Fit for purpose

Antiretroviral treatment optimisation

By Polly Clayden

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.

ABOUT HIV PIPELINE 2018: NEW DRUGS IN DEVELOPMENT

i-Base produces an annual HIV pipeline review as a companion to Fit for Purpose.

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Fit for purpose: antiretroviral treatment optimisation

Introduction

Fit for Purpose provides an overview of recent developments in antiretroviral treatment (ART) optimisation for HIV positive adults and adolescents in low- and middle-income countries (LMICs).

There have been several key developments since the July 2017 edition:

Two generic fixed dose combinations of tenofovir disoproxil fumarate (TDF), lamivudine (3TC) and dolutegravir (DTG) (TLD) were tentatively approved by the US Food and Drug Administration (FDA) in August 2017.[1]

A pricing agreement was announced in September 2017 that will speed up access to generic, DTG-based, fixed dose combinations. This will enable treatment of HIV in LMICs at an annual cost per person of around US $75.[2]

The Presidents Emergency Programme on AIDS Research (PEPFAR) has recommended rapid introduction of DTG in its priority countries and announced that it will soon stop procurement of efavirenz (EFV)-based treatment.[3]

The first generic fixed dose combination of tenofovir alafenamide (TAF), emtricitabine (FTC) and DTG was also tentatively approved by the US FDA in February 2018.[4]

The Third Conference on Antiretroviral Drug Optimisation (CADO 3) took place at the end of 2017. CADO 3 focused on optimised second- and third-line ART for adults and the sequencing and recycling of key products: TDF and TAF, DTG, and darunavir/r (DRV/r).[5]

But possibly interfering with all this progress was the news on 18 May 2018, when World Health Organisation (WHO) issued a statement, after a potential safety signal was identified relating to neural tube defects in infants who had been exposed to DTG at the time of conception.[6]

WHO guidance 2018

First-line

The 2016 WHO consolidated guidelines have recommended TDF/3TC or FTC (XTC)/EFV 600 mg as preferred adult and adolescent first-line ART regimen.[7]

DTG-based first-line ART was recommended as an alternative regimen due to evidence gaps for its use in pregnancy, preconception and with rifampicin (RIF)-based tuberculosis (TB) treatment and lack of generic formulations at that time.

WHO's most recent policy brief: Antiretroviral regimens for treating and preventing HIV infection and update on early infant diagnosis of HIV, July 2018,[8] cites its newly updated systematic review and meta-analysis (not yet published in full). This review confirmed the 2016 review findings, showing a regimen with two nucleoside reverse-transcriptase inhibitors (NRTIs) plus DTG to be more effective, with better viral suppression and CD4 count recovery and lower risk of treatment discontinuation compared with EFV-based ART in treatment-naive adults.

DTG has other advantages compared with EFV, including fewer drug-drug interactions, faster viral suppression and a higher genetic barrier to developing resistance. Unlike EFV, DTG is also effective against HIV-2.

But, WHO notes safety concerns with women and adolescent girls using DTG at conception. Although starting DTG in pregnancy appears to be safe. For women and adolescent girls of childbearing potential who do not wish to become pregnant, and are fully informed of the benefits and risks, DTG is recommended with consistent contraception. DTG and hormonal contraception do not have documented or expected drug-drug interactions. This is based on limited data but is not at all likely.[9]

WHO recommends women and adolescent girls of child-bearing potential

receive EFV or protease inhibitor (PI)-based regimens if consistent and reliable contraception cannot be assured or if a woman wishes to become pregnant.

WHO also recommends that countries with pretreatment resistance to EFV or nevirapine (NVP) at 10% or above should urgently consider using an alternative regimen that does not contain non-nucleoside reverse- transcriptase inhibitors (NNRTIs). DTG with consistent and reliable contraception for women and adolescent girls or atazanavir/ritonavir (ATV/r) are suitable options.

Second-line

WHO recommends DTG for people who have failed an NNRTI or protease inhibitor (PI)-based first-line, with the same preconception safety caveats for women. PI-based treatment with an ATV/r or lopinavir/ritonavir (LPV/r)-based regimen is recommended for people who receive DTG first-line.

An optimised NRTI backbone should be used for second-line, such as zidovudine (AZT) following TDF or abacavir (ABC) failure and vice versa.

Table 1. Options for first-, second- and third-line ART regimens for adults (including pregnant women and adolescents)

FIRST-LINE	SECOND-LINE	THIRD-LINE
2 NRTIs + DTG	2 NRTIs + ATV/r or LPV/r	DRV/r + DTG + 1–2 NRTIs (consider genotyping if possible)
2 NRTIs + EFV	2 NRTIs + DTG	

Source: WHO policy brief. Antiretroviral regimens for treating and preventing HIV infection and update on early infant diagnosis of HIV. July 2018.

Early adopters, new prices, new approvals

Although many countries have changed or are in the process of making the transition to DTG-based first-line (and in fewer countries EFV 400 mg) more information is still needed on how they are likely to perform in real world, LMIC settings.[10, 11]

By the end of 2017 at least 60 LMICs had recommended DTG first-line in their national guidelines.[12] And several countries have already began providing DTG in their programmes including Botswana, Brazil, Kenya, Nigeria and Uganda. Countries have taken different approaches to the transition and use in pregnancy and with TB treatment.[13] Since the potential safety signal with DTG preconception, countries are now reviewing their guidance for women of child-bearing age.

PEPFAR has recommended fast introduction of TLD in its priority countries. Before the DTG potential safety signal, the programme was stopping the procurement of EFV-based treatment. And by 2021 approximately 15 million people were predicted to be taking TDF/3TC/DTG – according to CHAI forecasts.[14]

Kenya was the first country to start providing generic DTG in its national programme – launched 28 June 2017.[15]

CHAI and UNITAID are working on a three-year large-scale initiative to speed up the introduction and access to optimal antiretrovirals.[16]

To speed things up further, a new pricing agreement was announced that will help to accelerate access to generic, DTG-based, fixed dose combinations.[17] This will enable treatment of HIV with modern ART in LMICs at an annual per person cost of around US $75.

