Universal children’s day – let’s improve current interventions to reduce vertical transmission of HIV now

Mark F Cotton§ and Helena Rabie

§Corresponding author: Mark F Cotton, Tygerberg Academic Hospital, Francie van Zyl Avenue, Tygerberg, 7505, South Africa. Tel: + 2721 938 4298. (mcot@sun.ac.za)
*Both the authors have contributed equally to this work.

Received 22 October 2014; Accepted 28 October 2014; Published 20 November 2014

Copyright: © 2014 Cotton MF and Rabie H; licensee International AIDS Society. This is an Open Access article distributed under the terms of the Creative Commons Attribution 3.0 Unported (CC BY 3.0) License (http://creativecommons.org/licenses/by/3.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Introduction

By 2013, there was a 40% decline in new paediatric infections compared to 2009. Prevention of mother to child transmission (PMTCT) of HIV continues to reduce the frequency of HIV in infants through wider and earlier implementation of antenatal combination antiretroviral therapy (ART). Postnatally, breastfed infants are now protected from HIV infection through maternal ART and/or infant nevirapine (NVP) [1]. The ultimate aim is the elimination of vertical transmission of HIV.

Should HIV infection occur in infants, the focus is on early detection and treatment. The children with HIV early antiretroviral (CHER) trial established the benefit of initiating ART at a median of seven weeks of age [2,3]. The narrative of the Mississippi child focussed attention on very early diagnosis and therapy. This infant, whose mother was diagnosed as HIV-positive in labour, initiated ART 31 hours after delivery. After ART discontinuation from 15 to 21 months of age due to poor adherence, plasma HIV RNA remained undetectable on standard assays until almost four years of age, with only traces of HIV DNA being found using sophisticated assays [4,5].

Optimization of antenatal and post-natal maternal HIV diagnosis

The main driver of mother to child transmission is the maternal viral load. Although in utero infection has been observed from 12 weeks’ gestation [6], it is likely that the majority occur in the last two months of pregnancy [7]. Therefore, antenatal ART is most effective when commenced by week 20 of pregnancy [8]. Pregnancy is time-limited. Every week of delayed diagnosis increases the risk of vertical transmission. Using data from studies until 2010, Johnson and colleagues calculated that seroconversion late in pregnancy or during breastfeeding contributes 28% of vertical infections, which could be reduced through testing at 32 weeks’ gestation, and at the six-week post-natal visit [9]. Many of these recommendations have now been incorporated in MTCT guidelines, with additional testing in seronegative breastfeeding mothers at three-monthly intervals thereafter recommended [10]. Testing of sexual partners of HIV uninfected pregnant and breastfeeding women may further prevent new acquisition. While the rapid antibody tests are effective, the window period for developing sufficient antibodies for a positive test is between two and eight weeks, with almost 100% being positive after 12 weeks [11]. A new innovation is the point of care virological test, which will substantially increase diagnosis of acute HIV [12]. Dried blood spots offer an appropriate alternative for more resource-constrained settings [13]. Expanded testing should be offered for women where significant risk of acute HIV is identified, for example, those presenting with acute seroconversion illness or in high prevalence settings (Table 1 – see suggested approach to improving maternal diagnosis and ART success).

Infant post-exposure prophylaxis when there is a high risk of vertical transmission

For new HIV diagnosis in late pregnancy or labour, there is a possibility of reducing risk of vertical transmission through enhanced post-exposure prophylaxis. A randomized study of post-exposure prophylaxis for infants born to women from high prevalence settings where HIV was diagnosed late in pregnancy and who received no antenatal ARVs, has contributed many insights. The main objective was to determine the best post-exposure regimen for infants at extremely high risk for vertical HIV infection. Two antiretrovirals (ARVs) (zidovudine [ZDV] for six weeks plus three doses of NVP in the first week or three ARVs (ZDV, lamivudine [LMV] and nevirapine) for two weeks performed equally well and were superior to ZDV given for six weeks in formula-fed infants [14]. Given the superior efficacy of three ARVs compared to two ARVs for treatment, many would have hoped that the three-drug regimen would be better. Reasons for equivalence include inability to achieve therapeutic exposure for nevirapine in 46% of infants, although nearly all had trough levels above 0.05 μg/ml, 10 times the upper limit of nevirapine IC50 for wild type HIV [15]. Also, the standard duration of post-exposure prevention is four weeks, rather than the two weeks used in this study [16]. Post-exposure prophylaxis for 28 days rather than a shorter period is supported by rhesus macaque studies after simian immunodeficiency virus infection [17,18]. A recent cohort analysis from Europe showed...
that a three-ARV regimen for 28 days in post-exposure prophylaxis is being used more frequently in circumstances where there is a high risk of vertical transmission [19]. This strategy is being widely adopted subsequent to the report of the Mississippi baby [4] and experience in Canada [20].

