



New Entry Inhibitors and Dug Classes

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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 ?**
- **Fostemsavir**
- **Capsid inhibitors**
- **Other inhibitors of viral entry and maturation**

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

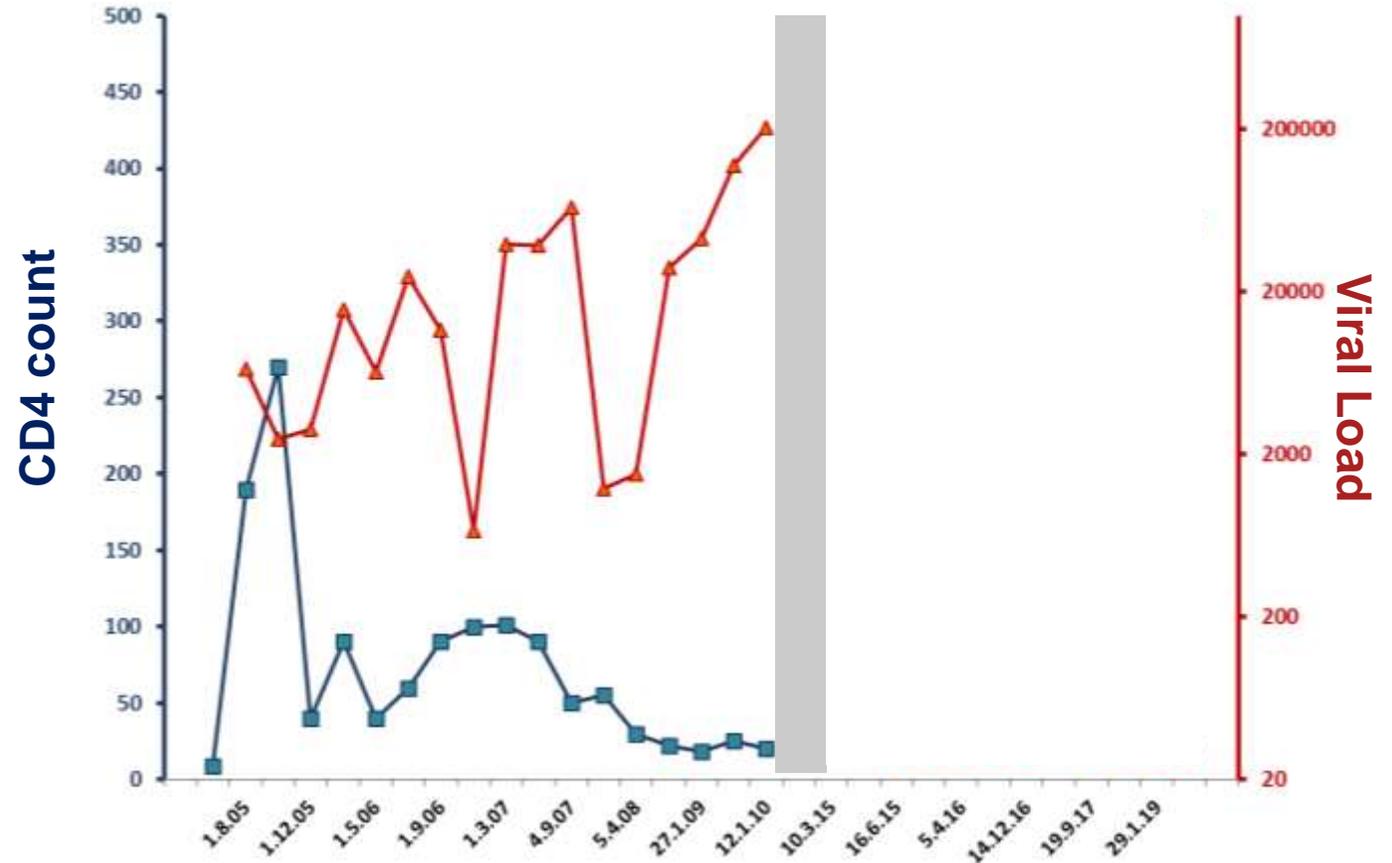
Advanced disease, falling CD4

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

K65R x L74I x V90I x K103N x V106M x

Y181C x Input mutation(s)

Protease

V32I x L33F x M36I x M46I x I54L x L63P x

L76V x V82I x I84V x I93L x

Input mutation(s)

Integrase

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

Nucleoside Reverse Transcriptase Inhibitors

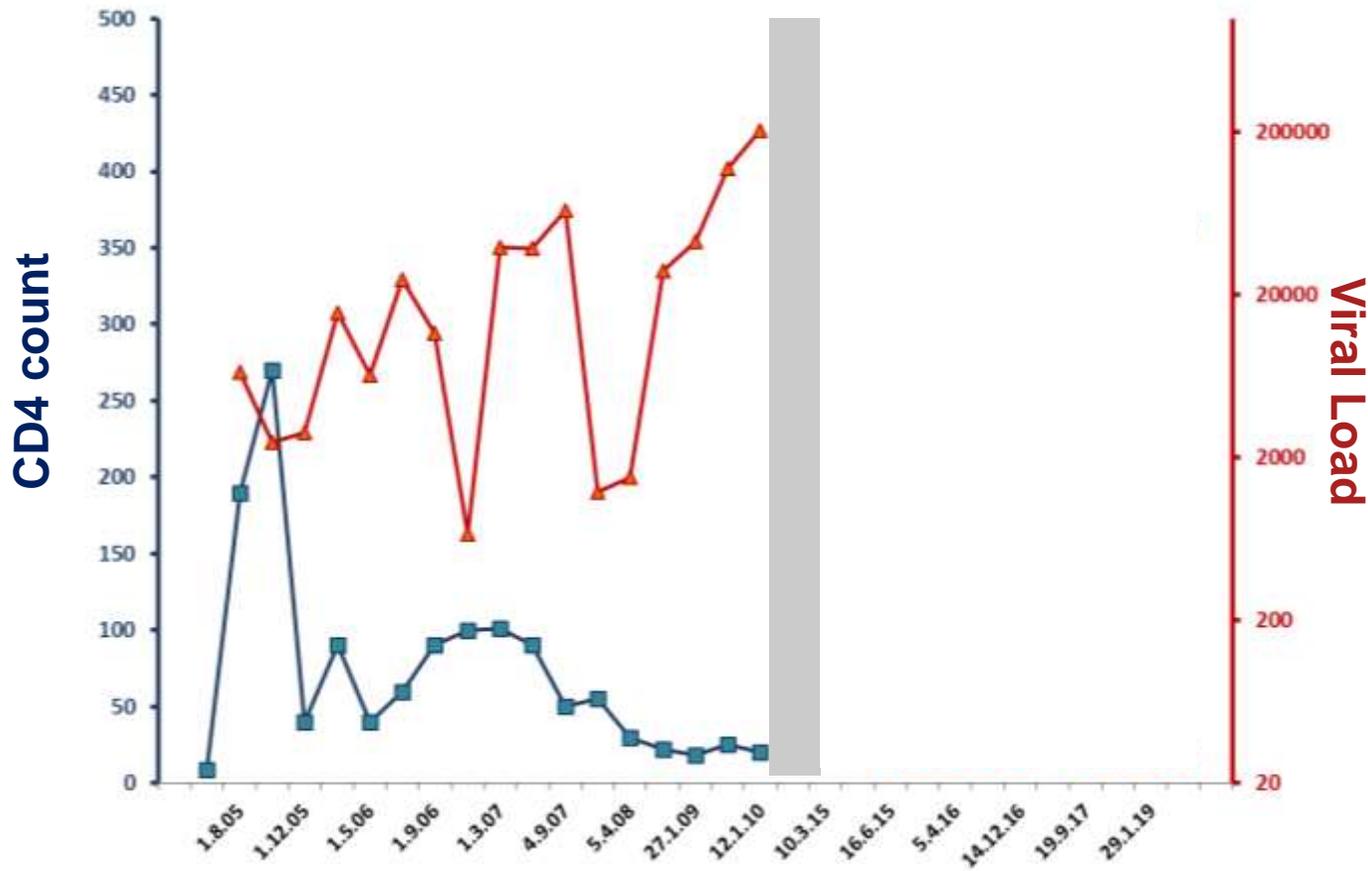
abacavir (ABC)	High-Level Resistance
zidovudine (AZT)	Susceptible
emtricitabine (FTC)	Intermediate Resistance
lamivudine (3TC)	Intermediate Resistance
tenofovir (TDF)	High-Level Resistance

Integrase Strand Transfer Inhibitors

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



2014

2020 ?

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

Reverse Transcriptase	Protease	Integrase
<input type="checkbox"/> K65R <input type="checkbox"/> L74I <input type="checkbox"/> V90I <input type="checkbox"/> K103N <input type="checkbox"/> V106M <input type="checkbox"/> <input type="checkbox"/> Y181C <input type="checkbox"/> Input mutation(s)	<input type="checkbox"/> V32I <input type="checkbox"/> L33F <input type="checkbox"/> M36I <input type="checkbox"/> M46I <input type="checkbox"/> I54L <input type="checkbox"/> L63P <input type="checkbox"/> <input type="checkbox"/> L76V <input type="checkbox"/> V82I <input type="checkbox"/> I84V <input type="checkbox"/> I93L <input type="checkbox"/> <input type="checkbox"/> Input mutation(s)	<input type="checkbox"/> Y143CHRY <input type="checkbox"/> Input mutation(s)



Patient 2

25y man

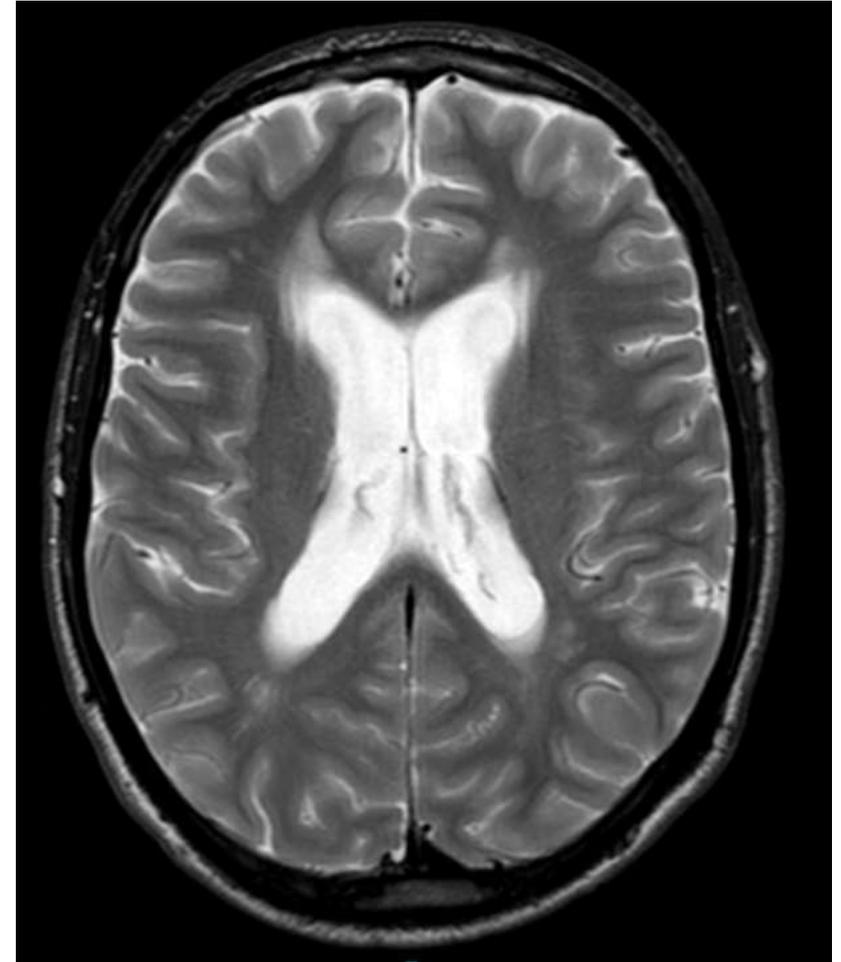
2018 Tested HIV+ (baseline testing K219KQ)

