Fit for purpose

Antiretroviral treatment optimisation

HIV i-Base
March 2020

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.

www.i-base.info

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 2020: NEW DRUGS IN DEVELOPMENT

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

http://i-base.info/hiv-pipeline-report-march-2020

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Innovation in Global Health
Funded by Unitaid.

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An HTB South supplement ISSN 2046-9373

Design & typesetting: *the earth is round*, Cape Town, RSA

Introduction

HIV i-Base produces Fit for Purpose – a review of antiretroviral therapy (ART) optimisation – annually for distribution at the International AIDS Society (IAS) conferences, with updates to coincide with other key HIV meetings.

This update of the July 2019 edition was for the Conference on Retroviruses and Opportunistic Infections (CROI) 2020 and the Conference on Antiretroviral Drug Optimisation (CADO) 4. We also highlight relevant data presented at CROI.

The frequently-updated Op-ART trial tracker summarises the progress of key research is available at:
http://i-base.info/op-art/

The full Pipeline Report – looking at investigational HIV drugs – is available at:
http://i-base.info/htb/37221

i-Base's HIV Treatment Bulletin (HTB) reports from CROI 2020 and affiliated meetings are available at:
http://i-base.info/htb/

The next edition of Fit for Purpose will include adult and paediatric ART optimisation and pipeline drugs and will be released at the 23rd International AIDS Conference (AIDS 2020) in July.

Fit for purpose: antiretroviral treatment optimisation

By Polly Clayden

Fit for Purpose provides an overview of research and development in ART optimisation for people living with HIV in low- and middle-income countries (LMICs).

This prioritises investigation into drugs, regimens and strategies that support or help to change current and future global HIV treatment recomendatations.

Important recent developments include:

- World Health Organization (WHO) guidance recommending dolutegravir (DTG)-based regimens as preferred first-and second-line ART.
- Week 48 data from ADVANCE and NAMSAL – two key ART optimisation trials of first-line DTG vs efavirenz (EFV) showing non-inferiority of DTG regimens in African settings.
- Update from Tsepamo study showing a declining rate of neural tube defects in Botswana but still slightly elevated compared to other ART regimens.
- Reports of weight gain among people receiving DTG-based ART that appears to be most pronounced in black women and those receiving tenofovir alafenamide (TAF).

What does the World Health Organization recommend?

Current WHO guidelines – Update of recommendations on first- and second-line antiretroviral regimens. World Health Organization 2019 [1] – recommend tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or emtricitabine (FTC) (XTC)/DTG as preferred first-and second-line ART regimen for adults and adolescents (and children with approved DTG dosing). See Table 1.

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

Since then, more information has accumulated on the use of DTG both first- and second-line, including some that helps to fill the evidence gaps.

The guidelines include a note of caution on using DTG during the periconception period among women and adolescent girls of childbearing potential. Effective contraception should be offered to those who do not wish to become pregnant and those who do should be fully informed of the slight increase in risk of neural tube defects.

EFV 400 mg is now recommended for adults and adolescents as an alternative first-line ART. But guidelines do not recommend EFV-based ART in settings with national estimates of pretreatment resistance to EFV of 10% or more.

TAF is only recommended in special circumstances: it may be considered for

people with established osteoporosis and/or kidney impairment as part of a first-line regimen.

Darunavir/ritonavir (DRV/r) is recommended as part of an alternative second-line regimen.

Table 1: WHO ART recommendations 2020

FIRST-LINE		
PREFERRED	ALTERNATIVE	SPECIAL CIRCUMSTANCES
TDF + 3TC (or FTC) + DTG	TDF + 3TC + EFV 400 mg	TDF + 3TC (or FTC) + EFV 600 mg AZT + 3TC + EFV 600 mg TDF + 3TC (or FTC) + PI/r TDF + 3TC (or FTC) + RAL TAF + 3TC (or FTC) + DTG ABC + 3TC + DTG
SECOND-LINE		
FAILING FIRST-LINE REGIMEN	PREFERRED	ALTERNATIVE
TDF + 3TC (or FTC) + DTG	AZT + 3TC + ATV/r (or LPV/r)	AZT + 3TC + DRV/r
TDF + 3TC (or FTC) + EFV (or NVP)	AZT + 3TC + DTG	AZT + 3TC + ATV/r (or LPV/r or DRV/r)
AZT + 3TC + EFV (or NVP)	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)

Key: ABC, abacavir; ART, antiretroviral treatment; ATV/r, atazanavir/ritonavir; AZT, zidovudine; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; PI/r; ritonavir-boosted protease inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Source: Update of recommendations on first- and second-line antiretroviral regimens. World Health Organization 2019

What we know and the evidence gaps

Dolutegravir

DTG-based regimens are now WHO-preferred for first- and second-line and many countries have transitioned to and others are planning to transition to DTG.

Week 48 data from two key ART optimisation studies looking at DTG regimens were presented in late 2018 and 2019.

ADVANCE

Forty-eight week results from the ADVANCE study were presented at IAS 2019, alongside a simultaneous publication in the New England Journal of Medicine (NEJM).[2, 3] In this study, first-line ART regimens TAF/emtricitabine (FTC)/DTG and tenofovir disoproxil fumarate (TDF)/FTC/DTG showed non-inferior efficacy compared with TDF/FTC/EFV at week 48.

Unlike registrational studies, ADVANCE participants reflect the population that will be treated in LMICs.

Among participants who remained on their study ART, TDF/FTC/EFV potency was equivalent to that of the DTG regimens, despite significant reported background resistance in South Africa.

Participants receiving TAF/FTC/DTG had a higher risk of developing obesity.

ADVANCE is a 96-week phase 3, investigator-led, open-label randomised trial, comparing TAF/FTC/ DTG and TDF/FTC/DTG with the local standard-of-care of TDF/FTC/EFV.

The study enrolled ART-naive adults and adolescents ages 12 years and above with viral load greater than 500 copies/mL. The primary endpoint is the proportion with viral load less than 50 copies/mL at 48 weeks.

A total of 1053 participants were randomised between February 2017 and May 2018: 99% black, 59% female, mean age 32 years, with mean CD4 count 337 cells/mm3.

At week 48, the respective proportions of participants with viral load less than 50 copies/mL were: 84% for TAF/FTC/DTG, 85% for TDF/FTC/DTG, and 79% for TDF/FTC/EFV, confirming non-inferiority.

All three regimens were well tolerated, with slightly greater toxicity and rate of discontinuation in the TDF/FTC/EFV arm. There were no differences in sleep or clinical events between arms, and modest differences in laboratory measures.

TAF/FTC/DTG had less effect on bone density and renal function than other regimens. Weight increase (both lean and fat mass) was greater when DTG and TAF were used together and for women.

Week 96 data from ADVANCE will be presented in 2020.

The investigators are planning to continue the study beyond 96 weeks, particularly to look at weight gain and whether this can be reversed.

NAMSAL

NAMSAL results were first presented in 2018 and published in the NEJM in 2019.[4,5,6] like ADVANCE, participants reflect the population that will be treated in LMICs. NAMSAL also includes a considerable proportion with high baseline viral load who are less likely to achieve a fully suppressed viral load.

Findings from the study were shown at Glasgow 2018: at week 48, DTG-based first-line ART was non-inferior, but not superior, to that with EFV 400 mg.

Of 613 participants, approximately 70% achieved viral load suppression. But

people with high viral load at baseline (greater than 500,000 copies/mL) had poor virological response with less than 60% achieving less than 50 copies/mL in both arms.

