PHC Chapter 6: Obstetrics & gynaecology

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OBSTETRICS

6.1 BLEEDING IN PREGNANCY

6.1.1 PREGNANCY, ECTOPIC

See Section 6.10: Pregnancy, ectopic.

6.2 MISCARRIAGE

O02.1/O03.4/O03.9

DESCRIPTION

Bleeding from the genital tract < 22 weeks' gestation, which may or may not be associated with lower abdominal pain (LAP).

» Miscarriage is classified as follows:

Cervix closed on digital examination	Cervix dilated on digital examination
» Threatened miscarriage: – mild vaginal bleeding, usually no associated LAP – fetus is still in the uterus	» Inevitable miscarriage: – moderate vaginal bleeding with associated LAP – fetus is still in the uterus
» Complete miscarriage: – complete passage of all products of conception – bleeding and pain have settled – usually still requires referral for confirmation	» Incomplete miscarriage: – vaginal bleeding often with clots – partial expulsion of products of conception

» Miscarriage is considered to be safe or unsafe (septic) miscarriage:

Safe miscarriage	Unsafe (septic) miscarriage
– Normal vital signs: pulse, BP, temperature, respiratory rate, Hb – No clinical signs of infection, e.g. chills, malaise – Uterus < 12 weeks in size – No offensive products of conception – No purulent vaginal discharge	– History of interference – Abnormal vital signs: any of tachycardia, hypotension, pyrexia, tachypnoea, pallor – Persistent heavy bleeding – Clinical signs of infections, e.g. chills, malaise – Uterus palpable abdominally (≥ 12 weeks in size) – Offensive vaginal discharge/ products of conception

For perinatal mortality audit and statistics (DHIS or PPIP), all fetuses ≥ 500 g are included.

GENERAL MEASURES

» Monitor vital parameters, e.g. Hb, pulse, BP, temperature.
» Treat for shock if indicated.
» Counselling and support.

» There is no specific treatment for threatened miscarriages: reassure the patient that bleeding usually stops spontaneously. Advise to return if bleeding worsens or persists or abdominal pain develops.

MEDICINE TREATMENT

For inevitable/incomplete miscarriages:

- Oxytocin, IV, 20 units, diluted in 1000 mL sodium chloride 0.9% and infused at 125 mL/hour (avoid where threatened miscarriage is suspected).

For all Rh-negative non-sensitised women who had a surgical procedure to manage a miscarriage:

- Anti-D immunoglobulin, IM, 50 mcg preferably within 72 hours but may be given up to 7 days following management of miscarriage.

Do not offer Anti-D prophylaxis to women who:

» only received medical management for a miscarriage or
» had a threatened miscarriage or
» had a complete miscarriage.

LoE:IVb[1]

If unsafe (septic) miscarriage is suspected, also give before referral:
O03.0/O08.0 + (A41.9/R57.2)

- Ceftriaxone, IV, 1 g as a single dose

CAUTION: USE OF CEFTRIAXONE
Do not administer calcium-containing fluids, e.g. Ringer-Lactate, concurrently with ceftriaxone.

AND

- Metronidazole, oral, 400 mg as a single dose.

REFERRAL

Urgent

» All patients with unsafe miscarriage
» Suspected ectopic pregnancy.
» Previous miscarriage or previously diagnosed incompetent cervix.

Note: For patients with safe miscarriage the need for referral is determined by skills and facilities at the primary health care level. A local referral policy should be in place. Ideally, midwife obstetric units and community health centres should be able to manage safe miscarriage using manual vacuum aspiration or medical management.

6.2.1 MANAGEMENT OF INCOMPLETE MISCARRIAGE IN THE 1ST TRIMESTER, AT PRIMARY HEALTH CARE LEVEL

O02.1/O03.4

Both Manual Vacuum Aspiration (MVA) and medical evacuation are equally effective for miscarriage.

GENERAL MEASURES

» Counselling.
» Evacuation of the uterus.

MEDICINE TREATMENT

Medical evacuation:

- Misoprostol, SL/PV/buccal, 800 mcg immediately as a single dose.
  - Repeat after 24 hours if necessary. *LoE:IIIb*[2]

Manual vacuum aspiration:

Routine analgesia for vacuum aspiration:

- Morphine, IM, 0.1 mg/kg 30 minutes before aspiration procedure, to a maximum of 10 mg (Doctor prescribed). *LoE:IVb*[3]

Alternatively, consider paracervical block if trained in technique. See the Adult Hospital Level STGs and EML, section 5.9.1: TOP: management of pregnancies ≤14 weeks of gestation (doctor only).

Oral analgesia as required for 48 hours:

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

AND

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, for 2–3 days.

Follow up after one week to ensure that bleeding has stopped, or sooner if worsening symptoms.
Perform a pregnancy test three weeks after medical management.

LoE:IIIb[4]

REFERRAL

» Unsafe miscarriage.
» Miscarriage ≥ 13 weeks' gestation.
» Anaemia.
» Haemodynamic instability.
» Failed medical evacuation
» Positive pregnancy test 3 weeks after medical management.

6.2.2 ANTEPARTUM HAEMORRHAGE

O46.0/O46.8-9

DESCRIPTION

Vaginal bleeding in pregnancy from 22 weeks' gestation.
Important causes include the following:

» abruptio placentae
» placenta praevia
» uterine rupture (particularly when misoprostol was used to attempt an unlawful TOP).

GENERAL MEASURES

» Monitor vital parameters, e.g. Hb, pulse, BP, temperature.

» Treat for shock if indicated.
Avoid digital vaginal examination, unless placenta praevia excluded with ultrasound.

MEDICINE TREATMENT

- Sodium chloride 0.9%, IV.

REFERRAL

Urgent
All patients.

6.3 TERMINATION OF PREGNANCY (TOP)

DESCRIPTION

Under the Choice of Termination of Pregnancy Act, 1996, as amended, a TOP may be carried out in the following circumstances:

Women eligibility

If gestation ≤ 12 weeks and 0 days:
» On request.

If gestation 12 weeks and 1 day to 20 weeks and 0 days:
If doctor is satisfied that:
» Pregnancy was from rape or incest, or
» There is a substantial risk that the fetus would suffer from a severe mental or physical abnormality, or
» The continued pregnancy would pose a risk to mother's physical or mental health, or
» Continued pregnancy will significantly affect the social or economic circumstances of the woman.

If gestation ≥ 20 weeks and 0 day:
» If the doctor after consulting with a second doctor or registered midwife or registered nurse is satisfied that continuing the pregnancy would endanger the mothers' life, pose a risk of injury to the fetus, or result in a severe fetal malformation.

Venue
Any facility that has a 24-hour maternity service can provide TOP service without specific designation - *The Choice on Termination of Pregnancy Act, 1996 (as amended by Act 38 of 2004), expanded access to abortions, allows registered nurses, as well as registered midwives, to perform abortions up to the twelfth week of pregnancy.*

Practitioner

If gestation ≤ 11 weeks and 6 days:
» Doctor, midwife or registered nurse with appropriate training.

If gestation ≥ 12 weeks and 0 day:
» Doctor is responsible for decision and prescription of medication. Registered nurse/midwife may administer medication according to prescription.

GENERAL MEASURES

» Pre- and post-termination counselling is essential.

» Consent for TOP and related procedures (e.g. laparotomy) may be given by minors. Minors are encouraged to consult parents or others, but parental consent is not mandatory.
» Consent of spouse/partner is not necessary.
» Offer contraception post TOP.

REFERRAL

» If service not available, refer to appropriate district or regional facility as soon as possible (within 2 weeks).
» If gestation ≥ 12 weeks and 0 day.

6.3.1 MANAGEMENT OF TERMINATION OF PREGNANCY AT PRIMARY HEALTH CARE LEVEL: GESTATION UP TO 12 WEEKS AND 0 DAYS

O04.9

GENERAL MEASURES

» Confirm pregnancy with urine pregnancy test.
» Determine gestational age with ultrasound. If ultrasound is unavailable, use dates (LMP) and bimanual (pelvic) examination.
» If unsure of dates, or examination disagrees with dates, or uterus palpable abdominally, or the woman is obese or difficult to examine, arrange pre-procedure ultrasound.
» Ultrasound is mandatory if suspected ectopic pregnancy – refer if uncertain.
» Counselling.
» Outpatient procedure by nursing staff with specific training.
» Screen for STIs (if treatment needed, do not delay TOP).
» Arrange Pap smear if needed.
» Check HIV status, Hb and blood group (Rh).
» Counsel and start contraception post TOP, before leaving facility. Arrange contraception follow-up.

MEDICINE TREATMENT

Medical TOP - if gestation ≤ 12 weeks and 0 days:

- Mifepristone, oral, 200 mg, immediately as a single dose. *LoE:IIIb*[5]

Followed 24–48 hours later by:

- Misoprostol, SL, 800 mcg by self-administration at home*.
  - If expulsion does not occur within 4 hours of misoprostol administration, a second dose of misoprostol 400 mcg, oral/PV may be given.
  - *From >9 weeks to ≤ 12 weeks- return to the facility within 48 hours to take misoprostol on-site (early morning) due to the risk of heavy bleeding.

LoE:IIIb[6]

Note: Bleeding may persist for up to 1 week. If there is no bleeding after the second dose of misoprostol, the woman must return to the facility as soon as possible as there is a possibility of an incomplete procedure or ectopic pregnancy. *LoE:IIIb*[7]

For pain:
After administration of mifepristone, start:

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

LoE:IVb[8]

ADD
After expulsion is complete:

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, as needed for 2–3 days.

LoE:IVb[9]

OR

TOP using manual vacuum aspiration (MVA) - if gestation ≤ 12 weeks and 0 days:

- Misoprostol, PV, 400 mcg 3 hours before vacuum aspiration of the uterus.

LoE:IVb[10]

Routine analgesia for vacuum aspiration:

- Morphine, IM, 0.1 mg/kg 30 minutes before aspiration procedure, to a maximum of 10 mg (Doctor prescribed).

LoE:IVb[11]

Alternatively, consider paracervical block if trained in technique. See the Adult Hospital Level STGs and EML, section 5.9.1: TOP: management of pregnancies ≤14 weeks of gestation (doctor only).

Oral analgesia as required for 48 hours:

- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

LoE:IVb[12]

AND

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, as needed for 2–3 days.

LoE:IVb[13]

For both medical and surgical TOPs (MVA):

In Rh-negative, non-sensitised women: (O36.0)

- Anti-D immunoglobulin, IM, 50 mcg preferably within 72 hours but may be given up to 7 days following TOP.

LoE:IIIb[14]

Contraception:
Counsel all women on effective contraception, especially long-acting reversible methods.
All methods can be given at the time of the procedure, with the exception of the IUCD at a medical TOP.

LoE:IVb[15]

Review all patients after 7 days: if bleeding persists, arrange urgent ultrasound.

REFERRAL

» If gestation ≥12 weeks and 1 day.
» If gestation uncertain.
» If any signs or symptoms of ectopic pregnancy or other early pregnancy complications.

» Co-morbid conditions (heart disease, asthma, diabetes, anaemia, clotting disorder, seizure disorder, substance abuse, hypertension).
» Large fibroids (may interfere with determining gestation age and/or MVA).
» Any signs of sepsis (tachycardia, hypotension, pyrexia, tachypnoea, offensive vaginal discharge).
» If gestation ≥ 9 weeks and 1 day and MVA not available or declined, refer.

6.4 ANTENATAL CARE

6.4.1 ANTENATAL SUPPLEMENTS

Z36.9 + (Z29.9)

DESCRIPTION

Supplements before and during pregnancy and lactation can help to prevent, or lessen the effect of, a number of conditions or complications associated with pregnancy. Specifically:

» Folic acid, given for at least one month before conception and during pregnancy (particularly the first 12 weeks) can help to prevent neural tube defects (abnormal development of spinal cord/brain).
» Iron can help to prevent anaemia.
» Calcium can help to prevent pre-eclampsia.

GENERAL MEASURES

» Eat a balanced diet to prevent nutritional deficiency.
» Avoid unpasteurised milk, soft cheeses, raw or undercooked meat or poultry, raw eggs, and shellfish.
» Cut down on caffeine. Reduce intake of tea. Do not drink tea within 2 hours of taking iron tablets.

MEDICINE TREATMENT

<u>Prevention of Neural Tube Defects (NTD)</u>

- Folic acid, oral, 5 mg daily:
  - All women intending to become pregnant or pregnant women (first trimester of pregnancy).
  - If high risk, throughout pregnancy, i.e.:
    - on anticonvulsants - especially valproic acid and carbamazepine
    - previous child with NTD; or
    - family history of NTD.

LoE:Ia[16]

CAUTION

Children born to women taking valproic acid are at significant risk of birth defects (10%) and persistent developmental disorders (40%).

Valproic acid is contra-indicated and should be avoided in pregnancy and women of child-bearing potential.

LoE:IIb[17]

Prevention of anaemia:
During pregnancy, after delivery and during lactation:

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

OR

- Ferrous fumarate, oral, 200 mg once daily (± 65 mg elemental iron).
  - Taking iron tablets with meals decreases iron absorption, but improves tolerability. (Note: Do not take iron tablets with milk).

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

- 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).

Note: Established anaemia i.e. Hb < 10 g/dL, see Section 3.1: Anaemia and and 6.4.3: Anaemia in pregnancy. *LoE:IVb*[18]

Prevention of pre-eclampsia:
From confirmation of pregnancy:

- Calcium, elemental, oral, 1 g daily (given as calcium carbonate), 12 hourly.
  - Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women. See Section 6.4.2.4: Pre-eclampsia.
  - Calcium reduces iron absorption from the gastro-intestinal tract. Take supplements 4 hours apart from each other. *LoE:IIIb*[19]

6.4.2 HYPERTENSIVE DISORDERS IN PREGNANCY

DESCRIPTION

Hypertension in pregnancy, pre-eclampsia and eclampsia may have very serious and fatal consequences for both the mother and the baby.
Hypertension is defined by:

» A systolic BP ≥ 140 and/or a diastolic BP ≥ 90 mmHg measured on 2 occasions, 4 hours apart.

OR

» A systolic BP ≥ 160 and/or a diastolic BP ≥ 110 mmHg measured on a single occasion.

(Always measure BP in the left lateral or sitting position (and not supine position).

Hypertensive disorders of pregnancy can be classified as:

» **Chronic hypertension:**
  - Hypertension diagnosed before pregnancy or < 20 weeks of pregnancy.

» **Gestational hypertension:**
  - Hypertension without proteinuria, with onset ≥ 20 weeks of pregnancy.

» **Pre-eclampsia:**
  - Hypertension with proteinuria, with onset ≥ 20 weeks of pregnancy (high risk patients include: nulliparity, obesity, multiple pregnancy, chronic hypertension,

kidney disease, diabetes, pre-eclampsia in a previous pregnancy, advanced maternal age or adolescent pregnancy).

» **Eclampsia:**
  - Generalised tonic-clonic seizures in women with pre-eclampsia.

» **Chronic kidney disease:**
  - Proteinuria with/without hypertension, diagnosed at < 20 weeks of pregnancy.

Categorising hypertensive disease:

» A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but with **NO** symptoms or organ dysfunction is classified as hypertensive disease without severe features.

» Maternal features of severe hypertensive disease are any or more of the following:
  - Acute severe hypertension (diastolic BP of 110 mmHg and/or systolic >160 mmHg).
  - Thrombocytopenia (platelet count <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 µl and LDH >600 µl).
  - Serum creatinine ≥120 micromol/L.
  - Pulmonary oedema.
  - New-onset severe headache unresponsive to medication.
  - Visual disturbances.

REFERRAL

Urgent

» Hypertension with severe features (refer to high risk labour ward urgently)
» Pre-eclampsia with or without severe features (refer to high risk labour ward, urgently if severe features present)

Non-urgent

» Chronic hypertension.
» Chronic kidney disease.

6.4.2.1 CHRONIC HYPERTENSION

O10.0

Stop oral antihypertensive medicines when pregnancy is planned or as soon as pregnancy is diagnosed, change to methyldopa and refer for assessment and management.

MEDICINE TREATMENT

- Methyldopa, oral, 250 mg 8 hourly.
  - Titrate to a maximum dose: 750 mg 8 hourly.
  - When using iron together with methyldopa, ensure that iron and methyldopa are not taken concurrently.

LoE:IIIb[20]

REFERRAL

Urgent (within 2 days)

All cases.

6.4.2.2 GESTATIONAL HYPERTENSION: NO SEVERE FEATURES

O13

DESCRIPTION

Hypertension occurring for the first time at ≥ 20 weeks' gestation with no proteinuria.

GENERAL MEASURES

» May be managed without admission < 38 weeks' gestation, provided no proteinuria.
» Review the following on a weekly basis:
  - BP
  - weight
  - urine analysis
  - height of fundus (every two weeks)
  - fetal heart rate and movements

» Educate on signs requiring urgent follow-up (headache, epigastric pain, visual disturbances, vaginal bleeding etc.).

