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Towards a Universal Antiretroviral Regimen: Special Considerations of Pregnancy and Breast Feeding

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Abstract

Purpose of review—As optimized antiretroviral therapy (ART) regimens are prepared for introduction in low and middle income countries (LMIC), we consider the current evidence related to dosing, efficacy and safety during pregnancy and breastfeeding of next generation first- and second-line ART regimens proposed for imminent introduction in the global marketplace.

Recent findings—Pregnancy pharmacokinetic considerations include potentially insufficient efavirenz exposure if dosed at 400mg/day, the need for twice daily darunavir dosing and the paucity of data related to tenofovir alafenamide and dolutegravir dosing, safety and efficacy. Increasingly evidence suggests an association with adverse birth outcomes, particularly in women conceiving on ART, and with varying risk by drug and drug combination. Clinical trials and studies are in progress or planned that aim to determine dosing, safety and efficacy of several new antiretrovirals.

Summary—Having a universal, highly potent and safe ART regimen for all individuals living with HIV in LMIC including pregnant women is clearly the most beneficial strategy to keep mothers alive and healthy and to prevent transmission of HIV to their children. It will have to be determined whether use of this next generation of optimized antiretrovirals will also optimize health outcomes of pregnant women and their children.

Keywords

HIV; optimized antiretroviral therapy; pregnancy and breast feeding; vertical HIV transmission

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Introduction

It is estimated that 1.5 million women living with HIV (HIV+) are pregnant annually and in 2015 77% received lifelong antiretroviral therapy (ART) or antiretroviral (ARV) prophylaxis for prevention of vertical HIV transmission (VT) during pregnancy, labor and delivery and postnatally during breastfeeding [1]. As global guidelines for universal treatment for pregnant women and, most recently, all individuals living with HIV are implemented, increasingly HIV+ women will either conceive on or initiate ART during pregnancy [2, 3]. The goal of finding an optimized, harmonized universal ART regimen for all people living with HIV, including pregnant and breastfeeding women, presents many individual and programmatic opportunities to ensure optimal health outcomes in pregnant women and further reduce VT risk. Selection of an appropriate ART regimen in pregnancy requires consideration of regimen efficacy for maternal health and prevention of VT, pregnancy pharmacokinetic changes as well as maternal and fetal safety. Considering that ARVs have been prescribed for pregnant women for more than two decades, the paucity of data relating to efficacy and safety for pregnant women and their ARV-exposed children is striking [4]. We consider the current evidence related to dosing, efficacy and safety during pregnancy and breastfeeding of next generation first- and second-line ART regimens proposed for imminent introduction in the global marketplace including the following drugs: emtricitabine (FTC), lamivudine (3TC), tenofovir disoproxil fumarate (TDF), tenofovir alafenamide (TAF), efavirenz 400 mg (EFV_{400}), dolutegravir (DTG) and darunavir (DRV).

Importance of a maximally suppressive regimen for maternal health and prevention of vertical transmission

In 2015 the health and survival benefits of early ART initiation for HIV+ adults with CD4 counts >500 cells/mm^3 were established [5**, 6**]. Multiple studies have demonstrated that ARVs to the mother (and/or infant) throughout the entire period of VT risk (pregnancy, delivery and the duration of breast feeding) are critical to prevent new infant infections [7, 8**, 9–11]. The Promoting Maternal and Infant Survival Everywhere (PROMISE) trial recently finally provided randomised trial evidence for the beneficial effect on early VT of maternal ART initiated during pregnancy compared to zidovudine (ZDV) prophylaxis in women with high CD4 counts [12**]. The French Perinatal Cohort (EPF) demonstrated that women on ART pre-conception have the lowest risk of perinatal HIV transmission, with increasing risk of transmission by each advancing trimester of ART initiation [8**]. Additionally, independent of timing of ART initiation, HIV viral load (VL) at delivery of 50–400 copies/ml was associated with a 4-fold greater odds (95% CI 1.9-8.2) of VT compared with VL < 50 copies/ml [8**]. Undergoing an ART regimen change during pregnancy, shorter duration on ART and height of pre-ART viral load have all been associated with viral non-suppression at the end of pregnancy [13, 14]. Furthermore, CD4 counts may not be adequately sensitive to identify viral non-suppression and pregnant women at highest risk of VT [15]. The need to switch ART regimens during pregnancy to avoid maternal or fetal adverse events can jeopardize maternal and infant health outcomes and is counter to the goal of an optimized, harmonized universal ART regimen. Having a universal, highly potent and safe ART regimen for all individuals living with HIV in low and

middle-income countries (LMIC) including pregnant women is clearly the most beneficial strategy to keep HIV+ mothers alive and healthy and to prevent transmission of HIV to their children.

