HIV treatment in pregnancy

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Abstract

Almost 25 years since antiretroviral therapy (ART) was first shown to prevent mother-to-child transmission, 76% of pregnant women living with HIV receive ART annually, amounting to over 1 million women). This reflects recent successes in universal ART scale-up in low and middle-income countries. Alongside unprecedented ART-related benefits to maternal and child health, challenges remain with regard to ART adherence, retention in care and uneven access to ART. Implementation research is ongoing to understand and address obstacles leading to loss-to-follow-up. Biological mechanisms underlying observed associations between antenatal ART and adverse pregnancy and birth outcomes are incompletely understood, with further research needed alongside strengthening of systems to assess safety of antiretroviral drugs for the mother and exposed child. In the treat all era, as duration on treatment and ART options expand, pregnant women will remain a priority population for treatment optimisation, to promote their health and that of their ART-exposed child.

Introduction

Of 34.5 million adults living with HIV globally in 2016, 15.3 million (44%) were women of reproductive age; thus, nearly half of the population on or in need of antiretroviral therapy (ART) may become pregnant[1]. Provision of ART to women prior to and during pregnancy and breastfeeding prevents mother-to-child transmission (MTCT) and improves the health and survival of the mother[2], which itself benefits the health of her children[3]. Treatment of pregnant women living with HIV is key to achievement of overall global health goals (including Sustainable Development Goal 3 and UNAIDS 90-90-90) as well as those relating specifically to maternal and child health, notably the UNAIDS Super Fast-Track Target of fewer than 20,000 new paediatric HIV infections by 2020.

Pregnant women are considered a special population from a treatment perspective, largely due to the opportunity to prevent MTCT with antiretroviral drugs and the need to consider safety for the woman herself and the exposed foetus/child. Pregnancy was the first situation where "treatment as prevention" was applied programmatically, nearly 25 years ago, following the ACTG 076 randomised clinical trial (RCT) results in 1994[4]. Thus, prior to the 2015 WHO "Treat All" recommendation, pregnancy has been a period where provision of ART to reduce MTCT has occurred in women not needing treatment for their own health. Pharmacokinetics (PK) is a further consideration: physiological changes in pregnancy (e.g. blood volume expansion; gastrointestinal, enzymatic and hormonal alterations) may alter PK properties of antiretroviral drugs, and can lead to altered absorption, reduced protein binding and increased elimination[5].

Preventing mother-to-child transmission of HIV-1

Maternal HIV RNA load is the foremost risk factor for MTCT of HIV, and suppressive ART in pregnancy and breastfeeding thus the principal intervention to prevent transmission [6-8]. Without any maternal ART 15-30% of formula-fed babies will become infected and up to 45% of those breastfed[9]. Rapid adoption of Zidovudine (ZDV) monotherapy (given antenatally, intrapartum and to the neonate) in high-income countries (HICs) after the ACTG 076 trial, which found a 68% reduced MTCT[4], was followed by clinical trials in lower and middle income countries (LMICs), initially assessing abbreviated, simpler antiretroviral regimens and then combination ART prophylaxis[10]. Subsequent randomized and observational data showed that ZDV-monotherapy was inferior to ART in preventing MTCT[11,12]. WHO guidelines for treatment of HIV in pregnant women have evolved in the context of accumulating evidence of the effectiveness and safety of ART, changing drug

affordability and the need to simplify treatment programmes for programmatic scale-up[2]. Key milestones are presented in Figure 1.

In HICs, implementation of ART has reduced MTCT rates to <1-2% since 2000[13,14] with extremely low rates being reported among women conceiving on ART, e.g. 0.2% in France in 2000-10[15] and on a population level, e.g. 0.27% in the UK in 2012-2014[16]. In LMICs, MTCT rates of <5% have been achieved in clinical trials[11,12,17] and four Global Plan priority countries where women primarily breastfeed (South Africa, Uganda, Swaziland and Namibia; data up to 2016)[9]. Expanding coverage of ART in pregnancy in LMICs from 50% in 2010 to 75% in 2016 led to a 47% reduction in new paediatric HIV infections[1].

PMTCT services also play an important role in primary prevention for pregnant women who screen negative, particularly for those identified as being at high risk for HIV acquisition. For HIV-negative women in sero-discordant partnerships, the peri-conception period and pregnancy may be a time of heightened HIV acquisition risk due to reduced use of barrier protection and biological factors[18], while risk of MTCT is elevated if incident maternal HIV infection does occur due to high HIV RNA load and lost opportunities for ARV prophylaxis[19]. Pre-exposure prophylaxis (PrEP)[20] is one strategy of several that can be considered to support safer conception in serodiscordant couples, alongside a range of behavioural and biomedical interventions including fully suppressive treatment of partner(s) HIV infection[21]; current evidence, albeit limited, supports the safety of PrEP in the peri-conception period and during pregnancy[22,23].

ART coverage in pregnancy: temporal trends

In HICs, where antenatal HIV prevalence is low compared with high prevalence LMIC settings, the vast majority of diagnosed pregnant women receive ART. This reflects high coverage of antenatal HIV screening alongside the increasing proportion of women already on ART at conception[16,24]. For example, in the UK and Ireland, 85% of pregnant women delivering in 2012-2014 were diagnosed before conception and 60% conceived on ART[16]. Among the minority of women starting ART during pregnancy, ART is being started progressively earlier, for example, at a median of 22 weeks in a European pooled analysis of more than 7000 deliveries in 2008-14[25].

