New Entry Inhibitors and Dug Classes

Saye Khoo

University of Liverpool, UK

Declaration of Interests

www.hiv-druginteractions.org & *www.hep-druginteractions.org*

Receives sponsorship from AbbVie, Merck, BMS, Janssen, Gilead, ViiV.
Editorial content remains independent.

Research funding, travel grants, speakers bureau from Gilead, AbbVie, ViiV, Merck, Janssen
Consultancy: ViiV Healthcare, Merck

See https://www.liverpool.ac.uk/translational-medicine/staff/saye-khoo/external-engagement/

Menu

- Why new drugs ? - Case History
- Inhibitors of viral entry and maturation
- Fostemsavir
- Capsid inhibitors

Why Do We Need New Drugs ?

30y male

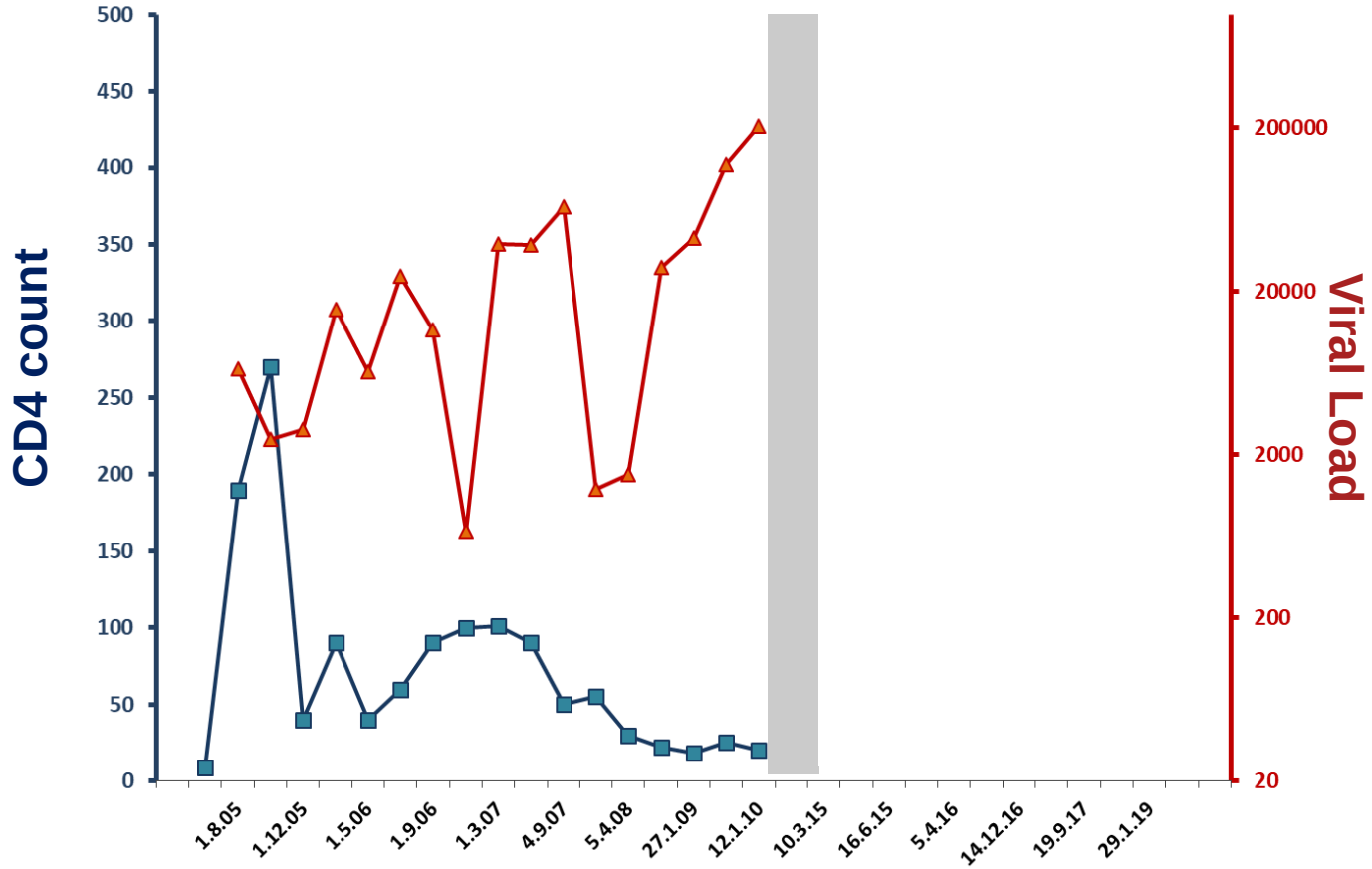
Vertically infected (diagnosed aged 12)
Diarrhoea, wasted, CD4 9 cells

Poor adherence for next 13 years
VL not suppressed
Accumulating resistance

Advanced disease, falling CD4
Weight loss
Night sweats

Severe psoriasis

Anal sphincter dysfunction



Start	Stop	Regimen	Reason
Jan 2003	Mar 2003	ABC, 3TC, EFV	CNS toxicity
Apr 2003	Jan 2004	ABC, 3TC, NVP	V Failure with resistance
Jan 2004	Jan 2006	ZDV, ddI, TDF, LPVr	V Failure with resistance
Jan 2006	Sep 2007	ZDV, LPVr, FPV	V Failure
Sep 2007	Jan 2010	ZDV, DRVr, ETR	TI, V Failure
Jul 2011	Jan 2013	TDF, FTC, EFV	V Failure
Jan 2013	Aug 2014	DRVr, RAL	V Failure with resistance
Aug 2014	Nov 2014	DRVr	V Failure

	RT	Protease	INI	Other
Jul 2004	K65R, V106M, Y181C	M36I, D60E, L63P, V82I, I93L		
Sep 2004	nil	M36I, L63P		
Dec 2005	nil	M36I, D60E, L63P, I93L		
Dec 2006	nil	M36I, M46I, L63P		
Jun 2007	nil	M46I, L76V		
Dec 2008	K65R, V90I, K103N, Y181C	L33F, M46I, L76V, I84V		
Oct 2014	L74I	V32I, M46I, I54L, I84V	Y143CHRY	R5 virus

Reverse Transcriptase	Protease	Integrase
K65R x L74I x V90I x K103N x V106M x Y181C x Input mutation(s)	V32I x L33F x M36I x M46I x I54L x L63P x L76V x V82I x I84V x I93L x Input mutation(s)	Y143CHRY x Input mutation(s)

Analyze

Protease Inhibitors

atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	High-Level Resistance
lopinavir/r (LPV/r)	High-Level Resistance

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Susceptible
dolutegravir (DTG)	Susceptible
elvitegravir (EVG)	Potential Low-Level Resistance
raltegravir (RAL)	High-Level Resistance

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Intermediate Resistance
lamivudine (3TC)	Intermediate Resistance
tenofovir (TDF)	High-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

doravirine (DOR)	High-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

Nucleoside Reverse Transcriptase Inhibitors

abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Intermediate Resistance
lamivudine (3TC)	Intermediate Resistance
tenofovir (TDF)	High-Level Resistance

Non-nucleoside Reverse Transcriptase Inhibitors

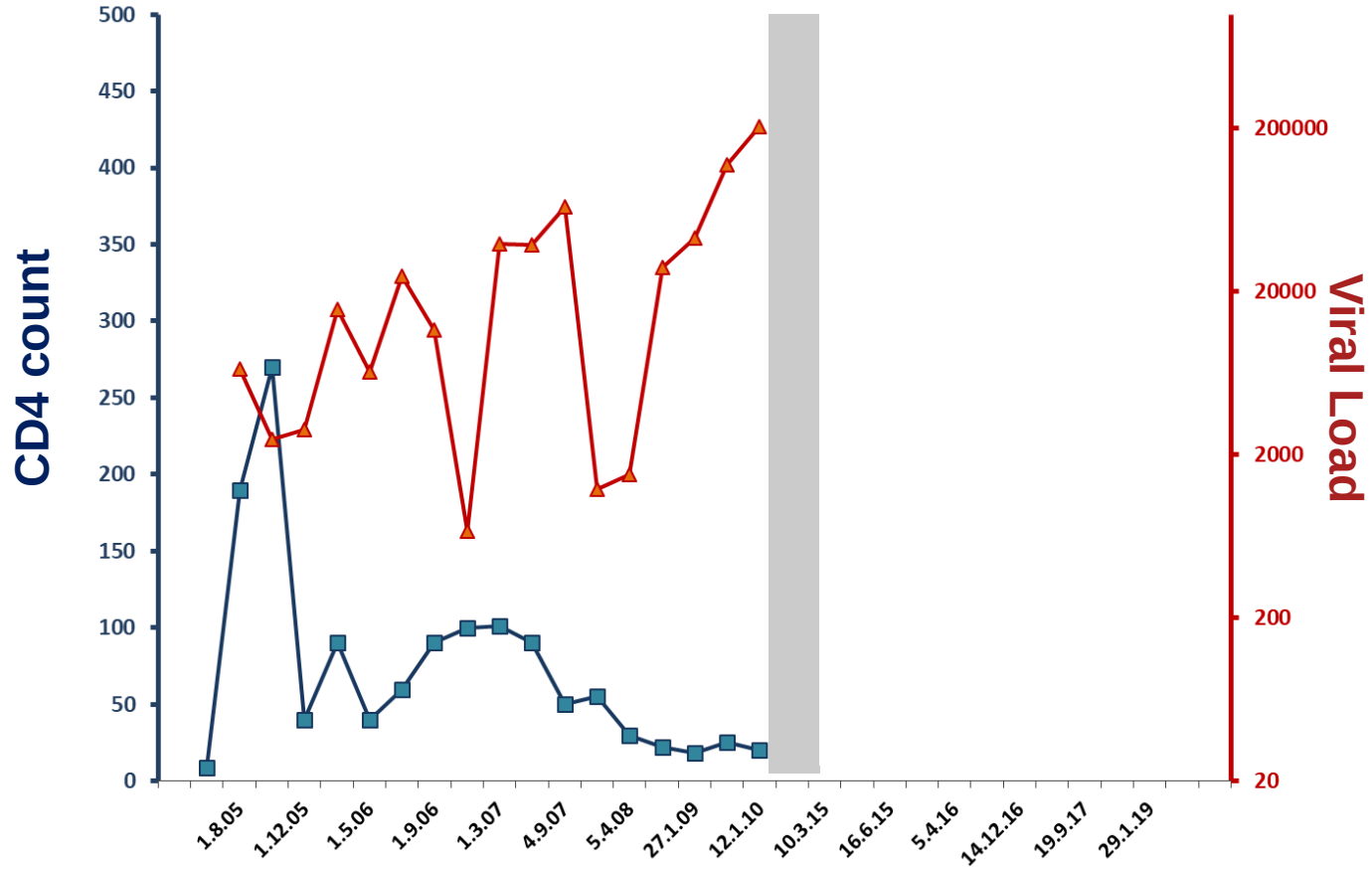
doravirine (DOR)	High-Level Resistance
efavirenz (EFV)	High-Level Resistance
etravirine (ETR)	Intermediate Resistance
nevirapine (NVP)	High-Level Resistance
rilpivirine (RPV)	Intermediate Resistance

Protease Inhibitors

atazanavir/r (ATV/r)	High-Level Resistance
darunavir/r (DRV/r)	High-Level Resistance
lopinavir/r (LPV/r)	High-Level Resistance

Integrase Strand Transfer Inhibitors

bictegravir (BIC)	Susceptible
dolutegravir (DTG)	Susceptible
elvitegravir (EVG)	Potential Low-Level Resistance
raltegravir (RAL)	High-Level Resistance



