfeed [14]. Several other programs too reported that even after the benefits of HIV prevention were taken into account worse or, at best, no benefit of artificial feeding were observed [14, 17–20].

Two study teams in Malawi, one in Kenya and one in Uganda recommended early weaning (complete stoppage of breastfeeding) to women participating in their trials and subsequently found marked elevations in diarrheal morbidity and mortality [21–24], compared, in some cases, to earlier cohorts when no specific recommendations were given to shorten breastfeeding duration. All these studies included close monitoring and follow-up, as well as education and counseling which theoretically should minimize risks of weaning. Two of the studies were interrupted by their Data Safety and Monitoring Boards concerned about the elevations in morbidity after weaning. Although it could be argued that historical comparisons are a weak study design, these observations are biologically plausible and increased rates of diarrheal morbidity among nonbreastfed children are consistently reported even in settings such as the UK and the USA without barriers to clean water and healthcare [25–27]. These increases in child morbidity and mortality were all the more palpable as access to antiretrovirals as well as other child-related services improved over time. Epidemiologic analyses of mortality among breastfed and nonbreastfed infants and young children between birth and 24 months in two trials in Malawi revealed that breastfeeding was associated with a 2.9-fold lower risk of mortality among exposed-uninfected infants after adjustment for confounders [28]. For a selection of some of the adverse effects, see Table 20.2.

Using HIV-free survival as the primary outcome also serves to neglect and overlook mortality among HIV-infected children. It is now well-established that HIV-infected children who are formula-fed

Table 20.2 Effects on morbidity and mortality of uninfected infants born to HIV-infected mothers when breastfeeding was curtailed

	Study design	Comparisons	Morbidity and mortality in uninfected children
Randomized trials			
Nairobi, Kenya [8]	Randomized trial ($n=401$)	Formula vs. breastfeeding	Trend towards higher 2-year mortality (24%) in formula (24%) vs. breastfeeding (20%) group
Botswana (MASHI) [11]	Randomized trial ($n=1,200$)	Formula vs. short breastfeeding	Higher mortality at 7 months in formula (9.3%) vs. breastfeeding (4.9%) groups
Lusaka, Zambia (ZEBS) [29, 87, 88]	Randomized trial ($n=958$)	Early weaning vs. long breastfeeding	Two to fourfold increase in uninfected child mortality due to weaning through 18 months
Historical controls			
Kampala, Uganda [23]	Observations during a trial vs. previous study ($n=1,307$)	Early weaning vs. longer breastfeeding	Higher diarrhea-related and all cause mortality in cohort encouraged to wean earlier
Malawi [21]	Comparison to prior trial with longer breastfeeding ($n=3,845$)	Early weaning vs. long breastfeeding	Higher diarrhea-related morbidity and mortality and all cause mortality in cohort encouraged to wean early
Kisumu, Kenya [24, 36]	Comparison to prior study with longer breastfeeding ($n=491$)	Early weaning vs. longer breastfeeding	Higher diarrhea-related morbidity Water safety intervention ineffective
Epidemiologic studies			
South Africa [13]	Program evaluation	Formula vs. breastfeeding	Formula had higher adverse outcomes (HIV and uninfected death combined) if poor socioeconomic status
Cote d'Ivoire [12]	Self-selected feeding choice ($n=557$)	Formula vs. short breastfeeding	Equivalent HIV-free survival
Malawi [28]	Combined studies ($n=2,000$)	Multivariate analysis of actual feeding practices	Significant reduction (hazard ratio = 0.44) in mortality if breastfed (both infected and uninfected children)
Rakai, Uganda [14]	Program evaluation ($n=182$)	Formula vs. breastfeeding	Sixfold increase in mortality if formula-fed
Rwanda [18]	Self-selected feeding choice ($n=532$)	Formula vs. short breastfeeding	Nonsignificant trend towards higher mortality in formula (5.6%) vs. breast-fed (3.3%)
Pune, India [20]	Program evaluation ($n=148$)	Formula vs. breastfed	Significant higher risks of hospitalization if formula-fed
Rural Uganda [17]	Self-selected feeding practices ($n=109$)	Early weaning vs. longer breastfeeding	Sixfold increase in death if wean before 6 months
Western Kenya [19]	Program evaluation ($n=2,477$ but high drop-out)	Formula vs. short breastfeeding	Equivalent HIV-free survival
Botswana [32, 34]	Public Health outbreak investigation	Actual practices	25-fold increase in diarrhea deaths if not breastfed