The announcement was made on 21 September 2017 at UNGA by the

governments of South Africa and Kenya with UNAIDS, CHAI, the Bill & Melinda Gates Foundation, Unitaid, DFID, PEPFAR, USAID, and the Global Fund, in collaboration with Mylan Laboratories Limited and Aurobindo Pharma.

The new TLD products were developed by Mylan and Aurobindo under licensing agreements from ViiV Healthcare, the originator of DTG. Both generic manufacturers received tentative approval from the US FDA for TLD in August of last year.[18]

The agreements, which set ceiling prices for TLD, apply to public sector purchasers in generic accessible countries. They will offer big reductions compared with the price of EFV-based fixed dose combinations (around US $100 per person per year).[19]

This could lead to savings of up to US $900 million over the next six years in South Africa – although transition to TLD has been delayed and is only likely to start in April 2019.[20]

Across the 92 countries covered under ViiV's DTG licensing agreement, six-year savings have been estimated at US $1 billion.

Another DTG-based product swiftly followed TLD: FDA granted Mylan tentative approval for its fixed dose combination DTG/FTC/TAF on 9 February 2018.[21, 22]

DTG/FTC/TAF 50/200/25 mg will be the first TAF-based fixed dose combination available in LMICs) for first-line ART. Mylan manufactures this generic product under licenses from the Medicines Patent Pool (DTG) and Gilead Sciences (FTC/TAF), respectively.

The tablet will be the smallest sized single tablet regimen available for people in LMICs. It will be offered in a 90-day package as well as a 30-day one.

But, although this combination of antiretrovirals is currently recommended in the US and Europe, TAF is not yet recommended (or even mentioned) in WHO guidelines. Several data gaps remain before its recommendation is likely, particularly on safety in pregnant women.

Third Conference on Antiretroviral Drug Optimisation (CADO 3)

CADO 3 took place at the end of 2017.[23, 24] The meeting focused on optimised second- and third-line ART for adults and the sequencing and recycling of key products: TDF and TAF, DTG, and DRV/r. The discussions assumed that DTG/XTC (3TC or FTC)/TAF will be first-line standard care in five years' time.

As ever, missing evidence is typically for pregnant women, people with HIV/TB coinfection and people who have not had resistance testing before starting ART.

Key messages and, in turn research priorities, from the meeting were:

- Trials to evaluate the transition from EFV-based to DTG-based regimens are needed to ensure safety and efficacy for the nearly nine million people on NNRTI based ART in LMICs who have either detectable or unknown viral loads. These should include
- DTG vs PI second-line after EFV-based first-line failure (possibly with a factorial on NRTI use).
- Can DTG be given without dose adjustment (50 mg) during co-treatment with RIF?
- Is it necessary to switch from TDF to AZT (current standard of care) vs maintaining TDF second-line after failing a first-line TDF-containing regimen?
- More evidence is needed on the use of TAF in pregnant women (in this case, considerably more evidence) and people with HIV-TB coinfection

taking RIF-based treatment to support widespread use of the new TAF/3TC/DTG combination in LMICs.

- Is it possible to use once-daily DRV/r 400/100 mg vs 800/100 mg (standard of care) second-line? Such investigations should also consider a factorial looking at NRTI use.
- Data from randomised phase 3 GEMINI trials of DTG/3TC will be available at in 2018, but the overall disadvantages of this approach appear to outweigh the advantages for people with HIV in the setting of LMICs.
- For new drugs, there is substantial additional research required to evaluate an antiretroviral for widespread use in LMICs. This should be important for new HIV drugs in development.

CADO 3 participants looked at the growing body of programme data on the safety of DTG in first-line – particularly from Botswana and Brazil – and agreed that these data support further expansion of a DTG regimen as a preferred first-line option. But they also agreed that a robust research programme to provide the remaining missing evidence to support its widespread use, as well as careful collection and analysis of programme data, were essential in parallel to countries' transition.

The strategy of universally switching people who are currently stable an EFV-based regimen and DTG's role in second-line was still debatable.

Participants judged EFV 400 mg to be the alternative first-line option for people who cannot tolerate DTG or for countries where it cannot be accessed because of cost and patent protection.

They did not support the use of two-drug regimens for adults based on the trial data currently available. As ever, recent and ongoing studies of two-drug regimens do not consider the usual important populations who will be treated in LMICs: pregnant women, people with TB and HBV co-infections, people diagnosed in advanced HIV infection; and populations with no or limited access to viral load and/or resistance testing.

Many of the two-drug investigations are switching studies. In real-life such strategies would require both widespread use of viral load testing as well as the procurement of two products – there would be many programmatic challenges.

The role of DTG in people who previously failed NNRTI-based regimens and whether or not TDF and TAF could be recycled were defined as key priorities. Following the DAWNING results, showing DTG-based ART to outperform LPV/r in second-line – there was much discussion at CADO 3 on whether these results could be duplicated in a public health setting without genotyping.[25] Trials to answer this question, and whether DTG will perform similarly to a PI in the context of NRTI resistance, or will need to be combined with different NRTIs, were judged to be essential.

Dose optimisation studies on use of low dose DRV/r in second-line for people who either failed first-line or were stable on another second-line regimen was also considered to be a priority.

Long acting drugs (oral, injection or implants) and nanoformulations were judged high-priority in the longer term. But, once again, in order for these or any pipeline products to be usable in LMICs, studies will need to include pregnant and women of child-bearing age, adolescents, people coinfected with TB and on treatment, and other co-morbidities.

And any investigations should consider the circumstances in which these products are likely to be given, such as no or limited viral load monitoring nor access to other tests, highly trained experts or laboratories.

If programmes begin implementation before clinical trial results are available – as is happening with DTG: enhanced monitoring protocol and only progress with good viral load monitoring.

CADO 3 also defined a prioritised portfolio of new adult ARV products. See table 2. This product portfolio will be updated on a regular basis, like the Paediatric Antiretroviral Drug Optimisation (PADO) list,[26] as new information is made available on existing products or on new products.

