

## HIV and Pregnancy

a report by

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HIV-1 is an RNA virus or retrovirus, which targets the cell-associated immune system (particularly CD4 cells), crucial for normal immune functioning. There is a strong relationship between viral load and the rate of CD4 decline, along with the development of clinical symptoms. The risk of opportunistic infections and other serious clinical symptoms becomes greater once immunodeficiency is established, with AIDS diagnosed according to specific clinical and immunological criteria.<sup>1</sup> Although the period of symptom-free infection varies between individuals, in most cases there is a 10-year period until development of serious manifestations of HIV disease in the absence of antiretroviral therapy and one to two years between AIDS diagnosis and death.<sup>2</sup> Antiretroviral drugs, which delay the progression of HIV through the inhibition of viral replication, were first approved for use in adults in 1987.

In 1996, the first evidence became available showing that combinations of three or more antiretroviral drugs are considerably more effective than single or double combinations in preventing viral replication and, hence, immunological and clinical deterioration.<sup>3,4</sup> Subsequently, such potent combinations (also called highly active antiretroviral therapy (HAART) usually containing at least two nucleoside analogue drugs combined with a protease inhibitor or a non-nucleoside reverse transcriptase) have become the standard of care in developed countries. The rapid uptake and widespread use of HAART has meant that HIV infection has been transformed into a chronic disease in these settings, with significant improvements in AIDS-free survival and quality of life<sup>5,6</sup> as a result.

### Epidemiology of HIV Infection in Women Globally and in Europe

An estimated 17 million women were living with HIV/AIDS at the start of 2004. Most of these women live in developing countries where the HIV epidemic has become generalised, largely in sub-Saharan Africa, and each year at least two million women become infected with HIV.<sup>7</sup> Women acquire HIV infection through heterosexual contact

with an infected partner, parenterally through injection drug use and through contaminated blood or blood products. Heterosexual contact is the predominant route of transmission globally among women;<sup>7</sup> in Europe and the US, injection drug use was initially the most important mode of acquisition among women, but was superseded by heterosexual transmission approximately a decade ago.<sup>8</sup> Women are not only more biologically vulnerable to the heterosexual acquisition of HIV infection than men, but are also socially vulnerable.<sup>9</sup> As expected for a sexually-transmitted infection (STI), most HIV-infected women are in their child-bearing years.

### Mother-to-Child Transmission of HIV

In 2004, 640,000 children were estimated to have acquired HIV infection, mostly through mother-to-child transmission (MTCT),<sup>7</sup> which can take place *in utero*, around labour and delivery and post-natally through breast-feeding. Prior to the introduction of interventions to reduce vertical transmission risk, reported rates of MTCT varied from 15–20% in Europe, 16–30% in the US, 25–40% in Africa to 13–48% in south and south-east Asia.<sup>10–13</sup> The MTCT rate at 24 months in the Kenyan breast-feeding versus formula-feeding trial was 37%, compared with 20% in formula-feeding.<sup>14</sup> Maternal viral load (HIV RNA) is the best individual predictor of MTCT risk *in utero*, intrapartum and through breast-feeding,<sup>15–18</sup> and other factors increasing risk include AIDS, primary infection and low CD4 count (for all routes of transmission) and vaginal delivery (for intrapartum transmission).<sup>19,20</sup>

### Prevention of MTCT

Interventions to prevent MTCT can only be applied if HIV-infected women are promptly identified in pregnancy – antenatal HIV screening is therefore a vital component of prevention of MTCT (PMTCT) programmes.<sup>21,22</sup> The benefits of early identification not only relate to PMTCT, but also allow the woman's own HIV disease and health to be monitored and appropriately managed. Rapid HIV testing in labour allows the identification of infected women who have not previously had a test, for example because of lack

of antenatal care, and allows the immediate provision of prophylactic antiretroviral therapy (ART) and the avoidance of breastfeeding.<sup>22,23</sup>

### Antiretroviral Prophylaxis

Antiretroviral (ARV) prophylaxis reduces MTCT by decreasing viral replication in the pregnant woman, thus reducing plasma HIV RNA load and, for ARV drugs that cross the placenta, through post-exposure prophylaxis of the neonate.<sup>24</sup> Prophylactic ART was first shown to be effective in reducing MTCT risk in the American–French Paediatric AIDS Clinical Trial Group (PACTG) 076 clinical trial in 1994, which investigated the use of zidovudine monotherapy in pregnancy (from 14 weeks), intrapartum and in the neonate for six weeks.<sup>25</sup> Over the subsequent decade, there have been considerable changes regarding the use of ARVs in pregnancy, both for PMTCT and for delaying HIV disease progression in the mother, with the introduction of HAART.<sup>24</sup>