or who are weaned off breast milk early are at high risk of dying prematurely [11, 28, 29]. It is not practical to make infant feeding recommendations based on the child's HIV status. Decisions about infant feeding are usually made during pregnancy and, if avoidance of breastfeeding or early weaning is selected, may be difficult to reverse. Even with the availability of early infant diagnosis, the child's

status is not known to the mother for weeks. Moreover, incorrect information about theoretical risks of "super-infection" and drug resistance and toxicity has been used to discourage women with newly identified infected children from breastfeeding. To its credit, the WHO has clearly stated that known HIV-infected children should breastfeed without any equivocation about duration or AFASS. As HIV-infected children can progress rapidly [30], breastfeeding is essential for these infants to survive long enough to access pediatric HIV care and treatment programs to benefit from antiretroviral therapy.

The Myth of AFASS: Can Formula Ever Be Safe?

Implicit in the concept of AFASS is that formula feeding is safe under certain circumstances. To attempt to unpack this myth in more detail, we consider the potential mechanisms whereby breastfeeding protects infants' health. For heuristic purposes, we separate the biological basis for the harm of nonbreastfeeding into three overarching mechanisms: (1) contamination, i.e., artificial feeding places the infant at risk through introducing environmental contaminants and creating a less hygienic feeding method; (2) poor nutrition, i.e., abstinence from breastfeeding could compromise an infant's nutritional status if formula is not mixed correctly or not given in appropriate quantities; and (3) the absence of immune protection.

Contamination: One of the most commonly stated reasons for why breastfeeding needs to be protected among HIV-infected women in sub-Saharan Africa is lack of clean water. It is certainly true that lack of clean water and inadequate sanitation facilities exaggerate the dangers of artificial feeding [31]. The dramatic epidemic of diarrhea-related deaths that occurred in Botswana among formula-fed infants after a period of severe flooding is a clear example of the dangers of contaminated water even in settings that usually have safe water supply [32–34]. Provision of a sustained supply of adequate clean water at the point of use in the household is clearly a major priority for public health [35]. But if safe water is available is formula feeding safe?

An exemplary demonstration of the multifactorial nature of breastfeeding's benefits came from an interesting confluence of circumstances in a clinical trial in rural Kenya. During a study to evaluate, the effects of antiretroviral therapy during lactation on the prevention of postnatal HIV transmission, HIV-infected women were encouraged to stop all breastfeeding by 6 months which was the time when antiretroviral therapy was also stopped. The study was temporarily suspended when elevated rates of diarrhea morbidity were noticed around the time of weaning [24]. A state-of-the-art home water quality improvement program was introduced. Despite the known benefits of this intervention in other settings, for weaning-related morbidity it was ineffective. The intervention reduced diarrhea while infants were being breastfed but not once they had stopped [36]. These results clearly demonstrate that while water contamination plays a role in exacerbating the risks of artificial feeding [31], clean water is insufficient to fully mitigate artificial feeding's risks.

Training around "safe" preparation of formula feeds has featured prominently in infant feeding programs in sub-Saharan Africa. The assumption is that if women can simply be sufficiently motivated to boil all water, wash their hands and follow all hygiene rules, infant formula can be given safely. In practice, following these guidelines in most homes in low resource settings, often without indoor water sources or electricity, is extremely difficult [37, 38]. In a study conducted in KwaZulu-Natal, South Africa, about 80% of formula samples mothers prepared at home after instructions from the counselors were contaminated with fecal bacteria [39]. About 20% of the samples that the counselors prepared at the clinic while showing the mothers how to do everything correctly were also contaminated [39].

