REVIEW ARTICLE

Intrapartum Management for Prevention of Mother-To-Child Transmission of HIV in Resource-Limited Settings: A Review of the Literature

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Abstract

Prevention of mother-to-child transmission (PMTCT) of HIV guidelines in resource-limited settings focus on antenatal and postnatal management. In this review of the literature, we present findings from select studies, highlight best practices, and present evidence-based guidelines for intrapartum PMTCT management that are applicable to resource-limited settings. We discuss the roles of intrapartum HIV testing, intrapartum antiretroviral medications, mode of delivery in settings with and without HIV RNA testing, other delivery practices, and infant care in the immediate postnatal period. With the advent of Option B+, which recommends all HIV-infected pregnant women commence lifelong combination antiretroviral therapy (ART), the potential impact for intrapartum interventions will be greatest for those women who recently have seroconverted and those with unknown HIV status. Research on intrapartum PMTCT interventions should focus on these populations. *Afr J Reprod Health 2013 (Special Edition); 17[4]: 107-117).*

Keywords: labor and delivery, pregnancy, PMTCT

Résumé

La prévention de la transmission du virus VIH de la mère à l'enfant (PTME) dans les lignes directrices dans les milieux à ressources limitées met l'accent sur la gestion prénatale et postnatale. Dans cette revue de la documentation, nous présentons les résultats de certaines études, les meilleures pratiques ainsi que les lignes directrices fondées sur des preuves pour la gestion de la PTME de l'intrapartum qui sont applicables aux pays à ressources limitées. Nous discutons le rôle du dépistage du VIH pendant l'accouchement, les médicaments antirétroviraux de l'intrapartum, le mode de prestation dans des milieux avec et sans dépistage de l'ARN du VIH, d'autres pratiques d'accouchement et les soins aux nourrissons pendant la période postnatale immédiate. Avec l'avènement de l'option B +, qui recommande à toutes les femmes enceintes infectées par le VIH commencent la poly thérapie antirétrovirale continue (TAR), l'impact potentiel des interventions pendant l'accouchement sera plus grand pour les femmes qui ont récemment présenté une séroconversion et ceux dont l'état du VIH est inconnu. La recherche sur les interventions de PTME intrapartum devrait se concentrer sur ces populations. *Afr J Reprod Health 2013 (Special Edition); 17[4]: 107-117).*

Mots-clés: travail et accouchement, grossesse, PTME

Introduction

Since its original release in 2000, the World Health Organization (WHO) has revised its guidelines for the prevention of mother-to-child HIV transmission (PMTCT) four times. Rapid advances in clinical and implementation science research have prompted such policy changes[1]. The most recent WHO update for PMTCT in 2012 recommends initiating all HIV-infected pregnant women on lifelong triple-drug antiretroviral therapy (ART) regardless of $CD4^+$ cell count or WHO clinical stage[2]. The policy aims to eliminate mother-to-child transmission by simplifying the management of HIV-infected pregnant women[2,3]. Despite constant interest in and alterations made to

the WHO PMTCT guidelines, and subsequently to national policies, relatively little attention has been paid to the management of HIV infection during the intrapartum period in resource-limited settings[4].

Labour and delivery is a critical time for PMTCT. Interventions initiated during the intrapartum period can improve the health of HIV-infected mothers and their newborns substantially. This review of the literature presents findings from select studies, best practices, and evidence-based guidelines for intrapartum management of the HIV-infected pregnant woman in resource-limited settings.

Intrapartum HIV Testing

Every pregnant woman should be tested for HIV at least once during her pregnancy; labor and delivery at the health facility provides a window of opportunity for testing. For example, in Cameroon, 10.1% of women with unknown HIV status tested positive during labour[5]. Trained counsellors and laboratory technicians offered counselling and HIV testing around the clock to labouring women with unknown HIV status. 80.5% of the 2,413 study participants had attended at least one antenatal care visit. Women with antenatal care were less likely to accept intrapartum HIV testing (adjusted odds ratio [AOR]: 0.42, 95% confidence interval [CI]: 0.26-0.66 for those with 1-2 antenatal visits and AOR: 0.47, 95% CI: 0.31-0.70 for those with 3 or more antenatal visits). Despite the inverse association, 87.0% of women who either refused or missed HIV testing during antenatal care accepted intrapartum HIV testing; 11.0% of this subpopulation was HIV-infected. Such findings demonstrate the potential impact of intrapartum HIV testing, even in those with previous interaction with the health system. Overall, 88.3% of labouring women with unknown HIV status accepted HIV testing[5].

