When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO Think Tank

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Purpose of review
To discuss barriers and opportunities for the introduction of new antiretrovirals into national treatment programmes in low-income and middle-income countries to support further treatment scale-up. Invitees to a WHO Think Tank in February 2017 evaluated recently published results.

Recent findings
There is not sufficient clinical experience of dolutegravir (DTG), tenofovir alafenamide (TAF) or efavirenz 400 mg (EFV_{400}) to recommend their use in pregnancy. Outcomes from births and assessment of congenital anomalies need to be evaluated from several hundred pregnant women. Clinical experience of these treatments during rifampicin-based treatment for tuberculosis is also required. This could be difficult for TAF, which is currently contraindicated with TAF. Changes in second-line treatment from two nucleoside analogues + protease inhibitor plus ritonavir will require new randomized trials of alternative combinations.

Conclusion
Additional safety and efficacy data on DTG, TAF and EFV_{400} in some subpopulations are needed before a large introduction in national treatment programmes. There is currently limited support for the introduction of TAF as part of first-line antiretroviral treatment in low-income and middle-income settings. There was an overall agreement for 6-monthly reviews of safety and efficacy data, in parallel with a phased introduction of the new antiretrovirals.

Keywords
antiretroviral treatment, drug–drug interactions, HIV–TB coinfection, pregnant women

INTRODUCTION

WHO guidelines currently recommend first-line treatment for HIV with tenofovir disoproxil fumarate (TDF) and lamivudine (3TC) or emtricitabine (FTC) and either the nonnucleoside efavirenz (EFV) or the integrase inhibitor dolutegravir (DTG) [1]. Treatment guidelines in high-income settings have recently been revised to recommend first-line use of integrase inhibitors in preference to EFV [2–4]. The recommended second-line treatment is with two nucleos(t)ide analogues and a boosted protease inhibitor: this is consistent across treatment guidelines.

DTG, the new nucleotide analogue tenofovir alafenamide (TAF), and the NNRTI EFV at the reduced 400 mg once daily dose (EFV_{400}) are becoming available as low-cost generics. Widespread use of these new options could lower the unit costs of antiretroviral treatment and enhance the treatment coverage capacity in countries [5,6,7▪]. However, evidence for the efficacy and safety of these drugs in pregnant women, children and tuberculosis (TB) coinfection is limited [8▪▪]. In addition, the role of

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KEY POINTS

- The WHO convened an expert panel in February 2017 to discuss how new antiretrovirals should be introduced into national treatment programmes for low-income and middle-income countries.
- It was agreed that additional safety and efficacy data on DTG, TAF and EFV_{400} in some subpopulations are needed, particularly for pregnant women and people with HIV–TB coinfection.
- At the meeting, there was limited support for the introduction of TAF as part of first-line antiretroviral treatment in low-income and middle-income settings.
- There was an overall agreement for 6-monthly reviews of safety and efficacy data, in parallel with a phased introduction of the new antiretrovirals.

DTG in second-line treatment, after first-line virological failure, is unclear. Several clinical trials are underway to assess the pharmacokinetics, efficacy and safety of these new antiretrovirals in pregnant women and TB-coinfected patients and to compare DTG with EFV, and TDF with TAF in low-income and middle-income countries (LMICs). Most of these trials will not generate results until 2019–2020. By that time, it is possible that several million people will already have been started on DTG, TAF and other new antiretrovirals.

The risks of adverse outcomes in pregnancy, or congenital anomalies in the infants, need to be considered when introducing new antiretroviral drugs into national programmes. Several recent studies have reported associations between use of certain antiretrovirals during pregnancy and adverse birth outcomes. An analysis of 6500 women in Botswana showed that those treated with TDF/3TC/EFV before conception were significantly less likely to have preterm deliveries or infants low birth weight, compared with mothers treated with the protease inhibitor lopinavir/ritonavir (LPV/r) [9]. In the randomized PROMISE study, women treated with TDF/3TC + LPV/r were significantly more likely to have adverse birth outcomes than those treated with zidovudine/3TC + LPV/r [10].

Another consideration is the compatibility of new antiretroviral drugs with rifampicin-based TB treatment. People with TB coinfection are typically under-represented in Phase 3 clinical development programmes for new antiretrovirals. However, HIV–TB coinfection is common in LMICs, and this drug interaction with rifampicin-based treatment is an important issue to be considered by HIV treatment programmes in these settings [8▪▪].

