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Introduction

Multidisciplinary management of HIV-1 in pregnancy has reduced the mother-to-child-transmission (MTCT) rate from 25-30% to <2% in the developed world. An audit of the outcome of HIV positive pregnancies in Ireland found that in the 9 year period, January 1999 to December 2007, of 874 live births, including 9 twin pregnancies, the vertical transmission rate was 1% [95% CI 0.98 – 1.019][1].

The most recent report on voluntary antenatal HIV testing indicates that between 2002 and 2006 uptake rates for antenatal HIV screening have consistently been >90%. In 2006, of 53,802 women offered antenatal HIV testing, 51,144 proceeded with testing giving an uptake rate of 93.5%. 116 were identified as HIV positive and of these, 36 (31%) were previously unaware of their HIV status, giving a HIV prevalence of 0.23% in pregnant women[2]. The prevalence is higher in the HSE Eastern region (0.33%) compared to the rest of the country (0.14%). The successful nationwide implementation of antenatal screening for HIV coupled with the policy of geographic dispersal of asylum seekers adopted in 2000 has resulted in HIV infected women delivering in obstetric units throughout the country. There is a need for clear and accessible, nationally relevant guidelines for the management of HIV in pregnancy so that the current success in preventing vertical transmission can be maintained.

These guidelines replace previously published guidelines for the management of HIV in pregnancy in Ireland[3], and offer a broad management outline for HIV positive pregnant women. Ultimately, each woman must be assessed by a multidisciplinary team and an individualised plan determined.

Methods

There are few randomised controlled trials to guide the management of HIV in pregnancy. Nonetheless both antiretroviral therapy prescribing and obstetric management of HIV infected women have changed significantly since the publication of the pivotal PACTG 076 study in 1994[4]. Many of these changes have been informed by observational data coupled with international expert opinion.

These guidelines are based on currently available peer-reviewed international data (both published and conference data). They have been developed with reference to international guidelines and with the input of adult and paediatric HIV physicians and obstetricians. The experience gained and lessons learned from the management of HIV infection in pregnancy in Ireland are used to provide nationally relevant management options.

Various scenarios have been drawn up to reflect the diversity of clinical presentations.

Prior to publication, these guidelines were available for a period of consultation by Obstetricians, adult HIV physicians and paediatric HIV physicians in Ireland.

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Principles of Management

1. ANTENATAL SCREENING

In Ireland, the opt-out antenatal HIV screening programme, first introduced in April 1999, recommends that all women booking for antenatal care are offered an HIV test The latest available data report uptake rates of >90% over the years 2002 to 2006.

- There should be a clear mechanism for informing HIV positive women of their test result in a timely manner and for onward referral to adult HIV services.
- Women who decline testing should be made aware of the benefits of knowing their HIV status and encouraged to proceed with testing. Maternal testing for HIV where consent has been explicitly refused is not recommended.
- Women who decline testing for themselves should be offered, and encouraged to avail of, HIV testing of their infant following delivery and when the infant is three months of age. Consideration should be given to proceeding with testing the infant for HIV even in the absence of parental consent.
- Women with ongoing risk factors for acquisition of HIV (active injecting drug use, known HIV infected partner, partner from high prevalence country, or partner with identified risks for HIV infection and unknown HIV status) and an initial negative test should be offered repeat testing throughout pregnancy. In the future repeat HIV testing in the third trimester, preferably prior to 36 weeks, may be considered for all women.
- Women who book for antenatal care after fetal viability should have their HIV test performed urgently with a clear mechanism for management of positive results. In the event of a positive HIV test in pregnancy, refer the woman to adult HIV services as soon as possible, without waiting for the results of a confirmatory HIV test.

- Women presenting unbooked in labour should have a HIV test performed urgently with availability of results within 24 hours (in larger obstetric units availability of a result within hours can be anticipated but this may be unrealistic in smaller units). Point of care HIV tests are now commercially available and offer good sensitivity and specificity. Where it is not possible to have rapid laboratory testing for HIV, use of rapid point of care HIV testing should be considered.

2. Maternal HIV care

The delivery of HIV care to women in pregnancy requires a multidisciplinary approach to optimise the chances of ensuring good maternal health and a HIV negative infant.

2(a) Assessment of maternal health

All HIV infected pregnant women should be assessed and managed at a specialist adult HIV service. In the non-pregnant population the need for antiretroviral therapy is guided by the CD4 count and presence of HIV related symptoms. International antiretroviral guidelines are available and regularly updated[5] [6].

Current US and British guidelines for the management of HIV in pregnancy recommend that initiation of antiretroviral therapy be in line with the guidelines for the non-pregnant population[7] [8]. Current guidelines recommend antiretroviral therapy for those with a CD4 count of $<350 \times 10^6$/L and opportunistic infection prophylaxis for those with a CD4 count of $<200 \times 10^6$/L.

That the physiological changes of pregnancy predispose to a temporary decline in maternal CD4 count in pregnancy, through haemodilution has been reported in cohorts of HIV infected pregnant women in Ireland and SubSaharan Africa[9] [10]. Therefore some pregnant women with a pre-treatment CD4 count of $<350 \times 10^6$/L but $>200 \times 10^6$/L may not need antiretroviral therapy beyond pregnancy. For women with

a pre-treatment CD4 count of <200 x 10^6/L opportunistic infections prophylaxis should be as for the non-pregnant population.

HIV-1 RNA levels (viral load) are measured at baseline and in response to antiretroviral therapy. There are a number of different assays available which generally correlate but differences in RNA copy number of 0.5 to 1.0 log have been described[11]. Therefore it is important that the same assay be used when determining response to antiretroviral therapy. Where this is not possible, the results should be interpreted with caution.

There have been reports that some assays underestimating the HIV viral load in nonB virus subtypes. Where there is discrepancy between the anticipated HIV viral load, CD4 count and clinical status (i.e. undetectable viral load in an untreated patient or low viral load in an individual with low CD4 count or symptomatic disease) in an individual infected with nonB virus, it is advisable to use an alternative assay so that significant viremia is not missed.

Genotypic antiretroviral ARV resistance testing should be performed at baseline in all newly diagnosed HIV infected people in Ireland. Between 2002 and 2003, of over 1200 new HIV diagnoses across Europe, the prevalence of acquired HIV resistance was 9.1%[12]. In pregnancy, all women should have baseline genotypic resistance testing performed, where possible before initiation of antiretroviral therapy. However, where a woman presents at an advanced gestational age, initiation of antiretroviral therapy should not be delayed pending results of baseline genotypic resistance testing.

For women failing antiretroviral therapy in pregnancy, genotypic resistance testing is indicated as for the non-pregnant population. Results may need to be sought urgently in order to optimise the chances of achieving virological control before delivery.

Short term antiretroviral therapy in pregnancy can predispose to development of antiretroviral resistance. Development of resistance in 13% women following temporary exposure to a non-nuceloside reverse transcriptase inhibitor regimen in

pregnancy has been reported[13]., Resistance testing should be performed around six weeks after delivery for women who discontinue antiretroviral therapy to inform selection of future antiretroviral ARV regimens.

2(b) Maternal antiretroviral therapy

The single most important determinant of whether or not a woman transmits HIV to her infant is maternal ARV therapy. In the non-pregnant HIV population the hallmarks of effective antiretroviral ARV therapy are complete virological suppression and immunological recovery. There are currently five licensed classes of antiretroviral agents: Nucleoside Reverse Transcriptase Inhibitors (NRTIs); Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs); Protease Inhibitors (PIs); Fusion Inhibitors and Integrase Inhibitors. Highly active antiretroviral ARV therapy (HAART) usually consists of 3 drugs from 2 classes. In individuals initiating therapy for the first time HAART will usually consist of 2 NRTIs plus 1 NNRTI or 1 PI. In pregnancy HIV infected women may require antiretroviral therapy for their own health or solely to reduce the risk of vertical transmission of HIV.

