Fit For Purpose: Antiretroviral Treatment Optimization

By Polly Clayden

The most striking news since the *2014 Pipeline Report* is from the START (Strategic Timing of AntiRetroviral Treatment) study.[1] We now have evidence from a large, randomized, controlled trial to show that CD4 count is no longer a barrier to starting antiretroviral treatment (ART).

START results mean that guidelines worldwide should soon recommend ART to all HIV positive people. This will bring on the mammoth task of starting and keeping 35 million on treatment.[2] If ever there was a time when ART needs to be optimized – that is safe, effective, tolerable, durable, simple and affordable – it is now.[3]

One way to optimize antiretrovirals is by dose reduction.[4] The rationale is that when new drugs are developed, the highest tolerated doses in phase II are often selected for phase III and approval. In some cases lower doses might have equivalent efficacy and better tolerability. It might also be possible to reduce the amount of active pharmaceutical ingredient (API) with improved bioavailability through reformulation – and reduced API means reduced cost.

Since discussions on treatment optimization began the field has evolved and newer antiretrovirals have been approved.[5, 6, 7] Focus has shifted from merely making older drugs more efficient. Speeding up the introduction of generic versions of newer drugs – in appropriate regimens and formulations – into low-and middle-income countries is likely to produce the best options.[8, 9, 10]

Treatment optimization is one critical component to achieving universal access to ART. Last year's report provided more background on optimizing treatment and how this might be achieved.[11]

Important steps towards optimized treatment over the past year include:

- The first generic version of dolutegravir (DTG) submitted to the US Food and Drug Administration (FDA) for tentative approval.[12]
- Published 96-week data from ENCORE1 – continuing to show that a lower dose of efavirenz (EFV) is non-inferior to the currently approved one. [13, 14]
- A new formulation of tenofovir alafanemide fumarate (TAF)[15] submitted to the FDA and the European Medicines Agency (EMA) – albeit within a fixed dose combination (FDC) and a co-formulation with agents that complicate its recommendation in low- and middle-income settings. [16, 17, 18]

This chapter gives an update on antiretroviral treatment optimization trials and strategies – both ongoing and planned – and pipeline products for low- and middle-income countries. It also looks at missing evidence that is needed to change current recommendations.

Can We Do Better With What We Have?

As we go to press, discussions about the recommendations for the 2015 World Health Organization (WHO) guidelines are afoot. For adults the current (2013) guidelines include the regimens in Table 1.[19]

Table 1. WHO recommended adult ART regimens 2013

First line	TDF + 3TC (or FTC) + EFV preferred (including pregnant women) AZT alternative to TDF NVP alternative to EFV
Second line	ATV/r or LPV/r preferred + TDF + 3TC preferred backbone (if AZT or d4T first-line) + AZT + 3TC preferredm(if TDF first-line)
Third line	No specific recommendations: Integrase inhibitor (INI) or second-generation PI or NNRTI are mentioned

ATV/r, atazanavir/ritonavir; AZT, zidovudine; d4T,stavudine; EFV,efavirenz; FTC,emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Several dose optimization trials and a reformulation program, relevant to these recommendations, are ongoing or have been completed. Some require more information before the new dose or formulation can be widely recommended. See Table 2.

TABLE 2. Antiretrovirals with potential for optimization

Compound/Approved dose	Class	Sponsor/approach	Outcomes	Status
TDF 300 mg once daily	NtRTI	CHAI in partnership with generic companies Reformulation	Approx 33% reduction anticipated Target 200 mg TDF-containing FDC tablet	TDF (xb) Bioequivalence completed Results available August 1015
AZT 300 mg twice daily	NRTI	Geneva University Hospital Dose optimization RCT	Dose reduced to 200mg twice daily	MiniZID Phase III Completed January 2014 No difference between arms in overall anemia rate at 24 weeks
d4T 30 mg twice daily	NRTI	Wits Reproductive Health Institute Dose optimization and comparison with TDF RCT	Dose reduced to 20mg twice daily	WHCS-001 Phase III To be completed end 2015/early 2016
EFV 600 mg once daily	NNRTI	Kirby Institute Dose optimization RCT	Dose reduced to 400 mg once daily	ENCORE 1 400 mg non-inferior to 600 mg at 96 weeks
ATV/r 300/100 mg once daily	PI	HIVNAT/Kirby Institute RCT	Dose reduced to 200/100	LASA III Phase IV to be completed June 2015

