Management of pregnancy in WLWH:
Belgian guidelines

Deborah Konopnicki, Marc Hainaut and Dimitri Van der Linden
On behalf of the working group

11th BREACH Symposium
30/11/2023
Dolce – La Hulpe

Working group: methodology

Starting point: Breach meeting in November 2021

EACS guidelines

Table on antiretroviral regimen for ART naïve patients: preferred or alternative

Questions:

what about women already treated with other ARV?

What about viral cut off for C section, retrovir infusion perpartum?

What about breastfeeding?...etc

After the Breach meeting in November 2021: set up a working group on pregnancy in WLWH

Methods

- ✓ Call to all Breach member to gather HCW involved in the management of pregnancy in WLWH
- ✓ **4 groups**: Pregnancy (Deborah Konopnicki), Infants (Marc Hainaut), Breastfeeding (Dimitri Van der Linden), Ethical issues

WLWH: Treatment before and during Pregnancy, FU during pregnancy and delivery	**Infant/Child** management: Treatment at birth, FU	**Breastfeeding**: Include a midwife specialized in breastfeeding	**Ethical issues:** Upon request

- ✓ Created a shared drive with literature and consensus drafts
- ✓ 8 live and online meetings

  2022: March 17, Sept 20th

  2023: Feb 9 and 14th, March 9th, 23rd and 28th and November 14th

- ✓ September 29th 2023: open to comments from all Breach members

BREACH

Working groups

- Pregnancy Group

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LAURENT France
KONOPNICKI Deborah
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- Infants Group

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- Breastfeeding group

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VANDERSCHUEREN Patricia
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DAELEMANS Siel
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NAGEL Julie
ROUSSEAU Charlotte

30 Virologists, Infectiologists, gynecologists, obstretricians, pediatrician, neonatologists, mid-wives, nurses, psychologists

CHU Saint-Pierre, Cliniques universitaires Saint Luc, Hôpital Ambroise Paré de Mons, Hôpital de la Citadelle, Hopital Erasme, ITG, LHUB-ULB, UZ Antwerp, UZ Brussel, UZ Gent, UZ Leuven

1. Management of pregnancy in WLWH

- **Ideal situation**

Viral load <50 cp/ml before the pregnancy and throughout the whole pregnancy

- When HIV is diagnosed at time of pregnancy or the WLWH is not treated for HIV at time of pregnancy:

Starting ARV triple therapy as soon as possible for all women:

