Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline

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Population

Pregnant women living with HIV

Already receiving combination antiretroviral therapy (cART)

New diagnosis / not receiving cART

Intrapartum antiretroviral therapy only

AZT mono-therapy

Combination antiretroviral therapy (cART)

TDF + FTC + at least one additional antiretroviral

ATZ + 3TC + at least one additional antiretroviral

CD4 ≥ 350

CD4 < 350

Drug names

There are a large number of different antiretroviral drugs used by people with HIV. These drug names and abbreviations will be used throughout this article.

Nucleoside reverse transcriptase inhibitors (NRTIs)

- TDF Tenofovir
- FTC Emtricitabine
- AZT Zidovudine
- 3TC Lamivudine
- ABC Abacavir

Protease inhibitors (PIs)

- LPV/r Lopinavir (boosted with ritonavir)
- ATZ/r Atazanavir (boosted with ritonavir)
- DRV/r Darunavir (boosted with ritonavir)

Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

- EFV Efavirenz
- RPV Rilpivirine

Integrase inhibitors

- RAL Raltegravir

This recommendation compares different combined antiretroviral medications that may be given to women during pregnancy, to reduce the risk of vertical transmission to the child.
Rapid Recommendations

Comparison 1

Favours TDF + FTC cART

TDF + FTC-based therapy
Tenoforv + emtricitabine-based antiretroviral therapy.

Treatment backbone:
TDF + FTC

Compared with one of:
ATZ/r
DRV/r
EFV
RAL
RPV

AZT + 3TC-based therapy
Zidovudine + lamivudine-based antiretroviral therapy.

Treatment backbone:
AZT + 3TC

Compared with one of:
LPV/r
DRV/r
ATZ/r
RAL
EFV
RPV

Favours AZT + 3TC cART

We suggest a zidovudine and lamivudine-based antiretroviral regimen over one that includes tenofovir and emtricitabine.

Comparison of benefits and harms

| All settings | HIV vertical transmission | Maternal laboratory AEs | Maternal clinical AEs | Premature births (>34 weeks) |
|--------------|---------------------------|------------------------|----------------------|-----------------------------|
| Events per 1000 people | 4 | 117 | 20 | 74 |
| Favor TDF + FTC cART | Favor AZT + 3TC cART |

Comparative benefits and harms

| All settings | Evidence quality |
|--------------|------------------|
| HIV vertical transmission | Low |
| Maternal laboratory AEs | Low |
| Maternal clinical AEs | Moderate |
| Premature births (>34 weeks) | Low |

Comparative benefits and harms by settings

Low/medium resourced settings

| Hepatitis B vertical transmission | Stillbirth/neonatal mortality |
| Events per 1000 people | Evidence quality |
|-----------------------------|------------------|
| Favor TDF + FTC cART | Favor AZT + 3TC cART |

Comparative benefits and harms by settings

| Evidence quality |
|------------------|
| Low |

High resourced settings

| Hepatitis B vertical transmission | Stillbirth/neonatal mortality |
| Events per 1000 people | Evidence quality |
|-----------------------------|------------------|
| Favor TDF + FTC cART | Favor AZT + 3TC cART |

Comparative benefits and harms by settings

| Evidence quality |
|------------------|
| Moderate |

Preferences and values

Women in these situations might be more likely to choose regimens with a tenofovir/emtricitabine backbone:
- Severe anemia
- Lamivudine-resistant hepatitis B
- Drug allergy
- Lamivudine-resistant HIV
- Alternatives are not available
- Zidovudine-resistant HIV
- Women taking other medications with serious interactions
- Women who place a high value on a once-daily regimen

Other considerations

The evidence applies less in areas with high hepatitis B disease activity, high resource settings, or where access to one of the options is limited.

