Fit for purpose

Antiretroviral treatment optimisation

HIV i-Base
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ABOUT HIV i-BASE

HIV i-Base is a London-based HIV treatment activist organisation. i-Base works in the United Kingdom and internationally to ensure that people living with HIV are actively engaged in their own treatment and medical care and are included in policy discussions about HIV treatment recommendations and access.

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ABOUT FIT FOR PURPOSE

i-Base's annual *Fit for Purpose* summarises key developments in antiretroviral treatment optimisation for low- and middle-income countries.

ABOUT HIV PIPELINE 2018: NEW DRUGS IN DEVELOPMENT

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

http://i-base.info/hiv-pipeline-2018/

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Unitaid
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HIV i-Base
107 The Maltings
169 Tower Bridge Road
London SE1 3LJ
Tel: +44 (0) 208 616 2210
www.i-base.info
admin@i-base.org.uk

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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 HIV positive adults, in low- and middle-income countries (LMICs).

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. This abbreviated version – looking at optimised ART for adults and including the HIV pipeline – was released at the annual Conference on Retroviruses and Opportunistic Infections (CROI) 2019.

Key developments since the July 2018 edition include:

- Interim World Health Organisation guidelines recommending dolutegravir (DTG)-based regimens for all adults and children (for whom approved DTG dosing is available) as preferred first- and second-line ART published December 2018.
- Week 48 results from the NAMSAL study – a key ART optimisation trial of first-line DTG vs efavirenz (EFV) in an African setting – presented October 2018.
- Week 48 results from a second-line switch study of people stable on a twice-daily lopinavir/ritonavir (LPV/r)-based who switched to a once-daily 400/100 mg darunavir/ritonavir (DRV/r) one – presented July 2018.
- Pharmacokinetc data on tenofovir alafenamide (TAF) pregnancy from IMPAACT P1026s – presented July 2018.

The July 2019 update will include ART optimisation for both adults and children and a new section on long acting formulations.

World Health Organisation guidance 2018

WHO released interim guidelines: *Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV*, in December 2018.[1]

The guidelines are a supplement to the *2016 consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV.*[2]

The 2016 guidelines recommended TDF/3TC or FTC (XTC)/EFV 600 mg as preferred adult and adolescent first-line ART regimen. DTG-based first-line ART was recommended as an alternative regimen due to evidence gaps for its use in pregnancy, preconception and with rifampicin (RIF)-based tuberculosis (TB) treatment and lack of generic formulations at that time.

Since the 2016 guidelines were released, information has accumulated on the use of DTG both first- and second-line, including some that (partly) helps to fill the evidence gaps.

But, during the process of reviewing evidence to support the guidelines, an important potential safety concern was reported suggesting DTG might be associated with an increased risk of neural tube defects in infants born to women receiving DTG during the periconception period.

The Interim guidelines provide a complete assessment of the use of DTG across all populations, considering the full range of known and potential benefits and risks, that emphsisises women's autonomy in decision-making, provision of information and options to enable women to make informed choices.

As more data become available on the potential risk of using DTG in women of child-bearing potential – and more is expected in the upcoming months – the guidelines will be updated as the evidence suggests.

Table 1. WHO first-line recommendations

1. A DTG-based regimen is recommended as the preferred first-line regimen for people living with HIV starting ART (conditional recommendation)

- Adults and adolescents (moderate-certainty evidence)
- Women and adolescent girls of childbearing potential (very-low-certainty evidence)
- Infants and children with approved DTG dosing (low-certainty evidence)

Note of caution on using DTG during the periconception period among women and adolescent girls of childbearing potential

- Exposure to DTG at the time of conception may be associated with neural tube defects among infants.
- DTG appears to be safe when started later in pregnancy: after the period of risk of neural tube defects and after the rst trimester.
- Adolescent girls and women of childbearing potential who do not currently want to become pregnant can receive DTG together with consistent and reliable contraception; hormonal contraception and DTG have no reported or expected drug–drug interactions although data are limited.
- An EFV-based regimen is a safe and effective first-line regimen recommended for use by the WHO 2016 ARV guidelines and can be used among women of childbearing potential during the period of potential risk for developing neural tube.
- Key considerations for national programmes when selecting the optimal ARV drug regimen for women and adolescent girls of childbearing potential include fertility levels, availability and coverage of contraceptives, pretreatment resistance to non-nucleoside reverse-transcriptase inhibitors at the population level, drug availability and the maternal and infant toxicity profile.
- A woman-centred approach to healthcare should be taken that consciously adopts the perspectives of women and their families and communities, with care provided in ways that respect women's autonomy in decision-making. Services must provide information and options to enable women to make informed choices.

Other remarks

- This recommendation applies to all infants and children for whom an approved DTG dosing is available.
- Because of limited long-term experience with DTG among both children and adults, active toxicity monitoring should be considered. WHO has developed specific guidance and tools

2. A raltegravir (RAL)-based regimen may be recommended as an alternative first-line regimen for infants and children for whom approved DTG dosing is not available (conditional recommendation, low-certainty evidence).

3. A RAL-based regimen is recommended as the preferred first-line regimen for neonates (conditional recommendation, very-low-certainty evidence)

Source: WHO. Updated recommendations on first-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. December 2018

WHO also published a policy brief earlier in the year: *Antiretroviral regimens for treating and preventing HIV infection and update on early infant diagnosis of HIV*, July 2018.[3]

And more implementation guidance will be available in WHO's forthcoming publication: *Programmatic considerations for countries transitioning to new ARV regimens*.[4]

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

Dolutegravir

Results from the NAMSAL study

NAMSAL results have been eagerly awaited as this is the first study to look at DTG in a real-life African setting. Unlike registrational studies, participants reflect the population that will be treated in LMICs, including those with high baseline viral load who are less likely to achieve a fully suppressed viral load.

Findings from the study were presented at Glasgow 2018: at week 48, DTG-based first-line ART was non-inferior, but not superior, to that with EFV 400 mg.[5,6]

Of 613 particiapnts, 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 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 preconception 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% compares with a 0.1% risk of neural tube defects in infants born to women taking other ARVs at the time of conception.

WHO's May statement was followed by several others, including from PEPFAR, US FDA, European Medicines Agency (EMA), US Department of Health and Human Services (DHHS), as well as a Dear Doctor letter from ViiV Healthcare. [11, 12, 13, 14] The recommendations advised varying degrees of caution.

Tsepamo data were 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%.

Tsepamo has expanded from eight to 18 sites, covering 72% of births in Botswana. The next comprehensive assessment of the data will take place in April this year. Approximately 1600 women with preconception DTG exposure are expected to be included. This will remain the most informative dataset on which to base guidance and policy in the near future.

Preclinical safety data did not show developmental toxic effects or teratogenicity – although these categories are no longer used, DTG is FDA category B.[15, 16]

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. [17, 18, 19]

As far as other early adopter countries are concerned, similar programmes to Tsepamo are in place in Uganda and Malawi.[20] 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.[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 report through to 31 July 2018 included supplementary information on preconception integrase inhibitor exposure. Only a small number of preconception DTG exposures (201) have been reported to date among which there were no neural tube defects.[23]

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).

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 are 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. There will be a presentation looking the complexity of extracting information from databases at CROI 2019.[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 Tsempamo 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]

Final results from DolPHIN1 were presented at AIDS 2018 and there might be some advantages to using DTG late in pregnancy.[33] 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.

In the meantime WHO recommends DTG for women of child-bearing potential with contraception 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,[34] 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.[35, 36] 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 pharmacokinetic sub-study of the NAMSAL study with DTG 50 mg given twice daily in the presence of RIF also supports this strategy.[37]

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.[38, 39]

A pharmacokinetic study in healthy volunteers looked at the effect of RIF on the pharmacokinetic 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.[40]

Whether DTG 100 mg once daily with RIF will be safe and effective in people with HIV/TB coinfection remains unclear from the pharmacokinetic results so far and further studies (including with 50 mg) are planned.

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

Dolutegravir and adverse events

DTG was better tolerated than EFV or DRV/r in its registrational studies but there was an increased risk of insomnia. More serious central nervous system (CNS) side effects (depression, suicide ideation) were rare.[41]

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.[42] 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.[43]

A recent meta-analysis, as well as several anecdotes, suggests that treatment with integrase inhibitors appears to lead to greater increases in body weight than with other antiretrovirals.[44] 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.

Ongoing African studies – including ADVANCE, NAMSAL and DolPHIN 1 and 2 – comparing DTG to EFV, with predominately black and female populations, have started reporting results or will do so this year. These studies will provide more information on whether or not this potential effect differs by sex and ethnicity.

Clearly this phenomenon needs to be carefully monitored given the widespread introduction of DTG globally.

Efavirenz 400 mg

The ENCORE 1 study, showed EFV 400 mg to be non-inferior to 600 mg (both plus TDF/FTC) as first-line ART.[45] The lower dose resulted in a reduction in EFV-related side effects 38% versus 48% with the standard dose.

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

Efavirenz 400 mg and pregnancy

Results from a pharmacokinetic study of EFV 400 mg during pregnancy, showed lower drug concentrations in the third trimester, compared with post-partum.[46] 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.[47, 48]

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

Efavirenz and TB

A pharmacokinetic 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.[49]

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

Efavirenz expected to remain an option

EFV is likely to remain a recommended first-line antiretroviral for a while.

In countries where generics are not accessible until a drug is off patent it is likely to be used for some time. The EFV/TDF/3TC regimen has been generic in

most countries worldwide since 2017, but DTG and TAF patents extend for at least another 10 years. This will mean many middle-income countries that do not qualify for minimum prices – including swathes of South America, South East Asia, and Eastern Europe, where countries can pay four times as much for antiretrovirals than African ones with similar Gross National Incomes – will encounter significantly higher (likely prohibitive) ones.[50]

And some countries are now discussing EFV for women of child-bearing potential – with varying shades of conservatism. And some women wishing to have children might prefer this option to DTG.

Tenofovir alafenamide

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

TAF doses are one tenth or less than that of TDF and give intracellular levels of the active metabolite, tenofovir diphosphate, which are four to seven times higher and plasma concentrations that are 90% lower than those with TDF.[51] It is dosed at 25 mg unboosted and 10 mg in a boosted regimen. This reduced dose gives TAF the potential to be produced at a much lower cost to TDF.