Around 90% of the annual 1.4 million pregnancies in HIV-positive women occur in sub-Saharan Africa (SSA), where ART scale-up among pregnant women was initially slow but with rapid acceleration in recent years (Figure 1). However, progress has been uneven, with coverage of 89% in Eastern and Southern Africa, 50% in West and Central Africa and 20% in North Africa and the Middle East[1]. The 2015 WHO recommendation of lifelong ART for all those diagnosed with HIV, regardless of CD4 count, had been adopted by 83% of LMICs and 94% of Fast Track countries by the end of 2017[26]. This has resulted in a rapid rise of women on ART at conception in many LMICs, such as Botswana, where 48% were on ART at conception in 2014 compared to only 19% in 2009[27].

ART in pregnant women: challenges in uptake, adherence and engagement

Experience in the Option B+ era has highlighted the multiple challenges in delivering and sustaining ART, on an individual and programmatic level, for women in pregnancy and postnatally[24,28-36]. Multiple individual, community, health system and other structural factors may positively or negatively influence access to HIV testing and treatment, adherence to ART and engagement in HIV care in pregnant women. Key barriers for initiation of and adherence to ART are outlined in Table 1, some of which are context-dependent and many of which are not unique to pregnancy. Of note, some barriers may result in delay in ART start rather than non-initiation, or gaps in treatment; these are of importance in the context of pregnancy where there is a limited time to achieve an undetectable HIV RNA level prior to delivery.

Malawi was the innovator of the Option B+ approach in 2011 and thus the first country experiencing the related challenges of adherence and retention; a recent analysis showed that loss to follow-up (LTFU) was highest in the first year of ART, with 77% of women retained in care at 12 months after initiation, and that early signs of poor adherence were markers of subsequent LTFU[33]. A systematic review of studies investigating retention in care during pregnancy and the postnatal period in Africa

during the Option B+ era (with more than 60,000 women included), recently reported a pooled estimate of 6 month retention of 73% [37]; of note, half of the studies were from Malawi and initiation of ART on the same day that HIV diagnosis took place was a risk factor for LTFU.

Various delivery models for Option B+ have been assessed, alongside implementation research to understand and address obstacles leading to LTFU[28,34]; interventions include use of mentor mothers, lay counsellors, home visits, adherence groups, mobile health (mHealth) reminders, including SMS messages, and quality improvement strategies[38]. The MoMent Study in Nigeria showed significant benefits of a mentor mother intervention for retention in care (62% at six months post-partum versus 25% in controls) and viral load suppression (nearly five times more common at six months post-partum in women with mentor mother support)[39]. In Malawi, the PURE Study (a cluster RCT) showed that community- or facility-based expert peer support resulted in significantly greater retention in care at 24 months post-ART initiation[40]. In Mozambique, a stepped wedge cluster RCT evaluated workflow modifications and active patient tracking (including improved patient flow, continuous quality improvement, enhanced counselling and adherence committees) to promote Option B+ retention: 71% of women were retained for 30 day refills in the intervention period versus 52% in the control period, but by 90 days only around 40% of women were retained in both groups[41].

Adherence is also critical in pregnancy, as missed ART may lead to virological failure, increased risk of MTCT and potential transmission of drug resistant virus to the baby [42,43]. Programmatic changes to address adherence in pregnancy include a move to simplify ART with once-daily and fixed-dose combination regimens which has been associated with better adherence. However, studies from Europe have reported that 14-20% of pregnant women conceiving on ART have an unsuppressed viral load, with younger women, those with two or more children already and those diagnosed for longer periods at increased risk[44,45]. A recent study from rural South Africa reported that among pregnant women who had been on ART for ≥6 months prior to conception, 18% had detectable viral loads (>50 copies/ml) around this time[46], with consistent findings from an earlier Cape Town study where 22% of women conceiving on ART had viral loads >50 copies/ml[47]. Even with multiple interventions ART adherence (≥90%, based on pharmacy refills) was only 23% for all women over a 90 day period in the Mozambique cluster RCT referenced above[41]. These findings underscore the need for optimised regimens as well as appropriate interventions to maximize adherence before, during and after pregnancy as well as scale-up of viral load monitoring in pregnancy[2].

Issues around postnatal LTFU and ART adherence are also experienced in both low/middle income and resource-rich settings. In a systematic review and meta-analysis of >20,000 pregnant and

postnatal women with HIV from 51 studies, no difference in adherence levels according to setting (high versus low income) was found, with a pooled estimate of 74% of pregnant women having ART adherence above 80% ("adequate")[32]. In a recent Swiss study, 34% of women did not return for an HIV care visit until 6-12 months after delivery and 12% were LTFU for >12 months[48], whilst a single-site study in the United States (US) reported only 39% of women being engaged in care one year post-delivery[49]. Disengagement from HIV care means interruption of ART, which has important implications for maternal health, for MTCT (for current and future infants) and horizontal transmission, while similar problems exist for those remaining in care postnatally but with deteriorating ART adherence; among 523 women starting ART during pregnancy in South Africa as Option B+ and achieving viral suppression during follow-up, there was an 11% increased incidence of subsequent viremia for each additional month postpartum[50].

