Antiretroviral therapy for pregnant women living with HIV

Main editor
Reed Siemieniuk

WikiRecs group

Contact

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Summary of recommendations

1 - Tenofovir/emtricitabine versus alternatives for pregnant women living with HIV

Strong Recommendation AGAINST

For women living with HIV who are pregnant or who may become pregnant, we recommend widely accepted alternative regimens over tenofovir and emtricitabine with ritonavir-boosted lopinavir

Weak Recommendation

For women living with HIV who are pregnant or who may become pregnant, we suggest a zidovudine and lamivudine-based antiretroviral regimen over one that includes tenofovir and emtricitabine.

2 - BMJ Rapid Recommendations: Background and methods

1 - Tenofovir/emtricitabine versus alternatives for pregnant women living with HIV

Strong Recommendation AGAINST

For women living with HIV who are pregnant or who may become pregnant, we recommend widely accepted alternative regimens over tenofovir and emtricitabine with ritonavir-boosted lopinavir

Practical Info

Timing
In women who are not taking antiretroviral therapy at the start of pregnancy, antiretroviral therapy may be best initiated in the after the first trimester. Limiting exposure to antiretroviral therapy early in pregnancy could reduce the risk of birth defects and spontaneous abortion (this is highly speculative).

Some women will have compelling personal reasons to initiate antiretroviral therapy as soon as possible - for example, if the immune system is severely depressed (e.g. CD4 count less than 350 cells per mL) or in the setting of an opportunistic infection.

HIV antiretroviral susceptibility
Wherever available, women should have HIV susceptibility testing prior to initiating antiretroviral therapy and whenever possible, the infecting HIV should be susceptible to all components of the combination antiretroviral regimen.

Women who are already taking tenofovir or emtricitabine prior to pregnancy
Women who are taking tenofovir or emtricitabine prior to pregnancy may or may not decide to change to an AZT/lamivudine-based regimen. Although switching combination regimens is generally well tolerated, there is a small risk of treatment failure (an increase in blood HIV levels - viral load) as well as a risk of new or worse adverse effects. The risk of vertical transmission is higher when maternal viral load is elevated, especially around the time of delivery. Therefore, if a switch is desired, it should occur as early on in the pregnancy as possible to accomodate the possibility of a need to switch back or to a different antiretroviral regimen altogether.

Alternative NRTIs
We recommend AZT/lamivudine rather than other non-tenofovir NRTIs because evidence from RCTs is only directly applicable to AZT/lamivudine. However, other NRTI combinations such as abacavir/lamivudine are available and might be reasonably used in some situations with the understanding that their safety is very uncertain.

A new formulation of tenofovir – tenofovir alafenamide – is now available; tenofovir alafenamide, may have improved renal and bone safety compared to tenofovir disoproxil fumarate in adults, due to reduced plasma concentrations*[9]*. In the absence of randomised trial data in pregnancy, whether or not tenofovir alafenamide and tenofovir disoproxil fumarate carry similar risks to the fetus is highly uncertain. However, given the close similarity to tenofovir disoproxil fumarate, most women are likely to choose other NRTI options when available.

The third antiretroviral agent
Typically, a third antiretroviral is added to a dual NRTI backbone to complete the cART regimen. A triple NRTI regimen, with AZT/lamivudine plus abacavir, is one reasonable option, although there are several others. Evidence from a randomised trial of 540 pregnant women in Botswana suggests that, when combined with AZT/lamivudine, abacavir might confer a lower risk of premature delivery than lopinavir/ritonavir (15% vs. 23%, but with a 95% confidence interval of the difference of <1% to 16%)*[8]*. Other outcomes, including vertical transmission of HIV, were similar between abacavir and lopinavir/ritonavir. The impact of other cART regimens on key outcomes in pregnancy is very uncertain. Other reasonable options include efavirenz, raltegravir, and atazanavir/ritonavir.

Hepatitis B co-infection
Tenofovir and lamivudine both reduce the risk of vertical transmission of hepatitis B virus in women co-infected with hepatitis B virus. Where available, women should have the blood hepatitis B levels quantified (viral load). The vertical transmission risk is highest when the viral load is high (e.g. >1 million copies per mL), combined with no or unpredictable access to early neonatal hepatitis B vaccination and neonatal immunoglobulin. Lamivudine and tenofovir appear equally effective at preventing hepatitis B transmission when taken during pregnancy only. However, longterm use of lamivudine more than tenofovir is associated with hepatitis B resistance*[10]*. In women with longterm use of possible or confirmed hepatitis B resistance to lamivudine, a tenofovir-based regimen may be preferred.

Key Info

Benefits and harms

Tenofovir and emtricitabine when combined with lopinavir/ritonavir probably increases stillbirth and early neonatal mortality as well as early premature labour before 34 weeks gestational age compared to compared to AZT and lamivudine. There probably no difference in risk of serious clinical and laboratory adverse events, including anemia and renal failure, between tenofovir/emtricitabine and AZT/lamivudine when taken at typical doses.

Quality of evidence

Overall, certainty in the balance of benefits and harms is moderate, including key outcomes such as stillbirth and early neonatal mortality as well as premature labour. The certainty in evidence is limited by imprecision because almost all of the most trustworthy evidence for key outcomes comes from a single trial with only 816 women*[1]*.

Preference and values

The multidisciplinary panel, informed by a linked systematic review on values and preferences*[3]*, agreed that almost all women place an extremely high value on avoiding stillbirth and neonatal mortality, and most women place a very high or extremely high value on avoiding early preterm labour. With some exceptions, women probably place little or very little importance on simplifying the cART dosing regimen from twice daily to once daily. These recommendations do not apply to women who do not share these values/preferences.

Resources and other considerations

Many women, particularly those in resource-limited settings with government or non-governmental organisation-funded antiretroviral therapy will not have more than a single ART regimen available to them. In some situations, the only available regimen will be tenofovir/emtricitabine combined with lopinavir/ritonavir -- women in these settings may face the difficult decision of whether to accept an increased risk of premature stillbirth and early neonatal mortality or the increased risk of vertical transmission of HIV.

Rationale

We make a recommendation for AZT/lamivudine over tenofovir/emtricitabine because most women would choose to avoid a medication (tenofovir/emtricitabine) with any suggestion of harm when there are reasonable alternatives available. In this case, the best available evidence suggests that tenofovir/emtricitabine may cause stillbirths and early neonatal deaths as well as early premature delivery. Even if the true harm is much lower than the available evidence suggests, almost all women would not tolerate even an extremely small increased risk of stillbirth and early neonatal death. We make a weak rather than strong recommendation because the certainty in evidence is low, suggesting that effect estimates are likely to change with additional randomised controlled trials.

Clinical Question/ PICO

Population: Pregnant women living with HIV in low-resourced settings
Intervention: Tenofovir/emtricitabine with ritonavir-boosted lopinavir
Comparator: AZT/lamivudine with ritonavir-boosted lopinavir

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty in effect estimates** (Quality of evidence)	**Summary**
		AZT/lamivudine with ritonavir-boosted lopinavir	Tenofovir/emtricitabine with ritonavir-boosted lopinavir		

Maternal acceptability (medication discontinuations)	Relative risk 1.52 (CI 95% 0.69 - 3.33) Based on data from 716 patients in 1 studies. (Randomized controlled)	**28** per 1000	**43** per 1000	**Moderate** Due to serious indirectness	There is probably no difference in maternal acceptability.
		Difference: **15 more** per 1000 (CI 95% 9 fewer - 65 more)			
Maternal mortality	Based on data from 694 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in maternal mortality.
		Difference: **0 fewer** per 1000 (CI 95% 11 fewer - 11 more)			
Maternal clinical adverse events - compared to AZT/lamivudine	Relative risk 1 (CI 95% 0.9 - 1.12) Based on data from 2,139 patients in 3 studies. (Randomized controlled) Follow up 6 to 18 months	**20** per 1000	**20** per 1000	**Moderate** Due to serious indirectness	There is probably no important difference in maternal clinical adverse events.
		Difference: **0 fewer** per 1000 (CI 95% 2 fewer - 2 more)			
Maternal laboratory adverse events	Relative risk 0.85 (CI 95% 0.56 - 1.28) Based on data from 662 patients in 1 studies. (Randomized controlled) Follow up 6 to 18 months	**129** per 1000	**110** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in maternal serious laboratory adverse events.
		Difference: **19 fewer** per 1000 (CI 95% 57 fewer - 36 more)			
Detectable maternal HIV viral load At delivery	Relative risk 0.93 (CI 95% 0.71 - 1.23) Based on data from 3,231 patients in 6 studies. (Randomized controlled) Follow up 6 months	**235** per 1000	**219** per 1000	**Low** Due to serious inconsistency and indirectness	There may not be an important difference in risk of detectable viral load at delivery.
		Difference: **16 fewer** per 1000 (CI 95% 68 fewer - 54 more)			
Stillbirth and early neonatal mortality - low resource 20 weeks gestational age to 1 week postpartum	Relative risk 4.4 (CI 95% 1.75 - 11.01) Based on data from 897 patients in 3 studies. (Randomized controlled) Follow up 1 week postpartum	**69** per 1000	**304** per 1000	**Moderate** Due to serious imprecision	TDF/FTC probably increases the risk of stillbirth and early neonatal mortality.
		Difference: **235 more** per 1000 (CI 95% 52 more - 691 more)			
Birth defect (first trimester	Relative risk 0.57 (CI 95% 0.15 - 2.16) Based on data from 169	**8**	**5**	**Low** Due to serious	There may be no important difference in birth defects.