MEDICINE TREATMENT

- Methyldopa, oral, 250 mg 8 hourly.
  - Titrate to a maximum dose: 750 mg 8 hourly.
  - When using iron together with methyldopa, ensure that iron and methyldopa are not taken concurrently.

LoE:IIIb[21]

REFERRAL

» All patients with gestational hypertension at 38 weeks for delivery.
» Pre-eclampsia (all levels of severity).
» Poor control of hypertension.
» Hypertension with severe features (urgent referral)

6.4.2.3 GESTATIONAL HYPERTENSION: WITH SEVERE FEATURES

O13

Management is the same as for treatment of pre-eclampsia with severe features – See Section 6.4.2.4: Pre-eclampsia.

6.4.2.4 PRE-ECLAMPSIA

O11/O14.0-2/O14.9

DESCRIPTION

» A systolic BP ≥ 140 and/or diastolic BP ≥ 90 mmHg with proteinuria, after 20 weeks of pregnancy (significant proteinuria defined as ≥ 1+ proteinuria).
» Pre-eclampsia with severe features is a life-threatenig condition and needs urgent stabilsation and referral.
» The following indicate a higher risk of developing pre-eclampsia: nulliparity, obesity, multiple pregnancy, chronic hypertension, kidney disease, diabetes, pre-eclampsia in a previous pregnancy, advanced maternal age or adolescent pregnancy.

GENERAL MEASURES

» Advise all pregnant patients to urgently visit the clinic if severe persistent headache, visual disturbances, epigastric pain (not discomfort).

» If severe features are present:

- Insert a Foley's catheter and monitor urine output hourly.
- Monitor BP every 30 minutes.
- Check reflexes every hour.

MEDICINE TREATMENT

Prevention of pre-eclampsia

From confirmation of pregnancy:

- Calcium, elemental, oral, 1 g daily (given as calcium carbonate), 12 hourly Although the benefit is greatest in high-risk women, consider use of this agent in all pregnant women.
- Calcium reduces iron absorption from the gastro-intestinal tract. Take supplements 4 hours apart from each other.

LoE:Ia[22]

Treatment if severe features are present

- Magnesium sulfate, IV, 4 g as a loading dose diluted with 200 mL sodium chloride 0.9% and infused over 20 minutes.

FOLLOWED BY

LoE:Ia[23]

- Magnesium sulfate, IM, 10 g given as 5 g in each buttock.
  - Then IM, 5 g every 4 hours in alternate buttocks.

CAUTION: USE OF MAGNESIUM SULFATE

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 > 5 mL/minute.

AND

If systolic BP ≥ 160 and/or a diastolic BP ≥ 110 mmHg:

- Nifedipine, oral, 10 mg (not sublingual) as a single dose.
  - May be repeated after 30 minutes if diastolic BP remains ≥ 110 mmHg or if systolic BP remains ≥ 160 mmHg.

LoE:Ia[24]

REFERRAL

Urgent

» Pre-eclampsia with severe features

Non urgent

» Pre-eclampsia without severe features (within 24 hours).

6.4.2.5 ECLAMPSIA

O15.0-2/O15.9

GENERAL MEASURES

» Stabilise prior to urgent referral.

» Ensure safe airway.
» Place patient in left lateral position.
» Insert a Foley's catheter and monitor urine output hourly.
» Monitor BP and check reflexes every 30 minutes.

MEDICINE TREATMENT

- Administer oxygen.
- Magnesium sulfate, IV, 4 g as a loading dose diluted with 200 mL sodium chloride 0.9% and infused over 20 minutes.

AND

- Magnesium sulfate, IM, 10 g given as 5 g in each buttock
  - Then IM, 5 g every 4 hours in alternate buttocks.

CAUTION: USE OF MAGNESIUM SULFATE

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 >5 mL/minute. *LoE:IVb*[25]

If recurrent eclamptic seizures despite magnesium sulfate loading dose administration:

- Magnesium sulfate, IV, 2 g, diluted with 100 mL sodium chloride 0.9%, over 10 minutes. *LoE:IVb*[26]

If seizures still persist and are continuous, there may be another cause of the seizures: treat as for status epilepticus (see Section 21.2.11: Seizures and status epilepticus).

AND

If systolic BP ≥ 160 and/or a diastolic BP ≥ 110 mmHg and patient becomes alert:

- Nifedipine, oral, 10 mg (not sublingual) as a single dose.
  - May be repeated after 30 minutes if diastolic BP remains ≥ 110 mmHg or if systolic BP remains ≥ 160 mmHg. *LoE:Ia*[27]

REFERRAL

Urgent

All cases.

6.4.3 ANAEMIA IN PREGNANCY

O99.0 + (D64.9)

DESCRIPTION

Anaemia in pregnancy is a Hb < 11 g/dL, most commonly due to iron deficiency. Hb levels should be checked at the booking visit, between 28 and 32 weeks, and at ± 36 weeks.

Treatment is recommended when the Hb falls below 10 g/dL.

Women with iron deficiency often have 'pica', e.g. eating substances such as soil, charcoal, ice, etc.

GENERAL MEASURES

» A balanced diet to prevent nutritional deficiency.
» Reduce intake of tea.
» Do not drink tea within 2 hours of taking iron tablets.

MEDICINE TREATMENT

Established anaemia with Hb < 10 g/dL:

Continue for 3 months after the Hb normalises in order to replenish body iron stores. Hb is expected to rise by at least 1.5 g/dL in two weeks.

- Ferrous sulfate compound BPC (dried), oral, 170 mg (± 55 mg elemental iron) 12 hourly with meals.
  - Taking iron tablets with meals decreases iron absorption, but improves tolerability (Note: Do not take iron tablets with milk).

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.
  - Taking iron tablets with meals decreases iron absorption, but improves tolerability. (Note: Do not take iron tablets with milk). *LoE:IIb*[28]

REFERRAL

Urgent (same day)

» Hb < 6 g/dL.
» Hb = 6-7.9 g/dL with symptoms (dizziness, tachycardia, shortness of breath at rest).

Non-urgent (within 1 week)

» Hb = 6-7.9 g/dL without symptoms (to high-risk clinic if available).
» Hb = 8-9.9 g/dL and no improvement after one month of treatment (to high-risk clinic, if available).
» Hb < 10 g/dL at 36 weeks' gestation or more: transfer to hospital for further antenatal care and delivery.

6.4.4 SYPHILIS IN PREGNANCY

O98.1

DESCRIPTION

A sexually transmitted infection with many manifestations that has a latent phase and may be asymptomatic in pregnant women. It is caused by the spirochaete, T pallidum. Vertical transmission to the fetus occurs in up to 80% of cases in untreated mothers. Untreated maternal syphilis may lead to miscarriage, stillbirth, non-immune hydrops fetalis, or congenital syphilis in the newborn.

DIAGNOSIS

» All pregnant women should have a syphilis test at the first booking visit.
» Women who booked in the first trimester and tested negative should have a repeat test done around 32 weeks' gestation.
» Diagnosis is made by positive serology. Clinical signs and symptoms are most recognisable in secondary syphilis. These include rash on palms of the hand and/or soles of the feet; and condylomata lata on genital areas.

» There are 2 types of diagnostic tests:

Specific treponemal test (e.g. TPAb//TPHA/FTA-ABS):	**Non-treponemal test** (e.g. RPR):
» Specifically diagnoses syphilis. » Available as rapid on-site finger-prick syphilis tests or laboratory-based assays. » Dual HIV/syphilis rapid on-site test may be used when HIV status is negative/unknown. » Once positive, a specific treponemal test generally remains positive for life, and therefore the presence of specific treponemal antibodies cannot differentiate between current and past infections. » A person with previously successfully treated syphilis will retain lifelong positive specific treponemal test results. » Thus a positive test should be immediately followed by an RPR test to confirm active disease; however treatment can be started while awaiting the RPR result.	The RPR can be used: » To determine if the patient's syphilis disease is active or not, » To measure a successful response to therapy (at least a fourfold reduction in titre, e.g. 1:256 improving to 1:64), or » To determine a new re-infection. **Note:** – False RPR positive reactions may occur, notably in patients with connective tissue disorders (these are usually low titre < 1:8). For this reason, positive RPR results should be confirmed as due to syphilis by further testing of the serum with a specific treponemal test; if the specific test result cannot be obtained the same day, start treatment while awaiting the result. – If specific treponemal test e.g. TPAb is performed first and gives a positive result, serum can be further tested for RPR to determine the presence of active syphilis (reverse testing algorithm). – Some patients, even with successful treatment for syphilis, may retain life-long positive RPR results at low titres (≤ 1:8), which does not change by more than one dilution difference over time (so-called serofast patients).

GENERAL MEASURES

» Encourage partner notification and treatment after confirmon the diagnosis
» Provide counselling and promote HIV testing.
» Educate on treatment adherence.
» Promote condom use.

MEDICINE TREATMENT

Pregnant woman

- Benzathine benzylpenicillin, IM, 2.4 MU weekly for 3 weeks.
  - Reconstitute with 6 mL of lidocaine1% without adrenaline (epinephrine).
  - Follow up at 3 months after the last injection to confirm a fourfold (i.e. 2 dilution) reduction in RPR titres, provided the initial titre was ≥ 1:8. If initial titre < 1:8, further reductions may not occur (serofast reaction).

LoE:IVb[29]

Severe penicillin allergy:
Z88.0
Refer for in-patient penicillin desensitisation.

Newborn baby

If baby asymptomatic, well and mother not fully treated > 1 month before delivery, give:

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

CAUTION

Benzathine benzylpenicillin (depot formulation) must never be given intravenously.

REFERRAL (BABY)

» Mother was not treated.
» Mother has received < 3 doses of benzathine benzylpenicillin.
» Mother delivered within 4 weeks of commencing treatment.
» Baby has any of the following:
  - Hepatosplenomegaly
  - Snuffles
  - Jaundice
  - Purpura
  - Pseudoparesis
  - Oedema
  - Anaemia
  - Desquamative rash (especially involving palms and soles)

6.4.5 URINARY TRACT INFECTION, IN PREGNANCY

6.4.5.1 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 and/or leukocytes; protein and/or blood may also be detected.

GENERAL MEASURES

» Encourage oral fluid intake.
» Midstream urine for microscopy, culture and sensitivity (start empiric treatment while awaiting results).

MEDICINE TREATMENT

See section 8.4: Urinary tract infection.

REFERRAL

» No response to treatment, or resistant organism on culture.
» Features of pyelonephritis (See Section 6.4.5.2: Pyelonephritis, acute, in pregnancy).

6.4.5.2 PYELONEPHRITIS

O23.0

DESCRIPTION

Features of pyelonephritis include: temperature ≥38°C, renal angle tenderness, vomiting, tachypnoea, tachycardia, hypotension, confusion.

This condition is more serious and may result in preterm labour.

GENERAL MEASURES
» Collect midstream urine for microscopy and culture and sensitivity.
» Ensure adequate hydration with IV fluids while awaiting transfer.

MEDICINE TREATMENT
Empiric therapy:
- Ceftriaxone, IV, 1 g as a single dose.

CAUTION: USE OF CEFTRIAXONE

Do not administer calcium-containing fluids, e.g. Ringer-Lactate, concurrently with ceftriaxone. *LoE:IVb*

REFERRAL
All cases.

6.4.6 LISTERIOSIS
A32.0-1/A32.7-9

Note: If you have any questions or concerns, visit www.nicd.ac.za or call the NCID hotline on 082 883 9920.

DESCRIPTION
Listeriosis is a preventable and treatable bacterial disease spread through food. Most listerial infections are sporadic but outbreaks do occur. Pregnancy is a predisposing factor for developing serious Listeriosis.
Patients present with a flu-like illness (with fever). They may also have sore joints, backache, diarrhoea and vomiting, and/or signs of meningitis (headache, neck stiffness, confusion).
Listeriosis has been added to the national list of notifiable diseases.

GENERAL MEASURES
Educate your patients on how to prevent it: wash hands, knives, and cutting boards after handling uncooked food, avoid luncheon meats/delicatessen meats, wash raw vegetables thoroughly, avoid unpasteurised milk, thoroughly cook raw food from animal sources.

MEDICINE TREATMENT
During outbreaks, if signs of meningitis are present, give pre-referral treatment (see Section 15.4.2: Meningitis, acute). *LoE:IVb*[30]

REFERRAL
All cases.

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

6.4.7.1 PRETERM LABOUR (PTL)

O60.0

DESCRIPTION

Regular painful contractions: 3 per 10 minutes, occurring < 37 weeks of gestation.

Note: Women with a previous spontaneous preterm delivery are at higher risk for preterm delivery in the next pregnancy. Refer the following high-risk cases for cervical screening:

» A history of 2nd trimester miscarriage (between 16 and 26 weeks).
» Previous history of spontaneous preterm birth between 27 and 34 weeks.
» No need to refer previous late preterm deliveries (34-37 weeks). *LoE:IVb*[31]

GENERAL MEASURES

<26 weeks:
» Refer without tocolysis (medicines to inhibit uterine contractions). *LoE:IVb*[32]

26–34 weeks of gestation:
» Refer with initial tocolysis and corticosteroids.

>34 weeks of gestation:
» Allow labour to continue at midwife obstetric unit.

MEDICINE TREATMENT

To improve fetal lung maturity at 26–34 weeks:
Z29.2
- Betamethasone, IM, 12 mg, 2 doses 24 hours apart. *LoE:Ia*[33]

Tocolysis:
Z29.2
Preload with:
- Sodium chloride 0.9%, IV, 200 mL.

THEN
- Nifedipine, oral, 20 mg as a single dose.
  - Follow with 10 mg after 30 minutes, if contractions persist.
  - Then 10 mg every 4 hours until patient is transferred.
  - Maximum duration: 24 hours.

REFERRAL

All cases before 34 weeks.

6.4.7.2 PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

O42.0-1/O42.9

DESCRIPTION

Rupture of the membranes before 37 weeks' gestation.
Confirmed with a sterile speculum examination demonstrating leakage of amniotic fluid.
If there is clinical uncertainty test for pH – liquor is alkaline.
Avoid digital vaginal examination.

MEDICINE TREATMENT

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

- Betamethasone, IM, 12 mg, 2 doses 24 hours apart. *LoE:Ia*[34]

Initiate 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 1 g orally as a single dose. *LoE:IIa*[35]

Severe penicillin allergy:(Z88.0)

- Azithromycin 1 g orally as a single dose and refer urgently.

REFERRAL

All cases, but refer **urgently** if PPROM < 34 weeks or cases of severe penicillin allergy.

6.4.7.3 PRELABOUR RUPTURE OF MEMBRANES AT TERM (PROM)

O42.0-1/O42.9

DESCRIPTION

Rupture of membranes before the onset of labour at term (>37 weeks).
A sterile speculum examination is required to visually confirm amniotic fluid draining through the cervical os.

GENERAL MEASURES

» If PROM is followed by uterine contractions at >34 weeks' gestation, allow labour to proceed.
» If the woman does not develop uterine contractions within 12 hours of PROM, commence antibiotics and transfer for induction of labour.

MEDICINE TREATMENT

Prolonged pre-labour rupture of membranes >12 hours/ suspected chorio-amnionitis:

Initiate antibiotic therapy and refer urgently:
O41.1

- Ampicillin, IV, 1 g as a single dose.

AND

- Metronidazole, oral, 400 mg as a single dose and refer.

Severe penicillin allergy:
Z88.0

- Azithromycin, oral, 500 mg as a single dose.

AND

- Metronidazole, oral, 400 mg as a single dose and refer.

LoE:IIa[36]

REFERRAL

Urgent

» Suspected chorio-amnionitis (refer after starting antibiotics).
» Prolonged pre-labour rupture of membranes (>12 hours).
» Meconium stained liquor.

6.5 INTRAPARTUM CARE

O80.0-1/O80.8-9

For the comprehensive management of women in labour refer to the most recent National Maternity Care and Intrapartum Care Guidelines.

DESCRIPTION

Labour is divided into 4 stages:

» First stage
  - onset of regular painful uterine contractions at term to full dilatation of cervix.
» Second stage
  - full dilatation to delivery of the baby.
» Third stage
  - delivery of the baby to delivery of the placenta.
» Fourth stage
  - 1 hour post-delivery of the placenta.

GENERAL MEASURES

» Encourage companion support.
» Ensure that the mother is adequately hydrated (can be done orally).
» Monitor progress of labour on partogram.

MEDICINE TREATMENT

First stage with cervical dilatation <10 cm:

Analgesia:
O62.9 + (Z51.2)

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

LoE:IVb[37]

OR

Especially in advanced first stage of labour:

- Nitrous oxide 50% mixed with oxygen 50%, given by mask.

AND

For nausea and sedation, if needed:

- Promethazine, IM, 25 mg 4 hourly.

Second stage

If episiotomy is needed, local anaesthetic:
O62.9 +(R10.2+Z51.2)
- Lidocaine1%.
  - Do not exceed 20 mL.