According to EACS guidelines table

INSTI-based regimen allows reaching VL<50 cp/ml more rapidly

EACS guidelines 2023

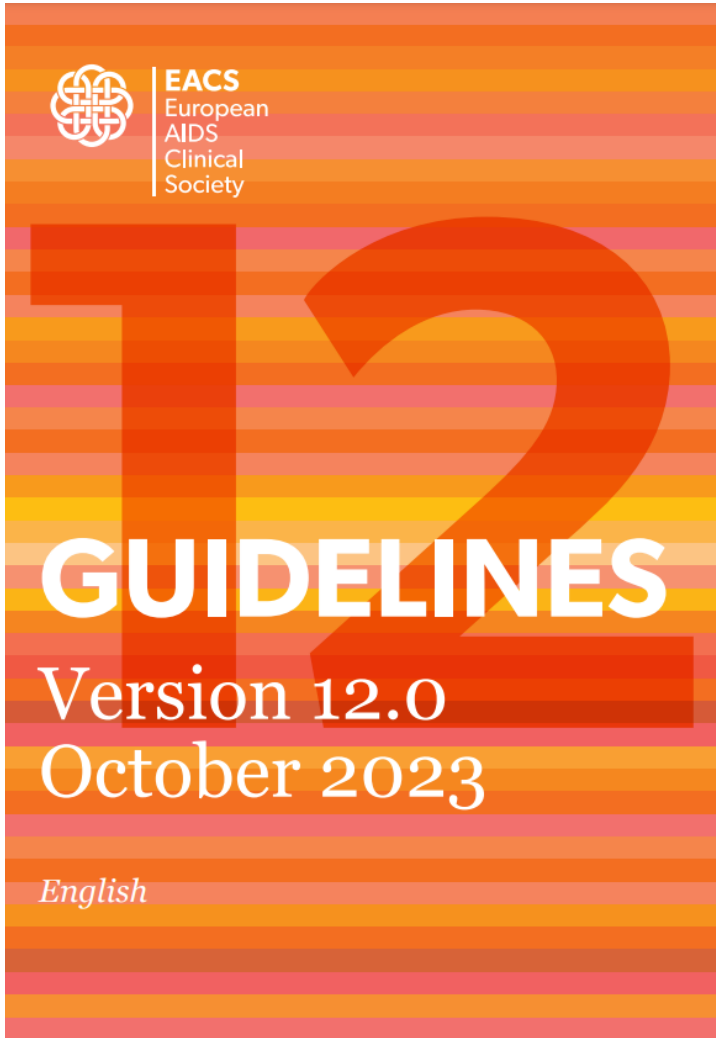

Table 1. Antiretroviral regimen for ART-naïve pregnant women

ART-naïve pregnant women should initiate treatment as soon as possible. The decision of ART regimen should be discussed with the person and individualized taking into account tolerability, possible adherence issues, as well weighed against potential risk coming from ART exposure or suboptimal pharmacokinetics in pregnancy.

Pregnant women starting ART should be monitored monthly or bimonthly (depending on adherence and length of virological suppression) and as close as possible to the predicted delivery date. HIV-VL should be tested every two months of pregnancy and including 36 weeks of gestation

Regimen	Main requirements	Additional guidance (see footnotes)
Recommended regimens		
2 NRTIs + INSTI (PREFERRED)		
TDF/XTC or TAF/FTC + DTG		I (Tenofovir salts)
TDF/XTC or TAF/FTC + RAL 400 mg bid		I (Tenofovir salts) II (RAL in pregnancy, bid dosing)
2 NRTIs + PI/r		
TDF/XTC or TAF/FTC + DRV/r 600 mg/100 mg bid	With food	I (Tenofovir salts) III (DRV dosing) IV (COBI boosting)
Alternative regimens		
2 NRTIs + INSTI		
ABC/3TC + DTG or ABC/3TC/DTG	HLA-B*57:01 negative HBsAg negative	V (ABC: HLA-B*57:01, may delay starting ART)
ABC/3TC + RAL 400 mg bid	HLA-B*57:01 negative HBsAg negative	II (RAL in pregnancy, bid dosing) V (ABC: HLA-B*57:01, may delay starting ART)
2 NRTIs + NNRTI		
ABC/3TC + EFV	HLA-B*57:01 negative HBsAg negative HIV-VL < 100,000 copies/mL At bedtime or 2 hours before dinner	V (ABC: HLA-B*57:01, may delay starting ART) VI (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + EFV or TDF/FTC/EFV	At bedtime or 2 hours before dinner	I (Tenofovir salts) VI (EFV HIV-2 & group O)
TDF/XTC or TAF/FTC + RPV or TDF/FTC/RPV or TAF/FTC/RPV	CD4 count > 200 cells/µL HIV-VL < 100,000 copies/mL Not on gastric pH increasing agents With food	I (Tenofovir salts) VII (RPV exposure during 2nd and 3rd trimester, HIV-2) VIII (Interactions)
2 NRTIs + PI/r		
ABC/3TC + DRV/r 600 mg/100 mg bid	HLA-B*57:01 negative HBsAg negative With food	III (DRV dosing) IV (COBI boosting) V (ABC: HLA-B*57:01, may delay starting ART)

Additional guidance

I Some generic forms of TDF use phosphate, maleate, and succinate salts instead of fumarate. They may be used interchangeably. In certain countries, TDF is labelled as 245 mg rather than 300 mg to reflect the amount of the prodrug (tenofovir disoproxil) rather than the fumarate salt (tenofovir disoprox- il fumarate)

II There were no reports of neural tube defects among 1991 prospective reports of RAL exposure in pregnancy, 456 of which were in the periconception period. No data on RAL 1200 mg qd: not recommended

III DRV/r 800/100 mg qd not recommended as initial ART during pregnancy due to decreased levels, but could be continued if the woman has already undetectable VL. DRV/c is not recommended during pregnancy due to significant lower exposures of DRV and COBI in the second and third trimester of pregnancy

IV Boosting with COBI is not recommended after the second trimester of pregnancy (insufficient drug levels)

V ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. If testing for HLA-B*57:01 results in delay of ART initiation, consider other recommended backbone

VI EFV not active against HIV-2 and HIV-1 group O strains

VII Lower RPV exposure during second and third trimesters; Consider monitoring VL more frequently. RPV is not active against HIV-2