Women diagnosed with HIV infection in pregnancy are clinically and immunologically evaluated to determine whether or not they need HAART for their own health. Such decisions are usually based on clinical and immunological indicators (and increasingly HIV RNA viral load), but policies and practices vary within and between countries. In Western Europe, an increasingly large proportion of HIV-infected women are already being given HAART when they become pregnant; for example, in one European cohort study, 85% of women delivering in 2003 were already being given HAART when they became pregnant.<sup>26</sup> HIV-infected women who do not need to start taking HAART for their own health should be offered ARV prophylaxis for PMTCT, which may be zidovudine monotherapy as per the PACTG 076 regimen (combined with an elective Caesarean section (CS));<sup>25</sup> however, such women are more likely to be offered short-term HAART for PMTCT reasons alone, as per current guidelines in the US and Europe.

The increasing use of HAART in pregnancy in developed countries has resulted in a growing proportion of women achieving undetectable levels of the virus by the time of delivery, which has had a substantial impact on vertical transmission. MTCT rates are currently at their lowest ever levels, at approximately 1–2%, as evidenced by the results from cohort studies.<sup>17,27–29</sup> In less developed countries, ARV prophylaxis for PMTCT has, until recently, been dominated by the use of short-course zidovudine (starting from 28 to 36 weeks' gestation) and single-dose nevirapine (sdNVP) intrapartum for the mother and post-natally for the infant, based on clinical trials that showed an approximate 37% efficacy in reducing

MTCT associated with abbreviated zidovudine regimens, and a 44% reduction with sdNVP.<sup>16,30–34</sup> Not only are these interventions less effective than those used in resource-rich settings, but sdNVP also selects for viral resistance,<sup>35,36</sup> which could have detrimental consequences for maternal response to future ART. Resistance is of particular concern given that the World Health Organization's (WHO's) recommended first-line HAART regimen for use in developing countries contains nevirapine.

Strategies to reduce the development of nevirapine resistance in women receiving PMTCT prophylaxis are being investigated. In particular, the addition of up to one week of post-natal prophylaxis with zidovudine and lamivudine to the sdNVP doses significantly reduces the prevalence of NVP resistance at four to six weeks' follow-up.<sup>37,38</sup> It has also been recommended that, where possible, PMTCT programmes should try to introduce more complex prophylactic regimens, including HAART.<sup>39</sup> Peripartum ART, although reducing risk of the early post-natal acquisition of infection, has no effect on late post-natal transmission after the initial weeks of life.<sup>40–42</sup> Several studies are currently under way in breast-feeding populations in resource-poor settings to evaluate the use of HAART for mothers in pregnancy and post-natally, and for uninfected infants during the breast-feeding period.<sup>43–45</sup>

### Elective CS

In 1999, results from a trial<sup>46</sup> and a large international meta-analysis<sup>47</sup> confirmed observational findings that elective CS (performed before onset of labour and before rupture of membranes) was associated with MTCT risk more than halving, independent of prophylactic zidovudine use. Subsequent recommendations were for all HIV-infected pregnant women to be offered an elective CS in Europe and rates of elective CS delivery of up to 82% among infected women were reported.<sup>29,48</sup>

However, the added benefit of elective CS as an intervention among women on successful HAART is uncertain and difficult to assess given the large numbers required for appropriate analysis. Nonetheless, a reduction of two-thirds in MTCT risk associated with elective CS, independent of maternal viral load and CD4 count was found in the HAART era in one European cohort study.<sup>26</sup> Although a significant effect of elective CS in reducing MTCT among women with undetectable viral loads at delivery was seen, the analysis did not adjust for HAART use.<sup>26</sup> National and local policies vary regarding recommendations for mode of delivery in HIV-infected women on HAART without obstetric indications for elective CS. However, it is strongly recommended that women with detectable viral loads

at delivery and those not receiving HAART (i.e. instead receiving zidovudine monotherapy as per the 076 regimen) should be offered this mode of delivery. HIV-infected women are generally at increased risk of postpartum complications compared with uninfected women, regardless of mode of delivery<sup>49,50</sup> and therefore require careful obstetric management. All HIV-infected women undergoing elective or emergency CS procedures should be provided with antibiotic prophylaxis, which may also be of benefit to women undergoing vaginal deliveries.

