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HIV in pregnancy – An update

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ABSTRACT

Human immunodeficiency virus (HIV) is an infection with a global prevalence and currently no cure or vaccine. Women living with HIV who become pregnant or who acquire the virus during pregnancy are at risk of both maternal and perinatal morbidity and mortality mainly if the virus is poorly controlled. Furthermore, there is a risk of vertical transmission to the fetus during pregnancy labour and postpartum through breastfeeding.

Appropriate management must be instituted to reduce the consequences of HIV in pregnancy, ideally starting with preconception counselling and planning pregnancies when the viral load is minimum. During pregnancy, an appropriate combined anti-retroviral (cART) medication is mandatory with very close monitoring of the viral load, cluster of differentiation 4 (CD4) cell counts, blood counts, liver and kidney function tests.

Planning delivery should not be different in women on cART and suppressed viral loads. However, special care must be taken to limit vertical transmission in those who present late and in whom viral load is unknown or not controlled at the time of delivery.

Breastfeeding remains a potential source of infection for the baby and is being discouraged in high-income countries for women living with HIV; however, in low-income countries, the recommendation is exclusive breastfeeding. If breastfeeding must happen, it is best when viral load is suppressed, and cART continued until weaning.

Serodiscordant couples present unique problems, and their management should begin with the planning of pregnancy. Emphasis should be on taking steps to prevent HIV transmission to the negative partner and vertical transmission to the new-born.

Introduction

Human immunodeficiency virus (HIV) was shown to be the cause of acquired immunodeficiency syndrome (AIDS) in 1983 [1]. Although AIDS was first reported in the United States in 1981, mainly amongst homosexuals, HIV infection has now been reported in every country world-wide and has become a global epidemic [2]. Approximately 37.9 million people across the globe were living with HIV/AIDS in 2018, and 1.7 million of these were children (<15 years old) [3]. An estimated 1.7 million individuals worldwide became newly infected with HIV in 2018 [3]. In recent times, the existence of HIV seems to be entirely overshadowed by the current coronavirus pandemic causing COVID 19 [4]. COVID 19 like other coronavirus infections (e.g., SARs, MERs, etc.) are likely to flare and disappear with survivors returning to a healthy life. HIV, on the other hand, seems to be here to stay and once a person is infected, will have to deal with the consequences of living with the virus for life as there is still no known cure or vaccine to protect from it.

Sub-Saharan Africa has some of the highest incidences of HIV, accounting for more than 60 % of all new infections [3]. Other regions currently bearing an increased burden of infections include Asia, Latin America, the Caribbean, Eastern Europe, and Central Asia [3].

The prevalence in the ante-natal population in most high income (HIC) countries varies between 0.1–2/1000 [5] whereas, in some low income (LIC) countries, it could be as high as 29 % [6]. However, with the global action on HIV/AIDS, these trends seem to be decreasing [3]. HIV infection in pregnancy has an impact for both the mother and child if untreated and therefore requires prudent management antenatally intrapartum and postpartum.

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The primary aims of managing HIV infection in pregnancy are the prevention of mother-to-child transmission (MTCT) of the virus, maintaining maternal health, and offering a safe and healthy environment for delivery for mother and child.

Disease description – HIV/AIDS

There are two serotypes of the human immunodeficiency (HIV) virus – HIV 1 and 2. The virus belongs to the family of retroviruses with three major classes:- M (main), N (new), and O (outlier) [7]. The M group of viruses accounts for more than 90 % of HIV infections worldwide and has nine subtypes, called clades, designated by the letters A–D, F–H, J, and K, as well as many recombinant forms [7]. The most prevalent subtype in West Africa is Clade A, while Clade B is commoner in the Americas and Western Europe [8]. Viral diversities are highest in sub-Saharan Africa [9]. HIV-2 which is found more commonly in West Africa and is associated with a lower viral load, a slower rate of both CD4 cell decline and clinical progression is much more prevalent than HIV-2 as a causative agent for AIDS. When compared with HIV-1, HIV-2 is less transmissible (5−8-fold less efficient than HIV-1 in early-stage disease and an about 20−30-fold lower rate of vertical transmission) [10].

HIV infection begins with the binding of the virus particle (virion) to the host cell, followed by replication and integration into the host genome. This then causes progressive depletion of CD4 cells [11], compromises the immunity of the host and creates the potential for opportunistic infections and tumours, and if unchecked can result in full-blown AIDS.