The first generic TAF-containing FDC was tentatively approved by the US FDA last year: DTG)/FTC/TAF.[52, 53] 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).[54]

But, lack of evidence, particularly for use in pregnancy and with TB coinfection, has meant that TAF is not yet included in WHO guidelines or Essential Medicines List (EML).[55, 56] TAF is also not included in the WHO transition document.[57] And participants of the Third Conference on Antiretroviral Drug Optimisation (CADO3) did not consider TAF to be supported by sufficient evidence to inform use in LMICs.[58, 59]

TAF vs TDF

Results from a meta-analysis of TDF versus TAF showed TDF, boosted with ritonavir or cobicistat, led to higher risks of bone and renal adverse events and lower rates of viral load suppression, compared with TAF.[60, 61] 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 pharmacokinetic studies in healthy volunteers suggest that TAF 25 mg could be given once daily with RIF. Both studies found the concentrations of TFV-diphosphate (DP) for TAF with RIF were higher than for people receiving standard TDF 300 mg.

In the first, twice-daily TAF plus RIF provided similar drug exposure to once-daily TAF.[62, 63]

This parallel design pharmacokinetic 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 pharmacokinetic study, plasma concentrations of once-daily TAF AUC were decreased by 55% and intracellular TFV-DP concentrations by 36% when given with RIF.[64, 65, 66]

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 pharmacokinetic 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.[67]

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 pharmacokinetic 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.

This group plan to look at 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 Antiretroviral Pregnancy Registry (APR) to detect at least a 1.5-fold increase in risk of overall birth defects and a 2-fold increase in risk of birth defects in the more common classes, cardiovascular and genitourinary systems, compared to the population-based rate.[68]

There are 3/110 and 0/50 birth defects reported to APR after first and second/third trimester 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 pharmacokinetic data are needed.

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

Darunavir/ritonavir

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

DRV/r remains a potential candidate for dose optimisation. Results from the original dose finding studies and two with 600/100 mg once daily, plus one showing the recommended dose of cobicistat results in a significantly lower DRV Cmin than when it is boosted with ritonavir (in which the investigators say a reduction of up to 50% in Cmin should not make a difference to efficacy), suggest that a dose reduction to DRV/r 400/100 mg might be feasible.[69, 70, 71]

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.[72]

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

Unexpectedly total blood plasma exposure of ritonavir trended to be higher in 400/100mg once-daily, than in 800/100mg once-daily due to a change in the inducer/inhibitor balance between DRV and RTV.[73]

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.[74]

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 in 2019.

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.[75, 76] There is sufficient data for DRV/r to exclude a two-fold increased risk of birth defects. Like other protease inhibitors it crosses the placenta poorly.

Darunavir and TB

There have been no previous drug interaction studies with DRV/r and RIF. One has recently been conducted with results expected at CROI 2019.

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 in ongoing.

The studies are: ADVANCE, a three-arm randomised comparison between two DTG-based regimens (one with TDF/FTC and the other with TAF/FTC) and EFV 600 mg (with TDF/FTC); and NAMSAL (which presented 48 week results last year, see above) comparing DTG-based to EFV 400 mg based regimens, conducted in South Africa and Cameroon respectively[77, 78, 79, 80]

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

Table 3: First-line ongoing

STUDY/ COHORT	DESIGN	PURPOSE	STATUS
ADVANCE WRHI 060 Wits RHI (USAID, Unitaid)	Phase 3 DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF non-inferiority, open label 1050 ART-naive adult participants >12 years randomised 1:1:1 Johannesburg, South Africa	Establish non-inferior efficacy for DTG/FTC/TAF compared to other study arms Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 96 weeks, CD4 changes, tolerability, safety and efficacy	Started January 2017 Fully recruited (May 2018) Week 48 data available Q2 2019 Completion Q1 2020
NAMSAL ANRS 12313 Inserm-ANRS (Unitaid)	Phase 3 DTG/3TC/TDF vs EFV400 mg /3TC/ TDF non-inferiority, open label 606 ART-naive participants (303 per arm) Yaoundé, Cameroon	Establish non-inferior efficacy for DTG/3TC/ TDF compared to EFV 400 mg/3TC/TDF Primary outcome number of participants with VL <50 copies/mL at 48 weeks Secondary outcomes include: VL <50 copies/mL at 24 weeks, CD4 changes, tolerability, safety and efficacy	Week 48 data 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: 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

Pregnancy

VESTED (IMPAACT P2010) is recruited and ongoing. The study is making the same three-arm comparison as ADVANCE but in pregnant women.[81,82]

DolPHIN2 is looking at DTG pharmacokinetic, safety and efficacy in pregnant women presenting in the third trimester, postpartum, and during breast feeding until weaning or 18 months.[83, 84] First results with all deliveries will be presented at CROI 2019.[85]

IMPAACT P1026s and PANNA – the respective American and European studies that look at pharmacokinetic of antiretrovirals in pregnancy and post-partum include women receiving DTG and TAF.[86, 87, 88, 89] 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.[90, 91] Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.

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

ADVANCE gives women who become pregnant during the study the option to continue on their study drugs.[92]

Table 4: Pregnancy dolutegravir – ongoing

STUDY	DESIGN	PURPOSE	STATUS
DolPHIN2 UoL (UCT, MU, LSTM, RU) (Unitaid)	Phase 3 DTG PK, safety and efficacy in pregnant women in 3rd trimester and PP during BF until weaning or 18 months 250 late presenting women (28 weeks' gestation to delivery) Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs South Africa and Uganda	Primary efficacy endpoint: proportion VL <50 at delivery Primary safety endpoint: safety of DTG in pregnancy Secondary: time to undetectable VL, CD4 response, VL in breastmilk, genital HIV shedding, health economics	Recruited First results to be 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 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 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 6: 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 10/16 recruited Primary completion December 2020
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; Wits RHI, Wits Reproductive Health and HIV Institute

Tuberculosis

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

Serious toxicities were seen in healthy volunteers in a drug-drug interaction study of once-weekly INH and RIF with once-daily DTG.[93] As such toxicities are not usually predictive of those in patients, the IMPAACT-4TB programme includes a single-arm phase 1/2 pharmacokinetic and safety study of DTG-based ART and once-weekly INH and RIF in HIV positive adults with latent TB infection.[94] Results will be presented at CROI 2019.[95]

Table 7: Dolutegravir and TAF TB – ongoing + planned

STUDY	DESIGN	PURPOSE	STATUS
DTG 50 mg/RIF UCT (Wellcome Trust)	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	Finalsing protocol
IMPAACT 4TB Aurum Institute	Phase 1/2 Group 1: 1st 12 participants (Group 1a) PK DTG 50mg once daily + 2NRTIs + once weekly RPT/INH Next 18 participants (Group 1B) PK either DTG 50mg or a higher or more frequent dose, if adjustment is needed, + RPT/INH Group 2: Next 30 participants will PK DTG as Group 1B VL measured at protocol-defined intervals	PK, safety, and tolerability of once-weekly RPT/INH (3HP) for the treatment of latent tuberculosis infection in HIV + DTG-based ART	Results CROI 2019
EPITAF Wits RHI/UCT (Unitaid)	30 HIV/TB-coinfected participants	TAF/RIF PK in HIV/TB coinfection	Finalising protocol

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.[96, 97]

Participants were genotyped at screening and only those with at least one predicted active NRTI were included. The study was stopped early, at 24 weeks, after the DTG arm showed greater viral suppression rates than the LPV/r arm. Week 48 data, where these are available, will be shown at AIDS 2018.[98]

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

The D2EFT study is investigating DRV/r 800/100 mg + DTG (which would have no overlapping resistance with EFV + 2 NRTI) vs DTG + 2 predetermined NRTIs vs DRV/r 800/100 mg + 2 NRTIs.[99]

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

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

Data to guide the use of DRV/r with TB treatment are missing and the DARifi pharmacokinetic study is comparing 1600/200 mg once daily with RIF and DRV/r 800/100 mg 12 hourly with RIF to DRV/r 800/100 mg without RIF. First data will be shown at CROI 2019.[100]

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.

Table 9: Second-line dolutegravir and darunavir/r – ongoing + planned

STUDY	DESIGN	PURPOSE	STATUS
DAWNING	Phase 3b Open label study to evaluate the safety and efficacy of DTG + 2 NRTIs (genotype guided) vs LPV/r + 2 NRTIs in participants failing first-line NNRTI + 2 NRTIs 624 participants Multicountry: Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russian Federation, South Africa, Thailand, Ukraine	Primary endpoint: proportion with VL <50 copies/mL at week 48	IDMC conducted an ad hoc review of week 24 data Recommended discontinuation of LPV/r arm due to differences in rates of virological nonresponse and increasing differences in rates of virological failure favouring the DTG arm 82% of participants on DTG vs 69% on LPV/r achieved viral load <50 copies/mL Week 48 data AIDS 2018 Superior efficacy DTG arm
Evaluation of low dose darunavir in a switch study WRHI052 Wits RHI (USAID, MRC SA)	Phase 3 300 participants stable on LPV/r + 2 NRTI twice daily randomised to stay or switch to DRV/r 400/100 mg once daily 48 weeks	400/100 mg DRV/r is non-inferior to LPV/r in virologically suppressed participants Primary endpoint VL <50 copies/mL at 48 weeks Secondary endpoints include clinical and laboratory markers	Week 48 data AIDS 2018 Non-inferior efficacy DRV/r 400/100 mg once daily arm
D2EFT Kirby Institute (Unitaid, US National Institute of Allergy and Infectious Disease, National Health and Medical Research Council, Australia)	Phase 3b/4 1,010 participants who failed first-line regimen randomised to DRV/r 800/100 mg + DTG vs DTG + 2 predetermined NRTIs vs DRV/r 800/100 mg + 2 NRTIs 96 weeks Multicountry: Argentina, Brazil, Chile, Colombia, Mexico, Guinea, Mali, Nigeria, South Africa, Zimbabwe, India, Malaysia, Thailand, Indonesia	To compare two DTG-based second-line regimens with standard of care and with each other Primary endpoint VL <50 at 48 weeks Secondary endpoints include differences in VL using different thresholds, time to VL <50 copies, changes in baseline CD4 count	Recruiting Primary completion December 2020
NADIA Coordinated by MU	Phase 3 Approx 420 participants with virological failure on EFV-based 1st line randomised to DTG vs DRV/r once daily + (second factorial) TDF/XTC vs AZT/3TC 96 weeks Uganda + multicountry	Compare DTG and DRV/r based regimens Compare TDF/XTC vs AZT/backbone without genotype Primary endpoint: VL <200 at 96 weeks Interim analysis at 48 weeks	Finalising ethics approval