Monotherapy

The seminal breakthrough in the development of strategies for the prevention of MTCT was the PACTG076 study, published in 1994[3]. This randomised controlled trial demonstrated that compared with placebo, oral antenatal zidovudine, intravenous peripartum zidovudine and oral postpartum zidovudine reduced the risk of MTCT by 66%. The efficacy of zidovudine monotherapy has been reproduced in several clinical trials and epidemiological studies since then[14 15 16]. Following the advent of HAART circa 1997 there was a move towards use of more combination antiretroviral therapy in pregnancy with some data suggesting that the more complex the regimen the lower the risk of transmission[17]. However recently published data on over 5000 mother-child pairs in the UK and Ireland did not demonstrate a difference

between zidovudine monotherapy coupled with an elective caesarean section and HAART in preventing MTCT[18]. Another concern surrounding the use of zidovudine monotherapy was the potential for monotherapy to promote evolution of antiretroviral resistance. In selected women with low pre treatment HIV viral loads, the risk of emergence of antiretroviral resistance is low when assessed with genotypic population sequencing and more sensitive cloning[19 20]. At the GUIDE clinic between 1997 and 2003, 20 women received antenatal zidovudine monotherapy. Maternal reluctance for more complex antiretroviral exposure, difficulty with pill burden, and very low level pre-treatment viraemia and normal CD4 counts were amongst reasons cited for opting for zidovudine monotherapy. The recent data from the Institute of child health[17] support the use of zidovudine monotherapy, coupled with elective caesarean section, in selected women with normal pre-treatment CD4 counts and low pre-treatment HIV viral loads.

Nevirapine a non-nucleoside reverse transcriptase inhibitor has proven efficacy in reducing MTCT when used as a single agent. It rapidly crosses the placenta, has a long half life, and has been shown to reduce the risk of MTCT in breastfeeding populations when given as a single dose to the mother in labour and to the neonate within the first 72 hours of life[21 22]. Unfortunately, nevirapine has a low genetic barrier to resistance and viral resistance to nevirapine has been demonstrated in up to 40% of exposed women after a single dose[23]. Single dose nevirapine monotherapy to the mother and neonate is therefore not routinely recommended in Ireland. Because nevirapine rapidly crosses the placenta and nevirapine containing regimens can result in very brisk decline in viremia, the addition of a single dose nevirapine to a standard regimen can be a useful option for women who present late in pregnancy. Similarly a single dose nevirapine may also be considered in women with high HIV viral loads and previously documented NNRTI resistance who present late in pregnancy. In both these situation, it is thought that the value of nevirapine is not

only to impact on maternal viremia but also, via placental transfer, to load the unborn infant and thus offer the infant pre exposure prophylaxis.

Dual therapy

The use of dual antiretroviral therapy with zidovudine and lamivudine is not recommended because of the potential to induce lamivudine resistance with this strategy[24].

Triple therapy

Since January 2001, in Ireland the standard approach has been to offer all HIV infected pregnant women triple antiretroviral therapy regardless of immunological well being[2]. For women not requiring antiretroviral therapy treatment is discontinued following delivery.

When to start therapy in pregnancy?

Timing of initiation of antiretroviral therapy depends on maternal well being and obstetric factors. In general for women requiring antiretroviral therapy for their own health, wait until after the first trimester to initiate antiretroviral therapy in order to minimise potential teratogenicity. Where the sole indication for antiretroviral therapy is prevention of MTCT, the optimum time for initiation of antiretroviral therapy is that which offers the best chance of avoiding transmission balanced against minimisation of exposure (both in utero and maternal) and toxicity whilst ensuring preservation of future maternal therapeutic options. Previous Irish guidelines have recommended that antiretroviral therapy be started at approximately 28 weeks in women not requiring antiretroviral therapy for their own health. In the recent report of over 5000 pregnancies in Ireland and the UK, there were 3 transmissions in women with an undetectable HIV viral load at delivery[17]. All three were the result of in utero transmission, which could possibly have been prevented by earlier initiation of

antiretroviral therapy. These data also demonstrated that the risk of transmission reduced by 0.9% for every additional week of antenatal antiretroviral therapy. Furthermore as the rates of MTCT have declined, the proportion of in utero transmissions has increased[25]. In Thailand, initiation of antiretroviral ARV therapy after 31.4 weeks gestation was an independent risk factor for transmission of HIV[26]. British guidelines recommend that therapy be initiated between 20 and 28 weeks and suggest that initiation before fetal viability (24 weeks) may be prudent[7]. Current US guidelines suggest initiating antiretroviral therapy any time after 10 to 12 weeks of pregnancy in those requiring therapy solely to reduce the risk of MTCT[6].

Initiation of antiretroviral therapy around fetal viability probably offers the optimum balance between limiting in utero and maternal exposure, limiting the potential for prematurity with more prolonged exposure whilst offering enough protection against in utero and peripartum transmission. Confounding factors such as a history of previous spontaneous preterm delivery, multiple pregnancy, maternal infections (eg. malaria or infectious syphilis) may warrant even earlier initiation of antiretroviral therapy in order to achieve adequate antenatal suppression of HIV viral load.

What therapy to start in pregnancy?

All HIV infected women should be offered antiretroviral therapy in pregnancy, regardless of gestational age at first presentation or pre-treatment immunological and virological parameters. Furthermore all women should be appraised of the potential and unknown risks associated with antiretroviral therapy in general and in pregnancy. For women requiring antiretroviral therapy for their own well being, the choice of regimen is based on maternal CD4 count, HIV viral load, co-morbidities and previous antiretroviral exposure and resistance. Whilst there is limited data around the use of many antiretroviral drugs in pregnancy, particularly newer agents, the absence of data should not preclude use of agents for which there is a clear maternal indication.

In circumstances where the primary indication for therapy is reducing MTCT, the objective is to minimise fetal exposure to virus, whilst maintaining future maternal antiretroviral options.

In general zidovudine should be included in antenatal antiretroviral regimens where possible. Reasons for this include that zidovudine is triphosphorylated to its active form in the placenta and is readily transmitted to the foetus. In the foetus it may act as pre-exposure prophylaxis around the time of labour and delivery, when the risk for exposure to HIV is greatest. Additionally international experience with zidovudine use in pregnancy is greater than for other agents.

Vaginal delivery is a realistic option for HIV positive women provided the woman is receiving triple antiretroviral therapy and has achieved viral suppression and there are no obstetric indications for surgical delivery. Where women do not have a requirement for antiretroviral therapy and the pre treatment viral load is <5000 copies, zidovudine monotherapy coupled with elective caesarean section may be an option (for timing of elective caserean section see 3 (c).

Currently, the most frequently used antiretroviral regimen in pregnancy is combivir (fixed dose formulation zidovudine 300mg plus lamivudine 150mg) 1 tablet BD coupled with a boosted protease inhibitor (lopinavir/ritonavir, saquinavir/ritonavir or atazanavir/ritonavir).

In Ireland, the use of nevirapine as part of combination therapy in pregnancy has been associated with an increased risk of serious hepatotoxicity (including 2 maternal deaths from fulminant hepatitis) in women with higher pre treatment CD4 counts[27]. The inclusion of nevirapine in antenatal antiretroviral regimens is best reserved for women with pre-treatment CD4 counts of <250 x 10^6/L. Nevirapine containing regimens may be particularly useful for women initiating antiretroviral therapy late in pregnancy as it is associated with more rapid viral decay than the protease inhibitors[28]. Furthermore, nevirapine is efficiently transferred across the placenta,

thus offering pre-exposure prophylaxis to the fetus/neonate. These features, rapid decline in viremia and excellent transplacental transfer, are particularly useful when trying to prevent peripartum transmissions in women initiating antiretroviral therapy late in pregnancy. They form the basis for the recommendation to add a single maternal dose of nevirapine to combination therapy in this setting.