All pregnant women with unknown HIV status who present in labour should be offered point-of-care HIV antibody testing[6]. In areas of high HIV prevalence, HIV-uninfected pregnant women without a HIV test result within the past 3 months should be offered repeat testing in labour to account for the window period[7]. Maternal acquisition of HIV infection during pregnancy increased the risk of vertical transmission by 15-fold from 1.8% to 22% (AOR 15.19, 95% CI: 3.98-56.30) in a US cohort, highlighting the importance of detecting incident HIV infections during pregnancy to eliminate MTCT[8]. Repeat testing at delivery is a cost-effective strategy. Using a decision analytic model, Kim et al period showed that point-of-care HIV testing at first antenatal care visit and again at delivery was cost effective in Uganda. This model assumed 10% HIV prevalence in the antenatal population, 3% incidence during pregnancy, and cost effectiveness definition of ≤ 3 times the gross domestic product per capita (USD 3300 in 2008) per life year gained[9].

Point-of-care HIV testing should be offered in an opt-out approach without the barriers of written consent and additional documentation[10]. Opt-out testing is associated with increased acceptance of HIV testing[11-13]. A systematic review and meta-analysis of 44 studies from 15 African countries demonstrated 94% (95% CI: 92-95%) acceptance in pregnant women offered opt-out HIV testing compared to 58% (95% CI: 40-75%) in those offered opt-in testing[14]. Positive HIV test results should be confirmed with a second test. The screening test should have high sensitivity while the second test high specificity. Counselling is always partnered with testing, but need not be prohibitively time-consuming. Acceptance of intrapartum HIV testing was significantly increased in 474 labouring women in the Democratic Republic of Congo when counselling lasted ≤ 5 minutes (AOR 5.8, 95% CI: 2.6-13)[15].

Intrapartum HIV testing allows for important interventions to be implemented in order to decrease mother to child transmission. The risk of vertical transmission in a US cohort increased with intrapartum HIV diagnosis (AOR 3.24, 95% CI: 1.15-8.15) and lack of intrapartum antiretroviral medication (crude OR [COR] 4.49, 95% CI: 2.67-7.59), demonstrating the potential impact of PMTCT drugs[8]. Rapid diagnosis coupled with intrapartum antiretroviral medications (ARVs) and caesarean delivery can drastically decrease the risk of perinatal HIV transmission. For the woman who is HIV-uninfected, post-test counselling can focus on HIV prevention, especially during the

breastfeeding period, when sero-conversion often results in high levels of viremia and postnatal transmission[16].

Intrapartum Antiretroviral Medications

Antiretroviral (ARV) medications reduce the risk of vertical HIV transmission from as high as 45% to less than 5% in breastfeeding populations[17]. ARVs should be given to every HIV-infected pregnant woman during labour and delivery, including those newly diagnosed in labour.

In the future, most HIV-infected pregnant women are expected to be on ART rather than ARV prophylaxis as increasing numbers of developing countries adopt the WHO "Option B+" guidelines for lifelong antiretroviral therapy in HIV-infected pregnant women regardless of CD4+ cell count[2]. However, until then, a thorough medical history can help determine whether the woman is taking ARV prophylaxis or triple-drug ART, which can be dispensed as one tablet once daily or multiple tablets twice daily. Women may not remember the exact names of medications, and so it is important to be familiar with the generic and brand names of the more common antiretroviral medications. These differ from region to region. In addition, knowledge of what the pills look like and how often one takes them is useful. Posters of the different antiretroviral medications may assist patients in recalling their specific drugs[18,19].

For HIV-infected pregnant women taking ART, treatment should be continued on schedule throughout labour and/or delivery, including for scheduled caesarean delivery. Women should be encouraged to bring their medications from home to the health facility so that stock-outs do not impact medication adherence.

