Fit for purpose

Antiretroviral treatment optimisation for adults and children

HIV i-Base
July 2017

ABOUT HIV i-BASE

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

www.i-base.info

ABOUT FIT FOR PURPOSE

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

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CHAPTER 1

Fit for purpose: antiretroviral treatment optimisation for adults and children

By Polly Clayden

Introduction

This year's edition of Fit for Purpose has expanded. We include treatment for children as well as adults in our annual review of optimised antiretroviral treatment (ART).

We have also included reviews of the HIV pipeline for both adults and children.

A full version of the adult pipeline, reporting key research in detail for each drug, is also available on the i-Base website.[1]

Adults

WHO 2016 Consolidated Guidelines

The preferred and alternative first-line ART regimens recommended in the 2016 World Health Organisation (WHO) Consolidated Guidelines are shown in Table 1.[2]

A fixed dose combination (FDC) of EFV 600 mg plus tenofovir disoproxil fumarate (TDF) and XTC – meaning either emtricitabine (FTC) or lamivudine (3TC) remains the preferred first-line regimen for adults and adolescents. The alternatives include EFV 400 mg and DTG based regimens.

Table 1: WHO 2015 preferred and alternative first-line adult ART regimens

FIRST LINE ART	PREFERRED REGIMENS	ALTERNATIVE REGIMENS
Adults	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + DTG TDF + 3TC (or FTC) + EFV400 TDF + 3TC (or FTC) + NVP
Pregnant/breastfeeding women	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine.

Recommendations for second-line ART are shown in Table 2. Those include DRV/r or raltegravir (RAL) as alternatives to boosted lopinavir (LPV/r).

Third-line includes new drugs (if available) with the least risk of cross-resistance to those used already.

Table 2: WHO 2016 preferred and alternative second- and third-line adult ART regimens

FIRST LINE ART	PREFERRED REGIMENS	2ND-LINE REGIMENS	3RD-LINE REGIMENS
Adults	2 NRTIs + EFV	2 NRTIs +ATV/r or LPV/r	DRV/r + DTG (or RAL) + 1-2 NRTIs
		2 NRTIs + DRV/r	
	2 NRTIs + DTG	2 NRTIs +ATV/r or LPV/r	DRV/r + 2 NRTIs + NNRTI
		2 NRTIs + DRV/r	Optimise regimen using genotype profile
Pregnant/ breastfeeding women	2 NRTIs + EFV	2 NRTIs +ATV/r or LPV/r	DRV/r + DTG (or RAL) + 1-2 NRTIs
		2 NRTIs + DRV/r	

Key: ATV/r, atazanavir/ritonavir; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; LPV/r, lopinavir/ritonavir; NRTI, nucleoside/nucleotide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir.

Early adopters

EFV 400 mg, DTG and tenofovir alafenamide (TAF) (the later not yet recommended by WHO but studies in LMICs are on the way) are expected to make up a large slice of the adult first-line market over the next five years, and contribute to ART cost reductions, according to projections by The Clinton Health Access Initiative (CHAI).[3]

Although several countries have changed or are in the process of making the transition to DTG-based first-line (and in fewer countries EFV 400 mg) more information is needed on how they are likely to perform in real world, low- and middle-income country (LMIC) settings for these drugs to be recommended in WHO guidelines without restriction.[4,5]

To date at least 15 LMICs have recommended DTG first-line in their national guidelines.[6] And five countries have already began providing DTG in their programmes: Botswana, Brazil, Kenya, Nigeria and Uganda. The countries have taken different approaches to the transition, use in pregnancy and with TB treatment.

Several countries are also considering EFV 400 mg first-line: China, Cambodia, Kenya, Nigeria and Zimbabwe, among others.

Kenya was the first country to start providing generic DTG in its national programme – launched 28 June 2017.[7] Single DTG was tentatively approved by the FDA in September 2016 – and is now being rolled out.[8] DTG-based FDCs with TDF and FTC/3TC should be approved later this year.

EFV 400 mg based products will also be available in the not-too-distant future.

CHAI and Unitaid are working on a three-year large-scale initiative to speed up the introduction and access to optimal ARVs.[9]

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

Dolutegravir

With a low 50 mg once daily dose that does not require boosting, a high barrier to resistance, good efficacy, minimal toxicity,[10,11,12,13] and the potential to be low-cost and coformulated, DTG looks like it will be an important potential option for use in LMICs. It is beginning to replace EFV first-line.

DTG studies have not yet included significant numbers of people who would be treated in LMICs – although several are now underway as is its use in early adopter countries. The registrational trials for DTG comprised approximately 80% men and few non-white participants and hardly anyone co-infected with other diseases (a few with hepatitis B and none with TB or malaria). People with baseline NRTI resistance were not included.

Partly because of insufficient data in pregnancy and with TB co-treatment, WHO 2016 guidelines recommend DTG as an alternative rather than preferred first-line option.

Dolutegravir and pregnancy

Pharmacokinetic (PK) data from women enrolled in IMPAACT P1026s and PANNA studies suggest DTG exposures in pregnancy are similar to that in non-pregnant adults but lower compared with postpartum.[14,15,16]

In IMPAACT P1026s DTG infant elimination half-life was more than twice that of the mothers in the study and historical non-pregnant adult controls.

Both studies reported good viral suppression in mothers and all evaluable infants were HIV negative.

Pre-clinical studies did not show any toxicities.[17] In the DTG registrational trials and compassionate use programmes, congenital anomalies were seen in six of 97 births.[18] But reports from postmarketing surveillance could be subject to reporting bias, as clinicians are more likely to report infants with anomalies.

Five of 15 DTG-exposed babies in IMPAACT P1026 were reported to have congenital anomalies (and two babies with findings considered to be "normal variants").

The investigators deemed that, based on the nature of the anomalies and the timing of first exposure in pregnancy, the association with DTG can be ruled out for all but two of the five anomalies (renal cysts). Because of the gestational age at which DTG was started and the nature of the renal cysts, the investigators also consider it unlikely that they are related to DTG-exposure.

The most recent (to 31 January 2017) Antiretroviral Pregnancy Registry (APR) reported two birth defects out of 77 pregnancies with first trimester exposure to DTG (2.7%) and two out of 56 pregnancies with second trimester exposure.[19,20] This is consistent with rates reported for other ARVs to the APR (2.8%) but the denominator of 200 or more live births with first trimester exposure, needed to rule out a two-fold increase in the rate of birth defects, has not been reached.

The European Pregnancy and Paediatric HIV Cohort Collaboration (EPPICC) analyses outcomes from observational studies of HIV positive pregnant women and their infants in Europe.

EPPICC reported two congenital anomalies out of 29 (6.9%) pregnancies with first trimester DTG exposure and one out of 32 (3.1%) with second/third trimester exposure.[21] The preterm delivery rate was 7% and 27% for infants with first and second/third trimester exposure respectively.

Small numbers preclude firm conclusions and no patterns of anomalies have been observed across these data sets reporting safety of DTG in pregnancy.

Observational data from Botswana – which changed from EFV-based to DTG-based first-line ART in 2016 including for pregnant women – reported similar adverse birth outcomes for the two regimens when started during pregnancy.[22] There were 845 pregnancies among women receiving DTG of which 116 were first trimester exposures. There were no major congenital anomalies among DTG exposed infants.

Dolutegravir and TB

Information about treating HIV/TB coinfection with a DTG-based regimen is limited. A phase I study has been conducted in healthy volunteers of DTG given with rifampicin and with rifabutin.[23] The study suggested that 50 mg twice daily dosing is likely to be required when it is co-administered with rifampicin to overcome UGT1A/CYP3A induction by this drug, which is used in standard first-line TB treatment.

Studies to look at DTG and TB treatment are ongoing or planned.

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.[24] Some recent observational studies have reported increased risk of CNS side effects with DTG.

Immune Reconstitution Inflammatory Syndrome (IRIS) could be a risk for people with low CD4 counts starting DTG as integrase inhibitors suppress viral load faster than other classes of ARVs.[25, 26]

Efavirenz 400 mg

EFV 600 mg – the currently approved and recommended dose – fulfils many of the desirable characteristics profile as part of an ideal ART regimen. For those

who tolerate the drug, it is safe and effective, can be used in pregnancy and in people also receiving TB treatment and needs minimal laboratory monitoring.

But it has a low genetic barrier to resistance. It is also associated with CNS side effects, which can lead to drug discontinuation.[27] And there is an interaction between EFV and some hormonal contraceptives that can reduce their efficacy.[28]

The ENCORE 1 study, showed EFV 400 mg to be non-inferior to 600 mg (both plus TDF/FTC) as first-line ART.[29] The lower dose resulted in a reduction in EFV-related side effects 38% versus 48% with the standard dose.

But questions about whether or not 400 mg would be robust in the third trimester of pregnancy and with TB treatment have delayed recommendations from WHO and national guidelines.

Efavirenz 400 mg and pregnancy

PK modelling, conducted to simulate EFV exposure using 600 mg and 400 mg during the third trimester of pregnancy, suggested that although pregnancy decreases total exposure of EFV the unbound fraction is predicted to be unchanged. This study indicates that a dose reduction to 400 mg might be feasible in pregnancy.[30]

Preliminary results from the SSAT063 study, in progress to look at EFV 400 mg PK in pregnancy, suggest that the lower dose can be used in pregnant women.[31,32]

Efavirenz and TB

For rifampicin, there have been seven short-term PK studies with EFV 600 mg (less than two weeks) showing reduction in plasma concentrations. It is unclear how useful these results are when EFV has not reached steady state. Five longer-term studies in HIV positive people have shown increased Cmin or no effect.[33]

A study in progress in London and Kampala is looking at the PK of EFV 400 mg in the presence of rifampicin and isoniazid.[34]

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 this is likely to be for some time. The EFV/TDF/3TC regimen will be generic in most countries worldwide by 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.[35]

While it does remain an option, it is important that the lower dose is recommended without restriction as soon as results from the PK studies support this, to ensure that people who need it receive the most optimised version.

Tenofovir alafenamide

TAF's low milligram dose and potential to be low cost and coformulated could offer benefits to generic accessible LMICs.

TAF is a novel prodrug of tenofovir. 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.[36] It is dosed at 25 mg unboosted and 10 mg in a boosted regimen.

The reduction in plasma concentrations with TAF could mean less tenofovir accumulation in bone and kidneys and, in turn, fewer bone and kidney associated toxicities compared with TDF.

There were no significant differences in efficacy or clinical side effects between TAF and TDF across phase 2 and 3 studies at 48 and 96 weeks. At 48 weeks, participants receiving TAF had statistically significant less renal toxicity and reduced bone mineral density compared to those receiving TDF. But TAF was also associated with increases in low-density lipoprotein (LDL) cholesterol and total cholesterol plasma levels. It is unclear whether or not these differences will have clinical significance long-term.

A recent meta-analysis conducted to compare TAF versus TDF, that included 10 trials, did not reveal statistically significant differences in virological outcomes, adverse events, lab abnormalities or deaths.[37] But the analysis reported significantly less detrimental effects from TAF on bone and renal markers. The trials included were largely conducted in white, male participants around 40 years old with baseline CD4 count greater than 50 cells/mm^3.

The authors concluded that the use of TAF in LMICs requires more data on pregnancy, TB and in people with advanced HIV.

TAF is notable for its absence in the WHO transition document.[38]

Tenofovir alafenamide and pregnancy

The APR reports only one defect among eight pregnancies with first trimester exposure and no defects with 10 second and third trimester exposures.[39] Obviously falling short of the 200 pregnancies threshold.