VIII Pregnant women are often prescribed anti-H2 or proton pump inhibitors for nausea. Careful review of concomitant medicines at each visit and providing pregnant women with information on potential interactions is recommended

ARV therapy before pregnancy

1. Insufficient data - Safety - Pharmacokinetic - Bitherapy as opposed to the 3 drugs dogma	Bictegravir Doravirine Raltegravir 1200 mg QD Cabotegravir/rilpivirine Dolutegravir/lamivudine Dolutegravir/rilpivirine	• Discussion with the patient to inform her: **shared decision** ➢ If VL<50 cp/ml, therapy well tolerated, and the patient wishes to continue her therapy, continue During pregnancy: monitoring VL frequently (at least at T1, T2, every month during T3) ➢ If VL >50 cp/ml, or if the patient prefer to have cART with sufficient data background: switch for a recommended therapy (See EACS guidelines)
2. Not recommended - Pharmacokinetic - Risk of viral rebound	Elvitegravir Cobicistat (significant decrease in blood concentrations at T3) Atazanavir (risk of hyperbilirubinemia, risk of viral failure)	• Discussion with the patient to inform her: **shared decision** and based on a case to case evaluation ➢ Propose to **switch to another regimen** (as there are a lot of alternatives) ➢ If VL<50 cp/ml and well tolerated, continue and during pregnancy: monitoring VL frequently (at least at T1, T2, every month during T3)
3. Not recommended Risk of congenital abnormalities	Efavirenz	Propose to switch to another regimen before pregnancy
4. Drugs that are ok		Dolutegravir based triple (or double regimen) Raltegravir 400 bid based triple regimen Prezista **800/rito 100** based triple regimen Rilpivirine or Viramune based triple regimen

ARV therapy during pregnancy

1. Insufficient data - Safety - Pharmacokinetic - Bitherapy as opposed to the 3 drugs dogma	Bictegravir Doravirine Raltegravir 1200 mg QD Cabotegravir/rilpivirine Dolutegravir/lamivudine Dolutegravir/rilpivirine	• Discussion with the patient to inform her: **shared decision** ➢ If VL<50 cp/ml, therapy well tolerated, and the patient wishes to continue her therapy, continue During pregnancy: monitoring VL frequently (at least at T1, T2, every month during T3) ➢ If VL >50 cp/ml, or if the patient prefer to have cART with sufficient data background: switch for a recommended therapy (See EACS guidelines)
2. Not recommended - Pharmacokinetic - Risk of viral rebound	Elvitegravir Cobicistat (significant decrease in blood concentrations at T3) Atazanavir (risk of hyperbilirubinemia, risk of viral failure)	• Discussion with the patient to inform her: **shared decision** and based on a case to case evaluation ➢ Propose to switch to another regimen **BEFORE T3** (as there are a lot of alternatives) ➢ If VL<50 cp/ml and well tolerated, continue and during pregnancy: monitoring VL frequently (at least at T1, T2, every month during T3)
3. Not recommended Risk of congenital abnormalities	Efavirenz	Propose to switch to another regimen as soon as possible at first T1 but until the end
4. Drugs that are ok		Dolutegravir based triple (or double regimen) to be started or continued Raltegravir 400 bid based triple regimen to be started or continued Prezista /rito based triple regimen to be started or continued Rilpivirine based triple regimen to be started or continued (Viramune based triple regimen to be continued, not started)

ARV therapy during Pregnancy:

Should we switch Darunavir/r 800/100mg QD to 600/100 mg bid ?

➡ Not if the woman has VL<50 cp/ml

There is a theoretical risk based on PK studies but they measured total darunavir and not unbound fraction so the clinical relevance of these measures are not evident

Large cases series and our own experiences are reassuring

ARV therapy during Pregnancy:

Is TAF safe on pregnancy outcome ? What about weight gain?

- Review of the guidelines
- Pharmacokinetic of tenofovir alafenamide during pregnancy
- Animal studies (Fertility, teratogenicity, placental and breast milk passage)
- Clinical efficacy
- Safety
- Weight gain

Is TAF safe on pregnancy outcome ?

