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

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Comparison 1

TDF + FTC-based therapy

Tenofovir + emtricitabine-based antiretroviral therapy.

Treatment backbone:

TDF + FTC

Combined with one of:

DRV/r
ATZ/r RAL
EFV RPV

or

AZT + 3TC-based therapy

Zidovudine + lamivudine-based antiretroviral therapy.

Treatment backbone:

AZT + 3TC

Combined with one of:

LPV/r DRV/r
ATZ/r RAL
EFV RPV

ABC

Favours TDF + FTC cART

Favours AZT + 3TC cART

Applies to

All

Strong

Weak

Weak

Strong

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

Comparison of benefits and harms

Favours TDF + FTC cART

No important difference

Favours AZT + 3TC cART

All settings

	Events per 1000 people		Evidence quality
HIV vertical transmission	4	No important difference 5	★★★★ Low
Maternal laboratory AEs	117	No important difference 138	★★★★ Low
Maternal clinical AEs	20	No important difference 20	★★★★ Moderate
Premature births (<34 weeks)	74	42 fewer 32	★★★★ Low

Low/medium resourced settings

	Events per 1000 people		Evidence quality
Hepatitis B vertical transmission	29	No important difference 111	★★★★ Low
Stillbirth/neonatal mortality	304	235 fewer 69	★★★★ Low

High resourced settings

	Events per 1000 people		Evidence quality
Hepatitis B vertical transmission	3	No important difference 10	★★★★ Moderate
Stillbirth/neonatal mortality	66	51 fewer 15	★★★★ Low

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

TDF + FTC + LPV/r

The specific combination of drugs tested in the PROMISE trial

Treatment backbone:

TDF + FTC

Combined with:

LPV/r

or

AZT + 3TC-based therapy

Zidovudine + lamivudine-based antiretroviral therapy.

Treatment backbone:

AZT + 3TC

Combined with one of:

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ATZ/r RAL
EFV RPV
ABC

Favours TDF + FTC + LPV/r

Favours AZT + 3TC cART

Applies to

All

Strong

Weak

Weak

Strong

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

Comparison of benefits and harms

Favours TDF + FTC cART

No important difference

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Alternatives are not available Zidovudine-resistant HIV

Women taking other medications with serious interactions

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Resourcing

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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 2016.¹ 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.¹ 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.² Without any intervention, approximately 15–45% of children born to mothers with HIV acquire HIV in the antenatal, intrapartum, and postpartum periods.³

Women may be offered antiretroviral therapy while pregnant to prevent vertical transmission⁴ and, in some cases, to reduce the maternal risk of AIDS defining events.⁵ 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.⁷ 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.^{8–10}

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).¹⁶

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.¹⁷

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, Dillmitis 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

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 section⁶
- Infant antiretroviral therapy prophylaxis
- Formula feeding rather than breastfeeding
- Maternal antiretroviral therapy during breastfeeding
- Infant nevirapine therapy during breastfeeding

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.¹⁸ The transmission rate is reduced to about 1% in children who receive prophylaxis with hepatitis B immunoglobulin and early hepatitis B vaccination.¹⁹ 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).^{19 20}

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?²¹
- What evidence describes the values and preferences of women considering antiretroviral therapy?²²

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

Fig 1 | Trends in the use of nucleoside or nucleotide reverse transcriptase inhibitors. ART=antiretroviral therapy; NRTI=nucleoside or nucleotide reverse transcriptase inhibitor; TDF=tenofovir disoproxil fumarate; AZT=zidovudine; 3TC=lamivudine; FTC=emtricitabine Dashed lines represent NRTI use in 18 low and middle income countries¹⁴; solid lines represent NRTI use in North America.¹⁵

tenofovir/emtricitabine or zidovudine/lamivudine.¹ 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.