For HIV-infected pregnant women taking twice daily oral zidovudine (ZDV), ZDV should be continued until delivery, and single dose nevirapine (sd-NVP) should be taken when labour first begins[20,21]. The health care worker should ask whether the woman has already taken sd-NVP on the way to the health facility. If so, this should be documented in the medical file. If not, the health care worker should prescribe sd-NVP. Because sd-NVP has been associated with increased drug resistance due to the longer half-life of NVP compared to ZDV, it is also recommended that women receive a zidovudine/lamivudine (ZDV/3TC) "tail" for 7 days[21,22]. The 7-day tail significantly reduced the emergence of non-nucleoside reverse-transcriptase inhibitor resistance mutations from 59.2% to 7.3% at 6 weeks postnatal in an open-label, randomized control trial of 406 pregnant women in South Africa; the control arm received sd-NVP only[22]. Women who have been adherent to antenatal ZDV for ≥ 4 weeks do not need sd-NVP with the ZDV/3TC tail[21], but countries may recommend the NVP and ZDV/3TC booster in case the woman was not adherent. Similarly, an HIV-infected pregnant woman who has not initiated any medications, or who is newly diagnosed during labour and delivery, should receive sd-NVP with the ZDV/3TC tail for 7 days.

Intrapartum intravenous (IV) ZDV also decreases the risk of vertical transmission. In the PACTG 076 trial, a package of ZDV-based interventions (antenatal oral ZDV and intrapartum IV ZDV for the woman, as well as oral ZDV syrup for the infant) decreased vertical HIV transmission by 66%[23]. For women with virological failure (HIV viral load ≥ 10,000 copies/mL) in the French Perinatal Cohort, no intrapartum ARV medications increased the risk of vertical transmission (AOR 4.72, 95% CI: 1.42-15.71, p=0.011) compared to intrapartum IV ZDV (and/or sd-NVP)[24]. This finding was confirmed in a recent analysis of women on antenatal ART in the same French cohort. In women with HIV viral load ≥ 1,000 copies/mL, the risk of vertical transmission was 7.5% in those who did not receive IV ZDV compared to 2.9% in those who did (p=0.01)[25]. However, intrapartum IV ZDV (and/or sd-NVP) was not associated with decreased risk of transmission in women with plasma HIV RNA < 400 copies/mL in the French Perinatal Cohort[24]. Furthermore, there are no randomized clinical trials evaluating the efficacy of intrapartum IV ZDV in women already on ART. Similarly, a cohort of 66 pregnancies in Ireland, with 3 cases of MTCT, demonstrated that IV ZDV did not significantly reduce the risk of vertical transmission in women with plasma HIV RNA < 1000 copies/mL[26]. The intervention of intrapartum

IV ZDV is mostly practiced in resource-rich settings, for all women[27-31] or only those with HIV RNA ≥ 50-400 copies/mL[6,26].

In the PACTG 076 trial, IV ZDV was administered as a loading dose of 2 mg/kg current body weight over 1 hour followed by continuous infusion of 1 mg/kg per hour until delivery[23]. In resource-limited settings, the logistics of mixing IV ZDV and administering a continuous infusion are complex. At Luanda Municipal Hospital, a tertiary hospital in Angola, only 40 (64.5%) of 62 women with available records received IV ZDV at delivery even though it was part of standardized procedures[32]. This missed opportunity possibly reflects challenges in administering this medication in resource-limited settings. Intrapartum oral ZDV in lieu of IV ZDV has been studied in small numbers but with mixed results regarding therapeutic plasma concentrations[33,34].

Mode of Delivery in Resource-Limited Settings

Elective caesarean delivery coupled with ZDV prior to the onset of labour and rupture of membranes significantly decreases vertical HIV transmission in women[35,36]. A meta-analysis of 15 prospective cohort studies, all conducted in Europe or North America, looked at risk factors for vertical transmission in 7840 mother-child pairs. This meta-analysis demonstrated the protective effect of elective caesarean delivery compared to vaginal delivery (AOR 0.42, 95% CI: 038.-0.55), after adjusting for zidovudine prophylaxis given during the prenatal, intrapartum, and neonatal time periods - not triple-drug ART[35]. In addition, a randomized controlled trial conducted between 1993 and 1998 showed 80% reduction in vertical transmission with elective caesarean delivery compared to vaginal delivery[36]. This trial enrolled 370 Italian, French, British, Spanish, Swiss, and Swedish women. In this study, 7 (3.4%) of 203 infants born by caesarean delivery and 15 (10.2%) of 167 infants born vaginally (p=0.009) were HIV-infected. The protective effect of caesarean delivery was more pronounced when looking at intention to treat analysis (1.8% in caesarean delivery vs. 10.5% in vaginal delivery). However, 36% of all women were not on antenatal ART[36]. Based on these findings, the United States National Institutes of Health guidelines recommend caesarean delivery in HIV-infected pregnant women with HIV RNA ≥ 1,000 copies/mL[6].

