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Review article

The impact of highly active antiretroviral therapy on obstetric conditions: A review

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ABSTRACT

HIV is the leading cause of maternal and neonatal morbidity and mortality in resource constrained countries. Highly active antiretroviral treatment (HAART) initiated in pregnancy has now almost eliminated mother to child transmission of the virus, and is beginning to show the desired effect of reducing HIV related maternal mortality. By modulating host immunological responses HAART has the potential to alter infections during pregnancy, in addition to modifying clinical conditions such as preeclampsia. There is increasing evidence of the benefits of HAART given to pregnant women, however there is paucity of data that distinguishes HIV or HAART as the cause or exacerbation of pre-existing medical conditions or conditions specific to pregnancy.

Anaemia is the commonest haematological disorder seen in HIV infected women and is more pronounced during pregnancy. The use of HAART has the potential to reduce the incidence and severity of the disease. Tuberculosis (TB) is the commonest chest infection amongst HIV infected people, being more common amongst pregnant than non-pregnant women. It is the leading cause of death from infectious diseases amongst women of reproductive age, and accounts for at least a quarter of all cases of maternal deaths associated with non-pregnancy related infections (NPRI). TB can manifest at any stage of the HIV infection, including during treatment with HAART. The latter (ie TB manifestation during HAART treatment) is thought to be the commonest manifestation of what is now known as immune reconstitution inflammatory syndrome (IRIS). In a South African report on maternal deaths, 55% of women who died of TB were on HAART, and a further 35% of women in the NPRI category died from other pneumoniae, notably pneumocystis jorevicci, which is also related to HIV infection. With regards to puerperal sepsis, studies are yet to show the impact of HAART independent of antibiotics in reducing infectious morbidity in HIV infected women.

Preeclampsia has been associated with HIV infection, where most studies point towards a reduced risk in HIV infected women. There is increasing evidence that this reduced risk is reversed in the presence of HAART, with women accessing HAART having almost the same risk as HIV uninfected women. HIV or its treatment may be associated with increased risk of obstetric haemorrhage, and an increasing trend of obstetric haemorrhage as a cause of maternal deaths has been recently reported, proportionally in line with the introduction and increasing availability of HAART for pregnant women The mechanism by which this may occur remains elusive since pregnancy is a pro-thrombotic state, however, HIV-related thrombocytopenia or vasculitis could account for the association, if found. HAART would then be expected to reverse this.

HAART especially protease inhibitor containing combinations, have been associated with preterm deliveries and low birth weight, particularly when initiated prior to the index pregnancy.

With these overall findings of the effect of HAART on obstetric conditions, this review is intended to encourage heightened surveillance of adverse events associated with HAART use in pregnant women.

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Introduction

Human Immunodeficiency Virus (HIV) is the leading cause of maternal mortality in resource poor countries accounting for approximately 40% of all deaths [1]. In addition, there are reports of considerable maternal morbidity arising from co-infections, in particular tuberculosis [2,3]. The use of highly active antiretroviral treatment (HAART) in the last decade has been hailed as one of the most effective interventions which has almost eliminated mother-to-child-transmission (MTCT) of the virus and associated with the reduction of maternal deaths [1,4]. Given the positive impact of the increased coverage of HAART on both the reduction in absolute numbers and ratio of maternal deaths, the focus is now shifting to HIV issues such as the direct and indirect effects of HAART on other pregnancy related co-morbidities. The era before the widespread use of HAART in pregnancy had a plethora of literature documenting serious morbidity and mortality due to the HIV disease and its co-infections. However, apart from the reports on perinatal outcomes, there has not been an equal enthusiasm in tracking the improvements in maternal and possibly obstetric conditions in the era of HAART particularly in countries with the highest burden of HIV disease.