Table 2: CADO 3 prioritised optimised products

SHORT-TERM 1–2 YEARS	MEDIUM-TERM 2–5 YEARS	LONG-TERM 5+ YEARS
TDF/XTC/DTG	TAF/XTC	Long-acting formulations (entry inhibitors and INSTIs)
TDF/3TC/EFV400	TAF/XTC/DTG	Maturation and capsid inhibitors
DRV/r 400/50 mg	New DRV/r formulations*	bNAbs

*Low dose standard formulation (400/100 mg) or standard dose nanoformulation (800/100 mg).

Other lower priority products might be considered if data suggests superiority to existing products.

The ones to watch: what we know and the evidence gaps

Dolutegravir

Generic DTG-based FDCs are now available and are starting to replace EFV-based first-line.

Dolutegravir preconception and pregnancy

On 18 May 2018, the WHO issued a statement after a potential safety signal with DTG was identified relating to neural tube defects in infants who had been exposed to this antiretroviral at the time of conception.[27]

The potential safety signal was found at a preliminary, unscheduled analysis of an ongoing observational study in Botswana. The Tsepamo study is a birth surveillance programme, started after the introduction Option B+ (lifelong ART for all pregnant women) in Botswana. When it was designed, there was still some uncertainty about EFV and birth defects.

Tsepamo compares birth outcomes with exposure from conception and/or during pregnancy to the most common ART regimens used in the country since 2014. Surveillance is conducted at eight maternity wards in government hospitals, representing about 45% of all births. Data are extracted from all consecutive births at 24 weeks or more gestational age, using obstetric records. Livebirth and stillbirth outcomes in HIV positive are also compared to those in HIV negative women.

The study had previously reported reassuring data (similar to that with EFV) with DTG started during pregnancy.[28, 29] The most recent figures, published in Lancet Global Health in June 2018, includes 1729 pregnant women who started DTG-based ART and 4593 EFV-based ART in pregnancy.[30] The risk for any adverse birth outcome among women on DTG versus EFV was similar: 33·2% vs 35·0%. As was the risk of any severe birth outcome: 10·7% vs 11·3%.

But adverse pregnancy outcomes among HIV positive women continue to be

elevated compared with HIV negative women, despite ART. When these data were released the Tsepamo investigators emphasised that the findings were reassuring but not the whole story: birth outcomes with DTG exposure from conception still needed to be evaluated.

The preconception analysis revealed four cases of neural tube defects (spina bifida, anencephaly, encephalocele, iniencephaly) out of 426 births to women who became pregnant while taking DTG.

This rate of approximately 0.9% compares with a 0.1% risk of neural tube defects in infants born to women taking other ARVs at the time of conception.

WHO's May statement was followed by several others, including from PEPFAR, US FDA, European Medicines Agency (EMA), US Department of Health and Human Services (DHHS), as well as a Dear Doctor letter from ViiV Healthcare.[31, 32, 33, 34] The recommendations suggest varying degrees of caution.

The WHO statement advises that pregnant women who are already taking DTG should not stop ART and should speak with their health care provider for additional guidance. For women of childbearing age starting ART, including pregnant women, it says, treatment should be based on drugs for which adequate efficacy and safety data are available; an EFV-based regimen is a safe and effective first-line regimen. DTG can be considered in cases where consistent contraception can be assured.

PEPFAR encourages countries to continue with their transition to TLD, but states that transition times might be altered to allow for the use of EFV-based regimens for certain women. Until further data are available, it recommends that women with HIV who wish to become pregnant should take EFV-based regimens. Any mention of contraception for women who do not wish to become pregnant is notable by its absence.

Many LMICs have already begun to transition (or are in the process of transitioning) to DTG-based regimens and are reviewing their policies based on this new information. Unfortunately, it appears that several countries are taking a conservative approach and giving all women of reproductive age EFV-based

first-line irrespective of their circumstances. The Kenyan Ministry of Health has pretty much banned DTG for women aged 15–49.[35]

WHO is working with many stakeholders worldwide to follow pregnant women with preconception DTG exposure to ensure more information is available to inform countries' recommendations.[36]

Preclinical safety data did not show developmental toxic effects or teratogenicity – although these categories are no longer used, DTG is FDA category B.[37, 38]

Currently there is a flurry of activity to try and determine whether the potential safety signal from Botswana was a chance finding.

There are data from a few women who became pregnant in DTG phase 3 trials and post marketing but these are not in sufficient numbers to pick up a rare adverse event such as a neural tube defect, nor have a comparator.[39, 40, 41]

There are about 600 more women who became pregnant on DTG before the warnings came out and are expected to deliver babies at one of the Tsepamo sites. Data on these women should be available in 9–12 months.

As far as other early adopter countries are concerned, similar programmes to Tsepamo are in place in Uganda and Malawi.[42] But the transition to DTG is only just beginning so neither country will have much to report yet.

Brazil has been using DTG in its national programme since early 2017, and has an excellent reporting system, but it is unlikely that the numbers of exposures will be substantial.[43]

Data from high-income countries are frequently collected and there has been longer term DTG use – although far fewer women with HIV.

This includes reports to the Antiretroviral Pregnancy Registry (APR).[44] APR is an international (although largely US), voluntary, prospective registry that monitors prenatal antiretroviral exposures to detect potential increases in the risk of birth defects. The APR produces twice-yearly reports.

Antiretroviral exposure is classified by earliest trimester, which means starting ART any time in the first three months. Due to the narrow exposure window of interest for neural tube defects, the current interim report through to 31 January 2018 (published June 2018) included supplementary information on preconception DTG exposure. Only a small number of exposures (121) have been reported to date among which there were no neural tube defects.[45]

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) is a network of cohort and surveillance studies conducting epidemiologic research on pregnant women and children with HIV and children exposed to HIV during pregnancy.

Data for 81 infants presented in 2017 reported defects in four infants – these are from any pregnancy exposures (55 mothers ART preconception) and not neural tube defects.[46,47] EPPICC is currently analysing preconception exposures to date across participating European countries.