ATV/r, atazanavir/ritonavir; AZT, zidovudine; d4T, stavudine; EFV, efavirenz; TDF, tenofovir disoproxil fumarate.

NRTI, nucleoside reverse transcriptase inhibitor; NRtI, nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor,

With the exceptions of TDF (xb), EFV 400 mg and darunavir/ritonavir (DRV/r) – discussed in the following section – since the trials began, optimizing existing antiretrovirals has become less relevant.

Lower dose AZT (400 mg) did not show an improvement in overall anaemia rate – the primary endpoint – compared with the standard dose (600mg) in a randomized trial conducted in Cameroon.[20]

The trial that dare not speak its name – of lower dose d4T (20 mg) – will yield more data from a low- or middle-income country on TDF. But d4T has not been recommended at higher doses anywhere for some time and we are not anticipating a revival. By 2018, d4T is expected to be only 2% of the nucleos(t)ide reverse transcriptase inhibitor (NRTI) market.[21]

The results of the low dose atazanavir/ritonavir (200/100 mg) trial are not expected to be applicable outside Thailand, where it is being conducted. [22]

What Are The Ones To Watch?

In the Clinton Health Access Initiative's (CHAI) *2014 ARV Market Report* the authors write: "The global community is coalescing around a short list of products that have shown superior or non-inferior efficacy compared to existing alternatives but also offer improved durability and tolerability, higher bioavailability, lower pill burden, and the potential for lower frequencies of adverse events." [23]

These products are: EFV 400 mg, DTG, TDF(xb), TAF and DRV/r, which have also featured annually in this Pipeline Report chapter.

Despite having coalesced for quite a while now, at a WHO Think Tank convened in February 2015, [24] the expert group recognized that a greater body of evidence supports the use of EFV 600 mg first-line (an estimated 15 million patient years when combined with TDF/XTC – meaning either FTC or 3TC).[25] The group suggested that this evidence provides a level of confidence that is not currently there with the alternatives: EFV 400 mg and DTG.

Both TDF (xb) and TAF are still in development and a WHO recommendation for DRV/r has been delayed due to a lack of a heat stable co-formulated generic version (which has been delayed due to a lack of a WHO recommendation).

Efavirenz 400 mg

EFV 600 mg 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 receiving concomitant 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.[26] There is also an interaction between EFV and some hormonal contraceptives that can reduce their efficacy.[27]

A recent 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.[28] But CNS side effects were more frequent with this antiretroviral compared to a number of others. People with HIV and activists have reported these adverse events as flaws of EFV since it was first approved.[29]

The ENCORE 1 study, showing 400 mg EFV to be non-inferior to 600 mg, was completed in July 2013. The 48-week results were published in The Lancet in April 2014.[30] There have been no surprises at 96 weeks. [31]

The study found a reduced dose of 400 mg EFV non-inferior to the 600 mg standard dose (both plus TDF/FTC) in 636 treatment-naive participants at 48 weeks. It was conducted in Europe, Australasia, Latin America, Asia, and Africa.

Significantly fewer participants (2% versus 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.

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

Results from a pharmacokinetic sub-study of ENCORE 1 suggest that the current targets for EFV could be too high.[32] There has also been a suggestion from the FDA that the original approved dose might be too high.[33]

Since the announcement of the trial results in 2013, there has been much discussion about recommending the reduced dose, particularly in low- and middle-income countries where the resulting cost savings would be considerable.

