HIV and pregnancy: how to manage conflicting recommendations from evidence-based guidelines

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In resource rich settings transmission of HIV from mother to child during pregnancy and post partum has been significantly reduced by access to interventions such as maternal and neonatal antiretroviral therapy, avoidance of breast feeding and consideration to caesarean section. Accumulating observational and randomised controlled studies provide the evidence for development of guidelines for the clinical management of these women. However, despite referencing the same studies, differences exist between recommendations originating from the United States versus the United Kingdom. The particular areas of controversy include use of efavirenz, dose adjustment of antiretrovirals during pregnancy, mode of delivery according to maternal viral load, duration of neonatal zidovudine, use of PJP prophylaxis and number of antiretrovirals to prescribe in a neonate considered high risk of acquiring HIV infection. This article summarises these differences and suggests ways of approaching and adapting these conflicting recommendations to the local setting.

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Background

Optimal management of HIV and pregnancy is essential to maximize the mother's health, minimize transmission to partners, and to prevent HIV transmission to the newborn. In resource-rich settings the reported rate of transmission, with interventions inclusive of maternal and neonatal antiretroviral therapy, avoidance of breastfeeding, and consideration to caesarean section is between 1 and 0.1% [1].

Over the past 10 years there have been increasing data available from clinical trials to guide in decision-making regarding the above interventions. To aid in the management of these women various authorities produce and regularly update guidelines encompassing this evidence. In the past 6 months two comprehensive sets of guidelines have been updated; those produced by the Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission from the US [2] and those produced by the British HIV Association (BHIVA) [3].

For many clinicians in similar resource-rich settings, outside the countries where these guidelines originate, they form an invaluable tool and reference to guide clinical care. However, with the recent iterations there are a number of conflicting recommendations which may lead to confusion and uncertainty.

The purpose of this commentary is to highlight the key differences between these two sets of guidelines and suggest ways of approaching this and adapting these differences for the individual's local situation. The author

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of this opinion piece is not a member of any of the guideline committees referenced. The key differences including the WHO guidelines are summarized in Table 1.

Key differences in antiretroviral therapy

The key differences in antiretroviral therapy can be divided into recommendations regarding specific drugs and pharmacokinetics.

Specific drugs: efavirenz

With regard to particular agents, efavirenz is not recommended in the guidelines from the US, especially in the first trimester [2]. If a woman is on efavirenz and found to be pregnant in this timeframe then there is no longer a recommendation to switch from efavirenz to another antiviral agent if this is likely to compromise virological control. The concerns about teratogenicity are based on a combination of animal data and human case reports. In preclinical studies three of 20 cynomolgus monkeys who received efavirenz from day 20–150 gestation at comparable plasma doses to humans developed malformations (anencephaly and anophthalmia, microphthalmia and cleft palate) [4]. Prospective reports of first trimester human exposure to the Antiretroviral Pregnancy Registry, up to January 2011, have not found an increase in birth defects compared with the background population rate [5]. Similarly, a meta-analysis which included data from nine cohorts and 1132 prospective reports of first trimester exposure found no overall increase in birth defects [6]. This was updated in 2011 and reported 39 defects in 1437 women receiving first trimester efavirenz, a relative risk of defects 0.85 [95% confidence interval (CI) 0.61–1.2]. One neural tube defect was reported giving an incidence of 0.07% (95% CI 0.002–0.39) [7]. In contrast two publications have reported high rates of birth defects in offspring exposed to efavirenz *in utero*, 15.6% [8] and 12.8% [9], respectively. There have been six retrospective case reports in humans of central nervous system defects [4].

In contrast to the American guidelines, the BHIVA guidelines state that the emerging prospective data reports no evidence for teratogenicity [3]. With regards to the high rates of birth defects reported by Brogly and Knapp they argue that these rates are inflated and cite issues of recruitment bias, small absolute numbers of exposure and no pattern to the malformations.

How do you incorporate these differing recommendations regarding efavirenz into local clinical practice?

