Fit for purpose

Antiretroviral treatment optimisation

HIV i-Base
July 2019

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 2018: 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-2018/

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Introduction

HIV i-Base produces Fit for Purpose annually for distribution at the International AIDS Society (IAS) conferences, with updates to coincide with other key HIV meetings.

We include a summary of new compounds in the pipeline.

This edition is for the the IAS 2019 Conference in Mexico City 21–24 July 2019.

The frequently-updated Op-ART trial tracker is available at:
http://i-base.info/op-art/

A more detailed version of the adult pipeline is available at:
http://i-base.info/htb/36278

i-Base's HIV Treatment Bulletin (HTB) reports from IAS 2019 and affiliated meetings will be available at:
http://i-base.info/htb/

A dedicated paediatric Fit for Purpose ART optimistaion review and pipeline will be available following IAS 2019 and the International Workshop on HIV Pediatrics 2019.

Fit for purpose: antiretroviral treatment optimisation

By Polly Clayden

Introduction

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

Key developments since July 2018 include:

- Week 48 data from ADVANCE and NAMSAL – two key ART optimisation trials of first-line dolutegravir (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
- World Health Organization (WHO) guidance recommending DTG-based regimens for adults and children (for whom approved DTG dosing is available) as preferred first-and second-line ART

World Health Organization guidelines 2019

New World Health Organization (WHO) recommendations, released on 22 July 2019 at IAS 2019, include dolutegravir (DTG) as the preferred antiretroviral drug in first- and second-line regimens. [1]

This recommendation recognises the declining estimate DTG-associated neural tube defect risk and observed efficacy.

The new policy brief is entitled: Update of recommendations on first- and second-line antiretroviral regimens July 2019. It is a forerunner to the revised 2019 WHO consolidated antiretroviral guidelines to be released later this year.

WHO now recommends tenofovir disoproxil fumarate (TDF)/lamivudine (3TC) or emtricitabine (FTC) (XTC)/DTG as the preferred first-and second-line ART regimen for adults, adolescents and children (with approved DTG dosing). Low dose efavirenz (EFV 400 mg) is now recommended for adults and adolescents as the alternative first-line ART.

Tenofovir alafenamide (TAF) is recommended in special circumstances for adults with established osteoporosis and/or impaired kidney function. It is recommended as part of an alternative first-line regimen for children of age and weight groups with approved dosing.

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, rapidly evolving evidence of safety and efficacy as well as programmatic data has accumulated on the use of DTG and efavirenz (EFV) 400 mg in pregnant women and people coinfected with TB.

Although risk of neural tube defects, associated with DTG, has declined since May 2018 it still remains slightly higher than with other ART exposure groups.

The new recommendations lift any previous restrictions on DTG for women of child-bearing potential. And WHO continues to emphasise the importance of a women-centred approach, providing women with up-to-date information on risks and benefits to make an informed choice.

The recommendations also highlight potential DTG-associated weight gain and the importance of a healthy diet and regular exercise to help manage weight.

See WHO ART recommendations Tables 1, 2 and 3.

Table 1: WHO recommendations July 2019

FIRST-LINE ART
1. DTG in combination with a nucleoside reverse-transcriptase inhibitor (NRTI) backbone may be recommended as the preferred first-line regimen for people living with HIV starting ART • Adults and adolescents (*strong recommendation, moderate-certainty evidence*) • Infants and children with approved DTG dosing (*conditional recommendation, low-certainty evidence*) 2. Efavirenz at low dose (EFV 400 mg) in combination with an NRTI backbone is recommended as the alternative first-line regimen for adults and adolescents living with HIV initiating ART (*strong recommendation, moderate-certainty of evidence)* 3. A raltegravir (RAL)-based regimen may be recommended as alternative first-line regimen for infants and children for whom approved DTG dosing is not available (*conditional recommendation, low-certainty evidence*) 4. A RAL-based regimen may be recommended as the preferred first-line regimen for neonates (*conditional recommendation, very-low-certainty evidence*)
SECOND-LINE ART
1. DTG in combination with an optimised NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom non-DTG- based regimens are failing. • Adults and adolescents (conditional recommendation, moderate certainty evidence) • Children with approved DTG dosing (conditional recommendation, low-certainty evidence) 2. Boosted protease inhibitors in combination with an optimised NRTI backbone may be recommended as a preferred second-line regimen for people living with HIV for whom DTG-based regimens are failing (strong recommendation, moderate-certainty evidence)

Table 2: Preferred and alternative first-line ART regimens

POPULATION	PREFERRED FIRST-LINE REGIMEN	ALTERNATIVE FIRST-LINE REGIMEN	SPECIAL CIRCUMSTANCES
Adults and adolescents	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + 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
Children	ABC + 3TC + DTG	ABC + 3TC + LPV/r TDF + 3TC + RAL TAF + 3TC (or FTC) + DTG	ABC + 3TC + EFV (or NVP) AZT + 3TC + EFV (or NVP) AZT + 3TC + LPV/r (or RAL)
Neonates	AZT + 3TC + RAL	ABC + 3TC + NVP	AZT + 3TC + LPV/r

Key: AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LPV/r, ritonavir-boosted lopinavir; NVP, nevirapine; PI/r, ritonavir-boosted protease inhibitor; RAL, raltegravir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine

Table 3: Preferred and alternative second-line ART regimens

POPULATION	FAILING FIRST-LINE REGIMEN	PREFERRED SECOND-LINE REGIMEN	ALTERNATIVE SECOND-LINE REGIMEN
Adults and adolescents	TDF + 3TC (or FTC) + DTG	TDF + 3TC + ATV/r (or LPV/r)	ABC + 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 (or FTC) + EFV (or NVP)	TDF + 3TC (or FTC) + DTG	TDF + 3TC (or FTC) + ATV/r (or LPV/r or DRV/r)
Children and infants	ABC + 3TC + DTG	ABC (or AZT) + 3TC + LPV/r (or ATV/r)	ABC + 3TC + DRV/r
	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + DTG	ABC (or AZT) + 3TC + RAL
	ABC (or AZT) + 3TC + EFV	ABC (or AZT) + 3TC + DTG	ABC (or AZT) + 3TC + LPV/r (or ATV/r)
	ABC + 3TC + NVP	ABC + 3TC + DTG	ABC (or AZT) + 3TC + LPV/r (or ATV/r or DRV/r)

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

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

Dolutegravir

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

Week 48 data from two key ART optimisation studies looking at DTG regimens were recently presented.