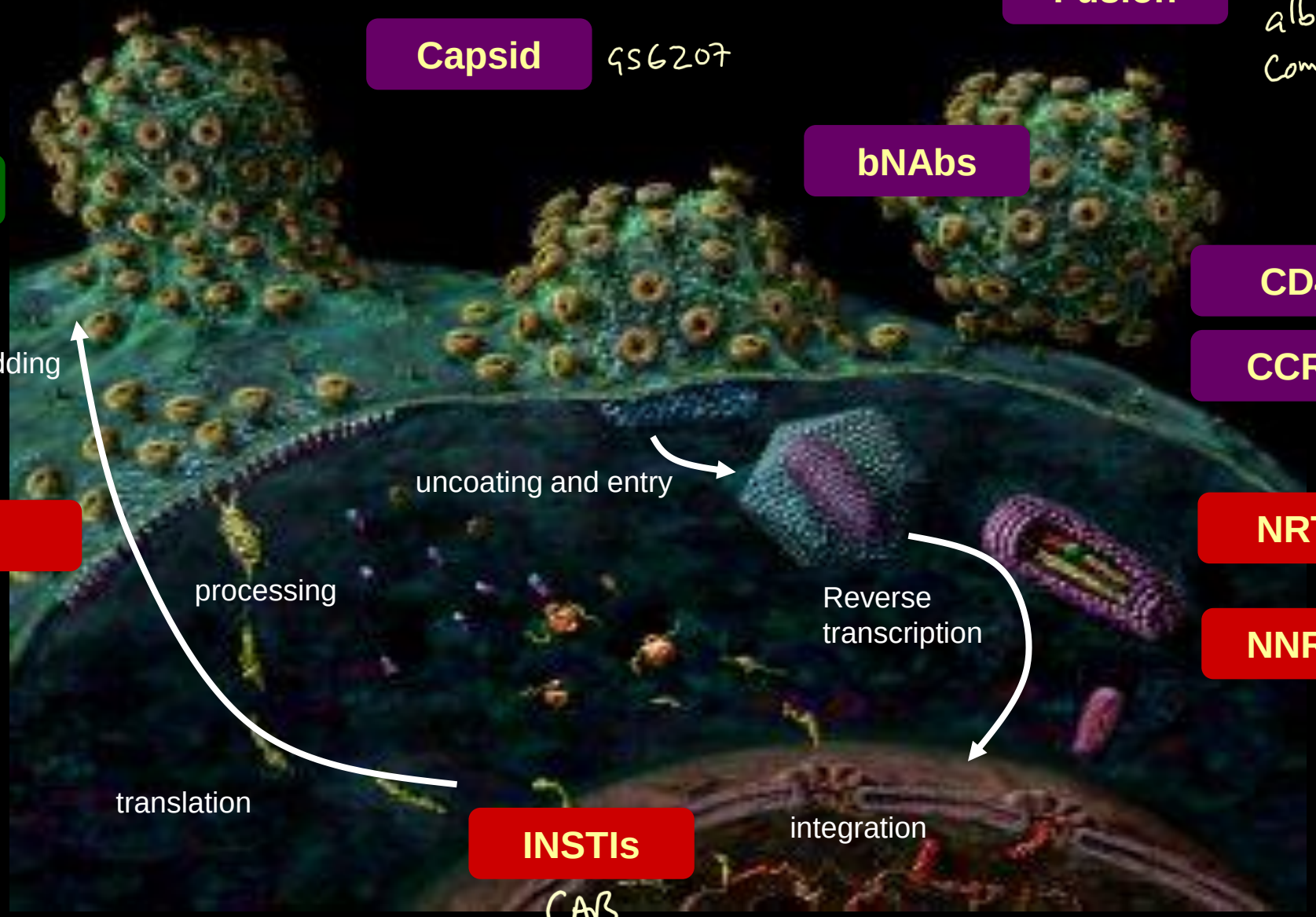
Reverse Transcriptase	Protease	Integrase
K65R × L74I × V90I × K103N × V106M × Y181C × Input mutation(s)	V32I × L33F × M36I × M46I × I54L × L63P × L76V × V82I × I84V × I93L × Input mutation(s)	Y143CHRY × Input mutation(s)

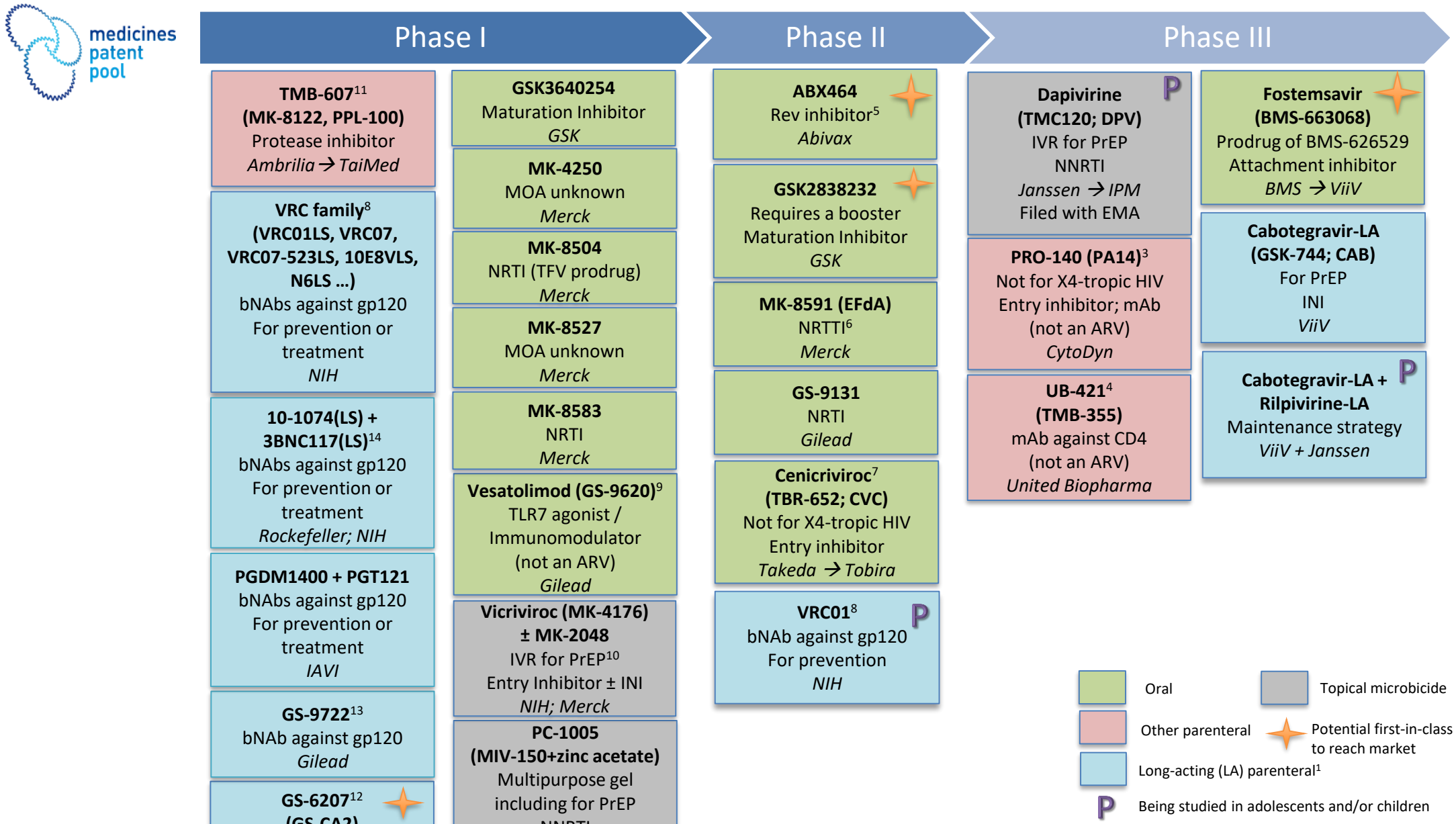
2014

- DTG 50 bd
- T20 90 bd sc
- TDF/FTC
- MVC

2020 ?

The HIV Pipeline in 2020

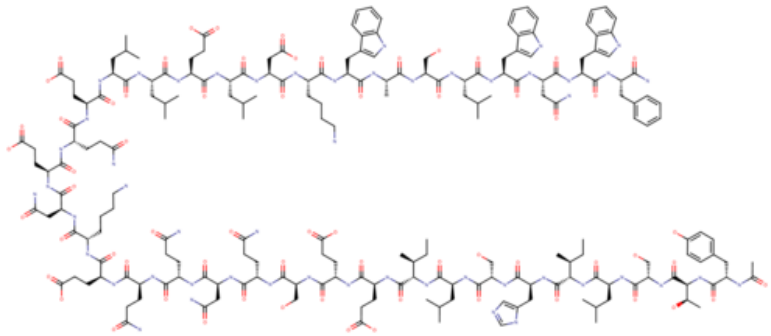




Medicines Patent Pool
List not exhaustive. Last updated on: 10/2018

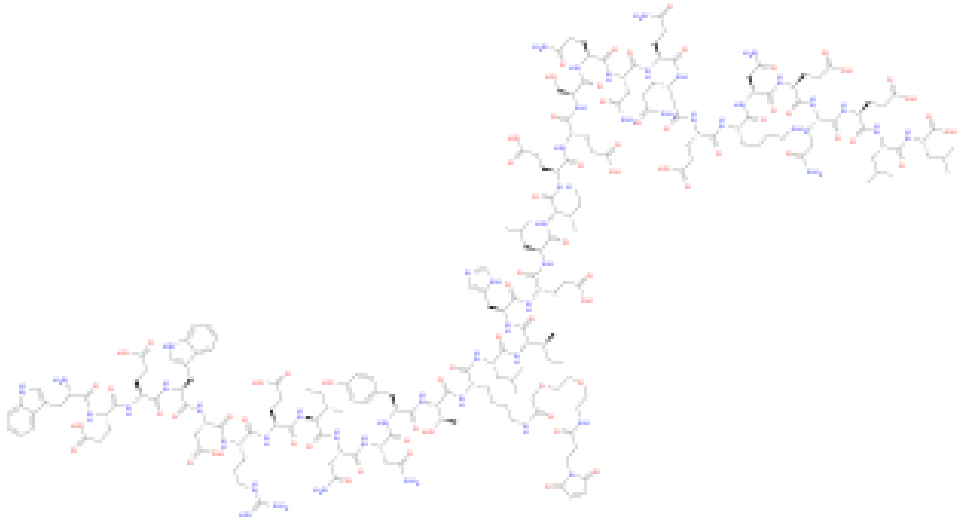
Fusion Inhibitors

Enfuvirtide



Targets gp41
Active against HIV-1 only
Administered 90 mg bd sc injection
Half-life 3.2h

Albuvirtide



Targets gp41 (HIV-1)
3-maleimimidopropionic acid (MPA) group irreversibly conjugates with albumin
Administered IV weekly
Half-life 10-13 days
Some activity against enfuvirtide-resistant strains
In-vitro selection of resistance requires mutations at 36,40,126 &144

