cART nel prossimo futuro: ruolo degli inibitori dell'entry

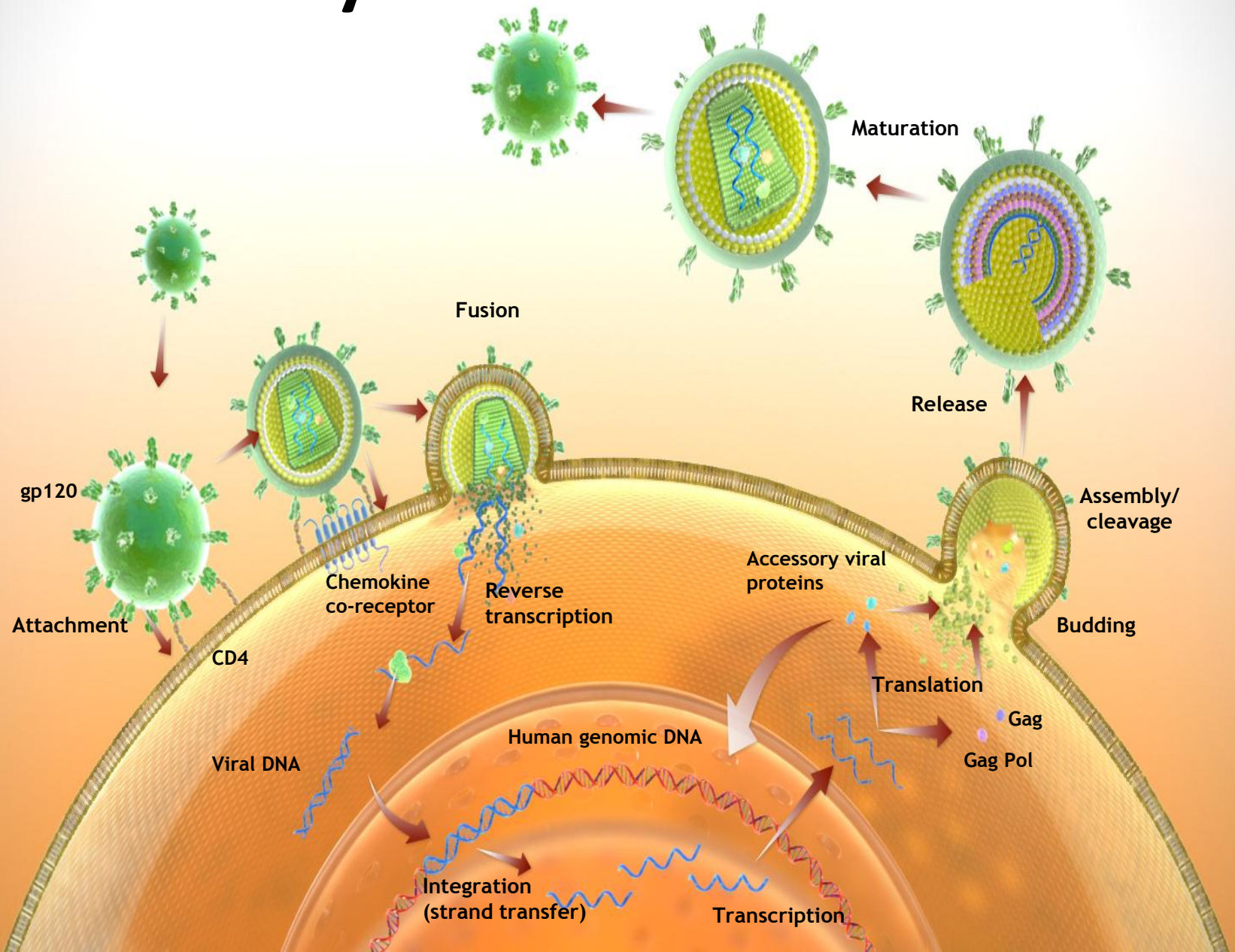
Stefano Rusconi

Divisione Clinicizzata di Malattie Infettive
DIBIC "Luigi Sacco"
Università degli Studi di Milano

