CHAPTER 6
OBSTETRICS

Note: For medical complications during pregnancy, refer to the relevant chapters. Only common conditions specific to pregnancy or requiring special management in pregnancy are included in this chapter.

6.1 ANAEMIA IN PREGNANCY

O99.0 + (D50.9/D64.9)

DESCRIPTION

Haemoglobin (Hb) <11 g/dL. Anaemia in pregnancy is most commonly due to iron deficiency. Hb levels in pregnancy should be checked routinely on-site at the first antenatal visit, and again at 30 weeks and 38 weeks. If Hb falls below 10g/dL, commence treatment with iron and do a FBC.

LoE:IVb[i]

GENERAL MEASURES

A balanced diet to prevent nutritional deficiency.
Advise against eating soil, clay, charcoal, and excessive consumption of tea and coffee.

MEDICINE TREATMENT

Prophylaxis Z34.9 + (Z29.9)

- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) twice daily.

OR

LoE:IVb[ii]

Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) daily.

<u>If daily iron is poorly tolerated (e.g., epigastric pain, nausea, vomiting, and constipation), intermittent iron supplementation may be administered:</u>

- Ferrous sulfate compound BPC (dried), oral, 340 mg per week, (± 110 mg elemental iron), with meals.

OR

- Ferrous fumarate, oral, 400 mg per week (± 130 mg elemental iron).

LoE:IVb[iii]

(For folic acid supplementation guidance to prevent neural tube defects, see Primary Health Care STGs and EML, section 6.4.1: Antenatal supplements).

Treatment: Iron deficiency (Hb <10g/dL)

- Ferrous sulfate compound BPC, oral (dried), 170 mg (± 55 mg elemental iron) 12 hourly.

OR

LoE:IIb[iv]

Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.
- Continue for 3-6 months after Hb reaches normal to replenish iron stores.
- Hb is expected to rise by at least 1.5 g/dL in two weeks.
- When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.
- If Hb has not increased after 4 weeks of therapy, do a FBC to confirm hypochromic microcytic anaemia.

LoE:IIIb[y]

Parenteral iron - See section: 2.1.1 Anaemia, iron deficiency.
If there is no response to oral iron, and iron deficiency is confirmed, review adherence to oral iron, and consider:

- Iron, IV, e.g.:
- Iron sucrose, IV, 200 mg in 200 mL sodium chloride 0.9%, over 30 minutes, given on alternate days until the total dose has been given**.**
  - **Note:** Test dose is not required but administer only where personnel and therapies are readily available to manage anaphylactic-type reactions.
  - An initial total dose of 600 mg is usually adequate to raise the Hb to acceptable levels.
  - For markedly anaemic or very obese women, consult the package insert on the total dose of iron infusion.

LoE:IVb

REFERRAL/CONSULTATION
No response to management.

6.2 DIABETES MELLITUS IN PREGNANCY
O24.0-4/O24.9
This condition should ideally be managed in consultation with a specialist.

DESCRIPTION
Established diabetes: Diabetes (type 1 or 2) predating pregnancy.
Gestational diabetes mellitus (GDM): carbohydrate intolerance first recognised during pregnancy. It does not exclude the possibility that diabetes preceded the pregnancy.

Diagnostic criteria for GDM
Either a fasting plasma glucose ≥5.6 mmol/L **OR** a plasma glucose of ≥7.8 mmol/L two hours after a 75 g oral glucose tolerance test.

The following women should be screened for GDM, between 24 and 28 weeks of gestation:
» Women of Indian ethnic origin.
» BMI >35 kg/m^2.
» Age >40 years of age.
» GDM in previous pregnancy.
» Family history (first degree relative) of diabetes.

» Previous unexplained third trimester fetal death.
» Previous baby with birthweight >4.5 kg.
» Polyhydramnios in index pregnancy.
» Glycosuria (≥1+ glucose in urine on 2 or more occasions).
» A fetus that is large for gestational age. *LoE:IIIb*[vi]

GENERAL MEASURES

» Stop smoking.
» Moderate exercise.
» Dietary advice.

Elective delivery at about 38 weeks' gestation.

MEDICINE TREATMENT

If fasting glucose is <7 mmol/l at diagnosis, promote lifestyle changes (diet and moderate exercise).
Assess after 2 weeks. *LoE:IIIb*[vii]

Fasting glucose ≥7 mmol/l, or no response to lifestyle changes:

- Metformin, oral, 500 mg daily.
  - Increase dose to 500 mg 12 hourly after 7 days.
  - Titrate dose to a maximum of 850 mg 8 hourly according to glucose control.
  - Contra-indications to metformin: liver or renal impairment.
  - If not tolerated, change to insulin.

Do capillary (fingerprick) glucose profiles, i.e. pre-prandial and 1-hour or 2-hour (2-hours more practical) post-prandial for breakfast, lunch and supper.
Aim for:

» Preprandial level <5.3 mmol/L and either
» 1-hour postprandial <7.8 mmol/L or
» 2-hour postprandial <6.4 mmol/L

LoE:IVb[viii]

Abnormal profiles

Women with diabetes treated with metformin but with poor glucose control should be admitted.
Add insulin.
Insulin requirements may increase with increasing gestation and later readmission may be necessary.

Preferred insulin regimen

- Insulin, short-acting with all 3 meals to maintain the 2-hour postprandial glucose levels <6.4 mmol/L.

AND

- Insulin, intermediate-acting at bedtime (with a bedtime snack) to maintain the fasting (morning) preprandial glucose levels <5.3 mmol/L.

Insulin dosing (in addition to metformin):

- Total daily dose: SC, 0.1 units/kg/day.

- One third of the total dose: intermediate acting insulin at bedtime.
- The remaining two thirds divided into three equal doses: short-acting insulin given before each meal (breakfast, lunch and supper).
- Adjust insulin dosage daily according to blood glucose profiles, until control is adequate.

LoE:IIIb[ix]

Where the above recommended regimen is not feasible

Twice-daily regimen with biphasic insulin.

- Insulin, biphasic.
  - Daily dose: SC, 0.5 units/kg/day, two thirds, 30 minutes before breakfast and one third 30 minutes before supper.
  - Titrate to achieve target capillary (fingerprick) glucose as above. *LoE:IIIb*[x]

Delivery

Plan induction of labour at 38 weeks' gestation, provided glucose control is adequate, or earlier with maternal co-morbid conditions, or if glycaemic control is poor. If the estimated fetal weight (EFW) on ultrasound is >4 kg, offer elective Caesarean delivery.

During labour:

Monitor glucose hourly.

Stop subcutaneous insulin.

Administer short-acting insulin to maintain physiological blood glucose levels.

- Insulin, short-acting, continuous IV infusion, 20 units plus 20 mmol potassium chloride in 1 L dextrose 5% at an infusion rate of 50 mL/hour, i.e. 1 unit of insulin/hour.
  - If blood glucose <4 mmol/L, discontinue insulin.
  - If >7 mmol/L, increase infusion rate to 100 mL/hour.

Postpartum insulin requirements decrease rapidly.

During the first 48 hours give insulin 4-hourly according to blood glucose levels.

Resume pre-pregnancy insulin or oral hypoglycaemic regimen once eating a full diet.

The newborn is at risk of:

» hypoglycaemia
» hyperbilirubinaemia
» respiratory distress syndrome
» congenital abnormalities

Postpartum management

Contraception Z30.0 + (O24.3-4/O24.9)

Tubal ligation should be considered.

Consider:

- Low-dose combined contraceptive in well-controlled cases.
- Progestin-only preparation **or** intra-uterine contraceptive device if planning to breastfeed.

See Primary Health Care chapter 7: Family planning.

Need for ongoing anti-diabetic therapy

Offer women diagnosed with GDM during the index pregnancy an oral glucose tolerance test after 6 weeks postpartum to assess whether they have diabetes needing ongoing therapy.

REFERRAL/CONSULTATION

» Obese women (BMI > 40 kg/m^2)
» Excessive fetal growth despite adequate diabetes control.
» Poor glucose control despite adequate insulin.

6.3 HEART DISEASE IN PREGNANCY

O99.4 + (I51.9)

All women with heart disease require referral for specialist evaluation and risk assessment. The risk is particularly high in women with mechanical valves, Eisenmenger's syndrome or pulmonary hypertension. Termination of pregnancy (TOP) is an option for women with severe heart disease if recommended by a specialist.

GENERAL MEASURES

All pregnant women with haemodynamically significant heart disease require multidisciplinary management in consultation with both obstetrician and physician/cardiologist.
Consider thyrotoxicosis, anaemia, and infection, which may precipitate cardiac failure.
Spontaneous delivery is usually preferable to Caesarean delivery, unless there are obstetric reasons for surgery.
Women with prosthetic heart valves should be counselled about the risks of pregnancy to themselves and their fetus; and offered effective contraception.

During labour:

» Nurse in semi-Fowler's position.
» Avoid unnecessary intravenous fluids.
» Give adequate analgesia.
» Give antibiotic prophylaxis for infective endocarditis, guided by the nature of the heart lesion (for cardiac indications and antibiotic recommendations see section 3.5: Endocarditis, Infective). Procedures for which endocarditis prophylaxis is indicated include:
  – Vaginal delivery in the presence of suspected infection.
  – Caesarean delivery.
  – Assisted vaginal delivery.
  – Prelabour rupture of membranes.
» Avoid a prolonged second stage of labour by means of assisted delivery with forceps (preferably) or ventouse.
» Avoid ergometrine after delivery of the newborn.
» Observe in a high care area for 24 hours post-delivery, as the risk of pulmonary oedema is highest in this period.

Contraception, including the option of tubal ligation should be discussed during the antenatal period and after delivery in all women with significant heart disease.
Women who had life-threatening complications during pregnancy should be advised not to become pregnant again.

Anticoagulation during pregnancy:
Indications for full anticoagulation during pregnancy (high risk):

» *Valvular disease with atrial fibrillation*: Women with valvular heart disease should be guided to consider completing their family early and then consider family planning including tubal ligation, before progressing to requiring mechanical valves.
» *Mechanical prosthetic heart valves:* Women with mechanical prosthetic heart valves should be offered contraception (preferably a LARC not containing estrogen); see PHC STGs and EML, chapter 7: Family planning. If they conceive, offer the option of TOP or refer to tertiary centre for anticoagulation management by a multi-disciplinary team.

MEDICINE TREATMENT

A. Thromboprophylaxis for pregnant women with valvular disease and atrial fibrillation:

1. First trimester

- Enoxaparin SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin, IV, 5 000 units as a bolus.
  - Followed by 1 000–1 200 units/hour as an infusion.

OR

- Unfractionated heparin, SC, 15 000 units 12 hourly.
  - Adjust the dose to achieve a mid-target PTT at 2–3 x control.

Practise strict infection control if using multi-dose vials, with one vial per patient and use of needle-free adaptor.

2. Second trimester until 36 weeks

- Warfarin, oral, 5 mg daily.
  - Adjust dose to keep INR within the therapeutic range of 2–3.

3. After 36 weeks until delivery

- Enoxaparin SC, 1 mg/kg 12 hourly.

OR

- Unfractionated heparin, IV, 5 000 units as a bolus.
  - Followed by 1 000–1 200 units/hour as an infusion.

OR

- Unfractionated heparin, SC, 15 000 units 12 hourly.

- Adjust dose to keep aPTT 2–3 x control.

4. Delivery
Stop heparin on the morning of elective Caesarean delivery (6 hours before scheduled surgery) or when in established labour, and re-start 6 hours after vaginal delivery or 12 hours after Caesarean delivery, as long as there is no concern that the patient is bleeding.

Secondary prophylaxis for venous thromboembolism - see chapter 2: Blood and blood forming organs, section 2.8.1: VTE during pregnancy and the puerperium.

B. Cardiac failure during pregnancy O99.4 + (I50.9)
See section 3.4: Congestive Cardiac Failure.
Treatment is as for non-pregnant women, except that **ACE-inhibitors, ARBs and spironolactone are contra-indicated.** *LoE:IVb*[xi]

If a vasodilator is needed:
- Hydralazine, oral, 25 mg 8 hourly.
  - Maximum dose: 200 mg daily.

AND
- Isosorbide dinitrate, oral, 20 mg 12 hourly.
  - Maximum dose: 160 mg daily.

C. Delivery by a cardiac patient O99.4 + (I51.9)
Contraction and retraction of the uterus after delivery increases the total peripheral resistance, and causes a relative increase in circulating volume. This may precipitate pulmonary oedema.

In women with NYHA grade II dyspnoea or more, consider the use of furosemide:
- Furosemide, IV, 40 mg with delivery of the baby.
  - Monitor for 48 hours thereafter for pulmonary oedema.

REFERRAL
» All pregnant women with mechanical prosthetic heart valves requiring anticoagulation.

Pregnant women with mechanical prosthetic valves should not receive LMWH unless antifactor Xa levels can be monitored reliably weekly. Therapeutic range is pre-dosing level 0.6 units/mL and a 4-hour peak level of 1–1.2 units/mL

6.4 HYPERTENSIVE DISORDERS IN PREGNANCY
O10.0/O11/O14.0-2/O14.9/O16

DESCRIPTION
Hypertensive disorders are one of the most common direct causes of maternal

mortality and are responsible for significant perinatal and maternal morbidity. These disorders include chronic hypertension, pre-eclampsia, eclampsia and HELLP Syndrome. Early detection and timely intervention is essential to prevent maternal and perinatal complications.

GENERAL MEASURES

Bed rest, preferably in hospital.
Lifestyle adjustment and diet.
Monitor BP, urine output, renal and liver function tests, platelet count, proteinuria, and fetal condition.
Consider delivery when risks to mother outweigh risks of prematurity to baby.

MEDICINE TREATMENT

Treatment

Antihypertensives

Medicine treatment will be dictated by blood pressure response.
Monitor progress until a stable result is achieved.
In general, diuretics are contra-indicated for hypertension in pregnant women.
When needed, combine drugs using lower doses when BP >160/100 mmHg, before increasing single medication doses to a maximum.

- Methyldopa, oral, 250 mg 8 hourly as a starting dose. *LoE:IVb*[xii]
  - Increase to a maximum of 750 mg 8 hourly, according to response.

AND/OR

- Long-acting calcium channel blocker, e.g.:
- Amlodipine, oral, 5 mg daily.
  - Increase to 10 mg daily. *LoE:IIb*[xiii]

Preeclampsia

Preeclampsia is defined as hypertension with significant proteinuria developing for the first time after 20 weeks' gestation, and can also be superimposed on chronic hypertension - evidenced by the new onset (after 20 weeks' gestation) of persistent proteinuria in a woman who had an initial diagnosis of chronic hypertension.

Pre-eclampsia without severe features:
A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but no symptoms or organ dysfunction.

Maternal features of severe disease:

» Acute severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic ≥160 mmHg).
» Thrombocytopenia (platelet <100 000/µL).
» Impaired liver function (ALT or AST >40 IU/L).
» Severe persistent right upper quadrant or epigastric pain.
» HELLP syndrome (platelets <100 000 and AST >70 U/L and LDH >600 U/L).
» Serum creatinine ≥120 micromol/L.
» Pulmonary oedema.

» New-onset severe headache unresponsive to medication.
» Visual disturbances.

Hypertensive emergency O10.0/9
SBP ≥160 mmHg and/or DBP ≥110 mmHg. Admit to a high-care setting for close monitoring.

- Nifedipine, oral, 10 mg.
  - Repeat after 30 minutes if needed, until systolic blood pressure <160 mmHg and diastolic blood pressure <110 mmHg.
  - Swallow whole. Do not chew, bite or give sublingually.

LoE:IIIb[xiv]

If unable to take oral or inadequate response:

- Labetalol, IV infusion, 2 mg/minute to a total of 1–2 mg/kg.
  - Reconstitute solution as follows:
    - Discard 40 mL of sodium chloride 0.9% from a 200 mL container.
    - Add 2 vials (2 x 100 mg) of labetalol (5 mg/mL) to the remaining 160 mL of sodium chloride 0.9% to create a solution of 1 mg/mL.
    - Start at 40mL/hour to a maximum of 160 mL/hour.
    - Titrate against BP – aim for BP of 140/100 mmHg.
  - Once hypertensive crisis has resolved, switch to an oral preparation.

LoE:Ia[xv]

Delivery

- Oxytocin, IM, 10 units as a single bolus after delivery of the baby.

LoE:IVb[xvi]

Ergot-containing medicines are contraindicated in hypertensive women, including pre-eclampsia, following delivery of the baby.
Pre-eclamptic and eclamptic women are often hypovolaemic, particularly when the haematocrit exceeds 40%, but are also susceptible to pulmonary oedema. Consequently, hypotension is a risk during anaesthesia. Careful infusion of IV fluids is important. Limit blood-loss at Caesarean section.

6.4.1 PREECLAMPSIA

O11/O14.0-2/O14.9

DESCRIPTION

Preeclampsia is defined as hypertension with significant proteinuria developing for the first time after 20 weeks' gestation, and can also be superimposed on chronic hypertension - evidenced by the new onset (after 20 weeks' gestation) of persistent proteinuria in a woman who had an initial diagnosis of chronic hypertension.

Pre-eclampsia without severe features:
A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but no symptoms or organ dysfunction.

Maternal features of severe disease:
» Acute severe hypertension (diastolic BP ≥ 110 mmHg and/or systolic ≥160

mmHg).
» Thrombocytopenia (platelet <100 000/µL).
» Impaired liver function (ALT or AST >40 U/L).
» Severe persistent right upper quadrant or epigastric pain.
» HELLP syndrome (platelets <100 000 and AST >70 U/L and LDH >600 U/L).
» Serum creatinine ≥120 micromol/L.
» Pulmonary oedema.
» New-onset severe headache unresponsive to medication.
» Visual disturbances.

Prevention of pre-eclampsia Z29.2 + O10.0/O24.0-3/O99.1/O99.8 + (D68.6/M32.9)
For women at high risk of pre-eclampsia, e.g. pre-eclampsia in a previous pregnancy, chronic hypertension, diabetes, antiphospholipid syndrome, or SLE.

From 6 weeks' gestation onwards, preferably starting before 16 weeks' gestation:
- Aspirin, oral, 150 mg daily until 36 weeks. *LoE:Ia*[xvii]

At confirmation of pregnancy
- Calcium, oral.
  - For high-risk patients: Calcium (elemental), oral, 1 gram daily.
  - Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women.
  - When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.

LoE:Ia[xviii]

Prevention of eclampsia
To prevent eclamptic seizures, magnesium sulfate is recommended for patients with severe features. In some cases this allows for delivery to be delayed to improve neonatal outcome. When used for prevention of eclampsia, magnesium sulfate is administered for 24 hours, and then stopped. The same dose regimens are used as for eclampsia. Women with severe features should be managed under specialist care.

6.4.2 ECLAMPSIA
O15.0-2/O15.9

DESCRIPTION
Generalised tonic-clonic seizures after 20 weeks of pregnancy or within 7 days after delivery associated with hypertension and proteinuria. Exclude any other obvious cause of the seizure before making the diagnosis. Management will include preventing further seizures, controlling the blood pressure, referral to a high-care unit, and delivery of the baby if not already post-delivery.

GENERAL MEASURES
Place patient in left-lateral position.

Clear airway. If necessary, insert oropharyngeal airway.
Abort seizures with magnesium sulfate.

MEDICINE TREATMENT

If necessary:

- Oxygen via nasal prongs or face mask to maintain a saturation of >90%.

Treatment

Where infusion pumps are not available:

- Magnesium sulfate, IV, 4 g in 200 mL sodium chloride 0.9% over 20 minutes.

Follow with:

- Magnesium sulfate, IM, 5 g every 4 hours administered at different sites, until 24 hours after delivery or following the last convulsion.

In high-care setting:

- Magnesium sulfate, IV, 4 g in 200 mL sodium chloride 0.9% over 20 minutes (loading dose).

Follow with:

- Magnesium sulfate, IV infusion, 1 g every hour, until 24 hours after delivery, or after the last convulsion (maintenance dose).

STOP MAGNESIUM SULFATE IF KNEE REFLEXES BECOME ABSENT OR IF URINE OUTPUT <100 ML/ 4 HOURS OR RESPIRATORY RATE <16 BREATHS/MINUTE.

IF RESPIRATORY DEPRESSION OCCURS:

- Calcium gluconate 10%, IV, 10 mL given slowly at a rate not exceeding 5 mL/minute.

Recurrent eclamptic seizure despite magnesium sulfate loading dose administration:

- Magnesium sulfate, IV, 2 g over 10 minutes.

For agitated and restless women with eclampsia:

- Lorazepam, IV/IM, 4 mg.
  - May be repeated after 10-15 minutes.
  - Maximum dose: 8 mg.

OR

Clonazepam, IV, 2 mg.

- May be repeated after 5 minutes.
- Maximum dose: 4 mg.

OR

If above not available:

Diazepam, IV, 10–20 mg, not faster than 2 mg/minute.

Notify the person who will resuscitate the newborn that a benzodiazepine and/or magnesium has been given to the mother.

REFERRAL
Refer all eclampsia cases to a high or intensive care facility.

6.4.3 CHRONIC HYPERTENSION
O10.0-4/O10.9

GENERAL MEASURES
Lifestyle modification
» No alcohol should be taken.
» Regular moderate exercise, e.g. 30 minutes brisk walking at least 3 times a week.
» Smoking cessation.
» Aim to keep BP <140/90 mmHg.

Screen for end-organ damage.
Fetal surveillance by symphysis-fundus height (SFH) growth. Umbilical artery Doppler screening (where available) at 24-26 weeks.
Ask mother about fetal movements at each antenatal visit. *LoE:IIb*[xix]

Consider labour induction if:
» BP persistently ≥160/110 mmHg, or
» pregnancy of ≥38 weeks duration, or
» in the presence of maternal or fetal compromise, e.g., poor SFH growth and oligohydramnios, etc.

MEDICINE TREATMENT
See prevention and treatment of pre-eclampsia.
Switch ACE-inhibitors and diuretics to methyldopa and/or amlodipine. Women should be advised that there is an increased risk of congenital abnormalities if ACE-inhibitors were taken during pregnancy.

6.4.4 GESTATIONAL HYPERTENSION
See to PHC STGs and EML, Chapter 6: Obstetrics and gynaecology, sections 6.4.2.2: Gestational hypertension: no severe features, and 6.4.2.3: Gestational hypertension: with severe features.

6.5 CORONAVIRUS DISEASE-19 (COVID-19) IN PREGNANCY
U07.1/U07.2
*Notifiable medical condition.

ANTENATAL CARE:

» Antenatal care is an essential service and should not be scaled down during lockdown periods.
» Screening and testing criteria for SARS-CoV-2 infection during pregnancy is the same as for the general population.
» Vaccination against Covid-19 and influenza is safe at all gestations of pregnancy and during COVID-19 pandemic it is important that pregnant women take up the COVID-19 and influenza vaccine to reduce their risk of contracting either. (See PHC STGs and EML, Section 13.7: Other vaccines).
» The clinical course and outcome of COVID-19 is not different in pregnancy and most pregnant women who are infected with SARS-CoV-2 will experience only mild or moderate symptoms.
» Up to 75% of infected women in pregnancy may be asymptomatic, and appropriate PPE must be used for all deliveries, regardless of the status of the mother. All pregnant women attending hospital, including women in labour, should wear masks.
» Maternal COVID-19 is associated with an approximately three times greater risk of preterm birth and women should be counselled on warning signs of spontaneous preterm labour. *LoE:IIIb*[xx]
» Risk factors for more severe disease or admission to hospital with COVID-19 include: *LoE:IIIb*[xxi]
  - Obesity (pre-pregnancy BMI >30 kg/m^2).
  - Co-morbidity, such as pre-existing diabetes (see section 6.2: Diabetes mellitus in pregnancy) and chronic hypertension (see section 6.6: Chronic hypertension).
  - Age >35 years
» SARS-CoV-2 infection is not associated with an increase in the incidence of congenital abnormalities..

THROMBOPROPHYLAXIS:

All pregnant women admitted with confirmed or suspected COVID-19 should be offered prophylactic LMWH or unfractionated heparin for 10 days, unless birth is expected within 12 hours. See section 2.8: Venous thrombo-embolism.

DELIVERY:

» COVID-19 infection is not an indication for delivery, unless delivery is required as part of maternal resuscitation to improve maternal oxygenation.
» When a woman with COVID-19 presents with spontaneous preterm labour, suppression of labour (to delay delivery in order to administer antenatal corticosteroids) should not be done.
» All women with confirmed or suspected SARS-CoV-2 infection must preferably deliver in a dedicated COVID-19 hospital or ward.

MEDICINE TREATMENT

Observe oxygen saturation measurement hourly.

- Oxygen, if saturation is <94%.

Symptomatic relief of headache:

- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Note: Avoid morphine analgesia if patient is respiratory compromised.

In pregnant patients who require supplemental oxygen:

» Corticosteroids crosses the placenta and may have long-term deleterious effects on the child.

If corticosteroids are also needed to accelerate fetal lung maturity: See section 6.12: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM).

If corticosteroids are not needed for fetal lung maturity:

- Corticosteroids, e.g.:
- Dexamethasone, IV, 6 mg daily for up to 10 days, or until discharge.

If there is a concern over in-utero steroid exposure, use alternative therapy (with less placental transfer):

- Prednisone, oral 40 mg daily, for up to 10 days, or until discharge.
  OR
  Hydrocortisone, IV, 80 mg 12 hourly for up to 10 days, or until discharge.

LoE:IIa[xxii]

Anaesthetic:

- Spinal anaesthesia is the anaesthetic of choice in the absence of contra-indications. See section 12.7: Anaesthesia, spinal (intrathecal). The patient should wear a surgical facemask for the duration of the perioperative period.

POSTPARTUM:

» Infection with SARS-CoV-2 is not a contra-indication to breast feeding.

» There is no contra-indication to the use of post-partum contraception (See PHC STGs and EML, Chapter 7: Family planning).

6.6 HIV IN PREGNANCY

O98.7 + (Z21/B24)

Consult the most recent National Department of Health Guideline for Vertical Transmission Prevention of Communicable Infections

All pregnant women should receive routine counselling and voluntary HIV testing at their very first antenatal visit.

All women who test negative or who decline testing, should be offered repeat HIV testing at every routine visit throughout pregnancy (8 visits in all), at labour/delivery, at the 6-week EPI visit, and three monthly throughout breastfeeding.

WLHIV should be clinically staged and have a blood sample taken for CD4 cell count and serum creatinine on the same day as diagnosis. The results must be obtained within a week.

Initiate lifelong ART in all pregnant or breastfeeding women on the same day of diagnosis regardless of CD4 count or infant feeding practice.

Provide adequate support and counselling, particularly addressing ART adherence.

Discuss postpartum contraceptive use in the antenatal period.

Educate all women during the antenatal period about the benefits of exclusive breastfeeding for the first 6 months and breastfeeding with complimentary feeding from 6 months until at least 2 years after delivery. (Only in circumstance where the mother has confirmed 2nd or 3rd line ART regimen failure (VL >1000 copies/mL), advise not to breastfeed and prescribe replacement feeds).

Perform a TB symptom screen for all pregnant women at each visit. If any of the answers to the screening questions are positive, do further TB investigations. A TB-NAAT test must be done for all pregnant women with a new diagnosis of HIV disease, or known HIV positive women with a new pregnancy.

Screen and treat all patients for syphilis and other STIs, in line with basic antenatal care.

Test partner for HIV and perform routine cervical cancer screening.

Assist women with unwanted pregnancies <20 weeks' gestation with access to TOP services.

MEDICINE TREATMENT

» Patients should receive ART at the first antenatal visit, whether newly diagnosed or known to be living with HIV but not on ART.

» Tenofovir should not be used in pregnant women with a serum creatinine ≥85 micromol/L (a more sensitive measure of renal impairment in pregnancy than calculated creatinine clearance).

» Pregnant women may be initiated on/switched to a dolutegravir-containing regimen.

LoE:IIb[xxiii]

» Initiate antenatal supplementation (see PHC STGs and EML, section 6.4.1: Antenatal supplements), noting that calcium and DTG should not be taken together on an empty stomach, but can be taken together with food.

1st ANC visit	
Pregnant women not on ART, with normal renal function, **without** TB.	• TDF, oral, 300 mg daily. **AND**

	• 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC).
Pregnant women not on ART, with normal renal function, **with** TB. (DTG requires boosting with TB treatment)	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC). **WITH** DTG, oral 50 mg 12 hours later.
Pregnant woman on TDF + FTC + EFV	Switch to TDF+3TC+DTG
Pregnant woman already on ART with a VL between 50-1000 copies/ml	See section 10.1: Antiretroviral Therapy
2nd ANC visit (1 week later)	
Creatinine ≤85 micromol/L	Continue ART as a FDC
Creatinine >85 micromol/L (TDF is contraindicated)	Replace TDF with ABC as part of a FDC: • ABC, oral, 600 mg daily **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily.

LoE:IIIb[xxiv]

Caesarean Delivery (CD):
Provide antibiotic prophylaxis to all pregnant women, including HIV-infected pregnant women prior to surgery (See chapter 11: Surgical antibiotic prophylaxis).

Women with the following risk factors may be at higher risk of infection post Caesarean delivery:
» Advanced immunosuppression.
» Prolonged rupture of membranes (>18 hours).
» Multiple vaginal examinations during labour (>5 PVs).
» Second stage CD.
Monitor carefully and treat infection appropriately.

HIV-infected pregnant women not on ART undergoing elective Caesarean delivery/or in labour:
- NVP, oral, 200 mg as a single dose.

WITH
- TDF, oral, 300 mg as a single dose.

AND
- 3TC, oral, 300 mg as a single dose.

AND
- DTG, oral, 50 mg as a single dose (as a FDC 4 hours before Caesarean delivery).

Followed by lifelong:
- TDF+3TC+DTG (provided as a FDC).

For management of the HIV-exposed infant, see PHC STG and EML, section 11.5.

For more information on HIV management, see section 10.1: Antiretroviral Therapy.

6.7 SYPHILIS

O98.1

DIAGNOSTIC CRITERIA

Most pregnant women infected with syphilis are asymptomatic.
See Primary Health Care STGs and EML, section 12.8: Syphilis serology and treatment.

GENERAL MEASURES

Inform contact(s).

MEDICINE TREATMENT

Mother (treat as either early or late latent/unknown stage of syphilis):

For late latent syphilis or syphilis of unknown duration
- Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), weekly for 3 doses.

Note: If the mother has received <3 doses, treat the baby for congenital syphilis.

For early syphilis *LoE:IIIb*[xxv]
- Benzathine benzylpenicillin (depot formulation), IM, 2.4 million units diluted in 6 mL 1% lidocaine without adrenaline (epinephrine), immediately as a single dose.

Severe penicillin allergy (Z88.0)
For penicillin sensitive pregnant women: penicillin desensitisation.
Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured. See "How to Use These Guidelines" for detailed information.

Oral penicillin desensitisation protocol

A: Prepare stock solution of oral phenoxymethylpenicillin 250mg/ 5mL and dilutions for steps 1-7 and 8-10 B: Administer increasing doses of penicillin strictly at 15 minutes intervals		
Step	**Medicine mg/mL**	**Amount to administer (mL)**
To make 0.5 mg/mL solution: Add 0.5 mL of stock phenoxymethylpenicillin solution to 49.5 mL water (total volume 50mL)		
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL orally
2		0.2 mL orally
3		0.4 mL orally
4		0.8 mL orally
5		1.6 mL orally
6		3.2 mL orally
7		6.4 mL orally
To make 5 mg/mL solution: Dilute 1 mL of stock phenoxymethylpenicillin solution with 9 mL water (total volume 10mL)		
8	5 mg/mL solution (10000 units/mL)	1.2 mL orally
9		2.4 mL orally
10		4.8 mL orally
Stock phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL		
11	50 mg/mL (80000 units/mL)	1.0 mL orally
12		2.0 mL orally
13		4.0 mL orally
14		8.0 mL orally

After step 14, observe for 30 minutes, then administer desired dose of intramuscular penicillin.

Note:

- Repeat desensitisation is not required for subsequent doses of the same treatment course (e.g., to complete 3 doses of benzathine benzylpenicillin for late latent syphilis or syphilis of unknown duration).
- However, second and third doses must be administered in a hospital setting.

Asymptomatic, well baby:

Mother has syphilis and has not been treated, or was only partially treated:

- Benzathine benzylpenicillin (depot formulation), IM, 50 000 units/kg as a single dose into the antero-lateral thigh.

Symptomatic baby

- Procaine penicillin, IM, 50 000 units/kg daily for 10 days. (Not for IV use).

OR

Benzylpenicillin (Penicillin G), IV, 50 000 units/kg, 12 hourly for 10 days.

6.8 HEPATITIS B IN PREGNANCY

O98.4

DESCRIPTION

Hepatitis B virus (HBV) is transmitted sexually or by percutaneous exposure to infectious body fluids, i.e., blood, saliva, vaginal fluid, and semen. Diagnosis is confirmed serologically by a positive hepatitis B surface antigen (HBsAg).

Screening in pregnancy for HBsAg should ideally be performed in the first trimester. HBeAg positive pregnant women are more infectious than HBsAg positive women, as they have higher rates of HBV replication.

GENERAL MEASURES

Screen sexual contact(s); if they are sero-negative, give hepatitis B vaccination.
All infected patients should be counselled with regard to lifestyle modifications to reduce hepatotoxicity, including alcohol, substance abuse, and co-prescription of herbal and traditional medicines.

MEDICINE TREATMENT

Indications for medical therapy in HIV-uninfected pregnant women are the same as for non-pregnant adults.

» For management of chronic hepatitis B, **without** chronic HIV infection, see section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection).
» For management of chronic hepatitis B **with** chronic HIV infection, see chapter 10: HIV and AIDS. (ART for women with chronic Hepatitis B should always include ARVs active against hepatitis B).

Note:

» Ensure normal renal function before starting treatment with TDF (serum creatinine <85 micromol/L or creatinine clearance >60 mL/minute).
» Monitor ALT and HBV DNA viral load at 6 months after commencing treatment.
» An adequate virological response is an HBV DNA VL<2000 IU/mL.