Based on the linked systematic review,²¹ the panel judged that there was moderate certainty that tenofovir/emtricitabine—when combined with lopinavir/ritonavir in the doses used in the PROMISE trial—increases stillbirth and early neonatal mortality compared with zidovudine/lamivudine, as well as early premature labour before 34 weeks gestational age (see infographic). Certainty is moderate rather than high because of imprecision around the best estimate of the absolute effect and because most of the evidence comes from a single study where the event rate in the zidovudine/lamivudine arm may have been lower than expected.¹ The authors of the PROMISE trial argued that the event rate in the zidovudine/lamivudine arm might have been lower than expected because of “some unknown confounder” that resulted in fewer early premature deliveries and early infant deaths in the zidovudine/lamivudine arm during the second phase of the study when tenofovir/emtricitabine was available—and that the confounder was not present before the introduction of the tenofovir/emtricitabine arm.¹ The panel think this is unlikely, and, even if there was an unknown confounder in the study, until that confounder is identified, the risk estimates apply to all pregnant women living with HIV. The available evidence suggested that there was no difference for any of the other pre-specified outcomes (low to moderate certainty; see infographic).

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 ¹⁰	TDF/FTC TAF/FTC ABC/3TC	—	d4T ddl	Lopinavir/ritonavir Atazanavir/ritonavir Rilpivirine
US DHHS, 2016 ⁹	TDF/FTC TDF/3TC ABC/3TC	AZT/3TC	TAF d4T ddl	Atazanavir/ritonavir Darunavir/ritonavir Raltegravir
WHO, 2016 ⁸	TDF/FTC TDF/3TC	AZT/3TC	—	Efavirenz
BHIVA, 2014 ¹¹	TDF/FTC ABC/3TC AZT/3TC	—	—	Lopinavir/ritonavir Atazanavir/ritonavir Efavirenz
Ireland, 2011 ¹²	AZT/3TC HBV co-infection: TDF/FTC TDF/3TC	—	—	Lopinavir/ritonavir Saquinavir/ritonavir Atazanavir/ritonavir Nevirapine
Thailand, 2010 ¹³	AZT/3TC	d4T/3TC	—	Lopinavir/ritonavir

EACS=European AIDS Clinical Society; US DHHS=US Department of Health and Human Services; WHO=World Health Organization; BHIVA=British HIV Association.
TDF= tenofovir disoproxil fumarate; FTC=emtricitabine; 3TC=lamivudine; AZT=zidovudine; ABC=abacavir; TAF=tenofovir alafenamide; d4T=stavudine; ddl=didanosine; HBV=hepatitis B virus.

HOW THE RECOMMENDATIONS WERE CREATED

This independent international panel included women living with HIV, adult and paediatric infectious disease specialists, general practitioners, paediatricians, obstetricians, a hepatologist, a pharmacist, and research methodologists (see appendix 1 on bmj.com for list of panel members). Panel members were recruited based on their work on the topic, with the focus on achieving a balanced panel representing all viewpoints. No person had any financial conflicts of interest; intellectual and professional conflicts were minimal (see appendix 2 on bmj.com).

The panel followed the *BMJ* Rapid Recommendations process for creating a trustworthy recommendation, such as using the GRADE approach to evaluate the evidence and create recommendations (appendix 3).³¹⁻³⁵ The panel considered the typical and expected variation in patient values and preferences, the balance of benefits, harms and burdens of the combination antiretroviral regimens, the quality of the evidence for each outcome, and treatment acceptability. With GRADE, recommendations can be strong or weak.^{36,37} Weak recommendations imply that there is likely to be variation in what informed patients would choose, thus emphasising the need for an explicit shared decision-making process between patient and healthcare provider.

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

Fig 2 | Characteristics of patients and details of PROMISE study

	PRACTICAL ISSUES		
	<div>TDF + FTC</div> <div>Tenofovir + Emtricitabine</div>	<div>AZT + 3TC</div> <div>Zidovudine + lamivudine</div>	<div>ABC + 3TC</div> <div>Abacavir + lamivudine</div>
DOSING	Once daily	Twice daily	Once daily
ART CO-FORMULATIONS AS SINGLE ONCE PER DAY TABLET	Several	No	Several
COST PER YEAR, USA*	\$22,574	\$11,179	\$16,722
COST PER YEAR, CANADA*	\$7,481	\$938	\$682
COST PER YEAR, LOWER INCOME COUNTRIES*	Lowest income: \$319 Low-middle income: \$548	\$161	\$225
COST PER YEAR, CHEAPEST GENERIC AVAILABLE*	\$64†	\$73	\$161
KEY DRUG-DRUG INTERACTIONS THAT SHOULD BE AVOIDED (TYPICAL INDICATION)	<div>Ledipasvir (hepatitis C)</div> <div>Atazanavir (HIV)</div> <div>Diclofenac & nonsteroidal anti-inflammatories (pain)</div>	<div>Amodiaquine (malaria)</div> <div>Ribavirin (hepatitis)</div> <div>Clarithromycin (bacterial infections)</div>	
MONITORING	Regular blood and urine tests for kidney function	Regular blood tests for anaemia	HLA*B5701 testing prior to initiating