In February 2017, the WHO held a 'Think-Tank' meeting in Seattle, the United States of America. There were 60 experts invited, including members of the WHO HIV Guidelines committee, specialists in paediatrics and HIV drug resistance, UNITAID, the Clinton Health Access Initiative, USAID, Centres for Disease Control and PEPFAR.

The two main questions discussed at this WHO Think-Tank meeting were

(1) Is there already enough evidence to support the efficacy and safety of DTG, TAF and EFV_{400} to justify their use in millions of people in LMICs?
(2) What clinical trials and pharmacovigilance studies are needed to assess drug safety when these new treatments are used more widely?

DOLUTEGRAVIR: OVERALL EFFICACY AND SAFETY

DTG is recommended as an alternative first-line treatment to EFV in the current WHO-consolidated ARV guidelines [1]. The efficacy of DTG has been established in studies of naïve and pretreated patients [11–15]. This alternative status from WHO reflects the limited information about the use of DTG in pregnant women and TB coinfection available in end of 2015, when these guidelines were formulated. In addition, there might be additional safety concerns with the use of this integrase inhibitor in real-life settings, beyond the controlled environment and selected patient population of clinical trials.

DOLUTEGRAVIR IN PREGNANT AND BREASTFEEDING WOMEN

In the registrational trials programme for DTG, there is very little clinical experience of treatment during pregnancy, reflecting the general precautionary approach to enroling pregnant women, and women in general in clinical trials of antiretrovirals [16]. DTG has high penetration across the placenta, unlike some other antiretrovirals [17]. High DTG concentrations in the developing embryo might protect against vertical HIV transmission, but might also increase the risk of adverse birth outcomes. In animal toxicology studies, there was no evidence for adverse effects from DTG treatment during pregnancy [18].

During the original clinical trials programme for DTG, women were advised to use contraception, and any women who became pregnant were discontinued from treatment with DTG [11,12].

Table 1. Congenital anomalies for infants after in-utero exposure to dolutegravir

Study	Congenital anomalies
IMPAACT P1026s (2/15)	Multicystic dysplastic right kidney
	Cyst, left kidney
DTG Phase 3 studies (1/30)	Right ventricular septal defect
DTG postmarketing (5/67)	Polydactyly
	Polydactyly and syndactyly
	Polydactyly
	Intracranial calcifications, intrauterine growth retardation
	Bilateral hydroureter, right hydronephrosis, pyelocaliectasis

DTG, dolutegravir.

These measures, although typical for early clinical development studies, mean that there are few women with treatment outcome data available.

Safety data for DTG during pregnancy is currently from the originator company database of Phase 2 and 3 clinical trials, postmarketing surveillance and from one prospective study – IMPAACT P1026s [19]. There have been 112 live births from these sources of data. Table 1 shows the congenital anomalies recorded in these infants. In addition to the outcomes from live births, there was one case of spontaneous abortion with foetal dystrophy after use of DTG in the first trimester. In the IMPAACT P1026s study, there was one additional case of polydactyly that was not included in the summary because it was not judged to be related to treatment.

It is not possible to evaluate the safety of DTG in pregnancy from the current database because the sample size is too small and potential confounders have not been assessed. The reports from postmarketing surveillance could be subject to reporting bias, if clinicians are more likely to report results from infants with congenital anomalies. Overall birth outcomes, such as spontaneous abortion or premature birth, also need to be evaluated.

At the 2017 WHO Think-Tank meeting, only a minority of participants considered that the safety database in pregnancy was sufficient to recommend giving pregnant women DTG in national treatment programmes in LMICs. The Brazilian Ministry of Health is starting to introduce DTG nationally but not for pregnant women or those with TB coinfection. Botswana is currently the only LMIC where DTG is being widely used for pregnant women. There are three randomized clinical trials of DTG versus EFV in pregnancy in progress: DOLPHIN-1, DOLPHIN-2 and VESTED [20,21]. A pharmacokinetic study is also in progress [22]. The details of these studies are shown in Table 2. These randomized studies will not report results until 2019–2020. Until then, results will only be available from nonrandomized studies, which could be more difficult to interpret.