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

Table 9: Additional darunavir/r studies

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

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

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 Organisation

1. WHO. Updated recommendations on rst-line and second-line antiretroviral regimens and post-exposure prophylaxis and recommendations on early infant diagnosis of HIV. December 2018 https://apps.who.int/iris/bitstream/handle/10665/277395/WHO-CDS-HIV-18.51-eng.pdf
2. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition. June 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/.
3. WHO policy brief. Antiretroviral regimens for treating and preventing HIV infection and update on early infant diagnosis of HIV. July 2018. Forthcoming.
4. WHO.Programmatic considerations for countries transitioning to new ARV regimens. Forthcoming.
5. Cournil A et al. Dolutegravir- versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Oral abstract O342.
6. ANRS/Unitaid press release. Dolutegravir, an alternative first-line HIV treatment for low and middle-income countries. 31 October 2018. https://unitaid.org/news-blog/dolutegravir-an-alternative-first-line-hiv-treatment-for-low-and-middle-income-countries/#en
7. WHO statement on DTG. 18 May 2018. http://www.who.int/medicines/publications/drugalerts/Statement_on_DTG_18May_2018final.pdf (PDF)
8. Zash R et al. Dolutegravir/tenofovir/emtricitabine (DTG/TDF/FTC) started in pregnancy is as safe as efavirenz/tenofovir/emtricitabine (EFV/TDF/FTC) in nationwide birth outcomes surveillance in Botswana. IAS 2017. 23–26 July 2017. Paris. Oral abstract MOAX0202LB. http://programme.ias2017.org/Abstract/Abstract/5532
9. Clayden P. Preliminary results on dolutegravir use in pregnancy are reassuring. HTB. 10 August 2017. http://i-base.info/htb/32182
10. Zash, R et al. Comparative safety of dolutegravir-based or efavirenz-based antiretroviral treatment started during pregnancy in Botswana: an observational study. Lancet Glob Health. Published online 4 June 2018. https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30218-3/fulltext

11. PEPFAR statement on potential safety issue affecting women living with HIV using dolutegravir at the time of conception. https://www.pepfar.gov/press/releases/282221.htm
12. US FDA. FDA Drug Safety Communication: FDA to evaluate potential risk of neural tube birth defects with HIV medicine dolutegravir (Juluca, Tivicay, Triumeq). 18 May 2018. https://www.fda.gov/Drugs/DrugSafety/ucm608112.htm
13. EMA press release. New study suggests risk of birth defects in babies born to women on HIV medicine dolutegravir. 18 May 2018. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/05/news_detail_002956.jsp&mid=WC0b01ac058004d5c1
14. 9. GSK Dear Doctor letter. Tivicay (dolutegravir), Triumeq (dolutegravir, abacavir, lamivudine), Juluca (dolutegravir, rilpivirine): neural tube defects reported in infants born to women exposed to dolutegravir at the time of conception. Ref: IE/DLG/0001/18. (22 May 2018). http://www.hpra.ie/docs/default-source/default-document-library/important-safety-information—tivicay-(dolutegravir)-triumeq-(dolutegravir-abacavir-lamivudine)-juluca-(dolutegravir-rilpivirine).pdf?sfvrsn=0
15. ViiV Healthcare. Full prescribing information: dolutegravir; 2013. www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf
16. Kandel CE et al. A review of the pharmacology, efficacy, and safety in the treatment of HIV. Drug Des Devel Ther 2015; 9: 3547– 3555. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4500604/
17. Hill A et al. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. J Virus Erad. 2018 Apr; 4(2): 66–71.
18. World Health Organization Transition to new antiretrovirals in HIV programmes; 2017. http://apps.who.int/iris/bitstream/handle/10665/255888/WHO-HIV-2017.20-eng.pdf https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5892677/
19. Vitoria M et al. When could new antiretrovirals be recommended for national treatment programmes in low-income and middle-income countries: results of a WHO think tank. Curr Opin HIV AIDS 2017; 12: 414– 422. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5459586/toxic
20. Mofensen L. In utero ART exposure and the need for pharmacovigilance. Lancet Glob Health. Published online 4 June 2018. https://www.thelancet.com/journals/langlo/article/PIIS2214-109X(18)30272-9/fulltext
21. 24. Clayden P. Brazil to start using dolutegravir first-line in its national programme. HTB. 1 October 2016. http://i-base.info/htb/30673
22. The Antiretroviral Pregnancy Registry http://www.apregistry.com
23. Antiretroviral Pregnancy Registry Steering Committee. Antiretroviral Pregnancy Registry Interim Report for 1 January 1989 through 31 July 2018. Wilmington, NC: Registry Coordinating Center; 2018. http://www.apregistry.com/forms/interim_report.pdf
24. Thorne C et al. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. IAS 2017. 23–26 July 2017. Paris. Poster abstract MOPEC0609. http://programme.ias2017.org/Abstract/Abstract/4549
25. Thorne C et al. Pregnancy and neonatal outcomes following prenatal exposure to dolutegravir. 9th International Workshop on HIV Pediatrics 2017. 21–22 July 2017. Paris. Oral abstract 10. http://regist2.virology-education.com/2017/9HIVped/26_Thorne.pdf
26. Money D et al. An analysis of congenital anomalies in pregnant women living with HIV in Canada: no signal for neural tube defects in women exposed to dolutegravir. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P001.
27. Weisman D et al. Use of integrase inhibitors in HIV-positive pregnant women: data from the Frankfurt HIV Cohort . HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P002.
28. Kowalska J et al. Exposure to dolutegravir in pregnant HIV-positive women in Central and Eastern Europe and neighbouring countries: data from the ECEE Network Group. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Poster abstract P004.
29. 29. FDAable http://www.fdable.com/basic_query/aers
30. Hill A et al. Reports of neural tube defects for 8 arts, in FDA, WHO, EMA, and UK safety databases. CROI 2019. Seattle. 4–7 March. Oral abstract 40 LB. Poster abstract 746.
31. Hill A et al. Safety and pharmacokinetics of dolutegravir in HIV-positive pregnant women: a systematic review. J Virus Erad. 2018 Apr; 4(2): 66–71.
32. Waitt C et al. DolPHIN-1: dolutegravir vs efavirenz when initiating treatment in late pregnancy. 25th CROI. Boston. 4–7 March 2018. Poster abstract 807. http://www.croiconference.org/sessions/dolphin-1-dolutegravir-vs-efavirenz-when-initiating-treatment-late-pregnancy (abstract and poster)
33. Orrell C et al. DolPHIN-1: Randomised controlled trial of dolutegravir (DTG)- versus efavirenz (EFV)-based therapy in mothers initiating antiretroviral treatment in late pregnancy. AIDS 2018. 23–27 July 2018. Oral abstract THAB0307LB. http://programme.aids2018.org/Abstract/Abstract/13144
34. IAS Forum on the risks of periconceptional dolutegravir exposure FAQs. https://www.iasociety.org/Portals/0/Files/DTG_FAQ.pdf
35. Dooley K et al. Safety and efficacy of dolutegravir-based art in TB/HIV coinfected adults at week 24. 25th CROI. Boston. 4–7 March 2018. Oral abstract 33. http://www.croiconference.org/sessions/safety-and-efficacy-dolutegravir-based-art-tbhiv-coinfected-adults-week-24 (abstract) http://www.croiwebcasts.org/console/player/37073 (webcast)
36. Dooley K et al. Safety and efficacy of dolutegravir-based ART in TB/HIV co-infected adults at week 48. AIDS 2018. Amsterdam. 23–27 July 2018. Oral abstract TUAB0206. http://programme.aids2018.org/Abstract/Abstract/6122 (abstract) https://www.youtube.com/watch?v=7XQjSgZKyyY (webcast)
37. Le M et al. Pharmacokinetic and efficacy of dolutegravir (50 mg BID) containing regimen in association with rifampin in HIV-infected patients using Dried Blood Spot:

ANRS-12313 NAMSAL sub-study in Cameroon. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 7. http://regist2.virology-education.com/presentations/2018/Antiviralpk/23_le.pdf (PDF)

38. FDA. TIVICAY (dolutegravir) tablets for oral use initial US approval: 2013. https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/204790lbl.pdf
39. Dooley K et al. Safety, tolerability, and pharmacokinetics of the HIV integrase inhibitor dolutegravir given twice daily with rifampin or once daily with rifabutin: results of a phase 1 study among healthy subjects. J Acquir Immune Defic Syndr. 2013 Jan 1;62(1):21-7. https://journals.lww.com/jaids/Abstract/2013/01010/Safety,_Tolerability,_and_Pharmacokinetics_of_the.4.aspx
40. Wang X et al. Pharmacokinetics of dolutegravir 100 mg once-daily with rifampicin. 19th International Workshop on Clinical Pharmacology. Baltimore. 22–24 May 2018. Oral abstract 11. http://regist2.virology-education.com/presentations/2018/Antiviralpk/22_boffito.pdf (PDF)
41. WHO technical update. Transition to new antiretroviral drugs in HIV programmes: clinical and programatic considerations. July 2017. http://apps.who.int/iris/bitstream/10665/255887/1/WHO-HIV-2017.23-eng.pdf
42. Hill AM et al. Risks of cardiovascular or central nervous system adverse events and immune reconstitution inflammatory syndrome, for dolutegravir versus other antiretrovirals: meta-analysis of randomised trials. Curr Opin HIV AIDS. 13 (2) March 2018. https://journals.lww.com/co-hivandaids/Abstract/2018/03000/Risks_of_cardiovascular_or_central_nervous_system.3.aspx
43. Elliot E et al. Relationship between dolutegravir plasma exposure, quality of sleep and its functional outcome in patients living with HIV over the age of 60 years. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy, 14- 16 June 2017, Chicago. Oral abstract O8. http://regist2.virology-education.com/2017/18AntiviralPK/11_Boffito.pdf (PDF)
44. Hill A et al. Are new antiretroviral treatments increasing the risks of clinical obesity? Journal of Virus Eradication 2019;5: e45–e47. http://viruseradication.com/journal-details/Are_new_antiretroviral_treatments_increasing_the_risks_of_clinical_obesity^
45. ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, doubleblind, placebo-controlled, non-inferiority trial. Lancet. April 2014. 383(9927):1474–82.
46. Boffito M et al. Pharmacokinetics, pharmacodynamics and pharmacogenomics of efavirenz 400mg once-daily during pregnancy and postpartum. IAS 2017. 23–26 July 2017. Paris. Poster abstract TUPDB0203LB. http://programme.ias2017.org/Abstract/Abstract/5612
47. Schalkwijk S et al. Pharmacokinetics of efavirenz 600 mg QD during pregnancy and postpartum. CROI 2016. 22–25 February. Boston. Poster abstract 433. http://www.croiconference.org/sites/default/files/posters-2016/433.pdf (PDF)
48. Puls R et al. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naive adults (ENCORE1): a randomised, double-blind, placebo-controlled, non-inferiority trial. Lancet. 2014 Apr 26;383(9927):1474-82. https://www.ncbi.nlm.nih.gov/pubmed/24522178
49. Cerrone M et al. Pharmacokinetics of efavirenz 400mg with isoniazid/rifampicin in people with HIV. 25th CROI. Boston. 4–7 March 2018. Poster abstract 457. www.croiconference.org/sites/default/files/posters-2018/1430_Cerrone_457.pdf
50. Ford N et al. Is the pricing of antiretrovirals equitable? Analysis of antiretroviral drug prices in 20 low- and middle-income countries. 7th IAS Conference on HIV Pathogenesis Treatment and Prevention, 30 June – 3 July 2013, Kuala Lumpur, Malaysia. Oral abstract WELBDO. http://pag.ias2013.org/flash.aspx?pid=596. http://pag.ias2013.org/Abstracts.aspx?SID=72&AID=3102.
51. Sax PE et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of HIV-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. Lancet. 27 Jun 2015;385(9987):2606-15.
52. FDA tentative approval letter dolutegravir, emtricitabine, and tenofovir alafenamide. 9 February 2018. https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/210237Orig1s000TAltr.pdf
53. Clayden P. FDA grants tentative approval to first DTG/FTC/TAF FDC. HTB. 21 February 2018. http://i-base.info/htb/33537
54. CHAI. ARV market report. Issue 8. 28 September 2017. https://clintonhealthaccess.org/content/uploads/2017/09/2017-ARV-Market-Report_Final.pdf (PDF)
55. WHO. Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach – Second edition. June 2016. http://www.who.int/hiv/pub/arv/arv-2016/en/
56. WHO model list of essential medicines. August 2017. http://www.who.int/medicines/publications/essentialmedicines/20th_EML2017_FINAL_amendedAug2017.pdf
57. WHO. Transition to new antiretrovirals in HIV programmes. July 2017. http://apps.who.int/iris/bitstream/10665/255888/1/WHO-HIV-2017.20-eng.pdf
58. Vitoria et al. The transition to dolutegravir and other new antiretrovirals in low- and middle- income countries – what are the issues? AIDS, Publish ahead of print 9 May 2018. DOI: 10.1097/QAD.0000000000001845. https://journals.lww.com/aidsonline/Abstract/publishahead/The_transition_to_dolutegravir_and_other_new.97225.aspx
59. WHO. Third conference on antiretroviral drug optimisation (CADO 3): summary meeting report, 29 November to 1 December 2017, Rosebank Crowne Plaza, Johannesburg, South Africa. http://apps.who.int/iris/bitstream/handle/10665/272291/WHO-CDS-HIV-18.6-eng.pdf