Prevention of perinatal transmission

» Caesarean delivery is reserved for obstetric indications only.
» Delivery should take place in a facility that can offer Hepatitis B vaccination to the baby at birth.
» Administration of ARVs active against HBV from 28 weeks of pregnancy will further reduce risk of vertical transmission.

Pregnant women who are HBsAg/ HBeAg positive and HIV negative

» All HIV negative pregnant women are eligible for HIV Pre-exposure prophylaxis (PrEP) (see PHC STGs and EML, section 11.11: Pre-exposure prophylaxis (PrEP)). TDF, which is included in the oral PrEP

regimen, has anti-HBV activity, and will reduce the risk of vertical transmission of HBV.
» Women who are HIV negative and HBsAg positive who decline PrEP must be counselled that TDF will reduce risk of vertical transmission of Hepatitis B to the baby, particularly if HBeAg is positive or HBV viral load is high.
» TDF 300 mg daily should be administered from 28 weeks of pregnancy until birth to women with a high hepatitis viral load (≥200 000 IU/mL), or positive HBeAg, or where HBeAg/viral load result is unavailable at 28 weeks.
» For care of babies born to: (1) mothers with acute hepatitis B infection at the time of delivery, (2) mothers who are HBsAg-positive, or (3) mothers who are HBeAg-positive, see Primary Health Care STGs and EML, section 6.6.5: Hepatitis B exposed infant.
» Obtain infectious disease specialist or internal medicine physician opinion before stopping TDF as there is a risk for postpartum hepatitis flare.
» Consider continued treatment for HBV after delivery where indicated (see section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection)).

For Pregnant women who are HBsAg/ HBeAg positive and HIV negative

- TDF, oral, 300 mg daily (from 28 weeks of pregnancy until birth).

LoE:IVb[xxvi]

REFERRAL
» Cirrhosis.
» Liver failure.
» Renal dysfunction (TDF is contraindicated in renal impairment. Tenofovir alafenamide (TAF) should be prescribed in place of TDF).
» Refer all infected babies to a specialist paediatrician for further management.

6.9 JAUNDICE IN PREGNANCY
O26.6

DESCRIPTION
The most common causes of jaundice in pregnancy are not pregnancy-specific. They include viral hepatitis, and adverse drug reactions.
Pregnancy-specific causes include:
» intrahepatic cholestasis of pregnancy,

» acute fatty liver of pregnancy (acute yellow atrophy of the liver),
» severe pre-eclampsia or eclampsia, and
» hyperemesis gravidarum.

REFERRAL
All, as certain causes of jaundice in pregnancy have a high mortality.

6.10 HYPEREMESIS GRAVIDARUM
O21.0/1/9

DESCRIPTION
Recurrent vomiting leading to ketosis, generally in the first trimester.
Exclude:
» medical causes, e.g., thyrotoxicosis, and
» molar pregnancy.

GENERAL MEASURES
Counselling.
Frequent small, dry meals.
Avoid fatty and spicy foods.
Restrict oral intake for 24–48 hours, but ensure adequate intravenous hydration.

MEDICINE TREATMENT
Correct electrolyte imbalance with IV fluids.

- Pyridoxine, oral, 25 mg 8 hourly.

AND

- Vitamin B complex, IV, 10 mL.

AND

- Promethazine, oral/IM/IV 25 mg 8 hourly as needed.

LoE:IIIb[xxvii]

If no/poor response:

ADD

- Metoclopramide, oral/IV, 10–20 mg 6 hourly as needed.

LoE:IIIb[xxviii]

In refractory cases:

Administer daily until hyperemesis is controlled:

- Dexamethasone, IM/IV, 4–8 mg daily.

AND

- Ondansetron, IV, 4–8 mg over 5 minutes, daily.
  - **Note:** There is uncertainty regarding the safety of ondansetron in the first trimester. Use with caution and only when necessary. *LoE:IIIb*[xxix]

6.11 PRETERM LABOUR

6.11.1 PRETERM LABOUR (PTL) AND PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

O60.0/O42.0-2/O42.9

DESCRIPTION

Preterm: <37 weeks' gestation.
Most problems occur at <34 weeks' gestation.
Confirm ruptured membranes by sterile vaginal speculum.
Preterm labour confirmed by regular uterine contractions with progressive cervical changes.

GENERAL MEASURES

Assess fetal wellbeing.
Estimate fetal weight.
Deliver if chorio-amnionitis suspected.

MEDICINE TREATMENT

If gestation <34 weeks:
Pre-hydrate before administration of nifedipine:

- Sodium chloride 0.9%, IV, 200 mL.

AND

- Nifedipine, oral, 20 mg.
  - If contractions persist, follow with 10 mg after 30 minutes then 10 mg 4 hourly for up to 48 hours.

If gestation <32 weeks and where nifedipine contra-indicated:

- Indomethacin, oral, 50 mg immediately then 25 mg 4 hourly for up to 48 hours.
  Note: Indomethacin may cause oligohydramnios, and its use is associated with a risk of premature closure of the ductus arteriosus. Use only if there is intolerance to nifedipine.

LoE:Ia[xxx]

To improve fetal lung maturity at 26–34 weeks: (Z29.2)

- Betamethasone, IM, 12 mg, 2 doses 24 hours apart.

LoE:Ia[xxxi]

If betamethasone is not available:

- Dexamethasone, IM, 8 mg, 3 doses 8 hours apart.

LoE:Ia[xxxii]

Note: Corticosteroids are maximally effective about 24 hours after administration of the first dose. Therefore, give as soon as possible following diagnosis of PTL or PPROM.

Antibiotic therapy (Z29.2)

- Ampicillin, IV, 1 g 6 hourly for 48 hours.

Follow with:

- Amoxicillin, oral, 500 mg 8 hourly for a further 5 days.

AND

- Azithromycin 1g orally as a single dose. *LoE:IIIa*[xxxiii]

Severe penicillin allergy: (Z88.0)

- Clindamycin, IV, 600 mg 8 hourly for 48 hours.

Follow with:

- Clindamycin, oral, 450 mg 8 hourly for a further 5 days.

AND

- Azithromycin 1g orally as a single dose. *LoE:IIIa*[xxxiv]

Prepare for appropriate care of preterm infant.

REFERRAL

» Fetus that may require neonatal intensive care, e.g. estimated weight <1.5 kg or gestation <32 weeks.
» Fetus requiring specialised treatment after birth, e.g. surgery.
» Severely ill mother.

6.11.2 PREVENTION OF PRETERM LABOUR (SINGLETON PREGNANCIES ONLY)

Z35.2

DESCRIPTION

Women with a previous spontaneous preterm delivery are at higher risk for preterm delivery in the next pregnancy. In certain high-risk cases, pregnancy may be prolonged by the careful consideration of either cervical cerclage or vaginal progesterone therapy.

The following high-risk women should undergo cervical screening and offered a choice of cerclage or progesterone:

» A history of 2nd trimester miscarriage (between 16 and 26 weeks) suggestive of cervical incompetence: (Painless dilatation with a quick labour, and birth of a live baby or fresh stillbirth) after excluding other causes of mid-trimester losses, e.g. intra-uterine death that required induction, abruptio placentae, fetal abnormalities, polyhydramnios, and medical terminations.
» Previous history of spontaneous preterm birth between 27 and 34 weeks (exclude non-spontaneous causes e.g. iatrogenic delivery for pre-eclampsia, or syphilis). No need to refer previous late preterm deliveries (34-37 weeks).

Do not screen low-risk women routinely, as it is not cost-effective.

GENERAL MEASURES

Cervical length must be measured by a skilled operator using transvaginal ultrasound.
Cervical measurement can be done between 16 and 24 weeks.
A cervical length of ≤25 mm indicates a higher risk for recurrent preterm labour.

Discuss the risks and benefits of both options with the patient to make an informed shared decision of the most appropriate treatment.

MEDICINE TREATMENT

Women should be counselled that 20 cerclage procedures will prevent one preterm delivery (NNT 17 to 20) and that progesterone is successful in 1 out of every 8 cases (NNT 6 to 8), to assist them in making an informed decision. *LoE:IIb*[xxxv]

Consider prophylactic vaginal progesterone ***or*** cervical cerclage (MacDonald suture) for women with:

» history of spontaneous preterm birth (27-34 weeks) or mid-trimester loss (16-24 weeks), ***and***
» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks).

- Progesterone, PV, 200 mg daily. *LoE:IIb*[xxxvi]
  - Stop treatment at 34 weeks and refer to antenatal services at primary level of care for further management.

(**Note**: Vaginal progesterone may be considered for high-risk women with a normal cervix length on ultrasound).

Consider prophylactic cervical cerclage (MacDonald suture) ***only*** for women with:

» cervical length ≤ 25 mm confirmed on ultrasound (16-24 weeks),

AND

» history of preterm prelabour rupture of membranes (PPROM), ***or***
» history of cervical trauma.

Rescue cerclage:

» If the cervix is already open and the membranes exposed, but unruptured, consider a rescue cervical cerclage (16-27 weeks).
» Do not insert a rescue cerclage if there are contractions, active vaginal bleeding or signs of infection.

Cerclage should be removed at 36 weeks, and thereafter the patient can be referred to antenatal services at primary level of care. *LoE:IIb*[xxxvii]

REFERRAL

Women with recurrent losses and previous cerclage that tore out (severe cervical trauma), as they may require an abdominal cerclage.

6.12 SUPPRESSION OF LABOUR FOR FETAL DISTRESS

O68.0-3/8-9 + (Z51.2)

DESCRIPTION

Tocolysis is useful to treat fetal distress in labour and to suppress labour in women needing transfer or awaiting Caesarean delivery. Also used prior to external cephalic version.

MEDICINE TREATMENT

- Salbutamol bolus, 250 mcg IV, slowly over 2 minutes.
  - Reconstitute the solution as follows:
    - Add 1 mL (i.e., 0.5 mg/mL) salbutamol to 9 mL sodium chloride 0.9% to make a solution of 50 mcg/mL. Administer 5 mL (250 mcg) of this solution.
    - Monitor pulse. Do not administer if mother has cardiac disease.
    - Place the mother in the left lateral position.
    - If pulse increases >120 bpm, discontinue salbutamol.

LoE:IIb[xxxviii]

6.13 LABOUR INDUCTION

Z35.9/Z51.2

If induction of labour is indicated, for medical reasons, for example pre-eclampsia, diabetes, or post-term pregnancy.

GENERAL MEASURES

Counsel the woman about the risks: failed induction or uterine hyperstimulation syndrome, which may require emergency Caesarean delivery.

Cervix favourable and confirmed HIV-uninfected mother
Artificial rupture of the membranes.

Cervix unfavourable (Bishop score <7)
Extra-amniotic Foley catheter with/without saline infusion:
Pass a Foley catheter with 30 mL bulb through cervix with sterile technique.
Inflate bulb with 50 mL water or sodium chloride 0.9%.
Tape catheter to thigh with light traction.
Alternatively, attach sodium chloride 0.9% 1 L with giving set to catheter, and infuse sodium chloride 0.9% at 50 mL/hour. Remove after 24 hours.

LoE:IVb

MEDICINE TREATMENT

Cervix unfavourable (Bishop score <7)
Extra-amniotic Foley catheter (as above) **PLUS** one of the options below:

LoE:IIb[xxxix]

Prostaglandins, e.g.:

- Dinoprostone gel, intravaginally, 1 mg.
  - Repeat after 6 hours.
  - Do not exceed 4 mg.

OR

- Dinoprostone tablets, intravaginally, 1 mg.
  - Repeat after 6 hours.
  - Do not exceed 4 mg.

LoE:IIIb[xl]

OR

- Misoprostol, oral, 20 mcg 2 hourly until in labour, or up to 24 hours.
  - Oral misoprostol may be given as freshly made-up solution of one 200

mcg tablet in 200 mL water, i.e., 1 mcg/mL solution. Give 20 mL of this solution 2 hourly.
- Stop misoprostol administration when in established labour.
- Maximum 24 hours.
- Never use oxytocin and misoprostol simultaneously.
- Misoprostol and other prostaglandins are contraindicated in women with previous Caesarean sections and in grand multiparous women.

LoE:IIIb[xli]

Note:
» Misoprostol in larger doses than indicated here for labour induction at term, may cause uterine rupture.
» Only to be prescribed by a doctor experienced in Maternal Health.

Non-stress test and cardiotocography:
Note: Perform a non-stress test (NST), before starting the induction, and cardiotocography (CTG) within an hour of each dinoprostone insertion, to evaluate the fetal condition during labour induction.
When using oral misoprostol, do a baseline NST before commencing IOL, followed by CTG 4-hourly (prior to every alternate dose).
Repeat CTG once contractions have started, or more frequently only if clinically indicated.

LoE:IVb

Cervix favourable (Bishop score ≥7)
Amniotomy followed 2 hours later by:

- Oxytocin, IV, 2 units in 200 mL sodium chloride 0.9%.

LoE:IIIb[xlii]

  - Start at an infusion rate of 12 mL/hour (i.e. 2 milliunits/minute). If absent or inadequate contractions, increase infusion rate according to the table below:

Time after starting (minutes)	Oxytocin dose (milliunits/minute)	Dilution: 2 units in 200 mL sodium chloride 0.9% (mL/hour)
0	2	12
30	4	24
60	6	36
90	8	48
120	10	60
150	12	72
180	14	84
210	16	96
240	18	108
270	20	120

Note:
» It is safe to perform amniotomy in pregnant women living with HIV on ART who have an undetectable plasma VL at delivery.

LoE:IIIb[xliii]

» Avoid oxytocin in women with previous Caesarean section or parity ≥5.

» Continuous electronic fetal heart rate monitoring is essential.
» Aim for adequate uterine contractions (3–5 contractions in 10 minutes). Once adequate contractions achieved, do **not** increase rate further.
» Most women will experience adequate contractions at a dose of 12 milliunits/minute.
» If tachysystole develops (>5 contractions in 10 minutes), reduce or stop the oxytocin infusion to achieve 3-5 contractions in 10 minutes. If there are fetal heart rate abnormalities which persist despite stopping the oxytocin, administer salbutamol as above.

6.14 LABOUR PAIN, SEVERE

O62.9 +(Z51.2)

GENERAL MEASURES

Antenatal counselling.
Psychological support from family member, friend or volunteer 'doula'.
The need for analgesics may be reduced by keeping the woman informed about the progress of labour, providing reassurance and carefully explaining the procedures performed.
Anticipate the need for analgesia rather than waiting for severe distress.

MEDICINE TREATMENT

- Morphine, IM, 0.1 mg/kg 4 hourly as needed, to a maximum of 10 mg.

Titrate dose and dose frequency according to pain. *LoE:IVb*[xliv]
Supplement with premixed nitrous oxide 50%/ oxygen 50% in late first stage.

Epidural anaesthesia
Offer this service only at hospitals with anaesthetic expertise, monitoring, capacity and equipment for epidural. (See chapter 12: Anaesthesiology, pain and intensive care).

Perineal analgesia: R10.2

- Lidocaine, 1 or 2%, infiltration, locally or by a pudendal block.

Postpartum and post-episiotomy pain O90.9 + (R10.2 + Z51.2)

- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

OR

- NSAID, e.g.:
- Ibuprofen, oral, 400 mg 8 hourly with meals.

OR

- Morphine, IM, 0.1 mg/kg 4 hourly as needed, to a maximum of 10 mg.

LoE:IVbl[iv]

6.15 DEHYDRATION/KETOSIS IN LABOUR

O99.2 + (E86)

DESCRIPTION

Subclinical dehydration is often missed in labour.

GENERAL MEASURES

Encourage adequate oral fluid intake.

MEDICINE TREATMENT

Mild dehydration

Give oral fluids.

Moderate/severe dehydration

Administer intravenous fluids, e.g.:

- Sodium chloride 0.9%, IV, 250 mL/hour.

Re-evaluate hydration hourly.

6.16 POSTPARTUM FEVER

O85/O86.0-4/O86.8

DESCRIPTION

During delivery the woman's protective barrier against infections is temporarily reduced and this may lead to infections.

The cause of fever may be a serious complication.

Consider excessive use of misoprostol for PPH (doses >600 mcg) as a possible non-infectious cause of postpartum fever.

GENERAL MEASURES

Prevent deep vein thrombosis.

Complete evacuation of uterine contents.

Hysterectomy may be indicated in severe uterine sepsis.

Attention to breast engorgement.

MEDICINE TREATMENT

Antibiotic treatment, where appropriate, should be guided by the presumed source of infection.

Empiric antibiotic therapy

- Amoxicillin/clavulanic acid, IV, 1.2 g 8 hourly, until patient apyrexial for 24 hours.

Follow with: *LoE:IVb*

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly.

REFERRAL

» No clinical response to 48 hours of antibiotic treatment.
» Septic shock.

6.17 POSTPARTUM HAEMORRHAGE

O72.1-3 + (Z51.2)

DESCRIPTION

Blood loss >500 mL after birth of the baby or any blood loss which results in haemodynamic instability (tachycardia and/or hypotension).

GENERAL MEASURES

Bimanual compression of the uterus.
Ensure delivery of placenta is complete.
Check for local causes of bleeding.
Balloon tamponade of the uterine cavity should be considered if the patient is to be transferred to another facility.

MEDICINE TREATMENT

Prevention Z29.2

Active management of the 3rd stage of labour:

- Oxytocin, IM, 10 units.

Note:

» Delay cord clamping and cutting (after 1 minute)
» Deliver the placenta by controlled cord traction.

Treatment

Resuscitate.
Put up two IV lines of crystalloid, one of which should contain oxytocin 20 IU.
Cross match and hold blood for transfusion.
Monitor BP and pulse, and response to uterotonics every 15 minutes.

- Oxytocin, IV, 20 units in 1 L sodium chloride 0.9% at 250 mL/hour.

If uterus remains atonic (palpable above the umbilicus) after the oxytocin infusion has started:

- Ergometrine, IM, 0.5 mg.
  or
  a combination of oxytocin, IM, 5 units and ergometrine, IM, 0.5 mg.
  - Avoid ergometrine in women with hypertension or cardiac disease, except in severe cases where the benefit is considered to outweigh the risk (discuss with a specialist).
  - Repeat ergometrine 0.5 mg IM after 15 minutes if no response.

AND *LoE:Ia*[xlvi]

- Tranexamic acid 1 g, IV, slowly over 10 minutes.
  - Repeat after 30 minutes if there is ongoing vaginal bleeding.

In settings where oxytocin had NOT been administered as prophylaxis at birth:

- Misoprostol, sublingual, or rectal, 600 mcg as a single dose.

LoE:IIb[xlvii]

6.18 THE RHESUS NEGATIVE WOMAN

O36.0 + (Z29.1)

GENERAL MEASURES

Maternal serum antibodies absent

Prevention

Test for maternal serum antibodies at 'booking', 28 and 34 weeks' gestation.
During pregnancy, give prophylactic anti-D immunoglobulin to the mother within 72 hours of a potentially sensitising event.

MEDICINE TREATMENT

After a termination of pregnancy (TOP), miscarriage, ectopic pregnancy or amniocentesis <20 weeks:

- Anti-D immunoglobulin, IM, 50 mcg.

LoE:IIIb[xlviii]

After external cephalic version or potentially sensitizing event ≥20 weeks:

- Anti-D immunoglobulin, IM, 100 mcg.

At birth, determine the Rh status of the cord blood and request a Coomb's test:
Cord blood Rh negative - no treatment.
Cord blood Rh positive, Coomb's negative:

- Anti-D immunoglobulin, IM, 100 mcg.

If a large feto-maternal haemorrhage is suspected:

- Anti-D immunoglobulin, IM, 300 mcg for every 30 mL haemorrhage.
  - Maximum dose: 1 200 mcg.

AND

Do a maternal blood Kleihauer test (consult a specialist).

Rh positive, Coomb's positive:
In these cases, the mother will also have antibodies.
Do not administer anti-D immunoglobulin.

Maternal serum antibodies present.
Consult a specialist.

6.19 URINARY TRACT INFECTION (UTI) IN PREGNANCY

6.19.1 CYSTITIS

O23.1

DESCRIPTION

This condition usually presents with lower abdominal pain, frequency of micturition, and/or dysuria. There are no features of sepsis, e.g., fever. Urine dipstick testing usually shows nitrites, with/without leukocytes; and/or blood.

GENERAL MEASURES

Encourage oral fluid intake.
Midstream urine for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Empiric treatment (symptoms present with nitrites positive **AND** leukocytes positive on dipstick):

- Fosfomycin, oral, 3 g as a single dose — *LoE:IIIb*[xlix]

OR

- Nitrofurantoin, oral, 100 mg, 6 hourly for 5 days. — *LoE:Ib*[l]

LoE:IIb[li]

REFFERAL/CONSULTATION

No response to treatment, or resistant organism on culture.

6.19.2 PYELONEPHRITIS, ACUTE

O23.0

DESCRIPTION

This condition is more serious than cystitis and may result in preterm labour.
Features of pyelonephritis include:

» temperature ≥ 38ºC
» renal angle tenderness (often bilateral)
» other features of sepsis, i.e., vomiting, tachypnoea, tachycardia, confusion and hypotension

GENERAL MEASURES

Admit to hospital.
Ensure adequate hydration with intravenous fluids, up to 3 L of sodium chloride 0.9% over 24 hours.
Midstream urine for microscopy, culture and sensitivity.

MEDICINE TREATMENT

Empiric therapy:

- Ceftriaxone, IV, 1 g, daily for 48 hours, or until fever subsides.

OR

- Gentamicin, IV, 6 mg/kg, daily (ensure normal renal function).

Switch to oral therapy as soon as the patient is able to take oral fluids:

- Amoxicillin/clavulanic acid, oral, 875/125 mg 12 hourly for 7 days.

Change antibiotics according to culture and sensitivity results. After treatment, ensure that two urine specimens are negative to confirm eradication.

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SOUTH AFRICAN ADULT HOSPITAL HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 6: OBSTETRICS
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020-4)

Medicine amendment recommendations, with supporting evidence and rationale are listed below.
Kindly review the medicine amendments in the context of the respective standard treatment guideline (STG).

SECTION A: NEW STANDARD TREATMENT GUIDELINE

SECTION	CONDITION	MEDICINE MANAGEMENT	MEDICINE ADDED
6.5	Coronavirus disease-19 (COVID-19) in pregnancy	Yes	Oxygen
			Corticosteroids *(therapeutic class)*
			Dexamethasone, parenteral *(example of corticosteroids therapeutic class)*
			Prednisone, oral *(if concerned with in-utero steroid exposure)*
			Hydrocortisone, parenteral *(if concerned with in-utero steroid exposure)*
			Corticosteroid, oral/IV *(cross referral to infections chapter)*
			Paracetamol, oral *(Dose range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain)*
	- *thromboprophylaxis*		LMWH *(cross referral to section 2.8: Venous thrombo-embolism)*
			Unfractionated heparin *(cross referral to section 2.8: Venous thrombo-embolism)*

6.5 CORONAVIRUS DISEASE-19 (COVID-19) IN PREGNANCY

The following STG was developed, aligned with the Royal College of Obstetricians and Gynaecologists clinical guidelines[1], which were assessed independently by two Committee members using the AGREE II tool[2]. The assessors generally agreed that the guideline could be used with adaptation for the South African setting, noting that this is a living guideline, which is updated as new evidence emerges. Thus, the guideline recommendations should strengthen as more robust evidence becomes available. The recommendations need re-evaluation as the guidelines are updated. However, the ethical challenges of studies performed amongst pregnant women was duly acknowledged.

ANTENATAL CARE:

» Antenatal care is an essential service and should not be scaled down during lockdown periods.
» Screening and testing criteria for SARS-CoV-2 infection during pregnancy is the same as for the general population.
» Vaccination against Covid-19 and influenza is safe at all gestations of pregnancy and during COVID-19 pandemic it is important that pregnant women take up the COVID-19 and influenza vaccine to reduce their risk of contracting either. (See PHC STGs and EML, Section 13.7: Other vaccines).
» The clinical course and outcome of COVID-19 is not different in pregnancy and most pregnant women who are infected with SARS-CoV-2 will experience only mild or moderate symptoms.
» Up to 75% of infected women in pregnancy may be asymptomatic, and appropriate PPE must be used for all deliveries, regardless of the status of the mother. All pregnant women attending hospital, including women in labour, should wear masks.
» Maternal COVID-19 is associated with an approximately three times greater risk of preterm birth and women should be counselled on warning signs of spontaneous preterm labour.
» Risk factors for more severe disease or admission to hospital with COVID-19 include:
  - Obesity (pre-pregnancy BMI >30 kg/m^2).
  - Co-morbidity, such as pre-existing diabetes (see section 6.2: Diabetes mellitus in pregnancy) and chronic hypertension (see section 6.6: Chronic hypertension).
  - Age >35 years
» SARS-CoV-2 infection is not associated with an increase in the incidence of congenital abnormalities.

THROMBOPROPHYLAXIS:

All pregnant women admitted with confirmed or suspected COVID-19 should be offered prophylactic LMWH or unfractionated heparin for 10 days, unless birth is expected within 12 hours. See section 2.8: Venous thrombo-embolism.

[1] Royal College of Obstetricians & Gynaecologists. Coronavirus (COVID-19) Infection in Pregnancy Guidelines, 7 March 2022 https://www.rcog.org.uk/guidance/coronavirus-covid-19-pregnancy-and-women-s-health/vaccination/

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DELIVERY:

» COVID-19 infection is not an indication for delivery, unless delivery is required as part of maternal resuscitation to improve maternal oxygenation.
» When a woman with COVID-19 presents with spontaneous preterm labour, suppression of labour (to delay delivery in order to administer antenatal corticosteroids) should not be done.
» All women with confirmed or suspected SARS-CoV-2 infection must preferably deliver in a dedicated COVID-19 hospital or ward.

MEDICINE TREATMENT

Observe oxygen saturation measurement hourly.

- Oxygen, if saturation is <94%.

Symptomatic relief of headache:

- ~~Paracetamol, oral, 1 g 4–6 hourly when required.~~
- Paracetamol, oral, 500 mg–1 g, 4–6 hourly as required (to a maximum of 4 g in 24 hours).
  - Maximum dose: 15 mg/kg/dose.

Note: Avoid morphine analgesia if patient is respiratory compromised.

In pregnant patients who require supplemental oxygen:

» Corticosteroids crosses the placenta and may have long-term deleterious effects on the child.

If corticosteroids are also needed to accelerate fetal lung maturity: See section 6.12: Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM).

If corticosteroids are not needed for fetal lung maturity:

- Corticosteroids, e.g.:
- Dexamethasone, IV, 6 mg daily for up to 10 days, or until discharge.

If there is a concern over in-utero steroid exposure, use alternative therapy (with less placental transfer):

- Prednisone, oral 40 mg daily, for up to 10 days, or until discharge.
  OR
  Hydrocortisone, IV, 80 mg 12 hourly for up to 10 days, or until discharge.

Anaesthetic:

- Spinal anaesthesia is the anaesthetic of choice in the absence of contra-indications. See section 12.7: Anaesthesia, spinal (intrathecal). The patient should wear a surgical facemask for the duration of the perioperative period.

POSTPARTUM:

» Infection with SARS-CoV-2 is not a contra-indication to breast feeding.
» There is no contra-indication to the use of post-partum contraception (See PHC STGs and EML, Chapter 7: Family planning).

Level of Evidence: Guidelines

Pain:

Nitrous oxide: *not added*

There is much controversy on the potential danger of nitrous oxide in an aerosol generating device. No consensus could be reached amongst the Cochrane review group[3].

NEMLC MEETING OF 9 DECEMBER 2021:
Aerolisation with nitrous oxide for pain was raised as a concern in pregnant women with COVID-19.
Recommendation: NEMLC recommended that nitrous oxide not be used in this clinical setting.

Level of Evidence: Expert opinion

The following statement was also added to the STG text:

Note: Avoid morphine analgesia if patient is respiratory compromised.

In pregnant patients who require supplemental oxygen:

Corticosteroids: *added as a therapeutic class*

[3] Devane D, Kellie F, Finucane E, Hanrahan V, Papageorghiou AT. COVID-19 Review of National Clinical Practice Guidelines for Key Questions Relating to the Care of Pregnant Women and Their Babies, 10 April 2020.
https://pregnancy.cochrane.org/sites/pregnancy.cochrane.org/files/public/uploads/covid_pcg_powerpoint_results_final_0.pdf

Dexamethasone, parenteral: *added as an example of corticosteroids therapeutic class*
Prednisone, oral: *added if concerned with in-utero steroid exposure*
Hydrocortisone, parenteral: *added if concerned with in-utero steroid exposure*

The NEMLC-accepted narrative aligned with the infections chapter,[4]amended specifically for the obstetrics setting.
Level of Evidence: II Moderate certainty evidence[5, 6]

SECTION B: MEDICINE AMENDMENTS:

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
6.1 Anaemia in pregnancy *- prophylaxis*	Ferrous sulfate, oral	Directions for use added for poor tolerance with daily iron
	Ferrous fumarate, oral	Directions for use added for poor tolerance with daily iron
	Therapeutic response	Criteria not amended
6.2 Diabetes mellitus in pregnancy	Criteria for screening for gestational diabetes mellitus	Amended
	Treatment protocol	Amended
	Insulin	Dose amended
6.4 Hypertensive disorders in pregnancy	Long-acting calcium channel blockers, oral	Added as a therapeutic class
	Amlodipine, oral	Retained as an example of class in the STG
	Nifedipine, oral	Not added to the STG, but added to the therapeutic interchange database
6.4.3 Chronic hypertension	Doppler screening	Added
6.6 HIV in pregnancy	Tenofovir + lamivudine + dolutegravir, oral	Indication expanded from ≥6 weeks gestation to ALL women
6.10 Hyperemesis gravidarum	Promethazine, oral/IM/IV	Added as first line option
	Metoclopramide, oral/IV	Amended to second line option
6.11.1 Preterm labour (PTL) and preterm prelabour rupture of membranes (PPROM)	Ampicillin, IV	Added
	Amoxicillin, oral	Amended
	Metronidazole, oral	Deleted
	Azithromycin, oral	Added
	Clindamycin, IV	Added
	Clindamycin, oral	Added
	Indomethacin, oral	Dose not amended
6.13 Labour induction	Dinoprostone, oral/gel	Directions for use not amended
6.14 Labour pain, severe	Morphine, IM	Retained
	Pethidine, IM	Deleted
	Postpartum and post-episiotomy pain: Paracetamol, oral	Retained *(Dose range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain)*
6.17 Postpartum haemorrhage	Tranexamic acid, parenteral	Directions for use amended
6.18 The Rhesus negative woman	Rh-antibody testing	Not amended

The content of the Adult Hospital Level obstetrics chapter has been aligned to the PHC obstetrics and gynaecology chapter, wherever appropriate.

6.1 ANAEMIA IN PREGNANCY

Prophylaxis

Ferrous sulfate, oral: *directions for use added for poor tolerance with daily iron*
Ferrous fumarate, oral: *directions for use added for poor tolerance with daily iron*

[4] Minutes of the NEMLC meeting of 3 December 2020
[5] National Department of Health: Affordable Medicines, EDP-NEMLC COVID-19. Rapid review: Corticosteroids for COVID-19: evidence review of the clinical benefit and harm, 24 October 2020. https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
[6] WHO Rapid Evidence Appraisal for COVID-19 Therapies (REACT) Working Group, Sterne JAC, Murthy S, Diaz JV et al. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020 Sep 2;324(13):1–13. https://pubmed.ncbi.nlm.nih.gov/32876694/

Dosing of iron was aligned with the PHC STGs and EML, noting that Cochrane review[7] of daily iron supplementation during pregnancy reviewed studies using daily doses of 9 mg to 900 mg of elemental iron; whilst intermittent dosing may be a feasible option for those who cannot tolerate daily iron (e.g. epigastric pain, nausea, vomiting and constipation). **Level of Evidence: Low to low certainty evidence**[8]

Therapeutic response: *criteria not amended*
The guidance in the STG is aligned with the UK Guidelines on the Management of Iron Deficiency in Pregnancy[9] that cites the British National Formulary[10], that states, *"Therapeutic response: The haemoglobin concentration should rise by about 100–200 mg/100mL (1–2 g/litre) per day or 2 g/100mL (20 g/litre) over 3–4 weeks. When the haemoglobin is in the normal range, treatment should be continued for a further 3 months to replenish the iron stores".*

6.2 DIABETES MELLITUS IN PREGNANCY

Criteria for screening for gestational diabetes mellitus: *amended*
The following was amended to align with the NICE Guidelines:

The following women should be screened for GDM, between 24 and 28 weeks of gestation:
» ……..
» Previous baby with birthweight ~~>4 kg~~ 4.5 kg.
» Polyhydramnios in index pregnancy.
» Glycosuria (≥1+ glucose in urine on 2 or more occasions).
……

Treatment protocol: *amended*
The STG text was amended to align with the step-wise treatment protocol as recommended in the NICE 2020 Guidelines[11] (i.e. lifestyle modification, then add metformin, then add insulin). The statement in the STG text, "the mainstay of therapy for gestational diabetes is insulin" was also deleted.

Insulin: *dose amended*
NICE Guidelines[12] mentions that the majority of studies have reported a total insulin dose ranging from 0.7 to 2 units per kg (present pregnant weight). In the first trimester, the total daily insulin requirement is 0.7 units/kg/day, in the second trimester it is 0.8 units/kg/day, and in the third trimester it is 0.9-1.0 units/kg/day. In a morbidly obese woman, the initial doses of insulin may need to be increased to 1.5-2.0 units/kg to overcome the combined insulin resistance (IR) of pregnancy and obesity. Furthermore, initiation at a lower dose of insulin for step-up treatment from metformin monotherapy is recommended.
Level of Evidence: III Guidelines

The STG text was amended from:

Preferred insulin regimen
- Insulin, short-acting with all 3 meals to maintain the postprandial levels.

AND
- Insulin, intermediate-acting at bedtime (with a bedtime snack) to maintain preprandial levels. Insulin dosing:
  - o Total daily dose: 0.5 units/kg/day.
  - o One third of the total dose: intermediate acting insulin at bedtime.
  - o The remaining two thirds divided into three equal doses are given before each meal (breakfast, lunch and supper). Adjust insulin dosage daily according to blood glucose profiles, until control is adequate.