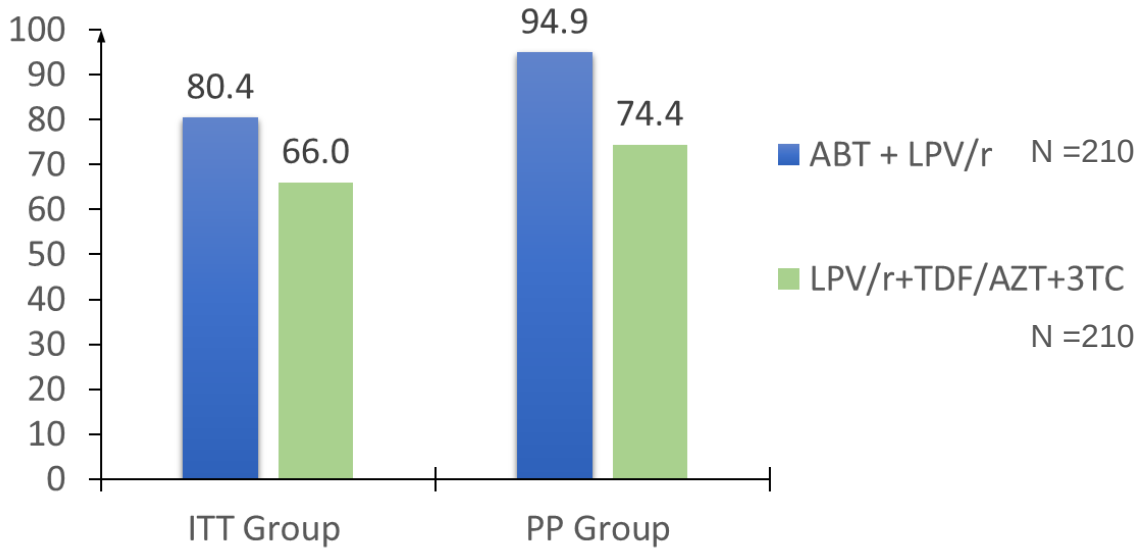
Long-acting Fusion Inhibitor - Albuvirtide

- Synthetic peptide
- High barrier to resistance
- Dosed iv q weekly
- Binds irreversibly to albumin
- Low DDI potential
- TALENT study (Glasgow 2016):

  Albuvirtide + LPVr vs

  TDF/ZDV + 3TC + LPVr
- Market authorization in China
- Exploratory: Albuvirtide + 3BNC117

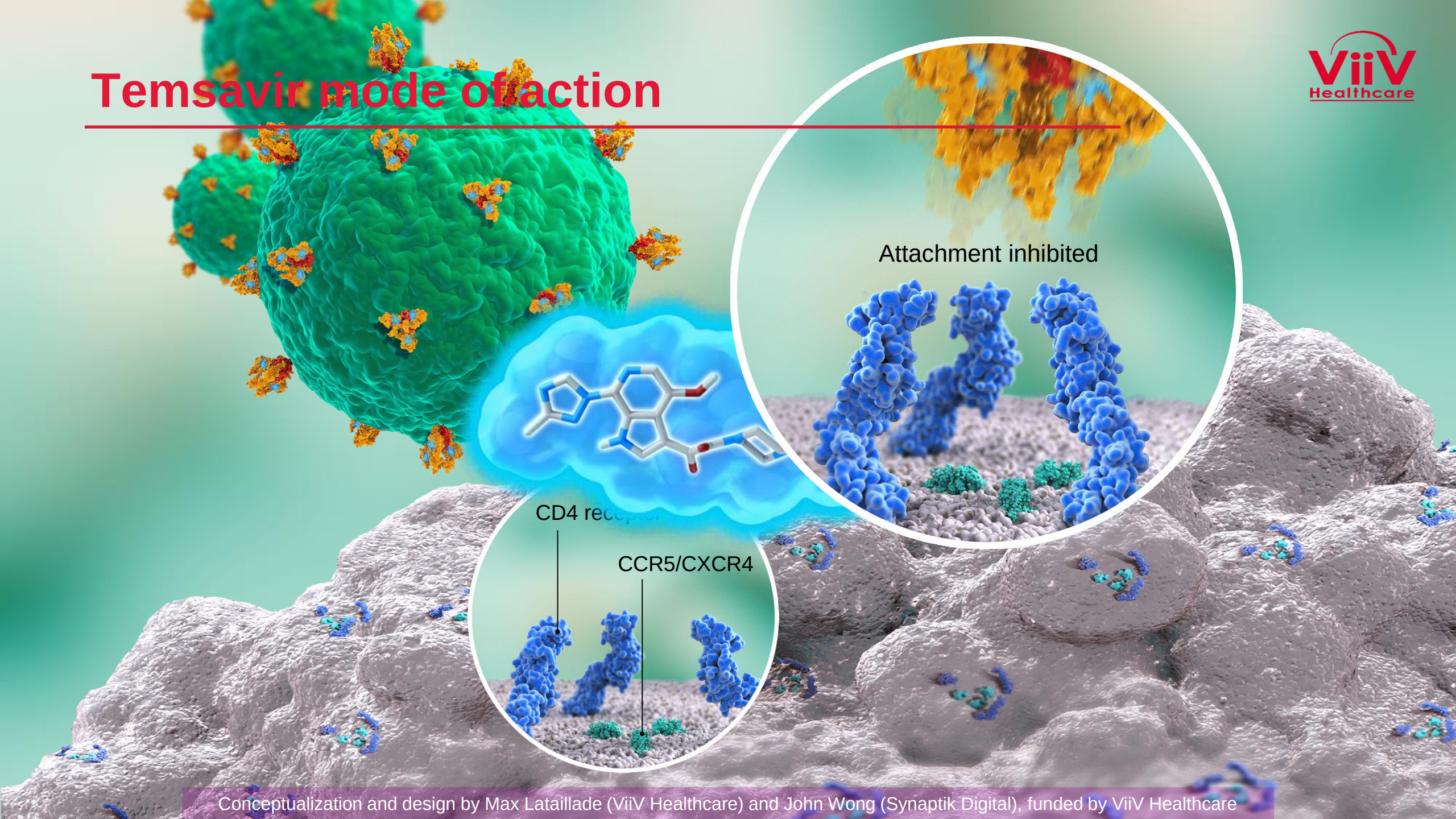
Virologic success: ***80.4% in ABT+LPV/r*** group *vs.* 66.0% in the control group



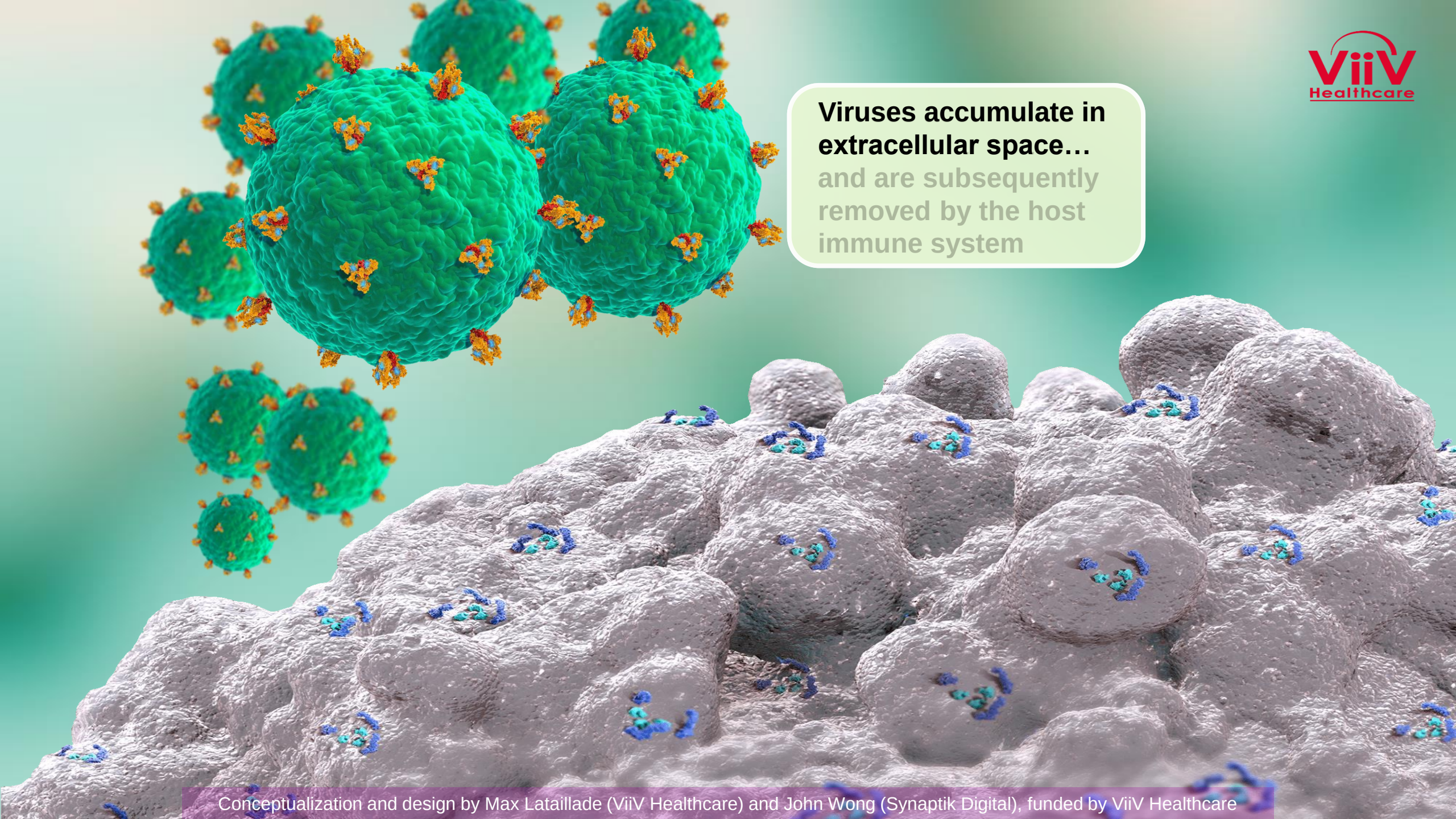
ABT/LPVr non-inferior to triple therapy

Wu H et al.. Glasgow Congress on HIV Therapy, 2016. Oral abstract O336

Temsavir mode of action



Conceptualization and design by Max Lataillade (ViiV Healthcare) and John Wong (Synaptik Digital), funded by ViiV Healthcare

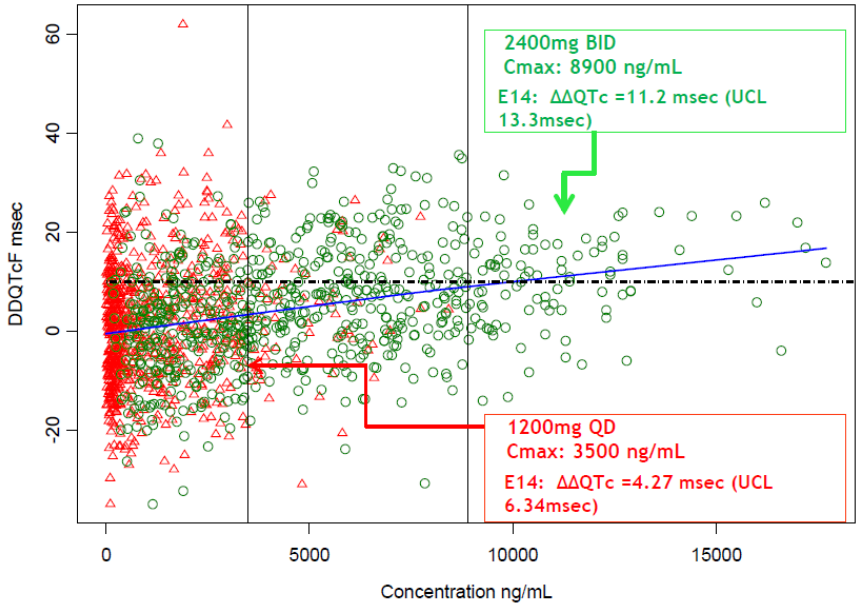


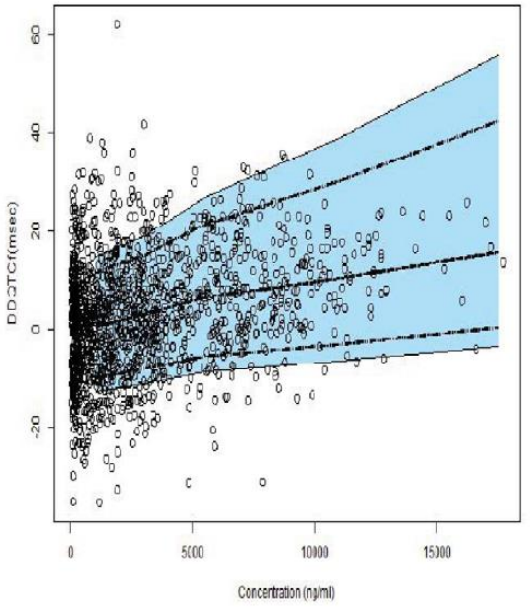
Conceptualization and design by Max Lataillade (ViiV Healthcare) and John Wong (Synaptik Digital), funded by ViiV Healthcare

