The Paediatric ART Pipeline

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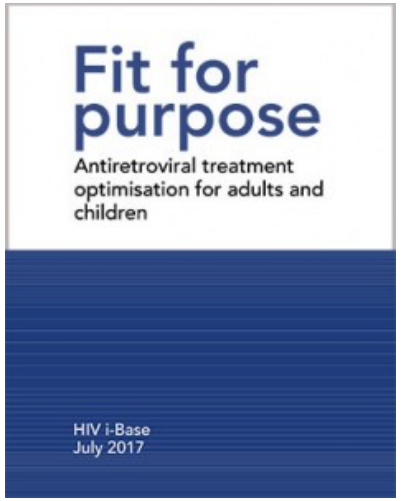


As I only have 15 minutes: ART optimisation including paediatric/ adult pipeline http://i-base.info/htb/31974

Neonates and young infants

- As paediatric investigation typically goes from eldest to youngest – last age group in which studies are conduced
- Can take about 10 years from adult approval
- Often does not include very youngest
- Limited treatment and prophlylactic options

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 (in development)	P1026s washout (in development)	
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	

Table adapted from Ruel T IMPAACT

Nucleotide reverse transcriptase inhibitor: tenofovir alafenamide (TAF)

Compound	Sponsor	Formulation/dose	Status
Emtricitabine/tenofovir alafenamide (F/TAF)	Gilead	Reduced strength, co-formulated tablets 120/15mg FTC/TAF for children 17 to <25 kg (<6 years) Non-solid formulation in development TAF palatability expected to be a problem	Approved >12 years Phase 2/3 switch study in children and adolescents stable on FTC/TDF and 3rd agent 6 to <18 years Study in infants and children 4 weeks to 6 years planned
Emtricitabine/cobicistat/ elvitegravir/tenofovir alafenamide E/C/F/TAF	Gilead	Reduced strength 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 PK within adult range at 24 weeks 12 to 18 years Waiver <6years

Nucleotide reverse transcriptase inhibitor: tenofovir alafenamide (TAF)

Compound	Sponsor	Formulation/dose	Status
Rilpivirine (RPV)/ emtricitabine/ tenofovir alafenamide R/F/TAF	Gilead/ Janssen	Reduced strength FDC tablets planned	Approved >12 years Dependent on development of RPV and F/ TAF
Bictegravir BIC/F/TAF	Gilead	Adult formulation >6 years and 25 kg Reduced strength tablet <6 years Powder for younger children	PIP 4 weeks to 18 years Switching study 6 to 18 (enrolling 12 to 18) Adult formulation NDA submitted to FDA for priority review (>12 years)

Non-nucleoside reverse transcriptase inhibitors

Compound	Sponsor	Formulation/dose	Status
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 with viral load < 100,000 copies/mL 2 to < 12 years planned (combination products with F/TAF and with DTG)
Doravirine	Merck	Single agent and FDC with TDF/3TC planned Formulation development underway	PIP/PSP submitted for single (all age groups), waiver < 2 years FDC First study in adolescents using adult tablets to open in 2017

Integrase inhibitors

Compound	Sponsor	Formulation/dose	Status
Raltegravir (RAL)	Merck	Granules for suspension 6mg/kg (100 mg sachet) Chewable 25 and 100 mg tables	FDA-approval for use in children >4 weeks Passive PK study ongoing: neonates born to women who received RAL in pregnancy and during labour Neonates PK and safety study for prophylaxis ongoing in high-risk HIV-exposed neonates from birth to six weeks Can we use chewable in younger age group? PK
Elvitegravir (EVG) (E/C/F/TDF and E/C/F/TAF)	Gilead	Reduce strength tablets and suspension in development XXX	EVG PK completed, RTV boosted 12 to <18 years RTV-boosted EVG to be studied in all age groups
Bictegravir BIC/F/TAF	Gilead	Adult formulation >6 years and 25 kg Reduced strength tablet <6 years Powder for younger children	PIP 4 weeks to 18 years Switching study 6 to 18 (enrolling 12 to 18) Adult formulation NDA submitted to FDA for priority review