Resourcing

Zidovudine/lamivudine is available as a low-cost generic around the world, while tenofovir/emtricitabine remains on patent in several countries.
Comparison 2

**Favours TDF + FTC + LPV/r**
- Treatment backbone: TDF + FTC
  - Combined with: LPV/r

**Favours AZT + 3TC cART**
- Treatment backbone: AZT + 3TC
  - Combined with one of: LPV/r, DRV/r, ATZ/r, EFV, RAL, RPV, ABC

We recommend a zidovudine and lamivudine-based antiretroviral regimen over tenofovir and emtricitabine with ritonavir-boosted lopinavir.

**Comparison of benefits and harms**

- **All settings**
  - HIV vertical transmission: 4 vs 5
  - Maternal laboratory AEs: 117 vs 138
  - Maternal clinical AEs: 20 vs 20
  - Premature births (<34 weeks): 74 vs 42 fewer

- **Low/medium resourced settings**
  - Hepatitis B vertical transmission: 29 vs 111
  - Stillbirth/neonatal mortality: 304 vs 235 fewer

- **High resourced settings**
  - Hepatitis B vertical transmission: 3 vs 10
  - Stillbirth/neonatal mortality: 66 vs 51 fewer

**Evidence quality**
- Low
- Moderate

**Preferences and values**
- Women in these situations might be more likely to choose regimens with a tenofovir/emtricitabine backbone:
  - Severe anemia
  - Lamivudine-resistant hepatitis B
  - Drug allergy
  - Lamivudine-resistant HIV
  - Alternatives are not available
  - Zidovudine-resistant HIV
  - Women taking other medications with serious interactions
  - Women who place a high value on a once-daily regimen

**Other considerations**
- The evidence applies less in areas with high hepatitis B disease activity, high resource settings, or where access to one of the options is limited.

**Resourcing**
- Zidovudine/lamivudine is available as a low-cost generic around the world, while tenofovir/emtricitabine remains on patent in several countries.
Approximately 1.4 million women living with HIV become pregnant every year. Most women use antiretroviral therapy, to reduce the risk of vertical transmission or for personal health reasons. Using the GRADE framework according to the BMJ Rapid Recommendation process, we make recommendations for optimal choice of combination antiretroviral regimen considering patient values and preferences, the balance of desirable and undesirable outcomes, their uncertainty, and practical issues. We suggest a zidovudine and lamivudine-based regimen over one that includes tenofovir or emtricitabine (weak recommendation). We recommend alternatives over the combination of tenofovir, emtricitabine, and lopinavir/ritonavir (strong recommendation).

The use of the most common combination antiretroviral medicines in pregnancy was questioned when the results of the Promoting Maternal and Infant Survival Everywhere (PROMISE) trial were published in late 2016. The primary efficacy outcome demonstrated that two common combination antiretroviral therapy regimens confer similar reductions in vertical HIV transmission compared with zidovudine (AZT) monotherapy. However, a planned analysis of a composite safety outcome raised the possibility that the combination regimen with tenofovir plus emtricitabine (FTC) may increase early prematurity, stillbirth, and neonatal death compared with zidovudine plus lamivudine when combined with ritonavir-boosted lopinavir. We aimed to appraise the totality of evidence about combination antiretroviral therapy for pregnant women infected with HIV and make women-centred recommendations.

Every year, about 1.4 million women living with HIV become pregnant and 1.1 million pregnant women use antiretroviral therapy. Without any intervention, approximately 15-45% of children born to mothers with HIV acquire HIV in the antenatal, intrapartum, and postpartum periods.

Women may be offered antiretroviral therapy while pregnant to prevent vertical transmission and, in some cases, to reduce the maternal risk of AIDS defining events. Combination antiretroviral therapy is the most effective among several options to reduce the risk of vertical transmission. Many of these options can be implemented simultaneously (box 1). They have different burdens and adverse effects.

Maternal combination antiretroviral therapy, when initiated before the third trimester, confers a vertical transmission rate of less than 5 per 1000 births. Most combination antiretroviral therapy regimens include a “backbone” of two nucleoside or nucleotide reverse transcriptase inhibitors (NRTIs) in combination with a third antiretroviral, often with a different mechanism of action.