Wherever HIV RNA PCR testing is available, HIV-infected pregnant women should have a viral load drawn at 34-36 weeks gestation[37], or a few weeks earlier in order to accommodate turnaround time for laboratory results in resource-limited settings. If an HIV-infected pregnant woman has a documented HIV RNA ≥ 1,000 copies/mL at 34 weeks gestation or above, then she should be offered a scheduled caesarean delivery at 38 weeks gestation in order to decrease the risk of vertical HIV transmission before the spontaneous onset of labour and rupture of membranes[6,38]. With regard to the unsuppressed viral load, she should be referred to a trained HIV care provider for assessment of adherence and possible drug resistance testing. In the meantime, the appropriate ART regimen should be initiated immediately[37].

For HIV-infected pregnant women with high HIV viral load who present in labour, preterm or term, or with ruptured membranes, the protective effect of caesarean delivery is less clear[36,39]. In the pre-ART era, the Mothers' and Infants' Cohort Study enrolled 207 HIV-infected mother-infant pairs in the USA between 1986 and 1991 and had complete data regarding duration of ruptured membranes and at least one antenatal CD4+ cell count on 127 participants. After adjusting for CD4+ cell count, longer durations of ruptured membranes in those delivered by caesarean was no longer associated with risk of vertical transmission[40]. In general, there is a paucity of data on the efficacy of caesarean delivery in the setting of labour and/or ruptured membranes[39]. Management in these situations needs to be individualized.

Intrapartum HIV Management Algorithm in Resource-Limited Settings

Currently, most HIV-infected pregnant women in resource-limited settings do not have access to HIV RNA testing. FIGURES 1-4 are algorithms for determining the mode of delivery for HIV-infected pregnant women in resource-limited settings. These algorithms are based on expert opinion. For

women with low viral loads while on ART, the risk of vertical transmission is low regardless of mode of delivery and duration of ruptured membranes[41-45]. In Zambia, antenatal ART use for at least 13 weeks has been associated with significant reductions in vertical transmission compared to ≤ 4 weeks. In this retrospective cohort study of 1813 HIV-infected pregnant women, women on ART for ≤ 4 weeks had a 5.5-fold increased odds of vertical transmission compared to those on ART for at least 13 weeks (95% CI: 2.6-11.7)[46]. According to a national surveillance study of HIV-infected pregnancies in the United Kingdom and Ireland, each additional week of ART during pregnancy conferred a 10% reduction in odds of vertical transmission (AOR=0.90 per week 95% CI: 0.84-0.97, p=0.007) among women on ART after adjusting for viral load, mode of delivery, and sex[42]. Thus, we recommend caesarean delivery for any HIV-infected pregnant woman with symptoms or signs of high HIV viremia: CD4+ cell count ≤ 350 cells/mL, WHO Stage III/IV, new opportunistic infections, and <13 weeks of antenatal ARVs or ART. Although the effectiveness of intrapartum IV ZDV is largely unknown in settings where women are on ART without HIV RNA results, we suggest it as a possible alternative to sd-NVP with ZDV/3TC in women undergoing caesarean delivery.

Because HIV seroconversion during pregnancy is associated with high viremia, the HIV-infected pregnant woman who had a negative HIV test during pregnancy and has a positive intrapartum HIV test should be offered ARVs and caesarean delivery. For the labouring woman with unknown HIV status whose intrapartum HIV test is positive, testing may not reflect an acute infection. However, intrapartum interventions can decrease the risk of transmission. Thus, we recommend mode of delivery to be dependent on WHO Stage since point-of-care CD4 is uncommon in resource-limited settings.

