Fit for purpose

Antiretroviral treatment optimisation

HIV i-Base
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ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organisation. i-Base works in the United Kingdom and internationally to ensure that people living with HIV are actively engaged in their own treatment and medical care and are included in policy discussions about HIV treatment recommendations and access.

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ABOUT FIT FOR PURPOSE

i-Base's annual *Fit for Purpose* summarises key developments in antiretroviral treatment optimisation for low- and middle-income countries.

Fit for purpose: antiretroviral treatment optimisation

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Fit for purpose: antiretroviral treatment optimisation

By Polly Clayden

Introduction

Although 2016 was a mortifying year for global politics, it was quite a bumper one for progress in antiretroviral treatment (ART) optimisation.

This commentary is an interim update of the 2016 i-Base booklet *Fit for Purpose*, an annual review of development in ART optimisation for low- and middle-income countries (LMIC).

Experts now agree on a short list of antiretrovirals that have shown superior or non-inferior efficacy compared to existing recommended ones. These drugs offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for fewer side effects.[1, 2] The antiretrovirals are: dolutegravir (DTG), tenofovir alafenamide (TAF), efavirenz (EFV) 400 mg, and darunavir/ritonavir (DRV/r).

Since the last version of this booklet there have been further steps towards optimised treatment using these priority drugs:

- Several key ART optimisation studies, that will provide evidence for future first- and second-line recommendations, have begun recruiting (or are almost recruiting). See pages 18-31.
- The first generic version of DTG was tentatively approved by the US Food and Drug Administration (FDA).[3]
- Two new initiatives from UNITAID and the United States Agency for International Development (USAID) OPTIMIZE are providing donor support to speed up the introduction and access to optimised antiretrovirals. These programmes include both clinical trials and product introduction. [4,5]

For regular *Fit for Purpose* readers, all similarities to the previous edition are entirely intentional as ART optimisation priorities are largely unchanged. But some of the content and the trial tables have been updated to reflect recent developments.

Watch this space

The next edition of *Fit for Purpose* will be distributed at IAS2017. This version will expand to review developments and plans for ART optimisation in adolescents, children and infants.

i-Base is also launching the online *Op-ART Trial Tracker* which will provide an ongoing update in ART optimisation research and progress as this unfolds.

WHO 2016 guidelines

The most recent World Health Organisation (WHO) *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV*,[6] include10 new recommendations since the 2013 iteration. Universal eligibility for ART (Treat all) is the most important of these – so more people will start ART earlier.

The preferred and alternative first-line ART regimens are shown in Table 1. The preferred regimens remain the same as 2013 recommendations. This is unsurprising: at a WHO Think Tank convened in February 2015,[7] the expert group recognised that a greater body of evidence supports the use of EFV 600 mg first-line (an estimated 15 million patient years when combined with tenofovir disoproxil fumarate[TDF] and XTC – meaning either emtricitabine [FTC] or lamivudine [3TC]). The group suggested that this evidence provides a level of confidence that is not currently there with the alternatives. A year later the same group arrived at much the same conclusion.[8]

For adults and adolescents the alternatives include the introduction of EFV 400 mg and DTG. More information is needed on how they are likely to perform in real world, LMIC settings for these two alternatives to be recommended in WHO guidelines without restriction. Populations in such settings include larger proportions of women of childbearing age, children, and people with tuberculosis (TB), malaria, and other coinfections.[9]

Table 1: WHO 2015 preferred and alternative first-line adult ART regimens

FIRST LINE ART	PREFERRED REGIMENS	ALTERNATIVE REGIMENS
Adults	TDF+3TC (or FTC)+EFV	AZT+3TC+EFV (or NVP) TDF+3TC (or FTC)+DTG TDF+3TC (or FTC)+EFV400 TDF+3TC (or FTC)+NVP
Pregnant/breastfeeding women	TDF+3TC (or FTC)+EFV	AZT+3TC+EFV (or NVP) TDF+3TC (or FTC)+NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

New recommendations for second-line ART are shown in Table 2. Those include DRV/r or raltegravir (RAL) as alternatives to boosted lopinavir (LPV/r).

Similarly to the 2013 guidelines, third-line includes new drugs (if available) with the least risk of cross-resistance to those used already.

Table 2: WHO 2015 preferred and alternative second- and third-line adult ART regimens

FIRST LINE ART	PREFERRED REGIMENS	2ND-LINE REGIMENS	3RD-LINE REGIMENS
Adults	2 NRTIs + EFV	2 NRTIs +ATV/r or LPV/r	DRV/r + DTG (or RAL) + 1-2 NRTIs
		2 NRTIs + DRV/r	
	2 NRTIs + DTG	2 NRTIs +ATV/r or LPV/r	DRV/r + 2 NRTIs + NNRTI
		2 NRTIs + DRV/r	Optimise regimen using genotype profile
Pregnant/ breastfeeding women	2 NRTIs + EFV	2 NRTIs +ATV/r or LPV/r	DRV/r + DTG (or RAL) + 1-2 NRTIs
		2 NRTIs + DRV/r	

Key: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir.

New drugs and formulations will support the guidelines and drive the next major drop in ART costs

EFV 400 mg, DTG and TAF (the later not yet recommended by WHO but studies in LMIC are on the way) are expected to make up a large chunk of the adult first-line market over the next five years, and contribute to ART cost reductions, according to projections by The Clinton Health Access Initiative (CHAI).[10]

The latest CHAI report on the state of the ART market in LMIC reveals that of nearly 37 million people needing ART, 46% received it in 2015. This proportion included a growth of two million people receiving ART that year – one of the biggest annual increases ever.