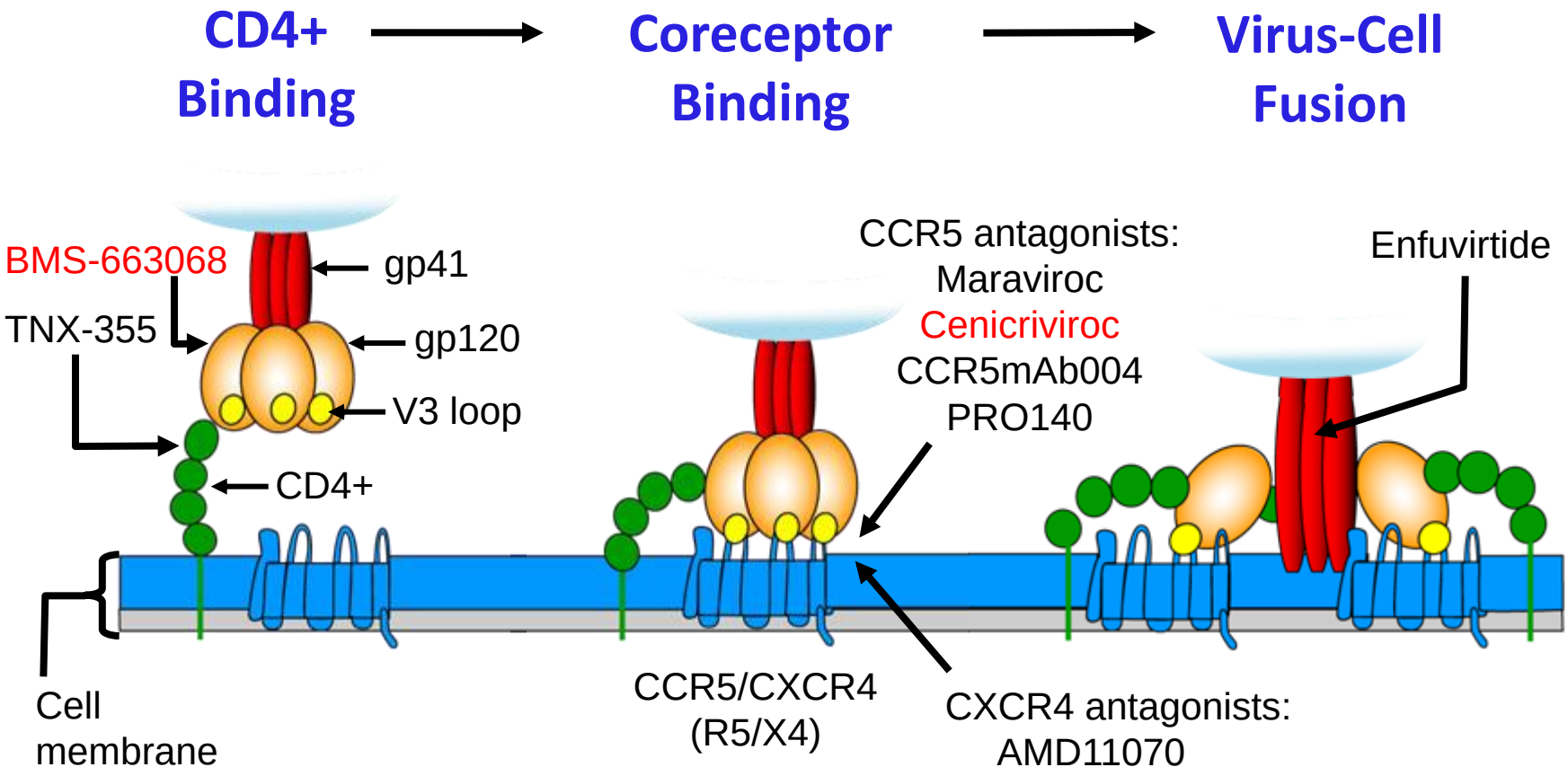
PANDORA 2.0

5 ottobre 2015

HIV-1 Lifecycle

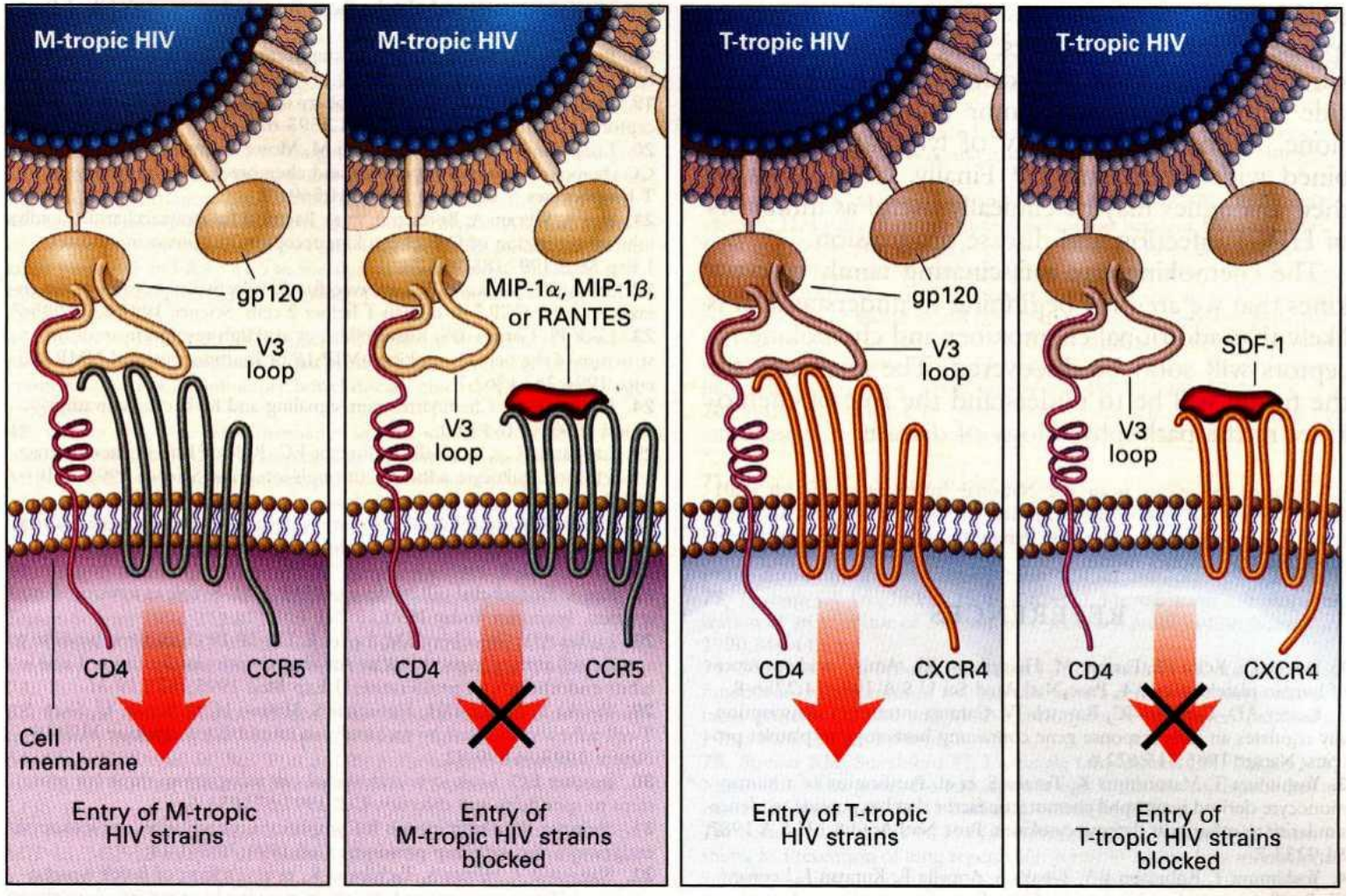


HIV-1 Entry Inhibitors



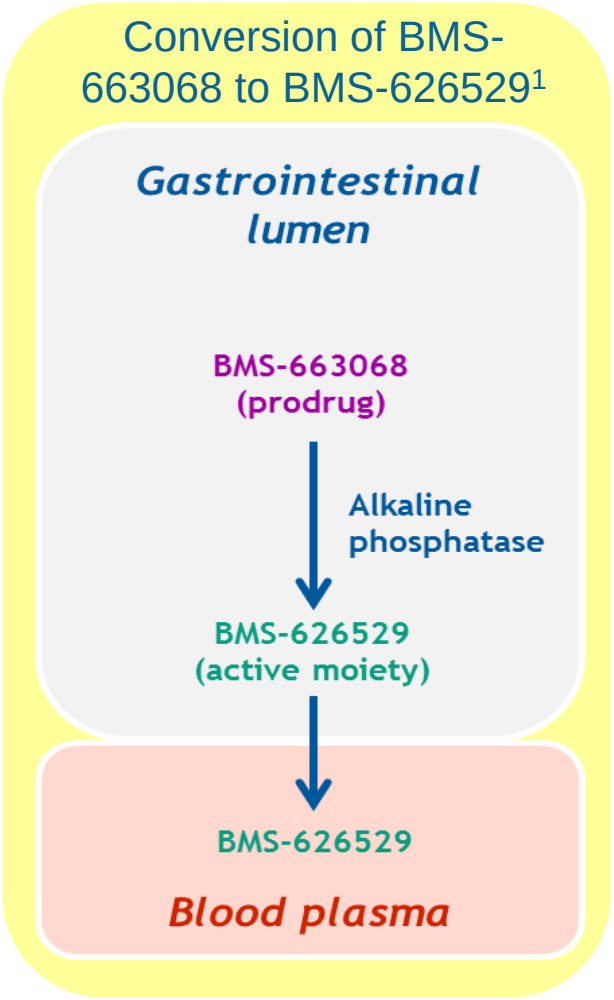
Rusconi, ottobre 2015

Chemokines' Ability to Block HIV Infection



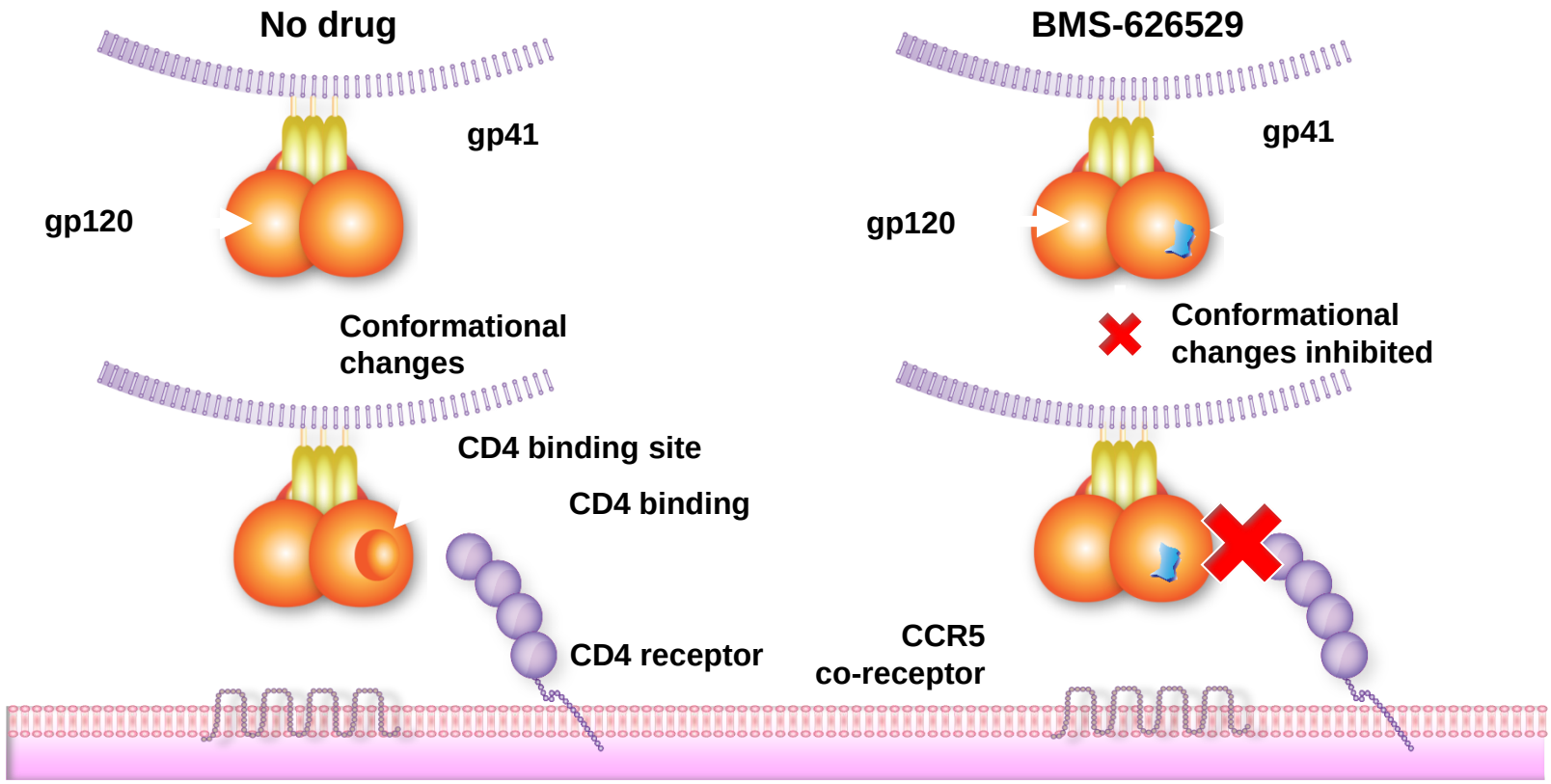
BMS-663068

- Prodrug metabolised to BMS-626529, a first-in-class attachment inhibitor that binds to HIV-1 gp120, preventing initial viral attachment and entry into the host CD4+ T-cell[1,2]
- In vitro activity against HIV-1 viruses, with the exception of subtype AE and Group O[3]
- Active against CCR5-, CXCR4- and dual-tropic (R5X4) strains of HIV-1[3–6]
- Unique resistance profile with no *in vitro* cross-resistance to other classes of antiretrovirals[3,6]
- Phase IIb study: subjects in a 7 day monotherapy substudy showed a mean decline in HIV-1 RNA of 0.7–1.5 $\log_{10}$ copies/mL



1. Brown J et al. J Pharm Sci 2013; 102:142–511; 2. Langley DL et al. Manuscript in development; 3. Nowicka-Sans B et al. AAC 2012; 56:3498–507; 4. Ray N et al. JAIDS 2013; 64:7–15; 5. Zhou N et al. JAC 2014; 69:573–81. 6. Li Z et al. AAC 2013; 57:4172–80.

BMS-626529 Attachment Inhibitor: Proposed Mechanism of Action

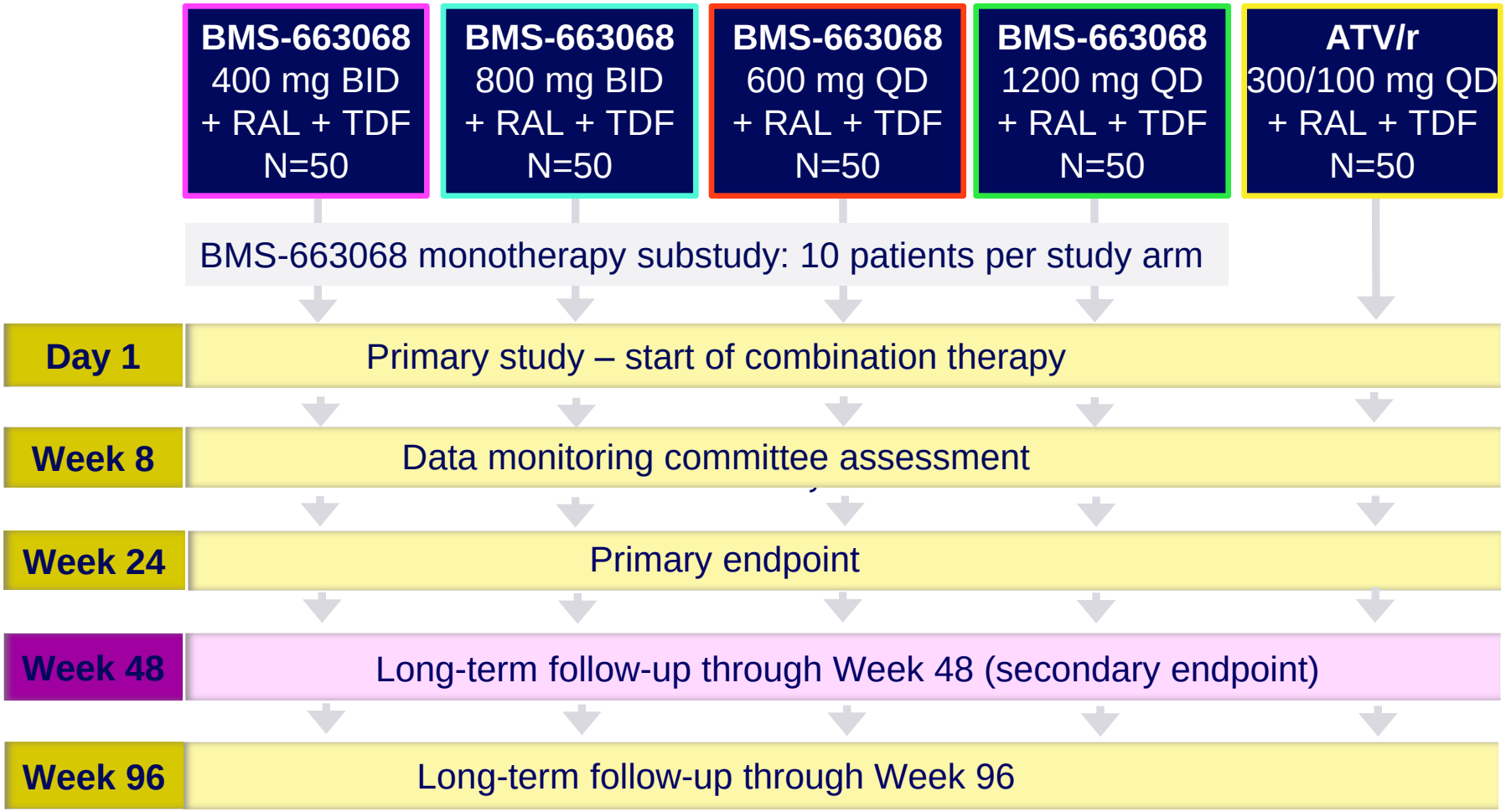


1. Langley DL et al. Manuscript in development.

AI438011: Key entry criteria

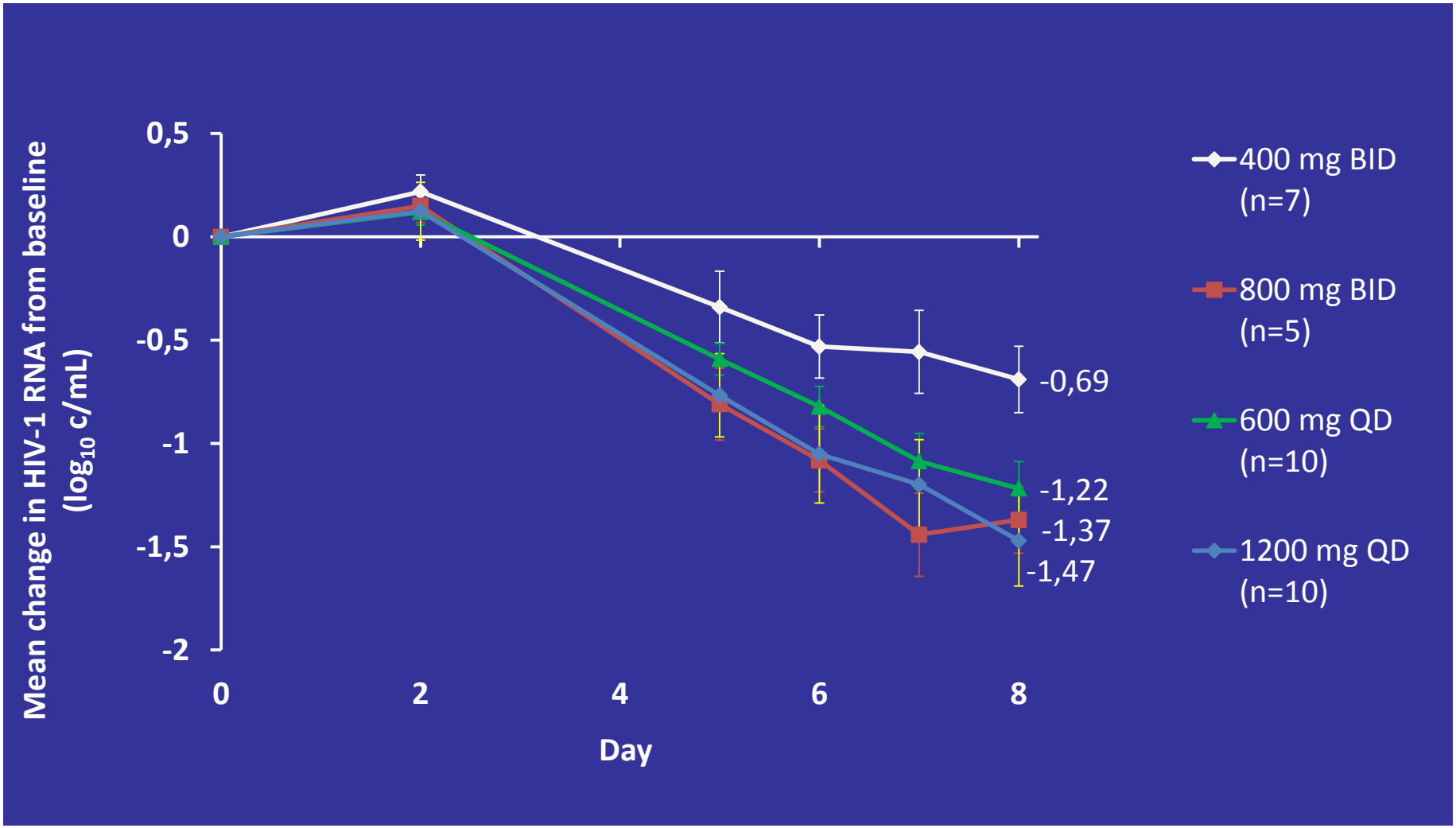
- Antiretroviral treatment-experienced (current or previous exposure to ≥1 antiretroviral for ≥1 week).
- Plasma HIV-1 RNA ≥1000 copies/mL.
- CD4+ T-cell count >50 cells/mm3.
- Susceptibility to RAL, TDF, and ATV.
- BMS-626529 IC50 <100 nM as determined by screening PhenoSense® Entry Assay (Monogram Biosciences - LabCorp).

AI438011 study design



* Blinded to BMS-663068 dose. Subjects and investigators blinded to Week 48

AI438011: BMS-663068 Monotherapy Substudy: Mean Change in HIV-1 RNA from Baseline*



* Error bars represent standard error of the mean.