By July 2017, the current database on pregnant women should be supplemented by analysis of the Antiretroviral Pregnancy Registry, a European study of

Table 2. Key randomized clinical trials evaluating new antiretrovirals: pregnant women

Clinical trial	Treatment arms	Inclusion	Objective	Results
Dolphin-1	2NRTI + EFV	Pregnant women	Efficacy	2018
$N = 60$	2NRTI + DTG	(Uganda)	Birth outcomes	
Dolphin-2	2NRTI + EFV	Pregnant women	Efficacy	2020
$N = 250$	2NRTI + DTG	(Uganda)	Birth outcomes	
VESTED	TDF/FTC/EFV	Pregnant women	Efficacy	2020
$N = 549$	TDF/FTC/DTG	(International)	Birth outcomes	
	TAF/FTV/DTG			
SSAT 063	2NRTI + EFV_{400}	Pregnant women	PK, outcomes	4Q17
$N = 25$				

DTG, dolutegravir; EFV, efavirenz; EFV_{400}, efavirenz 400 mg; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate.

Table 3. Key randomized clinical trials evaluating new antiretrovirals: TB coinfection

Clinical trial	Treatment arms	Inclusion	Objective	Results
SSAT 062	EFV_{400} + rifampicin	Healthy volunteers	PK	4Q17
N = 20				
RADIO	DTG + rifampicin	Healthy volunteers	PK	4Q17
N = 20				
NIH	DTG + rifapentine	Healthy volunteers	PK	Suspended
N = 20				
INSPIRING	DTG + 2NRTIs	HIV–TB coinfection	48-week efficacy	4Q17
N = 125	EFV + 2NRTIs	With rifampicin		
RIFT	TAF + rifampicin	Healthy volunteers	PK	4Q17
N = 20				

DTG, dolutegravir; EFV, efavirenz; EFV_{400}, efavirenz 400 mg; TAF, tenofovir alafenamide.

pregnancy outcomes (EPPIIC) and data from over 400 pregnant women treated in Botswana. A review of this larger dataset in late 2017 could inform considerations on the use of pregnant women with DTG in LMICs.

DOLUTEGRAVIR AND TB COINFECTION

When used with rifampicin, the dose of DTG needs to be increased to 50 mg twice daily [23] because of drug–drug interactions. DTG is being evaluated with rifampicin in several new studies [24–26], as shown in Table 3. This issue is discussed in other parts of the supplement.

USE OF INTEGRASE INHIBITORS AND THE RISK OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME

Immune reconstitution inflammatory syndrome (IRIS) occurs most often among people with low CD4 cell count initiating first-line antiretroviral treatment. Integrase inhibitors suppress HIV RNA levels more quickly than other antiretroviral drug classes [27]. A rapid recovery of immune function during first-line antiretroviral treatment can cause immune reactions to existing infections, often with severe and paradoxical effects. Inflammatory symptoms such as severely swollen lymph nodes (lymphadenopathy), tachycardia, fever and the worsening of symptoms of opportunistic infections can emerge and may require hospitalization and/or corticosteroid treatment.

Data from two recent studies from nonrandomized cohort studies in France and The Netherlands reported an association between the use of integrase inhibitors and a higher risk of IRIS.

In the Dutch study [28▪], IRIS was either diagnosed by a clinician or classified by the French 2004 definition (atypical tumour or opportunistic infection presentation accompanied by viral load decline or CD4 increase). According to these definitions, 38% of those who started integrase inhibitor treatment and 16% of those starting any other treatment regimen developed IRIS. Patients taking integrase inhibitor treatment were significantly more likely to develop IRIS according to either definition [odds ratio 3.25, 95% confidence interval (CI) 1.83–5.80].

In the French study [29▪], severe IRIS leading to hospitalization developed in 3% of patients in the integrase inhibitor group versus 1.5% in the non-integrase inhibitor group, a relative risk of 1.99 (95% CI 1.09–3.47). IRIS was most frequently related to tuberculosis, to *Mycobacterium avium* and to progressive multifocal leukoencephalopathy.

These two cohort studies are not randomized trials, so there is the potential for bias and confounding in the reported association with IRIS. However, randomized clinical trials comparing first-line treatment with integrase inhibitors and other treatment classes have typically excluded people with the highest risk of IRIS (patients with low CD4 cell counts, active TB or other opportunistic infections) [11,12]. It will therefore be important to monitor the risk of IRIS in national treatment programmes using first-line DTG in case a rise in its occurrence is observed.