Optimised regimens and newer antiretrovirals

WHO guidelines currently recommend a fixed dose combination of Tenofovir disoproxil fumarate (TDF) with either Lamivudine (3TC) or Emtricitabine (FTC) plus the non-nucleoside reverse transcriptase inhibitor (NNRTI) Efavirenz (EFV) as first-line therapy[2]. In 2016, new alternative options for ART for non-pregnant adults were included – with Dolutegravir (DTG), an integrase inhibitor, and EFV 400mg recommended for first line therapy and the Ritonavir (RTV, r) boosted protease inhibitor (PI) Darunavir (DRV/r) and Raltegravir (RAL), an integrase inhibitor, recommended for second or third line therapy, so called "optimised antiretroviral regimens"[2]. The rationale for this transition is to increase use of regimens that are highly effective, have low toxicity and high genetic barrier to resistance, few drug-drug interactions, taking into account key optimisation criteria including simplification, harmonization and cost, alongside safety considerations for special populations including pregnant women.

WHO does not yet recommend DTG within preferred first-line regimens in pregnancy because of a lack of safety data and a recent concern about birth defects (see later section)[51]. While more than 20 countries have updated their national guidelines to include DTG as a first-line option, with many adopting a phased transition, most are not recommending DTG for pregnant women or women planning to conceive. The exception is Botswana, where DTG-based ART has been rolled-out to all HIV-infected adults including pregnant women. Nationwide implementation of TDF/FTC/DTG for all new initiations was completed rapidly over a few months 2016 and there are plans to transition older regimens to DTG pending further data on birth defects.

In HICs, recommended or preferred options (particularly for third agents) for initial regimens for ART-naïve pregnant women vary somewhat and guidelines are frequently updated. Currently, the European AIDS Clinical Society (EACS) guidelines recommends RTV-boosted Atazanavir (ATV)/r as boosted PI, whilst the US and UK guidelines also recommend DRV/r. For integrase inhibitors, DTG is a recommended/preferred option in the UK and EACS guidelines, but remains an alternative option in the US[52-54].

Today, the majority of pregnant women in HICs are already on ART at conception; guidelines recommend review of their ART regimen, but it is generally recommended that a woman remains on her existing regimen if there are no tolerability issues and she has suppressed viral load[52-54].

Table 2 provides information on preclinical data, trans-placental passage, PK, clinical studies and the summary of product characteristics (SmPC) for four recently authorized antiretrovirals: Rilpivirine (RPV), a NNRTI authorized in 2011; Cobicistat (COBI, c), a booster authorized in 2013; DTG, authorized in 2014 and Tenofovir Alafenamide (TAF), a NRTI authorized in 2015. Of note, the SmPCs regarding pregnancy are mostly based on preclinical findings, with limited data on human pregnancy, mainly recommending avoiding use in pregnancy. However, real-world evidence shows significant increased use of these drugs over time, largely reflecting preconception initiation. For example, in the UK and Ireland National Study of HIV in Pregnancy and Childhood, exposure to any combination containing RPV or DTG increased more than 10-fold in 2013-2016 and 2015-2016 respectively[55]. Increasing real-world use thus provides not only the rationale but also the means to address the gap between regulatory recommendations and real-world experience.

Although dosing changes are rarely required for most currently recommended drugs, recent data on RPV has underscored the importance of PK studies in the context of pregnancy, with RPV area under the curve and trough concentration reduced in the second half of pregnancy compared with postpartum[56]; concerns regarding increased risk of virological failure has led to regulatory recommendations advising closer monitoring of viral load and/or to switch to another ART regimen in pregnancy.

HIV treatment considerations in specific populations

Late presenters

For women not on ART at conception, prompt ART initiation is key to preventing MTCT as probability of transmission is strongly associated with duration of ART prior to delivery and particularly important for women with high baseline viral load[52,54]. To illustrate, in the French Perinatal Cohort,

the MTCT rate among women starting ART in the third trimester was 2.2% in 2000-2011, versus 0.7% in the entire cohort[15]. In HICs, a substantial proportion of women diagnosed with HIV antenatally are diagnosed late, for example, 32% in a European pooled analysis were diagnosed at 20 weeks gestation or later[57], largely driven by late presentation. RAL is recommended in the scenario of late presentation to antenatal care and/or high viral loads in late pregnancy in a number of guidelines (within a three-drug regimen or with RAL intensification to an existing three-drug regimen) due to its transplacental transfer efficiency and rapid reduction in viral load[52,54].

In Thailand, RAL intensification for high risk pregnant women is now within national guidelines. A pilot study demonstrated the operational feasibility of adding RAL to standard ART in women presenting late (starting ART after 32 gestational weeks) or with viral load >1000 copies/ml at 34-38 gestational weeks; viral load declined by a median 1.6 $\log_{10}$ copies/mL during a median 3 weeks intensification, with a 3.9% MTCT rate reported[58].