ADVANCE

Eagerly-awaited results from the ADVANCE study were presented at IAS 2019.[2] In this study, first-line ART regimens tenofovir alafenamide (TAF)/FTC/DTG and 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, and CD4 count approximately 500 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 presented last year,[3,4] like ADVANCE, participants reflect the population that will be treated in LMICs. NAMSAL 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 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 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 periconception 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.[5]

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 women 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.[6, 7] 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.[8] 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 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.[9, 10, 11, 12] 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[13], reported 5/1683 neural tube defects among births to women receiving DTG at conception, a rate of 0.30%.

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 0.30% (95% CI 0.13, 0.69) and for non-DTG at conception 15/14792, 0.10% (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 0.01% 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.[14,15]

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. [16, 17, 18]

Similar programmes to Tsepamo are in place in Uganda and Malawi.[19] 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.[20] No neural tube defects among 382 women on DTG at conception were reported in Brazil at IAS 2019.[21]

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

Antiretroviral exposure is classified by earliest trimester, which means starting ART any time in the first three months. Due to the narrow exposure window of interest for neural tube defects, the current interim reports now include supplementary information on periconception integrase inhibitor exposure.

Data presented at IAS 2019 show one neural tune defect out of 248 periconception DTG exposures, giving a prevalence of 0.40% for DTG and (0.14% for integrase inhibitors overall).[23] This higher than for other drugs/classes classes – but based on one neural tube defect in a relatively small number of exposures.

The overall prevalence of neural tube defects in 8,546 periconception antiretroviral exposures was 0.03%. Most of the reports in the APR come from North America, 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.

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.[24,25] 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. Others like the French Perinatal Cohort do not (but there are very few pregnancy exposures there because their guidelines were very cautious about the use of DTG in pregnancy).

The presentations at HIV Glasgow 2018 showed data from analyses of DTG use in pregnancy from Canada, Frankfurt and Eastern/Central Europe.[26, 27,28] Although none of these reports found further neural tube defects, the numbers are small, so at best these findings were faintly reassuring.

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). [29] 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.[30]

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

But using DTG later in pregnancy appears safe.[31]

And DolPHIN1, the pilot study to DolPHIN2, confirmed that standard dose of DTG should be used in the third trimester. [32]

DolPHIN1 and DolPHIN2 studies suggest there might be some advantages to using DTG late in pregnancy.[33, 34] 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,[35] 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 poised to become a massively-used antiretroviral worldwide this includes 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.[36, 37] 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.[38]

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.[39, 40]

A pharmacokinetic (PK) study in healthy volunteers looked at the effect of RIF on the PK of DTG 100mg once daily. The study was conducted to evaluate whether doubling the DTG dose over 24 hours could offer an easier option than 50mg twice daily to manage the drug interaction.[41]

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.[42]

Dolutegravir and adverse events

DTG was better tolerated than EFV or daunavir/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.[43]

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.[44] 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.[45]

Another meta-analysis, suggested that treatment with integrase inhibitors appears to lead to greater increases in body weight than with other antiretrovirals.[46] 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 data presented at CROI 2019 on this topic.[47]

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.[48]

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.

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

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.

The ENCORE 1 study, showed EFV 400 mg to be non-inferior to 600 mg (both plus TDF/FTC) as first-line ART.[49] The lower dose resulted in a 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.[50] 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 ENCORE 1.[51, 52]

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.[53]

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 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.[54]

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

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

The first generic TAF-containing FDC was tentatively approved by the US FDA last year: DTG/FTC/TAF.[55, 56] The new FDC might offer several programmatic benefits to LMICs where generics are accessible including lower cost and smaller tablet size (easier to swallow, transport and store).[57]

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 Essential Medicines List (EML).[58] TAF is also not included in the previous WHO transition document.[59] And participants of the Third Conference on Antiretroviral Drug Optimisation (CADO3), held at the end of 2017, did not consider TAF to be supported by sufficient evidence to inform use in LMICs.[60, 61]

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.[62, 63] But, unboosted, there were no differences between the two versions of tenofovir for efficacy and only slight differences in safety.

Boosting agents significantly increase plasma AUC concentrations of TDF (25–37%). Higher plasma tenofovir levels are linked to higher risks of renal and bone adverse events. The TAF dose is reduced from 25 to 10 mg daily when boosted but TDF remains at 300 mg daily. TDF is most commonly used worldwide in unboosted regimens, combined with 3TC and either EFV or DTG. TAF is expected to replace TDF and likewise will largely be used unboosted.

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

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

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

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

TAF and rifampicin

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

Two PK studies in healthy volunteers suggest that TAF 25 mg could be given once daily with RIF. Both studies found the concentrations of 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.[64, 65]

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.[66, 67, 68]

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.

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

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 pharmacokinetics in HIV positive pregnant women.[69]

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 manufactured by Gilead, the originator company, as part of a fixed dose combination either with or without the pharmacokinetic booster cobicistat (COBI). TAF is given at a dose of 25 mg unboosted and 10 mg when boosted with 150 mg COBI.

Those eligible to enroll in the TAF arms were receiving the drug as part of routine clinical care at an IMPAACT site.

Steady state PK profiles of TAF were obtained following once-daily dosing of either rilpivirine/emtricitabine/TAF (R/F/TAF) 25/200/25 mg or elvitegravir/COBI/emtricitabine/TAF (E/C/F/TAF) 150/150/200/10 mg during the second and third trimesters and 6–12 weeks postpartum. Maternal plasma and cord blood samples were collected at delivery

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

There were 31 participants enrolled in the TAF 25 mg and 27 in the TAF/COBI 10/150 mg arms.

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 pseudoarthrosis clavicle in one infant and renal cyst in another.

At the time of analysis 46 infants were HIV negative, 8 indeterminate and 4 pending.

Analyses of all maternal delivery samples, cord blood samples and infant washout samples are not yet complete but TAF was below the limit of quantification (3.95 ng/mL) in all 15 cord blood samples tested to date.

