Fit for purpose

Antiretroviral treatment optimisation

i-Base/TAG
Pipeline Report 2014

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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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The i-Base/TAG Pipeline Report is an annual review of HIV, Hepatitis C Virus (HCV), and tuberculosis (TB) drugs, diagnostics, vaccines, preventive technologies, research toward a cure, and immune-based and gene therapies in development.

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Fit for purpose: antiretroviral treatment optimisation

By Polly Clayden

Since we first added a chapter looking at optimising antiretroviral treatment for low- and middle-income countries to the Pipeline Report in 2012 [1] – Retrofitting for purpose: treatment optimisation – this work has continued to gain traction. In the last year, results from one of the key dose optimisation trials ENCORE 1 – showing a lower dose of efavirenz (EFV) is non-inferior to the currently approved one – were published, [2] and dolutegravir (DTG) – one of the most promising pipeline drugs for this purpose – was approved for use in rich countries. [3, 4]

The importance of making the necessary investment to generate data – that will not come out of trials required for approval in rich countries – to inform recommendations for low- and middle-income countries is being discussed widely than before. And real life trial designs are being finessed, including in countries where the results will determine treatment strategies, and some are even being funded.[5]

Current Opinion in HIV and AIDS devoted an issue to treatment optimisation in November 2013.[6] In one opinion paper from this journal the authors note that an "entirely nontoxic combination of antiretroviral drugs for first-line and second-line use would be an important advance for this field" and suggest that lamivudine (3TC), emtricitabine (FTC) and raltegravir (RAL) each provide clinical proof-of-concept that regimens with long-term safety and minimal side effects are a possibility. [7]

And, World Health Organization (WHO) released a March 2014 Supplement to the 2013 Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection, which includes discussion on optimised treatment and the role of the evolving science. [8]

Sharp-eyed readers will notice a subtle title change from the original Pipeline Report chapter title to the one for this update, written with optimism that joined up research and guidance seems to be happening: more fit and less retro.

The story so far

Treatment 2.0 – a strategic approach by WHO and UNAIDS to achieving universal access to antiretroviral treatment and maximising the role of antiretrovirals in preventing new infections – includes treatment optimisation as one of its critical components. [9]

Discussions about optimisation of approved antiretrovirals – particularly through appropriate dose reduction – have been ongoing for over a decade. [10, 11] The rationale for possible lower doses being that when new drugs are developed, the highest tolerated doses in phase II are often selected for phase III and, in turn, approval, where in some cases lower ones may have equivalent efficacy. Efficiencies can also be achieved by reducing the amount of active pharmaceutical ingredient (API) with improved bioavailability through reformulation, or by improving the manufacturing process.

There are several ways that treatment optimisation can be done:

Dose reduction. In order to achieve regulatory approval for a dose lower than that currently approved, fully powered non-inferiority studies (phase III) – similar to those conducted by industry for the approval of a new drug – need to be done. It would take about three to six years to generate sufficient data to file with regulatory agencies, plus time to approval (about three months to a year). The estimated cost would be US$15 to 22 million.

Reformulation. This strategy makes use of technologies and/or inactive ingredients to increase the bioavailability of a drug, which enables reduction of the approved dose. A reformulated compound will need bioequivalence studies with the approved formulation (phase I). The estimated time frame to regulatory filing is two to three years, at a cost of US$2 to 8 million.

Process chemistry. It may also be possible to alter the manufacturing process leading to more efficient and less expensive API production. For this strategy to be successful, regulatory authorities would need to see only equivalent stability and purity data. This would take about one to two years, at an estimated cost of US$1 to 2 million.

Other factors in price reduction:

- Sourcing less expensive raw materials. This price depends on the volume needed, an increase in demand can attract new suppliers and in turn competition.
- Improvements in the manufacturing process can mean raw materials are converted to API more efficiently.
- Shelf life extension. To extend a typical two-year shelf life, real-time stability testing would be required with clear regulatory pathways.

The Conference on Dose Optimisation (CADO) – a collaborative project of the Clinton Health Access Initiative (CHAI), the Johns Hopkins University School of Medicine, and the Bill & Melinda Gates Foundation, held in 2010 and attended by process chemists, clinical pharmacologists, infectious disease specialists and experts in regulatory and ethical issues – led to a consensus statement on optimising the manufacturing, formulation, and dosage of antiretroviral drugs for more cost-efficient delivery in low- and middle-income settings. [12, 13]

As the statement explains, the API is the largest part of the cost of generic drugs; a reduction in this would potentially decrease the total cost of the product. The cost of a marketed generic drug typically consists of: API (65% to 75% of the total market price), formulation (10% to 20%), and packaging and profits (5% to15%).

In 2011, WHO held a follow up meeting to the first CADO, to work out ways to incorporate treatment optimisation into future guidelines and the Treatment 2.0 initiative. [14] This yielded a number of short-term research priorities and recommendations including increased harmonisation of adult and paediatric regimens, through FDCs and other simplified formulations.

Subsequent discussions at meetings led by Médecins Sans Frontières (MSF) and WHO, as well as the 2nd Conference on Dose Optimisation (CADO2), have explored medium- and longer-term horizons for future treatment strategies.[15, 16, 17]

The plans, established at CADO 1 to increase cost-efficiencies, remain unchanged, and this research continues to gain momentum. In the four years since the original meeting, there has been an increasing emphasis on patient acceptability and preferences. Discussions have included a broader group of representatives from the community and caregivers with consensus that improved efficiencies need, not only reduce costs, but also improve tolerability and outcomes for people with HIV. It is acknowledged that these factors will be increasingly critical as indications for treatment grow and more asymptomatic people with HIV are offered antiretroviral treatment. All potential treatment options must be measured against these factors.