In keeping with this increase, the overall LMIC market expanded to almost $US 2 billion in 2015. And cost of ART for adults per person year (pppy) decreased by 6–10% in 2015 from 2014 for adults and second-line for children in generic accessible countries. It now costs about $US110 to treat an adult with a preferred ART regimen.

CHAI report that over 70% people received WHO preferred regimens (or optimal paediatric formulations for children as defined by the Interagency Task Team [IATT]). So, cost of treatment generally fell with higher volumes, while quality of treatment rose in generic accessible countries.

More countries have adopted Treat all policies – including Botswana, Cambodia, Lesotho, Kenya and South Africa.

The first generic DTG has now been tentatively approved by the FDA. Botswana became one of the first countries to include DTG in its national guidelines and several others will follow. EFV 400 mg should be available in 2017 and TAF is also likely to come on to the market over the next two or three years.

A previous CHAI analysis showed that by the end of 2025 the introduction of TAF, EFV 400 mg, and DTG into ART programmes in LMIC could mean savings up to a whopping US $3 billion.[11]

Using their forecast for currently available products as baseline, CHAI modelled differences in prices of new and current products. Their assumptions were: TAF would displace TDF and zidovudine (AZT), and EFV 400 mg and DTG would displace EFV 600 mg and nevirapine (NVP) in first-line; and DTG would replace TDF and AZT-based backbones in second-line.

They estimated price discounts of new products over time using: costs of raw material (either directly from manufacturers or from the India Import/Export database); API process costs (from patents or literature; and formulation costs (assumed API accounts for 70–90% of the cost of formulation and packaging); volumes needed for economies of scale (chemistry inputs based on patents/scientific literature); and manufacturer profit margins (assumed approximately 25%).

The estimated pppy price savings at launch and scaled up with new products are shown in Table 3. Market share of new products and cumulative savings to 2025 are shown in Table 4.

Table 3: Estimated pppy savings with new products

ARV	VS	AT LAUNCH	AT SCALE
TAF	TDF	$0–2	$20–24
EFV400	EFV600	$10–11	$10–14
	NVP	<$1	$0–2
DTG	EFV600	Parity-slight premium	$17–21
	NVP	Parity-slight premium	$1–2

Key: DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV400, efavirenz 400 mg; EFV600, efavirenz 600 mg; NVP, nevirapine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate

Table 4: Market share and cumulative savings 2025

ARV	MARKET SHARE	SAVING
TAF	95% of first-line	$1.8 billion
DTG	80-90% of first-line and second line	$1.1 billion
EFV400	10-15% of first-line	$0.3 billion

Key: DTG, dolutegravir; EFV400, efavirenz 400 mg; TAF, tenofovir alafenamide

CHAI expect EFV 400 mg to peak at approximately 25% market share in 2021 before DTG takes over.

After all this good news on potential price savings, one important concern for access to Indian generic products is that the department within the Indian Central Drugs Standard Organisation of the Ministry of Health, responsible for regulating medical devices and drugs, the Drug Controller General of India (DCGI), requests clinical trials in India for all new drugs.[12] This request can also affect the export of new drugs.

The use of Indian generics to treat HIV is global: Mylan has 30% of the most recent South African tender, covering the three-year period from 1 April 2015 to 31 March 2018. [13]

But the DCGI can waiver the local clinical trial requirement for drugs, where the need is considered sufficiently urgent or important. This occurred with sofosbuvir for hepatitis C,[14] and has recently been granted for the Aurobindo DTG 50 mg single.[15]

The DCGI recently agreed on two conditions that will allow sponsors waivers on any drug, co-formulation or FDC that has been approved in countries included in the International Council for Harmonisation, covering the US, Europe and Japan, among others.

The conditions are: India's CDCO must perform inspections of batches manuafactured for regulatory approval; and bioavailability and bioequivalence studies of the drugs will be required.

But devil and details, according to FDAnews: "It may also be confirmed that the drug is being marketed in its country of origin, according to minutes from the board's meeting".[16] It is not clear whether or not this will pose problems for generic FDCs that do not have an originator equivalent or a market in their country of origin.

DTG, EFV 400 mg, and TAF will enable programmmes in LMIC to put more people on ART. These findings support advocacy for speeded up research and development of these products – which has now been a priority for sometime. And swift product uptake once they are available to realise their savings potential.

The ones to watch

Efavirenz 400 mg

EFV 600 mg – the currently approved dose – fulfils many of the characteristics in the target product profile as part of an ideal ART regimen. For those who tolerate the drug, it is safe and effective, can be used in pregnancy and in people also receiving TB treatment and needs minimal laboratory monitoring.

But it has a low genetic barrier to resistance. It is also associated with central nervous system (CNS) side effects, which can lead to drug discontinuation, reported in as many as half the people receiving it in settings with access to alternatives.[17] There is also an interaction between EFV and some hormonal contraceptives that can reduce their efficacy.[18]

A meta-analysis found that over 90% of treatment-naive people remained on an EFV-based first-line regimen after an average follow up of 78 weeks.[19] But CNS side effects were more frequent with this antiretroviral compared to a number of others. HIV positive people and activists have reported these adverse events as flaws of EFV since it was first approved.[20]

The ENCORE 1 study, showing 400 mg EFV to be non-inferior to 600 mg (both plus TDF/FTC), was completed in July 2013. The 48-week results were published in The Lancet in April 2014.[21] There were no surprises at 96 weeks.[22] The researchers recommend replacing the current EFV dose with the lower one.