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.[70]

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

There is an insufficient number of first trimester exposures (minimum of 200) reported to the APR to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems, compared to the population-based rate.[71]

There are 6/162 and 0/62 birth defects reported to APR after first and second/third trimester TAF exposure respectively.

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) as well as intracellular PK data 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. Both a heat-stable, co-formulated generic version (hopefully this year) and a recommendation from WHO took their time.

DRV/r remains a potential candidate for dose optimisation. Results from the original dose finding studies and two with 600/100 mg once daily, plus one showing the recommended dose of cobicistat results in a significantly lower DRV Cmin than when it is boosted with ritonavir (in which the investigators say a reduction of up to 50% in Cmin should not make a difference to efficacy), suggest that a dose reduction to DRV/r 400/100 mg might be feasible.[72, 73, 74]

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.[75]

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).[76]

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.[77]

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.

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

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.[78, 79]

There are 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. [80]

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

What is planned or ongoing?

First-line

Two African investigator-led studies to look at DTG-based regimens in closer-to-real-life settings are ongoing.

The studies are: ADVANCE, a three-arm randomised comparison of two DTG-based regimens (one with TDF/FTC and the other with TAF/FTC) and EFV 600 mg (with TDF/FTC); and NAMSAL comparing DTG-based to EFV 400 mg based regimens, conducted in South Africa and Cameroon respectively.[81, 82, 83, 84, 85] Both studies have presented 48-week data recently, at IAS 2019 and HIV Glasgow 2018 respectively.

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

Table 1: First-line ongoing and planned

STUDY/ COHORT	DESIGN	PURPOSE	STATUS
ADVANCE WRHI 060 Ezintsha, Wits RHI (USAID, Unitaid, SA MRC)	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 Q2 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 at 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: ART, antiretroviral treatment; BL, baseline; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; Wits RHI, Wits Reproductive Health and HIV Institute; 3TC, lamivudine

Pregnancy

VESTED (IMPAACT P2010) is recruited and ongoing. The study is making the same three-arm comparison as ADVANCE but in pregnant women.[86,87]

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.[88, 89] First results with all deliveries were presented at CROI 2019.[90]

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.[91, 92, 93, 94] 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.[95, 96] Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.

Table 2: 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 copies/mL 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. 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 copies/mL at delivery; VL <200 copies/mL 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 Primary completion 31 July 2020

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

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

Table 3: 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

STUDY	DESIGN	PURPOSE	STATUS
VESTED IMPAACT P2010 NIH (NIAID)	Phase 3 DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 639 mother/infant pairs Treatment-naive women starting ART at 14–28 weeks' gestation 50 weeks of maternal and infant follow-up PP Multicountry: IMPAACT sites (US, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania, Thailand, Uganda, Zambia, Zimbabwe)	Primary endpoints: VL <200 copies/mL at delivery; adverse pregnancy outcomes; maternal toxicity; infant toxicity Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks PP; renal toxicity; bone toxicity; adverse pregnancy outcomes; resistance (women with VF, and HIV infected infants)	Recruited Primary completion 31 July 2010
TAF switch study pregnancy Wits RHI	Switch study evaluating PK, dosing and tolerability, pre- and post-switch from TDF (EFV/FTC/TDF FDC >3 months) to TAF 25 mg, through 6 months PP 26 women (and infants), 14-28 weeks' gestation, stable (VL suppressed, tolerating well, no co-infection) on TDF-based ART	Primary endpoint: TFV-DP levels during pregnancy (baseline, 4 weeks post-switch, 2nd TM, 3rd trimester) and PP (birth, 6–8 weeks) Secondary endpoints: tolerability, safety, VL outcomes of TAF, adverse, pregnancy outcomes, infant TFV-DP levels, infant safety PP, BM TFV-DP at 6 weeks and 6 months PP	Funding application stage Earliest Q4 2019 (funding dependent)

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

Tuberculosis

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

Table 4: 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	Starting Q 2/3 2019
EPiTAF UCT/ Ezintsha, Wits RHI (Unitaid)	30 HIV/TB-coinfected participants	TAF/RIF PK in HIV/TB coinfection	Awaiting SAHPRA approval

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.[97, 98]

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.[99]

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, to be conducted in Cape Town, will be 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 will be 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 will compare TDF/3TC/DTG (50 mg) to the WHO-recommended second-line regimen (AZT/3TC/DTG).

VISEND, to be conducted in Zambia and Zimbabwe, will compare short- (24 and 48 weeks) and long-term (72, 96 and 144 weeks) virologic 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.[100]

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 due to start this year, 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. 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.[101]

The NADIA study is investigating DTG vs DRV/r once daily with a second factorial with TDF/XTC vs AZT/3TC.[102]

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.[103]

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

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

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

Table 5: Second-line dolutegravir and darunavir/r – ongoing + planned

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

STUDY	DESIGN	PURPOSE	STATUS
ARTIST UCT (MSF/ Wellcome Trust)	Phase 3 195 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	Awaiting SAHPRA approval
VISEND University Teaching Hospital, Lusaka/ Parirenyatwa Hospital, Harare (Global Fund/Mylan)	2346 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=482) Arm A2: TAF/3TC/DTG, BL VL <1000 copies/mL (n=482) Arm B1a: TDF/3TC/DTG, BL VL >1000 copies/mL (n=482) Experimental Arm B1b: TAF/3TC/DTG, BL VL >1000 copies/mL (n=482) 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	Start Q 2/3 2019

STUDY	DESIGN	PURPOSE	STATUS
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	Starting Q2/3

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

Conclusion

As ever, results from ART optimisation studies, as well as observational data, highlight the importance of conducting well-designed trials (with long-term follow up) and having good surveillance systems in LMICs. Data from registrational trials, largely conducted in men, are simply not sufficient to inform widespread use of new drugs in millions of people from different populations.

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

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HIV pipeline-lite 2019: new drugs in development

By Simon Collins

Introduction

Over the last year there were three new approvals of new drugs or fixed dose combinations (FDCs) in Europe and the US.

These included the new NNRTI doravirine (also in an FDC) and the dual FDC of dolutegravir/lamivudine.