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.[34] 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.[35] A detectable viral load at delivery was more common among pregnant women with TB, but antiretroviral treatment 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.[36]

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.[37]

In order to make a universal recommendation for EFV 400 mg results from pharmacokinetic studies with rifampicin and in pregnant women are necessary.

Results from a pharmacokinetic substudy of ENCORE1 suggest that although 400 mg gives cerebrospinal fluid exposure (CSF) exposure of EFV above that required for HIV suppression, exposure of metabolites might still be within the concentration range associated with toxicities.[38] Although significant, the reduction in EFV-associated adverse events was modest in ENCORE1 and the pharmacokinetic study suggests this possible explanation.

Last year, three leading HIV doctors suggested that the dominant role of EFV in first-line therapy should be reconsidered.[39] They wrote that "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 non-governmental organisations".

But for low- and middle-income countries, EFV is likely to remain a recommended first-line antiretroviral for a while. For countries where generics are not accessible until a drug is off patent this is likely to be for

some time. While EFV remains an option, it is important that the pharmacokinetic studies to look at TB and pregnancy are funded and conducted to ensure that the most optimized dose is given.

CHAI is working with suppliers to develop and file EFV 400 mg as part of an FDC with TDF and 3TC.[40] ENCORE1 data will be filed as an Investigational New Drug (IND), be cross-referenced in the suppliers' New Drug Applications (NDA) and be used as the basis for FDA tentative approval. The first filing is anticipated in the first quarter of 2016. FDA has agreed to the filing strategy for the product.

Dolutegravir

Excitable reviewers have found it hard to swerve from describing DTG as: "game-changing".[41] 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, it looks like it will be an important potential option for use in low- and middle-income countries. It could replace EFV first-line. It is also predicted to cost about US$30 per patient per year (pppy) to manufacture.

DTG was superior to EFV at 48 weeks in antiretroviral naive patients in phase III trials (and remained so at 96 weeks).[42, 43] 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 raltegravir (RAL) and in people with resistance to other integrase inhibitors [44, 45] were used to gain approval for a broad indication in adults and adolescents aged 12 and above.[46] The indication for 12 to 18 year olds is based on a 24-week open-label label study in integrase inhibitor-naive participants.

DTG studies have not yet included significant numbers of people who would be treated in low-and middle-income countries. 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.[47] 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.

As yet information about DTG in pregnant women is scarce. Although animal reproduction studies are not always predictive of human response, no safety issues were revealed in preclinical studies. So far only one first trimester and four second/third trimester exposures have been reported to the Antiretroviral Pregnancy Registry (APR) to 31 July 2014.[48]

For DTG to be recommended in WHO guidelines without restriction, more information is needed on how it is likely to perform in real world, low- or middle-income settings. Populations in these settings include larger proportions of women of childbearing age, children, and people with TB, malaria, and other coinfections.[49]

ViiV Healthcare (the originator of DTG), Aurobindo Pharma, and CHAI recently announced that Aurobindo has submitted an Abbreviated New Drug Application (ANDA) for generic DTG 50mg, to the FDA for tentative approval.[50]

This is the first ANDA for a generic version of DTG and has been made within two years from FDA approval of originator DTG for the US. ViiV has provided a selective waiver to the FDA for the five-year period of New

Chemical Entity exclusivity, which would have prevented tentative approval of Aurobino's ANDA. This product is expected to gain tentative approval in the first quarter of 2016. Several generic manufacturers are working on FDCs of DTG /TDF/3TC.

ViiV has also licensed DTG to the Medicines Patent Pool (MPP).[51] The agreements for both adult and pediatric treatment were signed just two months after DTG was approved by the EMA and eight months after FDA approval.

New and Better Versions of Tenofovir

TDF (xb)

Tenofovir disoproxil fumarate (TDF) – the current formulation of tenofovir – is recommended globally as part of first-line treatment and used widely in high-, low- and middle-income settings.

The downside of TDF is its potential for renal and bone toxicity. There are limits to the lowest possible price of TDF with the current formulation, due to its high milligram dose (300 mg).