There are several biologically plausible mechanisms why HAART may have unforeseen consequences on common conditions in pregnancy. Some of the antiretroviral drugs, such as zidovudine, a nucleoside reverse transcriptase inhibitor, can lead to mitochondrial toxicity and affect blood cell counts particularly reticulocytes, and thereby worsen the anaemia commonly associated with pregnancy itself. Other drugs are nephrotoxic or hepatotoxic, and can therefore affect the course of diseases such as preeclampsia and diabetes mellitus. Additionally, the immune reconstitution following the use of HAART may trigger or unmask certain inflammatory conditions, such as tuberculosis (TB), as well as preeclampsia, which is thought to involve an exaggerated inflammatory response as part of its pathogenesis Moreover, pregnancy related factors, such as changes in blood volume, body mass, elevations in hormonal level and alterations in enzyme activity may impact on the expected response to antiretroviral drugs.

The following is a narrative review of the current evidence regarding the use of HAART and its impact on obstetric conditions.

Medical conditions during pregnancy

Haematological disorders in pregnancy

In 2011, the WHO estimated the global prevalence of anaemia in pregnancy to be 38.2% [95% confidence intervals (CI): 33.5–42.6], much higher than that for all women of reproductive age, (29.4%, 95% CI: 24.5–35.0) [5]. Anaemia is said to be the most common hematological abnormality in HIV infected patients, and in pregnancy, it can be as high as 88.5% [6]. Several mechanisms have been suggested to explain the association between HIV and anaemia and these include direct infection of the bone marrow, which may inhibit growth of hematopoietic cells, with subsequent reticulopenia, or low endogenous erythropoietin concentrations, and rarely, deficiencies of iron or folic acid or Vitamin B12 [7].

The effect of HAART to possibly improve the prevalence or severity of anemia in pregnancy has also not been explicitly reported. A South African study, found no difference in the prevalence of anemia in those who were treated with HAART compared to those who received zidovudine alone (ZDV) during pregnancy [8]. The authors noted that, after adjusting for antiretroviral regimen, age and gravidity, only the CD4 count remained a significant risk factor for anaemia in pregnancy and post-delivery. However, regardless of CD4 counts, following the use of HAART and prophylactic iron supplementation during pregnancy, there was a 2.5 times less incidence of anaemia at 2 weeks postpartum compared to the time of antenatal registration. The latter implies that HAART has the potential to improve anaemia of pregnancy in HIV treated women. Even though anaemia in pregnancy is predominantly characterised as normocytic and normochromic (82.8%), possibly due to reduced erythropoietin production during states of HIV related chronic inflammation [8], this is probably a mixed picture of chronic HIV disease and micronutrient deficiencies, including iron. Hence not all women will respond to iron supplementation in pregnancy.

Thrombocytopenia (TCP) has been reported as another common haematological complication of HIV, and is said to affect at least 21% of patients with AIDS defining conditions [9]. However, in another study, there was no difference in the prevalence of TCP amongst HIV uninfected pregnant women, compared to those who were infected but untreated, (4.7% compared to 6%, $p = 0.292$) [10]. It is unlikely therefore that the effects of HAART would be easily appreciable.

Tuberculosis in pregnancy

Tuberculosis (TB) is said to be the leading cause of deaths in women aged 15–44 years globally [2,11]. It remains the single most common cause of maternal deaths from non-pregnancy related infections (NPRI). In the latest South African report on maternal deaths, 35% of which were due to NPRI, it accounted for 26% of deaths in this category [1]. In subSaharan Africa where both epidemics of TB and HIV co-exist, dual infections were found to be

the major cause of maternal mortality [2,12]. In the days prior to the availability of HAART, Ramogale et al. showed an increasing maternal mortality rate (MMR) amongst HIV infected and untreated women from 434 to 1023/100 000 births over a 7 year period, mainly due to end stage HIV disease, chest infections such as pneumonia and TB, and puerperal sepsis [12]. A study in Zambia also documented non-obstetric infections especially TB (and malaria) as the leading causes of maternal deaths. In this cohort, HIV was a co-infection in 92% of TB related deaths, compared to 37% in those with malaria [3].