Firstly, it is important to appreciate that for many HIV-positive women, taking antiretroviral medication during pregnancy can cause them significant anxiety particularly regarding drug exposure by their fetus. Recognizing this, it is important that healthcare providers are sensitive to these concerns but emphasize the overwhelming benefit in terms of maternal health and prevention of HIV transmission. A healthy mother and an undetectable HIV viral load are two extremely important factors in optimizing the best outcome for the child. Therefore, ideally a prepregnancy discussion around the conflicting data, animal and human case report data regarding potential teratogenicity of efavirenz should be had with every woman commencing antiretroviral therapy in light of her reproductive intent. This is also applicable to the large number of newer antiretroviral agents, many of which have an US Food and Drug Administration (FDA) classification B. This classification suggests either no evidence of risk in humans although for many of the newer antiretroviral drugs this actually means that in the absence of adequate human studies, animal studies show no fetal risk. Whether or not these are safer than efavirenz is unknown. If there are other effective, tolerable, affordable options then these should be considered. In addition, timing of 'pregnancy' diagnosis is important. Closure of the neural tube occurs at 6 weeks gestation, so if switching is to prevent the theoretical possibility of neural tube defects then this is not indicated after 6 weeks, the very gestation when many women recognize themselves as being pregnant. If a woman becomes pregnant on efavirenz, the diagnosis of anatomical defects, particularly neural tube defects, is usually made after 16 weeks. In the rare event that this may occur, the role of ultrasound for diagnosis (or amniocentesis for causality) may be useful in assisting decision making regarding further obstetric management during pregnancy including the continuation or not of the pregnancy. With increasing prospective reports of exposure and decreasing evidence for teratogenicity in humans, women who do conceive on efavirenz should be overwhelmingly reassured rather than automatically referred for consideration of termination of pregnancy or automatically switched to another antiretroviral agent especially if this is likely to compromise virological control.

Pharmacokinetics

The BHIVA guidelines do not recommend any routine dose alterations during pregnancy with the exception of darunavir, which should be dosed twice daily and consideration for therapeutic drug monitoring during the third trimester if on atazanavir and tenofovir [3]. The US guidelines also recommend twice daily dosing of darunavir based on a study of pregnant women which reported reduced plasma concentrations and trough concentrations during the third trimester with once-daily dosing [10]. In contrast to the British guidelines which do not recommend routine dose alterations, the US guidelines recommend increasing lopinavir/ritonavir in the second and third trimester, especially if protease inhibitor experienced, and atazanavir (if antiretroviral experienced and also on tenofovir or a H2 antagonist) [2].

Table 1. Key differences in recommendations between three sets of guidelines.

	DHHS guidelines	BHIVA guidelines	WHO guidelines
Antiretroviral therapy: efavirenz	Not recommended first trimester but if a woman is on it don't switch if this is likely to compromise virological control	No evidence for teratogenicity	Efavirenz-based regimens should not be initiated during first trimester of pregnancy. Efavirenz is listed as one of the preferred agents as a component of triple therapy for antiretroviral naive women in need of treatment for their own health. If a woman is on efavirenz and pregnancy recognized in first 28 days it should be stopped and substituted with nevirapine or a protease inhibitor, if pregnancy recognized after 28 days continue the efavirenz.
Therapeutic drug monitoring (TDM)	Increase lopinavir/ritonavir second and third trimester especially if protease inhibitor experienced	Routine dose alteration not recommended	No recommendations
	Increase atazanavir dose if antiretroviral experienced and also on tenofovir or a H2 antagonist	Consider TDM third trimester if on atazanavir and tenofovir	
	Darunavir should be dosed twice daily	Darunavir should be dosed twice daily	
Mode of delivery	Vaginal birth if maternal viral load <1000 copies/ml	Vaginal birth if maternal viral load <50 copies/ml	No recommendations
Intrapartum zidovudine	Recommended in all women if viral load >400 copies/ml	Recommended if viral load >10 000 copies/ml	Recommended with lamivudine (intrapartum and 7 days postpartum tail) to reduce nevirapine drug resistance among mothers and infants who receive single dose nevirapine at labour and birth
Duration of antiretroviral prophylaxis in the exposed neonate	6 weeks	4 weeks	4–6 weeks (this may be extended in breastfeeding infants whose mother's do not continue treatment)
Number of antiretroviral agents for neonate if mother has detectable viral load at time of delivery	2 drugs	3 drugs	No recommendations
Pneumocystis jirovecii pneumonia	From 6 weeks unless adequate test information to exclude HIV infection in the neonate	Only recommended in high risk infants from four weeks (for example if viral load unknown or >1000 copies/ml)	No recommendations