Tenofovir alafenamide and TB

TAF is a minor CYP3A4 substrate and a substrate of p-glycoprotein, both of which are induced by rifampicin, so there is likely to be an interaction with rifampicin. Use of TAF-based products and rifampicin together are currently contraindicated. Gilead has not yet conducted any interaction studies with TAF and rifampicin – although these are now planned. Co-administration with carbamazepine leads to a 55% decrease in TAF in plasma; results from modelling to predict the interaction with rifampicin predict this reduction will be 73% in plasma.[40] The intracellular concentrations of tenofovir-diphosphate when TAF is co-administered with rifampicin need to be investigated clinically.

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, coformulated 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.[41, 42, 43]

Darunavir 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.[44,45] 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 drug interaction studies with DRV/r and rifampicin; one is now planned.

What is planned or ongoing?

First-line

A DTG-based preferred first-line regimen is the current goal for first-line ART. As well as offering clinical advantages, in combination with TAF and FTC the total daily dose would be 275 mg (375 mg with 3TC) compared to 1200 mg with the current WHO preferred first-line: EFV 600 mg/TDF/3TC.

For people who cannot access (or tolerate) DTG, EFV 400 mg based regimens should be an alternative first-line.

Table 3: New first-line regimen studies

STUDY	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
ADVANCE WRHI 060 NCT03122262	Wits RHI (USAID, Unitaid)	DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF non-inferiority, open label 1110 treatment naive adult participants (370 per arm) Of these 60–90 treatment naive 12–15 year olds weighing > 40 kg (20 per arm analysed separately) Johannesburg, South Africa	Phase 3 Started January 2017 48-week data available Q1 2019 Completion Q4 2019	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
NAMSAL (Efficacy and safety of a dolutegravir-based regimen for the initial management of HIV infected adults in resource-limited settings) ANRS 12313 NCT02777229	Inserm-ANRS (Institute de Recherche pour le development) (Unitaid)	DTG/3TC/TDF vs EFV 400 /3TC/TDF non-inferiority, open label 606 treatment naive participants (303 per arm) Yaoundé, Cameroon	Phase 3 Started June 2016 48-week data available October 2018	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
ADVANZ-4 dolutegravir NCT02337322	Hospital Clinic of Barcelona	DTG/ABC/3TC vs DRV/r +ABC/3TC, randomised, open label 108 treatment naive participants with less than 100 CD4 cells/mm^3 Barcelona, Spain	Phase 4 Completion Q4 2017	Compare immunological reconstitution and virological efficacy during 96 weeks in people with advanced HIV Primary endpoint is the median increase in CD4 cell count at 48 weeks

Key: DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; Inserm-ANRS, French National Institute for Health and Medical Research-French National Agency for Research on AIDS and Viral Hepatitis; NIH, United States National Institutes of Health; NRTI, nucleos(t)ide reverse transcriptase inhibitor; PK, pharmacokinetic; TAF, tenofovir alafenamide fumarate; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine; 3TC, lamivudine

Two African investigator-led studies to look at these regimens in closer-to-real-life settings are in progress. 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 comparing DTG-based to EFV 400 mg based regimens, conducted in South Africa and Cameroon respectively.[46, 47, 48]

Although not conducted in an African setting, ADVANZ-4, a study currently underway in Spain will also provide information on DTG use in people with less than 100 CD4 cells/mm^3.[49]

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

Pregnancy

TABLE 4: First-line pregnancy studies

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Dolutegravir				
DolPHIN1 NCT02245022	University of Liverpool (University of Cape Town, University of Makerere)	Pilot study of DTG PK in pregnant women in third trimester and post-partum during 2 weeks breastfeeding 60 late presenting women (28 to 36 weeks gestation) Women randomised 1:1 to receive DTG (50 mg once daily) or standard of care (EFV) plus two NRTIs South Africa and Uganda	Phase 2 Started March 2017 Primary completion December 2017	Primary endpoint: PK 3rd trimester Secondary endpoints: safety and tolerability of DTG up to 2 weeks post-partum and VL at delivery
PK and safety study in pregnant women with HIV ING200336 NCT02075593	ViiV Healthcare	PK and safety single arm study of women with unintended pregnancies while participating in ARIA study of DTG/ABC/3TC FDC vs ATV/ r +TDF/FTC in 474 treatment naive women (NCT01910402) to be completed in 2018 Estimated enrolment 25 women (approx 237 receive study drug in ARIA) Multicountry (US, Russian Federation, Spain, UK)	Phase 3 Started Jan 2015 (recruiting) Primary completion February 2019	Primary endpoints: PK 2nd /3rd trimester Secondary endpoints: PK in neonates, maternal:cord blood ratio, maternal and infant AEs; adverse pregnancy outcomes
DolPHIN2 Dolutegravir in Pregnant HIV Mothers and Neonates	University of Liverpool (University of Cape Town, University of Makerere)	DTG PK, safety and efficacy in pregnant women in 3rd trimester and post-partum during breastfeeding 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	Phase 3 Planned to start Q3 2017 Primary completion Q1 2021	Primary endpoints: PK third trimester Secondary endpoints: VL at delivery, safety, tolerabilty and breast milk sterilisation
Tenofovir alafenamide				
WAVES (OLE) Women's AntiretroViral Efficacy and Safety (Open Label Extension) NCT01705574	Gilead Sciences	EVG/COBI/FTC/TDF vs TDF/FTC + ATV/r in treatment naive women with OLE in ATV/r arm re-randomised to remain or switch to EVG/COBI/FTC/TAF 583 women total, those that become pregnant can remain on study regimen Multicountry (US, Belgium, Dominican Republic, France, Italy, Mexico, Portugal,Puerto Rico, Russian Federation, Thailand, Uganda, UK)	Phase 3 Started February 2016 (ongoing) Primary completion March 2017	Safety, efficacy and tolerability in naive PW Safety and efficacy of EVG/COBI/FTC/TAF vs TDF/FTC + ATV/r

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Dolutegravir and tenofovir alafenamide				
VESTED IMPAACT P2010 NCT01302847	NIH (NIAID)	DTG/TAF/FTC vs DTG/TDF/FTC vs EFV/TDF/FTC in 549 mother/infant pairs Treatment-naive women starting ART at 14 to 28 weeks gestation Randomised 1:1:1 open label Only study that evaluates DTG/TAF/FTC in pregnancy Multicountry: IMPAACT sites (US, Botswana, Brazil, Haiti, India, Malawi, South Africa, Tanzania,Thailand, Uganda, Zambia, Zimbabwe)	Phase 3 Planned to start August 2017 Primary completion December 2019	Comparative data on safety and virologic efficacy during pregnancy and through 50 weeks of maternal and infant follow-up postpartum Superiority (virologic endpoint); comparison by arm for difference (adverse pregnancy outcome, toxicity endpoints) Primary endpoints: VL <200 copies/mL at delivery; adverse pregnancy outcomes (SAB, foetal death, PTD or SGA); maternal toxicity; infant toxicity Main secondary endpoints: VL <50 at delivery; VL <200 at 50 weeks postpartum; renal toxicity (mothers and infants); bone toxicity by DXA (subset of mothers and infants); adverse pregnancy outcomes including congenital anomaly; resistance (among women with VF, and among HIV-infected infants)

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
IMPAACT P1026s NCT00042289	IMPAACT network, NIH (NIAID)	PK properties of antiretroviral and related drugs during pregnancy and postpartum Each study arm 12–25 (target) women with evaluable 3rd trimester PK data Pregnant women > 20 weeks gestation receiving DTG (1 arm) and TAF (3 arms – within FDCs) as part of clinical care Washout PK in drug exposed infants Multicountry: IMPAACT sites (US, Argentina, Botswana, Brazil, Puerto Rico, South Africa, Thailand, Uganda)	Phase 4 Started in September 2014 (enrolment completed in DTG arm, recruiting for TAF arms) Primary completion June 2017 (DTG) and June 2018 (TAF)	Primary endpoint: PK 2nd /3rd trimester Secondary endpoints: PK in neonate, maternal:cord blood ratio, maternal and infant adverse events; adverse pregnancy outcomes
PANNA study NCT00825929	Radboud University (PENTA Foundation, ViiV Healthcare)	Pregnant women <33-week gestation receiving DTG as part of clinical care Each study arm 16 with evaluable 33-week data Multicountry: PANNA sites (Belgium, Germany, Ireland, Italy, Netherlands, Spain, UK)	Phase 4 Started in July 2015 (recruiting) Primary completion December 2020	Primary endpoint: PK at 33 weeks and 4-6 weeks after delivery Secondary endpints: PK in neonates, safety, VL and transmission

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Efavirenz 400 mg				
SSAT063 PK of EFV 400 mg Once daily during pregnancy in HIV positive women NCT02499874	SSAT (Mylan Inc.)	PK single arm 25 women stable on 2 NRTI plus EFV 600 mg for >12 weeks, switch to EFV 400 mg at gestational age 28 weeks UK and Uganda	Phase 1 Started September 2016 (ongoing) Primary completion October 2017	Primary endpoint: PK (AUC 24h and Ctrough) EFV 400 mg 3rd trimester pregnancy and post partum Secondary endpoints: Safety and tolerability, genetic influences on EFV PK

AE, adverse event; ABC, abacavir; ATV/r, atazanavir/ritonavir; BF, breast feeding; COBI, cobicistat; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; IMPAACT, International Maternal Pediatric Adolescent AIDS Trials Network; NAID, NIH, United States National Institutes of Health; NRTI, nucleos(t)ide reverse transcriptase inhibitor; OLE, open label extension; PANNA, Study on Pharmacokinetics of Newly Developed ANtiretroviral Agents in HIV-infected pregNAnt Women; PK, pharmacokinetic; PTD, preterm delivery; SGA, small for gestational age; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; VL, viral load; XTC, lamivudine or emtricitabine; 3TC, lamivudine

A ViiV-sponsored study is enrolling ART-naive women only and comparing first-line DTG regimens to boosted atazanavir (ATV/r) ones.[50,51] Women who become pregnant in the study will remain on their randomly assigned regimen and roll over into a pregnancy study.

DolPHIN 1 and 2 will look at DTG PK, safety and efficacy in pregnancy and post-partum, the pilot study is ongoing and the larger one is now supported by the Unitaid programme.[52,53]

The women-only Gilead study WAVES includes an open label extension in which women are re-randomised to remain on a boosted atazanavir-based regimen or switch to one that includes TAF.[54] Women who become pregnant in the study can stay on their ART regimen.