Integrase inhibitors and combinations

Compound	Sponsor	Formulation/dose	Status
Dolutegravir (DTG)	ViiV	Dispersible 5 mg tablets 10 and 25 mg tablets	Approved for children and adolescents 6 years and above weighing >30kg in US 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 >6 years weighing >30/15 kg FDA/ EMA Dependent on ongoing studies confirming DTG dose and establishment of appropriate dosing ratios for components
DTG/RPV	ViiV/Janssen	Paediatric formulation development planned	To be studied as maintenance regimen 6 to <18 years and virologically suppressed PIP waiver <2 years, PSP <6 years

Booster

Booster	Sponsor	Formulation/dose	Status
Cobicistat (COBI)	Gilead	75 mg tablets 20 mg tablets for oral suspension	Booster (also part of E/C/F/ TAF and E/C/F/TDF)
Atazanavir/cobicistat (ATV/r)	Gilead/BMS	Reduced dose and dispersible tablets planned	Phase 2/3 treatment experienced children 3 months to <18 years
Darunavir/cobicistat (DRV/c)	Gilead/Janssen	Reduced dose and dispersible tablets planned	Phase 2/3 treatment experienced children 3 to <18 years
DRV/COBI/FTC/TAF (D/C/F/TAF)	Gilead/Janssen	Reduced dose and dispersible tablets planned	Phase 3 6 to <18 years

Attachment inhibitor

Compound	Sponsor	Formulation/dose	Status
Fostemsavir	ViiV	Prolonged-release film coated tablets (30 April 2021) Prolonged-release granules (31 May 2022)	Waiver <2 years Studies in very treatment experienced children and adolescents (dual or triple class resistance) with OBT Mini weight band cohorts Completion February 2024

Long acting formulations

Compound	Sponsor	Formulation/dose	Status
Cabotegravir/rilpivirine LA (treatment)	ViiV/Janssen	IM nanosuspension same as adults Development of an age appropriate formulation orally disintegrating tablets (ODT)	PIP (October 2014) Waiver <2 years treatment, <12 years prevention/ deferral 2 to <18 years
Cabotegravir LA (PrEP)	ViiV	IM nanosuspension same as adults Development of an age appropriate formulation (ODT)	PIP (July 2016) Waiver <12 years/deferral 12 to <18 years Modelling and simulation study using data from adult treatment and prevention and adolescent treatment programmes

HIV neutralising monoclonal antibody

Compound	Sponsor	Formulation/dose	Status
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.

First-line ART optimisation trials for adults

Study	Sponsor	Design	Status	Purpose
ADVANCE	Wits RHI	DTG/FTC/TAF vs DTG/FTC/ TDF vs EFV 600/FTC/TDF non-inferiority 1050 treatment naive adult participants (350 per arm) 60 treatment naive 12-15 year olds (20 per arm) Johannesburg	Phase 3 Enrolling	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
NAMSAL ANRS 12313	Inserm-ANRS (Institute de Recherche pour le development)	DTG/3TC/TDF vs EFV 400 / 3TC/TDF 606 treatment naive participants Cameroon	Phase 3 Enrolling	Establish non-inferior efficacy for DTG/3TC/TDF compared to EFV 400 mg/ 3TC/TDT Primary outcome number of participants with VL <50 copies/mL at 48 weeks

