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Mitochondrial DNA and sperm quality in patients on antiretroviral therapy – response

We read with interest the observations of Diehl *et al.* [1], but would question the validity of their conclusion that 'sperm are not useful in monitoring mitochondrial toxicity'. We have previously published in this journal, which they did not refer to, evidence of multiple mitochondrial DNA deletions in three patients who were on highly active antiretroviral therapy, including stavudine or didanosine, for longer than 18 months [2]. Diehl *et al.* [1] did not, however, state how long their patients had taken highly active antiretroviral therapy nor the nucleosides taken. Even if mtDNA depletion does not occur, mitochondrial function could still be affected by multiple mtDNA deletions. Whether or not sperm can be used to monitor mitochondrial toxicity therefore remains unclear and deserves further study.

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Long-term infant health outcomes critical in feeding decisions by HIV-positive mothers

A recent paper by Brahmabhatt and Gray [1] attempted to answer the question of whether breastfeeding is best for HIV-positive mothers.

The authors implied that formula feeding is better than breastfeeding for infants of HIV-positive mothers in less

developed countries. They based this on their finding that, in less developed countries, outside the HIV context, babies of mothers who chose to formula feed because of preceding morbidity in either mother or infant had lower mortality rates than babies of mothers who chose to formula feed for other reasons. This

conclusion was drawn despite their finding that mortality, in all cases in which infants were artificially fed, was at least 3.7 times higher than among breastfed babies who were voluntarily weaned.

There are several sources of confusion in this analysis. These include combining previous maternal morbidity with previous infant morbidity, and combining data from countries with different levels of wealth and access to healthcare systems. The high death rates from formula may be partly caused by pre-existing morbidity, partly by a lack of access to healthcare (to prevent formula-related morbidity turning into mortality), and partly by the use of formula in a particular environment. The weight of each component may vary from place to place. No estimates were given in their paper.

The authors assumed that the higher mortality levels would not occur among the babies of HIV-positive women because they would not be formula feeding because of preceding morbidity. However, this assumes that all HIV-positive women are healthy (i.e. that HIV infection does not constitute 'morbidity'). Even if none of them has AIDS, many HIV-positive women will have other forms of morbidity, such as low CD4 cell counts [2] or vitamin A deficiency [3]. Even those with no observable symptoms may have an abnormally high death rate [4]. The authors also neglected to define breastfeeding properly, and did not distinguish between exclusive breastfeeding for 6 months (as recommended by the World Health Organization and United Nations Children's Fund) and mixed and short-term breastfeeding. This led to general statements about breastfeeding which blurred the very different health outcomes associated with exclusive and various types of non-exclusive breastfeeding.

The authors assumed that HIV-positive mothers who choose to formula feed are comparable with those outside the HIV/AIDS context who formula feed for reasons other than preceding mother or child morbidity. If this is incorrect, mortality among babies of formula feeding HIV-positive mothers could be much higher.

It is invalid to compare rates of HIV infection, which will have health consequences throughout the life of a child, with the negative effects of formula feeding,

which can also have health consequences throughout the life of a child, but that are only measured for a short time period. What HIV-positive mothers need to help them decide whether breastfeeding or formula feeding is the best feeding alternative is to have information on long-term health outcomes.

Expectant mothers should be made aware of the extremely high infant mortality rate among babies who were formula fed because of preceding morbidity (326.8/1000 over 2 years), and also be told that exclusive breastfeeding may minimize HIV transmission as well as maximizing overall health outcomes [5]. Women who are fully informed about the issues around HIV transmission and maternal and child health issues relating to infant feeding strategies would be in a better position to select the feeding method that will be best for their individual situation.

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In the HIV era, is breast always best? Response to 'Long-term infant health outcomes critical in feeding decisions by HIV-positive mothers' by Crowe *et al.*

We thank Drs Crowe and colleagues for their comments.

The authors state that our paper claims that 'formula

feeding is better than breastfeeding for infants of HIV-positive mothers in less developed countries' because 'babies of mothers who chose to formula feed because of preceding morbidity in either mother or infant had lower

mortality rates than babies of mothers who chose to formula feed for other reasons'. This is incorrect, we clearly showed that mortality associated with formula feeding as a result of preceding morbidity is higher than formula feeding for voluntary reasons. We repeatedly reported higher child mortality rates in children who were never breastfed, compared with children who had been weaned. Our fundamental point is that the reason for not breastfeeding or weaning is important because mortality was consistently higher among children who were never breastfed or were weaned because of a preceding illness. There is clear evidence of reverse causality, whereby pre-existing morbidity may cause mothers not to breastfeed or to wean, and the resultant higher mortality risk arises from the preceding illness, rather than the mode of feeding *per se*. Such self-selection and reverse causality is also evident in other studies.

The authors also suggested confusion as a result of conflation between previous infant with maternal illness, and a combination of data across countries at different levels of development and healthcare access. The majority of reasons for not breastfeeding or weaning were a result of the child's preceding illness. Omitting cases of maternal illness did not change our findings. The country-specific estimates demonstrated similar patterns, and were therefore combined to get an aggregate measure. They suggest that we disaggregate the excess mortality into components such as health access, as well as formula-related risks. Unfortunately, the DHHS survey data do not provide this information and we have stated this as a limitation of the study. However, it is striking that the findings were consistent in all countries examined, which indicates a consistent effect, irrespective of the level of development or healthcare. They also suggest that maternal immune status, micronutrient deficiencies and maternal symptomatology could increase the risk to the infant via maternal morbidity. We cannot speculate on this question because no data are available. They also recommend that we differentiate between exclusive and partial breastfeeding, but again, DHHS data are not available to address this issue.

The authors also question whether our findings can be applied to children of HIV-infected mothers who voluntarily decide not to breastfeed. We suggest that counselling HIV-positive mothers on methods of feeding should recognize that current child mortality estimates for non-breastfeeding are biased overesti-

mates, because they do not adjust for the reverse causality described above. Although breastfeeding results in lower infant and child mortality rates than formula feeding in non-HIV-infected women, this risk/benefit is reversed with HIV because of the high rates of mother-to-child HIV transmission via breast milk. Although we agree with the authors that a more specific definition of breastfeeding (i.e. mixed or exclusive) is important, this information is not available in cross-sectional surveys such as the DHHS and we suggest that prospective studies are needed on methods of feeding and reasons for weaning or the non-initiation of breastfeeding.

Finally, it is argued that it is invalid to compare rates of HIV infection, which have long-term consequences for survival with the possible adverse effects of formula feeding, which are likely to be short term. We profoundly disagree with this view. The median survival time of HIV-infected children in Rakai, Uganda, is 2 years [1]. In the absence of antiretroviral therapy, all pediatric HIV infections are likely to be fatal. Given the high rates of mother-to-child transmission via breast milk, and the unconfirmed efficacy of exclusive breastfeeding for the prevention of mother-to-child transmission, based on one observational study [2], we believe that it is only reasonable to offer women the alternative of not breastfeeding in order to select the safest method for feeding infants.

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Intentional self-inoculation with HIV-positive blood: a case series from the Centers for Disease Control and Prevention HIV/AIDS Surveillance System

Up to December 2001, 816 149 patients with AIDS were reported to the Centers for Disease Control and

Prevention (CDC) and 256 cases with an unusual transmission mode have been documented [1]. These