60. Hill A et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety? Fourth Joint Conference of BHIVA/BASHH. Edinburgh. 17–20 April 2018. Poster abstract P27.
61. Hill A et al. Tenofovir alafenamide versus tenofovir disoproxil fumarate: is there a true difference in efficacy and safety. Journal of Virus Eradication 4: 73-80, 2018. http://viruseradication.com/journal-details/Tenofovir_alafenamide_versus_tenofovir_disoproxil_fumarate:_is_there_a_true_difference_in_efficacy_and_safety%5E/
62. Custodio JM et al. Twice daily administration of tenofovir alafenamide in combination with rifampin: potential for tenofovir alafenamide use in HIV-TB coinfection. 16th European AIDS Conference (EACS). October 25–27 2017. Milan. Oral abstract PS13/4.
63. Clayden P. Once-daily tenofovir alafenamide appears sufficient when dosed with rifampicin. HTB. 14 March 2018. http://i-base.info/htb/33633
64. Cerrone M et al. Rifampin effect on tenofovir alafenamide (TAF) plasma/ intracellular pharmacokinetics. 25th CROI. Boston. 4–7 March 2018. Oral abstract 28LB.
65. Clayden P. Twice-daily tenofovir alafenamide dose might overcome interaction with rifampicin. HTB. 28 November 2017. http://i-base.info/htb/32909
66. National Institutes of Health. RIFT: Effect of rifampicin on plasma PK of FTC, TAF and intracellular TFV-DP and FTC-TP. https://clinicaltrials.gov/ct2/show/NCT03186482
67. Momper JD et al. Tenofovir alafenamide pharmacokinetics with and without cobicistat in pregnancy.AIDS 2018. Amsterdam. 23–27 July 2018. Oral abstract THAB0302. http://programme.aids2018.org/Abstract/Abstract/5960 (abstract) https://www.youtube.com/watch?v=djY2rjG_F-c (webcast)
68. Antiretroviral Pregnancy Registry International Interim Report for 1 January 1989 through 31 July 2018. http://www.apregistry.com/forms/interim_report.pdf
69. Molto J et al. Reduced darunavir dose is as effective in maintaining HIV suppression as the standard dose in virologically suppressed HIV-infected patients: a randomised clinical trial. J Antimicrob Chemother. 2015 Apr;70(4):1139-45
70. Lanzafame M et al. Efficacy of a reduced dose of darunavir/ ritonavir in a cohort of antiretroviral naive and experienced HIV-infected patients: a medium-term follow-up. J. Antimicrob. Chemother. 2015 Feb;70(2):627-30.
71. Kakuda TN et al. Pharmacokinetics of darunavir in fixed dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. J Clin Pharmacol. 2014 Aug;54(8):949-57.
72. Molina JM et al. Efficacy and safety of 400 mg darunavir/100 mg ritonavir with TDF/FTC or ABC/3TC in virologically suppressed HIV-1 infected adults: an open-label study – ANRS-165 Darulight. IAS 2017. 23–26 July 2017. Paris. Poster abstract MOPEB0313. http://programme.ias2017.org/Abstract/Abstract/1075
73. Lê MP et al. Pharmacokinetic modelling of darunavir/ritonavir dose reduction (800/100 mg to 400/100mg once daily) containing regimen in virologically suppressed HIV-infected patients as maintenance treatment: ANRS-165 DARULIGHT sub-study. Poster abstract MOPEB0329. http://programme.ias2017.org/Abstract/Abstract/1586
74. Venter F et al. Non-inferior efficacy for darunavir/ritonavir 400/100 mg once daily versus lopinavir/ritonavir, for patients with HIV RNA below 50 copies/mL in South Africa: The 48-week WRHI 052 study. IAS 2018. 23–27 July 2018. Oral abstract TUAB0107LB. http://programme.aids2018.org/Abstract/Abstract/13192
75. Khoo S et al. Pharmacokinetics and Safety of darunavir/Ritonavir in HIV-Infected Pregnant Women. AIDS Rev 2017 Jan-Mar;19(1):16-23.
76. Slogrove AL et al. Toward a universal antiretroviral regimen: special considerations of pregnancy and breast feeding. Current Opinion in HIV & AIDS. 12(4):359-368, July 2017. http://journals.lww.com/co-hivandaids/Fulltext/2017/07000/Toward_a_universal_antiretroviral_regimen__.10.aspx
77. US National Institutes of Health. ADVANCE Study of DTG + TAF + FTC vs DTG + TDF + FTC and EFV + TDF+FTC in first-line antiretroviral therapy (ADVANCE) https://clinicaltrials.gov/ct2/show/NCT03122262
78. Venter WDF et al. The ADVANCE study: a groundbreaking trial to evaluate a candidate universal antiretroviral regimen. Current Opinion in HIV & AIDS. 12(4):351-354, July 2017. http://journals.lww.com/co-hivandaids/Fulltext/2017/07000/The_ADVANCE_study___a_groundbreaking_trial_to.8.aspx
79. US National Institutes of Health. Efficacy and safety of a dolutegravir-based regimen for the initial management of HIV infected adults in resource-limited settings (NAMSAL) https://clinicaltrials.gov/ct2/show/NCT02777229
80. Cournil A et al. Dolutegravir- versus an efavirenz 400 mg-based regimen for the initial treatment of HIV-infected patients in Cameroon: 48-week efficacy results of the NAMSAL ANRS 12313 trial. HIV Glasgow. 28–31 October 2018. Glasgow, UK. Oral abstract O342.
81. VESTED/IMPAACT 2010 protocol. Final version 1.0. 1 December 2016. http://www.impaactnetwork.org/DocFiles/IMPAACT2010/IMPAACT2010_FINALv1.0_01DEC2016.pdf
82. US National Institutes of Health. Evaluating the efficacy and safety of dolutegravir-containing versus efavirenz-containing antiretroviral therapy regimens in HIV-1-infected pregnant women and their infants. (VESTED) https://clinicaltrials.gov/ct2/show/NCT03048422
83. US National Institutes of Health. Dolutegravir in pregnant HIV mothers and their neonates (DolPHIN-2). https://clinicaltrials.gov/ct2/show/NCT03249181
84. DolPHIN 2 website. https://www.dolphin2.org

85. Kintu K et al. RCT of dolutegravir vs efavirenz-based therapy initiated in late pregnancy: DolPHIN-2. CROI 2019. Seattle. 4–7 March. Oral abstract 40 LB.
86. US National Institutes of Health. Pharmacokinetic study of antiretroviral drugs and related drugs during and after pregnancy. https://clinicaltrials.gov/ct2/show/NCT00042289
87. Mulligan N et al. Dolutegravir pharmacokinetics in HIV-infected pregnant and postpartum women. Conference on Retroviruses and Opportunistic Infections (CROI) 2016. 22–25 February 2016. Boston, Massachusetts. Poster abstract 438. http://www.croiconference.org/sessions/dolutegravir-pharmacokinetics-hiv-infected-pregnant-and-postpartum-women-0
88. US National Institutes of Health. Pharmacokinetics of antiretroviral agents in HIV-infected pregnant women. (PANNA). https://clinicaltrials.gov/ct2/show/NCT00825929
89. Bollen P et al. A comparison of the pharmacokinetics of dolutegravir in pregnancy and postpartum. 18th International Workshop on Clinical Pharmacology of Antiviral Therapy. 14-16 June 2017. Chicago. Oral abstract 0_7. http://regist2.virology-education.com/2017/18AntiviralPK/10_Bollen.pdf
90. US National Institutes of Health. A study to determine safety and efficacy of dolutegravir/abacavir/lamivudine (DTG/ABC/3TC) in human immunodeficiency virus (HIV)-1 infected antiretroviral therapy (ART) naive women (ARIA). https://clinicaltrials.gov/ct2/show/NCT01910402
91. Clayden P. Dolutegravir is superior to boosted atazanavir in women in the ARIA study. HTB. 1 August 2016. http://i-base.info/htb/30376
92. US National Institutes of Health. ADVANCE Study of DTG + TAF + FTC vs DTG + TDF + FTC and EFV + TDF+FTC in first-line antiretroviral therapy (ADVANCE) https://clinicaltrials.gov/ct2/show/NCT03122262
93. Brooks KM et al. Cytokine-mediated systemic adverse drug reactions in a drug-drug interaction study of dolutegravir with once-weekly isoniazid and rifapentine. Clin Inf Dis Feb 3 2018. https://academic.oup.com/cid/advance-article-abstract/doi/10.1093/cid/ciy082/4836314
94. US National Institutes of Health. Safety tolerability DDI short course treatment of LTBI infection with high-dose rifapentine isoniazid in HIV+ patients (IMPAACT4TB). https://clinicaltrials.gov/ct2/show/NCT03435146
95. Dooley K et al. Safety & PK of weekly rifapentine/isoniazid (3HP) in adults with HIV on dolutegravir. CROI 2019. Seattle. 4-7 March. Oral abstract 80 LB.
96. US National Institutes of Health. Comparative efficacy and safety study of dolutegravir and lopinavir/ritonavir in second-line treatment. https://clinicaltrials.gov/ct2/show/NCT02227238
97. Aboud M et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/RTV) plus 2 NRTIs in second-line treatment: interim data from the DAWNING study. IAS 2017. 23–26 July 2017. Paris. Oral abstract TUAB0105LB.
98. Aboud M et al. Superior efficacy of dolutegravir (DTG) plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) compared with lopinavir/ritonavir (LPV/r) plus 2 NRTIs in second-line treatment – 48-week data from the DAWNING Study. AIDS 2018. 23–27 July 2018. Poster abstract THAB0302. http://programme.aids2018.org/Abstract/Abstract/5633
99. US National Institutes of Health. A phase IIIB/IV randomised open-label trial comparing dolutegravir with pharmaco-enhanced darunavir versus dolutegravir with predetermined nucleosides versus recommended standard of care ART regimens in patients with HIV-1 infection failing first line. https://clinicaltrials.gov/ct2/show/NCT03017872
100. Ebrahim I et al. Pharmacokinetics and safety of adjusted darunavir/ritonavir with rifampin in PLWH. CROI 2019. Seattle. 4–7 March. Oral abstract 80 LB. 81 LB.