IMPAACT P1026s and PANNA (both have presented preliminary data for DTG described earlier) – the respective American and European studies that look at PK of antiretrovirals in pregnancy and post-partum include women receiving DTG and TAF.[55,56,57,58]

VESTED (IMPAACT P2010) will make the same three-arm comparison as ADVANCE but in pregnant women.[59]

ADVANCE will give women who become pregnant during the study the option to continue on their study drugs.[60]

And for EFV 400 mg, the safety concerns in pregnancy were resolved with wide use of EFV 600 mg, and we can expect results from the ongoing SSAT063 pregnancy PK study later this year.[61]

Tuberculosis

Table 5: First-line HIV/TB co-treatment studies

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Dolutegravir				
INSPIRING Open label study of DTG vs EFV for HIV/TB coinfection ING117175 NCT02178592	ViiV Healthcare	50 mg DTG twice daily vs 600 mg EFV (open label, randomised 3:2 ratio) during TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) 125 treatment naive participants Multicountry (Argentina, Brazil, Mexico, Peru, Russian Federation, South Africa, Thailand)	Phase 3 Start Jan 2015 (ongoing) Primary completion December 2017	Establish antiviral activity of DTG or EFV containing regimens with TB treatment 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

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
RADIO PK DTG 50 mg and 100 mg once daily with rifampicin NCT03199690	SSAT (Wits RHI)	DTG 50 mg once daily with food for 1 week, PK on day 7 Then DTG 100 mg once daily for 1 week, PK on day 14 Then 7-day wash out period Start RIF on day 22 for 35 days and add DTG 50 mg on day 44, PK day on day 44 Then increase DTG to 100 mg OD for another 7 days, PK day on day 57 20 HIV negative participants UK	Phase 1 Planned start September 2017 Primary completion January 2018	Primary objective: investigate the PK of rifampicin 600 mg once daily and DTG 50 or 100 mg once daily in HIV negative participants Secondary objective: investigate the safety and tolerability of rifampicin 600 mg once daily and DTG 50 or 100 mg once daily in HIV negative participants Results will inform a bigger study that will be conducted in South Africa in people with HIV and TB who will be given rifampicin-containing regimens and DTG, ideally once daily

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Efavirenz 400 mg				
Steady state PK of efavirenz in the presence of rifampicin and isoniazid SSAT062 NCT02832778	SSAT (Mylan Inc)	Sequential: 98 days (stage 1) and 28 days (stage 2) open label PK study Stage 1 (London) PK in 25 HIV positive participants on established EFV 600 mg containing ART switch to EFV 400 mg plus rifampicin and isoniazid for 12 weeks (2 weeks after reduced EFV dose) Stage 2 (Kampala) PK in 10 participants with HIV and TB on established EFV 600 mg containing ART switch to EFV 400 mg plus rifampicin and isoniazid for 28 weeks (2 weeks after reduced EFV dose) UK and Uganda	Phase 1 Start September 2016 (recruiting) Primary completion October 2017	Evaluate steady state PK of EFV 400 mg during co-administration with rifampicin and isoniazid Secondary endpoints: safety and tolerability; Relationship between genetic polymorphisms and EFV exposure

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
Tenofovir alafenamide fumarate				
RIFT The effect of rifampicin on the plasma pharmacokinetics of emtricitabine (FTC) and tenofovir alafenamide fumarate (TAF) and intracellular tenofovir-diphosphate (TFV-DP) and FTC triphosphate (FTC-TP) SSCR101 NCT03186482	SSAT (Wits RHI, Gilead Sciences)	Stage A 20 participants: Phase 1 : TAF/FTC 25/200 mg once daily for 28 days (days 1-28) Phase 2 : TAF/ FTC 25/200 mg once daily plus rifampicin 600 mg once daily for 28 days (days 29-56) Phase 3: TDF 245 mg once daily for 28 days (days 57-84) If Stage A is only partially informative, Stage B will follow where a similar study will be undertaken with modified doses of TAF (eg 50 mg once daily or 25 mg twice daily with double dose of FTC too) and/or potential P-gp inhibitors (eg cobicistat). Stage B will be submitted as a protocol amendment. United Kingdom	Phase 1 Started June 2017 Primary completion October 2017	Primary objective: PK of TAF, plasma tenofovir, Intracellular TFV-DP, FTC, and FTC-TP, during co-administration of TAF/FTC or TDF with rifampicin in HIV negative participants Secondary objective: safety and tolerability of the co-administered drugs in HIV negative participants

DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; FTC-TP, FTC triphosphate; PK, pharmacokinetic; SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate; Wits RHI, Wits Reproductive Health and HIV Institute

ViiV is sponsoring INSPIRING, an open label study of regimens containing 50 mg DTG twice daily or EFV 600 mg once daily during first-line TB treatment, which begun enrolling early 2015.[62]

As it would be better to be able to take DTG once daily, the RADIO study will look at the drug concentrations in the presence of rifampicin at doses of 50 mg and 100 mg in HIV negative people.[63] This will inform a study in people with HIV/TB coinfection.

SSAT062 is in progress to investigate the PK of EFV 400 mg in HIV positive people in the presence of rifampicin and isoniazid in London and in HIV and TB coinfected participants receiving full anti-TB treatment in Kampala.[64]

For TAF the key PK parameter is intracellular tenofovir diphosphate in plasma and peripheral blood mononuclear cells. The RIFT study will measure this in the presence of rifampicin in HIV negative people.[65] Once this has been established then studies can be conducted in HIV/TB coinfected people.

It might be that EFV/TDF/3TC remains the recommended regimen during TB co-treatment if studies suggest that adjusting the dose of DTG (and possibly TAF) is necessary, as this can get a bit too complicated.

Two drugs first-line

There is currently interest, including from the AIDS Clinical Trial Group (ACTG) in looking at DTG/3TC dual therapy, as a potential new strategy to reduce ART cost and toxicity (discussed in detail in the adult pipeline section).

The main problems with two-drug treatment in LMIC are coinfection with Hepatitis B, underlying resistance to 3TC, reduced concentrations of DTG in third trimester of pregnancy and with TB treatment.[66]

It would be hard to extrapolate the results of the studies to date to routine LMIC programme settings where viral load data may be less available, and where resistance tests are unlikely.

In order for this strategy to be considered for LMICs there would need to be robust data from large pragmatic studies in unselected African populations, including TB and pregnancy. Both TB and pregnancy occur at incidence rates around 5% on ART in Southern Africa, so it is critical that the preferred first-line regimen is effective in these populations.

Although preliminary data from IMPAACT P1026s and PANNA suggest DTG exposures in pregnancy will be sufficient to suppress maternal viral load and prevent transmission in three drug regimens, some PK parameters are reduced in the third trimester. There is also considerable reduction in DTG exposure with rifampicin. Using it with only 3TC would likely scupper the possibility that DTG might still be effective at the standard dose with TB co-treatment, despite this reduction, which will be investigated further along the line.

Although every rand, pound or dollar saved in ART programmes is important at scale, the projected annual difference adding TAF to the regimen is about US $10–15 per person, which would have to be considered against the cost impact of potential first-line failure.

At the moment, it seems that the potential risks outweigh the potential benefits. The studies would need to be designed to make sure these potential risks could be ruled out, before this regimen could be considered for global guidelines.

Second-line

Table 6: Second-line DTG and DRV/r studies

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
DAWNING	ViiV	612 participants who failed 1st line (NNRTI + 2 NRTI) randomised to DTG + 2 NRTI vs LPV/r + 2 NRTIs 2nd line NRTIs genotype guided 48 weeks Multicountry: Argentina, Brazil, Chile, China, Colombia, Kenya, Mexico, Peru, Romania, Russian Federation, South Africa, Thailand, Ukraine	Phase 3b Ongoing 24-week results July 2017 Primary completion August 2017	Primary endpoint VL <50 copies/mL at 48 weeks Secondary endpoints include VL <50 copies/mL at 48 weeks; time to virological failure; AEs and laboratory markers
DRV/r 400/100 mg vs LPV/r WRHI052	Wits RHI (USAID, MRC SA)	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 South Africa	Phase 3 Ongoing Primary completion September 2017	Primary endpoint VL <50 copies/mL at 48 weeks, AEs Secondary endpoints time to virological failure

TRIAL	SPONSOR (COLLABORATORS)	DESIGN	STATUS	PURPOSE
D²EFT	UNSW (Unitaid, National Health and Medical Research Council, Australia ViiV, Janssen)	610 participants who failed 1st line regimen randomised to DRV/r + DTG vs DRV/r + 2–3 NRTIs 96 weeks Multicountry: Argentina, Chile, Colombia, India, Indonesia, Malaysia, Mexico, Peru, South Africa, Thailand, Zimbabwe	Phase 4 Starting September 2017	Primary endpoint VL <50 at 48 weeks Secondary endpoints differences in VL using different thresholds, time to VL <50 copies, changes in baseline CD4 count
Low dose DRV/r pilot	SSAT	120 treatment-naive participants randomised to DRV/r 800/100 mg vs 600/100 mg vs 400/100 mg + TDF/FTC UK and Uganda	Phase 2 pilot Funding application stage	PK and VL
Low dose DRV/r	SSAT	600 1st line treatment-experienced participants randomised to DRV/r 800/100 mg vs 600/100 mg vs 400/100 mg + TDF/FTC 96 weeks UK and Uganda	Phase 3 Funding application stage	PK and VL

Key: AEs, adverse events; DRV/r, darunavir/ritonavir; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ritonavir, MRC SA, Medical Research Council South Africa; NRTI, nucleoside/tide reverse transcriptase inhibitor; PK, pharmacokinetic; SSAT, St Stephens AIDS Trust; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; UNSW, University of New South Wales, VL, viral load; Wits RHI, University of Witwatersrand

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 is comparing DTG plus 2 NRTIs to LPV/r plus 2 NRTIs and 24-week data looks promising for DTG.[67, 68] Choice of NRTIs in DAWNING is genotype guided, so in order to consider this second-line strategy more information will be needed about taking this approach without resistance testing.

A regimen of DRV/r plus DTG has the potential to be a second-line option with no cross-resistance to an EFV/TDF/3TC first-line. Although with the current DRV/r mg dose of 800/100 mg a single pill daily regimen is less likely than two 400/50 mg ones. The D²EFT study will compare this regimen to DRV/r plus NRTIs.[69]

There is also the potential for a dose reduction of DRV/r to 400/100 mg and one study is underway and others are planned.[70]

PK data to guide the use of DRV/r with TB treatment are missing and plans to look at this are underway. The best option for second-line after a DTG-based first-line regimen will also be important. More research is needed to determine the best options for optimised second-line ART.

Paediatrics

The development of new antiretroviral drugs and appropriate formulations for children continues to be far too slow. Scale up of access for children is no better: in 2015, only 51% of children with HIV received ART; only half of those who did received optimal regimens.[71]

Few optimal regimens mean limited options for newborns, few appropriate FDCs, and paediatric regimens that cannot harmonise with those recommended for adults.

Treating paediatric HIV requires different regimens for different age groups. As children grow and the mechanisms by which they metabolise drugs mature, doses and often regimens must be changed. Such complexities have led to poor uptake and slow revision of recommendations as better ARVs become available for LMICs.

For manufacturers, there is scant incentive to develop appropriate ARVs for children. The vast success of maternal treatment and prevention of vertical transmission – although in every way a global victory – has led to an ever-shrinking market for paediatric ARVs.

There is still some way to go with formulations and regimens appropriate to children. Despite some advances in the last few years, innovation and access in antiretrovirals for children still lags behind that for adults.

Recent recommendations from the Paediatric Antiretroviral Working Group (PAWG) of the WHO suggest ways in which research can speed up the availability of new drugs and formulations.[72]

These include: the simultaneous enrolling of different age cohorts (rather than taking a de-escalated staggered approach see the paediatric pipeline section), the investigation of WHO weight bands in any paediatric development plan, the assessment of acceptability and feasibility while products are developed, and the use of PK modelling to inform dosing, as well as more efficient study designs. Prioritising optimal drugs and formulations needs to happen early and take programmatic constraints into account.

WHO 2015 guidelines

Recommendations for adolescents are the same as those for adults, guidance for younger children and infants is determined by age group. See tables 7 and 8.

But, as with the 2013 recommendations, there are no suitable generic formulations yet to support this guidance (except for adolescents who will be able to take DTG and EFV 400 mg based FDCs on the way for adults).

Only one regimen (that is not preferred), zidovudine (AZT) plus lamivudine (3TC) plus nevirapine (NVP) is currently available as an FDC.