[7] Peña-Rosas, Juan Pablo, Luz Maria De-Regil, Maria N. Garcia-Casal, and Therese Dowswell. Daily Oral Iron Supplementation during Pregnancy. Cochrane Database of Systematic Reviews, no. 7 (2015). https://doi.org/10.1002/14651858.CD004736.pub5.
[8] Peña-Rosas JP, De-Regil LM, Gomez Malave H, Flores-Urrutia MC, Dowswell T. Intermittent oral iron supplementation during pregnancy. Cochrane Database Syst Rev. 2015 Oct 19;(10):CD009997. https://www.ncbi.nlm.nih.gov/pubmed/26482110
[9] Pavord S, Daru J, Prasannan N, Robinson S, Stanworth S, Girling J; BSH Committee. UK guidelines on the management of iron deficiency in pregnancy. Br J Haematol. 2020 Mar;188(6):819-830. https://pubmed.ncbi.nlm.nih.gov/31578718/
[10] Joint Formulary Committee. British National Formulary. 80. London: BMJ Group and Pharmaceutical Press; 2020.
[11] NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3
[12] NICE. Guideline: Diabetes in pregnancy: management from preconception to the postnatal period, 16 December 2020. https://www.nice.org.uk/guidance/ng3

Where the above recommended regimen is not feasible Twice-daily regimen with biphasic insulin

- Insulin, biphasic.
  o Daily dose: 0.5 units/kg/day, two thirds, 30 minutes before breakfast and one third 30 minutes before supper. o Titrate to achieve target blood glucose as above.

To:

Preferred insulin regimen

- Insulin, short-acting with all 3 meals to maintain the 2-hour postprandial glucose levels <6.4 mmol/L.

AND

- Insulin, intermediate-acting at bedtime (with a bedtime snack) to maintain the fasting (morning) preprandial glucose levels <5.3 mmol/L.

Insulin dosing (in addition to metformin):

- Total daily dose: SC, 0.1 units/kg/day.
- One third of the total dose: intermediate acting insulin at bedtime.
- The remaining two thirds divided into three equal doses: short-acting insulin given before each meal (breakfast, lunch and supper).
- Adjust insulin dosage daily according to blood glucose profiles, until control is adequate.

Where the above recommended regimen is not feasible

Twice-daily regimen with biphasic insulin.

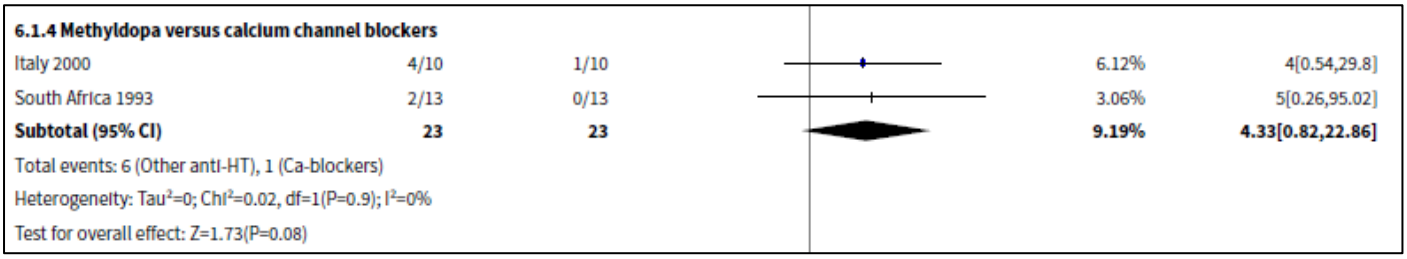
- Insulin, biphasic.
  - Daily dose: SC, 0.5 units/kg/day, two thirds, 30 minutes before breakfast and one third 30 minutes before supper.
  - Titrate to achieve target capillary (fingerprick) glucose as above.

6.4 HYPERTENSIVE DISORDERS IN PREGNANCY

Long acting calcium channel blockers, oral: *added as a therapeutic class*
Amlodipine, oral: *retained as an example of class in the STG*
Nifedipine, oral: *not added to the STG, but added to the therapeutic interchange database*

Evidence:

International Society for the Study of Hypertension in Pregnancy (ISSHP)[13] and South African Guideline on Hypertension in Pregnancy[14] recommends nifedipine as a second line drug (methyldopa/labetalol considered first line); whist authors of a Cochrane review[15] concluded that there is insufficient evidence to recommend any specific antihypertensive agent over another. A sub analysis in this review showed that calcium channel blockers appear to be more effective than methyldopa in avoiding an episode of severe hypertension (RR 4.33, 95%CI 0.82 to 22.86) – however, this was a pooled analysis of 2 small RCTs:



Forest plot of Analysis comparing methyldopa vs calcium channel blocker for the outcome: Severe hypertension (Albalos et al, 2018)

Level of Evidence: Low certainty evidence

Price comparison:

The current tender price for amlodipine compared to the SEP of generic nifedipine.

[13] Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Ananth Karumanchi S et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertension in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021). https://doi.org/10.1016/j.preghy.2021.09.008

[14] Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 National guideline. S Afr Med J. 2019 Sep 13;109(9):12723. https://pubmed.ncbi.nlm.nih.gov/31635598/

[15] Abalos E, Duley L, Steyn DW, Gialdini C. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. Cochrane Database Syst Rev. 2018 Oct 1;10(10):CD002252. https://pubmed.ncbi.nlm.nih.gov/30277556/

Medicine	Tender price[16]	SEP[17] (100%)	SEP (60%)
Calcium channel blockers – low dose			
Amlodipine 5 mg daily, 28 tabs	R3.78	-	-
Nifedipine 30mg daily, 30 tabs	-	R3.60	R2.16
Calcium channel blockers – standard dose			
Amlodipine 10 mg daily, 28 tabs	R5.23	-	-
Nifedipine 60mg daily, 30 tabs	-	R5.16	R3.10

Recommendation: Nifedipine be added as a therapeutic alternative to amlodipine on the therapeutic interchange database, to encourage therapeutic tendering (low and standard dose) – refer to table above.

6.4.3 CHRONIC HYPERTENSION

Doppler screening: *added*

ISSHP recommends that, "*Doppler ultrasound of the umbilical artery may reduce perinatal death and obstetric intervention in high-risk pregnancies, but the evidence is not definitive; it is important to note that near or at term, a normal umbilical artery Doppler does not exclude fetal compromise".* [18]

Level of Evidence: III Guidelines

6.6 HIV IN PREGNANCY

Aligned with the PHC STGs and EML – section 6.8: HIV in pregnancy and NEMLC approved HIV chapters including alignment to NDOH program guidelines.

Tenofovir + lamivudine + dolutegravir, oral: *indication expanded from ≥6 weeks gestation to ALL women*

Refer to the medicine review: Dolutegravir in pregnancy, June 2021, below:

NDoH_PHC-Adult Medicine review_DT

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential (WOCP). The existing contra-indication in pregnancy should be removed from the STG.

Rationale: The risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.

Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is unlikely to be clinically relevant.

Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.

A standardised regimen for all adults and adolescents living with HIV is likely to be easier for nurses to provide.

Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks.

Level of Evidence: Moderate certainty of evidence

Review indicator: New evidence of harms

[16] Contract circular HP09-2021SD (Accessed November 2021) – weighted average prices

[17] SEP database, 26 November 2021 – cheapest generic price

[18] Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Ananth Karumanchi S et al. The Hypertensive Disorders of Pregnancy: The 2021 International Society for the Study of Hypertension in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021). https://doi.org/10.1016/j.preghy.2021.09.008

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

6.10 HYPEREMESIS GRAVIDARUM

Promethazine, oral/IM/IV: *added as first line option*
Metoclopramide, oral/IV: *amended to second line option*

The Royal College of Obstetricians and Gynaecologists (RCOG) states that "*Metoclopramide is safe and effective, but because of the risk of extrapyramidal effects it should be used as second-line therapy",* the STG was amended accordingly.

The Royal College of Obstetricians and Gynaecologists provides guidance [19]as follows:

First line
- Cyclizine 50 mg PO, IM or IV 8 hourly
- Prochlorperazine 5–10 mg 6–8 hourly PO; 12.5 mg 8 hourly IM/IV; 25 mg PR daily
- Promethazine 12.5–25 mg 4–8 hourly PO, IM, IV or PR
- Chlorpromazine 10–25 mg 4–6 hourly PO, IV or IM; or 50–100 mg 6–8 hourly PR

Second line
- Metoclopramide 5–10 mg 8 hourly PO, IV or IM (maximum 5 days' duration)
- Domperidone 10 mg 8 hourly PO; 30–60 mg 8 hourly PR
- Ondansetron 4–8 mg 6–8 hourly PO; 8 mg over 15 minutes 12 hourly IV

Third line
- Corticosteroids: hydrocortisone 100 mg twice daily IV and once clinical improvement occurs, convert to prednisolone 40–50 mg daily PO, with the dose gradually tapered until the lowest maintenance dose that controls the symptoms is reached

The STG was amended as follows, aligned with RCOG Guidelines, and amended from:

- ~~Pyridoxine, oral, 25 mg 8 hourly.~~

~~**AND**~~

- ~~Metoclopramide, oral/IV, 10–20 mg 6 hourly as needed.~~

~~**AND**~~

- ~~Vitamin B complex, IV, 10 mL.~~

To:

- Pyridoxine, oral, 25 mg 8 hourly.

AND

- Vitamin B complex, IV, 10 mL.

AND

- Promethazine, oral/IM/IV 25 mg 8 hourly as needed.

If no/poor response:
ADD
- Metoclopramide, oral/IV, 10–20 mg 6 hourly as needed.

Level of Evidence: III Guidelines

6.11.1 PRETERM LABOUR (PTL) AND PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

Antibiotic therapy
Ampicillin, IV: *added*
Amoxicillin, oral: *amended*
Metronidazole, oral: *deleted*

[19] The Royal College of Obstetricians and Gynaecologists. The Management of Nausea and Vomiting of Pregnancy and Hyperemesis Gravidarum (Green-top Guideline No. 69), 22 June 2016. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/gtg69/

Azithromycin, oral: *added*
Clindamycin, IV: *added*
Clindamycin, oral: *added*

Aligned with Centers for Disease Control and Prevention (CDC) guidelines, noting that ampicillin, IV, clincamycin, IV and clindamycin, oral are included on the Adult Hospital Level EML.

NEMLC REPORT OF PHC OBSTETRICS AND GYNAECOLOGY CHAPTER, 2022-3 REVIEW:
Antibiotics for PPROM reduces maternal and neonatal complications – a Cochrane review[20] showed that any antibiotic vs placebo results in:

- *Less chorioamnionitis - any antibiotic vs placebo, RR 0.57; 95% CI 0.37 to 0.86.*
- *Less preterm birth - any antibiotics vs plaebo; delivery within 7 days after admission RR 0.8; 95% CI 0.71 to 0.9.*
- *Less neonatal infection - any antibiotic vs placebo; neonatal infection RR 0.68; 95% CI 0.53 to 0.87.*

However, women with PPROM have a high risk of group B streptococcal (GBS) infection. The recommended antibiotic for intrapartum GBS prophylaxis is penicillin .[21] Broad spectrum antibiotics are recommended to prolong latency (due to the colonization with vaginal and rectal organisms). [22]
Of note is that the Cochrane review[25] included 22 RCTs, of which only one RCT (from 1997) used metronidazole. From the available evidence, the Cochrane review recommends that erythromycin appears to be a better choice. When different regimens of azithromycin or erythromycin were compared, there was no difference in latency to delivery, incidence of chorioamnionitis, or neonatal outcomes. There also appears to be no additional benefit for an extended course of azithromycin beyond the single-day dosing.[23]

Level of Evidence: III Guidelines

Indomethacin, oral: *dose not amended*
Network meta-analysis ranked prostaglandin inhibitor as the most efficacious tocolytic – compared to placebo, prostaglandin inhibitors shown to be more effective in delaying delivery by 48 hours: OR 5.94, 95% CI 2.14 to 12.34. The dose of indomethacin for labor inhibition is 50 to 100 mg loading dose (may be given orally or per rectum), followed by 25 mg orally every four to six hours up to 48 hours). However, due to its side effect profile, administered in women <32 weeks' gestation with normal renal function and normal amniotic fluid volume.
Level of Evidence: II Moderate certainty evidence[24]

6.13 LABOUR INDUCTION

Dinoprostone, oral/gel: *directions for use not amended*

The package insert for dinoprostone ora/gel[25] as well as the NICE Guidelines[26] cautions against the use of dinoprostone and misoprostol to induce labour, after previous caesarean birth.
Cochrane review[27] concludes that "RCT evidence on methods of induction of labour for women with a prior caesarean section is inadequate, and studies are underpowered to detect clinically relevant differences for many outcomes. High-quality, adequately-powered RCTs would be the best approach to determine the optimal method for induction of labour in women with a prior caesarean birth. However, such trials are unlikely to be undertaken due to the very large numbers needed to investigate the risk of infrequent but serious adverse outcomes (e.g. uterine rupture). Observational studies (cohort studies), including different methods of cervical ripening, may be the best alternative".

[20] Kenyon S, Boulvain M, Neilson JP. Antibiotics for preterm rupture of membranes. Cochrane Database Syst Rev. 2013 Dec 2;(12):CD001058. https://pubmed.ncbi.nlm.nih.gov/24297389/
[21] Verani JR, McGee L, Schrag SJ; Division of Bacterial Diseases, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention (CDC). Prevention of perinatal group B streptococcal disease--revised guidelines from CDC, 2010. MMWR Recomm Rep. 2010 Nov 19;59(RR-10):1-36. https://pubmed.ncbi.nlm.nih.gov/21088663/
[22] ACOG. Prelabor Rupture of Membranes: ACOG Practice Bulletin, Number 217. Obstet Gynecol. 2020 Mar;135(3):e80-e97. https://pubmed.ncbi.nlm.nih.gov/32080050/
[23] Navathe R, Schoen CN, Heidari P, Bachilova S, Ward A, Tepper J et al. Azithromycin vs erythromycin for the management of preterm premature rupture of membranes. Am J Obstet Gynecol. 2019 Aug;221(2):144.e1-144.e8. https://pubmed.ncbi.nlm.nih.gov/30904320/
[24] Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ. 2012 Oct 9;345:e6226. https://pubmed.ncbi.nlm.nih.gov/23048010/
[25] Pfizer: Prandin E_2 vaginal gel package insert.
[26] NICE. Guideline: Inducing labour, 4 November 2021. https://www.nice.org.uk/guidance/NG207
[27] West HM, Jozwiak M, Dodd JM. Methods of term labour induction for women with a previous caesarean section. Cochrane Database Syst Rev. 2017 Jun 9;6(6):CD009792. https://pubmed.ncbi.nlm.nih.gov/28599068/

Observational studies in the second trimester suggests that dinoprostone (prostaglandin E_2) is safe[28].

6.14 LABOUR PAIN SEVERE

Morphine, IM: *retained*
Pethidine, IM: *deleted*

Aligned with the PHC STGs and EML, 2020 edition

NEMLC REPORT OF PHC OBSTETRICS AND GYNAECOLOGY CHAPTER, 2016-2018 REVIEW:
Analgesia:
Recommendation: *Morphine, IM replaces pethidine, IM as analgesia during first stage of labour with cervical dilatation < 10 cm.*
Rationale: Regulation 31 replaces regulation 47 of the Medicines and related substances Act 101 of 1965 i.e. access to pethidine is replaced by access to access to schedule 5 and 6 medicines in order to provide intrapartum care. ***In addition, there are safety concerns regarding pethidine's active metabolite, normeperidine that is potentially neurotoxic.***
Level of Evidence: Regulations[29], Guidelines[30]

Postpartum and post-episiotomy pain

Paracetamol: *retained (Dose range amended and maximum dose reiterated and aligned to AHL Chapter 25: Pain)*

6.17 POSTPARTUM HAEMORRHAGE

Tranexamic acid, parenteral: *directions for use amended*
The treatment protocol with tranexamic acid for the management of PPH was corrected.

The WOMAN trial states, "*Our results suggest that if tranexamic acid is used in the treatment of post-partum haemorrhage it should be* ***given soon after the onset of post-partum haemorrhage alongside uterotonics****. First, our findings show that a significant proportion of mothers die within hours of post-partum haemorrhage onset. In such circumstances, waiting to see if uterotonics fail to stop the bleeding could put some mothers' lives at risk. We found no evidence of adverse effects with tranexamic acid and it has also been shown to be safe and effective in trauma and surgery. Second, our data suggest that early administration is most effective*".

The STG was amended from:

~~• If uterus remains atonic (palpable above the umbilicus):~~
~~**ADD**~~
- ~~Ergometrine, IM, 0.5 mg.~~

~~**OR**~~
~~• Oxytocin, IM, 5 units.~~
AND
~~• Ergometrine, IM, 0.5 mg.~~
  - ~~Avoid ergometrine in women with hypertension or cardiac disease, except in severe cases where the benefit is considered to outweigh the risk (discuss with a specialist).~~
  - ~~Repeat ergometrine 0.5 mg IM after 15 minutes if no response~~

~~If still no response after 15 minutes:~~
- ~~Tranexamic acid 1 g, IV, slowly over 10 minutes.~~
  - ~~Repeat after 30 minutes if there is ongoing vaginal bleeding.~~

To:

If uterus remains atonic (palpable above the umbilicus) after the oxytocin infusion has started:
- Ergometrine, IM, 0.5 mg.

or

[28] Andrikopoulou M, Lavery JA, Ananth CV, Vintzileos AM. Cervical ripening agents in the second trimester of pregnancy in women with a scarred uterus: a systematic review and metaanalysis of observational studies. Am J Obstet Gynecol. 2016 Aug;215(2):177-94. https://pubmed.ncbi.nlm.nih.gov/27018469/
[29] Regulation 31 of the Medicines and related substances Act 101 of 1965.
[30] SAMF, 2022

a combination of Oxytocin, IM, 5 units and Ergometrine, IM, 0.5 mg.
- Avoid ergometrine in women with hypertension or cardiac disease, except in severe cases where the benefit is considered to outweigh the risk (discuss with a specialist).
- Repeat ergometrine 0.5 mg IM after 15 minutes if no response.

AND

- Tranexamic acid 1 g, IV, slowly over 10 minutes.
  - Repeat after 30 minutes if there is ongoing vaginal bleeding.

6.18 THE RHESUS NEGATIVE WOMAN

Rh-antibody testing: *not amended*
The STG recommended testing at booking', 28 and 34 weeks' gestation; whilst National Health Laboratory Services (NHLS) recommends testing at "20, 26 and 32 weeks".
NEMLC forwarded a letter to NHLS requesting alignment of the timing of the Rh-antibody testing.

MATERNAL MENTAL HEALTH
Similar to guidance in the PHC STGs and EML, the Adult Hospital Level **mental health chapter** contains appropriate content relating to maternal mental health, as required. Of note is that the PHC STGs and EML describes syndromic management; whilst the Adult Hospital Level STGs and EML guides on management following specific diagnosis as per the relevant ICD10 codes.

SECTION C: FURTHER CHANGES AFTER INITIAL PUBLICATION OF CHAPTER

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED/ NOT ADDED/ RETAINED
6.4.1 Preeclampsia	Calcium, oral	Retained with an amendment showing only the elemental calcium requirement i.e. not the calcium carbonate salt dose
6.6 HIV in pregnancy	VL requirement for switching pregnant woman from a TDF+FTC+EFV regimen to a TDF+3TC+DTG	Deleted
6.7 Syphilis	Penicillin desensitization	Clarified
6.8 Hepatitis B in Pregnancy	Prophylaxis for pregnant women who are HBsAG/HBeAG positive and HIV negative: TDF, oral	Added

6.4.1 PREECLAMPSIA

Calcium, oral: *Retained with an amendment showing only the elemental calcium requirement i.e. not the calcium carbonate salt dose*

A provincial query was received by NDOH requesting clarity on the STG dose for calcium which was regarded as ambiguous as it contained both the calcium carbonate salt dose & elemental calcium dose. It was also raised that the that calcium doses are not standardized in the PHC (Obstetrics & Gynecology) AHL (Obstetrics) & AHL (Nephrology) chapters. Going forward, NEMLC has recommended that the STG recommendation should only contain the elemental calcium requirement as this is the actual calcium content contained in the tablet (i.e. the calcium carbonate salt dose, should not be included in the STG). Additionally, the recommended elemental calcium dose is now in line with how the peadiatric Hospital STG is currently phrased.

The STG was updated as follows :

At confirmation of pregnancy

- Calcium, oral.
  - For high-risk patients: ~~Calcium carbonate, oral, 500 mg 12 hourly (equivalent to 1 g elemental calcium daily)~~ Calcium (elemental), oral, 1 gram daily.
  - Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women.
  - When using iron together with calcium supplementation, ensure that iron and calcium are taken at least 4 hours apart from one another.

6.6 HIV IN PREGNANCY

In April 2024, guidance indicating that switching pregnant woman from a TDF+FTC+EFV regimen to a TDF+3TC+DTG regimen requires a VL <50 copies/mL in the last 6 months was deleted from the STG in line with the 2023 NDOH Antiretroviral Therapy Clinical Guidelines[31]. Active psychiatric illness guidance regarding contraindication of EFV was removed as it applied when EFV was the treatment of choice; however now that DTG is the treatment of choice, patients on EFV would be switched to DTG. Additionally, clarification is provided regarding serum creatinine being a more sensitive measure of renal impairment in pregnancy rather than calculated creatinine clearance.

LOE: Guidelines

The STG was updated as follows:

MEDICINE TREATMENT

» Patients should receive ART at the first antenatal visit, whether newly diagnosed or known to be living with HIV but not on ART.
» Tenofovir should not be used in pregnant women with a ~~calculated creatinine clearance <60 mL/minute or~~ a serum creatinine ≥85 micromol/L (~~the latter is~~ a more sensitive measure of renal impairment in pregnancy than calculated creatinine clearance).
» Pregnant women may be initiated on/switched to a dolutegravir-containing regimen.
~~» Switching between TEE and TLD regimens requires a VL <50 copies/mL in the last 6 months. See section 10.1: Antiretroviral therapy~~
» Initiate antenatal supplementation (see PHC STGs and EML, section 6.4.1: Antenatal supplements), noting that calcium and DTG should not be taken together on an empty stomach, but can be taken together with food.

1st ANC visit	
Pregnant women not on ART, with normal renal function, **without** TB.	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC).
Pregnant women not on ART, with normal renal function, **with** TB. (DTG requires boosting with TB treatment)	• TDF, oral, 300 mg daily. **AND** • 3TC, oral, 300 mg daily. **AND** • DTG, oral, 50 mg daily. Provided as a fixed dose combination (FDC). **WITH** DTG, oral 50 mg 12 hours later.
Pregnant woman on TDF + FTC + EFV	Switch to TDF+3TC+DTG~~:~~ **~~» Switch only if VL is <50 copies/mL in the last 6 months~~**
Pregnant woman already on ART with a VL between 50-1000 copies/ml	See section 10.1: Antiretroviral Therapy
2nd ANC visit (1 week later)	
Creatinine ≤85 micromol/L	Continue ART as a FDC
Creatinine >85 micromol/L (TDF is contraindicated)	~~Stop FDC: TDF+FTC/3TC+EFV/DTG~~ Replace TDF with ABC as part of a FDC: • ABC, oral, 600 mg daily **AND** • 3TC, oral, 300 mg daily. **AND**

[31] South African National Department of Health. 2023 Antiretroviral Therapy Clinical Guidelines for the Management of HIV in Adults, Pregnancy and Breastfeeding, Adolescents, Children, Infants and Neonates. April 2023. Accessible at https://knowledgehub.health.gov.za/system/files/elibdownloads/2023-07/National%20ART%20Clinical%20Guideline%20AR%204.5%2020230713%20Version%204%20WEB.pdf

	• DTG, oral, 50 mg daily.
~~Active psychiatric illness~~ ~~(EFV may be contraindicated; consult an HIV specialist and/or psychiatrist, if required)~~ ~~O98.7 + (Z21/B24 + 099.3 +F-ICD10 code)~~	~~Replace EFV with DTG~~ ~~If DTG not suitable:~~ ~~Replace EFV with LPV/r, oral, 400/100 mg 12 hourly~~

6.7 SYPHILIS

A potential safety issue was raised, after the initial publication of the chapter in the 2020-3 review cycle, for oral penicillin desensitisation procedure for penicillin allergic pregnant women with syphilis, as the oral desensitization table did not include explicit instruction on the preparation of the oral penicillin doses and route of administration to be used. Additionally, below the table the original instruction to administer 1gram IV was not clear as it was raised that readers could interpret that 1g of the ORAL phenoxymethylpenicillin formulation listed in the table, above the note, should be given intravenously which could result in a potentially catastrophic error. It was also raised that none of the IV formulations of penicillin are generally measured in grams and this may add to the confusion about what the 1g is referring to.

Therefore, the oral penicillin desensitisation table in the syphilis STG was clarified as follows:

- Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured..
- The desensitization protocol was introduced in a heading as an oral penicillin desensitization protocol.
- Explicit instruction provided to prepare a stock solution of oral phenoxymethylpenicillin 250mg/ 5mL.
- The amounts to be administered for steps 1 to 14 explicitly stated for oral route of administration.
- The note below the table was clarified to read that after the final step of oral penicillin desensitisation (i.e. after step 14) and an observation period of 30 minutes, the desired dose of intramuscular penicillin should be administered. Intravenous was revised to intramuscular as benzathine benzylpenicillin (depot formulation), for the management of syphilis is administered via the intramuscular route of administration.
- In keeping with evidence that if less than 5 half-lives have elapsed between repeat doses no repeat desensitisation is required[32]; a further note is elaborated below the table that repeat desensitisation is not required for subsequent doses of the same treatment course (e.g., to complete 3 doses of benzathine benzylpenicillin for late latent syphilis or syphilis of unknown duration). However, as a pragmatic way forward for safety it is reiterated in this hospital level chapter that second and third doses must be administered in a hospital setting to ensure adequate experience in management/resuscitation of anaphylaxis.

  The corresponding section in the "How to Use These Guidelines" for oral and parenteral penicillin desensitisation, referred to in the obstetrics chapter, has also been updated to provide specific instruction on preparation, route and for the parenteral table cumulative dose.

Level of Evidence: Guidelines & **Expert Opinion and (IV)**

The STG was updated from:

Severe penicillin allergy (Z88.0)
For penicillin sensitive pregnant women: penicillin desensitisation.
(See page xxxi for detailed information).

A: Reconstitute phenoxymethylpenicillin 250mg/ 5mL		
Step	**Medicine mg/mL**	**Amount to administer (mL)**
Strictly every 15 minutes	**B**: To make 0.5 mg/mL solution Dilute 0.5 mL of reconstituted phenoxymethylpenicillin solution in 49.5 mL water.	
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL
2		0.2 mL
3		0.4 mL
4		0.8 mL

[32] Macy E, Romano A, Khan D. Practical Management of Antibiotic Hypersensitivity in 2017. J Allergy Clin Immunol Pract. 2017 May-Jun;5(3):577-586. doi: 10.1016/j.jaip.2017.02.014. Epub 2017 Mar 29. PMID: 28365277.

5		1.6 mL
6		3.2 mL
7		6.4 mL
	C: To make 5 mg/mL solution Dilute 1 mL of reconstituted phenoxymethylpenicillin solution in 9 mL water.	
8	5 mg/mL solution (10000 units/mL)	1.2 mL
9		2.4 mL
10		4.8 mL
	D: Reconstituted phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL	
11	50 mg/mL (80000 units/mL)	1.0 mL
12		2.0 mL
13		4.0 mL
14		8.0 mL

After step 14, observe for 30 minutes, then 1.0 g IV; Interval between doses: 15 minutes.

To

Severe penicillin allergy (Z88.0)
For penicillin sensitive pregnant women: penicillin desensitisation.
Perform only in an ICU setting or in a setting where recognition and management of anaphylaxis can be assured.
See "How to Use These Guidelines" for detailed information.

Oral penicillin desensitisation protocol

A: Prepare stock solution of oral phenoxymethylpenicillin 250mg/ 5mL and dilutions for steps 1-7 and 8-10 B: Administer increasing doses of penicillin strictly at 15 minutes intervals		
Step	**Medicine mg/mL**	**Amount to administer (mL)**
To make 0.5 mg/mL solution: Add 0.5 mL of stock phenoxymethylpenicillin solution to 49.5 mL water (total volume 50mL)		
1	0.5 mg/mL solution (1000 units/mL)	0.1 mL orally
2		0.2 mL orally
3		0.4 mL orally
4		0.8 mL orally
5		1.6 mL orally
6		3.2 mL orally
7		6.4 mL orally
To make 5 mg/mL solution: Dilute 1 mL of stock phenoxymethylpenicillin solution with 9 mL water (total volume 10mL)		
8	5 mg/mL solution (10000 units/mL)	1.2 mL orally
9		2.4 mL orally
10		4.8 mL orally
Stock phenoxymethylpenicillin 250 mg/5 mL = 50 mg/mL		
11	50 mg/mL (80000 units/mL)	1.0 mL orally
12		2.0 mL orally
13		4.0 mL orally
14		8.0 mL orally

After step 14, observe for 30 minutes, then administer desired dose of intramuscular penicillin.

Note:

- Repeat desensitisation is not required for subsequent doses of the same treatment course (e.g., to complete 3 dos benzathine benzylpenicillin for late latent syphilis or syphilis of unknown duration).
- However, second and third doses must be administered in a hospital setting.

6.8 HEPATITIS B IN PREGNANCY

Tenofovir disoproxil fumarate, oral: *Added as prophylaxis for pregnant women who are HBsAG/HBeAG positive and HIV negative*

In line with the WHO Guidelines for prevention of mother-to-child transmission of hepatitis B virus[33,34,35] on the 27th June 2024 the Committee accepted and recommended:

- Tenofovir monotherapy for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive.
- Maternal TDF prophylaxis be pragmatically offered to all HBsAg positive pregnant woman even if the HBeAg or viral load result is unavailable.
- Consider TAF for people (including pregnant women) with impaired kidney function (eGFR 15-50mL/min) and/or osteoporosis noting that TAF is not recommended if eGFR is <15 ml/min).[36]

Level of Evidence: IV Guidelines *(Strong recommendation, moderate-certainty evidence)*

As per the maternity care guideline[37] regarding chronic kidney disease:

- Women with known renal disease should be referred to a specialist to evaluate for the presence and severity of renal impairment, proteinuria and/or hypertension.
- Women with hypertension and proteinuria prior to 20 weeks gestation should be referred for tertiary care for further work-up.
- Pregnancy is contra-indicated in women with stage 4-5 chronic kidney disease. (Glomerular filtration rate < 30 mL/minute and serum creatinine > 250 umol/L)

Referral criteria in the STG has been updated including renal dysfunction where it is noted that TDF is contraindicated in renal impairment and Tenofovir alafenamide (TAF) should be prescribed in place of TDF.

The STG was updated as follows:

From:

Prevention of perinatal transmission

» Caesarean delivery is reserved for obstetric indications only.
» Babies born to mothers with acute hepatitis B infection at the time of delivery or to mothers who are HBsAg-positive or HBeAg-positive, see Primary Health Care STGs and EML, section 6.6.5: Hepatitis B exposed infant.

REFERRAL

» Cirrhosis.
» Liver failure.
» Renal dysfunction (eGFR <60 mL/minute).
» Treatment failure.
» Refer all infected babies to a specialist paediatrician for further management.

To:

Prevention of perinatal transmission

» Caesarean delivery is reserved for obstetric indications only.
» Delivery should take place in a facility that can offer Hepatitis B vaccination to the baby at birth.
» Administration of ARVs active against HBV from 28 weeks of pregnancy will further reduce risk of vertical transmission.

Pregnant women who are HBsAg/ HBeAg positive and HIV negative

» All HIV negative pregnant women are eligible for HIV Pre-exposure prophylaxis (PrEP) (see PHC STGs and EML, section 11.11: Pre-exposure prophylaxis (PrEP)). TDF, which is included in the oral PrEP regimen, has anti-HBV activity, and will reduce the risk of vertical transmission of HBV.
» Women who are HIV negative and HBsAg positive who decline PrEP must be counselled that TDF will reduce risk of vertical transmission of Hepatitis B to the baby, particularly if HBeAg is positive or HBV viral load is high.
» TDF 300 mg daily should be administered from 28 weeks of pregnancy until birth to women with a high hepatitis viral load (≥200 000 IU/mL), or positive HBeAg, or where HBeAg/viral load result is unavailable at 28 weeks.

[33] Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024. Available at: https://www.who.int/publications/i/item/9789240090903, Accessed 2 June 2024).
[34] Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy.
Geneva: World Health Organization; 2020. Available at (https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hepatitis/prevention/mother-to-child-transmission-of-hepatitis-b, accessed 2 June 2024
[35] National Department of Health: Affordable Medicines, EDP- PHC and Adult Hospital level. Medicine Review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B, May 2024. http://www.health.gov.za/.
[36] TAF – eGFR 15-50: NDoH Evidence Summary: Use of TAF for adults with HIV. V4_14 March 2024.
[37] NDOH. National Maternity Care Guidelines. Updated 2024

» For care of babies born to: (1) mothers with acute hepatitis B infection at the time of delivery, (2) mothers who are HBsAg-positive, or (3) mothers who are HBeAg-positive, see Primary Health Care STGs and EML, section 6.6.5: Hepatitis B exposed infant.
» Obtain infectious disease specialist or internal medicine physician opinion before stopping TDF as there is a risk for postpartum hepatitis flare.
» Consider continued treatment for HBV after delivery where indicated (see section 1.2.4.2 Hepatitis B, chronic (non-HIV coinfection)).

For Pregnant women who are HBsAg/ HBeAg positive and HIV negative

- TDF, oral, 300 mg daily (from 28 weeks of pregnancy until birth).

REFERRAL
» Cirrhosis.
» Liver failure.
» Renal dysfunction (TDF is contraindicated in renal impairment. Tenofovir alafenamide (TAF) should be prescribed in place of TDF).
» Refer all infected babies to a specialist paediatrician for further management.