Fetal distress during labour
O68.0-3/O68.8-9/O75.9
Place the woman in the left lateral position.
Tocolysis, then refer:
- Salbutamol, IV, 0.5 mg/mL, 250 mcg administered slowly over 2 minutes.
  - Reconstitute as follows:
  - Salbutamol 1 mL (0.5 mg/mL) added to 9 mL of water for injection, to make a 50 mcg/mL solution. Monitor pulse.
  - Inject 5 mL (250 mcg) over at least 2 minutes. Monitor pulse.
  - If pulse increases > 120 beats/minute, discontinue the injection.
  - Do not administer if mother has cardiac disease.

Third stage

Prevention of post-partum haemorrhage (PPH):
Z29.2
» Check for twins.
- Oxytocin, IM, 10 units.

» Clamp and cut cord after 1 minute.
» Controlled cord traction of the placenta.
If > 500 mL blood loss, manage as postpartum haemorrhage (see Section 6.7.1: Postpartum haemorrhage (PPH)).

Rh-negative mother
O36.0
» Check baby's Rh status; do not given anti-D if the baby is Rh-negative, or if the mother has Anti-Rh antibodies.

Administer to Rh-negative mother, if baby is Rh-positive or baby's Rh group is unknown:
- Anti-D immunoglobulin, IM, 100 mcg, preferably within 72 hours but can be given up to 7 days after delivery.

Care of the newborn baby
If baby not crying/breathing well, see Section 6.6.2: Neonatal Resuscitation.
For routine care of the neonate, see Section 6.6.1: Routine care of the neonate.
Observe mother and neonate for 1–2 hours before transfer to the postnatal ward.

For pain after delivery
- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4 g in 24 hours.

If needed
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for up to 5 days. *LoE:IVb*

REFERRAL

» Prolonged labour according to charting on partogram.
» Fetal distress during labour
» Post-partum haemorrhage.
» Retained placenta.
» Other complications of mother or baby.

6.6 CARE OF THE NEONATE

6.6.1 ROUTINE CARE OF THE NEONATE

Z76.2

For the comprehensive management of the newborn refer to the most recent Newborn Care Charts.

GENERAL MEASURES

Routine care for baby after delivery

» Dry the baby thoroughly at birth.
» If there is meconium, clear the airway first.
» If baby is not crying
- Clear airway, stimulate.
- If baby not breathing well, clamp and cut the cord and start resuscitation (see Section 6.6.2: Neonatal Resuscitation).

» If the baby is crying and breathing well
- Place on mother's chest, keep warm and check breathing.
- Clamp and cut cord after 1 minute.
- Monitor with mother and initiate breastfeeding.

Check and record the Apgar score:

Apgar score	0	1	2
Heart rate	Absent	< 100/min	> 100/min
Respiration	Absent	Slow or irregular	Good, crying
Muscle tone	Limp	Slight flexion	Active, moves
Response to stimulation	No response	Grimace	Vigorous cry
Colour	Blue or pale	Body pink, limbs blue	Pink all over

Check baby from head to toe including baby's back

» Check weight and head circumference.
» If any of the following, provide immediate management (see Section 6.6.3: Care of sick and small neonates) and refer to a neonatal unit:
- Grunting or chest indrawing
- Central cyanosis
- Fast breathing
- Abnormal tone (floppy/stiff)
- Less than normal movements
- Major congenital abnormality
- Head circumference > 39 cm
- Birth weight < 2.0 kg

Identify the infant at risk or needing special treatment

- » Birth weight < 2.5 kg.
- » Suspected chorio-amnionitis (membranes ruptured for > 18 hours, offensive liquor at birth).
- » Neurological or congenital problem.
- » Hospital stay > 3 days after delivery.
- » Mother blood group O and/or Rh –ve.
- » Mother diabetic.
- » Mother syphilis positive (partially treated or untreated or treated < 1 month before delivery).
- » Mother HIV-infected.
- » Infant not breastfed.
- » Mother on TB treatment.
- » Possible social problem (mother has died or is ill, teenage caregiver, social deprivation).

Initiate bonding and feeding

» Place the baby skin-to-skin with mother and initiate breastfeeding immediately.

Identify and record

» Formally identify the baby with the mother.
» Place a label with the mother's name and folder number, baby's sex, and time and date of birth on the baby's wrist and ankle.
» After giving vitamin K and chloramphenicol eye ointment, give the baby back to the mother, unless there is a reason for the baby to be transferred to a neonatal unit.

MEDICINE TREATMENT

Bleeding prophylaxis

Z29.2

- Vitamin K, IM, 1 mg immediately after birth routinely.
  - Administer in the antero lateral aspect of the mid-thigh.

Neonatal conjunctivitis prophylaxis

Z29.2

- Chloramphenicol ophthalmic ointment 1%, applied routinely to each eye after birth.

Routine EPI immunisation:

- BCG vaccination, intradermal, once neonate is stable. (Z23.2)
- bOPV (polio vaccine), oral, once neonate is stable. (Z24.0)

No baby must be sent home without immunisation.

REFERRAL

Refer to a neonatal unit if:

» Baby needed resuscitation.
» Apgar score < 8 at 5 minutes.

6.6.2 NEONATAL RESUSCITATION

P29.8

Be prepared Be at the delivery Check the equipment and emergency medicines

» Follow the algorithm at the end of this section.

» Check that each step has been effectively applied before proceeding to the next step. The algorithm follows the assumption that the previous step was unsuccessful and the baby is deteriorating.
» Use oxygen concentration that alleviates central cyanosis, obtains target pulse oximetry readings (if pulse oximeter is available), and restores a heart rate >100 beats/minute. Bag and mask ventilation should be initially done with room air. (There is evidence that routine resuscitation with 100% oxygen is potentially harmful to the baby).

An unsatisfactory response to resuscitation includes:
» A sustained slow heart rate, usually ≤ 60 beats/minute or a progressive decrease in heart rate until cardiac arrest occurs.
» Episodes of cardiac arrest, with a progressively weaker response to chest compressions, positive pressure ventilation and medicines.
» A decreasing blood pressure, increasing acidosis, severe hypotonia with central cyanosis or intense pallor.
» Apnoea or weak, irregular and inefficient respiratory efforts.

MEDICINE TREATMENT

If baby's response to resuscitation is inadequate once ventilation and circulation are adequately supported the following steps should be carried out:

If the mother is known or suspected to have had narcotic pain relief and the baby has normal heart rate and colour response to bag-mask ventilation, but has not initiated sustained regular respiratory effort:

- Naloxone, IV, 0.1 mg/kg.

Naloxone is not routinely indicated for neonatal resuscitation.

Check the blood glucose of the baby.If hypoglycaemia is present:
E16.0-2/P70.4

- Dextrose 10%, IV, 2.5–5 mL/kg.

Medicines used during neonatal resuscitation

Medicine and dose	Indications	Effect
• Adrenaline (epinephrine) ○ 0.1 mL/kg of a 1:10 000 dilution IV, (0.01 mg/kg/dose) ○ ET, up to 1 mL/kg of a 1:10 000 dilution (0.1 mg/kg/dose)	» Asystole » Heart rate < 60 beats/minute	» ↑Heart rate » ↑Myocardial contractility. » ↑Arterial pressure
• Naloxone, IV/IM, 0.1 mg/kg ○ May need repeating after 2 hours	» Maternal administration of opiates with apnoeic infant	» Corrects apnoea and/or hypoventilation
• Dextrose,10% IV ○ 2.5–5 mL/kg of 10% dextrose (250–500 mg/kg) ○ 10% solution: draw up 4 mL of 50% dextrose into a 20 mL syringe then draw up 16 mL water for	» Hypoglycaemia (usually only occurs after acute resuscitation)	» Corrects hypoglycaemia

injection – mix by agitating the syringe		
Fluid for volume expansion: • Sodium chloride 0.9%, IV, 10–20 mL/kg, slow IV (5–10 minutes)	» Hypovolaemia (usually history of blood loss, child pale shocked with poor pulses and perfusion)	» ↑Blood Pressure and improve tissue perfusion

If no adequate response has occurred by this stage, a person skilled in neonatal resuscitation should be consulted and the baby transferred with ongoing resuscitation to a higher level of care:

» Discontinue resuscitation if the unsatisfactory response to resuscitation persists for > 20 minutes and underlying conditions e.g. pneumothorax, diaphragmatic hernia has been excluded or > 10 minutes of unresponsive cardiac arrest (asystole) and/or > 20 minutes of unsustained respiration.

» Babies requiring minimal resuscitation with prompt and complete response may be watched with their mothers.

» Babies with a favourable response to resuscitation should be referred to a neonatal high or intensive care unit, if available, for post resuscitation care.

» Babies, who, after resuscitation, are not completely normal, should be referred to a higher level for care using transport with necessary support, e.g. oxygen, temperature control.

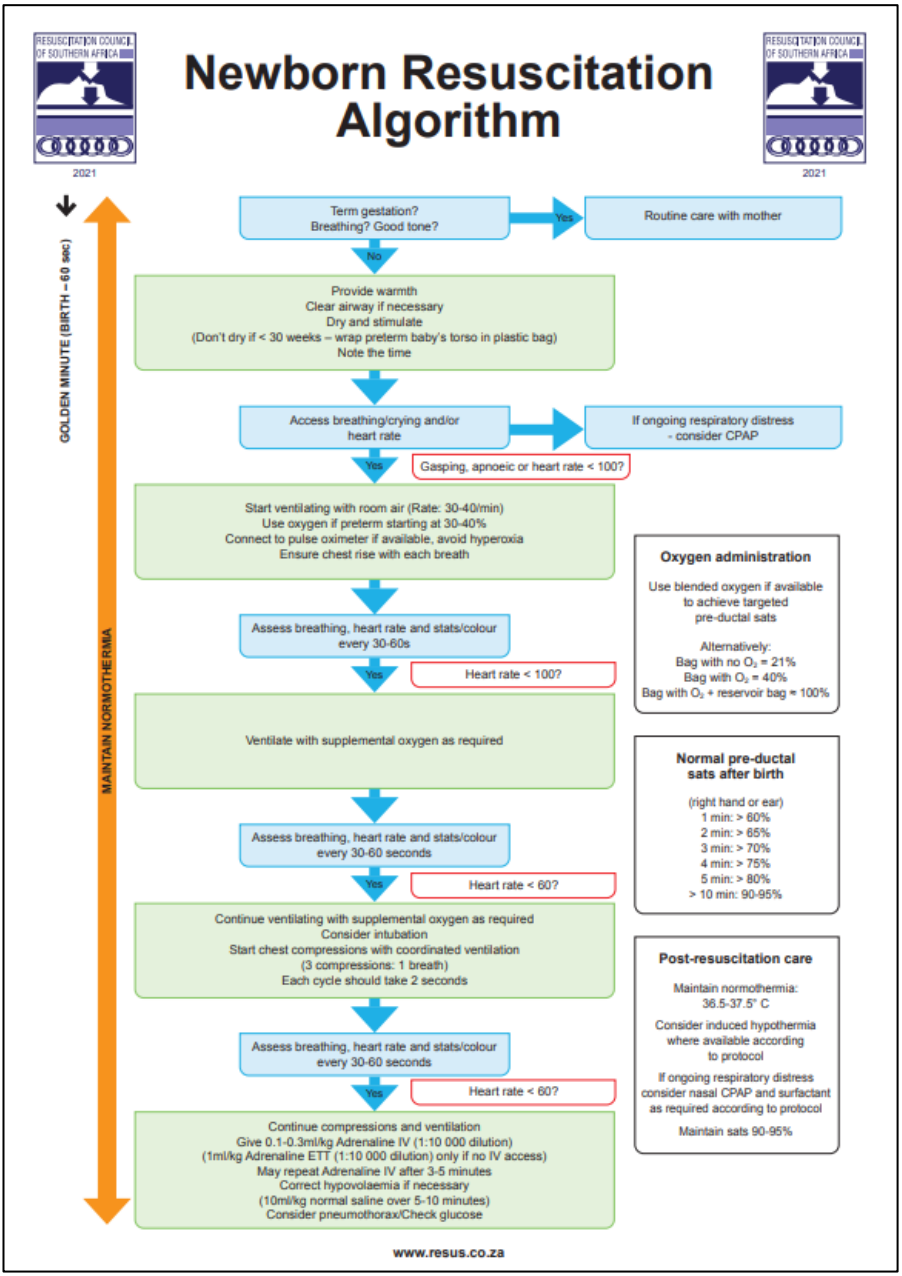

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Figure 6.1: Newborn resuscitation algorithm

6.6.3 CARE OF SICK AND SMALL NEONATES

DESCRIPTION

Neonates can become ill very rapidly and signs of disease are often not readily appreciated unless specifically looked for. Neonates should be referred urgently. Neonates < 2.5 kg are at higher risk of feeding and growth problems and need careful follow-up.

Urgently manage and refer neonates with any of the following signs of possible serious bacterial infection and/or jaundice:

- » Convulsions
- » Lethargic/ unconscious
- » Bulging fontanelle
- » Apnoea (< 30 breaths/min)
- » Severe chest indrawing
- » Nasal flaring or grunting
- » Swollen eyes; pus draining from eye
- » Low or high temperature
- » Not able to feed
- » Passing blood per rectum
- » Pallor
- » Jaundice in 1st 24 hours of life
- » Diarrhoea
- » Many or severe skin pustules
- » Fast breathing (> 60 breaths/min)
- » Vomiting everything/bile-stained vomitus
- » Only moves when stimulated
- » Umbilical redness extending to the skin and draining pus

GENERAL MEASURES

- » Keep the neonate warm (skin-to-skin/kangaroo mother care or in an incubator), the axillary temperature should be 36.5–37oC.
- » Check blood glucose concentration and treat if low (< 2.6 mmol/L). Check blood glucose concentration again after 15 minutes. If normal, feed 2-3 hourly. If still low, treat as severe hypoglycaemia (see below).
- » Check mother able to successfully establish breastfeeding in the small neonate and check health and weight gain more frequently.

MEDICINE TREATMENT

If grunting or severe chest indrawing

P22.0-1/P22.8-9

- Oxygen, using nasal catheter at 1 L/minute.

If infection is suspected and jaundice has been excluded

Z29.2

- Ceftriaxone, IM, 80 mg/kg/dose immediately as a **single dose**.
  - Administer into the lateral thigh.
  - Do not inject more than 1 g at one injection site.

CAUTION: USE OF CEFTRIAXONE IN NEONATES AND CHILDREN

- » If SUSPECTING SERIOUS BACTERIAL INFECTION in neonate, give ceftriaxone, even if jaundiced.
- » Avoid giving calcium-containing IV fluids (e.g. Ringer Lactate) together with ceftriaxone:
  - If ≤ 28 days old, avoid calcium-containing IV fluids for 48 hours after ceftriaxone administered.

- If > 28 days old, ceftriaxone and calcium-containing IV fluids may be given sequentially provided the giving set is flushed thoroughly with sodium chloride 0.9% before and after.
- Preferably administer IV fluids without calcium contents.

» Always include the dose and route of administration of ceftriaxone in the referral letter.

If blood glucose < 2.6 mmol/L and baby able to suckle or take orally:

» Breastfeed or give expressed breastmilk (only if breastfeeding is not possible, give replacement milk feed 10 mL/kg)

» If unable to take orally consider nasogastric tube feeding. Check blood glucose concentration again after 15 minutes. If normal, feed 2-3 hourly. If still < 2.6 mmol/L, manage as below.

If blood glucose < 1.4 mmol/L or remains < 2.6 mmol/L after an oral feed:

- Dextrose 10%, IV, 2 mL/kg as a bolus.

AND

- Dextrose 10%, IV, 3 mL/kg/hour. *LoE:IVb*[38]
  - Repeat in 15 minutes.
  - If blood glucose still low, repeat dextrose bolus.

REFERRAL

Urgent

» All neonates with a possible serious bacterial infection.

» All neonates with jaundice on the first day of life, with pallor or with poor feeding.

» All other neonates with increasing, deep or persistent (> 10 days) jaundice should be referred as soon as possible.

» All small neonates (< 2.5 kg) not able to feed.

» Persistent hypoglycaemia despite treatment.

(If possible, always send mother with the neonate as well as any clinical notes).

6.6.4 CARE OF THE HIV-EXPOSED INFANT

See Section 11.5: The HIV-exposed infant.

6.6.5 PERINATAL TRANSMISSION OF HEPATITIS B

P00.2

DESCRIPTION

Babies born to mothers with acute hepatitis B infection at the time of delivery or to mothers who are HBsAg-positive or HBeAg-positive.

MEDICINE TREATMENT

- Hepatitis B immunoglobulin, IM, 0.5 mL within 12 hours of delivery. *LoE:IVb*[39]

AND

- Hepatitis B vaccine, IM, 0.5 mL, first dose within 12 hours of delivery. *LoE:IVb*[40]
  - Continue hepatitis B immunisation according to the recommended immunisation schedule.

» Check the baby's hepatitis B surface antigen (HBsAg) and hepatitis B surface antibody (HBsAb) at 9 months:
  - If HBsAg positive: baby has hepatitis B infection – refer.
  - If HBsAg negative and HBsAb negative: repeat vaccination with hepatitis B containing vaccine, with a repeat dose in 1 month. Repeat HBsAb one month after the second dose; if still HBsAb negative then refer.
  - If HBsAb positive: baby is immune to hepatitis B. Reassure parents, no further testing required.