As the universal ART strategy expands, the incidence of horizontally and vertically acquired HIV infection is expected to decline further. However, a rising prevalence of transmitted HIV drug resistance in LMIC is a concern, particularly resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) [16]. Issues related to drug resistance, drug efficacy and antiretroviral regimens are addressed elsewhere in this issue [17, 18]. The implications of this for VT are unclear. Perinatal transmission of resistant virus is unusual and previous reports have shown that in the presence of mixed resistant and wild-type virus populations in the mother only wild-type and not resistant virus was vertically transmitted [19].

Universal ART regimens: considerations for pregnant and breastfeeding women

Pregnancy pharmacokinetic considerations

Pregnancy results in dramatic physiologic alterations that may impact on drug disposition, including absorption, distribution and elimination [20]. Even with substantial pregnancy-induced changes to drug metabolism, ARV exposure adequate to achieve viral suppression is most often reached, with the exception of boosted-protease inhibitors (PI) (Table 1) [21, 22**].

Nucleos(t)ide reverse transcriptase inhibitors (NRTIs), including FTC, 3TC and TDF, undergo increased renal elimination during pregnancy due to elevated renal blood flow and glomerular filtration particularly during the third trimester [22**]. Despite demonstrated increased clearance, pregnant women still met drug exposure targets for FTC, 3TC and TDF comparable to that during the post-partum period or in non-pregnant adults [23–29*]. NRTIs, including FTC, 3TC and TDF rapidly cross the placenta, with cord-to-maternal-blood ratios >1 [23, 25, 29*]. This has theoretical advantages for fetal pre-exposure prophylaxis, but also greater potential for negative fetal, infant and life-course effects. There are currently no pharmacokinetic data on TAF in pregnant women to inform appropriate pregnancy dosing or safety, however studies are planned.

With standard dosing of EFV (600mg/day), pregnancy trough concentrations are reduced due to increased metabolism by hepatic cytochrome P450 (CYP450) enzymes that are induced by elevated progesterone during pregnancy [21, 22**, 30, 31]. Despite this, 88% of pregnant women remained within the therapeutic range for EFV in the third trimester [30]. EFV crosses the placenta, but less well than the NRTIs, with cord-to-maternal-blood ratios of 0.5 [30]. Pharmacokinetic studies of lower dose EFV (400mg/day) are currently underway in pregnant women. Considering pregnancy-induced increased EFV metabolism, these studies are critical to be certain that EFV_{400} still meets the required exposure targets to achieve viral suppression during pregnancy.

As a result of pregnancy induced CYP450 enzyme induction, the standard adult dose of ritonavir (RTV)-boosted DRV (DRV/r) of 800mg/100mg daily results in inadequate DRV

exposure during the third trimester [21, 32*, 33*]. A twice daily dose of DRV/r (600mg/100mg) is recommended instead, and although this dose also results in reduced exposure during the third trimester compared to post-partum, it is thought to be adequate [34]. An increased dose of 800mg twice daily does not result in improved DRV exposure and is not recommended in pregnant women [35*]. PIs cross the placenta poorly, with the possible advantage of having fewer negative effects for the fetus, but are therefore not suitable agents for fetal pre-exposure prophylaxis.

Like NNRTIs and PIs, integrase strand transfer inhibitors (INSTIs), including DTG, raltegravir (RAL) and elvitegravir (EVG) undergo metabolism by the CYP450 enzymes. PK data on DTG use in pregnancy is limited to a single study demonstrating reduced DTG exposure during the third trimester compared to post-partum measurements in the same women [36**]. Third trimester exposure was similar though to non-pregnant historic controls and adequate viral suppression was achieved in all 15 women [36**]. EVG/cobicistat exposure was substantially lower during pregnancy than post-partum and only 75% (14/19) of women were virologically suppressed at delivery [37]. RAL is known to readily cross the placenta [38, 39] and DTG and EVG have also been identified in measurable concentrations in neonates following *in utero* exposure [36**, 37, 40].