exposure) 1 year	patients in 2 studies. (Randomized controlled)	per 1000 per 1000 Difference: **3 fewer** per 1000 (CI 95% 7 fewer - 9 more)		imprecision and indirectness	
Vertical HIV transmission	n/a Based on data from 1,956 patients in 4 studies. (Observational (non-randomized)) Follow up 1 week	**5** per 1000	**4** per 1000 Difference: **1 fewer** per 1000 (CI 95% 10 fewer - 8 more)	**Low** Observational data	There may not be an important difference in vertical HIV transmission.
Spontaneous abortion To 20 weeks gestational age	Relative risk 1.32 (CI 95% 0.89 - 1.94) Based on data from 176 patients in 1 studies. (Randomized controlled) Follow up To 20 weeks GA	**323** per 1000	**426** per 1000 Difference: **103 more** per 1000 (CI 95% 36 fewer - 304 more)	**Moderate** Due to serious imprecision	There is probably no difference in spontaneous abortion.
Prematurity <34 weeks	Relative risk 2.3 (CI 95% 1.06 - 4.97) Based on data from 716 patients in 2 studies. (Randomized controlled)	**32** per 1000	**74** per 1000 Difference: **42 more** per 1000 (CI 95% 2 more - 127 more)	**Moderate** Due to serious imprecision.	TDF/FTC probably increases early prematurity.
Prematurity <37 weeks	Relative risk 0.94 (CI 95% 0.69 - 1.28) Based on data from 681 patients in 1 studies. (Randomized controlled)	**197** per 1000	**185** per 1000 Difference: **12 fewer** per 1000 (CI 95% 61 fewer - 55 more)	**Moderate** Due to serious imprecision	There is probably no important difference in prematurity.
Neonatal laboratory adverse events 1st week of life	Relative risk 1.08 (CI 95% 0.59 - 1.99) Based on data from 687 patients in 1 studies. (Randomized controlled) Follow up 1 week	**59** per 1000	**64** per 1000 Difference: **5 more** per 1000 (CI 95% 24 fewer - 58 more)	**Moderate** Due to serious imprecision	There is probably no difference in serious biochemical adverse events.
Low birth weight <2500g at delivery	Relative risk 0.83 (CI 95% 0.6 - 1.16) Based on data from 620 patients in 1 studies. (Randomized controlled)	**204** per 1000	**169** per 1000 Difference: **35 fewer** per 1000 (CI 95% 82 fewer - 33 more)	**Moderate** Due to serious imprecision	There is probably no difference in low birth weight <2500g.

Very low birth weight <1500g at delivery	Relative risk 3.61 (CI 95% 0.76 - 17.28) Based on data from 681 patients in 1 studies. (Randomized controlled)	**6** per 1000	**22** per 1000	**Moderate** Due to serious imprecision	There may be an increased risk of very low birth weight with TDF/FTC.
		Difference: **16 more** per 1000 (CI 95% 1 fewer - 98 more)			
Vertical hepatitis B transmission - low resource 1 year postpartum	Relative risk 0.26 (CI 95% 0.01 - 4.77) Based on data from 1,037 patients in 9 studies. (Randomized controlled) Follow up neonate to 12 months	**111** per 1000	**29** per 1000	**Low** Due to very serious imprecision	There is probably no important difference in vertical hepatitis B transmission.
		Difference: **82 fewer** per 1000 (CI 95% 110 fewer - 418 more)			
Hepatitis B flare during pregnancy and in the antenatal period	Relative risk 0.48 (CI 95% 0.06 - 3.7) Based on data from 789 patients in 5 studies. (Observational (non-randomized))	**91** per 1000	**44** per 1000	**Very Low** Due to serious inconsistency, imprecision, and indirectness	We are uncertain whether TDF increases or decreases the risk of hepatitis B flares.
		Difference: **47 fewer** per 1000 (CI 95% 86 fewer - 246 more)			

Practical issues	AZT/lamivudine with ritonavir-boosted lopinavir	Tenofovir/emtricitabine with ritonavir-boosted lopinavir	Both
Medication routine Medication routine	Once daily medication Available in several one pill once a day co-formulations	AZT is a twice daily medication Available with lamivudine and abacavir as a on pill twice daily co-formulation Other cART regimens will require at minimum 3 pills total per day	
Costs and access Availability	Tenofovir-based cART regimens are routinely available in low resource settings that have limited available options.	AZT and abacavir-based cART regimens may be more or less available, depending on funding decisons made by treatment programmes.	In many settings, especially where cART is paid by a central funder, women may have access to a single first-line regimen prescribed to all patients initiating cART.
Costs and access Cost	• Tenofovir remains on patent in many settings until at least 2018 - longer for certain formulations. • In the USA, typical cost is $22,000 USD per year. • In settings with generic formulations available, cost is as low as $64 USD per year.	• AZT and lamivudine are off of patent protection around the world. • In the USA, typical cost is $11,000 USD per year. • In low-income settings, cost is as low as $73 USD per year.	In most settings, individuals do not pay for cART directly.

Adverse effects, interactions and antidote Common adverse effects	Some experience: • mild headache, • nausea and vomiting	With AZT, some experience: • Some experience mild headache, • nausea and vomiting; • in black patients, reversible skin changes in nailbeds		
Adverse effects, interactions and antidote Drug-drug interactions	Tenofovir interacts with (potentially serious interactions): • Ledipasvir (hepatitis C) • Atazanavir (HIV) • Diclofenac & nonsteroidal anti-inflammatories (pain)	AZT interacts with (potentially serious interactions): • Amodiaquine (malaria) • Ribavirin (hepatitis) • Clarithromycin (bacterial infections)	Not all drug-drug interactions are listed here, and many remain unknown or uncertain.	
Tests and visits Additional specific blood testing required for monitoring	Regular blood and urine tests for kidney function when taking tenofovir	Regular blood tests for anaemia with AZT. HLA*B5701 testing prior to initiating abacavir.	Regular blood monitoring of HIV viral load and CD4 cell count, in addition to other regular blood and urine testing.	
Food and drinks Dietary restrictions	No dietary restrictions Can take medication with food or with an empty stomach	No dietary restrictions Can take medication with food or with an empty stomach		

Details about studies used and certainty down- and upgrading

Maternal acceptability (medication discontinuations)	**Intervention reference:** Primary study **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: No serious** **Indirectness: Serious** Outcome is a surrogate for acceptability, but there may have been other reasons to withdraw from the trial. ; **Imprecision: No serious** Single study ; **Publication bias: No serious**
Maternal mortality	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Maternal clinical adverse events - compared to AZT/ lamivudine	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias and inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious**

	reference used for intervention	**Indirectness: Serious** Studies primarily from non-pregnant adults ; **Imprecision: No serious** **Publication bias: No serious**
Maternal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: No serious** ; **Imprecision: Serious** Wide confidence intervals ; **Publication bias: No serious**
Detectable maternal HIV viral load	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: Serious** Point estimates vary widely and confidence intervals have minimal overlap ; **Indirectness: Serious** Studies in non-pregnant adults to 6 months follow-up ; **Imprecision: No serious** **Publication bias: No serious**
Stillbirth and early neonatal mortality - low resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** CI includes important harm and important benefit ; **Publication bias: No serious**
Birth defect (first trimester exposure)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** **Imprecision: Serious** **Publication bias: No serious**
Vertical HIV transmission	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias ; **Inconsistency: No serious** **Indirectness: No serious** 1 week follow-up only ; **Imprecision: No serious** **Publication bias: No serious**
Spontaneous abortion	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Prematurity <34 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**

	intervention	
Prematurity <37 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Neonatal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Only data from one study ; **Publication bias: No serious**
Low birth weight <2500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Very low birth weight <1500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Vertical hepatitis B transmission - low resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Very Serious** Low number of patients - only one study with 6 total events that compared tenofovir to placebo; very wide confidence intervals ; **Publication bias: No serious**
Hepatitis B flare	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: Serious** **Indirectness: Serious** From HIV-negative mothers living with HBV ; **Imprecision: Serious** **Publication bias: No serious**