CHAI is developing a dosage form of TDF called TDF (xb) in partnership with companies performing the preclinical work, formulation screening and Good Manufacturing Practice (GMP), and a generic manufacturer. [52]

With the current TDF 300 mg formulation only 25% of tenofovir is absorbed into the bloodstream. By reformulating the excipients CHAI aims to increase bioavailability and, in turn, lower the dose to an anticipated 200 mg, while maintaining equivalent exposure to that achieved with the current formulation.

Bioequivalence studies will compare TDF (xb) to the 300 mg originator formulation of TDF to provide evidence for tentative FDA approval of TDF (xb)-containing FDCs. The goal is to reach the market with a TDF (xb)-containing FDC in 2017.

TAF

Gilead Sciences has developed a new version of tenofovir: tenofovir alafenamide fumarate (TAF).

TAF is not yet approved but it has been submitted to the FDA and EMA as a component of an FDC with elvitegravir/cobicistat and FTC (E/C/F/TAF) and a co-formulation with FTC (F/TAF).[53, 54, 55, 56] The FDA applications were filed in November 2014 with expected approval November 2015 and April 2015 with expected approval November 2016, respectively.

Besides Gilead's incestuous combinations, other TAF-containing FDCs in development are collaborations with Janssen: darunavir/cobicistat/FTC/TAF (D/C/F/TAF) and rilpivirine/FTC/TAF (R/F/TAF).

Both TDF and TAF are prodrugs 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.[57, 58, 59]

It is possible that 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. [8]

Due to a drug-drug interaction between TAF and cobicistat (or ritonavir) that increases the levels of tenofovir 2.5-fold, a dose of 10 mg is being used in regimens with boosting agents and 25 mg in un-boosted ones.

F/TAF will be produced in 10 mg and 25 mg TAF plus 200 mg FTC co-formulated tablets.

The reduced dose means less API and potentially considerable reductions in generic prices (this could eventually be an annual patient cost of less than US$20);[60, 61] it will also mean smaller tablet sizes.

The regulatory applications for F/TAF (described in the antiretroviral chapter of this *Pipeline Report*) are supported by the phase III trials of E/C/F/TAF [62] and an adolescent study,[63] plus bioequivalence data for F/TAF and E/C/F/TAF.

Results from these trials might not be sufficient to inform the production of generic FDCs without boosting agents, as identified as a potential optimized first-line regimen in several expert consultations.[64, 65]

Ongoing studies combining F/TAF with third agents are switching participants on stable treatment from TDF to TAF.[66, 67] Although DTG might be the third agent in the open label switch study, it would probably not generate appropriate data in treatment-naive people to allow WHO recommendation for first-line regimens. So even if the FDA and EMA approve TAF in 2015/2016, guidance and uptake in low- and middle-income countries could be delayed.

Independent investigators, generic manufacturers and organizations such as CHAI and UNITAID might be better placed to establish this evidence and take on the development of a DTG and TAF-based FDC than the originator manufacturers. One study is in the planning stage.

There are potential licensing hurdles with possible combination products under the current Gilead/MPP license.[68] CHAI is working with Gilead and MPP to clarify the licensing of TAF to allow specific FDCs for low- and middle-income countries.

At least one generic manufacturer plans to develop and file a DTG-containing FDC with FTC and TAF, anticipated in 2018.

Darunavir/ritonavir

Darunavir/ritonavir (DRV/r) is generally considered to be the most potent and tolerable protease inhibitor, but as yet there is no generic formulation, and cost has been a barrier to its wide use. WHO has not yet recommended DRV/r for second-line treatment and there has been limited work on its optimization.

This drug has different approved doses for treatment-naive (and treatment- experienced without DRV-associated mutations) and protease inhibitor-experienced patients. Treatment-naive patients receive DRV/r at an 8:1 (800/100 mg) ratio once daily, and experienced patients at a 6:1 ratio (600/100 mg) twice daily.