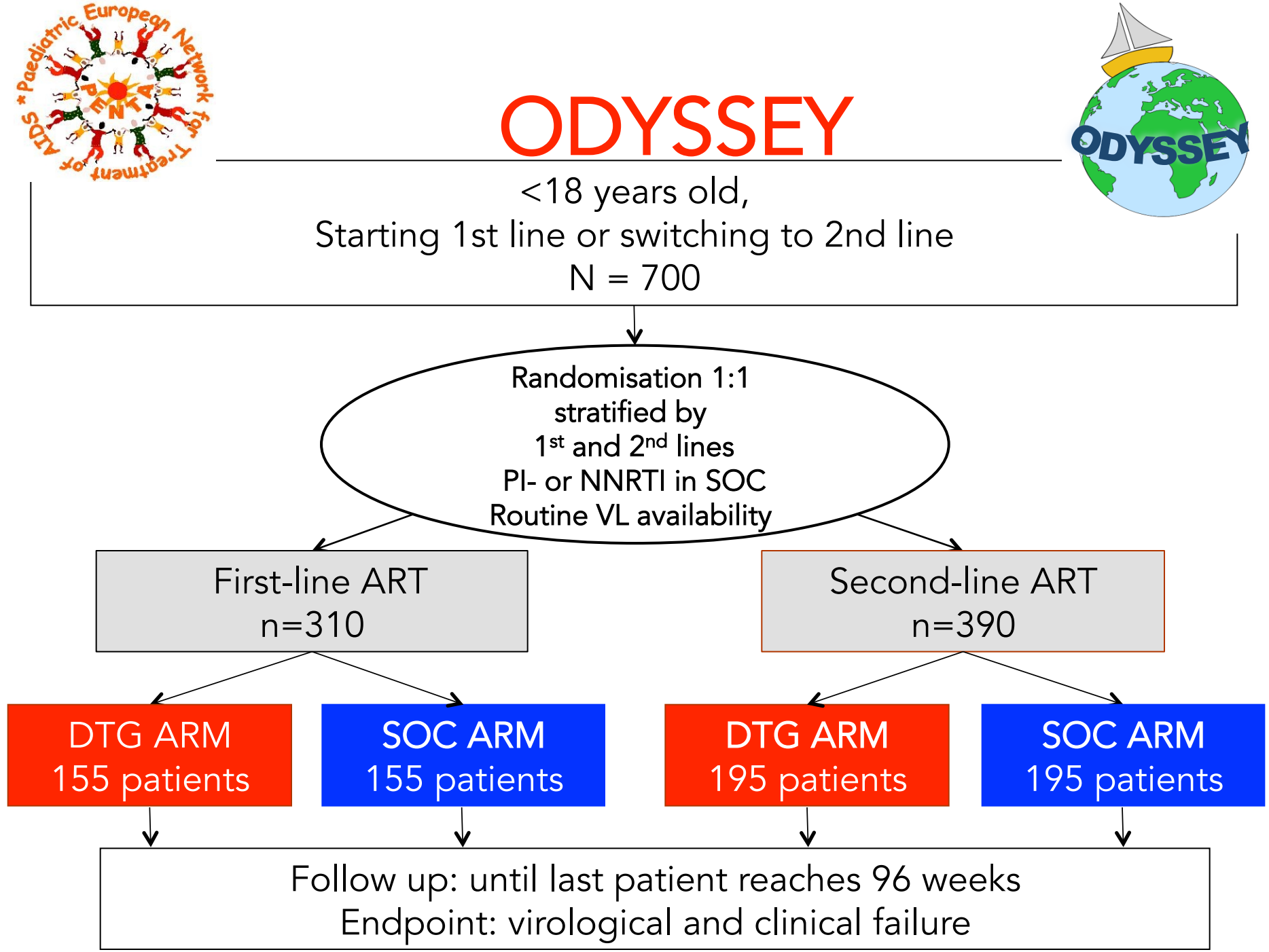
First-line ART optimisation trials for adults

Study	Sponsor	Design	Status	Purpose
VESTED IMPAACT P2010	NIH (NIAD)	DTG/FTC/TAF vs DTG/FTC/TDF vs EFV 600/FTC/TDF in 549 mother/infant pairs Multicountry (IMPAACT sites)	Phase 3 Enrolling	Establish safety and efficacy for DTG/FTC/TAF in pregnancy compared to other study arms Primary outcome number of participants with VL <200 copies/mL at delivery and 50 weeks PP, adverse outcomes