The scale up of HAART is expected to improve general clinical outcomes, particularly from infectious diseases. In the South African report on maternal deaths, the number of deaths from TB fell by 24.6% compared to the previous triennium. This was attributed to the increasing access to HAART in that period as more women with higher CD4 (<350 cells/mm^3) were now eligible. Within this same category of NPRI, with 92% HIV co-infection, other forms of pneumonia contributed 35% of the maternal deaths. These were community acquired pneumonia, pneumocystis jirovecii pneumonia (known also to be related to HIV), and possibly other missed cases of TB [1]. It has been noted that TB diagnosis can be difficult in HIV infected women, where 60% of the infected were found to be acid fast bacillus (AFB) smear positive compared to 100% of the HIV uninfected [13]. This can be improved by simultaneous TB screening at antenatal visits, with further testing for those who are symptom-screen positive. This, together with the use of isoniazid prophylaxis therapy (IPT), has potential to reduce morbidity due to TB and further augment the beneficial effects of HAART on TB outcomes during pregnancy.

Obstetric conditions

Obstetric haemorrhage

The evidence regarding the effect of HIV on obstetric hemorrhage is conflicting, and there has not been many studies examining the effect of HAART. Kourtis et al. found no increased odds of antepartum haemorrhage (APH) in HIV untreated women, [odds ratio (OR) = 1.06, 95% CI = 0.75–1.49] in the early years of antiretroviral treatment (ART) [14]. In subsequent years, though there was a significant reduction in APH amongst HIV uninfected women (OR = 0.93, 95% CI = 0.89–0.98), the authors showed a slight increase in the incidence of APH from 2.3% to 3.6% amongst HIV infected treated women, (OR = 1.27, 95% CI = 0.76–2.14)[15]. With regards to postpartum hemorrhage (PPH), Chanrachakul in India found an increased risk of PPH in nulliparous women with untreated HIV, OR = 2.75 (95%CI = 1.13–6.66) [16].

The recent meta- analysis suggested a doubled odds of APH (OR = 2.06, 95% CI = 1.42–2.97), but no evidence that HIV increases the odds of PPH (OR = 1.28, 95%CI = 0.69–2.38) [17]. However, this meta- analysis included studies in which women were HAART treated and in other studies they were untreated. In a re-analysis of the maternal deaths due to obstetric hemorrhage in the last South African (SA) triennial report, we argued that there was an excess of estimated 200 more deaths during the triennium where HAART was introduced, and this figure persisted subsequently. This link could possibly be coincidental, however, amongst women who were HIV infected, there were significantly more women who were receiving HAART than those not on HAART [10.1% versus 6.2%, relative risk (RR) = 1.61, 95% (CI = 1.15–2.25)] [18]. Most of the hemorrhage occurred postpartum, particularly at or after a cesarean delivery. Other studies comparing women on HAART and uninfected women showed increased odds of APH [13,19], but not PPH [19,20].

There is no clear pathophysiological basis for this apparent link between an increased risk of obstetric haemorrhage and HIV or HAART. Bearing in mind that pregnancy is a pro-thrombotic state, HIV or its treatment would have to counter this effect in order for it to be associated with increased obstetric hemorrhage. Others have described increased haemostatic disorders in HIV infected women which include hyperfibrinogenaemia, low prothrombin time, as well as thrombocytopenia, but with no increased risk of bleeding [21]. Vascular factors at the utero-placental interface would probably manifest with higher antepartum hemorrhage, such as abruptio placentae. This calls for further studies to examine not only the effect of HIV on obstetric haemorrhage, but also the effect of HAART on the incidence of antepartum or postpartum haemorrhage.