Most European countries have their own surveillance, some like the UK and Ireland NSHPC (National Study of HIV in Pregnancy and Childhood) and the Swiss MoCHiV (Mother and Child HIV Cohort Study) contribute to EPPICC. Others like the French Perinatal Cohort do not (but there are very few pregnancy exposures there because their guidelines were very cautious about the use of DTG in pregnancy).

Most impenetrable are adverse event reporting systems. Accessing FAERS (AERS) data (data within the FDA's drug Adverse Event Reporting System) requires the investigative skills of a sleuth (plus US $420 for a drug safety analysis). [48] Obviously, there is no denominator from spontaneous reporting but it is also tricky to work out whether or not events have been reported more than once under different descriptions.

So, despite much global commitment to hunting down neural tube risk data – where registries have not yet been established, numbers are too few or data are impossible to interpret – this might be easier said than done.

Using DTG later in pregnancy appears safe.[49]

In the meantime, WHO recommends DTG for women and adolescent girls with consistent and reliable contraception. Hopefully countries will follow suit and not restrict DTG for women who do not wish to become pregnant. Improving family planning services, rather than banning DTG for huge numbers of people who could benefit from it is key.

Dolutegravir and TB

Treating TB and HIV is complicated by drug interactions, overlapping toxicities, and immune reconstitution inflammatory syndrome (IRIS). As DTG is poised to become a massively-used antiretroviral worldwide this includes in settings where TB is common.

Interim week 24 results from the INSPIRING study – to look at safety and efficacy of DTG in ART naive adults with HIV/TB – suggest that DTG 50 mg twice daily seems effective and well-tolerated in HIV/TB co-infected adults receiving RIF-based TB treatment.[50] This study is not powered to make a comparison with EFV but conducted to obtain some data in people with HIV/TB. Week 48 data should be available later in the year.

Data from a PK sub-study of the NAMSAL study (that compares a DTG-based regimen to an EFV 400 mg one) with DTG 50 mg given twice daily in the presence of RIF also supports this strategy.[51]

The DTG label already recommends twice-daily dosing in the presence of RIF based on a previous drug-drug interaction study in HIV negative participants.[52, 53]

A PK study in healthy volunteers looked at the effect of RIF on the PK of DTG 100mg once daily. The study was conducted to evaluate whether doubling the DTG dose over 24 hours could offer an easier option than 50mg twice daily to manage the drug interaction.[54]

Whether DTG 100 mg once daily with RIF will be safe and effective in people

with HIV/TB coinfection remains unclear from the PK results so far and further studies (including with 50 mg) are planned.

For large scale programmes, such as South Africa, the logistics involved in procuring and dispensing DTG single tablets as well as DTG-based FDCs (which are less vulnerable to stock outs etc), might prove too complex. Another strategy could be to switch to an EFV-based fixed dose combination during TB treatment and back to DTG after this is completed. How countries approach HIV/TB co-treatment is likely to vary according to the size and capacity of the programme.

Dolutegravir and adverse events

DTG was better tolerated than EFV or DRV/r in its registrational studies but there was an increased risk of insomnia. More serious central nervous system (CNS) side effects (depression, suicide ideation) were rare.[55]

A meta-analysis of 6647 patient-years follow up showed no significant effect of DTG on the risk of cardiac, IRIS or suicide-related serious adverse events.[56] There was a higher risk of insomnia with DTG-based ART.

Anecdotes suggest that taking DTG in the morning overcomes difficulties with insomnia in most cases, without causing additional problems during the day.[57]

Efavirenz 400 mg

The ENCORE 1 study, showed EFV 400 mg to be non-inferior to 600 mg (both plus TDF/FTC) as first-line ART.[58] The lower dose resulted in a reduction in EFV-related side effects 38% versus 48% with the standard dose.

EFV 400 mg is an alternative first-line option in WHO guidelines.

Efavirenz 400 mg and pregnancy

Results from a PK study of EFV 400 mg during pregnancy, showed lower drug concentrations in the third trimester, compared with post-partum.[59] But, these were within adequate ranges achieved with EFV 600 mg during the third trimester and those measured in ART-naive participants receiving EFV 400 mg in ENCORE1.[60, 61]

All participants in the PK study maintained an undetectable viral load, suggesting that EFV 400 mg can be used in pregnant HIV positive women.

Efavirenz and TB

A PK study in HIV positive people without TB found isoniazid (INH)/RIF was associated with limited changes in EFV 400 mg exposure. EFV concentrations were sufficient to maintain virological suppression.[62]

The investigators concluded that EFV 400 mg can be co-administered with anti-TB treatment and this is being confirmed in people with HIV/TB coinfection.

Efavirenz expected to remain an option

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 it is likely to be used for some time. The EFV/TDF/3TC regimen will be generic in most countries worldwide by 2017, but DTG and TAF patents extend for at least another 10 years. 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 – will encounter significantly higher (likely prohibitive) ones.[63]

And some countries are now discussing EFV for women of reproductive age – with varying shades of conservatism.

While it does remain an option, it is important that the lower dose is recommended, to ensure that people who need it receive the most optimised version.

Tenofovir alafenamide

TAF is a nucleotide reverse transcriptase inhibitor. It is being considered as a replacement for TDF – the older prodrug of tenofovir currently recommended first-line.

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.[64] It is dosed at 25 mg unboosted and 10 mg in a boosted regimen. This reduced dose gives TAF the potential to be produced at a much lower cost to TDF.

The first generic TAF-containing FDC was tentatively approved by the US FDA earlier in the year: DTG)/FTC/TAF.[65, 66] The new FDC could offer several programmatic benefits to LMICs where generics are accessible including lower cost and smaller tablet size (easier to swallow, transport and store).[67]

But, lack of evidence, particularly for use in pregnancy and with TB coinfection, has meant that TAF is not yet included in WHO guidelines or Essential Medicines List (EML).[68, 69] TAF is also not included in the WHO transition document.[70] And CADO 3 participants did not consider TAF to be supported by sufficient evidence to inform use in LMICs.[71, 72]

TAF vs TDF

Results from a recent meta-analysis of TDF versus TAF showed TDF, boosted with ritonavir or cobicistat, led to higher risks of bone and renal adverse events and lower rates of viral load suppression, compared with TAF.[73, 74] But, unboosted, there were no differences between the two versions of tenofovir for efficacy and only slight differences in safety.