Clinical Question/ PICO

Population: Pregnant women living with HIV in high-resourced settings

Intervention: Tenofovir/emtricitabine with ritonavir-boosted lopinavir

Comparator: AZT/lamivudine with ritonavir-boosted lopinavir

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** AZT/lamivudine with ritonavir-boosted lopinavir	**Absolute effect estimates** Tenofovir/ emtricitabine with ritonavir-boosted lopinavir	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Maternal acceptability (medication discontinuations)	Relative risk 1.52 (CI 95% 0.69 - 3.33) Based on data from 716 patients in 1 studies. (Randomized controlled)	**28** per 1000	**43** per 1000	**Moderate** Due to serious indirectness	There is probably no difference in maternal acceptability.
		Difference: **15 more** per 1000 (CI 95% 9 fewer - 65 more)			
Maternal mortality	Based on data from 694 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in maternal mortality.
		Difference: **0 fewer** per 1000 (CI 95% 11 fewer - 11 more)			
Maternal clinical adverse events - compared to AZT/lamivudine	Relative risk 1 (CI 95% 0.9 - 1.12) Based on data from 2,139 patients in 3 studies. (Randomized controlled) Follow up 6 to 18 months	**20** per 1000	**20** per 1000	**Moderate** Due to serious indirectness	There is probably no important difference in maternal clinical adverse events.
		Difference: **0 fewer** per 1000 (CI 95% 2 fewer - 2 more)			
Maternal laboratory adverse events	Relative risk 0.85 (CI 95% 0.56 - 1.28) Based on data from 662 patients in 1 studies. (Randomized controlled) Follow up 6 to 18 months	**129** per 1000	**110** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in maternal serious laboratory adverse events.
		Difference: **19 fewer** per 1000 (CI 95% 57 fewer - 36 more)			
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		Difference: **16 fewer** per 1000 (CI 95% 68 fewer - 54 more)			
Stillbirth and early neonatal mortality - high resource 20 weeks	Relative risk 4.4 (CI 95% 1.75 - 11.01) Based on data from 897 patients in 3 studies. (Randomized controlled)	**15** per 1000	**66** per 1000	**Moderate** Due to serious imprecision	TDF/FTC probably increases the risk of stillbirth and early neonatal mortality.
		Difference: **51 more** per 1000			

gestational age to 1 week postpartum	Follow up 1 week postpartum	(CI 95% 11 more - 150 more)			
Birth defect (first trimester exposure) 1 year	Relative risk 0.57 (CI 95% 0.15 - 2.16) Based on data from 169 patients in 2 studies. (Randomized controlled)	**8** per 1000	**5** per 1000	**Low** Due to serious imprecision and indirectness	There may be no important difference in birth defects.
		Difference: **3 fewer** per 1000 (CI 95% 7 fewer - 9 more)			
Vertical HIV transmission	n/a Based on data from 1,956 patients in 4 studies. (Observational (non-randomized)) Follow up 1 week	**5** per 1000	**4** per 1000	**Low** Observational data	There may not be an important difference in vertical HIV transmission.
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Spontaneous abortion To 20 weeks gestational age	Relative risk 1.32 (CI 95% 0.89 - 1.94) Based on data from 176 patients in 1 studies. (Randomized controlled) Follow up To 20 weeks GA	**323** per 1000	**426** per 1000	**Moderate** Due to serious imprecision	There is probably no difference in spontaneous abortion.
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Vertical hepatitis B transmission - high resource 1 year postpartum	Relative risk 0.26 (CI 95% 0.01 - 4.77) Based on data from 1,037 patients in 9 studies. (Randomized controlled) Follow up neonate to 12 months	**10** per 1000	**3** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in vertical hepatitis B transmission.
		Difference: **7 fewer** per 1000 (CI 95% 10 fewer - 38 more)			
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Practical issues	AZT/lamivudine with ritonavir-boosted lopinavir	Tenofovir/emtricitabine with ritonavir-boosted lopinavir	Both
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Costs and access Availability	Tenofovir-based cART regimens are routinely available in low resource settings that have limited available options.	AZT and abacavir-based cART regimens may be more or less available, depending on funding decisons made by treatment programmes.	In many settings, especially where cART is paid by a central funder, women may have access to a single first-line regimen prescribed to all patients initiating cART.

Costs and access Cost	• Tenofovir remains on patent in many settings until at least 2018 - longer for certain formulations. • In the USA, typical cost is $22,000 USD per year. • In settings with generic formulations available, cost is as low as $64 USD per year.	• AZT and lamivudine are off of patent protection around the world. • In the USA, typical cost is $11,000 USD per year. • In low-income settings, cost is as low as $73 USD per year.	In most settings, individuals do not pay for cART directly.
Adverse effects, interactions and antidote Common adverse effects	Some experience: • mild headache, • nausea and vomiting	With AZT, some experience: • Some experience mild headache, • nausea and vomiting; • in black patients, reversible skin changes in nailbeds	
Adverse effects, interactions and antidote Drug-drug interactions	Tenofovir interacts with (potentially serious interactions): • Ledipasvir (hepatitis C) • Atazanavir (HIV) • Diclofenac & nonsteroidal anti-inflammatories (pain)	AZT interacts with (potentially serious interactions): • Amodiaquine (malaria) • Ribavirin (hepatitis) • Clarithromycin (bacterial infections)	Not all drug-drug interactions are listed here, and many remain unknown or uncertain.
Tests and visits Additional specific blood testing required for monitoring	Regular blood and urine tests for kidney function when taking tenofovir	Regular blood tests for anaemia with AZT. HLA*B5701 testing prior to initiating abacavir.	Regular blood monitoring of HIV viral load and CD4 cell count, in addition to other regular blood and urine testing.
Food and drinks Dietary restrictions	No dietary restrictions Can take medication with food or with an empty stomach	No dietary restrictions Can take medication with food or with an empty stomach	

Details about studies used and certainty down- and upgrading

Maternal acceptability (medication discontinuations)	**Intervention reference:** Primary study **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: No serious** **Indirectness: Serious** Outcome is a surrogate for acceptability, but there may have been other reasons to withdraw from the trial. ; **Imprecision: No serious** Single study ; **Publication bias: No serious**

Maternal mortality	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Maternal clinical adverse events - compared to AZT/ lamivudine	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias and inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: Serious** Studies primarily from non-pregnant adults ; **Imprecision: No serious** **Publication bias: No serious**
Maternal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: No serious** ; **Imprecision: Serious** Wide confidence intervals ; **Publication bias: No serious**
Detectable maternal HIV viral load	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: Serious** Point estimates vary widely and confidence intervals have minimal overlap ; **Indirectness: Serious** Studies in non-pregnant adults to 6 months follow-up ; **Imprecision: No serious** **Publication bias: No serious**
Stillbirth and early neonatal mortality - high resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** CI includes important harm and important benefit ; **Publication bias: No serious**
Birth defect (first trimester exposure)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** **Imprecision: Serious** **Publication bias: No serious**
Vertical HIV transmission	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias ; **Inconsistency: No serious** **Indirectness: No serious** 1 week follow-up only ; **Imprecision: No serious** **Publication bias: No serious**
Spontaneous	**Intervention reference:**	**Risk of bias: No serious**

abortion	Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Prematurity <34 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Prematurity <37 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Neonatal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Only data from one study ; **Publication bias: No serious**
Low birth weight <2500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Very low birth weight <1500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Vertical hepatitis B transmission - high resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Low number of patients - only one study with 6 total events that compared tenofovir to placebo. ; **Publication bias: No serious**
Hepatitis B flare	**Intervention reference:** Systematic review **Baseline/comparator**	**Risk of bias: No serious** **Inconsistency: Serious** **Indirectness: Serious** From HIV-negative mothers living with HBV ;

	reference: Control arm of reference used for intervention	**Imprecision: Serious** **Publication bias: No serious**

Weak Recommendation

For women living with HIV who are pregnant or who may become pregnant, we suggest a zidovudine and lamivudine-based antiretroviral regimen over one that includes tenofovir and emtricitabine.

Practical Info

Timing
In women who are not taking antiretroviral therapy at the start of pregnancy, antiretroviral therapy may be best initiated in the after the first trimester. Limiting exposure to antiretroviral therapy early in pregnancy could reduce the risk of birth defects and spontaneous abortion (this is highly speculative).

Some women will have compelling personal reasons to initiate antiretroviral therapy as soon as possible - for example, if the immune system is severely depressed (e.g. CD4 count less than 350 cells per mL) or in the setting of an opportunistic infection.

HIV antiretroviral susceptibility
Wherever available, women should have HIV susceptibility testing prior to initiating antiretroviral therapy and whenever possible, the infecting HIV should be susceptible to all components of the combination antiretroviral regimen.

Women who are already taking tenofovir or emtricitabine prior to pregnancy
Women who are taking tenofovir or emtricitabine prior to pregnancy may or may not decide to change to an AZT/lamivudine-based regimen. Although switching combination regimens is generally well tolerated, there is a small risk of treatment failure (an increase in blood HIV levels - viral load) as well as a risk of new or worse adverse effects. The risk of vertical transmission is higher when maternal viral load is elevated, especially around the time of delivery. Therefore, if a switch is desired, it should occur as early on in the pregnancy as possible to accomodate the possibility of a need to switch back or to a different antiretroviral regimen altogether.