Once safety data on DTG accumulates, it is likely to replace RAL for late presenters as it should have similar efficacy but only needs to be taken once daily (RAL is twice daily). The DolPHIN-2 trial is investigating in Uganda and South Africa whether a DTG-based regimen is superior to EFV-based regimens in preventing MTCT for women initiating ART in the third trimester of pregnancy, with results expected in 2021.

Hepatitis B virus co-infection

Part of the WHO's rationale for choosing XTC (3TC or FTC)+TDF as the NRTI backbone in first-line ART was its anti-HBV activity. In SSA, prevalence of HBV co-infection in pregnant women with HIV ranges from 2% to 16%, with up to 30% being HBeAg positive and thus at high risk of vertical HBV transmission[59]; meanwhile only around 40% of the world's infants receive HBV vaccine at birth [60]. Treating HIV/HBV co-infected pregnant women with a XTC+TDF-based regimen thus has potential to reduce vertical transmission of both infections, regardless of whether maternal HBV has been diagnosed [60]. This public health aspect, alongside the HBV therapeutic benefit, requires consideration in future policy decisions regarding NRTI, including recycling in second-line therapies.

Pregnant women who inject drugs

There are an estimated 3.5 million WWID worldwide, with a higher HIV prevalence than seen among males who inject drugs[61]. WHO Guidelines present the key principles of HIV treatment and care for WWIDs, namely access to essential harm reduction (i.e. needle and syringe exchange programmes, opioid substitution therapy) and the same access to ART as other populations[2]. Pregnancy can be a strong motivator for reducing drug use, but discrimination, stigma, punitive drug policies and lack of

targeted/tailored services are major barriers to pregnant WWID accessing services[61]. Increased risk of non-receipt of antenatal ART has been described among WWID in an Eastern European setting[62], whilst late presentation to antenatal care and high preterm delivery rates may contribute to shorter duration of antenatal ART in pregnant WWID accessing care. In terms of therapeutic management, interactions between methadone and some antiretrovirals (eg EFV, boosted PIs) may require methadone dose adjustment.

Safety issues

There remain some large gaps regarding the safe use of ART in pregnancy for newer antiretroviral drugs [27,63]. A major factor has been the exclusion of pregnant women or women planning a pregnancy from registrational and strategic trials of ART (i.e. ineligibility for enrolment or exclusion of women who become pregnant). Furthermore, data relating to use in non-pregnant women is also limited, due to the predominance of male participants in clinical trials of new antiretroviral drugs/regimens, with only a quarter of patients in such trials being female[64]. For some recent trials, women becoming pregnant have been allowed to continue on study drug, with appropriate follow-up of pregnancy and infant outcome[65]. Although this is a welcome trend, it remains the case that pregnancy-specific safety data can be very slow to accumulate for newer drugs, given the dependence on observational data (Table 2).

Teratogenicity

As increasing proportions of women are conceiving on ART, attention continues to be focused on the potential for human teratogenicity, particularly for newer drugs. Prior to 2018, studies of antenatal ART use demonstrated an overall similar prevalence of birth defects in ART-exposed infants compared with the general population, with no association between first trimester exposure to any ART and major birth defects[66,67]. To inform the development of the first harmonized WHO guidelines, and in response to case reports of neurological birth defects associated with EFV use, a series of systematic reviews were conducted. The most recent assessed first trimester exposure, finding no increased risk of birth defects in EFV-exposed infants [68].

The Antiretroviral Pregnancy Registry (APR) collects prospective data where ART exposure is assessed prior to birth outcomes being reported, predominantly through voluntary reports from mainly US-based healthcare providers. The APR reports sufficient mother-infant pairs reported to rule out at least a 1.5-times increase in overall birth defects in infants exposed to ZDV, 3TC, TDF, abacavir, FTC, nevirapine, RTV, lopinavir (LPV) and ATZ, and a 2-times increase in those exposed to

DRV, RPV, EFV and RAL compared with the general US population[69]. Some studies have identified potential signals which require continued monitoring. For example, a US study reported a significantly increased risk of congenital abnormalities associated with ATZ exposure in the first trimester, and a relative increase in skin and musculoskeletal defects[67], while the French Perinatal Cohort reported a two-fold increased risk of congenital heart defects associated with first trimester ZDV exposure [70] (although this was not found in the APR[71]).

In May 2018, there were four reported cases of infants with neural tube defects (NTDs) among 426 births to women who started DTG-based ART prior to conception in Botswana[51], nearly 10 times higher than the expected prevalence of NTDs. These results are based on a small number of events and further data are needed to confirm or refute the findings, from the Tsepamo Study in Botswana and elsewhere. Other published studies of congenital defects in DTG-exposed pregnancies are limited at present. In the APR, among 133 live births reported (77 with first trimester exposure), 3.0% had a birth defect[72] (with 2.7% and 2.8% birth defect prevalence among infants with first and second/third trimester exposure respectively in the APR overall[69]). In the European Pregnancy and Paediatric HIV Cohort Collaboration, prevalence of birth defects was 4.9% (95% CI 1.4, 12.2%) among 81 live births, of whom 42 had first trimester exposure[73]; national data from HIV-exposed pregnancies in the UK indicate a 2.9% birth defect rate[74].