How to stop antiretroviral therapy post partum?

Women taking antiretroviral therapy solely to reduce the risk of MTCT, can stop treatment post partum. When stopping therapy, consideration must be given to the individual half lives of the agents. If in the combination, one agent has a more prolonged half life than the other two, stopping all three agents at the same time will effectively result in monotherapy with the agent with the longer half live. This situation promotes selection of resistant strains and should be avoided. In general, with protease inhibitor based regimens all agents can be stopped at the same time. In women taking nevirapine based regimens, the long half life of nevirapine must be taken into consideration and a staggered cessation of the regimen is recommended. Here it is hoped that discontinuation of nevirapine immediately post partum and continuing the nucleoside back bone for a further 7 days will avoid effective nevirapine monotherapy and reduce the risk of developing NNRTI resistance. In the Irish setting, despite this strategy, 5 of 39 (13%) women exposed to temporary ART in pregnancy developed significant resistance post partum[12]. In the non-pregnant population staggered cessation of NNRTI containing regimens has not been associated with the development of significant resistance[29].

In situations where women initiate antiretroviral therapy late in pregnancy, It may be prudent to continue antiretroviral therapy until virological suppression has been achieved to reduce the risk of emergence of resistance.

Adverse effects of antiretroviral therapy in pregnancy

Potential adverse effects associated with antiretroviral therapy include teratogenicity; toxicity (both fetal/neonatal and maternal) and its effect on prematurity rates.

The antiretroviral pregnancy registry is an international voluntary, prospective reporting system that tracks congenital abnormalities in children exposed to antiretroviral therapy in utero. Reports are issued twice a year and are accessible at www.apregistry.com. The most recent report is covers the period January 1st 1989 to July 31st 2007.

Previous guidelines suggested that efavirenz be substituted with an alternative agent if a woman conceives while taking efavirenz. This recommendation was based on the reported association of in utero efavirenz exposure and neural tube defects in cynomolgous monkeys. Additionally, four retrospective case reports of neural tube type defects associated with human in utero exposure to efavirenz prompted the FDA to reclassify efavirenz as a class D drug (ie positive evidence of harm) in December 2004. The antiretroviral pregnancy registry has not demonstrated any increased risk of teratogenicity in prospective reporting of in utero first trimester exposure to efavirenz. Importantly there are now sufficient numbers reported to the registry to give sufficient power to detect a two-fold increased risk of teratogenicity compared to the general population. Thus, it may be reasonable to continue efavirenz in some women who conceive whilst taking an efavirenz containing regimen. Furthermore efavirenz has a long half life and can persist at detectable levels for up to 3 weeks following discontinuation[30]. A woman with a 28 day cycle it will be approximately the 15th day of intrauterine life when her period is late. The process of neural tube closure is complete by day 22-24 of intrauterine life and therefore despite stopping efavirenz when a period is missed there will be ongoing in utero exposure to efavirenz that may extend beyond the period of neural tube closure. Additionally stopping efavirenz and substituting an alternative agent may risk loss of virological

control with the potential for evolution of antiretroviral resistance and an increased transmission risk.

Fetal/Neonatal toxicity

Detailed anatomic survey should be offered to all women expose to antiretroviral therapy in the first trimester.

Anticipated side effects associated with zidovudine include anaemia and neutropenia which usually resolve by 12 weeks of age[31].

Nucleoside reverse transcriptase inhibitors (NRTIs) can inhibit mitochondrial DNA polymerase-gamma and the association between NRTI exposure and mitochondrial toxicity is well recognised. In a prospective French perinatal cohort eight cases, including two deaths, have been attributed to mitochondrial toxicity following in utero exposure to NRTIs[32]. A subsequent retrospective review of HIV negative or indeterminate children (n=223) that were exposed to ART and died determined that none of the deaths were likely attributable to mitochondrial dysfunction[33].

Notwithstanding the absence of a clear association in this large series there is evidence that mitochondrial DNA is reduced in infants exposed to NRTIs in utero[34 35 36]. The long term effects of asymptomatic mitochondrial DNA depletion are unknown, highlighting the importance of maintaining these children in long term surveillance.

Tenofovir crosses the placenta and has been associated with alterations in bone biomarkers in rhesus monkeys exposed to tenofovir in utero[37].

Atazanavir has been shown to cross the placenta with therapeutic atazanavir levels in cord blood of exposed infants[38 39]. Atazanavir inhibits the uridine diphosphate-glucuronosyl transferase 1A1 enzyme resulting in an unconjugated hyperbilirubinemia in exposed people. Exposed neonates should be monitored for hyperbilirubinemia but the available evidence to date suggests that dangerous hyperbilirubinemia in exposed neonates is not common[40 41].

Maternal toxicity

In the developed world, zidvudine is no longer recommended as part of first line ARV therapy. Notwithstanding this, based short term tolerability, safety and track record of efficacy, zidovudine remains one of the recommended first line agents for the management of HIV in pregnancy. For those taking short term zidovudine, associated toxicities, anaemia and neutropenia, are generally transient and reversible. For women continuing antiretroviral therapy following delivery a switch from zidovudine to either tenofovir or abacavir after delivery should be considered. More data on the use of tenofovir and abacavir in pregnancy may lead to a change in future recommendations.

As in the non-pregnant population, didanosine and stavudine should be avoided where possible. It is not clear whether or not pregnancy increases the risk of serious toxicity associated with these agents but maternal mortalities have been reported[42 43]

Fulminant hepatitis is a rare but well recognised side effect associated with nevirapine. This may be gender related and is increased in women with a pre-treatment CD4 count of >250 x 10^6/L[44 45]. In the context of pregnancy nevirapine is generally reserved for women requiring HAART for their own health.

Following initiation of antiretroviral therapy in pregnancy it is recommended that women should be seen twice within the first month of therapy and monthly thereafter to monitor for potential toxicity and assessment of virological (and immunological) response.

In both pregnant and non-pregnant populations protease inhibitor use has been associated with impaired glucose tolerance[46 47]. There are conflicting data around the risk of developing gestational diabetes in women taking protease inhibitor

containing regimens in pregnancy[48 49]. This should be considered when evaluating a woman's risk for development of gestational diabetes and some centres now perform glucose tolerance tests in women taking protease inhibitor containing regimens in pregnancy.

Adverse effects on *pregnancy duration*

Epidemiological data from the European Collaborative Study indicates an increased incidence of prematurity with a temporal relation to increasing HAART use in pregnancy. Furthermore this risk, in women delivering vaginally or by emergency Caesarean section, is greatest when HAART has been started pre-pregnancy (AOR 4.0, 95% CI 2.26 – 7.08)[50]. A recent report from a single site in the United States found that the risk of prematurity in women receiving combination therapy was greater for those on combination therapy with a protease inhibitor (AOR 1.8, 95% CI 1.1 – 3.0, p=0.03)[51].

Therapeutic drug monitoring in pregnancy

Physiologic change in pregnancy can significantly change drug handling and pharmacokinetic data in pregnancy must be interpreted with caution as the correlation between plasma total concentrations, plasma free concentrations and intracellular concentrations of drugs may be significantly altered.

Studies in different pregnant populations have demonstrated varying results with respect to the pharmacokinetics of the protease inhibitors.

Lopinavir/ritonavir is one of the more commonly used boosted protease inhibitors in pregnancy. Differing results have been reported for lopinavir/ritonavir soft gel capsules at standard dosing in pregnancy. Low lopinavir levels in the third trimester have been described in a multicentre study from the Unites States[52], while a single centre report from the United Kingdom suggested better steady state levels in the third trimester[53]. Pharmacogenomic differences in the handling of lopinavir/ritonavir

in the different cohorts may explain these differing results, highlighting the importance of exercising caution in applying results from one population to another.