South African National Essential Medicine List
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: HIV and AIDs

TITLE: DOLUTEGRAVIR IN PREGNANT WOMEN AND WOMEN OF CHILD-BEARING POTENTIAL (WOCP)

Date: 17 June 2021

Key findings

- This review is a second update of the 2017 review. In this update, we review evidence of safety and efficacy of dolutegravir (DTG) containing ART, compared with efavirenz (EFV) containing ART in women of child-bearing potential (WOCP) and pregnant women.
- The estimate of prevalence of neural tube defects (NTDs) in infants born to women on dolutegravir (DTG) has declined since the original safety signal from the Botswana Tsepamo study as more data in that cohort has accrued. The current estimate is approximately 2 NTDs per 1000 births.
  - In the July 2020 update from this study there were 7 NTDs in 3591 births with DTG exposure (0.19%; 95%CI 0.09% to 0.40%), and 8 NTDs in 10,958 births with EFV exposure from conception (0.07%; 95%CI 0.03% to 0.17%).
  - There was no significant difference in NTD prevalence between DTG and EFV at conception (difference 0.12%; 95%CI -0.001% to 0.33%).
  - In HIV-uninfected women there were 87/119,630 with NTD (0.07%; 95%CI 0.06, 0.09%)
- The Dolphin 2 study, randomised pregnant women of 28 or more weeks to DTG (n=129) or EFV (n=128)
  - HIV viral load < 50 copies/mL at delivery: DTG 74.2% vs EFV 42.7%
- A multicentre trial, including 643 pregnant women at 14-28 weeks gestation, randomised women to DTG/FTC/TAF (n=217), DTG/FTC/TDF (n=215) or EFV/FTC/ TDF (n=211).
  - At delivery, more participants were virally suppressed at in the combined DTG containing groups than the EFV group, 98% vs 91%, difference 6·5% (95% CI 2.0% to 10.7).
  - Neonatal mortality was highest in the EFV group: DTG/FTC/TAF group 1% vs DTG/FTC/TDF 2% vs EFV 5%.
  - Composite adverse pregnancy outcome (preterm delivery/ small for gestational age/stillbirth/ spontaneous abortion) was lower in the DTG/FTC/TAF group: DTG/FTC/TAF group 24% vs DTG/3TC/TDF 33% vs EFV 33%
  - Preterm deliveries were most common in the EFV group: DTG/FTC/TAF 6% vs DTG/3TC/TDF 9% vs EFV 12%.
  - Mean weight gain was highest in the DTG/FTC/TAF group: DTG/FTC/TAF 0.378kg/week vs DTG/FTC/TDF 0.319 kg/week vs EFV/FTC/TDF 0.291kg/week. Mean weight gain in all 4 groups was lower than that recommended by the Institute of Medicine during the 2nd and 3rd trimester.
- In a RCT comparing TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV, 10% of women were obese at baseline. At 48 weeks 20% of women on TAF/FTC/DTG , 11% on TDF/FTC/DTG 9% on TDF/FTC/EFV had new onset obesity.
- In an observational cohort study in Botswana including data from 1235 HIV exposed infants whose mothers took DTG/TDF/FTC in pregnancy, and 2411 whose mothers took EFV/TDF/FTC, mother to child transmission (MTCT) was rare when either regimen started before conception: DTG 0/213 (0%, 95% CI 0.00% to 1.72%) vs EFV 1/1497 (0.07%, 95% CI 0.00% to 0.37%). MTCT rates were similar when ART was started during pregnancy DTG 8/999 vs EFV 8/883 Risk difference 0.11% (95% CI -0.79 to 1.06%).

PHC/ADULT HOSPITAL LEVEL COMMITTEE AND NEMLC RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

Recommendation: The PHC/Adult Hospital Level Committee recommends that dolutegravir should be part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of child-bearing potential. The existing contra-indication in pregnancy should be removed from the STG.

Rationale: The estimated risk of neural tube defects in infants exposed to dolutegravir in early pregnancy that was first identified in the Tsepamo observational study in Botswana has diminished over time, with the accumulation of further data. The risk difference between dolutegravir and efavirenz is no longer significant.
Dolutegravir (especially when combined with tenofovir alafenamide) is associated with more weight gain during pregnancy than efavirenz, but the difference is of uncertain clinical relevance.
Randomised controlled trials have shown non-inferiority in terms of maternal viral suppression rates at 48 weeks. Dolutegravir causes more rapid viral suppression than efavirenz, resulting in increased viral suppression rates by time of delivery in randomised controlled trials of ART initiation in the second and third trimester of pregnancy. This has not yet translated into a demonstrable difference in mother-to-child transmission risk, but event rates are very low with both regimens.
A standardised regimen for all adults and adolescents living with HIV is likely to be easier to provide.
Based on those findings and observations, the PHC/Adult Hospital Level Committee feel that the potential long-term benefits to pregnant women and WOCP, as well as potential short-term benefits to their infants, outweigh the risks.
Level of Evidence: Moderate certainty of evidence
Review indicator: New evidence of harms
(Refer to appendix 2 for the evidence to decision framework)

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: The NEMLC accepted the recommendation as proposed by the PHC/Adult Hospital Level Committee, which would support the universal test-and-treat (UTT) strategy of the National HIV Programme.
It was also duly noted that the South African Health Products Regulatory Authority were currently reviewing the label of dolutegravir products registered on the South African market.

Monitoring and evaluation considerations

Research priorities

BACKGROUND

The first review of dolutegravir (DTG) was conducted by the Primary Health Care (PHC) Expert Review Committee (ERC) in 2017, and was updated in 2019. In 2019 NEMLC recommended that DTG be included in South African antiretroviral therapy (ART) guidelines as a first-line agent, based on evidence of superior efficacy to efavirenz, and higher barrier to emergence of resistance. The paucity of evidence for use in pregnancy was noted, and NEMLC recommended that DTG should be avoided in early pregnancy and in women of child-bearing potential (WOCP) who are not on reliable contraception because of concerns regarding increased risk of neural tube defects (NTDs) with periconception and early first trimester exposure (Zash, Makhema, and Shapiro 2018).

A pooled sequence analysis found pretreatment HIV-1 Drug Resistance in less than 5% of antiretroviral therapy-naive adults in South Africa before 2009 (Chimukangara et al. 2019). By 2015 this had increased to 11·9% (95% confidence interval (CI) 9.2 to 15.0) in 2015. Pooled annual prevalence of non-nucleoside reverse-transcriptase inhibitor (NNRTI) resistance pre-therapy increased from below 5% in 2011 to 10.0% (95% CI 8.4 to 11.8) by 2014. In the 2017 national HIV household survey, 15 % of respondents not on ART, and 56% of ART defaulters had NNRTI resistance (Moyo et al. 2020) The increased prevalence of pre-treatment NNRTI resistance may put both antiretroviral naïve and previously ART exposed patients initiated on efavirenz at increased risk of treatment failure.

Phillips et al (2019) modelled risks and benefits of tenofovir (TDF), lamivudine (3TC), and DTG in sub-Saharan patients, including WOCP (Phillips et al. 2019). The model included drug resistance, efficacy in reducing viral load and clinical treatment outcomes, as well as potential for NTDs (based on the 12 times higher risk of NTD with DTG compared to non-DTG ART in the first Tsepamo report). In the model, benefits of averted disability adjusted life years (DALYs) of transitioning to a regimen of TDF, 3TC, and DTG for all people on ART, considerably outweighed the risks. The model projected that the reduction in risk of mother-to-child transmission was greater than the increased risk of NTD with the TDF, 3TC, and DTG for all on ART. Substantially more DALYs were averted with the TDF, 3TC, and DTG for all individuals on ART. Additionally, DTG for all on ART regimen was cost-effective in most (83% of setting scenarios) compared with the same regimen dependent on viral load suppression and intention to have more children (cost effective in <1% of setting scenarios). Dugdale *et al*., (2019) modelled three outcomes in South African women with HIV (age 15 to 49 years) starting or continuing first-line ART, and their children: (1) maternal and infant mortality, (2) sexual and pediatric HIV transmissions, and (3) NTDs (estimate of increased risk from 1st Tsepamo report) for three strategies i.e. (1) DTG for all, (2) EFV for all, or (3) EFV without contraception or DTG with contraception (WHO approach at the time)(Dugdale et al. 2019). Combined deaths among women and children were lowest with DTG (358,000) compared to the WHO approach (362,800) or EFV (367,300). DTG averted 13,700 women's deaths (0.44% decrease) compared to EFV. Over the 5-year time horizon DTG increased total pediatric deaths compared to EFV by 4,400 and WHO by 4,100 due to more NTDs. However, the combined maternal and infant mortality was more favorable for DTG compared to EFV because DTG resulted in 3.1-fold fewer deaths (13,700) among women. Clinical outcomes for woman were better in the DTG group than the EFV group (70,400 more women were virologically suppressed and 39,700 fewer severe opportunistic infections). DTG was superior to the WHO approach for all outcomes in woman. DTG resulted in fewer projected sexual transmissions to partners over five years compared with EFV or the WHO approach. Similarly, DTG averted more pediatric HIV transmissions compared to EFV and the WHO approach; 7,100 and 6,700 respectively. Compared to EFV, DTG resulted in 2,100 fewer non-NTD related deaths but 6,400 more projected NTDs. In the WHO approach most conceptions occurred among women on EFV resulting in the outcomes for WHO group being like the EFV group. Overall, in the DTG group, 3,000 more children were alive and HIV-free at five years. Both of these modelling analyses suggested considerable benefit from DTG containing ART, despite including a higher risk of NTD than more recent data suggests.

In 2019, the World Health Organisation updated its guidance to recommend DTG containing regimens as the preferred option for first line and second-line antiretroviral treatment for all populations, including pregnant women and WOCP(World Health Organization 2019).

This update focuses on use of DTG in women of childbearing potential, including pregnancy women, and reviews evidence that has emerged since the last NEMLC recommendation in 2019.**Error! Bookmark not defined.**

QUESTION: In pregnant woman and WOCP living with HIV taking first-line antiretroviral therapy, is dolutegravir more efficacious, better tolerated, and of similar safety compared to efavirenz?

METHODS

We updated the previous NEMLC DTG review (26 January 2017 (first update 11 February 2019). The original review and 2019 update included data on all adult patients. In this update, we focused on first-line treatment with DTG in pregnant woman and WOCP. We searched from June 2018, to give 6 months of overlap with the previous update. For the search strategy see Appendix 1. PubMed and the Clinical Trials.gov Register were systematically searched on 3 June 2021 (Appendix 1). Records retrieved from PubMed were extracted to Covidence while the Clinical Trials.gov results were extracted to Microsoft Excel. Screening of titles and abstracts were conducted in duplicate (ND, MR) with disagreement handled through discussion and a tie breaker (LF). Full texts were reviewed in duplicate (ND, LF) with disagreements handled by a tie breaker (KC). Records were excluded based on eligibility criteria. Data from relevant articles was extracted by 5 reviewers (KC, ND, RdW, LF, MR) into a narrative table of results.

Eligibility criteria for review

Population: Pregnant HIV positive women, WOCP

Intervention: DTG-containing ART

Comparators: EFV-containing ART

Outcomes: Viral suppression rates, mortality, development of resistance mutations, rates of perinatal transmission, adverse pregnancy outcomes (miscarriages, preterm delivery, small for gestational age, still birth, neonatal death), congenital anomalies, terminations for congenital anomalies, neural tube defects adverse events, adverse reactions.

Study designs:

- Efficacy: Systematic Reviews of Randomized Control Trials (RCTs), RCTs
- Harms: RCTs, prospective cohort studies, retrospective cohort studies, pregnancy registries, systematic reviews

RESULTS

RESULTS OF THE SEARCH

The search retrieved 134 PubMed records after removing duplicates. The Clinical Trials.gov search retrieved 13 records none of which were relevant as the studies did not meet the eligibility criteria, were ongoing or had already been retrieved in the PubMed search. After reviewing titles and abstracts in duplicate, we excluded 95 records, leaving 39 studies for full text review. After full text review, 18 reports met our inclusion criteria, of which 2 were already included in the 2019 update of this review. We also included an AIDS 2020 conference abstract and presentation which presented updated results for one of the included studies.

Table 1 reports the main characteristics and outcomes reported in the 16 study reports included in this update Table 2 summarizes the 2 papers reported initial findings from the Tsepamo study in Botswana (the previous update did not include summary tables for included studies of safety in pregnancy, so we have included these summaries to give context to the updates of this study data included in this review update). Table 3 outlines excluded studies with reasons for exclusion.

DESCRIPTION OF INCLUDED STUDIES

We included 3 RCTs comparing DTG and EFV-based ART initiated in pregnancy (Waitt et al. 2019; Kintu et al. 2020; Lockman et al. 2021).

We included 2 RCTs comparing DTG and EFV-based ART in non-pregnant adults, including WOCP (Venter et al. 2020; Venter et al. 2019; NAMSAL ANRS 12313 Study Group 2019).

We included data on pregnancy adverse outcomes from a network meta-analysis which included DTG and EFV-based ART(Kanters et al. 2020).

We included a cohort study comparing fetal biometry between DTG and EFV exposed pregnancies in Botswana(Banda et al. 2020), and a comparison of rates of gestational diabetes with DTG and EFV exposure from the same cohort(Mmasa et al. 2021)

We included two updates of the Tsepamo study analysis of prevalence neural tube defects (NTDs) with exposure to DTG and EFV at time of conception(Zash et al. 2019; Zash et al. 2020). We included a report of prospective surveillance for NTDs set up by the Botswana ministry of health in response to the initial Tsepamo signal (Raesima et al. 2019). We included an analysis of rates of NTDs within the Canadian perinatal HIV Surveillance programme (Money et al. 2019), and retrospective cohort analysis of prevalence of NTDs with DTG exposure conducted in the Brazilian antiretroviral therapy database(Pereira et al. 2021).

We included a cohort study comparing weight gain in pregnant women taking DTG and EFV(Caniglia et al. 2020).

We included an observational cohort study in Botswana compared rates of mother to child transmission (MTCT) between women on DTG and women on EFV in pregnancy(Davey et al. 2020).

Randomised controlled trials of DTG in pregnancy

The DolPHIN-1 study randomised HIV positive ART naive women in South Africa and Uganda at 28 to 36 weeks of gestation to DTG -containing ART (n=29) or EFV-containing ART (n=31) (Waitt et al. 2019). The primary endpoint was pharmacokinetics of DTG in women and breastfed infants.

- DTG resulted in significantly faster viral suppression compared to EFV, median time to viral load (VL)<50 copies/mL 32 vs 72 days.

The DolPHIN-2 study randomised HIV positive women of 28 weeks or more weeks gestation to DTG (n=129) or EFV based regimen (n=128) (Kintu et al. 2020) . Co-primary endpoints were virological suppression at 1st post-partum visit, and drug related adverse effects. Median duration of ART was 55 days (IQR 33 to 77)

Efficacy DTG vs EFV:

- HIV viral load < 50 copies/mL at delivery: 74.2% vs 42.7%
- Median time to VL < 50copies/mL: 28 days (95% CI 28–34) vs 82 days (55–97)
- Median time to VL < 1000 copies/ml: 7 days (7–20) vs 23 days (21–27)

Adverse events DTG vs EFV:

- Drug-related serious adverse event (SAE 0 in 1 (<1%) vs 0)
- Stillbirths: 3/124 (2·2%) vs 1/120 (<1%)
- No significant difference in proportion of preterm /late-preterm births
- Congenital abnormalities did not differ between groups. No NTDS in either arm
- 4/123 (3%) infant deaths vs 2/119 (2%)

Mother to child transmission:

- 3 transmissions in DTG group, zero in EFV group

Lockman et al (IMPAACT) randomised 643 pregnant women from 9 countries at 14 to 28 weeks gestation and with less than 14 days of ART exposure to DTG/ emtricitabine(FTC)/ tenofovir alafenamide (TAF) (n=217), DTG/FTC/ tenofovir dispoproxil fumerate (TDF) (n=215) or EFV/FTC/ TDF (n=211) (Lockman et al. 2021). The primary efficacy outcome was the proportion of participants with viral suppression, (HIV-1 VL< 200 copies per mL), at or within 14 days of delivery. VL available for 605 (94%) participants. Median weight was 63 kg (56 to 73) and median BMI was 25 (95% CI 22 to 28).

Efficacy

- 98% in the combined DTG-containing groups had VL suppression at delivery compared with 91% in the EFV group, estimated difference 6.5% (95% CI 2.0 to 10.7).

Adverse events

- Composite adverse pregnancy outcome (preterm delivery/ small for gestational age/stillbirth/ spontaneous abortion): DTG/FTC/TAF group 24% vs DTG/FTC/TDF 33% vs EFV/FTC/TDF 33%
- Preterm deliveries in DTG/FTC/TAF 6% vs DTG/FTC/TDF 9% vs EFV/FTC/TDF 12%.
  - Significant difference between DTG/FTC/TAF and EFV groups, difference –6·3% (95%CI –11·8 to –0·9)
- Neonatal mortality higher in EFV group: DTG/FTC/TAF 1% vs DTG/FTC/TDF 2% vs EFV/3TC/TDF 5%.

Weight gain

- Mean weight gain was highest in the DTG/FTC/TAF group: DTG/FTC/TAF 0.378kg/week vs DTG/FTC/TDF 0.319 kg/week vs EFV/FTC/TDF 0.291kg/week. Mean weight gain in all 4 groups was lower than that recommended by the Institute of Medicine during the 2nd and 3rd trimester.

RANDOMISED TRIALS THAT INCLUDED WOMEN OF CHILDBEARING POTENTIAL

Venter et al (ADVANCE study) randomised 1053 participants, 59% of them female, median age 32 years, to DTG plus emtricitabine (FTC) plus tenofovir dispoproxil fumerate (TDF) or DTG plus emtricitabine (FTC) plus tenofovir alafenamide (TAF) or TDF plus FTC plus EFV(Venter et al. 2019). EFV-based ART was standard of care in 2017 when the trial commenced. Primary end point was virological suppression (<50 copies/mL at week 48.

Efficacy

- HIV-1 viral load< 50 copies/mL at 48 weeks: 84% in the TAF-DTG group, 85% in the TDF-DTG group, and 79% in the EFV group (meeting non-inferiority definition). Efficacy results are not presented disaggregated by sex.

Safety

- Deaths: 1 in TAF-DTG, 1 in TDF-DTG, 2 in EFV
- Weight increase (both lean and fat mass) was greatest in the TAF-DTG group and among female patients. At 48 weeks 26/133 (20% of TAF-DTG group, 13/123 (11%) of the TDF-DTG group, and 9/104 (9%) of the EFV group had new onset obesity. 10% of women in the study were obese at baseline.
- 1 discontinuation in TAF-DTG group because of asymptomatic increase in aminotransferases.
- 8 EFV-linked discontinuations because of adverse reactions: 5 with liver dysfunction of which 2 symptomatic, 2 rash, 1 with neuropsychiatric adverse effects.
- No resistance to integrase inhibitors identified in patients failing the DTG-containing regimens. Four patients on EFV and 1 on DTG were found to have new NNRTI resistance.

Pregnancy outcomes

- There were 78 pregnancies (12.5% of included women), 50 on DTG-containing ART. There were no NTDs. There was 1 neonatal death (TAF/FTC/DTG arm) and 1 stillbirth in the EFV arm.

Week 96 of the IMPAACT study(Venter et al. 2020)

Efficacy

- Viral suppression to <50 copies/mL was 79%, 78%, and 74% in the TAF-DTG, TDF-DTG, and EFV groups, respectively.
- Two patients in the TDF-DTG group and 16 patients in the EFV group had resistance mutations (none to INSTIS).

Safety

- Amongst the 623 women in the study, 28%, 18%, and 12% developed obesity in the TAF-DTG, TDF-DTG, and EFV groups, respectively.
- By 96 weeks, there were 29, 25, and 34 pregnancies, with 6, 2, and 9 miscarriages in women on TAF-DTG, TDF-DTG, and EFV, respectively.

The NAMSAL study randomised 613 participants, 65.9% of them female, to DTG or EFV 400mg-based ART(NAMSAL ANRS 12313 Study Group 2019).

- Efficacy results are not presented disaggregated by sex. Primary end point was proportion of participants with VL<50 copies/mL at week 48. This was achieved in 74.5% of the DTG group and 69% of the EFV group, difference 5.5%, (95% CI -1.6 to 12.7).
- 6.2% of female participants fell pregnant during the trial, including 13 in the DTG group, all of whom were born live and without congenital anomalies.
- There was more weight gain in the DTG group than the EFV group overall.
  - Weight gain of 10% or more was observed in 147/379 (38.8%) of women vs 44/192 (22.9 %) of men.

ADVERSE PREGNANCY OUTCOMES AND CONGENITAL ANOMALIES

The Kanters et al network meta-analysis (which included data from Tsepamo and several smaller studies) found no significant differences between DTG and EFV in terms of rates of preterm birth, low birth weight, stillbirth, small for gestational age, or congenital anomalies.

A prospective cohort study (Tshilo Dikotla) in Botswana enrolled 469 pregnant women between 16 and 36 weeks gestation, including 182 on TDF.FTC/ DTG, 127 on TDF/FTC/ EFV based regimen and 160 who were HIV negative Banda et al. 2020). There was no difference in fetal biometry between the 3 groups (Banda et al. 2020).

RISK OF NEURAL TUBE DEFECTS

Tsepamo study

The risk period for neural tube defects (NTDs) is the first 28 days post-conception. Botswana transitioned to DTG in 2016. The Tsepamo cohort study in Botswana prospectively captured birth outcomes at 8 hospitals from August 2014. In 2018, they compared outcomes in women commencing DTG or non-DTG containing-ART prior to conception- this analysis was included in the 2019 update of this review. At that stage, 89,064 births had accrued of which 88,755 (99.7%) had a surface examination at birth.

- Prevalence of neural tube defects was higher in those exposed to DTG periconception than those on non-DTG containing ART: 4/426 (0.94%) versus 14/11300 (0.12%).
- At the time of this first analysis, there were no NTDs in 2812 women who started DTG during pregnancy.
- NTDs in 61 of 66057 (0.09%) infants born to HIV negative women (Zash, Makhema, and Shapiro 2018).

Tsepamo included 8 public hospital maternity wards from August 2014 to June 2018. Ten additional sites were added between July 2018 and March 2019, giving coverage of approximately 70% of births in Botswana.

Tsepamo 2019 update (Zash et al. 2019)

As at March 31, 2019 there were 119,477 deliveries, 119,033 (99.6% had an infant surface examination. This included 1683 on DTG from conception, 14792 on non-DTG ART from conception, of which 7959 were on EFV from conception, and 3840 who started DTG pregnancy. There was data from 89272 HIV negative mothers.

- There were 98 NTDs (0.08% of deliveries)
- The prevalence of NTDS remained slightly higher in association with DTG exposure at conception than with other types of ART exposure at conception (3 per 1000 deliveries vs. 1 per 1000 deliveries).
  - 5 NTDs in 1683 deliveries in mothers taking DTG at conception, (0.30% of deliveries; 95% CI 0.13 – 0.69). (2 myelomeningocele, 1 anencephaly, 1 encephalocele, 1 iniencephaly)
  - 15 NTDs in 14792 women taking non DTG ART from conception (0.10%; 95% CI 0.06 – 0.17) infants. Prevalence difference was 0.20 (95% CI 0.01 – 0.59) vs the reference DTG from conception.
  - 3 NTDs in 7959 women taking EFV from Conception: (0.04%; 95% CI 0.01 – 0.11) infants. Prevalence Difference: 0.26 (95% CI 0.07 – 0.66) vs the reference DTG from conception
  - 1 NTD in 3840 women who commenced DTG during pregnancy (0.03%; 95% CI 0.00 – 0.15) infants. Prevalence Difference: 0.27 (95% CI 0.06 – 0.67) vs the reference DTG from conception
  - 70 NTDs in 89372 HIV negative women (0.08%; 95% CI 0.06– 0.10) infants. -Prevalence Difference: 0.22 (95% CI 0.05 – 0.62) vs the reference DTG from conception

Tsepamo 2020 update(Zash et al. 2020)

An update was presented at the AIDS conference in July 2020, including data from 39,200 additional births, which included 1908 additional DTG conception exposures.

- Since August 2014, 158,244 deliveries; 153,899 (97.2%) with infant surface exam
- 126 NTDs (0.08%, 95%CI 0.07%,0.09%)
- Prevalence of NTDs in infants born to women on DTG decline since the original safety signal. Prevalence estimate seems to be stabilizing at approximately 2 per 1000.
  - No significant difference between DTG and non-DTG- ART at conception (0.09% difference; 95%CI -0.03%, 0.30%).
  - No significant difference between DTG and EFV at conception (0.12% difference; 95%CI -0.001%, 0.33%).
  - DTG at conception, 7/3591 with NTD (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephaloceles, and 1 iniencephaly
  - Non DTG-ART 21/19 with NTD,361 (0.11%; 95%CI 0.07%, 0.17%)
  - EFV from conception 8/10,958 with NTD (0.07%; 95%CI 0.03%, 0.17%)
  - DTG started in pregnancy 2/4,581 with NTD (0.04%; 95%CI 0.1%, 0.16%)
  - HIV-uninfected women 87/119,630 with NTD (0.07%; 95%CI 0.06, 0.09%)

In response to the signal from the Tsepamo study, the Botswana ministry of health expanded surveillance for NTDs to 22 non-Tsepamo facilities (Raesima et al. 2019). Midwives conducted surface examination of liveborn and stillborn infants.

- From October 2018- 31 March 2019 there were 3076 deliveries, of which 2328 (76%) HIV negative, 742 (24%) HIV positive, and 6 (<1%) HIV unknown.
- There were 544 (73% with ART exposure at conception, of which 152 (28%) were DTG exposed.
- There were 3 confirmed/probable NTDs, 1 in DTG exposed, 2 in HIV negative.

- NTD prevalence with DTG exposure was 0.66% (95%CI 0.02-3.69)
- NTD prevalence in babies born to HIV negative mothers was 0.09% (95% CI 0.01-0.31)
- Difference between DTG based ART and non-DTG based NTD prevalence was 0.66% (95% CI -0.48-3.63)

This study lacked power for precise estimate of NTD prevalence with DTG-exposure at conception.

The Canadian perinatal HIV Surveillance programme collects data on pregnant women living with HIV (WLWH), and their babies (Money et al. 2019).

- Between 2007 and 2017, 85 of 2423 WLWH (3.5%, 95% CI 2.85–4.36%) had non-chromosomal congenital anomalies.
- Rates of congenital anomalies were similar between women who were on ART in their first trimester (3.9%, CI 1.7–7.6%) and those without 1st trimester ART exposure (3.9%, 95% CI 2.6–5.6%)
- 4/80 (5.0%, 95% CI 1.4–12.3%) neonates born to WLWH on DTG during the first trimester had congenital anomalies, none were neural tube defects (95% CI0.00–3.10%). There were very few first trimester DTG exposures and this study lacked power to detect rare events such as NTDs. The cohort included women on efavirenz, but rate of congenital anomalies not reported for EFV-containing ART.

A retrospective cohort analysis was conducted in the Brazilian antiretroviral therapy database(Pereira et al. 2021). Women with DTG exposure within 8 weeks of estimated conception between Jan 1, 2017, and May 31, 2018 were matched 3:1 with pregnant women exposed to EFV between Jan 1, 2015, and May 31, 2018. Primary outcomes were NTD and a composite measure of NTD, stillbirth, or miscarriage.

- 382/ 1427 were exposed to DTG within 8 weeks of estimated date of conception. During pregnancy, 183 (48%) of 382 DTG-exposed and 465 (44%) of 1045 EFV-exposed women received folic acid supplementation.
- There were no NTDs in either DTG-exposed (0, 95% CI 0–0.0010) or efavirenz-exposed groups (0, 95% CI 0–0·0036).
- There were 23 (6%) stillbirths or miscarriages in 384 DTG-exposed fetuses and 28 (3%) in the 1068 EFV-exposed fetuses (p=0·0037).
- After study closure, 2 NTDs in fetuses with periconception DTG exposure were reported to public health officials. Estimate of NTD incidence incorporating these cases and the estimated number of additional DTG-exposed pregnancies between Jan 1, 2015, and Feb 28, 2019, was 1.8 (95% CI 0·5–6·7) per 1000 DTG-exposed pregnancies.

MOTHER TO CHILD TRANSMISSION

An observational cohort study in Botswana compared rates of mother to child transmission (MTCT) between women on DTG and women on EFV in pregnancy(Davey et al. 2020). The analysis included data from 1235 HIV exposed infants whose mothers took DTG/TDF/FTC in pregnancy, and 2411 whose mothers took EFV/TDF/FTC.

- Mother to child transmission (MTCT) was rare when either regimen started before conception: DTG 0/213 (0%, 95% CI 0.00% to 1.72%) vs EFV 1/1497 (0.07%, 95% CI 0.00% to 0.37%).
- MTCT rates were similar when ART was started during pregnancy DTG 8/999 (0.80%, 95% CI 0.35 to 1.57%) vs EFV 8/883 (0.91, 95% CI 0.39 to 1.78%) Risk difference 0.11% (95% CI -0.79 to 1.06%).
- Most transmissions were in women starting ART <90 days before delivery: DTG 4/8 vs EFV 6/9.

ADVERSE EVENTS FROM NON-RANDOMISED STUDIES

<u>Weight gain in mothers during pregnancy</u>

Weight gain during pregnancy was explored in pregnant women commencing DTG or EFV-based ART before 17 weeks of gestation in the Tsepamo cohort in Botswana(Caniglia et al. 2020). The analysis included 1683 women on DTG, 1464 on EFV, and 21 917 HIV uninfected women.

- Women on DTG and EFV both gained less weight during pregnancy compared to uninfected people.
- DTG was associated with decreased risk of insufficient weight gain.
- EFV was associated with less risk of excessive weight gain.

<u>Gestational diabetes</u>

The Tshilo Dikotla prospective cohort in Botswana screened 468 pregnant women for gestational diabetes using a 75g oral glucose tolerance test, of which 486 were PLWHA(Mmasa et al. 2021). Women known to be diabetic were excluded.

- 8.4% of women had gestational diabetes, this was similar between PLWHA and HIV negative women.
- PLWHA taking DTG-containing ART had lower risk of gestational diabetes than those on EFV; 6.1% vs 13.5%.

- adjusted odds ratio 0.40, 95%CI 0.18 to 0.92), in a model including age, BMI, gravidity, CD4 count, and whether or not patient was on ART at the time of conception.

CONCLUSION

The Tsepamo study (Botswana) surveying birth outcomes in infants born to woman on DTG regimens provided the signal of harm (increased NTDs) in 2018(Zash et al. 2018). The updates in 2019 and 2020 have been reassuring - as more data has accrued the difference observed in the rate of NTDs between women taking DTG-based regimens at the time of conception compared to other antiretroviral drugs has shrunk, and is no longer significantly different(Zash et al. 2019; Zash et al. 2020). The current estimate of prevalence of NTDs in pregnancies with DTG exposure at time of conception in Botswana is 2 per 1000. The estimated prevalence in a recent retrospective cohort study in Brazil was similar (1.8 per 1000 DTG exposed pregnancies), but the study is underpowered and the estimate lacks precision(Pereira et al. 2021).

DTG causes more rapid viral load suppression in pregnancy than efavirenz. This could potentially reduce the risk of vertical HIV transmission in mothers who are initiated on DTG treatment in late pregnancy. However, rates of MTCT were similar for DTG and EFV-based ART in a cohort study in Botswana, and transmission event were rare(Davey et al. 2020).

In RCTS, both pregnant and non-pregnant women gained more weight in the DTG than the EFV arm(Venter et al. 2019; Venter et al. 2020; Lockman et al. 2021), especially in those on concomitant tenofovir alafenamide. The mechanism postulated for this difference is impaired weight gain in individuals taking EFV who have the slow metaboliser cytochrome P450 2B6 genotype, which is common in African patients(Griesel et al. 2020). Slow metabolizers have higher EFV concentrations than extensive metabolizers, which may result in increased mitochondrial toxicity from EFV. In the Tsepamo study, DTG in pregnancy was associated with decreased risk of insufficient weight gain and EFV was associated with less risk of excessive weight gain (Caniglia et al. 2020). However, women on either drug gained less weight than HIV negative women.

Based on the benefits to women in terms of viral suppression and reduced risk of drug resistance, and the fact that the risk of neural tube defects in infants exposed to dolutegravir in early pregnancy is no longer significantly different to those exposed to non-dolutegravir-based regimens, dolutegravir should form part of the preferred first line ART regimen for all adults and adolescents living with HIV, including pregnant women and women of childbearing potential, even if not on reliable contraception.

Reviewers: Karen Cohen, Natasha Davies, Lee Fairlie, Milli Reddy, Renee de Waal.

Declaration of interests: KC (Division of Clinical Pharmacology, Department of Medicine, Groote Schuur Hospital, University of Cape Town), ND (Anova Health Institute), MR (Better Health Programme, South Africa), RdW (Centre for Infectious Disease Epidemiology and Research, School of Public Health and Family Medicine, University of Cape Town) have nothing to declare in respect of dolutegravir in HIV. LF (WITS RHI) co-authored HIV publications of which some are included in this review, ND (Anova Health Institute) received a scholarship from Gilead to attend the International AIDS Society conference, in Mexico City in July 2019 and discloses involvement with Southern African HIV Clinicians' Society in development and updating of adult ART guidelines and statements pertaining to the use of dolutegravir in pregnant women and women of child-bearing potential following release of the Tsepamo data update July 2020.