Table 7: WHO recommended first-line ART for children and adolescents

FIRST LINE ART	PREFERRED REGIMENS	ALTERNATIVE REGIMENS
Adolescents	TDF + 3TC (or FTC) + EFV	AZT + 3TC + EFV (or NVP) TDF (or ABC) + 3TC (or FTC) + DTG TDF (or ABC) + 3TC (or FTC) + EFV 400 mg TDF (or ABC) + 3TC (or FTC) + NVP
Children 3 years to less than 10 years	ABC + 3TC + EFV	ABC + 3TC + NVP AZT + 3TC + EFV (or NVP) TDF + 3TC (or FTC) + EFV (or NVP)
Children less than 3 years	ABC (or AZT) + 3TC + LPV/r	ABC (or AZT) + 3TC + NVP

Key: ABC, abacavir; AZT, zidovudine; DTG, dolutegravir; EFV, efavirenz; FTC, emtricitabine; LVP/r, lopinavir/ritonavir; NVP, nevirapine; TDF, tenofovir disoproxil fumarate; 3TC, lamivudine

Table 8. WHO recommended second- and third-line ART for children and adolescents

FIRST LINE ART	PREFERRED REGIMENS	2ND-LINE REGIMENS	3RD-LINE REGIMENS
Children	2 NRTIs + LPV/r	Less than 3 years: 2 NRTIs + RAL	DTG + 2 NRTIs DRV/r + 2 NRTIs DRV/r + DTG + 1-2 NRTIs
		Older than 3 years: 2 NRTIs + EFV or RAL	
	2 NRTIs + EFV	2 NRTIs + ATV/r or LPV/r	

Key: ATV/r, atazanavir/ritonavir; DTG, dolutegravir; DRV/r, darunavir/ritonavir; EFV, efavirenz; FTC, emtricitabine; LPV/r, lopinavir/ ritonavir; NVP, nevirapine; NRTI, nucleos(t)ide reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; RAL, raltegravir

Missing paediatric formulations

Several gaps remain in available products for children that need to be filled before longstanding recommendations from the 2013 WHO guidelines (you read that right) can be implemented in most LMICs.[73]

Where possible these should be reduced strength tablets, and dispersible tablets for young children and infants. For compounds that cannot be formulated in this way (large and/or insoluble molecules like LPV/r) pellets are preferable to liquids.

Two priority formulations still needed to treat children according to the guidelines remain in slowly advancing development: abacavir/lamivudine/efavirenz (ABC/3TC/EFV) (150/75/150 mg), and lopinavir/ritonavir (LPV/r) 4-in-1 (30/15/40/10 mg).

Currently ABC/3TC/EFV can only be given by using ABC/3TC coformulated tablets with EFV tablets. A one-pill, once-daily regimen for children aged three to 10 years (less than 35 kg) would be useful.

LPV/r-based formulations are still in development and are needed to make it possible to give FDCs to children younger than three.

In May 2015, the big news for paediatric HIV was that finally heat-stable oral pellets of LPV/r (a finite number of LPV/r 40/10 mg pellets in a capsule, which is opened and sprinkled on soft food) suitable for infants and young children less than three years old were approved by the FDA.[74] These became available for country procurement mid-2016.

Less good news is that there is concern that currently forecasted demand for the pellets might exceed the production capacity for the manufacturer (though efforts are being made to increase capacity in the near future).[75]

The LIVING study is an implementation study using the LPV/r pellets ongoing in Kenya and starting soon in several other sub-Saharan African countries.[76]

The 4-in-1 granule formulation (finer than the 0.8mm pellets and more sand-like in texture) [77] has an anticipated approval date in early 2019.

Newborns

LPV/r is not suitable for neonates.[78] This age group is the least well-served by current options, meanwhile evidence for treating as early as possible continues to grow.

From birth to less than four weeks, there is currently no alternative to nevirapine (NVP) plus 3TC plus AZT. Although very early treatment is being explored for infants, data for this very young age group are scarce. Data from population modelling can help to predict dosing regimens in this age group.

IMPAACT have presented population modelling and PK simulations predicting dosing regimens to achieve target NVP treatment concentrations in term and late preterm infants.[79]

NVP clearance is low in term neonates, and lower still in preterm ones, because of immaturity in CYP2B6 and CYP3A4 activity. Clearance is also autoinduced in proportion to the size of the NVP dose in the first years of life.

PK data are available to guide NVP dosing for treatment of HIV in infants after one month of life: trough concentration target 3.0 ug/mL (target). Less than one month old evaluations of dosing regimens are limited to prophylaxis for HIV-exposed: trough concentration target 0.1 ug/mL.

The model revealed that typical NVP clearance in term infants increased by nearly 6-fold from birth to 6 months due to maturation and by an additional 79% due to induction. Simulated doses of 6 mg/kg twice daily for term and 4mg/kg twice daily for one week followed by 6 mg/kg twice daily for late preterm infants achieved NVP targets.

The dosing regimens supported by these simulations and NVP PK in preterm infants are being studied in the IMPAACT 1115 and 1106 protocols.

More missing data for priority antiretrovirals will be provided by ongoing IMPAACT trials:

- P1026s – phase 4, prospective, PK study in pregnancy and post partum that obtains infant antiretroviral washout data.[80]
- P1093 – phase 1/2, open label, non-comparative, intensive pharmacokinetics and safety study of DTG down to four weeks.[81]
- P1097 – washout pharmacokinetic study of RAL including in low birth weight (<2500 g) infants.[82]
- P1106 – phase 4 prospective pharmacokinetic study in low birth weight infants receiving NVP prophylaxis, tuberculosis (TB) prophylaxis or treatment and/or LPV/r-containing ART.[83]
- P1110 – phase 1 open label, non-comparative pharmacokinetic dose-finding study of RAL in high risk, HIV-exposed neonates.[84]
- P1115 – phase 1/2 proof of concept study of very early intensive ART in infants to achieve HIV remission.[85]

Table 9: Newborn treatment options (or lack of options to date): including ongoing and planned IMPAACT trials

COMPOUND	PRETERM	TERM	2 WEEKS
Nucleos(t)ide Reverse Transcriptase Inhibitor			
ABC	P1106 < 2500 g		
AZT	√	√	√
ddI			√
d4T	P1106 < 2500 g	√	√
FTC		√	√
TAF	P1026s washout	P1026s washout	
3TC	P1106 < 2500 g	√	√
Non-nucleoside Reverse Transcriptase Inhibitor			
Doravirine	P1026s washout	P1026s washout	
EFV	P1026s washout	P1026s washout	
ETR	P1026s washout	P1026s washout	
NVP	P1106 < 2500 g	P1115 >34 weeks GA	√
RPV			
Protease Inhibitors			
ATV			
DRV	P1026s washout	P1026s washout	
LPV	P1026s washout P1106 <2500 g	P1026s washout	√
Integrase Inhibitors			
DTG	P1026s washout	P1026s washout P1093 dosing (in development)	P1093 dosing (in development)
EVG	P1026s washout	P1026s washout	
RAL	P1097 washout	P1097 washout P1110 dosing	
CCR5 Receptor Antagonist			
Maraviroc		In development	

Updated from Ruel T. IMPAACT 2015.

Key: ABC, abacavir; ATV, atazanavir; AZT, zidovudine; ddI, didanosine; DTG, dolutegravir; d4T, stavudine: EFV, efavirenz; FTC, emtricitabine; ETR, etravirine; LPV/r, lopinavir/ritonavir; NVP, nevirapine; RAL, raltegravir; RPV, rilpivirine; TAF, tenofovir alafenamide fumarate; 3TC, lamivudine. GA, gestational age.

Recommendations from PADO 3

WHO has led several consultations, to advance the discussion on drug and formulation development for children, resulting in a more collaborative and coordinated response among key stakeholders. A third WHO meeting on Paediatric ARV Drug Optimisation (PADO 3) took place on 6–7 December 2016.[86, 87]

As with adults, DTG and DTG FDCs are a big priority for paediatric use and future first-line regimens in treatment-naive children and second-line for ART-experienced children are likely to be DTG-based. (See table 10 for PADO 3 priorities; for more details and references on drugs and formulations currently in development for children see the paediatric pipeline section)

Table 10: PADO 3 priorities

ADVANCE DEVELOPMENT	MID-TERM PRIORITY (3–5 YEARS)	LONG-TERM PRIORITY (5–10 YEARS)
Lopinavir/ritonavir (LPV/r) 4-in-1 30/15/40/10 mg	Nevirapine/zidovudine (NVP/AZT) neonates	Dolutegravir/lamivudine (DTG/3TC)
Abacavir/lamivudine/efavirenz (ABC/3TC/EFV) 150/75/150 mg	Darunavir/ritonavir (DRV/r) (120/20 mg)	
	Raltegravir (RAL) 50 mg scored	Long acting oral/ injectable
	Dolutegravir (DTG) 5 mg	
	DTG/3TC/ABC (5/30/60 mg)	
	F/TAF	Neutralising antibodies
	DTG/FTC or 3TC/TAF	
	DTG/DRV/r	

Source: WHO. PADO 3 meeting report. December 2016.

DTG is under investigation in IMPAACT 1093 and is also being evaluated in children and adolescents the PENTA trial ODYSSEY.[88,89]

IMPAACT 1093 is now enrolling younger children and infants and children aged 4 weeks to <2 years (and also assessing WHO weight band dosing), and preliminary results are anticipated later in 2017.

ODYSSEY is a multi-centre randomised trial of DTG-based regimens versus standard of care for first- and second-line. It includes a PK sub-study to validate weight band dosing and will also look at PK in TB co-treatment. 100 participants are now recruited in ODYSSEY and results are expected in 2020.

RAL could be a useful drug to fill a gap for infants and children until DTG development for children is completed and it becomes available. It is the only integrase inhibitor recommended down to 4 weeks of age and is being investigated for neonates.

PADO 3 participants also discussed TAF and its potential for future use in paediatrics – including the issue of taste-masking. A first-line regimen with DTG and TAF (plus XTC) has the potential to harmonise across age and weight bands and with adults.

A reduced strength version of the boosted PI DRV/r is another priority.

The group also looked at two-drug regimens, such as DTG/3TC, for which adult phase 3 trials are ongoing. There was also concern with this regimen, particularly in the setting with high levels of NRTI resistance; with hepatitis B, during the third trimester of pregnancy and with TB treatment.

Longer term still there was also interest in the potential for long-acting formulations for infants, children and adolescents.

WHAT NEEDS TO BE DONE?

- **Upgrade the new first-line adult regimen.** Sufficient evidence to change WHO guidelines to recommend DTG (which is now starting to be provided in national programmes) and TAF as part of the preferred first-line regimen needs to be generated. A recommendation from WHO is the strongest signal to generic manufacturers to take the risk and produce new FDCs. Such WHO recommendations will require results from the studies discussed here.
- **Originators donate drugs to strategy studies for LMICs.** Originator manufacturers must take responsibility and supply prioritised antiretrovirals to key investigator-led studies (as well as the supporting substudies) to generate evidence to support their use in LMICs. And not after several years of deliberation. The lack of information on use of new drugs and doses in pregnancy and with TB treatment – that is critical to treating populations in LMICs – will continue to be a barrier to the recommendation and of any new regimen, however impressive the results from the phase 3 trials are.
- **Countries get ready to switch.** Countries with high volume ART programmes, need their guideline committees briefed as results are generated (even before they are publicly released), so that they can make new recommendations, hopefully before final WHO decisions.
- **Donors must support switch to new drugs and regimens.** Donors can play a huge part in changing standard of care in countries. Unitaid bought large volumes of TDF and helped to bring down the price and speed up the switch from d4T – so called market dynamics.
- **Timely approval.** Regulatory agencies in LMICs, need to register new originator and generic formulations for adults and children, as swiftly as possible. The Indian regulatory agency needs to waiver the request for Indian trials before prioritised ARV products can be exported. Ideally this should happen before new WHO and national recommendations.