Major guidelines currently recommend the NRTI combination of tenofovir disoproxil fumarate and emtricitabine as a first line therapy in pregnant women (table 1). For simplicity, we refer to tenofovir disoproxil fumarate as tenofovir, recognising that the discussion may not apply to the related agent tenofovir alafenamide. Tenofovir is usually combined with emtricitabine and is currently the most widely used antiretroviral worldwide (fig 1). In 2016, revenues from tenofovir and tenofovir-containing products reached US$13bn (approximately £10bn).

Some antiretrovirals, including tenofovir and lamivudine, also have activity against hepatitis B virus (HBV). HBV infection is common among women with HIV, especially in women born in areas where HBV is endemic.

**WHAT YOU NEED TO KNOW**

- The guideline panel make a weak recommendation for zidovudine and lamivudine instead of tenofovir or emtricitabine for pregnant women living with HIV when they are combined with most antiretrovirals, and a strong recommendation when these drugs are combined with lopinavir/ritonavir
- Tenofovir and emtricitabine probably increase the risk of early neonatal death and preterm delivery <34 weeks compared with zidovudine and lamivudine; this is more certain when they are combined with lopinavir/ritonavir
- Almost all women place an extremely high value on avoiding early neonatal deaths, and most do not consider pill burden very important in pregnancy
- Women with active hepatitis B and high risk of vertical hepatitis B transmission, severe anaemia, drug allergies or intolerances, or zidovudine or lamivudine resistant HIV or hepatitis B may be more likely to choose treatment based on tenofovir and emtricitabine
- Recommendations that take a public health perspective (rather than an individual patient perspective) need to consider resource use and might make different recommendations based on the same evidence

**LINKED ARTICLES IN THIS BMJ RAPID RECOMMENDATIONS CLUSTER**

- Siemieniuk RAC, Lytvyn L, Mah Ming J, et al. Antiretroviral therapy in pregnant women living with HIV: a clinical practice guideline. BMJ 2017;358:j3961. doi:10.1136/bmj.j3961
  - Summary of the results from the Rapid Recommendation process
- Siemieniuk RA, Foroutan F, Mirza R, et al. Antiretroviral therapy for pregnant women living with HIV or hepatitis B: a systematic review and meta-analysis. BMJ Open 2017;7:e019022. doi:10.1136/bmjopen-2017-019022
  - Systematic review of antiretroviral therapies in pregnant women
- Lytvyn L, Siemieniuk RA, Dilmitsis S, et al. Values and preferences of women living with HIV who are pregnant, postpartum, or considering pregnancy on choice of antiretroviral therapy during pregnancy. BMJ Open 2017;7:e019023. doi:10.1136/bmjopen-2017-019023
  - Systematic review of values and preferences
- MAGICapp (www.magicapp.org/goto/guideline/VLpr5E)
  - Expanded version of the evidence with multilayered recommendations, evidence summaries, and decision aids for use on all devices
Vertical transmission of HBV occurs in approximately 38% of children born to mothers with active HBV infection in settings where prophylactic measures are not available. The transmission rate is reduced to about 1% in children who receive prophylaxis with hepatitis B immunoglobulin and early hepatitis B vaccination. When transmission does occur, it is almost always in the minority of mothers with high HBV disease activity—such as a detectable serum hepatitis B envelope antigen (found in the early phase of infection) or high HBV viral load (>1 million copies/mL).

The evidence

To inform the recommendations, the panel requested two systematic reviews, which are linked to this publication (see linked articles in this cluster) on the following questions:

- What are the relative benefits and harms of different NRTI regimens for pregnant women with HIV?
- What evidence describes the values and preferences of women considering antiretroviral therapy?