Nov VL 429,000 copies, CD4 10 cells

Cryptococcal meningitis – culture positive

Treated (AmB + 5FC) → Fluconazole po

ART commenced with **ABC/3TC/DTG**

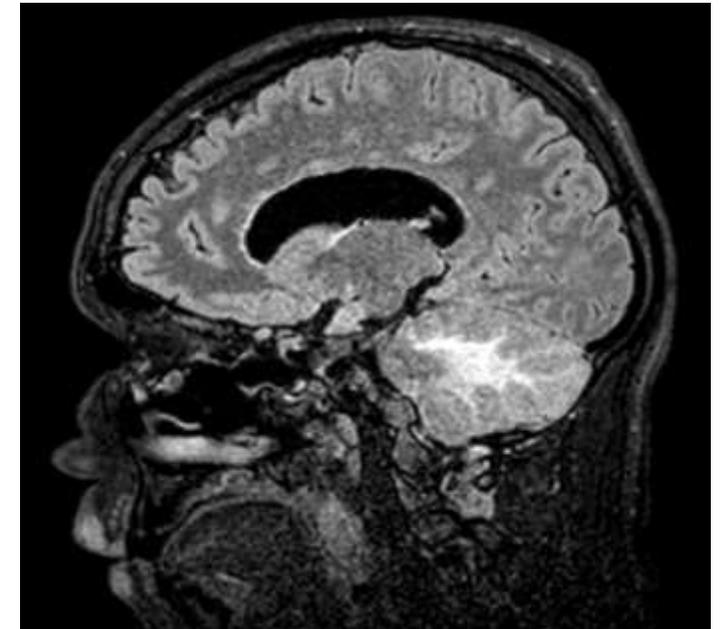
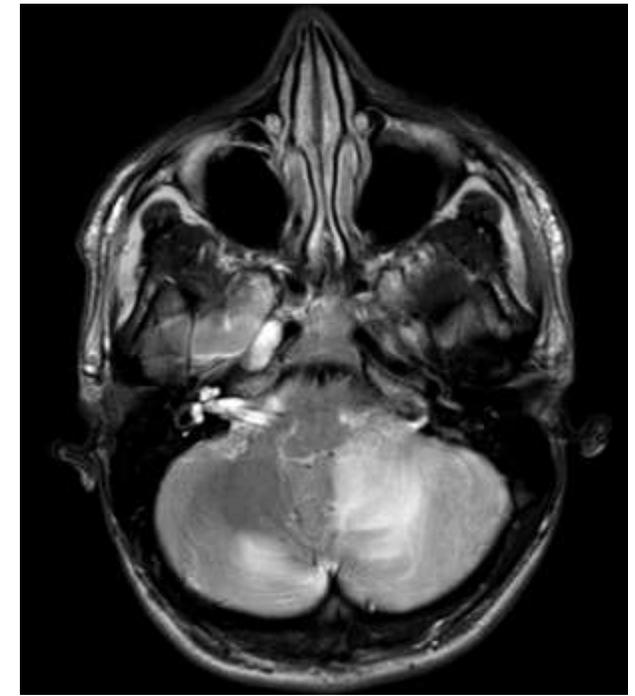
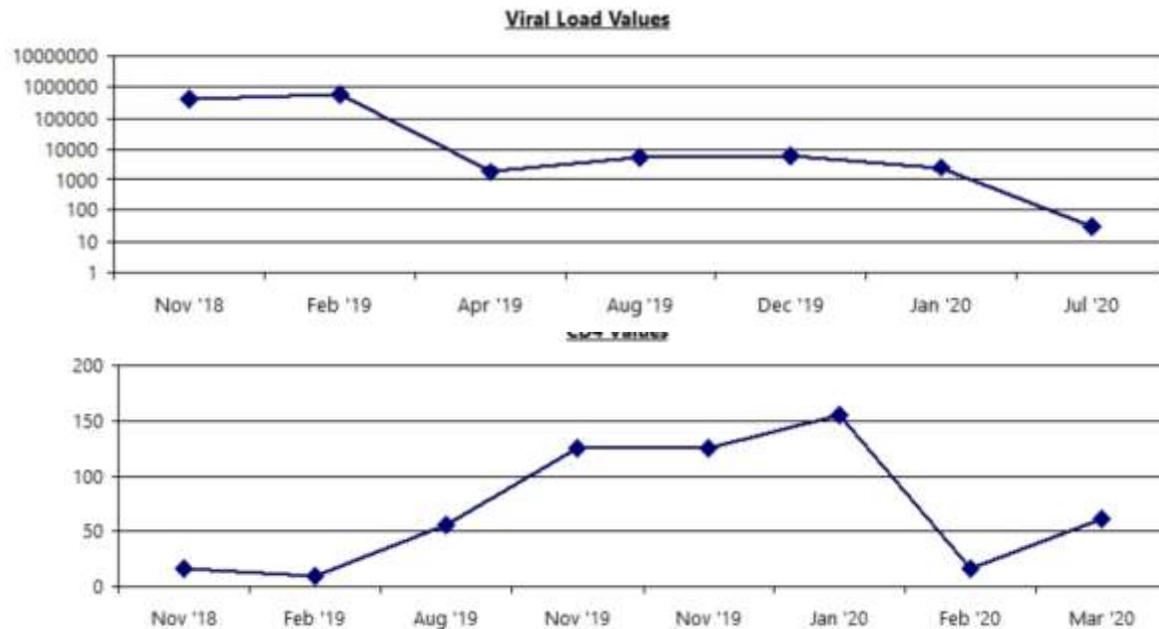


Patient 2

25y man

2019 Cryptococcal IRIS (? relapsing meningitis)
Steroids (Dexamethasone)
re-treatment of cryptococcal meningitis

Persistent **detectable VL** 1000-5800 copies
CD4 80-156 cells



Patient 2

25y man

2020 obstructing hydrocephalus
Jan Ventriculo-peritoneal shunt inserted

Fluctuating clinical signs and CrAg titre

Multiple admissions and LPs

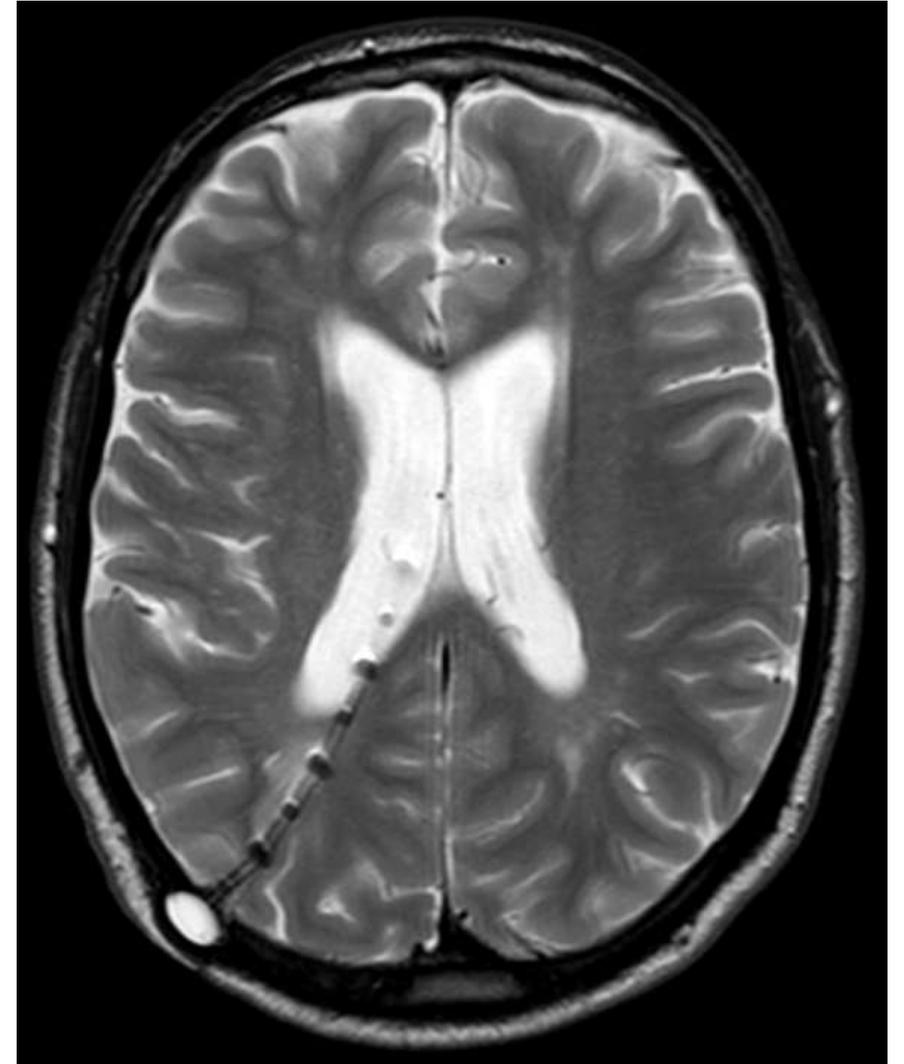
Relapsing Crypto IRIS

Steroids for 24 months

HIV resistance – M184V, V106I and R263K

Symtuza + DTG (50 bid)