The US FDA decision on the first injectable ART is expected by December 2019 with approval expected based on results from phase 3 studies. However, EU filing is only planned in Q32019 with a decision 12 months later.

And intriguing results from some broadly neutralising monoclonal antibodies (bNAbs) – notably those with long-acting formulations – show the potential to maintain viral suppression after ART has been stopped.

Although approved in the US last year as a treatment for people with HIV multidrug resistance, the monoclonal antibody ibalizumab is still awaiting a decision from the EMA in the EU.

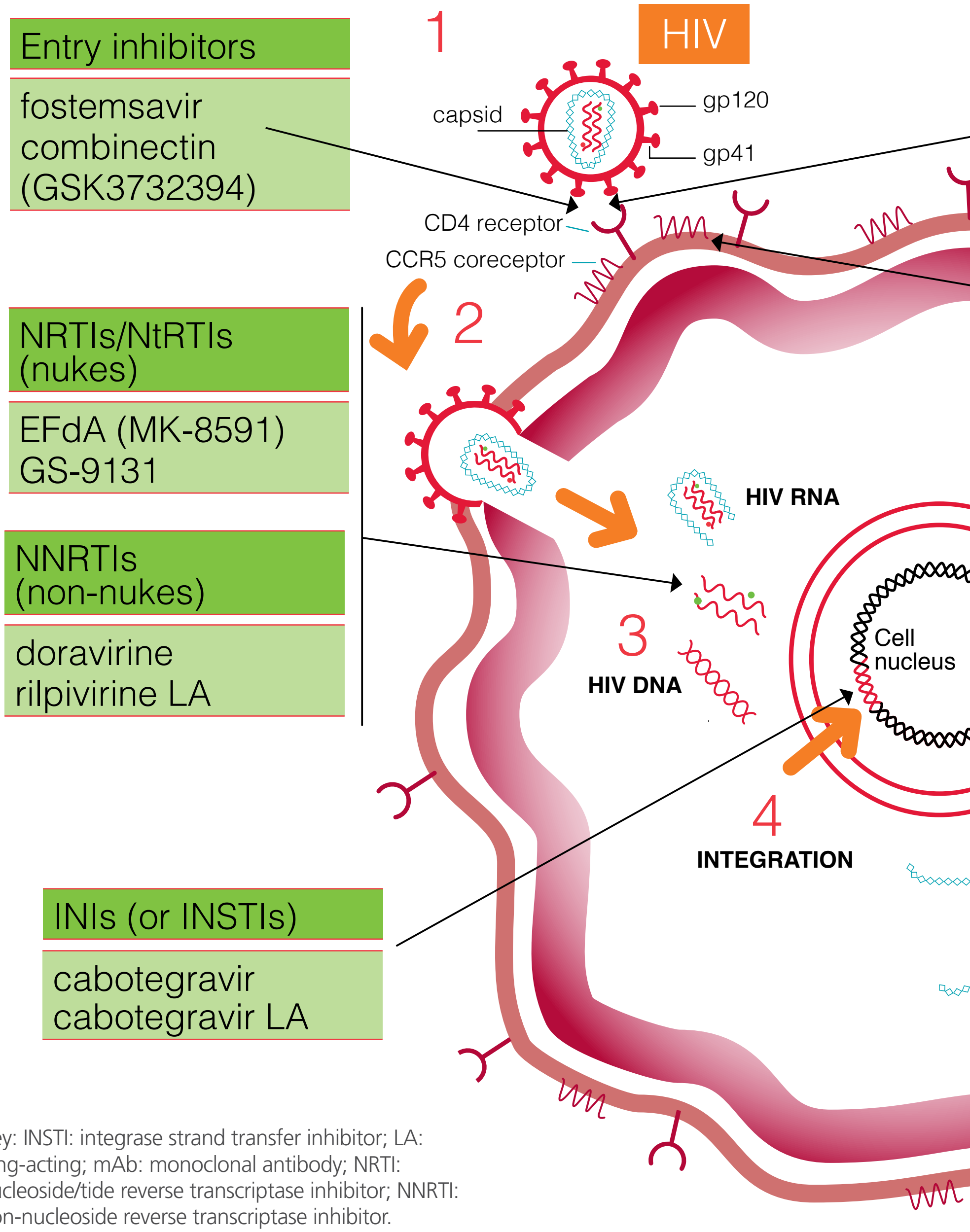
As with long-acting ARVs, these long-acting bNAbs also have important potential as PrEP.

The most quickly progressing compound is islatravir (MK-8591), a newly-named NRTI with extremely high potency, in development both as treatment and PrEP and with a slow-release implant formulation that allows once-a-year administration.