HIV pipeline 2019: new drugs in development

By Simon Collins, HIV i-Base

Introduction

The last year has been important for HIV research. There were five new approvals of new drugs or fixed dose combinations (FDCs), including the first in class monoclonal antibody. But, not all drugs have been approved yet in both the US and the EU and one was only approved in China.

After a long development history, the first monoclonal antibody (mAb) was approved for HIV treatment. Other compounds in the class are already in development with potential for treatment, prevention and cure. Not only does this class offer hope for people with difficult multidrug resistance, but several mAbs are being studied for their potential to control HIV without ART.

While mAbs are expensive, newer more potent compounds will be discovered (including biphasic 10E8.4/iMab) that have broader coverage and potency.[1, 2] Easier ways to deliver mAbs are an important research focus that with time might allow lower cost alternatives to IV infusions that can easily be self-administered. Developing the best antibody combination will also be challenging, including the differences in sensitivity by HIV sub-clade, especially for prevention research.[3]

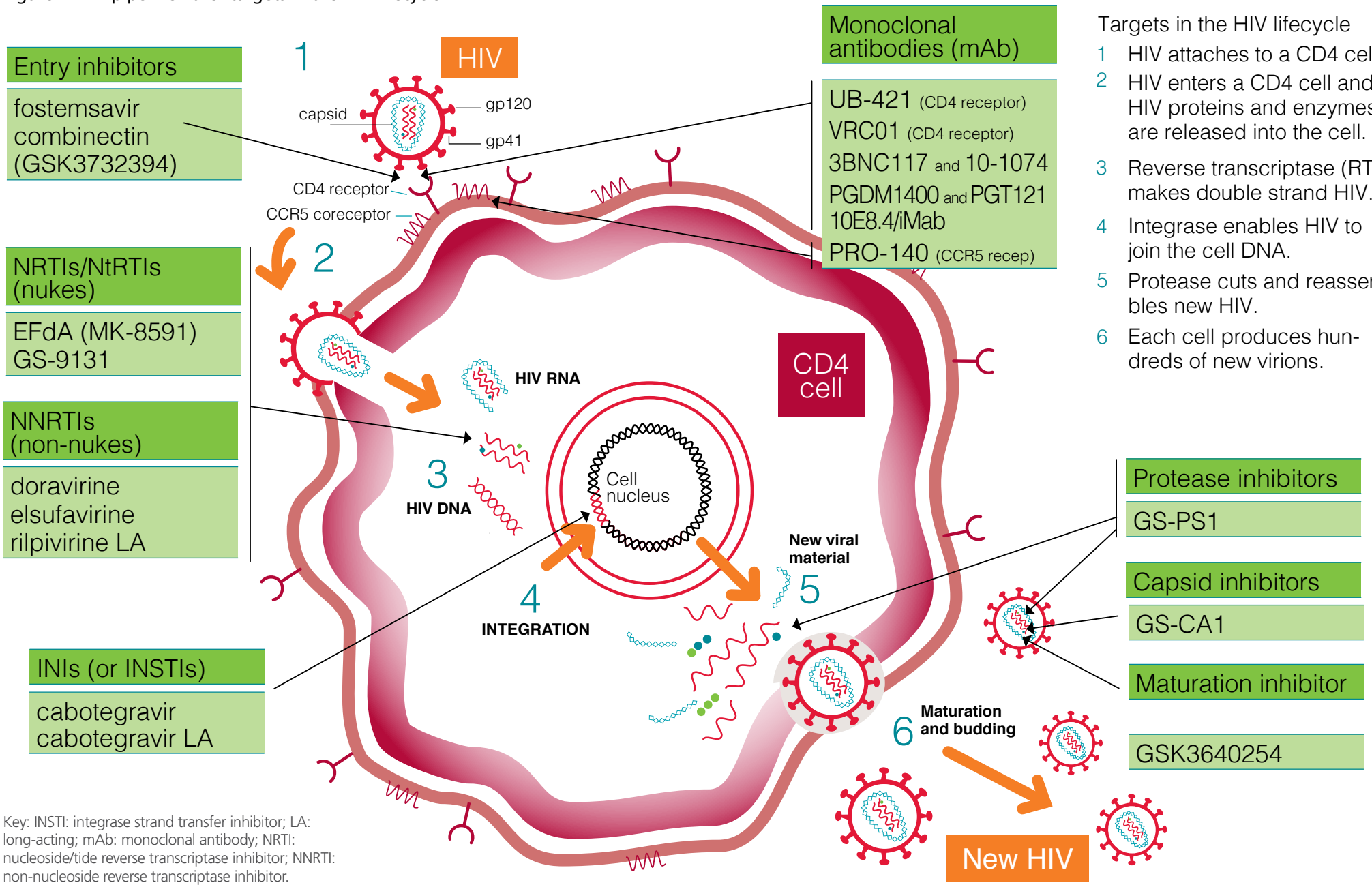
Several other compounds have been submitted with regulatory decisions expected later in 2019.

This report reviews these recently approved compounds and others in the HIV pipeline.

Figure 1 updates the HIV pipeline by target and Tables 1 and 2 summarise compounds by development stage and likely use.

This report is a reduced version of the 2018 pipeline report, updated tor CROI 2019.

Figure 1: HIV pipeline 2019: 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. Each cell produces hundreds of new virions.

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

Recently approved new HIV drugs

Over the last year, in different regions, five new drug or FDCs were approved

Darunavir/cobicistat/FTC/TAF (Symtuza)

The first protease inhibitor based FDC was approved in July 2018 in the US (although approved in six months earlier in the EU.[4, 5]

This once-daily FDC combines darunavir 800 mg, cobicistat 150 mg, emtricitabine 200 mg and tenofovir alafenamide 10 mg (D/C/F/TAF).

It was developed through a collaboration between Janssen and Gilead and is marketed by Janssen-Cilag with the brand name Symtuza.

- The indication is for HIV positive adults and adolescents aged 12 years and older.
- The combination needs to be taken once-daily with food.
- Approval is based on phase 3 studies showing bioequivalence to the individual components being taken as single drugs.

Bictegravir/FTC/TAF (Biktarvy)

In February 2018, the US FDA approved a new FDC containing bictegravir, emtricitabine and tenofovir alafenamide (TAF), with approval in the EU following in June.[6, 7]

Bictegravir is an integrase inhibitor with a 50 mg dose that does not need to be boosted or taken with food. It is coformulated with 200 mg emtricitabine and a 25 mg dose of TAF.

The FDC is manufactured by Gilead Sciences and will be marketed with the brand name Bictarvy.

Numerous additional studies are listed on the US clinical trials registry as ongoing or recruiting, often looking at bictegravir as a switch option. These include a phase 2 dose-finding of Gilead's investigational NRTI GS-9131 that is being studied in HIV positive women on failing ART at baseline in Uganda. This is also of interest as the optimised ART regimen uses GS-9131 with bictegravir and boosted darunavir.[8]

Ibalizumab (Trogarzo) – mAb

In March 2018, the US FDA approved ibalizumab as the first monoclonal antibody to treat HIV positive people with multidrug resistance who are currently on failing ART.[9]

The company is actively engaged with the EMA to pursue the regulatory pathway for ibalizumab in the EU.

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. [10

The ibalizumab programme was led by David Ho at the Aaron Diamond AIDS Research Centre who has recently identified a new bispecific monoclonal antibody 10E8.4/iMab. This molecule has greater potency and coverage than most other

bNAbs and an ongoing phase 1 study included both HIV positive and negative participants, reflecting its potential use as both treatment and prevention.[11]

Albuvirtide (Aikening)

Albuvirtide injections are marketed by Frontier Biotech with the trade name Aikening, but it is only approved in China.[12]

This is a rare example of an HIV treatment not being first approved in either the US or EU.

Albuviride works at an early stage of the HIV lifecycle by blocking attachment to CD4 cells. It has a similar structure and mechanism to an earlier HIV fusion inhibitor called enfuvirtide (T-20, Fuzeon) that was developed for people who had run out of treatment options.

In July 2017, the company announced a licensing agreement with Rockefeller University in the US to coformulated albuvirtide with the broad neutralising monoclonal antibody 3BNC117.

Doravirine and doravirine/TDF/3TC

Doravirine was approved in both the US and the EU, together with an FDC combined with generic tenofovir DF (TDF) and generic lamivudine (3TC).[13, 14]

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).

Although current guidelines have moved to recommending integrase inhibitor-based regimens as preferred first-line treatment, NNRTIs are likely to still be used before protease inhibitors as alternatives.

Doravirine has a better tolerability profile compared to efavirenz (which is still widely-used despite the guidelines), but its use might depend on being a less expensive option (including to integrase inhibitors). For this, doravirine will need to be priced very competitively.