Dolutegravir adult FDCs

- Two DTG/TDF/3TC FDCs (Mylan and Aurobindo) received FDA tentative approval August 2016
- New pricing agreement – ceiling price US $75 per person year in 92 LMICs
- PEPFAR to purchase
- DTG/TAF/XTC on the way…

ODYSSEY


<18 years old,
Starting 1st line or switching to 2nd line
N = 700
Randomisation 1:1
stratified by
1st and 2nd lines
PI- or NNRTI in SOC
Routine VL availability
First-line ART
n=310
Second-line ART
n=390
DTG ARM
155 patients
SOC ARM
155 patients
DTG ARM
195 patients
SOC ARM
195 patients
Follow up: until last patient reaches 96 weeks
Endpoint: virological and clinical failure

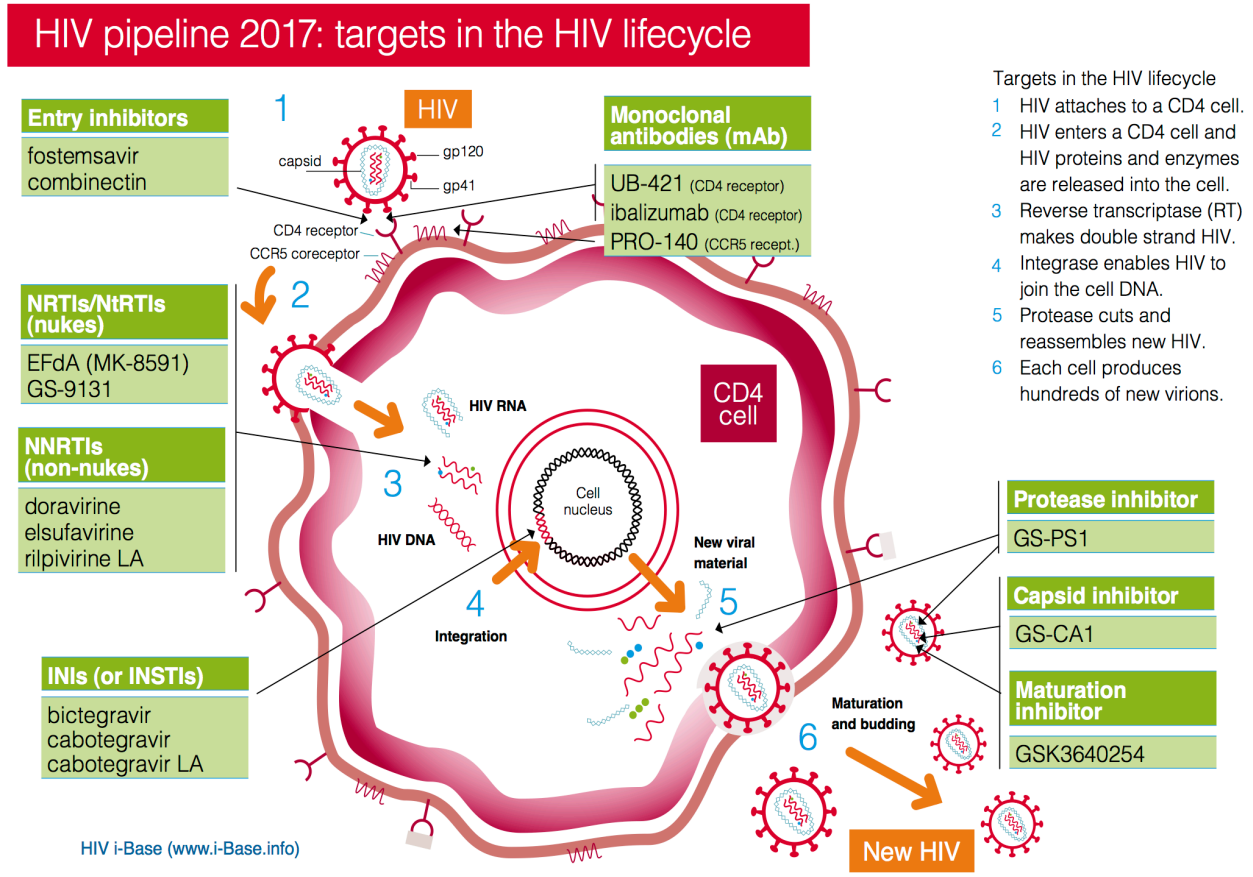
Tenofovir alafenamide

- Only being investigated within Gilead co-formulations and FDCs – switching studies
- TAF/FTC, E/C/F/TAF and RPV/F/TAF approved >12 years
- Nasty bitter taste like TDF – taste masking, formulation

Dolutegravir and TAF PK with rifampicin

Study	Sponsor (collaborators)	Design	Status	Purpose
INSPIRING Open label study of DTG vs EFV for HIV/TB coinfection	ViiV	50 mg DTG twice daily vs 600 mg EFV (randomised 3:2 ratio) during TB treatment (rifampicin, isoniazid, pyrazinamide and ethambutol) 125 treatment naive participants Multinational sites including South Africa	Phase 2b Ongoing Primary completion July 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
RADIO PK DTG 50 and 100 mg once daily with rifampicin	SSAT	PK of 50 mg and 100 mg DTG PK when added to rifampicin 20 HIV negative participants UK	Phase 1 Started September 2017 Primary completion December 2017	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
RIFT TAF (intracellular tenofovir diphosphate, TFV-DP) and FTC triphosphate	SSAT	TFV-DP after 28 days of TAF/FTC followed by 14 days of TAF/FTC/ rifampicin followed by 28 days of TDF with PK on days 28, 42, and 70 in HIV negative participants	Phase 1 Started June 2017	Establish potential decrease in TFV-DP when TAF is given with rifampicin compared to TAF alone and TDF