Breastfeeding considerations

3TC and FTC are readily excreted in breast milk and occur in biologically meaningful concentrations resulting in infant plasma concentrations within the range for the concentration required of these drugs to inhibit 50% of wild-type HIV replication (IC_{50}) [40, 41]. This raised caution that monitoring for acquisition of viral resistance is warranted in the rare HIV-infected child exposed to FTC or 3TC via breast milk [41, 42]. TDF and EFV occur at much lower levels in breast milk resulting in negligible exposure to the breastfeeding infant [41, 43]. Although there are no data on breast milk passage of DRV, LPV has been observed to have very low to undetectable levels in breast milk [44, 45]. There are no data on breast milk excretion of INSTIs.

Considerations for *in utero* antiretroviral exposed children

Teratogenicity

Drug exposure during critical early stages of embryonic development poses the potential for teratogenicity and development of congenital anomalies. Of all ARVS, EFV has presented the most concern regarding teratogenic potential as animal studies in conjunction with isolated human case-reports raised the possibility of neural tube defects with first trimester EFV exposure [46]. With time, the accumulating evidence has been reassuring that first trimester EFV exposure poses no additional risk compared with second or third trimester exposure for congenital anomalies in general or for central nervous system defects specifically [47, 48**]. The multi-country prospective Antiretroviral Pregnancy Registry (APR) has accumulated sufficient numbers of first trimester exposures to detect at least a 1.5-fold increase in risk of overall birth defects for FTC, 3TC, LPV, RTV and TDF, and a 2-fold increase in risk for DRV, EFV and RAL. No such increases have been detected as of July 2016 [48**]. Insufficient numbers of DTG exposures have been reported to make

similar comparisons and there have been no cases of TAF exposure reported to the APR [48**]. Similarly, the French EPF has observed no association between overall birth defects and first trimester exposure to FTC, TDF, LPV or RTV [49]. The EFP has not yet reported on DRV, DTG or TAF exposures.

Birth outcomes

HIV+ compared to HIV-negative women experience high rates of adverse birth outcomes including stillbirth, preterm birth (PTB), low birth weight (LBW) and small for gestational age (SGA) that persist despite maternal ART [50*, 51]. Although some reports implicate protease-inhibitor based ART [52, 53], a recent meta-analysis including 19,189 mother-infant pairs from 11 studies, showed a significantly increased risk in women conceiving on ART, irrespective of ART regimen, compared to those initiating ART during pregnancy for PTB (relative risk (RR) 1.20, 95% CI 1.01-1.04), very PTB (RR 1.53, 95% CI 1.22-1.92) and LBW (RR 1.30, 95% CI 1.04-1.62) [54**]. SGA did not differ and risk of stillbirth was increased but not significantly different (RR 1.30, 95% CI 0.99-1.69) by pre- or post-conception ART initiation [54**]. Restricted to LMIC studies only, the strength of the association between PTB and pre-conception ART was stronger (RR 1.41, 95% CI 1.22-1.63), with no difference in high income country studies (RR 0.89, 95% CI 0.54-1.47). The authors qualify these findings with caution that the quality of evidence is low to very low and that potential confounding differences in women initiating ART pre-conception may not be completely taken into account. Importantly, spontaneous versus induced preterm delivery for maternal or fetal indication was not differentiated in any studies and this may be a valuable piece in understanding the drivers of PTB in HIV+ women on ART.

Repeated birth surveillance studies in Botswana have observed elevations in adverse birth outcomes in HIV+ women whether conceiving on or initiating ART regimens during pregnancy [51, 55**, 56**]. Women on TDF+FTC+EFV during pregnancy less often had SGA newborns compared to women on any other 3-drug ART or ZDV-monotherapy, and PTB and stillbirth were no different [55**]. Recently, a closer look at birth outcomes in Botswana specifically comparing type of ART regimen at conception demonstrated that TDF +FTC+EFV was safer than all other ART regimens (NVP-based or LPV/r-based) in terms of all or severe adverse birth outcomes [56**]. In attempts to overcome potential confounding by HIV disease severity, indication for ART pre-conception and temporal changes, multiple sensitivity analyses were conducted that did not alter these findings [55**, 56**]. Similarly, in the United Kingdom and Ireland women on NNRTI-based regimens at conception had a lower probability of PTB compared to women on PI-based regimens [57].