HIV virions have been isolated from a number of human bodily fluids (in both cell-free and cell-associated fractions) including blood, seminal plasma, pre-ejaculate, cerebrospinal fluid, saliva, tears and breast milk. There are four stages of HIV disease (1–4) – Stage 1 being asymptomatic while Stage 4 is fully blown AIDS (WHO). [12]

Impact of HIV on pregnancy and pregnancy outcomes

HIV infection is associated with varying rates of adverse pregnancy outcomes. Some of the known associated poor outcomes include increased spontaneous miscarriages, stillbirths, increased perinatal mortality, intrauterine growth restriction, low birth weight, and chorioamnionitis [13]. Because of immunosuppression, HIV can adversely affect the frequency and course of many infections in pregnancy, including genital herpes simplex, human papillomavirus, vulvovaginal candidiasis, bacterial vaginosis, syphilis, trichomonas vaginalis, cytomegalovirus, toxoplasmosis, hepatitis B and C, malaria, urinary tract infections and bacterial pneumonia. Besides, parasitic infestations and HIV-related opportunistic infections - such as tuberculosis, pneumocystis jerovecii pneumonia seem to be frequent during pregnancy and in the puerperium [8].

Pregnancy does not seem to adversely affect the course of HIV infection, progression or survival. The decline in the CD4 cell count in women with HIV during pregnancy resolves typically in the postpartum period and is attributable to haemodilution [14]. HIV RNA levels seem to remain stable during pregnancy, although some studies suggest an increase in viral load in the postpartum period.

In HIC countries, HIV infection is a rare cause of maternal mortality because of available and specialised healthcare services whereas, in LIC countries especially in sub-Saharan Africa, it is an important and a leading contributor to maternal morbidity and mortality [15].

Screening for HIV in pregnancy

The effects of HIV on pregnancy and the risk of Mother-to-Child-Transmission (MTCT) make screening for infections an essential part of antenatal care for all pregnant women. The World Health Organisation recommends that in high-prevalence settings (>5% prevalence), provider-initiated testing and counselling (PITC) for HIV should be considered a standard component of the package of care in all antenatal care settings. In low-prevalence settings (<5%), PITC can be considered as a vital component of the effort to eliminate MCTC and integrate it with testing for syphilis and other relevant tests depending on the setting to strengthen the underlying maternal and child health systems [16].

The "opt-out" approach to HIV testing may be offered to all women as part of routine antenatal tests during the first antenatal visit. The women in this approach reserve the right to decline the test without any sanctions from the provider. Women who decline the test initially often accept to be tested later in pregnancy with more detailed counselling. HIV testing may also be offered late in pregnancy (about 36 weeks) or in labour to women whose status is unknown or who had tested negative earlier in pregnancy but remain at risk of a new infection. HIV testing and counselling should be voluntary with the principles of consent, confidentiality, counselling, and ensuring that test results are linked with appropriate care, treatment and preventive services. HIV screening and counselling involve pre-test information, HIV testing, post-test and follow-up counselling [5].

Screening in pregnancy goes beyond having a simple blood test as a positive result is likely to have a life-long impact on the patient since there is yet no real cure or vaccination for HIV infection. In HIC countries, a large proportion of women would know about their HIV status before the onset of pregnancy, but some will have to learn for the first time during the course of pregnancy. In the UK, for example between 2012 and 2014, of the pregnancies in women with HIV, 85 % of deliveries were to those who knew their HIV status before pregnancy, and about 50 % of them were having a second or subsequent baby since diagnosis [5].

The psychosocial impact of having a positive HIV test and living with HIV can be overwhelming for new mothers, and British HIV Association (BHIVA) strongly recommend psychosocial assessment and support for these women [5]. This should be done through a well-constituted and dedicated Multi-Disciplinary Team (MDT). Besides, they should also be screened for other sexually transmitted infections as well as bacterial vaginosis, herpes simplex infections and offered cervical cytology [5].

Preconception counselling

All women in the reproductive age group who are HIV positive should seek counselling before starting a pregnancy so that a detailed discussion on pregnancy and childbearing can be established. Pregnancy should be carefully planned, and contraception should be an integral part of this plan.