No dose-finding studies have ever been conducted with DRV/r in treatment- naive people and the original studies were conducted in people who were highly protease inhibitor-experienced.[69, 70] Results from these trials of DRV/r, as well as two with 600/100 mg,[71, 72] suggest that a dose reduction to DRV/r 400/100 mg might be feasible.

There are also potential cost efficiencies to be gained through process chemistry and reformulation.

Several generic manufacturers have been developing a co-formulation of DRV/r 400/50 mg (800/100 mg once daily, two pills). As ritonavir is tricky to make in a heat stable formulation there have been technical hitches with this product development. One manufacturer seems to have overcome these obstacles and anticipates an FDA filing for tentative approval in the second quarter of 2016.[73]

What Is Planned Or Needed To Recommend The New Drugs And Formulations?

Several trials are underway or planned (see table 3) that should fill some of the remaining evidence gaps.

TABLE 3: Ongoing or planned ART optimization trials

Trial	Implementer/ Sponsor	Design	Status	Information gained
LOW DOSE EFAVIRENZ				
EFV 400 mg pregnancy	SSAT/Mylan	PK EFV 400 mg in third trimester pregnancy and post partum in 25 women Sites in London and Kampala	Starting July 2015	Supporting data to ENCORE1
EFV 400 mg TB	SSAT	PK EFV 400 mg with isoniazid and rifampicin in 26 participants Sites in London and Kampala	Funding application stage	Supporting data to ENCORE1
ULTRA-HAART EFV 200 vs 400 vs 600 mg	UK MRC	EFV 200 vs 400 vs 600 mg once daily, non-inferiority plus superior tolerability with reduced doses 96 weeks Multinational	Funding application stage	Further experience with EFV400mg plus 200 mg
DOLUTEGRAVIR				
DTG/FTC/TDF vs DTG/FTC/TAF	Wits RHI	DTG/FTC/TDF vs DTG/FTC/TAF in 600 ART-naive participants Phase III Few exclusion criteria – adults according to WHO 2015 guidelines No baseline resistance testing Percentage with HIV RNA<200 copies/mL at 48 Weeks (FDA snapshot algorithm) South Africa	Funding application stage	Data on safety and efficacy of DTG-based regimens first line Comparison TAF vs TAF 25 mg Support inclusion in 2017 WHO guidelines
NAMSAL ANRS 12313	HIV OPD (Central Hospital) and CNPS Hospital (Yaounde) ANRS	DTG vs EFV 400mg, both plus 3TC/TDF in 550 ART-naive participants Phase III Few exclusion criteria – adults according to WHO 2013 guidelines No baseline resistance testing Percentage with HIV RNA<200 copies/mL at 48 Weeks (FDA snapshot algorithm) Two sites in Cameroon	Fully funded by ANRS Awaiting DTG supply	Data on TDF/3TC/DTG as 1st line ART in low-income country
DolPHIN1 (dolutegravir in pregnant HIV mothers and neonates)	University of Liverpool/ Makere University/ ViiV	DTG PK in pregnant women in third trimester and post partum during breastfeeding Phase II 60 late presenting women (after 28 weeks gestation) Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs Sites in Uganda	Start July 2015 Completion July 2016	Data on 3rd trimester PK Secondary outcomes include: safety and tolerability of DTG up to 6 months post partum and VL at delivery