Note: Do not check hepatitis B serology before 9 months of age as antibodies from the birth dose of immunoglobulin might still be present. Refer if hepatitis B serology is not available.

6.7 POSTPARTUM CARE

6.7.1 POSTPARTUM HAEMORRHAGE (PPH)

O72.0-3

DESCRIPTION

Primary postpartum haemorrhage (PPH) is blood loss >500 mL that occurs within 24 hours of birth.
Secondary PPH occurs 24 hours to 12 weeks after delivery (late or delayed PPH).
The most common cause of primary PPH is an atonic uterus.

GENERAL MEASURES

» Massage fundus and expel clots from vagina.
» Empty the bladder.
» Two intravenous lines (wide bore if possible).
» Bimanually compress the uterus to stop the bleeding.
» If no response to medicine treatment, insert a condom catheter (an open condom slipped over a large Foley's catheter and secured at its base with string to provide a makeshift balloon catheter) into uterus, inflate with 400-500mL of saline and clamp. Pack vagina with swabs to prevent expulsion and refer urgently.

MEDICINE TREATMENT

Replace fluids:

- Sodium chloride 0.9%, IV, infused as fast as possible in one IV line.

AND

- Oxytocin, IV 20 units in 1 000 mL sodium chloride 0.9% infused at 250 mL/hour in 2nd IV line. *LoE:IIb*[41]

<u>If no response:</u>

- Ergometrine, IM, 0.5 mg. *LoE:IVb*

OR

- Oxytocin/ergometrine, IM, 5 units/0.5 mg.
  - Avoid ergometrine in hypertensive women and those with heart disease, unless haemorrhage is life threatening (woman haemodynamically unstable).

- Repeat after 10–15 minutes if no response to 1st dose, while arranging referral.

Only in settings where oxytocin is not available:

- Misoprostol, sublingual/rectal, 600 mcg as a single dose. *LoE:IIa*[42]

REFERRAL

All cases.

6.7.2 PUERPERAL SEPSIS

O85/O86.0-4/O86.8

DESCRIPTION

Clinical features include a temperature ≥ 38°C (usually ≥ 2 days after delivery), often accompanied by offensive vaginal discharge (lochia) and/or abdominal pain within the first 10 days postpartum. In post caesarean section (CS) cases, there may additionally be tenderness around the CS wound and offensive discharge from the wound.

GENERAL MEASURES

» Monitor vital parameters, e.g. Hb, pulse, BP, temperature.
» Treat for shock if indicated.

MEDICINE TREATMENT

- Ceftriaxone, IV, 1 g as a single dose.

CAUTION: USE OF CEFTRIAXONE

Do not administer calcium-containing fluids, e.g. Ringer-Lactate, concurrently with ceftriaxone.

AND

- Metronidazole, oral, 400 mg as a single dose.

REFERRAL

All cases.

6.7.3 CRACKED NIPPLES DURING BREASTFEEDING

O92.1

DESCRIPTION

The areola and nipple are protected by the secretion of a lubricant from Montgomery's glands. Cracked nipples may lead to infection and mastitis.

Causes of cracked nipples include:

» poor positioning of the baby and incorrect attachment to the breast
» removing the baby from the breast before suction is broken
» the four signs of good attachment are:
  - chin touching breast (or very close)
  - mouth wide open
  - lower lip turned outward
  - more areola visible above than below the mouth

GENERAL MEASURES
» Apply expressed breast milk to the nipples between feeds and air dry.
» If too painful, express the milk and nurse the baby on the other breast until improvement.
» Keep areola and nipple clean and dry.
» Avoid use of soap, creams and lotions on the nipples.

MEDICINE TREATMENT
- Zinc and castor oil ointment.
  - Apply between feeds.

If oral thrush is present, treat neonate with:
- Nystatin solution, oral. See Section 1.2: Candidiasis, oral (thrush).

REFERRAL
No improvement after 2 days.

6.7.4 MASTITIS
O91.2

DESCRIPTION
Inflammation of the breast tissue surrounding the milk ducts.
Risk factor includes retrograde infection from a fissured nipple and milk stasis. Commonly isolated pathogens include S. aureus and S. epidermidis. Presentation includes painful breast(s), fever, erythema and malaise.

GENERAL MEASURES
Compresses.
Regular expressing of breast milk.
Do not stop breastfeeding, unless a breast abscess has developed.
If breast abscess present, refer for incision and drainage.

MEDICINE TREATMENT
- Flucloxacillin, oral, 500 mg 6 hourly for 5 days.

<u>Severe penicillin allergy:</u>
Z88.0
Macrolide, e.g.:
- Azithromycin, oral, 500 mg daily for 3 days.

<u>Pain:</u>
- Paracetamol, oral, 1 g 4–6 hourly when required.
  - Maximum dose: 15 mg/kg/dose.
  - Maximum dose: 4g in 24 hours.

REFERRAL
» Breast abscess.
» No improvement after 2 days.

6.8 HIV IN PREGNANCY

O98.7

DESCRIPTION

HIV is currently the commonest cause of maternal deaths in South Africa. Transmission of HIV from mother to infant may occur during pregnancy, delivery and/or breastfeeding. Without intervention, 25–40% of infants born to HIV-infected women may become infected. With appropriate interventions, maternal mortality as well as perinatal transmission of HIV can be substantially reduced. 4% of women who were initially HIV-negative become positive later during pregnancy. Repeat HIV testing is essential.

For comprehensive information on the care of HIV-infected pregnant women refer to the current National Consolidated Guidelines for the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the management of HIV in Children, Adolescents and Adults as well as the current Guidelines for Maternity Care in South Africa. See Chapter 11: HIV and AIDS.

GENERAL MEASURES

HCT in all pregnant and breastfeeding women

» Provide routine counselling and voluntary HIV testing to all pregnant women (if HIV status is negative or unknown) at their very first antenatal visit, and treat other STIs if necessary.
» All women who test negative must be offered repeat HIV testing at every routine visit throughout pregnancy, at labour/delivery, at the 6-week EPI visit and 3 monthly throughout breastfeeding.
» Perform a TB symptom screen at each visit

Women who choose not to be tested

» Provide with individual 'post-refusal' counselling and offer HIV testing at every subsequent visit.
» Perform a TB symptom screen at each visit.
» Counsel on risks of MTCT to unborn baby, HIV risk reduction behaviour and offer HIV prevention services.

Pregnant women who test HIV positive

» Confirm result with a 2nd rapid HIV test of another type in compliance with current HCT policy.
» If results are discordant, repeat both first and confirmatory rapid HIV tests and if still discordant, send blood for a laboratory HIV ELISA.
  - All confirmed HIV-infected women must be fast-tracked for ART regardless of CD4 count.
» Perform clinical staging and TB symptom screen, and take a blood sample for CD4 cell count and creatinine, on the day of testing. Obtain results within a week.
  - If CD4 < 100 cells/mm3, do a serum cryptococcal antigen (CrAg) test.
» Start ART on the day of diagnosis (unless there are symptoms of TB).
» Investigate all those with TB symptoms before ART initiation. If TB treatment is started, defer ART for 2 weeks.
» HIV-infected women (WLHIV) must return 1 week after their initial ANC visit to get their creatinine, and CD4 cell count results and be managed accordingly.

» Refer women with unwanted pregnancies < 20 weeks' gestation for termination of pregnancy (TOP) services.
» Perform a TB symptom screen at each visit

Pregnant women already known to be HIV-infected
» If not on ART, do clinical staging; take blood for CD4 count (to determine eligibility for cotrimoxazole prophylaxis) and creatinine. If CD4< 100 cells/mm3, do a serum cryptococcal antigen (CrAg) test.
  - Start ART the same day if no contraindication.
» If already on ART for > 3 months, take blood for viral load measurement irrespective of when it was last done.
» Perform a TB symptom screen at each visit

Antenatal support
» Counsel about the importance of adherence and virological suppression for PMTCT.
» Counsel on infant feeding, safer sex, family planning, postnatal contraception, partner testing, routine cervical cancer screening.
» Provide appropriate nutritional care and support including iron, folate and calcium supplementation and Hb testing.

Postpartum support
» Provide adequate support and counselling, particularly addressing ART adherence during breastfeeding.
» Educate mothers about the benefits of breastfeeding. Only in circumstance where the mother has confirmed 2nd or 3rd line ART regimen failure, advise not to breastfeed and prescribe replacement feeds.
» Refer mother to appropriate services to continue lifelong ART as part of the general adult ART population.

MEDICINE TREATMENT

Opportunistic infection treatment and prophylaxis for HIV-infected pregnant women:

Pregnant women diagnosed with pulmonary TB:
» First line TB treatment is safe and effective in pregnant women.
» See Section 17.4.1: Pulmonary tuberculosis (TB) in adults.

Pregnant women on ART with no symptoms of TB:
» See Section 11.2.2: Tuberculosis preventive therapy (TPT).

Women with CD4 ≤ 200 cells/mm3 or WHO clinical stage 2, 3 or 4:
- Cotrimoxazole, oral, 160/800 mg daily, until CD4 > 200 cells/mm3.

If CrAg-positive, consult an infectious disease expert, and refer.
See Section 11.3.4: Cryptococcosis.
Note: All CrAg positive women need a LP, unless contra-indicated, regardless of symptoms.

CAUTION

» Although fluconazole should be avoided in the 1st trimester, pregnant women should be counselled that the benefits of fluconazole outweigh the risks in the management of cryptococcosis.

» All pregnant women <20 weeks gestation exposed to fluconazole should have an ultrasound scan to detect congenital abnormalities. *LoE:IIIb*[43]

» Fluconazole is present at concentrations similar to maternal plasma concentrations in breast milk. *LoE:IVb*[44]

FIRST-LINE ART REGIMENS *(Also see Section 11.1 Antiretroviral therapy)*		
1ST ANC VISIT		
Pregnant women	• Tenofovir, oral 300 mg daily **AND** • Lamivudine, oral, 300 mg daily **AND** • Dolutegravir, oral, 50 mg daily **Note:** Provide as a fixed dose combination (FDC) *LoE:IIa*[45]	» Contraindication to TDF: renal insufficiency, other nephrotoxic medicines e.g. aminoglycosides.
If renal insufficiency or other nephrotoxic medicines e.g. aminoglycosides (TDF may be contraindicated)	Start alternative regimen (Doctor consult): • Abacavir, oral, 600 mg, daily **AND** • Lamivudine, oral, 300 mg, daily **AND** • Dolutegravir, oral, 50 mg daily *LoE:IIIb*[46]	
Pregnant women currently on ART	• Continue current ART regimen.	» Do a VL as soon as pregnancy is confirmed.
Pregnant women not currently on ART but ART exposed (previous PMTCT or ART loss to follow-up)	<u>If previous VL (while on ART) < 50 c/mL:</u> • Tenofovir, oral, 300 mg daily **AND** • Lamivudine, oral, 300 mg daily **AND** • Dolutegravir, oral, 50 mg daily **Note:** Provide as a fixed dose combination (FDC) <u>If previous VL (while on ART) > 50 c/mL, or no VL result available:</u> Switch/ continue current regimen whilst investigating and managing cause of elevated VL: • Tenofovir, oral, 300 mg daily **AND** • Lamivudine, oral, 300 mg daily **AND**	*LoE:IIIb*[48] » Resistance testing for WLHIV failing a DTG-based regimen and who meet the definition of confirmed virological failure may be authorized by an expert on a case-by-case basis.

	• Dolutegravir, oral, 50 mg daily **DTG- based 1st line regimen failure for >2 years:** • Tenofovir, oral, 300 mg daily. **AND** • Emtricitabine, oral, 200 mg daily **AND** • Atazanavir/ritonavir, oral, 300/100 mg daily If HBsAg positive: ensure patient is on TDF-containing regimen. *LoE:IIb*[47]	
2ND ANC VISIT (1 WEEK LATER)		
Creatinine ≤ 85 mmol/L	• Continue FDC: TDF+3TC+DTG	
Creatinine > 85 mmol/L (TDF is contra-indicated)	• Stop tenofovir Start alternative regimen (Doctor consult): • Abacavir, oral, 600 mg, daily **AND** • Lamivudine, oral, 300 mg, daily **AND** • Dolutegravir, oral, 50 mg daily *LoE:IIIb*[49]	» High-risk pregnancy: change to alternate triple therapy within 2 weeks (doctor consult) **and refer for renal dysfunction investigation**.
VL < 50 c/mL (Pregnant women currently on ART)	If still on EFV-based ART, offer switch to: • Tenofovir, oral, 300 mg daily **AND** • Lamivudine, oral, 300 mg daily **AND** • Dolutegravir, oral, 50 mg daily	
VL ≥ 50 c/mL (Pregnant women currently on ART)	Continue current regimen whilst investigating and managing cause of elevated VL. Determine if the client should switch to 2nd line.	» Doctor/ expert consult or refer for expert advice. » Pregnant women with confirmed 2nd or 3rd line ART regimen failures should not breastfeed their infants, if they can safely formula feed.
WOMEN DIAGNOSED HIV POSITIVE IN LABOUR		
All unbooked women who test positive during labour should be given prophylactic ART during labour and initiated on lifelong ART before being discharged.	• Nevirapine, oral, 200 mg single dose as early as possible in labour. **AND** • Tenofovir, oral, 300 mg daily **AND** • Lamivudine, oral, 300 mg daily **AND** • Dolutegravir, oral, 50 mg daily	Before discharge: Start lifelong ART the day after delivery, if there are no contraindications, regardless of CD4: • TDF+3TC+DTG as a FDC

	Note: Provide TDF + 3TC + DTG as a FDC	
POST-DELIVERY		
The mother should start ART within 24 hours of delivery to protect the baby during breastfeeding.	Start lifelong ART regardless of CD4: TDF+3TC+DTG as a FDC	
BABY		
See Section 11.5: The HIV-exposed infant to decide whether infant is low risk or high risk and what HIV prophylactic management is needed.		

LoE:IIIb[50]

Note:

» eGFR and creatinine clearance are not reliable for diagnosing renal impairment in pregnancy.
» Monitor response to ART within 3 months of ART initiation with a plasma VL. If VL is not suppressed, refer or consult for expert advice.

Viral load monitoring for 1st line regimen in pregnant and breastfeeding women:
Newly diagnosed and initiated ART for the first time:

» Do 1st VL at 3 months on ART.
» If VL < 50 c/mL, repeat VL at delivery.

Known HIV-positive women already on ART:

» Measure VL at first/booking visit in ANC,
» If VL < 50 c/mL, repeat VL at delivery. *LoE:IIIb*[51]

Known HIV-positive women, who are not currently on ART, but are ART exposed (e.g. previous PMTCT, or ART loss to follow-up) and who are initiating a DTG-containing regimen:

» Do 1st VL at 3 months on ART.
» If VL < 50 c/mL, repeat VL at delivery.

REFERRAL

» Refer mothers suspected of non-adherence early.

Urgent

» Creatinine > 85 mmol/L.
» ALT > 100 IU/L.
» Pregnant women who are CrAg+, and
  - LP cannot be performed, or
  - symptomatic (headache, confusion), or
  - asymptomatic, but in the 1st trimester.

6.9 MATERNAL MENTAL HEALTH

In vulnerable women, pregnancy exacerbates the risk of developing a mental illness. Approximately one in three women in South Africa have depression and/or anxiety in the perinatal period. Globally, postpartum psychosis affects 1 to 2 women in every 1000 after childbirth .

Risk factors for maternal mental illness include past history of mental illness, recent major life event, (e.g. bereavement) early childhood adversity/ abuse, domestic violence, a history of trauma, displacement from home of origin, low socio-economic status, food insecurity. Women who learn that they are HIV positive during pregnancy have a particular vulnerability to mental health conditions.

Untreated maternal mental illness is associated with the following:

» unplanned and unwanted pregnancy
» poor adherence to health advice; poor uptake of antenatal services
» tobacco, alcohol and other substance use
» self-harm and suicide
» relapse of the mental illness during the pregnancy or postpartum
» gestational hypertension and/or diabetes
» poor pregnancy outcomes, including preterm labour and low birth weight
» increased risk of neonatal morbidity and stillbirth in mothers with bipolar and psychotic disorders
» poor engagement with the infant
» poor family relationships; paternal mental health conditions
» behavioural and neurodevelopmental disorders in the offspring

Suspect maternal mental illness if:

» unreliable antenatal clinic attendance
» continued smoking and/or other substance use during pregnancy
» any odd or eccentric speech or behaviour
» screened positive using the 3-item tool in the Maternity Case Record

Pre-conception care:

» Identify at-risk women – any current or past symptoms of mental illness, emotional problems, substance use, poor social support, abusive relationships, recent trauma, socio-economic deprivation.
» Initiate management for mental disorders/ substance use/ psychosocial stress as needed.
» Use medicines which are safe in pregnancy, unless benefit outweighs risk and patient consents to use (if valproate use, sign acknowledgement of risk form https://www.sahpra.org.za/6-28_valproate_annual_risk_acknowledgement_form_dec18_v1/
» Discuss planning for pregnancy and initiate contraception according to individual choice.