The study was conducted in 636 treatment-naive participants in Europe, Australasia, Latin America, Asia, and Africa.

A very high proportion (approximately 90%) of participants had an undetectable viral load in ENCORE1. Extended follow up to 96-weeks continued to demonstrate non-inferiority of 400 mg EFV.

Significantly fewer participants (2% vs 6%, p=0.01) discontinued treatment due to EFV-related side effects (rash, CNS, gastrointestinal, but not psychiatric) in the 400 mg arm compared to the 600 mg arm and 10% fewer reported these side effects.

Results from a pharmacokinetic substudy of ENCORE1 suggest that although

400 mg gives cerebrospinal fluid (CSF) exposure of EFV above that needed to suppress HIV exposure of metabolites might still be within the concentration range associated with toxicities.[23] Although statistically significant, the reduction in EFV-associated side effects was modest in ENCORE1 and the pharmacokinetic study suggests this possible explanation.

Questions about whether or not 400 mg would be robust in the third trimester of pregnancy and with TB treatment have delayed recommendations from WHO and national guidelines.

There are six studies that include 235 women treated with 600 mg EFV in pregnancy in which drug concentrations were not significantly affected and there were high rates of viral load suppression in the mothers at the time of delivery.[24] The results suggest that pregnancy has slight if any clinically important effects on EFV pharmacokinetics.

A South African study of 97 pregnant women (44 with TB) found that pregnancy increased the rate of low EFV plasma concentrations, but vertical transmission was rare.[25] A detectable viral load at delivery was more common among pregnant women with TB, but ART was generally started later in this group. Another small study also found lower EFV plasma concentrations during pregnancy but the authors suggested that the clinical implications are unknown.[26]

Pharmacokinetic modelling, conducted to simulate EFV exposure using 600 mg and 400 mg during the third trimester of pregnancy, suggested that although pregnancy decreases total exposure of EFV the unbound fraction is predicted to be unchanged.[27] This study indicates that a dose reduction to 400 mg might be feasible in pregnancy.

For rifampicin, there have been seven short-term pharmacokinetic studies with EFV 600 mg (less than two weeks) showing reduction in plasma concentrations. It is unclear how useful these results are when EFV has not reached steady state. Five longer-term studies in HIV positive people have shown increased Cmin or no effect.[28]

Three leading HIV doctors suggested that the dominant role of EFV in first-line ART should be reconsidered,[29] and wrote: "this should not only happen in high-income countries but ideally also in low-income settings, if alternative drugs are available, and this recommendation should be reflected in the treatment guidelines of the WHO and both governmental and nongovernmental organisations."

But EFV is likely to remain a recommended first-line antiretroviral for a while. In countries where generics are not accessible until a drug is off patent this is likely to be for some time. The EFV/TDF/3TC regimen will be generic in most countries worldwide by 2017,[30] but DTG and TAF patents extend for at least another 10 years.[31] This will mean many middle-income countries that do not qualify for minimum prices – including swathes of South America, South East Asia, and Eastern Europe, where countries can pay four times as much for antiretrovirals than African ones with similar Gross National Incomes[32] – will encounter significantly higher (likely prohibitive) ones.

While EFV remains an option, it is important that the pharmacokinetic studies to look at the lower dose with TB treatment and in pregnancy are conducted to ensure that people receive the most optimised version.

Dolutegravir

With a low 50 mg once daily dose that does not require boosting, a very high barrier to resistance, good efficacy, minimal toxicity, pregnancy category B, and the potential to be low-cost and co-formulated, DTG looks like it will be an important potential option for use in LMIC. It is expected to replace EFV first-line.

DTG was superior to EFV at 48 weeks in antiretroviral naive participants in phase 3 trials (and remained so at 96 weeks).[33, 34] At 48 weeks the proportion of participants who discontinued treatment due to adverse events was lower in the DTG group than in the EFV group (2% vs 10%). Rash and CNS events frequently associated with EFV were significantly more common in the EFV group.

Data from this comparison and from studies comparing DTG to RAL and in people with resistance to other integrase inhibitors[35, 36] were used to gain approval for a broad indication in adults and adolescents aged 12 and above.[37] The indication for 12–18 year olds is based on a 24-week open-label label study in integrase inhibitor-naive adolescents.

DTG studies have not yet included significant numbers of people who would be treated in LMIC. The registrational trials for DTG comprised approximately 80% men and few non-white participants and hardly anyone co-infected with other diseases (a few with hepatitis B and none with TB or malaria). People with baseline NRTI resistance were not included.

Information about treating HIV/TB coinfection with a DTG-based regimen is limited. A phase I study has been conducted in healthy volunteers of DTG given with rifampicin and with rifabutin.[38] The study suggested that 50 mg twice daily dosing is likely to be required when it is co-administered with rifampicin to overcome UGT1A/CYP3A induction by this drug, which is used in standard first-line TB treatment.

To date information about DTG in pregnant women is also scarce. Although animal reproduction studies are not always predictive of human response, no safety issues were revealed in preclinical studies.