Alternative NRTIs
We recommend AZT/lamivudine rather than other non-tenofovir NRTIs because evidence from RCTs is only directly applicable to AZT/lamivudine. However, other NRTI combinations such as abacavir/lamivudine are available and might be reasonably used in some situations with the understanding that their safety is very uncertain.

A new formulation of tenofovir – tenofovir alafenamide – is now available; tenofovir alafenamide, may have improved renal and bone safety compared to tenofovir disoproxil fumarate in adults, due to reduced plasma concentrations*[9]*. In the absence of randomised trial data in pregnancy, whether or not tenofovir alafenamide and tenofovir disoproxil fumarate carry similar risks to the fetus is highly uncertain. However, given the close similarity to tenofovir disoproxil fumarate, most women are likely to choose other NRTI options when available.

The third antiretroviral agent
Typically, a third antiretroviral is added to a dual NRTI backbone to complete the cART regimen. A triple NRTI regimen, with AZT/lamivudine plus abacavir, is one reasonable option, although there are several others. Evidence from a randomised trial of 540 pregnant women in Botswana suggests that, when combined with AZT/lamivudine, abacavir might confer a lower risk of premature delivery than lopinavir/ritonavir (15% vs. 23%, but with a 95% confidence interval of the difference of <1% to 16%)*[8]*. Other outcomes, including vertical transmission of HIV, were similar between abacavir and lopinavir/ritonavir. The impact of other cART regimens on key outcomes in pregnancy is very uncertain. Other reasonable options include efavirenz, raltegravir, and atazanavir/ritonavir.

Hepatitis B co-infection
Tenofovir and lamivudine both reduce the risk of vertical transmission of hepatitis B virus in women co-infected with hepatitis B virus. Where available, women should have the blood hepatitis B levels quantified (viral load). The vertical transmission risk is highest when the

viral load is high (e.g. >1 million copies per mL), combined with no or unpredictable access to early neonatal hepatitis B vaccination and neonatal immunoglobulin. Lamivudine and tenofovir appear equally effective at preventing hepatitis B transmission when taken during pregnancy only. However, longterm use of lamivudine more than tenofovir is associated with hepatitis B resistance*[10]*. In women with longterm use of possible or confirmed hepatitis B resistance to lamivudine, tenofovir may be preferred.

Key Info

Benefits and harms

Tenofovir and emtricitabine – when combined with antiretrovirals other than lopinavir/ritonavir – may increase stillbirth and early neonatal mortality as well as early premature labour before 34 weeks gestational age compared to compared to AZT and lamivudine. There probably no difference in risk of serious clinical and laboratory adverse events, including anemia and renal failure, between tenofovir/emtricitabine and AZT/lamivudine when taken at typical doses.

Quality of evidence

Overall, certainty in the balance of benefits and harms is low, including key outcomes such as stillbirth and early neonatal mortality as well as premature labour. The certainty in evidence is limited by imprecision because almost all of the most trustworthy evidence for key outcomes comes from a single trial with only 816 women*[1]*. When applying the evidence to patients who choose a third antiretroviral other than lopinavir/ritonavir, the certainty in evidence is further lowered because of indirectness.

Preference and values

The multidisciplinary panel, informed by a linked systematic review on values and preferences*[3]*, agreed that almost all women place an extremely high value on avoiding stillbirth and neonatal mortality, and most women place a very high or extremely high value on avoiding early preterm labour. With some exceptions, women probably place little or very little importance on simplifying the cART dosing regimen from twice daily to once daily. These recommendations do not apply to women who do not share these values/ preferences.

Resources and other considerations

Tenofovir/emtricitabine is available as a once per day medication, and is co-formulated into several one pill once a day options. AZT/ lamivudine is a twice daily medications and is not co-formulated with as many options: the dosing regimen will typically be more complex with AZT/lamivudine.

Many women, particularly those in resource-limited settings with government or non-governmental organisation-funded antiretroviral therapy will not have more than a single ART regimen available to them.

Rationale

We make a recommendation for AZT/lamivudine over tenofovir/emtricitabine because most women would choose to avoid a medication (tenofovir/emtricitabine) with any suggestion of harm when there are reasonable alternatives available. In this case, the best available evidence suggests that tenofovir/emtricitabine may cause stillbirths and early neonatal deaths as well as early premature delivery. Even if the true harm is much lower than the available evidence suggests, almost all women would not tolerate even an extremely small increased risk of stillbirth and early neonatal death. We make a weak rather than strong recommendation because the certainty in evidence is low, suggesting that effect estimates are likely to change with additional randomised controlled trials.

Clinical Question/ PICO

Population: Pregnant women living with HIV in low-resourced settings
Intervention: Tenofovir/emtricitabine based antiretroviral therapy
Comparator: Alternative NRTI-based antiretroviral therapy

Outcome	Study results and	Absolute effect estimates	Certainty in	Summary

Timeframe	measurements	Alternative NRTI-based antiretroviral therapy	Tenofovir/ emtricitabine based antiretroviral therapy	effect estimates (Quality of evidence)	
Maternal acceptability (medication discontinuations)	Relative risk 1.52 (CI 95% 0.69 - 3.33) Based on data from 716 patients in 1 studies. (Randomized controlled)	**28** per 1000	**43** per 1000	**Moderate** Due to serious indirectness	There is probably no difference in maternal acceptability.
		Difference: **15 more** per 1000 (CI 95% 9 fewer - 65 more)			
Maternal mortality	Based on data from 694 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in maternal mortality.
		Difference: **0 fewer** per 1000 (CI 95% 11 fewer - 11 more)			
Maternal clinical adverse events - compared to AZT/lamivudine	Relative risk 1 (CI 95% 0.9 - 1.12) Based on data from 2,139 patients in 3 studies. (Randomized controlled) Follow up 6 to 18 months	**20** per 1000	**20** per 1000	**Moderate** Due to serious indirectness	There is probably no important difference in maternal clinical adverse events.
		Difference: **0 fewer** per 1000 (CI 95% 2 fewer - 2 more)			
Maternal laboratory adverse events	Relative risk 0.85 (CI 95% 0.56 - 1.28) Based on data from 662 patients in 1 studies. (Randomized controlled) Follow up 6 to 18 months	**129** per 1000	**110** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no important difference in maternal serious laboratory adverse events.
		Difference: **19 fewer** per 1000 (CI 95% 57 fewer - 36 more)			
Detectable maternal HIV viral load At delivery	Relative risk 0.93 (CI 95% 0.71 - 1.23) Based on data from 3,231 patients in 6 studies. (Randomized controlled) Follow up 6 months	**235** per 1000	**219** per 1000	**Low** Due to serious inconsistency and indirectness	There may not be an important difference in risk of detectable viral load at delivery.
		Difference: **16 fewer** per 1000 (CI 95% 68 fewer - 54 more)			
Stillbirth and early neonatal mortality - low resource 20 weeks gestational age to 1 week postpartum	Relative risk 4.4 (CI 95% 1.75 - 11.01) Based on data from 897 patients in 3 studies. (Randomized controlled) Follow up 1 week postpartum	**69** per 1000	**304** per 1000	**Low** Due to serious imprecision and indirectness	TDF/FTC probably increases the risk of stillbirth and early neonatal mortality.
		Difference: **235 more** per 1000 (CI 95% 52 more - 691 more)			

Birth defect (first trimester exposure) 1 year	Relative risk 0.57 (CI 95% 0.15 - 2.16) Based on data from 169 patients in 2 studies. (Randomized controlled)	**8** per 1000	**5** per 1000	**Low** Due to serious imprecision and indirectness	There may be no important difference in birth defects.
		Difference: **3 fewer** per 1000 (CI 95% 7 fewer - 9 more)			
Vertical HIV transmission	n/a Based on data from 1,956 patients in 4 studies. (Observational (non-randomized)) Follow up 1 week	**5** per 1000	**4** per 1000	**Low** Observational data	There may not be an important difference in vertical HIV transmission.
		Difference: **1 fewer** per 1000 (CI 95% 10 fewer - 8 more)			
Spontaneous abortion To 20 weeks gestational age	Relative risk 1.32 (CI 95% 0.89 - 1.94) Based on data from 176 patients in 1 studies. (Randomized controlled) Follow up To 20 weeks GA	**323** per 1000	**426** per 1000	**Moderate** Due to serious imprecision	There is probably no difference in spontaneous abortion.
		Difference: **103 more** per 1000 (CI 95% 36 fewer - 304 more)			
Prematurity <34 weeks	Relative risk 2.3 (CI 95% 1.06 - 4.97) Based on data from 716 patients in 2 studies. (Randomized controlled)	**32** per 1000	**74** per 1000	**Low** Due to serious imprecision and indirectness	TDF/FTC probably increases early prematurity.
		Difference: **42 more** per 1000 (CI 95% 2 more - 127 more)			
Prematurity <37 weeks	Relative risk 0.94 (CI 95% 0.69 - 1.28) Based on data from 681 patients in 1 studies. (Randomized controlled)	**197** per 1000	**185** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no important difference in prematurity.
		Difference: **12 fewer** per 1000 (CI 95% 61 fewer - 55 more)			
Neonatal laboratory adverse events 1st week of life	Relative risk 1.08 (CI 95% 0.59 - 1.99) Based on data from 687 patients in 1 studies. (Randomized controlled) Follow up 1 week	**59** per 1000	**64** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no difference in serious biochemical adverse events.
		Difference: **5 more** per 1000 (CI 95% 24 fewer - 58 more)			

