A matter of context – time to clinically validate 9-month infant HIV testing in South Africa(?)

To the Editor: In their recent article, Fairlie *et al.*[1] rightly point out the need for increased identification and early treatment of postnatally HIV-infected infants, and suggest that testing at 9 months of age using HIV rapid tests (HRTs) will assist in this regard. While I agree with them on this point, I am less certain that such a practice will reduce the number of HIV polymerase chain reaction (PCR) tests done with resultant cost savings, as they have concluded. All HRTs that are positive at 9 months will have to be confirmed with HIV PCR testing, as maternal antibodies may persist well beyond this time point. Delayed seroreversion at >18 months of age in HIV-uninfected infants has been described in Malawi, Vietnam, Brazil and the USA. The US study detected anti-HIV antibodies by enzyme-linked immunosorbent assay (ELISA) testing in 14% of uninfected infants >18 months of age, with the median time to seroreversion occurring at >13 months of age.[2] The slower time to seroreversion from previously established cut-offs appears to be related to the introduction of combination antiretroviral therapy for prevention of mother to-child transmission during pregnancy, although the exact mechanisms of anti-HIV antibody clearance remain unclear.

Whereas there are anecdotal observations of delayed seroreversion in uninfected infants >18 months of age from South Africa (SA), to the best of my knowledge there are no local published data regarding time to loss of antibodies using rapid tests in infants exposed to World Health Organization Option B/B+. Hence there is concern that if routine use of HRTs is implemented at 9 months for all HIV-exposed infants, without clinical validation of HRT kits beforehand, a considerable proportion of these infants may require further HIV PCR testing. Furthermore, those infants who are still breastfeeding will require additional HIV testing 6 weeks after cessation of breast-feeding, with further repeat HIV PCR testing being required if seroreversion still has not occurred at this time. This will not only add to the escalating costs of infant diagnosis but will probably have a negative impact on the throughput and turnaround time of very early infant testing, which should remain the priority, at least for the time being. Fairlie *et al.*[3] base their findings on data suggesting that HRTs are able to detect seroreversion in the majority of HIV-exposed uninfected infants by 8 - 10 months of age. Whereas this may have been the case 10 years ago, it does not necessarily hold true today. Before a multicentre nationwide pilot study, as suggested by the authors, clinical validation of different HRTs needs to be prioritised within the current Option B+ context.

Ahmad Haeri Mazanderani
Centre for HIV and Sexually Transmitted Infections, National Institute for Communicable Diseases, Johannesburg, South Africa, and Department of Medical Virology, University of Pretoria, South Africa
ahmadh@nicd.ac.za

1. Fairlie L, Madevu-Matson CA, Black V, Sherman GG. Time to implement 9-month infant HIV testing in South Africa. S Afr Med J 2015;105(9):765-768. [http://dx.doi.org/10.7196/SAMJnew.8175]
2. Gutierrez M, Ludwig DA, Khan SS, et al. Has highly active antiretroviral therapy increased the time to seroreversion in HIV exposed but uninfected children? Clin Infect Dis 2012;55(9):1255-1261. [http://dx.doi.org/10.1093/cid/cis662]
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Fairlie *et al.* respond: We thank Dr Haeri Mazanderani for his interest in our article and for the opportunity to raise the profile of the debate on early infant diagnosis (EID) of HIV.

While we acknowledge that the SA Department of Health (DoH) guidelines[1] are excellent in terms of establishing EID, there is a gap once infants exit the current 18-week visit.[2] If they are breastfeeding and test negative before 18 weeks or their mothers previously tested HIV negative and seroconvert during breastfeeding, they usually do not get tested again until they become ill many years later. Despite numerous efforts, measles immunisation rates decrease by 18 months; HIV testing rates are low at 18 months, and post-breastfeeding HIV testing rates are unknown but are assumed to be low.[3] Since measles immunisation rates at 9 months are high[3] and many infants have discontinued breastfeeding by then, the 9-month visit presents a perfect opportunity for an Expanded Programme on Immunisation (EPI)-integrated HRT.

We agree that delayed seroreversion in infants would affect the model we described by increasing the number of HIV PCR tests required at 9 months.[2] Gutierrez *et al.*[4] ask 'Has highly active antiretroviral therapy increased the time to seroreversion in HIV exposed but uninfected children?' and describe an older median age (13.9 months) at seroreversion than previous studies. Their study was a retrospective record review of children exposed to maternal combination antiretroviral therapy (cART) in the USA.[4] They were unable to define a clear mechanism to explain these findings, but noted a significant association between late seroreversion and protease inhibitor (PI)-based ART (p=0.026) and caesarean section (p=0.0052), respectively.[4] The majority of SA pregnant women on Option B+ receive first-line cART (a non-nucleoside reverse transcriptase inhibitor, usually efavirenz, and not PI-based therapy) and SA DoH guidelines do not recommend routine caesarean section for HIV-infected women, most of whom give birth vaginally, which is associated with earlier seroreversion.[1] In our article we proposed using HRTs that have been shown to detect seroreversion at an earlier age than the more sensitive laboratory-based HIV ELISA test used by Gutierrez *et al.*[2,4,5] Although unknown, the differences in ART, delivery method and proposed rapid test used in SA suggest that our HIV-exposed uninfected infants will seroревert at an earlier age.

In the absence of data on the timing of seroreversion in HIV-exposed infants in the SA context, it is imperative that we do not disadvantage children by assuming that the findings of one study conducted under different field conditions in a different population will apply elsewhere. Even with lower rates of seroreversion at 8 - 10 months, negative HRTs would be expected to predominate in HIV-exposed, uninfected infants if appropriate HRTs are used. A test to screen children at <1 year on site, at a routine, well-attended EPI visit. would provide an additional opportunity to diagnose HIV-infected children early and initiate ART at a high-risk time, reducing morbidity and mortality.

We believe that the time is right to include, rather than exclude, children from HIV testing beyond early infant diagnosis. Adults are able to test frequently in the health system and are encouraged to do so, whereas HIV testing in children errs on the side of fewer tests, yet children have the highest morbidity and mortality if not diagnosed early.

Piloting 9-month HRTs at EPI visits in SA for HIV-exposed infants will encourage maternal retesting postpartum, as recommended in the guidelines, provide an opportunity for infant HIV PCR testing in those with a positive HRT, and allow for monitoring of seroreversion rates in the context of Option B+ in our local population using a different HRT. Furthermore, if maternal HIV antibodies persist in 14% of HIV-exposed children aged 18 months and seroreversion is incomplete at 24 months in HIV-exposed and uninfected children,[4] additional HIV PCR testing is urgently required in HRT-positive children aged >18 months in SA to prevent lifelong cART in uninfected children.

In summary, while we appreciate the points made, we believe that the current infant testing strategy lacks an EPI-based test at a fixed time point after 18 weeks and under 1 year, and that 9-month HIV testing could enhance EID and earlier ART initiation and replace the

post-weaning HIV test in HRT-negative infants who are no longer breastfeeding. Additional research and monitoring are essential.

Lee Fairlie
Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa
lfairlie@wrhi.ac.za

Caitlin Anna Madevu-Matson
Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa, and ICAP at Columbia University, Mailman School of Public Health, Columbia University, New York, USA

Vivian Black
Wits Reproductive Health and HIV Institute, University of the Witwatersrand, Johannesburg, South Africa

Gayle G Sherman
Department of Paediatrics and Child Health, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, and Centre for HIV and STI, National Institute for Communicable Diseases, Johannesburg, South Africa

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