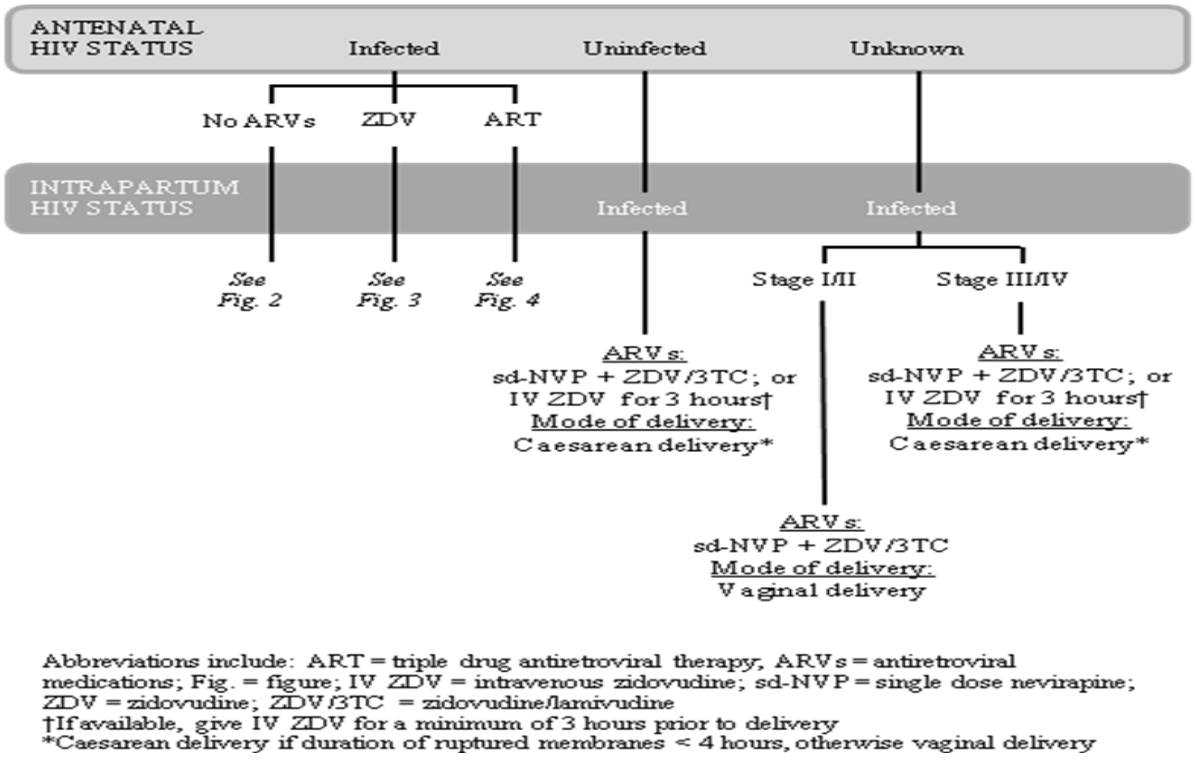


Figure 1: Algorithm for intrapartum interventions in resource-limited settings, starting with HIV status and intrapartum testing; based on expert opinion