HIV successfully suppressed

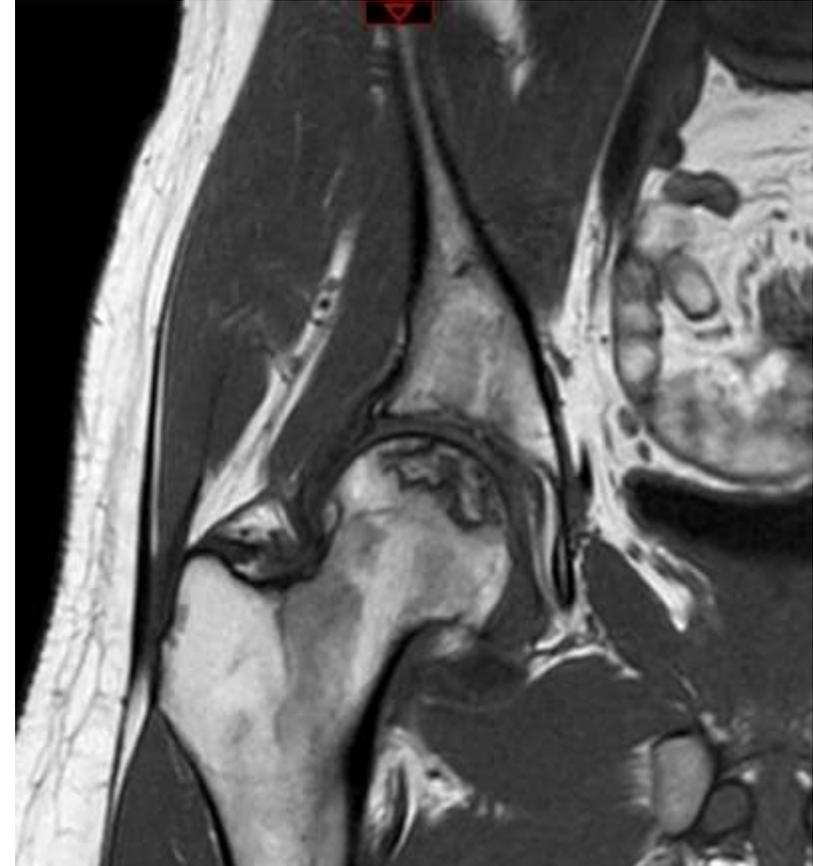


Patient 2

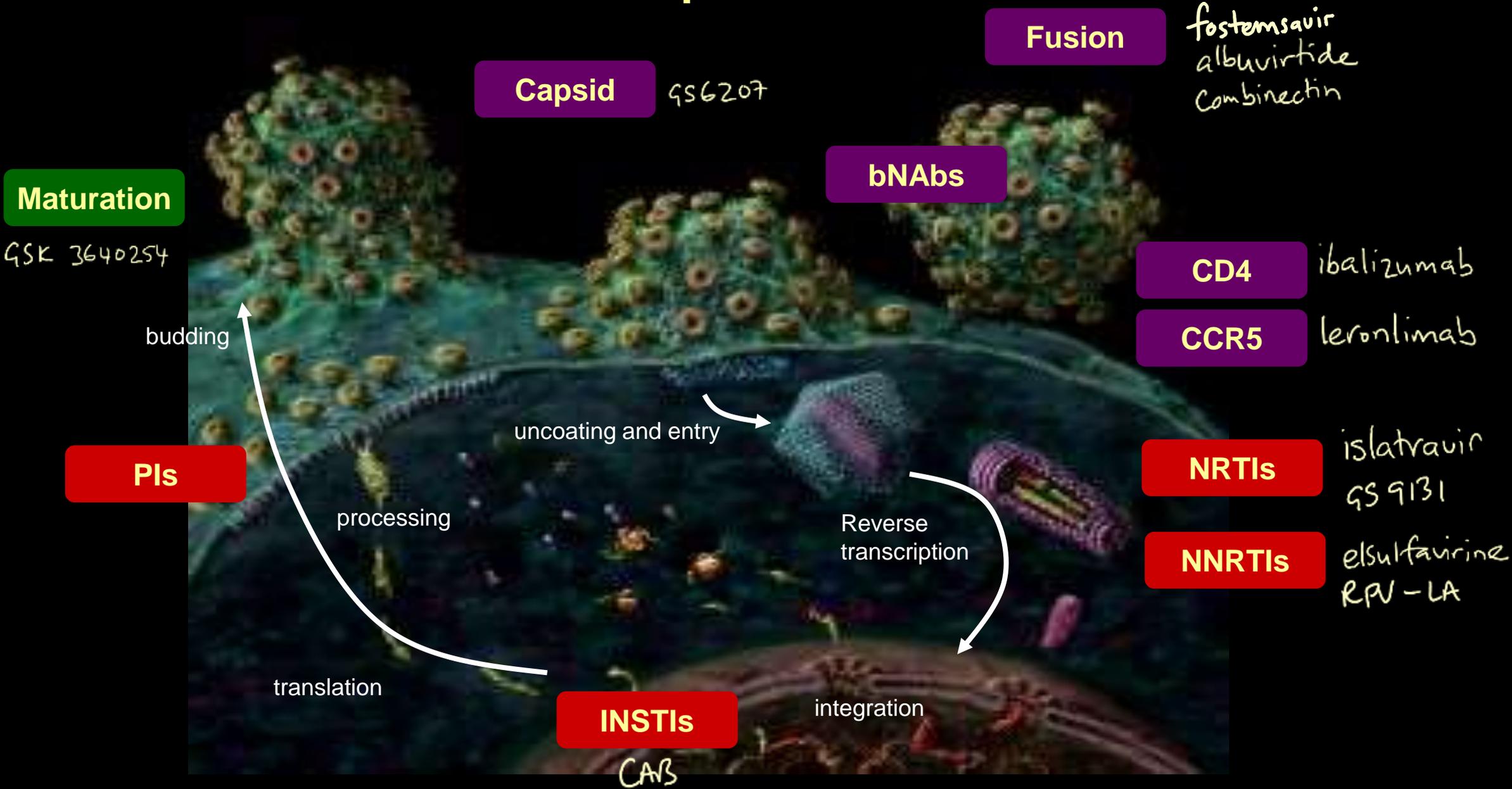
25y man

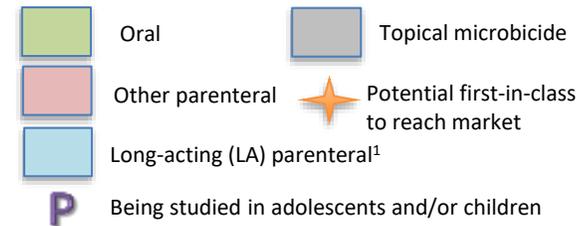
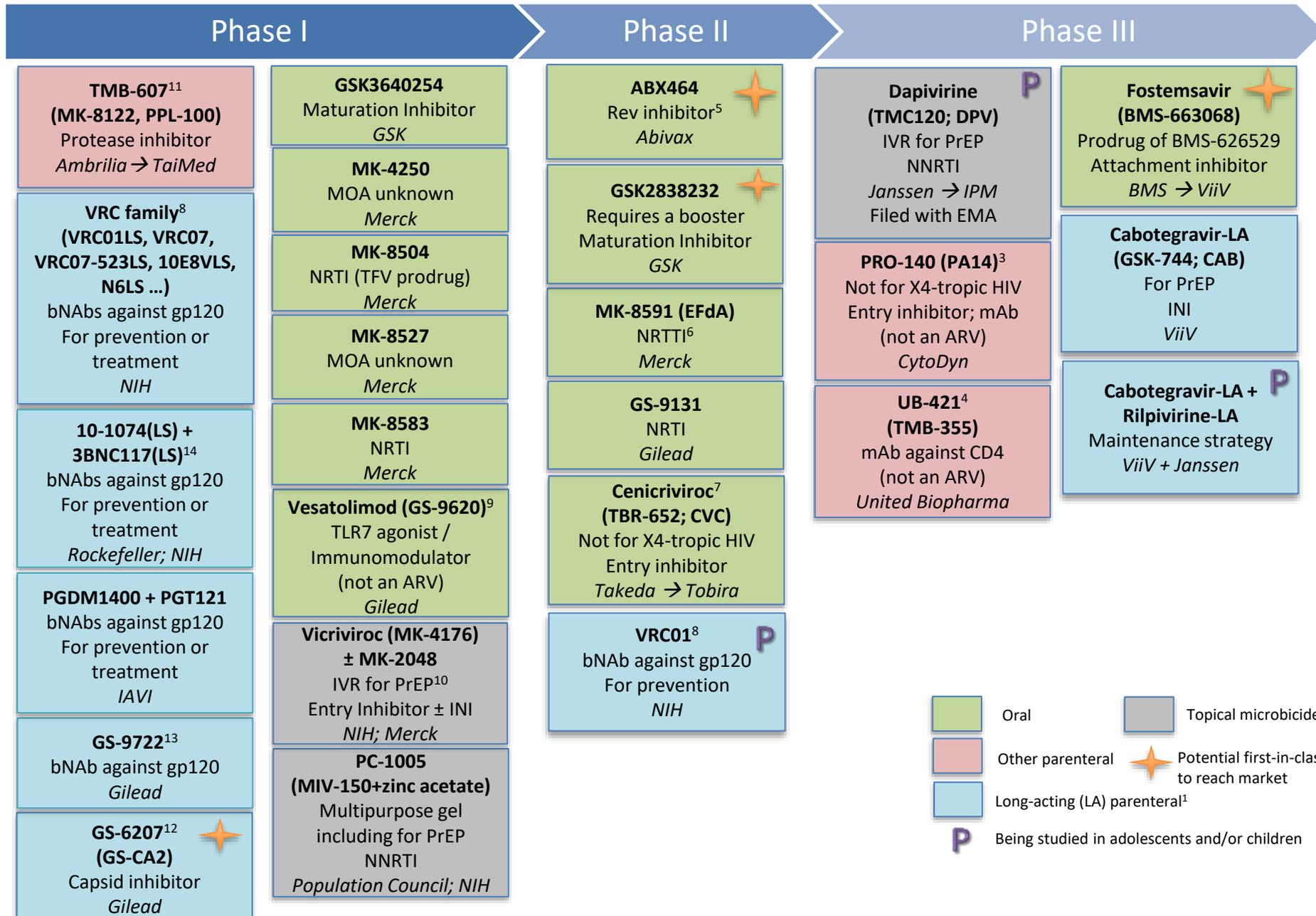
2021 Bilateral hip pain

Jan MRI scans show bilateral avascular necrosis
chronic steroid use, likely DDI



The HIV Pipeline in 2021



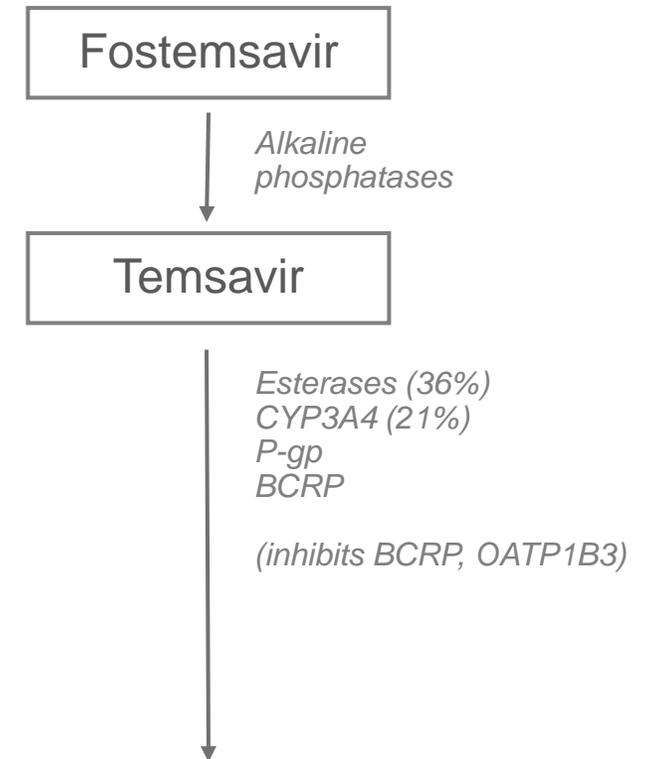


Fostemsavir

- Prodrug of temsavir (TMR- binds gp120)
- 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).