The following need to be considered when new drugs are evaluated for pregnancy: pharmacokinetic differences, possible increased risk and viral suppression in pregnant women; safety for infant (teratogenicity, birth outcomes and longer term toxicities); and prevention of vertical transmission.

In the DTG registrational trials and compassionate use programmes, among 39 pregnancies, there were: one congenital anomaly; 21 live births without anomalies; 10 elective terminations without anomalies; and three spontaneous abortions without anomalies. Post marketing surveillance of 141 pregnancies to 16 July 2016 reported: 31 live births without anomalies, three live births with congenital anomalies; 17 spontaneous abortions without anomaly; one spontaneous abortion with anomaly; one stillbirth without anomaly and 88 pregnancies ongoing or lost to follow up.[39]

Preliminary pharmacokinetic data from 15 women enrolled in IMPAACT P1026s suggests DTG exposures in pregnancy are similar to that in non-pregnant adults but lower compared with postpartum.[40]

DTG AUC was 25–30% lower in the second and third trimester compared with paired postpartum – the differences were not significant. DTG Cmax was significantly lower in the third trimester compared with postpartum. C24 was 41% lower in the second and third trimester but differences were not significant.

In this evaluation, 6/9 (67%) women in the second trimester, 12/15 (80%) in the third trimester and 8/9 (89%) postpartum had an AUC above the 10th percentile (37.5 mcg*hr/mL) of non-pregnant adults (historical controls).

All 15 women had viral load <50 copies/mL at delivery.

DTG infant elimination half-life was more than twice that of the mothers in the study and historical non-pregnant adult controls. All evaluable infants were HIV negative.

As of June 2016, five DTG-exposed babies in IMPAACT P1026 were reported to have congenital anomalies (and two babies with findings considered to be "normal variants") of approximately 15 born.[41]

The investigators deemed that, based on the nature of the anomalies and the timing of first exposure in pregnancy, the association with DTG can be ruled out for all but two of the five anomalies (renal cysts).

Because of the gestational age at which DTG was started and the nature of the renal cysts, the investigators also consider it unlikely that they are related to DTG-exposure.

The DTG arm of IMPAACT 1026s is now fully enrolled.

As of 31 January 2017, 61 pregnancies with exposure to DTG were reported to the Antiretroviral Pregnancy Registry (APR) but it is likely these data overlap with the company data above (IMPAACT P1026s is not included in the ViiV data set).[42]

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPIC) will is collecting data on DTG pregnancy outcomes to be presented later this year.[43] And Botswana will also be collecting maternal infant data as it rolls out DTG in its national programme.

Tenofovir alafenamide

TAF is another prodrug of tenofovir. TAF doses are one tenth or less than that of TDF and give intracellular levels of the active metabolite, tenofovir diphosphate, which are four to seven times higher and plasma concentrations that are 90% lower than those with TDF.[44]

The reduction in plasma concentrations with TAF could mean less tenofovir accumulation in bone and kidneys and, in turn, fewer bone and kidney associated toxicities compared with TDF.

There were no significant differences in efficacy or clinical side effects between TAF and TDF across phase II and III studies at 48 and 96 weeks. At 48 weeks, participants receiving TAF had statistically significant less renal toxicity and reduced bone mineral density compared to those receiving TDF. But TAF was also associated with increases in low-density lipoprotein (LDL) cholesterol and total cholesterol plasma levels. It is unclear whether or not these differences will have clinical significance long-term.

As with DTG, TAF badly needs to be evaluated in pregnancy and in the presence of rifampicin-based TB treatment before it can be used in LMIC.

TAF is a minor CYP3A4 substrate and a substrate of p-glycoprotein, both of which are induced by rifampicin, so there is likely to be an interaction. Gilead has not conducted any interaction studies with TAF and rifampicin. Co-administration with carbamazepine leads to a 55% decrease in TAF in plasma[45]; results from modelling to predict the interaction with rifampicin predict this reduction will be 73% in plasma.[46] But the intracellular concentrations of tenofovir-diphosphate when TAF is co-administered with rifampicin need to be investigated clinically.

TAF might give safety benefits over TDF and it could offer considerable benefits in price to generic accessible LMIC.

Darunavir/ritonavir

The WHO guidelines finally recommend DRV/r for second-line treatment. DRV/r is generally considered to be the most potent and tolerable protease inhibitor, but the generic formulation has taken its time, and cost has been a barrier to its wide use.

No dose-finding studies have ever been conducted with DRV/r in treatment-naive populations. The original studies were conducted in people that were highly protease inhibitor-experienced.[47, 48] The approved doses are DRV/r 800/100 mg once daily and 600/100 mg twice daily for people with no protease inhibitor resistance and with protease inhibitor resistance respectively.

Results from the dose finding studies and two with 600/100 mg once daily,[49, 50] plus one showing the recommended dose of cobicistat results in a significantly lower DRV Cmin than when it is boosted with ritonavir[51, 52] (in which the investigators say a reduction of up to 50% in Cmin should not make a difference to efficacy), suggest that a dose reduction to DRV/r 400/100 mg might be feasible.

What is planned or ongoing?

First-line

Experts agree that a DTG-based preferred first-line regimen is the current goal. As well as offering the advantages described earlier, in combination with TAF and FTC the total daily dose would be 275 mg (375 mg with 3TC) compared to 1200 mg with the current WHO preferred first-line: EFV 600 mg/TDF/3TC.