Preeclampsia

Preeclampsia is believed to be due to the loss of immune tolerance to the fetal antigens which result in immune hyperactivity and a subsequent exaggerated systemic inflammatory response [22]. Hence, HIV infection through its immunosuppressive characteristic is thought to alter the prevalence of preeclampsia. Studies exploring a possible relationship between HIV and preeclampsia have provided conflicting evidence [23,24], however, a recent systematic review and a meta-analysis found no significant association between HIV (or its treatment) with pregnancy induced hypertension (RR = 1.26, 95% CI = 0.87-1.83), pre-eclampsia (RR = 1.01; 95% CI = 0.87- 1.18) or eclampsia (RR = 1.62, 95% CI = 0.14-18.68) [25]. However, an earlier meta- analysis did find that the risk of pregnancy induced hypertension (PIH) but not preeclampsia/eclampsia syndrome, was higher in HIV infected women [18]. Both meta-analyses included studies of both HAART treated and untreated women. In another recent SA study, Tooke et al. studied mothers who delivered very low birth weight babies, majority of whom had pre-eclampsia, and found that although HIV was not independently associated with preeclampsia ($p = 0.13$), mothers who received more than 4weeks of HAART were more likely to develop severe forms of pre-eclampsia ($p = 0.007$) [26]. Other studies that compared HIV infected women receiving HAART with HIV uninfected women, found an increased odds of development of preeclampsia in HIV infected women receiving HAART [14,19]. Whilst a reduced risk for pre-eclampsia has also been reported, in women on HAART, this reduction was only statistically significant in a study by Mattar's et al. [23], but not others [27,28]. We re- analysed the maternal deaths from hypertensive disorders (of which >80% were preeclampsia/eclampsia), as reported in the recent Saving Mothers Report and demonstrated that immune-deficient women (untreated AIDS) were least at risk of developing preeclampsia, more than those receiving HAART (with treated AIDS) or immune competent (those HIV infected but not requiring HAART) [29]. Compared to HIV uninfected women, the increasing protective effect in HIV infected was from 32% (HIV infected not requiring treatment), to 61% (AIDS patients receiving HAART) with the greatest reduction of 79% prevalence of preeclampsia amongst individuals with untreated AIDS'. This report used the definition of AIDS as those women with WHO clinical stage 4, or CD4 counts <200 cells/mm^3 [1].

Thus it seems that the risk of preeclampsia is reduced in HIV infected women, and the latest evidence suggests that HAART can reverse this, thus increasing the risk. This therefore calls for further heightened surveillance of pregnancy complications and clinical outcomes among women receiving HAART.

Pregnancy related infections – intrauterine and puerperal sepsis

Studies have found conflicting evidence of the association between endometritis or other forms of puerperal sepsis and HIV infection. In a prospective study of women recruited from 36

weeks of gestation, observed through labour and up to 6 weeks postpartum, we found no increased risk of postpartum infectious morbidity amongst 241 HIV infected women compared to 427 HIV uninfected women, (20.7% compared to 20.8% infectious morbidity rate, p = 0.977) [30]. All women underwent vaginal delivery, and HIV infected women had a median CD4 count of 402cell/microL with only 2/241 being on HAART. Another study, in the absence of HAART and a 15% cesarean delivery rate, found no definite association between puerperal infection and HIV sero-positivity., OR = 1.02 (95% CI = 0.13-7.68)[16]. Others have had similar findings [14]. However, the meta-analysis by Calvert and Ronsmans [2013], found that intrauterine infections were increased in association with HIV, (OR = 2.51, 95% CI = 1.5–4.21) [17]

In the presence of HAART, Fiore et al., prospectively studied women who underwent vaginal deliveries, and reported a non-significant association between HIV and endometritis, (OR = 2.56, 95%CI = 0.77–6.59) [31]. In another study with a high cesarean delivery (CD) rate, (30% amongst HIV infected and 51% in HIV negative groups), women on HAART had a nonsignificant reduction in odds of endometritis, OR = 0.21, (95% CI = 0.01-4.01) [32]. Kourtis et al., showed an increased odds of major puerperal sepsis in HIV infected women in the early period of HAART use (OR = 2.27, 95% CI1.46–3.52) [14]. However, in the later analysis of hospitalizations in the HAART era, the authors did not show any clear pattern of increased or reduced odds, (OR = 1.24, 95% CI = 0.65–2.36) for earlier period of HAART use [2004] and OR = 0.95 (95% CI = 0.48–1.89) in later years [2011][15]. The conflicting evidence depends mainly on different settings and background c/section rates. In the same meta-analysis, 4 of the 5 studies which looked at women accessing HAART showed an increased risk of infectious morbidity (endometritis or puerperal sepsis), however this was only statistically significant in 2 of these [17]. In view of the possible residual infectious morbidity despite the use of HAART, caution and use of prophylactic antibiotics should be used until further evidence from prospective studies which control for the mode of delivery and the use of antibiotics.