6.9.1 PERINATAL DEPRESSION AND/OR ANXIETY

O28.8-9/ O90.9 + (F32.0-3/F32.8-9/ F33.0-4/F33.8-9/F34.1/F53.0-1/F53.8-9)

DESCRIPTION

See Sections 16.4.1: Depressive disorders and 16.3 Anxiety disorders, for symptoms of depression and/or anxiety. Note that these conditions may occur together in the same person.

» Depression and /or anxiety may be antenatal or postpartum. Postpartum depression usually begins within a month of delivery but can present up to a year after delivery.
» Anxiety disorders may present as fear of labour and childbirth, or other fears e.g. needle phobia. Such fears may interfere with antenatal and postnatal care if they are not addressed.
» Postpartum blues last less than a week, are characterised by irritability, tearfulness, anxiety beginning by day 3-5 postpartum. Usually resolve with gentle support but may progress to depression.

CAUTION: Suicide

» Highest risk period is from 6 weeks before to 12 weeks after delivery.
» Adolescent mothers are at particular risk.
» Those with a prior history of self-harm at particular risk.
» See PHC STGs and EML, 2018 – section 16.7: Suicide risk assessment.
» Inform all healthcare providers involved of suicide risk.
» Ensure psychosocial support – partner/ family/ NGO/ welfare support.
» Optimise treatment of mental illness.
» Do not leave unattended if high risk of self-harm.

GENERAL MEASURES

Antenatal

» Don't stop psychiatric medication if stable on treatment: assess course of illness, severity, and suicide risk. Refer if any or increasing signs of severity.
» Discuss potential benefits/harms of medication to patient and baby as well as alternatives (see Adult Hospital Level STGs and EML, Sections 15.2: Anxiety and obsessive-compulsive disorders and 15.3.1: Depressive disorders).
» Antenatal care: provide active adherence support; provide regular, frequent CHW home visits; watch for preterm labour and/or SGA baby; follow-up on any up-referral.
» Explore and address psychosocial stressors: *LoE:IIIb*[52]
  - Mobilise patient's support system.
  - Stress management/coping skills – refer for counselling e.g. at www.sadag.org
  - Relationship and family issues – refer for counselling, e.g. at www.famsa.org.za
  - Abuse or interpersonal violence - refer to a social worker and for support, e.g. by www.genderjustice.org.za or www.powa.co.za

Postnatal

» Continue close home-based support of mother and baby for at least the first year
» Encourage breastfeeding, if not contraindicated medically (Breastfeeding difficulties may also be associated with depression and anxiety).
» Optimise treatment of mental illness and co-morbid physical health conditions. *LoE:IIIb*[53]
» Optimise psychosocial and parenting support – utilise support groups e.g. at www.sadag.org Refer to Social Welfare if suspect child-care is seriously impaired.

MEDICINE TREATMENT

See Sections 16.4.1: Depressive disorders and 16.3: Anxiety disorders, for treatment of depression and/or anxiety.

» Mild to moderate anxiety – refer for psychotherapy if available (and/or psychosocial support from mothers' groups, NGOs, counsellors) and monitor response.
» Moderate – severe anxiety and/ or depression - antidepressant (SSRI) treatment for early symptom control and prevention of relapse is generally necessary.

REFERRAL

» All severe depression where functioning is severely impaired.
» Poor response to psychological and supportive medication.
» Poor response to first line SSRI (antidepressant) medication.
» Factors requiring urgent admission, invoke the MHCA if necessary:
  - Suicide risk
  - Any possible psychotic features
  - Risk to infant

6.9.2 BIPOLAR, SCHIZOPHRENIA, AND RELATED DISORDERS

O28.8-9/ O90.9 + (F28/F29/F53.0-1/F53.8-9)

DESCRIPTION

Bipolar disorders (BD):

See Adult Hospital STG Sections 15.3.2: Bipolar and related disorders for description and management in the perinatal period.

Note that:

» BD may present with antenatal or postnatal depression, hypomania, mania or psychosis.
» the index episode often occurs postpartum – may be no prior history of mental illness.
» risk of relapse in those known to have BD is increased in pregnancy and postpartum.
» women with bipolar disorder have a 1 in 4 chance of postpartum psychosis.
» BD is associated with increased risk of pre-eclampsia, placental abnormalities, preterm delivery, LBW and SGA babies, neonatal morbidity, and maternal suicide.

Schizophrenia and related disorders:

See PHC STG Section 16.5: Psychosis and Adult Hospital STG Section 15.5: Psychotic disorders for description and management.

Note that:

» Psychotic disorders are associated with poor pregnancy outcomes as with BD plus increased risk of diabetes, stillbirth, sudden infant death syndrome.
» The rate of deterioration from a non-psychotic to psychotic state may be more rapid in the postpartum period than usual. Take any reports of unusual behaviour by family members as serious and urgent.

CAUTION: Psychosis

» Is a medical emergency; requires urgent hospitalisation.
» Always exclude delirium due to puerperal sepsis.
» May present with subtle, odd behaviour and/or thoughts; women may be blunted, withdrawn, agitated, or aggressive.
» High risk for harm to self or others, suicide, infanticide.
» May severely impair mother-infant bonding and child-care.
» Manage aggressive or disruptive behaviour (See Section 16.1.2: Aggressive disruptive behaviour in adults).

GENERAL MEASURES

» Manage all pregnancies as high-risk in conjunction with obstetrician and psychiatrist.
» Don't stop psychiatric medication – discuss with doctor/ psychiatrist.
» Actively monitor adherence to antenatal care and hospital referrals.
» Provide regular, frequent CHW home visits.
» Arrange for hospital delivery.
» Postpartum – keep in hospital, monitor mother and new-born, and ensure home-based care and outpatient follow-up before discharge

Factors requiring urgent admission, invoke the MHCA if necessary:

» Suicide risk.
» Any possible psychotic features.
» Risk to infant.

REFERRAL

All patients.

GYNAECOLOGY

6.10 ECTOPIC PREGNANCY

O00.0-2/O00.8-9

DESCRIPTION

Pregnancy outside the uterus, usually presenting with the combination of:

» amenorrhoea (missed menstrual period)
» sudden lower abdominal pain/ pelvic pain
» vaginal bleeding (os closed)
» dizziness
» shock
» anaemia
» urine pregnancy test usually positive
» shoulder tip pain

Note: Consider ectopic pregnancy in young women who complain of lower abdominal pain.

GENERAL MEASURES

» Monitor vital parameters, e.g. Hb, pulse, BP, temperature.
» Treat for shock if indicated.

MEDICINE TREATMENT

- Sodium chloride 0.9%, IV.

REFERRAL

Urgent

All suspected cases of ectopic pregnancy.

6.11 VAGINAL BLEEDING

Note: Women should receive regular screening for cervical cancer after the age of 30 years. Any opportunity to perform screening should be taken; this includes taking pap smears during pregnancy.

6.11.1 ABNORMAL VAGINAL BLEEDING DURING REPRODUCTIVE YEARS

N92.0-2/3-6

DESCRIPTION

Increased vaginal blood flow in either volume, duration, and/or frequency, including menorrhagia or dysfunctional uterine bleeding.

GENERAL MEASURES

» Assess current contraceptives used.
» Exclude pregnancy complication or organic disease e.g. cervical cancer, fibroids.

MEDICINE TREATMENT

- Combined oral contraceptive pill (ethinylestradiol/levonorgestrel) for 3–6 months.
- Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for 2–3 days.
  - Ibuprofen may reduce blood loss in menorrhagia associated with intrauterine contraceptive device (IUCD) or chronic salpingitis (See Chapter 12: Sexually transmitted infections).

If blood loss has been severe or there are signs of anaemia:

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

OR

- Ferrous fumarate, oral, 200 mg (± 65 mg elemental iron) 12 hourly.

  - Continue for 3 months after Hb normalises - to replenish body iron stores.
  - Taking iron tablets with meals decreases iron absorption, but improves tolerability (**Note:** Do not take iron tablets with milk).

LoE:IIb[54]

REFERRAL

» No improvement.
» Girls < 12 years of age with vaginal bleeding before the development of their secondary sexual characteristics.
» For investigation of other causes such as:
  - sexual abuse
  - foreign bodies
  - tumours of the genital tract
» Severe anaemia.

6.11.2 POST-MENOPAUSAL BLEEDING

N95.0

DESCRIPTION

Vaginal bleeding six months following the complete cessation of menstruation.
Note: If bleeding is profuse, stabilise before referral.

REFERRAL

All cases, to exclude underlying malignancy and other pathology.

6.12 DYSMENORRHOEA

N94.4-6

DESCRIPTION

Pain associated with menstrual cycles. In primary dysmenorrhoea there is no known cause. Secondary dysmenorrhoea usually has an organic cause.

GENERAL MEASURES

» Advise and reassure women with primary dysmenorrhoea about the nature of the condition.

» Encourage patient to carry on with normal everyday activities.

MEDICINE TREATMENT

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal as needed for 2–3 days.

ADD

- Combined oral contraceptive pill, if symptoms still problematic, and if pregnancy is not planned.

Treat for pelvic infection when present.

REFERRAL

» Poor response to treatment.
» If an organic cause is suspected, e.g. fibroids.

6.13 HORMONE THERAPY (HT)

N95.1-2/N95.8-9

Indications:

Short-term symptomatic relief for severe menopausal symptoms.
For menopausal women, treatment should be ≤ 5 years.
Risk-benefit assessment should be individualised in all patients.

Contra-indications include:

» Known or suspected estrogen-dependent malignant tumours (such as endometrial cancer).
» Coronary heart disease.
» Active liver disease.
» Women ≥ 60 years of age.
» Current, past or suspected breast cancer.
» Thrombophilia.
» Undiagnosed genital bleeding.
» Previous idiopathic or current venous thromboembolism.
» Untreated endometrial hyperplasia.
» Porphyria cutanea tarda.

GENERAL MEASURES

Prior to starting HT:

» Do breast and gynaecological examination.
» Cervical screening.

MEDICINE TREATMENT (Doctor initiated)

Uterus present (no hysterectomy)

HT can be offered as sequentially opposed or continuous combined preparations. Continuous combined preparations are often preferred if the woman had her last menstrual period (menopause) over a year ago, as they will not usually cause bleeding then. For women who are still menstruating or have recently stopped, sequentially opposed preparations are preferred and will result in regular menstrual periods, whereas continuous combined may result in irregular bleeding.

CONTINUOUS COMBINED THERAPY
• Estradiol/norethisterone acetate, oral, 1mg/0.5mg for 28 days.
OR
• Estradiol/norethisterone acetate, oral, 2mg/1mg for 28 days.
OR
• Conjugated estrogens, oral, 0.3–0.625 mg for 28 days. **AND** • Medroxyprogesterone acetate, oral, 2.5–5mg daily for 28 days.

OR

SEQUENTIALLY OPPOSED THERAPY
• Estradiol valerate/cyproterone acetate, oral: • Estradiol valerate, oral, 2 mg for 11 days. • Estradiol valerate/cyproterone acetate, oral, 2mg/1mg for 10 days. • Placebo, oral, for 7 days.
OR
• Estradiol valerate, oral, 1–2 mg daily for 21 days. **ADD** • Medroxyprogesterone acetate, oral, 5 -10 mg daily from day 12–21. Followed by no therapy from day 22–28.
OR
• Conjugated estrogens, oral, 0.3–0.625 mg daily for 21 days. **ADD** • Medroxyprogesterone acetate, oral, 5–10 mg daily from day 12–21. Followed by no therapy from day 22–28.

LoE:IVb[55]

Note: Where a dose range is provided start at the lowest possible dose to alleviate symptoms. The need to continue HT should be reviewed annually.

Women with no uterus (post-hysterectomy)

- HT is given as estrogen only, e.g.:
- Estradiol valerate, oral, 1–2 mg daily.

OR

- Conjugated estrogens, oral, 0.3 mg daily to a maximum of 1.25 mg daily.

REFERRAL

» Premature menopause, i.e. < 40 years of age.
» Severe osteoporosis
» Management difficulties, e.g. where oestrogen therapy is contra-indicated, poorly tolerated, or ineffective.
» Post-menopausal bleeding.
» If HT needed (symptoms persist) after 5 years of HT or woman ≥ 65 years.

6.14 VAGINAL ULCERS

See Section 12.5: Genital ulcer syndrome (GUS).

6.15 VAGINAL DISCHARGE/LOWER ABDOMINAL PAIN IN WOMEN

See Sections 12.1: Vaginal discharge syndrome (VDS) and 12.2: Lower abdominal pain (LAP).

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REPUBLIC OF SOUTH AFRICA

2030 NDP

SOUTH AFRICAN PRIMARY HEALTHCARE LEVEL ESSENTIAL MEDICINES LIST
CHAPTER 6: OBSTETRICS & GYNAECOLOGY
NEMLC RECOMMENDATIONS FOR MEDICINE AMENDMENTS (2020 -2023 REVIEW CYCLE)

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).
All reviews and costing reports may be accessed at: https://www.knowledgehub.org.za/content/standard-treatment-guidelines-and-essential-medicines-list
(Please note that section 6.8: HIV in pregnancy will be updated if required to align with the pending 2023 National HIV Guidelines).

MEDICINE AMENDMENTS:

SECTION	MEDICINE/MANAGEMENT	ADDED/DELETED/AMENDED
6.2 Miscarriage	Anti-D immunoglobulin, IM	Amended
6.2.1 Management of incomplete miscarriage in the 1st trimester, at primary health care level *- medical evacuation*	Misoprostol, SL/PV/buccal	Directions for use amended
	Ibuprofen, oral	Directions for use amended
	Pregnancy test	Added
	Paracervical block (lidocaine 1%)	Added
6.3 Termination of pregnancy (TOP) *- venue*	TOP criteria	Amended
6.3.1 Management of termination of pregnancy at primary health care level: gestation up to 12 weeks and 0 days	Mifepristone, oral	Directions for use not amended
	Misoprostol, SL	Directions for use amended
	Paracervical block (lidocaine 1%)	Added (doctor only)
	Ibuprofen, oral	Directions for use amended
6.4.1 Antenatal supplements	Iron, oral	Not amended
	Calcium, oral	Not amended
6.4.2 Hypertensive disorders in pregnancy	Categories of gestational hypertension	Amended
6.4.2.1 Chronic hypertension	Methyldopa, oral	Dose and directions for use not amended
6.4.2.5 Eclampsia	Labetalol, IV	Not added
6.4.4 Syphilis in pregnancy	Lidocaine 1%, parenteral	Not amended
6.4.7.1 Preterm labour (PTL) *and* **6.4.7.2 Preterm pre-labour rupture of membranes (PPROM)**	Betamethasone, parenteral	Dosing amended
6.4.7.2 Preterm prelabour rupture of membranes (PPROM) *- Antibiotic therapy*	Ampicillin, IV	Added
	Amoxicillin, oral	Retained
	Metronidazole, oral	Deleted
	Aztihromycin, oral	Added
- Severe penicillin allergy	Metronidazole, oral	Deleted
	Aztihromycin, oral	Dose amended
	Clindamycin, oral	Not added
6.4.7.3 Prelabour rupture of membranes at term (PROM): *>12 hours*	Antibiotic prophylaxis	Retained
6.5 Intrapartum care	Morphine, parenteral	Retained
	Pethidine, parenteral	Not added
	Anti-D immunoglobulin	Directions for use amended
6.6.2 Neonatal resuscitation	Naloxone, IV	Retained
	Resuscitation algorithm	Amended
6.7.1 Postpartum haemorrhage (PPH)	Tranexamic acid, parenteral	Not added
6.8 HIV in pregnancy	Tenofovir + lamivudine + dolutegravir, oral	Indication amended
	HIV testing	Amended
- DTG- based 1st line regimen failure for >2 years	Tenofovir+emtricitabine+ atazanavir/ ritonavir, oral	Added
- CrAg positive	Lumbar puncture	Added
6.13 Hormone therapy	Mammogram	Deleted
	Transdermal hormone therapy patches	Not added to the STG, but added to the therapeutic interchange database

6.2 MISCARRIAGE

Anti-D immunoglobulin, IM: *amended*

Local resource constraints of Anti-D immunoglobulin warrants restricted use of Anti-D immunoglobulin, from "*all Rh-negative women who had a surgical procedure*" to "*only in Rh-negative, non-sensitised women who had surgical procedure for miscarriage*".

The STG was amended as follows:

~~For all miscarriages in Rh-negative, non-sensitised women:~~

For all Rh-negative non-sensitised women, who had a surgical procedure to manage a miscarriage:

- Anti-D immunoglobulin, IM, 50 mcg preferably within 72 hours but may be given up to 7 days following management of miscarriage.

~~Omit anti-D in the first trimester when there are supply constraints~~

Do not offer Anti-D prophylaxis to women who:

» only received medical management for a miscarriage or
» had a threatened miscarriage or
» had a complete miscarriage.