Doravrine is also part of a very interesting FDC with 3TC plus the investigational (and highly potent) NRTI MK-8591. Results are expected mid-2019.[15]

Submitted applications or completed phase 3

Dolutegravir/lamivudine

A dual combination of the integrase inhibitor dolutegravir with a single NRTI lamivudine has already been submitted for regulatory decisions based on phase 3 studies presented at AIDS 2018.[16]

The GEMINI studies showed that dual therapy with DTG/3TC was non-inferior to the triple ART, with these particular drugs.

The disadvantages of dual therapy (for example, when HBV is a concern) are currently likely to outweigh advantages in low- and middle-income settings.

But, in high-income settings, with easier access to monitoring, the use for DTG/3TC is likely to be very different. The results are also encouraging for people who have complication related to use of current NRTIs.

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.

This compound is being developed by ViiV after being acquired from BMS (BMS-663068).

Updated 48-week results were presented at Glasgow 2018 from the phase 3 BRIGHTE study.[17]

This was an advanced patient group with CD4 count at screening less than 200 cells/mm3 and 50 cells/mm3 in 72% and 41% of the group respectively. Previous use of integrase inhibitors and protease inhibitors were reported for 80% and 96% respectively.

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.

Currently, the dosier is being prepared for submission to regulatory agencies. The company is also working on scaling up manufacturing capacity.

Compounds in phase 3 development

Several 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 oral and long acting

Cabotegravir (CAB) is a second-generation integrase inhibitor being developed both as an oral tablet and a long-acting (CAB-LA) injectable formulation.

The oral formulation is primarily to use as a lead-in safety drug before switching to CAB-LA injections. CAB-LA is being studied both as treatment (coformulated with rilpivirine LA) and as single drug for use as PrEP.

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

CAB-LA has an extremely long half-life: a single injection resulted in drug levels that were still detectable in some people after more than a year. This requires an essential oral dosing lead-in phase before using the injection to screen for risk of a hypersensitivity reaction. The long half-life means that anyone stopping CAB-LA when it is 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.

However, a presentation at the HIVR4P conference in October 2018 reported cases where therapeutic levels of CAB could still be detected after 2.5 years in men and 3.5 years in women.[18]

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

Although the potential to use injections rather than oral drugs generates a lot of interest, there is little new data to add to last years pipeline report. This is mainly 96-week results from the phase 2b LATTE-2 study that were presented at IAS 2017 (and simultaneously published in the Lancet) that were comparable to 48-week data.[19, 20]

The 96-week results presented at IAS 2017 showed CAB maintained viral suppression to <50 copies/mL in 94%, 87% and 84% of participants in the 8 week, 4 week and oral groups respectively. Both injection schedules were non-inferior to oral dosing: 8 week: difference +10.0% (95%CI: –0.6% to +20.5%) and 4 week: +3.0% (95%CI: –8.4% to +14.4%). This compared to viral suppression rates at week 48 of 92%, 91% and 89%, respectively.

Serious adverse events occurred in 10%, 10% and 13% in the 8 week, 4 week and oral groups respectively, but none were judged drug-related.

Injection site reactions (ISRs) were common (>80% at day 1 and at ~30 to 40% in injection arms throughout follow-up), occurring slightly more in the 8 week group, but 84% overall were mild and 15% were moderate. Most common ISR events were pain (66%), nodules (8%), swelling (6%), and pruritus (6%). Median duration of ISRs was 3 days, with 89% resolving in <7 days. Only two participants (both in the 8 week group) discontinued due to ISRs.

Several phase 3 studies are already recruited and ongoing. These include the ATLAS, FLAIR and the ATLAS-2M study with top-line results from ATLAS reported in August 2018.[21]

ViiV have also announced a compassionate access/named patient programme for CAB-LA for people who are either not eligible for the phase 3 study or who need CAB to construct a new combination. This is an international study, with sites in the US, Canada, France, Portugal, Switzerland and the UK.[22]

Several international phase 3 studies of CAB-LA for PrEP are also underway using oral TDF/FTC as the control group. New nanoformulations of CAB-LA are also in development.

Results from a macaque study included encouraging data for CAB-LA use as PrEP were presented at CROI 2018 showing protection from penile infection.

PRO 140 – mAb

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

PRO 140 has been in development for more than a decade, but that has been designated by the FDA for fast-track status, for potential to treat MDR HIV.

When used as a switch treatment, after viral suppression on oral ART, the weekly infusion of PRO 140 monotherapy has maintained viral suppression in some participants for more than two years.

Although new data have not been presented since CROI 2017, in February 2018, CytoDyn issued a press release reporting that a new phase 2/3 study had reached the primary endpoint (reduction of >0.5 log copies/mL at one week compared to placebo).[23, 24]

This ongoing study includes 52 treatment-experienced participants on currently failing ART (viral load > 400 copies/mL) who had drug resistance to three classes and limited treatment options. After adding PRO 140 or placebo monotherapy for one week, all participants continue with weekly infusions of the active drug plus optimised ART for 24 weeks. Results are expected later in 2019.[25]

The other ongoing phase 2b/3 study is a monotherapy switch study in 300 participants who have been on stable ART with viral load <50 copies/mL for >24 weeks, with a primary endpoint of viral suppression at 48 weeks. Although the clinical trials registry lists this study as still open to recruitment – all sites are in the US – it also states the expected end date of 2018.[26]

Several other studies, both with ART and as monotherapy, are ongoing to collect longer follow-up.

PRO 140 is also being studied in non-HIV settings as prophylaxis against graft vs host disease (GVHD) in people undergoing allogenic stem cell transplant.[27]

UB-421 – mAb

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

It is being developed by the Taiwanese company United BioPharma, with research sites in Taiwan. Although two phase 3 studies were listed to start in 2018, these are not yet open to recruitment.

One is a randomised (1:2) open label study in 375 participants on stable ART who will continue on their current treatment or switch to monotherapy with UB-421.[28]

The second will add UB-421 or placebo to currently failing ART in 20 treatment experienced participants with drug resistance, followed by optimised background ART and open label UB-421 to all participants out to 435 weeks.[29]

The most recent data were presented at CROI 2017 from a phase 2 study in 29 virally suppressed participants on ART who used UB-421 monotherapy during an 8-week treatment interruption. UB-421 was given by infusion either 10 mg/kg weekly or 25 mg/kg every two weeks.[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

MK-8591 (EFdA) – NRTI

MK-8591 is a very interesting NRTI in development by Merck. It is notable for high potency (currently using a 10 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.

Its profile suggests that a daily of 0.25 mg would retain full potency as part of an FDC for treatment.[31]

MK-8591 is fully active against NRTI mutations K65R and Q151M (although the M184V variant conferred 10-fold resistance) and is active against both HIV-1 and -2 (with greater potency against HIV-2).

EFdA achieves good drug levels in vaginal and rectal tissue – supporting further PrEP studies.

A single dose of MK-8591 (30 mg, 10 mg, 2 mg, 1 mg or 0.5 mg) in 30 treatment-naive participants (n=6 for each arm), 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).[32, 33]

The study also looked at the pharmacokinetics of different doses, especially drug levels in plasma and PBMCs and the impact on plasma and intracellular half-life for potential dosing schedules.

Both plasma and intracellular drug levels were dose-related, with higher doses achieving levels approximately 1 log higher with the half-life in PBMCs ranging from 78 to 128 hours, allowing for a wide range of potential dosing schedules.

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.[34]

The results were pretty remarkable: all animals receiving the placebo became infected within 1 to 4 challenges compared to none of the MK-8591 animals, even after 12 challenges and continued follow-up for a further three months. MK-8591 resulted in a 41.5-fold lower risk of infection (95% CI: 7.3 to 237.9) compared to placebo ($p < 0.0001$).

MK-8591 is also included in an FDC with 3TC and doravirine that is currently in an ongoing phase 2 study.[35]

Merck also have three compounds in phase 1 studies (MK-4250, MK-8583 and MK-8504) that might lead to future FDCs, although the trial lists do not include details on drug class.

GS-9131 – NRTI

GS-9131 is a prodrug of GS-9148 with early animal and in vitro drug resistance studies presented 13 years ago at CROI 2006.[36]

Other published studies highlight the potential for low risk of toxicity in animal studies and retention of in vitro phenotypic sensitivity to broad NRTI resistance including mutations at K65R, L74V and M184V and multiple TAMS.[37]

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 for GS-9131 in combination with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF. [38]

Currently, the only ongoing study with GS-9131 is a phase 2 dose-finding trial in 58 treatment-experienced women who have detectable viral load >500 copies/mL on current NRTI-including ART. GS-9131 will be added as monotherapy (using 30 mg, 60 mg and 90 mg doses) for 10 days after which background ART will be changed to bictegravir plus darunavir and ritonavir, with continued GS-9131.[39] This study only has sites in Uganda.

VRC01 – mAb

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 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]

Another study reported tentatively positive safety results from using a single injection in infants after birth to limit risk of vertical transmission and a potential role of additional injections for breastfed infants.[42]

Unfortunately, in a phase 1 study in adults, VRC01 produced no additional impact on reducing the latently infected viral reservoir after being added to ART. VRC01 also had little impact on time to viral rebound after stopping ART, as part of a strategy in cure research.

A new long-acting formulation – VRC01LS – is also in phase 1 studies, designed to improve the half-life of the antibody, administered IV.[43, 44]

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. The elsulfavirine arm reported similar viral suppression to <50 copies/mL (81% vs 73%), including those with baseline viral load >100,000 copies/mL (78% vs 62%), with fewer CNS side effects (32% vs 62%).[45]

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.[46]

ABX464 – Rev inhibitor

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

Although there are limited data for HIV treatment, results from a phase 2a dose-ranging study in 80 treatment-naive participants in Thailand reported 0.5 log copies/mL in 4/6 people at day 14 using the highest 150 mg dose as monotherapy (but with no response in 2/6).[47]

A phase 2b study looking at reducing the viral reservoir showes a reduction in viral DNA (the marker for the viral reservoir) was observed in 8/15 (53%) participants, there was no change in time to viral rebound: 13 vs 14 days for days ABX464 vs placebo.[48]

An open-label phase 2 pharmacokinetic study in 36 HIV positive participants is currently ongoing, looking at 50 mg and 150 mg once-daily dosing.[49]

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.[50, 51]

The development of an earlier maturation inhibitor, BMS-955176, also acquired from BMS, was discontinued in October 2016, based on 24-week results from the phase 2b AI468-038 study in treatment naive participants. This was due to gastrointestinal intolerability and treatment-emergent drug resistance. The ongoing studies with BMS-955176 (AI468-038 and AI468-048) were also ended early. Although discontinued, a poster at IAS 2017 on tolerability and side effects was important for the lack of signal for neuropsychological side effects with this class.[52, 53]

Other mAbs 3BNC117 and 10-1074; PGDM1400 and PGT121

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

Several phase 1 studies are using these compounds individually and together and also in longer-acting versions that have an FcRn binding site mutation (LS) to improve pharmacokinetics.