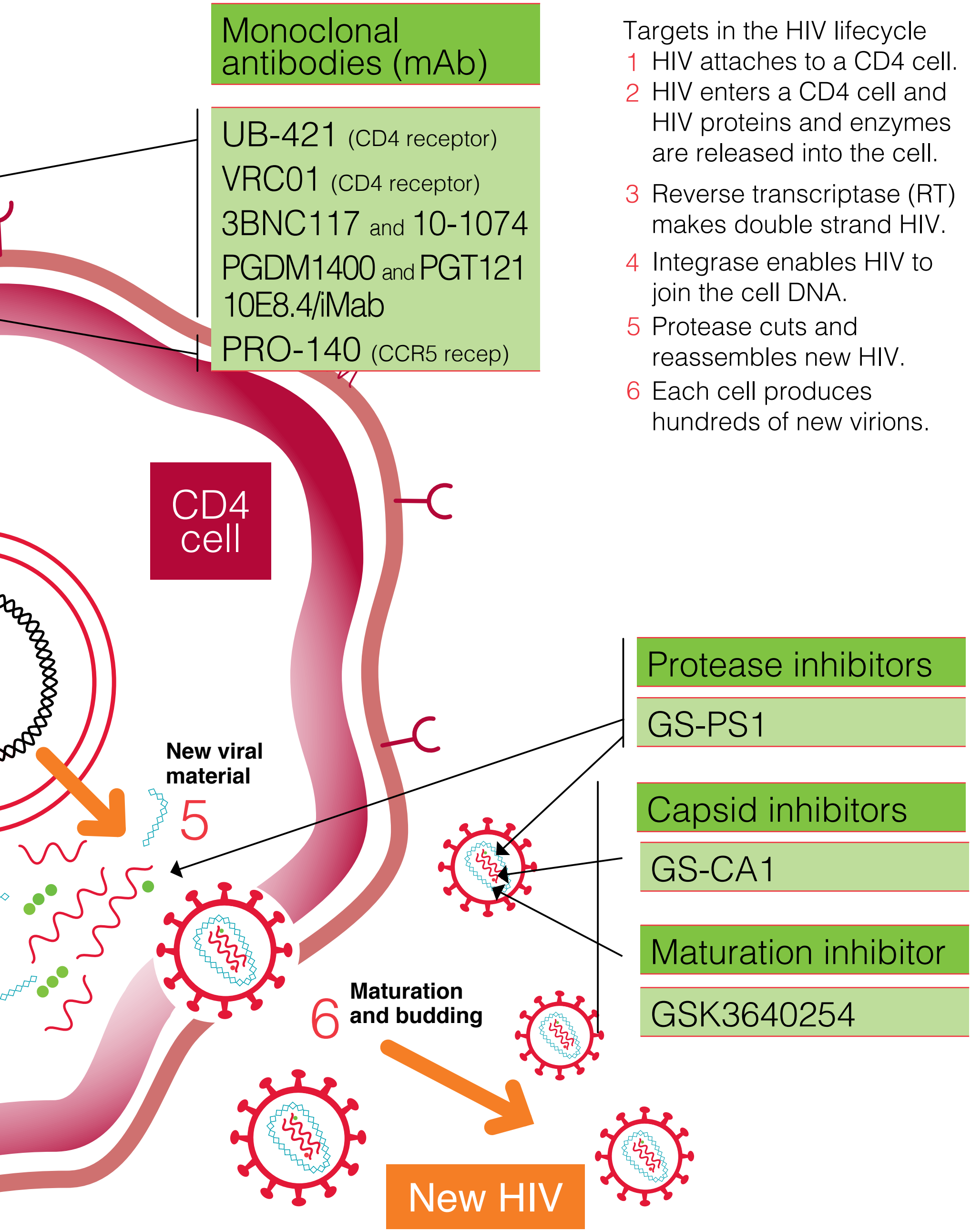
Figure 1 updates the HIV pipeline by target. Table 1 summarises compounds by development stage and Table 2 highlights long-acting compounds.

Over the next 5–10 years ART might become much simpler than taking a single pill once a day – with some compounds showing the potential for weekly, monthly, and perhaps even annual dosing.

Figure 1: HIV pipeline 2019: targets in the HIV lifecycle



Key: INSTI: integrase strand transfer inhibitor; LA: long-acting; mAb: monoclonal antibody; NRTI: nucleoside/tide reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor.


Monoclonal antibodies (mAb)
UB-421 (CD4 receptor)
VRC01 (CD4 receptor)
3BNC117 and 10-1074
PGDM1400 and PGT121
10E8.4/iMab
PRO-140 (CCR5 recep)
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 Each cell produces hundreds of new virions.
CD4 cell
New viral material
5
Protease inhibitors
GS-PS1
Capsid inhibitors
GS-CA1
Maturation inhibitor
GSK3640254
6
Maturation and budding
New HIV

Recently approved new HIV drugs

Over the last year, three new drugs or FDCs were approved.

Doravirine (Pifeltro) and doravirine/ TDF/3TC (Delstrigo)

The NNRTI doravirine (Pifeltro) was approved in the US (August 2018) and the EU (November 2018) together with an FDC (Delstrigo) combined with generic tenofovir DF (TDF) and generic lamivudine (3TC).[4, 5]

Doravirine is a once-daily NNRTI from Merck that can be taken with or without food. It has few drug interactions and retains activity against common first generation NNRTI mutations (K103N, Y181C, G190A and E138K).

Doravirine has a better tolerability profile compared to efavirenz.

Doravrine is being studied as part of a three-drug combination with 3TC plus the investigational NRTI MK-8591. It is also being studied in dual combination with MK-8591.

Results from both these studies are due to be presented at IAS 2019 in two late-breaker presentations.[6, 7]

Dolutegravir/lamivudine (Dovato)

A dual combination of the integrase inhibitor dolutegravir with a single NRTI, 3TC, was approved in the US in April 2019 and in Europe in July 2019.[8, 9]

This was based on phase 3 studies presented at AIDS 2018.[10]

The GEMINI studies showed that dual therapy with DTG/3TC was non-inferior to triple ART. A sub-study from the phase 3 ASPIRE study showed no differences in low levels viraemia <50 copies/mL in 2-drug vs 3-drug arms.[11]

GEMINI 96-week results are due to be presented at IAS 2019 together with another analysis of viral dynamics at low levels.[12, 13]

Ibalizumab (Trogarzo) – mAb – EU pending

Ibalizumab was approved by the US FDA in March 2018. Although given a positive opinion in the EU in April 2019, it is currently still awaiting a final decision in the EU.[75, 76]

Ibalizumab as the first monoclonal antibody to treat HIV positive people with multidrug resistance who are currently on failing ART.

Ibalizumab was developed by TaiMed Biologics. It is marketed in the US and Canada with the trade name Trogarzo by Theratechnologies. The US list price for ibalizumab is US $ 118,000 (WAC/Wholesale Acquisition Cost), which does not include costs for providing the infusions (the product is not self-administered). Easier to use formulations are also being studied.

Although this development took many years – with Phase 1b efficacy results first reported in 2008 – it is a considerable achievement for any compound to be the first drug approved in a new class.

Submitted applications or completed phase 3

Two new drugs and coformulations are already in late-stage development with regulatory applications submitted to the FDA and EU or phase 3 studies already completed.

Cabotegravir/rilpivirine long-acting (LA) injections

On 29 April 2019, the long-acting two-drug injection formulation of cabotegravir/rilpivirine was submitted to the US FDA based on 48-week results from the phase 3 FLAIR and ATLAS studies presented at CROI 2019.[14, 15]

These studies reported >90% viral suppression to <50 copies/mL at week-48 meeting criteria for non-inferiority compared to three-drug oral therapy.