Baseline characteristics were similar across both arms: 68% of participants were women, median age was 36 years, CD4 count was 281 cells/mm3, and viral load was 5.3 log copies/mL. A considerable proportion of participants had high viral load at baseline: 66% had greater than 100,000 copies/mL and 30% had greater than 500,000 copies/mL.

At week 48, the proportion of participants with viral load less than 50 copies/mL was 74.5% in the DTG arm and 69.0% in the EFV 400 mg arm: p=0.13 for the superiority test.

Among participants with baseline viral load less than 100,000 copies/mL, the respective proportions were 91.3% and 83.5%.

And for participants with greater than 100,000 copies/mL at baseline, the respective proportions were 66.2% and 61.5%.

Of participants with greater than 500,000 copies/mL at baseline only 54.8% and 57.9% in the DTG and EFV 400 mg arms respectively, achieved viral load suppression.

Viral load greater than 100,000 copies, CD4 count less than 200 cells/mm3, and male sex were associated with viral load greater than 50 copies/mL at week 48.

Among participants presenting with high viral load at baseline, the investigators observed persistently low viral replication rates in both arms.

Adherence was good in the study – greater than 80% in both arms.

NAMSAL will continue until 2021 to ensure long-term monitoring of participants who started DTG.

Dolutegravir preconception and pregnancy

On 18 May 2018, 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.[7]

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.[8, 9] 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.[10] 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 periconception analysis revealed four cases of neural tube defects out of 426 births to women who became pregnant while taking DTG.

This rate of approximately 0.9% compared 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 2018 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. [11, 12, 13, 14] The recommendations advised varying degrees of caution.

Tsepamo data were previously updated on 1 May 2018 to include 596 births to women receiving DTG at conception. No additional neural tube defects were reported in this group, bringing the interim reported rate to 4/596, 0.67%.

The most recent update, presented at IAS 2019 and published in the NEJM [15,16] reported 5/1683 neural tube defects among births to women receiving DTG at conception, a rate of 0.3%.

Since 1 May 2018 and as of 31 March 2019 the study accrued data on an additional 29,979 deliveries including 1,257 to women on DTG at conception.

Of the total study population there were 98/119,033 neural tube defects, a rate of 0.08% (95% CI 0.07 to 0.10). For DTG at conception the rate was 0.3% (95% CI 0.13 to 0.69) and for non-DTG at conception 15/14792, 0.1% (95% CI 0.06 to 0.17).

The prevalence of neural tube defects with DTG at conception remains higher than all other exposure groups but the estimated difference is small (0.2–0.27%). Compared with all other ART at conception, the 95% CI indicates that this difference is as low as 0.1% and as high as 0.67%.

Tsepamo surveillance continues and DTG at conception exposures continue to accrue without notable decrease (240 since 31 March 2019).

Tsepamo remains the most informative dataset on which to base guidance and policy.

As far as other datasets are concerned, programmes have been looking at this issue for DTG (as well as other integrase inhibitors) and some data from small,

and mostly high-income country cohorts were presented at HIV Glasgow 2018 and CROI 2019.[17,18]

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. [19, 20, 21]

Similar programmes to Tsepamo are in place in Uganda and Malawi.[22] But the transition to DTG is only just beginning so neither country has much to report yet.

Brazil has been using DTG in its national programme since early 2017, and has an excellent reporting system and is analysing these data.[23] No neural tube defects among 382 women on DTG at conception were reported in Brazil at IAS 2019.[24]

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).[25] 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 interim reports now include supplementary information on periconception integrase inhibitor exposure.

Data presented at EACS 2019 [26] showed that by 31 July 2019, 667 pregnancies with exposure to DTG were prospectively reported to APR: 357 periconception (defined as 2 weeks before through 28 days after conception) exposures, 67 later during the first trimester, and 243 during the second/third trimesters.

Among the 667 DTG exposed pregnancies there were 614 live singleton births: 312 with periconception exposure, 63 later during the first trimester, and 239 during the second/third trimesters.

There were 21/614 defects overall: prevalence 3.4% (95% CI 2.1 to 5.2). With

periconception exposure there were 10/312 defects: prevalence 3.2% (95% CI 1.6 to 5.8). Defect prevalence for later first trimester and second/third trimester were both similar and not above the expected population rate.

There was 1/312 neural tube defect case of anencephaly with periconception DTG exposure.

Although 1/312 gives an neural tube defect prevalence of 0.3%, similar to data from the Tsepamo study, the number of periconception outcomes is not sufficient (2000 needed to rule out a 3-fold increase) to refute or confirm an association between DTG and neural tube defects.

Most of the reports in the APR come from US, where there is national food folic acid fortification which has been shown to reduce neural tube defect risk by 36–68% in the general population.

And, although one neural tube defect is reported in this data set, the denominator is too small to draw any conclusions about an association between periconception DTG and neural tube defectss.

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 no neural tube defects.[27, 28, 29] EPPICC is 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.

Reports from Canada, Frankfurt and Eastern/Central Europe found no neural tude defects.[30, 31,32] But the numbers are very small.

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). [33] 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. A presentation at CROI 2019 looked at the complexities of extracting information from such databases.[34]

But using DTG later in pregnancy appears safe.[35]

And DolPHIN1, the pilot study to DolPHIN2, confirmed that standard dose of DTG should be used in the third trimester. [36]

DolPHIN1 and DolPHIN2 studies suggest there might be some advantages, in terms of viral suppression, to using DTG late in pregnancy.[37, 38] A significantly greater proportion of women achieved undetectable viral load starting a DTG-based regimen late in pregnancy, compared with one based on EFV. Median time to undetectable viral load with DTG was approximately half of that with EFV.

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.

WHO recommends DTG for women of child-bearing potential and recognition of their autonomy and right to make this choice with the relevant information.

And the IAS Forum on the risks of periconceptional dolutegravir exposure published FAQs,[39] also supporting access to DTG for women of child-bearing potential, designed to help provide context and to support public health and clinical decision-making bodies until there are more data available.

Dolutegravir and TB

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

Week 24 and 48 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.[40, 41] This study was not powered to make a comparison with EFV but conducted to obtain some data in people with HIV/TB.

Data from a PK sub-study of the NAMSAL study with DTG 50 mg given twice daily in the presence of RIF also supports this strategy.[42]

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.[43, 44]

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 50 mg twice daily to manage the drug interaction.[45]

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.

DTG can be given with short-course TB preventive therapy of 12 once-weekly rifapentine/isoniazid (3HP) without dose adjustment, according to data from the DOLPHIN (not to be confused with DolPHIN 1 and 2) trial, presented at CROI 2019.[46]

Dolutegravir and adverse events

DTG was better tolerated than EFV or darunavir/ritonavir (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.[47]

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.[48] 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.[49]

Another meta-analysis, suggested that treatment with integrase inhibitors appears to lead to greater increases in body weight than with other antiretrovirals.[50] The effect seems to be more pronounced for women and black people. There also might be an additional effect with NRTIs. But it is unclear yet whether these changes are clinically significant.

No clear conclusions emerged from (largely high-income country) data presented at CROI 2019 on this topic.[51]

But a pooled analysis of the ADVANCE and NAMSAL studies, presented at IAS 2019, found weight gain and clinical obesity for TAF/FTC/DTG and TDF/FTC/DTG compared with TDF/FTC/EFV.[52]

In this analysis, first-line DTG was associated with rises in body weight, clinical obesity, and increased trunk fat. Increased weight gain was higher in women and if used in combination with TAF/FTC. Rises in body weight on TAF/FTC/DTG appear to be progressive in black women.

Futher analysis from ADVANCE was presented at EACS 2019 and included 531 participants who had reached week 96.[53]

Approximately 25% of participants were overweight and 12% obese before starting ART.