The results from randomized trials in an appropriate patient population are not yet available and so cannot be used to evaluate the risk of IRIS from use of integrase inhibitors in LMICs. The Spanish ADVANZ-4 trial is evaluating first-line treatment with DTG versus darunavir plus ritonavir (DRV/r) in 108 patients with baseline CD4 counts below 100 cells/μl [30]. This trial is limited in sample size to a statistically significant risk of clinical IRIS, but includes detailed evaluations of immune function and is expected to produce results in late 2017. As

Table 4. Key randomized clinical trials evaluating new antiretrovirals: first-line and second-line treatments

Clinical trial	Treatment arms	Inclusion	Objective	Results
First-line treatment				
ADVANCE	TDF/FTC/EFV	Naïve	48-week efficacy	2019
N = 1100	TDF/FTC/DTG	(South Africa)		
	TAF/FTC/DTG			
NAMSAL	TDF/3TC/EFV_{400}	Naïve	48-week efficacy	2019
N = 606	TDF/3TC/DTG	(Cameroun)		
ADVANZ-4	ABC/3TC/DTG	Naïve	48-week efficacy	4Q17
N = 108	ABC/3TC/DRV/r	(Spain)	IRIS	
Second-line treatment				
WHRI 052	2NRTI + LPV/r	Switch	48-week efficacy	2018
N = 300	2NRTI + DRV/r 400 mg	(South Africa)		
DAWNING	2NRTI + DTG	First-line failure	48-week efficacy	3Q17
N = 612	2NRTI + PI/r	(International)		
D2EFT	DTG + DRV/r	First-line failure	48-week efficacy	
N = 610	2NRTI + DRV/r	(International)		

3TC, lamivudine; DTG, dolutegravir; EFV, efavirenz; EFV_{400}, efavirenz 400 mg; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; TAF, tenofovir alafenamide TDF, tenofovir disoproxil fumarate.

shown in Table 4, the other large randomized trials of first-line DTG versus EFV that could include patients with low CD4 cell counts and/or Centres for Disease Control (CDC) stage C disease – ADVANCE and NAMSAL – will not report 48-week results until 2019 [31,32].

Until more evidence becomes available on this issue, strict clinical monitoring for IRIS may be required for patients starting first-line, integrase-based treatment with known risk factors for IRIS, to check for evidence of emerging IRIS.

USE OF DOLUTEGRAVIR AND OTHER SIDE EFFECTS

Results from nonrandomized cohort studies suggest a higher risk of CNS adverse events for DTG compared with other integrase inhibitors [33–37]. In addition, there has been a report of two cases of myocarditis on DTG [38], with one additional case of myocarditis in the FLAMINGO trial, part of the Phase 3 development programme [12]. These results need to be evaluated in the context of the overall safety profile of DTG from randomized clinical trials: there have been fewer discontinuations for all adverse events on DTG compared with either EFV in the SINGLE study [11] or with DRV/r in the FLAMINGO study [12].

TENOFOVIR ALAFENAMIDE: OVERALL SAFETY AND EFFICACY

In a recent meta-analysis of randomized clinical trials comparing TAF versus the original prodrug of TDF, there was no difference in the risk of adverse events, serious adverse events or discontinuations for adverse events between the two forms of the drug [39]. However, there were significant differences in mean change in bone and renal laboratory markers, favouring TAF, whereas mean changes in blood lipids showed a benefit for TDF [8▪▪]. The clinical significance of these mean changes in laboratory markers for patients in mass treatment programmes in LMICs is unclear. There is very limited clinical experience of TAF in pregnancy.

TENOFOVIR ALAFENAMIDE IN PREGNANT AND BREASTFEEDING WOMEN

The intracellular concentration of tenofovir diphosphate is four to five times higher for TAF compared with TDF [40]. It is unclear whether this higher intracellular concentration could lower the risk of vertical HIV transmission and/or increase the risk of adverse birth outcomes. There is currently very little clinical experience of TAF in pregnancy. No data are available on placental or breast milk passage of TAF in humans [41▪].

The safety database of TAF from the originator company included birth outcomes in only 12 live infants, of whom two had a congenital anomaly. One infant was born with tricuspid atresia, a large ventricular septal defect and died within 10 min of birth. The other infant was born with patent *foramen ovale*. The trial investigators did not consider either of these anomalies as related to their antiretroviral treatment. In addition, there were 17 induced terminations,

with two congenital anomalies. One embryo had Trisomy 18 (Edwards' syndrome) that was considered possibly related to TAF because the mother was taking TAF at the time of conception. The other embryo had Trisomy 21 (Down's syndrome) that was not considered to be treatment-related because the mother was not taking TAF at the time of conception.

It is not clear whether there is a clinical trial programme in place to properly evaluate the safety of TAF in pregnant women. Results from the Antiretroviral Pregnancy Registry are accumulating slowly, and the clinical trial database is limited in size. The VESTED study will compare TAF with TDF in over 500 pregnant women and their infants [21]. There should be approximately 180 pregnant women treated with TAF in this study. However, results will not be available until 2020. Other studies such as IMPAACT P1026s may only provide a small number of mother–infant pairs with outcome data [19].