Cabotegravir (CAB) is a second-generation integrase inhibitor being developed as both an oral tablet and long-acting (CAB-LA) injectable formulation. The oral formulation is primarily to use before using CAB-LA injections to screen for risk of a hypersensitivity reaction. CAB-LA is being studied both as treatment (coformulated with rilpivirine LA) and as single-drug for use as PrEP.

CAB-LA has an extremely long half-life. A presentation at the HIVR4P conference in October 2018 reported cases where therapeutic levels of cabotegravir could still be detected after 2.5 years in men and 3.5 years in women.[16]

The long half-life means that anyone stopping CAB-LA when used as treatment needs to switch to alternative ART (rather than interrupting treatment). When used as PrEP, current studies recommend switching to daily oral PrEP for a year.

The oral formulation has a similar drug resistance profile to dolutegravir.

Pooled results from the FLAIR and ATLAS studies will be presented at IAS 2019, including presentations about participant quality of life using injections.[17, 18, 19]

Results will also be presented for a sustained release long acting cabotegravir implant to be used for PrEP.[20]

Both CAB formulations are being developed by ViiV Healthcare with the FDC in collaboration with Janssen.

Fostemsavir – attachment inhibitor

Fostemsavir (GSK3684934) is an attachment inhibitor that binds to gp120 and prevents conformational changes needed for attachment. It is active against nearly all HIV-1 subtypes, though not sub-type AE or group O and has no in vitro cross resistance to drugs from other classes.

Updated 48-week results were presented at Glasgow 2018 from the phase 3 BRIGHTE study.[21]

In this advanced patient group, at week 48, by snapshot analysis, 54% participants in the randomised study (146/272) and 38% (38/99) in the open label study had viral load <40 copies/mL. These were similar to rates at week 24.

Two presentations at CROI 2019 showed data supporting activity in treatment-experienced participants.[22, 23]

Currently, the submission is still being prepared for regulatory agencies, the timeline might be related to issues linked to scaling up manufacturing capacity. FDA submission planned Q4 2019 and EU in 2020. No information about priority review means likely 12 month decisions.

Two presentations at IAS 2019 will show 96-week results from the BRIGHTE study.[24, 25]

This compound is being developed by ViiV Healthcare.

Compounds in phase 3 development

Two bNAbs are in phase 3 development although there have been little new data on both these compounds over the last year.

Leronlimab – mAb

Leronlimab (previously PRO 140) is a humanised IgG4 monoclonal antibody that blocks HIV entry by binding to CCR5 but is active against maraviroc-resistant virus.

Leronlimab has been in development for more than a decade, but that has been designated fast-track status, for potential to treat MDR HIV.

In addition to use as an ARV in combination leronlimab is also beings studied as a switch treatment after viral suppression on oral ART. Unfortunately, preliminary results from a phase 2 study using this strategy, presented at CROI 2019 reported a high failure rate at the initial 350 mg dose that was not overcome with 525 mg and 700 mg doses.[26]

Leronlimab is also being studied in non-HIV setting as prophylaxis against graft vs host disease (GVHD) in people undergoing allogenic stem cell transplant.[27]

Leronlimab is being developed by CytoDyn.

UB-421 – mAb

UB-421 is a broadly neutralising mAb that targets CD4 binding with in vitro data that suggest comparable or greater potency compared to other compounds, including VRC01 and 3BNC117. No new clinical data has been presented since 2017.

It is being developed by the Taiwanese company United BioPharma, with research sites in Taiwan. Although two phase 3 studies are listed to start in 2020, they were previously both due to start in 2018. Neither study is currently open to recruitment. [28, 29]

The most recent data were presented at CROI 2017 but published in April 2019 in the NEJM. This was a phase 2 study in 29 virally suppressed participants on ART who used UB-421 monotherapy during an 8-week treatment interruption.[30]

Although there were no cases of viral rebound during the monotherapy phase, viral load rebounded at 35 to 62 days after the last UB-421 dose in five participants who delayed restarting ART. All five later restarted ART and viral load became undetectable.

Compounds in phase 1/2 studies

The compounds in this section include some that are likely to advance quickly into phase 3 studies and some where there has been little progress over the last year.

MK-8591 (EFdA) – NRTI

MK-8591 is a very interesting NRTI in development by Merck that is notable for high potency (currently using a 0.25 to 2.25 mg oral daily dose), a long plasma half-life that allows once-weekly oral dosing, a slow-release removable implant that might only require annual dosing and ongoing studies looking at use for both treatment and PrEP.

A single dose of MK-8591 in treatment-naive participants, produced mean viral load reductions at day 7 that were dose-related and ranged from approximately –1.2 logs (for the 0.5 mg, 1.0 mg and 2.0 mg groups) to approximately –1.6 logs (for the 10 mg and 30 mg group).

The latest results relating to potency and activity against drug resistance virus were presented in a poster at CROI 2019.[31]

This showed 4-fold lower IC50 for MK-8591 triphosphate than any other marketed NRTI with potential to use doses of 0.25 mg daily or 10 mg weekly. Common NRTI mutations, including M184I/V, K65R, and K70E, only confer low fold-shifts in antiviral potency and MK-8591 has greater inhibitory quotients against these drug-resistant mutations than those of TDF, TAF, and 3TC with WT HIV.

The potential for PrEP was shown using weekly oral doses of MK-8591 or placebo for three months in 16 macaques who were then exposed to rectal

SIV (on day 6 of every weekly cycle) for 12 weeks, protecting all animals in the active arm.[32]

Preliminary results also suggested that a slow release implant might provide protection as PrEP for more than one year.