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)



Sevinski et al IWCPAVT 2017 (Abst 23)

Savant et al CROI 2015 Abstr P509

Landry et al IWCPHT 2015 Abstr O9

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

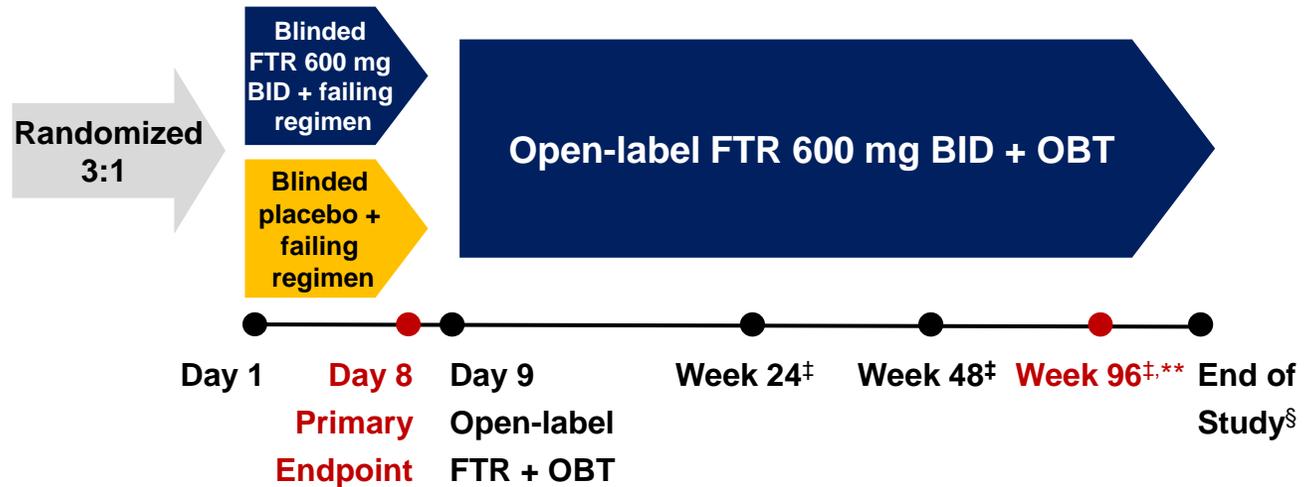
Study design

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:

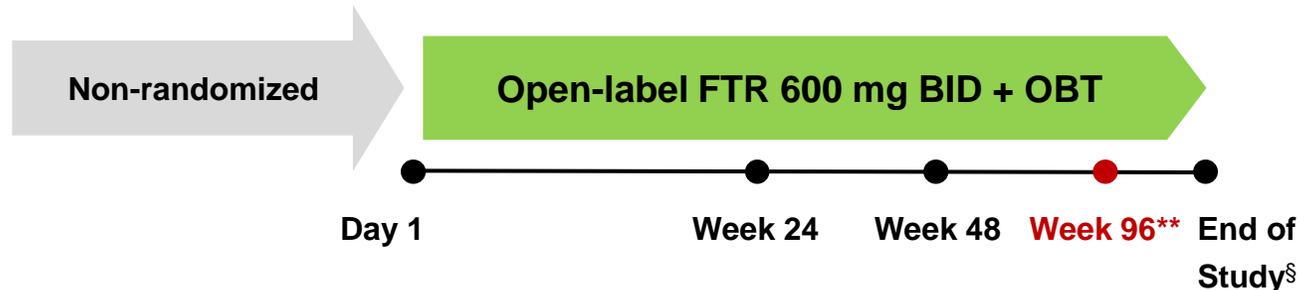
- 1 or 2 ARV classes remaining with ≥ 1 fully active[†] approved agent per class
- Unable to construct viable regimen from remaining agents



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 IC₅₀ 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.

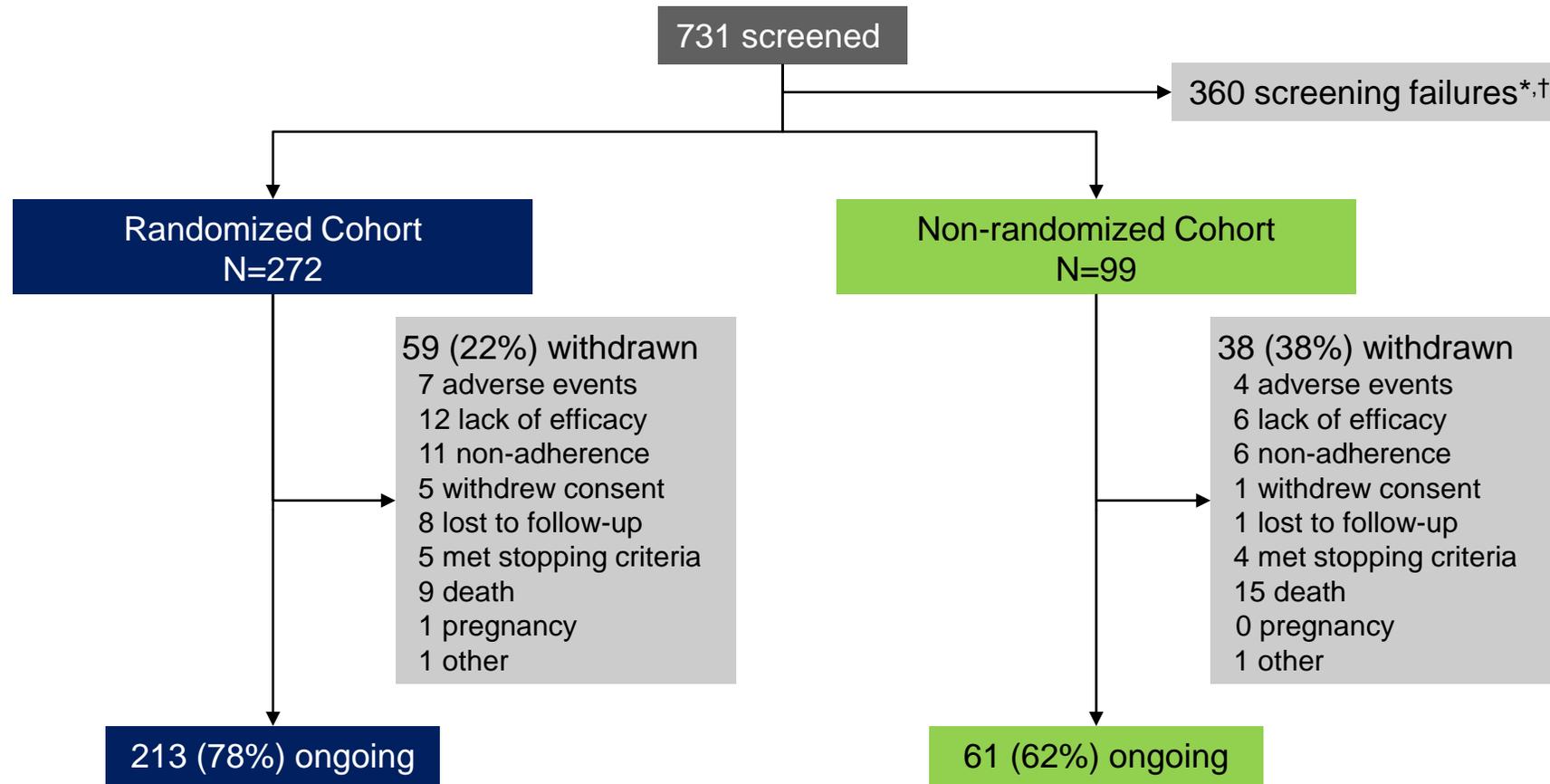
[¶]Use of investigational agents as part of OBT was permitted. ^{**}Week 96 database lock August 14, 2018.

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.

Baseline characteristics

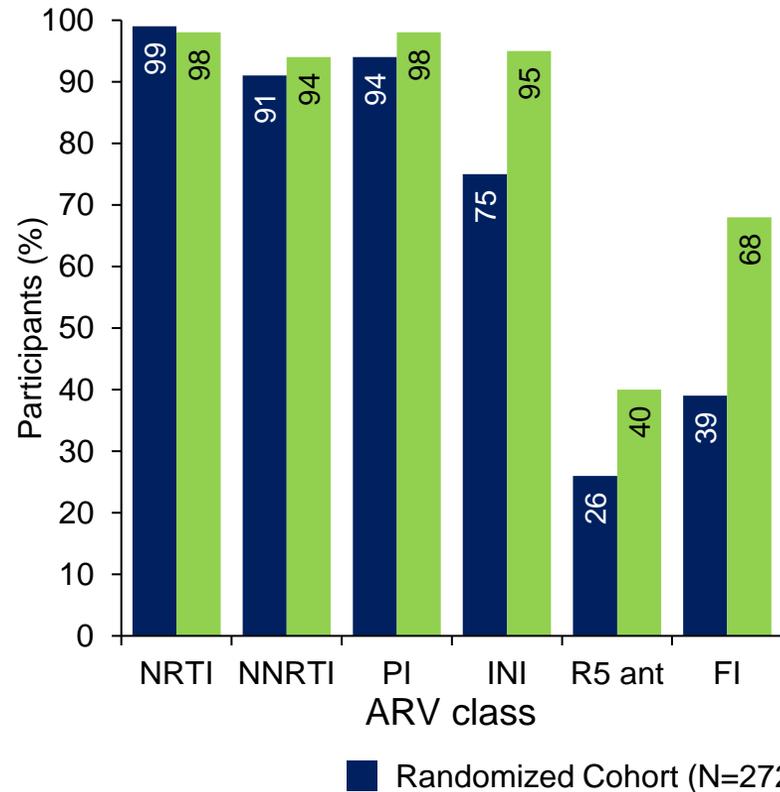
Parameter	Randomized Cohort			Non-randomized Cohort	Total treated participants (N=371)
	Placebo BID (N=69)	FTR 600 mg BID (N=203)	Total randomized (N=272)	FTR 600 mg BID (N=99)	
Age , years, median (range)	45 (19–66)	48 (18–73)	48 (18–73)	50 (17–72)	49 (17–73)
<50 years, n (%)	46 (67)	116 (57)	162 (60)	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 log₁₀ 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.