Taken together, what these results demonstrate is that infant formula is not the only source of exposure to pathogens among infants and young children, especially in contaminated environments. Much to

their parents' chagrin, young children explore their world with their hands and mouths. Breast milk has evolved to protect children from these pathogens [40]. Some breastfeeding, even if it is nonexclusive, is more protective against diarrhea morbidity and mortality than no breastfeeding [41], even if the quantity of breast milk consumed is relatively small [42]. It is noteworthy that breastfeeding reduces the risk of respiratory illness and pneumonia, outcomes where contaminated water plays little or no role [25, 43–45]. Breastfeeding also protects against severe infectious disease in settings with a predominantly safe water supply [25–27].

Poor nutrition: The cost of infant formula places it beyond the financial reach of all but small elites in most sub-Saharan African countries. Lack of access to formula or limited access resulting in overdilution to stretch the available formula as far as possible is often invoked as the explanation as to why HIV-infected women need to breastfeed. This concern gives rise to the inference that simply providing adequate quantities of infant formula would solve the challenges of infant feeding for HIV-infected women since infant formula is specifically developed to mirror the nutritional composition of breast milk as closely as possible. Theoretically, health service provision of formula should be able to address the affordability challenge but given the reality of weak health service infrastructures, ensuring a sustained supply has been a challenge in many programs. Audits of the South African national formula program have described stock-outs and rationing in both urban and rural sites [46]. Population mobility introduces further complications for sustained access.

Other than these gross limitations in terms of access to formula, even from a nutritional point of view the product falls short in other respects. Breast milk is physiologically regulated such that the content varies from the beginning to the end of the feed so that a child can be most quickly satiated even with a short feed but can continue to feed for comfort and not become overfed on longer feeds [47]. The composition of human milk also varies even between feeds based on the amount the child consumes and over time being regulated to adapt to the unique needs of a specific child [48]. This individualization cannot be achieved with formula. Obesity and metabolic syndrome in children and young adults are now increasingly recognized as being linked to formula feeding [49–52] indicating that even with adequate access and sufficient quantities, infant formula remains nutritionally substandard. There are burgeoning efforts in the infant formula industry to make formula more like human milk by adding immunologically active components, such as long chain fatty acids and probiotics [53–55]. Breast milk is more than food and attempting to achieve only nutritional parity will not bring formula to the level of protection of infant health that breast milk can provide.

Absence of immune protection: Since neither clean water nor adequate supplies can explain the benefits of breastfeeding we are left with the clear inference that it is not so much what breastfeeding *keeps out* that is important, but what breastfeeding *puts in*. Breast milk contains a vast spectrum of immunologically active components that include antigen-specific antibodies and cellular immune components as well as almost every soluble factor known to have immunologic activity to protect against disease [56–58]. Passive transfer of maternal antibodies across the placenta is now well known to be an important means by which the infant, whose immune system is not fully mature at the time of birth, is protected immunologically. This process continues during breastfeeding with passive transfer of immunologic components as well as immunomodulatory effects of breast milk components on the infant gut and developing immune system [56, 57]. A substantial component of this activity is by dampening the immune response creating "tolerance" in the infant and preventing activation after exposure to pathogens [59]. Since HIV has so many dysregulatory effects on the human immune system, theoretically the immunologic quality of breast milk from HIV-infected women might be compromised. Although this topic needs considerable more study, one study from Botswana showed that HIV-infected and uninfected women had similar quantities of the immunologic components that they measured [60] suggesting that despite HIV infection, breast milk immunologic quality is not compromised.

Paying Close Attention to the Numbers

Despite the decades of research into the adverse effects of artificial feeding and the considerable body of basic science, clinical and epidemiologic research that do not support the safety of formula feeding, the argument by analogy is often invoked: namely, women in the USA formula feed their infants all the time and those babies are doing just fine. Or, the n-of-one argument: I (or my child) was formula-fed and I (he/she) am (is) doing just fine.