Saquinavir/ritonavir is also widely used as part of short term HAART in pregnancy. At the GUIDE clinic the majority of a cohort of 45 women achieved adequate levels of saquinavir in the third trimester with a median HIV viral load of <50copies/ml at standard saquinavir (1g soft gel capsules BD with ritonavir 100mg BD) dosing[54]

At present there is a multicentre study of the pharmacokinetics of protease inhibitors in pregnancy ongoing in Irish and United Kingdom sites, when available these results will provide nationally relevant data.

2 (c) Management of co-morbidities

All pregnant HIV infected women should have serological screening for hepatitis B, hepatitis C and syphilis. All pregnant HIV infected women should have at least one STI screen performed in pregnancy. Syphilis serology should be repeated in the third trimester and a repeat STI screen considered if the history identifies a new risk for acquisition of an STI.

Hepatitis B

Hepatitis B transmission from mother to baby is related to the level of Hepatitis B viraemia and can be prevented by vaccination and administration of hepatitis B immunoglobulin to the neonate. It is not clear whether or not HIV co-infection increases the risk of hepatitis B transmission but HIV co-infection may increase the level of hepatitis B DNA.

When co-infected surface Ag positive women are commencing combination antiretroviral therapy in pregnancy it is prudent to include two agents with hepatitis B

activity (tenofovir with lamivudine or emtricitabine). Additionally the use of antiretroviral agents with activity against hepatitis B may reduce the risk of hepatitis B transmission[55]

Hepatitis B surface antigen is a very sensitive marker of viral activity in individuals who are hepatitis B core antibody positive (indicating previous hepatitis B exposure). Therefore it is not necessary to use antiretroviral agents with hepatitis B activity in women who are hepatitis B core antibody positive but hepatitis b surface antigen negative.

Children born to women who are hepatitis B surface antigen positive should receive hepatitis B immunoglobulin and hepatitis B vaccination as soon as possible following delivery. To complete the course, further hepatitis B vaccinations will be given as a component of the hexavalent vaccine at 2, 4 and six months of age as part of the national primary immunisation programme. Infants born to hepatitis B surface antigen positive mothers should have blood drawn 6 – 8 weeks following completion of hepatitis B vaccination to exclude hepatitis B infection and to ensure adequacy of the vaccination response.

Hepatitis B is a statutorily notifiable disease and should be must be reported to public health. Household contacts of people who are Hepatitis B surface antigen positive should be screened and offered hepatitis B vaccination if appropriate.

Hepatitis C

In hepatitis C monoinfected women vertical transmission rates of up to 6% have been reported[56 57]. In the monoinfected group up to ~20% of Hepatitis C infected children will later spontaneously clear infection. Maternal HIV/Hepatitis C co-infection

increases the risk of hepatitis C transmission with transmission rates to up to 20% reported. This risk increases with higher hepatitis C viral loads[58] [59].

Little is known about the mechanism(s) and timing of vertically transmitted hepatitis C infection but transmission risk may increase the longer the membranes are ruptured suggesting that intrapartum transmission is significant[60]. As yet, a clear protective benefit of ELCS in preventing vertical Hepatitis C transmission from hepatitis C infected women to their infants has not been proven [61] [62]. In HIV/HCV co-infected women ELCS may reduce the risk of Hepatitis C transmission but data is inconsistent. The use of HAART in HIV/Hepatitis C co-infected women may reduce the risk of hepatitis C transmission (OR 0.26, 95% CI 0.07 – 1.01) [63]. In Ireland, HIV/ hepatitis C co-infected women with ongoing hepatitis C viral replication have generally been offered an ELCS to reduce the risk of hepatitis C transmission.

Syphilis

Untreated early infectious syphilis in pregnancy can lead to still birth in up to 33% of cases. Treatment of syphilis in HIV infected pregnant women should be in accordance with treatment guidelines for syphilis in pregnancy and syphilis in HIV infected persons. Maternal syphilis infection may increase the risk of HIV MTCT and this risk appears to be greater with active syphilis infection[64] [65]. Syphilis serology should be repeated in the third trimester in all HIV infected women. All infants born to women with positive syphilis serology should undergo a syphilis risk assessment. Unless there is a documented history of appropriate maternal treatment **and** response, infants should undergo evaluation and treatment with a single dose of benzathine penicillin. Where the possibility of neurosyphilis is not definitively excluded neonates should receive 10 days intravenous benylpenicillin.

Genital herpes infection

Maternal genital herpes can rarely result in disseminated neonatal herpes simplex virus infection. The risk of neonatal infection is greatest with a primary episode of genital herpes in the third trimester of pregnancy, particularly if there are active lesions at the time of delivery. The presence of genital ulcers or a clinical diagnosis of genital herpes has been associated with an increased risk of transmission of HIV from mother to baby[66] [67]. In HIV positive non-pregnant populations herpes suppressive therapy has been associated with a reduction in both plasma and genital tract HIV viral loads[68] [69]. It is not known whether or not the use of herpes suppressive therapy in HIV infected women in pregnancy reduces the risk of vertical transmission of HIV.

HIV infected women with genital herpes in pregnancy should be managed as per the HIV negative population. Given the evidence that the HIV viral load can be reduced with herpes suppressive therapy it may be prudent to routinely give all HIV pregnant women with a previous history of recurrent genital herpes, anti herpes suppressive therapy in the last four weeks of pregnancy (for example valacyclovir 500mg once daily PO).

Other sexually transmitted infections

All pregnant HIV infected women should have an STI screen performed at baseline in pregnancy. STI screens should be repeated thereafter if risk of a new infection is identified. Infections should be treated and managed as per the HIV negative population with contact tracing to prevent onward transmission and re-infection.

2 (d) Management of opportunistic infections in pregnancy

In Ireland the majority of HIV infected women in pregnancy have been relatively immune competent and the incidence of opportunistic infections in pregnancy low.

Opportunistic infections in pregnancy should be managed as for the non-pregnant population. Where possible medications with less teratogenicity should be used but efficacy should not be compromised.

2 (e) Psycho-social support

Whilst antenatal HIV screening is integral to a strategy to reduce MTCT, a new diagnosis of HIV in pregnancy is traumatic for those diagnosed and their families. Qualitative research in African women diagnosed with HIV through antenatal screening in Ireland has demonstrated that they experience significant trauma requiring support, education and counselling at this time and highlighted the need to develop culturally appropriate support mechanisms for this group of women[70].

For asylum seekers in "direct provision" attendance for hospital appointments can be limited by inability to pay for transport, particularly for women dispersed to centres in rural areas.

Pregnant HIV infected women with a history of past or current substance abuse often find themselves in challenging social circumstances with multiple stressors. This can have a negative impact on their attendance for hospital appointments and adherence with antiretroviral therapy.

A new diagnosis of HIV brings with it the need to identify, inform and offer HIV testing to other parties, potentially at risk for HIV infection and for HIV infected women in pregnancy this will include sexual partners and other children, born before the diagnosis of HIV was made. The Irish Medical Council gives clear guidance on the need for disclosure where a party may be at risk of an infection. Every effort must be made to facilitate self disclosure in a timely manner but where this is not possible the Irish Medical Council endorses breaching an individual's confidentiality in order to inform at risk individuals[71]. It is important to recognise that a newly diagnosed pregnant woman may face abandonment or domestic violence following disclosure of

HIV and that inappropriate handling of disclosure could result in the woman losing trust in the multidisciplinary team and defaulting from care.

The identification, management and alleviation of the many psychosocial challenges facing HIV infected pregnant women requires a multidisciplinary team approach with clear channels of communication between members of the multidisciplinary team.