Caesarean delivery rates in the era of HAART

In a systematic review and a meta- analysis, a caesarean delivery (CD) was shown to result in at least 80% reduction in vertical transmission compared to vaginal delivery. This was a review of mainly studies prior to the use of HAART, where zidovudine was used as a single agent throughout pregnancy for the purpose of prevention of mother to child transmission (MTCT) of the virus [33]. This led to an increase in CD rates amongst HIV infected women, despite a possibility of increased infectious morbidity. Subsequent studies began to examine this protective effect with the use of HAART, and though the results were not always consistent, the majority showed that the pre-eminent and independent risk factor for MTCT was the viral load at the time of delivery. Viral load (VL) of > 1 000 copies/ml was associated with a 12-fold increase in the risk of MTCT. [34] The study found that elective CD in women of undetectable VL secondary to HAART use was associated with approximately 90% reduction in the risk of MTCT, compared to vaginal delivery, [34], (OR 0.10; 95% CI, 0.03–0.33). We recently reviewed the evidence, which points towards safe vaginal delivery amongst women on HAART with virological suppression. It has been shown that the number needed to prevent one case of MTCT in the presence of HAART exceeds a hundred, [35,36]. The risk of MTCT has been found to be directly related to the duration of HAART use, with a sharp reduction observed after the first 12 weeks of treatment. The authors found that each week of HAART use reduced the risk of transmission by 6% (with OR calculated per week as 0.94, 95% CI: 0.90-0.99) [37]. Most authorities therefore recommend that a viral load (VL) test be performed after the 36th week of pregnancy, and if >1000 copies/ml, a woman be counselled for a planned cesarean section to prevent vertical transmission [38]. However, another study showed that mode of delivery remains important even with VL levels as low as 50 copies/ml [39]. The authors found that "for all modes of delivery, the risk of transmission was significantly higher when viral load was 50–399 copies/ml than when fully suppressed (<50 copies/ml)", however, they did not find a statistically significant reduction in the risk of vertical transmission amongst women delivering by planned c/section compared to vaginal delivery in this group for VL >50-399, (0.77% versus 1.6%, p = 0.39). Therefore a detectable VL, even though <1000 cp/ml, cannot be treated as one which is undetectable. The issue becomes more complex as different settings use undetectable range of <50 and others <20cp/ml. Therefore, individual counselling is necessary, also taking into account the duration of HAART, the maternal CD 4 count and the presence of other co-morbidities.

HAART and perinatal outcomes

The effects of HAART on the fetus and pregnancy outcomes remain uncertain. There has been increasing documentation of adverse outcomes particularly preterm deliveries and low birth weight infants associated with the use of HAART. However, this needs to be interpreted in the background of HIV as a possible risk factor, without the administration of HAART. In earlier studies, low birth weight (LBW) and small for gestational age were associated with maternal HIV infection [40], with conflicting evidence of the association with preterm deliveries (PTD), [41]. A recent meta-analysis of 52 cohort studies [42] confirmed the findings of the earlier analysis [43], and showed that HIV was associated with LBW and PTD.

It is against this background that the effect of HAART on these outcomes have to be interpreted. An earlier meta- analysis did not find an association between HAART and risk of PTD, however, the use of combination regimens before or early in pregnancy were found to slightly increase the risk of prematurity [44]. In the recent report of trends in hospitalizations, Ewing et al. did not observe any significant increase in the rate of preterm labour and PTD amongst HIV infected women receiving HAART over the periods 2004, 2007 and 2011 [15]. However, in the latest systematic review, Alemu et al. reiterated that the type of HAART (especially protease inhibitor based therapy) and timing of initiation are responsible for the adverse perinatal outcomes observed [45]. The use of HAART before pregnancy has consistently being found to be associated with preterm delivery.