For people who cannot access (or tolerate) DTG, EFV 400 mg based regimens should be an alternative first-line.

Two investigator-led studies to look at these regimens in closer-to-real-life African settings have started enrolling. The studies are: ADVANCE, a three arm randomised comparison between two DTG-based regimens (one with TDF/FTC and the other with TAF/FTC) and EFV 600 mg (with TDF/FTC);[53] and NAMSAL comparing DTG-based to EFV 400 mg based regimens, conducted in South Africa and Cameroon respectively.[54] See table 5.

There are also a number of ongoing or planned studies to help to address some of the evidence gaps associated with use in pregnant women and people receiving TB treatment.

Table 5: New first-line regimen studies

STUDY	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
ADVANCE WRH1060	Wits RHI (USAID, UNITAID)	DTG/FTC/TAF vs DTG/FTC/ TDF vs EFV 600/ FTC/TDF non-inferiority, open label 1050 treatment naive adult participants (350 per arm) 60–90 treatment naive 12–15 year olds weighing > 40 kg (20 per arm) Johannesburg, South Africa	Phase 3 Started January 2017 48-week data available Q1 2019 Completion Q2 2020	Establish non-inferior efficacy for DTG/FTC/TAF compared to other study arms Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 96 weeks, CD4 changes, tolerability, safety and efficacy
NAMSAL (Efficacy and safety of a dolutegravir-based regimen for the initial management of HIV infected adults in resource-limited settings) ANRS 12313 NCT02777229	Inserm-ANRS (Institute de Recherche pour le development) (UNITAID)	DTG/3TC/TDF vs EFV 400 /3TC/TDF non-inferiority, open label 606 treatment naive participants (303 per arm) Yaoundé, Cameroon	Phase 3 Started June 2016 48-week data available October 2018	Establish non-inferior efficacy for DTG/3TC/TDF compared to EFV 400 mg/3TC/TDF Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 24 weeks, CD4 changes, tolerability, safety and efficacy

Key: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; Inserm-ANRS, French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis; NIH, United States National Institutes of Health; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PK, pharmacokinetic; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine; 3TC, lamivudine

Pregnancy

TABLE 6: First-line pregnancy studies

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Dolutegravir				
DolPHIN1 Dolutegravir in Pregnant HIV Mothers and Neonates: a pilot study NCT02245022	University of Liverpool (University of Cape Town, University of Makerere)	DTG PK in pregnant women in third trimester and post-partum during 2 weeks breastfeeding 60 late presenting women (28 to 36 weeks gestation) Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs South Africa and Uganda	Phase 2 Planned start March 2017 Primary completion December 2017	PK 3rd trimester Secondary outcomes include: safety and tolerability of DTG up to 2 weeks post-partum and VL at delivery
PK and safety study in pregnant women with HIV ING200336 NCT02075593	ViiV Healthcare	PK and safety single arm study of women with unintended pregnancies while participating in ARIA study of DTG/ ABC/3TC FDC vs ATV/ r +TDF/FTC in 474 treatment naive women (NCT01910402) to be completed in 2018 Estimated enrolment 25 women (approx 237 receive study drug in ARIA) Multicountry (United States, Russian Federation, Spain, United Kingdom)	Phase 3 Started Jan 2015 (recruiting) Primary completion February 2019	Impact of pregnancy on DTG PK in mother disease progression and maternal foetal transmission PK 2nd /3rd trimester PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes
DolPHIN2 Dolutegravir in Pregnant HIV Mothers and Neonates	University of Liverpool (University of Cape Town, University of Makerere, UNITAID)	DTG PK, safety and efficacy in pregnant women in 3rd trimester and post-partum during breastfeeding until weaning or 18 months 250 late presenting women (28 weeks gestation to delivery) Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs South Africa and Uganda	Phase 3 Planned to start Q3 2017 Primary completion Q1 2021	Primary endpoints: viral load at delivery, safety and tolerability Secondary endpoints: safety and breast milk sterilisation
Tenofovir alafenamide				
WAVES (OLE) Women's AntiretroViral Efficacy and Safety (Open Label Extension) NCT01705574	Gilead Sciences	EVG/COBI/FTC/ TDF vs TDF/FTC + ATV/r in treatment nave women with OLE with women in ATV/r arm re-randomised to remain or switch to EVG/COBI/FTC/TAF 583 women total, those that become pregnant can remain on study regimen Multicountry (United States, Belgium, Dominican Republic, France, Italy, Mexico, Portugal,Puerto Rico, Russian Federation, Thailand, Uganda, United Kingdom)	Phase 3 Started February 2016 (ongoing) Primary completion March 2017	Safety, efficacy and tolerability in naive PW in a two-phase study: double blind treatment phase (48 weeks) and open label extension phase (48 weeks) Safety and efficacy of EVG/COBI/FTC/TAF vs TDF/FTC + ATV/r