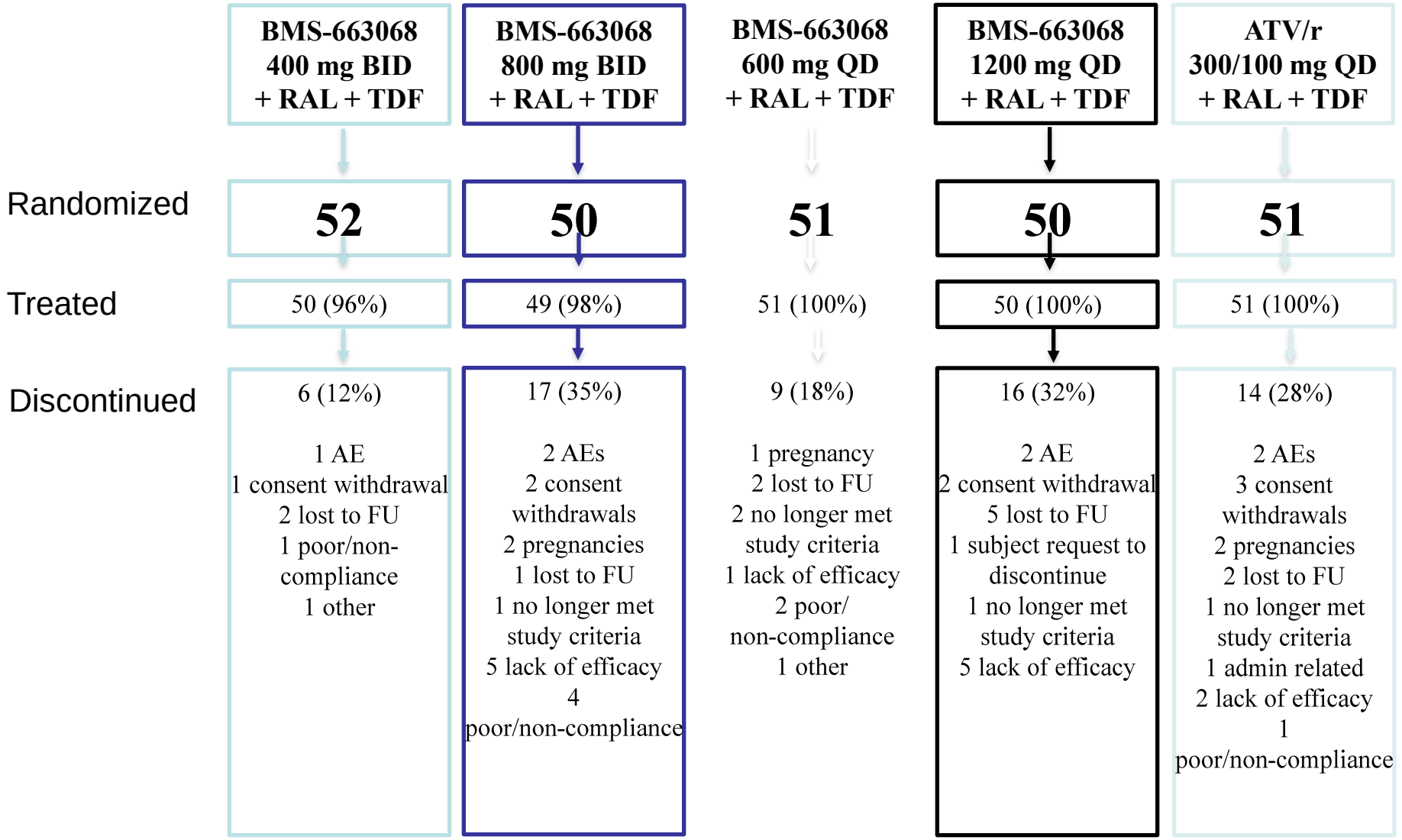
Lalezari J *et al.* CROI 2014 (Abstract 86)

Subject disposition

- 581 subjects were screened, 254 randomized and 251 treated.
- Most common reason for screen failure was a screening plasma HIV-1 RNA <1000 copies/mL (29%).
- The PhenoSense® Entry Assay, only used in Phase II studies, failed to produce a result in 26% of screening samples in this study.
- Of the samples successfully tested in the PhenoSense® Entry Assay, approximately 6% had a BMS-626529 IC_{50} >100 nM at screening.
- Of those receiving treatment, 48/201 (24%) across the BMS-663068 arms and 14/51 (28%) in the ATV/r arm failed to complete 48 weeks' treatment.

Thompson *et al.* CROI 2015 (Abstract 545)

Subject disposition through Week 48*



*581 patients screened.
AE, adverse event ; FU, follow-up.

Thompson *et al.* CROI 2015 (Abstract 545)

Baseline characteristics

					ATV/r +TDF + RAL
	400 mg BID N=50	800 mg BID N=49	600 mg QD N=51	1200 mg QD N=50	300 mg/100 mg QD N=51
Median age, years (range)	39 (22–57)	37 (23–60)	40 (26–58)	40 (20–67)	39 (20–68)
Male, %	62.0%	57.1%	56.9%	68.0%	56.9%
Race, %					
White	40.0%	38.8%	33.3%	32.0%	45.1%
Black/African-American	28.0%	30.6%	31.4%	36.0%	25.5%
Other*	32.0%	30.6%	35.3%	32.0%	29.4%
HIV subtype, %					
B	70.0%	59.2%	68.6%	64.0%	66.7%
C	16.0%	24.5%	21.6%	20.0%	17.6%
Other	14.0%	16.2%	9.9%	16.0%	15.6%
HIV-1 RNA					
Median, $\log_{10}$ c/mL	4.97	5.01	4.88	4.78	4.78
≥100,000 c/mL, %	46.0%	51.0%	45.1%	36.0%	35.3%
CD4+ T-cell count					
Median, cells/μL	214	237	226	224	249
<200 cells/μL, %	38.0%	32.6%	41.2%	42.0%	37.3%
BMS-626529 IC_{50} median, nM	0.68	0.65	0.43	0.82	0.73

•Majority of subjects within the "other" category reported themselves as multiracial. Previously presented by Lalezari *et al.*[8]

•~50% of subjects had ≥1 major protease inhibitor (PI), nucleoside reverse transcriptase inhibitor or non-nucleoside reverse transcriptase inhibitor resistance-associated mutation at baseline (M184V/I, 31%; K103N, 29%; thymidine analogue mutations, 13%; major PI mutations, 2%).

Thompson *et al.* CROI 2015 (Abstract 545)

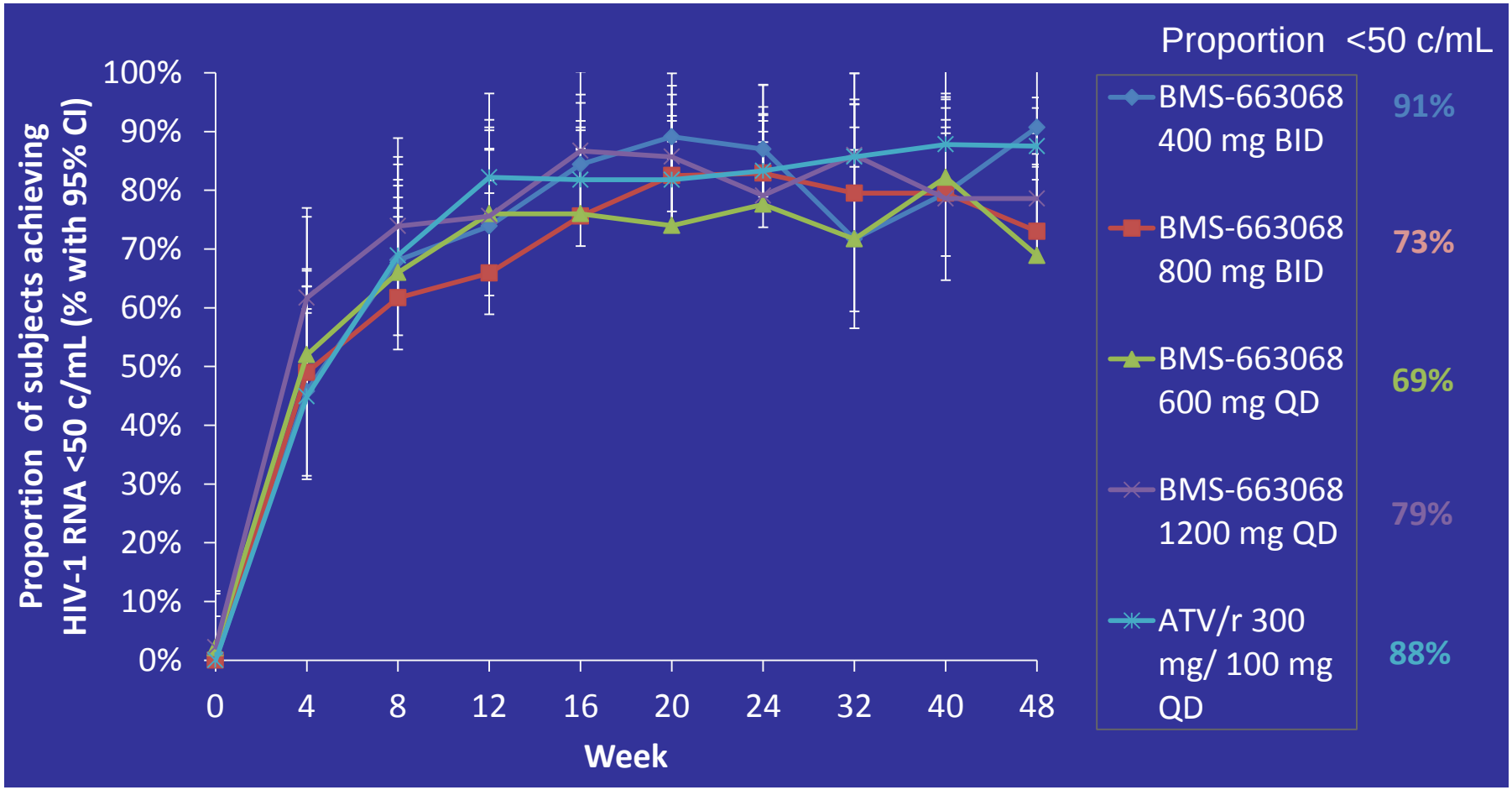
Proportion of subjects achieving HIV-1 RNA <50 or <400 c/mL (Week 48 Snapshot): mITT

	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
Parameter	400 mg BID N=50	800 mg BID N=49	600 mg QD N=51	1200 mg QD N=50	300 mg/100 mg QD N=51
HIV-1 RNA <50 c/ mL, %	82.0%	61.2%	68.6%	68.0%	70.6%
HIV-1 RNA ≥50 c/ mL, %	4.0%	18.4%	19.6%	16.0%	9.8%
Discontinued (lack of efficacy), %	0%	4.1%	0%	2.0%	0%
Discontinued (other reasons), %	6.0%	2.0%	5.9%	12.0%	5.9%
No virologic data at Week 48					
Discontinued due to AE or death, n (%)	1 (2.0%)	2 (4.1%)	0	1 (2.0%)	2 (3.9%)
Discontinued for other reasons, n (%)	2 (4.0%)	5 (10.2%)	3 (5.9%)	0	5 (9.8%)
Missing data during window but on-study, n (%)	1 (2.0%)	0	0	0	0
HIV-1 RNA <400 c/mL, %	86.0%	75.5%	84.3%	80.0%	74.5%

mITT, modified intent-to-treat

Thompson *et al.* CROI 2015 (Abstract 545)

Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 (observed)



CI, confidence interval

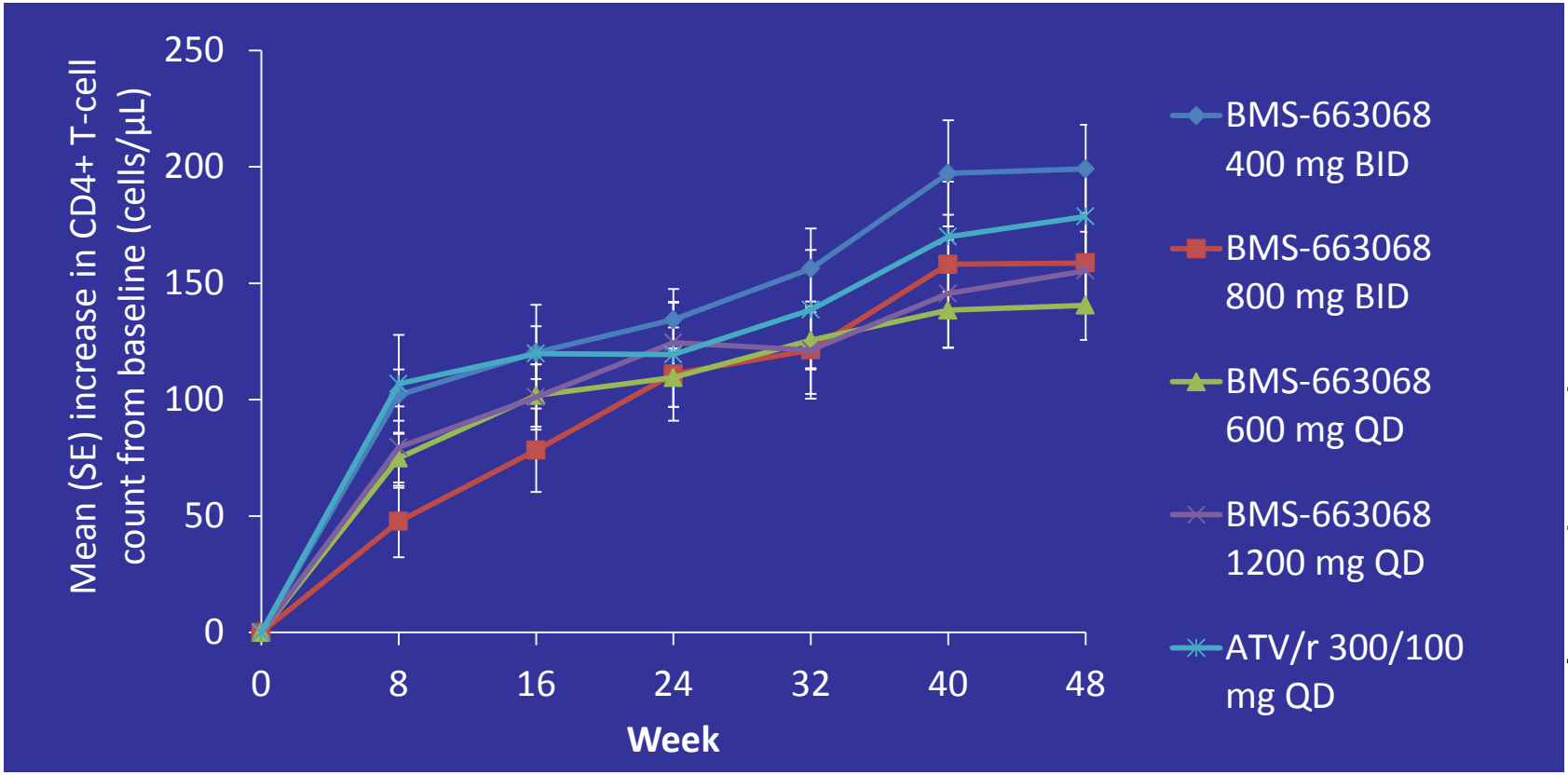
Thompson *et al.* CROI 2015 (Abstract 545)

Proportion of subjects achieving HIV-1 RNA <50 c/mL through Week 48 by baseline BMS-626529 IC_{50} category: observed

Baseline BMS-626529 IC_{50} category, n (%)	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
	400 mg BID N=43	800 mg BID N=39	600 mg QD N=45	1200 mg QD N=42	300 mg/100 mg QD N=41
<0.1 nM	2/2 (100%)	1/1 (100%)	2/3 (67%)	2/2 (100%)	0
≥0.1 nM	39/41 (95%)	29/38 (76%)	33/42 (79%)	32/40 (80%)	36/41 (88%)
<1.0 nM	24/26 (92%)	16/19 (84%)	21/30 (70%)	17/21 (81%)	24/26 (92%)
≥1.0 nM	17/17 (100%)	14/20 (70%)	14/15 (93%)	17/21 (81%)	12/15 (80%)
<10 nM	34/36 (94%)	28/33 (85%)	30/39 (77%)	30/37 (81%)	35/38 (92%)
≥10 nM	7/7 (100%)	2/6 (33%)	5/6 (83%)	4/5 (80%)	1/3 (33%)

Thompson *et al.* CROI 2015 (Abstract 545)

Mean change in CD4+ T-cell counts from baseline through Week 48: observed



Mean increase through Week 48, cells/µL

+199.1

+158.7

+140.5

+155.4

+178.7

SE, Standard error

Thompson *et al.* CROI 2015 (Abstract 545)

Safety endpoints

- A summary of safety data through Week48:
  - AEs leading to discontinuation that were related to study drug(s):
    - BMS-663068 arms: TDF-induced acute renal failure
    - ATV/r arm: abdominal distension, flatulence, nausea, jaundice
    - None were related to BMS-663068.
  - SAEs that were related to study drug(s):*
    - BMS-663068 800 mg BID: TDF-induced acute renal failure
    - ATV/r 300/100 mg QD: Influenza-like symptoms.