The main issue should centre on the prevention of MTCT of HIV. There should also be the need to review medications to initiate appropriate combined anti-retroviral treatment (cART) that is appropriate for pregnancy [17]. This will be the period to emphasise the importance of compliance with medications during pregnancy and the postpartum period and identify potential barriers that may affect antenatal, intra and postpartum care [18]. It is also important to stress that successfully achieving maximal viral suppression before conception and throughout pregnancy is the most predictive means of ensuring the lowest risk of potential MTCT [17]. Part of preconception counselling should also be aimed at identifying women who may be victims of domestic violence, depression, and other psychosocial or psychiatric illnesses that may serve as barriers to preventing MTCT. It may be essential to treat and achieve effective control/management of these co-morbidities prior to becoming pregnant [17].

Table 1
Tests and diagnosis of HIV.

HIV Test	Time to availability of result	What is tested	Window Period*	Sensitivity	Specificity
ELISA	2 days–2 weeks	HIV antibodies	3 Months	>99	>98
Antigen test (p24)	2 days–1 week	P24 viral proteins	11 days–1 month	90	100
4th generation tests	2 days–2 weeks	Antibodies and p24	11 days–1 month	>99.7	>99.3
PCR/NAAT tests	2 days–1 week	Genetic material of HIV	12 days	>99	99
Rapid test	Within 20 min	Antibodies	3 months	>99	>98

* Window period – period from infection (exposure) to having a positive result.

Ante-natal management of HIV: (Table 3)

Diagnosis

The diagnosis of HIV infection can be made either directly from the detection of the viral particles or components or indirectly by the detection of antibodies against the virus. Screening is usually done by traditional HIV testing modalities - either an HIV 1/2 Antigen/Antibody test or a Fourth Generation test with the reflex ability of multi-type (combi) detection which essentially establishes a diagnosis of HIV infection [19]. Newer testing modalities have also been introduced. An example of this is the reflex Multispot rapid HIV test, which provides for a combined HIV-1/HIV-2 rapid test to distinguish between HIV-1 and 2 infections [20]. Recently a more rapid test has become available that can make the diagnosis within 1–2 h and can be self-performed. If the Multispot test is negative, additional reflex testing should be done to confirm the negative test and then rule out HIV infection with a polymerase chain reaction (PCR) test [21] (Table 1). The rapid test has a sensitivity close to 100 %, but the positive predictive value is dependent on the prevalence of HIV in the population [21]. It is particularly useful on delivery suites for women of unknown HIV status. If positive in a labouring patient, interventions should be instituted immediately without waiting for a confirmatory test. Table 1 shows the currently available tests and the time to results.

Monitoring

Women with HIV must be carefully monitored all through pregnancy on the effects of infections as well as the effects of cART (Tables 2 & 3). Those who are newly diagnosed with HIV do not require any additional baseline investigations compared with nonpregnant women living with HIV other than those routinely performed in the general antenatal clinic [5].

It will, however, be essential to have monthly assessments of viral loads to monitor the progress and efficacy of management. In women who commence cART in pregnancy, an HIV viral load should be performed 2–4 weeks after initiating treatment, and later at least once every trimester, and at 36 weeks and at delivery [5].

Most cART drugs are metabolised in the kidneys and the liver. It is therefore prudent to monitor the liver function tests and serum creatinine with a complete metabolic profile (CMP). This will detect early renal or liver insufficiency that might require management. This can be done more frequently at the onset of treatment and spaced out more as they stabilise on their medications.

A monthly complete blood count is also recommended with particular emphasis on the haemoglobin concentration and platelet counts. This is because some cART drugs cause bone marrow suppression [22]. A cluster of differentiation 4 (CD4) cell count should be monitored approximately every three months as is recommended in nonpregnant women. An additional CD4 count at delivery should be done even if the CD4 count was higher than 350cells/mm, at the first test in pregnancy [3,] [5].

A baseline HIV genotype and hepatitis panel is necessary to assess for any viral resistance and hepatic disease, both of which are important to know before initiating antiretrovirals [22].