Boosting agents significantly increase plasma AUC concentrations of TDF (25–37%). Higher plasma tenofovir levels are linked to higher risks of renal

and bone adverse events. The TAF dose is reduced from 25 to 10 mg daily when boosted but TDF remains at 300 mg daily. TDF is most commonly used worldwide in unboosted regimens, combined with 3TC and either EFV or DTG. TAF is expected to replace TDF and likewise will largely be used unboosted.

The meta-analysis evaluated 11 randomised head-to-head trials of TDF vs TAF – including 8110 participants. Those included were largely young to middle aged, with no pre-existing osteoporosis or kidney damage and mostly from high-income countries.

Nine trials compared TDF vs TAF in HIV positive people and two in people with hepatitis B. There were 4,574 participants who received boosting agents (with both TDF and TAF) representing 7,198 person years (p/y) follow up. The remaining 3,537 participants received unboosted regimens, giving 3,595 p/y follow up.

The analysis revealed boosted TDF treated participants had marginally lower viral load suppression rates, more bone fractures, lower bone mineral density and more discontinuation for bone or renal adverse events.

In contrast, there were no significant differences in viral load suppression rates or clinical safety endpoints (except bone mineral density) between unboosted TDF and TAF.

TAF and rifampicin

TAF is a substrate of drug transporters and RIF is a potent inducer and associated with drug-drug interactions and in turn lower drug exposures. Currently TDF is indicated for use with RIF but once-daily TAF is not.

Two PK studies in healthy volunteers suggest that TAF 25 mg could be given once daily with RIF. Both studies found the concentrations of TFV-diphosphate (DP) for TAF with RIF were higher than for people receiving standard TDF 300 mg.

In the first, twice-daily TAF plus RIF provided similar drug exposure to once-daily TAF.[75,76]

This parallel design PK study showed when twice-daily TAF was given with RIF 600 mg intracellular TFV-DP decreased by 24% and plasma TAF by 15% compared with once-daily TAF alone.

The evaluation found that with twice-daily administration of TAF plus RIF, exposures over 24 hours of TAF total plasma, overall systemic plasma TFV and intracellular PBMC-associated TFV-DP are expected to be reduced by less than 15%, about 20%, and about 24%, respectively, compared with once-daily TAF.

Notably, after twice-daily administration of TAF plus RIF, the mean steady-state trough concentration of TFV-DP was above the historical steady state TFV-DP concentrations achieved with TDF 300 mg.

In the second PK study, plasma concentrations of once-daily TAF AUC were decreased by 55% and intracellular TFV-DP concentrations by 36% when given with RIF.[77, 78, 79]

But although RIF co-administration decreased the plasma TAF by 55% and intracellular TFV-DP AUC by 36%, intracellular TFV-DP AUC were 76% higher with TAF plus RIF than with TDF (300 mg once daily) alone.

These PK data support further evaluation of TAF plus RIF in people with HIV and TB.

TAF and pregnancy

No adequate and well-controlled studies have been conducted on the use of TAF in pregnant women.

In preclinical studies, there was no evidence of adverse developmental outcomes with TAF at exposures that were either not maternally toxic (rabbits) or greater than (rats and mice) those in humans at the recommended dose.

Clinical data reported so far have not been sufficient to recommend TAF for pregnant women.

There is an insufficient number of first trimester exposures (minimum of 200) reported to the Antiretroviral pregnancy registry (APR) to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems, compared to the population-based rate.[80]

There are 3/56 and 0/29 birth defects reported to APR after first and second/third trimester exposure respectively.

GS-US-236-0128 (WAVES), a phase 3 study, evaluating the safety and efficacy of two TDF-containing regimens in treatment-naive women, allowed women who became pregnant to remain on study if they re-consented following diagnosis of pregnancy. After 48 weeks, there was an open-label extension phase (WAVES OLE) where 212 women were re-randomised 3:1 to switch to a TAF-based regimen or remain on their TDF-based one.[81] A total of 159 women received TAF and there were 14 pregnancies with the following outcomes: 5 live births, 4 elective abortions, and 5 spontaneous abortions.

Following the potential preconception safety signal with DTG, programmes are likely to be more cautious about new drugs with limited preconception and pregnancy data.

Darunavir/ritonavir

DRV/r is generally considered to be the most potent and tolerable protease inhibitor but cost has been a barrier to its wide use. Both a heat-stable, co-formulated version and a recommendation from WHO took their time.

DRV/r remains a potential candidate for dose optimisation. Results from the original dose finding studies and two with 600/100 mg once daily, plus one showing the recommended dose of cobicistat results in a significantly lower DRV Cmin than when it is boosted with ritonavir (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.[82, 83, 84]

A 400/100 mg once-daily DRV/r dose plus two NRTIs maintained virologic efficacy through 48 weeks in participants previously suppressed with DRV/r 800/100 mg ANRS-165 Darulight study.[85]

A PK sub study of Darulight conducted in 15 men found total and unbound blood and seminal plasma exposure of DRV to be not significantly different between doses, despite 50% dose reduction.

Unexpectedly total blood plasma exposure of ritonavir trended to be higher in 400/100mg once-daily, than in 800/100mg once-daily due to a change in the inducer/inhibitor balance between DRV and RTV.[86]

In the meantime, a heat-stable, formulation of DRV/r is expected to be available in 2018.

Darunavir/ritonavir in pregnancy

Standard once-daily 800/100 mg dosing of DRV/r leads to reduced trough levels in third trimester – although it has been effective in some reports – 600/100 mg twice daily is recommended.[87, 88] There is sufficient data for DRV/r to exclude a two-fold increased risk of birth defects. Like other protease inhibitors it crosses the placenta poorly.

Darunavir and TB

There have been no drug interaction studies with DRV/r and RIF; one is now ongoing.

What is planned or ongoing?