Understanding the recommendation

Benefit and harm

The most credible and relevant evidence comes from the PROMISE study, which randomised 816 women from Africa, who were at least 14 weeks pregnant, to tenofovir/emtricitabine or zidovudine/lamivudine. Both groups also received the protease inhibitor combination of lopinavir/ritonavir at a standard dose until the third trimester, when the dose was increased by 50% until delivery. Fig 2 shows details of the study and characteristics of included patients.

Box 1 | Interventions that reduce vertical transmission of HIV

- Maternal antiretroviral therapy:
  - Antiretroviral monotherapy
  - Combination antiretroviral therapy
  - Intrapartum antiretroviral therapy
- Pre-labour, pre-rupture of membranes caesarean section
- Infant antiretroviral therapy prophylaxis
- Formula feeding rather than breastfeeding
- Maternal antiretroviral therapy during breastfeeding
- Infant nevirapine therapy during breastfeeding

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Table 1 | Statements from current guidelines on antiretroviral therapy for pregnant women living with HIV

| Guideline               | Preferred options | Alternative options | Recommend against | Preferred third antiretroviral |
|-------------------------|-------------------|---------------------|-------------------|--------------------------------|
| EACS, 2016              | TDF/FTC           | —                   | d4T, ddI          | Lopinavir/ritonavir           |
|                         | TAF/FTC           | —                   | d4T, ddI          | Atazanavir/ritonavir          |
|                         | ABC/3TC           | —                   | d4T, ddI          | Rilpivirine                   |
| US DHHS, 2016           | TDF/FTC           | AZT/3TC             | TAF, d4T, ddI     | Atazanavir/ritonavir          |
|                         | TDF/3TC           | —                   | d4T, ddI          | Datinavir/ritonavir           |
|                         | ABC/3TC           | —                   | d4T, ddI          | Raltegravir                   |
| WHO, 2016               | TDF/FTC           | AZT/3TC             | —                 | Elvitegravir                  |
| BHIVA, 2014             | TDF/FTC           | —                   | —                 | Lopinavir/ritonavir           |
|                         | TDF/3TC           | —                   | —                 | Atazanavir/ritonavir          |
|                         | ABC/3TC           | —                   | —                 | Elvitegravir                  |
| Ireland, 2011           | AZT/3TC           | —                   | —                 | Lopinavir/ritonavir           |
|                         | HIv co-infection  | —                   | —                 | Saquinavir/ritonavir          |
|                         | TDF/FTC           | —                   | —                 | Atazanavir/ritonavir          |
|                         | TDF/3TC           | —                   | —                 | Newtr inevapine               |
| Thailand, 2010          | AZT/3TC           | d4T/3TC             | —                 | Lopinavir/ritonavir           |

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EACS=European AIDS Clinical Society; US DHHS=US Department of Health and Human Services; WHO=World Health Organization; BHIVA=British HIV Association.

For a full list of abbreviations, see linked articles in this cluster.
NRTIs are often combined with antiretrovirals other than lopinavir/ritonavir (table 1). It is possible but unlikely that a drug-drug interaction between lopinavir/ritonavir and tenofovir contributed to the increase in infant mortality. When tenofovir and lopinavir/ritonavir are used together, serum lopinavir/ritonavir concentrations are not increased and tenofovir levels are only marginally increased (much less than normal variation between patients).23 Moreover, the increased lopinavir/ritonavir dose used in the third trimester in the PROMISE study provided serum drug concentrations similar to those of non-pregnant women taking the typical dose,24 although some experts argue that no dose increase is required during pregnancy.25 For combinations with a third antiretroviral agent other than lopinavir/ritonavir, the best evidence informing the comparison of tenofovir/emtricitabine versus alternative NRTIs is therefore indirect because the best evidence comes almost entirely from a study that used lopinavir/ritonavir. In this circumstance, certainty in the evidence was rated down from moderate to low for several key outcomes, including stillbirth and early neonatal death.