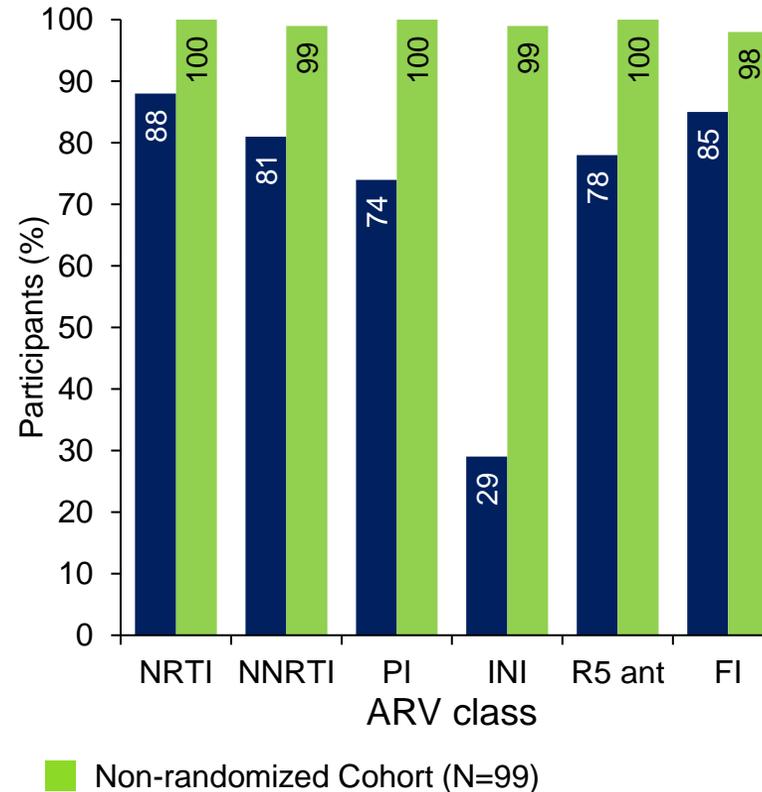
Lataillade et al. IAS 2019; Mexico City, Mexico. Slides MOAB0102 <http://bit.ly/brighte96wk>

Baseline prior ARV exposure and resistance

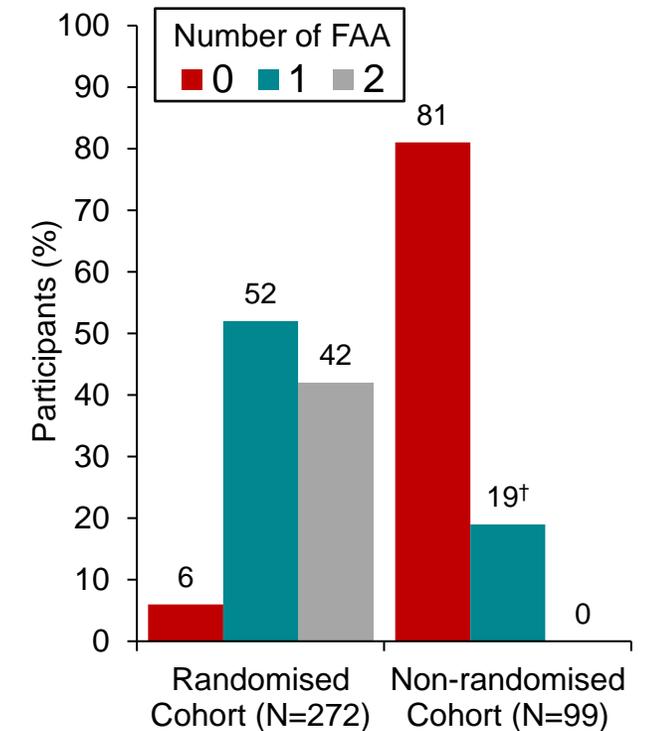
Prior exposure to ARV classes



ARV classes exhausted at baseline*



FAA in initial OBTT

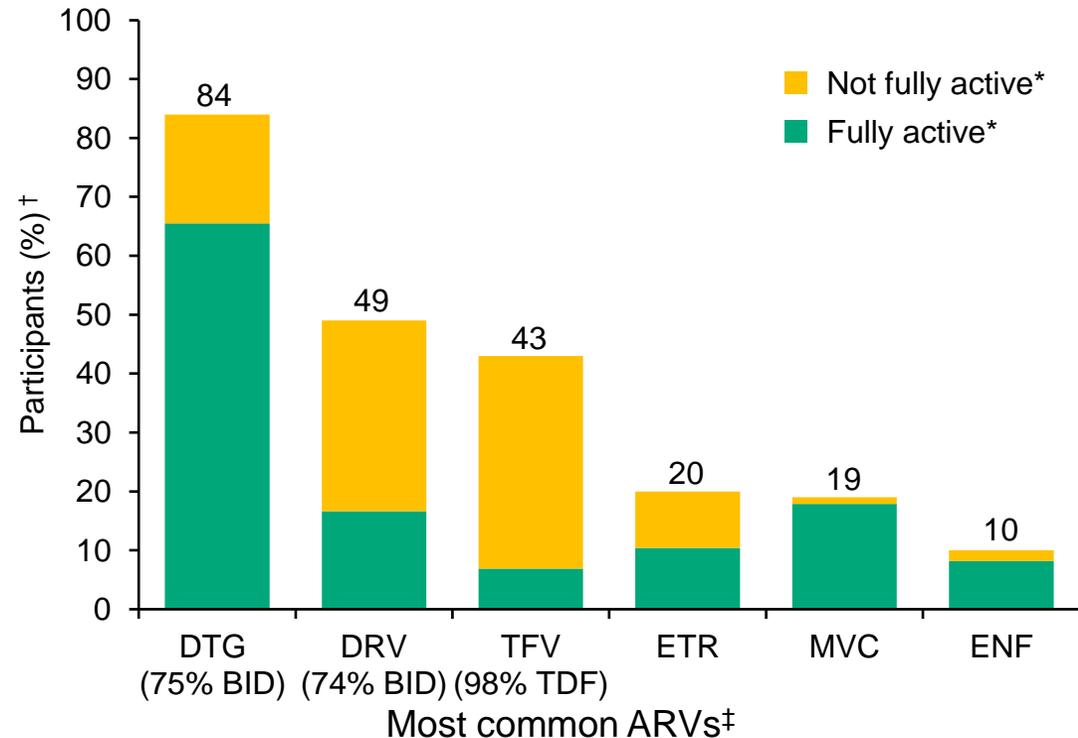


*Proportions of participants for whom there are no remaining FAAs within the indicated ARV class, based on Monogram assays (PhenoSense® GT Plus Integrase, Trofile®, and PhenoSense® Entry), historical resistance, eligibility, and tolerability. [†]15/19 received investigational ARV ibalizumab and 4/19 were incorrectly assigned to the Non-randomized Cohort.

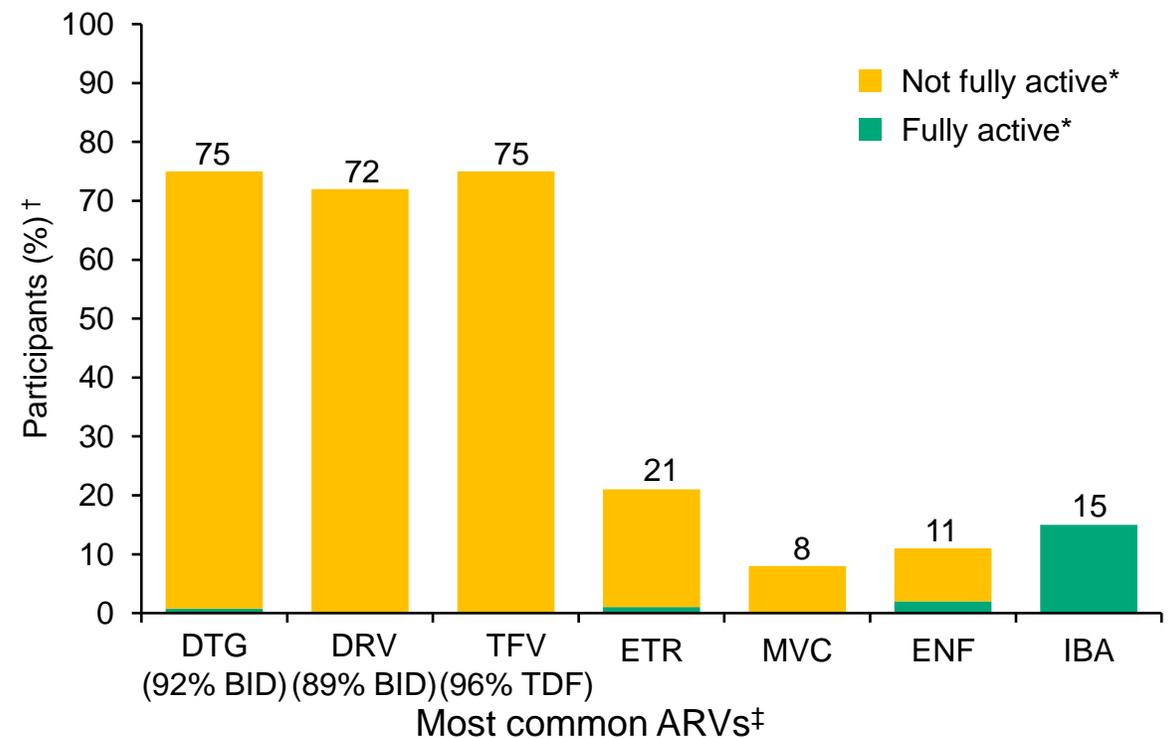
FAA, fully active ARV; FI, fusion inhibitor; INI, integrase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-NRTI; PI, protease inhibitor; R5 ant, CCR5 antagonist.

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.