One of the challenges of obtaining sufficient data on the risk of birth defects by ART regimen is that most of these exposures are occurring in LMIC where there has been a lack of systematic surveillance of drug safety in pregnancy. In these settings, surveillance can be difficult because of lack of reliable medical and pharmacy records, home births and insufficient training to recognize birth defects. However, recent efforts by several African countries to implement birth surveillance has shown early success and WHO is coordinating a system to pool this data to improve efficiency and reach[27].

Adverse birth outcomes

Untreated HIV infection in pregnancy is associated with increased risk of a range of adverse birth outcomes including preterm delivery (PTD), low birthweight, small for gestational age (SGA) and stillbirth, with highest risk among women with advanced HIV disease/immunosuppression[75]. While ART reduces the risk of adverse birth outcomes associated with poor maternal health or infant HIV infection, combination ART can simultaneously increase the risk, particularly of PTD, via other incompletely understood mechanisms, with greater risk of adverse pregnancy outcome observed than with NRTI mono/dual therapy in both LMICs and HICs[12,76]. Proposed potential mechanisms include ART-induced disruption or reversal of the Th1 to Th2 shift that is a normal feature of

pregnancy, resulting in predisposition to early labour, and an increase in the inflammatory response following ART initiation as a result of immune reconstitution syndrome[77].

Combination ART was first associated with PTD in Europe in 1998, with subsequent studies showing presence/magnitude of association to differ by ART regimen, timing of initiation and setting. PIs (particularly when boosted with ritonavir) have been widely implicated in observational studies[78-81] and in the Mma Bana trial in Botswana which showed a PTD rate of 21.4% among women randomised to ZDV-3TC-LPV/r at 26-34 gestation weeks vs 11.8% among those randomised to ZDV-3TC-ABC[82]. Progesterone levels may be reduced by PIs, resulting in growth restriction[83] and providing a potential mechanistic link between PIs and increased PTD risk (spontaneous or iatrogenic), with progesterone supplementation for women on PIs being explored[84]. Data from the PROMOTE trial also show the impact of ART on estradiol levels, with LPV/r-based ART associated with an increase and EFV-based ART with a decrease in estradiol and correlations with SGA risk in both directions[85].

The PROMISE trial found an increased risk of very PTD <34 weeks and neonatal death <14 days in women randomised to LPV/r-TDF-FTC compared with LPV/r-ZDV-3TC, but not compared with ZDV monotherapy[12], resulting in a focus on the safety of TDF-containing regimens. However, a recent meta-analysis of 17 studies found that TDF was associated with a reduced risk of PTD (RR 0.90, 95%CI 0.81-0.99) and stillbirth (RR 0.60 95%CI 0.43-0.84) with increased risk of neonatal death <14 days found only in the PROMISE study[86]. These results may indicate an issue with TDF-FTC used in combination with LPV/r, for example relating to the increased TDF levels seen when co-administered with LPV/r, or reflect a low rate of adverse outcomes in the ZDV-3TC arm of the PROMISE study rather than an elevated rate in the TDF-FTC arm[2].

National surveillance data on safety of TDF from Botswana are also reassuring, showing significantly reduced SGA among women initiating TDF/FTC/EFV in pregnancy and among women on TDF/FTC/EFV from conception compared to other ART regimens including ZDV/3TC/NVP and ZDV/3TC/LPV-r[81,87]. Women on TDF/FTC/EFV at conception also had a lower risk of SGA compared with women on TDF/FTC/NVP and TDF/FTC/LPV-r at conception, suggesting (like PROMISE) that it is difficult to isolate the fetal effect of individual antiretrovirals when used in combinations. Surveillance in Botswana also found a concerning risk for stillbirth among women on ZDV/3TC/NVP compared to other ART[81]. Together, this underscores the need to evaluate the comparative safety of specific ART regimens in future research and surveillance.

Uncertainties remain around the role of timing of ART initiation and adverse birth outcomes. Results from the UK/Ireland showed an association between LPV/r and PTD risk, but only if LPV/r was initiated before conception[74]. A meta-analysis of 19,189 mother-child pairs indicated a 20%

increased risk of PTD in pregnancies conceived on ART vs those with ART initiated during pregnancy, alongside a 53% increased risk of very PTD <34 weeks, and 30% increased risk of low birthweight[88].

Maternal disease stage is a key confounder of the association between timing of ART initiation and adverse outcomes, as illustrated in the UK/Ireland study where those conceiving on ART with a CD4 >350 cells/mm^3 had a lower unadjusted PTD rate (8.7%) than the groups initiating ART in pregnancy (11.3% if CD4 ≤350 cells/mm^3, 10.7% if CD4 >350 cells/mm^3)[74]. Interpretation of observational data on ART safety is complicated by the potential role of confounding by indication or channelling bias, changes over time in treatment guidelines and comparator groups, inaccuracies in ascertainment of gestational age in some studies (especially in settings without routine confirmation by ultrasound) and the fact that women starting ART later in pregnancy have less time on ART at risk of preterm delivery than those conceiving on treatment. In the "treat all" era, as more women conceive on ART with relatively high CD4 counts, safety data are needed that are relevant to the changing HIV-positive pregnant population and to newer antiretroviral drugs, and that address limitations in the existing evidence base (for example around gestational age ascertainment). A more complete understanding of mechanistic links between antiretroviral drugs and adverse outcomes will, if found to be causal, provide the basis for development of interventions or risk-stratification strategies.