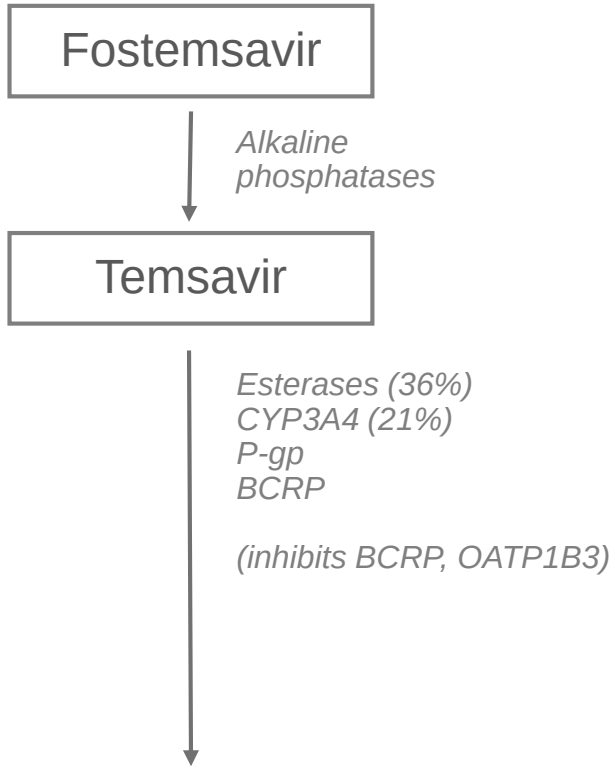
Fostemsavir

Fostemsavir (FTR)

- **Prodrug of temsavir (TMR), extended release formulation**
- **Temsavir binds gp120 subunit**
- **FTR 600mg bd**
- **Administered with/without food**
- **Protein binding 88.4% (wide tissue distribution)**
- **T1/2 11h**
- **prolongs QT at supratherapeutic doses (2400 mg BID).**







Sevinski et al IWCPAVT 2017 (Abst 23)
Savant et al CROI 2015 Abstr P509
Landry et al IWCPHT 2015 Abstr O9

Fostemsavir DDIs

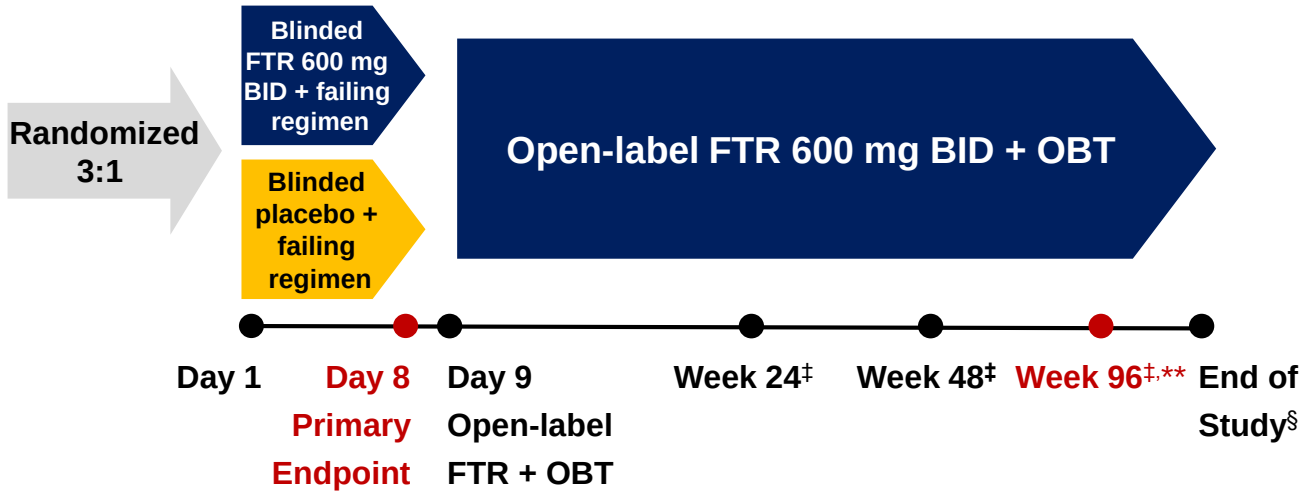
- **Relatively few DDIs (no effect on CYPs or UGT)**
- **TMR inhibits BCRP, OATP1B3**
- **RTV (TMR ↑+50%), cobi (TMR ↑+100%)**
- **ETR (TMR ↓50%)**
- **RIF (TMR ↓82%)**
- **RBT (TMR ↓30%), RBT + RTV (TMR ↑+66%)**
- **Rosuvastatin ↑+69%**
- **Ethinyl estradiol ↑+40% (?BCRP)**

Vakkaladda et al ICAAC 2015 Abstr 1676
Magee et al 9th IAS HIV Science 2017 Abs MOPEB0339
Landry et al CROI 2016 Abstr 460
Adamczyk et al 8th IAS HIV Pathogenesis 2015 Abstr TUPEB277

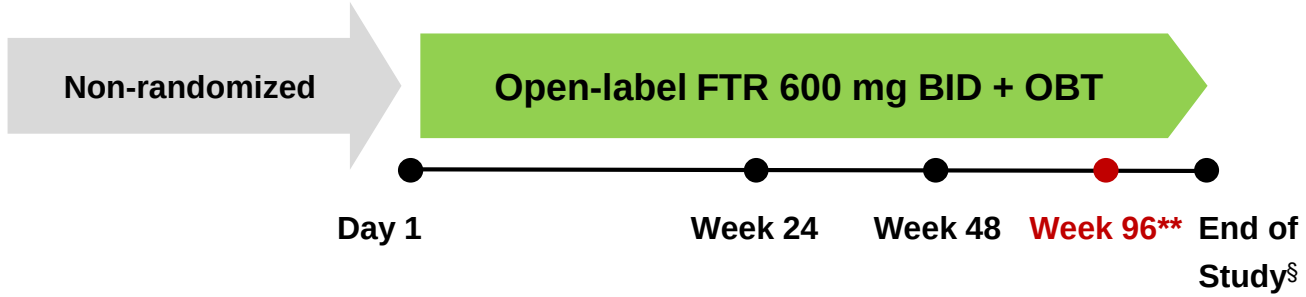
Study design

BRIGHTE is an ongoing Phase 3 randomized, placebo-controlled, double-blind trial

Randomized Cohort:*
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
- 1 or 2 ARV classes remaining with ≥1 fully active† approved agent per class
- Unable to construct viable regimen from remaining agents



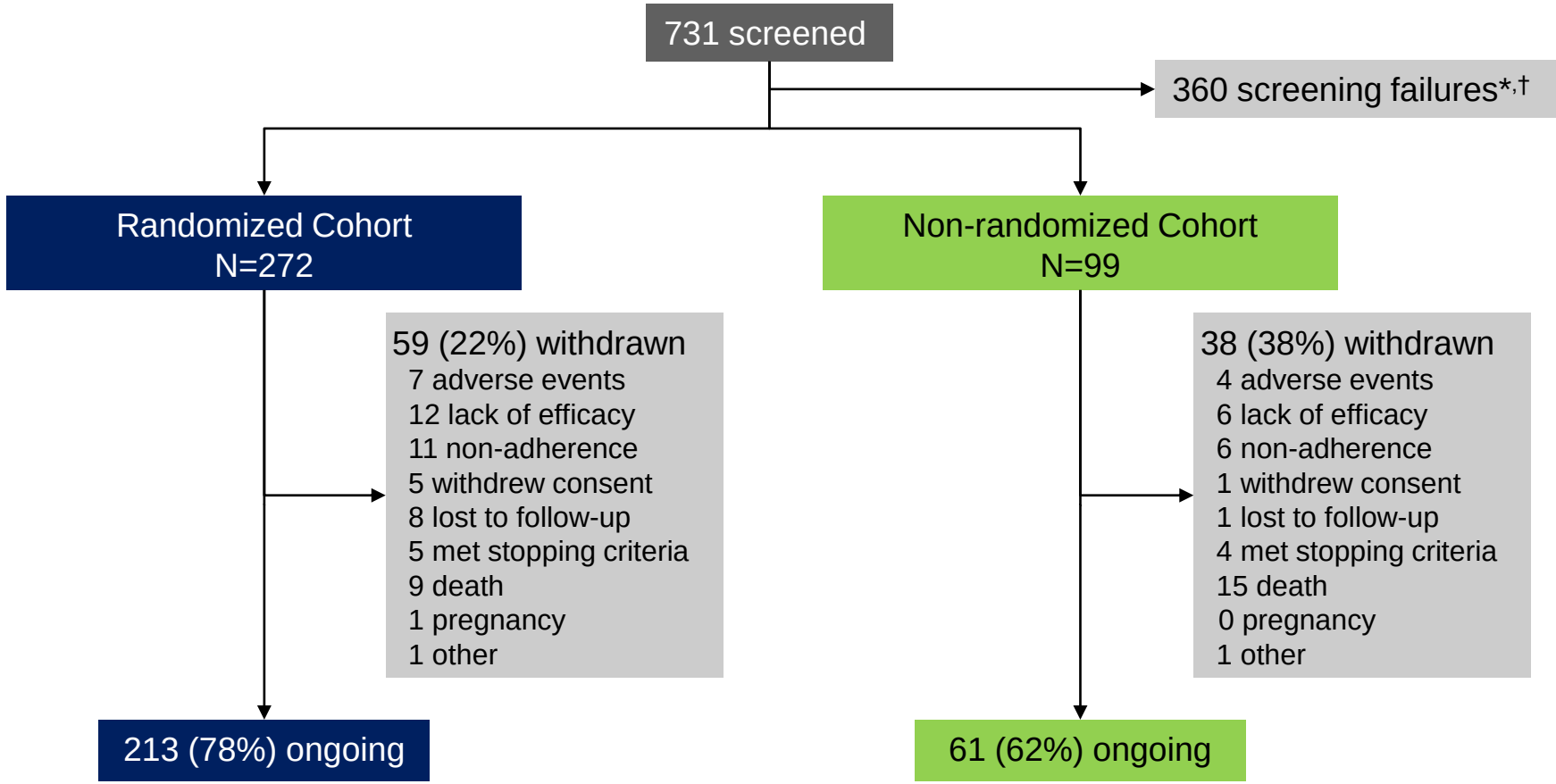
Non-randomized Cohort:*
HTE participants failing current regimen with confirmed HIV-1 RNA ≥400 c/mL and:
- 0 ARV classes remaining and no remaining fully active† approved agents¶