Apart from the HIV-specific monitoring, the antenatal management should be as close to normal as possible [5]. Fetal ultrasound imaging should be performed as per national guidelines regardless of maternal HIV status. The combined screening test for fetal aneuploidies and non-invasive prenatal testing (NIPT) for those who screen as high risk is recommended as this has the best sensitivity and specificity and will minimise the number of women who may need invasive testing [5]. Invasive prenatal diagnostic testing should be deferred until after the HIV status of the woman is known, and even then, should ideally be deferred until HIV viral load has been adequately suppressed to <50 HIV RNA copies/mL. There is limited data that suggests that amniocentesis might be safe in women on cART [23]. If not on cART and an invasive diagnostic test procedure cannot be delayed until viral suppression is achieved, it is recommended that women are commenced on cART to include raltegravir and be given a single dose of nevirapine 2–4 h before the procedure [5]. The risks need to be balanced with the benefits and advice taken from the HIV physicians and an informed consent taken from the patient. Table 2 summarises the monitoring tests on women with HIV in pregnancy.

Antiretroviral treatment in pregnancy

The only ART licensed for use in pregnancy is zidovudine in the third trimester. There is, however, a global consensus that women who conceive on effective cART should continue cART throughout pregnancy and then lifelong [5]. This can, of course, be modified if the regimen is non-standard (e.g. monotherapy with protease inhibitors) or with drugs showing lower pharmacokinetics in pregnancy such as darunavir/cobicistat and elvitegravir/cobicistat etc. [5].

Table 2
Monitoring HIV in pregnancy.

	Interval	Reason
Viral loads	Monthly every 2–4 weeks on initiation of treatment and space out later.	Progress and efficacy of management
Liver Function tests and Renal Functions	Weekly at onset of treatment and spaced out when stable.	Detect early liver of kidney compromise secondary to drugs.
Full Blood Count	Monthly (attention to Hb and platelets)	Marrow suppression by cART Medications
Cluster of differentiation 4 (CD4) count	Every 3 months	Disease progression

Table 3
Summary of AN Care.

Investigations:
All Routine AN investigation as other clients
Viral Load: 2–4 weekly at onset and once every trimester if stable)
Liver and Renal Functions: Weekly at onset and spaced out when stable.
Full Blood Count: Monthly
Cluster of differentiation 4 (CD4) count: Every 3 months.
HIV Genotype: Baseline at onset.
Monitoring:
All AN Monitoring as in non-HIV patients
USS as per national guidelines
Combined screening test for fetal aneuploidies
Non-invasive prenatal testing (NIPT)
Invasive tests:
Defer until the HIV status of the woman is known and HIV viral load has been adequately suppressed to <50 HIV.
If not Consider cART (Start on raltegravir and give single dose of nevirapine 2–4 h before procedure)

In treating pregnant women, consideration should be given not only to their health but also that of their unborn babies with particular attention to congenital abnormalities. The aim of drug therapy here is to induce and maintain maximum viral load suppression; hence triple-drug therapy is recommended, which may not always be appropriate for use in standard adult treatment outside of pregnancy. The World Health Organisation recommends that all pregnant and breastfeeding women with HIV irrespective of CD4 cell count, viral load, and clinical stage should have triple antiretroviral drugs, which should be maintained throughout the period of risk of MTCT (late pregnancy, labour and breastfeeding) and continued for life [24] as for other patients with living HIV. The choice of drugs should depend on whether the woman is treatment naïve (i.e. those who have never had treatment before), drug-resistance, toxicity of the drugs and co-morbidities including hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. It is of great advantage if one of the drugs is able to cross the placenta to provide pre-exposure prophylaxis for the fetus.

BHIVA recommends the use of two nucleoside backbone combinations, including tenofovir/emtricitabine and abacavir/lamivudine, or zidovudine/lamivudine combinations [5,25] (Table 4). In choosing the backbone combinations, considerations should be given to the side-effect profile, frequency of dosing, interactions with the third agent, adverse outcome profiles and prior cART experience, including resistance profile where available [5] (Table 5). The combination of tenofovir/emtricitabine and lopinavir/r (especially high-dose lopinavir/r), should be used with care in light of the reported increased risk of neonatal death and prematurity in a recent trial [26].

Drug toxicities are not uncommon with ARTs and can manifest as anaemia, mitochondrial toxicity (lactic acidosis, pancreatitis, peripheral neuropathy, myopathy, and cardiomyopathy), hyperlipidemia, fat redistribution, and insulin resistance. Bone disorders as osteopenia, osteoporosis and osteonecrosis have all been documented. Nevirapine has been associated with mucus membrane /skin eruptions, including Steven Johnson's syndrome [27]. It is therefore essential to monitor haematological and clinical chemistry parameters for patients on antiretroviral.