* In the BMS-663068 1200 mg QD arm one episode of overdose was listed as related to study medications. This was changed to unrelated after the Week 48 database lock

Thompson *et al.* CROI 2015 (Abstract 545)

Safety summary*

Parameter, n (%)	BMS-663068 + TDF + RAL 400 mg BID N=50	BMS-663068 + TDF + RAL 800 mg BID N=49	BMS-663068 + TDF + RAL 600 mg QD N=51	BMS-663068 + TDF + RAL 1200 mg QD N=50	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
SAEs†	3 (6.0%)	5 (10.2%)	4 (7.8%)	3 (6.0%)	5 (9.8%)
AEs leading to discontinuation‡	1 (2.0%)	2 (4.1%)	0	2 (4.0%)	2 (3.9%)
Grade 2–4-related clinical AEs					
Total subjects with an event	4 (8.0%)	4 (8.2%)	3 (5.9%)	6 (12.0%)	15 (29.4%)
Present in ≥2 subjects					
Abdominal pain	0	0	0	1(2.0%)	2 (3.9%)
Nausea	0	0	0	0	2 (3.9%)
Hyperbilirubinemia	0	0	0	0	4 (7.8)
Jaundice	0	0	0	0	2 (3.9%)
Blood bilirubin increased	0	0	0	0	3 (5.9)
Headache	0	1(2.0%)	0	0	2 (3.9%)

*As reported by investigators

† Anal abscess, herpes encephalitis, overdose (3), extrapulmonary tuberculosis (2), herpes zoster, abdominal pain, myalgia, spontaneous abortion, acute renal failure, cellulitis (2), lymphangitis, chronic cholecystitis, back pain, influenza, pneumonia, pyelonephritis, diarrhea, cholelithiasis, migraine

‡ Illegal substance use; extrapulmonary tuberculosis (3); acute renal failure; abdominal distension, flatulence, nausea; jaundice

AE, adverse event; SAE, serious AE

Grade 3–4 laboratory abnormalities (≥2 subjects)

Parameter, n (%)	BMS-663068 + TDF + RAL 400 mg BID N=50*	BMS-663068 + TDF + RAL 800 mg BID N=49	BMS-663068 + TDF + RAL 600 mg QD N=51*	BMS-663068 + TDF + RAL 1200 mg QD N=50*	ATV/r + TDF + RAL 300 mg/100 mg QD N=51*
Neutrophils (absolute)	1 (2.1%)	1 (2.0%)	2 (3.9%)	1 (2.1%)	1 (2.0%)
Alkaline phosphatase	0	0	0	1 (2.1%)	0
Alanine aminotransferase	0	0	0	2 (4.2%)	1 (2.0%)
Aspartate aminotransferase	1 (2.1%)	1 (2.0%)	0	2 (4.2%)	2 (4.0%)
Total bilirubin	0	0	0	0	29 (58.0%)
Creatine kinase	0	1 (2.0%)	1 (2.0%)	2 (4.2%)	2 (4.0%)
Glucose fasting serum	0	1 (2.0%)	2 (3.9%)	0	0
Uric acid	0	0	0	2 (4.2%)	0

* Data not available for all subjects

Thompson *et al.* CROI 2015 (Abstract 545)

ID Week 2014
(Presentation 540)

HIV-1 Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Week 24 Subgroup Analysis

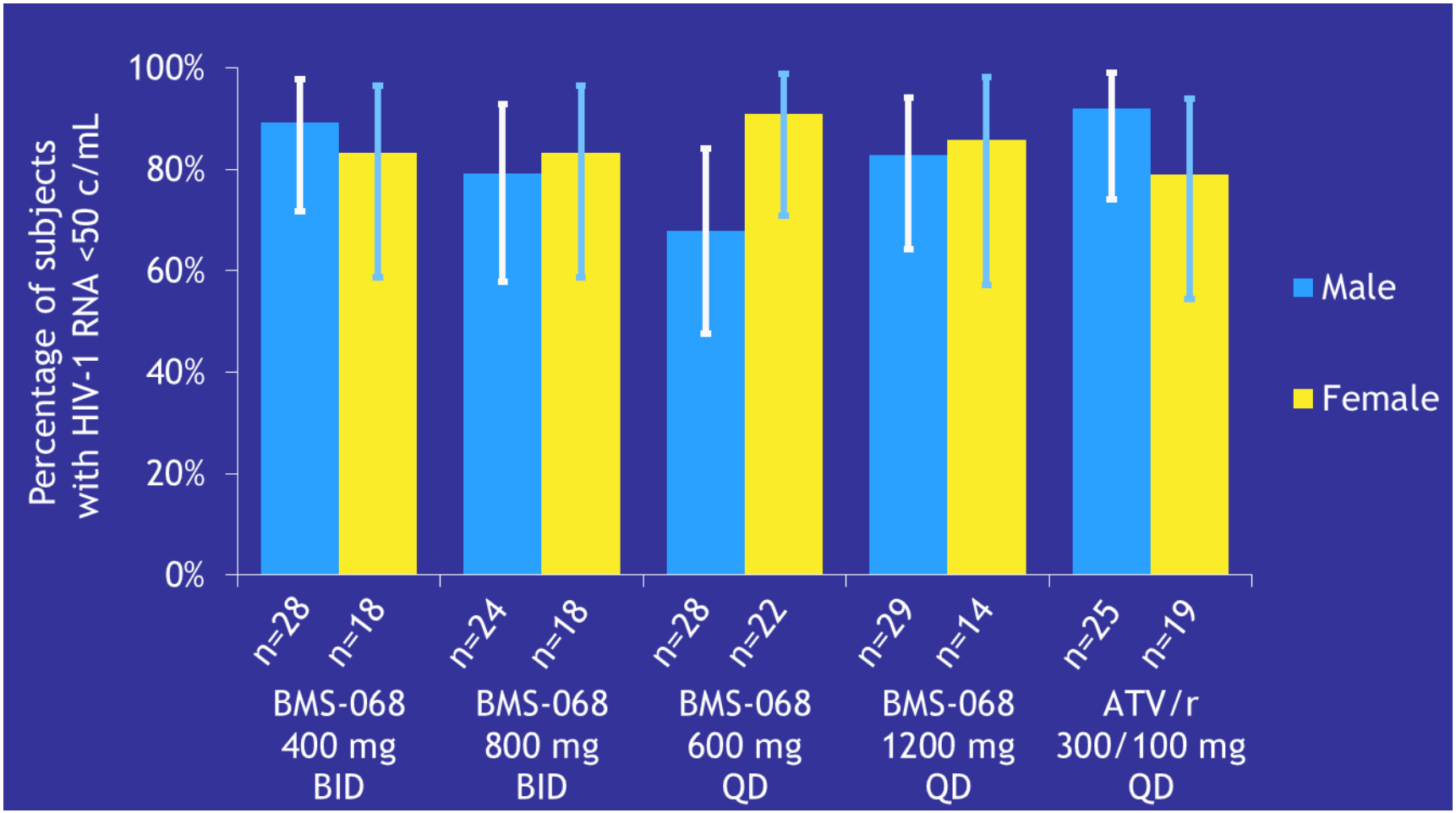
C Brinson,[1] J Lalezari,[2] GH Latiff,[3] M Thompson,[4] J Echevarría,[5]

S Treviño-Pérez,[6] D Stock,[7] SR Joshi,[7] GJ Hanna,[8] M Lataillade[7]

for the AI438011 study team

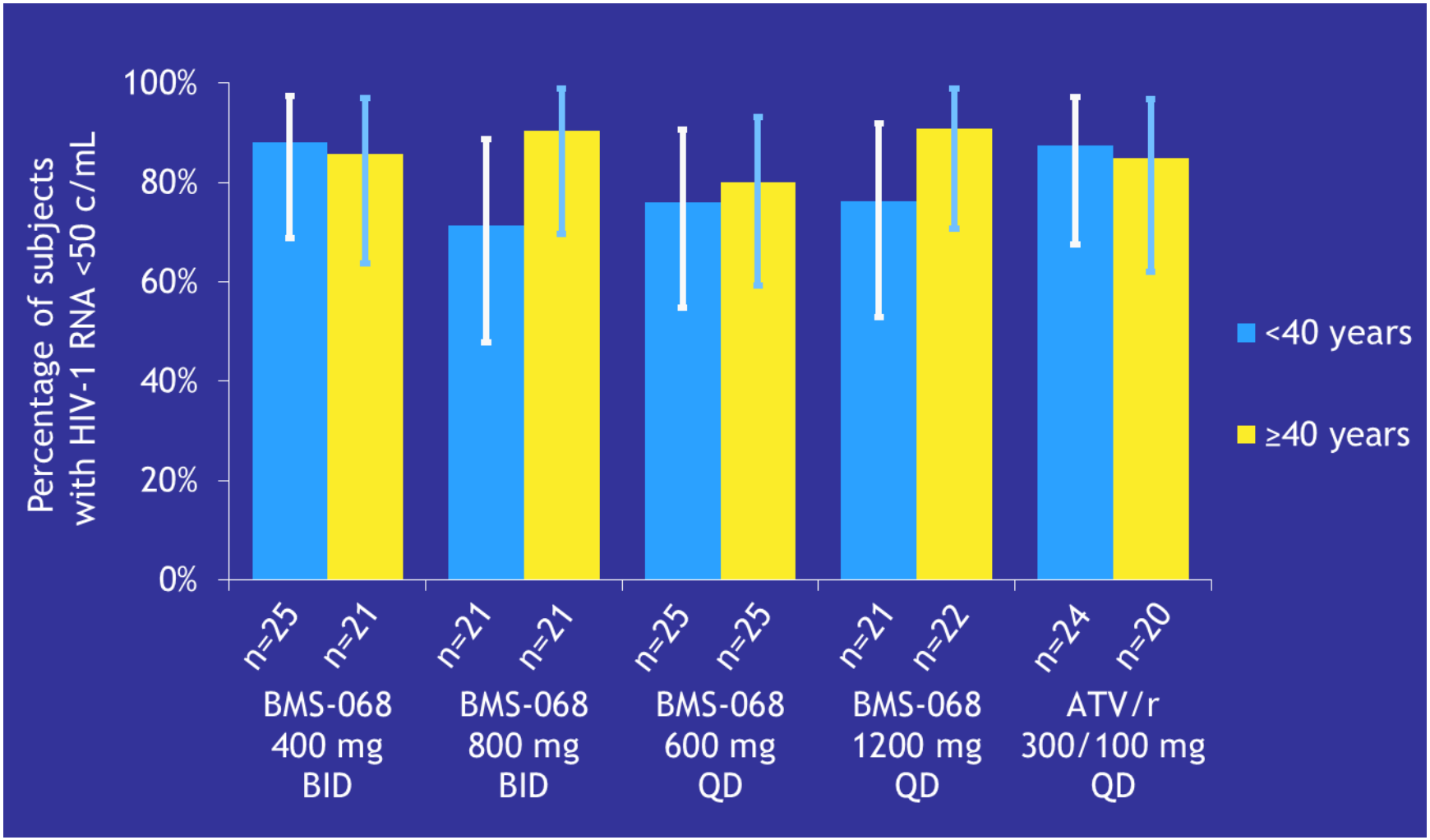
1. Central Texas Clinical Research, Austin, TX, USA; 2. Quest Clinical Research, San Francisco, CA, US; 3. Maxwell Clinic, Durban, South Africa; 4. AIDS Research Consortium of Atlanta, Atlanta, USA; 5. Hospital Nacional Cayetano Heredia, Lima, Peru; 6. Mexico Centre for Clinical Research, Mexico City, Mexico; 7. Bristol-Myers Squibb, Wallingford, CT, USA; 8. Bristol-Myers Squibb, Princeton, NJ, USA.