*There were no screening TMR IC_{50} criteria. †Fully active = no current or historical evidence of resistance & the participant is tolerant of, eligible for, and willing to take (in the case of enfuvirtide) the ARV. ‡Measured from the start of open-label FTR 600 mg BID + OBT. §The study is expected to be conducted until an additional option, rollover study, or marketing approval is in place. ¶Use of investigational agents as part of OBT was permitted. **Week 96 database lock August 14, 2018.
BID, twice daily; OBT, optimized background therapy.
ClinicalTrials.gov Identifier: NCT02362503; EudraCT Number: 2014-002111-41

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

Study disposition through Week 96



*Including 12 individuals who met screening criteria but were not randomized or treated (4 withdrew consent, 2 lost to follow-up, 6 other).
†The two most common reasons for screening failure were: i) >2 ARV classes remaining, ii) failing the current ARV regimen with plasma HIV-1 RNA <400 copies/mL.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

Baseline characteristics

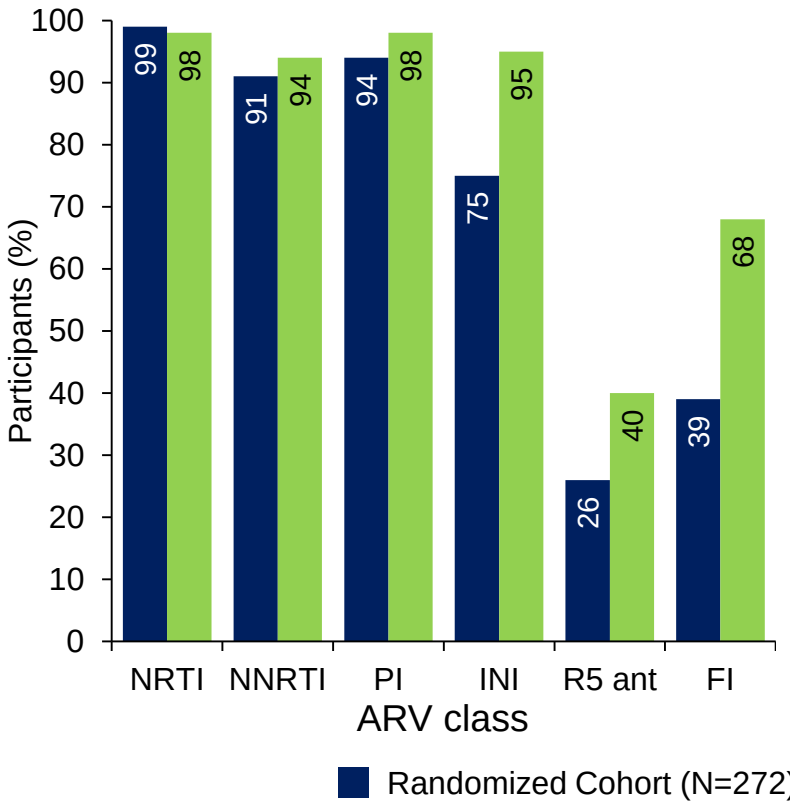
Parameter	Randomized Cohort			Non-randomized Cohort	Total
	Placebo BID (N=69)	FTR 600 mg BID (N=203)	Total randomized (N=272)	FTR 600 mg BID (N=99)	treated participants (N=371)
Age, years, median (range)	45 (19–66)	48 (18–73)	48 (18–73)	50 (17–72)	49 (17–73)
<50 years, n (%)	46 (67)	116 (57)	162 (60)	44 (44)	206 (56)
Gender, n (%) Female	12 (17)	60 (30)	72 (26)	10 (10)	82 (22)
Race, n (%)					
White	48 (70)	137 (67)	185 (68)	74 (75)	259 (70)
Black/African American	18 (26)	42 (21)	60 (22)	23 (23)	83 (22)
HIV-1 RNA log_{10} c/mL, median (IQR)	4.5 (3.6–5.2)	4.7 (4.0–5.1)	4.7 (3.9–5.1)	4.3 (3.6–4.8)	4.6 (3.9–5.0)
HIV-1 RNA c/mL, n (%)					
<400	7 (10)	14 (7)	21 (8)	5 (5)	26 (7)
400 to <1000	3 (4)	7 (3)	10 (4)	4 (4)	14 (4)
1000 to <100,000	35 (51)	126 (62)	161 (59)	75 (76)	236 (64)
≥100,000	24 (35)	56 (28)	80 (29)	15 (15)	95 (26)
CD4+ T cells/µL, median (IQR)	100 (23–244)	99 (15–203)	99 (15–203)	41 (6–161)	80 (11–202)
CD4+ T cells/µL, n (%)					
<20	17 (25)	55 (27)	72 (26)	40 (40)	112 (30)
20 to <50	6 (9)	19 (9)	25 (9)	14 (14)	39 (11)
50 to <200	26 (38)	76 (37)	102 (37)	25 (25)	127 (34)
200 to <500	16 (23)	42 (21)	58 (21)	18 (18)	76 (20)
≥500	4 (6)	11 (5)	15 (6)	2 (2)	17 (5)
AIDS history,* n (%)	61 (88)	170 (84)	231 (85)	89 (90)	320 (86)

*AIDS history recorded if a participant has nadir CD4+ count <200 cells/µL, or prior history of AIDS defining illness.

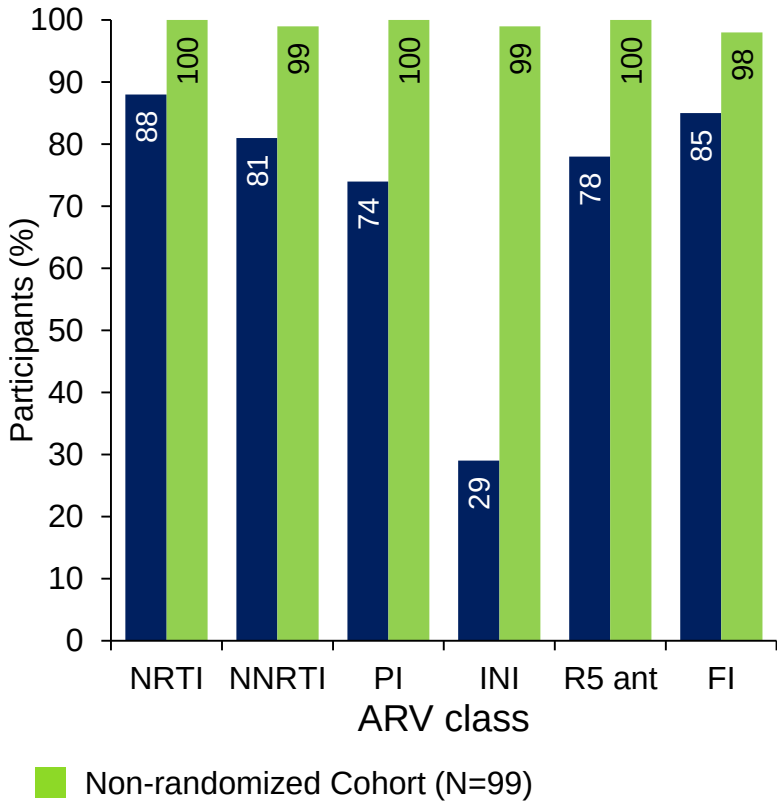
Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

Baseline prior ARV exposure and resistance

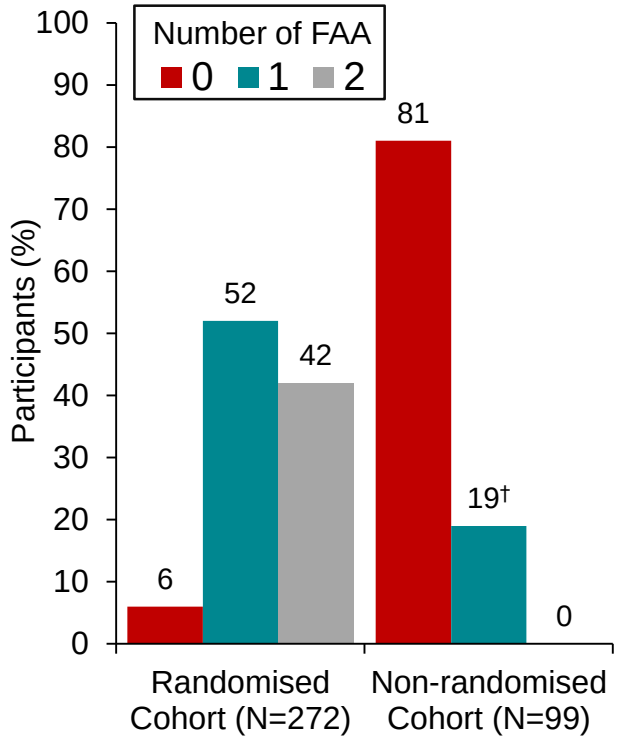
Prior exposure to ARV classes



ARV classes exhausted at baseline*



FAA in initial OBT

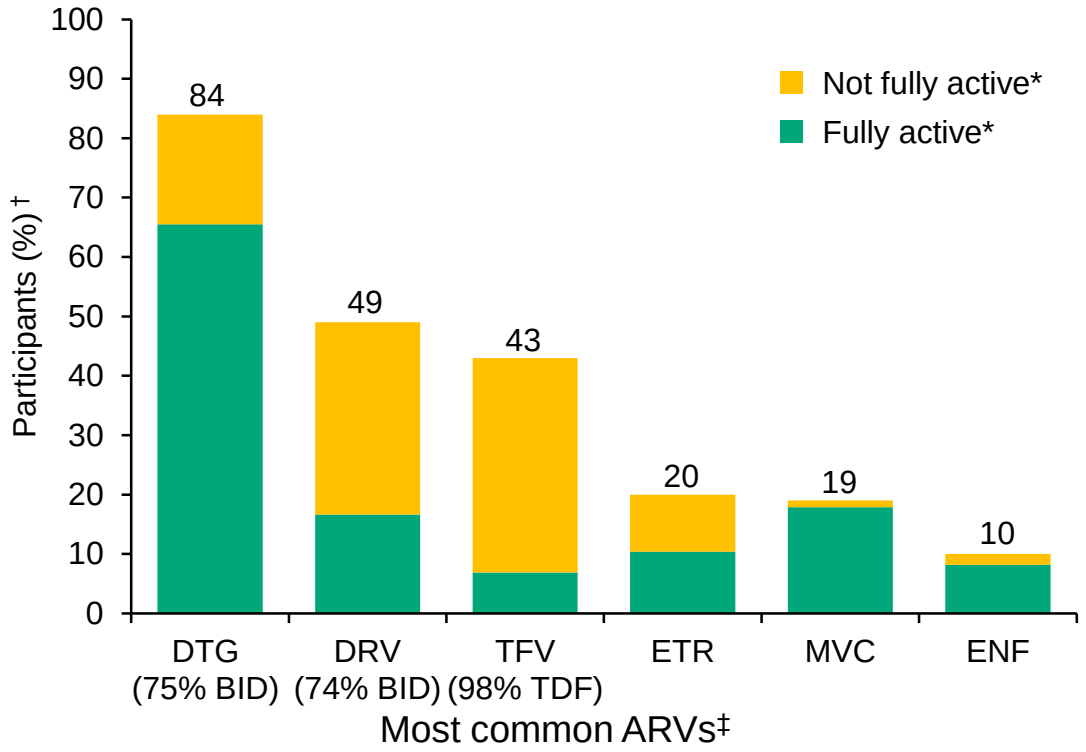


*Proportions of participants for whom there are no remaining FAAs within the indicated ARV class, based on Monogram assays (PhenoSense® GT Plus Integrase, Trofile®, and PhenoSense® Entry), historical resistance, eligibility, and tolerability. †15/19 received investigational ARV ibalizumab and 4/19 were incorrectly assigned to the Non-randomized Cohort.
FAA, fully active ARV; FI, fusion inhibitor; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; R5 ant, CCR5 antagonist.