Starting cART

Once a diagnosis of HIV has been made in pregnancy, antiretroviral treatment should be started as soon as possible to achieve maximal viral load suppression before delivery. While achieving this should be the priority, some consideration should be given to the issue of nausea and vomiting in early pregnancy and the potential for teratogenicity hence, if the immune status is good, there may be a case for delaying treatment till the end of the first trimester. The duration of therapy affects vertical transmission. In a French cohort, the median duration of therapy of 9.5 weeks was observed in women where vertical transmission occurred, compared with 16 weeks with no transmission [28].

Good advice would be to start on cART [5]

a) as soon as possible in the second trimester where the baseline viral load $\leq$30,000 HIV RNA copies/mL;

Table 4
Classes of antiretroviral drugs.

	Drug Class	Examples
1	Nucleoside/nucleotide reverse-transcriptase inhibitors (NRTIs/NtRTIs)	Azidothymidine (AZT) or Zidovudine (ZDV), Lamivudine (3TC), Abacavir (ABC), Emtricitabine (FTC), Stavudine (d4T), Tenofovir (DF)
2	Non-nucleoside reverse-transcriptase inhibitors (NNRTIs)	Efavirenz (EFV), Nevirapine (NVP) and Etravirine (ETV)
3	Protease inhibitors (PIs)	Lopinavir (LPV), Ritonavir (RTV), Atazanavir (ATV), Indinavir (IDV), Saquinavir (SQV), Nelfinavir (NFV)
4	Integrase strand transfer inhibitors (INSTIs)	Raltegravir (RAL), Dolutegravir (DTG)

Table 5
Recommended and alternative cART agents in pregnancy and breastfeeding.

BHIVA 2019 [5]		
	Recommended	**Alternative**
Nucleoside reverse transcriptase inhibitor (NRTI) backbone	Abacavir/lamivudine Tenofovir DF/emtricitabine	Zidovudine/lamivudine
Third agent	Efavirenz Atazanavir/r	Rilpivirine, Darunavir/r, Raltegraviror Dolutegravir (after 8 weeks' gestation)
WHO 2018 [68]		
	Preferred Regimen	**Alternative Regimen**
First-line ART	Tenofovir + Lamivudine (or Emtricitabine) + Dolutegravir	Tenofovir + Lamivudine (or Emtricitabine) + Efavirence Azidothymidine + Lamivudine + Dolutegravir
Second-line ART	Azidothymidine + Lamivudine (or Emtricitabine) + Lopinavir/r (or Atazanavir/r)	Tenofovir + Lamivudine (or Emtricitabine) + Dolutegravir
Third-line ART	Darunavir /r + Dolutegravir (or Raltegravir) + 1–2 NRTIs	

b) at the start of the second trimester, or as soon as possible thereafter in those with a baseline viral load of 30,000–100,000 HIV RNA copies/mL;
c) in the first trimester if viral load >100,000 HIV RNA copies/mL and/or CD4 cell count is less than 200 cells/mm^3.
d) All women should have commenced cART by the 24th of pregnancy.

Most drugs are considered to be reasonably safe in pregnancy, but recent surveillance of dolutegravir in Botswana linked it to a slightly higher than expected rates of neural tube defects [29]. It will, therefore, be better to avoid using it in the first trimester and if possible, switching to other medications in women who are trying to conceive [5].

Special circumstances

Any woman who presents after 28 weeks of pregnancy should commence cART without delay, and if her viral load is unknown or >100,000 HIV RNA copies/mL a three or four-drug regimen that includes raltegravir is suggested. This is because integrase inhibitor-based cART regimens tend to induce a more rapid viral load decline compared to other drug combinations [30]. The aim will be to suppress viral load maximally at the time of delivery.

External cephalic version (ECV) can be offered to women at term from 37^{+0} weeks of pregnancy if the plasma viral load is <50 HIV RNA copies/mL. This is, however, not supported by robust clinical evidence, but there is some theoretical evidence to support ECV. There is evidence that feto-maternal haemorrhage occurs in about 2.4 % of patients after ECV, but this represents new fetal blood cells in the maternal circulation (not the reverse). It has been postulated that, due to the structure and function of the placenta, the risk of maternal blood entering the fetal circulation due to ECV is even much lower [31].