3. Obstetric care

3 (a) Antenatal care

In general there is no need for increased antenatal surveillance for HIV infected women as HIV itself does not appear to have a detrimental effect on pregnancy outcome. There may be an increased risk of pre-eclampsia associated with immune reconstitution in pregnancy[72] [73] and as outlined earlier protease inhibitors are known to impair glucose tolerance. As with all pregnant women periconceptual folic acid is recommended as a measure to reduce the risk of neural tube defects.

Reports that predate the HAART availability suggest that invasive prenatal testing might increase the risk of vertical transmission of HIV[74]. More recently data in the HAART era reported lower transmission rates, suggesting that antiretroviral therapy may reduce the risk of HIV transmission associated with invasive pre natal testing[75] [76]. We recommend, where possible, women should be in receipt of antiretroviral therapy before invasive prenatal testing is performed. In women opting for Down's Syndrome screening, HIV infection and antiretroviral therapy can alter serum human chorionic gonadotrophin and alpha fetoprotein levels rendering interpretation of serum markers difficult[77].

In most circumstances the management of obstetric problems in HIV positive women is as for the HIV negative population. The use of antenatal steroids to promote fetal

lung maturity should be administered where obstetrically indicated. Potential toxicity associated with administration of antiretroviral therapy may be difficult to distinguish from obstetric disorders such as cholestasis of pregnancy or the HELLP (Haemolysis, elevated liver enzymes, low platelets) syndrome.

Prematurity remains an independent risk factor for HIV transmission[78]. The management of women presenting in premature labour or with threatened premature labour needs to be individualised, balancing the potential morbidity and mortality associated with early delivery against the risk of HIV infection. Where there is a clear obstetric indication tocolysis can be used and the management of the HIV risk can then be tailored to the situation (see scenarios, section 5). Genital tract infection increases the risk of prematurity and women presenting in premature labour or with premature rupture of the membranes should be screened for genital tract infection.

In the general obstetric population, because of an increased risk of intrauterine death associated with prolonged pregnancy, arrangements are made for delivery once a pregnancy has gone beyond 41+ weeks. Delivery can be achieved by induction of labour with the administration of vaginal prostaglandins, artificial rupture of the membranes and intravenous syntocinon or by elective caesarean section. In the context of HIV, there is an association between transmission of HIV and longer duration of ruptured membranes. This data predates the widespread use of HAART in pregnancy and the impact of duration of ruptured membranes on transmission in women on HAART with an undetectable viral load is unknown, although transmission in this setting has occurred (personal communication). As in the general obstetric population the risk for ascending infection and development of chorioamnionitis increases the longer the membranes are ruptured. The presence of inflammation in the genital tract may lead to an increase in the HIV viral load in the genital tract, despite undetectable levels in the plasma and HAART. Thus, there are multiple

reasons why it may be prudent to avoid early elective rupture of the membranes in the context of HIV infection.

For women on HAART with an undetectable viral load who wish to have a vaginal delivery, in whom the cervix is favourable for induction (perhaps particularly women who have delivered vaginally before), a pragmatic approach may be to commence intravenous zidovudine, induce labour with a view to delivery as quickly as possible with minimum duration of ruptured membranes. Where the membranes have been ruptured for longer than anticipated, consideration should be given to triple neonatal antiretroviral therapy (see 4 (b) infant antiretroviral therapy).

3 (b) Intrapartum care

In Ireland HIV infected pregnant women are offered the option of a vaginal delivery where there has been an adequate duration of and response to antiretroviral therapy in pregnancy.

Previous Irish guidelines have recommended peripartum intravenous zidovudine regardless of antenatal antiretroviral therapy and peripartum HIV viral load. Furthermore this is an achievable objective with 85% of all the women that attended the GUIDE clinic in pregnancy between 1996 and 2003 receiving intravenous zidovudine before delivery. The current British guidelines suggest that in women on HAART with an undetectable HIV viral load, there may not be an additional benefit in administering peripartum intravenous zidovudine although US guidelines continue with the recommendation regardless of antiretroviral therapy history. Recent data from the French cohort did not identify a significant difference in transmission rate in women with a delivery HIV-1RNA <400 copies/ml by whether or not they received peripartum zidovudine (0% vs 0.6%, p=1)[73]. Conversely there was a significant benefit in administering intravenous zidovudine where the delivery HIV RNA was >/=10,000 copies/ml (22.7% vs 5.3%, p=0.009). On logistic regression analysis no

intrapartum prophylaxis was associated with an increased risk of transmission (OR 4.72, 95% CI 1.42 – 15.71, p=0.011) in women with a delivery viral load of >/= 10,000 copies/ml.

In the absence of definitive data on the need for intravenous zidovudine in women who have been on HAART for at least 4 weeks with a HIV viral load of <50 copies/ml, it is reasonable to continue with this recommendation, particularly in situations where the membranes have spontaneously ruptured or have been artificially ruptured to induce or augment labour. For women being delivered by elective caesarean section, intravenous zidovudine should be started approximately 4 hours before the anticipated delivery time.

Transmission risk increases the longer the membranes are ruptured. Therefore it is best to avoid artificial rupture of the membranes where possible in HIV infected women in labour. Triple antiretroviral therapy should be given to the neonate if the membranes have been ruptured for more than 12 hours. Interventions that could be associated with a risk of transmission in labour, namely fetal scalp electrodes and fetal blood sampling are best avoided. Where an instrumental delivery is deemed necessary, consideration should be given to triple neonatal antiretroviral therapy if there is any evidence of trauma with breach of the neonate skin at delivery.

3 (c) Elective Caesarean section

When is an elective caesarean section of benefit?

In the pre HAART era, elective caesarean section was shown to significantly reduce transmission in women not on antiretroviral therapy and in women on zidovudine monotherapy[79] [80] [81]. Now that transmission rates are low it has been estimated that a randomised trial would require over 6000 mother-child pairs in each arm to

determine if there was an additional transmission benefit associated with elective caesarean section in the setting of suppressive HAART[82] . Recent data from the UK and Ireland of over 5000 mother child pairs failed to demonstrate a difference in transmission rates between women on HAART who were delivered vaginally or by elective caesarean section[17]. Similarly the French cohort did not show an additional benefit associated with elective caesarean section in women with a delivery viral load of <400 copies/ml (0.4% for elective caesarean section versus 0.5% for other modes of delivery, p = 0.35)[73].

Elective caesarean section is indicated for women receiving zidovudine monotherapy. For women on HAART, the optimum duration of therapy before delivery and the delivery viral load threshold below which elective caesarean section is unlikely to be of benefit is not known. In the recent report from the UK and Ireland, the overall transmission rate in women who received at least 14 days of any type of antiretroviral therapy was 0.8% and the risk of transmission in women on HAART declined with each additional week of antiretroviral therapy (AOR = 0.90 per week of HAART, p=0.007)[17]. Interestingly in the French cohort[73], the proportion of in utero transmissions was higher in women transmitting with low viral loads at delivery (42% with delivery viral load of <400 copies/ml; 43% for delivery viral load of 400 – 9999 copies/ml and 21% for delivery viral load of >10,000copies/ml), suggesting that in this circumstance an elective caesarean section may not be of additional benefit as transmission has already occurred. The previous guidelines recommended that women be offered an elective caesarean section if they had not received at least 4 weeks of antiretroviral therapy and if the 36 week viral load is >1000 copies/ml. Cautiously extrapolating from the UK and Ireland and French cohort data it may be reasonable to reduce the minimum requirement for antiretroviral therapy from 4 weeks to 2 weeks but reduce the viral load threshold for elective caesarean section from <1000 copies/ml to <400 copies/ml. This position would place the Irish

guidelines between that taken in the current British (elective caesarean section for all if viral load >50 copies/ml at 36 weeks) and US (elective caesarean section if viral load >1000copies/ml at 36 weeks) guidelines for management of HIV in pregnancy. [KB1]

Is an elective caesarean section safe in HIV infected women?