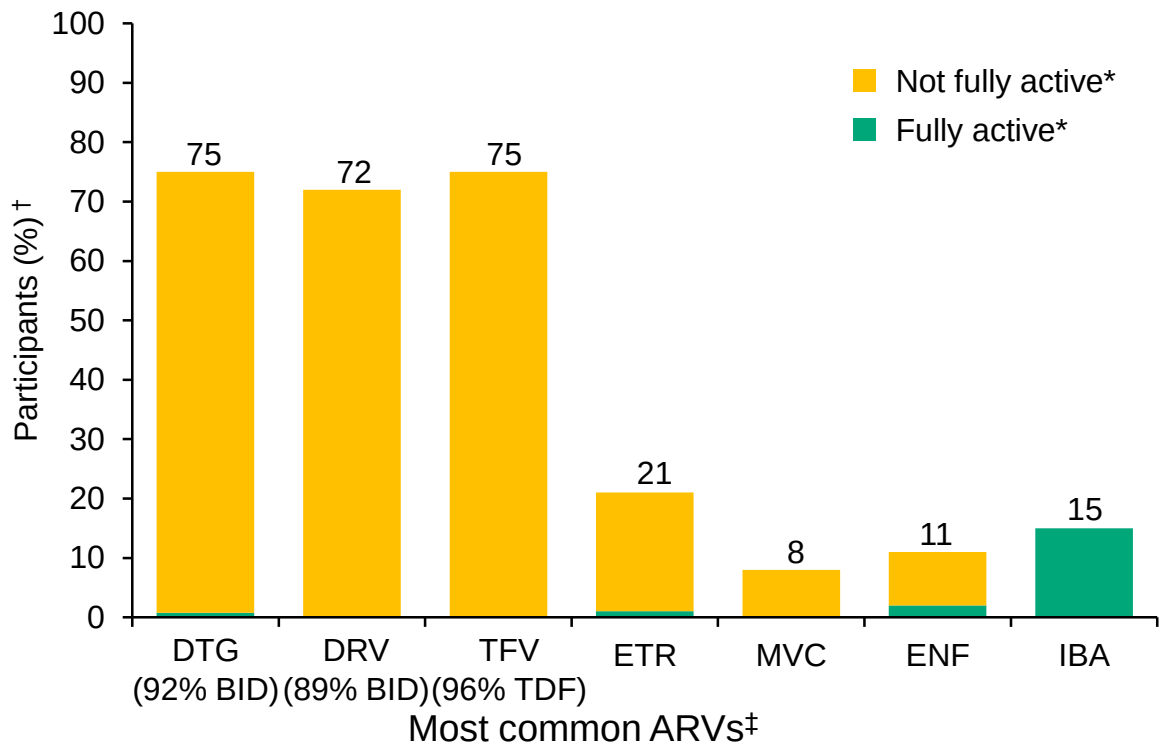
Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

Most common ARV agents in initial OBT

Randomized Cohort (N=272)



Non-randomized Cohort (N=99)

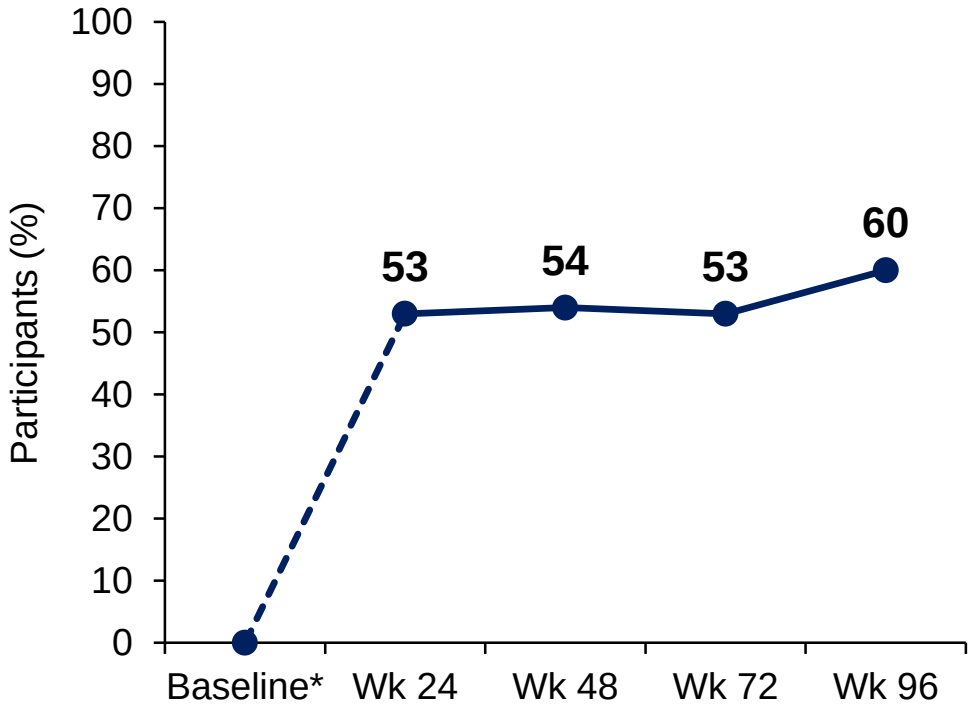


*Based on Monogram assays (PhenoSense® GT Plus Integrase, Trofile®, and PhenoSense® Entry), historical resistance, eligibility, and tolerability.
†Numbers at the top of the bars show the percent of all participants in the cohort who included the ARV in their OBT.
‡ARVs that were included in the OBT for at least 10% of study participants in either cohort.
DRV, darunavir; DTG, dolutegravir; ENF, enfuvirtide; ETR, etravirine; IBA, ibalizumab; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

HIV-1 RNA <40 copies/mL through Week 96 Snapshot analysis, ITT-E*

Randomized Cohort (N=272)



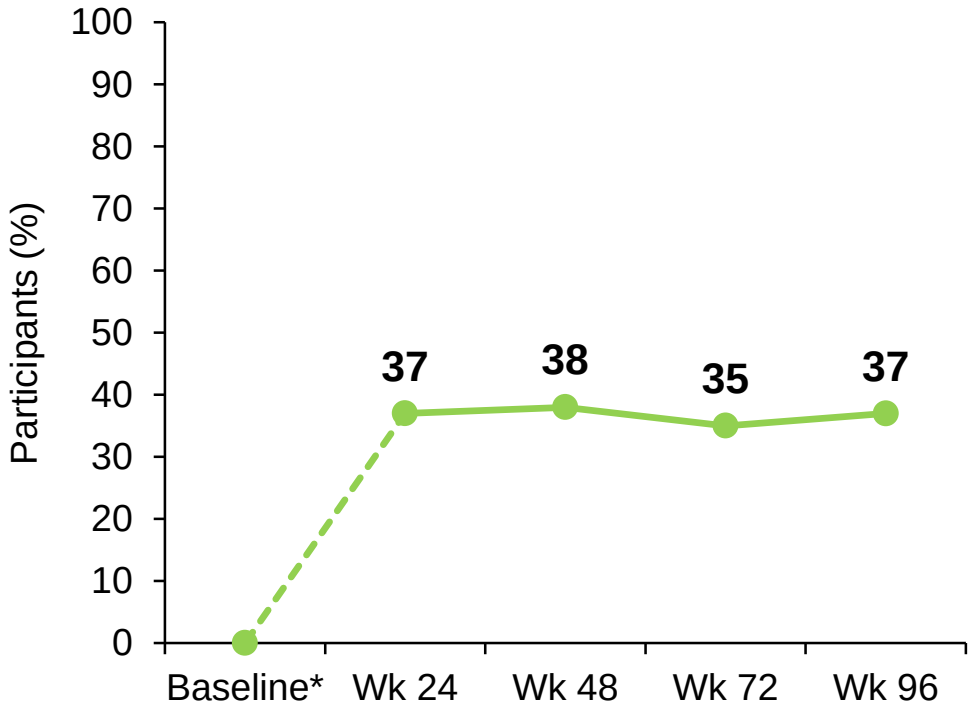
Week 96 outcome, n (%)	Randomized Cohort (N=272)
HIV-1 RNA <40 copies/mL	163 (60)
HIV-1 RNA ≥40 copies/mL	81 (30)
Data in window not below threshold	33 (12)
D/C for lack of efficacy	10 (4)
D/C for other reason while not below threshold	17 (6)
Change in ART†	21 (8)
No virologic data	28 (10)
D/C study due to AE or death	15 (6)
D/C study for other reasons	8 (3)
Missing data during window	5 (2)

*Snapshot analysis did not include baseline. One participant had HIV-1 RNA <40 copies/mL at baseline.
†Change in OBT for efficacy reasons were considered virologic failures in this analysis.
AE, adverse event; ART, antiretroviral therapy; D/C, discontinued; ITT-E, intent-to-treat exposed population.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

HIV-1 RNA <40 copies/mL through Week 96 Snapshot analysis, ITT-E*

Non-randomized Cohort (N=99)



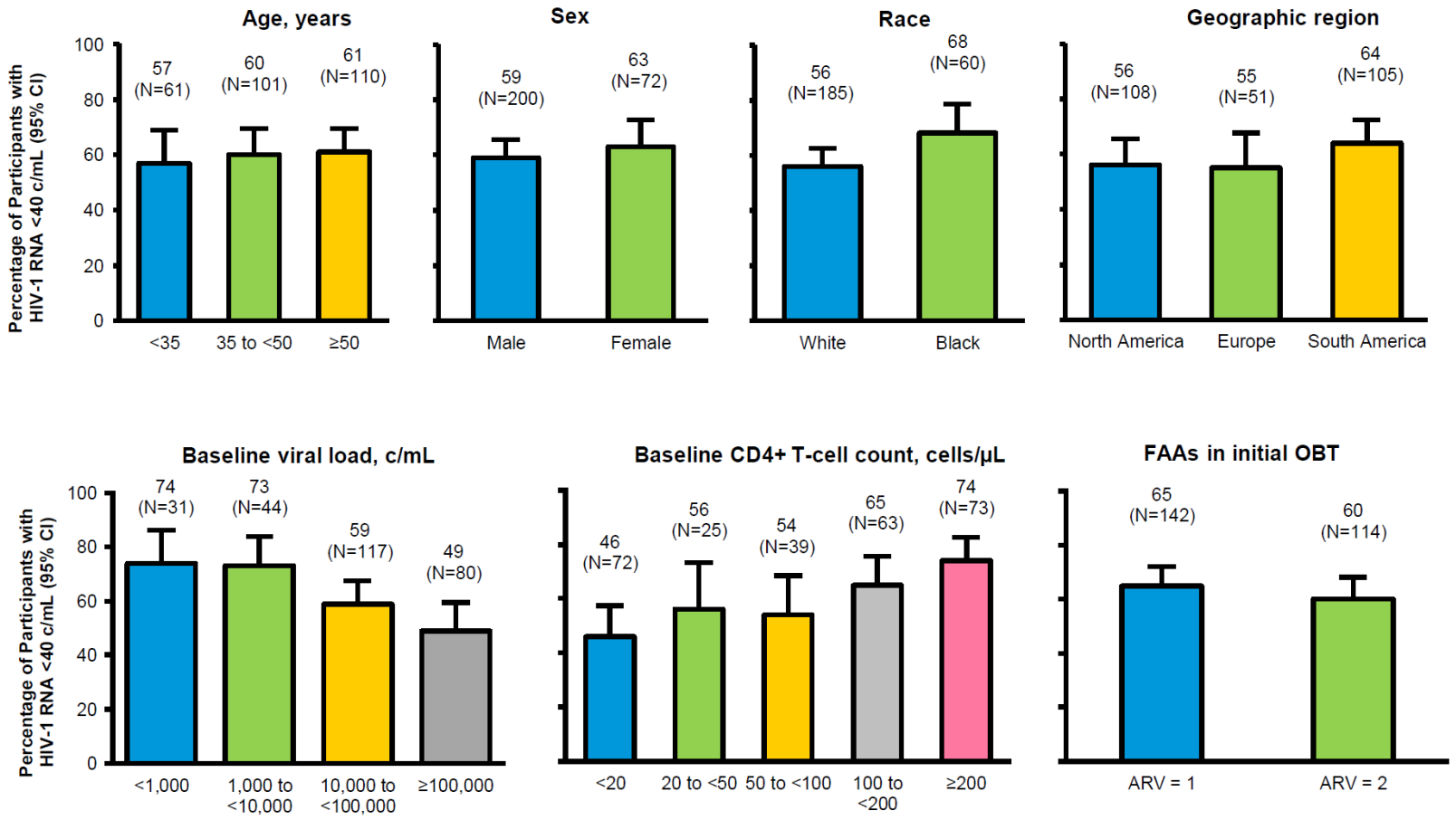
Week 96 outcome, n (%)	Non-randomized Cohort (N=99)
HIV-1 RNA <40 copies/mL	37 (37)
HIV-1 RNA ≥40 copies/mL	43 (43)
Data in window not below threshold	15 (15)
D/C for lack of efficacy	3 (3)
D/C for other reason while not below threshold	6 (6)
Change in ART†	19 (19)
No virologic data	19 (19)
D/C study due to AE or death	14 (14)
D/C study for other reasons	4 (4)
Missing data during window	1 (1)