Low birth weight <2500g at delivery	Relative risk 0.83 (CI 95% 0.6 - 1.16) Based on data from 620 patients in 1 studies. (Randomized controlled)	**204** per 1000	**169** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no difference in low birth weight <2500g.
		Difference: **35 fewer** per 1000 (CI 95% 82 fewer - 33 more)			
Very low birth weight <1500g at delivery	Relative risk 3.61 (CI 95% 0.76 - 17.28) Based on data from 681 patients in 1 studies. (Randomized controlled)	**6** per 1000	**22** per 1000	**Low** Due to serious imprecision and indirectness	There may be an increased risk of very low birth weight with TDF/ FTC.
		Difference: **16 more** per 1000 (CI 95% 1 fewer - 98 more)			
Vertical hepatitis B transmission - low resource 1 year postpartum	Relative risk 0.26 (CI 95% 0.01 - 4.77) Based on data from 1,037 patients in 9 studies. (Randomized controlled) Follow up neonate to 12 months	**111** per 1000	**29** per 1000	**Low** Due to very serious imprecision	There is probably no important difference in vertical hepatitis B transmission.
		Difference: **82 fewer** per 1000 (CI 95% 110 fewer - 418 more)			
Hepatitis B flare during pregnancy and in the antenatal period	Relative risk 0.48 (CI 95% 0.06 - 3.7) Based on data from 789 patients in 5 studies. (Observational (non-randomized))	**91** per 1000	**44** per 1000	**Very Low** Due to serious inconsistency, imprecision, and indirectness	We are uncertain whether TDF increases or decreases the risk of hepatitis B flares.
		Difference: **47 fewer** per 1000 (CI 95% 86 fewer - 246 more)			

Practical issues	Alternative NRTI-based antiretroviral therapy	Tenofovir/emtricitabine based antiretroviral therapy	Both
Medication routine Medication routine	Once daily medication Available in several one pill once a day co-formulations	AZT is a twice daily medication Available with lamivudine and abacavir as a on pill twice daily co-formulation Other cART regimens will require at minimum 3 pills total per day	
Costs and access Availability	Tenofovir-based cART regimens are routinely available in low resource settings that have limited available options.	AZT and abacavir-based cART regimens may be more or less available, depending on funding decisons made by treatment programmes.	In many settings, especially where cART is paid by a central funder, women may have access to a single first-line regimen prescribed to all patients initiating cART.

Costs and access Cost	• Tenofovir remains on patent in many settings until at least 2018 - longer for certain formulations. • In the USA, typical cost is $22,000 USD per year. • In settings with generic formulations available, cost is as low as $64 USD per year.	• AZT and lamivudine are off of patent protection around the world. • In the USA, typical cost is $11,000 USD per year. • In low-income settings, cost is as low as $73 USD per year.	In most settings, individuals do not pay for cART directly.
Adverse effects, interactions and antidote Common adverse effects	Some experience: • mild headache, • nausea and vomiting	With AZT, some experience: • Some experience mild headache, • nausea and vomiting; • in black patients, reversible skin changes in nailbeds	
Adverse effects, interactions and antidote Drug-drug interactions	Tenofovir interacts with (potentially serious interactions): • Ledipasvir (hepatitis C) • Atazanavir (HIV) • Diclofenac & nonsteroidal anti-inflammatories (pain)	AZT interacts with (potentially serious interactions): • Amodiaquine (malaria) • Ribavirin (hepatitis) • Clarithromycin (bacterial infections)	Not all drug-drug interactions are listed here, and many remain unknown or uncertain.
Tests and visits Additional specific blood testing required for monitoring	Regular blood and urine tests for kidney function when taking tenofovir	Regular blood tests for anaemia with AZT. HLA*B5701 testing prior to initiating abacavir.	Regular blood monitoring of HIV viral load and CD4 cell count, in addition to other regular blood and urine testing.
Food and drinks Dietary restrictions	No dietary restrictions Can take medication with food or with an empty stomach	No dietary restrictions Can take medication with food or with an empty stomach	

Details about studies used and certainty down- and upgrading

Maternal acceptability (medication discontinuations)	**Intervention reference:** Primary study **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: No serious** **Indirectness: Serious** Outcome is a surrogate for acceptability, but there may have been other reasons to withdraw from the trial. ; **Imprecision: No serious** Single study ; **Publication bias: No serious**

Maternal mortality	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Maternal clinical adverse events - compared to AZT/ lamivudine	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias and inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: Serious** Studies primarily from non-pregnant adults ; **Imprecision: No serious** **Publication bias: No serious**
Maternal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** Wide confidence intervals ; **Publication bias: No serious**
Detectable maternal HIV viral load	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: Serious** Point estimates vary widely and confidence intervals have minimal overlap ; **Indirectness: Serious** Studies in non-pregnant adults to 6 months follow-up ; **Imprecision: No serious** **Publication bias: No serious**
Stillbirth and early neonatal mortality - low resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** CI includes important harm and important benefit ; **Publication bias: No serious**
Birth defect (first trimester exposure)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** **Imprecision: Serious** **Publication bias: No serious**
Vertical HIV transmission	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of	**Risk of bias: No serious** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias ; **Inconsistency: No serious** **Indirectness: No serious** 1 week follow-up only ;

	reference used for intervention	**Imprecision: No serious** **Publication bias: No serious**
Spontaneous abortion	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Prematurity <34 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**
Prematurity <37 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**
Neonatal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** Only data from one study ; **Publication bias: No serious**
Low birth weight <2500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**
Very low birth weight <1500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious**

		Publication bias: No serious
Vertical hepatitis B transmission - low resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Very Serious** Low number of patients - only one study with 6 total events that compared tenofovir to placebo; very wide confidence intervals ; **Publication bias: No serious**
Hepatitis B flare	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: Serious** **Indirectness: Serious** From HIV-negative mothers living with HBV ; **Imprecision: Serious** **Publication bias: No serious**

Clinical Question/ PICO

Population: Pregnant women living with HIV in high-resourced settings
Intervention: Tenofovir/emtricitabine based antiretroviral therapy
Comparator: Alternative NRTI-based antiretroviral therapy

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates** Alternative NRTI-based antiretroviral therapy	**Absolute effect estimates** Tenofovir/ emtricitabine based antiretroviral therapy	**Certainty in effect estimates** (Quality of evidence)	**Summary**
Maternal acceptability (medication discontinuations)	Relative risk 1.52 (CI 95% 0.69 - 3.33) Based on data from 716 patients in 1 studies. (Randomized controlled)	**28** per 1000	**43** per 1000 Difference: **15 more** per 1000 (CI 95% 9 fewer - 65 more)	**Moderate** Due to serious indirectness	There is probably no difference in maternal acceptability.
Maternal mortality	Based on data from 694 patients in 1 studies. (Randomized controlled)	**0** per 1000	**0** per 1000 Difference: **0 fewer** per 1000 (CI 95% 11 fewer - 11 more)	**Moderate** Due to serious imprecision	There is probably no important difference in maternal mortality.
Maternal clinical adverse events - compared to AZT/lamivudine	Relative risk 1 (CI 95% 0.9 - 1.12) Based on data from 2,139 patients in 3 studies. (Randomized controlled)	**20** per 1000	**20** per 1000 Difference: **0 fewer** per 1000	**Moderate** Due to serious indirectness	There is probably no important difference in maternal clinical adverse events.