Higher morbidity rates following delivery have been reported in HIV infected women compared to the general population[83 84]. One case control study did not identify an increased rate of postoperative morbidity in HIV infected women undergoing spinal anaesthesia compared to the general population[85]. Many studies describe more postnatal morbidity in HIV infected women following abdominal delivery versus vaginal delivery[86 87]. Within the study from the Women and Infants Transmission Study[81] there was a decrease in all postnatal morbidity over time, most likely reflecting improved maternal health and routine use of prophylactic perioperative antibiotics. A recently published study suggests that elective Caesarean section is associated with similar postnatal morbidity to vaginal delivery (OR 1.16, 95% CI, 0.5 – 2.7)[88]. It is noteworthy that many of these studies have been carried out in very different populations at different times and extrapolation to the current Irish situation must be made with caution. Whilst most of the reported morbidity is minor, postnatal morbidity must remain a consideration in mode of delivery decision making in HIV infected women. This is of particular relevance at a time when the additional benefit of elective caesarean section in the setting of suppressive HAART is unknown. Furthermore in an environment where more and more asylum seekers are being repatriated, it is important to recognise that women who have a scar on their uterus may be at greater risk in a future pregnancy, without access to antenatal care.

Timing of elective caesarean section

In the general obstetric population, elective caesarean section is scheduled for 39 completed weeks in recognition of the reduced risk of transient tachypnea of the newborn associated with an additional week in utero[89]. Current British and US guidelines recommend that where an elective caesarean section is being performed to reduce the risk of transmission of HIV that it be performed at 38 rather than 39 weeks in order to avoid spontaneous rupture of the membranes or labour in a woman scheduled for a caesarean section. There is an association between antiretroviral therapy and earlier onset of labour with a concern that longer exposure to more complex antiretroviral therapy increases the risk of premature delivery (see section 2 (b) maternal antiretroviral therapy – *adverse effects pregnancy length*). The experience at the GUIDE clinic has been that there was not an increased risk of prematurity with more complex antiretroviral therapy (none, one, two or three drugs) and the median gestational age at delivery in 242 pregnancies between 1996 and 2003 was 39 weeks. [KB2]This supports the previous recommendation for scheduling of elective caesarean sections for 39 weeks rather than 38 weeks in the Irish setting. In situations where an elective caesarean section is anticipated and where there is a concern that a woman may go into spontaneous labour or have spontaneous rupture of the membranes between 38 and 39 weeks it would be prudent to schedule delivery for 38 weeks.

4. Infant care

4 (a) General

HIV exposed infants should in general be managed as other infants. HIV exposure per se is not an indication for admission to a special care baby unit. Infants should be bathed before leaving the labour ward to remove any maternal blood. Consideration should be given to the need for Hepatitis B vaccination and Hepatitis B immunoglobulin (if the mother is Hepatitis B surface antigen positive) and any other maternal coinfections that might impact on infant management (hepatitis C, syphilis,

cytomegalovirus, toxoplasmosis, tuberculosis or other STI's). Infants should commence antiretroviral therapy as soon as possible following delivery (see below)

4 (a) Infant Feeding

Although breast milk is the ideal nutritional source for infants, breastfeeding is associated with a 10 – 15 % increased risk of HIV transmission. The risk appears greatest in the first 6 – 8 weeks post partum but continues throughout all of the time of breastfeeding. Seroconversion during breastfeeding is associated with a particularly high transmission risk. Studies have shown that mixed feeding is associated with the significantly higher transmission rate compared with exclusive breast or formula feeding[90] [91]. However in some settings, the benefit of preventing breast feeding associated HIV transmission is effectively negated by the excess mortality in children undergoing replacement feeding. In resource constrained countries this additional risk of breastfeeding has to be balanced against the very significant morbidity that can be associated with replacement feeding[92]. Feeding recommendations for infants born to HIV infected will therefore vary depending on the local setting. Feeding recommendations will therefore vary depending on the local setting. Studies are ongoing to determine the impact of either maternal or infant antiretroviral therapy in preventing breastfeeding associated transmission[93] [94].Pending the results of these studies, the recommendation must stand that in Ireland, as in other developed countries, where there are safe alternative options, infants of HIV positive mothers should not be breast fed.

4 (b) Infant antiretroviral therapy

After delivery, infants commence ART as soon as possible, at least within 4 hours of birth and continue for 4 weeks. The regimen chosen is determined by maternal antiretroviral exposure and HIV viral load close to delivery. In general infants born to mothers who are at low risk for transmission receive zidovudine syrup as

monotherapy. This is administered twice daily for four weeks. Triple ART, usually with zidovudine, lamivudine and nevirapine, is recommended for infants at higher risk of transmission i.e.

- where the mother has received <4 weeks of combination ART
- where there have been concerns for maternal adherence to antiretroviral therapy
- where the maternal HIV viral load is >1000 copies/ml prior to delivery
- where there has been ruptured membranes for more than 12 hours
- or where other factors associated with increased risk of transmission are identified

Infants who are unable to tolerate zidovudine syrup orally should receive intravenous zidovudine. For infants prescribed triple therapy, lamivudine is given orally at the same time as zidovudine for four weeks. Nevirapine is the third agent in common use for neonatal triple antiretroviral therapy. The timing of neonatal nevirapine administration depends of whether or not the mother has received nevirapine. If the mother has not been prescribed nevirapine a first dose is given to the infant as soon as possible following delivery and a second dose given 24 – 48 hours later. If the mother has received nevirapine the first neonatal dose is given at 48 to 72 hours with a second dose the following day. Two doses only of nevirapine are used. The efficacy of the programme has been demonstrated with a vertical transmission rate of just 1% in 874 deliveries in Ireland over the years 1999 to 2007 inclusive. In selected situations, e.g. where there is evidence of maternal antiretroviral resistance, alternative neonatal antiretroviral regimens may be used.

Although the data is limited, there is evidence to support initiation of antiretroviral therapy as post exposure prophylaxis for HIV exposed infants even where mothers have received no antiretroviral therapy[95] [96] . Thus infants of women diagnosed at

delivery or in the immediate (<72hrs) postpartum period should receive triple ARV therapy as post exposure prophylaxis. The value of ARV in preventing HIV transmission if > 72 hours post delivery had elapsed is not proven. In this situation the emphasis should be on avoiding breast feeding and early HIV testing for infection in the infant.

4 (c) Monitoring for toxicity

Anticipated side effects associated with zidovudine include anaemia and neutropenia which usually resolve by 12 weeks of age. A full blood count should be obtained on Day 1, at 2, 6 and 12 weeks of age. Liver transaminases should also be checked post delivery. Although asymptomatic hyperlactatemia has been reported in infants exposed to ARV therapy in utero, routine monitoring of lactate levels is not indicated.

4 (d) Infant vaccination and prophylaxis

BCG vaccine should be deferred until HIV PCR test results are available. Infants with negative HIV PCR tests at birth, 2 and 6 weeks of age can proceed to BCG vaccination.

HIV exposed infants should receive all of the routine primary immunisations including the hexavalent (6 in 1) vaccine (DaPT/HIB/HBV/IPV), meningococcal C, Prevnar and MMR vaccines.

As outlined earlier infants born to hepatitis B surface antigen positive mothers should receive their first dose of hepatitis B vaccine together with hepatitis B immunoglobulin as soon as possible following delivery. Further doses of HBV vaccine will be given as components of the hexavalent vaccine at 2, 4, and 6 months of age. Testing for Hepatitis B surface antigen (to exclude infection) and hepatitis B surface antibody (to ensure adequacy of protective response) should be carried out between 8 and 12 months of age.