AI438011: HIV-1 RNA <50 c/mL by Gender: Observed



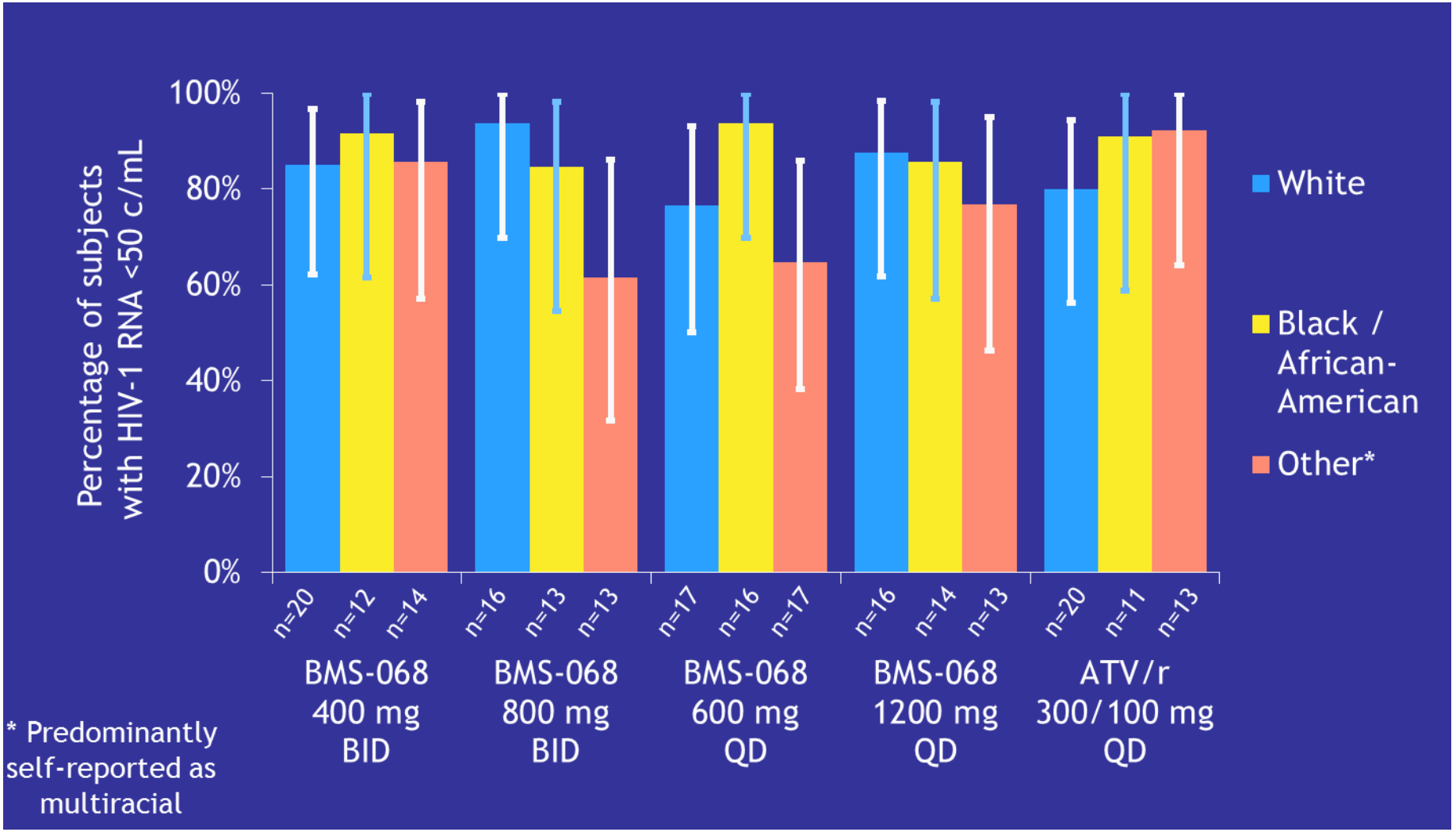
BMS-068, BMS-663068. Observed population: subjects receiving ≥1 dose of study drug and with plasma HIV-1 RNA data within the Week 24 window.
Errors bars show 95% confidence intervals.

AI438011: HIV-1 RNA <50 c/mL by Age: Observed



BMS-068, BMS-663068. Observed population: subjects receiving ≥1 dose of study drug and with plasma HIV-1 RNA data within the Week 24 window.
Errors bars show 95% confidence intervals.

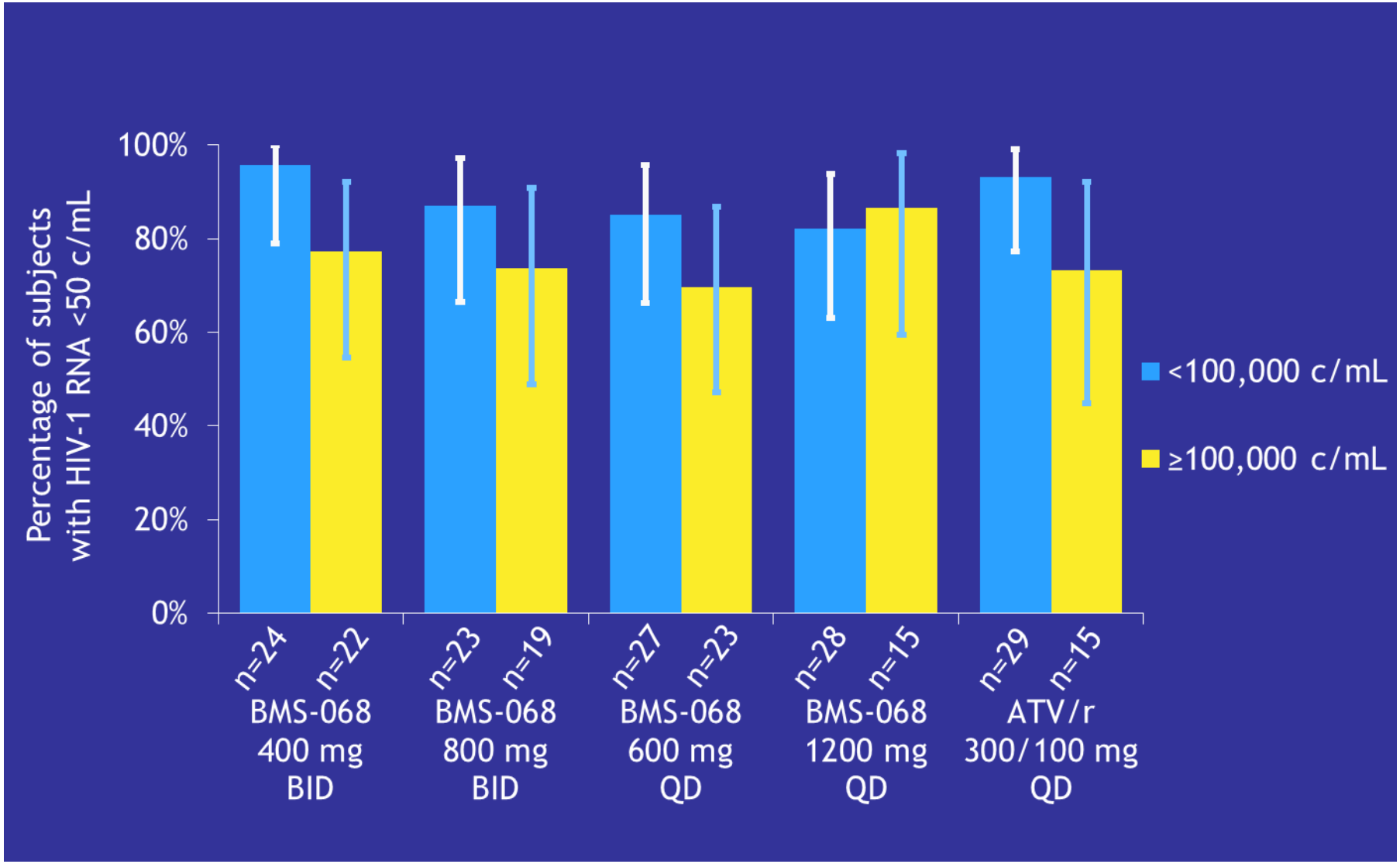
AI438011: HIV-1 RNA <50 c/mL by Race: Observed



BMS-068, BMS-663068. Observed population: subjects receiving ≥1 dose of study drug and with plasma HIV-1 RNA data within the Week 24 window.
Errors bars show 95% confidence intervals.

Brinson *et al.* ID Week 2014 (Abstract 540)

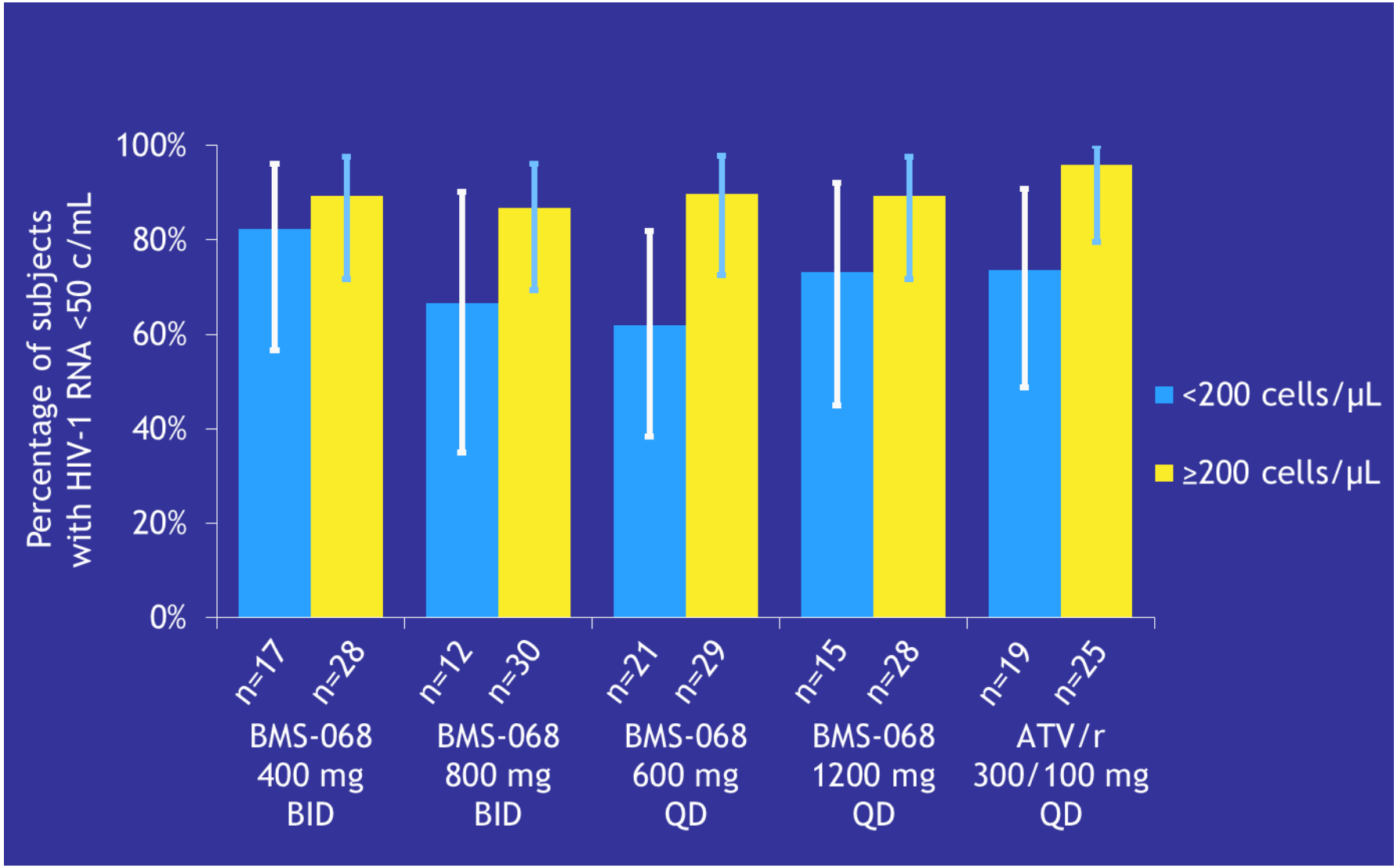
AI438011: HIV-1 RNA <50 c/mL by Baseline Viral Load: Observed



BMS-068, BMS-663068. Observed population: subjects receiving ≥1 dose of study drug and with plasma HIV-1 RNA data within the Week 24 window.
Errors bars show 95% confidence intervals.

Brinson *et al.* ID Week 2014 (Abstract 540)

AI438011: HIV-1 RNA <50 c/mL by Baseline CD4+ T-cell Count: Observed



BMS-068, BMS-663068. Observed population: subjects receiving ≥1 dose of study drug and with plasma HIV-1 RNA data within the Week 24 window.
Errors bars show 95% confidence intervals.