- **Generic companies need time to plan for high volume manufacture.** Generic manufacturers need to be briefed on when data from key studies are expected to be released, guideline changes, and tender timing in countries, so that they can start planning to compete to supply the newly recommended regimens.
- **Pre-empt possible chaos.** Before introducing new drugs, issues such as stockpiling (and stock outs) need to be discussed and planned, so that hitches with switching from old to new regimens are kept to a minimum.
- **Adult second-line needs more consideration.** Although there is consensus on the likely best optimised first-line regimen, second-line is not quite there yet and requires more discussion and research and development to ensure best regimens and formulations.
- **Speed up development for children.** The gap needs to be narrowed between approval of new drugs for adults, children, and neonates. Simultaneous enrolling of different age cohorts, use of PK data and modelling and the consideration of weight bands. Speeding up research and in turn availability will require building on existing partnerships and research networks and collaboration between the research community, pharmaceutical companies, regulators and policy makers.
- **Speed up approval for children.** Harmonisation of regulatory requirements (including age categories and weight bands) between stringent authorities, WHO prequalification, and national authorities is also needed to help speed up availability.
- **Implement WHO recommendations.** As simpler formulations identified to implement the paediatric guidelines become available (most topically LPV/r pellets), countries must ensure that they are swiftly approved and distributed, with appropriate training for health workers. And manufacturers need to ensure availability meets demand.
- **Coordinate paediatric procurement.** Guidance on optimal formulations for children needs to be easily available to countries and updated as better ones become available. Companies need to be informed of the priority formulations. Plans need to be in place to phase out suboptimal paediatric formulations and phase in new ones. Donors need to ensure the availability of low volume products in a diminishing market.

CHAPTER 2

HIV pipeline 2017: new drugs in development

By Simon Collins

Introduction

This has been a lively year for HIV research.

Even though only one new drug was approved (a once-daily version of raltegravir) several key generic approvals (dolutegravir and tenofovir/FTC) are perhaps just as important. Three new fixed-dose combinations (FDCs) have been submitted to the US Food and Drug Administration (FDA)/European Medicines Agency (EMA) with expected decisions soon, including one with a new integrase inhibitor (bictegravir).

Early data presented for several new compounds, including from new drug classes that are in early stages of research, are an optimistic sign that HIV is still a potential market for new drugs.

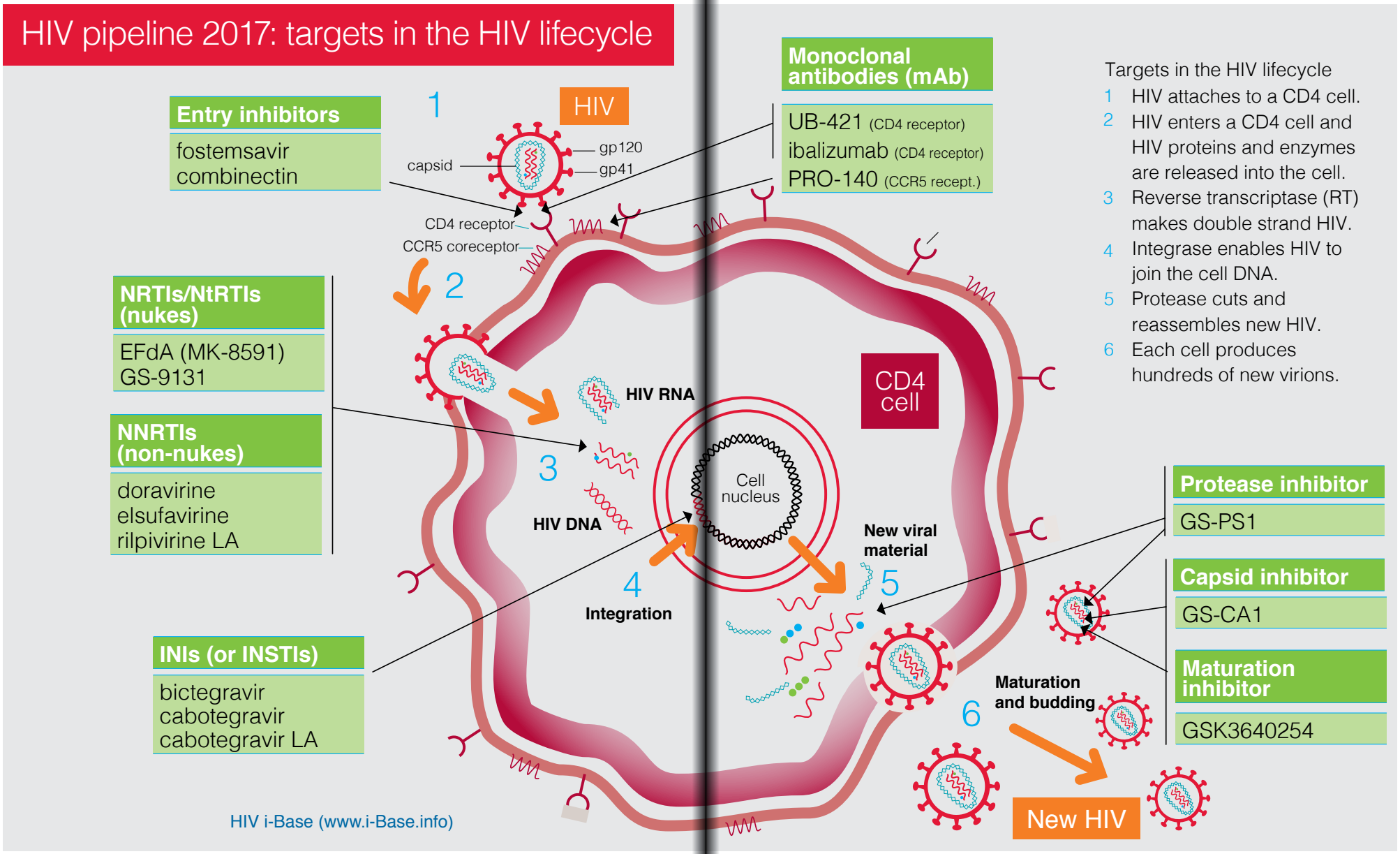
While current ART is safe and effective there are ways it could become better still: formulations with smaller pills, less frequent dosing, long-acting compounds (weekly, monthly, yearly), with lower doses, fewer side effects and drug interactions, stronger resistance profiles – and it could be cheaper and more accessible. Some of these factors feature in compounds already filed for regulatory approval.

This year the pipeline includes compounds in current classes (NRTIs, NNRTIs, PIs and integrase inhibitors) and compounds with new targets and mechanisms of action (including a capsid inhibitor and several monoclonal antibodies), see Figure 1. It also includes a two-drug combination submitted with an indication as maintenance therapy (dolutegravir/rilpivirine).

Importantly, compounds from new classes – monoclonal antibodies (mAbs), entry inhibitors, maturation inhibitors and capsid inhibitors – are all expected to work for people with multiple drug resistant (MDR) HIV who are dependent on new drugs.

Some of these drugs have potential to be used in very different ways – as treatment, as part of a cure strategy and for prevention as PrEP.

Figure 1: HIV pipeline 2017: targets in the HIV lifecycle



Key: INSTI: Integrase strand transfer inhibitors; NRTI: Nucleoside/tide reverse transcriptase inhibitors; NNRTI Non-nucleoside reverse transcriptase inhibitors.

Recently approved new HIV drugs

Raltegravir HD

The only new HIV drug approval since the pipeline report in July 2016 was for a once-daily formulation of raltegravir.[1]

The new version still requires a two-pill dose (2 x 600 mg) but has improved pharmacokinetic (PK) properties that allow once-daily dosing without regard to food. Approval was based on 48-week results from the phase 3 treatment-naive ONCEMRK study.[2] See study details.

The improved PK profile also results in lower peak drug concentrations and higher trough levels, and less interpatient variability.

The regulatory approval of several generic formulations over the last year is also important.

Generic dolutegravir

In September 2016, tentative approval by the FDA of a generic formulation of dolutegravir has the potential to significantly improve treatment in countries who have access to in-patent generics. This will be especially true once the FDC (with TAF/FTC) also becomes available.[3]

Generic TDF/FTC

EMA approval of three generic formulations of TDF/FTC[4] that use a different base salt for tenofovir, but that has been referred to European courts to decide on patent issues.[5]

The FDA also approved a generic version of TDF/FTC.[6] The patent implications and timeline for US generic access and pricing is unclear and might take years: generic drugs are sometimes priced very highly in the US.[7]

Submitted applications: completed phase 3 results

Several compounds have already been submitted for regulatory evaluation based on primary endpoint results from phase 3 studies.

Darunavir/cobicistat/FTC/TAF: FDC

In September 2016, the first single pill protease-inhibitor based fixed dose combination (FDC) of darunavir/cobicistat/FTC/TAF (D/C/F/TAF) was submitted in both the US and Europe, with a decision expected later in 2017.[8]

The applications are based on studies with darunavir/cobicistat plus tenofovirDF/FTC as control[9] and at least one study at IAS will report on this FDC.[10]

The reduced milligram dose for TAF compared to TDF makes this formulation possible as a single tablet.

Bictegravir/FTC/TAF: FDC

On 12 June 2017, a new drug application to the US FDA for an FDC of bictegravir/emtricitabine/tenofovir alafenamide (BIC/FTC/TAF).[11] A similar submission to the EMA in Europe is expected during 3Q 2017.

Bictegravir (formerly GS-9883) is a once-daily integrase inhibitor, that (unlike elvitegravir) does not need to be boosted or to be taken with food. This is also a potent compound, used at low milligram dose (50 mg) leading to a small pill when combined with TAF, few drug-drug interactions and a similar resistance profile to dolutegravir.[12]

Four phase 3 studies include a treatment naive study comparing it to dolutegravir and several switch studies in people with viral suppression on current treatment.

The most recent publicly presented data were results from a small phase 2 non-inferiority study in 98 treatment-naive participants that showed very similar results compared to dolutegravir.[13]

Results from two phase 3 studies in treatment naive adults will be presented as late breaker abstracts at the IAS 2017 in Paris.[14, 15]

Dolutegravir/rilpivirine: two-drug FDC

Although both dolutegravir and rilpivirine are long-approved as oral drugs (in 2013 and 2011 respectively, in the US), in June 2017 a new oral coformulation with both drugs in a single pill was submitted for regulatory approval as an FDC for maintenance therapy.[16]

The application is for use as a switch option in people with suppressed viral load on earlier treatment and is notable for being the first FDC that doesn't include NRTIs. The application is based on results from the SWORD 1 and 2 studies presented at CROI 2017 that showed dual arm was non-inferior to continuing ART.[17]

Dolutegravir-based dual therapy with 3TC is also discussed below.

Compounds in phase 3 development

The unpredictability of drug development is always important to remember and this year included gains and losses of some compounds and the re-emergence of others.

Doravirine: NNRTI

Doravirine is a once-daily NNRTI that can be taken with or without food that has few drug-drug interactions and that retains activity against common first generation NNRTI mutations (K103N, Y181C, G190A and E138K). It is being developed in an FDC with generic TDF/3TC and has the compound name MK-1439A.[18]

Results from a two-part, dose-finding, phase 2 study in treatment-naive participants presented at CROI 2016 last year, reported doravirine to be non-inferior compared to efavirenz with 78% in each group having undetectable viral load at week 48.[19]

This year another randomised phase 3 study reported doravirine to be non-inferior compared to boosted darunavir with similar safety and efficacy results.[20]

New nanoformulations of this compound are also in development[21] and IAS 2017 will include phase 3 results comparing the MK-1439A FDC to efavirenz/TDF/FTC in people on first ART.[22]

Cabotegravir and cabotegravir/rilpivirine: long-acting (LA) FDC

Cabotegravir (CAB) is a second-generation integrase inhibitor being developed by ViiV Healthcare as both an oral tablet and long-acting (CAB-LA) injectable formulation. It has potential use as both treatment and, the injectable formulation, as PrEP.

CAB-LA has an extremely long half-life: a single injection results in drug levels that are still detectable in some people more than a year later. This requires that a lead-in phase using the oral formulation is essential before using the injection to screen for likely risk of hypersensitivity reaction. The long half-life means that anyone stopping CAB-LA when used as treatment needs to switch to alternative ART. When used as PrEP, current studies recommend switching to daily oral PrEP for a year.