- Among the 15 participants who received ibalizumab in their initial OBT, the response rate (HIV-1 RNA <40 copies/mL) at Week 96 was 33% (5/15)

*Snapshot analysis did not include baseline. One participant had HIV-1 RNA <40 copies/mL at baseline.
†Change in OBT for efficacy reasons were considered virologic failures in this analysis.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

BRIGHTE Subgroup analysis



Conclusions

- Virologic response in the ITT population continued to improve over time, including amongst participants with high baseline viral load and low baseline CD4+ count.
- Compared with their counterparts, comparable virologic outcomes were observed in older and Black participants, who are disproportionately represented within the HTE population.[11]
- Continued clinically meaningful improvement in CD4+ T-cell counts was seen across all subgroups, including those most immune suppressed at baseline.
- While FTR-containing regimens were well tolerated through Week 96, severe safety events (i.e. SAEs and deaths) were more frequent in the most immune compromised participants with the lowest baseline CD4+ T-cell counts.
- These results support the continued development of FTR as an important therapeutic option for a broad cross-section of the HTE population, including those who are most immune suppressed, have high baseline viral load, are older, female, and/or of Black race.

Ackerman et al IAS Conference 2019, Mexico MOPEB234

Week 96 safety summary

Parameter, n (%)	Randomized Cohort (N=272)*	Non-randomized Cohort (N=99)	Total treated participants (N=371)
Any event	249 (92)	98 (99)	347 (94)
Any Grade 2–4 AE	216 (79)	87 (88)	303 (82)
Drug-related Grade 2–4 AEs	57 (21)	22 (22)	79 (21)
Any Grade 3/4 AE	78 (29)	49 (49)	127 (34)
Any SAE†	92 (34)	48 (48)	140 (38)
Drug-related SAE‡	9 (3)	3 (3)	12 (3)
Any AE leading to discontinuation	14 (5)	12 (12)	26 (7)
Any CDC Class C event	23 (8)	15 (15)	38 (10)
Death§	12 (4)	17 (17)	29 (8)

All safety data reflect cumulative results collected through the data cutoff date of August 14, 2018. *Includes participants randomized to the placebo group who received FTR 600 mg BID during the open-label phase; only data from initiation of open-label FTR dosing are presented. †The only SAEs occurring in at least 2% of participants were pneumonia (n=15), cellulitis (n=8), and acute kidney injury (n=6). ‡Drug-related SAEs (16 events in 12 participants) included: nephrolithiasis (n=2); immune reconstitution inflammatory syndrome (n=3); and one each of acute kidney injury, renal impairment, hyperglycemia, hyperkalemia, loss of consciousness, myocarditis, hepatocellular injury, rhabdomyolysis, fetal growth restriction, disorientation, and rash. §18/29 deaths were due to AIDS-related events or acute infections (one case was considered treatment-related: immune reconstitution inflammatory syndrome, related to recurrent atypical mycobacterial infection). 5/29 deaths occurred after the participant had discontinued from the study. AE, adverse event; SAE, serious adverse event.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

Drug-related Grade 2–4 AEs and AEs leading to discontinuation

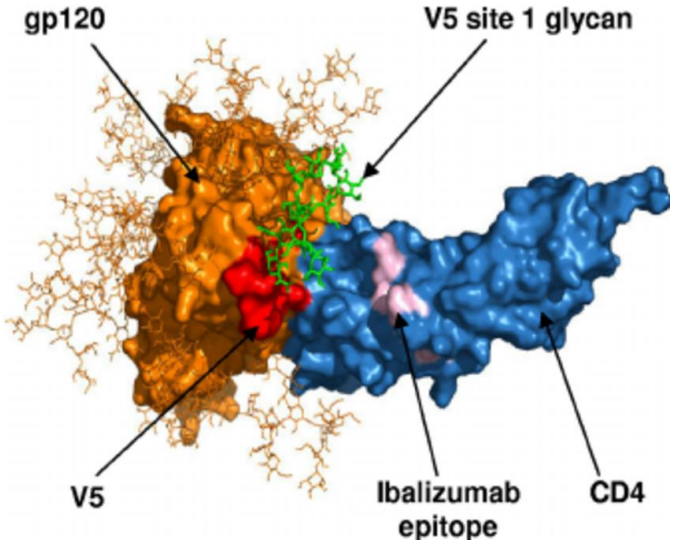
Parameter, n (%)	Randomized Cohort (N=272)*	Non-randomized Cohort (N=99)	Total treated participants (N=371)
Drug-related Grade 2–4 AEs	57 (21)	22 (22)	79 (21)
Occurring in ≥2% of participants in either cohort			
Nausea	9 (3)	5 (5)	14 (4)
Diarrhea	6 (2)	3 (3)	9 (2)
Headache	6 (2)	1 (1)	7 (2)
IRIS	7 (3)	0	7 (2)
Vomiting	4 (1)	2 (2)	6 (2)
Fatigue	3 (1)	2 (2)	5 (1)
Asthenia	2 (<1)	2 (2)	4 (1)
AE leading to discontinuation	14 (5)	12 (12)	26 (7)
In ≥2 participants			
Abdominal pain	2 (<1)	0	2 (<1)
Electrocardiogram QT prolonged	2 (<1)	1 (1)	3 (<1)
Non-cardiac chest pain	1 (<1)	1 (1)	2 (<1)
Hepatic failure	0	2 (2)	2 (<1)

All safety data reflect cumulative results collected through the data cutoff date of August 14, 2018. *Includes participants randomized to the placebo group who received FTR 600 mg BID during the open-label phase; only data from initiation of open-label FTR dosing are presented.
IRIS, immune reconstitution inflammatory syndrome.

Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 http://bit.ly/brighte96wk

Ibalizumab

- Humanised monoclonal – binds to CD4
- Active against HIV-1 resistant to all approved ARV agents
- Binds to CD4 to prevent HIV attachment
- Initial development as IV infusion to be administered every 2 weeks



Lewis et al. Croi 2017 Abstract #449LB

Ibalizumab

TNX 355.03

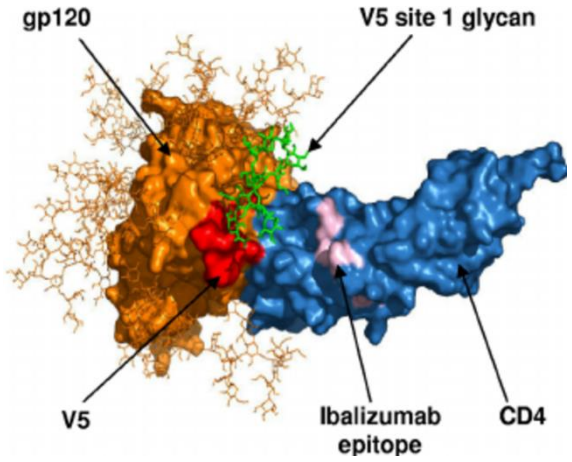
- Phase IIa patients failing therapy (N=82).
- 3-arm placebo controlled – OBR+IBA or placebo

TMB 202

- Phase IIb – dose-response randomised (N=113)

TMB 301

- Phase 3 open-label IBA+OBR in HTE patients (N=40) with MDR HIV.
- IV loading 2000mg, then 800 mg q2w for 24 weeks.
- OBR added @7d with at least 1 additional sensitive agent.



TMB 311

- After w24 TMB-301, patients continued TMB-311 for up to 48w
- Safety and efficacy were assessed until 48 weeks.

Beccari et al, AAC 2019
Lewis et al. Croi 2017 Abstract #449LB

TMB-301/-311: Key Results

Virologic Outcome With Ibalizumab	TMB-301		TMB-311
	Day 14[1] (N = 40)	Wk 24[2] (N = 40)	Wk 48[3] (N = 27)
≥ 0.5 log_{10} HIV-1 RNA decrease, %	83*	NR	NR
≥ 1.0 log_{10} HIV-1 RNA decrease, %	60	55	NR
≥ 2.0 log_{10} HIV-1 RNA decrease, %	NR	48	NR
Mean log_{10} HIV-1 RNA decrease	1.1	1.6	NR
HIV-1 RNA < 50 copies/mL, %	NR	43	59
HIV-1 RNA < 200 copies/mL, %	NR	50	63

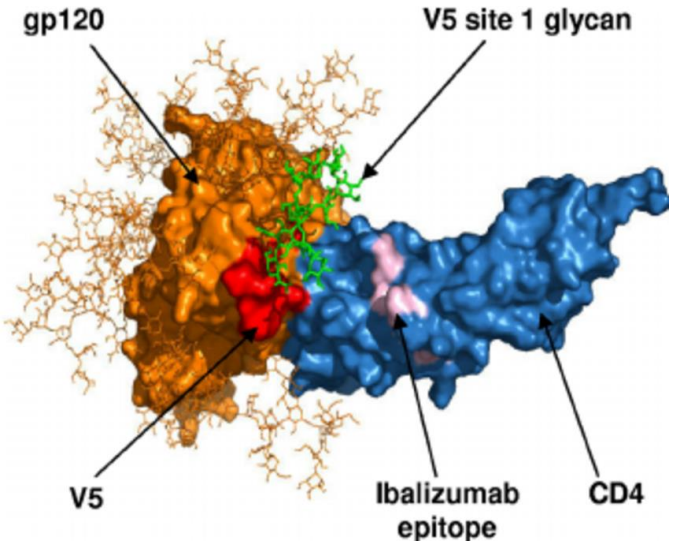
*P < .0001 vs 3% at end of control period.