Looking to the future

The benefits of ART for prevention of MTCT and for maternal, child and public health are indisputable. Harmonized, universal regimens have been key to the magnitude of scale-up of ART in LMICs, with 76% of all pregnant women with HIV receiving ART in 2016 and declining MTCT rates documented worldwide. Every year, over a million pregnancies/foetuses are exposed to ART, underscoring safety implications on a population level, as even a very small increased risk of an adverse outcome may affect a large number of women and/or children. The unprecedented scale of exposure to antivirals in pregnancy has been a catalyst for pharmacovigilance strengthening in LMICs, although this remains work in progress[27].

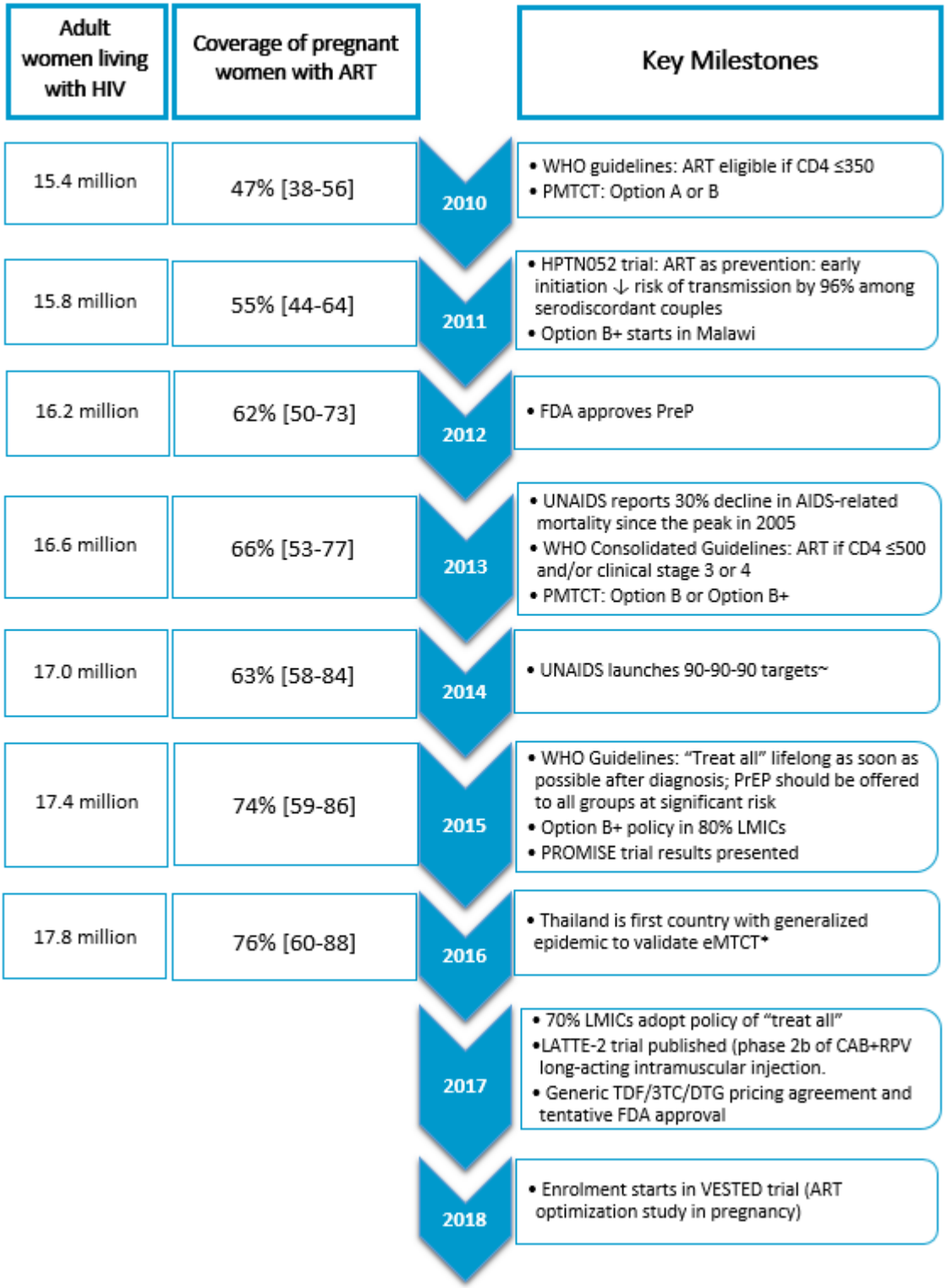
More data are needed regarding the PK, safety and toxicity of newly authorized antiretroviral drugs, particularly given the increasing numbers of women of reproductive age requiring second-line regimens[27,63]. Safety data based on observational, real-world evidence is accumulating for new drugs whilst the VESTED trial (Table 2) will provide much needed randomised data comparing EFV/FTC/TDF with DTG/FTC plus either TAF or TDF in women starting ART in pregnancy.