- Up to date data on use of TAF during pregnancy are reassuring
- There seems to have no contraindication during first trimester
  - No teratogenicity in animal studies with TAF exposure higher than in human with therapeutic dosage.
  - No increase in congenital abnormalities in different registry
- Even with decreasing plasma TAF/TFV during pregnancy, still within therapeutic range
- IMPACT/Vested trial is one of very few randomized ART trials in pregnancy: excellent efficacy and safety outcome
- TAF is associated with increasing weight gain during pregnancy (compared to TDF) but was under the normal weight gain expected during pregnancy so this should be monitored

Endorsed in the last the EACS guidelines October 2023

Monitoring of HIV VL during pregnancy

Patient diagnosed during pregancy T1 or T2 or LTFU before pregnancy	• VL + genotype at diagnosis; Start ARV before genotyping results • VL 1 month after treatment initiation • Then VL every 1 to 2 months • At 36 weeks and at birth
Patient diagnosed during late pregancy T3	• VL + genotype at diagnosis; Start ARV including Dolutegravir before genotyping results • VL every 1-2 weeks untill undetectable • At 36 weeks and at birth
Patient under regular follow-up and VL controlled (<50 cp/ml)	• VL at least once per trimester ; monthly in T3 if on not recommended cART • At 36 weeks and at birth
Patient under regular follow-up and VL not controlled	• Check for tolerability, nausea, pill size, etc.. • VL + genotype; • Consider adding INSTI (prefered= Dolutegravir) or switching to another ARV before genotyping results • Recheck VL at 1 month if T1 or T2 or after 2 weeks if T3 • If VL <50, recheck every 1-2 months thereafter • At 36 weeks and at birth

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What if VL not controlled?

Concentration	?	TDM
Resistance	?	Genotype
Observance	?	Anamnèse
Interactions	?	Anamnèse

Consider adding an INSTI or shifting to INSTI (prefered=dolutegravir)

Threshold of HIV VL Week 36 for prevention measures

	Programmed Cesarian section at 38 weeks		IV ZDV per partum	
	recommended	considered	recommended	considered
EACS Oct 2021 and 2023	>50 cp/ml		>50 cp/ml	
DHHS Dec 2020	>1000 cp/ml		>1000 cp/ml	50-1000 cp/ml
BHIVA 2020	> 400 cp/ml	50-399 cp/ml	>1000 cp/ml	50-1000 cp/ml

Threshold of HIV VL Week 36 for prevention measures

	Vaginal delivery	Elective C- section at 38 weeks	IV ZDV per partum
<50 cp/ml	**Recommend**	No	No
50-400 cp/ml	Favor*	Consider*	Yes
400-1000 cp/ml	Consider*	Consider*	Yes
>1000 cp/ml	No	**Recommend**	Yes

* decision on a case-by-case basis after shared decision with the patient

Belgian guidelines: we RECOMMEND

- an elective caesarean section (C-section) if VL > 1000 cp/ml (except imminent delivery)+IV zidovudine

- vaginal delivery if VL <50 cp/ml (and no other obstetrical condition needing C-section)

Between 50-400 and 1000 cp/ml: CONSIDER

a decision between vaginal delivery versus elective C- section should **be shared with the patient**.
The obstetrical future, the presence of other comorbidity, the history and the opinion of the patient will be taken into account for a decision on a case-by-case basis.

Based on:

- In this case, risk of vertical transmission between 1 and 3%
- Expected gain from an elective C Section: maximum 1% reduction in the risk of vertical transmission
- However, the increase in maternal and fetal morbidity in the event of elective C- section during the current pregnancy and during future pregnancies is >1%

=>we favor vaginal delivery between 50-400 cp/ml

Intravenous Retrovir will be given during caesarean section and/or labor if VL> 50 cp/ml.
In the event of a vaginal delivery, protective measures will be applied such as:

- Rupture of membranes as late as possible.
- No internal electrode or scalp pH
- No “routine” instrumental extraction or “routine” episiotomy
- (Consider disinfection of vagina, the cord and newborn with chloramine: scant data supporting that)

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2. Management of infants/children born from a mother living with HIV

Risk stratification

Lowest risk

- Full VL suppression before and throughout pregnancy

Intermediate risk

- Maternal VL detectable at some point during the pregnancy but <50 copies/mL before birth

High risk

- Maternal VL known or suspected to be >50 copies/mL at delivery

VL = viral load

Optimal scenario: Full VL suppression before and throughout pregnancy

- No post-exposure prophylaxis
- AZT 4 weeks could be offered at the request of the parents, mainly/only for parents who already have a child who received a PEP at birth
- Neonatal follow-up without breastfeeding:
  - DNA + RNA testing
    - At birth (0-2 days)
    - 6 weeks
    - 12 weeks
  - Serology screen test at ≥20 months