The aforementioned meetings and publications have described the target product profile (TPP) of a "dream regimen" of antiretrovirals – summarised in Table 1.

TABLE 1. Target product profile of a dream antiretroviral regimen

SAFE AND EFFECTIVE	Superior or equivalent to currently recommended drugs
SIMPLE	Possible to be given in decentralised facilities or the community. One pill, once a day (less frequently might be possible in the future). No lead-in dosing. No dose adjustments when given with other common medicines. Heat-stable. Shelf life of two or more years.
TOLERABLE	Minimal toxicity. Reformulation and/or dose reduction might improve tolerability.
DURABLE	High genetic barrier to resistance. Low pharmacokinetic variability. Forgiving of missed doses. Tolerable for easier adherence.
UNIVERSAL	Safe and effective across all CD4 strata; in people with high viral load; in men and women; during pregnancy; across age groups and with common coinfections such as tuberculosis (TB) or viral hepatitis.
AFFORDABLE	Antiretroviral coverage does not meet the estimated current need. Meanwhile, evidence is growing for earlier and wider use of treatment.

Current WHO recommendations

For adult first-line treatment, a one pill, once-a-day fixed dose combination (FDC) of EFV plus tenofovir disoproxil fumarate (TDF) plus 3TC is agreed –across all expert consultations as well as in the 2013 World Health Organization Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection[18] – to be the current preferred option in the short- and medium-term. See Table 2.

The key messages from the WHO guidelines are:

1. Once daily regimens are better than twice-daily regimens from both clinical and programmatic standpoints.
2. FDCs are preferred for simplification, convenience, adherence, more efficient procurement, lower risk of stock outs and resistance.
3. EFV is superior to nevirapine (NVP) in the long term, as studies showed less discontinuation. It is also associated with other clinical and programmatic advantages such as no need for a lead-in dose, simpler use with TB treatment and safety/availability as a once daily FDC.
4. For sequencing, TDF use has advantages over other NRTIs from both clinical and programmatic perspectives: once daily, better in terms of resistance, and limits the risk of interaction with PIs.

CHAI produces an annual list of ceiling prices available to countries participating in their procurement consortium. [19] These prices, alongside those published by MSF Access Campaign in their excellent Untangling the Web of Antiretroviral Price Reductions inform those quoted in this chapter. [20]

The 2013 CHAI ceiling price for the preferred first line FDC is now US$131 per patient per year (pppy), which is a 21% reduction since 2012. With successful optimisation work, this regimen could be expected to be less than $100 pppy. [21] Future changes to this regimen must either offer efficiencies with its components (such as a reduced dose with the same durability and improved tolerability), or superiority with new compounds.

The recommended second-line regimen is ritonavir (RTV)-boosted protease inhibitor-based and, unlike recommendations in rich countries, lopinavir/ritonavir (LPV/r) rather than darunavir/ritonavir (DRV/r) is included alongside atazanavir/ritonavir (ATV/r). An optimised ATV/r regimen could be expected to be less than $275 pppy.

TABLE 2. 2013 WHO guidelines: recommended ART regimens

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 preferred (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.

Treatment-limiting central nervous system (CNS) toxicities that are a concern with EFV could possibly be reduced with a lower dose. Fears about its use during pregnancy are steadily being assuaged, and more permissive recommendations – in line with the British HIV Association guidelines – are made in the WHO 2013 guidelines. [22, 23, 24, 25, 26]

Despite direct comparisons as monotherapy, 3TC and FTC are largely considered to be interchangeable in terms of efficacy and safety, and the WHO systematic review concluded this to be true. [27] Both are nucleoside reverse transcriptase inhibitors (NRTIs) and are structurally similar molecules with low toxicity, and both are effective against hepatitis B virus. Cost comparisons make 3TC the preferred option – using FTC instead in combination with EFV and TDF adds an annual patient cost of US$25 to a combined product. But this gap in price appears to be narrowing. Currently 3TC is available in more FDCs than FTC.

Updated systematic reviews looking at EFV in pregnancy and 3TC versus FTC are both included in the WHO March 2014 supplement to the guidelines.

Work on the bioavailability of TDF could bring down the price (currently US$54 pppy as a single agent). Further reductions still might be possible in the future with the pipeline pro-drug, tenofovir alafenamide (TAF) due to its low volume and, in turn, API.

LPV/r is still the most widely used protease inhibitor in second-line regimens in low- and middle-income countries, making up 84% of donor funded protease inhibitors procured in 2012. [28]

The US Food and Drug Administration (FDA) has tentatively approved a heat-stable formulation of ATV/r. [29, 30] This 300/100 mg one-pill, once-daily, formulation is now US$220 pppy, considerably cheaper than LPV/r costing US$300 pppy. LPV/r also has a higher pill burden than ATV/r and more complex dosing (four pills a day dosed twice-daily). Mylan Pharmaceuticals has developed a two pill once-a-day co-packaged regimen of ATV/r plus 3TC and TDF; the ceiling price is US$306 pppy. Although it is a better option than LPV/r

the uptake of ATV/r has been slow – CHAI predicts it will reach 34% in the protease inhibitor adult market by 2017.