At the 2017 WHO Think-Tank meeting, very few participants supported a recommendation to allow treatment of pregnant women with TAF in LMICs. The lack of pharmacokinetic and safety data from pregnant women was noted as a key concern.

TENOFOVIR ALAFENAMIDE IN HIV–TB COINFECTION

TAF is currently contraindicated for treatment with rifampicin, because the results of an interaction study with carbamezapine suggested that there would be significant reductions in tenofovir concentrations [41▪]. A new pharmacokinetic interaction study (RIFT, Table 3) is in progress, in 20 healthy volunteers, to investigate the effects of rifampicin on TAF. This study will include analysis of intracellular tenofovir diphosphate concentrations. At the 2017 Think-Tank meeting, there was no support for using TAF with rifampicin, given the current contraindication and lack of clinical evidence.

EFAVIRENZ 400 MG ONCE DAILY

The recommendation to use the 400-mg dose of EFV is supported by results from the ENCORE-1 study and the substudy of pharmacokinetics (PK)/PD [42,43]. There were significantly fewer EFV-related clinical adverse events at the 400-mg dose (38%) compared with the 600-mg dose (48%). A detailed PK/PD analysis of this study showed that the lower EFV concentrations at the 400-mg dose were not associated with a loss of virological efficacy [43].

EFAVIRENZ 400 MG IN PREGNANT WOMEN

There is extensive clinical experience of TDF/XTC/EFV in pregnant women, using the standard 600-mg once daily dose of EFV, which is recommended by WHO for treatment of pregnant women. The SSAT 063 study is in progress to evaluate the pharmacokinetics of EFV 400 mg in pregnant women (Table 2). At the meeting, some participants questioned the priority of adopting the low dose of EFV versus switching to DTG.

EFAVIRENZ 400 MG IN HIV–TB COINFECTION

Pharmacokinetic studies showed that rifampicin-based treatment leads to short-term reductions in EFV drug levels during the first 1–2 weeks of treatment, but after longer term treatment in combination with rifampicin-based combinations increases in EFV drug levels have been observed consistently across several studies [44]. However, these overall trends could differ by ethnicity, as suggested in the STRIDES study [45]. The efficacy of EFV-based treatment is similar for people either taking or not taking rifampicin-based treatment (in contrast to nevirapine, which shows lower efficacy when coadministered with rifampicin) [26].

There is a new pharmacokinetic study in progress – SSAT 062 – evaluating the interaction between EFV_{400} and rifampicin. The first phase of this study is in people with HIV infection in the United Kingdom and Uganda. The first results are expected by the end of 2017 (Table 3).

At the meeting, a minority of participants supported the use of EFV_{400} in combination with rifampicin. Most people wanted to see the results from the SSAT 062 study before making a firm recommendation.

The consensus was to continue using rifampicin-based treatment for HIV–TB coinfected people, despite the drug-interaction issues. The pharmacokinetic studies of DTG, TAF and EFV_{400} with rifampicin should generate results by the end of 2017. These results could allow planning of new clinical studies. For example, the pharmacokinetic interaction studies with TAF are likely to show lower concentrations of tenofovir diphosphate with rifampicin. However, if this concentration is still above the levels seen for TDF without rifampicin, this could still be therapeutic.

FIRST-LINE TREATMENT: CONTINUE WITH EFAVIRENZ OR SWITCH TO DOLUTEGRAVIR?

At the 2017 WHO Think-Tank meeting, there were equal numbers of participants who favoured a switch to first-line TDF/XTC/DTG in LMICs versus keeping country programmes using TDF/XTC/EFV.

The arguments in favour of switching to DTG included potential cost-savings, improved tolerability, encouraging evidence from treatment in North America and Europe and a higher barrier to drug resistance for DTG. The arguments supporting maintaining the *status quo* of EFV included TB coinfection, which was considered central to HIV infection in sub-Saharan Africa. The complexity of doubling the dose of DTG when using rifampicin was seen as a problem by some participants. Also, there was some concern over the emerging adverse event profile of DTG and the need for more intensive pharmacovigilance. Some participants favoured a phased introduction of DTG, excluding pregnant women and TB coinfected people from using DTG in national programmes until a more reliable safety database was available.