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Dolutegravir and tenofovir alafenamide				
VESTED IMPAACT P2010 Phase 3 Study of Virologic Efficacy and Safety of Dolutegravir-Containing versus Efavirenz Containing ART Regimens in HIV-1-Infected Pregnant Women and their Infants NCT01302847	NIH (NIAID)	DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 549 mother/infant pairs Treatment-naive women starting ART at 14 to 28 weeks gestation Randomised 1:1:1 open label Only study that evaluates DTG/TAF/FTC in pregnancy Multicountry: IMPAACT sites (United States, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania,Thailand, Uganda, Zambia, Zimbabwe)	Phase 3 Planned to start March 2017 Primary completion December 2019	Comparative data on safety and virologic efficacy during pregnancy and through 50 weeks of maternal and infant follow-up postpartum Superiority (virologic endpoint); comparison by arm for difference (adverse pregnancy outcome, toxicity endpoints) Primary endpoints: VL < 200 copies/mL at delivery; adverse pregnancy outcome (SAB, foetal death, PTD or SGA); maternal toxicity; infant toxicity Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks postpartum; renal toxicity (mothers and infants); bone toxicity by DXA (subset of mothers and infants); adverse pregnancy outcome including congenital anomaly; antiretroviral drug resistance (among women with VF, and among HIV-infected infants)

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
IMPAACT P1026s Pharmacokinetic Properties of Antiretroviral and Related Drugs During Pregnancy and Postpartum NCT00042289	IMPAACT network, NIH (NIAID)	PK properties of antiretroviral and related drugs during pregnancy and postpartum Each study arm 12–25 (target) women with evaluable 3rd trimester PK data Pregnant women > 20 weeks gestation receiving DTG (1 arm) and TAF (3 arms – within FDCs) as part of clinical care Multicounty: IMPAACT sites (United States, Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda)	Phase 4 Started in Sep 2014 (enrolment completed in DTG arm, recruiting for TAF arms) Primary completion June 2017 (DTG) and June 2018 TAF	PK data during pregnancy and to compare these parameters to a) historical PK data from non-pregnant women and b) postpartum PK data from the same women in the study cohorts. PK 2nd /3rd trimester PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes Washout PK in drug exposed infants
PANNA study Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women NCT00825929	Radboud University (PENTA Foundation, ViiV Healthcare)	Pregnant women < 33-week gestation receiving DTG as part of clinical care Each study arm 16 with evaluable 33-week data Multicountry: PANNA sites (Belgium, Germany, Ireland, Italy, Netherlands, Spain, United Kingdom)	Phase 4 Started in July 2015 (recruiting) Primary completion Dec 2020	PK data (PK curves) in pregnant HIV-infected women using newly developed antiretroviral agents. PK at 33 weeks and 4-6 weeks after delivery PK in neonate, safety, VL and transmission
Efavirenz 400 mg				
PK of EFV 400 mg once daily during pregnancy in HIV positive women SSAT063 NCT02499874	SSAT (Mylan Inc.)	PK single arm 25 women stable on 2 NRTI plus EFV 600 mg for >12 weeks, switch to EFV 400 mg at gestational age 28 weeks United Kingdom and Uganda	Phase 1 Started Sep 2016 (ongoing) Primary completion May 2017	PK (AUC 24h and Ctrough) EFV 400 mg during 3rd trimester pregnancy and post partum Safety and tolerability, genetic influences on EFV PK

Key: AE, adverse event; ABC, abacavir; ATV/r, atazanavir/ritonavir; BF, breast feeding; COBI, cobicistat; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Trials Network; NAID, NIH, United States National Institutes of Health; NRTI, nucleos(t)ide reverse transcriptase inhibitor; OLE, open label extension; PANNA, Study on Pharmacokinetics of Newly Developed ANtiretroviral Agents in HIV-infected pregNAnt Women; PK, pharmacokinetic; PTD, preterm delivery; SGA, small for gestational age; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine; 3TC, lamivudine

A ViiV-sponsored study is enrolling ART-naive women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.[55] Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.[56]

DolPHIN 1 and 2 will look at DTG pharmacokinetics, safety and efficacy in pregnancy and post-partum, the pilot study is on the verge of starting enrolment and the larger one is now supported by the UNITAID programme.[57, 58]

The women-only Gilead study WAVES includes an open label extension in which women are re-randomised to remain on a boosted atazanavir-based regimen or switch to one that includes TAF. Women who become pregnant in the study can stay on their ART regimen.[59]

IMPAACT P1026s (which has presented preliminary data for DTG described earlier)[60, 61] and PANNA [62] – the respective American and European studies that look at pharmacokinetics of antiretrovirals in pregnancy and post-partum include women receiving DTG and TAF.

VESTED (IMPAACT P2010) will make the three arm same comparison as ADVANCE but in pregnant women.[63, 64]

ADVANCE will give women who become pregnant during the study the option to continue on their study drugs.

And for EFV 400 mg – for which the safety concerns were resolved with wide use of EFV 600 mg – a pharmacokinetic study in pregnant women is ongoing.[65]