Once-daily heat-stable DRV/r would also offer a better option to LPV/r second line. At present a suitable formulation (and suitable price) remains elusive. Research is also required to establish optimal dosing. With expected comparable price to LPV/r (there is potential to reduce the current cost of DRV/r at $900 to below $350 pppy, if it was used in similar volumes to that of LPV/r currently) and a better profile, DRV/r should be a second-line option and not just considered for third-line treatment.

WHO recommendations for third-line treatment were introduced for the first time in 2010 and they remain much the same in 2013, suggesting that, in addition to DRV/r, RAL, and second-generation non-nucleoside reverse transcriptase inhibitor (NNRTI), etravirine (ETR) could be used in nucleos(t)ide (NRTI)-sparing regimens. None of these yet have generic versions, and the costs are considerable.

CADO2 recommendations

CADO-2 participants agreed that although first-line standard of care is hard to beat, CNS side effects associated with EFV; and renal and bone toxicities associated with TDF (as well as its high milligram dose of 300 mg) should be improved upon. Issues of tolerability might become increasingly unacceptable as the eligibility criteria for antiretroviral treatment continues to broaden and more people are likely to be asymptomatic when they start.

The group concluded that an FDC of TAF/3TC/DTG first-line could be a possible future option (or one with a lower dose of EFV). For people starting this DTG-based regimen second-line could be DRV/r plus two NRTIs or plus the NNRTI rilpivirine. People currently receiving EFV based first-line regimens might receive an FDC of DRV/r plus DTG second-line.

In the meantime can we do better with what we have?

Optimisation with some approved antiretrovirals might offer advantages over current doses and/or formulations, and work is underway with several compounds. [31] See Table 3.

TABLE 3. Approved antiretroviral compounds with potential for dose optimisation

COMPOUND/ APPROVED DOSE	CLASS	SPONSOR/ APPROACH	OUTCOMES	STATUS
Tenofovir disoproxil fumarate (TDF) 300 mg once daily	NtRTI	CHAI in partnership with generic companies Reformulation	Approx 33% reduction anticipated Target 200 mg TDF-containing FDC tablet Cost reduction $50 to $35 pppy	TDF (hx) Underway
Zidovudine (AZT) 300 mg twice daily	NRTI	Geneva University Hospital Dose optimisation RCT	Dose reduced to 200mg twice daily Cost reduction $89 to $60 pppy	MiniZID Phase III Completed January 2014 No difference between arms in overall anaemia rate at 24 weeks

COMPOUND/ APPROVED DOSE	CLASS	SPONSOR/ APPROACH	OUTCOMES	STATUS
Stavudine (d4T) 30 mg twice daily	NRTI	Wits Reproductive Health Institute Dose optimisation and comparison with TDF, RCT	Dose reduced to 20mg twice daily Cost reduction $25 to $20 pppy	WHCS-001 Phase III To be completed end 2015/early 2016
Efavirenz (EFV) 600 mg once daily	NNRTI	Kirby Institute Dose optimisation RCT CHAI Reformulation	Dose reduced to 400 mg once daily Potential additional 33% reduction by reformulation Cost reduction $63 to $31 pppy	ENCORE 1 400 mg non-inferior to 600 mg at 48 weeks
Atazanavir/ ritonavir (ATV/r) 300/100 mg once daily	PI	HIVNAT/Kirby Institute Dose optimisation RCT CHAI Process chemistry	Dose reduced to 200/100 Cost reduction $355 to $200 pppy Additional potential price reduction by process chemistry	LASA III Phase IV to be completed 2014

Tenofovir

TDF is universally recommended as part of first-line treatment. It is considered to be the best NRTI on the market, and this is likely to continue for several years.

The price of TDF has dropped considerably since its introduction into the generic market. This is largely due to efficiencies in raw material sourcing and improved processing, which led to a 57% drop in price between 2006 and 2010.[32, 33] It is now available for about US$50 pppy, a 74% drop since 2006: a TDF-based FDC regimen is now available for about US$125 pppy.

There are, however, limits to the lowest possible price of TDF due to its high milligram dose (300 mg) with the current formulation.

CHAI is developing a dosage form of TDF called TDF (hx) in partnership with companies performing the preclinical work, formulation screening and GMP work, and a generic manufacturer.

Through reformulation of the excipients, they aim to increase bioavailability and, in turn, lower the dose to an anticipated 200 mg, while maintaining equivalent exposure.

Bioequivalence studies will compare TDF (hx) to the 300 mg originator formulation of TDF (Viread) to provide evidence for tentative FDA approval of TDF (hx)-containing FDCs.

CHAI's goal is to reach the market with a TDF (hx)-containing FDC in late 2017.

As well as TAF, being developed by Gilead, Merck is developing CMX-157, another prodrug of tenofovir. [34, 35, 36]

A TAF-containing FDC is not expected to reach the market in low- and middle-income countries before 2020 and would take a while to completely replace TDF. There has been little news of CMX-157.

AZT

If TDF remains the preferred first-line NRTI, AZT is likely to be used second-line in the short term.

The initial dose of AZT was 1200 mg per day (300 mg every four hours). This was reduced to 250 to 300 mg twice daily, after similar efficacy and increased safety was demonstrated. [37]

Although AZT is generally better tolerated than d4T over a long-term period, its hematologic toxicities (anaemia/neutropenia) remain a concern in many low- and middle-income countries.

The MINIZID study looked at 200 mg versus 300 mg AZT twice daily (as part of a regimen with 3TC plus an NNRTI), with reduction of anaemia as the primary endpoint.