An ongoing phase 1, open label, dose-escalation study will enrol 30 participants and includes both HIV positive and HIV negative group.

Primary objectives are to evaluate the safety, tolerability and pharmacokinetics of a single infusion of 3BNC117-LS at 3 mg/kg, 10 mg/kg and 30 mg/kg doses.[54]

Three other phase 1 randomised studies are using a dual mAbs combination 3BNC117 with 10-1074 in HIV positive and negative participants.[55, 56, 57]

The first of these studies will evaluate the safety and antiretroviral activity of an infusion of 3BNC117 and 10-1074, administered intravenously at 30 mg/kg dose level in participants on ART, followed by six infusions of both antibodies at weeks 2, 4, 8, 12, 16 and 20 during an analytical treatment interruption (ATI).

The ATI lasts for 38 weeks if viral suppression is maintained, with ART restarted following two consecutive viral load results >200 copies/mL.

This compound is also being studied in a randomised phase 2 study with romedepsin in 30 HIV positive participants.[58]

Another ongoing phase 1 study involves using PGDM1400 and PGT121 with the potential for both HIV treatment and prevention.[59]

Preclinical compounds of interest

As many companies do not widely publicise pre-clinical work, this section is restricted to a few studies. It is notable that this section is largely unchanged from the 2017 pipeline report.

Combinectin (GSK3732394) – adnectin/fusion inhibitor

Combinectin (GSK3732394, previously BMS-986197) 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.[60]

However, no new data have been presented since and there are no listings on the clinical trials register for new studies.

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.[61]

However, no new data have been presented since and there are no listings on the clinical trials register for new studies.

GS-CA1 – capsid inhibitor

First data were presented on GS-CA1 at CROI 2017. It is the first compound in a new class of HIV capsid inhibitors, with a formulation that can be used for slow-release injections.[62]

Capsid is the cone-shaped structural core within the virion that protects HIV RNA and related enzymes. As part of a dynamic process, the capsid protein (p24) first breaks down to release viral contents into the CD4 cell to enable reverse transcription and also needs to reassemble inside new virions as part of the maturation process at the end of the lifecycle.

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 compound is potent with EC50 in target cells of 60 to 140 pM (compared to 1000 to 19000 for efavirenz, dolutegravir and atazanavir) with activity against drug resistance to current HIV classes. Although population sequencing showed the binding site to be highly conserved, capsid resistance can be generated from in vitro serial passaging.

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.

No new data have been presented since and there are no listings on the clinical trials register for new studies.

Conclusion

The high number of recent approvals and ending applications for new HIV drugs is impressive.

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 (see Table 1).

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	COMMENT
cabotegravir ViiV Healthcare	INSTI	Oral formulation of integrase inhibitor mainly used for lead-in dose before long-acting formulation.
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.
PRO 140 CytoDyn	mAb CCR5 target	Once-weekly (350 mg) sub-cutaneous injection being studied in addition to ART for multi-drug resistance and as monotherapy maintenance therapy (without ART).
GSK3684934 (Fostemsavir) ViiV	attachment inhibitor	Gp120 attachment inhibitor that is mainly being studied in treatment-experienced patients with MDR HIV in a large international study.
UB-421 United BioPharma	mAb CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption.
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 (currently submitted for regulatory approval, see above) with generic 3TC and new NRTI MK-8591 (EfDA)
GS-9131 Gilead	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.
VRC01 VRC01LS	mAb CD4 binding	Intravenous infusion (40 mg/kg) being studied in cure research and as PrEP (2 large phase 3 studies are ongoing). Sub-cutaneous dosing of infants to prevent transmission at birth or from breastfeeding. VRC01LS is a longer acting formulation.
elsulfavirine, prodrug of VM-1500A Viriom	NNRTI	NNRTI that is being developed for use in LMICs. Similar activity to efavirenz. Long-acting formulation being studied with potential for monthly IM/SC injections. 96-week phase 2 results at AIDS 2018.
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.
GSK3640254 ViiV Healthcare	Maturation inhibitor	Maturation inhibitor acquired from BMS that has just entered phase 1 studies.
Combinection (GSK3732394) ViiV Healthcare	Entry inhibitor gp41 and CD4	Combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action and the potential for self-administered once-weekly injections.
GSPI1 Gilead	Protease inhibitor	New QD unboosted PI, high potency, long half-life, potential as part of an FDC.
GS-CA1 Gilead	capsid inhibitor	Early stage for new class with activity at multiple stages of viral lifecycle. Sub-cutaneous injection with monthly or less frequent dosing.

References

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

Introduction (10E8.4/iMab refs)

1. Huang Y. Engineered bispecific antibodies with exquisite HIV-1-neutralizing activity. Cell. 2016 Jun 16; 165(7): 1621–1631. doi: 10.1016/j.cell.2016.05.024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4972332
2. Ho D. First in human clinical evaluation of 10E8.4/iMab, a potent and broad bispecific antibody against HIV. https://www.cavd.org/grantees/Pages/Grantee-Ho4.aspx
3. Wagh K et al. Potential of conventional & bispecific broadly neutralizing antibodies for prevention of HIV-1 subtype A, C & D infections. PLoS Pathogens. March 5, 2018. DOI: 10.1371/journal.ppat.1006860. http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006860
4. Janssen press statement. European Commission approves Symtuza for the treatment of HIV-1 in adults and adolescents in Europe. (27 September 2017). http://www.investor.jnj.com/releases.cfm http://files.shareholder.com/downloads/JNJ/5608440606x0x957933/0DD01932-2A31-43BE-8F35-FDF1DCF4791D/Approved_Symtuza_EC_approval_Press_Release.pdf (PDF)
5. European Summary of Product Charateristics (SPC) for Symtuza. (September 2017). http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/004391/human_med_002165.jsp&mid=WC0b01ac058001d124
6. U.S. Food and Drug Administration approves Gilead's Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) for treatment of HIV-1 infection. (07 February 2018). http://www.gilead.com/news/press-releases
7. European Commission grants marketing authorization for Gilead's Biktarvy (bictegravir, emtricitabine, tenofovir alafenamide) for the treatment of HIV-1 Infection. (25 June 2018). http://www.gilead.com/news/press-releases
8. ClinicalTrials.gov. Efficacy of GS-9131 functional monotherapy in HIV-1-positive adults failing a nucleos(t)Ide reverse transcriptase inhibitor-containing regimen. NCT03472326. https://clinicaltrials.gov/ct2/show/NCT03472326
9. FDA press release. FDA approves new HIV treatment for patients who have limited treatment options. (06 March 2018). https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm599657.htm?
10. Lalezari J et al. Primary efficacy endpoint and safety results of ibalizumab (IBA) in a phase 3 study of heavily treatment-experienced patients with multi-drugs resistant (MDR) HIV-1 infection. ID Week, 26-30 October 2016. Late breaker oral abstract LB-6. http://www.idweek.org http://www.natap.org/2016/IDSA/IDSA_06.htm
11. Ho D. First in human clinical evaluation of 10E8.4/iMab, a potent and broad bispecific antibody against HIV. https://www.cavd.org/grantees/Pages/Grantee-Ho4.aspx
12. Frontier Biotech press release. Frontier Biotech receives marketing authorization from China FDA for Aikening (albuvirtide for injection), China's first new drug for the treatment of HIV. (06 June 2018). http://www.frontierbiotech.com/en/news
13. Merck (MSD) press release. European Commission approves Merck's doravirine/lamivudine/tenofovir disoproxil fumarate (Delstrigo), a once-daily fixed-dose combination tablet as a complete regimen and doravirine (Pifeltro), an NNRTI, both for the treatment of HIV-1 in appropriate patients. (28 November 2018). https://www.mrknewsroom.com
14. Merck (MSD) press release. FDA approves Merck's Delstrigo (doravirine/lamivudine/tenofovir disoproxil fumarate), a once-daily fixed-dose combination tablet as a complete regimen and Pifeltrotm (doravirine), an NNRTI, both for the treatment of HIV-1 in appropriate patients. (30 August 2018). https://www.mrknewsroom.com
15. ClinicalTrials.gov. MK-8591 with doravirine and lamivudine in participants infected with HIV type 1 (MK-8591-011) (DRIVE2Simplify). NCT03272347. https://clinicaltrials.gov/ct2/show/NCT03272347
16. Cahn P et al. Non-inferior efficacy of dolutegravir (DTG) plus lamivudine (3TC) versus DTG plus tenofovir/emtricitabine (TDF/FTC) fixed-dose combination in antiretroviral treatment-naïve adults with HIV-1 infection – 48-week results from the GEMINI studies. AIDS 2018, 23-27 July 2018, Amsterdam. Late breaker oral abstract TUAB0106LB. http://programme.aids2018.org/Abstract/Abstract/13210 (abstract)
17. Aberg J et al. Week 48 safety and efficacy of the HIV-1 attachment inhibitor prodrug fostemsavir in heavily treatment-experienced participants (BRIGHTE study) . Glasgow HIV Congress 2018, 28 – 31 October 2018. Oral abstract O344A.
18. Landovitz R. Tail-phase Safety, Tolerability and Pharmacokinetics of Long-acting Injectable Cabotegravir in HIV-uninfected Individuals: HPTN 077 Final Results. Oral late-breaker abstract OA15.06LB. http://www.professionalabstracts.com/hivr4p2018/iPlanner/#/presentation/347 (abstract) http://webcasts.hivr4p.org/console/player/40424 (webcast)
19. Eron J et al. Safety and efficacy of long-acting CAB and RPV as two drug IM maintenance therapy: LATTE-2 week 96 results. IAS 2017, Paris. Late breaker oral abstract MOAX0205LB. http://programme.ias2017.org/Abstract/Abstract/5628
20. Margolis D et al. Long-acting intramuscular cabotegravir and rilpivirine in adults with HIV-1 infection (LATTE-2): 96-week results of a randomised, open-label, phase 2b, non-inferiority trial. The Lancet (24 July 2017). http://dx.doi.org/10.1016/S0140-6736(17)31917-7. http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)31917-7/fulltext