In men, the mean change in weight at 96 weeks was: 5.9 kg, 3.5 kg and 1.2 kg in the TAF/FTC/DTG, TDF/FTC/DTG TDF/FTC/EFV arms respectively.

In women, the mean change in weight at 96 weeks was: 8.3 kg, 5.3 kg and 3.4 kg in the TAF/FTC/DTG, TDF/FTC/DTG and TDF/FTC/EFV arms respectively.

Factors associated with 10% or more increase in body weight were: TAF/FTC/DTG, baseline CD4, baseline viral load, female sex, age, and baseline weight.

Twenty-seven per cent of women in ADVANCE developed clinical obesity by

week 96 and there is no sign of a plateau in weight gain. The investigators are now calculating the potential effects of this weight gain on increased future risks. These results will be shown at CROI 2020.

Hyperglycaemia was reported in Uganda among people switching first-line regimens to DTG-based ART, in a letter to Lancet HIV, publised in February 2020.[54]

The report showed 16 of 3417 (0·47%) people receiving DTG-based ART had new-onset hyperglycaemia compared with 1 of 3230 (0·03%) receiving non-DTG ART (p=0·0004). Over 12 months this gave an incidence of 4·7 per 1000 vs 0·32 per 1000, in the DTG and non-DTG groups respectively.

Among the cases, hyperglycaemia events were severe (in 15 of 16) and the majority were preceded by weight loss after starting DTG rather than weight gain.

Median time from starting DTG to onset of hyperglycaemia was 4 months.

Longer term follow up and re-analysis of these and other studies and cohorts – particularly those representative of the global epidemic – is needed to evaluate consequences of weight gain/clinical obesity, hyperglycaemia and metabolic disorders.

This is particularly important in settings where pharmacovigilance is poor.

Efavirenz 400 mg

EFV 400 mg with two NRTIs is now the is now recommended by WHO as the alternative first-line – EFV 600 mg is no longer recommended, except in special circumstances.

The ENCORE 1 study, showed EFV 400 mg to be non-inferior to 600 mg (both plus TDF/FTC) as first-line ART.[55] The lower dose resulted in a modest reduction in EFV-related side effects 38% versus 48% with the standard dose.

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.[56] 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.[57, 58]

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

Reassuring real-life data from 271 women in Lusaka, Zambia, presented at IAS 2019, showed EFV 400 mg to be associated with high levels of maternal viral suppression (92%) during pregnancy.[59]

Notably this rate was higher than the previously reported suppression rates of 75% with EFV 600 mg in the same Zambian population, which might be due to the slightly improved tolerability of the lower dose.

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.[60]

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.

Tenofovir alafenamide

The first generic TAF-containing FDC was tentatively approved by the US FDA in 2018: DTG/FTC/TAF.[61, 62] This FDC might offer some programmatic benefits to LMICs including lower cost and smaller tablet size (easier to swallow, transport and store).[63]

But, lack of evidence, particularly for use in pregnancy and with TB coinfection, has meant that TAF is only just included (with an honourable mention) in WHO guidelines and is not included in the WHO Essential Medicines List (EML).[64]

And participants of the Third Conference on Antiretroviral Drug Optimisation (CADO 3), held at the end of 2017, did not consider TAF to be supported by sufficient evidence to inform use in LMICs.[65, 66]

TAF vs TDF

Results from a meta-analysis of TDF vs 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[67, 68] 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 will largely be used unboosted in LMICs.

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 tenofovir-diphosphate (TFV-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.[69, 70]

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.[71, 72, 73]

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

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

The first publicly presented clinical data on TAF in pregnancy are from IMPAACT P1026s – an ongoing, non-randomised, open-label, multi-centre, phase 4 study conducted to characterise antiretroviral PK in HIV positive pregnant women.[74]

TAF exposures during pregnancy were within the typical range of those in non-pregnant adults but higher than expected postpartum when dosed at 25 mg – according to data presented at AIDS 2018.

TAF is given at a dose of 25 mg unboosted and 10 mg when boosted with 150 mg COBI in ART regimens.

Target TAF exposure was assessed relative to the 10th percentile value in non-pregnant adults.

There were 31 participants receiving TAF 25 mg and 27 TAF/COBI 10/150 mg. Postpartum sampling was performed at a median of approximately 9 weeks.

Plasma TAF exposures during pregnancy and postpartum were in the range of those observed in non-pregnant adults. TAF exposure with 25 mg was lower during pregnancy compared with postpartum but this difference was driven by higher than expected AUC postpartum.

Congenital anomalies, considered possibly related to study drugs, included left congenital pseudarthrosis clavicle in one infant and renal cyst in another.

In a further analysis from IMPAACT P1026s, plasma exposures to TAF 25 mg with PK boosters did not differ significantly between third trimester and postpartum, although confidence intervals were wide.[75]

This group plan to look at look at intracellular levels of TAF in pregnancy and postpartum.

TAF reached the threshold of 200 first trimester exposed cases during the most recent reporting period of the APR.[76]

Prevalence of birth defects was calculated for the first time: 12 birth defects / 233 live births, 5.2% (95% CI 2.7–8.8) in the first trimester compared with 1 birth defect / 84 live births, 1.2% (95% CI 0.0–6.5) in the second/third trimester.

Although the prevalence in first trimester exposures is elevated, the lower end of the 95% CI is within the bounds of the 95% CI for background population prevalence.

Before TAF can be recommended for use in pregnancy additional safety and outcome data from larger numbers of women and their infants (including preconception exposure) are needed.

Following the potential periconception safety signal with DTG, programmes are likely to be more cautious about new drugs with limited periconception 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. WHO recommendeds DRV/r as part of second-line ART a heat-stable, co-formulated generic version remains elusive.

Although there has been little progress, DRV/r appears to still be a potential candidate for dose optimisation (although this will be discussed at CADO 4).

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.[77, 78, 79]

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.[80]

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 ritonavir (RTV).[81]

Data from Johannesburg, presented at AIDS 2018, found stable participants on a twice-daily lopinavir/ritonavir (LPV/r)-based second-line regimen who switched to a once-daily 400/100 mg DRV/r one maintained similar virological suppression to those who remained on LPV/r at 48 weeks.[82]

In this study, 300 participants, stable on 2 NRTI + LPV/r with viral load less than 50 copies/mL, were randomised to 2 NRTI + DRV/r 400/100 mg once daily or to continue on their LPV/r-based regimen. The study defined treatment success as viral load less than 50 copies/mL at week 48.

At baseline participants were 68% women and 99.7% black, with median of age 42 years, and CD4 count greater than 600 cells/mm3.

In the primary efficacy analysis, viral load less than 50 copies/mL by week 48 was 95.3% in the DRV/r arm versus 93.4% in the LPV/r arm.

DRV/r at the lower dose of 400/100 mg once daily showed non-inferior efficacy to LPV/r in this switch study.

These results support further studies with low dose DRV/r, including in PI-naive second-line patients.

Optimised DRV/r 400/100 mg could be cheaper to produce than LPV/r and atazanavir/r.

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.[83, 84]

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

Giving DRV/r with RIF is complicated. Double doses of DRV/r with RIF were associated with unacceptable risk of hepatotoxicity and a reduction in DRV trough concentrations in a PK study, in HIV positive people without TB, conducted in South Africa, and presented at CROI 2019. [85]

The study was stopped before completion due to the high rates of hepatotoxicity.

What is planned or ongoing?

First-line

The main two African investigator-led studies to look at DTG-based regimens in closer-to-real-life settings have presented week 48 data (as shown above) and are ongoing.