**Early infant diagnosis of HIV**

In the post-exposure prophylaxis study by Nielsen-Saines et al., a polymerase chain reaction (PCR) test on the first day of life showed in utero infection in 5.7% of infants, illustrating the importance of an immediate PCR when the risk of transmission is high. There is a growing concern that both the accuracy of diagnostic testing and relying on a single test in the presence of ARV exposure are insufficient, leading to a false sense of security. In one report, a PCR at 4–6 weeks of age in formula-fed infants missed 32% of infections found at three months of age. Other studies have confirmed the inaccuracy of a single PCR at 4–6 weeks of age [21,22]. Point of care virological testing may be useful on the first day of life particularly where there is a high transmission risk but is not essential provided that at least two blood specimens are drawn for PCR in the first few days of life and triple ARV prophylaxis is initiated as soon as possible after birth. The latter should then be continued if the infant is HIV-infected. Also, for breastfed infants regular virological testing of the infant is essential until the infant is fully weaned (see Table 2).

**Conclusions**

PMTCT approaches in high prevalence settings require urgent adaptation to improve early infant diagnosis for the prevention and management of HIV.

---

### Table 1. Urgent maternal interventions to further reduce HIV PMTCT

| Phase          | HIV status | Intervention                                                                 | Rationale                                      | Comments                                      |
|----------------|------------|-----------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------|
| Antenatal      | Unknown    | Encourage first clinic visit and initial HIV testing in first trimester      | ART most effective when commenced by 20 weeks’ gestation | Initiate ART rapidly. Raltegravir can be added to more rapidly reduce viral load |
|                | Initial antibody test negative | Repeat HIV testing later in pregnancy and at delivery. If antibody negative, use point of care virological assay | Seroconversion in pregnancy can be detected and infants identified for triple ARV post-exposure prophylaxis. Stratification of tests allows rational usage of antibody and virological testing | Preventing maternal seroconversion |
|                | HIV +      | Check ART adherence through standard viral load assays at 32 weeks’ gestation and ensure no missed pharmacy visits | Standard viral load assay often easily available in many settings. Pharmacy visits easy to measure | Standard test can be replaced by point of care assay if standard test logistically difficult |
| During Delivery| HIV +      | Point of care virological test if assay at 32 weeks’ gestation above detectable limits | Identifies infants for ART prophylaxis and early diagnosis | |
|                | Previously HIV negative or unknown | Point of care antibody test if antibody test first; if negative, use point of care virological assay | As above | |

---

### Table 2. Urgent measures to increase early diagnosis, prevention and treatment in HIV-exposed infants

| Timing          | Intervention                                                                 | Comment                                                                 |
|-----------------|-----------------------------------------------------------------------------|-------------------------------------------------------------------------|
| At birth        | Commence post-exposure prophylaxis using three ARVs for 4 weeks            | Begin as soon as possible and take precedence over timing of diagnostic tests. Convert to continued ART for a positive early test |
|                 | 2 separate blood draws for diagnostic PCR tests or point of care virology test plus confirmatory PCR | Confirmation of HIV status essential                                       |
| 4–6 weeks       | Repeat diagnostic PCR                                                       | Delayed positive test possible                                           |
| 12 weeks        | Repeat diagnostic PCR if negative at 4–6 weeks                             |                                                                         |
| For continued breastfeeding | Repeat diagnostic PCR every 3 months Rapid antibody test or virological point of care test can be instituted at 9 months of age | This should continue until 6 weeks after fully weaned. A positive rapid antibody test at 9 months may reflect slow disappearance of maternal antibody and requires a diagnostic PCR or point of care virology test |
Authors’ affiliations
Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Stellenbosch, South Africa

Competing interests
Both authors have no competing interests.

Authors’ contributions
Mark F Cotton wrote the manuscript; Helena Rabie gave input, reviewed the manuscript and approved the final version.