First-line

A DTG-based regimen is the still the current goal for first-line ART. As well as offering many clinical advantages, in combination with TAF and FTC the total daily dose is 275 mg (375 mg with 3TC) compared to 1200 mg with the current 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 African investigator-led studies to look at these regimens in closer-to-real-life settings are in progress. 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); and NAMSAL comparing DTG-based to EFV 400 mg based regimens, conducted in South Africa and Cameroon respectively.[89, 90, 91]

Although not conducted in an African setting, ADVANZ-4, conducted in Spain will also provide information on DTG use in people with less than 100 CD4 cells/mm^3.[92]

There are 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 3: First-line ongoing

STUDY/COHORT	DESIGN	PURPOSE	STATUS
ADVANCE WRHI 060 Wits RHI (USAID, Unitaid)	Phase 3 DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF non-inferiority, open label 1050 ART-naive adult participants >12 years randomised 1:1:1 Johannesburg, South Africa	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	Started January 2017 Fully recruited (May 2018) Week 48 data available Q2 2019 Completion Q1 2020
NAMSAL ANRS 12313 Inserm-ANRS (Unitaid)	Phase 3 DTG/3TC/TDF vs EFV400 mg /3TC/TDF non-inferiority, open label 606 ART-naive participants (303 per arm) Yaoundé, Cameroon	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	Week 48 data expected HIV Glasgow 2018
ADVANZ-4 Hospital Clinic of Barcelona	Phase 4 DTG/ABC/3TC vs DRV/r + ABC/3TC, randomised, open label 108 ART-naive participants with less <100 CD4 cells/mm3 Barcelona, Spain	Compare immunological reconstitution and virological efficacy during 96 weeks in people with advanced HIV Primary endpoint: median increase in CD4 count at 48 weeks	Completion Q4 2017

Key: ABC, abacavir; ART, antiretroviral treatment; ARV, antiretroviral; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; Wits RHI, Wits Reproductive Health and HIV Institute; XTC, lamivudine or emtricitabine; 3TC, lamivudine

Pregnancy

VESTED (IMPAACT P2010) is recruiting and should be fully recruited by the end of this year. The study is making the same three-arm comparison as ADVANCE but in pregnant women.[93]

DolPHIN2 is also recruiting and looking at DTG PK, safety and efficacy in pregnant women presenting in the third trimester, postpartum, and during breast feeding until weaning or 18 months.[94, 95]

DolPHIN1, the pilot study to DolPHIN2, showed standard dose of DTG should be used in the third trimester.[96] But HIV positive women who start ART in late pregnancy are a vulnerable group with a higher risk of adverse outcomes and vertical transmission of HIV. Final results from DolPHIN1 will be presented at AIDS 2018.[97]

IMPAACT P1026s and PANNA – the respective American and European studies that look at PK of antiretrovirals in pregnancy and post partum include women receiving DTG and TAF.[98, 99, 100, 101] Data from both studies have been presented previously for DTG. Data on TAF PK in pregnancy from P1026s will be presented at AIDS 2018.[102]

A ViiV-sponsored study is enrolling ART-naive women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.[103, 104] Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.

A switch study is being planned to look at PK, dosing and tolerability, pre- and post-switch from TDF-based to TAF-based ART.

ADVANCE gives women who become pregnant during the study the option to continue on their study drugs.[105]

Table 4: Pregnancy dolutegravir – ongoing

STUDY	DESIGN	PURPOSE	STATUS
DolPHIN2 UoL (UCT, MU, LSTM, RU) (Unitaid)	Phase 3 DTG PK, safety and efficacy in pregnant women in 3rd trimester and PP during BF 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	Primary efficacy endpoint: proportion VL <50 at delivery Primary safety endpoint: safety of DTG in pregnancy Secondary: time to undetectable VL, CD4 response, VL in breastmilk, genital HIV shedding, health economics	Recruiting Primary completion Q4 2021
VESTED IMPAACT P2010 NIH (NIAID)	Phase 3 DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 639 mother/infant pairs Treatment-naive women starting ART at 14–28 weeks' gestation 50 weeks of maternal and infant follow-up postpartum Multicountry: IMPAACT sites (US, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania, Thailand, Uganda, Zambia, Zimbabwe)	Primary endpoints: VL <200 copies/mL at delivery; adverse pregnancy outcomes; maternal toxicity; infant toxicity Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks postpartum; renal toxicity (mothers and infants); bone toxicity (subset of mothers and infants); adverse pregnancy outcomes; resistance (women with VF and HIV infected infants)	Recruiting Primary completion December 2019 First results expected Q3 2019

STUDY	DESIGN	PURPOSE	STATUS
ING200336 PK and safety study in pregnant women with HIV ViiV Healthcare	Phase 3 PK and safety single arm study of women with unintended pregnancies while participating in ARIA study of DTG/ABC/3TC vs ATV/ r +TDF/FTC in 474 treatment naive women to be completed in 2018 Estimated enrolment 25 women (approx 237 receive study drug in ARIA) Multicountry: US, Russian Federation, Spain, UK	Primary endpoints: PK 2nd /3rd trimester Secondary endpoints: PK in neonates, maternal:cord blood ratio, maternal and infant AEs; adverse pregnancy outcomes	Recruiting (started January 2015) Primary completion February 2019

Key: ABC, abacavir; ART, antiretroviral treatment; ATV/r, atazanavir/ritonavir; BF, breastfeeding; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network; LSTM, Liverpool School of Tropical Medicine; MU, Makerere University; NIH, US National Institutes of health; NRTIs, nucles/tide reverse transcriptase inhibitors; PK, pharmacokinetic; PP, postpartum; PTD, preterm delivery; PW, pregnant women; RU, Raboud University; SGA, small for gestational age; SoC, standard of care; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TM, trimester; UoL University of Liverpool; VL, viral load; 3TC, lamivudine