ADVANCE is 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 is comparing DTG-based to EFV 400 mg based regimens, conducted in South Africa and Cameroon respectively.[86, 87, 88, 89, 90]

Table 2: First-line ongoing and planned

STUDY/COHORT	DESIGN	PURPOSE	STATUS
ADVANCE WRHI 060 Ezintsha, Wits RHI (USAID, Unitaid)	Phase 3 DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF non-inferiority, open label 1053 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 Week 48 data presented IAS 2019 DTG-based regimens non-inferior to EFV-based Completion Q1 2020 Two years extension after 96 weeks (funding application stage)
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 presented HIV Glasgow 2018 DTG arm non-inferior to EFV 400 Concern about suppression rates in participants with high BL VL Long term follow up to 2021

Key: ABC, abacavir; ART, antiretroviral treatment; ARV, antiretroviral; BL, baseline; 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

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.

Pregnancy

VESTED (IMPAACT P2010) is recruited and ongoing. The study is making the same three-arm comparison as ADVANCE but in pregnant women.[91, 92]

The primary efficacy analysis will be presented at CROI 2020 as a late breaker.[93]

DolPHIN2 is 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] First results with all deliveries were presented at CROI 2019.[96]

These results showed, women living with HIV starting DTG-based ART after presenting in late pregnancy achieved more rapid virological suppression before delivery than those who started with an EFV-based one.

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.[97], [98], [99], [100] Data have been presented previously for DTG and TAF.

A ViiV-sponsored study is enrolling ART-naive women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.[101], [102] Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.

IMPAACT 2026, also looking at PK in pregnancy and post-partum,and starting imminently, will include TAF 10 mg boosted and 25 mg arms.[103]

Table 3: 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	Recruited First results presented at CROI 2019. More rapid virological suppression before delivery with DTG vs EFV 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)	Recruited First results CROI 2020 Primary completion 31 July 2020

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 4: 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 presented at AIDS 2018 TAF exposures during pregnancy within typical range in non-pregnant adults; higher than expected PP with 25 mg Looking at intracellular levels

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 11/16 recruited Primary completion December 2020
VESTED IMPAACT P2010	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)	Recruited First results CROI 2020 Primary completion 31 July 2020

IMPAACT 2026 NIH (NIAID)	Phase 4 PK properties of ARV and anti-TB drugs during pregnancy and PP TAF 10 mg boosted TAF 25 mg without boosting TAF 25 mg boosted Up to 28 women to achieve 25 (target) 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 (US and international)	Primary endpoint: PK 2nd /3rd trimester Secondary endpoints: PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes	Will begin recruiting 2020 Total study duration 5 years

Key: AIDS 2018, 22nd International AIDS Conference; ART, antiretroviral treatment; ARV, antiretroviral; 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

Tuberculosis

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

Table 5: Dolutegravir and TAF TB – ongoing + planned

STUDY	DESIGN	PURPOSE	STATUS
DTG 50 mg/RIF UCT (Wellcome)	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	Recruiting
EpiTAF UCT/ Ezintsha, Wits RHI (Unitaid)	30 HIV/TB-coinfected participants	TAF/RIF PK in HIV/TB coinfection	Recruiting

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.[104, 105]

Participants were genotyped at screening and only those with at least one predicted active NRTI were included. The LPV/r arm of 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, were shown at AIDS 2018 with similar results.[106]

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.

These discussions are also important for people currently on EFV-based first-line who will be switched to TDF/3TC/DTG in the absence of viral load monitoring.

Indirect evidence suggests that recycling the TDF/3TC backbone from first- to second-line could be achieved without resistance mutations to DTG.

The ARTIST study [107] – ongoing in Cape Town – is a randomised, open-label, controlled trial to determine the virological suppression in participants failing first-line TDF/XTC/EFV who are switched to a DTG based second-line with a recycled TDF/3TC backbone.

It is in two stages: stage 1 with a supplemental dose of DTG for 14 days to compensate for the enzyme-inducing effect of the discontinued EFV; and stage 2 compares TDF/3TC/DTG (50 mg) to the WHO-recommended second-line regimen (AZT/3TC/DTG).

VISEND – ongoing in Zambia and Zimbabwe – is comparing short- (24 and 48 weeks) and long-term (72, 96 and 144 weeks) virological outcomes in ART-treated adults switched from TDF/XTC/EFV or NVP-containing regimens to TDF or TAF/XTC/DTG-containing regimens with and without virologic suppression at time of switch.[108]

Importantly this study will also provide some real-life African data on TAF, including in a regimen with DTG.

ACTG 5381 is an observational cohort, also recruiting, that will assess efficacy and emergence of resistance following the initiation of TDF/3TC/DTG first- or second-line or with RIF-containing TB treatment.[109] The study is multinational with sites in: Haiti, Kenya, Malawi, South Africa, Uganda, and Zimbabwe.

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.[110]

The NADIA study is investigating DTG vs DRV/r once daily with a second factorial with TDF/XTC vs AZT/3TC.[111]

PK data to guide the use of DRV/r with TB treatment are missing and the DARifi PK study compared 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. First data was shown at CROI 2019, where the study was stopped for hepatoxicity, and this remains complicated.[112]

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.

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

STUDY	DESIGN	PURPOSE	STATUS
D2EFT Kirby Institute (Unitaid, NIAID, 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 12 years and above 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 copies at 96 weeks Interim analysis at 48 weeks	Recruiting Primary completion December 2020

ARTIST UCT (MSF/Wellcome Trust)	Phase 4 195 participants >18 years failing EFV-based 1st line Randomised, open-label, controlled trial Stage 1: TDF/3TC/DTG with an extra 50 mg DTG for 14 days (n=65) Stage 2: TDF/3TC/DTG (50 mg) vs AZT/3TC/DTG (n=130/65 per arm) 48 weeks Cape Town	VS in participants failing 1st-line TDF/XTC/EFV switched to a DTG based 2nd-line with recycled TDF/3TC Primary endpoint: Stage 1 VL <50 copies at 24 weeks Stage 2 VL <50 copies at 24 weeks	Recruiting Primary completion 31 December 2020
VISEND University Teaching Hospital, Lusaka/ Parirenyatwa Hospital, Harare (Mylan)	Phase 3 1254 participants >18 years switching from EFV- or NVP-based 1st line Randomised control trial Arm A1: TDF/3TC/DTG, BL VL <1000 copies/mL (n=209) Arm A2: TAF/3TC/DTG, BL VL <1000 copies/mL (n=209) Arm B1a: TDF/3TC/DTG, BL VL >1000 copies/mL (n=209) Experimental Arm B1b: TAF/3TC/DTG, BL VL >1000 copies/mL (n=209) Experimental Arm B2a: AZT/3TC/LPV/r, BL VL >1000 copies/mL (n=209) Arm B2b: AZT/3TC/ATV/r, BL VL >1000 copies/mL (n=209) 144 weeks Zambia and Zimbabwe	Compare short- (24 and 48 weeks) and long-term (72, 96 and 144 weeks) virologic outcomes in adults switched from TDF/XTC/EFV or NVP-containing ART to TDF or TAF/XTC/DTG-containing regimens with and without virologic suppression at time of switch Primary endpoint: >1,000 copies/mL at week 144	Recruiting

ACTG 5381 NIAID/PEPFAR	Observational cohort 1350 participants >10 years starting TDF/3TC/DTG: Group 1. Switch from NNRTI-based 1st line (n=540): 1a VL >1000 copies/mL; 1b VL< copies/mL Group 2 (n=540). Switch from PI-based 2nd-line: 2a VL >1000); 2b <1000 copies/mL Group 3 (n=90). With RIF-containing TB co-treatment + additional 50mg DTG. Group 4. ART-naive 10% adolescents 10–19 years Haiti, Kenya, Malawi, South Africa, Uganda, and Zimbabwe 36 months	Assess efficacy and emergence of resistance after starting TDF/3TC/DTG 1st- or 2nd-line ART or with RIF-containing TB treatment	Recruiting