To appreciate the reasons for why some of those babies in the USA might (or might not [61, 62]) be doing just fine, it is important to make the distinction between an *absolute* risk and a *relative* risk. An absolute risk is the frequency with which an event occurs in the population, e.g., the infant mortality rate might be 10 deaths per 1,000 live-births. A relative risk requires a comparison. For example, we might say the infant mortality rate is 10/1,000 live-births if women breastfeed, but 20/1,000 live-births if women avoid all breastfeeding, i.e., a twofold increased risk. The ratio of rates in the two groups is referred to as the relative risk. The *relative risk* associated with artificial feeding is elevated in all populations, but what makes the north different from the south is that the absolute rates of morbidity and mortality are generally low. Moreover, breastfeeding may protect against morbidity, but since most morbidity in these settings is not fatal, arguably the benefits can be ignored. For low resource settings, women face a double whammy: the absolute background rates of mortality are several fold higher, so even small elevations translate into large numbers of infant deaths, and the relative risks are higher too because environmental deprivation and barriers to health care exacerbate the biological inferiority of formula.

Benefits of breastfeeding are multifactorial. Although a strong public health program may be able to minimize risks of environmental contamination and poor nutrition, programs can do nothing to mitigate the risks conferred by the absence of the immunologically active components of breast milk. The fact that breastfeeding confers benefits to infant health even in wealthy countries [25, 26] suggests that there is a biological threshold below which it is not possible to go even with the strongest programs.

Clinical trial data are important in formulating policy but caution is required when extrapolating results on the risks of artificial feeding from clinical trials. In most clinical studies, participants are highly motivated, receive the best possible educational interventions and are provided with close monitoring and a health service safety set. In a rigorous and well-monitored clinical trial in urban Botswana, a country with some of the best economic indicators in sub-Saharan Africa, HIV-exposed, uninfected infants randomized to infant formula from birth had a twofold increase in mortality compared to those randomized to breastfeeding [11]. In contrast, in two separate programs in Uganda, infant mortality was increased more than sixfold among women who considered formula feeding an AFASS choice for themselves [14, 17]. Under the best-case scenario, when infant formula is provided under carefully monitored conditions, with adequate access to medical care and sufficient education and support and with optimal selection of women considered to have adequate personal resources to safely formula feed, there is still about a twofold increased risk of mortality. In programmatic settings, the risks of death are several fold higher.

The Subtext of Poverty and Human Rights

The subtext of poverty and human rights makes discourse around infant feeding and HIV complex. It is obviously, morally, and ethically unacceptable that some babies are born into poverty, into settings where there is no clean water, insufficient food at home and where there are background risks of fatal infections that make use of infant formula a foolhardy choice at best. The concept of AFASS attempted to be a gentle reminder to guard against the inappropriate promotion and use of formula. AFASS was

impractical and failed in the field because it required that HIV-infected women themselves make the determination for whether or not infant formula was AFASS for their circumstances. An interesting study in South Africa stratified participants based on objective socioeconomic criteria. Women who chose above their station, i.e., chose formula when their socioeconomic station would have precluded it had the worst outcomes [13]. Counseling to explain that breastfeeding should only be undertaken if you are too poor to afford to safely formula feed is likely to be a challenge for even the most tactful of counselors.

In addition to the insensitivity of such counseling, provision of free or subsidized formula poses complex ethical challenges [63, 64]. In situations of scarcity, infant formula is perceived as a valuable and precious commodity. When it is further endorsed by the health service, it is also perceived as a safe and superior method of feeding. Qualitative research has highlighted the coercive dynamics of free formula and there are many examples of confusion and misinformation [38, 46, 65–68]. AFAS – S (minus the last S) appears to make an ethical demand that formula be made available by programs, in an affordable, acceptable, and sustainable way, in all settings (especially those where they are *not* affordable to the population at large). Availability is set up as the limitation rather than the intrinsic lack of safety. The impulse to address the gross economic inequalities between the developed and the developing world by simply implementing the same "standard of care" (provision of formula) is an understandable one. However, in the field of HIV and breastfeeding this one-size-fits-all approach has now done considerable harm.