The oral formulation has a similar drug resistance profile to dolutegravir, and is also being studied as part of dual oral therapy with rilpivirine (see dolutegravir/rilpivirine above). Results from a phase 2b included 144-week results from 243 treatment-naive participants who started triple therapy ART (dose-ranging cabotegravir or efavirenz, plus background TDF/FTC NRTIs), and who switched to oral cabotegravir plus rilpivirine maintenance therapy at week 24 if viral load was undetectable.[23]

The phase 2 LATTE-2 study, using dual injection maintenance therapy (CAB-LA coformulated with rilpivirine LA) reported good efficacy and tolerability at week-48 with >90% of participants having undetectable viral load and high patient satisfaction with injections (even though these caused usually minor side effects).[24]

Several international phase 3 studies of cabotegravir LA for PrEP are already underway, with oral TDF/FTC as the comparison.[25, 26] New nanoformulations of cabotegravir LA are also in development.[27]

The phase 3 programme includes two large international studies in treatment-

naive and -experienced participants: FLAIR (First Long-Acting Injectable Regimen) and ATLAS (Antiretroviral Therapy as Long-Acting Suppression). IAS 2017 will include updated 96-week results from LATTE-2.[28]

Dolutegravir/lamivudine: two-drug FDC

Dolutegravir showed a higher barrier against drug resistance in treatment-naive studies than any other antiretroviral to date and this led to several independent research groups looking at whether dolutegravir could be used in combinations with less than three active drugs.

In addition to using dolutegravir with rilpivirine (see above), several studies are using dolutegravir with lamivudine (3TC) including with the two drugs coformulated in an FDC.

This includes use both as first-line ART and as a switch option in people who are stable on current ART (usually defined as having undetectable viral load for year).

Of these, the single-arm treatment naive PADDLE study reported rapid reductions in viral load, including in four people with baseline viral load >100,000 copies/mL with 18/20 maintaining undetectable viral load at week-48.[29] Results from week-96 of this study will be presented at IAS 2017.[30]

Several larger phase 2 and 3 studies are ongoing including the single arm LAMIDOL and ACTG A5353 studies and the randomised ASPIRE and TRULIGHT studies.[31, 32, 33, 34]

Of these, only the French ANRS 167 LAMIDOL single arm switch study has reported results. At CROI 2017, after 40 weeks of dual therapy, 101/104 participants remaining undetectable, with a single person with viral rebound (>50–200 copies/mL) who switched back to triple ART.[31] ACTG A5353 in 122 treatment-naive participants is due to report results at IAS 2017.[32]

Finally, in August 2016, ViiV announced two large international randomised phase 3 studies (GEMINI 1 and 2) that will compare dolutegravir/3TC FDC to dolutegravir plus separate TDF/FTC.[35] Together these will enrol 1400 treatment-naive participants and will quantify whether dual-NRTIs are still needed for some integrase-based regimens, with data collection for the primary endpoint (viral suppression at week-48) expected in 2018.[36, 37]

If these studies produce positive results, a modelling study published last year reported potential savings of $550 million in the US alone over five years if dolutegravir/3TC was used as maintenance therapy by 50% of people who suppressed viral load on triple ART and $800 million if used as initial ART. This increased to $3 billion if 25% of people currently on stable ART switch to dolutegravir/3TC dual therapy.[38]

It is also important that although several studies using dolutegravir as monotherapy maintained viral suppression in most participants, the unpredictable risk of viral rebound in some people with the development of integrase resistance means that monotherapy with dolutegravir is now clearly not recommended. All dolutegravir monotherapy studies should have now changed all participants back to dual or triple therapy.[39]

Ibalizumab: mAb

Ibalizumab is a monoclonal antibody that has been in development for over a decade. Previous development names included TMB-355 and TNX-355 and phase 1 efficacy results were first reported in 2008.[40]

Ibalizumab blocks initial HIV entry by attaching to CD4 receptors and stopping conformational changes that are needed for the virus to enter a CD4 cell. It is active against CCR5 and CXCR4-tropic virus. The half-life of >3 days enables the intravenous (IV) infusion to be given every two weeks.

For much of the development programme, access was limited to an open-label expanded-access study[41] but results from a small phase 3 study (TMB-301) were presented at CROI 2017. This study in 40 people with multidrug resistant HIV, reported a mean viral load decrease from baseline was –1.6 log copies/mL, with

55% and 48% having reductions >1 log and >2 log respectively.[42]

Results from an intramuscular formulation were also presented at CROI 2017 but although initial viral load reductions were similar to the IV version, rebound after one week suggests greater vulnerability to drug resistance.[43]

Ibalizumab is being developed by the Taiwanese company TaiMed but marketing and distribution rights for the US and Canada have been sold to Theratechnologies (who market tesamorelin for visceral hypertrophy). A press release from the developing companies reported that FDA had granted a priority review with an expected deadline for submission in January 2018.[44]

A further phase 3 study is also ongoing[45] and updated results in treatment-experienced patients are due to be presented at IAS 2017.[46]

PRO 140: mAb

PRO 140 is a humanised IgG4 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 ten years, but that paradoxically has been designated "fast-track" status, for having potential activity against MDR HIV.

The most recent phase 3 data were presented at CROI 2017 where a small number of people (n=41 originally and 16 in a follow up phase) switched to PRO140 monotherapy after stopping ART. PRO 140 uses weekly dosing of 350 mg self-administered sub-cutaneous injections of PRO 140 and 10/16 people continued to have undetectable viral load without ART for up to two years.[47]

Ongoing phase 3 studies include a monotherapy switch study in 300 participants with viral suppression >48 weeks on ART[48] and in addition to ART as part of salvage combination in 30 participants with multidrug resistance to other classes.[49] No new results are expected at IAS 2017.

Compounds in phase 2 studies

Fostemsavir (GSK3684934): attachment inhibitor

Fostemsavir (GSK3684934) is an attachment inhibitor that binds to gp120 that 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 but was previously a BMS compound (BMS-663068).

Results from a phase 2b randomised dose-ranging study in 251 treatment-experienced participants that used atazanavir/r in the control arm were presented at the Glasgow conference in 2016. Rather than using 2 NRTIs as background drugs, all participants used raltegravir (400 mg twice-daily) plus TDF (once-daily) as the background drugs. At 96-weeks, 61% vs 53% had undetectable viral load <50 copies/mL (GSK934 vs atazanavir) with no difference by baseline subgroups.[50]

Ongoing research is in a large international phase 3 study (enrolled, no longer recruiting) in treatment-experienced patients with drug resistance and who are sensitive to only two or fewer drug classes. This study was launched in 2015 with an estimated end date in 2020.[51]

Although no new clinical data are due to be presented at IAS 2017, two drug interactions studies are due to be presented as posters.[52, 53]

UB-421: mAb

UB-421 is a broadly neutralising mAb that targets CD4 binding with in vitro data suggest comparable or greater potency compared to other compounds, including VRC01 and 3BNC117.[5]

A phase 2 study in 29 virally suppressed participants on ART who used UB-421 monotherapy during an 8-week ART interruption had no cases of viral rebound during the monotherapy phase. UB-421 was given by infusion either 10 mg/kg weekly or 25 mg/kg every two-weeks.[54]

Two current phase 3 studies in people with MDR HIV are listed but not yet enrolling.[55, 56]

No new data are expected at IAS 2017.

VRC01: mAb

VRC01 is another 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, as part of cure research and for prevention.

One study at CROI reported no additional impact on reducing the latently infected viral reservoir from adding VRC01 to ART.[57] Other studies in cure research are ongoing.[58]

This includes using a single injection in infants after birth to limit risk of vertical transmission and a potential role of additional injections for breastfed infants.[59]

Two large international phase 2 PrEP studies are already ongoing.[60, 61]

Although new clinical data are expected at IAS 2017, a study on lack of effect on reservoirs will be presented, similar to published results from last year.[62, 63]

ABX464: Rev inhibitor

ABX464 is a molecule thought to work by blocking the end stages of viral assembly. A phase 2a dose-ranging study presented at CROI 2016 in 80 treatment-naive participants in Thailand reported modest antiviral activity (~0.5 log copies/mL) but only in 4/6 people using the highest 150 mg dose (with no responses in 2/6).[81]

The compound is also being studied for impact on viral reservoir and whether it can limit viral rebound in absence of ART, included a related study due to be presented at IAS 2017 in Paris.[82, 83]

Phase 1 and preclinical compounds of interest

As many companies do not widely publicise pre-clinical work, this section is restricted to a few studies.

MK-8591 (EFdA): NRTI

MK-8591 is a very interesting NRTI now in phase 1 development by Merck that 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.

MK-8591 is active against both HIV-1 subtypes and HIV-2, including against NRTI mutations K65R and Q151M (although the M184V variant conferred 10-fold resistance).[64]

EFdA reaches good drug levels in vaginal and rectal tissue – supporting further PrEP studies.[65]

IAS 2017 is expected to include important new results for both use as treatment and prevention.[66, 67]

GS-913: NRTI

GS-9131 was reported ten years ago at CROI 2006.[68]

Other published studies highlight the potential for low risk of toxicity in animal studies and retains in vitro phenotypic sensitivity to broad NRTI resistance including mutations at K65R, L74V and M184V and multiple TAMS.[69] The poster at CROI 2017 confirmed results from previously published studies into the activity against common NRTI mutations.[70]

No new data are expected at IAS 2017.

GSK3640254: maturation inhibitor

The maturation inhibitor GSK3640254 (previously BMS-986197) is in preclinical stages of development with GSK with a molecule acquired from BMS.[71]

An earlier maturation inhibitor, BMS-955176, also acquired from BMS was discontinued in October 2016 due to GI toxicity and drug resistance.[72]

New data on tolerability and side effects will be presented at IAS 2017.[73]

Combinectin: adnectin/fusion inhibitor

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

This compound was in preclinical development with BMS and was acquired by ViiV in late 2015.

Latest data presented at Glasgow 2016 summarised, in vitro activity and resistance data and virologic data from mouse studies.[74]

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 PK data from rat and dog studies.[75]

GS-CA1: capsid inhibitor

First data was presented on GS-CA1, the first compound in a new class of HIV capsid inhibitors, with a formulation that can be used for slow-release injections, with monthly or longer dosing.[76]

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.

Compounds developed for low- and middle-income markets

Although the following compounds are not being developed for use in high-income counties, they are progressing though clinical research.

Albuvirtide: fusion inhibitor

Albuvirtide is a second-generation fusion inhibitor similar to T-20 (enfuvirtide) that is being developed by Frontier Biotechnologies as an alternative second-line combination in China.

The long half-life enables once-weekly intravenous infusion (rather than twice-daily sub-cutaneous injections with T-20) and a side effect profile that does not include injection site reactions (ISRs).

Partial interim phase 3 results from 175/389 participants were presented in Glasgow in October 2016 included approximately 80% viral suppression at 24 weeks and generally good tolerability.[77]

Based on these results, albuvirtide has already been submitted for conditional approval in China and there are plans to run additional international studies in other countries next year, especially with other long-acting drugs. A sub-cutaneous formulation of albuvirtide is also in development that would allow self-injections at home, rather than weekly clinic visits needed in the current version.

Elsulfavirine: NNRTI

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

48-week results from a phase 2b study at CROI 2017 reported similar viral suppression compared to efavirenz (81% vs 73% <50 copies/mL) using TDF/FTC background NRTIs.[78]

A long-acting injectable formulation is being used in ongoing studies for treatment and PrEP with new results due at IAS 2017.[79]

Other compounds: trailing or lost

Several other compounds that featured in earlier pipeline reports have not led to new data being presented over the last year.

GS-9695 and GS-9822: integrase inhibitors

GS-9695 and GS-9822 were promising integrase inhibitor compounds that were discontinued due to unpredictable kidney/urothelial toxicity in monkeys.[80]

BMS-955176: maturation inhibitor

The decision to end the development programme for BMS-955176 due to gastrointestinal intolerability was mentioned earlier in this report.[71]

The follow-on compound GSK3640254 is still in development.

Conclusion

This is still an exciting time for HIV drug development.