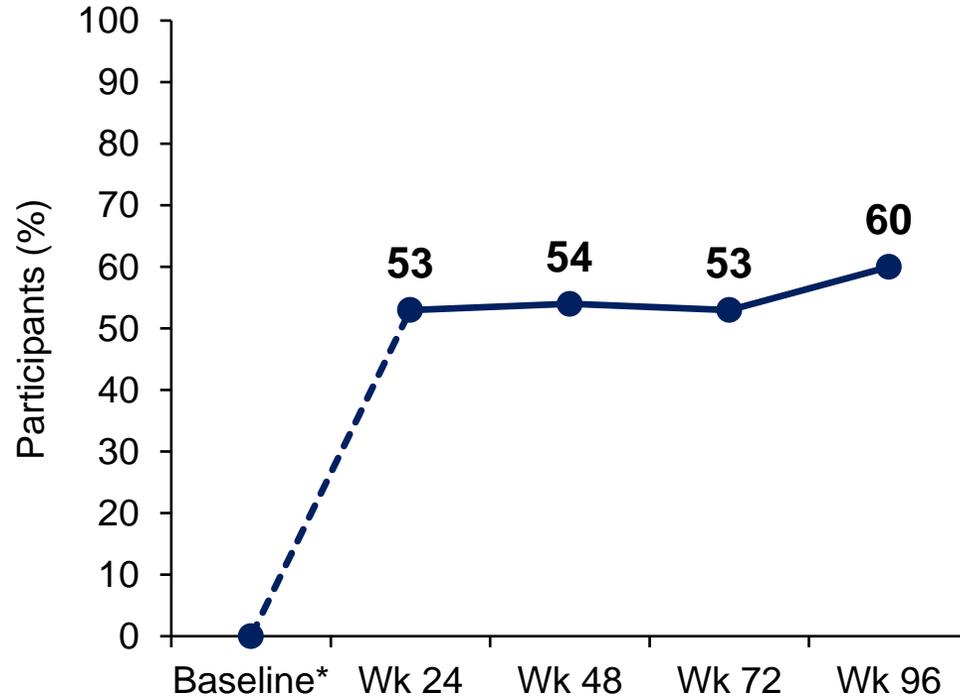
DRV, darunavir; DTG, dolutegravir; ENF, enfuvirtide; ETR, etravirine; IBA, ibalizumab; MVC, maraviroc; TDF, tenofovir disoproxil fumarate; TFV, tenofovir.

HIV-1 RNA <40 copies/mL through Week 96

Snapshot analysis, ITT-E*



Randomized Cohort (N=272)



	Randomized Cohort (N=272)
Week 96 outcome, n (%)	
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.

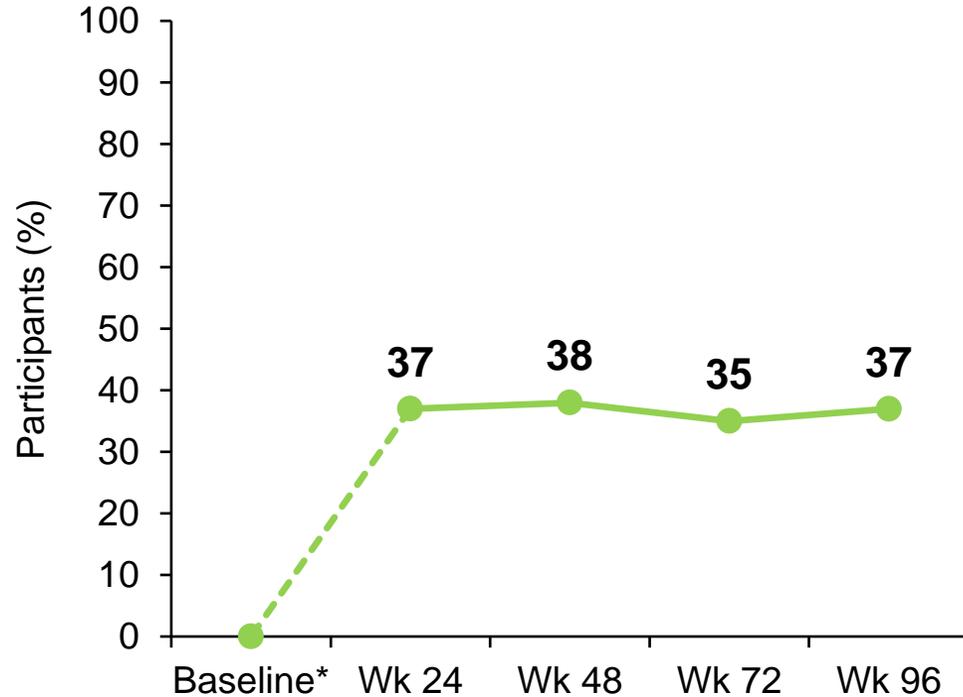
[†]Change in OBT for efficacy reasons were considered virologic failures in this analysis.

AE, adverse event; ART, antiretroviral therapy; D/C, discontinued; ITT-E, intent-to-treat exposed population.

HIV-1 RNA <40 copies/mL through Week 96

Snapshot analysis, ITT-E*

Non-randomized Cohort (N=99)



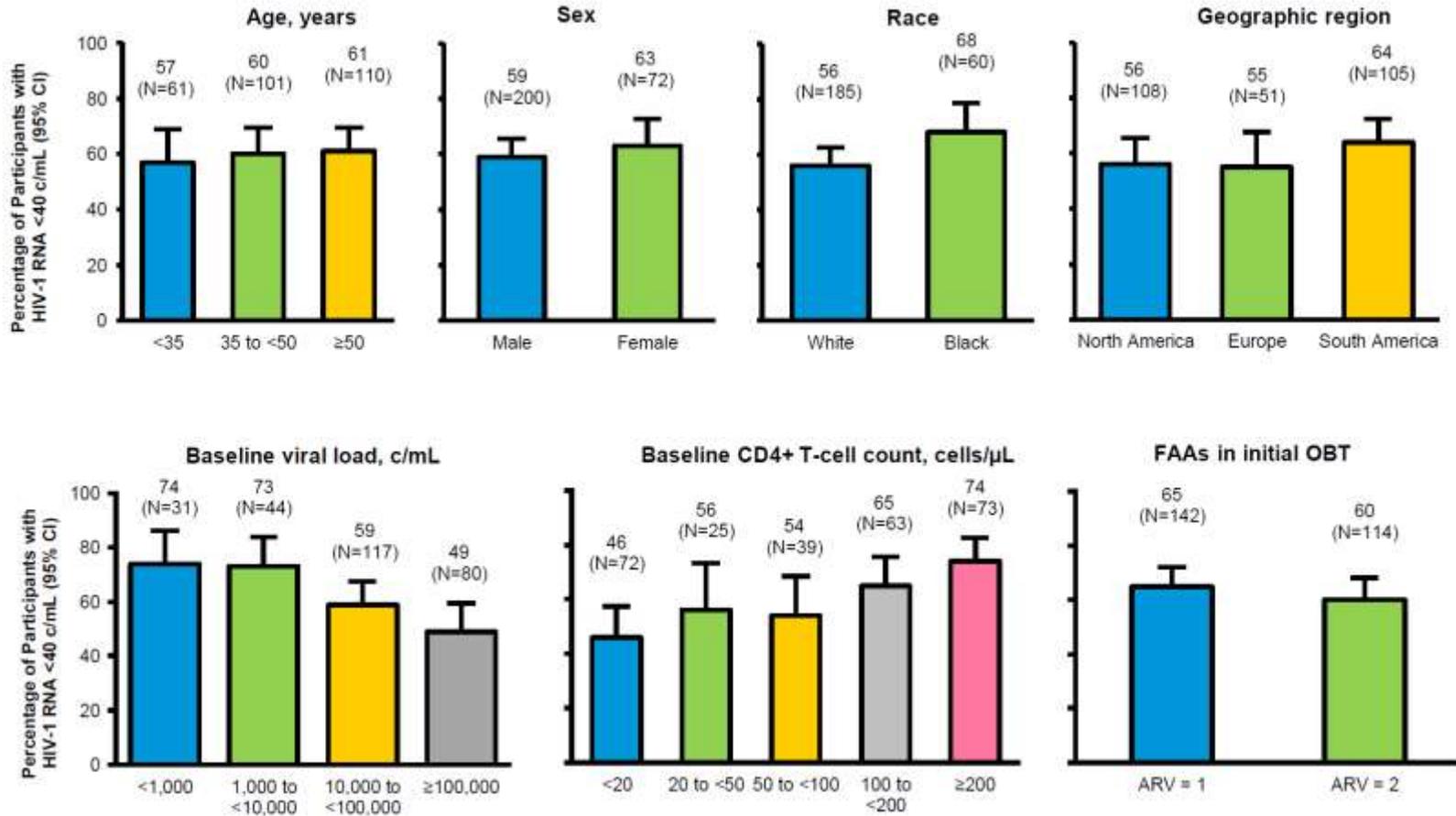
	Non-randomized Cohort (N=99)
Week 96 outcome, n (%)	
HIV-1 RNA <40 copies/mL	37 (37)
HIV-1 RNA ≥40 copies/mL	43 (43)
Data in window not below threshold	15 (15)
D/C for lack of efficacy	3 (3)
D/C for other reason while not below threshold	6 (6)
Change in ART [†]	19 (19)
No virologic data	19 (19)
D/C study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

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.

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.