	Follow up 6 to 18 months	(CI 95% 2 fewer - 2 more)			
Maternal laboratory adverse events	Relative risk 0.85 (CI 95% 0.56 - 1.28) Based on data from 662 patients in 1 studies. (Randomized controlled) Follow up 6 to 18 months	**129** per 1000	**110** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no important difference in maternal serious laboratory adverse events.
		Difference: **19 fewer** per 1000 (CI 95% 57 fewer - 36 more)			
Detectable maternal HIV viral load At delivery	Relative risk 0.93 (CI 95% 0.71 - 1.23) Based on data from 3,231 patients in 6 studies. (Randomized controlled) Follow up 6 months	**235** per 1000	**219** per 1000	**Low** Due to serious inconsistency and indirectness	There may not be an important difference in risk of detectable viral load at delivery.
		Difference: **16 fewer** per 1000 (CI 95% 68 fewer - 54 more)			
Stillbirth and early neonatal mortality - high resource 20 weeks gestational age to 1 week postpartum	Relative risk 4.4 (CI 95% 1.75 - 11.01) Based on data from 897 patients in 3 studies. (Randomized controlled) Follow up 1 week postpartum	**15** per 1000	**66** per 1000	**Low** Due to serious imprecision and indirectness	TDF/FTC probably increases the risk of stillbirth and early neonatal mortality.
		Difference: **51 more** per 1000 (CI 95% 11 more - 150 more)			
Birth defect (first trimester exposure) 1 year	Relative risk 0.57 (CI 95% 0.15 - 2.16) Based on data from 169 patients in 2 studies. (Randomized controlled)	**8** per 1000	**5** per 1000	**Low** Due to serious imprecision and indirectness	There may be no important difference in birth defects.
		Difference: **3 fewer** per 1000 (CI 95% 7 fewer - 9 more)			
Vertical HIV transmission	n/a Based on data from 1,956 patients in 4 studies. (Observational (non-randomized)) Follow up 1 week	**5** per 1000	**4** per 1000	**Low** Observational data	There may not be an important difference in vertical HIV transmission.
		Difference: **1 fewer** per 1000 (CI 95% 10 fewer - 8 more)			
Spontaneous abortion To 20 weeks gestational age	Relative risk 1.32 (CI 95% 0.89 - 1.94) Based on data from 176 patients in 1 studies. (Randomized controlled) Follow up To 20 weeks	**323** per 1000	**426** per 1000	**Moderate** Due to serious imprecision	There is probably no difference in spontaneous abortion.
		Difference: **103 more** per 1000 (CI 95% 36 fewer - 304 more)			

	GA				
Prematurity <34 weeks	Relative risk 2.3 (CI 95% 1.06 - 4.97) Based on data from 716 patients in 2 studies. (Randomized controlled)	**32** per 1000	**74** per 1000	**Low** Due to serious imprecision and indirectness	TDF/FTC probably increases early prematurity.
		Difference: **42 more** per 1000 (CI 95% 2 more - 127 more)			
Prematurity <37 weeks	Relative risk 0.94 (CI 95% 0.69 - 1.28) Based on data from 681 patients in 1 studies. (Randomized controlled)	**197** per 1000	**185** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no important difference in prematurity.
		Difference: **12 fewer** per 1000 (CI 95% 61 fewer - 55 more)			
Neonatal laboratory adverse events 1st week of life	Relative risk 1.08 (CI 95% 0.59 - 1.99) Based on data from 687 patients in 1 studies. (Randomized controlled) Follow up 1 week	**59** per 1000	**64** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no difference in serious biochemical adverse events.
		Difference: **5 more** per 1000 (CI 95% 24 fewer - 58 more)			
Low birth weight <2500g at delivery	Relative risk 0.83 (CI 95% 0.6 - 1.16) Based on data from 620 patients in 1 studies. (Randomized controlled)	**204** per 1000	**169** per 1000	**Low** Due to serious imprecision and indirectness	There is probably no difference in low birth weight <2500g.
		Difference: **35 fewer** per 1000 (CI 95% 82 fewer - 33 more)			
Very low birth weight <1500g at delivery	Relative risk 3.61 (CI 95% 0.76 - 17.28) Based on data from 681 patients in 1 studies. (Randomized controlled)	**6** per 1000	**22** per 1000	**Low** Due to serious imprecision and indirectness	There may be an increased risk of very low birth weight with TDF/FTC.
		Difference: **16 more** per 1000 (CI 95% 1 fewer - 98 more)			
Vertical hepatitis B transmission - high resource 1 year postpartum	Relative risk 0.26 (CI 95% 0.01 - 4.77) Based on data from 1,037 patients in 9 studies. (Randomized controlled) Follow up neonate to 12 months	**10** per 1000	**3** per 1000	**Moderate** Due to serious imprecision	There is probably no important difference in vertical hepatitis B transmission.
		Difference: **7 fewer** per 1000 (CI 95% 10 fewer - 38 more)			
Hepatitis B flare during pregnancy and in the	Relative risk 0.48 (CI 95% 0.06 - 3.7) Based on data from 789	**91**	**44**	**Very Low** Due to serious inconsistency,	We are uncertain whether TDF increases or decreases the risk of

antenatal period	patients in 5 studies. (Observational (non-randomized))	per 1000 Difference: **47 fewer** per 1000 (CI 95% 86 fewer - 246 more)	per 1000	imprecision, and indirectness	hepatitis B flares.

Practical issues	Alternative NRTI-based antiretroviral therapy	Tenofovir/emtricitabine based antiretroviral therapy	Both
Medication routine Medication routine	Once daily medication Available in several one pill once a day co-formulations	AZT is a twice daily medication Available with lamivudine and abacavir as a on pill twice daily co-formulation Other cART regimens will require at minimum 3 pills total per day	
Costs and access Availability	Tenofovir-based cART regimens are routinely available in low resource settings that have limited available options.	AZT and abacavir-based cART regimens may be more or less available, depending on funding decisons made by treatment programmes.	In many settings, especially where cART is paid by a central funder, women may have access to a single first-line regimen prescribed to all patients initiating cART.
Costs and access Cost	• Tenofovir remains on patent in many settings until at least 2018 - longer for certain formulations. • In the USA, typical cost is $22,000 USD per year. • In settings with generic formulations available, cost is as low as $64 USD per year.	• AZT and lamivudine are off of patent protection around the world. • In the USA, typical cost is $11,000 USD per year. • In low-income settings, cost is as low as $73 USD per year.	In most settings, individuals do not pay for cART directly.
Adverse effects, interactions and antidote Common adverse effects	Some experience: • mild headache, • nausea and vomiting	With AZT, some experience: • Some experience mild headache, • nausea and vomiting; • in black patients, reversible skin changes in nailbeds	
Adverse effects, interactions and antidote Drug-drug interactions	Tenofovir interacts with (potentially serious interactions): • Ledipasvir (hepatitis C) • Atazanavir (HIV) • Diclofenac & nonsteroidal anti-inflammatories (pain)	AZT interacts with (potentially serious interactions): • Amodiaquine (malaria) • Ribavirin (hepatitis) • Clarithromycin (bacterial infections)	Not all drug-drug interactions are listed here, and many remain unknown or uncertain.

Tests and visits Additional specific blood testing required for monitoring	Regular blood and urine tests for kidney function when taking tenofovir	Regular blood tests for anaemia with AZT. HLA*B5701 testing prior to initiating abacavir.	Regular blood monitoring of HIV viral load and CD4 cell count, in addition to other regular blood and urine testing.
Food and drinks Dietary restrictions	No dietary restrictions Can take medication with food or with an empty stomach	No dietary restrictions Can take medication with food or with an empty stomach	

Details about studies used and certainty down- and upgrading

Maternal acceptability (medication discontinuations)	**Intervention reference:** Primary study **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: No serious** **Indirectness: Serious** Outcome is a surrogate for acceptability, but there may have been other reasons to withdraw from the trial. ; **Imprecision: No serious** Single study ; **Publication bias: No serious**
Maternal mortality	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Maternal clinical adverse events - compared to AZT/ lamivudine	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias and inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: Serious** Studies primarily from non-pregnant adults ; **Imprecision: No serious** **Publication bias: No serious**
Maternal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias ; **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** Wide confidence intervals ; **Publication bias: No serious**
Detectable maternal HIV viral load	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of	**Risk of bias: No serious** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias ; **Inconsistency: Serious** Point estimates vary widely and confidence intervals have minimal overlap ;

	reference used for intervention	**Indirectness: Serious** Studies in non-pregnant adults to 6 months follow-up ; **Imprecision: No serious** **Publication bias: No serious**
Stillbirth and early neonatal mortality - high resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Primary study	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** CI includes important harm and important benefit ; **Publication bias: No serious**
Birth defect (first trimester exposure)	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** **Imprecision: Serious** **Publication bias: No serious**
Vertical HIV transmission	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** Inadequate sequence generation/ generation of comparable groups, resulting in potential for selection bias ; **Inconsistency: No serious** **Indirectness: No serious** 1 week follow-up only ; **Imprecision: No serious** **Publication bias: No serious**
Spontaneous abortion	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** **Publication bias: No serious**
Prematurity <34 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**
Prematurity <37 weeks	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**

Neonatal laboratory adverse events	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** Only data from one study ; **Publication bias: No serious**
Low birth weight <2500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**
Very low birth weight <1500g	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: Serious** Evidence comes entirely from the PROMISE trial, which combined both NRTI options with lopinavir/ritonavir. There may or may not be important drug-drug interactions between tenofovir and lopinavir and therefore, our certainty is lower when considering third antiretrovirals other than lopinavir and ritonavir. ; **Imprecision: Serious** **Publication bias: No serious**
Vertical hepatitis B transmission - high resource	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: No serious** **Indirectness: No serious** **Imprecision: Serious** Low number of patients - only one study with 6 total events that compared tenofovir to placebo. ; **Publication bias: No serious**
Hepatitis B flare	**Intervention reference:** Systematic review **Baseline/comparator reference:** Control arm of reference used for intervention	**Risk of bias: No serious** **Inconsistency: Serious** **Indirectness: Serious** From HIV-negative mothers living with HBV ; **Imprecision: Serious** **Publication bias: No serious**

2 - BMJ Rapid Recommendations: Background and methods

About *BMJ* Rapid Recommendations

Translating research to clinical practice is challenging. Trustworthy clinical practice recommendations are one useful knowledge translation strategy. Organisations creating systematic reviews and guidelines often struggle to deliver timely and trustworthy recommendations in response to potentially practice-changing evidence. *BMJ* Rapid Recommendations aims to create trustworthy clinical practice recommendations based on the highest quality evidence in record time. The project is supported by an international network of systematic review and guideline methodologists, people with lived experience of the diseases or conditions, clinical specialists, and front-line clinicians. This overview is one of a package that includes recommendations and one or more systematic reviews published by the *BMJ* group and in MAGICapp (http://www.magicapp.org). The goal is to translate evidence into recommendations for clinical practice in a timely and transparent way, minimizing bias and centred around the experience of patients. *BMJ* Rapid Recommendations will consider both new and old evidence that might alter established clinical practice.