MK-8591 is also included in an FDC with 3TC and doravirine and is also being studied as dual therapy with doravirine.[33]

Three studies on MK-8195 will be presented at IAS 2019 including two late-breaker presentations on efficacy as treatment.[6, 7]

A third late-breaker abstract will present data on formulation in an annual implant for use as PrEP, extending dosing out to one year.[34]

GS-9131 – NRTI

GS-9131 is a prodrug of GS-9148 with early animal and in vitro drug resistance studies presented 12 years ago at CROI 2006.[35] Other published studies highlight the potential for low risk of toxicity in animal studies and retains in vitro phenotypic sensitivity to broad NRTI resistance including mutations at K65R, L74V and M184V and multiple TAMS.[36]

The compound has good potency (EC50 = 25-200 nM) with activity against HIV-1 subtypes A, B, C, D, E, F, group O and N (EC50 0.29-113 nM), also against HIV-2. Synergistic activity was reported in combination with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TDF and TAF.[37]

The only ongoing study with GS-9131 is a phase 2 dose-finding trial Uganda in 58 treatment-experienced women who have detectable viral load >500 copies/mL on current NRTI-including ART.[38]

A poster presented at CROI 2019 reported on the high in-vitro threshold to drug resistance.[39]

VRC01, VRC01LS and VRC07-523LS – bNAbs

VRC01 is a broadly neutralising mAb that targets the CD4 binding site that can be given by infusion or sub-cutaneous injection and that is 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 are already ongoing that allow the option for participants to also use open-label oral TDF/FTC PrEP.[40, 41]

Although results are expected in 2019 there have always been concerns about using only a single mAb given the limited breadth and potency from one compound.[42]

A new long-acting formulation VRC01LS is also in phase 1 studies, designed to improve the half-life of the antibody, administered IV. 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.[43]

A new long-acting formulation VRC01LS is also in phase 1 studies.[44, 45]

Results from the LS formulation will be presented at IAS 2019 together with VRC07-523LS – a variant long-acting bNAb.[46]

Other bNAbs: 3BNC117 and 10-1074; PGDM1400 and PGT121; 10E8

3BNC117 and 10-1074 are two broadly neutralising mAbs that target CD4 binding that are in development at Rockefeller University.

Several phase 1 studies are using these individually and together and also in longer-acting LS versions, allowing monthly or two-monthly dosing.

An overview of latest results using this dual formulation was presented in one of the opening lectures to CROI 2019.[47]

This talk mainly looked at the potential for bNAbs to control HIV for extensive periods without ART, both in animal and human studies.[48, 49]

Another oral presentation at CROI 2019 included results from using a single subcutaneous injection of 10-1074 alone or in combination with 3BNC117 (10 mg each bNAb/kg) in a macaque study showed efficacy of these bNAbs as PrEP.[50]

3BNC117 is also included in a dual combination with the long-acting entry inhibitor albuvirtide that was approved last year in China. This phase 2 study with US study sites is looking at either 2-weekly or 4-weekly injection-based maintenance therapy.[51]

Also at CROI 2019, results from a phase 1 study using the bNAb PGT121 in 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. In two people starting with low baseline viral load (<400 copies/mL) a single infusion dropped viral load to undetectable where it remained, without ART, for at least eleven months.[52]

While the safety and tolerability of bNAbs are generally good, the highly potent bNAb 10E8 was recently put on hold due to grade 3 skin erythema in 7/8 participants.[53]

Preliminary results for a trispecific bNAb were presented at CROI 2019.[54]

Elsulfavirine – NNRTI

Elsulfavirine (a prodrug of VM-1500A) is an NNRTI being developed by Viriom for registration in some middle-income countries.

Although limited data are available, in a randomised, double-blind phase 2b study conducted in Russia in 120 treatment naive participants, elsulfavirine 20 mg was compared to efavirenz 600 mg, each with TDF/FTC background NRTIs.[55]

A long-acting injectable formulation in development, with results from an animal study presented at IAS 2017, showing the potential for monthly by intramuscular (IM) or subcutaneous (SC) injection.[56]

Phase 2 results at 96-week were presented at AIDS 2018.57 A second poster at IAS 2018 reported the potential for a long-acting injection formulation.[58]

ABX464 – Rev inhibitor

ABX464 is an anti-inflammatory molecule thought to work by blocking the end stages of viral assembly. No new clinical data has been presented since 2017.[59, 60]

An ongoing open-label phase 2 pharmacokinetic study in 36 HIV positive participants is currently ongoing, looking at 50 mg and 150 mg once-daily dosing.[61]

GSK3640254 – maturation inhibitor

The maturation inhibitor GSK3640254 (previously BMS-986197) is currently in two phase 1 studies in HIV negative adults that include bioavailability of different formulations.[62, 63]

Since the last pipeline report, results from an early phase 1 safety and telerability study were published last year.64 First results from a phase 2a study in HIV positive people were presented at CROI 2019. This included mean viral load reduction of –1.5 log copies/mL in the highest dose (200 mg/day) group.[65]

Preclinical compounds of interest

As many companies do not widely publicise pre-clinical work, this section is restricted to a few studies. Apart from a few new compounds, this section is largely unchanged from the 2018 pipeline report.

Combinectin (GSK3732394) – adnectin/fusion inhibitor

Combinectin (GSK3732394 is a 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-weekly injections.

A summary of in vitro activity and resistance data and virologic data from mouse studies were presented at Glasgow 2016.[66]

In June 2019 the first phase 1 study in HIV negative volunteers started enrolling, with results expected mid-2020.[67]

GS-PI1 – protease inhibitor

GS-PI1 is a once-daily unboosted protease inhibitor with high potency and a long half-life, and in vitro sensitivity against some second-generation PI resistance, in pre-clinical development by Gilead.

An oral presentation at CROI 2017 reported a high barrier to resistance both after in vitro passaging and against multiple resistance complexes from multiple PI-resistant clinical isolates, and pharmacokinetic data from rat and dog studies.[68]

GS-CA1 – capsid inhibitor

First phase I data was presented at CROI 2019 on GS-CA1.

This is the first HIV capsid inhibitors, with a formulation that can be used for slow-release injections.[69]

GS-CA1 acts in both the early and late stages by binding at a site that blocks both disassembly and assembly leading to defective new virions that are non-infectious.

The investigational compound is currently developed as a subcutaneous injection that in rat studies maintained plasma concentrations nine times above the protein adjusted EC95 ten weeks after a single injection. This suggests monthly or longer dosing intervals in humans.