Acknowledgements
Both authors received support from the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1AI069521. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

References
1. World Health Organization. Global update on the health sector response to HIV. 2014. Geneva: WHO; 2014.
2. Violari A, Cotton MF, Gibb DM, Babiker AG, Steyn J, Madhi SA, et al. Early antiretroviral therapy and mortality among HIV-infected infants. N Engl J Med. 2008;359:2233–44.
3. Cotton MF, Violari A, Otwombe K, Panchia R, Dobbelts E, Rabie H, et al. Early time-limited antiretroviral therapy versus deferred therapy in South African infants infected with HIV: results from the children with HIV early antiretroviral (CHER) randomised trial. Lancet. 2013;382:1555–63.
4. Persaud D, Gay H, Ziemniak C, Chen YH, Piatak M, Chun TW, et al. Absence of detectable HIV-1 viremia after treatment cessation in an infant. N Engl J Med. 2013;369:1828–35.
5. “Mississippi Baby” now has detectable HIV, researchers find. National Institute of Allergy and Infectious Diseases; 2014 [cited 2014 July 10]. Available from: http://www.niaid.nih.gov
6. Langston C, Lewis DE, Hammill HA, Papek EJ, Kojenis CZ, Kline MW, et al. Excess intrauterine fetal demise associated with maternal human immunodeficiency virus infection. J Infect Dis. 1995;172:1451–60.
7. Rouzioux C, Costagliola D, Burgard M, Blanche S, Mayaux M, Griscelli C, et al. Estimated timing of mother-to-child human immunodeficiency virus type 1 (HIV-1) transmission by use of a Markov model. The HIV Infection in Newborns French Collaborative Study Group. Am J Epidemio. 1995;142:1330–7.
8. Read PI, Mandalia S, Khan P, Harrison U, Naftalin C, Gilleece Y, et al. When should HAART be initiated in pregnancy to achieve an undetectable HIV viral load by delivery? AIDS. 2012;26:1095–103.
9. Johnson LE, Stinson K, Newell ML, Bland RM, Moultre H, Davies MA, et al. The contribution of maternal HIV seroconversion during late pregnancy and breastfeeding to mother-to-child transmission of HIV. J Acquir Immune Defic Syndr. 2012;59:417–25.
10. South African National AIDS Council (SANAC). The South African antiretroviral treatment guidelines 2013- PMTCT Guidelines revised: March 2013 [Internet]. 2013 [cited 2013 March 13]. Available from: http://www.nicd.ac.za/sanac/index.php/sections/pmtct-guidelines-

11. Panel on treatment of HIV-infected pregnant women and prevention of perinatal transmission. Recommendations for the use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmissions in the United States. USA: Department of Human Health Services; 2014 [cited 2014 Jun 30]. Available from: http://aidsinfo.nih.gov/guidelines
12. Emau P, Jiang Y, Agy MB, Tian B, Bekele G, Tsai CC. Post-exposure prophylaxis for SIV revisited: animal model for HIV prevention. AIDS Res Ther. 2006;3:29.
13. Tsai CC, Emau P, Folli KE, Beck TW, Benveniste RE, Bischoffberger N, et al. Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. J Virol. 1998;72:4265–73.
14. Chiappini E, Galli L, Giaquinto C, Ene L, Goetheheuer T, Judd A, et al. Use of combination neonatal prophylaxis for the prevention of mother-to-child transmission of HIV infection in European high-risk infants. AIDS. 2013;27:991–1000.
15. Bintun A, Samson L, Chun TW, Kakkar F, Brophy J, Murray D, et al. Early initiation of combination antiretroviral therapy in HIV-1-infected newborn infants can achieve sustained virologic suppression with low frequency of CD4+ T-cells carrying HIV in peripheral blood. Clin Infect Dis. 2014;59:1012–9.
16. Burgard M, Blanche S, Jasseron C, Descamps P, Alleron MC, Cirau-Vigneron N, Fisch C, et al. Performance of HIV-1 DNA or HIV-1 RNA tests for early diagnosis of perinatal HIV-1 infection during anti-retroviral prophylaxis. J Pediatr. 2012;160:60–6.661.
17. Mazaderani H, Ahmad F, Du Plessis BM, Rossi S, et al. Loss of detectability and indeterminate results: challenges facing HIV infant diagnosis in South Africa’s expanding ART programme. S Afr Med J. 2014;104:574.