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Table 1. Characteristics of included publications

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Banda FM et al. 2020.	Design: Prospective cohort study (Tshilo DIkotla cohort), Botswana, August 2016-May 2019 Funding: National Institute of Diabetes and Digestive and Kidney Disease (NIDDK) (R01DK109881) COI: none declared	• Pregnant WLHIV and pregnant women without HIV • Between 16-36 weeks gestation • Women on TDF/FTC with DTG or EFV during pregnancy • 469 women enrolled • 182 on DTG based regimen • 127 EFV based regimen • 160 HIV negative Exclusions • Multiple gestations Fetal demise	**Exposures** TDF/FTC/DTG TDF/FTC/EFV	• Head circumference, Biparietal diameter, Abdominal circumference, Femoral length Z scores • Measurements taken during single ultrasound performed in second trimester • Association of in-utero HIV/ART exposure with each fetal biometric Z score	Median Age: EFV based: 32 years (older) DTG based 28 years p<0.01 HIV negative: 24 years Parity: EFV based: 3 DTG based 2 p<0.01 HIV negative: 1 Tertiary education: EFV based: 7.9% DTG based 14.3% p<0.01 HIV negative: 33.1% Gestational age: HIV positive: 28 weeks HIV negative: 26 weeks p<0.01 Viral load and CD4 values similar in both ART groups No significant differences in Z scores between groups, even with adjustments for maternal age, height, education level, parity, alcohol use in pregnancy	• No significant differences in fetal biometry between DTG exposed, EFV exposed and HIV unexposed fetuses Limitations: • Single study site • Small sample size • Single ultrasound (not longitudinal) • No birth follow up to confirm any congenital anomalies at birth Conclusion: • Reassuring results supporting safety of use of DTG in pregnancy.
Caniglia et al, 2020	National birth outcomes surveillance, Botswana (Tsepamo) Funding: NIH No COI declared	Inclusion: • Pregnant women • First time ART initiators • ART start before 17 weeks' gestation • DTG- or EFV-based regimens • HIV-uninfected group for comparison DTG: n=1 683 EFV: n=1 464 HIV-uninfected: n=21 917	EFV DTG HIV-uninfected	**Primary** • Weekly weight gain from 18±2 weeks' gestation to 36±2 weeks' gestation • Total weight gain over 18 weeks **Secondary** • Weight gain >0.59 kg/week • Weight gain <0.18 kg/week (above 2 categories based on Institute of Medicine recommendations) • Weight loss	**Weekly weight gain**, mean (SD) kg: EFV: 0.31 (0.23) DTG: 0.35 (0.22) HIV-uninfected: 0.44 (0.23) Adjusted mean difference versus EFV (95% CI) kg: DTG: 0.05 (0.03 to 0.07) HIV-uninfected: 0.12 (0.10 to 0.14) **Total weight gain**, mean (SD) kg: EFV: 5.3 (4.35) DTG: 6.27 (3.96) HIV-uninfected: 7.95 (4.11) Adjusted mean difference versus EFV (95% CI) kg: DTG: 1.05 (0.61 to 1.49) HIV-uninfected: 2.31 (1.85 to 2.77)	• HIV-uninfected women were more likely to be nulliparous and primigravid than HIV-infected women; women on DTG were less likely to have CD4 measured, had lower CD4 counts, and initiated ART earlier than those on EFV; other baseline characteristics were similar. • Analyses adjusted for age, CD4, employment, education, parity, gravidity, marital status, site, smoking, alcohol use, pre-pregnancy weight, baseline weight, gestational age at ART initiation, medical history (results very similar for crude analyses). • The authors state that the clinical significance of their findings is uncertain, but that lower weight gain is associated with increased risk of preterm birth and lower birth weight, and higher weight gain is associated with pregnancy and delivery complications. They also conclude that HIV and/or ART might impact weight gain.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					Weekly weight gain >0.59 kg, adjusted risk ratio versus EFV (95% CI): EFV: 9.1% DTG: 12.9%, 1.44 (1.11 to 1.87) HIV-uninfected: 23.1%, 2.41 (1.81 to 3.21) **Weekly weight gain <0.18 kg**, adjusted risk ratio versus EFV (95% CI): EFV: 27.7% DTG: 20.2%, 0.73 (0.63 to 0.86) HIV-uninfected: 11.1%, 0.48 (0.41 to 0.57) **Weight loss**, adjusted risk ratio versus EFV (95% CI): EFV: 9.4% DTG: 4.4%, 0.43 (0.28 to 0.67) HIV-uninfected: 2.2%, 0.30 (0.19 to 0.47)	
Crowell et al, 2020.	Prospective cohort study (22 sites in United States including Puerto Rico; from 2007 to 2017) Follow-up duration: Youth followed up to 18 years Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development with co-funding from the National Institute of Dental and Craniofacial Research, the National Institute of Allergy and Infectious Diseases, the National Institute of Neurological Disorders and Stroke, the National Institute on Deafness and Other Communication Disorders, Office of AIDS Research, the National Institute of Mental Health, the National Institute on Drug Abuse, and the National Institute on Alcohol Abuse and Alcoholism, through Cooperative agreements	Sample size: 3747 children - HIV-exposed but uninfected (CHEU) and exposed *in utero* to ARVs Two cohorts: • Static cohort (enrolled from 2007–2009; 1–12 years; participated in prior studies with available pregnancy and birth data) • Dynamic cohort (enrolled during gestation or within 1 week after birth) Patient characteristics: 48% girls 68% black and 31% Hispanic. Maternal tobacco use: 17% Maternal alcohol use: 8% Maternal marijuana use: 8% Maternal Cocaine/opiates use: 3% Inclusion criteria: CHEU enrolled by 1 April 2017 and had a study visit for neurologic trigger assessment by 1 August 2017 (triggers for potential neurologic diagnoses defined as a febrile or afebrile	Exposures: •ARVs (3747) •EFV vs control (166 vs 3487) •DTG vs control (94 vs 688)	**Primary outcome:** Neurological adverse event associated with ARVs (febrile or afebrile seizure, microcephaly, or other neurologic or ophthalmologic disorders)	**Primary outcome:** All ARVs • ***Neurological cases:*** ○ 231/3747 (6.2%, 95% CI 5.4% to 7.0%) over a median follow-up of 4.3 years (IQR: 1.4–7.0). • ***Neurologic diagnoses*** ○ Microcephaly: 25.1% ○ Febrile seizure: 17.6% ○ Eye-related abnormalities (esotropia, exotropia,strabismus, ptosis, nystagmus, ambylopia, and optic nerve abnormalities: 16.5% ○ Nonfebrile seizure:13.5% **Sub-analyses:** EFV vs control • ***Neurological cases:*** ○ 15/166 (9%) vs 211/3487 (6.1%), adjusted RR (aRR) 1.53 (95% CI 0.94 to 2.51), p=0.090 ○ At conception: aRR = 1.92 (95% CI 1.09 to 3.36) DTG vs control • ***Neurological cases:*** ○ 15/166 (9%) vs 211/3487 (6.1%), aRR 43 (95% CI 0.75 to 7.84), p=0.14 ○ At conception: aRR = 3.47 (95% CI 0.74 to 16.36) ○ At conception: aRR = 2.95 (95% CI 0.79 to 11.1)	• An observational study to determine neurological harms associated with ARVs • As models were restricted to children born after 2007 for darunavir and raltegravir, after 2011 for rilpivirine, and after 2013 for DTG and elvitegravir – due to drug approval dates, the study cohorts for DTG (n=94) was not comparable in size to EFV (n=166) • Of 3747 children enrolled, 94 lacked detailed ARV information and was excluded from the analysis – missing information for 2.5% of study population; some concern of selection bias • Maternal substance use was through self-reporting questionnaires that may have contributed to reporting bias at baseline. • Assessors in the panel that classified neurological triggers in CHEU, were blinded to the ARVs their mothers used. • Information on the controls are not clearly reported. • Sensitivity analyses were done to account for possible bias, adjusting for confounders such as maternal factors (age, race, ethnicity, chronic health conditions, obstetrical complications, and substance use), birth cohort (<2011, 2011–2014, 2015–2017), and family/household factors (socioeconomic status, household income level, and caregiver education level). • Adjusting for confounders, resulted in persistent association of EFV exposure with a risk for neurological adverse events.

<table>
<tr><th>Citation</th><th>Study design</th><th>Population</th><th>Exposures and control</th><th>Outcomes</th><th>Effect sizes</th><th>Comments</th></tr>
<tr><td></td><td>with the Harvard T.H. Chan School of Public Health and the Tulane University School of Medicine.

Declarations: E.G.C. holds stock in Abbot and AbbVie. All other authors report no conflicts of interest.</td><td>seizure, microcephaly, or other neurologic or ophthalmologic disorders)

Exclusion criteria:
Neurologic diagnoses determined to be secondary to events occurring after birth (e.g. postnatal meningitis, trauma)</td><td></td><td></td><td></td><td>• In utero DTG exposure was associated with an increased risk of a neurologic diagnosis but imprecision was high, due to the small number of exposed cases.</td></tr>
<tr><td>Davey et al, 2020</td><td>National surveillance, Botswana.
Early Infant Treatment Study screened infants for HIV at 20% of delivery facilities in the country; those in Tsepamo registry were linked to establish ART regimen

Funding: NIH
No COI declared</td><td>Total infants screened:
n=10 622

Liked to Tsepamo:
Exposed to DTG: n=1 235
Exposed to EFV: n= 2 411
Exposed to other ART: n=1 246
Exposed to multiple ART regimens: n=37
No ART exposure: n=135</td><td>DTG
EFV
Other regimens
No ART</td><td>MTCT rates</td><td>MTCT, n, % (95%CI):
Overall
DTG: 8/1 235, 0.64 (0.28 to 1.27)
EFV: 9/2 411, 0.37 (0.17 to 0.71)
Other regimens: 2/1283, 0.16 (0.02 to 0.56)
No ART: 6/135, 4.44 (1.65 to 9.24)

ART initiated before pregnancy
DTG: 0/213, 0 (0 to 1.72)
EFV: 1/1 497, 0.07 (0 to 0.37)

ART initiated during pregnancy
DTG: 8/999, 0.80 (0.35 to 1.57)
EFV: 8/883, 0.91 (0.39 to 1.78)
Risk difference: 0.11%, 95% CI -0.79 to 1.06</td><td>• Those on ‘other’ ART regimens were less likely to be diagnosed during pregnancy, less likely to start ART during pregnancy, and had a longer duration of ART exposure than those on EFV or DTG.</td></tr>
<tr><td>Kanters et al, 2020</td><td>Systematic review and network meta-analysis

Funding: WHO HIV department</td><td>For pregnancy outcomes the authors included 54 references from 35 studies. Studies included RCTs, comparative and non-comparative observational cohorts, and population-level surveillance or registries.</td><td>DTG
EFV</td><td>Preterm birth
Low birth weight
Small for gestational age
Congenital abnormalities
Still birth
Maternal death
Neonatal death
MTCT
NTDs</td><td>Pregnancies with pre- and post-conception exposures to DTG versus EFV
<table><tr><th>Outcome</th><th>Odds ratio</th><th>95% credible interval</th></tr><tr><td>Preterm</td><td>0.99</td><td>0.85 to 1.14</td></tr><tr><td>LBW</td><td>0.93</td><td>0.80 to 1.08</td></tr><tr><td>SGA</td><td>0.93</td><td>0.80 to 1.07</td></tr><tr><td>CA</td><td>1.06</td><td>0.40 to 2.86</td></tr><tr><td>Stillbirth</td><td>1.03</td><td>0.72 to 1.46</td></tr><tr><td>M. death</td><td>0.09</td><td>0.00 to 39.39</td></tr><tr><td>N. death</td><td>1.03</td><td>0.65 to 1.62</td></tr><tr><td>MTCT</td><td>6.87</td><td>0.74 to 39.10</td></tr></table>
Any adverse birth outcome
DTG: 33.2%
EFV: 35%

Neural tube defects
DTG: 6/1835
EFV: 3/8220
Risk difference 0.29% (95% CI 0.10 to 0.68)</td><td>• Most data on pregnancy outcomes is from Tsepamo (the other studies were relatively small in comparison).
• The NTD estimate is based on Tsepamo and the Raesima et al study only, because of variability in folic acid supplementation and background event rates. Tsepamo data up until March 2019 was included.
• Other outcomes (efficacy) were reported overall, and not for women separately.</td></tr>
</table>

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Kintu et al, 2020. DolPHIN-2 Study Group.	Randomised, open-label trail in Cape Town, South Africa (8 PHC facilities) and Kampala, Uganda (8 PHC antenatal facilities); from January to August 2018 Funding: Funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.	Sample size: 268 screened, 128 randomised to DTG (n=129) or EFV based regimen (n=128) Inclusion criteria: Woman≥ 18 yrs with untreated but confirmed HIV, positive pregnancy test, ± gestation of ≥28 weeks, provided consent. Exclusion Criteria: ART in the preceding year or ever received integrase inhibitors; documented virological failure of a non-nucleoside containing ART; previous EFV toxic events or clinical history precluding randomisation; estimated glomerular filtration rate <50 mL/min; haemoglobin <8.0 g/dL; decompensated liver disease or alanine aminotransferase > 5x upper limit of normal (ULN); or alanine aminotransferase >3x ULN and bilirubin >2x ULN (with >35% direct bilirubin); severe pre-eclampsia; medical, psychiatric, or obstetric condition that might affect participation; receiving any drugs significantly interacting with EFV or DTG within the preceding 2 weeks. *In June 2018, protocol amended to exclude patients with pretreatment HIV VL of < 50 copies/ml	**DTG (50 mg) or EFV** plus TDF (300 mg) plus FTC (200 mg) in South Africa or 3TC (300 mg) in Uganda) Both administered as single tablet once daily.	**Primary outcomes:** **Efficacy:** HIV viral load < 50 copies/mL at birth **Safety:** Frequency of drug-related adverse events. **Secondary Outcomes:** -viral load of <1000 copies/mL at birth, -occurrence of mother-to-child transmission -safety & tolerability of DTG in mothers and breastfed infants	**Primary outcomes:** *DTG Vs EFV :* **HIV viral load < 50 copies/mL @ birth (mothers):** 89/120 (74·2%) vs 50/117 (42·7%) **Median time to VL < 50copies/mL:** 28 days (95% CI 28–34) vs 82 days (55–97) **Median time to VL < 1000 copies/ml:** 7 days (7–20) vs 23 days (21–27) **Frequency of drug-related adverse events:** • ≥1 SAE: 30 (22%) vs 14 (11%) • ≥1 drug-related SAE 1 (<1%) vs 0 • ≥1 or immune reconstitution inflammatory syndrome (IRIS)-related SAE 1 (<1%) vs 0 **Secondary outcomes:** **Viral load of <1000 copies/mL at birth:** 112/120 (93%) vs 96/117 (82%) **Mother-to-child transmission:** 3 transmissions in DTG group **Safety & tolerability of DTG in mothers and breastfed infants:** Higher frequency of pregnancy, puerperium, and perinatal events in mothers receiving DTG vs EFV: • Stillbirths: 3/124 (2·2%) vs 1/120 (<1%). • 123 vs 119 live births • Median gestation at birth of 39 weeks (IQR 37·3–40·3) - both groups • No significant difference in proportion of preterm, late-preterm births, frequency of serious adverse events, infant birthweights • Congenital disorders (umbilical hernias, birth marks, skin dimples, acrochordon, heterochromia iridis, laryngomalacia, strabismus, talipes, cleft palate, and polydactyly) did not differ between groups • 0 neural tube defects • 4/123 (3%) infant deaths vs 2/119 (2%)	• Women on DTG regimen more likely to achieve VL< 50 copies per/ml / less likely to have a VL of ≥50 copies/mL) at time of birth (initiated in the third trimester) • Undisclosed ART unlikely - mothers with a VL < 50 copies/mL excluded at baseline • 7 & 28 day visit days used as a measure of time from randomization to viral load suppression which might have biased the true time of viral load suppression (but same in both groups) • For this population, peripartum HIV transmission strongly correlated with prevailing maternal VL therefore DTG regimens might reduce HIV transmission around birth & potentially during breastfeeding, compared with EFV regimens • 3 HIV-infected infants were likely to have had in-utero infections, but peripartum transmission cannot be excluded because infants not tested within 2 days of birth • Higher proportion of mothers who received DTG had serious adverse events Finding driven by a higher overall frequency of pregnancy, puerperium, and perinatal events in mothers receiving DTG, who had prolonged pregnancy beyond term. • 4 stillbirths - related to obstetric & severe maternal infection. • Sample size not large enough to study differences in infant transmissions, but powered to detect virological superiority before or at time of birth (best validated proxy for vertical HIV transmission) • Results were robust in sensitivity analysis. The DolPHIN-2 results strongly support global transition to DTG use in first-line ART
Kouafack et al, 2019. New Antiretroviral and Monitoring	Open-label, multicenter, randomized, phase 3 noninferiority trial (48 weeks – July 2016 – August 2017).	Sample size: N=613 Patient characteristics:	**Exposures:** •DTG regimen •EFV (400-mg) regimen	**Primary outcome:** •Proportion of participants with a VL of <50 copies/ml at week 48 **Secondary outcomes:**	**Patient Characteristics:** -Baseline values balanced between groups. Median age - 37 years. **65.9% (n=404) of the participants were women.** Median baseline VL - 5.3 log_{10} copies/ml. 66.4% -baseline VL of at least 100,000 copies/milliliter. Median CD4+ T-cell count	• Study included both men and women (no pregnant women) • Results showed noninferiority of DTG to EFV400 with regard to viral suppression at week 48.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Strategies in HIV-Infected Adults in Low-Income Countries **(NAMSAL)**	Study Setting: Cameroon Two Arms: -n=310 DTG -n=306 EFV -Randomization, 1:1 ratio, to receive DTG/EFV400 Follow-up duration: follow-up until week 96	Adults, **both males & females**, HIV – infected, HIV treatment naïve. 66.4% had a viral load (VL) of ≥100,000 copies/ml milliliter, & 30.7% had a viral load of ≥500,000 copies/ml) Inclusion criteria: ≥18 years of age, had not received ART, and had HIV-1 group M infection with a viral load of at least 1000 copies/ml. WOCP had to agree to use effective contraceptive methods. Exclusion criteria: Pregnant, breast-feeding, severe hepatic impairment, renal failure, severe psychiatric illness, & unstable tuberculosis coinfection Funding: Supported by Unitaid and the French National Agency for AIDS Research (ANRS 12313) Declarations: None		•VL with other thresholds: - VL <200 copies/ml; & virologic failure, defined by the WHO as VL>1000 copies/ml after reinforcement of adherence) at weeks 24 & 48 •Drug resistance. •Change from baseline in the CD4+ T-cell count at weeks 24 & 48 •Morbidity (WHO stage) •Adherence to treatment, -Safety, & Patient-reported outcomes (depression, anxiety, & stress; HIV treatment symptoms, including EFV related symptoms; & quality of life)	was 281/cubic mm. Adherence to treatment was similar in both groups. **Primary Outcome:** Efficacy: DTG vs EFV **(males and females)** Week 48, n=231/310 (74.5%) vs n=209/303 (69.0%) - viral load < 50copies/ml. Difference between treatment groups was 5.5 % points (95% confidence interval [CI], −1.6 to 12.7), meeting criterion for noninferiority (P<0.001) but not superiority (P = 0.13). **Results Reported for Women: DTG vs EFV Women & viral suppression:** (n=157/197 [79.7%] vs. n=147/207 [71.0%]; difference, 8.7 % points; 95% CI, 0.3 to 17.0) (favoring DTG). **Secondary Outcomes:** -25/404 (6.2%) women became pregnant - (13 DTG vs 12 EFV400) **Delivery:** 4 (30.7%) vs (66.7%) **Miscarriage:** 6 (42.2%) vs 4(33.3%) **Voluntary abortion:** 3 (23.1) vs (0 (0%) -All deliveries (n=12) born alive, without reported congenital abnormalities. Significantly > median increase in body weight in DTG group vs EFV group (5.0 kg [interquartile range, 1.0-8.0] vs. 3.0 kg [interquartile range, 0.0 - 7.0], P<0.001). Weight gain of at least 10% observed in > women vs men (147/379 [38.8%] vs. 44/192 [22.9%], P<0.001)	• Adherence to treatment was high on the basis of scores on a validated questionnaire but this measure has limitations. • The relationship between DTG and obesity as well as risks associated with childbearing potential need exploration
Lockman et al, 2021.	Design: Multicentre, phase 3, open-label, randomised controlled trial Recruitment: Jan 19, 2018, to Feb 8, 2019 Funding: National Institute of Allergy and Infectious Diseases, the Eunice Kennedy Shriver National Institute of Child Health and Human Development, and the National Institute of Mental Health	Study population: Pregnant women gestation 14-28 weeks, less than 14 days of ART in sites in Botswana, Brazil, India, South Africa, Tanzania, Thailand, Uganda, the USA, and Zimbabwe 643 pregnant women enrolled: 217 to the dolutegravir, emtricitabine, and tenofovir alafenamide fumarate(TAF) group, 215 to the dolutegravir, emtricitabine, and tenofovir disoproxil fumarate (TDF) group, and 211 to the	Exposures DTG/FTC/TAF DTG/3TC/TDF Control EFV/TDF/FTC 1:1:1 randomisation	Primary efficacy outcome: proportion of participants with viral suppression (< 200 copies per mL, at or within 14 days of delivery prespecified non-inferiority margin of –10% in the combined dolutegravir-containing groups versus the efavirenz-containing group Primary safety outcomes: compared pairwise among treatment	Enrolment: • Median gestational age 21·9 weeks (IQR 18·3–25·3) • median HIV-1 RNA concentration 902·5 copies/mL (152·0–5182·5 • 181 [28%] of 643 participants HIV-1 VL <200 copies/mL) • Median CD4 count was 466 cells per µL (308–624) Delivery • VL available for 605 (94%) participants. • 395 (98%) of 405 participants in the combined dolutegravir containing groups had VL	• Study pause May 18 and Oct 12, 2018 due to NTD signal in Tsepamo • Direct comparison between DTG-based and EFV SOC-based ART in pregnancy, 14-28 weeks • Superior virological efficacy in DTG-containing regimen compared to efavirenz-containing regimen • DTG/DTC/TAF has lowest composite pregnancy outcomes • Efavirenz higher neonatal death

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
		efavirenz, emtricitabine, and TDF group Inclusion criteria: • ≥18 years • 14-28 weeks gestation • HIV-1 infection Exclusion criteria • Previous ART (except 14 days for current pregnancy) • Psychiatric illness • Multiple pregnancy • Known fetal anomaly		groups, occurrence of a composite adverse pregnancy outcome (ie, either preterm delivery, the infant being born small for gestational age, stillbirth, or spontaneous abortion) in all participants with a pregnancy outcome, and the occurrence of grade 3 or higher maternal and infant adverse events in all randomised participants.	suppression at delivery compared with 182 (91%) of 200 participants in the efavirenz group (estimated difference 6·5% [95% CI 2·0 to 10·7], p=0·0052 • Slightly fewer women in DTG/FTC/TAF arm with composite adverse pregnancy outcomes (52 [24%] of 216) DTG/3TC/TDF (70 [33%] of 213; estimated difference –8·8% [95% CI –17·3 to –0·3], p=0·043) or the TEE group (69 [33%] of 211; –8·6% [–17·1 to –0·1], p=0·047) • Infants with grade 3 outcomes not different between groups • Preterm delivery lower in DTG/FTC/TAF group (12 [6%] of 208) compared to efavirenz group (25 [12%] of 207; –6·3% [–11·8 to –0·9] p=0·023) • Neonatal mortality significantly higher in efavirenz group (ten [5%] of 207 infants) DTG/FTC/TAF two [1%] of 208; p=0·019) DTG/3TC/TDF (three [2%] of 202; p=0·050)	
Money D, et al; 2019.	Canadian Perinatal (CPHSP) HIV Surveillance Programme Study Setting: 22 sites, 19 HIV referral health centres, 3 health departments from all Canadian provinces & territories). Captures ± 95% of all pregnancies in WLWH, and 100% where infant is infected with HIV Funding: No specific funding secured for the analysis. Public Health Agency of Canada (PHAC) had no role in this study's conduct and design; collection, management, analysis, or write up. Declarations: Data presented annually at the Canadian Conference on HIV/AIDS Research and other meetings.	Live-born infants born in Canada to WLWH between 2007 and 2017	ART (at conception & pregnancy)	Congenital anomalies	**From 2007 to 2017** **Patient Characteristics:** - 2591 live infants born to WLWH - 2423 had congenital anomaly data - 81.9% deliveries at term - Mean gestational age 38.2 weeks. - 2306 of the mothers had timing of HIV diagnosis known; 272 (11.8%) diagnosed with HIV during pregnancy, 40 (1.7%) at or after childbirth, 1994 (86.5%) before pregnancy. 4/80 (5.0%, 95% CI 1.4 to 12.3%) neonates born to WLWH on DTG during the first trimester had congenital anomalies vs 3/46 (6.5%, 95% CI 1.4 to 17.9%) on EFV - Anomalies for DTG included urinary tract (n = 2), circulatory system (n = 1) & musculoskeletal system (isolated polydactyly, n = 1). -NTDs on DTG (0/117; 95% CI 0.00 to 3.10%) -3 cases of NTDs since 2007, overall incidence rate of 0.12% (95% CI 0.03 to 0.36%) – none on DTG or EFV	• Small sample size due to limited use of DTG in women of reproductive age in Canada • Looked at both DTG before conception and those initiated on DTG after conception • 5% of infants of Canadian women living with HIV on DTG at conception had congenital anomalies; none had neural tube defects

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Mmasa et al, 2021	Prospective cohort, Botswana Funding: NIH No COI declared	Pregnant women ≥18 years, 16-36 weeks' gestation, without diabetes n=486 DTG: 197 EFV: 126 HIV-uninfected: 163	DTG EFV HIV-uninfected	Gestational diabetes diagnosed on oral glucose tolerance test at 24-28 weeks' gestation, or earliest prenatal visit if after 28 weeks	**Gestational diabetes** DTG: 6.1% EFV: 13.5% aOR: 0.34 (95% CI 0.12 to 0.97), adjusted for age, BMI, gravidity, CD4, ART started before pregnancy aOR: 0.40 (95% CI 0.18 to 0.92), also adjusted for duration of ART exposure HIV-uninfected: 7.4% aOR versus HIV-infected on ART: 0.83 (95% CI 0.37 to 1.85), adjusted for age, education, BMI, and gravidity	• Those on EFV, compared to those on DTG, were older, were more likely to be on ART at conception, and had a longer duration of ART exposure; other baseline characteristics were similar

Pereira GFM, et al. 2021.	Design: retrospective, observational, national, cohort study
	
	Funding:
	Brazilian Ministry of Health and the United States' National Institutes of Health
	
	COI:
	BES, FM, CCMcG, and JLC declare receiving grants from the US National Institutes of Health. All other authors declare no competing interests.
		• 1468 women included
		• 382 any DTG exposure
		• 41 any RTG exposure
		• 1045 only EFV exposure All women with possible prenatal dolutegravir exposure from 1 Jan 2017 to 31 May 2018
		• All women potentially raltegravir exposed at conception (same timeline)
		• A pool of Efavirenz exposed women, geographically matched (comparative cohort)
		
		Inclusions:
		• Aall women with reported pregnancy and an immediately previous dolutegravir-based regimen
		• All women of childbearing age receiving dolutegravir who switched to a pregnancy-recommended regimen for unclear reasons
		• All women receiving dolutegravir who received injectable or oral solution zidovudine or nevirapine (or both) as an indication of a birth event.
		• Any DTG, EFV or RTG use at any point during the periconception window (8 weeks before or after
			Exposures:
			DTG
			RTG
			EFV
			
			Cases reviewed on 3:1 ratio for EFV:DTG
				Primary outcomes
				• NTD
				• Composite measure of NTD, stillbirth >22 weeks, miscarriage < 22 weeks
					Mean age:
					EFV only: 28.5 yrs
					DTG exposure: 26.6yrs
					
					CD4 count:
					EFV only: 604 cells/ml
					DTG exposure: 530 cells/ml
					
					Undetectable VL
					EFV only: 465 (75%)
					DTG exposure: 139 (36%)
					
					Primary Outcome:
					• No NTDs among birth outcomes of women periconceptionally exposed to DTG or EFV
					• Estimated NTD prevalence = 0
					• Composite outcomes (NTD+miscarriage+stillbirth):
					  ○ DTG-exposed: 25/384 = 7%, 95% CI 0.04 to 0.094
					  ○ EFV-exposed: 43/1068 = 4%, 95% CI 0.030 to 0.054
					• Miscarriages 6% vs 3% DTG vs EFV
					• No differences with sensitivity analyses and additional of prenatal variables for the composite outcome
					• 2 additional NTDs were reported just after the end of the study (May 2019).
					• This updated the incidence of NTD in DTG exposed women to 0.0018 - Equal to 1.8/1000 DTG exposed pregnancies (95% CI 0. To 6.7).
					
					Other outcomes:
					No significant differences in preterm labour, premature rupture of membranes, pre-eclampsia, diabetes/gestational diabetes, gestational
						• Sensitivity analyses conducted to see if any difference if women exposed to more than one ART during periconception period
						
						Conclusion
						• No occurrences of NTDs in Brazilian national cohort study of women with periconceptional DTG exposure
						• After inclusion of 2 NTDs reported after study close, incidence remained well below 1%
						• Increased rate of miscarriages in women exposed to DTG but finding inconclusive as attenuated once prenatal variables added to model
						
						Limitations:
						• Likely underpowered to detect difference in NTD risk because of rarity of event
						• Uncertainty of timing of conception relative to ART exposure
						• Many women received multiple ART regimens during periconception period
						• Retrospective analysis can introduce bias
						• Missing data for some women (birth outcome, ART exposure, timing of conception)

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
		estimated date of conception) Exclusions: • Women found not pregnant, with unknown birth outcome or ART exposure and with no periconceptional exposure to DTG/RTG/EFV • Women whose estimated date of conception could not be calculated			hypertension or average weight gain per week between the groups	
Raesima MM et al. 2019.	National surveillance, Botswana	Inclusion: • All pregnancies with live-born or stillborn delivered beyond 24 weeks • 22 non-Tsepamo facilities • Delivered from October 2018- 31 March 2019 Population: • 22 sites, Botswana • 3076 deliveries • 2328 (76%) HIV negative • 742 (24%) HIV positive • 6 (<1%) HIV unknown • 544 (73%) ART exposed at conception • 152 (28%) DTG exposed	DTG-based regimen exposure Non-DTG based regimen exposure	Data collected: Surface examination (midwife) Maternal HIV status ART exposure at conception Folate exposure NOT collected Primary outcome: Estimated prevalence of NTD according to maternal HIV status and ART exposures, including DTG	• 3 confirmed/probable NTDs amongst all infants • 1 in DTG exposed, 2 in HIV negative • DTG prevalence 0.66% CI 0.02 to 3.69 • HIV negative prevalence 0.09% CI 0.01 to 0.31 • Difference between DTG based ART and non-DTG based NTD prevalence = 0.66% CI -0.48 to 3.63	• Slightly higher prevalence of NTDs among HIV positive mothers with DTG exposure at time of conception • Magnitude of NTD risk with DTG exposure at time of conception remains <1% Limitations • Short duration of study • NTD rare event, only 3 cases • Unstable prevalence estimates resulted from small sample size
Venter WDF et al. 2019.	Design: Phase 3, investigator-led, open-label, randomized trial Funding: U.S. Agency for International Development, Unitaid, and the South African Medical Research Council. Investigational drugs were donated by Gilead Sciences and ViiV Healthcare. COI: WDFV reports lecture fees and travel support from Roche, grant support,	Study population: South Africans ≥ 12 years Randomized to triple-therapy combination of emtricitabine (FTC) and DTG plus either of TAF (TAF-based group) or tenofovir disoproxil fumarate (TDF) (TDF-based group) — against the local standard-of-care regimen of TDF–FTC–efavirenz (standard-care group). Population 1053 patients randomised February 2017 through May 2018.	Exposures DTG/FTC/TAF DTG/3TC/TDF Control EFV/TDF/FTC 1:1:1 randomisation	Efficacy: The primary end point was the percentage of patients with a 48-week HIV-1 RNA level of less than 50 copies per milliliter, non-inferiority margin -10 percentage points Safety data at 48 weeks also reported	Baseline characteristics: • Mean age 32 years, mean CD4 count 337 cells/mm^3. Week 48: **Efficacy** • Percentage of patients with an HIV-1 RNA level of < 50 cps/ml 84% in the TAF-based group, 85% in the TDF-based group, and 79% in the standard-care group • DTG-containing regimens were noninferior to the standard-care/EFV regimen. • The number of patients who discontinued the trial regimen was higher in the standard-care group than in the other two groups.	• DTG-based regimens non-inferior to EFV-based SOC • TAF-based regimen less bone mineral and renal issues compared to TDF