Whether the culprit medication is tenofovir or emtricitabine, and the circumstances in which an increase in stillbirths and neonatal death occurs, remain uncertain. Some evidence from observational studies might suggest that tenofovir/emtricitabine is safe in pregnancy.8 26 However, in addition to the inevitable residual confounding inherent to observational studies,27 the available studies also failed to adjust for important confounders, had inconsistent results, and their pooled estimate of effect was imprecise.21 The observational evidence thus provides only very low certainty evidence and does not provide reassurance that tenofovir/emtricitabine is safe in pregnancy. Indeed, even adequately powered observational studies that control for known and measurable confounders would be unlikely to provide adequate assurance of safety in the face of the current randomised trial evidence suggesting harm.

Hepatitis B co-infection—Tenofovir and lamivudine both have antiviral activity against HBV. In the linked network meta-analysis, there was no apparent difference between tenofovir and lamivudine for preventing vertical transmission of hepatitis B, but the certainty is low because there were very few patients and events in the single randomised controlled trial with tenofovir.21 The impact of tenofovir compared with lamivudine on the risk of antiviral resistance and flares in hepatitis B disease is uncertain in this context.

Practical issues
Tenofovir/emtricitabine (as well as abacavir/lamivudine) are typically administered once per day, whereas zidovudine/lamivudine is administered twice daily. Antiretrovirals are often co-formulated into single tablets for ease of administration in an attempt to optimise adherence. Tenofovir/emtricitabine and abacavir/lamivudine are available as co-formulations with several other antiretrovirals in single once daily tablets (tenofovir/emtricitabine is co-formulated with efavirenz, rilpivirine, or elvitegravir/cobicistat); zidovudine/lamivudine is not co-formulated into any single once daily tablets, and is instead available in a single tablet co-formulated with abacavir to be taken twice per day. Therefore, tenofovir based regimens may be simpler than zidovudine/lamivudine based combination antiretroviral therapy (see fig 3).

Values and preferences
Our linked systematic review of qualitative studies report several consistent themes that are important or very
important to women when considering combination antiretroviral therapy during pregnancy. These themes concur with the experience of those panellists living with HIV, as well as the healthcare worker panellists’ observations from interactions with patients.

Women described a strong desire to optimise the health of their child. This desire encouraged mothers to use antiretroviral therapy to reduce vertical HIV transmission, but also proved a barrier for some because of concerns about adverse effects on the child. More specifically, 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 combination antiretroviral therapy dosing regimen from twice daily to once daily. Thus our recommendations apply to women who share these values.

**Practical advice**

**Empowering women**

The recommendations are meant to support shared decision making between pregnant women and their healthcare provider. Healthcare providers should make all necessary efforts to inform women of all of the benefits and harms for all reasonable treatment options. The linked decision aids, available through MagicApp can help facilitate this conversation (www.magicapp.org/goto/guideline/VLpr5E). Patient support organisations can also play a critical role in patient education.
**RAPID RECOMMENDATIONS**

**Alternative NRTIs**
A reasonable NRTI backbone is zidovudine/lamivudine. This is because evidence from randomised controlled trials is directly applicable only to zidovudine/lamivudine as an alternative to tenofovir/emtricitabine, although other NRTI combinations such as abacavir/lamivudine are available.

A new formulation of tenofovir, tenofovir alafenamide, is now available; tenofovir alafenamide may have improved renal and bone safety compared with tenofovir disoproxil fumarate in adults because of reduced plasma concentrations. In the absence of randomised trial data in pregnancy, whether tenofovir alafenamide and tenofovir disoproxil fumarate carry similar risks to the fetus is speculative.

**The third antiretroviral agent**
Typically, a third antiretroviral is added to a dual NRTI backbone to complete the combination antiretroviral therapy regimen. A triple NRTI regimen, with zidovudine/lamivudine plus abacavir, is one reasonable option, although there are several others. Current guidelines differ substantially in their recommendations for the third antiretroviral agent (table 1). The linked systematic review did not formally address the third antiretroviral agent, but evidence from a randomised trial of 540 pregnant women in Botswana suggests that, when combined with zidovudine/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%). Other outcomes, including vertical transmission of HIV, were similar between abacavir and lopinavir/ritonavir. The impact of other combination antiretroviral therapy regimens on key outcomes in pregnancy is very uncertain.