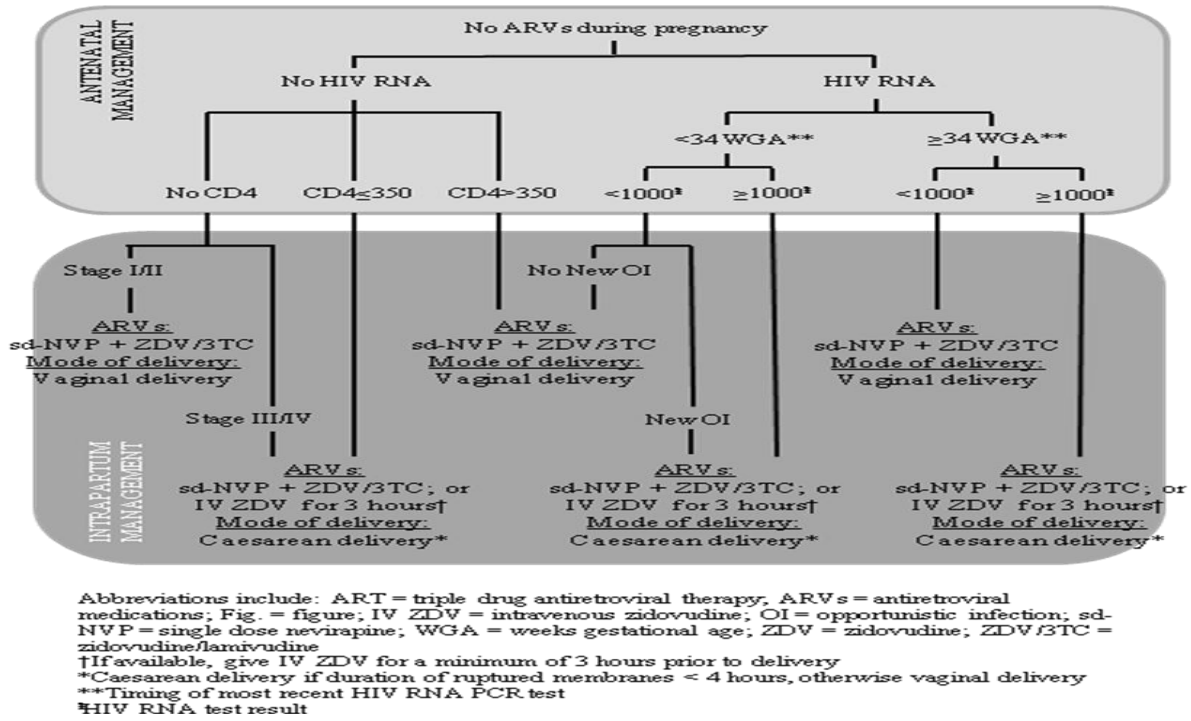


Figure 2: Algorithm for intrapartum interventions in resource-limited settings for women on no