SECOND-LINE TREATMENT: FUTURE ALTERNATIVES TO 2NRTI + PI/R

At the 2017 WHO Think-Tank meeting, there was strong consensus that second-line treatment should be with two nucleoside analogues (NRTIs) with a boosted protease inhibitor. This is because of the strong evidence base from randomized clinical trials, which has shown no advantage of other treatment strategies. For example, in the EARNEST and SECOND-LINE studies, there was no improvement in efficacy for using combinations of a protease inhibitor and an integrase inhibitor second-line, versus 2NRTI + protease inhibitor plus ritonavir (PI/r). This high efficacy for 2NRTI + PI/r combinations was seen despite the presence of high-level NRTI resistance at baseline in the EARNEST study [46,47].

There are three studies in progress that might change this paradigm. The DAWNING study is comparing 2NRTI + DTG with 2NRTI + LPV/r for patients who have failed virologically on first-line treatment but have at least one active NRTI, according to genotypic resistance analysis. Results from the DAWNING study are expected by September 2017 [15]. Even if this study does show similar efficacy for DTG and LPV/r as second-line treatment, it may be difficult to apply this strategy in LMICs where there is restricted availability of genotypic resistance testing.

The D2EFT trial [48] is comparing a new combination of DRV/r + DTG versus the standard of care 2NRTI + DRV/r treatment in patients who have failed virologically on first-line treatment. Resistance testing is also permitted in this study to guide the choice of NRTIs, if locally available – again this could limit the application of the results to LMICs where resistance testing is not available. Another issue with this treatment strategy is the prevalence of Hepatitis B in sub-Saharan Africa, which ranges from 6.5% in Zambia to 25% in Zimbabwe [49]. Combinations of protease inhibitors with integrase inhibitors would not suppress HBV DNA replication. Therefore, before starting PI-integrase combinations, there would need to be systematic screening for Hepatitis B to avoid flares among people previously taking TDF/FTC or TDF/3TC.

Finally, the WHRI 052 study is evaluating a switch from LPV/r to a lower dose of DRV/r 400/100 mg once daily for 300 patients on second-line treatment with HIV RNA suppression (Table 4). If successful, the results could justify widespread switching to the lower dose of DRV/r for people with HIV RNA suppression. However, it will be important to start other studies to evaluate the lower dose of DRV/r in people with virological failure on first-line treatment. Currently, DRV/r is not available as a heat stable coformulation and is significantly more expensive than either LPV/r or atazanavir/ritonavir, which limits its widespread use in LMICs [6]. A reduction of the DRV/r dose to 400/100 mg once daily could lower the price to the same range as the other protease inhibitors, while avoiding the gastrointestinal adverse events and twice daily dosing of LPV/r.

CONCLUSION

After review of the current clinical trial data, it was agreed that the evidence base for evaluating the safety and efficacy of DTG, TAF and EFV_{400} needs to be improved to justify expanding treatment with these new drugs in millions of people in LMICs. Results from several key randomized clinical trials, such as NAMSAL, ADVANCE, D2EFT and VESTED, are not expected for at least another 2 years. Therefore, it will be important to analyse other datasets, even if nonrandomized, in the interim.

The current evidence for the safety and efficacy of DTG, TAF and EFV_{400} was not considered strong enough to justify widespread introduction of these antiretrovirals in LMICs. This situation could change within the next 3 years, as results emerge from ongoing clinical trials.

By July 2017, there should be a large enough database of pregnant women treated with DTG for a first review of birth outcomes and congenital anomalies. This review could be repeated at the end of 2017, once the database has grown further. The outcomes from the pregnant mothers treated in Botswana will be of key interest in these reviews.

The reports of IRIS and CNS adverse events on DTG need to be followed up with a systematic review of clinical trials and cohort studies. The cohort studies could provide valuable information on the safety of DTG in patients typically excluded

from Phase 2 and 3 studies, because of CDC C disease, low CD4 cell counts or HIV–TB coinfection. These are the patients most likely to develop IRIS.

There was agreement that 6-monthly reviews of safety and efficacy should be started to be continued until the evidence is sufficient to change WHO recommendations on the use of these drugs in pregnant women, HIV–TB coinfection and people with low CD4 cell counts.

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List of participants for Think Tank 2017: HIV treatment transition and drug sequencing in the context of new ARVs.

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Conflicts of interest

A.H. has received consultancy payments from Janssen and Teva, not connected with this project. A.P. has received consultancy payments from Gilead, Janssen, BMS, Merck and ViiV and Cipla, not connected with this project. M.V., N.F. and P.C. report no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

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