Trial	Implementer/ Sponsor	Design	Status	Information gained
ARIA	ViiV	DTG/ABC/3TC FDC vs ATV/ r +TDF/FTC in 474 treatment naive women Phase IIIb Pregnancy and breast feeding are exclusion criteria but women who become pregnant in ARIA can rollover to ING200336 Multinational, sites in South Africa 48 weeks	Underway Start August 2013 Completion April 2018 Primary completion September 2015	Data on women
ING200336 Pharmacokinetic and safety study in pregnant women with HIV	ViiV	PK and safety single arm study of women with unintended pregnancies while participating in ARIA Estimated enrolment 25 (approx 237 receive study drug in ARIA) Multinational, sites in South Africa	Start October 2014 Completion February 2019	Data on 2nd/3rd trimester PK
IMPAACT 1026s V9 Pharmacokinetic properties of antiretroviral and related drugs during pregnancy and postpartum	NIH	PK Phase IV Pregnant women > 20 weeks gestation receiving DTG as part of clinical care Each study arm 12 to 25 (target) women with evaluable 3rd trimester PK data Open to all IMPAACT sites	September 2014 May 2016	Data on 2nd/3rd trimester PK
PANNA Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women	PANNA Network	PK, safety and efficacy Pregnant women receiving DTG as part of clinical care Target 16 women Open to all PANNA sites	June 2015 until target	PK data from 3rd and at 4 to 6 weeks post-partum.
Open label study of DTG vs EFV for HIV/TB coinfection	ViiV	50 mg DTG twice daily vs 600 mg EFV (randomised 3:2 ratio) during TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) in 125 treatment naive participants Phase IIIb 48 weeks Multinational, sites in South Africa	Start November 2014 Completion December 2018 Primary completion 2016 Not yet enrolling	Data on HIV/TB first line co-treatment

Trial	Implementer/ Sponsor	Design	Status	Information gained
TENOFOVIR ALAFENAMIDE 25 MG				
Switch study to evaluate F/TAF in HIV positive participants who are virologically suppressed on regimens containing FTC/TDF	Gilead	Double blinded study in 660 virologically stable adults receiving FTC/TDF plus open label 3rd agent randomised to continue vs switch to FTC/10mg or 25mg TAF (dosing will be dependent on 3rd agent) Phase III 48/96 weeks Sites in US, Canada and Europe	Start May 2014 Completion October 2016 Primary completion November 2015	Data on unboosted TAF (dolutegravir, efavirenz, raltegravir and rilpivirine allowed) Total number of participants receiving unboosted dose unknown
Switch study to evaluate the safety and efficacy of FTC/RPV/TAF FDC in HIV positive adults who are virologically suppressed on FTC/RPV/TDF	Gilead	Double blinded study in 550 virologically stable adults receiving RPV/FTC/TDF FDC randomised to continue vs switch to RPV/FTC/ 25mg TAF FDC Phase IIIb 48 weeks Sites in US, Canada and Europe	Start January 2015 Completion June 2017 Primary completion June 2016	Data on 25 mg TAF
IMPAACT 1026s V9 Pharmacokinetic properties of antiretroviral and related drugs during pregnancy and postpartum	NIH	PK Phase IV Pregnant women > 20 weeks gestation receiving TAF as part of clinical care Each study arm 12 to 25 (target) women with evaluable 3rd trimester PK data Open to all IMPAACT sites	September 2014 May 2016	Data on 2nd/3rd trimester PK
SECOND LINE LOW DOSE DRV/R (INCLUDING PLUS DTG)				
DRV/r 400/100 mg South Africa	Wits RHI/ SA DoH	200 2nd line participants stable on LPV/r+2 NRTI twice daily to stay or switch to DRV/r 400/100mg once daily 48 weeks	Seeking DRV/r supply	Clinical experience of low dose DRV in switch study
DRV/r 400/100 mg France	ANRS	Single arm 100 stable participants switch to DRV 400/100 once daily plus 2 NRTI	Ongoing	Clinical experience of low dose DRV in switch study
SL2 pilot	SSAT	DTG+DRV/r 400/100mg once-daily vs DTG+DRV/r 800/100 once daily vs TDF/FTC+DRV/r once daily in 120 treatment naive participants 48 weeks	Funding application stage	Preliminary data to support registration study
SL2 registration	SSAT	DTG+DRV/r 400/100 vs TDF/FTC+DRV/r 800/100 once daily in 600 1st line experienced participants Powered for non-inferiority 96 weeks Africa/SE Asia	Funding application stage	Data for FDA, PEPFAR and WHO approval

First-line

Experts agree that a DTG-based preferred first-line regimen is the current goal. In combination with TAF and FTC the total daily dose would be 275 mg 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.