In the PROMISE trial that established the superiority of maternal ART over ZDV monotherapy for prevention of VT among immunocompetent women, significantly more maternal adverse events and adverse birth outcomes occurred in both the ZDV-based (ZDV +3TC+LPV/r) and TDF-based (TDF+FTC+LPV/r) ART arms compared to ZDV alone [12**]. Furthermore, TDF-based ART was associated with significantly higher rates of severe adverse birth outcomes than ZDV-based ART (9.2% vs. 4.3%, p=0.02) and specifically a higher rate of very preterm delivery before 34 weeks (6.0% vs. 2.6%, p=0.04), with significantly more neonatal deaths in the first week of life (4.4% vs. 0.6%, p=0.001).

The authors hypothesized that pharmacologic interactions between TDF and LPV/r in pregnant women could have been responsible for the increase in severe adverse pregnancy outcomes in the TDF-based ART arm [12**].

Life course effects of perinatal antiretroviral exposure

There are indications that long term consequences may result from fetal ARV exposure. There has been evidence for some time of geno- and mitochondrial toxicity in infants following NRTI exposure [58**]. The clinical significance of these observations is unclear but has potential for poorer neurodevelopmental outcomes and myocardial aberrations [59, 60]. More recently genotoxicity, specifically aneuploidy and altered gene expression in DNA repair and telomere maintenance pathways, has been recognized in infants with *in utero* exposure to ZDV or TDF [61*]. It is unknown whether these genotoxic signatures persist, however they may represent predisposing factors for an oncogenic event and possibly later cancer [61*]. Reassuringly, an updated analysis from the EPF, including 15,163 HIV-exposed uninfected (HEU) children exposed to at least one NRTI *in utero* did not observe an increased risk of childhood cancer compared to the general population following any NRTI exposure (standardized incidence ratio (SIR) 0.8 [95% CI 0.47-1.24]) or specifically following exposure to TDF, FTC or TDF and FTC in combination [62**]. Didanosine (ddI) however, was associated with an elevated hazard for childhood cancer with first trimester compared to no ddI exposure (HR 5.5 [95% CI 2.1-14.4]) [62**]. Although ddI has been replaced with safer and less toxic drugs, these findings do emphasize the need for systematic long term surveillance of children and adults exposed *in utero* to ARVs.

Although there has been concern about *in utero* exposure to TDF specifically and its effects on the developing fetal skeletal structure, in two large US based cohorts there was no evidence of an association between *in utero* TDF exposure and fetal growth [63, 64]. However, lower length-for-age Z-score in TDF-exposed infants at age one year and a lower weight-for-age Z-score at six months of age were observed [63, 64]. In Ugandan and Zimbabwean infants exposed to TDF *in utero* there was no evidence of inferior growth at age two years compared to HIV exposed infants not exposed to TDF [65]. Furthermore, in a South African study there was no association with duration of TDF-exposure as part of an EFV-based regimen and fetal or postnatal length growth to 12 months of age [66, 67]. Significantly lower newborn bone mineral content has been described following late pregnancy TDF exposure compared to no TDF exposure in HIV-exposed newborns [68*]. The long term importance of these observations remains uncertain but highlights the need for further surveillance of TDF-exposed infants. With the lower renal toxicity profile of TAF it would be expected to have a lower potential for renal and bone toxicity following *in utero* exposure, however this is yet to be studied.

Additionally, HEU children appear to experience immune system differences, an increase in infectious disease severity and greater mortality compared to HIV-unexposed children [69–71]. Early studies suggested an association with advanced maternal HIV disease [72, 73], however more recent evidence indicates that these findings persist despite improving maternal health and safer breastfeeding in the context of maternal ART [71, 74, 75]. The role of specific ARVs or ART more generally in ameliorating or exacerbating this increased

morbidity and mortality is unclear and further work to understand the risks to HEU child health in the current context of new ART regimens is required [76].