Tuberculosis

Table 7: First-line HIV/TB co-treatment studies

STUDY	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Dolutegravir				
INSPIRING Open label study of DTG vs EFV for HIV/TB coinfection ING117175 NCT02178592	ViiV Healthcare	50 mg DTG twice daily vs 600 mg EFV (open label, randomised 3:2 ratio) during TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) 125 treatment naive participants Multicountry (Argentina, Brazil, Mexico, Peru, Russian Federation, South Africa, Thailand)	Phase 3 Start Jan 2015 (ongoing) Primary completion Dec 2017	Establish antiviral activity of DTG or EFV containing regimens with TB treatment Primary outcome number of participants with VL <50 copies/ mL at 48 weeks Secondary outcomes include: VL <50 copies/ mL at 24 weeks, CD4 changes, tolerability, safety and efficacy
PK DTG 50 mg and 100 mg once daily with rifampicin	SSAT (Wits University)	DTG 50 mg once daily with food for 1 week, PK day on day 7 Then DTG 100 mg once daily for 1 week, PK on day 14 Then 7-day wash out period Start RIF on day 22 for 35 days and add DTG 50 mg on day 44, PK day on day 44 Then increase DTG to 100 mg OD for another 7 days, PK day on day 57 20 HIV negative participants United Kingdom	Phase 1 Planning stage	Primary objective: investigate the PK of rifampicin 600 mg once daily and DTG 50 or 100 mg once daily in HIV negative partcipants Secondary objective: investigate the safety and tolerability of rifampicin 600 mg once daily and DTG 50 or 100 mg once daily in HIV negative participants Results will inform a bigger study that will be conducted in South Africa in people with HIV and TB who will be given rifampicin-containing regimens and DTG, ideally once daily

STUDY	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Efavirenz 400 mg				
Pharmacokinetics of Efavirenz in the Presence of Rifampicin and Isoniazid SSAT062 NCT02832778	SSAT (Mylan Inc)	Sequential: 98 days (stage 1) and 28 days (stage 2) open label PK study Stage 1 (London) PK in 25 HIV positive participants on established EFV 600 mg containing ART switch to EFV 400 mg plus rifampicin and isoniazid for 12 weeks (2 weeks after reduced EFV dose) Stage 2 (Kampala) PK in 10 participants with HIV and TB on established EFV 600 mg containing ART switch to EFV 400 mg plus rifampicin and isoniazid for 28 weeks (2 weeks after reduced EFV dose) United Kingdom and Uganda	Phase 1 Start Sep 2016 (recruiting) Primary completion May 2017	Evaluate steady state PK of EFV 400 mg during co-administration with rifampicin and isoniazid Secondary endpoints: safety and tolerability; Relationship between genetic polymorphisms and EFV exposure

STUDY	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Tenofovir alafenamide fumarate				
RIFT The effect of rifampicin on the plasma pharmacokinetics of emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) and intracellular tenofovir-diphosphate (TFV-DP) and FTC triphosphate (FTC-TP) SSCR101	SSAT (Wits University, Gilead Sciences)	Stage A 20 participants: Phase 1 : TAF/FTC 25/200 mg once daily for 28 days (days 1-28) Phase 2 : TAF/FTC 25/200 mg once daily plus rifampicin 600 mg once daily for 28 days (days 29-56) Phase 3: TDF 245 mg once daily for 28 days (days 57-84) If Stage A is only partially informative, Stage B will follow where a similar study will be undertaken with modified doses of TAF (eg 50 mg once daily or 25 mg twice daily with double dose of FTC too) and/or potential P- gp inhibitors (eg cobicistat). Stage B will be submitted as a protocol amendment. United Kingdom	Phase 1 Planned start Q1 2017 Primary completion end 2017/ early 2018	Primary objective: PK of TAF, plasma tenofovir, Intracellular TFV-DP, FTC, and FTC-TP, during co-administration of TAF/FTC or TDF with rifampicin in HIV negative participants Secondary objective: safety and tolerability of the co-administered drugs in HIV negative participants

Key: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; PK, pharmacokinetic;SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate

ViiV is sponsoring an open label study of regimens containing 50 mg DTG twice daily or EFV 600 mg once daily during first-line TB treatment, which begun enrolling early 2015.[66]

As it would be better to be able to take DTG once daily, another study will look at the drug concentrations in the presence of rifampicin at doses of 50 mg and 100 mg in HIV neagative people. This will inform a study in people with HIV/TB coinfection.

A study is recruiting to investigate the pharmacokinetics of EFV 400 mg in HIV positive people in the presence of rifampicin and isoniazid in London and in HIV and TB coinfected participants receiving full anti-TB treatment in Kampala.[67]

For TAF the key pharmacokinetic parameter is intracellular tenofovir diphosphate in plasma and peripheral blood mononuclear cells. A study to measure this in the presence of rifampicin is planned in HIV negative people. Once this has been established then studies can be conducted in HIV/TB coinfected people.

It might be that EFV/TDF/3TC remains the recommended regimen during TB co-treatment if studies suggest that adjusting the dose of DTG (and possibly TAF) is necessary, as this can get a bit too complicated.

If DTG/TAF/XTC fulfils its early promise, is recommended, and generic FDCs are made available, there will be questions to be answered on the pros and cons of a wholesale switch from the current EFV-based first-line versus a gradual transition.

Two drugs first-line

There is currently interest, including from the AIDS Clinical Trial Group (ACTG) in looking at DTG/3TC dual therapy, as a potential new strategy to reduce ART cost and toxicity. [68]

In order for this strategy to be considered for LMIC there would need to be robust data from large pragmatic studies in unselected African populations, including TB and pregnancy. Both TB and pregnancy occur at incidence rates around 5% on ART in Southern Africa, so it is critical that the preferred first-line regimen is effective in these populations.

Although preliminary data from IMPAACT P1026s suggests DTG exposures in pregnancy will be sufficient (in three drug regimens), some pharmacokinetic parameters are reduced in the third trimester.[69] There is also considerable reduction in DTG exposure with rifampicin. Using it with only 3TC would likely scupper the possibility that DTG might still be effective at the standard dose with TB co-treatment, despite this reduction, which will be investigated further along the line.