While data gaps remain, both compounds should, at the very least, have an honorable mention in the WHO 2015 guidelines.

ViiV is sponsoring a number of trials to help to address some of the evidence gaps with DTG – including use in pregnant women and people receiving TB treatment. An open label study of regimens containing 50 mg DTG twice daily or EFV 600 mg once daily during first-line TB treatment, begun enrolling early 2015.[74]

Another trial is enrolling ART-naive women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.[75] Women who become pregnant in the trial will remain on their randomly assigned regimen and roll over into a pregnancy study.[76]

A number of investigator-led studies are also planned in closer-to-real-life African settings. These include a randomized comparison between DTG and EFV 400 mg regimens, and another with two DTG-based regimens, one with TDF and the other TAF and FTC. NAMSAL, the trial of DTG versus EFV 400 mg regimens is fully funded but has been delayed now for some time due to the DTG supply (or lack of). The TAF versus TDF study is at the funding application stage and dependent of TAF being approved. A DTG pregnancy pharmacokinetics study is funded and scheduled to start enrollment in July 2015.[77]

IMPAACT P1026s and PANNA[78, 79] – the respective American and European studies that look at pharmacokinetics of antiretrovirals in pregnancy and post-partum – are both starting to enrol women receiving DTG (and TAF is planned).

For EFV 400 mg, a pharmacokinetic study in pregnant women is scheduled to start enrolment in July 2015. Funding for the TB pharmacokinetic study is still under discussion.

Un-boosted TAF for adults is only being investigated in two Gilead trials [80, 81] – so in order to recommend this drug widely the investigator-led study is important.

IMPAACT P1026s and PANNA will provide some pharmacokinetic data on TAF in pregnant women. For co-treatment of TB, TAF is a minor CYP3A4 substrate and a substrate of P-glycoprotein, both of which are induced by rifampicin, so there might be an interaction. Gilead has not looked at this.

If DTG/TAF/FTC 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.

Second-line

For people failing EFV-based first-line treatment – and this population is expected to swell with greater access to viral load testing – discussions about a one-pill, once daily, second-line regimen with DRV/r 400/100mg and DTG are underway. [82] Studies to investigate this regimen are designed and seeking funding.

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. Market forecasts suggest that such an FDC might be available at low cost: US$250 pppy. Making recommendations for DTG first- and second-line depending on the initial regimen is not mutually exclusive.

If DTG becomes preferred first-line, research into the best option for second-line following this regimen is needed. Early discussions have included the possibility of DRV/r with rilpivirine or doravirine. It might also be possible to use NRTIs again.[83, 84]

What Needs To Be Done?

The 2015 revised WHO guidelines must reflect recent research and approvals. DTG and EFV 400mg should be included as alternative first-line recommendations with restrictions where data are missing. DRV/r is overdue as a recommended second-line option. A recommendation from WHO is the biggest signal and incentive to generic manufacturers to produce new formulations and FDCs suitable for low- and middle-income countries.

Research must be funded. Donors need to step up and fund the trials that will generate data to fill the current knowledge gaps. We need the missing information to make first-line recommendations without restriction. We need information to guide switching from EFV to DTG regimens. We need studies to support recommendations for optimized second-line regimens.

Sustainable supply of generic antiretrovirals must be maintained. Three manufacturers (Mylan, Cipla, and Hetero) accounted for 51% of antiretroviral volume and 56% of revenue in low- and middle-income countries in 2013.[85] Mylan had the highest share of revenue at 24%. The company also has 30% of South African public sector market (the largest ART program in the world); and it supplies many of the APIs for antiretrovirals produced by South African generic companies.[86] So the recent moves by the Israeli pharmaceutical company Teva for a hostile takeover of Mylan are alarming.[87] Should this come about Teva must continue with the commitment to people with HIV in low- and middle-income countries.

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