BMS-626529:
No Cross-Resistance with other HIV Entry Inhibitors

- CD4 dependent activity
  - BMS-626529 retained activity against CD4-independent viruses
  - All site-directed BMS-626529-resistant viruses tested were CD4-dependent
  - Clinical envelopes from the monotherapy study that exhibited decreased susceptibility to BMS-626529 were CD4-dependent
  - Clinical use of BMS-663068 is unlikely to promote resistance via generation of CD4-independent viruses

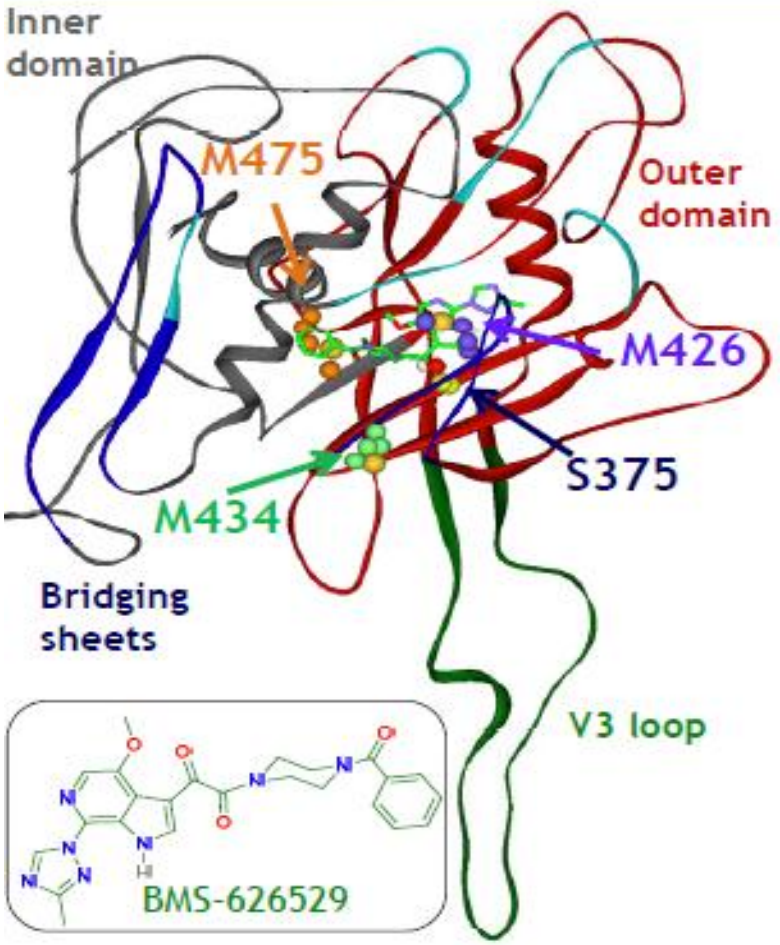
- Cross Resistance
  - Ibalizumab and ENF-resistant viruses retained susceptibility to BMS-626529
  - Although some MVC-resistant envelopes were resistant to BMS-626529, resistance to BMS-626529 is not directly linked to MVC resistance
  - All BMS-626529-resistant envelopes were susceptible to all other entry inhibitors

Li et al. XIX IAC, 2012. Poster TUPE015

Genotypic and Phenotypic Correlates of Virologic Response to BMS-626529[1,2]

- Resistance to BMS-626529 could be due to:
  - Decrease binding affinity to compound
    - M426L, M475I, S375M, M434I map at or around modeled binding site
  - Mutations that can stabilize CD4-bound conformation
    - M426L, M434I are bridging β-sheet that is stabilized in CD4 bound conformation
- Intra-subject variability of functional clones exhibited a broad spectrum of susceptibility to BMS-626529

Model of BMS-626529 bound to gp120 complex



1. Zhou et al. Glasgow, 2012. Poster P207
2. Zhou et al. International Workshop on HIV and Hepatitis Virus Drug Resistance, 2012. Poster 6

Clinical Resistance Summary: 8-Day Monotherapy in HIV-1-Infected Subjects (POC Study – AI438006)

- In a previous proof-of-concept study, HIV-1-infected subjects received BMS-663068 monotherapy for 8 days[1]
  - 6/48 subjects completing the study had a maximal decline in plasma HIV-1 RNA of <1.0 $\log_{10}$ c/mL[1,2]
  - <1.0 $\log_{10}$ c/mL decline in HIV-1 RNA was associated with:
    - an elevated BMS-626529 IC_{50} (>100 nM) at baseline[1,2]
    - the gp120 M426L substitution[2,3]
  - However, 2 subjects with the **M426L** substitution at baseline had a decline in HIV-1 RNA of >1 $\log_{10}$ c/mL following 8 days of monotherapy[3]
- Additional gp120 substitutions associated with reduced susceptibility to BMS-626529 included **S375M/T/H/N, M434I and M475I[3]**

1. Nettles R *et al*. J Infect Dis 2013; 206:1002–11. 2. Ray N *et al*. J Acquir Immune Defic Syndr 2013; 64:7–15. 3. Zhou *et al*. J Antimicrob Chemother 2014; 69:573-81. 4. Langley DL *et al*. CROI 2013. Poster 542.
POC, proof-of-concept.

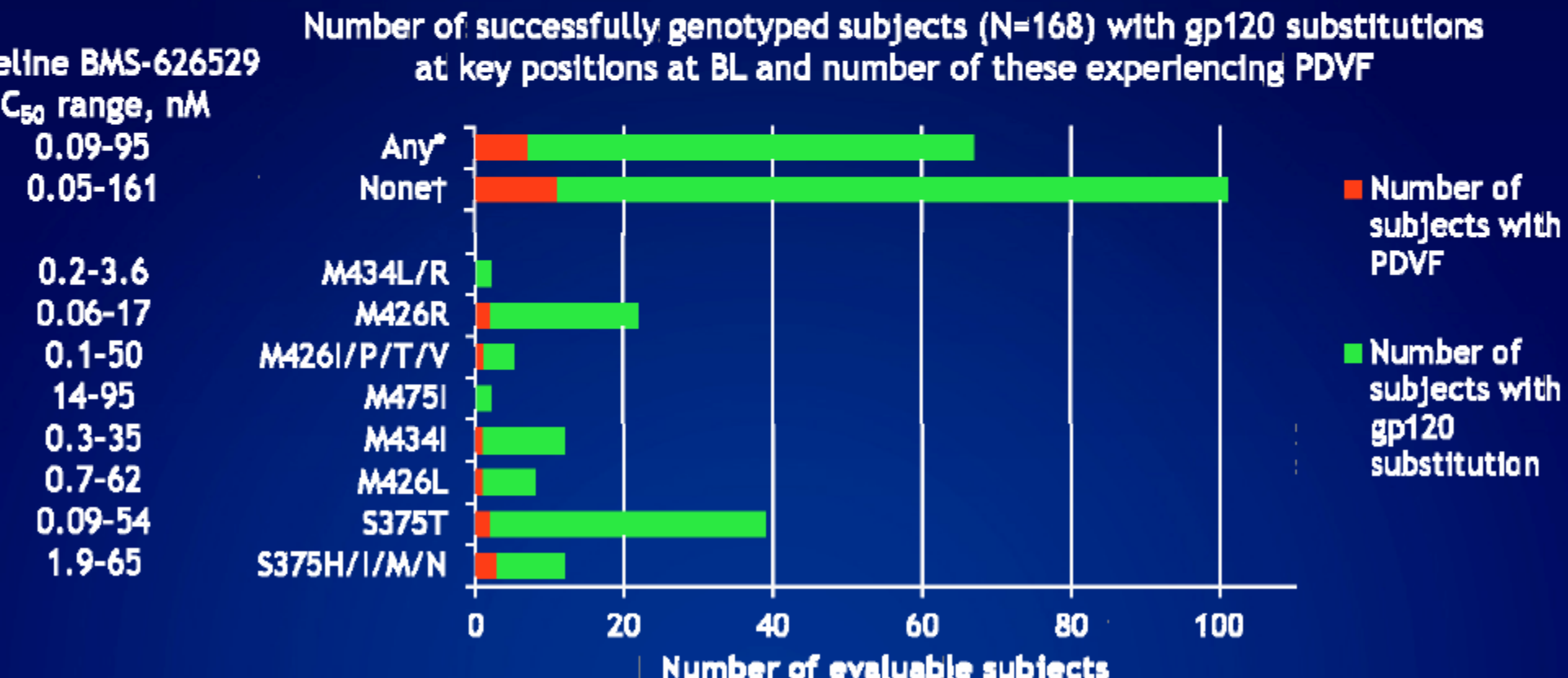
International Workshop on
Retroviral Drug Resistance 2014
(Abstract 21)

HIV-1 Attachment Inhibitor Prodrug BMS-663068 in Antiretroviral-Experienced Subjects: Primary Week 24 Analysis of Emergent Drug Resistance

Lataillade, N Zhou, SR Joshi, S Lee, D Stock, GJ Hanna and M Krystal
Bristol-Myers Squibb, Wallingford, CT and Princeton, NJ, USA

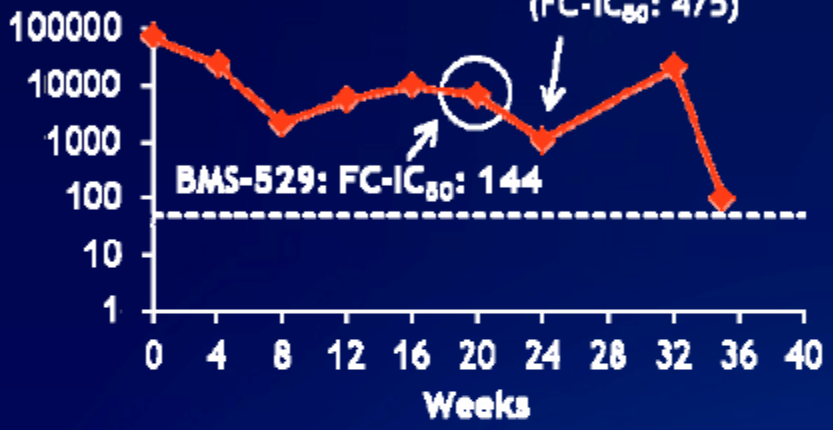
Association of Baseline gp120 Substitutions with Virologic Response

- Subjects were screened at baseline for substitutions in gp120 at key amino acid positions associated with reduced susceptibility to BMS-626529 (375, 426, 434, 475)[1,2]
- For subjects with BMS-626529 IC_{50} <100 nM, the presence of key gp120 substitutions at baseline (at positions 375, 426, 434 and 475) were not correlated with PDVF

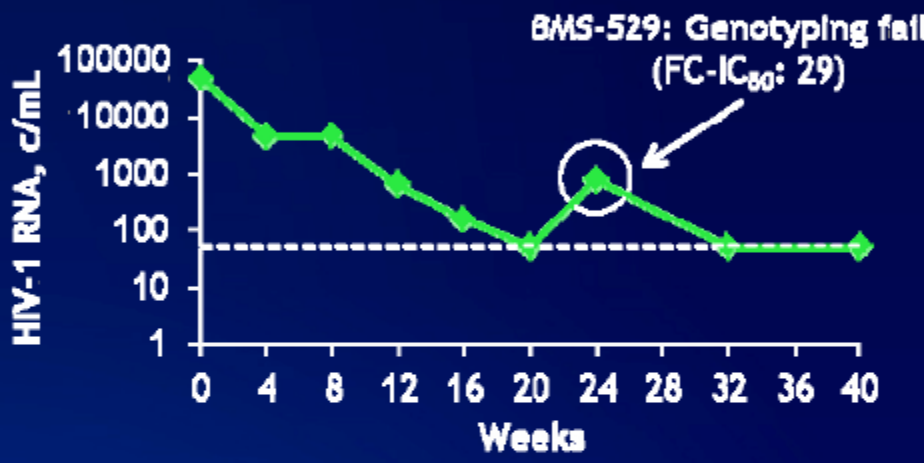


Subjects With Virologic Failure and >3-fold Change in BMS-626529 FC-IC_{50} w/o RAL Resistance

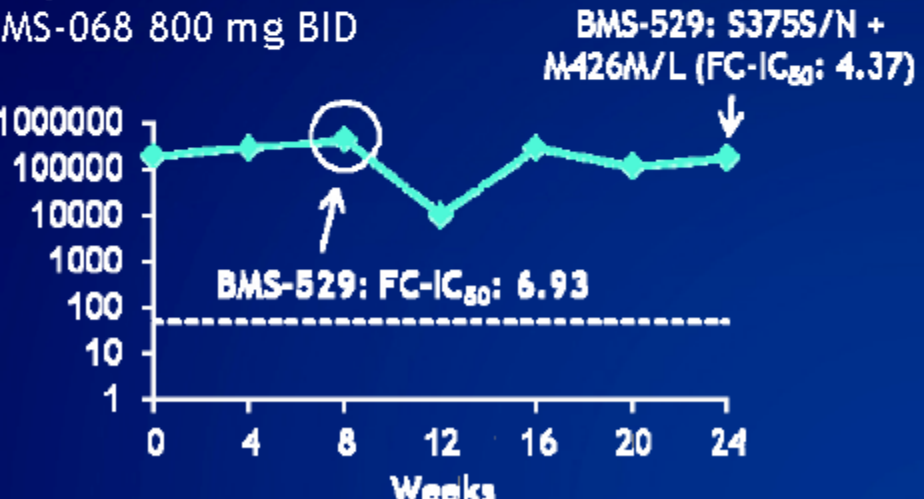
ubject 2:
MS-068 600 mg QD



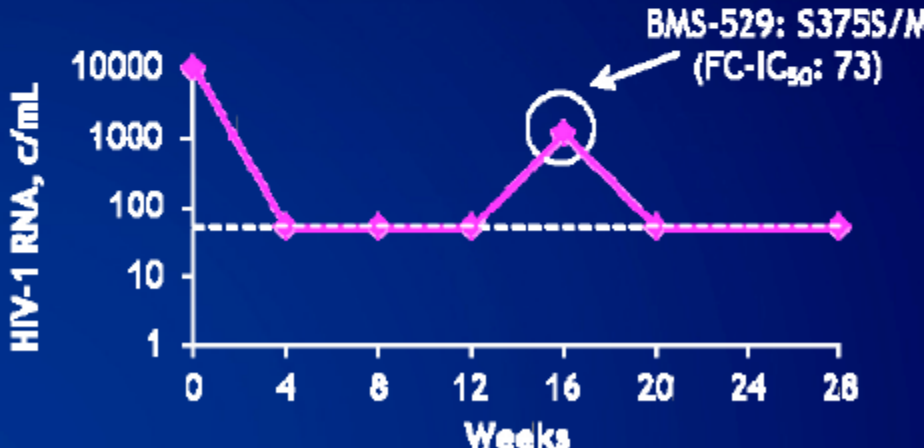
Subject 5:
BMS-068 1200 mg QD



ubject 6:
MS-068 800 mg BID

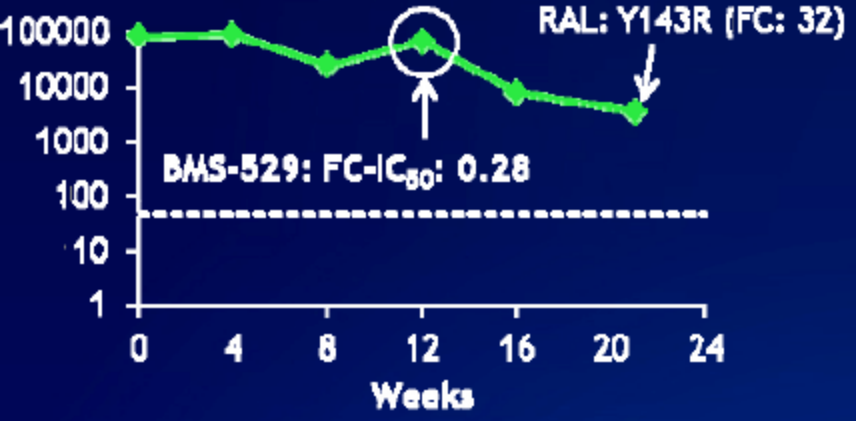


Subject 8 (M426L at BL):
BMS-068 600 mg QD

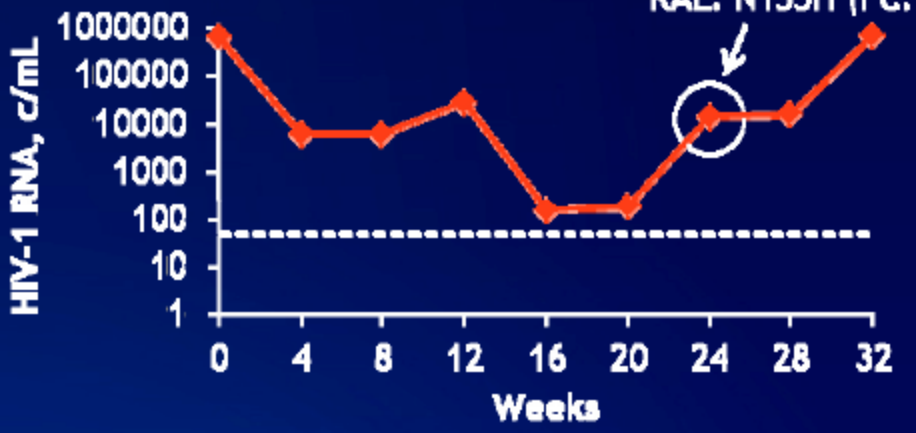


Subjects With Virologic Failure and >3-fold Change in BMS-626529 FC-IC_{50} + RAL Resistance