Table 5: TAF pregnancy – ongoing + planned

STUDY	DESIGN	PURPOSE	STATUS
IMPAACT 1026s NIH (NIAID)	Phase 4 PK properties of antiretroviral and related drugs during pregnancy and PP Each arm 12–25 (target) women with evaluable 3rd trimester PK data Pregnant women > 20 weeks' gestation receiving TAF (3 arms – within FDCs) as part of clinical care Washout PK in drug exposed infants Multicountry: IMPAACT sites (United States, Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda)	Primary endpoint: PK 2nd /3rd trimester Secondary endpoints: PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes	Results AIDS 2018
PANNA study Radboud University (PENTA Foundation, ViiV Healthcare)	Phase 4 Pregnant women <33-week gestation receiving TAF as part of clinical care Each study arm 16 with evaluable 33-week data Multicountry: PANNA sites (Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK)	Primary endpoint: PK at 33 weeks and 4–6 weeks after delivery Secondary endpoints: PK in neonates, safety, VL and transmission	Recruiting 3/16 recruited Primary completion December 2020

STUDY	DESIGN	PURPOSE	STATUS
VESTED IMPAACT P2010 NIH (NIAID)	Phase 3 DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 639 mother/infant pairs Treatment-naive women starting ART at 14–28 weeks' gestation 50 weeks of maternal and infant follow-up PP Multicountry: IMPAACT sites (US, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania, Thailand, Uganda, Zambia, Zimbabwe)	Primary endpoints: VL <200 copies/mL at delivery; adverse pregnancy outcomes; maternal toxicity; infant toxicity Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks PP; renal toxicity; bone toxicity; adverse pregnancy outcomes; resistance (women with VF, and HIV infected infants)	Recruiting Primary completion December 2019 First results expected Q3 2019
TAF switch study pregnancy Wits RHI	Switch study evaluating PK, dosing and tolerability, pre- and post-switch from TDF (EFV/FTC/TDF FDC >3 months) to TAF 25 mg, through 6 months PP 26 women (and infants), 14-28 weeks' gestation, stable (VL suppressed, tolerating well, no co-infection) on TDF-based ART	Primary endpoint: TFV-DP levels during pregnancy (baseline, 4 weeks post-switch, 2nd TM, 3rd trimester) and PP (birth, 6–8 weeks) Secondary endpoints: tolerability, safety, VL outcomes of TAF, adverse, pregnancy outcomes, infant TFV-DP levels, infant safety PP, BM TFV-DP at 6 weeks and 6 months PP	Funding application stage Earliest Q4 2019 (funding dependent)

Key: AIDS 2018, 22nd International AIDS Conference; ART, antiretroviral treatment; BF, breastfeeding; BM, breastmilk; DTG, dolutegravir; EFV, efavirenz; FDC, fixed dose combination; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Clinical Trials Network; NIH, US National Institutes of health; PK, pharmacokinetic; PP, postpartum; PTD, preterm delivery; PW, pregnant women; SGA, small for gestational age; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate; TM, trimester; VL, viral load; Wits RHI, Wits Reproductive Health and HIV Institute

Tuberculosis

Further PK studies to look at dosing of DTG and TAF with RIF and being planned in people with HIV and TB.

Serious toxicities were seen in healthy volunteers in a drug-drug interaction study of once-weekly INH and RIF with once-daily DTG.[106] As such toxicities are not usually predictive of those in patients, the IMPAACT-4TB programme includes a single-arm phase 1/2 PK and safety study of DTG-based ART and once-weekly INH and RIF in HIV positive adults with latent TB infection.[107]

Table 6: Dolutegravir and TAF TB – ongoing + planned

STUDY	DESIGN	PURPOSE	STATUS
DTG 50 mg/RIF UCT	Phase 2 Standard vs double dose DTG + RIF in HIV/TB coinfected participants Viral load endpoints + PK	Establish whether standard 50 mg dose DTG can be used with RIF	Funding application stage
IMPAACT 4TB Aurum Institute	Phase 1/2 Group 1: 1st 12 participants (Group 1a) PK DTG 50mg once daily + 2NRTIs + once weekly RPT/ INH Next 18 participants (Group 1B) PK either DTG 50mg or a higher or more frequent dose, if adjustment is needed, + RPT/INH Group 2: Next 30 participants will PK DTG as Group 1B VL measured at protocol-defined intervals	PK, safety, and tolerability of once-weekly RPT/INH (3HP) for the treatment of latent tuberculosis infection in HIV + DTG-based ART	Recruiting Estimated completion Q4 2018

STUDY	DESIGN	PURPOSE	STATUS
TAF/RIF PK Wits RHI/UCT (Unitaid)	30 HIV/TB-coinfected participants	TAF/RIF PK in HIV/TB coinfection	Protocol planning stage

Key: ART, antiretroviral treatment; DTG, dolutegravir; EFV, efavirenz; INH, isoniazid; PK, pharmacokinetics; RIF, rifampicin: RPT, rifapentine; UCT, University of Cape Town; VL, viral load; Wits RHI, The Wits Reproductive Health and HIV Institute

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 DTG and DRV/r second-line regimens.

The DAWNING study compared DTG + 2 NRTIs to the current standard second-line of LPV/r + 2 NRTIs.[108, 109]

Participants were genotyped at screening and only those with at least one predicted active NRTI were included. The study was stopped early, at 24 weeks, after the DTG arm showed greater viral suppression rates than the LPV/r arm. Week 48 data, where these are available, will be shown at AIDS 2018.[110]

Whether the results from DAWNING can be duplicated in settings without genotyping, questions about the role and dose of DRV/r, and whether NRTIs can be recycled, drive second-line ART optimisation studies.

The D2EFT study is investigating DRV/r 800/100 mg + DTG (which would have no overlapping resistance with EFV + 2 NRTI) vs DTG + 2 predetermined NRTIs vs DRV/r 800/100 mg + 2 NRTIs.[111]

The NADIA study will investigate DTG vs DRV/r once daily with a second factorial with TDF/XTC vs AZT/3TC.

WRHI052 has evaluated DRV/r 400/100 mg in a switch study and week 48 results will be shown at IAS 2018.[112]

A study of DRV/r-based ART in people with virological failure (rather than switching stable people) is under discussion.

PK data to guide the use of DRV/r with TB treatment are missing and the DARifi PK study is comparing 1600/200 mg once daily with RIF and DRV/r 800/100 mg 12 hourly with RIF to DRV/r 800/100 mg without RIF.