Level of Evidence: Low certainty evidence[1,2], Guidelines[3]

6.2.1 MANAGEMENT OF INCOMPLETE MISCARRIAGE IN THE 1ST TRIMESTER, AT PRIMARY HEALTH CARE LEVEL

Medical evacuation

Misoprostol, SL/PV/buccal: *directions for use amended*

The STG text was amended to align with NICE[4] and WHO[5] guidelines as follows:

- ~~Misoprostol, PV, 800 mcg every 3 hours for 2 doses.~~
  - ~~Repeat after 24 hours if necessary.~~

~~**OR**~~

- ~~Misoprostol, SL, 600 mcg every 3 hours for 2 doses~~
  - ~~Repeat after 24 hours if necessary~~
- Misoprostol, SL/PV/buccal, 800 mcg immediately as a single dose.
  - Repeat after 24 hours if necessary.

Level of Evidence: Low certainty evidence

Ibuprofen, oral: *directions for use amended*

The STG text was aligned with narrative within this chapter, noting harms associated with routine use of ibuprofen:

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, as needed for 2-3 days.

Pregnancy test: *added*

Pregnancy test as follow up management was added, aligned with NICE guidance.[6]A 3-week period before testing is recommended to minimise false-positives (bHCG 25miu/ml is the cut-off for a positive pregnancy test).[7] Women with a positive pregnancy test to be referred, accordingly.

Perform a pregnancy test three weeks after medical management

Level of Evidence: Low certainty evidence

6.2.1 MANAGEMENT OF INCOMPLETE MISCARRIAGE IN THE 1ST TRIMESTER, AT PRIMARY HEALTH CARE LEVEL *and*

[1] Karanth L, Jaafar SH, Kanagasabai S, Nair NS, Barua A. Anti-D administration after spontaneous miscarriage for preventing Rhesus alloimmunisation. Cochrane Database Syst Rev. 2013 Mar 28;(3):CD009617. https://pubmed.ncbi.nlm.nih.gov/23543581/

[2] Hamel C, Esmaeilisaraji L, Thuku M, Michaud A, Sikora L, Fung-Kee-Fung K. Antenatal and postpartum prevention of Rh alloimmunization: A systematic review and GRADE analysis. PLoS One. 2020;15(9):e0238844.

[3] Schmidt-Hansen M, Lord J, Hawkins J, Cameron S, Pandey A, Hasler E, et al. Anti-D prophylaxis for rhesus D (RhD)-negative women having an abortion of a pregnancy up to 13+6 weeks' gestation: a systematic review and new NICE consensus guidelines. BMJ Sex Reprod Health. 2020 Jan 20;bmjsrh-2019-200536.

[4] NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

[5] WHO. Guideline: Medical management of abortion, 2018. https://www.who.int/reproductivehealth/publications/medical-management-abortion/en/

[6] Medical abortion (follow-up pregnancy test): NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

[7] Barnhart K, Sammel MD, Chung K, Zhou L, Hummel AC, Guo W. Decline of serum human chorionic gonadotropin and spontaneous complete abortion: defining the normal curve. Obstet Gynecol. 2004 Nov;104(5 Pt 1):975–81. https://pubmed.ncbi.nlm.nih.gov/15516387/

6.3.1 MANAGEMENT OF TERMINATION OF PREGNANCY AT PRIMARY HEALTH CARE LEVEL: GESTATION UP TO 12 WEEKS AND 0 DAYS

Paracervical block (lidocaine 1%): *added*

Guidance was added for paracervical block with lidocaine 1%, parenteral with a cross-reference to the Adult Hospital Level STGs and EML, section 5.9.1: TOP: management of pregnancies ≤14 weeks of gestation, where detailed information is provided on directions for use.

The South African Nursing Council (SANC) *"maintains that Paracervical block is an invasive procedure which is outside the current Scope of Practice of Registered Nurses and Midwives. For this reason, training of nurses to perform such a procedure is not supported by SANC"*[8], and thus guidance for paracervical block has been included as "doctor only".

6.3 TERMINATION OF PREGNANCY (TOP)

Venue

TOP criteria: *amended*

The Choice on Termination of Pregnancy Act, 1996 (as amended by Act 38 of 2004), provides expanded access to abortions; allows registered nurses, as well as registered midwives, to perform abortions up to the twelfth week of pregnancy. The following additional STG text was added:

~~An accredited facility with staff trained in performing TOP, designated by the Member of Executive Council at provincial level.~~ Any facility that has a 24-hour maternity service can provide TOP service without specific designation - *The Choice on Termination of Pregnancy Act, 1996 (as amended by Act 38 of 2004), expanded access to abortions, allowed registered nurses, as well as registered midwives, to perform abortions up to the twelfth week of pregnancy.*

6.3.1 MANAGEMENT OF TERMINATION OF PREGNANCY AT PRIMARY HEALTH CARE LEVEL: GESTATION UP TO 12 WEEKS AND 0 DAYS

Medical TOP

Mifepristone, oral: *directions for use not amended*

Timing of administration of misoprostol, following mifepristone is recommended by RCOG Best Practice guide[9] as 24-48 hours; whilst NICE guidelines[10] recommends 36-48 hours (and a shorter time interval, based on women's preference). However, for pragmatic purposes 24-48 hours was retained.

Level of Evidence: Low certainty evidence

Misoprostol, SL: *directions for use amended*

The RCOG Best Practice guide[11] recommends that > 14 weeks medical TOP should be performed in a facility, but it can be presumed that in South Africa it may be unsafe to abort 9-12 weeks at home or en-route to a hospital. Therefore, the STG text was amended to include the additional pragmatic guidance:

- Misoprostol, SL, 800 mcg by self-administration at home*.
  - If expulsion does not occur within 4 hours of misoprostol administration, a second dose of misoprostol 400 mcg, oral/PV may be given.
  - *From >9 weeks to ≤ 12 weeks - return to the facility within 48 hours to take misoprostol on-site (early morning) due to the risk of heavy bleeding.

Level of Evidence: Low certainty evidence

Pain

Ibuprofen, oral: *directions for use amended*

The STG text was aligned with narrative within this chapter, noting harms associated with routine use of ibuprofen:

[8] The SANC Circular 8/2019: https://www.sanc.co.za/2019/11/26/circular-30-84-2/

[9] Royal College of Obstetrics and Gynaecology Guidelines. The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No. 7), 2011. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/the-care-of-women-requesting-induced-abortion/

[10] Medical abortion (follow-up pregnancy test): NICE. Guideline: Abortion Care, 25 September 2019. https://www.nice.org.uk/guidance/ng140

[11] Royal College of Obstetrics and Gynaecology Guidelines. The Care of Women Requesting Induced Abortion (Evidence-based Clinical Guideline No. 7), 2011. https://www.rcog.org.uk/en/guidelines-research-services/guidelines/the-care-of-women-requesting-induced-abortion/

- Ibuprofen, oral, 400 mg 8 hourly with or after a meal, as needed for 2-3 days.

6.4.1 ANTENATAL SUPPLEMENTS

Iron, oral: *not amended*

The STG currently provides guidance for dosing of oral iron in those with poor tolerance, supported by previously reviewed evidence.[12] [13]

Calcium, oral: *not amended*

Dosing for calcium was not amended. WHO guidance[14] recommends 1.5 - 2g in divided doses. The recent International Society for the Study of Hypertension in Pregnancy (ISSHP)[15] recommends 'at least 500g per day', assessed as 'weak evidence'. Authors of an updated Cochrane review[16] concluded, "*High-dose calcium supplementation (≥ 1 g/day) may reduce the risk of pre-eclampsia and preterm birth*", and that, "*The limited evidence on low-dose calcium supplementation suggests a reduction in pre-eclampsia, hypertension and admission to neonatal high care, but needs to be confirmed by larger, high-quality trials*".

Level of Evidence: Low certainty evidence

6.4.2 HYPERTENSIVE DISORDERS IN PREGNANCY

Categories of gestational hypertension: *amended*

Aligned with the Adult Hospital Level STGs and EML, 2019; Section 6.4: Hypertensive disorders in pregnancy.

STG text was amended from:

~~LEVELS OF SEVERITY OF HYPERTENSION~~

~~Level of hypertension~~	~~BP Level mmHg~~		
	~~Systolic~~		~~Diastolic~~
~~mild~~	~~140–149~~	~~or~~	~~90–99~~
~~moderate~~	~~150–159~~	~~or~~	~~100–109~~
~~severe~~	~~≥160~~	~~or~~	~~≥ 110~~

To:

Categorising hypertensive disease:

» A diastolic BP of 90-109 mmHg and/or systolic BP of 140-159 mmHg; but with **NO** symptoms or organ dysfunction is classified as hypertensive disease without severe features.

» Maternal features of severe hypertensive disease are any or more of the following:

- Acute severe hypertension (diastolic BP of 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 µl and LDH >600 µl).
- Serum creatinine ≥120 micromol/L.
- Pulmonary oedema.
- New-onset severe headache unresponsive to medication.
- Visual disturbances.

6.4.2.1 CHRONIC HYPERTENSION

Methyldopa, oral: *dose not amended*

[12] Ferrous (Iron) supplements, oral - intermittent dosing: National Department of Health: Affordable Medicines, EDP-Primary Health Care level. Medicine Review: Intermittent iron supplementation in pregnancy, 6 November 2017. https://www.knowledgehub.org.za/e-library

[13] Ferrous (Iron) supplements, oral - intermittent dosing: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

[14] WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia, 2011. http://www.who.int/reproductivehealth/publications/maternal_perinatal_health/9789241548335/en/

[15] 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 Hypertesion in Pregnancy Classification, Diagnosis & Management Recommendations for International Practice, Pregnancy Hypertension: An International Journal of Women's Cardiovascular Health (2021), doi: https://doi.org/10.1016/j.preghy.2021.09.008

[16] Hofmeyr GJ, Lawrie TA, Atallah ÁN, Torloni MR. Calcium supplementation during pregnancy for preventing hypertensive disorders and related problems. Cochrane Database Syst Rev. 2018 Oct 1;10(10):CD001059. https://pubmed.ncbi.nlm.nih.gov/30277579/

The dose of methyldopa for chronic gestational hypertension was not amended, as this is aligned to the Adult Hospital Level STGs and EML, 2019 – refer to the extract from the NEMLC report for the Adult Hospital Level Obstetrics chapter (2017-19 review cycle), below:

Methyldopa, oral: dosing not amended
Query regarding the discrepancy between the NDoH Maternal Health Care Guidelines, 2012 and Adult Hospital Level STGs and EML, 2015 for methyldopa for management of hypertension in pregnancy, was received.
FIGO Guidelines: NDoH Maternal Care Guidelines aligned with International Federation of Gynecology and Obstetrics (FIGO) guidelines[17], recommending methyldopa 500 mg 8 hourly, oral.
Pharmacokinetic study: Adult Hospital STGs and EML, recommends, "Methyldopa, oral, 250 mg 8 hourly as a starting dose - increase to a maximum of 750 mg 8 hourly, according to response". It is noted that this aligns with the SAMF, 2016[18]; whilst a pharmacokinetic study[19] suggests that 12 hourly dosing is feasible.
***Recommendation:** Methyldopa, oral dosing retained as, "250 mg 8 hourly as a starting dose - increase to a maximum of 750 mg 8 hourly, according to response".*
Level of Evidence: III Pharmacokinetic study, Guidelines

Level of Evidence: Low certainty evidence

Methyldopa, oral: *directions for use not amended*
The STG text was not amended as iron supplements have been found to decrease methyldopa absorption[20]. Taking methyldopa two hours before or after iron-containing products can help avoid this interaction.

6.4.2.5 ECLAMPSIA

Labetalol, IV: *not added*
The NEMLC had not approved this in the previous review cycle, due to affordability and pragmatic implications at primary level of care.

NEMLC report for the 2016-2018 review of the PHC STGs and EML, 2018 edition:
The focus of management of eclampsia at primary level of care is to control the seizures with urgent referral. Emergency dosing with oral nifedipine was added to the STG in cases where patient is alert and BP ≥ 110/160 mmHg; whilst labetalol IV was not considered appropriate for primary level of care.
Level of Evidence: III Guidelines, Expert opinion

6.4.4 SYPHILIS IN PREGNANCY

Lidocaine 1%, parenteral*: not amended*
Recommendations for the administration of lidocaine 1% which is used as a diluent for less painful administration of intramuscular benzathine benzylpenicillin were not amended. The volume of lidocaine 1% as a diluent is aligned with Amir et al's study[21] and the UK 2008 STI guidelines[22] as previously cited.

6.4.7.1 PRETERM LABOUR (PTL) *and* 6.4.7.2 PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

Betamethasone, parenteral: *dosing amended*
The administration of antenatal betamethasone has been shown to improve improve fetal lung maturity at 26–34 weeks, confirmed by the updated 2020 Cochrane review[23]. High certainty evidence showed that antenatal corticosteroids reduced the risk of:

- perinatal death (RR 0.85, 95% CI 0.77 to 0.93; 9833 infants; 14 RCTs; 2.3% fewer, 95% CI 1.1% to 3.6% fewer)

[17] International Federation of Gynecology and Obstetrics. The FIGO Textbook of Pregnancy Hypertension. http://www.safemotherhood.ucsf.edu/wpcontent/uploads/2013/01/FIGO-Pregnancy_Hypertension-Final.pdf
[18] SAMF, 2022
[19] Wright JM, Orozco-Gonzalez M, Polak G, Dollery CT. Duration of effect of single daily dose methyldopa therapy. Br J Clin Pharmacol. 1982 Jun;13(6):847-54. https://www.ncbi.nlm.nih.gov/pubmed/7093115
[20] Campbell NR, Campbell RR, Hasinoff BB. Ferrous sulfate reduces methyldopa absorption: methyldopa: iron complex formation as a likely mechanism. Clin Invest Med. 1990 Dec;13(6):329-32. https://pubmed.ncbi.nlm.nih.gov/2078911/
[21] Amir J, Ginat S, Cohen YH, Marcus TE, Keller N, Varsano I. Lidocaine as a diluent for administration of benzathine penicillin G. Pediatr Infect Dis J. 1998 Oct;17(10):890-3.
[22]Kingston M, French P, Goh B, Goold P, Higgins S, Sukthankar A, et al.; Syphilis Guidelines Revision Group 2008, Clinical Effectiveness Group. UK National Guidelines on the Management of Syphilis 2008. Int J STD AIDS. 2008 Nov;19(11):729-40. Erratum in: Int J STD AIDS. 2011 Oct;22(10):613-
[23] IM: McGoldrick E, Stewart F, Parker R, Dalziel SR. Antenatal corticosteroids for accelerating fetal lung maturation for women at risk of preterm birth. Cochrane Database Syst Rev. 2020 Dec 25;12(12):CD004454. https://pubmed.ncbi.nlm.nih.gov/33368142/

- neonatal death (RR 0.78, 95% CI 0.70to 0.87; 10,609 infants; 22 RCTs; 2.6% fewer, 95% CI 1.5% to 3.6% fewer)
- respiratory distress syndrome (RR 0.71, 95% CI 0.65 to 0.78; 11,183 infants; 26 RCTs; 4.3% fewer, 95% CI 3.2% to 5.2% fewer)

The dosing interval for commonly used regimen of two doses of betamethasone, IM 12 mg was corrected from "~~*12 hours apart*~~" to "*24 hours apart*", aligned with the International Federation of Gynecology and Obstetrics clinical practice guide on maternal-fetal medicine[24].

Level of Evidence: High certainty evidence

6.4.7.2 PRETERM PRELABOUR RUPTURE OF MEMBRANES (PPROM)

Ampicillin, IV: *added*
Amoxicillin, oral: *retained*
Metronidazole, oral: *deleted*
Aztihromycin, oral: *added*

Antibiotics for PPROM reduces maternal and neonatal complications – a Cochrane review[25] 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 placebo; 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.[26] Broad spectrum antibiotics are recommended to prolong latency (due to the colonization with vaginal and rectal organisms). [27]

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 erythromycin as 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.[28]

Level of Evidence: Moderate certainty evidence

Severe penicillin allergy
Metronidazole, oral: *deleted*
Aztihromycin, oral: *dose amended*
Clindamycin, oral: *not added*
As clindamycin is not currently included in the PHC EML, a single pre-referral dose of azithromycin 1 g is recommended with urgent referral (refer to discussion on azithromycin above).

6.4.7.3 PRELABOUR RUPTURE OF MEMBRANES AT TERM (PROM)

> 12 hours
Antibiotic prophylaxis*: retained*
Antibiotic prophylaxis for term or near-term premature rupture of membranes is not associated with any benefits in either maternal or neonatal outcomes. In women with latency longer than 12 hours, prophylactic antibiotics are

[24] FIGO Working Group on Good Clinical Practice in Maternal-Fetal Medicine. Good clinical practice advice: Antenatal corticosteroids for fetal lung maturation. Int J Gynaecol Obstet. 2019 Mar;144(3):352-355. https://pubmed.ncbi.nlm.nih.gov/30710360/
[25] 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/
[26] 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/
[27] 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/
[28] 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/

associated with significantly lower rates of chorioamnionitis by 51% and endometritis by 88%.[29] The STG recommends a pre-referral dose of antibiotics with urgent referral.