PCP prophylaxis

Cotrimoxazole, 240mg, given once daily every Monday, Wednesday and Friday should be initiated at 6 weeks of age for:-

- All HIV infected infants
- All HIV exposed infants considered at higher risk of infection (ie all infants who received triple ARV prophylaxis)

PCP prophylaxis is not required for HIV exposed infants born to mothers who were receiving HAART and who were virally suppressed at delivery.

4 (e) Testing for HIV infection

Cord blood sampling should be avoided

Blood for HIV PCR testing should be obtained on Day 1, week 2, 6, and 12 and 6 months of age. HIV antibody testing is carried out at 18 months of age.

An infant is considered "uninfected" if HIV is not detected by PCR testing of two blood samples, separated at least a 2 week interval, the second of which is at of after 3 months of age. The uninfected status is confirmed by testing for HIV antibody at 18 months of age, by which time seroreversion or loss of maternal antibody will generally have occurred. With the improved sensitivity of the new generations of HIV antibody test, on occasion, it is possible to detect some faint residual antibody at 18 months of age but this will has disappeared if testing is repeated at two years.

5. Scenarios

See Table 5

5 (a) Women on antiretroviral therapy at conception

In general women on suppressive HAART should not make any changes to their antiretroviral therapy during pregnancy.

It may be reasonable to continue efavirenz in pregnancy, particularly if the physician is not aware of the pregnancy until after the neural tube has closed and if a change in

antiretroviral therapy could lead to loss of virological control or exposure to other antiretrovirals with less data on teratogenicity. Efavirenz should be avoided in women of child bearing potential who are not using effective contraception. Recently presented audits from both London and Dublin demonstrated extremely poor documentation of contraception in women prescribed efavirenz, highlighting the need to include discussion regarding family planning in women of child bearing potential being prescribed antiretroviral therapy, particularly efavirenz[97] [98]

Women on a non-suppressive regimen should have genotypic resistance testing performed to guide further antiretroviral regimens with a view to achieving an undetectable viral load as soon as possible.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

5 (b) Women presenting before fetal viability

Baseline CD4 count <200 x 106/L, regardless of HIV viral load

Prophylaxis against Pneumocystis jiroveci (formerly pneumocystis carinii, PCP) infection should be initiated as soon as possible. Where co-trimoxazole is used consider co-administration of folic acid 5mg once daily to reduce theoretical risk of a neural tube defect secondary to inhibition of dihydrofolate reductase with co-trimoxazole. Antiretroviral therapy is indicated for maternal health and should be initiated as soon as possible after the first trimester. Baseline genotypic resistance testing should be performed to guide antiretroviral choices. Given the wealth of experience with zidovudine in pregnancy it should be included in antenatal

antiretroviral regimens wherever possible. A nevirapine based regimen may be an option in women with a baseline CD4 count of <250 x 10^6/L.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

Baseline CD4 count >200 x 10^6/L but <350 x 10^6/L

For some women in this situation the CD4 count may be spuriously low because of the physiological changes associated in pregnancy and for others there will be a clear need for antiretroviral therapy for maternal well being. Where the CD4 count is deemed spuriously low because of pregnancy, initiation of antiretroviral therapy can be delayed to between 20 and 24 weeks. Where there is a need for antiretroviral therapy for maternal well being, antiretroviral therapy should be initiated as soon as possible after the first trimester.

Baseline genotypic resistance testing should guide antiretroviral choices.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

Baseline CD4 count >350 x 10^6/L baseline HIV viral load <5000 copies/ml

In general women with a baseline CD4 count of >350 x 10^6/L will not require antiretroviral therapy for their own health and can initiate therapy between 20 and 24 weeks. Baseline genotypic resistance testing should guide antiretroviral choices. If the baseline HIV viral load is <5000 copies/ml women may opt for the choice

between zidovudine monotherapy and an elective caesarean section or HAART with a view to awaiting spontaneous onset of labour.

All women opting for zidovudine monotherapy should be delivered by elective caesarean section. In women opting for HAART final recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery (see Table 5.3).

Baseline CD4 count >350 x 10^6/L baseline HIV viral load >5000 copies/ml

In general women with a baseline CD4 count of >350 x 10^6/L will not require antiretroviral therapy for their own health but because the baseline HIV viral load is >5000 copies/ml, HAART is recommended and can be initiated between 20 and 24 weeks.

Baseline genotypic resistance testing should guide antiretroviral choices.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

5 (c) Women presenting after fetal viability

Women presenting for antenatal care after fetal viability should have their HIV test processed as quickly as possible. Where the initial test is positive it may be prudent to refer women for adult HIV assessment without waiting for the results of a second confirmatory HIV test.

Baseline CD4 count <200 x 106/L, regardless of HIV viral load

Prophylaxis against Pneumocystis jiroveci (formerly pneumocystis carinii, PCP) infection and HAART should be initiated as soon as possible. It may not be possible to wait for results of baseline genotypic resistance testing before initiating therapy and choices should be guided by potential previous antiretroviral exposure and likelihood of transmitted resistance at baseline. A nevirapine based regimen may be a prudent choice, particularly with presentation in the third trimester given its rapid onset of action and effective transfer across the placenta.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by duration of antiretroviral therapy, HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

Baseline CD4 count >200 x 10^6/L but <350 x 10^6/L, regardless of HIV viral load

For some women in this situation the CD4 count may be spuriously low because of the physiological changes associated in pregnancy and for others there will be a clear need for antiretroviral therapy for maternal well being. Regardless of maternal need HAART should be initiated as soon as possible in all women presenting for the first time after fetal viability. It may not be possible to wait for results of baseline genotypic resistance testing before initiating therapy and choices should be guided by potential previous antiretroviral exposure and likelihood of transmitted resistance at baseline.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by duration of antiretroviral therapy, HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

The decision to continue or discontinue HAART beyond pregnancy will be based on individual maternal need.

Baseline CD4 count >350 x 10^6/L, regardless of baseline HIV viral load

In general women with a baseline CD4 count of >350 x 10^6/L will not require antiretroviral therapy for their own health but because they have presented after fetal viability, HAART is recommended and should be initiated as soon as possible. It may not be possible to wait for results of baseline genotypic resistance testing before initiating therapy and choices should be guided by potential previous antiretroviral exposure and likelihood of transmitted resistance at baseline.

Recommendations regarding the mode of delivery and neonatal antiretrovirals will be determined by duration of antiretroviral therapy, HIV viral load at 36 weeks and duration of ruptured membranes prior to delivery.

5 (d) Women presenting in premature labour or threatened premature labour

In the HAART era, prematurity remains an independent risk for vertical transmission of HIV. Management of the HIV positive woman presenting in premature labour or threatened premature labour needs to be individualised, balancing the morbidity (and mortality) associated with prematurity with the risk for transmission of HIV and requires multidisciplinary consultation. Genital tract infection, which may have led to premature labour, should be identified and treated.

On effective HAART <34/40

Maternal steroids should be administered to promote fetal lung maturity and tocolysis may be indicated to allow steroids to work. Maternal antiretroviral therapy should be continued and an urgent HIV viral load test sent. A single dose of nevirapine given to the mother could be considered to pre-load the neonate with nevirapine. If tocolysis has successfully delayed delivery, consideration should be given to caesarean

section once steroids have taken effect, depending on the estimated fetal weight and gestational age and clinical scenario.

Neonatal triple antiretroviral therapy should be administered where the membranes have been ruptured for more than 12 hours before delivery or the urgent HIV viral load is >400 copies/ml but may be limited by unsuitability of some premature neonates for enteral therapy.

On effective HAART >34/40

Maternal antiretroviral therapy should be continued and an urgent HIV viral load test sent. Intravenous zidovudine should be commenced and if delivery is not imminent, particularly where the membranes have ruptured, consideration should be given to delivery by caesarean section. A single dose of nevirapine given to the mother should be considered to pre-load the neonate with nevirapine.