* All costs are approximate and reported in US Dollars. Data, in part, from the Medecins Sans Frontieres Access to Medicines Campaign²⁸
† Tenofovir/FTC remains on patent by Gilead Sciences, Inc. in most of Europe, the United States, Canada, and other countries.

Fig 3 | Practical issues about use of combination antiretroviral therapy

important to women when considering combination antiretroviral therapy during pregnancy.²² 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.²² 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.²² 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.

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.²⁹ 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% v 23%, but with a 95% confidence interval of the difference of <1% to 16%).³⁰ 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,³¹ take a patient centred perspective. Guidelines that take a public health perspective, such as the WHO guideline,⁸ may issue different recommenda-

tions 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”.⁸ The WHO currently recommends a single tablet combination of tenofovir/emtricitabine plus efavirenz as the first line combination antiretroviral therapy regimen for all adults.⁸ 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.^{9 10}

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.³² 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 a higher baseline risk of HBV transmission—particularly when there is high maternal HBV activity (such as >200 000 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,

Table 2 | New evidence which has emerged after initial publication

Date	New evidence	Citation	Findings	Implications for recommendation(s)
There are currently no updates to the article				

EDUCATION INTO PRACTICE

- How many women in your practice receive tenofovir or emtricitabine while pregnant?
- How will you share this information with women infected with HIV?
- To what extent might you use information in this article to alter the conversations you have with women living with HIV?

HOW PATIENTS WERE INVOLVED IN THE CREATION OF THIS ARTICLE

In addition to the systematic review of the values and preferences of women living with HIV, three women living with HIV were full panel members, participated in the teleconferences and email discussions, and met all authorship criteria. These panel members identified important outcomes, led the discussions about values and preferences, and helped to interpret and provide context for the evidence.

most information has been gleaned from observational studies, rather than randomised controlled trials. Even if adequately powered and carefully controlled for known confounders, observational studies are unlikely to provide sufficient reassurance on the safety of any particular regimen when randomised trial evidence suggests harm—even when the randomised trial data informs decisions indirectly and the effect estimates are imprecise. Speculative arguments about antiretroviral dosing, serum levels, drug interactions, and mechanisms that might cause antiretroviral therapy-related harm in pregnancy need further basic science and observational research, complemented by safety confirmation in randomised controlled trials. The PROMISE trial serves as a reminder of the importance of randomised evidence to inform treatment options in pregnant women with HIV.

The outcomes reported in many of the studies were narrow in scope. Future studies should consider all outcomes important to patients—such as medium to long term child development. Future primary studies and secondary reviews must consider all reasonable and available interventions, including zidovudine monotherapy, not simply combination antiretroviral therapy.

Implementation research and efforts may be required to overcome the current operational challenges so that availability of the right choice of combination antiretroviral therapy is aligned with the best available evidence for almost all pregnant women living with HIV.

Updates to this article

Table 2 shows evidence which has emerged since the publication of this article. As new evidence is published, a group will assess the new evidence and make a judgment on to what extent it is expected to alter the recommendation.

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Transparency: R A C Siemieniuk 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.