6.5 INTRAPARTUM CARE

Morphine, parenteral: *retained*
Pethidine, parenteral: *not added*
Morphine was approved by NEMLC in the previous review cycle, as it has less side effects/less effect on the baby.

NEMLC report for the 2016-2018 review of the PHC STGs and EML, 2018 edition:
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 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: III Regulations[30], Guidelines[31]

Anti-D immunoglobulin: *directions for use amended*
Rational use of Anti-D immunoglobulin is warranted due to continual supply challenges. The following additional text was added to the STG:

» Check baby's Rh status; do not given anti-D if the baby is Rh-negative, or if the mother has Anti-Rh antibodies.

6.6.2 NEONATAL RESUSCITATION

Naloxone, IV: *retained*
The PHC/Adult Hospital Level Committee noted that naloxone, IV was not used in practice for initial neonatal resuscitation in the delivery room anymore. Maternally administered opioids in this clinical setting may cause neonatal respiratory depression, but evidence could not be sourced for naloxone, noting that ventilation and oxygenation may be sufficient for neonatal resuscitation.

NEMLC MEETING OF 24 JUNE 2021:
NEMLC Recommendation: *The NEMLC recommended that naloxone be retained for the indication stated in the STG: If the mother is known or suspected to have had narcotic pain relief and the baby has normal heart rate and colour response to bag-mask ventilation, but has not initiated sustained regular respiratory effort".*
However, concern of irrational use of naloxone in clinical practice was raised, and NEMLC deliberated on removing naloxone from the STG. However, as maternal opioid misuse was considered to be relatively common, the NEMLC recommended that naloxone be retained for the indication above, but that a statement be added that ***"Naloxone is not routinely indicated for neonatal resuscitation".***

The Resuscitation Council of Southern Africa's newborn resuscitation algorithm was updated from the 2015 version to the 2021 version.[32]

6.7.1 POSTPARTUM HAEMORRHAGE (PPH)

Tranexamic acid, parenteral: *not added*
Previously reviewed by NEMLC and not approved for inclusion on the PHC EML.

NEMLC report for the 2017-2019 review of the Adult Hospital Level STGs and EML, 2019 edition:
TXA, IV at primary level of care:

[29] Saccone G, Berghella V. Antibiotic prophylaxis for term or near-term premature rupture of membranes: metaanalysis of randomized trials. Am J Obstet Gynecol. 2015 May;212(5):627.e1-9. https://pubmed.ncbi.nlm.nih.gov/25555659/
[30] Regulation 31 of the Medicines and related substances Act 101 of 1965.
[31] SAMF, 2022
[32] Published with permission from the Resuscitation Council of Southern Africa. https://resus.co.za/

The National Committee of Confidential Enquires into Maternal Deaths (NCCEMD) requested that consideration be made to access TXA injection at primary level of care for PPH cases not responding to oxytocin and ergometrine. Currently, TXA IV is only included in the Adult Hospital Level EML.
WOMAN trial: E-mail communication from the investigators verified that risk factors for PPH were not collected and that the trial was done in the emergency situation.[33]

Rationale provided for inclusion of TXA, IV on the PHC EML:
Savings Mother report (2011-2013)[34] *reported that 15.9% (684) PPH cases caused maternal deaths; of which 2% occurred at primary level of care; whilst 36.7% occurred at secondary level facilities. The PHC STG recommends that where blood loss is greater than 500 mL, oxytocin/ergometrine to be administered with referral to secondary level of care.*
CRASH-2 study: Both the CRASH-2[35] *and the WOMAN studies showed a mortality benefit if TXA IV was administered within 3 hours of trauma or PPH. The WOMAN trial showed no additional statistical significant benefit or harm if TXA, IV was administered to women with PPH due to uterine atony beyond 3 hours.*
Pragmatic implications: From a pragmatic perspective, early access to TXA IV at primary level of care may be beneficial due to the quick onset and severity of PPH and early administration of TXA, once it is clear that there has been no response to initial oxytocin/ergometrine treatment. Access to TXA at midwife obstetric units (MOUs) may reduce referrals for PPH up to a higher level of care. Furthermore, there may be considerable delay in transferring women with PPH from an MOU to a higher level of care, either due to the long distance to the nearest hospital, or the from delay awaiting arrival of emergency medical services (EMS) at the MOU. This would necessitate additional training regarding intrapartum and emergency obstetric care for primary level healthcare workers.

NEMLC RECOMMENDATION:
The NEMLC did not accept the proposal to include TXA IV on the primary health care EML. (However, inclusion on the Adult Hospital Level EML was acceptable).
Rationale:
- "The **composite primary endpoint of death** from all causes or hysterectomy was not reduced with tranexamic acid (534 [5·3%] deaths or hysterectomies in the tranexamic acid group vs 546 [5·5%]in the placebo group, RR 0·97, 95% CI 0·87-1·09; p=0·65)"; **statistically not significant.** Death due to bleeding where tranexamic acid was administered within 3 hours of birth was a secondary endpoint. The effect size was small: ARR of 0.5% with NNT of 200 (1.2% in the tranexamic acid group vs 1.7% in the placebo group).
- Generalisability of the results of the WOMANS Trial to the local primary health care setting was not possible, as the trial was done in an emergency hospital setting.
- Referral to higher level of care for appropriate management from primary level may be delayed.

Level of Evidence: I RCT
Review indicator: Evidence of efficacy and safety in primary care setting.

6.8 HIV IN PREGNANCY

(Note: Recommendations were aligned with chapter 11: HIV and AIDs, as appropriate).

Tenofovir + lamivudine + dolutegravir, oral: *amended*
Indication expanded from ≥6 weeks gestation to ALL women
Refer to the medicine review: Dolutegravir in pregnancy, June 2021:

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. The existing contra-indication in pregnancy should be removed from the STG.

[33] E-mail communication from WOMAN trial investigator, 28 November 2017, on file.
[34] National Department of Health: National Committee for the Confidential Enquiries into Maternal Deaths Saving Mothers Report, 2011-2013.
[35] CRASH-2 Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised placebo-controlled trial. Lancet 2010; 376: 23-32. https://www.ncbi.nlm.nih.gov/pubmed/20554319

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 (Women of Child Bearing Potential), 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

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.

DTG- based 1st line regimen failure for >2 years
Tenofovir + Emtricitabine + Atazanavir/ritonavir, oral: *added*
Aligned with the PHC chapter 11: HIV and AIDs, section 11.1: Antiretroviral therapy, adults and adolescents (10-19 years old).

HIV testing: *amended*
Guidance for HIV-testing was amended to align with guidance recommended in the Prevention of Mother-to-Child Transmission of HIV (PMTCT) and the management of HIV in Children, Adolescents and Adults, current Guidelines for Maternity Care in South Africa - i.e. at every Basic Antenatal Care (BANC) visit (8 in total).

CrAg positive
Lumbar puncture: *added*
The following was added to the STG text:

Note: All CrAg positive women need a LP, unless contra-indicated, regardless of symptoms.

6.13 HORMONE THERAPY (HT)

Mammogram: *deleted*
The following STG text was deleted, specifically noting that no facilities are available at primary level of care:

» ~~Where the facility is available, arrange mammography before starting HT. However, lack of access to mammography should not delay HT if indicated for severe menopausal symptoms if the woman has no other special risk factors for breast cancer (e.g.: family history of breast cancer in first degree relative).~~

Transdermal hormone therapy patches: *not added to the STG, but added to the therapeutic interchange database*
Refer to the evidence summary on transdermal HT patches, July 2021, v2:

Transdermal HT Patches_Evidence Sum

Evidence for alternative routes for HT administration was reviewed, owing to reported supply constraints with oral HT. Oral and transdermal HT were both effective in terms of management of menopausal symptoms. Observational

studies showed that the risk of thrombosis was higher with oral oestrogen compared to transdermal oestrogen. The PHC ERC therefore proposed that transdermal HT be added to the STG, but restricted to women at high risk of thrombosis, owing to cost. However, the two routes have not been compared directly in women with a high risk of thrombosis, and transdermal HT isn't specifically indicated/registered for this population.

NEMLC MEETING OF 19 DECEMBER 2021

Discussion: The risk for first time thrombosis was reported to be higher amongst women on oral HT compared to those using transdermal HT[36]. However, the number of women needing HT who have a high risk of thromboembolism was anticipated that this would be a small number[37]. Citalopram is recommended for treatment of menopausal symptoms in women at high risk of thromboembolism at secondary level of care. Furthermore, NEMLC raised concerns regarding the high price of transdermal HT.

Recommendation: NEMLC deliberated on the proposal suggested by the PHC/Adult Hospital Level Committee, and recommended that HT transdermal patches be removed from the STG, but be added to the therapeutic interchange database as an alternative to oral estrogens.

Rationale: The number of women requiring HT at high risk of thromboembolism is anticipated to be small. Transdermal HT is expensive compared to oral HT preparations. Citalopram is included on the secondary level EML for management of perimenopausal or menopausal syndrome where "oral" HT is contra-indicated, poorly tolerated or ineffective.

Level of Evidence: Conditional recommendation, moderate certainty evidence

Review: equivalence of hormones

Hormone replacement therapy (HRT) reduce vasomotor symptoms in a dose-dependent fashion, and the standard treatment guidelines recommend that prescribers start with the lowest dose available and titrate upwards according to symptoms.[38] There are no head-to-head comparisons of the various formulations in relieving vasomotor symptoms.

Estrogens: Conjugated estrogen (CE) 0.625mg orally is considered a 'standard dose' of HRT and is equivalent to 1-2mg of oral estradiol.[3] A serum estradiol concentration of 76.8 pg/mL is achieved with CE 0.625 mg daily. For 1 mg and 2 mg doses of oral estradiol, serum concentrations of estradiol attained are 65.8 pg/mL and 107.6 pg/mL respectively. Although the optimal range for serum estradiol concentration to achieve therapeutic efficacy has not been established, a serum estradiol concentration of 60 pg/mL is needed to prevent osteoporosis[39] and reduce 50% of hot flashes.[40] During a normal menstrual cycle in the mid-follicular phase plasma estradiol concentrations are 60-150pg/ml.[4] Experimental studies in castrated animals and human studies in postmenopausal women suggest that a plasma estradiol concentration of approximately 100 pg/ml is optimal for treatment of hot flushes, prevention of bone loss and cardiovascular protection.[4]

Progestogens: Serum progesterone concentrations greater than 5 ng/mL must be achieved to inhibit endometrial mitosis and to induce a secretory change (endometrial protection). This threshold concentration is based on the observation that during a normal menstrual cycle, the corpus luteum produces circulating progesterone concentrations that are in the range of approximately 5 to 20 ng/mL.[41]

[36] Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, et al.; Million Women Study Collaborators. Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012 Nov;10(11):2277-86. https://pubmed.ncbi.nlm.nih.gov/22963114/

[37] Previously, NEMLC had recommended venlafaxine, oral (for hormone with hormone-dependant cancers) not be included on the national EML for secondary level of care; but rather for consideration at tertiary and quaternary level of care – NEMLC minutes of the meeting of 14 December 2017.

[38] Kim S-M, Kim SE, Lee D-Y, Choi D. Serum estradiol level according to dose and formulation of oral estrogens in postmenopausal women. Sci Rep. 2021 Feb 11;11:3585.

[39] de Lignieres B. Hormone replacement therapy: clinical benefits and side-effects. Maturitas. 1996 May;23 Suppl:S31-36.

[40] Steingold KA, Laufer L, Chetkowski RJ, DeFazio JD, Matt DW, Meldrum DR, et al. Treatment of hot flashes with transdermal estradiol administration. J Clin Endocrinol Metab. 1985 Oct;61(4):627–32.

[41] Stanczyk FZ, Paulson RJ, Roy S. Percutaneous administration of progesterone: blood levels and endometrial protection. Menopause. 2005 Apr;12(2):232–7.

Norethisterone vs medroxyprogesterone acetate: The WHO 18th Expert Committee of the Selection and Use of Essential Medicines[42] systematically reviewed the evidence (1 systematic review[43] and 3 RCTs[44 45 46]) and concluded that low-dose HT be used to manage menopausal symptoms (doses of 5mg norethisterone not recommended as the risks outweigh the benefits). Combining estrogen with progestogen minimises the risk of endometrial hyperplasia which can develop into endometrial cancer in menopausal women with an intact uterus; and low dose estrogen plus progestogen (1 mg norethisterone or 1.5 mg medroxyprogesterone acetate) appears safe for the endometrium, taken either continuously or sequentially.[47]

The therapeutic interchange database for hormone therapy was updated as per the following table aligned with products currently available on the South African market listed in the SAMF, 2020 edition
NEMLC recommended that transdermal hormone therapy patches not be included on the PHC EML, but recommended that the patches should be added to the therapeutic interchange database and be grouped therapeutically with the other EML-recommended oral hormone preparations – the evidence (safety and efficacy) reviewed did not show value for investing in the transdermal HT patches, but could be considered as an alternative to the oral HT preparations when there are supply issues of the latter, or for scale of volume procurement purposes.

Indication	Therapeutic class	INN	Strength (mg)	formulation
Menstruation > 1 year ago	**Progestogens and estrogens, fixed combinations (lowdose)**	**Norethisterone/estrogen***	**0.5/1**	**oral**
Menstruation > 1 year ago	Progestogens and estrogens, fixed combinations (lowdose)	Norethisterone/estrogen**	0.62/2.7	transdermal patches
Menstruation > 1 year ago	**Progestogens and estrogens, fixed combinations (standard dose)**	**Norethisterone/estrogen***	**1/1**	**oral**
Menstruation > 1 year ago	Progestogens and estrogens, fixed combinations (standard dose)	Norethisterone/estrogen**	11.2/3.2	transdermal patches
Menstruation > 1 year ago	**Progestogens (used with estrogens) - continuous combined therapy**	**Medroxyprogesterone acetate***	**2.5 to 5**	**oral**
Menstruation > 1 year ago	Progestogens (used with estrogens) - continuous combined therapy	Norethisterone**	1.25 to 2.5	oral
Menstruation > 1 year ago	**Estrogens (used with progestogens) - continuous combined therapy**	**Estradiol***	**1 to 2**	**oral**
Menstruation > 1 year ago	Estrogens (used with progestogens) - continuous combined therapy	Conjugated estrogens**	0.3 to 0.625	oral
Menstruation < 1 year ago/present	**Progestogens and estrogens, sequential preparations (low dose)**	**Norethisterone+estrogen/estrogen***	**1/2**	**oral**
Menstruation < 1 year ago/present	Progestogens and estrogens, sequential preparations (low dose)	Dydrogesterone+estrogen/estrogen**	10/1	oral
Menstruation < 1 year ago/present	**Progestogens and estrogens, sequential preparations (standard dose)**	**Norgestrel+estrogen/estrogen***	**0.5/2**	**oral**
Menstruation < 1 year ago/present	Progestogens and estrogens, sequential preparations (standard dose)	Cyproterone+estrogen/estrogen**	1/2	oral
Menstruation < 1 year ago/present	Progestogens and estrogens, sequential preparations (standard dose)	Norethisterone+estrogen/estrogen**	1/2	oral
Menstruation < 1 year ago/present	**Progestogens (used with estrogens) - sequential opposed therapy**	**Medroxyprogesterone acetate***	**5 to 10**	**oral**
Menstruation < 1 year ago/present	Progestogens (used with estrogens) - sequential opposed therapy	Norethisterone**	1.25 to 2.5	oral
Menstruation < 1 year ago/present	**Estrogens (used with progestogens) - sequential opposed therapy**	**Estradiol***	**1 to 2**	**oral**
Menstruation < 1 year ago/present	Estrogens (used with progestogens) - sequential opposed therapy	Conjugated estrogens**	0.3 to 0.625	oral
Uterus absent (post hysterectomy)	**Estrogens**	**Estradiol***	**1 to 2**	**oral**
Uterus absent (post hysterectomy)	Estrogens	Conjugated estrogens**	0.3 to 0.625	oral
Uterus absent (post hysterectomy)	Estrogens	Estradiol**	25 to 75	transdermal patches

**Listed in the STG*
***Listed in the therapeutic interchange database*

[42] World Health Organization. 18th Expert Committee on the Selection and Use of Essential Medicines- Section 18.7: Progestogens, March 2011. [Accessed 17 March 2022] Available at: https://www.who.int/selection_medicines/committees/expert/18/applications/Norethisterone.pdf
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[46] Boschetti C, Cortellaro M, Nencioni T, Bertolli V, Della Volpe A, Zanussi C. Short- and long-term effects of hormone replacement therapy (transdermal estradiol vs oral conjugated equine estrogens, combined with medroxyprogesterone acetate) on blood coagulation factors in postmenopausal women. Thromb Res. 1991 Apr;62(1-2):1-8. doi: 10.1016/0049-3848(91)90663-h.
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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.