Process overview

1. On a daily basis, we monitor the literature for practice-changing evidence:
   a. Formal monitoring through McMaster Premium LiteratUre Service (PLUS)
   b. Informal monitoring the literature by *BMJ* Rapid Recommendations expert groups, including clinician specialists and patients
2. The *RapidRecs* executive team and editors at *The BMJ* choose which clinical questions to pursue among the identified potentially-practice changing evidence, based on relevance to a wide audience, widespread interest, and likelihood to change practice.
3. We incorporate the evidence into the existing body of evidence and broader context of clinical practice via:
   a. a rapid and high-quality systematic review and meta-analysis on the benefits and harms with a focus on the outcomes that matter to patients
   b. parallel rapid recommendations that meet the standards for trustworthy guidelines[1] by an international panel of people with relevant lived experience, front-line clinicians, clinical content experts, and methodologists.
   d. Further research may be conducted including:
      i. A systematic review of observational studies to identify baseline risk estimates that most closely represent the population at the heart of the clinical question, a key component when calculating the estimates of absolute effects of the intervention
      ii. A systematic review on the preferences and values of patients on the topic.
4. Disseminate the rapid recommendations through
   a. publication of the research in *BMJ* journals
   b. short summary of recommendations for clinicians published in *The BMJ*
   c. press release and/or marketing to media outlets and relevant parties such as patient groups
   d. Links to BMJ Group's *Best Practice* point of care resource
   e. MAGICapp which provides recommendations and all underlying content in digitally structured multilayered formats for clinicians and others who wish to re-examine or consider national or local adaptation of the recommendations.

Who is involved?
Researchers, systematic review and guideline authors, clinicians, and patients often work in silos. Academic journals may publish work from any one or combinations of these groups of people and findings may also be published in the media. But it is rare that these groups work together to produce a comprehensive package. *BMJ-RapidRecs* circumvents organisational barriers in order to provide clinicians with guidance for potentially practice-changing evidence.
Our collaboration involves
   a. The *RapidRecs* group with a designated Executive team responsible for recruiting and coordinating the network of researchers who perform the systematic reviews and the recommendation panels.. The *RapidRecs* group is part of MAGIC (www.magicproject.org), a non for profit organization that provides MAGICapp (www.magicapp.org) an authoring and publication platform for evidence summaries, guidelines and decision aids, which are disseminated online for all devices.[5]
   b. *The BMJ* helps identifiying practice-changing evidence on key clinical questions, coordinates the editorial process and publishes the package of content linking to the MAGICapp that is presented in a user friendly way.

METHODS FOR THE RAPID RECOMMENDATIONS

The formation of these recommendations adheres to standards for trustworthy guidelines with an emphasis on patient involvement, strict management of conflicts of interests, as well as transparent and systematic processes for assessing the quality of evidence and for moving from evidence to recommendations. [1,2,6]

Guidance on how the panel is picked and how they contribute
Panel members are sought and screened through an informal process.
The following panel members are important

- At least one author of the individual systematic reviews
- At least one patient representative with lived experience of the disease or condition. This person receives patient-oriented documents to explain the process and is allocated a linked panel member to empower their contribution.
- A full spectrum of practicing clinicians involved in the management of the clinical problem and patients it affects, including front-line clinicians with generalist experience and those with deep content clinical and research expertise in the particular topic.
- Methodological experts in health research methodology and guideline development

Any potential conflicts of interest are managed with extreme prudence:

- No panel member can have a financial interest – as assessed by the panel chair, the *Rapidrecs* executive team or *The BMJ* editors as relevant to the topic
- No more than two panel members with an intellectual interest on the topic (typically having published statements favouring one of the interventions).

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, the panel recruitment of content experts and community panel members was challenging. Content experts in this area are infectious diseases experts, many of whom have financial conflicts of interests through interactions with the pharmaceutical industry through advisory boards and participation in industry-funded trials. The group reached out to more than 17 potential panel members who were eventually excluded from participating because of conflicts – notably, all of these persons had not disclosed any relevant conflicts on related and recent publications in the topic area. Many more potential panel members were not recruited because of publicly declared conflicts. The chair and MAGIC team were able, with considerable effort and ingenuity, to recruit several excellent and unconflicted content experts.

How the panel meets and works

The international panel communicates via teleconferences and e-mail exchange of written documents throughout the process. Minutes from teleconferences are audiorecorded, transcribed, and stored for later documentation (available for peer-reviewers on request). Teleconferences typically occur at three timepoints, with circulated documents by e-mail in advance:

1. At the initiation of the process to provide feedback on the systematic review protocol (for example, on selection of patient-important outcomes and appropriate prespecified analysis of results) before it is performed.
2. At the evidence summary stage with discussion, feedback and agreement on draft evidence (GRADE evidence profile) prepared by the Chair and the methods editor based on the systematic review.
3. At the recommendation formulation phase with discussion, feedback and agreement on draft recommendations and other content underlying the recommendation (e.g. GRADE SoF-table, key information, rationale, practical advice)

Following the last teleconference the final version of the recommendations is circulated by e-mail specifically requesting feedback from all panel members to document agreement before submission to *The BMJ*. Additional teleconferences are arranged as needed.

Illustrative example: For the BMJ Rapid Recommendations on antiretroviral therapy for pregnant women living with HIV, two large-group teleconferences were arranged. First, content experts provided crucial input to evidence assessment (e.g. subgroups to identify). For the recommendation formulation phase the panel needed two teleconferences to discuss all elements in detail, followed by more than 100 e-mails with specific issues to be sorted out. Multiple teleconferences were held to allow the scheduling flexibility required so that all could participate.

How we move from research findings to recommendations

What information is considered?

The panel considers best current evidence from available research. Beyond systematic reviews - performed in the context of the *BMJ* Rapid Recommendations - the panel may also include a number of other research papers to further inform the recommendations.

How is a trustworthy guideline made?

The Institute of Medicine (IOM)'s guidance on out how trustworthy guidelines should be developed and articulated key standards as outlined in the table below.[1] The standards are similar to those developed by the Guideline International Network (G-I-N).[2] These standards have been widely adopted by the international guideline community. Peer reviewers of the recommendation article are asked whether they found the guideline trustworthy (in accordance with IOM standards). The table below lays out how we hope to meet the standards for our rapid recommendations:

1. Establishing transparency
"The processes by which a CPG is developed and funded should be detailed explicitly and publicly accessible"*

- This method is available and published as a supplementary file as well as in MAGICapp where all recommendations and underlying content is available.
- We ask the peer-reviewers to judge whether the guidance is trustworthy and will respond to concerns raised.

2. Managing conflicts of interest
"Prior to selection of the guideline development group, individuals being considered for membership should declare all interests and activities potentially resulting in COI with development group activity....",

- Interests of each panel member are declared prior to involvement and published with the rapid recommendations
- No one with any potential financial interests in the past three years, or forthcoming 12 months will participate - as judged by the panel chair and *The BMJ*
- No more than two panel members have declared an intellectual conflict of interest. Such conflicts include having taken a position on the issue for example by a written an editorial, commentary, or conflicts related to performing a primary research study or written a prior systematic review on the topic.
- The Chair must have methods expertise, a clinical background and no financial or intellectual interests.
- Funders and pharmaceutical companies have no role in these recommendations.

3. Guideline Development Group Composition
"The guideline development group should be multidisciplinary and balanced, comprising a variety of methodological experts and clinicians, and populations expected to be affected by the CPG"

- *The RapidRecs* group will aim to include representation from most or every major geographic region in the world, with specific efforts made to achieve gender-balance.
- We will facilitate patient and public involvement by including patient experience, via patient-representatives and systematic reviews addressing values and preferences to guide outcome choices and relative weights of each outcome, where available
- Patient-representatives will be given priority during panel meetings and will have an explicit role in vetting the panel's judgements of values and preferences.