Conclusion

Having a universal, highly potent and safe ART regimen for all individuals living with HIV in LMIC including pregnant women is clearly the most beneficial strategy to keep HIV+ mothers alive and healthy and to prevent transmission of HIV to their children. As the global community prepares to introduce optimized ART regimens in LMIC, special considerations for pregnant and breast feeding women take on increased importance. Pharmacokinetic considerations include potentially insufficient EFV exposure if dosed at 400mg/day, the need for twice daily DRV dosing and the paucity of data related to TAF and DTG dosing, safety and efficacy during pregnancy. Furthermore, while the benefit of ART during pregnancy is clear, it does not come without a price. Increasingly evidence suggests an association with adverse birth outcomes, particularly in women conceiving on ART, and with varying risk by drug and drug combination. Whether there is potential for long term harm incurred with these exposures also remains to be determined. There are a number of clinical trials and studies in progress or planned that aim to determine dosing, safety and efficacy of several of the new ARVs and ARV combinations (Table 2) [77]. These studies will provide crucial evidence to inform global guidance and to determine the safe use of these drugs among pregnant and breast feeding women. It will have to be determined whether use of this next generation of optimized ARVs will also optimize health outcomes of pregnant women and their children.

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Key Points

- The global market is poised to introduce several new antiretroviral medications to optimize HIV treatment outcomes
- Several issues need to be considered regarding use of these medications in pregnant and breastfeeding women
- Pregnancy pharmacokinetic considerations include potentially insufficient efavirenz exposure if dosed at 400 mg/day, the need for twice daily darunavir dosing and the paucity of data related to tenofovir alafenamide and dolutegravir dosing, safety and efficacy
- The potential for adverse pregnancy and birth outcomes needs to be assessed and monitored

Table 1

Summary of antiretroviral considerations for HIV-infected pregnant women and their antiretroviral exposed children

Drug	Pregnancy pharmacokinetics	Pregnancy dose changes	Placental and breast milk transfer	Teratogenicity	Other considerations
FTC	Increased renal clearance with lower exposure in 3rd trimester	Modest PK changes, but not large enough to warrant dose changes during pregnancy	High placental transfer; Excreted in breast milk with biologically meaningful exposure to the infant	Sufficient data to exclude a 1.5-fold increased risk of overall birth defects	
3TC	Increased renal clearance with lower exposure in 3rd trimester	Modest PK changes, but not large enough to warrant dose changes during pregnancy	High placental transfer; Excreted in breast milk with biologically meaningful exposure to the infant	Sufficient data to exclude a 1.5-fold increased risk of overall birth defects	Evidence of mitochondrial and genotoxicity in infancy
TDF	Increased renal clearance with lower exposure in 3rd trimester	Modest PK changes, but not large enough to warrant dose changes during pregnancy	High placental transfer; Excreted in breast milk at low levels	Sufficient data to exclude a 1.5-fold increased risk of overall birth defects	Reduced newborn bone mineral content; Evidence of genotoxicity in infancy
TAF	**No data**	**No data**	**No data**	**No data**	**No data**
EFV	Increased metabolism and **reduced trough concentrations at standard dose (600mg daily)**	Modest PK changes, but not large enough to warrant dose changes (at 600mg daily) during pregnancy	Moderate placental transfer Excreted in breast milk at low levels	Sufficient data to exclude a 2-fold increased risk of overall birth defects	
DRV/r	Reduced trough levels in 3rd trimester with standard once daily dosing	**600mg/100mg twice daily recommended**. 800mg/100mg twice daily does not improve pregnancy DRV exposure and is not recommended	Low placental transfer; No data on breast milk excretion (LPV low to undetectable levels in breast milk)	Sufficient data to exclude a 2-fold increased risk of overall birth defects	
DTG	Increased metabolism and reduced exposure during pregnancy	**Insufficient data to make a dosing recommendation**	High placental transfer No data on breast milk excretion	**Insufficient data**	

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Table 2

Active and planned clinical trials of dolutegravir, tenofovir alafenamide, efavirenz 400, in pregnant and breatfeeding women