Key: ACTG, AIDS Clinical Trials Group; ART, antiretroviral treatment; ATV/r, atazanavir/ritonavir; 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; MSF, Médecins Sans Frontières; MU, Makerere University; NIAID, National Institute of Allergy and Infectious Diseases; NNRTI, non-nucleoside reverse transcriptase inhibitor; NRTI, nucleos/tide reverse transcriptase inhibitor; NVP, nevirapine; PEPFAR, United States President's Emergency Plan for AIDS Relief; SAHPRA, South African Health Products Regulatory Authority; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UCT, University of Cape Town; VL, viral load; VS, virological suppression; XTC, lamivudine or emtricitabine; 3TC, lamivudine

What to watch out for at CROI 2020 and next steps

Results from key ART optimisation studies to look out for at CROI 2020:

- First safety and efficacy data from the VESTED trial (oral late breaker presentation) [113]
- Risks of metabolic syndrome, diabetes and cardiovascular disease in the ADVANCE trial (oral presentation) [114]
- Postpartum weight changes in women starting DTG vs EFV in pregnancy: DolPHIN2 trial (poster presentation) [115]
- Risk of treatment-emergent resistance and the effect of pretreatment resistance in the ADVANCE trial (poster presentations) [116], [117]

The conference will also show a wealth of related data on currently recommended drugs, regimens and strategies across populations as well as new componds in the pipeline (see below).

The upcoming CADO 4 meeting will examine what we know, the evidence gaps and potential roles for new drugs and strategies in LMICs. The meeting will produce a list of research recommendations and priority drugs and regimens.

We will include recommendations from CADO 4 in the next edition of Fit for Purpose.

References

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 Organization

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HIV pipeline 2020: new drugs in development

By Simon Collins, HIV i-Base

Introduction: eight months since IAS 2019

This report is based on new developments over the last eight months since we produced the pipeline report for the IAS conference in July 2019.[1]

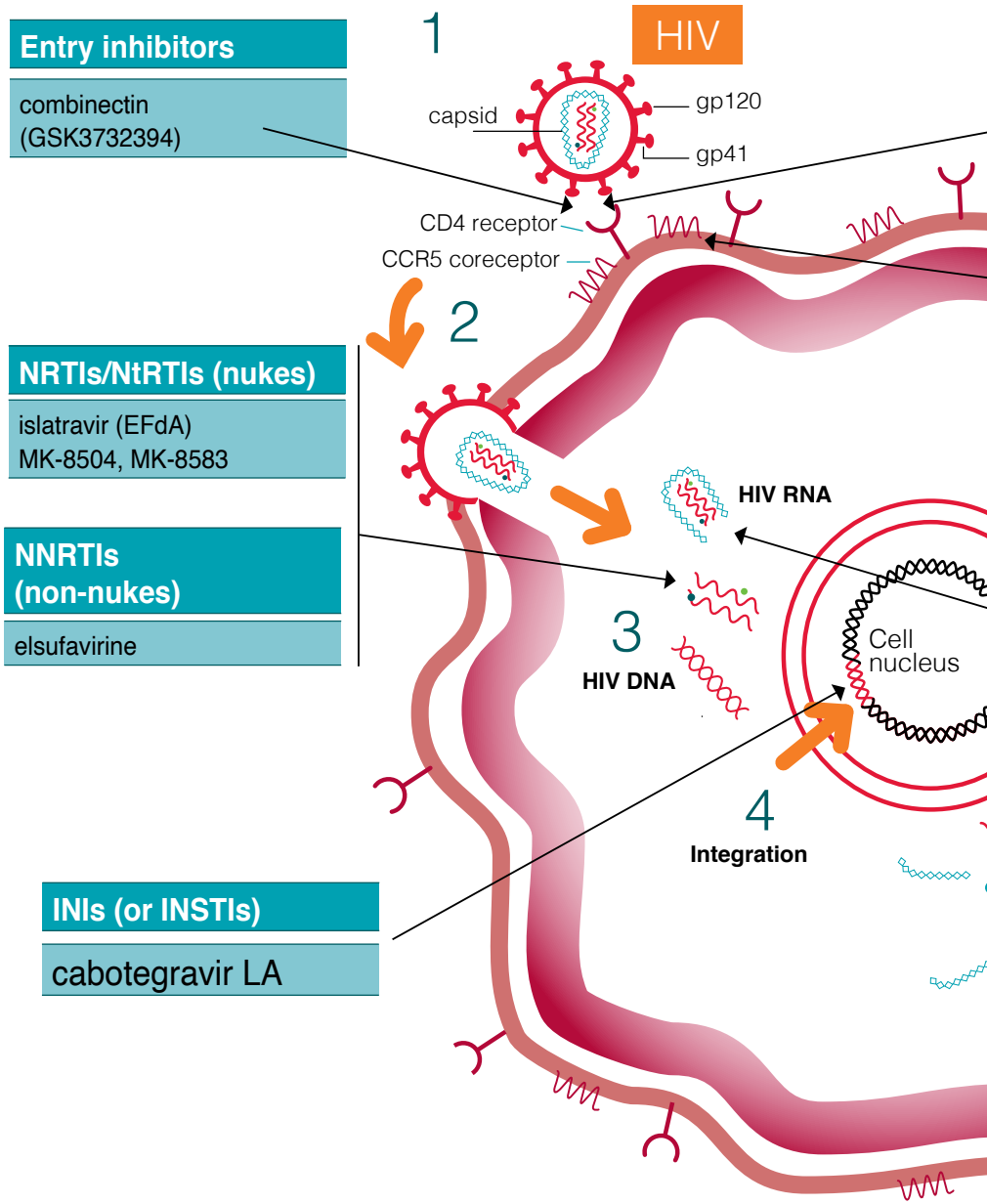
These include the move towards simplified ART and long-acting compounds in several drug classes that allows less frequent dosing than daily oral ARVs.