This year the HIV pipeline is remarkable for a potential range of drugs that could improve many aspects of the traditional approach to treating HIV using three-drug oral therapy.

It includes responses to the changing situation in which all countries now have access to some generic anitretrovirals – and drug pricing will continue to drive access in all countries. It also includes some compounds that are only developed for low- and middle-income countries, and coformulations that will not be available in high income-countries.

Table 11: HIV pipeline compounds by development phase

COMPOUND COMPANY	CLASS	COMMENT	REFS.
Submitted to FDA/EMA			
darunavir/cobicistat/ TAF/FTC Janssen and Gilead	Boosted PI and NRTI FDC	As phase 3 research used darunavir/cobicistat plus TDF/ FTC as a comparitor, the FDC is expected to be at least non-inferior.	8, 9
bictegravir Gilead	INSTI and NRTI FDC	Once-daily, unboosted, low mg FDC with FTC/TAF.	10, 11, 12, 13, 14, 15
dolutegravir/ rilpivirine FDC ViiV and Janssen	INSTI and NNRTI FDC	Already approved integrase inhibitor but now in a new two-drug coformulation with the NRTI rilpivirine.	16, 17
Phase 3			
doravirine Merck/MSD	NNRTI	Active against first generation NNRTI resistance. Non-inferior to efavirenz. Generic FDC with TDF/3TC in phase 3 studies.	18, 19, 20, 21, 22
cabotegravir ViiV Healthcare	INSTI	Oral formulation integrase inhibitor mainly used for lead-in dose before long-acting formulation.	23
cabotegravir/ 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.	24, 25, 26, 27, 28
dolutegravir/3TC ViiV	INSTI and NRTI FDC	Dual combination currently in Phase 3 studies as initial ART in naive participants and a switch option in people on stable ART.	29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39
Ibalizumab TaiMed and Theratechnologies	mAb CD4 binding	Intravenous infusion (800 mg every two weeks) being studied in addition to optimised ART in single arm study in people with multiclass HIV drug resistance.	40, 41, 42, 43, 44, 45, 46
PRO 140 CytoDyn	mAb CCR5 target	Once-weekly (350 mg) sub-cutaneous injection with potential to maintain viral suppression for more than two years after stopping ART. Also, with ART against multiclass resistance.	47, 48, 49
GSK3684934 ViiV	attachment inhibitor	Fostemsavir is a gp120 attachment inhibitor that is mainly being studied in treatment-experienced patients with MDR HIV in a large international study.	50, 51, 52, 53

COMPOUND COMPANY	CLASS	COMMENT	REFS.
Albuvirtide Frontier Biotech	Entry inhibitor	Similar to T-20 (enfuvirtide) but only requiring once-weekly infusion. Only in development for use in China.	77
Phase 2			
UB-421 United BioPharma	mAb CD4 binding	Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption.	54, 55, 56, 57, 63
VRC01	mAb CD4 binding	Intravenous infusion (40 mg/kg) being studied with ART for effect on reservoir and 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.	57, 58, 59, 60, 61, 62, 63
elsulfavirine, prodrug of VM-1500A Viriom	NNRTI	NNRTI that is being developed for use in low and middle income countries. Similar activity to efavirenz in Russian study. Long-acting formulation being studied with potential for weekly dosing.	78, 79
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.	81, 82, 83
Phase 1 and preclinical			
MK-8591 (EFdA) Merck/MSD	NRTIs	Highly potent, low dose, active against NRTI resistance. Long half-life, potential as oral (weekly dose) and implant (annual implant for PrEP).	64, 65, 66, 67

COMPOUND COMPANY	CLASS	COMMENT	REFS.
GS-9131 prodrug of GS-9141 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. Currently difficult to synthesise in bulk.	68, 69, 70
GSK3640254 ViiV Healthcare	Maturation inhibitor	Back-up compound to first of two maturation inhibitors acquired from BMS. Early preclinical research.	71, 72, 73
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.	74
GSPI1 Gilead	Protease inhibitor	New QD unboosted PI, high potency, long half-life, potential in FDC single table regimen (Gilead).	75
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.	76
Discontinued			
GS-9695 and GS-9822 Gilead	INSTI	Non-catalytic integrase inhibitors no longer being studied due to renal toxicity.	80
BMS-955176 ViiV Healthcare	Maturation inhibitor	Development stopped in October 2016 due to problems with GI toxicity and resistance.	72, 73

CHAPTER 3

The paediatric pipeline

By Polly Clayden

Introduction

Paediatric investigation plans (PIPs)[1] and paediatric study plans (PSPs)[2] – required by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) respectively – will be under discussion for all compounds in early phases of development for adults by originator manufacturers (described in the previous section).

PIPs are compulsory for all new drugs and FDCs before the marketing authorisation application is submitted – usually at the end of phase 1 development. PSPs must be agreed on before filing a new drug application (NDA) – at the end of phase 2.

Both regulatory agencies offer incentives and/or penalties to ensure that any new drug that might benefit children must be studied in this population. The EMA enforces penalties for companies that do not provide a PIP as part of their application (or request a waiver), and gives patent extensions for completing the PIP. The FDA also extends six-month patent protection to companies that perform the requested paediatric studies – though companies are not required to do this.

Paediatric development can be waived for specific drugs or classes of drugs that are likely to be ineffective or unsafe in all or some paediatric age groups. A waiver can also be obtained for products that are intended for conditions that only occur in adults, or that do not represent a benefit over existing paediatric treatments. In some cases, studies can be deferred until after the adult studies have been conducted.

Manufacturers must include PK data for all age groups of children, efficacy, tolerability, and differences in side effects. They must have stability and palatability data for formulations and demonstrate that they are able to achieve PK targets associated with efficacy in adults.

Studies are conducted in children as soon as there are sufficient data from those in adults. Most paediatric development programmes take an age staggered approach, starting with the older cohorts of children and working in de-escalated age bands: 12 to less than 18 years; 6 to less than 12 years; 2 to less than six years; 6 months to less than 2 years and below six months. Data are required in the youngest age groups – down to new-borns – unless a regulatory waiver is obtained. As the youngest age group is last to be studied and approved there are considerable delays in availability of new drugs for this population.

The problems with the age-staggered approach that results in delays in approval and availability of new drugs, particularly in the youngest age group where options are lacking, have been much discussed. World Health Organisation (WHO) uses a weight band dosing approach and it would make sense to investigate weight band dosing in paediatric antiretroviral development from the beginning, optimising the use of PK data and modelling. The dolutegravir (DTG) development programme, IMPAACT P1093, will try to capture enough data to inform weight band dosing, with the dispersible tablet in the younger cohorts.

Moving away from the age-staggered approach to weight bands could also make it possible to open multiple cohorts simultaneously, if formulations are available, which would speed up availability of new drugs for infants and children considerably.

It would be interesting to see if doses for younger children have changed dramatically from predicted milligrams per kilogram ones due to PK data from older cohorts.

If work on aligning age bands with WHO weight bands could be done as originator manufacturers conduct their paediatric development programmes, this would help generic manufacturers develop co-formulations and FDCs that allow dosing aligned with recommendations across the weight bands. It could help close the gap between when new drugs and regimens are available for adults and children.

Table 12. The paediatric antiretroviral pipeline

COMPOUND	SPONSOR	FORMULATION/S AND DOSE	STATUS AND COMMENTS
Nucleotide reverse transcriptase inhibitor and combinations			
Emtricitabine/tenofovir alafenamide (F/TAF)	Gilead	Reduced strength, coformulated tablets and non-solid formulation in development	Approved >12 years Phase 2/3 switch study in children and adolescents stable on FTC/TDF plus 3rd agent 6 to <18 years Study in infants and children 4 weeks to <6 years planned
Elvitegravir, cobicistat, emtricitabine, tenofovir alfenamide (E/C/F/TAF	Gilead	Reduced dose FDC tablets in development	Approved >12 years Phase 2/3 single arm, open label E/C/F/TAF treatment-naive children and adolescents 6 to <18 years Waiver <6 years
Rilpivirine (R)/F/TAF	Gilead/ Janssen	Reduced strength FDC tablets	Approved >12 years Dependent on development of RPV and F/TAF Waiver <2 years
Bictegravir (B)/F/TAF	Gilead	Reduced strength FDC tablets	12 to <18 years submitted to FDA Switch study in stable children and adolescents 6 to <18 years 4 weeks to <6 years planned

COMPOUND	SPONSOR	FORMULATION/S AND DOSE	STATUS AND COMMENTS
Non-nucleoside reverse transcriptase inhibitors			
Etravirine (ETR)	Janssen	Dispersible tablets 25 (scored), 100 mg	Approved >6 years Phase 1/2 treatment-experienced infants and children 2 months to <6 years and treatment-naive 2 months to <2 years enrolling Waiver <2 months
Rilpivirine (RPV)	Janssen	Tablet 25mg Granules 2.5 mg /g	Approved >12 years with viral load < 100,000 copies/mL 2 to <12 years planned
Doravirine	Merck	Single agent and FDC with TDF/3TC planned	Switch and treatment-naive studies planned Waiver for <2 years FDC
Integrase inhibitors and combinations			
Raltegravir (RAL)	Merck	Granules for suspension 6mg/kg (100 mg sachet) Chewable 25 and 100 mg tablets	Approved for use in children >4 weeks Studies underway in HIV infected and exposed infants <4 weeks
E/C/F/TDF (Stribild)	Gilead	Reduced dose tablets in development	Studies underway in treatment-naive 12 to <18 years 6 to <12 years planned Waiver <6 years

COMPOUND	SPONSOR	FORMULATION/S AND DOSE	STATUS AND COMMENTS
E/C/F/TAF See TAF above	Gilead	Reduced dose tablets in development	Studies underway in treatment naive 12 to <18 years 6 to <12 years planned Waiver <6 years
Dolutegravir (DTG)	ViiV Healthcare	Dispersible 5 mg tablets in development 10 mg and 25 mg tablets	Approved for children and adolescents >6 years, weighing >30/15 kg FDA/EMA Phase 1/2 study, 6 weeks to <18 years treatment-naive and -experienced children, ongoing
DTG/ ABC/3TC	ViiV	Reduced strength film coated and dispersible tablets	Approved for adolescents >12 years and >40 kg Dependent on ongoing studies confirming DTG dose in children and ability to establish appropriate dosing ratios for components Waiver <2 years
DTG/RPV	ViiV/Jansen	Reduced strength co-formulation	To be studied as maintenance regimen 6 to <18 years and virologically suppressed Waiver <6 years
DTG/3TC	ViiV	Reduced strength co-formulation	Waiver <2 years

COMPOUND	SPONSOR	FORMULATION/S AND DOSE	STATUS AND COMMENTS
Cabotegravir/RPV long acting (LA)	ViiV/ Janssen	Age appropriate liquid formulation for induction Intramuscular nanosuspension as for adults	Treatment and prevention phase 1/2 Waiver <2 years (treatment) <12 years prevention Deferral 2 to <18 years
B/F/TAF	Gilead	Reduced strength FDCs	See TAF above
Booster			
Cobicistat (COBI)	Gilead	75 mg tablets 20 mg dispersible tablets for oral suspension	Booster Also part of E/C/F/TDF and E/C/F/TAF
Atazanavir/cobicistat (ATV/c)	Gilead/ BMS	Reduced strength and dispersible tablets planned	Phase 2/3 treatment experienced children 3 months to <18 years (ATV/c) 3 to <18 years (DRV/c)
Darunavir/cobicistat (DRV/c)	Gilead/ Janssen		
Darunavir/cobicistat/ emtricitabine/tenofovir alafenamide (D/C/F/TAF)	Gilead/ Janssen	Reduced strength tablets planned	Phase 3 6 to < 18 years 6 years of age or weighing less than 25 kg
VRC01	IMPAACT	Single 20 or 40 mg/ kg subcutaneous dose within 72 hours of birth	Phase 1 At risk infants >36 weeks of gestation or >2 kg at birth

Nucleotide reverse transcriptase inhibitor

Tenofovir alafenamide

TAF is considered a priority for future generic FDCs for children. Early data in adults suggests that it might have a better safety profile than TDF. This has yet to be confirmed in children. TAF also has a low milligram adult dose: 25 mg without a boosting agent and 10 mg boosted.