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	advisory board fees, and provision of drugs from Gilead Sciences, advisory board fees from ViiV ealthcare, lecture fees from Merck and Adcock Ingram, and lecture fees and advisory board fees from Johnson & Johnson and Mylan; MM honoraria and conference attendance support from Johnson & Johnson, Cipla, and ViiV Healthcare, honoraria, advisory board fees, and conference attendance sponsorship from Gilead Sciences, advisory board fees from AbbVie, and conference attendance sponsorship from Merck; EA receiving advisory committee fees from ViiV Healthcare.	> 99% of the patients were Black, 59% female Inclusion criteria: • ≥12 years • no receipt of ART in the previous 6 months, • creatinine clearance of more than 60 ml per minute (>80 ml per minute in patients < 19 years • HIV-1 • VL ≥ 500 copies/ml Exclusion criteria: Pregnancy, current TB treatment			• In the per-protocol population, the standard-care regimen had equivalent potency to the other two regimens. **Safety** • The TAF-based regimen had less effect on bone density and renal function than the other regimens. • Weight increase (both lean and fat mass) was greatest in the TAF-based group and among female patients (mean increase, 6.4 kg in the TAF-based group, 3.2 kg in the TDF-based group, and 1.7 kg in the standard-care group). • No resistance to integrase inhibitors identified in patients receiving the DTG-containing regimens.	
Venter WDF, et al. 2020	ADVANCE study, as above. 96 week results	As above The trial included 623 women	As above	96-week outcomes reported separately for women: Viral suppression<50 copies/mL Obesity Pregnancy outcomes	**Women:** **Viral suppression <50 copies/mL** TAF/FTC/DTG: 168/214 (79%) TDF/FTC/DTG: 154/208 (74%) TDF/FTC/EFV: 147/201 (73%) **Obesity** TAF/FTC/DTG: 42/151 (28%) TDF/FTC/DTG: 23/129 (18%) TDF/FTC/EFV: 15/125 (12%) **Pregnancy outcomes** TAF/FTC/DTG: 29 pregnancies in 26 women; 6 miscarriages (21%); 1 infant death TDF/FTC/DTG: 25 pregnancies in 24 women; 2 miscarriages (8%); 0 infant deaths TDF/FTC/EFV: 34 pregnancies in 32 women; 9 miscarriages; 0 infant deaths **Overall (all trial participants, not only women):** **Viral suppression <50 copies/mL** TAF/FTC/DTG: 276/351 (79%)	• Subgroup analyses were presented for women overall, not necessarily only WOCP. The overall mean age of the study population was 32 years (range 13-62). • In the viral suppression results, patients with no viral load results were considered failures – the proportions with missing VL data weren't reported for women specifically, but were 18%, 18%, and 23% for the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV groups overall.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					TDF/FTC/DTG: 275/351 (78%) TDF/FTC/EFV: 258/351 (74%) **Drug discontinuation due to AE** TAF/FTC/DTG: 2 TDF/FTC/DTG: 1 TDF/FTC/EFV: 10 **Resistance mutations** In those with VF and a baseline and 96-week resistance data available, 2/16 patients in the TDF/EFV/DTG group had NRTI resistance mutations (M184V); and 13/21 patients in the EFV group had various mutations. No other resistance mutations were reported.	
Waitt et al, 2019.	Open – Label Randomized Control Trial (Uganda & South Africa between 9th March 2017 & 16th January 2018). Randomized 1:1 to DTG or EFV) containing ART until 2 weeks post-partum (2wPP). Study Setting: Mulago National Referral Hospital, Kampula, Uganda Gugulethu Community Health Care Centre, Cape Town Two Arms: -(n=29) pregnant women on DTG -(n=31) pregnant women on EFV Follow-up duration: 6 months until postpartum	Sample size: N=60 mothers initiating therapy in third trimester were randomised to receive EFV based (standard of care) or DTG regimen Patient characteristics: 100% Black African, HIV – infected treatment – ART treatment naïve pregnant women (28–36 weeks of gestation, age 26 (19–42), weight 67kg (45–119). Inclusion criteria: informed consent, comply with scheduled visits, treatment plans, other required study procedures, aged atleast 18 years, untreated HIV in late pregnancy, 28–36 weeks of gestation Exclusion criteria:Pregnant mothers who received ARVs in the previous 6 months, had ever received integrase inhibitors; anaemic (hb <than	Exposures: •DTG - ART (50mg) consisting of tenofovir disoproxil fumarate with either lamivudine/emtricitabine •EFV – ART (SOC) consisting of once daily EFV; tenofovir disoproxil fumarate with either lamivudine/ emtricitabine	Primary outcome: Pharmacokinetics of DTG in HIV infected women during the third trimester of pregnancy & after two weeks postpartum as defined by the area under the concentration-time curve of DTG between 0 & 24 hours (AUC_{0-24}). Secondary outcomes: Cord to maternal plasma DTG ratio (C:M ratio), maternal breast milk to plasma DTG ratio (M:P ratio), & infant DTG concentrations at maternal steady state & at 1, 3 & 3 days following discontinuation	DTG vs EFV No differences in baseline maternal age (median 27 vs 25 years), gestation (31 vs 30 weeks), weight (65 vs 68 Kg), obstetric history, viral load (4.5log10 copies/mL both arms) & CD4 count (343 vs 466 cells/mm^3). 28 DTG vs 31 EFV live births. Median (range) gestational age at delivery DTG 39 (35–43) weeks, vs EFV 38 (34–42) weeks. No significant differences for birth weight (3kg DTG) vs 3kg EFV) **Primary Outcome:** **Pharmacokinetic Data: Predose:** n=29 -intensive PK sampling. n=1 excluded - non – adherent due to undetectable DTG concentrations. n=28 in third trimester, Cmax, C_{24} & AUC_{0-24} (geometric mean, range) were 2435 (1462–3986) ng/mL, 642 (188–3088) ng/mL and 35322 (19196–67922) ng.h/mL respectively. **Pharmacokinectic Data: Post – Dose:** n=23 - intensive post-partum PK sampling following delivery; n=6 - sampling before 7 days postpartum excluded. n=17 sampled at a median of 10 (range 7–18) days following delivery, with C_{max}, C_{24} & AUC_{0-24} of 2899 (1397–4224) ng/mL, 777 (348–1210) ng/mL and 40127 (22795–59633) ng.h/mL respectively. No significant differences in the geometric mean ratios of C_{max}, C_{24} & AUC_{0-24} in 14	• DolPHIN-1 confirms that the superior virological responses observed with DTG-based combination therapy in non-pregnant adults is also seen in pregnancy. Differences show that DTG has a role in prevention of mother to child transmissions among women who are initiated on ART in the 3rd trimester. • Standard DTG dosing potentially safe & beneficial in late pregnancy. • High infant exposures to DTG in utero, & in first week of life, may offer additional prophylaxis against HIV transmission • **Discontinuations and Resistance:** n=1 participant in the DTG-ART arm discontinued for lack of efficacy after week 4 - undetectable DTG concentrations in 3rd trimester & admitted nonadherence. Another individual in the DTG-ART arm experienced resistance & had a viral load of 2217 copies/mL at the post-partum visit. Multi-class resistance demonstrated on baseline sample (M41L, L201W, T215Y, M184V, Y188L, M46I, I84V, I54V, V32I, V82A, L33F, K43T) & attained virological suppression after transition to a regimen containing DTG & ritonavir-boosted darunavir. The n=2 that discontinued prior to the post-partum visit for other reasons (1 in each arm) both had a VL <200 copies/mL at the point of discontinuation (4 weeks).

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
	Funding: DolPHIN-1 was funded by ViiV Healthcare through an investigator-initiated study scheme https://www.viivhealthcare.com/en-gb/advancinghiv- science-and-rd/we-collaborate-to-innovate/, award number 205785 awarded to SK. CW is funded by a Wellcome Postdoctoral Training Fellowship for Clinicians WT104422MA https:// wellcome.ac.uk/funding/schemes/postdoctoralresearch-training-fellowships-clinicians. Declarations: ML declared research grants from ViiV, Janssen and personal fees from Mylan.	8 g/dL); had elevations in serum levels of alanine aminotransferase (ALT) > 5 times the upper limit of normal (ULN) or ALT >3xULN and bilirubin >2xULN (with >35% direct bilirubin); active hepatitis B; history/ clinical suspicion of unstable liver disease (presence of ascites, encephalopathy, coagulopathy, hyperbilirubinaemia, oesophageal/gastric varices/persistent jaundice); severe pre-eclampsia, or other pregnancy related events such as renal/ liver abnormalities (grade 2/ above proteinuria, elevation in serum creatinine (>2.5 x ULN), total bilirubin, ALT or AST); / clinical depression/ evidence of suicidal ideation.		of DTG. Viral load (VL) in at delivery & the change in VL over the first four weeks of therapy. Two approaches to hanndle missing VL data : 1) missing VL = failure [>50 copies/mL] (M = F) in which subjects with missing data at two weeks post-partum were assessed as experiencing failure, and 2) missing viral load equals excluded (M = X)	mothers who underwent sampling in the third trimester of pregnancy & at post-partum visit. **Cord & Maternal Blood Samples**: Paired cord & maternal blood samples available in 16 mother-infant pairs. 1 individual, both samples were < limit of quantitation (BLQ), & non-adherence was reported. n= 15 samples - median C:M ratio of 1.21 (range 0.51–2.11). **DTG levels in Breastmilk:** DTG detectable in breast milk with a BM_{max} of 84.6 (43.8–171) ng/mL and a BM_{trough} of 22.3 (3.0–64.3) ng/mL. DTG detectable in plasma of breastfed infants with an $Infant_{max}$ of 66.7 (21–654) ng/mL and an $Infant_{trough}$ of 60.9 (16.3–479) ng/mL - median of 10 (range 7–18) days of age. Infant plasma to maternal plasma (IP:MP) ratios were 0.03 (0.00–0.06) at $Infant_{max}$ and 0.08 (0.00–0.17) at $Infant_{trough}$. After discontinuation of maternal DTG, detectable in 100%, 80% and 80% breastfed infants at 48, 72 & 96 hrs after final maternal dose, respectively. **Secondary Outcomes** Safety: Both regimens tolerated, no significant differences with adverse effects. • DTG-ART - 25 (86.2%) - caesarean section & 4 (13.8%) normal delivery • EFV-ART -21 (67.7%) caesarean section & 10 (32.3%), normal delivery. **Adverse events**: n=3 **Serious adverse events**: n=1 -2 in the DTG arm: i) low HB - unrelated, & ii) hospitalisation due to maternal malaria & urinary tract infection with raised ALT, bilirubin, hypokalemia & hyponatremia. (The mother took herbal medications at onset of event). Stillbirth related to umbilical cord around neck – not DTG related. EFV arm - 1 SAE - preeclampsia - unrelated. No **congenital anomalies** in DTG arm vs 2 in EFV arm (n=1 syndactyly -unlikely to be related to EFV and n=1 with multiple skeletal, limb & cardiac malformations (possibly TARP [Talipes equinovarus, Atrial septal defect, Robin sequence,	• DTG showed superior virological suppression vs EFV among women commencing ART in late pregnancy • Two limitations: (1) related to the requirement to initiate immediate EFV-ART at HIV diagnosis, and the need to limit exposure of newborn and breastfed infants to what was not a recommended first-line regimen during the study period. Randomisation would have balanced effect in the two arms. • Some women attended postpartum visit earlier than the proposed 2 weeks, potentially minimising differences in DTG exposure as a result of late pregnancy.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
					& Persistent left superior vena cava] syndrome) - not related EFV. n=1 infant in EFV arm - neonatal sepsis-not related to EFV, recovered **Virologic Response** **Proportion undetectable:** 69.0% (20/29) and 74.1% (20/27) DTG arm vs 38.7% (12/31) & 40.0% (12/30) EFV arm, in the M= F & M= X analyses, respectively. In analyses of log_{10} HIV RNA at 2wkPP, VL was significantly lower in the DTG arm vs EFV-ART (p = 0.007). n=3 discontinued prior to the 2-week post-partum visit (2 DTG-ART & 1 EFV-ART).	
Zash R, Holmes L, Diseko M, Jacobson DL, Brummel S, Mayondi G, Isaacson A, *et al*. 2019 Neural-Tube Defects and Antiretroviral Treatment Regimens in Botswana. N Engl J Med. 2019 Aug 29;381(9):827-840. doi: 10.1056/NEJMoa1905230. Epub 2019 Jul 22. PMID: 31329379; PMCID: PMC6995896.	Birth outcome surveillance study, Botswana (8 public hospital maternity wards from August 2014 to June 2018, 10 adiitonal sites added between July 2018 and March 2019	Sample Size: From August 15, 2014, to March 31, 2019, 119,477 deliveries, 119,033 (99.6%) had an infant surface examination Patient Characteristics: Baseline characteristics (delivery site, history of epilepsy, diabetes, and weight during pregnancy) between ART exposures groups were negligible. Folate supplementation and timing similar across the treatment groups. Funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD) Disclosures: Submitted with the publication	Exposures: •DTG from conception: (1683) •Any other non DTG ART from conception: (14792) •EFV from Conception (7959) •DTG started during pregnancy: (3840) HIV negative Mothers (89372)	**Primary Outcome:** Prevalence of neural-tube defects (NTDs) among infants	**Tsepamo Results from August 2014 to March 2019:** 98 NTDs (0.08%) **DTG from conception:** 5/1683 (0.30%; 95% CI 0.13 to 0.69) infants **Any other non DTG ART from conception:** 15/14792 (0.10%; 95% CI 0.06 to 0.17) infants. -Prevalence Difference: 0.20 (95% CI 0.01 to 0.59) vs the reference DTG from conception **EFV from Conception:** 3/7959(0.04%; 95% CI 0.01 to 0.11) infants. -Prevalence Difference: 0.26 (95% CI 0.07 to 0.66) vs the reference DTG from conception **DTG started during pregnancy**: 1/3840 (0.03%; 95% CI 0.00 to 0.15) infants. -Prevalence Difference: 0.27 (95% CI 0.06 to 0.67) vs the reference DTG from conception **HIV Negative:** 70/89372 (0.08%; 95% CI 0.06 to 0.10) infants. -Prevalence Difference: 0.22 (95% CI 0.05 to 0.62) vs the reference DTG from conception	• Prevalence of NTDs higher in association with DTG treatment at conception than with non DTG based ART at conception/ other types of ART.
Zash et al., 2020 Update on neural tube	Birth Outcomes Surveillance in government	Since August 2014 total of 158,244 deliveries; 153,899 (97.2%) had an evaluable infant surface exam, with	Exposures:	Prevalence of neural-tube defects (NTDs) among infants	**126 (0.08%, 95%CI 0.07%,0.09%) NTDs identified to date in cohort overall** **Cumulative results by group**	• After a decline since the original safety signal, the prevalence of NTD among infants born to women receiving DTG at conception seems to be stabilizing at approximately 0.2%.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
defects with antiretroviral. **This update from the Tsepamo study was presented at AIDS 2020. Abstract number OAXLB0102** ***Tsepamo Study*** https://www.natap.org/2020/IAC/IAC_112.htm	maternity sites, Botswana, since August 2014 August 2014 – July 2018 – 8 Sites (±45% of all births in Botswana) July 2018 to September 2018 – expanded to 18 surveillance sites (±72% of all births in Botswana) Since September 2019, maintained surveillance at 16 sites (±70% of all births in Botswana) Originally designed to assess NTD in infants whose mothers were exposed to exposed to EFV DTG was rolled out in Botswana in Mid 2016 Funding: National Institutes of Health &NICHD	1067 LATE BREAKER ABSTRACTS AUTHOR INDEX PUBLICATION ONLY ABSTRACTS	• DTG from conception: (1683) • Any other non DTG ART from conception: (14792) • EFV from Conception (7959) • DTG started during pregnancy: (3840) • HIV negative Mothers (89372)		**DTG at conception**, 7/3591 NTDs (0.19%; 95%CI 0.09%, 0.40%): 3 myelomeningoceles, 1 anencephaly, 2 encephaloceles, and 1 iniencephaly. **Non DTG-ART** NTD in 21/19,361 (0.11%; 95%CI 0.07%, 0.17%) EFV from conception 8/10,958 (0.07%; 95%CI 0.03%, 0.17%) DTG started in pregnancy 2/4,581 (0.04%; 95%CI 0.1%, 0.16%) HIV-uninfected women. 87/119,630 (0.07%; 95%CI 0.06, 0.09%) Difference between DTG and non-DTG- ART at conception not different (0.09% difference; 95%CI -0.03%, 0.30%). **Tsepamo Results as at March 2019:** From May 2018 to March 2019 1 NTD/1275 adiitonal exposures to DTG at conception **Tsepamo Results through to 30th April 2020: 1 April 2019 to 30 April 2020** **Number of NTDs:** Total 28/39,200 (0.07%) **DTG from conception:** 2/1908 (0.1%) **Any other non DTG ART from conception:** 6/4569 (0.1%) **EFV from Conception:** 5/2999 (0.2%) **DTG started during pregnancy**: 1/741 (0.1%) **HIV Negative:** 17/30,258 (0.1%)	• Two Women (started on DTG at conception) who delivered infants with NTDs had no medical history, did not receive other medication, and did not receive pre-conception folate supplementation

Table 2: Tsepamo study reports included in the previous review update

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
Zash *et al*. 2018 Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. 2018 Jul;6(7):e804-e810. doi: 10.1016/S2214-109X(18)30218-3. Epub 2018 Jun 4. PMID: 29880310; PMCID: PMC6071315.	Observational Study - Birth outcome surveillance study, Botswana (8 public hospital maternity wards from August 2014) Inclusion Criteria: DTG regimen started and delivery between Nov 1 2016 and Sep 3th 2017 for singleton pregnancy EFV regimen started and delivery between Aug 15th 2014 and Aug 15th 2016 for singleton pregnancy Exclusion criteria; births to mothers who switched ART regimens or stopped ART	Sample Size: Patient Characteristics: Age parity, socioeconomic indicators, timing of initiating of antenatal care and site of delivery were similar between EFV and DTG groups. HIV negative woman were younger, primiparous, higher education level compared to HIV positive woman. Similar timing of initiation and antenatal care for HIV infected and uninfected women. Funding: National Institutes of Health grants Disclosures: None declared	Exposures: •DTG based ART (1729) •EFV based ART (4593)	**Primary Outcome:** Combined endpoints of any adverse outcome **(**stillbirth, preterm birth (<37 weeks gestation), small for gestational age (SGA < 10th percentile of birthweight by gestational age) or neonatal death (withig 28 days of age) and very SGA (< 3rd percentile of birthweight by gestational age)	Aug 15th 2014 to Aug 15th 2016 n=11708 women with HIV delivered singletons -4593 (39%) on EFV based regimen after conception. Nov 1st 2016 to Sep 30th 2017, n=5418 women with HIV delivered singletons - 1729 (32%) began DTG regimen after conception. -51167 HIV negative woman had singleton pregnancies -total for both time periods Median CD4 count was similar between DTG and EFV group. Greater proportion of women in the EFV group had a CD4 count during pregnancy (2054 (44.7% vs 247 (14,2%) **Adverse outcomes**: -**Risk for any adverse outcome** among woman on DTG vs EFV was similar (n=574, 33·2% vs n=1606, 35·0%; aRR 0·95, 95% CI 0·88– 1·03), -**Risk of any severe birth outcome** was similar (n=185, 10·7% vs n=519, 11·3%; 0·94, 0·81–1·11). In 675 women (280 on DTG and 395 on EFV) with 1st trimester exposure to ART, 1 major congenital abnormality (skeletal dysplasia) in EFV exposed infant -No significant differences by regimen in individual outcomes of stillbirth, neonatal death, preterm birth, very preterm birth, SGA, or very SGA **HIV Negative Women** -134766 (28.9%) had any adverse birth outcomes -Severe adverse birth outcomes 5085 (9.9%) women	• Adverse birth outcomes were similar for DTG based ART vs FEV based ART during pregnancy • Sample size was large • Inability to fully evaluate CD4 cell count due to low number of woman in DTG group with CD4 reported (due to policy changes in testing) • Switch from EFV To DTG might put the data at historical bias (but short interval – 3 years) • Observational study – risk of confounding exists – however baseline characteristics of groups was similar, adjusted for confounding and conducted sensitivity analyses which were robust to changes • Unable to verify the data in medical records or validate gestational age dating (although any bias would be similar between the two treatment groups)
Zash R, et al, 2018. Neural-Tube Defects with Dolutegravir Treatment from the Time of Conception. N Engl J Med. 2018 Sep	Letter to the Editor outlining birth outcome surveillance (n=8 government hospitals, Botswana) Funding: National Institutes of Health (R01 HD080471-01 and K23 HD088230-01A1).	May 1, 2018 Sample Size: n=89,064 births included in surveillance n=88,755 (99.7%) had an infant surface examination	Exposures: •DTG from conception: (436) •Any other non DTG ART from conception: (11,300)	Prevalence of neural-tube defects (NTDs) among infants	**n=86 NTDs identified** (0.10% of births; 95% CI, 0.08 to 0.12) **Defects included:** -42 meningocele/myelomeningocele, 30 of anencephaly, 13 encephalocele, 1 of iniencephaly **DTG from conception:** 4/426 (0.94%; 95% CI 0.37–2.4) infants had a NTD (encephalocele, myelomeningocele (with	• Previously reported (2018) the risk of adverse birth outcomes or congenital abnormalities among women who started DTG based ART after conception (including therapy initiated during the first trimester of pregnancy) was not higher than the risk among women who started EFV based therapy after conception. • NTDs in DTG from conception: The 4 mothers delivered in 3 geographically separated hospitals over a 6-month period; none had epilepsy/diabetes/received folate supplementation at conception.

Citation	Study design	Population	Exposures and control	Outcomes	Effect sizes	Comments
6;379(10):979-981. doi: 10.1056/NEJMc1807653. Epub 2018 Jul 24. PMID: 30037297; PMCID: PMC6550482.	Declarations: Disclosure forms provided by authors		• DTG started during pregnancy: (2812) • HIV negative Mothers (66,065)		undescended testes), & iniencephaly (with major limb defect). **Any other non DTG ART from conception:** 14/11,300 (0.12%; 95% CI 0.07 – 0.21) infants -Prevalence Difference: -0.82 (95% CI, −0.24 to −2.3) vs the reference DTG from conception **DTG started during pregnancy**: 0 /2812 (0.00%; 95% CI 0.0 – 0.13) infants. Median gestational age at initiation of ART - 19 weeks (interquartile range, 14 to 25). 75 women started ART at gestational age < 6 weeks. -Prevalence Difference: -0.94 (95% CI, −0.35 to −2.4) vs the reference DTG from conception **HIV Negative:** 61/66,057 (0.09%; 95% CI 0.07– 0.12) infants -Prevalence Difference: -0.85 (95% CI, −0.27 to −2.3) vs the reference DTG from conception **7 additional infants with NTDs** -3 born to women who started non DTG ART during pregnancy -3 to (HIV)–infected women who did not receive ART during pregnancy -1 to a woman of unknown HIV infection status not on ART.	• Potential early signal for an increased prevalence of NTDs in association with DTG based ART from the time of conception. • Small number of events • Small difference in prevalence • Study is ongoing, and more data has since been collected which has refuted this signal

Table 3. List of excluded publications

No	Citation	Reason for Exclusion
1	Alhassan Y et al. Community acceptability of dolutegravir-based HIV treatment in women: a qualitative study in South Africa and Uganda. BMC Public Health. 2020 Dec 7;20(1):1883.	Wrong study design
2	Bollen P et al. Pharmacokinetics of ANtiretroviral agents in HIV-infected pregNAnt women Network. The Effect of Pregnancy on the Pharmacokinetics of Total and Unbound Dolutegravir and Its Main Metabolite in Women Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021 Jan 23;72(1):121-127.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
3	Chandiwana NC et al. Unexpected interactions between dolutegravir and folate: randomized trial evidence from South Africa. AIDS. 2021 Feb 2;35(2):205-211.	Wrong outcomes
4	Chouchana L et al. Is There a Safety Signal for Dolutegravir and Integrase Inhibitors During Pregnancy? J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):481-486.	No comparison with EFV
5	Chouchana L et al. Dolutegravir and neural tube defects: a new insight. Lancet Infect Dis. 2020 Apr;20(4):405-406.	Analysis of spontaneous reports from Vigibase. This is a pharmacovigilance database of spontaneous adverse drug reaction reports, not a pregnancy registry – did not meet study design
6	Crawford M et al. Postmarketing Surveillance of Pregnancy Outcomes With Dolutegravir Use. J Acquir Immune Defic Syndr. 2020 Jan 1;83(1):e2-e5.	No comparison with EFV
7	Dickinson L et al. Infant exposure to dolutegravir through placental and breastmilk transfer: a population pharmacokinetic analysis of DolPHIN-1. Clin Infect Dis. 2020 Dec 21:ciaa1861.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
8	Grayhack C et al. Evaluating outcomes of mother-infant pairs using dolutegravir for HIV treatment during pregnancy. AIDS. 2018 Sep 10;32(14):2017-2021.	No comparison to EFV-based ART
9	Hill A, Clayden P, Thorne C, Christie R, Zash R. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. J Virus Erad. 2018 Apr 1;4(2):66-71.	Review looking at safety and pharmacokinetics of DTG. Only one of the safety studies included in the review (one of the early Tsepamo reports) met PICO, and was already included
10	Kreitchmann R et al. Two cases of neural tube defects with dolutegravir use at conception in south Brazil. Braz J Infect Dis. 2021 Mar-Apr;25(2):101572.	Wrong Study Design
11	Mulligan N et al.; IMPAACT P1026s Protocol Team. Dolutegravir pharmacokinetics in pregnant and postpartum women living with HIV. AIDS. 2018 Mar 27;32(6):729-737.	Non-comparative pharmacokinetic study looking at outcomes not of relevance to our PICO
12	Nguyen B et al.. Pharmacokinetics and Safety of the Integrase Inhibitors Elvitegravir and Dolutegravir in Pregnant Women With HIV. Ann Pharmacother. 2019 Aug;53(8):833-844.	Review looking at safety and pharmacokinetics of DTG. Relevant studies already included.
13	Podany AT et al. Comparative Clinical Pharmacokinetics and Pharmacodynamics of HIV-1 Integrase Strand Transfer Inhibitors: An Updated Review. Clin Pharmacokinet. 2020 Sep;59(9):1085-1107.	NO - pharmacokinetic comparison between InSTIs
14	Rahangdale L et al; HOPES (HIV OB Pregnancy Education Study) Group. Integrase inhibitors in late pregnancy and rapid HIV viral load reduction. Am J Obstet Gynecol. 2016 Mar;214(3):385.e1-7.	Only 4 women on DTG
15	Reefhuis J et al. Neural Tube Defects in Pregnancies Among Women With Diagnosed HIV Infection - 15 Jurisdictions, 2013-2017. MMWR Morb Mortal Wkly Rep. 2020 Jan 10;69(1):1-5.	Wrong study design
16	Schomaker M et al. Assessing the risk of dolutegravir for women of childbearing potential. Lancet Glob Health. 2018 Sep;6(9):e958-e959.	Commentary
17	Slogrove AL et al. Toward a universal antiretroviral regimen: special considerations of pregnancy and breast feeding. Curr Opin HIV AIDS. 2017 Jul;12(4):359-368.	Commentary /opinion piece
18	van De Ven NS et al. Analysis of Pharmacovigilance Databases for Dolutegravir Safety in Pregnancy. Clin Infect Dis. 2020 Jun 10;70(12):2599-2606.	No denominator to contribute to incidence of NTD with DTG vs EFV exposure
19	van der Galiën R et al. Pharmacokinetics of HIV-Integrase Inhibitors During Pregnancy: Mechanisms, Clinical Implications and Knowledge Gaps. Clin Pharmacokinet. 2019 Mar;58(3):309-323.	3 relevant studies already included / duplication
20	Vannappagari V, Thorne C; for APR and EPPICC. Pregnancy and Neonatal Outcomes Following Prenatal Exposure to Dolutegravir. J Acquir Immune Defic Syndr. 2019 Aug 1;81(4):371-378. doi: 10.1097/QAI.0000000000002035. PMID: 30939532; PMCID: PMC6905407.	No comparison with EFV
21	Zipursky J et al. Dolutegravir for pregnant women living with HIV. CMAJ. 2020 Mar 2;192(9):E217-E218.	Commentary

Appendix 1: Search strategy

Date searched for the updated review: 3 June 2021

Database: PubMed

Search Strategy

Search	Query	Results
#6	Search: (#1 AND #4) NOT (animals[mh] NOT humans[mh]) Sort by: Most Recent	134
#5	Search: #1 AND #4 Sort by: Most Recent	136
#4	Search: #2 OR #3 Sort by: Most Recent	1,071,076
#3	Search: neural tube defects[mh] OR neural tube defect*[tiab] OR neurenteric cyst*[tiab] OR acrania*[tiab] OR craniorachischis*[tiab] OR diastematomyelia*[tiab] Sort by: Most Recent	31,975
#2	Search: pregnancy[mh] OR pregnant women[mh] OR pregnan*[tiab] Sort by: Most Recent	1,048,366
#1	Search: "dolutegravir" [Supplementary Concept] OR dolutegravir[tiab] Sort by: Most Recent	1,343

Number of studies: 134

Database: Clinical Trials.Gov

Search terms: dolutegravir AND (pregnancy OR pregnant women)

Records retrieved: 13

Appendix 2: Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large: ☐ Moderate: X Small: ☐ None: ☐ Uncertain: ☐	Compared with EFV, - viral suppression rates are non-inferior by 48 weeks; - viral suppression rates are superior by the time of delivery; - rates of vertical transmission are not significantly different, but event rates are very low with both regimens; - risk of insufficient weight gain in pregnancy is lower; and - risk of development of resistance mutations in those who fail first line regimens is lower.
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** Large: ☐ Moderate: ☐ Small: X Uncertain: ☐	Compared with EFV: - - Risk of NTD is not significantly different; -risk of other adverse pregnancy outcomes are not significantly different; - weight gain is higher, but the clinical significance of this is unknown (WLHIV on both regimens had less weight gain in pregnancy than HIV-uninfected women
BENEFITS & HARMS	**Do desirable effects outweigh undesirable harms?** Favours intervention: x Favours control: ☐ Intervention = Control *or* Uncertain: ☐	
QUALITY OF EVIDENCE	**What is the certainty/quality of evidence?** High: ☐ Moderate: x Low: ☐ Very low: ☐ *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	RCT data for efficacy, resistance, and some adverse events (eg weight). Observational data for NTDs is consistent.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes: X No: ☐ Uncertain: ☐	
RESOURCE USE	**How large are the resource requirements?** More intensive: ☐ Less intensive: X Uncertain: ☐	Price of medicines/ 28 days: **Medicine** | **Price** TDF+FTC+EFV (TEE) | R104.56 TDF+3TC+DTG (TLD) | R 98.18 Contract circular RT71-2019ARV
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor: X Major: ☐ Uncertain: ☐ **Is the option acceptable to key stakeholders?** Yes: X No: ☐ Uncertain: ☐	Standardised first line regimens for all adults and adolescents living with HIV is likely to be valued by prescribers. Access to DTG for WOCP has been advocated for by patient advocacy groups.
EQUITY	**Would there be an impact on health inequity?** Yes: x No: ☐ Uncertain: ☐	There is likely to be a positive effect in terms of reducing health inequity.

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South African National Essential Medicine List
Adult Healthcare Medication Review process
Component: Obstetrics

EVIDENCE REVIEW

Title: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B.

Date: 11 April 2024

Key findings

- The 2022 World Health Organization (WHO) Guideline: "Recommendations for prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy" were informed by a commissioned systematic review and meta-analysis and cost–effectiveness modelling.
- We performed GRADE-adolopment of these WHO guidelines.
- The WHO-commissioned systematic review and meta-analysis identified 129 studies that evaluated the efficacy of antiviral prophylaxis in Hepatitis B virus (HBV)-infected pregnant women to prevent mother-to-child transmission. After removal of duplicate studies n=89 studies were included in a meta-analysis. Most studies were performed in the Western Pacific Region. There were no studies available from the African Region or from the Americas.
- The majority of the 89 studies in the meta-analysis included hepatitis B immunoglobulin (HBIG) in both trial arms (in six studies use of HBIG was not reported). (In SA currently, when a pregnant mother is HepB positive and there is risk for transmission to the baby, HepB vaccine is administered to the baby at birth (instead of the Expanded Programme on Immunisation schedule administration at 6 weeks). Additionally, if HepB Immunoglobulin is available, it is given to the baby after birth.)
- The WHO-approved PICO listed seven antiviral interventions. The WHO systematic review identified studies administering the following antivirals: tenofovir (TDF) 300 mg, lamivudine (3TC) (100–150 mg), telbivudine (LdT) 100 mg and 600 mg, and adefovir dipivoxil (ADV) 10 mg and 500 mg. Neither telbivudine or adefovir are available in South Africa. The WHO review did not find any studies including antiviral treatment with emtricitabine (FTC), entecavir (ETV) or tenofovir alafenamide fumarate (TAF).
- The WHO-approved population of interest was pregnant women with chronic HBV infection. WHO planned subgroup analyses in women coinfected with hepatitis D virus (HDV) and/or human immunodeficiency virus (HIV). However, the WHO reviewers were not able to conduct a subgroup analysis by HIV coinfection status, as there were no eligible studies that reported results for this subgroup separately.
- **For TDF 300mg vs no treatment or placebo:**
  - RCTs and non RCTs showed lower proportion HBsAg positive at 6–12 months in the TDF treatment group
    - 5 RCTs: [(n=1 of 349 (0.3%) vs no treatment/placebo group (n=23 of 337(6.8%)] – ***moderate certainty evidence***.

        - 14 Non RCTs [n=21 of 723 (2.9%) (treatment group) vs n=88 of 499 (17.6%) (no treatment/placebo group [OR 0.17, 95% CI: 0.10–0.29] - ***low certainty evidence***
    - 5 RCTs included in the meta-analysis, moderate certainty evidence, suggests that there will be 80 fewer HBsAg positivity cases at 6–12 months per 1000 in infants whose mothers took TDF prophylaxis versus those who did not; (95% confidence interval 10–140 fewer).
    - HBV flares after treatment discontinuation were reported in six of the 19 included RCT and non RCT studies that administered TDF to mothers. Various definitions were used, including: "postpartum flare", "severe flare", "ALT >5 ULN", "moderate flare" and others. Within these studies, 34 of 418 mothers who were treated with TDF during pregnancy experienced an HBV flare at the time of treatment discontinuation, whereas 20 of 382 mothers who were not treated during pregnancy experienced an HBV flare at a matched time-point. The WHO panel was not able to fully examine the outcome of HBV flare, as standardised information was lacking across studies.
    - 3 RCTs that reported on HBV flares after TDF treatment discontinuation found a higher proportion with hepatitis flares in the TDF treatment groups vs no treatment/placebo [(n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group)] - ***moderate certainty evidence***.
    - Similar results were noted for flare after TDF treatment discontinuation in 3 Non RCTs [(n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group)] ***very low certainty evidence***.
    - For neonatal deaths (death within 28 days of life):
        - 5 RCTs in the meta-analysis reported n=2 deaths of 367 (0.5%) infants (treatment group) vs n=1 death of 350 infants (0.3%) (no treatment/placebo group)- ***moderate certainty evidence***.
        - 14 Non RCTs included in the meta-analysis deaths were reported for n=0 of 712 [(0.0%) (treatment group) vs n=0 of 518 (0.0%) mothers (control group)] - ***low certainty evidence***.