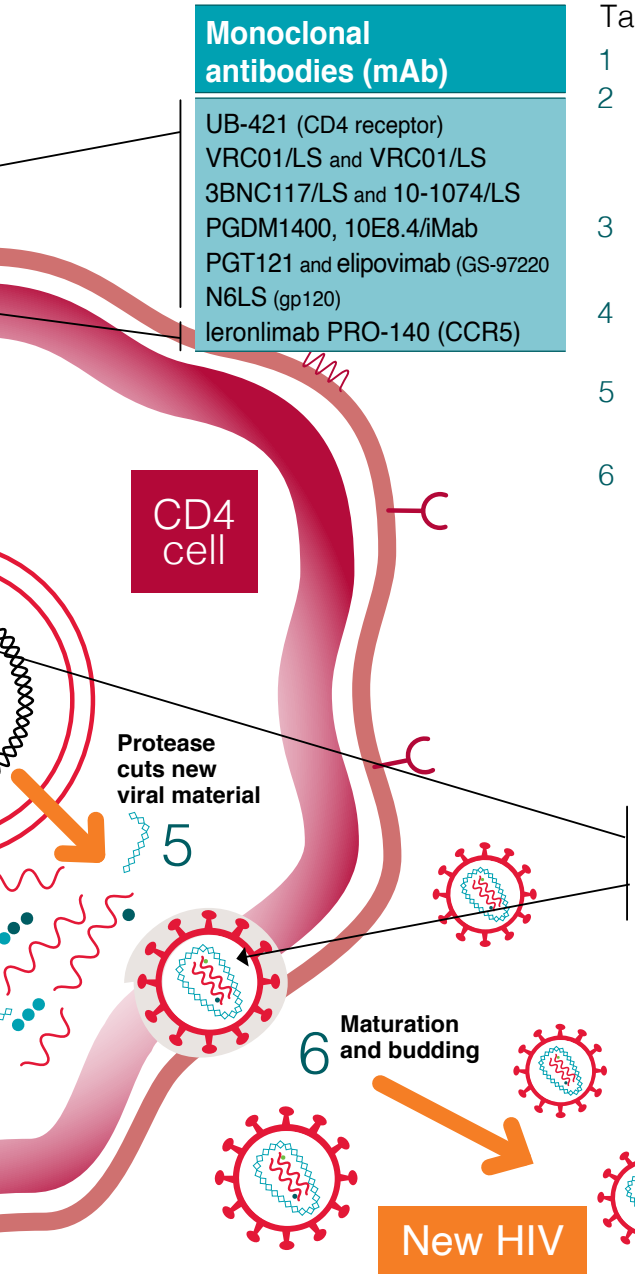
New developments also include using bNAbs as a rescue treatment for people with multiclass HIV resistance. So, while ibalizumab has already been approved with an orphan-drug designation for multidrug resistance, this potential is shared with dozens of other bNAbs and other new classes including long-acting capsid inhibitors.

It is notable that the companies developing new drugs for treatment and prevention are also investing in HIV cure.

The report also references 30 studies at CROI 2020 that cover a wide range of pipeline compounds. These include islatravir, MK-8504 and 8583, bNAbs (including VRC01, PGT-121, GS- 9722, 3BNC117, 10-1074, N6-LS), GS-6207 (capsid inhibitor), GSK3640254 (maturation inhibitor), elsulfavirine, combinectin, ABX464, BIT255 and GS- 9131.

Figure 1: HIV pipeline 2020: targets in the HIV lifecycle





Targets in the HIV lifecycle

1. HIV attaches to a CD4 cell.
2. HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
3. Reverse transcriptase (RT) makes double strand HIV.
4. Integrase enables HIV to join the cell DNA.
5. Protease cuts and reassembles new HIV.
6. Final stages include maturation and budding as each cell produces hundreds of new virions.

Rev inhibitor

GS-PS1

Capsid inhibitors

GS-6207
GSK (preclinical)

Maturation inhibitor

GSK' (oral)
GSK '937 (LA)

Regulatory approvals and submissions

Recent approvals include the HIV monoclonal antibody ibalizumab (Trogarzo) in the EU (18 months after approval in the US).[2, 3] See Table 1.

Table 1: Recent regulatory approvals and submissions

COMPOUND/ FORMULATION	CLASS	APPROVED / SUBMITTED	COMPANY
ibalizumab	bNAb.	Approved US: April 2018. Approved EU: Sep 2018.	Theratechnologies
fostemsavir	gp120 attachment inhibitor.	Submitted US: Dec 2019. Submitted EU: Jan 2020.	ViiV Healthcare
cabotegravir LA and rilpivirine LA injections	INSTI + NNRTI injections.	Submitted US: Apr 2019 Submitted EU: July 2019	ViiV Healthcare Janssen
Cabotegravir oral	INSTI - oral formulation used for lead-in dosing.	Submitted US: Apr 2019 Submitted EU: July 2019	ViiV Healthcare Janssen
elsulfavirine, prodrug of VM-1500A	NNRTI - similar activity to efavirenz. Long-acting monthly IM/SC injections. 96-week phase 2 results at AIDS 2018.	Apparently licensed in Russia. No published phase 3 data or submission to FDA or EMA.	Viriom

The gp-120 attachment inhibitor fostemsavir was submitted to the FDA in December 2019 and to the EMA in January 2020 based on 96-week results from the BRIGHTE study.[4, 5, 6]

However, the regulatory application for the long-acting injections of cabotegravir LA and rilpivirine LA (Cabenuva) was not approved by the FDA within the fast-track timeline.[7] This was unexpected given good results from the phase 3 FLAIR and ATLAS studies.[8] The decision was due to manufacturing problems from scaling up to industrial production and there are no safety and efficacy concerns. Ongoing studies are already looking at practical issues of using these injectable drugs.[9, 10, 11]

ViiV has also submitted a new application to the FDA for a switch indication for the dual combination of dolutegravir/lamivudine (Dovato), based on 48-week results from the phase 3 TANGO study, presented at IAS 2019.[12, 13]

Dolutegravir/lamivudine was approved in the EU as first-line ART in July 2019[14] and extended follow-up to 96-weeks for the GEMINI 1 and 2 studies in treatment naive participants were presented at IAS 2019.[15]

Updates from CROI 2020 include looking at the importance of other background drugs with ibalizubmab.[82] *It also includes results from the ATLAS-2M study reporting that cabotegravir/ rilpivirine LA injections can be used every two months and several studies*[83] *About a dozen posters will look at dual ART, largely dolutegravir/lamivudine, including updates from the phase 3 GEMINI and TANGO studies.*[84, 85, 86]

Compounds in development by class

Integrase inhibitors

cabotegravir LA

The 2019 pipeline report summarised the clinical efficacy and safety of long-acting cabotegravir and rilpivirine injections and the regulatory complications are discussed above.[1]

However, the US National Institute for Allergy and Infectious Diseases (NIAID) recently announced a new study using cabotegravir LA (without rilpivirine) in a dual combination with VRC07-523LS - a long-acting bNAb.[16, 17]

ViiV also recently announced an agreement to develop another bNAb developed by NIAID called N6LS (see later below).[18]

Cabotegravir is also being developed as a 6-monthly PrEP implant.

NRTIs

islatravir (EFdA)

Islatravir is an NRTI in development by Merck that is notable for very high potency, a long plasma half-life (~120 hours) that allows weekly and perhaps monthly oral dosing and a slow-release removable implant that might only require annual dosing.

Ongoing studies are for use as both treatment and PrEP. It is classified as a

nucleoside reverse transcriptase translocation inhibitor (NRTTI) and has multiple mechanisms of action.[19]

New results on islatravir both as treatment and PrEP were presented at IAS 2019.

A phase 2b dose-ranging study led to selecting the 0.75 mg daily dose. It also provided first data on dual therapy with islatravir and doravirine.[20, 21]

Phase 3 studies using a two-drug fixed dose combination of doravirine/islatravir are already planned or ongoing.[22, 23, 24]

Details on once-weekly oral dosing dual ART, with another long-acting compound in pre-clinical development not been announced (but see MK-8504 and MK-8683 below).

Islatravir PrEP studies include an ongoing phase 2 study using an oral formulation for once-monthly dosing.[25] If this is effective, it will have the potential to significantly expand the indication for PrEP from a relatively small group of people at high risk of HIV to the billions of people globally who are sexually active but whose HIV risk is much smaller.

IAS 2019 included results on an islatravir implant for PrEP (now at the 62 kg dose).[26]

Updates from CROI 2020 include a late breaking oral presentation on PrEP efficacy in a macaque study using weekly oral islatravir and two posters related to metabolic outcome and dose selection.[87, 88, 89]

MK-8504 and MK-8583

There are few details on the other long-acting compounds Merck plans to study islatravir with, but MK-8504 and MK- 8583 are two tenofovir prodrugs studies in HIV positive phase 1 studies.