Mode of delivery

Normal delivery should be offered to women with a plasma viral load of <50 HIV RNA copies/mL at 36 weeks, and in the absence of obstetric contraindications. Planned vaginal delivery should be supported, but if the viral load is ≥400 HIV RNA copies/mL at 36 weeks, a planned Caesarean section should be offered [5]. For women with a viral load of 50–399 HIV RNA copies/mL at 36 weeks, pre-labour Caesarean section should be considered, taking into account the actual viral load, the trajectory of the viral load, length of time on treatment, adherence issues, obstetric factors and detailed consultation with the patient [5]. There is very good evidence that the vertical transmission rate is consistently lower than 0.5 % in women with viral loads of <50 HIV RNA copies/mL taking cART, irrespective of the mode of delivery [32,33]. It is noteworthy that the risk of vertical transmission for women delivering vaginally is about twice that of those delivered by CS, and this rises to four-fold when *in-utero* transmissions are excluded [5,34].

There is no evidence to deny women with well suppressed viral load the chance for a vaginal birth after Caesarean Section (VBAC), and it should be offered for obstetric reasons in women with a viral load <50 HIV RNA copies/mL. Timing of Caesarean section for prevention of vertical transmission should be between 38 and 39 weeks' gestation, but planned Caesarean section in women with suppressed viral load should be performed at 39 weeks [5,35].

Management of labour and delivery

Once the decision for vaginal delivery has been made, the management of labour should be as near-normal as possible. Previously the advice had been to avoid amniotomy, fetal scalp electrodes and fetal blood sampling, instrumental delivery and episiotomy because of a theoretical risk of transmission. Most of these were developed in the pre-cART era, and current evidence does not support these conclusions. There is no doubt that cART has played a significant role in reducing MTCT of HIV. A Spanish retrospective study predominantly in the pre-cART era showed a vertical transmission of 26.3 % in infants exposed to fetal scalp monitoring with electrodes or pH sampling or both) compared with 13.6 % in those who had none of these [36]. In a more recent Swiss cohort, neither fetal scalp electrodes (RR 2.0; 95 % CI 0.58–6.91) nor pH blood sampling (RR 1.73; 95 % CI 0.58–5.15) were confirmed as independent risk factors [37]. In the Women and Infants Transmission Study (WITS) cohort (1989–1994) artificial rupture of membranes (RR 1.06; 95 % CI 0.74–1.53) and exposure to blood during labour (RR 0.7; 95 % CI 0.4–1.27) or delivery (RR 1.06; 95 % CI 0.74–1.52) were not associated with transmission [38]. Also, fetal skin lesions (RR 1.2; 95 % CI 0.7–1.8) and episiotomy/tear (RR 1.0; 95 % CI 0.7–1.3) have not been associated with transmission [39,27].

Instrumental delivery is no longer as risky with regards to MTCT as previously thought. Data from different sources have failed to identify instrumental delivery as a cause of vertical transmission [37,40]. The choice of instrument should be based on it, causing minimal fetal trauma. However, it is unlikely that there will be any significant difference in outcome between a low forceps and vacuum in women with well suppressed viral loads.

In all cases of term pre-labour spontaneous rupture of fetal membranes (PROM), delivery within 24 h should be the aim. Currently, there is no evidence of increased vertical transmission in women with undetectable viral load with SROM < 4 h and between 4 and 24 h [41]. There is, however, lack of data for transmission risk beyond 24 h, hence the advice to deliver within this time limit. One of the major factors associated with vertical transmission in this cases is acute or chronic chorioamnionitis [42,43] hence labour should be expedited for all women with PROM at term to avoid this. If the viral load is well suppressed, labour should be induced immediately with a low threshold to treat for chorioamnionitis. If the viral load is not well suppressed, an immediate Caesarean section should be considered. However, some benefit of doubt could be given to women with a viral load of 50–399 HIV RNA copies/mL considering the actual viral load and its trajectory, length of time on treatment, adherence issues, obstetric factors and the woman's own views [5].

As there is no good evidence to show that ruptured membranes for more than 4 h is associated with a higher risk of vertical transmission for women on cART and suppressed viral loads [44,45] the management of preterm SROM at ≥34 weeks should be the same as that of non-HIV women with term SROM, except that women at 34–37 weeks' gestation should be offered group B streptococcus prophylaxis in line with national guidelines [5]. Under 34 weeks, steroids should be given, and if HIV viral load is not controlled, it should be optimised, and a multidisciplinary discussion held on the timing of delivery.