Trial	Sponsor (collaborators)	Design	Status	Purpose
Dolutegravir				
DolPHIN1	University of Liverpool (University of Cape Town, Makerere University)	DTG PK in late presenting (28 to 36 weeks gestation) pregnant women in third trimester and postpartum during 2 weeks breastfeeding; randomised 1:1 to DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs	Started: March 2017 Primary completion: December 2017	Primary: PK 3rd trimester Secondary: safety and tolerability of DTG up to 2 weeks post-partum and VL at delivery
PK and safety study in pregnant women with HIV	ViiV Healthcare	Women with unintended pregnancies (estimated n=25) while participating in ARIA study of DTG/ABC/3TC FDC vs ATV/ r +TDF/FTC in 474 treatment naive women	Started: Jan 2015 Primary completion: February 2019	Primary: PK 2nd/3rd trimester Secondary: PK in neonate, maternal:cord blood ratio, maternal and infant AEs; adverse pregnancy outcomes
DolPHIN2	University of Liverpool (University of Cape Town, Makerere University, UNITAID)	DTG PK, safety and efficacy in 250 late presenting (≥ 28 weeks gestation) pregnant women in 3rd trimester and post-partum during breastfeeding until weaning or 18 months; randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs	Planned start: Q3 2017 Primary completion: Q1 2021	Primary: PK 3rd trimester Secondary: viral load at delivery, safety, tolerability breast milk sterilisation
Tenofovir alafenamide				
WAVES (OLE)	Gilead Sciences	EVG/COBI/FTC/TDF vs TDF/FTC + ATV/r in treatment naive women with OLE women in ATV/r arm re-randomised to remain or switch to EVG/COBI/FTC/TAF; those that become pregnant can remain on study regimen	Started: February 2016 Primary completion: March 2017	Safety, efficacy and tolerability in ART naive pregnant women
Dolutegravir and tenofovir alafenamide				
VESTED IMPAACT P2010	IMPAACT network NIH (NIAID and NICHD)	DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 549 mother/infant pairs Treatment-naive women starting ART at 14 to 28 weeks gestation	Planned start: March 2017 Primary completion: December 2019	Comparative data on safety and virologic efficacy during pregnancy and through 50 weeks of maternal and infant follow-up postpartum
IMPAACT P1026s	IMPAACT network NIH (NIAID and NICHD)	PK properties of antiretroviral and related drugs during pregnancy and postpartum; pregnant women > 20 weeks gestation receiving DTG (1 arm) and TAF (3 arms – within FDCs) as part of clinical care	Started: Sep 2014 Primary completion: June 2017 (DTG) and June 2018 (TAF)	Primary: PK 2nd /3rd trimester Secondary: PK in neonate, maternal:cord blood ratio, maternal and infant AEs; adverse pregnancy outcomes

Trial	Sponsor (collaborators)	Design	Status	Purpose
PANNA study	Radboud University (PENTA Foundation, ViiV Healthcare)	Pregnant women < 33-week gestation receiving DTG as part of clinical care Each study arm 16 with evaluable 33-week data	Started: July 2015 Primary completion: Dec 2020	Primary: PK at 33 weeks and 4–6 weeks after delivery Secondary: PK in neonate, safety, VL and transmission
Efavirenz 400 mg				
PK of EFV 400 mg once daily during pregnancy in HIV positive women	SSAT (Mylan Inc.)	PK single arm 25 women stable on 2 NRTI plus EFV 600 mg for >12 weeks, switch to EFV 400 mg at gestational age 28 weeks	Started: Sep 2016 Primary completion: May 2017	Primary: PK 3rd trimester and postpartum Secondary: Safety and tolerability, genetic influences on EFV PK

AE, adverse event; ABC, abacavir; ATV/r, atazanavir/ritonavir; COBI, cobicistat; DTG, dolutegravir; EFV, efavirenz; EVG, elvitegravir; FDC, fixed dose combination; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Trials Network; NAID, NIH, United States National Institutes of Health; NRTI, nucleos(t)ide reverse transcriptase inhibitor; OLE, open label extension; PANNA, Study on Pharmacokinetics of Newly Developed ANtiretroviral Agents in HIV-infected pregNAnt Women; PK, pharmacokinetic; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; 3TC, lamivudine

Adapted from Clayden P. Fit for Purpose. HIV i-Base. February 2017. [77]