4. Clinical Practice Guideline–Systematic Review Intersection
"CPG developers should use systematic reviews that meet standards set by the IOM. Guideline development group and systematic review team should interact regarding the scope, approach, and output of both processes".

- Each rapid recommendation will be based on one or more high-quality SRs either developed and published in parallel with our *BMJ* Rapid Recommendations or produced by other authors and available at the time of making the recommendaiton.
- The recommendation panel and SR teams will interact, with up to three members participating in both teams to facilitate communication and continuity in the process

5. Establishing Evidence Foundations for and Rating Strength of Recommendations
"For each recommendation: explain underlying reasoning, including a clear description of potential benefits and harms, a summary of relevant available evidence and description of the quality., explain the part played by values, opinion, theory, and clinical experience in deriving the recommendation, "provide rating of strength of recommendations"

- The GRADE approach will provide the framework for establishing evidence foundations and rating strength of recommendations.[6] For each recommendation systematic and transparent assessments are made across the following key factors:
  - Absolute benefit and harms for all patient-important outcomes through structured evidence summaries (e.g. GRADE Summary of Findings tables) [4]
  - Quality of the evidence [7]
  - Values and preferences of patients
  - Resources and other considerations (e.g. feasibility, applicability, equity)
- Each outcome will - if data are available through systematic reviews - include an effect estimate and confidence interval, with a measure of certainty in the evidence, as presented in Summary of Findings tables. If such data are not available narrative summaries will be provided.
- A summary of the underlying reasoning and all additional information (e.g. key factors, practical advice, references) will be available online in an interactive format at www.magicapp.org. This summary will include descriptions of how theory (e.g. patophysiology) and clinical experience played into the evidence assessment and recommendation development.
- Recommendations will be rated either weak or strong, as defined by GRADE. [8]
- If the panel members disagree regarding evidence assessment or strength of recommendations, we will follow a structured consensus process customized to the GRADE system and report any final differences in opinion, with their rationale, in the online supplement and online at www.magicapp.org.

6. Articulation of recommendations
"Recommendations should be articulated in a standardized form detailing precisely what the recommended action is, and under what circumstances it should be performed, and so that compliance with the recommendation(s) can be evaluated"

- Each recommendation will appear at the top of the guideline infographic, published in *The BMJ*, and will be available in standardised formats in MAGICapp, articulated to be actionable based on best current evidence on presentation formats of guidelines.[9]
- There will be a statement included in each summary article in *The BMJ* and in the MAGICapp that these are recommendations to provide clinicians with guidance. They do not form a mandate of action and should be contextualised in the healthcare system a clinician's works in, and or with an individual patient.

7. External review
"External reviewers should comprise a full spectrum of relevant stakeholders...., authorship should be kept confidential....., all reviewer comments should be considered....a rationale for modifying or not should be recorded in writing.... a draft of the recommendation should be made available to general public for

comment.."

- At least two external peer-reviewers and one patient reviewer will review the article for *The BMJ* and provide open peer review. Each will have access to all the information in the package. They will be asked for general feedback as well as to make an overall judgement on whether they view the guidelines as trustworthy
- A *BMJ* series adviser with methodological and/or statistical expertise will review the *BMJ* Rapid Recommendations publication and the systematic reviews.
- The *Rapidrecs* panel will be asked to read and respond to the peer review comments and make amendments where they judge reasonable
- *The BMJ* and *RapidRecs* executive team may, on a case-by-case basis, choose to invite key organizations, agencies, or patient/public representatives to provide and submit public peer-review.
- There will be post-publication public review process through which people can provide comments and feedback through MAGICapp (or through *The BMJ*). The Chair will, on behalf of panel authors, aim to respond to each publicly-available peer-review within 30 days, for a period of six months after publication.

8. Updating
"The date for publication, systematic review and proposed date for future review should be documented, the literature should be monitored regularly and the recommendation should be updated when warranted by new evidence"

- The *Rapidrecs* panel will, through monitoring of new research evidence for published *BMJ* Rapid Recommendations, aim to provide updates of the recommendations in situations in which the evidence suggests a change in practice. These updates will be initially performed in MAGICapp and submitted to *The BMJ* for consideration of publication of a new Rapid Recommendation.

References:
1. Laine C, Taichman DB, Mulrow C. Trustworthy clinical guidelines. *Annals of internal medicine.* 2011;154(11):774-775.
2. Qaseem A, Forland F, Macbeth F, et al. Guidelines International Network: toward international standards for clinical practice guidelines. *Annals of internal medicine.* 2012;156(7):525-531.
3. Guyatt GH, Oxman AD, Kunz R, et al. Going from evidence to recommendations. *Bmj.* 2008;336(7652):1049-1051.
4. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *Journal of clinical epidemiology.* 2011;64(4):383-394.
5. Vandvik PO, Brandt L, Alonso-Coello P, et al. Creating clinical practice guidelines we can trust, use, and share: a new era is imminent. *Chest.* 2013;144(2):381-389.
6. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *Bmj.* 2008;336(7650):924-926.
7. Balshem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of evidence. *Journal of clinical epidemiology.* 2011;64(4):401-406.
8. Andrews JC, Schunemann HJ, Oxman AD, et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. *Journal of clinical epidemiology.* 2013;66(7):726-735.
9. Kristiansen A, Brandt L, Alonso-Coello P, et al. Development of a novel, multilayered presentation format for clinical practice guidelines. *Chest.* 2015;147(3):754-763.

References

[1] Fowler MG, Qin M, Fiscus SA, Currier JS, Flynn PM, Chipato T, McIntyre J, Gnanashanmugam D, Siberry GK, Coletti AS, Taha TE, Klingman KL, Martinson FE, Owor M, Violari A, Moodley D, Theron GB, Bhosale R, Bobat R, Chi BH, Strehlau R, Mlay P, Loftis AJ, Browning R, Fenton T, Purdue L, Basar M, Shapiro DE, Mofenson LM, Benefits and Risks of Antiretroviral Therapy for Perinatal HIV Prevention.. The New England journal of medicine 2016;375(18):1726-1737-null Pubmed

[2] Siemieniuk R, Lytvyn L, Mah Ming J Antiretroviral therapy for pregnant women living with HIV or hepatitis B: systematic review. BMJ Open Co-submitted;

[3] Lytvyn L Values and preferences of pregnant women living with HIV who are initiating antiretroviral therapy. BMJ Open co-submitted;

[4] Cotter AM, Garcia AG, Duthely ML, Luke B, O'Sullivan MJ Is antiretroviral therapy during pregnancy associated with an increased risk of preterm delivery, low birth weight, or stillbirth?. The Journal of infectious diseases 2006;193(9):1195-201-null Pubmed

[5] D'Ubaldo C, Pezzotti P, Rezza G, Branca M, Ippolito G Association between HIV-1 infection and miscarriage: a retrospective study. DIANAIDS Collaborative Study Group. Diagnosi Iniziale Anomalie Neoplastiche AIDS.. AIDS (London, England) 1998;12(9):1087-93-null Pubmed

[6] Chen JY, Ribaudo HJ, Souda S, Parekh N, Ogwu A, Lockman S, Powis K, Dryden-Peterson S, Creek T, Jimbo W, Madidimalo T, Makhema J, Essex M, Shapiro RL Highly active antiretroviral therapy and adverse birth outcomes among HIV-infected women in Botswana.. The Journal of infectious diseases 2012;206(11):1695-705-null Pubmed Journal

[7] Keane E, Funk AL, Shimakawa Y Systematic review with meta-analysis: the risk of mother-to-child transmission of hepatitis B virus infection in sub-Saharan Africa.. Alimentary pharmacology & therapeutics 2016;44(10):1005-1017-null Pubmed Journal

[8] Shapiro RL, Hughes MD, Ogwu A, Kitch D, Lockman S, Moffat C, Makhema J, Moyo S, Thior I, McIntosh K, van Widenfelt E, Leidner J, Powis K, Asmelash A, Tumbare E, Zwerski S, Sharma U, Handelsman E, Mburu K, Jayeoba O, Moko E, Souda S, Lubega E, Akhtar M, Wester C, Tuomola R, Snowden W, Martinez-Tristani M, Mazhani L, Essex M Antiretroviral regimens in pregnancy and breast-feeding in Botswana.. The New England journal of medicine 2010;362(24):2282-94-null Pubmed Journal

[9] Wang H, Lu XI, Yang X, Xu N The efficacy and safety of tenofovir alafenamide versus tenofovir disoproxil fumarate in antiretroviral regimens for HIV-1 therapy: Meta-analysis.. Medicine 2016;95(41):e5146-null Pubmed

[10] Lok ASF, Lai C-L, Leung N, Yao G-B, Cui Z-Y, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M Long-term safety of lamivudine treatment in patients with chronic hepatitis B.. Gastroenterology 2003;125(6):1714-22-null Pubmed