A single dose of MK-8504 (100 mg or 240 mg) produced reductions in viral load of about –1.0 log (range +0.5 to –1.5) copies/mL.[27]

Results have not yet been published for MK-8583.[28]

Updates from CROI 2020 include a poster on these two compounds reporting on antiviral efficacy from single doses.[90]

GSK NRTTI

GSK have also filed several patents for NRTTI compounds that are currently pre-clinical stages with plans to formulate these as a long acting injection.

bNABs

A growing number of HIV broadly neutralising monoclonal antibodies (bNAbs) are now in development (with more to follow) engineered to improve potency, breadth of coverage and half-life etc.

They generally need to be used in combinations and also require sensitivity testing at baseline to know whether or not they are likely to be active. These sensitivity tests are also in early stage development.

Long-acting formulations – called LS from the two mutation changes – bring the potential of extended dosing schedules from 2 to 6 months.

Drug resistance has so far reported for all individual bNAbs, and strategies to reduce this risk include use of combination bNAbs and engineering bispecific or trispecific compounds.

Although there have been few new clinical studies presenting new data since CROI 2019, several new studies have been launched and both ViiV and Gilead have announced licensing rights to develop some of the most promising bNAbs.

The number of studies referenced below for each of the most promising bNAbs show the research interest in this field but is unlikely to be comprehensive. An updated table of these and other compounds is produced by Richard Jefferys at

TAG as part of a resource on cure-related trials.[29]

CROI 2020 includes several studies looking at bNAbs in general including baseline susceptibility, tissue penetration (including CSF). Several studies related to aspects of individual compounds in adults and infants, including leronlimab, VRC01, N6-LS and 3BNC117.[91, 92, 93, 94, 95, 96, 97, 98]

leronlimab (PRO140)

Leronlimab is a humanised IgG4 monoclonal antibody that blocks HIV entry by binding to CCR5 but is active against maraviroc-resistant virus.

This compound has been in development for more than a decade and is being studied as part of ART and as monotherapy after viral suppression on oral ART.

Ongoing studies include a phase 2/3 study in 25 treatment- experienced participants.[30]

A much larger US phase 2b/3 study has enrolled more than 550 HIV positive participants on stable ART.[31, 32]

According to a more recent press release from August 2019, more than 150 participants have maintained undetectable viral load out to one year. The study completion date is listed as July 2020.[33]

Leronlimab is also being studied in non-HIV setting as prophylaxis against graft vs host disease (GVHD) in people undergoing allogeneic stem cell transplant.[34]

Leronlimab is being developed by CytoDyn.

CROI 2020 includes a poster on use in four-class resistance.[92]

UB-421

UB-421 is a broadly neutralising mAb that targets CD4 binding. In vitro data suggest comparable or greater potency compared to other compounds, including VRC01 and 3BNC117.

Results from a phase 2 study were published in the New England Journal of Medicine in April 2019. This used UB-421 monotherapy during an 8-week treatment interruption. UB-421 was given by infusion every two-weeks.[35]

Several studies are listed as expected to start in 2020. Although the same studies have been listed since 2017 with the starting dates changing each year.[36, 37, 38] These include adding UB-421 to ART to reduce the HIV reservoir and a phase 3 switch study to UB-421 monotherapy.

UB-421 is being developed by United BioPharma with all sites in Taiwan.

No updates are expected at CROI 2020.

VRC01 and VRC01LS

VRC01 is an early broadly neutralising mAb (active against 80–90% HIV strains) that targets the CD4 binding site. It can be given by infusion or sub-cutaneous injection and has been studied in phase 1/2 development with multiple indications: for treatment, prevention and as a component of cure research.

Most ongoing studies are looking at VRC01 for HIV prevention, with two large international dose-finding, placebo-controlled phase 2 studies using VRC01 as PrEP.[39, 40]

Although results are expected in late 2020 there are concerns about using a single mAb given limited breadth and potency from one compound.[41]

VRC01 is being studied as part of a dual bNAb combination with 10-1074 in a phase 1 study in 75 HIV positive people on suppressed ART who will be asked to stop HIV treatment.[42]

A phase 1 study is looking at VRC01 with ART in 25 HIV positive people diagnosed during primary infection, with sites in Kenya, Tanzania and Thailand.[43]

The long-acting formulation VRC01LS is also in phase 1 studies. This includes using a single injection of VRC01LS in infants after birth to limit risk of vertical transmission and a potential role of additional injections for breastfed infants.[44, 45]

Another phase 1 study is looking at responses to VRC07 in eight people who received VRC01LS.[46]

CROI 2020 includes studies on VRC01 tissue penetration and use as infant prophylaxis.[93, 94, 95, 96]

VRC07 and VR07-523LS

VRC07 is an engineered clonal relative to VRC01 and includes VRC07-523LS which is a second-generation bMAb with improved potency, breadth, expression and a LS version to extend the half-life.

Results from a phase 1 safety study in 26 HIV negative participants was published in Lancet HIV in October 2019.[47]

It is now being studied alone and in combination with other bMAbs including 10E8VLS, PGT121 and PGDM140 in at least seven studies, usually phase 1 in HIV negative participants. However, this also includes a study in HIV-exposed infants and at least two studies in HIV positive adults.[45, 48, 49]

A new ACTG study (ACTG 5837) was announced that uses cabotegravir-LA every 4 weeks with VRC07-523LS every two months.[50]

NIAID have also granted TaiMed a non-exclusive license to develop VRC07-523LS in combination with the company's other bNAbs.[51]

No updates are expected at CROI 2020.

PGT-121 and GS-9722 (elipovimab)

PGT121 is an IgG1 mAb that targets the V3 Env epitope. Results from a randomised double blinded, dose escalation, placebo-controlled phase 1 study were presented at CROI 2019.[52]

Results in 15 treatment-naive participants, reported that a single infusion of PGT121 produced a median viral load reduction of –1.7 log copies/mL in participants with high baseline viral load, but breakthrough with bNAb resistance also occurred quickly when used as monotherapy.

Two phase 1 studies in HIV negative participants are ongoing but a third phase1/2 study with other bNAbs includes HIV positive participants.[49]

PGT-121 was licensed from IAVI/Theraclone to Gilead in 2014 who developed a derivative called elipovimab (GS-9722), which was also reported at CROI 2019.[53] No ongoing or planned studies are currently listed for elipovimab.

Studies at CROI 2020 include new animal data on PGT-121 and looking at the viral reservoir and viral rebound and results from a phase 1 PK study of GS-9722 in HIV positive people.[99, 100, 101, 102]

3BNC117, 10-1074 and LS formulations

3BNC117 targets the CD4 binding site and 10-1074 targets the base of the V3 loop of the HIV envelope protein so in combination there is no cross resistance.

Both bNAbs were developed at Rockefeller University. When used together, a study at CROI 2019 reported that 2/13 participants maintained viral load below detection for over a year after interrupting ART, with one person extending this to two years.[54]

Both bNAbs are now engineered into long-acting LS formulations that might enable 6-monthly infusions. It is significant that in January 2020, Gilead

announced it had signed licensing agreement for both exclusive and global development rights.[55, 56]

Several phase 1 studies are already ongoing using this combination in HIV positive participants, two of which include treatment interruptions.[57, 58, 59, 60]

A UK placebo-controlled study is also using both long-acting bNAbs to maintain viral suppression during a treatment interruption. The RIO study plans to enrol 75 HIV positive people who were diagnosed during primary infection and who started immediate ART.[61]

A phase 2 study uses 3BNC117 in combination with the fusion inhibitor albuvirtide (approved in China as a once-weekly formulation, similar to enfuvirtide) as maintenance therapy in 80 HIV positive participants on stable ART, in US sites.[62]

Studies at CROI 2020 on 3BNC117 include a reservoir study with romidepsin and on 10-1074 include a PK study on infant prophylaxis.[98, 94]

N6 and N6-LS

N6 is a bNAb also developed by the US NIH from the VRC01 class, engineered to have higher potency, active against 98% of isolates tested and also developed into a long-acting LS formulation.[63]

The only study currently listed is an ongoing phase 1 study in 40 HIV negative participants.[64]

In November 2019, ViiV Healthcare announced that it had negotiated an exclusive license to develop N6LS for both treatment and prevention of HIV.[65]

Studies at CROI 2020 include a phase 1 dose escalation study in HIV negative people, a CNS immune activation study in macaques and another looking at dynamics of viral rebound with TLR-7 antagonist GS-9620.[97, 99, 100]

Other bNAbs: 10E8, trispecific bNAbs, PGDM1400

Several other promising antibodies are in development.