- **For 3TC (100-150mg) no treatment or placebo:**
    - 8 RCTs (***moderate certainty evidence)*** and 32 non RCTs (***low certainty evidence)*** showed lower HBsAg positivity at 6–12 months in the 3TC treatment group respectively ((n=25 of 432 [(5.8%) (treatment group) vs n=105 of 389 (27.0%) (control group) [OR 0.16, 95% CI: 0.10–0.26]] and [(n=41 of 1575 (2.6%) (treatment group) vs n=233 of 1655 (14.1%) (control group) [OR 0.17, 95% CI: 0.12–0.24)]]
    - 1 RCT reported a lower proportion with a HBV flare after 3TC treatment discontinuation (n=16 of 83 (19.3%) (treatment group) vs the control group n= 15 of 46 (32.6%) mothers (control group)) - ***low certainty evidence***
    - Higher proportion for HBV flare up after 3TC treatment discontinuation vs control groups in 5 Non RCTs (n=32 of 287 (12.9%) (treatment group) vs n= 31 of 504 (6.2%) mothers (control group)) – ***low certainty evidence***
    - An equal percentage of neonatal deaths (death within 28 days of life) were noted in 8 RCTs (moderate certainty evidence) (n=1 deaths of 439 (0.2%) infants (treatment group) vs n=1 death of 407 infants (0.2%) (control group) and 31 Non RCTs (***low certainty evidence*** ((n=0 deaths of 1571 (0.0%) infants (treatment group) vs n=0 death of 1686 infants (0.0%) (control group))

- The meta-analysis indicated a protective effect for both TDF and lamivudine in preventing mother-to-child transmission (TDF 300 mg: odds ratio [OR] 0.16, 95% confidence interval [CI]: 0.10–0.26; lamivudine 100 mg: OR 0.17, 95% CI: 0.13–0.22).

- The WHO Guideline was rated as a high-quality clinical practice guideline (AGREE II score of 92% overall and 86% for rigour of development).

➡ To be noted; lamivudine has a low genetic barrier to drug resistance mutations, which may lead to the emergence of drug-resistant strains of HBV while TDF has a higher barrier to drug resistance. WHO recommends nucleos(t)ide analogues with a high barrier to resistance to treat HBV infection Thus, TDF was recommended by WHO as medicine of choice for prevention of vertical transmission of HBV from mother to child.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
					X

PHC/AHL ERC RECOMMENDATON: (11 APRIL 2024)

Recommendation: The committee recommends Tenofovir for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive. (moderate CoE, Strong recommendation).

Rationale: There was evidence of moderate benefit and trivial harms, increased equity, and negligible costs. The treatment was found to be feasible and acceptable to implement.

Level of Evidence: Moderate certainty of evidence
Review indicator: New high-quality evidence of a clinically relevant benefit

NEMLC RECOMMENDATION (16 May 2024):

The NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation of Tenofovir for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive.

Monitoring and evaluation considerations: see review indicators above

Research priorities: see review indicators above

1. Executive Summary

Date: 11 April 2024
Medicine (INN): Tenofovir Antiviral
Medicine (ATC): J05AR12
Indication (ICD10 code): B19.10 – Unspecified viral hepatitis B without hepatic coma
Patient population: Third trimester HBeAG positive, HIV negative pregnant women
Prevalence of condition: 0.67% prevalence of HBsAg in HIV negative pregnant women [Joseph Davey, D., Hsiao, Ny., Wendy Spearman, C. et al. Low prevalence of hepatitis B virus infection in HIV-uninfected pregnant women in Cape Town, South Africa: implications for oral pre-exposure prophylaxis roll out. BMC Infect Dis 22, 719 (2022). https://doi.org/10.1186/s12879-022-07697-5]
Level of Care: Adult Hospital Level
Prescriber Level: Medical Doctor
Motivator/reviewer name(s): n/a
PTC affiliation: n/a

2. Authors, affiliation and conflict of interest details:

Prof S Gebhardt (Stellenbosch University and Tygerberg Hospital)
Dr M Reddy (Supply Chain Technical Assistance)
Dr M McCaul (Centre for Evidence-Based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University and South African GRADE Network)

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Ms D Frank (Clinton Health Access Initiative) for assisting with the duplicate AGREE II assessment.

SG, MR, MM & DF have no interests to declare with regard to antivirals in the third trimester of pregnancy in women who are HIV Negative and HBeAG positive.

3. Introduction/ Background

Pregnant women who are hepatitis B virus (HBV) positive have a high risk of transmitting HBV to the baby. Maternal HBV infection may also result in higher rates of preterm births and gestational diabetes.[1]

National Department of Health, updated maternity guidelines (2024)
recommends that all pregnant woman should be offered a test for HBsAg at the first antenatal visit irrespective of gestational age.[2]

The World Health Organization recommends that pregnant women who test positive for HBV infection (HBsAg positive) receive tenofovir (TDF) prophylaxis from the 28th week of pregnancy until at least birth[3]. The Centers for Disease Control advise that all pregnant women should be tested for hepatitis B surface antigen (HBsAg) during each pregnancy and those testing positive should be tested for HBV DNA. Women with HBV DNA >200,000 IU/mL should receive antiviral therapy to prevent perinatal transmission.[4]

The NDOH Guideline for the Prevention of Vertical Transmission of Communicable Infections state that the ART drugs TDF and lamivudine (3TC) treat both HIV and HBV and reduce the risk of vertical transmission by decreasing the viral load of both HIV and Hepatitis B. The guideline recommends that health care workers need to be aware of the required management of a HBV-infected mother and her infant as outlined in the National Maternity Care Guidelines (update published in 2024).[2] The NDOH maternity guidelines (2024) indicate that HBsAg positive pregnant woman (irrespective of HIV status) should be referred to a specialist center for further serological evaluation, where they may be offered TDF. Additionally, PrEP (TDF and emtricitabine) is now routinely available and recommended for all pregnant women including adolescent girls[1]

The NDOH hepatitis guidelines are currently under review for an update for publication. (March 2024 communication from the NDOH program)

The current first line antiretroviral treatment regimen for HIV-positive adults, including pregnant woman, comprises TDF, 3TC and dolutegravir based regimens which provides protection against vertical transmission in HIV positive women who are HBeAG positive.[1, 2]

The WHO Global hepatitis report 2024 which calls for action for access in low- and middle-income countries states that combining routine screening and antiviral prophylaxis for treating pregnant women with hepatitis B, along with the hepatitis B birth-dose vaccination for infants, will be critical to eliminate the mother-to-child transmission of viral hepatitis B, especially in regions such as sub- Saharan Africa with a high disease burden of hepatitis B.[5]

Several local and international guidelines already recommend use of antivirals for HBeAG positive pregnant woman irrespective of HIV status. In order for recommendations to be informed by current evidence in the management of HIV negative and HBeAG positive pregnant woman, the PHC and AHL expert review committee requested a review and adolopment of a good quality guideline recommending management of pregnant woman who are HBeAG positive.

4. Purpose/Objective

Should antivirals be recommended for women in the third trimester of pregnancy who are HIV negative and HBeAG positive?

5. PICO eligibility criteria

Population	HIV negative pregnant women in third trimester who are HBeAg positive or have a viral load >200 000 IU/ml
Intervention	Antiviral therapy
Comparator	No treatment/placebo
Outcome	Efficacy outcome: • Vertical transmission of Hepatitis B Safety outcomes: • Adverse events in mother (e.g. Rebound hepatitis) Foetal death
Studies	Guidelines that employed GRADE (and/or have evidence to decision framework).

6. Methods

The GRADE-adolopment approach was used for efficiency purposes. The choice of source guideline was deliberated and selected by two of the reviewers (SG & MR) and assessed for relevance, credibility (AGREE II) and whether the evidence was sufficiently up-to-date. The GRADE-ADOLOPMENT process was used to adopt, adapt, adopt with minor changes, or exclude recommendations from the source guideline. The GRADE-ADOLOPMENT process briefly, includes 1) selection the guideline topic and question, 2) searching and identifying the source guidelines, 3) matching the source guideline recommendations and underlying evidence, 4) updating and reviewing the underling evidence and 5) populating and/or reassessing the EtD framework to develop recommendations (as either an adopted, adapted or de novo recommendation) [6]. We searched PubMed and google scholar for guidance, in March 2024, on the topic of management of pregnant woman who are HBeAG positive.

An AGREE II (Appraisal of Guidelines, for Research, and Evaluation)[7] assessment was planned in duplicate on the selected guideline to evaluate the process of guideline development and quality of reporting. Two reviewers (MR & DF) independently reviewed the guideline using the online AGREE II assessment tool.

7. Results

We identified the following guidelines: CDC, Australian, Fellow of the Royal College of Obstetricians and Gynecologists (FRCOG), Royal College of Obstetrics & Gynaecology (RCOG) and American College of Obstetricians and Gynecologists; but these focused more on vaccinations and not on our PICO question. We identified one World Health Organization (WHO) guideline addressing our PICO question, that utilised a Grading of Recommendations Assessment, Development and Evaluation (GRADE)[8] framework approach. The source guideline: "Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy (July 2020)" was reviewed for adoption and/ or adaptation.

The WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis In Pregnancy (July 2020) was selected for review for the following reasons:

- Use of Grading of Recommendations Assessment, Development and Evaluation (GRADE) methods
- Local familiarity
- Applicability
- Rigor as the guideline outlined the evidence and information that guided the recommendations

- Credibility
- Timeliness
- Acceptability
- Trustworthiness (whether it is likely to be up to date)

The AGREE II appraisal outcome is presented in Appendix 2. In summary the WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy (July 2020) guideline can be considered a high-quality clinical practice guideline (AGREE II score of 92% overall and 86% for rigour of development) and was considered up-to-date and relevant to the committee's question.

The applicable WHO review question was posed as follows: Are antiviral therapies efficacious and safe at reducing MTCT of HBV if administered during pregnancy in women with chronic HBV infection?

The following eligibility criteria was used for the WHO review question above and was in line with the current PHC & AH PICO:

Population: Pregnant women with chronic HBV infection

Intervention: Maternal treatment with antiviral therapy during pregnancy with or without infant birth dose vaccination and/or HBIG. The following antiviral therapies were considered for inclusion:

- adefovir dipivoxil (ADV)
- emtricitabine (FTC)
- entecavir (ETV)
- lamivudine (3TC/LAM)
- telbivudine (LdT)
- tenofovir alafenamide fumarate (TAF)
- TDF.

Comparators: No antiviral therapy or placebo. Timely administration of birth dose vaccine, timely administration of HBIG Completion of three or four doses of infant hepatitis B vaccines also considered in relation to no antiviral therapy or placebo.

Outcomes: The primary outcome of interest was MTCT of HBV, as indicated by infant HBsAg positivity at 6–12 months of life.

Secondary infant outcomes of interest, included:

- Infant HBV DNA positivity at 6–12 months of life
- Any infant adverse event, such as
    - neonatal death (within 28 days of life [WHO, 2006])
    - preterm birth (<37 weeks of gestational age [WHO, 2018])
    - congenital abnormality
    - Apgar score at 1 minute of life
    - measurement of bone density of infants.
- Maternal outcomes of interest, specified in the study protocol, included:
    - any maternal adverse event, including:
        - miscarriage (<28 weeks gestational age,
        - stillbirth (>=28 weeks gestational age,
    - HBV flare after discontinuation of treatment (e.g. elevated HBV DNA and/or elevated ALT)

- postpartum haemorrhage
- Antiviral resistance

The WHO-commissioned systematic review and meta-analysis identified 129 studies that evaluated the efficacy of antiviral prophylaxis in HBV-infected pregnant women to prevent mother-to-child transmission.

The WHO approved PICO included seven different treatments of interest. However, only studies including TDF 300 mg, 3TC (100–150 mg), Telbivudine (LdT) 100 mg and 600 mg, and adefovir dipivoxil (ADV) 10 mg and 500 mg were found eligible. The latter two ARVs are not routinely used in South Africa. No studies investigated any regimens with FTC, ETV, TAF and therefore these treatments were not included.

The WHO approved study population included pregnant women with chronic HBV infection. HIV status was not stipulated. Subgroup analyses were to include coinfection with hepatitis D virus (HDV) or human immunodeficiency virus (HIV). It was not possible to conduct a subgroup analysis by coinfection status, as there were eventually no eligible studies that included coinfected populations. The population studied was applicable to the current review question.

All studies in the meta-analysis (n=89) included HBIG in both trial arms, with the exception of six studies, in which the use of HBIG was not reported.

The systematic review and meta-analysis commissioned by the WHO showed that certain antiviral therapies may be efficacious if used during pregnancy for the prevention of vertical transmission of HBV, as indicated by the proportion of infants with HBsAg detected at 6–12 months of life:

- Meta-analysis of RCTs investigating TDF 300 mg had a protective, pooled OR of 0.10 (95% CI: 0.03–0.35), and
- Meta-analysis of RCTs investigating Lamivudine 100–150 mg had a protective pooled OR of 0.16 (95% CI: 0.10–0.26)

Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo

- N=19 studies (n=5 RCTs & n=14 non-randomized trials/observational studies)

Efficacy:

HBsAg positivity at 6–12 months

- 5 RCTs: n=1 of 349 (0.3%) (treatment group) vs n=23 of 337(6.8%) (control group) [OR 0.10, 95% CI: 0.03–0.35] – ***moderate certainty evidence***.
- 14 Non RCTs: n=21 of 723 (2.9%) (treatment group) vs n=88 of 499 (17.6%) (control group [OR 0.17, 95% CI: 0.10–0.29] - **low *certainty evidence.***

Safety:

Postpartum haemorrhage (3 RCTS)

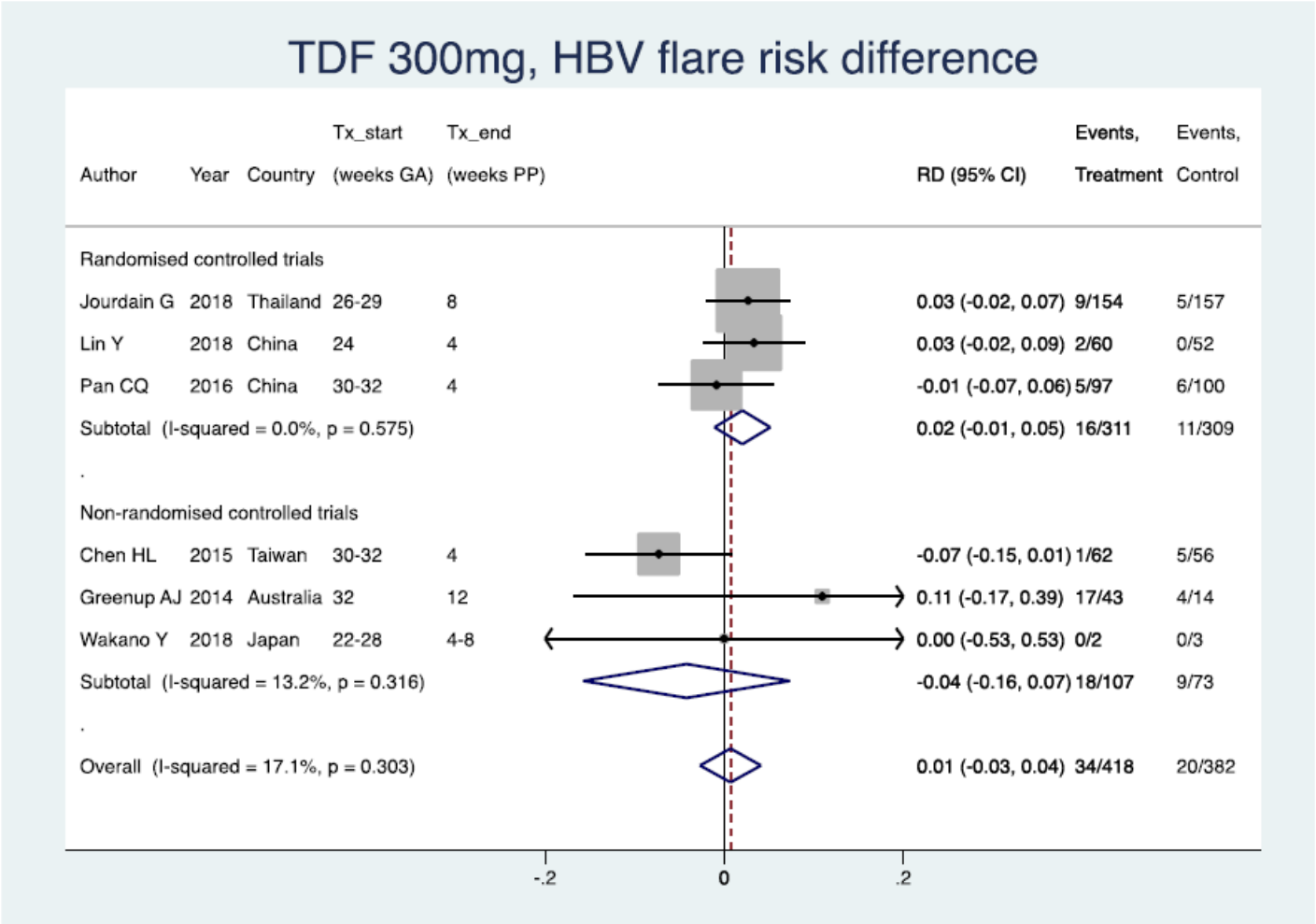
- 3 RCTs: n=4 of 177 (2.3%) (treatment group) vs n=5 of 172 (2.9%) (control group) – ***moderate certainty evidence.***
- 3 Non RCTs: n=5 of 188 (2.7%) (treatment group) vs n=3 of 84(3.6%) (control group) – **low *certainty***

evidence.

HBV Flare after treatment discontinuation (3 RCTs)

Information on HBV Flare after treatment discontinuation was available for six of the 19 included RCT and non RCT studies that administered TDF to mothers. Various definitions were used, including: "postpartum flare", "severe flare", "ALT >5 ULN", "moderate flare" and others. 3 RCTs: n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group) –***moderate certainty evidence.***

- 3 Non RCTs: n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group) – ***very* low *certainty evidence.***



34 of 418 (non-weighted average 8.1%) mothers who were treated with TDF during pregnancy experienced a type of HBV flare at the time of treatment discontinuation, vs 20 of 382 (non-weighted average 5.2%) mothers who were not treated during pregnancy.

The panel was not able to fully examine all important safety outcomes, such as HBV flare, as standardized information was lacking across studies.

- Flares were reported as follows in the six individual RCT and non RCT studies:

- n=1 RCT asymptomatic flares in the alanine aminotransferase level (level of >300 IU per liter) during pregnancy (9 of 154 women (6%; 95% CI, 3 to 11) in the TDF group vs 5 of 157 (3%; 95% CI, 1 to 7) in the placebo group),
- n=1 RCT: digestive tract reaction: vomiting (2 of 60 (3%) TDF group vs 0 of 52 (0%) control group) during pregnancy
- n=1 RCT: severe flare as ALT flare 5.1 to 10 times above the baseline value postpartum (5 of 97 (5%) TDF group vs 6 of 100 (6%) in the control group) & serious alanine aminotransferase flare of an ALT more than 10 times above the upper limit of normal postpartum (1 of 97 (1%) TDF group vs 3 of 100 (3%) in the control group)
- n=1 non RCT: 1 of 62 TDF group (2%) vs 5 of 56 (9%) in the control group
- n=1 non RCT: moderate postpartum flares postpartum (>95 IU/L ALT) (17 of 43 (40%) TDF group vs 4 of 14 (29%) in the control group)
- n=1 RCT: Serum transaminase flares (none reported)

Neonatal deaths (death within 28 days of life) (5 RCTs)

- 5 RCTs: n=2 deaths of 367 (0.5%) infants (treatment group) vs n=1 death of 350 infants (0.3%) (control group) -– ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 712 (0.0%) (treatment group) vs n=0 of 518 (0.0%) mothers (control group) – ***low certainty evidence.***

Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks]) (5 RCTs)

- 5 RCTs: n=3 cases of 372 (0.8%) (treatment group) vs n=0 of 362 (0.0%) (control group) – ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 570 (0.0%) (treatment group) vs n=1 of 520 (0.2%) mothers (control group) – ***low certainty evidence.***

Lamivudine (LAM) 100–150 mg versus no treatment or placebo

- n= 40 (n=8 RCTs & n=32 non-randomized trials/observational studies)

Efficacy:

HBsAg positivity at 6–12 months

- 8 RCTs: n=25 of 432 (5.8%) (treatment group) vs n=105of 389 (27.0%) (control group) [OR 0.16, 95% CI: 0.10–0.26] – ***moderate certainty evidence.***
- 32 Non RCTs: n=41 of 1575 (2.6%) (treatment group) vs n=233of 1655 (14.1%) (control group) [OR 0.17, 95%

CI: 0.12–0.24] – ***low certainty evidence.***

Safety

Postpartum haemorrhage

- 1 RCT: n=0 of 53 (2.3%) (treatment group) vs n=0 of 53 (0%) (control group) – ***low certainty evidence.***
- 7 Non RCTs: n=98 of 558 (17.6%) (treatment group) vs n=61 of 699 (8.7%) (control group) – ***low certainty evidence.***

HBV Flare after treatment discontinuation

Various definitions of HBV flare were used in the studies, including: "postpartum flare", "severe flare", "ALT >5 ULN", and others. The WHO panel was not able to fully examine s HBV flare, as standardised information was lacking across studies.

- 1 RCT: n=16 of 83 (19.3%) (treatment group) vs n= 15 of 46 (32.6%) mothers (control group) – ***very low certainty evidence.***
- 5 Non RCTs: n=32 of 287 (12.9%) (treatment group) vs n= 31 of 504 (6.2%) mothers (control group) – **very low *certainty evidence.***

Neonatal deaths (death within 28 days of life)

- 8 RCTs: n=1 deaths of 439 (0.2%) infants (treatment group) vs n=1 death of 407 infants (0.2%) (control group) – moderate ***certainty evidence.***
- 31 Non RCTs: n=0 deaths of 1571 (0.0%) infants (treatment group) vs n=0 death of 1686 infants (0.0%) (control group) – ***moderate certainty evidence.***

Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks])

- 8 RCTSs n=1 cases of 472 (0.2%) (treatment group) vs n=0 of 409 (0.0%) (control group) – ***moderate certainty evidence.***
- 31 Non RCTs n=0 cases of 1531 (0.0%) (treatment group) vs n=9 of 1678 (0.5%) (control group) – low ***moderate certainty evidence.***

Appendix 1 describes the evidence profile (GRADE tables) that informed the WHO Guideline recommendations (for RCTs and non RCTs).

From the studies included in the meta-analysis:

- RCTs: moderate certainty evidence suggests that there will be 80 fewer HBsAg positivity cases at 6–12 months per 1000 in infants whose mothers took TDF prophylaxis versus those who did not; (10–140 fewer). From the non RCTs included in the meta-analysis,
- Non RCTs: Low certainty evidence suggests that there will be 140 fewer HBsAg positivity cases at 6–12 months per 1000 in infants whose mothers took TDF prophylaxis versus those who did not; (80–200 fewer).

8. Discussion

The WHO working group made an overall conditional recommendation to use tenofovir prophylaxis to prevent mother-to-child transmission, acknowledging that most clinical trials that evaluated the efficacy of tenofovir prophylaxis had also included the use of HBIG in both arms. The WHO guideline development group set a viral load threshold of HBV DNA ≥5.3 log10 IU/mL (≥ 200,000 IU/mL) at which pregnant women are eligible to receive TDF prophylaxis. Additionally the panel recommended reassessing patients for long-term maternal TDF treatment after delivery.

WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis In Pregnancy (July 2020)

Prophylaxis	Recommendation	Strength of Recommendation
Tenofovir prophylaxis to prevent mother-to-child transmission of HBV	WHO recommends that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥ 5.3 $\log_{10}$ IU/mL (≥ 200,000 IU/mL)[1] receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth, to prevent mother-to-child transmission of HBV. This is in addition to three-dose hepatitis B vaccination in all infants, including timely birth dose	Conditional recommendation, moderate quality of evidence.

In March 2024, the WHO released Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection.[9] In this guideline the existing recommendation for use of TDF prophylaxis for HBsAg-positive pregnant women with HBV DNA levels ≥200 000 IU/mL or a positive HBeAg, in settings where there is ready access to these assays, is retained from the 2020 WHO hepatitis B antiviral prophylaxis guidelines for prevention of vertical transmission. Additionally, the guideline reiterated the 2020 WHO guidance to continue TDF for mothers who meet the criteria for antiviral therapy.

Conclusion

"The WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy (July 2020)" were suitable for adolopment.

The following recommendations were accepted from the WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis in Pregnancy (July 2020):

- Start maternal tenofovir prophylaxis from 28 weeks of Pregnancy until at least birth.
- Reassess for long-term maternal treatment after delivery and monitor (as per WHO HBV guidelines)

Appendix 1: GRADE SUMMARY OF FINDINGS (Taken from: World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission)

Table 1. GRADE evidence profile – TDF 300 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

(Taken from: World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission)

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity at 6–12 months												
5	*Randomized controlled trials (RCTs)*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	1/349 (0.3)	23/337 (6.8)	**0.10** (0.03–0.35)	**80 fewer** per 1000 (10–140 fewer)	Moderate[a]
14	*Non-RCTs*	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect	21/723 (2.9)	88/499 (17.6)	**0.17** (0.10–0.29)	**140 fewer** per 1000 (80–200 fewer)	Low[b]
HBV DNA positivity at 6–12 months												
4	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	1/319 (0.3)	20/307 (6.5)	**0.11** (0.03–0.43)	**70 fewer** per 1000 (0–150 fewer)	Moderate[c]
7	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine publication bias	Magnitude of the effect	0/451 (0.0)	38/308 (12.3)	**0.06** (0.02–0.19)	**110 fewer** per 1000 (50–170 fewer)	Moderate[d]
Infant safety: neonatal deaths												
5	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	2/367 (0.5)	1/350 (0.3)	-	**0** (10 fewer – 10 more)	Moderate[e]

14	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/712 (0.0)	0/508 (0.0)	-	**0** (10 fewer – 10 more)	Low[f]

Infant safety: prematurity												
4	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	11/337 (3.3)	16/320 (5.0)	-	**10 fewer** (30 fewer – 20 more)	Moderate[g]
4	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine publication bias	None	8/285 (2.8)	6/159 (3.8)	-	**10 more** (30 fewer to 40 more)	Low[h]
Infant safety: congenital abnormalities												
5	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	2/367 (0.5)	3/350 (0.9)	-	**0** (20 fewer – 10 more)	Moderate[i]
9	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine publication bias	None	2/435 (0.5)	2/337 (0.6)	-	**0** (20 fewer – 20 more)	Low[j]
Infant safety: bone mineral density												
1	*RCTs*	No serious	N/A	No serious	Serious	Not able to examine publication bias	N/A	N/A	N/A	-	**−0.006 g/cm²** (−0.019 to 0.007 g/cm²); p=0.38)	Low[k]
Maternal safety: miscarriage and stillbirth												
5	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	3/372 (0.8)	0/362 (0.0)	-	**10 more** (10 fewer – 20 more)	Moderate[l]
14	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/570 (0.0)	1/520 (0.2)	-	**0** (10 fewer – 10 more)	Low[m]
Maternal safety: postpartum haemmorhage												
3	*RCTs*	Serious	No serious	No serious	No serious	Not able to examine publication bias	N/A	4/177 (2.3)	5/172 (2.9)	-	**0** (30 fewer – 30 more)	Moderate[n]
3	*Non-RCTs*	No serious	No serious	No serious	No serious	Not able to examine	None	5/188 (2.7)	3/84 (3.6)	-	**0** (40 fewer	Low[o]

						publication bias					– 40 more)	
Maternal safety: HBV flare after treatment discontinuation												
3	*RCTs*	No serious	No serious	No serious	Serious	Not able to examine publication bias	N/A	16/311 (5.1)	11/309 (3.6)	-	**20 more** (10 fewer – 50 more)	Moderate[p]
3	*Non-RCTs*	No serious	No serious	No serious	Serious	Not able to examine publication bias	None	18/107 (16.8)	9/73 (12.3)	-	**40 fewer** (160 fewer – 70 more)	Very low[q]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to possible publication bias/small study effects, upgrading due to magnitude of effect.
[c]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[d]Upgrading due to magnitude of effect
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]No upgrading or downgrading
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to inability to examine certain elements (e.g. inconsistency), and for imprecision due to the fact that there was only one RCT included.
[l]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[m]No upgrading or downgrading
[n]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[o]No upgrading or downgrading [p]Downgrading due to imprecision
[q]Downgrading due to imprecision

Table 2: GRADE evidence profile: Lamivudine 100–150 mg during pregnancy to prevent HBV mother-to-child transmission (MTCT)

(Taken from: World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission)

Number of studies	Design	Quality assessment						Number of patients		Effect		Quality
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	AVT (%)	No AVT (%)	OR (95% CI)	Absolute (95% CI)	
HBsAg positivity at 6–12 months												
8	*Randomized controlled trials (RCTs)*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	25/432 (5.8)	105/389 (27.0)	**0.16** (0.10–0.26)	**190 fewer** per 1000 (90–280 fewer)	Moderate[a]
32	*Non-RCTs*	No serious	No serious	No serious	No serious	Evidence of possible publication bias/small study effects	Magnitude of the effect.	41/1575 (2.6)	233/1655 (14.1)	**0.17** (0.12–0.24)	**140 fewer** per 1000 (110–180 fewer)	Low[b]
HBV DNA positivity at 6–12 months												
5	*RCTs*	Serious	Serious I^2=39.8%	No serious	No serious	Not possible to examine publication bias	N/A	21/312 (6.7)	73/269 (27.1)	**0.22** (0.10–0.47)	**160 fewer** per 1000 (320 fewer to 4 more)	Low[c]
18	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	Magnitude of the effect.	22/1014 (2.2)	137/1057 (13.0)	**0.14** (0.09–0.23)	**140 fewer** per 1000 (90–190 fewer)	Moderate[d]
Infant safety: neonatal deaths												
8	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/439 (0.2)	1/407 (0.2)	-	**0** (10 fewer – 10 more)	Moderate[e]
31	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/1571 (0.0)	0/1686 (0.0)	-	**0** (10 fewer – 10 more)	Low[f]

Infant safety: prematurity												
2	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	0/123 (0.0)	0/93 (0.0)	-	**0** (30 fewer – 30 more)	Moderate[g]
8	*Non-RCTs*	Serious	Serious I^2=55.6%	No serious	No serious	Not possible to examine publication bias	None	14/486 (2.9)	11/306 (3.6)	-	**0** (40 fewer – 40 more)	Very low[h]
Infant safety: congenital abnormalities												
3	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/219 (0.5)	0/222 (0.0)	-	**0** (10 fewer – 20 more)	Moderate[i]
13	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	7/626 (1.1)	5/953 (0.5)	-	**0** (10 fewer – 20 more)	Low[j]
Maternal safety: miscarriage and stillbirth												
8	*RCTs*	Serious	No serious	No serious	No serious	Not possible to examine publication bias	N/A	1/472 (0.2)	0/409 (0.0)	-	**0 more** (10 fewer – 10 more)	Moderate[k]
31	*Non-RCTs*	No serious	No serious	No serious	No serious	No evidence of publication bias	None	0/1531 (0.0)	9/1678 (0.5)	-	**0** (10 fewer – 10 more)	Low[l]
Maternal safety: postpartum haemmorhage												
1	*RCTs*	Serious	Not applicable	No serious	No serious	Not possible to examine publication bias	N/A	0/53 (0.0)	0/53 (0.0)	-	**0** (40 fewer – 40 more)	Low[m]
7	*Non-RCTs*	No serious	No serious	No serious	No serious	Not possible to examine publication bias	None	98/558 (17.6)	61/699 (8.7)	-	**10 more** (10 less – 40 more)	Low[n]
Maternal safety: HBV flare after treatment discontinuation												

1	*RCTs*	Serious	Not applicable	No serious	Very serious	Not possible to examine publication bias	N/A	16/83 (19.3)	15/46 (32.6)	-	**130 less** (290 fewer – 30 more)	Very low[o]
5	*Non-RCTs*	Serious	Very serious I^2=87.8%	No serious	Very serious	Not possible to examine publication bias	None	37/287 (12.9)	31/504 (6.2)	-	**40 fewer** (200 fewer – 110 more)	Very low[p]

[a]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[b]Downgrading due to evidence of possible publication bias, however, upgrading due to magnitude of effect.
[c]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inconsistency >30%.
[d]Upgrading due to magnitude of effect
[e]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[f]No upgrading or downgrading
[g]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[h]Downgrading due to "serious" study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle–Ottawa scale), downgrading due to inconsistency >30%.
[i]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[j]No upgrading or downgrading
[k]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high).
[l]No upgrading or downgrading
[m]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included
[n]No upgrading or downgrading
[o]Downgrading due to "serious" study design limitations (all RCTs had <=4 of 8 criteria with low risk of bias, the rest being unclear or high), downgrading due to inability to examine certain elements (e.g. inconsistency) due to the fact that there was only one RCT included, downgrading due to serious imprecision.
[p]Downgrading due to "serious" study design limitations (the majority of non-RCTs had a score of 6 on the Newcastle–Ottawa scale), downgrading due to severe inconsistency >30%, downgrading due to imprecision.

Appendix 2: AGREE II Assessment

AGREE II assessment scores																							
WHO Prevention of Mother-To-Child Transmission of Hepatitis B Virus: Guidelines on Antiviral Prophylaxis In Pregnancy (July 2020)																							
Scoring the guidelines																							
	Scope and purpose			Stakeholder involvement			Rigour of development								Clarity of presentation			Applicability				Editorial independence		Overall assessment
	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Item 17	Item 18	Item 19	Item 20	Item 21	Item 22	Item 23	Overall
Appraiser 1	6	6	6	6	7	7	7	6	7	7	7	7	7	1	7	7	7	7	7	7	7	4	7	147
Appraiser 2	7	7	7	7	7	4	7	7	7	7	7	6	6	3	7	7	7	6	7	7	6	7	7	150
Item Total	13	13	13	13	14	11	14	13	14	14	14	13	13	4	14	14	14	13	14	14	13	11	14	297
Domain Total	39			38			99								42			54				25		297
Minimum possible score	6			6			16								6			8				4		46
Maximum possible score	42			42			112								42			56				28		322
Domain score	92%			89%			**86%**								100%			96%				88%		**92%**

Overall assessment: The Guideline is recommened for use in this context

Score: (e.g. domain 1)

$$\frac{\text{Maximum possible score = 7 (highest score) x no. of items x no. of appraisers}}{\text{Minimum possible score = 1 (lowest score) x no. of items x no. of appraisers}}$$

Score for each domain

$$\frac{\text{Obtained score - minimum possible score}}{\text{Maximum possible score - minimum possible score}} \times 100$$

Acknowledgement: Display of the AGREE II assessment taken from developers of the National Department of Health Technology Assessment Methods Guide. 2022-2027.