A phase I study in HIV positive participants in currently ongoing with sites in the US.[70]

MK-8583 (tenofovir prodrug). MK-8527, MK-8558

Three compounds being developed by Merck are currently in phase I studies. Although the first of these is an NRTI the trial listings do not include the mechanism of action.[71, 72, 73]

Conclusion

The high number of recent approvals and ending applications for new HIV drugs is impressive. (see Table 1)

It is also important that this includes new classes that will overcome drug resistance to other classes and that additional new compounds are in development, especially those that are long-acting (see Table 2).

This investment in formulations that use less than daily dosing could dramatically change the way that HIV is treated, with several of the compounds in this report already showing the potential for monthly or perhaps annual dosing.

Other companies are also looking to invest in similar technologies, reflecting that better HIV treatment is still seen as a competitative market.[74]

The global need for better HIV treatment also means that drugs developed in high-income countries need to have data to inform their use in all settings.

Table 1: HIV pipeline compounds by development phase

COMPOUND/ COMPANY	CLASS	NOTES
Phase 3		
cabotegravirViiV Healthcare	INSTI	Oral formulation of integrase inhibitor mainly used for lead-in dose before long-acting formulation. Submitted to FDA in April 2019. Also, long-acting implant for PrEP (phase1).
cabotegravir LA/ rilpivirine LA ViiV Healthcare and Janssen	INSTI	Injection with very long half-life – detectable after more than one year following single injection. Research as both treatment with rilpivirine LA and prevention as single compound. Submitted to FDA in April 2019.
fostemsavir ViiV Healthcare	attachment inhibitor	Fostemsavir is a gp120 attachment inhibitor that is mainly being studied in treatment-experienced patients with MDR HIV in a large international study. Updated results at CROI 2019. Regulatory submission expected soon.
leronlimab CytoDyn	mAb CCR5 target	Once-weekly sub-cutaneous injection being studied in addition to ART for multi-drug resistance and as monotherapy maintenance therapy (without ART). Results at CROI 2019 showed high failure rate as monotherapy switch.
UB-421 United BioPharma	mAb CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption. No recent results.
Phase 1/2		
MK-8591 (EFdA) Merck/MSD	NRTI	Highly potent, low dose, active against NRTI resistance. Long half-life, potential as oral (weekly dose) and implant (annual implant for PrEP).
MK-8591/3TC/ doravirine Merck/MSD	FDC: NNRTI + 2 NRTIs	FDC with NNRTI doravirine and generic 3TC. Also as dual therapy with doravirine. Results presented at CROI 2019 and with two late-breakers at IAS 2019.

COMPOUND/ COMPANY	CLASS	NOTES
GS-9131 Gilead Sciences	NRTI	Active against NRTI resistance. Synergy reported with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF. Will be coformulated with other Gilead drugs. Phase 2 dose-finding study in Ugandan women. Potency data presented at CROI 2019. No results expected at IAS 2019.
VRC01 VRC01LS VRC07-523LS	bNAb CD4 binding	VRC01 ntravenous infusion (40 mg/kg) is being studied in cure research and as PrEP (2 large phase 3 studies AMP are ongoing). Also sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding. VRC01LS is a long-acting formulation. Phase 1 results of VRC01LS and VRC07-523LS at IAS 2019.
3BNC117 and 10-1074; PGDM1400 and PGT121, 10E8 etc.	bNAb	Many other bNAbs are in development, often in dual or triple combinations and including trispecific molecules. Potential to be used as switch option without ART and in current studies for use as PrEP. No results expected at IAS 2019.
elsulfavirine, prodrug of VM-1500A Viriom	NNRTI	NNRTI that is being developed for use in low and middle income countries. Similar activity to efavirenz. Long-acting formulation being studied with potential for monthly IM/SC injections. 96-week phase 2 results at AIDS 2018 together with potential for long-acting injectable formulation. No results expected at IAS 2019.
ABX464 Abivax	Rev inhibitor	Compound with evidence of modest antiviral activity (~0.5 log in 4/6 people) that is also being studied for impact on the viral reservoir. Currently in phase 2. No new clinical data has been presented since 2017. No results expected at IAS 2019.

COMPOUND/ COMPANY	CLASS	NOTES
GSK3640254 ViiV Healthcare	Maturation inhibitor	Maturation inhibitor with phase IIa results in HIV positive participants presented at CROI 2019: mean viral load reduction of –1.5 log copies/mL in the highest dose (200 mg/day) group. No results expected at IAS 2019.
Phase 1 and preclinical		
combinectin (GSK3732394) ViiV Healthcare	Entry inhibitor gp41 & CD4	Combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action and the potential for self-administered once-weekly injections. No results expected at IAS 2019.
GSPI1 Gilead Sciences	Protease inhibitor	New QD unboosted PI, high potency, long half-life, potential in FDC single table regimen. No new clinical data has been presented since 2017. No results at IAS 2019.
GS-CA1 Gilead Sciences	Capsid inhibitor	New class active at multiple stages of viral lifecycle. Sub-cutaneous injection with monthly or less frequent dosing. Phase I results in HIV negative at CROI 2019. Phase I in HIV positive participants is ongoing. No results expected at IAS 2019.
MK-8583, MK-8527, MK-8558 Merck/MSD	NRTI and others	These three compounds are registered for phase I studies in HIV positive particiapants, but with limited details on their mechanism of action. They are plausibly likely to have potential to be long-acting. No results expected at IAS 2019.

Table 2: Compounds with long-acting formulations

COMPOUND	COMPANY
cabotegravir/rilpivirine	ViiV/Janssen
cabotegravir implant for PrEP	ViiV
MK-8591 (EfDA) yearly implant for PrEP. Potentially weekly or longer dosing as treatment.	Merck/MSD
bNAbs: 3BNC117 and 10-1074; PGDM1400 and PGT121, 10E8	Various including Rockefeller Institute.
conbinectin	ViiV Healthcare
elsulfavirine	Viriom (Russia)
Gilead compounds – including CA1 capsid inhibitor.	Gilead Sciences (in partnership with Lyndra) – compounds not specified [61]
MK-8583, MK-8527, MK-8558	Merck/MSD. No details on compounds but likely to be long-acting.

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Key: CROI: Conference on Retroviruses and Opportunistic Infections; IAS: International AIDS Society; HIV Glasgow: Glasgow Congress on HIV Therapy.

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