Acknowledgements: Tamara Kredo and Joy Oliver (Cochrane South Africa) supported the systematic literature search. Trudy Leong (National Department of Health) provided support for this review.

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.

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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.

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					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
Primary Healthcare and Adult Hospital Level Medication Review Process
Component: Gynaecology

EVIDENCE SUMMARY

Date: 22 July 2021

Reviewer: Prof GS Gebhardt

Affiliation and declaration of interests: GSG (Department of Obstetrics and Gynaecology, Stellenbosch University, PHC/Adult Hospital Level Committee member) has no interests to declare with respect to transdermal hormone patches.

RESEARCH QUESTION: Are Transdermal Patches an effective, acceptable and safe alternative route for hormone replacement therapy in women with vasomotor symptoms of menopause?

Eligibility criteria for inclusion of studies:
Population: Postmenopausal women with vasomotor symptoms

Intervention: Treatment with oral estrogen

Comparison: Treatment with transdermal estrogen

Outcome: Efficacy (relief of symptoms); safety and acceptability

Study designs: Systematic reviews of RCTs

BACKGROUND

Hormone replacement therapy (HT) for short-term symptomatic relief of severe menopausal symptoms are currently available in the STG as oral preparations only (estradiol valerate or conjugated oestrogens in various strengths) with or without progesterone. Women without a uterus (e.g. post-hysterectomy) use estrogen only, while women with an intact uterus needs additional progesterone for endometrial protection. This is given either as sequentially opposed or continuous combined regimens. Estrogen is available in many other forms, including transdermal patches, gels, emulsions and lotions, intravaginal creams and tablets, vaginal rings and subcutaneous implants, but currently only oral preparations are available on the EDL. There is a supply challenge with conjugated estrogen and the PHC/Adult Hospital Committee is exploring alternative formulations/routes for administration of HT.

Transdermal HT patches

The table below lists the transdermal HT options currently available on the South African market.

TRANSDERMAL HT PREPARATIONS - SEP					
Trade Name	**Contents**	**Usage**	**Tender price (28d) (ZAR)**	**SEP (28d) (ZAR)**	**60% of SEP (28d) (ZAR)**
Estradot 25 mcg®	Oestradiol hemihyd-25mcg	Estrogen only (unopposed)	-	180.21	108,13
Estradot 37.5 mcg®	Oestradiol hemihyd-37 5mcg	Estrogen only (unopposed)	-	180.21	108,13
Estradot 50 mcg®	Oestradiol hemihyd-50mcg	Estrogen only (unopposed)	-	207.21	124,32
Estradot 75 mcg®	Oestradiol hemihyd-75mcg	Estrogen only (unopposed)	-	207.21	124,32
Estradot 100 mcg®	Oestradiol hemihyd-100mcg	Estrogen only (unopposed)	-	207.21	124,32
Evorel 25 tts®	Oestradiol-1 6mg	Estrogen only (unopposed)	-	194.07	116,44
Evorel 50 tts®	Oestradiol-3 2mg	Estrogen only (unopposed)	-	209.71	125,82
Evorel 75 tts	Oestradiol-4 8mg	Estrogen only (unopposed)	-	218.87	131,32
Evorel 100 tts®	Oestradiol-6 4mg	Estrogen only (unopposed)	-	228.64	137,19
Climara 50®	Oestradiol-3 9mg	Estrogen only (unopposed)	-	180.13	108,08
Estalis 50/140®	Norethis acet-2 7mg; Oestradiol hemihyd-0 62mg	Continuous combined (estrogen with progesterone)	-	289.27	173.56
Evorel conti®	Oestradiol-3 2mg; Norethis acet-11 2mg;	Continuous combined (estrogen with progesterone)	-	345.36	207.21
Evorel sequi®	Oestradiol-3 2mg; Oestradiol-3 2mg; Norethis acet-11 2mg	Sequential use (estrogen with progesterone)	-	366.60	201.96

ORAL HT PREPARATIONS CURRENTLY ON TENDER					
Trade Name	**Contents**	**Usage**	**Tender price (28d) (ZAR)**	**SEP (28d) (ZAR)**	**60% of SEP (28d) (ZAR)**
Estrofem 1 mg®	Estradiol 1 mg	Estrogen only (unopposed)	40.31	154.97	92.98
Estrofem 2 mg®	Estradiol 2 mg	Estrogen only (unopposed)	75.78	168.92	101.35
Premarin 0.3 mg®	Conjugated oestrogens-0 3mg	Estrogen only (unopposed)	123.02	133.85	80.31
Activelle®	Estradiol-1mg Norethis acet-0 5mg	Continuous combined (estrogen with progesterone)	94.43	239.21	143.53
Kliogest®	Estradiol-2mg Norethis acet-1mg	Continuous combined (estrogen with progesterone)	109.53	308.02	184.51

METHODS:
Five data sources were searched: Pubmed, Cochrane Library, Epistemonikos, NICE Guidelines and Google scholar.

i. Pubmed

Search strategy
((("administration, cutaneous"[MeSH Terms] OR ("administration"[All Fields] AND "cutaneous"[All Fields]) OR "cutaneous administration"[All Fields] OR "transdermal"[All Fields] OR "transdermally"[All Fields] OR "transdermals"[All Fields] OR "transdermic"[All Fields] OR "transdermically"[All Fields]) AND ("estrogen s"[All Fields] OR "estrogene"[All Fields] OR "estrogenes"[All Fields] OR "estrogenic"[All Fields] OR "estrogenically"[All Fields] OR "estrogenicities"[All Fields] OR "estrogenicity"[All Fields] OR "estrogenization"[All Fields] OR "estrogenized"[All Fields] OR "oestrogen"[All Fields] OR "estrogens"[Pharmacological Action] OR "estrogens"[MeSH Terms] OR "estrogens"[All Fields] OR "estrogen"[All Fields] OR "oestrogen s"[All Fields] OR "oestrogenic"[All Fields] OR "oestrogenically"[All Fields] OR "oestrogenicity"[All Fields] OR "oestrogenization"[All Fields] OR "oestrogens"[All Fields]) AND ("vasomotor"[All Fields] OR "vasomotoric"[All Fields] OR "vasomotoricity"[All Fields] OR "vasomotors"[All Fields])) AND (clinicaltrial[Filter] OR meta-analysis[Filter] OR randomizedcontrolledtrial[Filter] OR systematicreview[Filter])

10 systematic reviews was retrieved, of which four (Corbelli et al(1) and Derzko et al(2) and Nelson et al(3) and Mohammed et al(4) was relevant to the PICO and two more (the NICE(5) guideline and the Marjoribanks(6) Cochrane review) was already retrieved (see below). 58 randomised control trials were retrieved, of which only one (Akhila et al) was recent and relevant to the PICO and not included in one of the systematic reviews.(7)

ii. Cochrane Library

Search strategy:
"transdermal" in Title Abstract Keyword AND “vasomotor” OR “menopausal” in Title Abstract Keyword - in Cochrane Reviews, Cochrane Protocols (Word variations have been searched)

76 Cochrane reviews and 6 Cochrane protocols were retrieved; of which 2 Cochrane reviews (Marjoribanks(6) et al, 2017) and Boardman(8) et al (2015) were reviewed (but see below) as other literature was not relevant to the PICO question.

iii. Epistemonikos

Search strategy:
(title:(TRANSDERMAL AND VASOMOTOR OR MENOPAUSAL) OR abstract:(TRANSDERMAL AND VASOMOTOR OR MENOPAUSAL))

15 primary studies and 17 systematic reviews were retrieved, but (apart from the two Cochrane reviews already mentioned) none of the systematic reviews were relevant to the PICO question and the primary studies were those already identified via PubMed, conducted in the 1990s. Two more recent primary studies were excluded as not relevant to the PICO (comparison was with placebo). A systematic review by Abdi(9) et al (Hormone Therapy for Relieving Postmenopausal Vasomotor Symptoms; 2015) were excluded as the comparator was placebo and the intervention any form of hormone therapy (oral, gels, spray and transdermal).

iv NICE guidelines

One NICE guideline (Menopause: diagnosis and management) contained information that was relevant to the PICO. One systematic review (Sweetland(10) et al) was identified from a reference search.

v: Google Scholar: The review by Grant(11) was found by a Google scholar search.

RESULTS

Description of studies

Transdermal HT is in general use for the last 30 years and the randomised trials and acceptability studies were mostly done in in the early 1990s (e.g. Pornell et al(12) and Gordon(13)). There were no recent (since 2010) randomised trials or systematic reviews comparing the transdermal route with the oral route.

The Nelson et al systematic review from 2004(3) included 32 trials with 14 trials meeting criteria for meta-analysis. All estrogen agents regardless of route significantly reduced the weekly number of hot flashes compared with placebo (conjugated estrogen, 1 trial: mean change, –19.1; 95% confidence interval [CI], –33.0 to –5.1; oral 17ß-estradiol, 5 trials: pooled weighted mean difference, –16.8; 95% CI, –23.4 to –10.2; transdermal 17-estradiol, 6 trials: pooled weighted mean difference, –22.4; 95% CI, –35.9 to –10.4). There was no significant differences between agents.

The Corbelli(1) systematic review was excluded as the comparator was placebo and the Derzko(2) review was excluded as the comparison was with estrogen gel and placebo.

The NICE guideline(5) on the diagnosis and treatment of menopause use the blanket term HT (hormone replacement therapy) and does not make individual recommendations for different routes of administration except in the case of women at higher risk for venous thromboembolism(VT) (including a BMI>30kg/m^2), where the transdermal route is recommended. The evidence for this is summarised in appendix H(14) of the NICE guideline and is based largely on the 2012 study by Sweetland et al(10) where more than 1 000 000 women on HT were assessed for risk for thromboembolism (for effectively more than 3 million person years of follow-up). The VT risk was significantly greater for oral estrogen-progestin than oral estrogen-only therapy (RR = 2.07 [95%CI, 1.86 to 2.31] vs. 1.42 [1.21 to 1.66]), with no increased risk with transdermal estrogen-only therapy (0.82 [0.64 to 1.06]). Current use of transdermal oestrogen only HT in women aged 50+ years had a RR for VT of 0.85 (95% CI 0.61 to 1.20), while current use of oral oestrogen only HT in women aged 50+ years had a RR of 1.33 (1.06 to 1.65) .

A systematic review and meta-analysis by Mohammed et al on oral vs transdermal estrogen therapy and vascular events included the Sweetland study with 14 more observational studies at moderate risk of bias.(4) When compared to transdermal estrogen, oral estrogen was associated with increased risk of a first episode of VT (RR, 1.63; 95% CI, 1.40 to 1.90; I^2 = 53%), deep vein thrombosis (RR, 2.09; 95% CI, 1.35 to 3.23; I^2 = 0 %), and possibly stroke (RR, 1.24; 95%CI, 1.03 to 1.48; a single case-controlled study). The meta-analysis appears below – see figure 1.

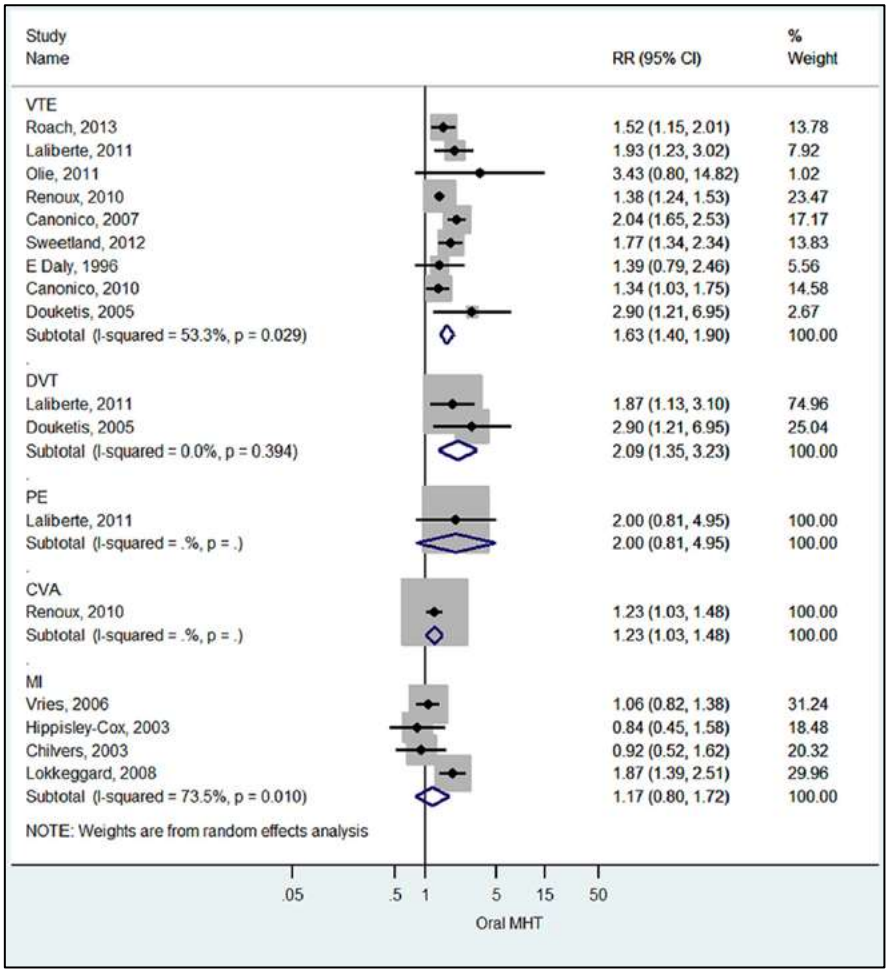

Figure 1: Forest plot comparing oral vs other HT therapies, assessing associated vascular adverse effects.

Grant et al prepared a comprehensive analysis of the comparative effectiveness of therapies for menopausal symptoms for the Agency for Healthcare Research and Quality by Grant and co-workers (11) of 238 trials, concluded that there is considerable certainty that estrogens are the most effective treatment for relieving vasomotor symptoms and are accompanied by the greatest improvement in quality-of-life measures. They again used any available route of estrogen (high dose or low dose) as a comparator and did not compare various estrogen routes with each other.

The two Cochrane reviews identified did not address the PICO directly- the Marjoribanks(6) review looked at safety (mortality, cardiovascular outcomes, cancer, gallbladder disease, fracture and cognition) with any type of hormonal preparation. The one metanalysis of patch data and risk of possible venous thromboembolism (Women without major health problems (selected outcomes: death, CVD, cognition, QOL), Outcome Venous thromboembolism (DVT or PE): oestrogen-only HT did not show a significant increased risk in any of the studies included (for patch the relative risk versus placebo was 0,4 with 95% CI 0.02-9.73).

The Boardman(8) Cochrane review was excluded as it only investigated oral preparations and the risk for cardiovascular with no comparison to patches.

SUMMARY

- Estrogen, regardless of route, is an effective method for relief of vasomotor menopausal symptoms.
- Only the oral route is currently available to women on the EML, and there are supply constraints.
- The transdermal route (patch) is as effective, it is acceptable and probably safer (less risk for thrombotic events in observational studies).

RECOMMENDATION

Based on this evidence summary, the PHC/Adult Hospital Level Committee proposes that transdermal estrogen patches be considered for inclusion on the EML for the management of vasomotor symptoms in menopause. Because of its higher cost, use may be restricted to women with previous history of thrombotic events.

Rationale: Available evidence shows that all estrogen agents regardless of route of administration significantly reduces vasomotor symptoms of menopause with improved quality-of-life measures, compared with placebo. When compared to transdermal estrogen, oral estrogen was associated with increased risk of a first episode of VT, deep vein thrombosis and possibly stroke.

Level of evidence: Moderate certainty evidence

Review indicator: Price (expand indication to all if price is reasonable)

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Discussion: The risk for first time thrombosis was reported to be higher amongst women on oral HT compared to those using transdermal HT. However, the number of women needing HT who have a high risk of thromboembolism was anticipated that this would be a small number[1]. Citalopram is recommended for treatment of menopausal symptoms in women at high risk of thromboembolism at secondary level of care. Furthermore, NEMLC raised concerns regarding the high price of transdermal HT.

Recommendation: NEMLC deliberated on the proposal suggested by the PHC/Adult Hospital Level Commitee and recommended that HT transdermal patches be removed from the STG, but be added to the therapeutic interchange database as an alternative to oral estrogens.

Rationale: The number of women requiring HT at high risk of thromboembolism is anticipated to be small. Transdermal HT is expensive compared to oral HT preparations. Citalopram is included on the secondary level EML for management of perimenopausal or menopausal syndrome where "oral" HT is contra-indicated, poorly tolerated or ineffective.

Level of Evidence: Conditional recommendation, moderate certainty evidence

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[1] Previously, NEMLC had recommended venlafaxine, oral (for hormone with hormone-dependant cancers) not be included on the national EML for secondary level of care; but rather for consideration at tertiary and quaternary level of care – NEMLC minutes of the meeting of 14 December 2017.

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