BHIVA, British HIV Association; DHHS, Department of Health and Human Services.

Protease inhibitors are highly protein-bound with limited placental transfer. During the third trimester there is a reduction in protein binding and even if this is small, it can lead to increased free drug level. The clinical significance of these changes, particularly in the third trimester, is not clear, but the magnitude of change appears to be smaller than the total lopinavir concentration decrease reported in other studies [11]. For example, pharmacokinetic studies have reported that an increased dose (three tablets twice daily) in the third trimester is required to achieve a similar average area under the curve (AUC) as the standard dose of two tablets twice daily [12]. This study was based in the US and the majority of women in this study were Hispanic with a median weight at delivery 77.8 kg. In comparison, a similar pharmacokinetic study undertaken in Thailand reported that 81% of women achieved above the target AUC with standard dosing (400/100 mg twice daily) [13]. The median weight of this group was 59.5 kg with a BMI of 26. In the group who did have reduced lopinavir exposure during the third trimester, this was approximately half that observed in the American population studied by Best *et al.* [12].

There are conflicting data regarding pharmacokinetic changes of atazanavir with pregnancy. Some studies report similar concentrations during the third trimester compared with post partum [14]. In contrast, other studies have reported a reduction ranging from 28%, up to 50% if also on concomitant tenofovir [15]. In addition, a European study found that despite a 33% reduction in AUC during the third trimester with standard 300 mg

doses of atazanavir, drug levels when measured were still above the recommended minimum plasma concentration for wild type virus [16].

How do you incorporate the differing pharmacokinetic guidelines into local clinical practice?
Key considerations include the patient population being treated and their characteristics such as weight, BMI, and ethnicity. These two factors may influence the magnitude of pharmacokinetic changes as evidenced by the study conducted in the US compared with Thailand. In a woman with a low BMI that remains virologically suppressed, routine dose changes in the third trimester may not be warranted. If therapeutic drug monitoring is available then this may be employed to guide this decision. In regions where this is not readily available in a timely, cost-effective manner, then routine dose increase may be considered particularly if the patient population is thought to reflect some of the characteristics of the population studied in the report by Best *et al.* [12].

In addition tolerability of medication is important. If a woman is experiencing significant side effects to lopinavir yet has suppressed viral load it is important to ensure increasing the dose does not potentially compromise adherence and therefore virological suppression. Similarly, if a woman is experiencing significant hyperbilirubinemia at a dose of 300 mg atazanavir, then a routine increase in the dose which may worsen the hyperbilirubinemia and theoretically risk neonatal hyperbilirubinemia may not be warranted if she remains fully virologically suppressed.

Overall, it is important to note that to date there has been no correlation between standard dosing of antiretroviral therapy during the third trimester of pregnancy, virological failure, and increased perinatal HIV transmission. In addition, it is not clear whether it is the free or the bound drug concentration that is the most important. Therefore the approach should be individualized according to the patient population, tolerability and availability of viral load monitoring and therapeutic drug monitoring.