antenatal antiretroviral medications; based on expert opinion

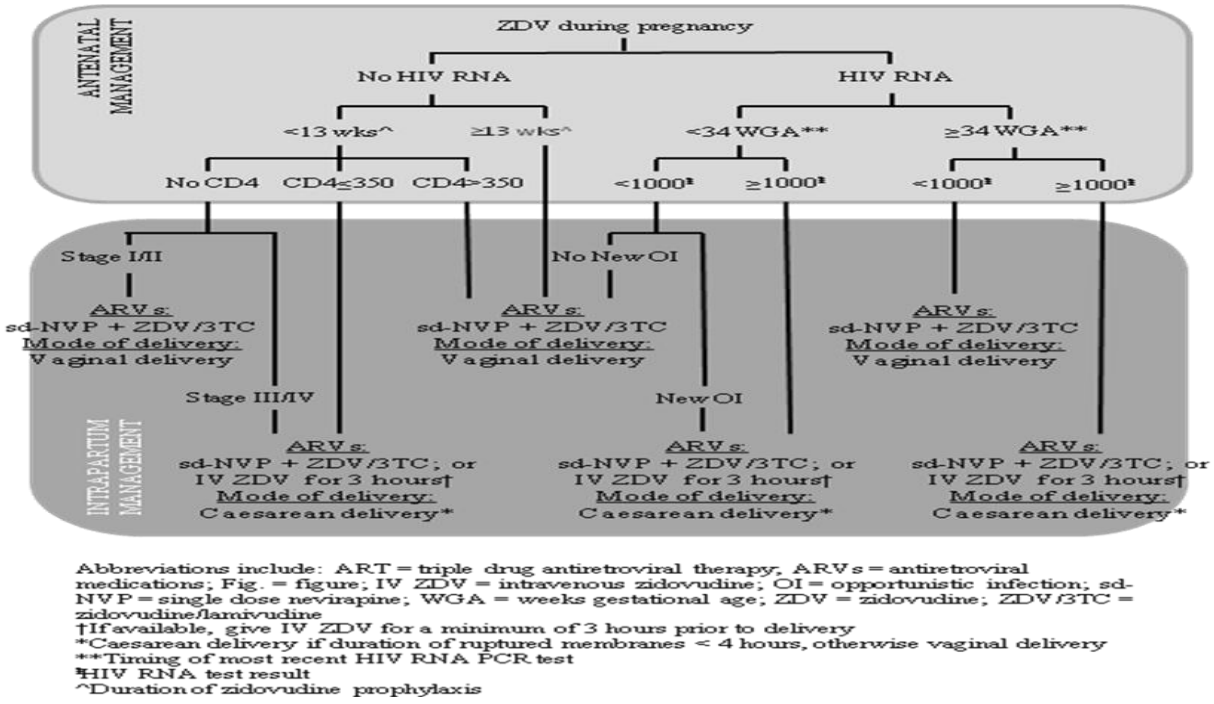
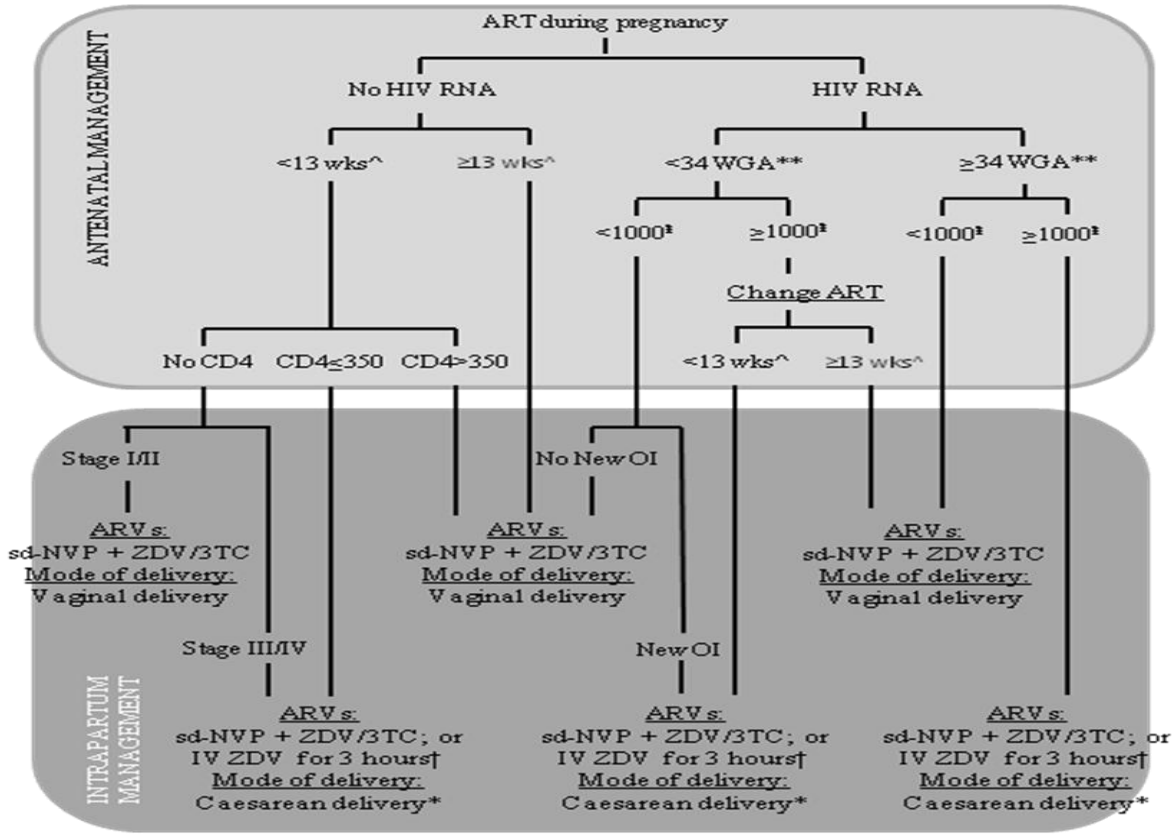