Misunderstandings About Exclusive Breastfeeding

In a field of controversy and confusion, no single finding has generated as much of its own than the observation that exclusive breastfeeding is associated with reduced risk of HIV transmission. Initially, when first reported from Durban, South Africa that mothers who gave their infants only breast milk through 3 months of age were less likely to transmit HIV than mothers who breastfed and gave other solids or liquids before this age [69, 70], the average response was disbelief. How can *more* breastfeeding lead to *less* HIV transmission? A biological puzzle indeed, but when nature gives us clues as to some of the complexities of HIV pathogenesis it is worth paying attention [71]. But only few gave thought to the likely mechanisms involved [72], and the primary response was confusion as to why women in this study were counseled to breastfeed exclusively at all. It is hot in Durban, don't the babies get thirsty? So it took some time for infectious disease specialists to get up to speed with a standard midwifery syllabus that includes exclusive breastfeeding as one of the primary principles of lactation support, embedded in the baby-friendly principles endorsed by all international health agencies [73]. Since breast milk alone can support all of an infant's nutrition and fluid requirements through at least 6 months of age [74], supplements are unnecessary and potentially dangerous. Exclusive breastfeeding also establishes a regularity of breast milk supply and demand reducing mastitis and other breast problems [75, 76] which represent additional risk factors in HIV transmission. The finding that the *quality* of breastfeeding, ascertained by the extent of exclusive breastfeeding, is related to the risk of HIV transmission has now been confirmed in at least three additional large studies [70, 77–79]. Thus, estimates of postnatal transmission gathered from settings where support of exclusive breastfeeding is lacking or in communities with poor uptake of recommendations to breastfeed exclusively are likely to be higher than those collected in settings more favorable to and supportive of exclusive breastfeeding.

Exclusive breastfeeding also reminded us that although breastfeeding is a biological process, it is also a cultural practice [80]. What is healthiest and what is normative do not necessarily coincide. Cultural practices that displace breastfeeding, such as giving herbal supplements to infants, can be detrimental to both mother and infant [81]. The lament was then raised that exclusive breastfeeding

was too difficult and cultural barriers too entrenched to propose this as a viable strategy to reduce HIV transmission. Despite the fact that programs to support exclusive breastfeeding were being successfully developed and evaluated in Asia and Latin America during this time [27, 82–85], these new innovations were not incorporated into HIV programs. To our knowledge, no randomized study of how to support exclusive breastfeeding among HIV-infected women has yet been undertaken—a serious missed opportunity for operational prevention research.

An even more serious confusion that arose out of discussions of the observations that exclusive breastfeeding reduces HIV transmission was the conclusion that all breastfeeding should stop when breastfeeding is no longer exclusive. WHO in an attempt to be responsive to new scientific findings issued a specific recommendation about the importance of supporting exclusive breastfeeding for HIV-infected women who elected to breastfeed [86]. For reasons that remain unclear, almost everyone understood these recommendations to mean that exclusive breastfeeding should be supported for *no longer than* 6 months and then women should be encouraged to stop all breastfeeding abruptly. We stand accused as one of the teams of investigators who thought that it was so plausible that a short period of exclusive breastfeeding followed by abrupt cessation of breastfeeding was the optimal strategy to preserve HIV-free survival that we designed a randomized trial to test just that. Unfortunately, we were dead wrong. As we published our results showing that early weaning neither improved HIV-free survival nor was safe in terms of protecting survival of exposed-uninfected and infected infants [29], we found ourselves up against a community who had already begun implementing this approach thinking it was the recommendation of the WHO!

As part of our trial, 958 HIV-infected women in Lusaka, Zambia were randomized to either stop breastfeeding abruptly at 4 months or to continue breastfeeding for their own preferred duration. Infant formula and a specially developed, fortified weaning cereal was provided for infants in the intervention group. Since the cereal required cooking, contamination of water sources would, theoretically, be less of a concern. Infants in either study arm were weighed regularly and were provided with food supplements if there was any evidence of failure to thrive. Routine childhood interventions, including vaccines, vitamin A, and prophylactic cotrimoxazole was provided to children in both groups. The context of the trial also provided a health services safety net and intensive counseling and education, including about safe water and hygiene [29]. Despite our best educational efforts, early weaning was not well-accepted by the study population. Thus, it became essential, in the interpretation of our results, to analyze the data based on actual feeding behaviors. What we observed was that infants born to women who adhered to their assignment and weaned early as instructed, had worse outcomes than those whose mothers ignored their random assignment and continued breastfeeding; as did infants born to women who refused to adhere to their assignment to the control group and weaned early [87]. Benefits of breastfeeding on infant and young child survival persisted into the second year of life to around 18 months [88]. Benefits of continued breastfeeding were also observed for child growth [89] and for diarrheal morbidity and mortality [90].