The use of intrapartum intravenous infusion of zidovudine is no longer recommended for women with a viral load <50 HIV RNA copies/mL. However, it should be considered in those with a viral load of 50–1000 HIV RNA copies/mL and definitely offered if the viral load is >1000 HIV RNA copies/mL. It is also recommended for untreated women presenting in labour or with SROM in whom the current viral load is not known [5,46].

Breastfeeding

Breastfeeding is particularly important to some mothers, but it is essential for all to understand that HIV can be transmitted

through breast milk in erstwhile uninfected babies. In HIC countries, most women with HIV do not breastfeed, so there are hardly any more data coming from these countries. In low- to middle- income countries, the overall postnatal risk of HIV transmission through breast milk when women are treated with cART has been reported as 1.08 % (95 % CI 0.32–1.85) at six months and 2.93 % (95 % CI 0.68–5.18) at 12 months [47,48]. For women not on cART, the risk of infecting the baby is affected by detectable HIV viral load; advanced maternal HIV disease, longer duration of breastfeeding, breast and nipple infection/inflammation, infant mouth or gut infection/inflammation and mixed feeding, in particular solid food given to infants less than two months of age [49].

Many HIC countries like the United Kingdom actively discourage breastfeeding in HIV infected women because of the on-going risk. In the LIC countries, the advice is different and is related to higher mortality and morbidity from diarrhoea, malnutrition and pneumonia in formula-fed infants. These are the basis for the current WHO recommendation of exclusive breastfeeding for the first six months of life, introducing appropriate complementary foods thereafter, and continuing breastfeeding until the infant reaches 12 months of age. Breastfeeding can be discontinued once a nutritionally adequate and safe diet without breast-milk can be provided. There is, however, no doubt that the transmission rate will be better reduced if the mother stays on lifelong antiretroviral treatment or extended antiretroviral prophylaxis until one week after cessation of all breastfeeding.

The neonate

Treating the neonate is beyond the scope of this article, but babies born to HIV positive mothers require special attention that is worth mentioning. Their risk of acquiring vertical transmission should be objectively categorised depending on the duration of cART in the mother, documented suppression of viral load (<50 HIV RNA copies/mL), and if delivered beyond 34 weeks of gestation. Those categorised as very low risk will need two weeks of zidovudine monotherapy. In comparison, the low-risk ones will require four weeks of treatment, and the high-risk ones without good or unknown viral load suppression will require combination therapy [5]. Ideally, all medications should be started within 4 h of birth.

Management of serodiscordant couples

The term “serodiscordant couple” refers to an intimate partnership in which one person is HIV-positive, and the other is HIV-negative [50]. Such a relationship may be defined by marital, cohabitating, or co-parenting status or by the length of relationship (e.g., minimum of 3–6 months), intention to stay together, or reporting a certain minimum number of sexual acts with this partner within a given timeframe [51]. The frequency of such couples tends to reflect the prevalence of HIV in the community [52]. For instance, in Kenya, over 40 % of HIV infected individuals have HIV uninfected regular partners. Many of these couples are of reproductive age with strong desires to have children [52], which may put the HIV uninfected partner at risk of HIV acquisition as they pursue their pregnancy goals through unprotected sexual intercourse [53].

The management of such couples should precede pregnancy with safer conception strategies to offer affected couples the opportunity to conceive while reducing the risk of sexual transmission [53]. Some of these strategies include the use of antiretroviral therapy (ART) for viral suppression for the HIV uninfected partner - Pre-Exposure Prophylaxis (PrEP) [53]. Other useful methods include restricting condom-less sex to peak fertility periods [54,55], vaginal self-insemination for couples with HIV infected women [56] male circumcision for HIV uninfected men [57] and medically assisted reproduction by sperm washing [58]. When used singly or in combination, these interventions will reduce the risk of HIV transmission in serodiscordant couples seeking pregnancy [52,59]. There is good evidence to show that the lifetime risk of sexual HIV transmission for heterosexual serodiscordant couples is only 0–5 % if the HIV-positive partner achieves full viral suppression and do not have any other sexually-transmitted infection [60,61].

There is a lot of medical evidence on the efficacy of Pre-Exposure Prophylaxis (PrEP). In the PARTNERS study, 1166 couples of differing HIV statuses (both heterosexual couples and men who have sex with men) where the infected partner was kept on suppressive ART while having sex without using condoms, no cases of HIV transmission were reported after a median follow up of 1.3 years and approximately 58,000 condom-less sex acts [62].