New antiretroviral drugs may be licensed despite lack of data on key characteristics such as transplacental passage in human pregnancy, with SmPCs often recommending avoiding use in pregnancy (Table 2); however, the majority of women on ART are of reproductive age and at least half of pregnancies in HIV-positive women are likely to be unplanned[89,90]. This raises the question of whether more regulatory "push" is needed to ensure that pharmaceutical companies expedite the necessary studies to obtain pregnancy data, similar to the process for paediatric investigation plans. The potential safety signal with DTG at conception underscores the importance of large scale pharmacovigilance studies. Linked to this, clinical trials of new drugs, including long-acting injectables, should have provision to follow-up women becoming pregnant during the study, with consideration to remain on drug if appropriate. The Pregnancy and HIV/AIDS: Seeking Equitable Study (PHASES) initiative is an ongoing initiative to develop guidance for conducting ethical HIV research among pregnant women with the goal of providing accelerated access to treatment[91].

There are complex and incompletely understood relationships between antenatal ART and adverse pregnancy and birth outcomes as well as gaps in our understanding of any potential short to long-term effects of intra-uterine and breastmilk exposure to antiretrovirals among HIV-exposed, uninfected (HEU) children. Evaluating the potential health risks of such exposures is challenging, but important as the numbers of HEU children will continue to increase[27]. Adverse health outcomes in HEU children reported to date include increased mortality, greater infectious disease morbidity, impaired growth, metabolic alterations, neurodevelopmental delays, altered immunity and mitochondrial abnormalities[27,92,93]. For all these areas, a better understanding is needed of potential causal pathways in order to explore whether any health risks can be mitigated.

Treat all for life is a clear public health message, but not only demands adherence to ART and sustained engagement in HIV care on an individual level but also recognition of and interventions to overcome the structural barriers to effective long-term treatment. Pregnant women face specific challenges in this regard, particularly those newly diagnosed. Further implementation research is needed to ensure that the health of women living with HIV, and that of their families, is optimised.

Figure 1 Treatment of HIV: key milestones and global situation with a focus on pregnancy



Numbers of adult women living with HIV and ART coverage of pregnant women are UNAIDS estimates[1]
Footnote for Figure 1:

~ 90% of PLWH to be diagnosed, 90% of those to be accessing ART and 90% of those on ART to achieve undetectable VL by 2020; * eMTCT (elimination of MTCT): <50 cases of MTCT per 100,000 births and MTCT rate <5% in breastfeeding and <2% in non-breastfeeding populations)
Option A: ZDV monotherapy and single-dose nevirapine; Option B: triple ART prophylaxis during pregnancy and breastfeeding period; Option B+: lifelong ART

Table 1: Barriers for initiation and adherence to ART in pregnancy

Individual	• Poor knowledge or misconceptions regarding HIV, VT or ART • Fears around side effects and potential harms of ART for themselves and their foetus / infant • Denial of HIV status • Depression and other mental health problems; emotional stress • Substance misuse • Conflicting priorities (e.g. child care, other care-taking responsibilities, employment) • Undisclosed HIV status and/or fear of disclosure • Costs and perceived costs (including transport to clinic) • Younger age • Low self-efficacy • Pregnancy-related nausea / sickness • Lack of or late presentation for antenatal care • Cultural beliefs (e.g. use of traditional medicines)
Community / partner	• Intimate partner violence • Stigma • Lack of support from partner, family, community
Regimen	• Regimen with poor tolerability • Complex regimen and scheduling requirements (pill burden, frequency) • Running out of pills
Health system / delivery model	• Under-resourced health system (staffing, drug availability, stock-outs, waiting times, delays in test results) • Centralised HIV services, poor coverage in rural / remote settings • Poor coverage and/or lack of integrated antenatal care / PMTCT services • Insufficient adherence support • Initiation of ART on same day as HIV diagnosis
Other structural	• Logistical challenges in accessing health services

24,29-36

Table 2: Summary of pregnancy-related characteristics (preclinical, published product characteristics, pharmacokinetic, dosing and clinical studies) of newly authorized antiretrovirals

Drug	Preclinical safety data (animal studies)	Clinical data (pregnancy toxicity): statements from SmPC	Transplacental passage	PK / Dosing recommendations	Ongoing clinical studies
DTG Tivicay ABC/3TC/**DTG** Triumeq	No developmental toxicity, teratogenicity. In studies in combo with **3TC** *increased in early embryonic deaths in rabbits* at relatively low systemic exposures. DTG, 3TC, ABC: no effect on M/F fertility.	Limited data and effect on human pregnancy is unknown. Should be used only if the B> R to the foetus. See also [51]	High placental transfer (animal studies)[◊]	*PK*: AUC may decrease in III- trim compared to PP, but good VL suppression in III-trim recipients. *Dosing*: No change indicated.	*DolPHIN1*: safety+ PK study; *IMPAACT P1026s*: DTG PK pregnancy vs PP and infants; I*NG200336:* ARIA sub-study for incident pregnancies: safety+ PK of Triumeq; *DolPHIN-2*: efficacy of DTG-based vs EFV-based ART in women presenting late in pregnancy and their infants *VESTED/ IMPAACT 2010* (see below)
RPV Edurant FTC/TDF/**RPV** Eviplera FTC/TAF/**RPV** Odefsey	No reproductive toxicity, no teratogenicity in rats and rabbits. No effect on fertility in animals, not known in humans. RPV liver toxicity associated with liver enzyme induction in rodents.	Limited data. As a precautionary measure, preferable to avoid use in pregnancy. Odefsey: Effective contraceptives must be used; no adequate and well-controlled studies in pregnant women.	Moderate to high placental transfer (animal studies)[◊]	*PK*: highly variable, AUC 30% lower in pregnancy vs PP. Most pregnant women exceed target exposure, but those with detectable VL had lower RPV troughs. *Dosing*: RPV plasma concentration reduced but insufficient data to recommend dosing change.	Study *TMC114HIV3015* of 19 pregnant women during II+III trim+ PP. Ten women completed the study with no MTCT, RPV was well tolerated during pregnancy and PP; *IMPAACT P1026s*: large PK pregnancy vs PP and their infants study including RPV