Key differences in obstetric management including mode of delivery and intrapartum zidovudine

Mode of delivery

Currently, the BHIVA guidelines recommend a vaginal birth for women with a plasma HIV RNA level of less than 50 copies/ml at week 36 gestation [3]. In contrast, the US guidelines advise that a scheduled caesarean section should not be routinely recommended in women with a plasma HIV RNA level of less than 1000 copies/ml [2]. The difference in these viral load cut-offs reflects the change in sensitivity of HIV RNA assays over time, leading to lower and lower limits of detection. In addition, the threshold of 1000 copies/ml is largely based on data from the Womens and Infants Transmission Study in which none of the 57 women with a HIV RNA viral load below 1000 copies/ml transmitted HIV [17].

How do you approach this difference in cut-off if a woman has a reported plasma HIV RNA between 50 and 1000 copies/ml?
In 2008, a report from the National Surveillance System in the United Kingdom and Ireland reported HIV transmission in three of 2309 (0.1%) in women with a plasma HIV RNA below 50 copies/ml compared with 12 of 1023 (1.2%) in women with a plasma HIV RNA between 50 and 999 copies/ml [1]. Women therefore, with a plasma HIV RNA between 50 and 1000 copies/ml, should be advised that it is not clear whether a caesarean section will confer additional benefit in reducing the transmission rate below 1%. The decision needs to be individualized based on past obstetric history, standard obstetric indications, personal preference, access to medical/surgical resources and care, and the potential risk of morbidity associated with operative delivery.

Intrapartum zidovudine

Intrapartum intravenous zidovudine is recommended in the US guidelines to all women with a plasma HIV RNA viral load above 400 copies/ml [2]. The rationale for this is based on the initial PACTG 076 clinical trial and subsequent studies proving the efficacy of a three part zidovudine regimen, and its 'unique characteristics and proven track record'. In contrast, the BHIVA guidelines state that there is no evidence to support intrapartum, intravenous zidovudine in women with a plasma HIV RNA of below 10 000 copies/ml. This is primarily based on French data which found no evidence that intrapartum zidovudine further reduced risk of transmission in women on HAART with a viral load below 10 000 copies [18].

So, how do you decide whether to use intrapartum zidovudine?
Given the relative lack of data regarding benefit of intravenous intrapartum zidovudine in the HAART era, a suggested approach is to recommend it for women with a plasma HIV RNA viral load of more than 10 000 copies, consider it in women with a plasma HIV RNA viral load between 400 and 10 000 copies, and advise that it could be considered but is not essential in women with a plasma HIV RNA viral load below 400 copies on HAART.

Key differences in postnatal management of the infant

There are three key differences between the guidelines from the US compared with from the UK with regards to

postnatal management of the HIV-exposed neonate. These are the duration of antiretroviral therapy (6 versus 4 weeks), the number of agents used if the mother has a detectable plasma HIV RNA viral load (two versus three drugs), and the role of *Pneumocystis jirovecii* pneumonia (PJP) prophylaxis.

Duration of antiretroviral therapy

The US guidelines recommend all neonates receive 6 weeks of zidovudine starting within 6–12 h of delivery [2]. This stems from the original clinical trial PACTG 076 study [19] comprising of three parts to zidovudine prophylaxis (prenatal, intrapartum, and 6 weeks postpartum). In the absence of ongoing HIV exposure by the avoidance of breastfeeding and evidence that shorter postnatal regimens are effective in reducing transmission, many centres in resource rich settings have shortened this to 4 weeks.

How do you decide between 4 or 6 weeks of postexposure prophylaxis?

Important considerations when deciding between 4 and 6 weeks of treatment includes risk of transmission to the neonate including the potential for ongoing exposure after birth, adherence by the caregiver to administration of the medication, and potentially related to this, concern over toxicity. There is no evidence that 6 weeks of zidovudine postexposure prophylaxis (PEP) is superior to 4 weeks of PEP in neonates whose mother had an undetectable plasma HIV RNA viral load at delivery. In fact, a study of 916 infants receiving 4 weeks of zidovudine in the setting of maternal prenatal antiretroviral therapy reported transmission rates of 1.1% [20] similar to reported transmission rates in the US where standard duration of PEP is 6 weeks. However, there may be more toxicity associated with prolonged antiretroviral exposure as evidenced by a recent study which reported earlier recovery from anemia with a shorter regimen [21]. The clinical significance of this is uncertain but may be sufficient to cause anxiety among the carers administering the therapy and needs to be weighed against the lack of efficacy benefit in a neonate with no ongoing exposure after birth whose mother had an undetectable viral load at delivery.