The ideal chemoprophylactic drug should have a long half-life and high barrier for genetic resistance, achieve high levels of concentrations in monocytes, macrophages, and genital secretions, and be safe and inexpensive [63]. Most of these characteristics are reached by tenofovir (TDF). The FDA has approved the combination of TDF and emtricitabine (FTC) (Truvada TDF/FTC 300/200 mg) for PrEP against sexual HIV acquisition by men who have sex with men (MSM), as well as for heterosexually active serodiscordant women and men [64]. The CDC recommends that an individual who does not have HIV and who is planning a pregnancy with a partner who has HIV should start on PrEP about one month before conception is attempted and continue for another one month after conception occurs [65]. If they will continue having unprotected intercourse after conception, and the partner with HIV has not achieved sustained viral suppression, the partner without HIV should continue to take PrEP to decrease the risk of secondary transmission [65].

There are still a lot of issues about the cost-effectiveness of PrEP which depends on other factors including the prevalence and incidence of HIV in the population taking up PrEP (and therefore their age and their level of condom use), PrEP drug-cost, PrEP efficacy (sometimes expressed in terms of adherence to PrEP), rate of HIV diagnosis in the population and cost of antiretroviral treatment for the HIV-positive population [63]. The use of generic formulations of TDF/FTC (Truvada), if and where available, might help to improve the cost-effectiveness of PrEP, which is essential for use as a public health approach to reduce community HIV transmission.

Before attempting conception, it is essential that the partner with HIV should be on ART and should have achieved sustained viral suppression [59]. If the couple decides to take PrEP, they should be educated about the potential risks and benefits and all available alternatives for safer conception [65]. The implications of initiating therapy before conception goes beyond viral load suppression and entails the choice of proper ART compatible with pregnancy with expert counselling and the need to adhere to treatment through pregnancy, delivery and breastfeeding.

Monitoring pregnant women in serodiscordant relationships

HIV positive women living with HIV negative partners should be managed like other HIV positive woman with emphasis on preventing the partners and the babies from acquiring HIV.

Women who are HIV negative but living with n HIV positive partners should have a baseline HIV diagnostic test, renal function test, and pregnancy test done at baseline. HIV and pregnancy test should be repeated every three months, and renal functions every six months [59]. Testing for hepatitis B virus (HBV) infection should be performed, and individuals without HBV infection should be

vaccinated if previously not vaccinated or lack immunity to HBV [59,65].

When booking for ante-natal care, HIV testing should be repeated. Also, they should be counselled on the importance of their partners' adherence to ART and the need to achieve sustained virologic suppression to reduce the risk of sexual transmission of HIV during the course of pregnancy. HIV testing should be carried out in every trimester, and a Rapid test is done when the lady is admitted for delivery. HIV testing should then be carried on every three months after delivery at least throughout breastfeeding.

It is also necessary to discuss the symptoms of acute retroviral syndrome (i.e., fever, pharyngitis, rash, myalgia, arthralgia, diarrhoea, and headache) and the importance of seeking medical care and testing if they experience such symptoms. Acute HIV infection during pregnancy or lactation is associated with high viral load and increased risk of transmitting HIV to their infants [66,67].

Summary and conclusion

HIV infection remains very prevalent all over the world, with the highest prevalence in Sub-Saharan Africa and the LIC countries. It affects pregnant women and if not appropriately managed, carries significant morbidity and some mortality and the risk of vertical transmission to babies. All pregnant women should be presented with the option of an HIV test, and opting out should be managed as infected. Despite the immune status as evidenced by viral load and CD4 cell count, all pregnant women with HIV infection should receive cART during pregnancy. The duration of cART and suppression of the viral load and duration are essential factors in preventing MTCT. When the viral load is well suppressed, delivery should not be different from that of other women, and most interventions should be for obstetric indications. However, if the viral load is not suppressed or if the HIV status is unknown, special care should be taken in planning labour and delivery to prevent perinatal transmission of the virus to the baby. Serodiscordant couples present special problems, and ideal management should begin with the planning of pregnancy. Emphasis is on taking steps to prevent HIV transmission to the negative partner, thus preventing vertical transmission to the new-born.

Declaration of Competing Interest

None.

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