Figure 3: Algorithm for intrapartum interventions in resource-limited settings for women on zidovudine prophylaxis; based on expert opinion



Abbreviations include: ART = triple drug antiretroviral therapy, ARVs = antiretroviral medications; Fig. = figure; IV ZDV = intravenous zidovudine; OI = opportunistic infection; sd-NVP = single dose nevirapine; WGA = weeks gestational age; ZDV = zidovudine; ZDV/3TC = zidovudine/lamivudine
†If available, give IV ZDV for a minimum of 3 hours prior to delivery
*Caesarean delivery if duration of ruptured membranes < 4 hours, otherwise vaginal delivery
**Timing of most recent HIV RNA PCR test
¥HIV RNA test result
^Duration of antiretroviral therapy

Figure 4: Algorithm for intrapartum interventions in resource-limited settings for women on antiretroviral therapy during pregnancy, including pre-conception use; based on expert opinion

Other Delivery Practices

Before the widespread use of ART, duration of ruptured membranes ≥ 4 hours was associated with increased vertical HIV transmission[40]. We therefore recommend that routine, artificial rupture of membranes should be avoided. The Mothers' and Infants' Cohort Study showed duration of ruptured membranes ≥ 4 hours compared to < 4 hours increased vertical transmission rates significantly in women with CD4+ cell counts < 345 cells/mL (relative risk 4.53, 95% CI: 1.14-18.1, p=0.02). However, there was no association between duration of ruptured membranes ≥ 4 hours and increased mother to child transmission among women with high CD4+ cell counts[40]. Because of this study's questionable applicability to women on ART, artificial rupture of membranes for obstetric indications, such as induction or augmentation of labour, is appropriate. Studies in resource-rich settings have not shown a statistically significant increase in vertical transmission based on length of duration of ruptured membranes in women with low viral loads while on ART. The risk of vertical transmission did not differ based on duration of ruptured membranes (1% with duration of ruptured membranes < 4 hours vs. 1.9% with ≥ 4

hours) in a US-based prospective cohort study of 707 women on ART. Furthermore, there were no cases of perinatal transmission in the 493 women suppressed on ART (viral load < 1000 copies/mL) despite duration of membranes as long as 25 hours[44]. Even when duration of ruptured membranes stretched up to 4 days for latency in 10 cases of preterm premature rupture of membranes in women on antenatal ARVs, there were no cases of vertical transmission[47].

Invasive fetal monitoring (fetal scalp electrode or pH blood sampling) should be avoided, based on a study that showed intermittent or persistent HIV viral shedding in the genital tract of 22 (37%) of 59 women on ART whose plasma HIV viral load was undetectable[48]. In addition, episiotomy and vaginal examinations should be limited to those necessary for obstetric management in order to decrease the risk of puerperal infection. Episiotomy (incidence rate ratio (IRR) 2.05, 95% CI: 1.48-2.85, p<0.001) and number of vaginal examinations after rupture of membranes (IRR 1.09, 95% CI: 1.01-1.18, p =0.026) were associated with postpartum infectious morbidity in HIV-infected and HIV-uninfected women alike[49]. Instrumental deliveries should be also avoided unless obstetrically indicated; this recommendation is based on a pre-ART analysis of over 700 mother-infant pairs from 1984 to 1991[50]. Antenatal corticosteroids are associated only with benefits in the premature HIV-exposed fetus; available data do not suggest any increased risk of vertical HIV transmission with antenatal corticosteroids given for fetal health[51].

Infant Feeding and Prophylaxis in the Immediate Postnatal Period

In settings where replacement feeding with infant formula is not acceptable, feasible, affordable, sustainable, and safe (AFASS criteria), HIV-free survival appears higher in breastfed infants than in formula-fed infants[52,53]. Thus, HIV-infected women should be encouraged to breastfeed their infants soon after birth, similar to the HIV-uninfected woman[54]. A review by Vogler, Singh, and Wright includes studies conducted in southern and eastern Africa and illustrates the protective effect of maternal and infant ARV prophylaxis on risk of breastfeeding-related transmission (10-17% vs. 1.1-5.0%)[54]. HIV-exposed infants should receive nevirapine or zidovudine syrup at birth and daily (once or twice respectively) for a minimum of 6 weeks[21,55-59]. The length of infant ARV prophylaxis depends on which medications the mother is taking and whether she is breastfeeding the infant or not.

Conclusion

Vertical transmission of HIV can be effectively reduced by intrapartum interventions, namely: prompt detection of HIV-infection in those who have recently seroconverted and those with unknown status, use of intrapartum ARVs, caesarean delivery for women with HIV RNA > 1,000 copies/mL, and early initiation of infant ARV prophylaxis. Current data on mode of delivery in resource-limited settings where women are on ART but do not commonly have HIV RNA tests are inconclusive[60]. Therefore, clinical surrogates for suspected high viremia may warrant caesarean delivery. Individual management that includes discussion with the patient is critical.

With the advent of Option B+ and recommendation for all HIV-infected pregnant women to begin lifelong ART, the potential impact for intrapartum interventions will be greatest for those women who recently seroconverted and those with unknown status. Logistics and human resources need to be available to conduct HIV counselling and testing in maternity centers. The capacity to offer elective caesarean deliveries needs to be strengthened in resource-limited settings. Furthermore, the clinical impact and cost effectiveness of intrapartum interventions, such as IV ZDV, remain unclear, and additional research needs to be conducted. Bolstering health systems to implement intrapartum interventions will complement antenatal and postnatal efforts to eliminate mother to child transmission of HIV in resource-limited settings.

Acknowledgements

No funding institutions were involved in the writing of the review article.

Conflict of interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. K.C.L. conceived of the review, wrote the first draft, and was responsible for editing the final manuscript. C.J.C. guided the development of the review and contributed to subsequent drafts. Both authors approved of the final version.

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