ubject 1:
MS-068 1200 mg QD



Subject 3 (M434I at BL):
BMS-068 600 mg QD



ubject 4:
MS-068 800 mg BID

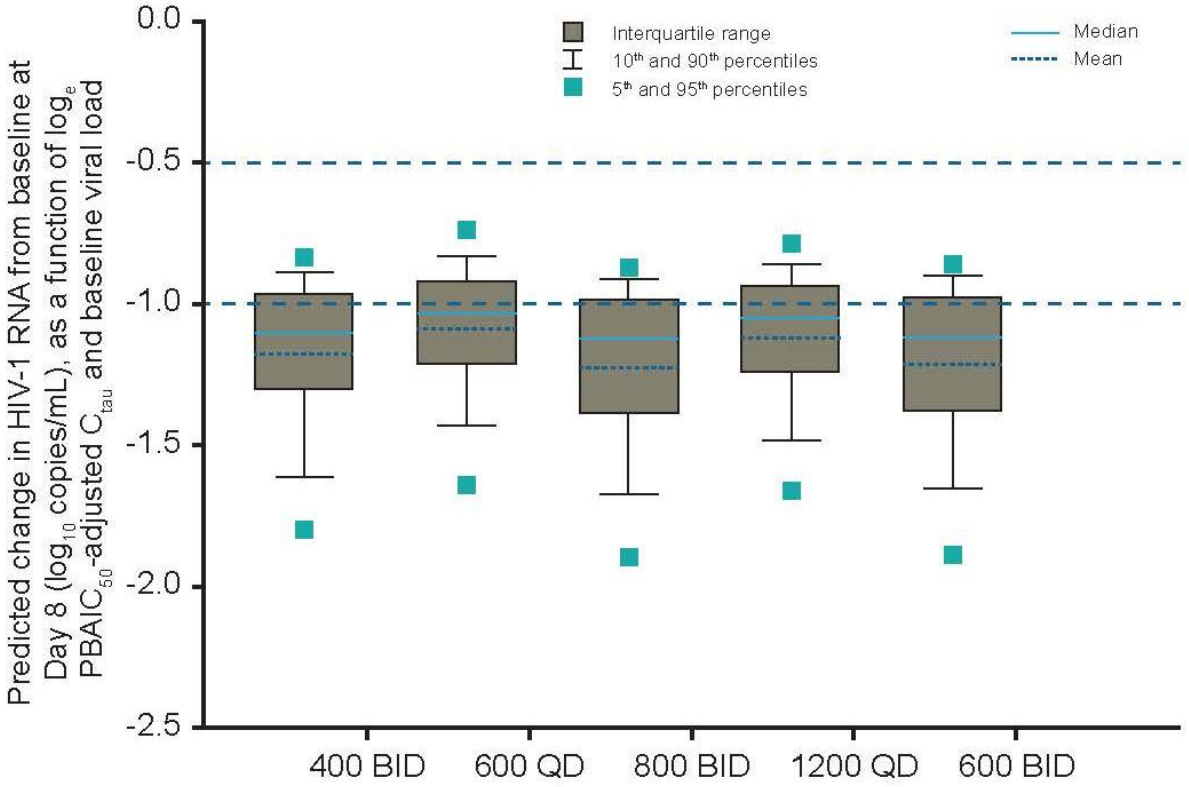
Subject 7 (S375M at BL):
BMS-068 1200 mg QD

Phase III dose: 600 mg BID

- Phase III dose of 600 mg BID was selected based on the following:
  - 600 mg BID dose had a similar or slightly higher probability of achieving a decline in HIV-1 RNA of >1 $\log_{10}$ copies/mL following 7 days of BMS-663068 monotherapy, when compared with the 800 mg BID and 1200 mg QD doses, respectively
    - A total daily dose of 1200 mg (1200 mg QD) showed comparable efficacy and safety to a total daily dose of 1600 mg (800 mg BID) when administered as cART for 24/48 weeks[1]
    - 400 mg BID dose excluded as an HIV-1 RNA decline of >1.0 $\log_{10}$ c/mL was not achieved after 7 days of monotherapy [1]

1 Lalezari J *et al*. CROI 2014: Oral Abstract 86; Savant Landry et al; CROI2015 Abstract 509

Model-based simulation of proposed BMS-663068 doses

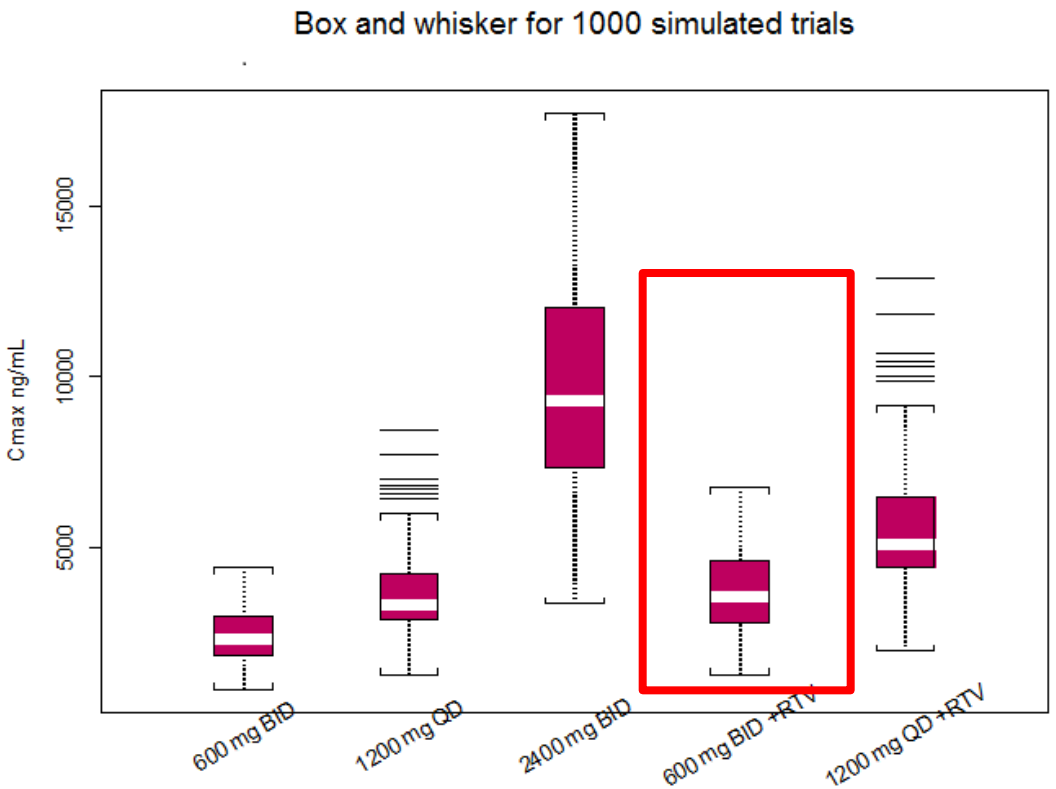


	400 BID	600 QD	800 BID	1200 QD	600 BID
Probability of >0.5 log_{10} c/mL decline, %	100	99.5	99.9	99.8	100
Probability of >1 log_{10} c/mL decline, %	68.0	57.4	72.6	60.8	71.1

Savant Landry et al; CROI2015 Abstract 509

Phase 3 Doses- BMS-663068 in combination with Boosted Protease Inhibitor: Cmax Simulation and Assessment of QTc risk

600mg BID with and without boosted protease inhibitor provides lower risk of Cmax approaching threshold where QTc risk may exist



Estimated ΔΔQTc at median Cmax	1.70	3.20	8.93	2.98	5.42
Upper confidence interval	4.15	5.61	12.15	5.58	7.94

Landry et al. IWCPHIV 2015

@ CROI 2013

Week 24 Primary Analysis of Cenicriviroc vs Efavirenz, in Combination with FTC/TDF, in Treatment-naïve HIV-1 Infected Adults with CCR5-tropic virus (Study 652-2-202; NCT01338883)

Joseph Gathe[1], Jerry Cade[2], Edwin DeJesus[3], Judith Feinberg[4], Jay Lalezari[5], Javier O. Morales-Ramírez[6], Anthony Scarsella[7], Michael Saag[8], Melanie Thompson[9], Eric Lefebvre[10]

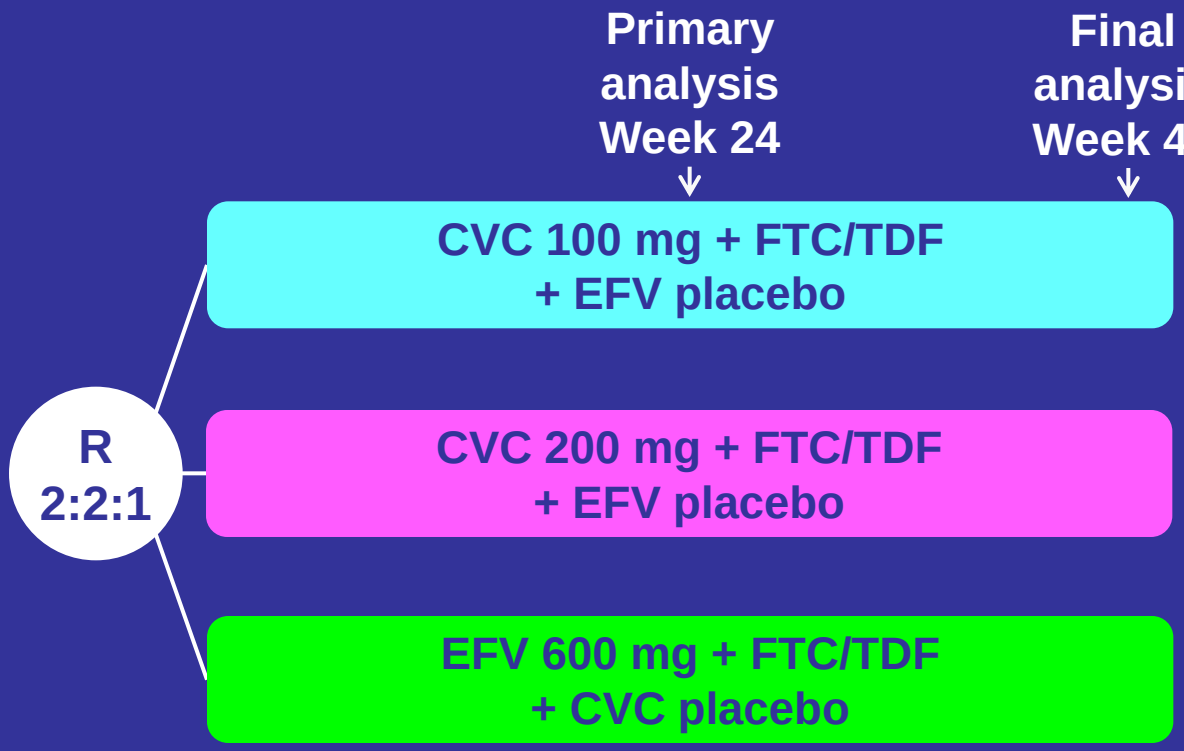
[1]Therapeutic Concepts, Houston, TX, US; [2]Nevada AIDS Res Ed Society, Las Vegas, NV, US; [3]Orlando Immunology Ctr, Orlando, FL, US; [4]Univ Cincinnati, Cincinnati, OH, US; [5]Quest Clin Res, San Francisco, CA, US; [6]Clin Res P.R., Inc., San Juan, Puerto Rico; [7]Pacific Oaks Med Grp, Beverly Hills, CA, US; [8]Univ Alabama at Birmingham, Birmingham, AL, US; [9]AIDS Res Consortium of Atlanta, Atlanta, GA, US; [10]Tobira Therapeutics Inc., San Francisco, CA, US

Cenicriviroc (CVC) Characteristics

- Oral CCR5/CCR2 receptor antagonist
  - In vitro protein-adjusted IC_{90} against HIV clinical isolates = 0.25 nM
  - Inhibits binding of MCP-1 to CCR2 at 5.9 nM (IC_{50})
- Once-daily dosing
  - Long plasma $t_{½}$ = 30–40 hours
- Low drug–drug interaction potential
  - Metabolized via CYP3A4 and CYP2C8
  - Not a known CYP inducer or inhibitor
- Additive to synergistic antiviral activity in vitro with
  - NRTIs, NNRTIs, PIs and INSTIs