Maternal VL detectable at some point during the pregnancy but <50 copies/mL before birth

- AZT 4 weeks
- Neonatal follow-up without breastfeeding:
  - DNA + RNA testing
    - At birth (0-2 days)
    - 6 weeks
    - 12 weeks
  - At least 2 tests after completion of PEP, ≥4 weeks apart
  - Serology screen test at ≥20 months

Maternal VL known or suspected to be >50 copies/mL at delivery

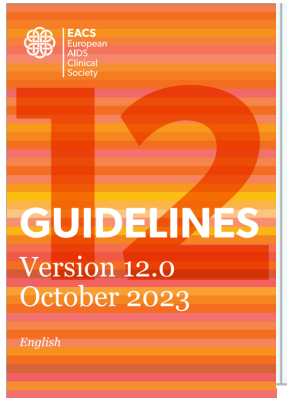
- Triple therapy 4 weeks – Preferred : AZT + 3TC + NVP
- If NVP not indicated (demonstrated/suspected maternal virus resistance): replace NVP with LPV/R or RAL

- If maternal viral load sampled at birth is <50 cp/mL, triple therapy could be simplified in favor of AZT alone for 4 weeks

Maternal VL known or suspected to be >50 copies/mL at delivery

- Neonatal follow-up without breastfeeding:
  - DNA + RNA testing
    - At birth (0-2 days)
    - 2 to 3 weeks
    - 6 weeks
    - 3 months
    - 6 months
  - The rationale to add a testing at 6 months of age is that combination ART has the potential to interfere with the sensitivity of the PCR tests for a prolonged period of time.
  - Serology screen test at ≥20 months

3. Breastfeeding infants born from a mother living with HIV



- **Breastfeeding is not recommended routinely**
- **In situations where there is persistently undetectable maternal HIV viral load and very low risk of transmission, breastfeeding may be facilitated by joint decision making and with appropriate close monitoring of mother and infant. Please see the section on General Principles of Postnatal Prophylaxis and Infant Feeding for details, on page 157**

World Health Organization

FULL LENGTH ARTICLE | VOLUME 283, P86-89, APRIL 2023 Download Full Issue

Successful implementation of new Swiss recommendation breastfeeding of infants born to women living with HIV

Pierre Alex Crisinel • Katharina Kusejko • Christian R Kahlert • ... Andri Rauch • Paolo Paioni • Karoline Aebi-Popp • Show all authors • Show footnotes

Open Access • Published: February 14, 2023 • DOI: https://doi.org/10.1016/j.ejogrb.2023.02.013 •

BHIVA British HIV Association

BREACH

Breastfeeding is not routinely recommended

When women decide to breastfeed, despite having been informed about the potential harms, as professionals it is our duty to offer proper guidance and follow-up in a supportive environment

Eligibility criteria

- Long-term follow-up with undetectable viral load on cART
- Proof of excellent adherence

= OPTIMAL SCENARIO (LOW RISK)

- Women in the INTERMEDIATE RISK group : discourage B/F but same service/support should be offered if decision to B/F

Prenatal preparations

- **Multidisciplinary** prenatal consultation to discuss the pros and cons.
- **Involve the father** in the decision process if possible.
- An **information leaflet** must be available to the parents to help them to make a decision. This document should be signed, ideally by both parents.
- Lack of financial resources **should not be** the main motivation to breastfeed. In that case, financial/material support should be sought.

Post-natal follow-up

MAX 6 MONTHS EXCLUSIVE BREASTFEEDING IS RECOMMENDED

BABY	MOTHER
• Clinical f/up and PCR/6 weeks until 3 months post weaning • Serology ≥ 20 months • AZT could be proposed to parent's request • In case of INTERMEDIATE RISK →AZT 4 weeks	• VL/6 weeks as baby • Special attention to adherence • B/feeding-nipples supervision by a specialized nurse • HIV VL in milk can be performed if available

BREACH

When and how to interrupt breasfeeding

1. Gastro-enteritis, cracked nipples, candidiasis, mastitis
   - Express milk, throw it away and restart B/F when healing
   - Use contralateral breast if healthy (in case of mastitis/cracked nipples)
2. Blip > 50 copies/ml : stop B/F and discourage resuming
   - If minor blip 50-100 copies/ml and VL undetectable again a case-by-case discussion to consider resuming B/F
   - If viral detection in milk, stop B/F even if undetectable VL in plasma
3. When weaning is decided : cabergoline should be proposed (if not contraindicated). Frozen breastmilk could be used to facilitate the transition.