This was a 24-week phase II/III study in 142 treatment-naive patients, sponsored by the University of Geneva and being conducted at the Hôpital de la Caisse Nationale de Prévoyance Sociale, Yaoundé, Cameroon. Recruitment began in August 2011 and it was completed in January 2014. [38]

The results were presented recently and showed no difference in overall rate of anaemia with the lower dose but demonstrated improved safety and similar efficacy compared to standard dose. [39]

Several countries such as Thailand and India already use the AZT 250 mg tablet twice daily, and Thailand is currently using 200 mg twice daily in patients weighing less than 50 kg.

d4T

Of all the dose optimisation strategies proposed or ongoing, the decision to use d4T is the most controversial. Unlike the other antiretrovirals for which these strategies are being suggested or conducted, d4T is no longer a preferred option in any guideline, anywhere, due to its toxicity profile. For several years, WHO has issued guidance for phasing out d4T.

The Wits Reproductive Health Institute in South Africa is leading a phase IIIb trial comparing 20 mg d4T twice daily to 300 mg TDF once daily in approximately 1,000 patients in South Africa, India and Uganda. The trial is supported by the Bill & Melinda Gates Foundation.

The primary objective is to demonstrate the non-inferiority of 20 mg d4T to 300 mg TDF (both in a regimen with 3TC plus EFV) in treatment-naive patients. The proportion of patients receiving each regimen with undetectable viral load (less than 200 copies/mL) at 48 weeks, will determine this. The secondary endpoints are to evaluate the tolerability, overall safety, and efficacy of 20 mg d4T compared to 300 mg TDF.

The trial is concerning, as it will not answer long-term toxicity questions associated with d4T. The 20 mg d4T dose might be acceptable in a short-term 48- or even 96-week virological endpoint study. But, because mitochondrial toxicity is both dose- and time-dependent – and treatment with d4T is associated with more severe mitrochondrial DNA depletion and fat wasting over time compared with AZT therapy [40] – many of its most serious side effects would not necessarily emerge until after such a study was completed. Although it looks at lipoatrophy, this study does not include monitoring of surrogate markers for mitochondrial toxicity, so it cannot shed light on the incidence of this serious adverse event.

The d4T parallel track programme – which randomised over 10,000 patients to receive 40 (30) mg or 20 (15) mg (between October 1992 and February 1994) – showed a higher incidence of neuropathy in the high-dose arm (21%).

Nonetheless, the incidence of neuropathy observed in the lower dose arm was also unacceptably high (15%). [41]

In addition to concerns about cumulative toxicities, d4T-related cost savings might become irrelevant by the time the trial ends. Through other dose optimisation strategies and perhaps promising newly approved and pipeline compounds, alternatives are likely to become available that could drive regimen costs down with less risk to patient safety.

Activists from all over the world have opposed this trial. [42, 43, 44, 45, 46, 47, 48]

Since the trial was designed the price of TDF has come down more than was originally anticipated – TDF (hx) could reduce this even further – and uptake of TDF-containing FDCs has increased.

The most useful data from this trial will be on the safety of TDF in a resource limited setting.

Efavirenz

EFV fulfils many of the desirable characteristics for the TPP. But it is associated with CNS side effects, which can lead to drug discontinuation, reported in as much as half the people receiving it in settings with access to alternatives. [49]

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. [50,]

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 patients at 48 weeks. The study was conducted in Europe, Australasia, Latin America, Asia, and Africa.

Significantly fewer patients (approximately 3%) discontinued treatment due to EFV-related side effects (rash, CNS, gastrointestinal, but not psychiatric) from the 400 mg arm compared to the 600 mg arm and 10% fewer participants reported these side effects.

A very high proportion (approximately 90%) of participants had an undetectable viral load in this study.

Results from a pharmacokinetic sub-study of ENCORE 1 suggest that the current targets for EFV might be too high. [51, 52]

That comparable efficacy was achieved at reduced dose of EFV in ENCORE 1 (and potentially reduced cost) is an important finding.

The ENCORE 1 investigators suggest, "Lower dose efavirenz should be recommended as part of routine care". WHO and the Adults ART Working Group question whether the lower dose would be robust in the presence of rifampicin (which reduces concentrations of EFV due to a drug-drug interaction) in treatment of TB/HIV coinfection and in the third trimester of pregnancy.

It seems that to recommend 400 mg EFV widely pharmacokinetic studies with rifampicin and in pregnant women will have to be conducted. One question will be, what pharmacokinetic targets are appropriate for treatment success?

The high API of EFV is due in part to its poor water solubility. CHAI is looking at reformulation, targeting the inactive ingredients, to improve this.

Nanosuspensions of EFV, using freeze-drying technology are also in development, which could result in improved bioavailability and possibly greater antiviral activity. [53, 54]

The research group at the University of Liverpool is developing a nanosuspension of EFV. [55]

Atazanavir

Dose reduction might also be possible with ATV/r, and the HIV Netherlands Australia Thailand Research Collaboration, with some support from the Kirby Institute, is conducting a trial that might provide some evidence for this strategy.[56]

The low-dose ATV/r versus standard-dose ATV/r (LASA) study is comparing the efficacy and safety of ATV/r at either 200/100 mg or 300/100 mg once daily in 560 Thai patients in combination with two NRTIs. This non-inferiority, phase IV study with about 600 patients began recruiting in March 2011 and results should be announced this year.