Neonatal triple antiretroviral therapy should be administered where the membranes have been ruptured for more than 12 hours before delivery or the urgent HIV viral load is >400 copies/ml but may be limited by unsuitability of some premature neonates for enteral therapy.

Failing HAART or not on antiretroviral therapy <34/40

Maternal steroids should be administered to promote fetal lung maturity and tocolysis may be used to allow the steroids to work. Intravenous zidovudine should be administered as soon as possible. Maternal HAART should be commenced or optimised (in the setting of a failing regimen) as soon as possible with baseline bloods sent for urgent HIV viral load and CD4 count. Where the CD4 count is known to be $<250 \times 10^6$/L and there is no history of NNRTI resistance a nevirapine based regimen should be considered given rapid onset of action and effective placental transfer. Where the CD4 count if known to be $>250 \times 10^6$/L or there is known NNRTI resistance a protease inhibitor based regimen should be initiated as soon as possible

and there may be value in administering a single dose of nevirapine to the mother even in the setting of previously documented NNRTI resistance. If tocolysis has successfully delayed delivery, consideration should be given to caesarean section once steroids have taken effect, depending on the estimated fetal weight and gestational age and clinical scenario.

Neonatal triple antiretroviral therapy should be administered to the neonate but may be limited by unsuitability of some premature neonates for enteral therapy.

Failing HAART or not on antiretroviral therapy >34/40

An urgent HIV viral load (and genotypic resistance testing) should be sent and for newly diagnosed women an urgent CD4 count should be sent. Intravenous zidovudine should be administered as soon as possible. Where time permits maternal HAART should be commenced or optimised (in the setting of a failing regimen) as soon as possible. Where the CD4 count is known to be $<250 \times 10^6$/L and there is no history of NNRTI resistance a nevirapine based regimen should be considered given rapid onset of action and effective placental transfer. Where the CD4 count if known to be $>250 \times 10^6$/L or there is known NNRTI resistance a protease inhibitor based regimen should be initiated and there may be value in administering a single dose of nevirapine to the mother even in the setting of previously documented NNRTI resistance. If delivery is not imminent, consideration should be given to delivery by caesarean section, particularly if the membranes have ruptured.

Neonatal triple antiretroviral therapy should be administered to the neonate but may be limited by unsuitability of some premature neonates for enteral therapy.

5 (e) Pre-labour rupture of membranes

The risk of transmission increases with the duration of membrane rupture. This has

been clearly demonstrated for women in active labour but definitive studies on women with premature rupture of the membranes (i.e. rupture of the membranes without onset of labour) are not available. It is advisable, however, to minimise duration of membrane rupture i.e. expedite delivery unless the risk to the infant from premature delivery outweighs the risk of HIV acquisition. Genital tract infection should be identified and treated.

<34/40 on effective HAART

Maternal steroids should be administered to promote fetal lung maturity. Maternal antiretroviral therapy should be continued and an urgent HIV viral load test sent. Consideration should be given to caesarean section once steroids have taken effect, depending on the estimated fetal weight and gestational age and clinical scenario. Intravenous zidovudine should be administered around delivery and a single dose of nevirapine given to the mother should be considered to pre-load the neonate with nevirapine.

Triple neonatal antiretroviral therapy should be administered where the membranes have been ruptured for more than 12 hours before delivery or the urgent HIV viral load is >400 copies/ml but may be limited by unsuitability of some premature neonates for enteral therapy.

<34/40 failing HAART or not on antiretroviral therapy

Maternal steroids should be administered to promote fetal lung maturity. Intravenous zidovudine should be administered as soon as possible. Maternal HAART should be initiated or optimised (in the setting of a failing regimen) as soon as possible. Where the CD4 count is known to be <250 x 10^6/L and there is no history of NNRTI resistance a nevirapine based regimen should be considered given rapid onset of action and effective placental transfer. Where the CD4 count if known to be >250 x 10^6/L or there is known NNRTI resistance a protease inhibitor based regimen should

be initiated and there may be value in administering a single dose of nevirapine to the mother even in the setting of previously documented NNRTI resistance. Consideration should be given to caesarean section once steroids have taken effect, depending on the estimated fetal weight and gestational age and the clinical scenario.

Triple antiretroviral therapy should be administered to the neonate but may be limited by unsuitability of some premature neonates for enteral therapy.

>34/40 on effective HAART

Maternal antiretroviral therapy should be continued and an urgent HIV viral load test sent. Intravenous zidovudine should be commenced and delivery should be expedited by caesarean section or induction of labour.

Neonatal triple antiretroviral therapy should be administered where the membranes have been ruptured for more than 12 hours before delivery or the urgent HIV viral load is >400 copies/ml but may be limited by unsuitability of some premature neonates for enteral therapy.

>34/40 failing HAART or not on antiretroviral therapy

An urgent HIV viral load (and genotypic resistance testing) should be sent and for newly diagnosed women an urgent CD4 count should be sent. Intravenous zidovudine should be administered as soon as possible. Where time permits maternal HAART should be commenced or optimised (in the setting of a failing regimen) as soon as possible. Where the CD4 count is known to be $<250 \times 10^6$/L and there is no history of NNRTI resistance a nevirapine based regimen should be considered given rapid onset of action and effective placental transfer. Where the CD4 count if known to be $>250 \times 10^6$/L or there is known NNRTI resistance a protease inhibitor based regimen should be initiated and there may be value in administering a single dose of nevirapine to the mother even in the setting of

previously documented NNRTI resistance. If delivery is not imminent, consideration should be given to delivery by caesarean section, particularly if the membranes have ruptured.

Neonatal triple antiretroviral therapy should be administered to the neonate but may be limited by unsuitability of some premature neonates for enteral therapy.

5 (f) Women presenting in labour at term

Labour may represent the first opportunity to implement measures to reduce transmission of HIV in two circumstances: either a woman presents unbooked in labour and has an urgent HIV test performed or where a positive result was identified earlier in the pregnancy but the woman did not attend for the result. Where a woman has defaulted from antenatal care and is thus unaware of her HIV status, the delivery suite and neonatal staff should be aware of the situation and a proposed management plan should be in place before the estimated due date for the woman. Intravenous zidovudine should be commenced as soon as possible and consideration given to a single dose of nevirapine to the mother. If the membranes have been ruptured every effort should be made to deliver as quickly as possible. The neonate should be commenced on triple antiretroviral therapy as soon as possible after birth. The mother's HIV status should be confirmed as soon as possible with early referral to an adult HIV service.

5 (g) Women diagnosed post partum

Women who are delivered before admission to hospital or shortly after admission, should have their HIV test sent urgently to ensure that there is an opportunity to initiate neonatal triple antiretroviral therapy as soon as possible and before 72 hours of life. The mother's HIV status should be confirmed as soon as possible with early referral to an adult HIV service.

5 (h) Women refusing interventions to reduce MTCT

Where women refuse to engage in care it is important that they understand and appreciate the benefits associated with interventions to reduce MTCT. It is important to give culturally competent verbal and written information with access to an interpretive service when required. Where women have refused interventions the Irish Courts have made these infants a ward of court to ensure administration of antiretroviral therapy and avoidance of breastfeeding. It is prudent to have a management plan in place well in advance of the anticipated date of delivery.

6. Conclusion

The overall management of HIV in pregnancy requires a multidisciplinary approach between adult and paediatric HIV specialists and obstetric services. The changing demographics of the population in Ireland provide medical, social and cultural challenges for the management of HIV. Equally, the management of subsequent pregnancies in mothers who have previously received short term antiretrovirals to reduce MTCT adds further complexities to their management.

While these guidelines can be used as a model for the management of HIV in pregnancy, ultimately each patient is managed individually, and a unique antenatal, intrapartum, and postpartum path is determined for each patient

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