Belgian guidelines

- Available
  - On the BREACH web site
  - BVIKM/SBIMC
  - Pediatric society

- Will be submited to publication

- Reviewed by the group at least once a year and whenever there will be a breaking change

Perspectives

- Belgian registry for delivery
- Belgian registry collecting prospectively breastfeeding cases

Thank you for your attention

EACS guidelines 2023

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III DRV/r 800/100 mg qd not recommended as initial ART during pregnancy due to decreased levels, but could be continued if the woman has already undetectable VL. DRV/c is not recommended during pregnancy due to significant lower exposures of DRV and COBI in the second and third trimester of pregnancy

IV Boosting with COBI is not recommended after the second trimester of pregnancy (insufficient drug levels)

V ABC contraindicated if HLA-B*57:01 positive. Even if HLA-B*57:01 negative, counselling on HSR risk still mandatory. If testing for HLA-B*57:01 results in delay of ART initiation, consider other recommended backbone

VI EFV not active against HIV-2 and HIV-1 group O strains

VII Lower RPV exposure during second and third trimesters; Consider monitoring VL more frequently. RPV is not active against HIV-2

VIII Pregnant women are often prescribed anti-H2 or proton pump inhibitors for nausea. Careful review of concomitant medicines at each visit and providing pregnant women with information on potential interactions is recommended

Treatment of Pregnant Women Living with HIV or Women Considering Pregnancy

Scenarios for pregnant women or women who wish to conceive

1. Women planning to be pregnant or becoming pregnant while already on ART	- Maintain ART: The main goal of ART during pregnancy is maintaining treatment efficacy, both for the women's benefit and HIV transmission risk. - ART may be switched temporarily for the duration of pregnancy to the preferred combinations recommended for ART naïve pregnant women, see table 1 - The decision on switching ART should be individualized taking into account the person's history of treatment, adherence and tolerability, and weighed against potential risk coming from ART exposure or suboptimal pharmacokinetics in pregnancy - If the purpose for switching is insufficient data about safety and efficacy in pregnancy, it should be explained to the pregnant woman and her decision/ willingness to switch current regimen taken into account: • Lower serum concentration was observed in persons on therapies boosted with COBI, DRV/r qd and RPV • There is insufficient data in pregnancy for BIC, DOR, RAL qd, and dual regimens - Pregnant women should be monitored monthly or bimonthly (depending on adherence and length of virological suppression) and as close as possible to the predicted delivery date. HIV-VL should be tested every two months of pregnancy and including 36 weeks of gestation
2. Women becoming pregnant while treatment-naïve	Starting ART as soon as possible is highly recommended, see table 1
3. Women whose follow-up starts late in the second or in the third trimester	Start ART immediately (see table 1) and consider RAL or DTG as the preferred choice to obtain rapid HIV-VL decline and to ensure the HIV-VL is undetectable by the time of delivery
4. Women whose HIV-VL is not undetectable at third trimester	Perform resistance testing and consider changing to or adding INSTI (RAL or DTG) if not on this class to obtain rapid HIV-VL decline
5. Women whose HIV-VL is > 50 copies/mL at week 34-36 of pregnancy	Elective cesarean section to be planned at week 38, see labour and breastfeeding
6. Women diagnosed with HIV in labour	See labour and breastfeeding
7. Labour	**1) Women whose HIV-VL is > 50 copies/mL at week 34-36:** • Elective cesarean section to be planned at week 38 • iv ZDV: During labour and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery - Scheduled cesarean delivery: start iv ZDV 3 hours before surgery - Unscheduled cesarean delivery: consider administering loading dose then proceed to delivery **2) Women diagnosed with HIV during labour:** • If possible, perform caesarean section • iv ZDV: During labour and delivery: 2 mg/kg loading dose followed by continuous iv infusion of 1 mg/kg/hour until delivery. Consider administering loading dose then proceed to delivery Postnatal prophylaxis (PNP) should be given to all newborns born to mothers living with HIV according to local guidelines. For antiretroviral therapy in children with HIV, See page 153
8. Breastfeeding	• **Breastfeeding is not recommended routinely** • **In situations where there is persistently undetectable maternal HIV viral load and very low risk of transmission, breastfeeding may be facilitated by joint decision making and with appropriate close monitoring of mother and infant. Please see the section on General Principles of Postnatal Prophylaxis and Infant Feeding for details, on page 157**