And it might be possible to lower the overall dose of DRV (and potentially RTV) needed to achieve therapeutic steady state blood concentrations, using nanoparticles to improve drug absorption – and this work is also ongoing.

The best option for second-line after a DTG-based first-line regimen will be key in the future and the work on DRV/r might also be important here.

More research is needed to determine the best options for optimised second-line ART – but some of the investigations recommended at CADO 3 are already getting started or under discussion.

Table 7: Second-line dolutegravir and darunavir/r – ongoing + planned

STUDY	DESIGN	PURPOSE	STATUS
DAWNING	Phase 3b Open label study to evaluate the safety and efficacy of DTG + 2 NRTIs (genotype guided) vs LPV/r + 2 NRTIs in participants failing first-line NNRTI + 2 NRTIs 624 participants Multicountry: Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russian Federation, South Africa, Thailand, Ukraine	Primary endpoint: proportion with VL <50 copies/mL at week 48	IDMC conducted an ad hoc review of week 24 data Recommended discontinuation of LPV/r arm due to differences in rates of virological nonresponse and increasing differences in rates of virological failure favouring the DTG arm 82% of participants on DTG vs 69% on LPV/r achieved viral load <50 copies/mL Week 48 data AIDS 2018 Superior efficacy DTG arm
Evaluation of low dose darunavir in a switch study WRHI052 Wits RHI (USAID, MRC SA)	Phase 3 300 participants stable on LPV/r + 2 NRTI twice daily randomised to stay or switch to DRV/r 400/100 mg once daily 48 weeks	400/100 mg DRV/r is non-inferior to LPV/r in virologically suppressed participants Primary endpoint VL <50 copies/mL at 48 weeks Secondary endpoints include clinical and laboratory markers	Week 48 data AIDS 2018 Non-inferior efficacy DRV/r 400/100 mg once daily arm

STUDY	DESIGN	PURPOSE	STATUS
D2EFT Kirby Institute (Unitaid, US National Institute of Allergy and Infectious Disease, National Health and Medical Research Council, Australia)	Phase 3b/4 1,010 participants who failed first-line regimen randomised to DRV/r 800/100 mg + DTG vs DTG + 2 predetermined NRTIs vs DRV/r 800/100 mg + 2 NRTIs 96 weeks Multicountry: Argentina, Brazil, Chile, Colombia, Mexico, Guinea, Mali, Nigeria, South Africa, Zimbabwe, India, Malaysia, Thailand, Indonesia	To compare two DTG-based second-line regimens with standard of care and with each other 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	Recruiting Primary completion December 2020
NADIA Coordinated by MU	Phase 3 Approx 420 participants with virological failure on EFV-based 1st line randomised to DTG vs DRV/r once daily + (second factorial) TDF/XTC vs AZT/3TC 96 weeks Uganda + multicountry	Compare DTG and DRV/r based regimens Compare TDF/XTC vs AZT/backbone without genotype Primary endpoint: VL <200 at 96 weeks Interim analysis at 48 weeks	Protocol finalisation stage

Key: AIDS 2018, 22nd International AIDS Conference; ART, antiretroviral treatment; AZT, zidovudine; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; IDMC, Independent Data Monitoring Committee; LPV/r, lopinavir/ritonavir; MCC SA, Medicines Control Council South Africa; MU, Makerere University; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos/tide reverse transcriptase inhibitor; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; Wits RHI, The Wits Reproductive Health and HIV Institute; XTC, lamivudine or emtricitabine; 3TC, lamivudine

Table 8: Additional darunavir/r studies

STUDY	DESIGN	PURPOSE	STATUS
DARifi UCT (USAID)	To compare steady state PK of DRV given in standard DRV/r doses of 800/100 mg without RIF to: 1. DRV/r 1600/200 mg once daily with RIF 2. DRV/r 800/100 mg 12 hourly with RIF 24 participants	Safety of adjusted doses of DRV/r + RIF in HIV+ (TB uninfected) participants on ART	Recruiting
DRV/r nanoformulation UoL (PEPFAR/USAID)	Preclinical evaluation in animal models	Lower overall dose of DRV (and potentially RTV) needed to achieve therapeutic steady state blood concentrations, using nanoparticles to improve drug absorption	Ongoing Formulations on stability testing to establish shelf life for first-in-human studies in 2019

Key: ART, antiretroviral treatment; DRV, darunavir; DRV/r, darunavir/ritonavir; PK, pharmacokinetic; RIF, rifampicin; RTV, ritonavir; UCT, University of Cape Town; UoL University of Liverpool

What needs to be done?

- **Originators donate drugs to strategy studies for LMICs.** Originator manufacturers must take responsibility and supply prioritised antiretrovirals to key investigator-led studies (as well as the supporting substudies) to generate evidence to support their use in LMICs. And not after several years of deliberation. The lack of information on use of new drugs and doses in pregnancy and with TB treatment – that is critical to treating populations in LMICs – will continue to be a barrier to the recommendation and of any new regimen, however impressive the results from the phase 3 trials are.
- **Timely approval.** Regulatory agencies in LMICs, need to register new originator and generic formulations as swiftly as possible. The Indian regulatory agency needs to waiver the request for Indian trials before prioritised antiretroviral products can be exported. Ideally this should happen before new WHO and national recommendations.
- **Countries get ready to switch.** Countries with high volume ART programmes, 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.

- **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.
- **Surveillance, surveillance, surveillance.** The DTG preconception signal has to be a clarion call. As new drugs are rolled out with gaps in information, systems need to be established in countries where DTG and, in the future, other new HIV drugs will be introduced. This includes long-acting ones that will need extra consideration in pregnancy. And enhanced monitoring for other adverse events should also be in place.
  Donors, particularly those supporting aggressive transition plans, need to ensure that accompanying surveillance programmes are also set up and supported.

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Key: CHAI, Clinton Health Access Initiative; CROI, Conference on Retroviruses and Opportunistic Infections; IAS, International AIDS Society; PEPFAR, Presidents Emergency Programme on AIDS Research; US FDA, US Food and Drug Administration; WHO, World Health Organisation

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