Number of agents recommended if the mother has a detectable plasma HIV RNA viral load

Triple combination neonatal therapy is advised in the BHIVA guidelines for infants born to mothers with a detectable plasma HIV RNA viral load above 50 copies/ml or infants born to untreated mothers [3]. In contrast, the US guidelines recommend a two-drug antiretroviral regimen for infants born to untreated mothers rather than three. This is based on the findings from a randomized controlled trial of 6 weeks of zidovudine combined with three doses of nevirapine for the first week that found dual therapy to be as effective but less toxic than a three-drug regimen (zidovudine, nelfinavir, lamivudine) [22]. Importantly, both the two and three drugs regimens were more effective in preventing transmission compared with zidovudine monotherapy in these infants considered at 'high risk' (women who did not receive any antiretroviral drugs during pregnancy).

Given these data, and conflicting advice, when do you prescribe two or three antiretroviral drugs to the neonate?

For untreated women, recently published randomized controlled data provide evidence for the use of two antiretrovirals in these infants at high risk of infection, but have not found this to be superior to three antiretrovirals [22]. For women on treatment but who have suboptimal viral suppression at delivery, there are limited data to guide the optimal duration and number of antiretrovirals. Although speculation, it would seem unlikely that three drugs would be superior to two drugs in the setting of suboptimal viral suppression for a woman on therapy when there is no evidence of improved efficacy when a woman is on no treatment at all (presumably a higher risk situation). Therefore this needs to be discussed at length and in the absence of randomized controlled data, individualized taking into consideration the maternal viral load at delivery, potential benefit in terms of reduced transmission, and the potential toxicity of multiple drugs. Although long-term, irreversible toxicity secondary to antiretroviral therapy used for infant prophylaxis has not been reported there are some reports of toxicity in HIV-infected children requiring continuation of antiretroviral therapy for treatment of disease, such as bone density reductions with tenofovir [23]. Therefore, any discussion regarding potential benefit versus risk must also include a discussion around what is known and currently unknown.

Pneumocystis jirovecii pneumonia prophylaxis

The US guidelines recommend all infants receive PJP prophylaxis from 6 weeks (when PEP is completed) unless there is adequate test information to presumptively exclude HIV infection [2]. In contrast the BHIVA guidelines only recommend PJP prophylaxis for high risk infants from 4 weeks (when PEP is completed) such as those born to mothers who are not fully virologically suppressed at delivery (viral load >1000 copies despite HAART or if viral load unknown) [3].

How do you decide whether to recommend *Pneumocystis jirovecii* pneumonia prophylaxis?

The most important consideration when incorporating these contrasting recommendations into local clinical practice is the availability and reliability of viral load testing in the mother and HIV diagnostic testing in the neonate. If maternal viral load is known and low and diagnostic testing of the neonate is reliable and can be accessed soon after birth (to exclude intrapartum transmission) and between 4 and 6 weeks of age, and there is no ongoing risk of transmission (e.g. by

breastfeeding) then it would seem reasonable to not prescribe PJP prophylaxis.

In conclusion, for clinicians involved in the care of HIV-infected pregnant women and their exposed neonates, evidence-based guidelines are a vital source of information to guide management. However, despite referencing similar sources of evidence, variations exist in the current recommendations for resource-rich settings. It is important to highlight that many recommendations are made based on observational data rather than randomized controlled trials, therefore relying heavily on expert opinion. It is essential that healthcare providers, working in countries outside the US and the UK, who rely on these guidelines, understand the basis for the differing recommendations, and have an approach to adapt these for their local setting. What this equates to in many cases is individualizing recommendations based on perceived risk to the baby.

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Conflicts of interest

There are no conflicts of interest.

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