Adult pipeline: new targets



Adult pipeline

Compound	Sponsor	Class	Comment
PRO 140	CytoDyn	mAbCCR5 target	Phase 3 Once-weekly (350 mg) sub-cutaneous injection with potential to maintain viral suppression for more than two years after stopping ART. Also use with ART against multiclass resistance.
UB-421	United BioPharma	mAbCD4 binding	Phase 2 Infusion dosed either weekly or every two weeks as alternative to ART during treatment interruption.
ABX464	Abivax	Rev inhibitor	Phase 2 Evidence of modest antiviral activity (approx 0.5 log in 4/6 people) also being studied for impact on viral reservoir
MK-8591 (EFdA)	Merck/MSD	NRTI	Phase 1 Highly potent, low dose (10 mg), active against NRTI resistance. Long half life, potential as oral weekly dose and annual implant for PrEP
GS-9131	Gilead	NRTI	Pre-clinical Active against NRTI resistance. Synergy reported with AZT, FTC, abacavir, efavirenz, bictegravir, dolutegravir and lopinavir, and additive activity with TFV and TAF. Will be co-formulated with other Gilead drugs. Currently difficult to synthesise in bulk.

Adult pipeline

Compound	Sponsor	Class	Comment
Combinectin	ViiV Healthcare	Entry inhibitor gp41 and CD4	Preclinical Combined adnectin/fusion inhibitor that stops viral entry by targeting multiple sites of action and the potential for self-administered once-weekly injections.
GSPI1	Gilead	Protease inhibitor	Preclinical New once-daily unboosted PI, high potency, long half-life, potential in FDC
GS-CA1	Gilead	Capsid inhibitor	Preclinical Early stage for new class with activity at multiple stages of viral lifecycle. Sub-cutaneous slow release injection with monthly or less frequent dosing.

Thank you

- Simon Collins, HIV i-Base