This study enrolled patients who were already virologically suppressed to switch to the lower or standard dose of ATV/r. This research is important for Thailand as patients tend to have a lower body weight, and hyperbilirubinemia occurs quite frequently. It will be difficult to generalise the results from this research beyond the study population, but positive results would provide good reason to conduct a study in treatment-naive patients from a broader population.

CHAI is also working on optimising the process chemistry of ATV/r.

Research gaps and planned trials to address them

For the recommendations from CADO 2 and the Adults ART Working Group to be realised, new trials are needed to address gaps in information on how optimised doses, recently approved or pipeline drugs will perform in public health programmes in low- and middle-income counties. Table 4 summarises research gaps and what is needed and Table 7 describes trials in the planning stage or about to start.

Table 4: Action needed for antiretroviral treatment optimisation

OPTIMISED STRATEGY	TOLERABILITY	RESISTANCE	CONVENIENCE	PW, TB, CHILDREN	COST REDUCTION	ACTION NEEDED	ESTIMATED TIMELINE (YEARS)
Low dose EFV	√	?	√	?	√	PK studies (PW and TB)	1-2
Low dose DRV/r	√	?	√	?	√	PK studies (titration of best DRV:RTV ratio) RCT (comparative studies standard vs low dose)	2-5
Use of DTG	√	√	√	?	√	Studies in PW, TB and children Comparative trials (TDF/TAF) first line RCT (DRV/r+DTG second line)	2-5
Use of TAF	√	?	√	?	√	Comparative trials using DTG Studies in PW, TB and children	2-5
Long-acting formulations	√	?	√	?	√	Phase II/III studies (treatment and preventative)	>5

Source: Adapted from Marco Vitoria. Global Access to New HIV Therapies. WHO. June 2014.

First-line studies are needed to determine FDC regimens that are equally or more potent and more durable, tolerable and affordable than TDF/ XTC (refers to either 3TC or FTC)/EFV 600mg, including TAF/ XTC/DTG and TAF/XTC/EFV 400mg.

For second-line, studies are needed to identify improved regimens, particularly looking at the role of DRV/r in replacing LPV/r or ATV/r. Studies of reduced dose DRV/r, in combination with recycled NRTIs or DTG are important.

A one pill, once a day option is desirable for second-line.

Several trials are either at the planning stage or a bit further along the pipeline.

Low dose efavirenz

Pharmacokinetic-pharmacodynamic modelling of the data from ENCORE1 is currently ongoing to help better understand predictors of EFV pharmacokinetics and response in a heterogeneous population.

Since the announcement of the trial results last year, there has been a lot of discussion about recommending the reduced dose, particularly in low-income countries where the resulting cost savings would be considerable.

Questions about whether or not 400 mg will be robust enough in the third trimester of pregnancy and in the presence of concomitant treatment for TB have delayed recommendations from WHO and national guidelines.

There are five 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. [57] The results suggest that pregnancy has slight if any clinically important effects on EFV pharmacokinetics.

For rifampicin, there have been a number of short-term pharmacokinetic studies with 600 mg EFV showing reduction in plasma concentrations. It is unclear how useful these results are when EFV has not reached steady state. Longer-term studies in HIV positive people have shown increased Cmin or no effect. [58] In order to determine whether the pharmacokinetic interaction

between rifampicin and EFV is different using the 400mg dose (there may be different induction effects) a new study is considered necessary.

It seems that to recommend 400 mg EFV widely pharmacokinetic studies with rifampicin and in pregnant women will have to be conducted and these are in the planning stage.

It is also important to remember that in the early DMP-266 005 trial of EFV there was no difference in viral suppression between people receiving 200 mg, 400 mg and 600 mg at 16 weeks. [59] There is talk of exploring the 200 mg dose compared to 400 mg and 600 mg in Africa, Latin America and Thailand. A UK study is also planned to compare 200 mg EFV once daily to 400 mg RAL twice daily. [60]

Dolutegravir

With a low 50 mg once-daily dose that does not require boosting, very good efficacy, minimal toxicity, pregnancy category B, and the potential to be low cost and co-formulated, DTG might be an option for use in low- and middle-income countries. It could replace EFV first-line or be used second-line. It is also predicted to cost US$30 pppy to manufacture: 90% cheaper than RAL.

DTG was superior to EFV at 48 weeks in antiretroviral naive patients in phase III trials. [61] Data from this comparison and from studies comparing DTG to RAL and in people with resistance to other integrase inhibitors [62, 63] were used to gain approval for a broad indication in adults and adolescents aged 12 and above. [64] The indication for 12 to18 year olds is based on a 24-week open-label label study in integrase inhibitor-naive patients.

Some of the registrational trials were open label and included people that received a TDF/FTC backbone (as opposed to ABC/3TC from the originator company) so there are some preliminary data on this potential preferred regimen. See table 5.

Table 5: Numbers of people receiving TDF/FTC in DTG arms of phase III clinical trials

TRIAL	NUMBER AND PERCENTAGE ON TDF/FTC
SPRING-2	242 (59%)
SINGLE	All received ABC/3TC (regimen comparison study)
FLAMINGO	163 (67%)
SAILING	Not in publication. Numbers will be small as most people has a boosted PI in their background regimen plus one other antiretroviral

Although some of the registrational trials now have two years data, how DTG is likely to perform in a real world, low- or middle-income setting still poses questions. Populations in these settings include significantly larger proportions of women of childbearing age, children, and people with TB, malaria, and other coinfections, but research is conducted in order to provide information to register drugs for rich countries.[65]

DTG has been studied in several treatment scenarios and regimens, but so far this has not included key populations who would be treated with DTG in low- and middle-income countries. The registrational trials for DTG were about 80% men and few non-white participants and hardly anyone co-infected with other diseases (a few hepatitis B and none with TB or malaria). People with baseline NRTI resistance were excluded. Table 6 shows the number of women in phase III DTG trials.