For children TAF might be an alternative to abacavir. It could help to harmonise paediatric and adult ART regimens, particularly if it could be coformulated with DTG and 3TC or FTC.

The originator company Gilead Sciences is developing a co-formulation with FTC (F/TAF) and TAF-containing FDCs of elvitegravir (EVG)/cobicistat (COBI)/FTC/TAF (E/C/F/TAF) and bictegravir (B/F/TAF). In collaboration with Janssen there is also an FDC with rilpivirine (R/F/TAF).

Emtricitabine/tenofovir alafenamide

F/TAF is approved for adolescents aged 12 and above at the adult doses: 200/25 mg.[3,4]

It is being investigated in a phase 1/2 switch study enrolling children down to six years of age (200/25 mg unboosted and 200/10 mg boosted).[5,6]

Adolescents aged 12 to less than 18 years switch their current two nucleoside

reverse transcriptase inhibitor (NRTI) containing regimen to F/TAF (while continuing on their third antiretroviral agent) for 96 weeks. Children aged 6 to less than 12 are randomised to receive either F/TAF or FTC/TDF while continuing their third antiretroviral agent through 96 weeks.

A study in infants and children aged 4 weeks to 6 years is planned. Reduced strength tablets and a non-solid formulation are in development. As with the paediatric formulation of TDF, the taste of TAF is bitter and will need masking. This is particularly tricky and important for dispersible forms for children who cannot swallow tablets.

Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide

E/C/F/TAF is also approved for adolescents 12 years and above at the adult doses: 150/150/200/10mg.

E/C/F/TAF is being investigated in phase 2/3, single arm, open label studies treatment-naive adolescents and virologically suppressed children and adolescents aged 6 to less than18 years. There is a waiver for children below six years old.[7,8,9]

In 12 to less than 18 year olds receiving E/C/F/TAF, steady-state PK parameters of EVG, COBI, FTC, TAF and its metabolite tenofovir (TFV) were compared to adult exposures.[10] The study found TAF (as well as TFV, EVG, COBI, and FTC) PK parameters in adolescents to be consistent with those associated with safety and efficacy in adults.

In 6 to less than 12 year olds, at week 24, plasma PK of EVG, COBI, FTC, TAF and TFV were modestly higher (20–80%) than in adults, but were within safe and efficacious adult ranges.[11]

E/C/F/TAF was generally well tolerated in both studies with a favourable renal and bone safety profile and participants remained virologically suppressed.

Bictegravir/emtricitabine/tenofovir alafenamide

An NDA for the adult formulation of B/F/TAF 50/200/25 mg has recently been submitted to the FDA.[12] Gilead plans to submit a marketing authorisation to the EMA later this year.

A phase 2/3 switch study is ongoing in virologically suppressed adolescents and children aged 6 to less than 18 years.[13,14]

Formulation and trial design for infants and young children 4 weeks to less than 6 years of age and/or less than 25 kg are under discussion.

Rilpivirine/emtricitabine/tenofovir alafenamide

R/F/TAF 25/200/25 mg is approved for the treatment of adults and adolescents ages 12 years and older weighing at least 35 kg without NNRTI, TDF or FTC resistance, and with a viral load less than 100,000 copies/mL.[15]

The adult dose will also be investigated for children 6 to less than 12 years, and age appropriate formulations for ages 4 weeks to less than 12 years, but these are deferred until more is known about the individual components. There is a waiver for infants less than 4 weeks.[16]

Non-nucleoside reverse transcriptase inhibitors

Etravirine

A scored 25 mg etravirine (ETR) tablet with dosing recommendations for treatment-experienced children and adolescents aged 6 to less than 18 years and weighing at least 16 kg is currently approved.[17] The recommended dose is based on 5.2 mg/kg twice daily.

IMPAACT P1090 is evaluating the drug in treatment-naive and -experienced children aged 2 months to 6 years.[18,19,20] Phase 1/2 studies in the younger age groups are currently enrolling treatment-experienced children.

There is a waiver for infants from birth to less than two months.

Rilpivirine

Rilpivirine (RPV) is approved for treatment of adults and adolescents 12 years of age and above with viral load less than 100,000 copies/mL at 25 mg once daily.

Studies are ongoing or planned for children from two weeks to less than 12 years of age.[21,22] A granule formulation of RPV is in development.

RPV is also being developed as a co-formulation with DTG and an intramuscular long acting formulation for treatment and prevention (see below).

Doravirine

Once-daily 100 mg doravirine is currently under investigation in adults.[23] The originator company Merck has a full paediatric development plan for doravirine including the FDC of doravirine plus TDF plus 3TC (from birth to 18 years of age and the latter going down to 2 years of age).[24]

The studies will enrol populations similar to those in adult phase 3 studies: treatment-naive and stable experienced patients for switch studies.[25] The first study in adolescents is planned to open by the end of this year.

Reduced strength tablets and granules are in development.

Integrase inhibitors

Raltegravir

Raltegravir (RAL) is approved for infants and children from four weeks of age.[26]

For the youngest age group (four weeks to less than two years, weighing 3 kg to 20 kg) it is formulated as granules for oral suspension. The formulation comes in single-use packets of banana-flavoured granules containing 100 mg of RAL, which is suspended in 5 mL of water giving a final concentration of 20 mg/mL. Giving RAL to neonates currently requires a complex dosing regimen.

For older children, there is an orange-banana flavoured, chewable paediatric formulation: 25 and 100 mg tablets. Because the formulations are not bioequivalent, chewable tablets and the oral suspension are not interchangeable and have specific guidance.

There have been discussions about the possibility of using the chewable formulation in younger age groups, as the granules for oral suspension are complicated to use.

The chewable tablets can be prepared by wetting, crushing, and stirring in water, apple juice, or breast milk until dispersed. This could mean simpler administration to younger children following WHO weight bands.[27] Although in vitro data suggest this will result in therapeutic plasma levels, there are no efficacy/safety data to support this use.

A comprehensive development plan is ongoing with the IMPAACT Network including in neonates less than four weeks of age (both HIV infected and exposed) infants.[28, 29, 30, 31, 32, 33, 34, 35]

Elvitegravir

The development of EVG as a single formulation for children was recently stopped. EVG is being studied as part of E/C/F/TAF (see above) and E/C/F/TDF.

Dolutegravir

DTG is approved for children ages 6 years and above, weighing at least 30 kg (FDA) or 15 kg (EMA).[36, 37] Reduced strength formulations are 10mg and 25mg oral tablets.

DTG also has a very comprehensive development programme and is being studied in age groups down to 4 weeks in IMPAACT P1093.[38]

IMPAACT P1093 is an ongoing, phase 1/2, open label PK, safety and efficacy study in children and adolescents in age de-escalated cohorts of DTG plus optimised background regimen.[39, 40, 41]

A 5 mg dispersible tablet formulation of DTG is being developed (as an alternative to the granule formulation that was originally used in early studies) for infants and young children. The dispersible tablet and granule formulations are bioequivalent.[42] DTG PK is not affected by water mineral content or 30-minute delay in dispersed tablet consumption. The dispersible tablet can be given under these conditions.

Taste masking work on the dispersible tablets is ongoing. The tablets will be strawberry cream flavoured. Only the dispersible tablets will be available commercially.

Dolutegravir/abacavir/lamivudine

Development of a paediatric formulation of the FDC of DTG/ABC/3TC – currently approved for adults and adolescents aged 12 years and above in EU (adults 18 and above in US) [43, 44] – is also planned.

The DTG/ABC/3TC PIP requires data from IMPAACT P1093 in the 2 to less than 12 years of age group to inform DTG dosing.[45]

The investigation plan also requires the completion of a DTG/ABC/3TC FDC paediatric study in 2 to 12 year olds. This will be an open-label, switch design and enrol children who are fully suppressed on ART and integrase inhibitor-naive.

There is a waiver from birth to less than 2 years old.

Dolutegravir/rilpivirine

The current plan for a paediatric DTG/RPV FDC is as a maintenance regimen in children and adolescents aged six to less than18 years and virologically suppressed.[46]

Data from planned adult phase 3 studies and existing adolescent data from single agents will be used for the 12 to less than 18 years age group. Providing the adult data supports the maintenance strategy, dosing studies and paediatric FDC development will then go ahead in the 6 to 12 age group.

There is a waiver from birth to less than 6 years old.

Dolutegravir/lamivudine

The plan for DTG/3TC FDC is for ART naive adolescents above 12 to less than 18 years with viral load less than 500,000 copies/mL and virologically suppressed children and adolescents aged 2 to less than 18 years.[47]

There is a waiver from birth to less than 2 years old.

Bictegravir

In development as part of B/F/TAF (see above).

Cabotegravir and rilpivirine long-acting

Cabotegravir (CAB) is under investigation for adults as a long-acting formulation with RPV (CAB/RPV LA). An age appropriate formulation will be developed for induction and the intramuscular nanosuspension will be the same as for adults (adult/adolescent doses: 3mL loading, 2mL maintenance).

The PIP includes PK, safety, tolerability, durability, acceptability and maintenance of CAB and RPV in 2 to 18 year olds (prevention studies from 12 to less than 18 years).[48]

A waiver was granted for children from birth to less than two years and a deferral for 2 to 18 year olds.

IMPAACT 2017 – a phase 1/2 study will look at CAB/RPV LA in approximately 155 virologically suppressed children and adolescents aged 12 to less than 18 years. Antiviral activity will be assessed as part of safety evaluations. [49]

PK booster

Cobicistat and formulations

COBI is a CYP3A inhibitor with no antiretroviral activity. COBI 150 mg is approved for adults as a booster of atazanavir (ATV) 300 mg or DRV 800 mg and as part of several FDCs. It is under investigation for children and adolescents aged at least six years as a part of E/C/F/TDF and E/C/F/TAF.

A 50 mg paediatric immediate-release tablet and a 20 mg paediatric dispersible tablet are in development.[50]

COBI is being studied in treatment-experienced children aged three months to 18 years who are suppressed and on RTV boosted atazanavir (ATV)- or darunavir (DRV)-containing regimens. The study will switch children from RTV to COBI and look at steady state PK and confirm the dose. It will also evaluate the safety, tolerability, and efficacy of ATV/COBI or DRV/COBI.

Reduced dose COBI-boosted co-formulations (ATV/c and DRV/c) are planned as well as an FDC with DRV (D/C/F/TAF).[51, 52, 53]

There are waivers from birth to 3 months, 3 years and 6 years for ATV/c, DRV/c and D/C/F/TAF respectively.

HIV neutralising monoclonal antibody

VRCO1

As a slight departure from antiretrovirals, first data from VRC01 – an investigational HIV neutralising monoclonal antibody administered subcutaneously to neonates – were presented this year.[54]

Preliminary results from IMPAACT P1112 suggest that its half-life would support monthly injections for those at risk of HIV through breastfeeding.

This is an ongoing, prospective, open label, dose escalating study of VRC01, given to infants at increased risk of vertical transmission as a single 20 or 40 mg/kg subcutaneous dose within 72 hours of birth.

VRC01 is being investigated in IMPAACT P1112 and with ART to promote clearance of HIV infected cells in IMPAACT 2008 is planned.[55, 56]

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CHAPTER 1: FIT FOR PURPOSE

Key: CROI, Conference on Retroviruses and Opportunistic Infections; IAS, International AIDS Society

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CHAPTER 2: HIV PIPELINE

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CHAPTER 3: THE PAEDIATRIC PIPELINE

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