Other studies on the use of HAART during pregnancy show a protective effect in that the rates of low birth weight (LBW) and preterm birth were shown to decrease since the introduction of HAART [46]· In this recent retrospective study, even though the authors reported improved birth outcomes in HIV infected women receiving HAART compared to no treatment, (reduced odds of a SB (OR 0.08, 0.21 and 0.18 respectively)), PTD (OR 0.52, 0.68 and 0.56 respectively) and LBW(0.37, 0.61 and 0.52 respectively)., when compared to those who received ZDV only, there was no difference in rates of SGA ad preterm births, whereas LBW and stillbirths were slightly higher in HAART treated women, though not statistically different. The most recent prospective, open label, multicentre randomised trial (PROMISE), showed a significantly higher risk of very early preterm births and neonatal deaths in women receiving tenofovir containing HAART, compared to the zidovudine arm [47].

Adverse drug reactions specific to pregnancy

Zidovudine is the only antiretroviral drug that has been widely used during pregnancy, and continues to be used on its own (with

additional single dose nevirapine during labour), or as part of the 3 drug HAART regimen. Studies have linked zidovudine (ZDV) use with mitochondrial toxicity leading to myopathy [48]. It is thought that ZDV harms the mitochondria via impairment of the mitochondrial DNA (mtDNA), [48]. Additionally, it is the same toxicity on the mitochondrium which leads to the anemia associated with the use of the drug.

Tenofovir (TDF), is a pro-drug of nucleotide reverse-transcriptase inhibitors (NRTI). It is commonly used to treat patients with Hepatitis B, but is also preferred for HIV infected patients with renal or hepatic dysfunction, though by itself, it may cause renal impairment. It is thought to be a better and safer drug than ZDV in pregnancy, [48]. It is rated category B by the FDA, whereas ZDV is rated C.

Nevirapine binds to an enzyme rather than DNA, and therefore known as non-competitive non-nucleoside reverse transcriptase inhibitor. Its popularity in pregnancy followed evidence that a single administration during labor could reduce vertical transmission by almost 50% [49]. However, its use as part of combination antiretroviral treatment is associated with significant side effects such as skin rashes, (which in worst forms manifested as Steven-Johnson Syndrome), and impairment of hepatic function, which in some cases led to fatal hepatotoxicity. It has been reported that commencing NVP in ART-naive pregnant women with CD4 counts $\geq$250 cells/μl significantly increased the odds of toxicity [50]. The latter usually manifests within a few weeks following initiation of the drug.

Earlier reports on animal studies raised concern regarding the use of first-trimester efavirenz exposure and possible development of central nervous system congenital anomalies. A systematic review of studies reporting on birth outcomes of women exposed to efavirenz in the first trimester, compared to those with non-efavirenz-containing regimens, found no difference in overall risk of congenital anomalies between the two groups (RR = 0.78, 95% CI 0.56–1.08) [51].

Stavudine has been associated with lactic acidosis [52], however, there have not been many studies during pregnancy. A study of treatment-naïve women initiating stavudine-containing regimens during pregnancy, found few adverse reactions, however, the follow up was short, (10.4 weeks) [53].

Conclusion

HAART during pregnancy is associated with significant improvement in outcomes for both mother and infant. Since it works by modulating the immune response, conditions with an inflammatory basis (such as infectious diseases and preeclampsia) seem to be particularly affected by its use. Since fetal life involves extensive development and growth, this can also be affected. The effect on general obstetric conditions such as obstetric haemorrhage need to be monitored. As with the use of any drug in pregnancy, an enhanced level of maternal and fetal surveillance is necessary for women on HAART.

Conflict of interest

The authors declare no conflict of interest.

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