Table 6. Numbers of women in DTG arms of phase III clinical trials

TRIAL	NUMBER AND PERCENTAGE OF WOMEN
SPRING-2	63 (15%)
SINGLE	67 (16%)
FLAMINGO	31 (13%)
SAILING	107 (30%)
VIKING-3	42 (23%)

Information about treating HIV/TB coinfection with a DTG-based regimen is limited. So far a phase I study has been conducted in healthy volunteers of DTG given with rifampicin and with rifabutin. [66] This 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. A study of 50 mg DTG twice daily during TB treatment will begin in November 2014. [67]

As yet there is no information about DTG in pregnant women, although animal reproduction studies are not always predictive of human response, no safety issues were revealed in preclinical studies.

The originator company is sponsoring a number of trials to help to address some of these gaps and several investigator-led trials are also planned (see Table 7). [68, 69, 70] The company-sponsored research will not be entirely real world scenarios – as an example the second line study includes NRTI resistance testing to determine eligibility. It is essential that trials – such as NAMSAL that will generate real world data for DTG – are supported.

Low dose darunavir/ritonavir

DRV/r is generally considered to be the most durable protease inhibitor, but there is no generic formulation, and cost has been a barrier to its wide use. As it is not yet recommended for second-line treatment by WHO there has been limited work on its optimisation.

This drug has different approved doses for treatment-naive (including treatment- experienced but with no 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. [71, 72] Results from these trials of DRV/r, as well as a more recent one with 600/100 mg,[73] 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.

One-Pill, Two-Pill, Red-Pill, Blue-Pill

For people failing EFV-based first-line treatment – greater access to viral load monitoring is expected to swell this population – discussions about a one-pill once-daily second-line regimen with DRV/r and DTG are underway.

A regimen of DRV/r plus DTG has the potential to be a once daily, heat stable, co-formulated second-line option with no cross-resistance to the current recommended first line. The potential strategy using the once daily first-line followed by co-formulated DRV/r plus DTG is known as Pill A, Pill B (Pill 1, Pill 2 or Red Pill, Blue Pill). [74]

Market forecasts suggest that such a Pill B might be available at low cost: US$250 pppy.

The dose ranging (phase II) study for the proposed development programme would compare three once daily regimens: TDF/FTC plus DRV/r 400/100 mg vs DTG plus DRV/r 800/100 mg vs DTG + DRV/r 400/100 mg. This phase would be conducted in treatment naive participants over 48 weeks.

If 24-week phase II data justifies progression of the programme (no obvious safety or efficacy concerns), a 96-week phase III pivotal trial with 1050 NNRTI-experienced participants will follow.

Phase III – a non-inferiority study conducted in sites in Africa, South East Asia and Eastern Europe – would compare two NRTIs plus boosted protease

inhibitor (standard of care and control arm) vs DTG plus DRV/r 800/100 mg vs DTG plus DRV/r 400/100 mg.

The success of this programme should make switching people who are on current first-line regimens with virologic failure to second-line considerably simpler and more accessible.

The one criticism is that this strategy would lead to recommending DTG second-line when many experts believe it should be the preferred first-line option in the future. It is critical that work is funded to ensure that we have enough information to use DTG first-line in low-income settings, but research into first- and second-line DTG-based regimens should not be mutually exclusive. A better second line option is essential for the 5% of nearly 13 million people on first-line (and more as scaling up continues) that need to switch.

If a DTG/TDF/3TC (or even DTG/TAF/3TC) becomes the future Pill A, then Pill B might be DRV/r plus rilpivirine – which also needs to be investigated.

TABLE 7: Planned treatment optimisation trials

TRIAL	IMPLEMENTER/ SPONSOR	DESIGN	STATUS/ COMMENTS
Low dose EFV studies			
EFV 400 mg TB	SSAT/ BMGF	PK EFV 400 mg with isoniazid and rifampicin	Protocol in final stages
EFV 400 mg pregnancy	SSAT/ BMGF	PK EFV 400 mg in third trimester pregnancy and post partum	Protocol in final stages
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 approval phase
EFV 200 mg	NIHR	EFV 200mg once daily vs RAL 400 mg twice daily in 100 antiretroviral naive participants in UK Pilot data for full phase III study Virological and toxicity endpoints	Protocol in final stages

TRIAL	IMPLEMENTER/ SPONSOR	DESIGN	STATUS/ COMMENTS
Dolutegravir			
NAMSAL DTG vs 400 mg EFV	ANRS	400 mg EFV plus 3TC/ TDF vs DTG plus 3TC/TDF in 550 antiretroviral naive participants 48 weeks Sites in several African countries	First line, phase III investigator-led study Few exclusion criteria, includes people with TB co-infection and aims to be as close as possible to real life DTG supply under discussion
DOLphin (dolutegravir in pregnant HIV mothers and neonates)	University of Liverpool/ Makerere University/ ViiV	DTG PK in pregnant women in third trimester and post partum during breastfeeding 60 late presenting women (after 28 weeks gestation) Women randomized 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs. Sites in Uganda	Phase II investigator-led study Protocol in final stages
TB	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 48 weeks	Phase IIIb Will start November 2014