HIV transmission persists throughout the duration of breastfeeding but early weaning is a late starter as much of the transmission has already occurred by the time breastfeeding ends. The older the child when breastfeeding ends, the less there is to gain in terms of avoiding HIV infection. As a result, risks of early weaning take on greater weight. With only small benefits of HIV prevented, small increases in mortality easily offset this benefit. We have reported no benefit of cessation of breastfeeding at 4 months for the combined outcome of HIV infection or death (HIV-free survival) compared to standard practice of breastfeeding ad lib in the primary intent to treat analyses [29]. With further analysis of the actual practices, we have found that the magnitude of benefit associated with early weaning (i.e., the amount of HIV prevented) was almost identical to the magnitude of the harm caused by early weaning (i.e., the numbers of uninfected child deaths caused) [87]. Women who stopped breastfeeding by 5 months had an additional 1.1% transmission rate after 4 months but a 17.4% uninfected child mortality rate through 24 months. In contrast, women who continued to breastfeed for 18 months had an additional 11.2% transmission rate but an uninfected child mortality rate of 9.7% [87].

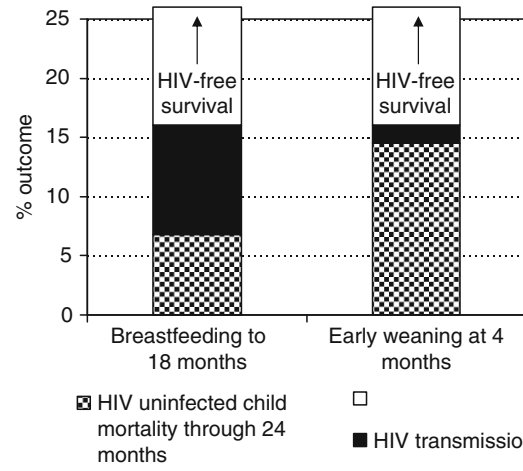

Fig. 20.1 Results from the Zambia exclusive breastfeeding study (ZEBS) which showed no net benefit for HIV-free survival of early weaning because reductions in HIV transmission were counter-balanced by increases in uninfected child mortality [93]

Thus, the total number of adverse events was almost identical between early weaning and prolonged breastfeeding but the composition was different with HIV making up a larger proportion of the adverse events in the breastfeeding women (Fig. 20.1).

Our data from Zambia were collected in the absence of either maternal antiretroviral treatment or extended antiretroviral prophylactic regimens that continue during breastfeeding. It is now clearly established that these interventions reduce postnatal HIV transmission considerably [91–93]. Thus, when antiretrovirals are given, the magnitude of mortality caused by artificial feeding is even larger than the magnitude of HIV transmission prevented. In our trial, among women who were not yet at an advanced enough disease stage to require antiretroviral therapy for their own health, stopping breastfeeding at 4 months led to a threefold *increase* in the combined outcome of child HIV infection or death occurring between 4 and 24 months [87].