- 1 Fowler MG, Qin M, Fiscus SA, et al. IMPAACT 1077BF/1077FF PROMISE Study Team. Benefits and risks of antiretroviral therapy for perinatal HIV prevention. *N Engl J Med* 2016;375:1726-37. doi:10.1056/NEJMoa1511691 pmid:27806243.
- 2 UNAIDS. AIDSInfo Data Sheets 2016. <http://aidsinfo.unaids.org/>.
- 3 The Working Group on Mother-To-Child Transmission of HIV. Rates of mother-to-child transmission of HIV-1 in Africa, America, and Europe: results from 13 perinatal studies. *J Acquir Immune Defic Syndr Hum Retrovirol* 1995;8:506-10. doi:10.1097/00042560-199504120-00011 pmid:7697448.
- 4 Siegfried N, van der Merwe L, Brocklehurst P, Sint TT. Antiretrovirals for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev* 2011;(7):CD003510.pmid:21735394.
- 5 Lundgren JD, Babiker AG, Gordin F, et al. INSIGHT START Study Group. Initiation of antiretroviral therapy in early asymptomatic HIV infection. *N Engl J Med* 2015;373:795-807. doi:10.1056/NEJMoa1506816 pmid:26192873.
- 6 European Mode of Delivery Collaboration. Elective caesarean-section versus vaginal delivery in prevention of vertical HIV-1 transmission: a randomised clinical trial. *Lancet* 1999;353:1035-9. doi:10.1016/S0140-6736(98)08084-2 pmid:10199349.
- 7 Forbes JC, Alimenti AM, Singer J, et al. Canadian Pediatric AIDS Research Group (CPARG). A national review of vertical HIV transmission. *AIDS* 2012;26:757-63. doi:10.1097/QAD.0b013e328350995c pmid:22210635.
- 8 World Health Organization. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: Recommendations for a public health approach. 2016. www.who.int/hiv/pub/arv/arv-2016/en/.
- 9 Panel on Treatment of HIV-Infected Pregnant Women and Prevention of Perinatal Transmission. Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV transmission in the United States. 2016. <https://aidsinfo.nih.gov/contentfiles/lvguidelines/PerinatalGL.pdf>.
- 10 European AIDS Clinical Society. EACS guidelines. 2017. www.eacsociety.org/guidelines/eacs-guidelines/eacs-guidelines.html.
- 11 de Ruiter A, Taylor GP, Clayden P, et al. British HIV Association. British HIV Association guidelines for the management of HIV infection in pregnant women 2012 (2014 interim review). *HIV Med* 2014;15(Suppl 4):1-77. doi:10.1111/hiv.12185 pmid:25604045.
- 12 Health Service Executive. Irish guidelines for antiretroviral treatment in children 2011. www.hse.ie/eng/about/Who/clinical/natclinprog/obsandynaeprogramme/guide10.pdf.
- 13 Phanuphak N, Lolekha R, Chokephaibulkit K, et al. Thailand national guidelines for the prevention of mother-to-child transmission of HIV: March 2010. 2010. www.researchgate.net/publication/317745187_Thailand_national_guidelines_for_the_prevention_of_mother-to-child_transmission_of_HIV_2016.
- 14 Habiymbere V, AIDS Medicines and Diagnostic Services (AMDS) Strategic Information and Planning Unit. WHO global ARVs and diagnostic use survey in 2015 in low & middle-income countries: ARV use situation by end of 2014 preliminary results. 2016. www.who.int/hiv/amds/amds2016-ppt-WHO-2015ARVUSeSurvey.pdf?ua=1.
- 15 North American AIDS Cohort Collaboration on Research and Design. ART use: international epidemiology database to evaluate AIDS. 2017. <https://statepiaps7.jhsph.edu/naaccord/>.
- 16 Gilead Sciences announces fourth quarter and full year 2016 financial results [press release]. 2017. www.gilead.com/news/press-releases/2017/2/gilead-sciences-announces-fourth-quarter-and-full-year-2016-financial-results.
- 17 Barth RE, Huijgen Q, Taljaard J, Hoepelman AI. Hepatitis B/C and HIV in sub-Saharan Africa: an association between highly prevalent infectious diseases. A systematic review and meta-analysis. *Int J Infect Dis* 2010;14:e1024-31. doi:10.1016/j.ijid.2010.06.013 pmid:20870439.
- 18 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. *Aliment Pharmacol Ther* 2016;44:1005-17. doi:10.1111/apt.13795 pmid:27630001.