10E8v2.0/iMab is a bispecific antibody that showed almost 100% neutralisation breadth across a 118-member pseudotyped panel with mean inhibitory concentration of 0.002 ug/mL. It has also prevented infection in mouse studies.[66]

A phase 1 dose escalation study using both IV and subcutaneous formulations includes HIV positive people not yet on ART (as well as HIV negative participants).[67]

However, while the safety and tolerability of bNAbs is generally good, one study using 10E8 was recently put on hold due to grade 3 skin erythema in 7/8 participants.[68]

Preliminary results for a trispecific bNAb were presented at CROI 2019. This is the result of a joint development by the Vaccine Research Centre at NIAID and Sanofi where a single molecule could interact with three independent envelope regions: the CD4 binding site, MPER and the V1V2 glycan site.[69]

PGDM1400-1412 is a range of bNAbs with high potency and PGDM 1400 is already included in two recruited ongoing phase 1 studies including HIV positive people in combinations with PGT- 121, VRC07-523LS and 10-1074.[70, 71]

A phase 1/2a study is also ongoing in HIV positive people in combination with PGT121, VRC07-523LS and PGDM1400.[49]

Capsid inhibitors

GS-6207

Capsid is the cone-shaped structural core within the HIV virion that protects HIV RNA and related enzymes. The capsid inhibitors are active in both early and later stages of the HIV lifecycle.

Phase 1 results with GS-6207 at IAS 2019 reported mean –2.2 log reduction at day 10 with GS-6207 monotherapy in treatment- naive participants (at which point ART was started).[72]

Further phase 1 results at EACS 2019 supported development of a modified six-monthly sub-cutaneous injection.[73]

A phase 2 study in 175 treatment naive participants will use oral GS-6207 to cover the first two weeks before using subcutaneous infusion of the capsid inhibitors, with oral F/TAF used throughout. However, when the infusion is repeated after six months, background F/TAF will be switched to dual ART with either daily oral TAF or daily oral bictegravir.[74]

A second study, also currently enrolling in US sites is a phase 2/3 study to GS-6207 with optimised ART in 100 treatment experienced people with multidrug resistance. A second cohort will run for people who don't meet criteria for initial randomisation, or for when this study is fully enrolled.[75]

Studies at CROI 2020 include an oral presentation and posters on antiviral activity and PK and another poster on resistance,[103, 104, 105, 106]

Maturation inhibitors

GSK3640254

The maturation inhibitor GSK3640254 works at the late stage of the viral lifecycle, by producing non-infectious, undeveloped HIV.

Results from two phase 1 studies in HIV negative adults that reported good safety outcomes and bioavailability of two different formulations were presented last year.[76] These supported further development as a once-daily oral pill.

A proof of concept, phase 2 dose-finding study is ongoing in 34 treatment-naive HIV positive participants.[77]

GSK 937 is a second maturation inhibitor compound in preclinical development as a long acting injectable formulation (both subcutaneous and intramuscular). Both compounds are being developed by GSK/ViiV.

Studies at CROI 2020 include a poster on preclinical development of second-generation maturation inhibitors.[107]

Other compounds

Although little data has been reported for the following compounds over the last year (at least), they are still in active development.

Elsulfavirine (VM1500-A)

Elsulfavirine (a prodrug of VM-1500A) is an NNRTI being developed by Viriom that is currently being used in Russia.[78]

A long-acting injectable formulation is in development, with results from an

animal study presented at IAS 2017, showing the potential for monthly by intramuscular (IM) or subcutaneous (SC) injection.[79]

CROI 2020 includes the first safety and PK results for the long- acting formulation of elsulfavirine.[108]

Combinectin (GSK3732394)

Combinectin (GSK3732394) is a biologic combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action on gp41 and CD4. This compound has the potential for self-administered once-monthly subcutaneous injections.

A summary of in vitro activity and resistance data and virologic data from mouse studies were presented at Glasgow 2016.[80]

In June 2019 the first phase 1 study in HIV negative volunteers started enrolling, with results expected mid-2020.[81]

CROI 2020 includes an oral presentation on combinectin.[109]

ABX464 - Rev inhibitor

ABX464 is an anti-inflammatory molecule thought to work by blocking the end stages of viral assembly.

HIV research is looking at strategies with compound to reduce the viral reservoir. The only other going studies related to use for ulcerative colitis, Crohn's disease and arthritis.

CROI 2020 includes a poster on ABX464 reducing HIV transcription and the viral reservoir.[110]

BIT225 - VPU

BIT225 is currently in phase 2 studies.

It is different to other experimental HIV drugs because it targets cells like macrophages and so is being used in addition to conventional ART to see whether it can reduce the viral reservoir.

CROI 2020 includes a poster on a phase 2 study of BIT225 in addition to ART.[111]

Development stopped or on hold

GS-9131 - NRTI

GS-9131 is an NRTI that is no longer being actively developed by Gilead.

CROI 2020 includes a poster on susceptibility of GS-9131 to drug resistant HIV-2.[112]

GS-PI1 - protease inhibitor

GS-PI1 is a once-daily unboosted protease inhibitor that is no longer being actively developed by Gilead.

Conclusion

Although there are now fewer large companies bringing new HIV drugs to market, Gilead, GSK/ViiV and Merck/ MSD all have long-acting molecules that cover both treatment and prevention, see Table 2. They are all running studies using dual-therapy ART.

Table 2: Compounds with long-acting formulations

COMPOUND	COMPANY
cabotegravir	ViiV Healthcare
islatravir	Merck/MSD
MK-8504 / MK-8583	Merck/MSD
bNAbs: including 3BNC117 and 10-1074; PGDM1400 and PGT121, 10E8.	Various including NIH/NIAID, Rockefeller University, ViiV Healthcare, Gilead Sciences.
GS-6207 (capsid)	Gilead Sciences
GSK '937 (maturation)	ViiV Heathcare
combinectin	ViiV Heathcare
elsulfavirine	Viriom

Although Janssen are not developing new HIV treatments, their HIV vaccine is currently in two large phase 3 studies.

It is notable that these companies are also focused on targeting the HIV reservoir and related cure research.

If successful, the compounds in the pipeline report should dramatically reduce HIV incidence and provide better treatment for people living with HIV who for whatever reason have difficulty with daily oral medicines. (See Table 3).

Table 3: Likely positioning for new drugs

INDICATION	NAME
treatment-naive	islatravir, doravirine/islatravir
switch options on ART	islatravir, doravirine/islatravir, cabotegravir LA/ rilpivirine LA, bNAbs,
multidrug resistance (MDR)	islatravir, bNAbs, new classes: capsid and maturation inhibitors.
PrEP	cabotegravir-LA; islatravir; VRC01, all other mAbs.
maintenance without ART	bNAbs - in combinations as switch after viral load suppressed on ART.

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