### Avoidance of Breast-feeding

Breast-feeding is associated with an approximate doubling of overall MTCT risk, with the risk remaining as long as breast-feeding continues.<sup>14</sup> In developed countries where formula feeding is safe, affordable and feasible, HIV-infected women should be advised to avoid breast-feeding, as recommended in the WHO/UNICEF/Joint United Nations Programme on HIV and AIDS (UNAIDS) guidelines.<sup>51</sup> There is only limited data on the effect of HAART on viral load in breast milk, which is known to be highly variable,<sup>52</sup> and so women on HAART should also be recommended to avoid breast-feeding.

### Safety of Antiretroviral Drugs in Pregnancy and as Neonatal Prophylaxis

Despite the undoubted effectiveness of HAART in PMTCT, there are few safety data from studies involving pregnant women, with all antiretroviral drugs having B, C or D US Food and Drug Administration (FDA) safety classification.<sup>24</sup> This is of particular importance given the increasing use of HAART in pregnancy, particularly at the time of organogenesis. Reports of adverse effects of antenatal HAART use for pregnancy outcome and/or the pregnant woman herself include increased risk of pre-eclampsia,<sup>53,54</sup> gestational diabetes<sup>55–57</sup> and prematurity.<sup>58–60</sup> There have been case reports of lactic acidosis (some fatal) in pregnant women on didanosine and stavudine-containing HAART;<sup>61–63</sup> therefore, this combination should be avoided. There is no evidence of an increased risk of hepatotoxicity with sdNVP; however, there have been reports of hepatotoxicity among adults on long-term NVP-containing regimens, particularly those only moderately immunosuppressed. Pregnant women with CD4 counts above 250cells/mm<sup>3</sup> should not start NVP-containing regimens due to the potentially increased risk of hepatotoxicity.<sup>64–67</sup>

To date, there appears to be no increased risk of congenital malformations associated with HAART

exposure in pregnancy,<sup>68</sup> with the exception of efavirenz, which has been associated with teratogenicity in animal<sup>69,70</sup> and human studies,<sup>69,71,72</sup> and should not be given to women who are or may become pregnant. However, there are concerns that uninfected infants born to infected mothers with *in utero* and neonatal ARV exposure may be at potential risk of adverse effects in the medium to long term, with regards to immunological, haematological and mitochondrial functioning. Anaemia (usually mild and reversible) in the neonate is the major toxicity usually associated with exposure to prophylactic zidovudine.<sup>73,74</sup> However, recent evidence from two European cohort studies suggests that there may be longer-term effects for other haematological parameters, with significantly reduced levels of platelets, lymphocytes and neutrophils in ARV-exposed compared with unexposed infants.<sup>75,76</sup> Clinical and sub-clinical mitochondrial dysfunction has been reported in a few ARV-exposed children from France,<sup>77,78</sup> with other studies reporting transient hyperlactataemia in such children,<sup>79–81</sup> which is a non-specific marker indicating possible mitochondrial damage. With regards to genotoxic and mutagenic potential, zidovudine has been shown to be incorporated into the DNA of leukocytes in infants with *in utero* zidovudine exposure,<sup>82</sup> but the persistence of this and its clinical significance are unknown.<sup>83</sup> Observational studies have been reassuring regarding lack of cancers in ART-exposed children,<sup>73,84,85</sup> although evidence to date does not exclude the possibility of increased risk of cancers at older ages. These potential adverse effects of exposure to ART *in utero* and early in life require further long-term monitoring; however, the tremendous benefits of ARV prophylaxis so far outweigh the potential costs.

### Conclusions

Elimination of vertically acquired HIV infection is now on the public health agenda in developed countries, as a result of the very low MTCT rates below 1–2%. However, barriers to this goal remain, including inadequate or late access to antenatal care, late or non-identification of HIV infection in pregnant women, sub-optimal application of PMTCT interventions and poor uptake of and/or adherence to PMTCT interventions. Although innovations in rapid HIV testing and post-exposure prophylaxis may prevent some transmissions in women with no or limited antenatal care, this should not be seen as an alternative to improving antenatal care for women at risk of HIV infection, including screening. Further research and monitoring are required regarding the safety aspects of ARV use in pregnancy and the neonatal period, particularly as

the number of infants exposed to potent combinations of ARV drugs in Europe and elsewhere is increasing.

In contrast, the majority of HIV-infected pregnant women in the developing world do not receive any PMTCT interventions, or receive interventions

that are substantially less effective than those used in resource-rich settings. Further research is needed to develop appropriate strategies for perinatal and subsequent ART for use in the developing world, particularly considering the impact of perinatal ART for PMTCT on the effectiveness of post-natal ART regimens. ■

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