- 19 Schillie S, Walker T, Veselsky S, et al. Outcomes of infants born to women infected with hepatitis B. *Pediatrics* 2015;135:e1141-7. doi:10.1542/peds.2014-3213 pmid:25896839.
- 20 Wiseman E, Fraser MA, Holden S, et al. Perinatal transmission of hepatitis B virus: an Australian experience. *Med J Aust* 2009;190:489-92. pmid:19413519.
- 21 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.
- 22 Lytvyn L, Siemieniuk RA, Dillmitis 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.
- 23 Kearney BP, Mathias A, Mittan A, Sayre J, Ebrahimi R, Cheng AK. Pharmacokinetics and safety of tenofovir disoproxil fumarate on coadministration with lopinavir/ritonavir. *J Acquir Immune Defic Syndr* 2006;43:278-83. doi:10.1097/01.qai.0000243103.03265.2b pmid:17079992.
- 24 Best BM, Stek AM, Mirochnick M, et al. International Maternal Pediatric Adolescent AIDS Clinical Trials Group 1026s Study Team. Lopinavir tablet pharmacokinetics with an increased dose during pregnancy. *J Acquir Immune Defic Syndr* 2010;54:381-8. doi:10.1097/QAI.0b013e3181d6c9ed pmid:20632458.
- 25 Salem AH, Jones AK, Santini-Oliveira M, et al. No need for lopinavir dose adjustment during pregnancy: a population pharmacokinetic and exposure-response analysis in pregnant and nonpregnant HIV-infected subjects. *Antimicrob Agents Chemother* 2015;60:400-8. doi:10.1128/AAC.01197-15 pmid:26525798.
- 26 Mofenson LM, Baggaley RC, Mameletzis I. Tenofovir disoproxil fumarate safety for women and their infants during pregnancy and breastfeeding. *AIDS* 2017;31:213-32. doi:10.1097/QAD.0000000000001313 pmid:27831952.
- 27 Agoritsas T, Merglen A, Shah ND, O'Donnell M, Guyatt GH. Adjusted analyses in studies addressing therapy and harm: users' guides to the medical literature. *JAMA* 2017;317:748-59. doi:10.1001/jama.2016.20029 pmid:28241362.
- 28 Médecins Sans Frontières Access Campaign. *Untangling the web of antiretroviral price reductions*. Médecins Sans Frontières, 2016.
- 29 Wang H, Lu X, 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 (Baltimore)* 2016;95:e5146. doi:10.1097/MD.00000000000005146 pmid:27741146.
- 30 Shapiro RL, Hughes MD, Ogwu A, et al. Antiretroviral regimens in pregnancy and breast-feeding in Botswana. *N Engl J Med* 2010;362:2282-94. doi:10.1056/NEJMoa0907736 pmid:20554983.
- 31 Siemieniuk RA, Agoritsas T, Macdonald H, Guyatt GH, Brandt L, Vandvik PO. Introduction to BMJ Rapid Recommendations. *BMJ* 2016;354:i5191. doi:10.1136/bmj.i5191 pmid:27680768.
- 32 Lok AS, Lai CL, Leung N, et al. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003;125:1714-22. doi:10.1053/j.gastro.2003.09.033 pmid:14724824.
- 33 Poolman RW, Agoritsas T, Siemieniuk RA, et al. Low intensity pulsed ultrasound (LIPUS) for bone healing: a clinical practice guideline. *BMJ* 2017;356:j576. doi:10.1136/bmj.j576 pmid:28228381.
- 34 Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. *BMJ* 2016;354:i5085. doi:10.1136/bmj.i5085 pmid:27680583.
- 35 Siemieniuk RAC, Harris IA, Agoritsas T, et al. Arthroscopic surgery for degenerative knee arthritis and meniscal tears: a clinical practice guideline. *BMJ* 2017;357:j1982. doi:10.1136/bmj.j1982 pmid:28490431.
- 36 Guyatt GH, Oxman AD, Kunz R, et al. GRADE Working Group. Going from evidence to recommendations. *BMJ* 2008;336:1049-51. doi:10.1136/bmj.39493.646875.AE pmid:18467413.
- 37 Guyatt GH, Oxman AD, Vist GE, et al. GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-6. doi:10.1136/bmj.39489.470347.AD pmid:18436948.

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