- Wk 24: 9 pts reported 17 serious AEs; 1 drug-related serious AE (IRIS) resulted in d/c
- Wk 48 TEAEs (all mild/moderate): upper respiratory tract infection, 15%; diarrhea, 11%; rashes, 7%

1. Lalezari J, et al. IDWeek 2016. Abstract LB-6. 2. Lewis S, et al. CROI 2017. Abstract 449LB.
3. Emu B, et al. IDWeek 2017. Abstract 1686.

Ibalizumab

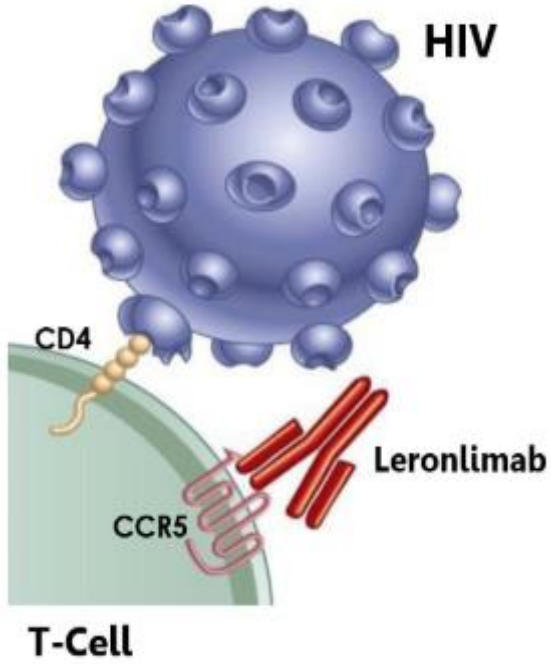
- In treatment-experienced patients (n=40) with resistance to approved ARV agents, After 24 weeks of treatment (with optimized background regimen):
  - Mean VL decrease of 1.6 log_{10} from Baseline (55% with ≥1 log_{10}; 48% with ≥2 log_{10})
  - 43% of patients had VL of <50 copies; 50% with <200 copies
- Adverse reactions were mild to moderate



Lewis et al. Croi 2017 Abstract #449LB

Leronlimab

Leronlimab (PRO140) - CytoDyn



- Humanised IgG4 monoclonal directed against CCR5
- Treatment-experienced HIV
- Weekly, self-administered injection
- >800 patients in Phase 1-3
- Data from Italian PRESTIGIO Registry Study Group expected CROI 2020
- a high failure rate at the initial 350 mg dose [CROI 2019]

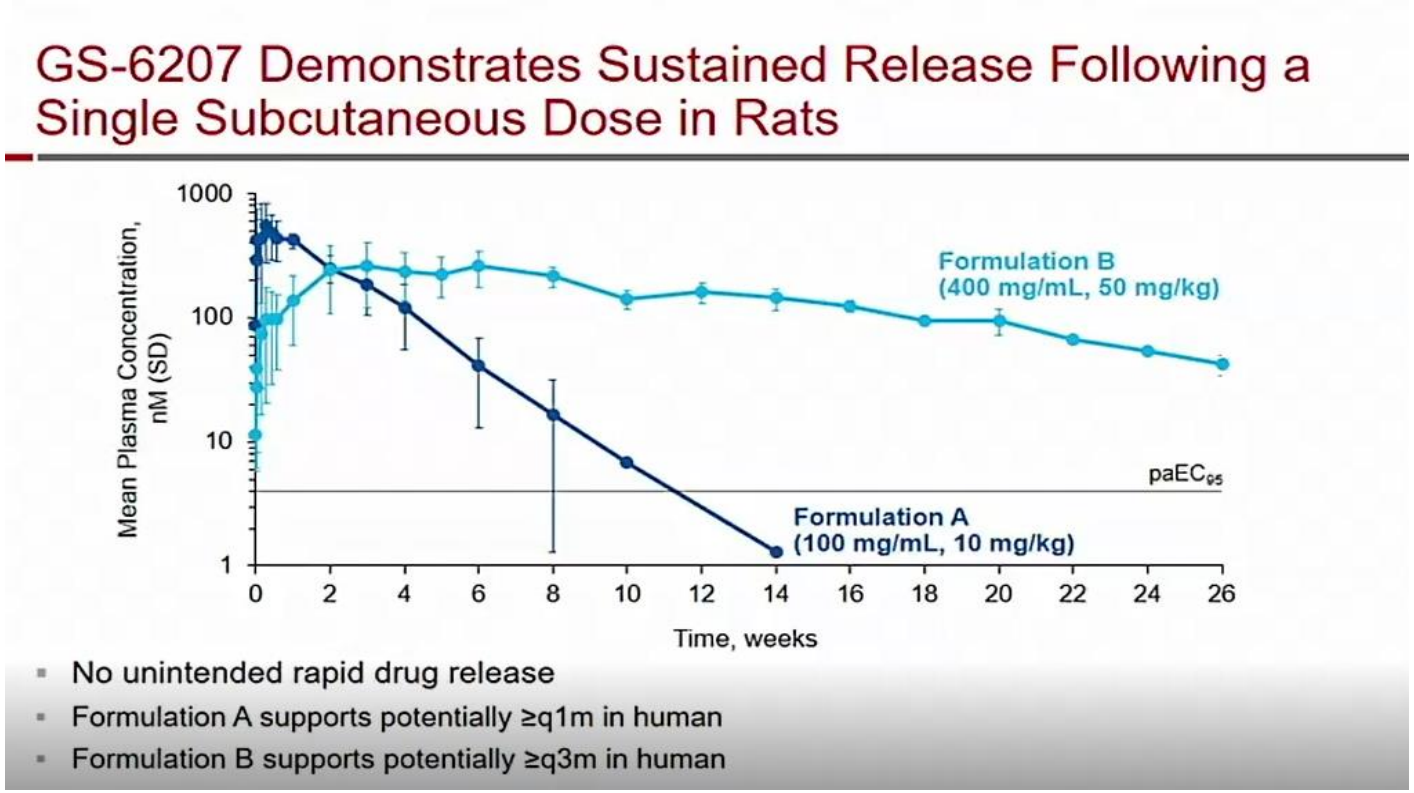
Approximately 65% (149/226) of participants in the 350 mg, 33% (38/115) in the 525 mg arm and 14% (6/14) in the 700 mg arm, had confirmed viral rebound >200 copies/mL.

- Also being assessed in metastatic cancer and GVHD in Allogeneic SST

Capsid Assembly Inhibitor – GS 6207

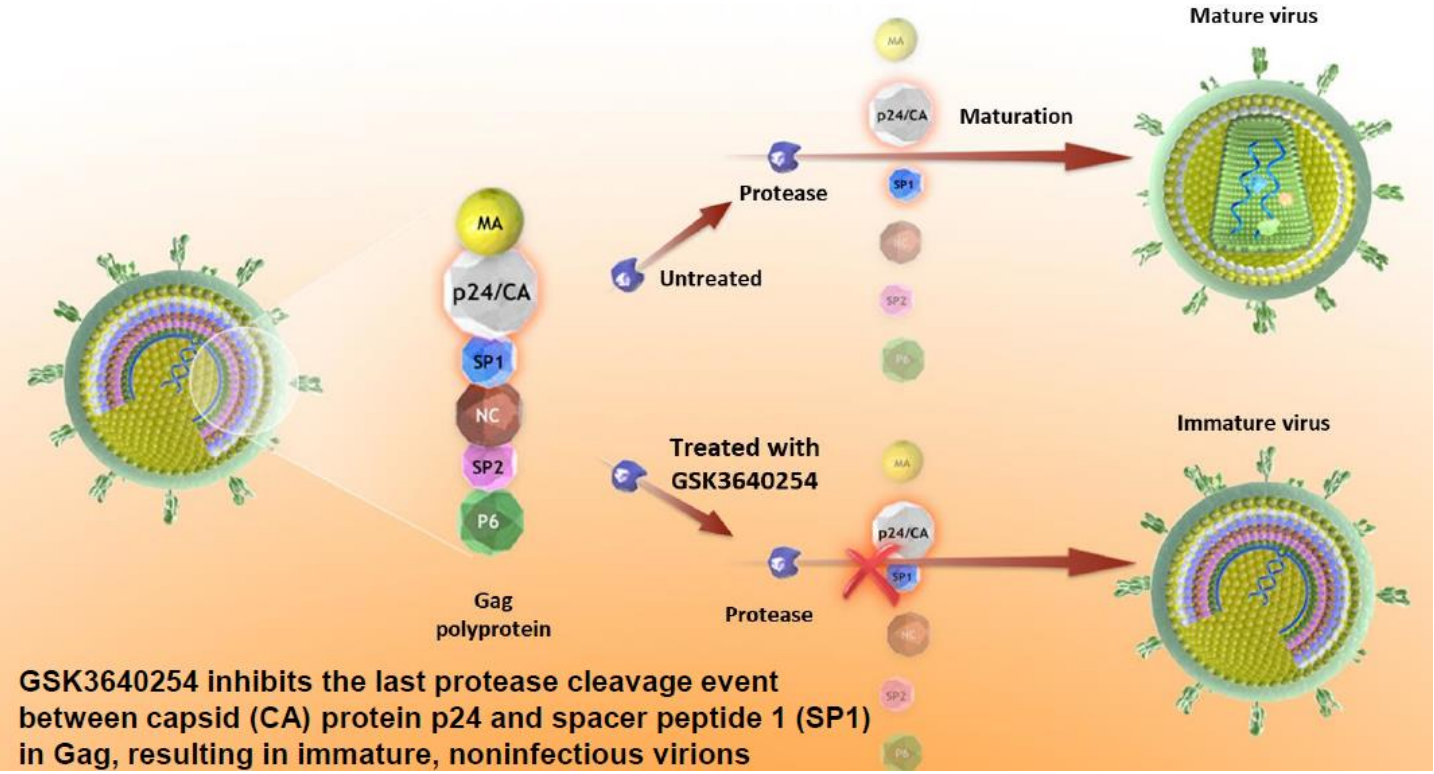
GS 6207

- Novel action, unique resistance profile
- High antiviral potency (EC50= 50 pM)
- Resistant variants have low fitness
- Low in-vivo clearance
- Poorly soluble
- Half-life: 30-43 days
- Healthy volunteer PK consistent with long-acting potential
- Given as a subcutaneous suspension



Sagar et al. CROI 2019: Abstract 141
Zheng. LEAP meeting Seattle 2019

GSK 3640254 – Maturation inhibitor



SAD / MAD data presented (IWCPAT 2019 Noordwijk)

- GSK 3640254 did not show nay clinically significant adverse tolerability findings through maximum 14d dosing
- PK supports od dosing
- Ongoing POC study NCT03784079 in HIV+ treatment naive

New Entry Inhibitors and Drug Classes

- **HTE patients with multi-resistance increasingly uncommon**
- **Unclear what patterns of mutations will predominate in future**
  - use of unboosted INSTIs first (and second) line
  - switch to TLD in LMICs without VL testing
- **bPIs retain their anchor role** *(is DRV the last word ?)*
- **New classes (Capsid, Maturation, Monoclonals, bNAbs) and improvements on existing classes very welcome**
- **HIV drug development very much alive !**

UNIVERSITY OF LIVERPOOL

David Back
Marco Siccardi
Andrew Owen
Catia Marzolini
Helen Reynolds

Sara Gibbons
Katie McAllister
Justin Chiong
Jasmine Martin
Katie Moss
Fiona Marra
Alison Boyle
Kay Seden

David Burger
Marta Boffito
Alan Winston
Mohamed Lamorde
Catriona Waitt
Charlie Flexner
Kim Scarsi
Jonathan Schapiro