Appendix 3: Adaptation of the World Health Organisation. 2020. PREVENTION OF MOTHER-TO-CHILD TRANSMISSION OF HEPATITIS B VIRUS: GUIDELINES ON ANTIVIRAL PROPHYLAXIS IN PREGNANCY

(Note: Where judgements differed, both WHO and PHC/Adult Hospital Level's assessments have been described)

Problem: Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	• 257 million people were living with chronic hepatitis B virus (HBV) infection worldwide (2015 statistics quoted) • 900 000 had died from HBV infection, mostly as a result of cirrhosis or hepatocellular carcinoma. • Most HBV-associated deaths among adults are secondary to infections acquired at birth or in the first five years of life. • World Health Assembly endorsed the Global Health Sector Strategy on viral hepatitis, which calls for the elimination of viral hepatitis as a public health threat by 2030 (defined as a 90% reduction in incidence of new infections and a 65% reduction in mortality). • Elimination of HBV infection as a public health threat requires a reduction in the prevalence of hepatitis B surface antigen (HBsAg) to below 0.1% in children 5 years of age. • This can be achieved through universal immunization of newborns against hepatitis B and other interventions to prevent mother-to-child transmission of HBV e.g. antiviral prophylaxis.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	In SA, over 1.9 million people are chronically infected with HBV; a significant burden on public health in SA despite the introduction of an infant immunization program implemented in 1995 and the availability of effective treatment for chronic HBV infection. Taken from: Maepa MB, Ely A, Kramvis A, Bloom K, Naidoo K, Simani OE, Maponga TG, Arbuthnot P. Hepatitis B Virus Research in South Africa. Viruses. 2022 Aug 31;14(9):1939. doi: 10.3390/v14091939. PMID: 36146747; PMCID: PMC9503375. The SA Expanded Programme on Immunisation schedule advises HepB vaccination at 6 weeks after birth. The WHO recommends that all babies should receive the hepatitis B vaccine as soon as possible after birth (within 24 hours).	
Desirable effects: How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
WHO Guideline panel		
○ Trivial ○ Small ○ Moderate ○ Large	• Meta-analysis of RCTs investigating TDF 300 mg had a protective, pooled OR of 0.10 (95% CI: 0.03–0.35), and • Meta-analysis of RCTs investigating Lamivudine 100–150 mg had a protective pooled OR of 0.16 (95% CI: 0.10–0.26) **<u>Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo</u>**	

○ Varies ○ Don't know	• N=19 studies (n=5 RCTs & n=14 non-randomized trials/observational studies) **Efficacy:** *HBsAg positivity at 6–12 months* • 5 RCTs: n=1 of 349 (0.3%) (treatment group) vs n=23 of 337(6.8%) (control group) [OR 0.10, 95% CI: 0.03–0.35] – ***moderate certainty evidence***. • 14 Non RCTs: n=21 of 723 (2.9%) (treatment group) vs n=88 of 499 (17.6%) (control group [OR 0.17, 95% CI: 0.10–0.29] - **low *certainty evidence.*** **Lamivudine (3TC) 100–150 mg versus no treatment or placebo** • n= 40 (n=8 RCTs & n=32 non-randomized trials/observational studies) **Efficacy:** *HBsAg positivity at 6–12 months (8 RCTS)* • 8 RCTs: n=25 of 432 (5.8%) (treatment group) vs n=105of 389 (27.0%) (control group) [OR 0.16, 95% CI: 0.10–0.26] – ***moderate certainty evidence.*** • 32 Non RCTs: n=41 of 1575 (2.6%) (treatment group) vs n=233of 1655 (14.1%) (control group) [OR 0.17, 95% CI: 0.12–0.24] – ***low certainty evidence.***	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know		
Undesirable effects: How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ○ Don't know	Panel was confident that the desirable effects of the intervention outweighed the undesirable effects and most or all patients would benefit from antiviral prophylaxis. **Tenofovir disoproxil fumarate (TDF) 300 mg versus no treatment or placebo** • N=19 studies (n=5 RCTs & n=14 non-randomized trials/observational studies) **Safety** *Postpartum haemorrhage (3 RCTS)*	

- 3 RCTs: n=4 of 177 (2.3%) (treatment group) vs n=5 of 172 (2.9%) (control group) – ***moderate certainty evidence.***
- 3 Non RCTs: n=5 of 188 (2.7%) (treatment group) vs n=3 of 84(3.6%) (control group) – **low *certainty evidence.***

HBV Flare after treatment discontinuation (3 RCTs)

- 3 RCTs: n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group) –***moderate certainty evidence.***
- 3 Non RCTs: n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group) – ***very* low *certainty evidence.***

Neonatal deaths (death within 28 days of life) (5 RCTs)

- 5 RCTs: n=2 deaths of 367 (0.5%) infants (treatment group) vs n=1 death of 350 infants (0.3%) (control group) -– ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 712 (0.0%) (treatment group) vs n=0 of 518 (0.0%) mothers (control group) – ***low certainty evidence.***

Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks]) (5 RCTs)

- 5 RCTs: n=3 cases of 372 (0.8%) (treatment group) vs n=0 of 362 (0.0%) (control group) – ***moderate certainty evidence.***
- 14 Non RCTs: n=0 of 570 (0.0%) (treatment group) vs n=1 of 520 (0.2%) mothers (control group) – ***low certainty evidence.***

Lamivudine (3TC) 100–150 mg versus no treatment or placebo

- n= 40 (n=8 RCTs & n=32 non-randomized trials/observational studies)

Safety

Postpartum haemorrhage

- 1 RCT: n=0 of 53 (2.3%) (treatment group) vs n=0 of 53 (0%) (control group) – ***low certainty evidence.***
- 7 Non RCTs: n=98 of 558 (17.6%) (treatment group) vs n=61 of 699 (8.7%) (control group) – ***low certainty evidence.***

HBV Flare after treatment discontinuation

- 1 RCT: n=16 of 83 (19.3%) (treatment group) vs n= 15 of 46 (32.6%) mothers (control group) – ***very low certainty evidence.***
- 5 Non RCTs: n=32 of 287 (12.9%) (treatment group) vs n= 31 of 504 (6.2%) mothers (control group) – **very low *certainty evidence.***

Neonatal deaths (death within 28 days of life)

- 8 RCTs: n=1 deaths of 439 (0.2%) infants (treatment group) vs n=1 death of 407 infants (0.2%) (control group) – moderate

	certainty evidence. • 31 Non RCTs: n=0 deaths of 1571 (0.0%) infants (treatment group) vs n=0 death of 1686 infants (0.0%) (control group) – ***moderate certainty evidence.*** <u>*Fetal demise (miscarriage [<28 weeks], stillbirth [>=28 weeks])*</u> • 8 RCTSs n=1 cases of 472 (0.2%) (treatment group) vs n=0 of 409 (0.0%) (control group) – ***moderate certainty evidence.*** • 31 Non RCTs n=0 cases of 1531 (0.0%) (treatment group) vs n=9 of 1678 (0.5%) (control group) – low ***moderate certainty evidence.***	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
o Large o Moderate o Small o Trivial o Varies o Don't know	○ 3 RCTs that reported on HBV flare after TDF treatment discontinuation showed a higher proportion with hepatitis flare-ups in the TDF treatment groups vs no treatment/placebo [(n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group)] - ***moderate certainty evidence.*** ○ Similar results were noted for flare after TDF treatment discontinuation in 3 Non RCTs [(n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group)] ***very low certainty evidence.***	
Certainty of evidence: What is the overall certainty of the evidence of effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
o Very low o Low o Moderate o High o No included studies	•Moderate certainty evidence	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
o Very low o Low o Moderate o High o No included studies		

Values: Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Guideline indicated that n=3 published studies and n=2 unpublished studies were identified that assessed the preferences of pregnant women related to interventions to prevent mother-to-child transmission. These studies indicated that most women were willing to have their infant given a timely birth dose, varying from 66% (251/380) of women in Vietnam, to 93% (195/209) in Ghana. • In Ghana, 93% of the surveyed women were willing to take antiviral prophylaxis. In a study in Burkina Faso, 100% of eligible women agreed to take antiviral prophylaxis (A. Guingane, unpublished data). • In China (the SHIELD project), 97% of women eligible for prophylaxis were willing to receive it (Dr Hou, unpublished data). However, one study conducted in Guangdong China found that only 17% (125/737) of women surveyed were willing to take antiviral prophylaxis).	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE'S JUDGEMENT**		
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability		
Balance of effects: Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Maternal tenofovir prophylaxis may prevent HBV infection in infants born to HBV infected women. This may protect these children from the risk of developing serious disease complications later in life. On a population level, prevention of transmission of HBV may reduce the reservoir for further transmission. The main potential harm is the risk of liver flare after discontinuation of prophylaxis. Although the risk of flare is low, reactivation has been reported in patients treated for hepatitis B after antiviral prophylaxis had been withdrawn. There is also the risk that a recommendation could lead to the false perception that tenofovir prophylaxis in HBV-infected pregnant women could replace the use of timely birth dose vaccination. ○ 3 RCTs that reported on HBV flare after TDF treatment discontinuation showed a higher proportion with hepatitis flare-ups in the TDF treatment groups vs no treatment/placebo [(n=16 of 311 (5.1%) (treatment group) vs n= 11 of 309 (3.6%) mothers (control group)] - ***moderate certainty evidence.***	

	○ Similar results were noted for flare after TDF treatment discontinuation in 3 Non RCTs [(n=18 of 107 (16.8%) (treatment group) vs n=9 of 73 (12.3%) mothers (control group)] ***very low certainty evidence.***	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention (compared to placebo) ○ Favors the intervention ○ Varies ○ Don't know		
Resources required: How large are the resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO GUIDELINE PANEL**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	The global cost of adding antenatal testing of pregnant women for HBsAg and providing tenofovir prophylaxis for those at increased risk of mother-to-child transmission (over scaled up timely birth dose) would be an extra US$ 2.2–2.7 billion over 10 years. The ICERs of this testing and prophylaxis strategy guided by HBV DNA, in addition to timely birth dose, varies between US$ 890 and US$ 7355 per DALY averted, depending on the world region. The regions with the lowest ICERs for antiviral scale up are East Asia, West Africa, Central Europe, Central Africa and East Africa with ICERs of US$ 890, US$ 1066, US$ 1069, US$ 1106 and US$ 1250 per DALY averted, respectively.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	TDF – 300MG – 28 Tablets – R 41.01 (March 2024 MHPL) i.e. R1.46 per tablet	Prevalence of condition: 0.67% prevalence of HBsAg in HIV negative pregnant women [Joseph Davey, D., Hsiao, Ny., Wendy Spearman, C. et al. Low prevalence of hepatitis B virus infection in HIV-uninfected pregnant women in Cape Town, South Africa: implications for oral pre-exposure prophylaxis roll out. BMC Infect Dis 22, 719 (2022). https://doi.org/10.1186/s12879-022-07697-5]
Certainty of evidence of required resources: What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

• **WHO Guideline panel**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	Compared to the status quo, scaling up timely birth dose was reported as the most cost-effective option that delivers the most health benefit for the lowest cost. However, in countries that have already scaled up the timely birth dose, adding antenatal testing of pregnant women and tenofovir prophylaxis is an additional opportunity to prevent perinatal infections and may be cost effective in some regions, depending on diagnostic costs and how such a strategy is implemented.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Very low ○ Low ○ Moderate ○ High ○ No included studies	It is noted that in South Africa, universal Hepatitis B antenatal testing is planned and underway. SA NDOH advises routine testing during antenatal care, but provinces have not started to implement this yet due to logistical and budgetary challenges.	
Cost effectiveness: Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies	Testing of pregnant women and tenofovir prophylaxis is an additional opportunity to prevent perinatal infections and may be cost effective in some regions, depending on diagnostic costs and how such a strategy is implemented.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ No included studies		

Equity: What would be the impact on health equity?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Increased equity for disadvantaged groups Emphasizing the need to increase access to cheaper HBV DNA tests and endorsement of HBeAg as an alternative marker for HBV DNA quantification could result in increased availability of affordable testing and subsequent access to tenofovir prophylaxis. This would reduce inequities in access for pregnant women in settings with poor access to testing and prophylaxis	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know		
Acceptability: Is the intervention acceptable to key stakeholders?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Global Hepatitis Programme conducted an online stakeholder consultation to gather the perspectives of programme managers, health-care workers and civil society organizations on introducing antiviral prophylaxis to prevent mother-to-child transmission of HBV. • Tenofovir prophylaxis is acceptable and feasible to implement according to the majority of respondents who answered the questionnaires. • Tenofovir prophylaxis is an opportunity to prevent HBV infection and integrate with and strengthen HIV and syphilis PMTCT services. • Reported concerns are availability and costs of diagnostics. Therefore, costs, cost–effectiveness and availability of tests will need to be taken into account. • Other perceived concerns are the safety of the mother and infant. Safety monitoring will need to be provided to address these concerns. • Confidentiality, stigma and discrimination remain a source of concern when pregnant women are routinely tested. Safeguards will need to be provided to address these issues.	.

• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no ○ Possibly/Probably yes ○ Yes ○ Varies ○ Don't know		

Feasibility: Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
• **WHO Guideline panel**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know	Global Hepatitis Programme conducted an online stakeholder consultation to gather the perspectives of programme managers, health-care workers and civil society organizations on introducing antiviral prophylaxis to prevent mother-to-child transmission of HBV. • Respondents were consulted to determine their views on the acceptability and feasibility of a policy to use tenofovir prophylaxis in eligible pregnant women to prevent mother-to-child transmission of HBV infection. Around 30% of respondents in the African Region. • 77% of respondents felt that it is feasible to implement tenofovir prophylaxis in eligible pregnant women. Perceived challenges to implementation were cost and availability of HBV DNA tests and tenofovir, education of health-care workers and women living with HBV infection, and the lack of infrastructure to test and treat pregnant women.	
• **PHC/ADULT HOSPITAL LEVEL COMMITTEE**		
○ No ○ Probably no ○ Probably yes ○ Yes ○ Varies ○ Don't know		

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	11 April 2024	SG, MR, MM	The committee suggests Tenofovir for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive. (moderate CoE, Strong recommendation).

1 NDOH. Guideline for the Prevention of Vertical Transmission of Communicable Infections August 2023.

2 NDOH. National Maternity Care Guidelines. Updated 2024.

3 World Health Organisation. 2020. Hepatitis B vaccination and prevention of mother-to-child transmission. Available at: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hepatitis/prevention/mother-to-child-transmission-of-hepatitis-b. Accessed 27 March 2024.

4 Centers for Disease Control. Hepatitis B Virus (HBV) infection. Available at: https://www.cdc.gov/nchhstp/pregnancy/overview.html

5 WHO. Global hepatitis report.2024.Available at: https://www.who.int/publications/i/item/9789240091672. Accessed 25 April 2024.

6 Martins RS, Hussain H, Chaudry M, Rizvi NA, Mustafa MA, Ayub B, Aamdani SS, Rehman AA, Pervez A, Nadeem S, Khalid R, Ali AS, Shahid S, Zubairi ABS, Haider AH, Irfan M. GRADE-ADOLOPMENT of clinical practice guidelines and creation of clinical pathways for the primary care management of chronic respiratory conditions in Pakistan. BMC Pulm Med. 2023 Apr 17;23(1):123. doi: 10.1186/s12890-023-02409-4. PMID: 37069600; PMCID: PMC10111762.

7 Appraisal Of Guidelines For Research & Evaluation II. Available at: https://www.agreetrust.org/wp-content/uploads/2013/10/AGREE-II-Users-Manual-and-23-item-Instrument_2009_UPDATE_2013.pdf. Accessed 19 April 2024.

8 Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94.

9 World Health Organisation. 2024. Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Available at: https://www.who.int/publications/i/item/9789240090903. Accessed 25 April 2024

South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Obstetrics & Gynaecology
Addendum to the NDoH review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B

Date: 21 May 2024
Reviewers: [1.] Prof Gebhardt, [2.] Dr M Reddy
Affiliation: [1.] Stellenbosch University and Tygerberg Hospital, [2.] Supply Chain Technical Assistance

Acknowledgements: Ms D Frank (Clinton Health Access Initiative) & Dr M McCaul (Centre for Evidence-Based Health Care, Division of Epidemiology and Biostatistics, Department of Global Health, Stellenbosch University and South African GRADE Network)

Prevention of Mother-to-Child Transmission of Hepatitis B by Using Antiviral Prophylaxis - World Health Organization 2024 Updates

Background

In 2023 the Primary Health Care and Adult Hospital Expert Review Committee was tasked with reviewing the use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive (at high risk of vertical transmission (VT), to prevent VT of Hepatitis B.

The following eligibility criteria was approved for the review.

Population	HIV negative pregnant women in third trimester who are at high risk for VT (either HBeAg positive or have a viral load >200 000 IU/ml)
Intervention	Antiviral therapy
Comparator	No treatment/placebo
Outcome	Efficacy outcome: • Vertical transmission of Hepatitis B Safety outcomes: • Adverse events in mother (e.g. Rebound hepatitis) Foetal death
Studies	Guidelines that employed GRADE (and/or have evidence to decision framework).

The GRADE-adolopment approach was used for efficiency purposes.

The 2020 WHO guideline on the Prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy guideline was adoloped and in May 2024 NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation of Tenofovir for the

prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are at high risk for VT (either HBeAg positive or have a viral load >200 000 IU/ml).[1]

At that time, in May 2024, a query was raised by NEMLC which was not part of the initial review question:

- How to manage HBsAg-positive pregnant women where HBeAg or viral loads are not available

Additionally following the ratification of the initial review by NEMLC in, May 2024, it was brought to the attention of NEMLC that:

- The WHO in March 2024 released updated guidance for the prevention of vertical transmission of hepatitis B in their guidelines for the prevention, diagnosis, care and treatment for people (including pregnant woman as a key priority topic) with chronic hepatitis B infection[2], including:
    - the use of TDF/3TC and TDF/FTC if TDF monotherapy is not available and
    - the use of TAF to be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis.
- Proposals for advancing triple elimination indicate that relying on the availability of HBeAg testing is no longer recommended; and that HbsAg is a more accurate test to apply.[3]

It should be noted that the NEMLC review considered HBeAg-positive in the eligibility criteria. However in 2019 from the existing recommendation on testing of pregnant women for HIV, syphilis and hepatitis B from the 2019 Consolidated guidelines on HIV testing services[4] and for hepatitis B from the 2017 WHO Guidelines on hepatitis B and C testing[5] WHO had recommended that all pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy.[1] (HIV standing recommendation since 2007; syphilis: strong recommendation, moderate-quality evidence; HBsAg: strong recommendation, low quality evidence).

In 2020, the WHO recommended that pregnant women testing positive for HBV infection (HBsAg positive) with an HBV DNA ≥5.3 log10 IU/mL (≥200,000 IU/mL) receive tenofovir prophylaxis from the 28th week of pregnancy until at least birth to prevent mother-to-child transmission of HBV. This is in addition to three-dose HBV vaccination, including timely birth dose (conditional recommendation, moderate quality of evidence). Furthermore, in 2020, the WHO recommended that in settings in which antenatal HBV DNA testing is not available, for example in the public sector in SA, HBeAg testing can be used as an alternative to HBV DNA testing to determine eligibility for tenofovir prophylaxis to prevent mother-to-child transmission of HBV (conditional recommendation, moderate quality of evidence). This is the recommendation that was adoloped by NEMLC in May 2024.

Following the publication of the WHO 2024 guidelines through personal communication by a NEMLC member, with the lead author, it was raised that there is an error in the summary guidance of the 2024 WHO guideline recommendation on page XXXI of the guideline[2] which would have bearing on the following closing statement in the NDOH review: *In March 2024, the WHO released Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection.[2] In this guideline the existing recommendation for use of TDF prophylaxis for HBsAg-positive pregnant women with HBV DNA levels ≥200 000 IU/mL or a positive HBeAg, in settings where there is ready access to these assays, is retained from the 2020 WHO hepatitis B antiviral prophylaxis guidelines for prevention of vertical transmission*. Additionally, the guideline reiterated the 2020 WHO guidance to continue TDF for mothers who meet the criteria for antiviral therapy. The summary guidance, as

included in the narrative of the guideline should have included that in settings where neither HBV DNA nor HBeAg testing is available, prophylaxis with TDF is recommended for all HBV-positive (HBsAg-positive) pregnant women (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.

Introduction

Historically, the WHO has recommended universal HBsAg screening of pregnant women and using antiviral prophylaxis to prevent vertical transmission of hepatitis B among those pregnant patients with a high HBV DNA (≥200 000 IU/mL) or positive HBeAg test.[6]

In the March 2024 update on guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection[2] the WHO acknowledged the challenges in accessing HBV DNA and/or HBeAg serology testing among HBsAg-positive pregnant women to determine eligibility for antiviral prophylaxis, especially in sub-Saharan Africa. The WHO further acknowledges that as a result, there has been no effective universal HBsAg screening of pregnant women and using antiviral prophylaxis to prevent vertical transmission among those pregnant patients with a high HBV DNA (≥200 000 IU/mL) or positive HBeAg test. Therefore a conditional recommendation to expand TDF prophylaxis to all HBsAg-positive pregnant women was made and based on an overall pragmatic approach.

Using the following eligibility criteria (Table 1) the WHO in March 2024 provide updated recommendations (Table 2 & Figure 1) for the research question: Among HBsAg-positive people, what is the efficacy and safety and cost–effectiveness of antiviral prophylaxis in all HBsAg-positive pregnant women to prevent mother-to-child transmission of HBV compared to those with HBV DNA levels >200 000 IU/mL?

Table 1: WHO Eligibility Criteria

PICO: Use of antiviral prophylaxis for PMTCT of HBV[2]

Population	All pregnant women with chronic HBV infection regardless of HBV DNA level
Intervention	Maternal treatment with antiviral therapy in all HBsAg-positive pregnant women regardless of HBV DNA level
Comparison	Maternal treatment with antiviral therapy in HBsAg-positive pregnant women with HBV DNA level >200 000 IU/mL (current 2020 recommendations)
Outcome	MTCT as indicated by infant HBsAg positivity at 6–12 months of life

Table 2: WHO Recommendations

Taken From: Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.

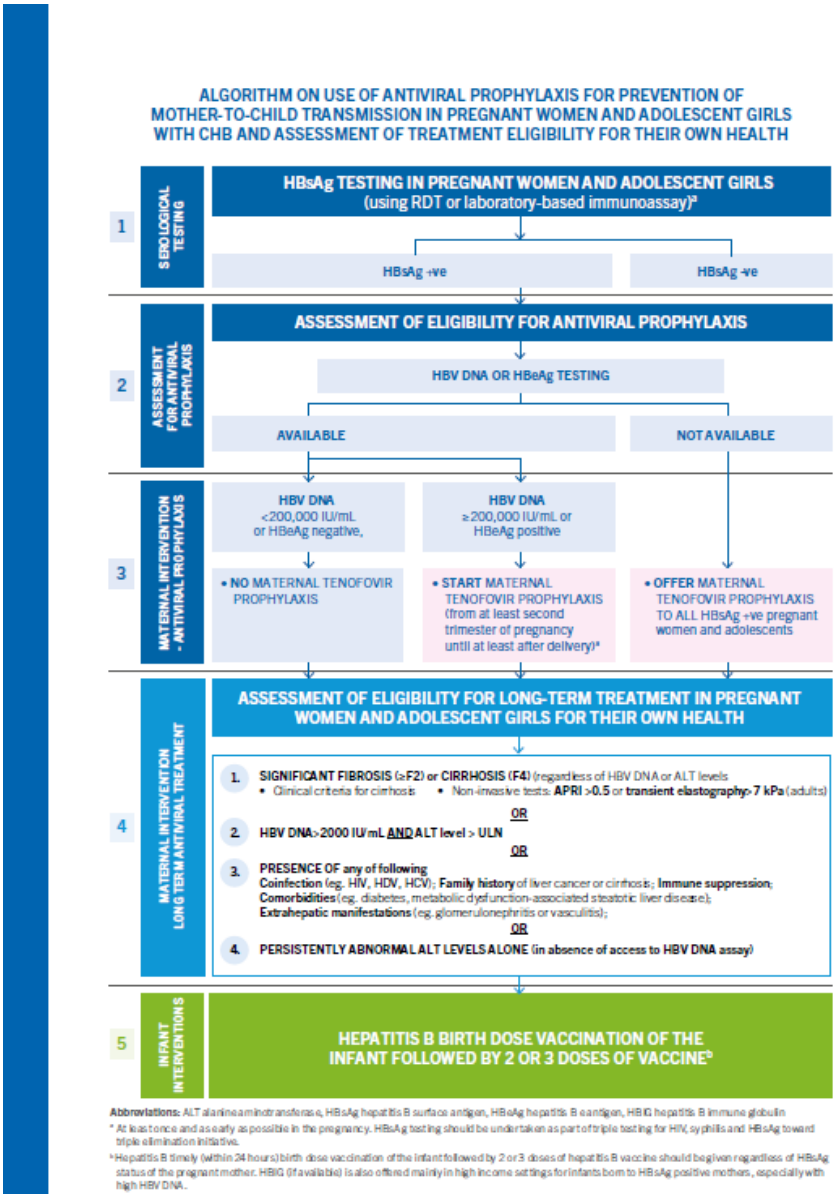
Existing and maintained recommendation (2019 guidelines on HIV testing)	HBsAg testing among pregnant women and adolescent girls	All pregnant women should be tested for HIV, syphilis and hepatitis B surface antigen (HBsAg) at least once and as early as possible during their pregnancy.	*strong recommendation, low-certainty evidence*
2020 guidelines on antiviral prophylaxis	Antiviral prophylaxis among pregnant women and adolescent girls	In settings where HBV DNA or HBeAg testing is available, prophylaxis with tenofovir disoproxil fumarate (TDF)b is recommended for all HBV-positive (HBsAg-positive) pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg[a] (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV.	*strong recommendation, moderate-certainty evidence*
New recommendation		In settings where neither HBV DNA nor HBeAg testing is available, prophylaxis with TDF[b] is recommended for all HBV-positive (HBsAg-positive) pregnant women (preferably from the second trimester of pregnancy until at least delivery or completion of the infant HBV vaccination series), to prevent the mother-to-child transmission (MTCT) of HBV. All interventions should be given in addition to at least three doses of hepatitis B vaccination for all infants, including a timely birth dose. Note: All pregnant women and girls of reproductive age should be assessed first for eligibility for long-term treatment for their own health. For women and adolescent girls of childbearing age planning additional pregnancies, TDF prophylaxis can also be maintained after delivery and during subsequent pregnancies, according to women's choice.	*strong recommendation, moderate-certainty evidence*

a The use of the HBeAg recommendation represents an additional option for determining eligibility, but HBeAg Rapid Diagnostic Tests have poor diagnostic performance, which limits their routine use in low- and middle-income countries.

b TAF may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not yet approved for hepatitis B treatment in pregnancy. TAF is not recommended if eGFR is <15 ml/min.

Figure 1: The Algorithm on Use of Antiviral Prophylaxis of Mother to Child Transmission in Pregnant Women and Adolescent Girls with Chronic Hepatitis B and Assessment of Treatment Eligibility for Their Own Health.

Taken From: Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection. Geneva: World Health Organization; 2024.



In summary start maternal TDF prophylaxis (from atleast second trimester of pregnancy until at least after delivery) if HBV DNA ≥200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination) and offer maternal TDF prophylaxis to all HBsAg positive pregnant woman and adolescents. Dual therapy is not included in the algorithm for prophylaxis but treatment only.

Summary of Evidence

Existing and Maintained Recommendation

Efficacy and safety of maternal TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination)
The maternal and infant efficacy and safety evidence quoted for the retention of the recommendation of TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive in the WHO 2024 Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection update comes from the WHO Commissioned Systematic review used in the 2020 Guideline for the prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy.

The 2020 WHO guideline for the prevention of mother-to-child transmission of hepatitis B virus: guidelines on antiviral prophylaxis in pregnancy guideline was adoloped and in May 2024 NEMLC accepted the proposed PHC/Adult Hospital Level ERC recommendation of Tenofovir for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive.[7]

Additional evidence mentioned in the 2024 guideline for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection

Efficacy and safety of maternal TDF prophylaxis to prevent mother-to-child HBV transmission among those with HBV DNA >200 000 IU/mL or HBeAg positive (alongside infant HBV vaccination)
In the WHO 2024 Guidelines for the prevention, diagnosis, care and treatment for people with chronic hepatitis B infection update, the WHO quote a recent study from the WHO African Region (Democratic Republic of the Congo) demonstrating high protective efficacy of TDF in addition to infant hepatitis B birth dose without hepatitis B immunoglobulin:

- n=0 cases of transmission among babies born to n= 9 treated women.[8]

TAF
In terms of safety WHO also report that the data on the safety of TAF during pregnancy are limited but also suggest an excellent safety profile.[9] However, the WHO 2024 Guideline**Error! Bookmark not defined.** in the narrative of the guideline indicates that TAF has not been approved yet for preventing MTCT of HBV and in a recommendation table (see Table 2 above) that TAF may be considered for people (including pregnant women) with impaired kidney function and/or osteoporosis but is not yet approved for hepatitis B treatment in pregnancy. Refer to the NDOH evidence summary on Tenofovir alafenamide (TAF) for the treatment of chronic hepatitis B (non-HIV co-infection) in patients with renal impairment[10] for additional evidence utilised by NEMLC in recommending TAF in renally impaired patients.

Feasibility of expanding antiviral prophylaxis access to all HBsAg-positive pregnant women
The WHO report that to date, no studies have been undertaken to examine the clinical impact and feasibility of expanding antiviral prophylaxis access to all HBsAg-positive pregnant women. Therefore, the WHO commissioned a modelling study of different scenarios of eligibility for antiviral prophylaxis.[11]

A systematic review and meta-analysis outlined eligibility of pregnant women for antiviral prophylaxis. The study reviewed the proportion of pregnant women with chronic hepatitis that were HBeAG positive with high viraemia (HBV DNA levels ≥200 000 IU/mL). This systematic review also included studies from Africa (while the systematic review commissioned by the WHO in 2020

evidence on TDF efficacy did not). The study concluded: "Approximately 20% of HBV-infected pregnant women are eligible for peripartum antiviral prophylaxis [PAP]".[12] The overall pooled proportion of high viraemia in the WHO Africa region was 12.45%. The study cautions that considering the significant regional variation, each country should define optimal strategies to incorporate HBsAg screening, risk stratification and PAP into routine antenatal care services.[12]

Modelling study of TDF prophylaxis for all HBsAg-positive pregnant women

- Adding HBsAg testing and TDF prophylaxis for eligible pregnant women to the scenario of HepB3 vaccination (three doses of hepatitis B vaccine given in infancy) and hepatitis B birth dose would prevent an additional 2.9–3.0 million neonatal infections over the same period.[12]
- A recent modelling study of 110 countries across all WHO regions assessed the impact and cost–effectiveness of universal TDF prophylaxis among all HBsAg-positive pregnant women regardless of HBV DNA level in settings without access to HBV DNA testing (i.e. excluding the existing recommendation for only those with a high HBV DNA level).[13]
    - **Cost–effectiveness of hepatitis B prophylaxis guided by HBV DNA levels or HBeAg status:**
        - Prophylaxis for HBsAg-positive pregnant women with HBV DNA ≥200 000 IU/mL or positive HBeAg strategy would probably be cost-effective in only 28 (26%) of 106 countries analysed, including:
            - China (incremental cost–effectiveness ratio US$ 8131, 95% CI US$ 3958–17 538),
            - South Africa (US$ 1431, 95% CI US$ 943–2494),
            - Vietnam (US$ 1374, 95% CI US$ 960–1832), and
            - Lower diagnostic and monitoring costs would make the strategy cost-effective in 74 (70%) of 106 countries, including 24 in the African Region.
    - **Impact and cost–effectiveness of expanded treatment for all HBsAg-positive pregnant women:**
        - Universal antiviral prophylaxis, regardless of HBV DNA level or HBeAg serostatus, would have great impact on HBV PMTCT, with about 4.9 million (95% CI: 4.7 million–5.1 million) neonatal infections averted. At central cost estimates and compared with hepatitis B birth dose, the universal "prophylaxis for all" strategy would probably only be cost-effective in 42 (40%) of 106 countries.
        - The relative cost–effectiveness of the universal and HBV DNA–driven strategies (each compared with sole hepatitis B birth-dose strategy) depended highly on the relative costs of treatment and diagnostic tests.

Proposal

- Retain the NEMLC ratified recommendation (16 June 2024) of tenofovir monotherapy for the prevention of vertical transmission of Hepatitis B in HIV Negative pregnant women with chronic active Hepatitis B infection who are HBeAG positive.
- Additionally, pragmatically, offer maternal TDF prophylaxis to all HBsAg positive pregnant woman even if the HBeAg or viral load result is unavailable.
- Consider TAF for people (including pregnant women) with impaired kidney function and/or osteoporosis noting that TAF is not recommended if eGFR is <15 ml/min).

PHC/Adult ERC Recommendation: 6 June 2024
The PHC /AHL ERC accepted the proposal as stated above.

NEMLC Recommendation: 27 June 2024

NEMLC accepted the proposal as recommended by the PHC/Adult ERC (see above)

[1] National Department of Health: Affordable Medicines, EDP- Adult Hospital level. Medicine Review: Use of antivirals in the third trimester of pregnancy, in HIV Negative women with chronic active Hepatitis B infection who are HBeAG positive, to prevent vertical transmission of Hepatitis B. http://www.health.gov.za/

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[10] TAF – eGFR 15-50: NDoH Evidence Summary: Use of TAF for adults with HIV. V4_14 March 2024.

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12 WHO. Web Annex C. Nayagam S, Hallet T, Schmit N, Shimakawa Y, Lemoine M, Thursz M. Impact and cost–effectiveness of HBV peripartum antiviral therapy. In: Prevention of mother-to-child transmission of hepatitis B virus (HBV): guidelines on antiviral prophylaxis in pregnancy. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO.

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