Some women may have other compelling reasons to choose a specific single or combination antiretroviral therapy regimen. The virus should be susceptible to the prescribed antiretrovirals. Further, specific antiretroviral therapy agents should be avoided if a woman is allergic, intolerant to side effects, or has had a serious adverse reaction to that agent in the past. Abacavir should be avoided in women with the HLA B*5701 genotype.

**Recommendations in context**
The number of antiretroviral therapy options that women can choose from and can be prescribed varies considerably throughout the world. The most widely available regimen in low resource settings is tenofovir with emtricitabine or lamivudine, combined with efavirenz. In many settings, zidovudine/lamivudine may not be available, despite it being older and generally cheaper. Our first recommendation can only apply to settings where women have access to zidovudine and lamivudine. In light of this evidence, healthcare administrators should be encouraged to prioritise making zidovudine and lamivudine available to pregnant women in settings where zidovudine/lamivudine based combination antiretroviral therapy regimens are not currently available.

These recommendations, like all BMJ Rapid Recommendations, take a patient centred perspective. Guidelines that take a public health perspective, such as the WHO guideline, may issue different recommendations based on the same evidence. Many HIV treatment programmes, especially in low resource settings, are underfunded and have difficulty meeting antiretroviral therapy demand. In some situations, these operational pressures have been partially alleviated by simplifying the treatment regimen to be used as first line therapy for all patients, including women with HIV who are pregnant or who may be expected to become pregnant. The 2016 WHO guidelines explicitly state that “simplifying operational demands” was one reason that “the same once-per-day combination pill is now recommended for all adults”. The WHO currently recommends a single tablet combination of tenofovir/emtricitabine plus efavirenz as the first line combination antiretroviral therapy regimen for all adults. Recommending alternative treatment options for women living with HIV who are pregnant may introduce operational challenges. For example, many treatment programmes negotiate more affordable medication purchases in bulk. Other influential guidelines either have not yet had the opportunity to consider the evidence from the PROMISE trial or did not have the opportunity to consider the evidence systematically.

**Hepatitis B co-infection**
In women co-infected with HBV, there is a risk that the HBV becomes resistant and that treatment fails, a risk that may be particularly important in women taking lamivudine for a prolonged period. Lamivudine may be less effective at preventing vertical transmission of HBV in mothers with lamivudine resistance than in mothers without resistance. However, the degree to which this is true is uncertain. In women with low HBV disease activity or who have access to neonatal hepatitis B immunoglobulin and early infant HBV vaccination, the risk of HBV transmission is already low (approximately 1 in 100), so any speculative difference in vertical transmission rates between tenofovir and lamivudine in lamivudine-resistant HBV will be small. On the other hand, the speculative benefit of tenofovir over lamivudine in Preventing vertical transmission in women with lamivudine-resistant HBV might be larger in situations with higher baseline risk of HBV transmission—particularly when there is high maternal HBV activity (such as >20000 IU/mL or 1 million copies/mL) and where there is unreliable infant access to hepatitis B immunoglobulin or early HBV vaccination.

**Cost and resources**
In the commonest situation, where women do not pay directly for antiretroviral therapy, cost is not their concern. In settings where tenofovir/emtricitabine and its one tablet once per day combination pills remain on patent, we expect there to be considerable cost savings to the payer with the routine use of zidovudine/lamivudine over tenofovir/emtricitabine. In settings where generic tenofovir/emtricitabine is available and routinely prescribed, the impact on costs to the payer is uncertain (fig 3).

**Uncertainty**
There is a lack of data on the safety and efficacy of most commonly used combination antiretroviral therapy regimens in pregnant women living with HIV. To date,
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Transparency: R A C Simieniuk affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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