A Parallel Antiretroviral Research Agenda

And so antiretrovirals stepped up to save the day. Parallel with the research on infant feeding and HIV was a systematic research agenda evaluating the use of antiretrovirals to prevent mother-to-child transmission [93]. Starting with the first proof of principle in 1996 [94], later studies investigated how to shorten the duration of prophylaxis as much as possible to make the interventions affordable and feasible in low resources settings. When the shortest possible intervention, single-dose nevirapine, was found to be almost 50% effective in reducing transmission peripartum (largely infections occurring in labor or during delivery) [95], a new age of implementation began which made the prevention of pediatric HIV infection a real possibility in low resource settings. Over almost 15 years, breastfeeding was a thorn in the side of antiretroviral prevention programs, since the short-course regimens were designed to attack transmission occurring peripartum with little to no coverage over the breastfeeding period. Breastfeeding simply added new infections after the antiretrovirals had ceased, eroding the benefits [95]. Eventually, the research agenda turned to evaluating longer courses of antiretrovirals continuing through the breastfeeding period. Prophylaxis of the infant with nevirapine proved to be an effective approach [91, 96, 97]; in contrast to prophylaxis with zidovudine which was not [11]. The first study evaluated 6 weeks of nevirapine, the second 14 weeks, and the third 24 weeks of daily nevirapine, all showing reductions in transmission when prophylaxis was given but resumption of transmission when prophylaxis was discontinued [91, 96, 97]. It was finally up to WHO to bravely

pull the plug and declare that there was now sufficient evidence that use of nevirapine as prophylaxis was effective whenever it was used during breastfeeding and endorsing its use over the duration of breastfeeding [98].

At the same time, as the agenda on how to use antiretrovirals to prevent mother-to-child transmission was unfolding, a parallel agenda to make antiretroviral therapy available to adults in low resource settings was gathering momentum. Rationing initially made drugs available only to the sickest individuals, with guidelines recommending treatment only for persons with CD4 counts below 200 cells/mm^3. Advocates were quick to motivate that pregnant women should be prioritized. As therapy needs to continue lifelong, its initiation during pregnancy would theoretically reduce postnatal HIV transmission via breastfeeding in addition to its established benefits for reducing peripartum transmission and protecting maternal health. Studies providing antiretroviral drugs to pregnant women who met treatment criteria reported low rates of transmission even when women continued to breastfeed [99, 100]. Studies then turned to evaluating antiretroviral drugs given to women with higher CD4 counts, or to all women regardless of CD4 count, with the goal less to protect maternal health but to prevent transmission through all routes [18, 92, 99, 101–105]. Prophylaxis using a usually therapeutic antiretroviral regimen would then be stopped when breastfeeding ended. To our knowledge, no study has yet to provide antiretrovirals over a normal duration of breastfeeding, i.e., 18 months or longer as most of these studies were designed in the era when early weaning was in place as the de facto recommendation. Nevertheless, one study with 6 months of breastfeeding has reported <1% postnatal transmission rate with antiretroviral therapy started during pregnancy indicating that maternal therapy can almost eliminate transmission occurring via breastfeeding [92].

There is a difference of opinion as to whether maternal therapy to all women regardless of CD4 count is a better public health approach to prevent mother-to-child HIV transmission than maternal therapy only to those who meet criteria with infant prophylaxis to the rest [106]. Since guidelines for who to treat have expanded to include all with CD4 counts <350 cells/mm^3 [107] the argument with respect to postnatal HIV is somewhat moot. More than 80% of postnatal transmission occurs among women with CD4 counts below 350 cells/mm^3 [108] so whatever interventions are given to the remaining women has only minor impact on the overall risk of transmission. The biggest "bang for the buck" is treating pregnant women with CD4 count <350 cells/mm^3. The challenge remains to meet the unmet needs for antiretroviral therapy among pregnant women since there is a limited time window and fragmentation of health services create further barriers for this priority population.

The Pendulum Swings Halfway Back

New WHO guidelines now support breastfeeding to 12 months for HIV-infected women albeit with some equivocation related to setting [98]. The success of antiretrovirals in reducing postnatal transmission to very low levels facilitated this partial swing back to arguably a reasonable middle-ground position. The now growing reports of the adverse consequences of shifts away from breastfeeding among HIV-infected women are grim reminders of why antiretrovirals during breastfeeding are so essential. The challenge now is implementation: both in terms of providing access to antiretrovirals and in terms of supporting breastfeeding. Effective use of antiretroviral drugs can now reduce HIV transmission to such low levels that there are few circumstances where replacement feeding can be justified.

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