TRIAL	IMPLEMENTER/ SPONSOR	DESIGN	STATUS/ COMMENTS
Malaria	University of Liverpool/ Makerere University	PK DTG and artemisinin-based combination therapies for in 46 healthy volunteers	Phase I investigator-led study Under discussion
Second line	ViiV	DTG vs LPV/r in approximately 600 1st line treatment experienced participants with virological failure in LMIC Multinational	Phase IIIb Participants screened for NRTI resistance Not yet open for recruitment
ARIA	ViiV	DTG/ABC/3TC vs. ATV/ r+TDF/FTC in 474 treatment naive women Pregnancy is an exclusion criterion Multinational, sites in South Africa 48 weeks	Phase IIIb study Underway
Pregnancy	ViiV	Pharmacokinetic and safety single arm study of women with unintended pregnancies while participating in a trial of DTG/ABC/3TC FDC Maximum number of women: all randomised to study drug (approx 237) but unintended pregnancies in all women not anticipated Multinational, sites in South Africa	Phase III Not yet open for recruitment

TRIAL	IMPLEMENTER/ SPONSOR	DESIGN	STATUS/ COMMENTS
Darunavir/ritonavir			
DRV/r once daily trial (South Africa)	WRHI	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	Funding approval stage
DRV/r once daily (France)	ANRS	Single arm 100 stable participants switch to DRV 400/100 once daily plus 2 NRTI	Starting later 2014
Dolutegravir plus darunavir/ritonavir			
SL2 pilot	SSAT/BMGF	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 naïve participants 48 weeks	Funding approval phase
SL2 registration	SSAT/BMGF	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 approval phase Data for FDA, PEPFAR and WHO approval

ANRS, National Agency for AIDS Research, France; BMGF, Bill & Melinda Gates Foundation; NIHR, National Institute for Health Reserch; SSAT, St Stephen's AIDS Trust, UK; UK MRC, UK Medicines Research Council; WRHI, Wits Reproductive Health and HIV Institute, South Africa

*Arm conditional on favourable results from DRV/r 400/100 mg

Tenofovir alafenamide

TAF is not yet approved and in phase III – it could also be a useful new drug. With doses 10 times or more lower than that of TDF, the cost of TAF is predicted to be appropriately lower, and could come in at an annual patient cost of as little as US$20.[75]

Gilead are hopeful that this compound will have a better safety profile at a much lower dose than TDF. It is critical that Gilead recognises the potential for this compound as a future component of generic FDCs.

At present the Gilead is prioritising the development of TAF in potential FDCs with elvitegravir (EVG, its own integrase inhibitor that needs to be boosted), the boosting agent cobicistat (COBI) and FTC. It is also developing an FDC with boosted DRV/r. (See Appendix 1, Table 1).

Due to a drug-drug interaction with COBI that increases the levels of tenofovir 2.5-fold, a dose of 10 mg is being used in regimens with boosted agents.

The information generated by the development programme might not be sufficient inform the production of a generic FDC of TAF/DTG/3TC, as prioritised by CADO-2.

Close to 300 activist organisations and individuals signed letter to Gilead demanding that the company conducts investigations into dosing of TAF in unboosted regimens. [76]

Recent discussions have been more promising and the company is developing a 10mg and/or 25mg TAF plus 200mg FTC co-formulated tablet(s). The TAF dose will depend on the results of pharmacokinetic evaluations. From the original dose ranging studies where 8 mg monotherapy was non-inferior to 300 mg TDF, 10mg might be sufficient for un-boosted regimens.

This drug-drug interaction work is currently ongoing.

In future it will be important to include TAF in real life trials, in place of TDF.

Long acting formulations

There is a lot of excitement about the possibility of long acting formulations for resource limited settings and their potential to vastly change standard of care.

As yet there is not clarity on the target product profile – both for the molecules and for patient acceptability – for these formulations. Nor is it clear if the right combination of compounds required to construct a suitable regimen are available or even in development.

What needs to be done?

1. Treatment optimisation must best serve people with HIV

This deserves emphasis. The d4T trial remains an example of a widely unpopular strategy. Acceptability for HIV positive people and activists is always important. This will become increasingly so as indications for starting become broader and more asymptomatic people with HIV are offered treatment.

There is some concern that DTG might only being prioritised for second-line treatment. If DTG is as good a drug as it appears (and a better and more tolerable one than EFV) it should also be recommended first-line. These two strategies are not mutually exclusive. There will be sufficient numbers of people who fail first-line treatment with the currently recommended EFV-based regimen to justify the DRV/r plus DTG second-line strategy. Research and formulation work needed to make first-line DTG regimens an option must be conducted.

2. Plan phase III and subsequent trials to generate necessary data

As far as possible, when trials are being designed for registration, drug development plans need to be designed with broader populations in mind.

Where information is not going to be forthcoming from these, the originator companies and independent investigators need to fill the gaps in a timely fashion.

3. Investments must be made

In order to generate data to provide evidence to make it possible to use new drugs and strategies that will not come from registrational trials additional research will be needed. Funding and support for complementary studies for low- and middle-income countries is critical.

4. Speed up the time between approvals

There are still big gaps between full FDA/EMA approval and WHO prequalification, FDA tentative approval, and approval by local regulatory agencies.

Delays with the registration process, in addition to production by generic manufacturers and recommendations in national guidelines, means that it takes years from promising results in trials and initial approval to wide availability for the majority of people in need of antiretroviral treatment.

5. Joined up planning and thinking

This is happening more and more. It is unfortunate that after ENCORE 1 results were announced additional information is still needed before the lower dose EFV can be recommended. For future optimisation work, additional research needs to be done simultaneously with the main trials and not considered afterwards.