When this DTG/3TC was raised at the WHO Think-Tank meeting earlier this year, only a minority were in favour.[70] The other concerns were lack of coverage for people co-infected with hepatitis B, and baseline antiretroviral resistance.

Although every rand, pound or dollar saved in ART programmes is important at scale, the projected annual difference adding TAF to the regimen is about US $10–15 per patient, which would have to be considered against the cost impact of potential first-line failure.

At the moment it seems that the potential benefits outweigh the potential risks. The studies would need to be designed to make sure these potential risks could be ruled out, before this regimen could be considered for global guidelines.

Second-line

For people failing EFV-based first-line treatment – and this population is expected to grow with greater access to viral load testing – there have been discussions about a second-line regimen with low dose DRV/r.[71]

A regimen of DRV/r plus DTG has the potential to be once daily, heat-stable, co-formulated second-line option with no cross-resistance to an EFV/TDF/3TC first-line. Although with the current DRV/r mg dose of 800/100 mg a single pill daily regimen is less likely than two 400/50 mg ones. The D_2EFT study will compare this regimen to DRV/r plus NRTI.

There is also the potential for a dose reduction of to DRV/r 400/100 mg and one study is underway and other are planned.

Table 8: DRV/r second-line studies

STUDY	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
DRV/r 400/100 mg vs LPV/r WRHI052	Wits RHI (USAID, MCC SA)	300 participants stable on LPV/r + 2 NRTI twice daily randomized to stay or switch to DRV/r 400/100 mg once daily 48 weeks South Africa	Phase 3 Ongoing	Primary endpoint VL <50 copies/mL at 48 weeks Secondary endpoints include clinical and laboratory markers
D_2EFT	UNSW (UNITAID)	610 participants who failed 1st line regimen randomised to DRV/r + DTG vs DRV/r + 2–3 RTIs 96 weeks Multicountry: Argentina, Chile, Colombia, Mexico, Peru, South Africa, Zimbabwe, India, Malaysia, Thailand, Indonesia	Phase 3 Starting September 2017	Primary endpoint VL <50 at 48 weeks Secondary endpoints include differences in VL using different thresholds, time to VL <50 copies, changes in baseline CD4 count
Low dose DRV/r pilot	SSAT	120 treatment naive participants randomised to DRV/r 800/100 mg vs 600/100 mg vs 400/100 mg + TDF/FTC United Kindom and Uganda	Phase 2 pilot Funding application stage	PK and VL
Low dose DRV/r	SSAT	600 1st line treatment experienced participants randomized to DRV/r 800/100 mg vs 600/100 mg vs 400/100 mg + TDF/FTC 96 weeks United Kingdom and Uganda	Phase 3 Funding application stage	PK and VL

Key: DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; PK, pharmacokinetic; MCC SA, Medicines Control Council South Africa; SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UNSW, University of New South Wales, VL, viral load

If DTG becomes preferred first-line, research into the best option for second-line after this regimen is needed. Discussions have included using NRTIs again or combining DRV/r with rilpivirine or doravirine.

More research is needed to determine the best options for optimised second-line ART.

WHAT NEEDS TO BE DONE?

- **Upgrade the new first-line regimen.** Sufficient evidence to change WHO guidelines to recommend DTG and TAF as part of the preferred first-line regimen (replacing EFV and TDF) needs to be generated in order to convince generic manufacturers to invest in new production for the new regimens. A recommendation from WHO is the strongest signal to generic manufacturers to take the risk and produce new FDCs. Such WHO recommendations will require results from the studies discussed here.
- **Originators donate drugs to strategy studies for LMIC.** Originator manufacturers must take responsibility and supply prioritised antiretrovirals to key investigator-led studies (as well as the supporting substudies) to generate data to support their use in LMIC. And not after several years of deliberation. The lack of information on use of new regimens in pregnancy and with TB treatment – that is critical to treating populations in LMIC – will continue to be a barrier to their universal recommendation however impressive the results from the phase III trials are.
- **Countries get ready to switch.** Countries with high volume ART programmes such as South Africa, Kenya, and Uganda, need their guideline committees briefed as results are generated (even before they are publically released), so that they can make new recommendations, hopefully before final WHO decisions.
- **Donors must support switch to new drugs and regimens.** Donors can play a huge part in changing standard of care in countries. UNITAID bought large volumes of TDF and helped to bring down the price and speed up the switch from d4T – so called market dynamics.
- **Timely approval.** Regulatory agencies in LMIC, such as the South African Medicines Control Council, need to register new originator and generic formulations, as swiftly as possible. The DCGI in India needs to waiver the request for Indian trials before prioritised antiretrovirals products can be exported. Ideally this should happen before new WHO and national recommendations.
- **Generic companies need time to plan for high volume manufacture.** Generic manufacturers need to be briefed on when data from key studies are expected to be released, guideline changes, and tender timing in countries, so that they can start planning to compete to supply the newly recommended regimens.
- **Pre-empt possible chaos.** Before introducing new drugs, issues such as stockpiling (and stock outs) need to be discussed and planned, so that hitches with switching from old to new regimens are kept to a minimum.
- **Second-line needs more consideration.** Although there is consensus on the likely best optimised first-line regimen, second-line is not quite there yet and requires more discussion and research and development to ensure best regimens and formulations.

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