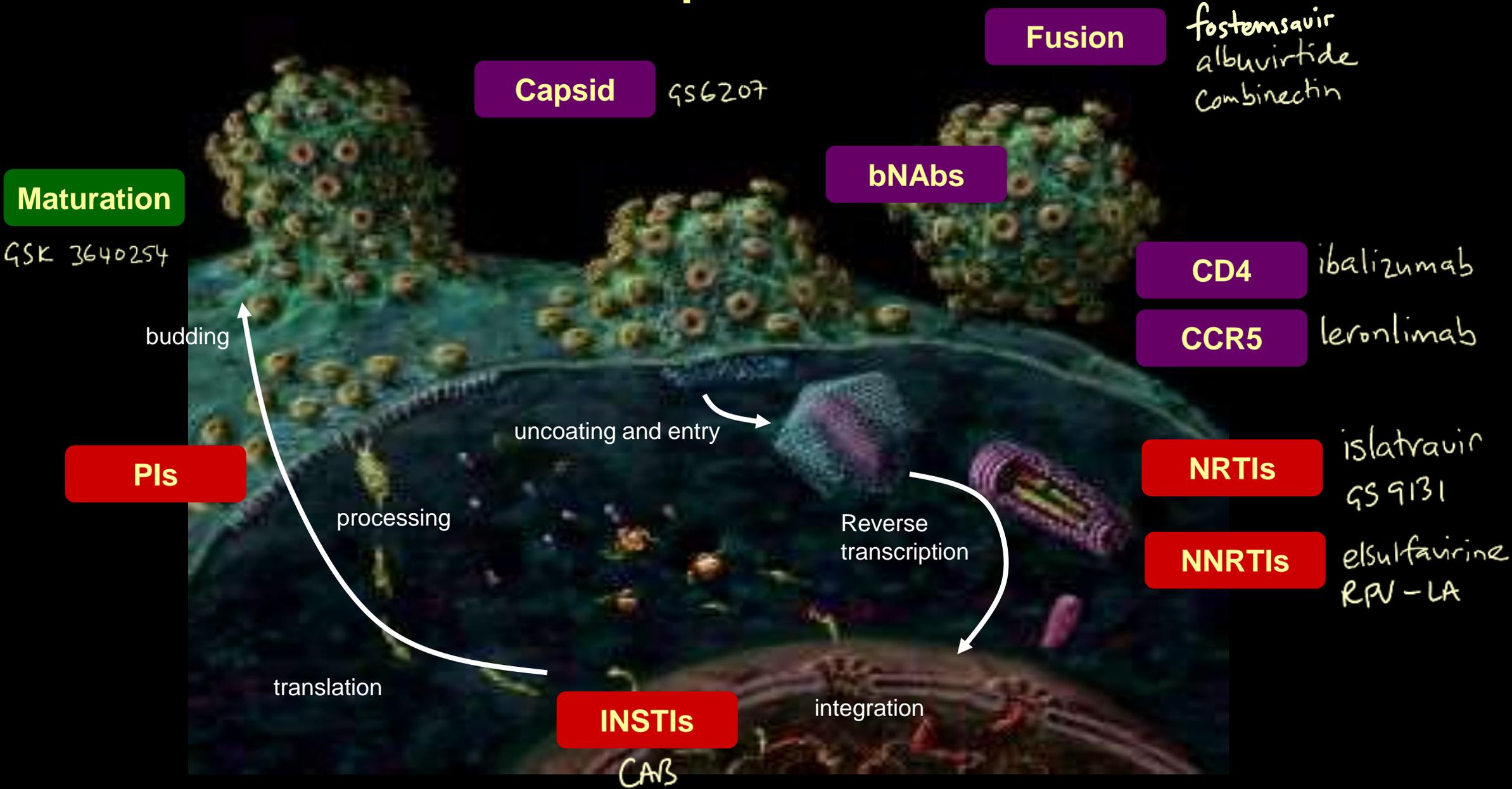
Drug-related Grade 2–4 AEs and AEs leading to discontinuation

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.

The HIV Pipeline in 2021

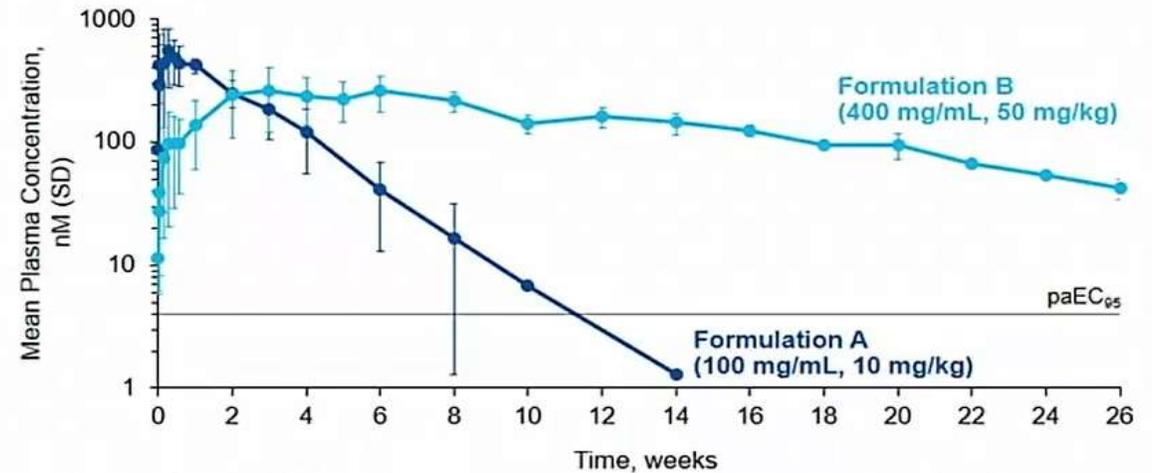


Lenacapavir (GS 6207) - Capsid Assembly Inhibitor

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

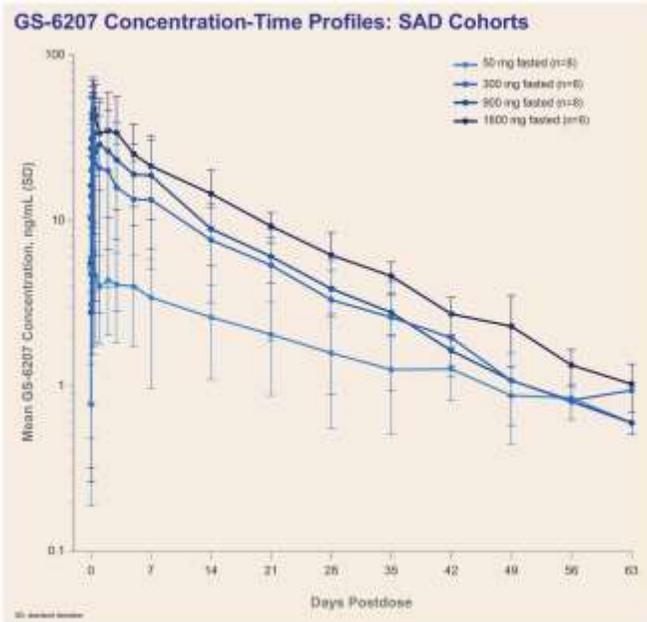
GS-6207 Demonstrates Sustained Release Following a Single Subcutaneous Dose in Rats



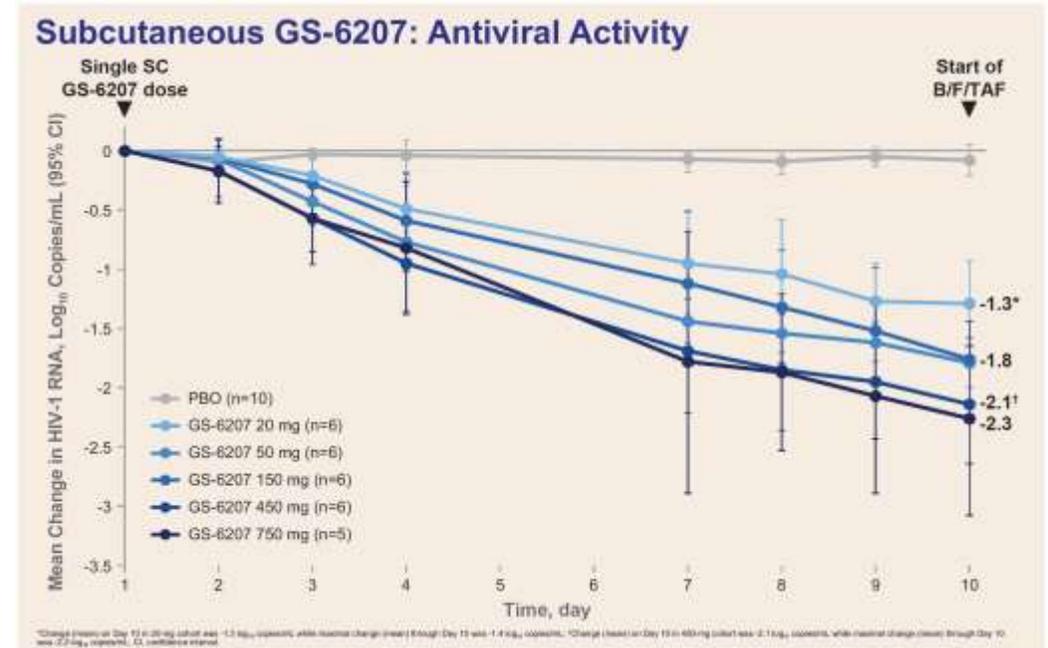
- No unintended rapid drug release
- Formulation A supports potentially \geq q1m in human
- Formulation B supports potentially \geq q3m in human

Lenacapavir (GS 6207) SAD studies

Oral



Subcutaneous



- Oral formulation being assessed for lead-in dosing (2w)
- SC injection 50-750mg > 20mg
- Well-tolerated (mild-mod ISR, some CK/amylase elevations)
- Phase II (175) oral lead-in (+FTaf) then sc q6m (+ po Taf or BIC)
- Phase II/III (100) MDR HIV – OBT +/- Lenacapavir q6m sc (after 2w monotherapy lead-in)



HIV pipeline 2020: targets in the HIV lifecycle

Entry inhibitors

combinectin
(GSK3732394)

NRTIs/NRTTIs (nukes)

islatravir (EFdA)
MK-8504, MK-8583

NNRTIs (non-nukes)

elsulfavirine

INIs (INSTIs)

cabotegravir LA

Monoclonal antibodies (mAb)

UB-421 (CD4 receptor)
VRC01/LS and VRC07/LS
3BNC117/LS and 10-1074/LS
PGDM1400, 10E8.4/iMab
PGT121 and elipovimab (GS-9722)
N6LS (gp120)
Ieronlimab PRO-140 (CCR5)

Targets in the HIV lifecycle

- 1 HIV attaches to a CD4 cell.
- 2 HIV enters a CD4 cell and HIV proteins and enzymes are released into the cell.
- 3 Reverse transcriptase (RT) makes double strand HIV.
- 4 Integrase enables HIV to join the cell DNA.
- 5 Protease cuts and reassembles new HIV.
- 6 Final stages include maturation and budding as each cell produces hundreds of new virions.