Appendix 1

Table 1. Summary of pipeline compounds in 2014

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
cobicistat	Gilead	PK booster	Approved in E.U.; NDA refiled for U.S. approval	In September 2013, European Commission approved cobicistat as a pharmacokinetics enhancer of atazanavir 300 mg once daily or darunavir 800 mg once daily as part of a complete ART regimen in adults
elvitegravir	Gilead	INSTI	Approved in E.U.; NDA refiled for U.S. approval	In November 2013, European Commission approved elvitegravir for use in combination with ritonavir-boosted PIs for individuals without evidence of resistance to elvitegravir

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
darunavir plus cobicistat (co-formulation)	Janssen	PI plus PK booster	Application filed in E.U.; NDA filed in U.S.	EMA application filed October 2013; NDA filed April 2014
atazanavir plus cobicistat (co-formulation)	BMS	PI plus PK booster	NDA filed in U.S.	NDA filed April 2014
darunavir plus abacavir plus 3TC (co-formulation)	ViiV Healthcare	INSTI plus two NRTIs	NDA filed in U.S.; application filed in E.U.	US. and EU applications filed in October 2013
tenofovir alafenamide (TAF, GS-7340)	Gilead	NtRTI (tenofovir prodrug)	Phase III	In development as FDC component with elvitegravir, cobicistat, and FTC for treatment-naive and –experienced patients. Also as a component of FDC with darunavir, cobicistat, and emtricitabine. Co-formulation with emtricitabine, as follow-up to Truvada, also in development

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
raltegravir (once-daily formulation)	Merck	INSTI	Phase III	PK data from phase I once-daily formulation (2 x 600 mg tablets) studies presented at EACS 2013 and CROI 2014. A phase III study is expected to begin in 2014
dolutegravir plus rilpivirine (coformulation)	ViiV Healthcare, Janssen	ISNTI plus NNRTI	Phase II/III	Clinical trials evaluating the safety and efficacy of the FDC as two-drug maintenance therapy are expected to begin in early 2015.
darunavir plus cobicistat plus FTC plus TAF (co-formulation)	Gilead	PI plus PK booster plus NtRTI and NRTI	Phase II	Phase II study has been completed. A phase III study of the FDC has not yet been announced

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
apricitabine	Avexa	NRTI	Phase II	3TC-like molecule, stalled at phase IIb with no new studies listed since a phase III study was halted in 2009. A potential role for multiclass-resistant HIV. Partnership announced in December 2013 with NextPharma
BMS-663068	BMS	Attachment inhibitor (gp120)	Phase II	Phase II data presented at CROI 2014
cenicriviroc (TBR-652)	Tobira	CCR5 inhibitor (also active against CCR2)	Phase II	Phase II study results reported at EACS 2013. Tobira plans to study FDC of cenicriviroc plus 3TC in combination with third drug in phase III programme
doravirine (MK-1439)	Merck	NNRTI	Phase II	Phase II data reported at CROI 2014

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
PRO 140	CytoDyn	CCR5-specific humanized monoclonal antibody	Phase II	No new data since 2010. Phase III trials, including treatment substitution protocol, are planned by CytoDyn
ibalizumab (TMB-355; formerly TNX-355)	TaiMed Biologics	CD4-specific humanized IgG4 monoclonal antibody	Phase II	No data from treatment studies in several years; potential as long-acting preexposure prophylaxis
S/GSK1265744 oral and long-acting parenteral (LAP) formulations	ViiV Healthcare	INSTI (follow-up to dolutegravir)	Phase II	Preliminary data supporting daily oral dosing as maintenance therapy, paired with oral rilpivirine, presented at CROI 2014. Demonstrates potential for once-monthly dosing with rilpivirine-LA

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
rilpivirine-LA (long-acting formulation)	Janssen	NNRTI	Phase II	Preliminary data supporting daily oral dosing as maintenance therapy, paired with oral S/ GSK1265744, presented at CROI 2014. Demonstrates potential for once-monthly dosing with S/ GSK1265755 LAP
OBP-601 (formerly BMS-986001)	Oncolys	NRTI	Phase II	d4T-like molecule in phase II, with no new clinical data reported since 2012. Licensing agreement between Oncolys and BMS has been terminated and the compound returned to Oncolys for continued development
albuvirtide	Chongquing Biotechnologies	Long-acting fusion inhibitor	Phase I	No new data or studies announced since 2013 Pipeline Report

COMPOUND	COMPANY	CLASS/ TYPE	STATUS	COMMENTS
CMX157	Merck	NtRTI (similar to TAF)	Phase I	No new data or studies announced since 2013 Pipeline Report
EFdA	Merck	NRTI	Phase I	No new data or studies announced since 2013 Pipeline Report

BMS: Bristol-Myers Squibb; CROI: Conference on Retroviruses and Opportunistic Infections; EACS: European AIDS Conference; E.U.: European Union; FDA: U.S. Food and Drug Administration; FDC: fixed-dose combination; GSK: GlaxoSmithKline; IM: intramuscular; INSTI: integrase strand transfer inhibitor (integrase inhibitor); MDR-HIV: multidrug-resistant HIV; NDA: new drug application; NRTI: nucleoside reverse transcriptase inhibitor; NtRTI: nucleotide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor; PK: pharmacokinetic; PI: protease inhibitor; STR: single-tablet regimen; U.S.: United States

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Notes


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