TAF Vemlidy FTC/**TAF** Descovy	No reproductive toxicity (rats, rabbits), no effect on fertility, pregnancy or foetal parameters. Bone & kidney as main toxicity target with reduced mineral density (dogs, rats)	No adequate and well controlled studies in pregnancy. Should be used only if B>R to the foetus.	No data available on placental transfer◊	*PK:* No PK studies in human pregnancy. *Dosing:* Insufficient data to make dosing recommendation.	*VESTED / IMPAACT 2010*: Safety + efficacy of DTG/FTC/TAF, EFV/FTC/TDF, DTG/FTC/TDF in ART-naïve pregnant women and infant
COBI Tybost FDCs: ATV/**c**, Evotaz DRV/**c**, Rezolsta EVG/**c** +FTC/TDF Stribild EVG/**c** +FTC/TAF Genvoya	No Reproductive toxicity, no teratogenic effects (rats, rabbits), *only in rats ossification changes* (spinal column and sternebra) of foetuses at maternal toxic doses. Stribild**:** in rats *increased post-implantation loss and decreased foetal weights*	No or limited clinical data. Consider use only if B> R. ATV/c, DRV/c, FTC/TAF: No data in pregnant women. EVG/c FTC/TDF and EVG/c FTC/TAF: effective contraceptives should be used.	Low placental transfer (animal studies)◊	PK: Exposure and boosting effect markedly reduced in pregnancy. *Dosing*: Not yet studied. When in combo with TDF, FTC no change in dose is indicated.	*IMPAACT P1026s*: EVG/c, DRV/**c,** ATV/**c**, PK pregnancy vs PP and their infants; *PANNA*: large PK study on ART including EVG/c, DRV/c
DTG= Dolutegravir; ABC: Abacavir; 3TC= Lamivudine; RPV= Rilpivirine; FTC=Emtricitabine; TDF=Tenofovir Disoproxil Fumarate; TAF= Tenofovir Alafenamide; COBI /c=Cobicistat; ATV= Atanazavir; DRV= Darunavir; EVG= Elvitegravir; combo= combination; M/F= male/female; B>R= Benefit >Risk; PP= postpartum;; AUC= Area under the curve; VL= viral load; trim=trimester; SmPC: summary of product characteristics ◊ Placental transfer categories- Mean or median cord blood/maternal delivery plasma drug ratio: High >0.6; Moderate 0.3-0.6; Low <0.3 European Medicines Agency. Available from: http://www.ema.europa.eu/ema/ ; AIDS info, U.S. Department of Health and Human Services. Available from: https://aidsinfo.nih.gov/guidelines/htmltables/3/5947; i-base. Available from: http://i-base.info/htb/33406; NIH, U.S. Clinical Trials. Available at: https://clinicaltrials.gov/					

Panel: search strategy

We searched PubMed for publications using the following search terms: pregnan*, HIV, human immunodeficiency virus, antiretroviral, mother-to-child transmission, vertical transmission, treat*, fet*, foet*, birth defect, preterm, adverse birth outcome, adherence, loss-to-follow-up, Option B+ and retention. We screened reference lists of identified studies and searched recent HIV conference abstracts and the grey literature including WHO and UNAIDS publications.

We selected articles published in English from 1994 to 2017 judged to be most relevant, prioritising systematic reviews and meta-analyses as well as clinical trials, cohort/surveillance and PK studies pertinent to contemporary questions around use of ART in pregnancy. We focused on articles published in the last 10 years.

Author contributions

HB, VR, CT and RZ all contributed to the literature search and drafting sections of the text. HB, VR, CT and RZ made crucial revisions to and approved the final draft of the manuscript. VR and CT prepared the Figure and Tables.

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Conflicts of Interest

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APR Advisory Committee Consensus statement: In reviewing all reported defects from the prospective registry, informed by clinical studies and retrospective reports of antiretroviral exposure, the Registry finds no apparent increases in frequency of birth defects with first trimester exposures compared to exposures starting later in pregnancy and no pattern to suggest a common cause. While the Registry population exposed and monitored to date is not sufficient to detect an increase in the risk of relatively rare defects, these findings should provide some assurance when counseling patients. However, potential limitations of registries such as this should be recognized. The Registry is ongoing. Given the use of new therapies about which data are still insufficient, health care providers are strongly encouraged to report eligible patients to the Registry at SM_APR@INCResearch.com via the data forms available at www.APRegistry.com.

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