Rev inhibitor

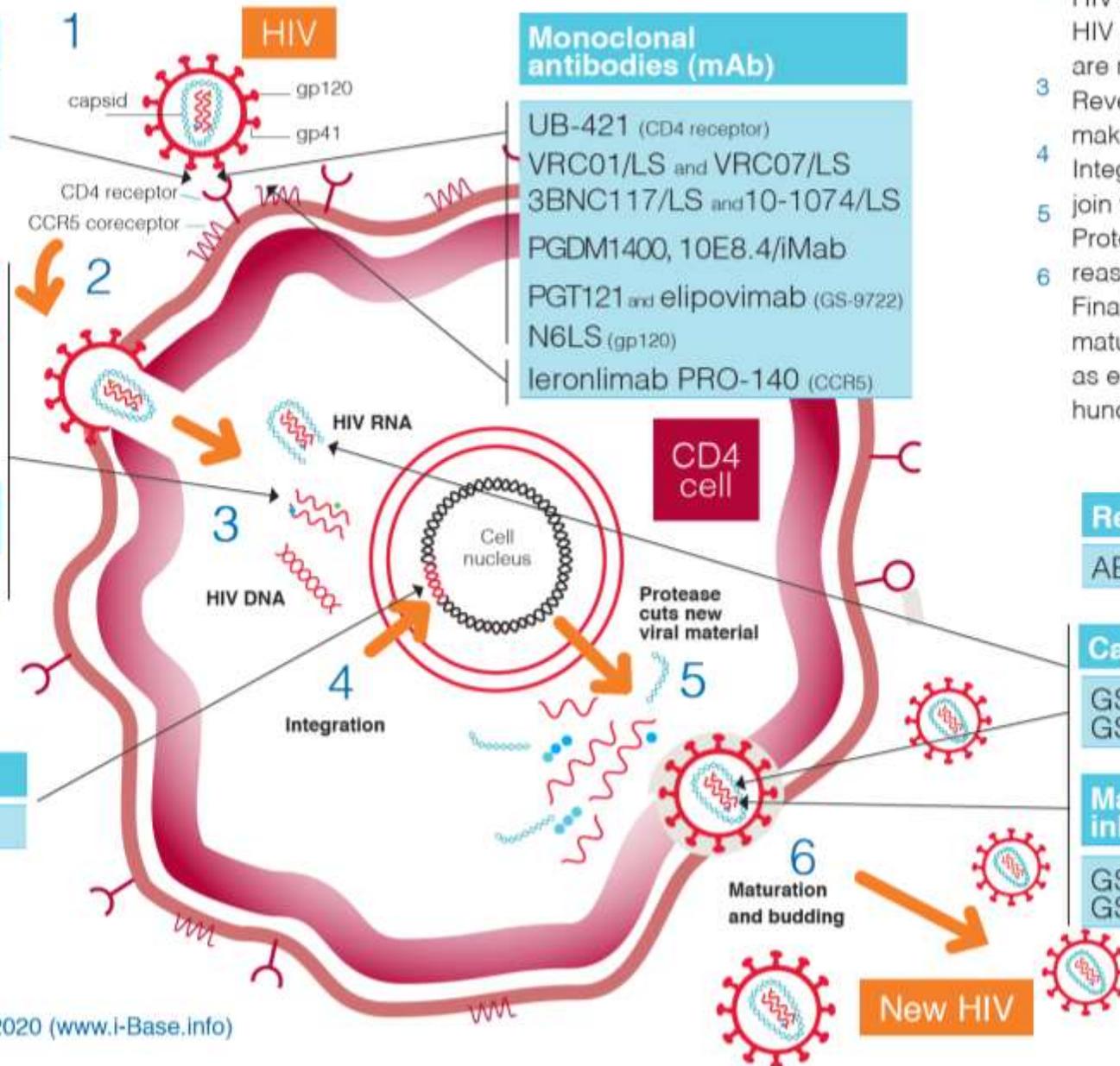
ABX-464

Capsid inhibitors

GS-6207
GSK (pre-clinical)

Maturation inhibitors

GSK '254 (oral)
GSK '937 (LA)



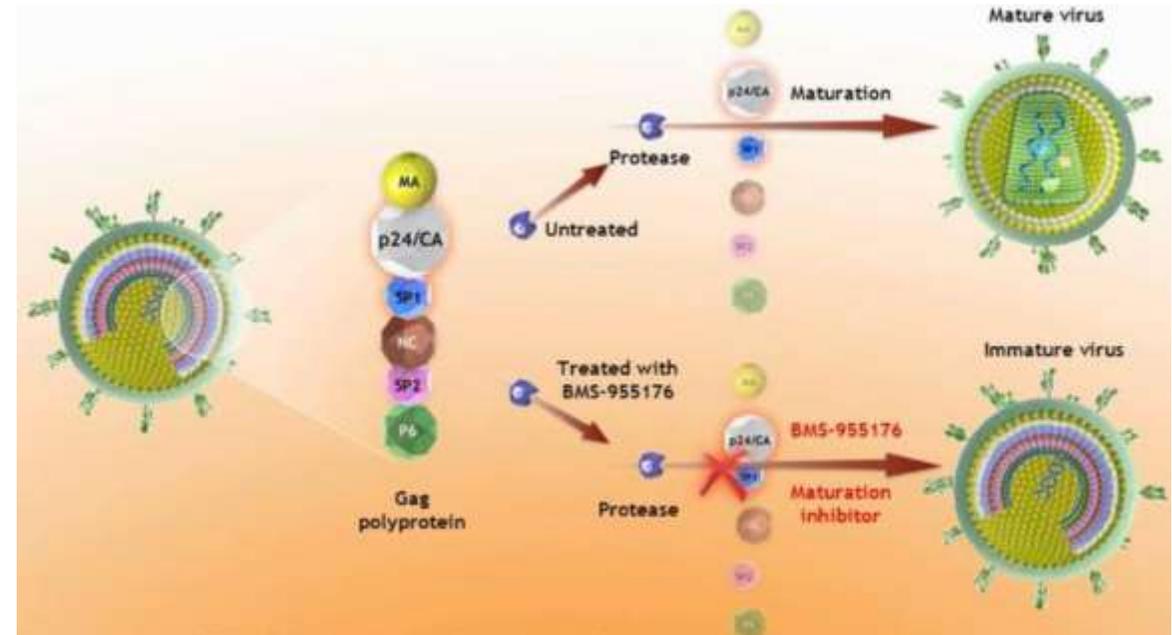
GSK3640254 – Maturation Inhibitor

- 1st generation (Bevirimat) discontinued. Single amino acid polymorphisms confer resistance
- 2nd generation maturation inhibitors in development

GSK3640254

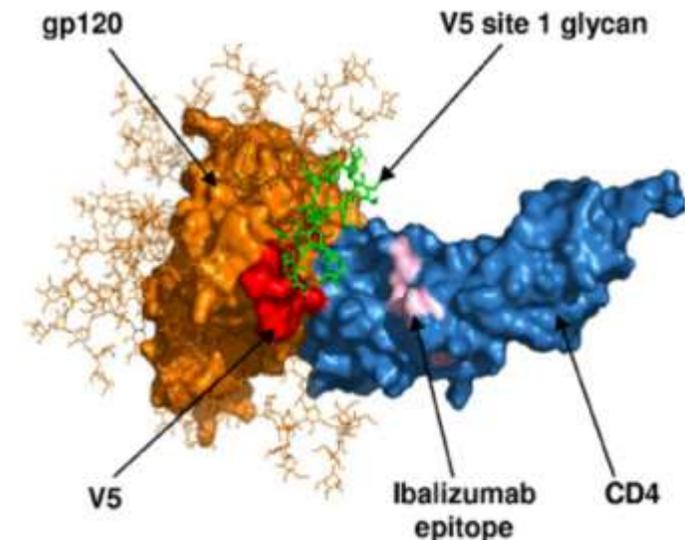
- Phase I (2 formulations) published (Dec 2020)
- Phase II in progress (5-100mg); dosing with food.

Another maturation inhibitor in development for LA use



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



Ibalizumab

TNX 355.03

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

TMB 202

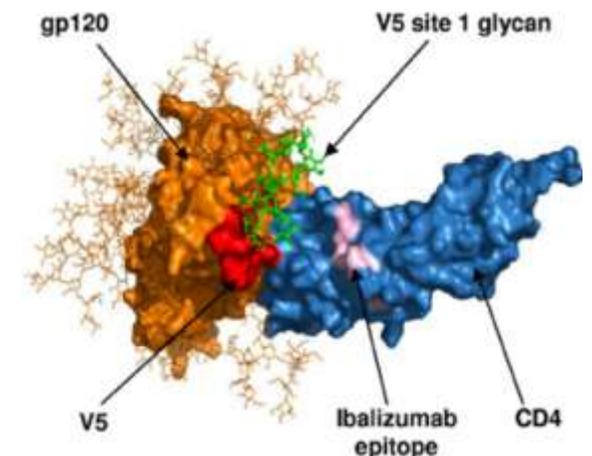
- Phase IIb – dose-response randomised (N=113)

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.

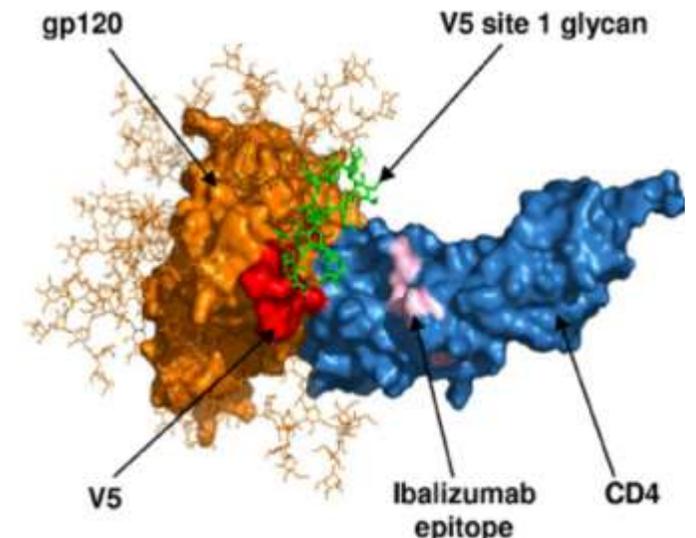
TMB 311

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



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 log₁₀ from Baseline (55% with ≥1 log₁₀; 48% with ≥2 log₁₀)
 - 43% of patients had VL of <50 copies; 50% with <200 copies
- Adverse reactions were mild to moderate



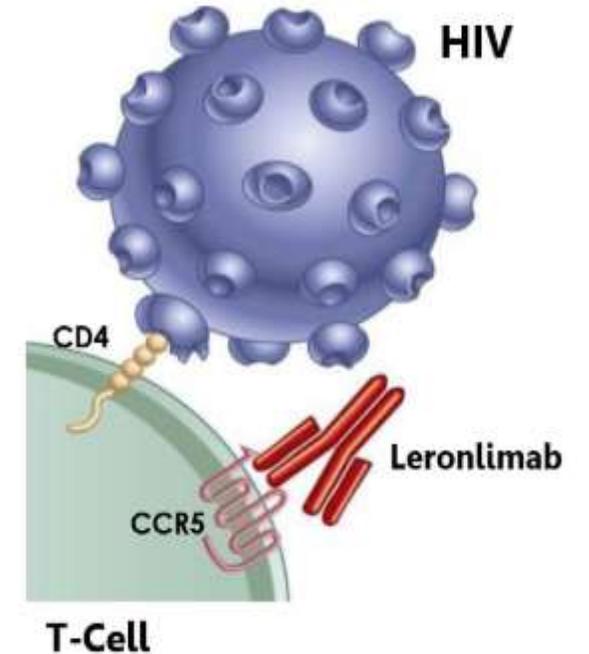
Leronlimab

Leronlimab (PRO140) - CytoDyn

- Humanised IgG4 monoclonal directed against CCR5
- Treatment-experienced HIV
- Weekly, self-administered injection
- >800 patients in Phase 1-3
- 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 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



New Entry Inhibitors and Drug Classes

- **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 and new drugs still needed for treatment**

- Highly resistant virus
- Moderately resistant virus, intolerant of bPIs

- **HIV drug development very much alive !**



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