21. ViiV press release. ViiV Healthcare reports positive 48-week results for first pivotal, phase III study for novel, long-acting, injectable HIV-treatment regimen. (15 August 2018)
https://www.viivhealthcare.com/media/press-releases/2018/viiv-healthcare-reports-positive-48-week-results-for-first-pivotal-phase-iii-study-for-novel-long-acting-injectable-hiv-treatment-regimen.aspx
22. clinicaltrials.gov. Study evaluating the efficacy, safety, and tolerability of switching to long-acting cabotegravir plus long-acting rilpivirine from current antiretroviral regimen in virologically suppressed HIV-1-positive adults. NCT02951052.
https://www.clinicaltrials.gov/ct2/show/NCT029510521
23. Lalezari J et al. PRO140 single-agent maintenance therapy for HIV-1 Infection: a 2-year update. CROI 2017, 13-16 February, Seattle. Poster abstract 437.
http://www.croiconference.org/sessions/pro140-single-agent-maintenance-therapy-hiv-1-infection-2-year-update (abstract and poster)
24. CytoDyn press release. CytoDyn reports primary endpoint achieved in PRO 140 pivotal combination therapy trial in HIV infection. (20 February 2018)
https://www.cytodyn.com/media/press-releases/detail/271/cytodyn-reports-primary-endpoint-achieved-in-pro-140
25. A randomized, double-blind, placebo-controlled trial, followed by single-arm treatment of PRO 140 in combination w/ optimized background therapy in treatment-experienced HIV subjects (PRO 140). NCT02483078.
https://clinicaltrials.gov./ct2/show/NCT02483078
26. ClinicalTrials.gov. A phase 2b/3, multicenter study to assess the treatment strategy of using PRO 140 SC as long-acting single-agent maintenance therapy for 48 weeks in virologically suppressed subjects with CCR5-tropic HIV-1 infection. NCT02859961.
https://clinicaltrials.gov./ct2/show/NCT02859961
27. ClinicalTrials.gov. Study of PRO 140 for prophylaxis of acute GVHD in patients with AML or MDS undergoing allogeneic stem-cell transplant. (GVHD). NCT02737306.
https://clinicaltrials.gov./ct2/show/NCT02737306
28. ClinicalTrials.gov. To investigate the efficacy and safety of UB-421 monotherapy in HIV-1 infected adults. NCT0314921.
https://clinicaltrials.gov/ct2/show/NCT0314921
29. ClinicalTrials.gov. UB-421 combine with optimized background therapy regimen in multi-drug resistant HIV-1 infection patients. NCT03164447.
https://clinicaltrials.gov/ct2/show/NCT03164447
30. Wang C-Y et al. A phase 2 open-label trial of antibody UB-421 monotherapy as a substitute for HAART. CROI 2017, 13-16 February, Seattle. Poster abstract 450 LB.
http://www.croiconference.org/sessions/phase-2-open-label-trial-antibody-ub-421-monotherapy-substitute-haart (abstract and poster)
31. Matthews RP et al. Multiple daily doses of MK-8591 as low as 0.25 mg are expected to suppress HIV. CROI 2018, Boston. Oral abstract 26.
www.croiconference.org/sessions/multiple-daily-doses-mk-8591-low-025-mg-are-expected-suppress-hiv (abstract)
www.croiwebcasts.org/console/player/37063 (webcast)

32. Collins S. MK-8591: further compelling early results for both treatment and prevention. HIV Treatment Bulletin. (10 august 2017)
http://i-base.info/htb/32246
33. Matthews RP. Single doses as low as 0.5 mg of the novel NRTTI MK-8591 suppress HIV for at least seven days. IAS 2017, Paris. Late breaker poster abstract TUPDB020.
http://programme.ias2017.org/Abstract/Abstract/5525
34. Markowitz M et al. Low dose MK-8591 protects rhesus macaques against rectal SHIV infection. CROI 2018, Boston. Oral abstract 89LB.
www.croiconference.org/sessions/low-dose-mk-8591-protects-rhesus-macaques-against-rectal-shiv-infection (abstract)
www.croiwebcasts.org/console/player/37191 (webcast)
35. ClinicalTrials.gov. MK-8591 with doravirine and lamivudine in participants infected with HIV type 1 (MK-8591-011) (DRIVE2Simplify). NCT03272347.
https://clinicaltrials.gov/ct2/show/NCT03272347
36. Cihlar T et al. GS9148: A novel nucleotide active against HIV-1 variants with drug-resistance mutations in reverse transcriptase. 13th Conference on Retroviruses and Opportunistic Infections, 5-8 February 2006, Denver. Oral abstract 45. (Abstract no longer online).
37. Cihlar T et al. Design and profiling of GS-9148, a novel nucleotide analog active against nucleoside-resistant variants of HIV Type 1, and its orally bioavailable phosphonoamidate prodrug, GS-9131. Antimicrob Agents Chemother. 2008 Feb; 52(2): 655–665. Published online 2007 Dec 3. doi: 10.1128/AAC.01215-07.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2224772
38. White KL et al. GS-9131 is a novel NRTI with activity against NRTI-resistant HIV-1. CROI 2017, 13-16 February, Seattle. Poster abstract 436.
http://www.croiconference.org/sessions/gs-9131-novel-nrti-activity-against-nrti-resistant-hiv-1
39. ClinicalTrials.gov. Efficacy of GS-9131 functional monotherapy in HIV-1-positive adults failing a nucleos(t)ide reverse transcriptase inhibitor-containing regimen. NCT03472326.
https://clinicaltrials.gov/ct2/show/NCT03472326
40. ClinicalTrials.gov. Evaluating the safety and efficacy of the VRC01 antibody in reducing acquisition of HIV-1 infection in women. NCT02568215.
https://www.clinicaltrials.gov/ct2/show/NCT02568215
41. ClinicalTrials.gov. Evaluating the safety and efficacy of the VRC01 antibody in reducing acquisition of HIV-1 infection among men and transgender persons who have sex with men. NCT02716675.
https://www.clinicaltrials.gov/ct2/show/NCT02716675
42. Cunningham CK et al. Safety & pharmacokinetics of the monoclonal antibody, VRC01, in HIV-exposed newborns. CROI 2017, 13-16 February, Seattle. Poster abstract 760.
http://www.croiconference.org/sessions/safety-pharmacokinetics-monoclonal-antibody-vrc01-hiv-exposed-newborns (abstract and poster)

43. ClinicalTrials.gov. Evaluating the safety and pharmacokinetics of VRC01 and VRC01LS, potent anti-HIV neutralizing monoclonal antibodies, in HIV-1-exposed infants. NCT02256631. https://clinicaltrials.gov/ct2/show/NCT02256631
44. ClinicalTrials.gov. Safety and virologic effect of a human monoclonal antibody, VRC-HIVMAB080-00-AB (VRC01LS), with broad HIV-1 neutralizing activity, administered intravenously to HIV-positive adults. NCT02840474. https://clinicaltrials.gov/ct2/show/NCT02840474
45. Murphy R et al. Elsulfavirine as compared to efavirenz in combination with TDF/FTC: 48-week study. CROI 2017, 13-16 February, Seattle. Late breaker abstract 452LB. http://www.croiconference.org/sessions/elsulfavirine-compared-efavirenz-combination-tdfftc-48-week-study
46. Bichko V et al. Pre-clinical pharmacokinetics of elsulfavirine/VM1500A long acting injectable formulations. IAS 2017, 23-26 July, Paris. Poster abstract WEPEA0190. http://programme.ias2017.org/Abstract/Abstract/1515
47. Scherrer D et al. Early evidence of antiviral activity & safety of ABX464 in HIV treatment-naïve patients. CROI 2016, February 22–25, Boston, Late breaker poster abstract 461LB. http://www.croiconference.org/sites/default/files/posters-2016/461LB.pdf (PDF)
48. Paredes R et al. ABX464 decreases total HIV DNA in PBMC´s when administered during 28 days to HIV-infected patients who are virologically suppressed. IAS 2017, 23-26 July, Paris. Poster abstract TULBPEB22. http://programme.ias2017.org/Abstract/Abstract/5650
49. ClinicalTrials.gov. An open-label study of the safety, pharmacokinetics, and pharmacodynamics of ABX464 in HIV-1 seronegative and seropositive adults. NCT02990325. https://clinicaltrials.gov/ct2/show/NCT02990325
50. ClinicalTrials.gov. GSK3640254 first time in human (FTIH) study in healthy volunteers. NCT03231943. https://clinicaltrials.gov/ct2/show/NCT03231943
51. ClinicalTrials.gov. A study to compare the relative bioavailability of two different formulations of GSK3640254. NCT03575962. https://clinicaltrials.gov/ct2/show/NCT03575962
52. GSK discontinues development of maturation inhibitor BMS-955176. (October 2016). http://i-base.info/htb/30865
53. Joshi SR et al. An analysis of neurologic and psychiatric adverse events of subjects receiving the investigational HIV-1 maturation inhibitor (MI) GSK3532795/BMS-955176. IAS 2017, Paris. Poster abstract WEPEB0540. http://programme.ias2017.org/Abstract/Abstract/2917
54. ClinicalTrials.gov. 3BNC117-LS first-in-human phase 1 study. NCT03254277. https://clinicaltrials.gov/ct2/show/NCT03254277
55. ClinicalTrials.gov. 3BNC117 and 10-1074 in ART-treated Individuals. NCT03526848. https://clinicaltrials.gov/ct2/show/NCT03526848
56. ClinicalTrials.gov. Combination therapy with 3BNC117 and 10-1074 in HIV-infected individuals. NCT03571204. https://clinicaltrials.gov/ct2/show/NCT03571204
57. ClinicalTrials.gov. First-in-human Study of 10-1074-LS Alone and in Combination With 3BNC117-LS. NCT03554408. https://clinicaltrials.gov/ct2/show/NCT03554408
58. ClinicalTrials.gov. A phase 2a, randomized study of romidepsin with or without 3BNC117 to evaluate the effects on the HIV-1 reservoir (ROADMAP) NCT02850016. https://clinicaltrials.gov/ct2/show/NCT02850016
59. ClinicalTrials.gov. A clinical trial of PGDM1400 and PGT121 monoclonal antibodies in HIV-infected and HIV-uninfected adults. NCT03205917. https://clinicaltrials.gov/ct2/show/NCT03205917
60. Krystal M et al. HIV combinectin GSK3732394: a long-acting inhibitor with multiple modes of action. Glasgow 2016. http://www.natap.org/2016/GLASGOW/GLASGOW_27.htm
61. Link JO et al. Novel HIV PI with high resistance barrier and potential for unboosted QD oral dosing. CROI 2017, 13-16 February, Seattle. Late breaker abstract 433. http://www.croiwebcasts.org/p/2017croi/croi33636
62. Tse WC et al. Discovery of novel potent HIV capsid inhibitors with long-acting potential. CROI 2017, 13-16 February, Seattle, Washington. Oral abstract 38. http://www.croiconference.org/sessions/discovery-novel-potent-hiv-capsid-inhibitors-long-acting-potential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