Design: Phase 2b, Randomized, Double-Blind, Double-Dummy, Dose-Finding Study

Subjects (N=143)
- Tx-naïve adults
- CCR5-tropic only HIV (genotype and phenotype)
- HIV RNA ≥1000 copies/mL
- CD4+ cell count ≥200 c/mm^3
- No primary NRTI/NNRTI resistance
- Stratified by baseline viral load (< or ≥100 000 copies/mL)



Primary endpoint: Subjects (%) with HIV-1 RNA <50 copies/mL at Week 24 in the ITT population (FDA Snapshot algorithm)

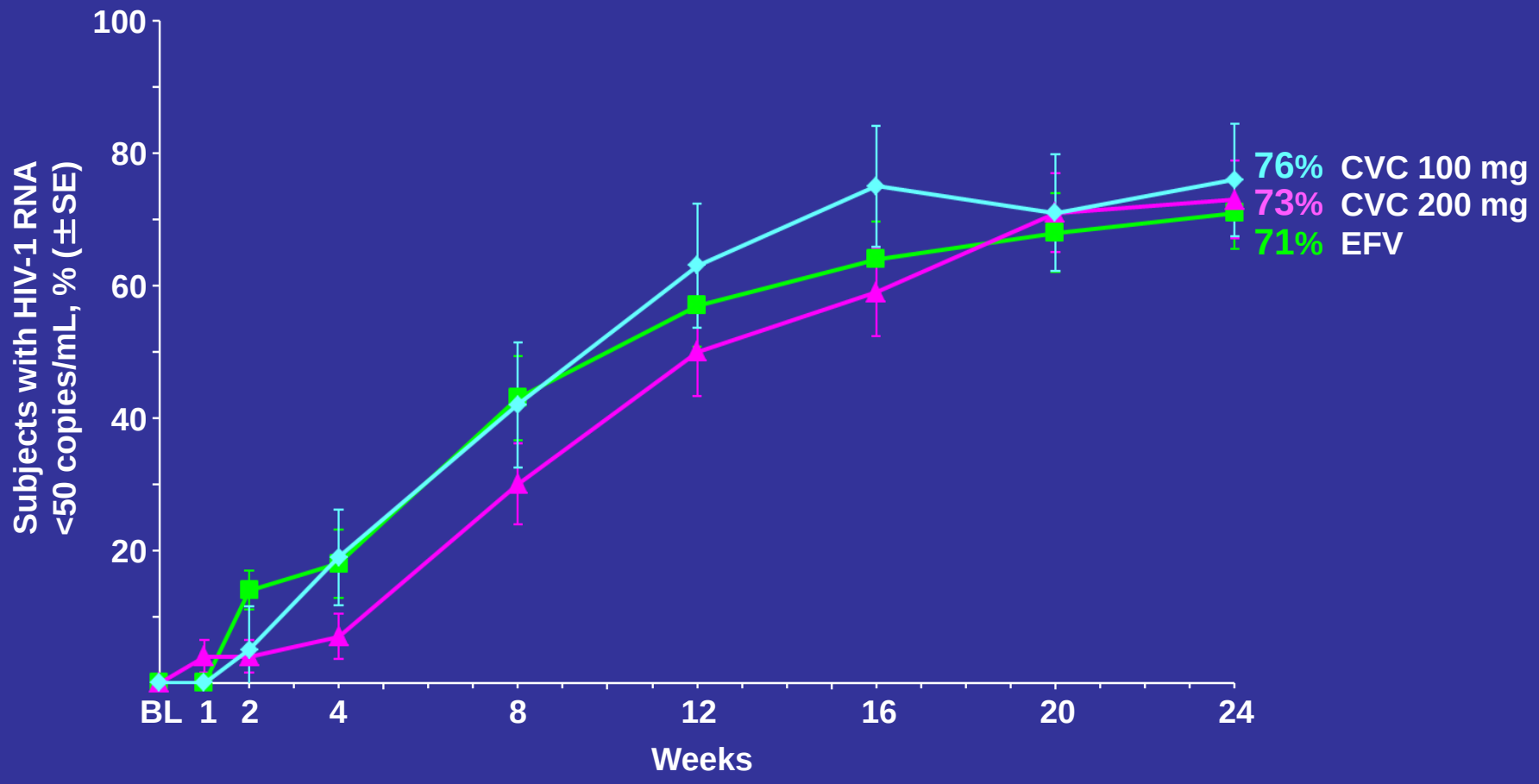
Dosing Instructions of Blinded Study Drugs

Treatment arm	CVC 50 mg	CVC placebo	EFV 600 mg	EFV placebo	FTC/TDF (Truvada®)
	Blinded: Taken with breakfast		Blinded: Taken on empty stomach at bedtime		Open-label: At anytime
CVC 100 mg					
CVC 200 mg					
EFV					

Demographics and Baseline Characteristics

Baseline characteristics	CVC 100 mg (N=59)	CVC 200 mg (N=56)	EFV (N=28)
Male	**92%**	**100%**	**89%**
Mean age, years (min–max)	**36 (19–63)**	**36 (21–57)**	**32 (19–49)**
Race			
Caucasian	58%	64%	64%
Black/African American	41%	23%	32%
Ethnicity			
Hispanic	12%	32%	36%
Mean HIV-1 RNA, log_{10} copies/mL	**4.43**	**4.59**	**4.47**
Mean CD4 cells/mm^3 (min–max)	**414 (188–749)**	**410 (77–1090)**	**359 (191–641)**
Baseline HIV-1 RNA copies/mL ≥100 000	**17%**	**25%**	**14%**

HIV-1 RNA <50 copies/mL (ITT-FDA Snapshot)



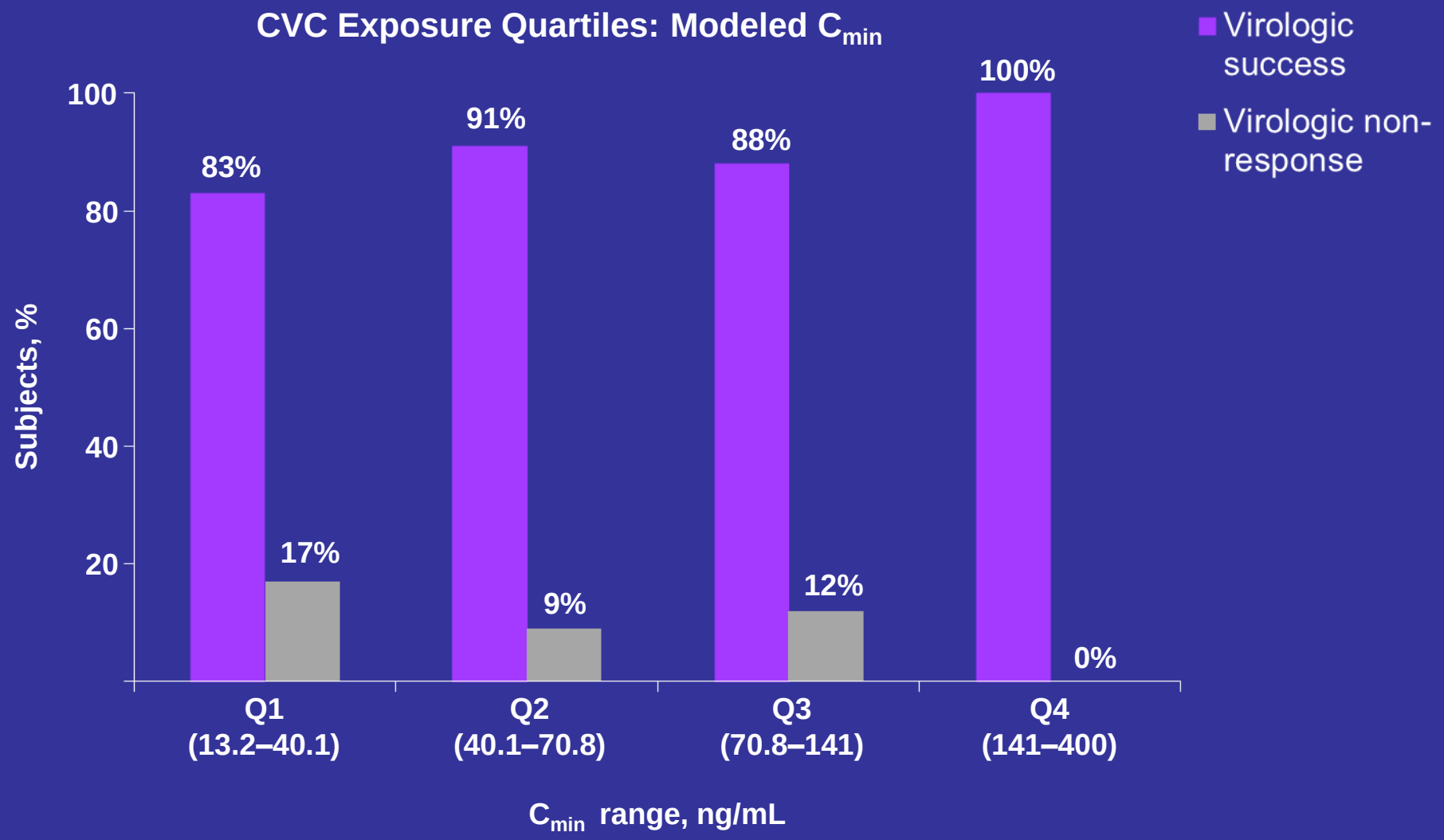
CVC 100 mg (N=59) ◆	0	3	11	25	37	44	42	45
CVC 200 mg (N=56) ▲	2	2	4	17	28	33	40	41
EFV (N=28) ■	0	4	5	12	16	18	19	20

Week 24 Virologic Outcomes by Stratification (ITT-FDA Snapshot)

Category	Baseline HIV RNA (copies/mL)					
	<100 000			≥100 000		
	CVC 100 mg (N=49)	CVC 200 mg (N=42)	EFV (N=24)	CVC 100 mg (N=10)	CVC 200 mg (N=14)	EFV (N=4)
Virologic success	80%	81%	71%	60%	50%	75%
Virologic non-response	10%	10%	0%	20%	29%	25%
No virologic data in Week 24 window	10%	9%	29%	20%	21%	0%

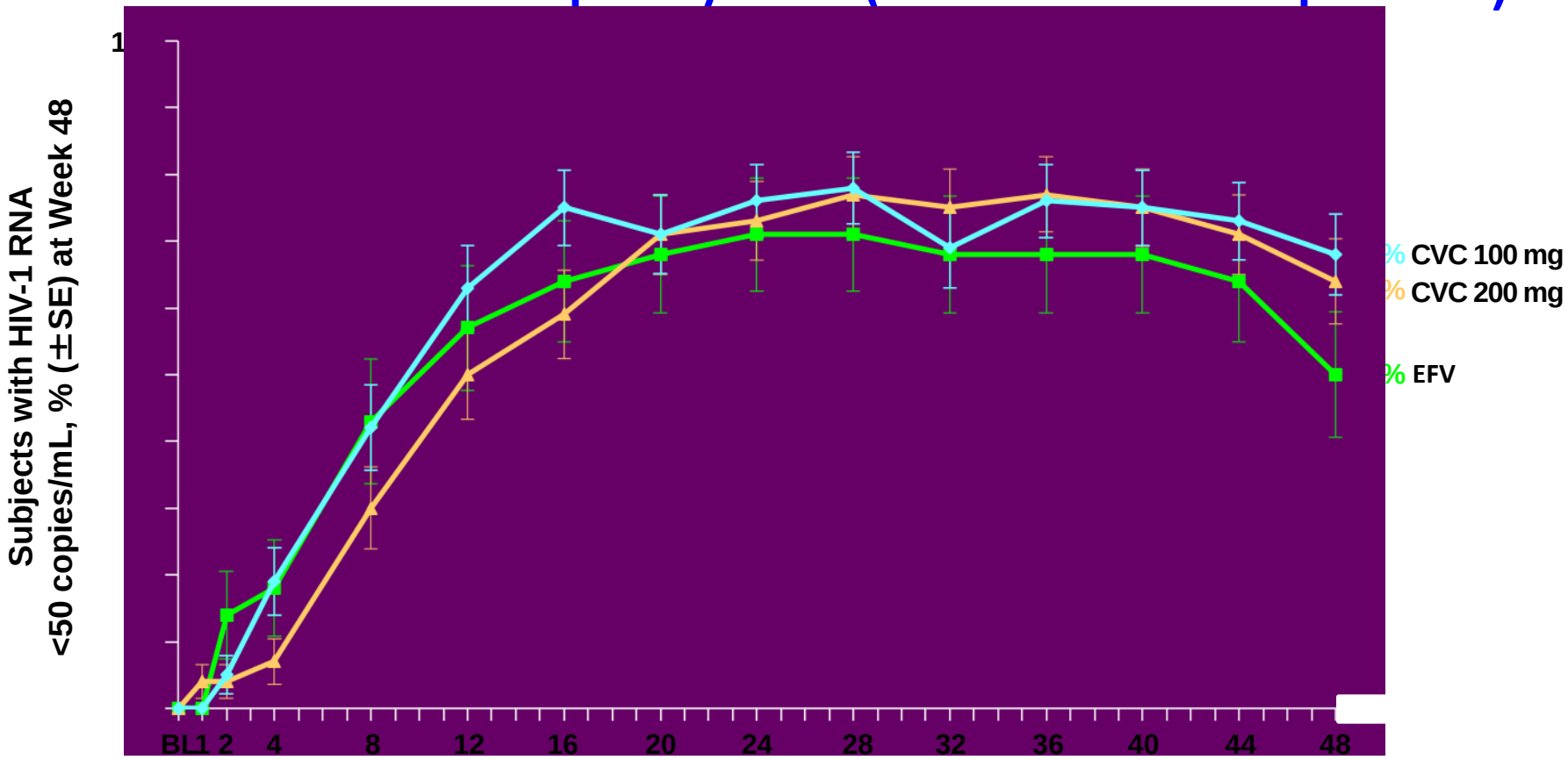
Discontinued (Other) includes: consent withdrawn, non-compliance, lost to follow-up, other reasons

Week 24 PK/PD Efficacy Analyses



Week 48 Final Analysis

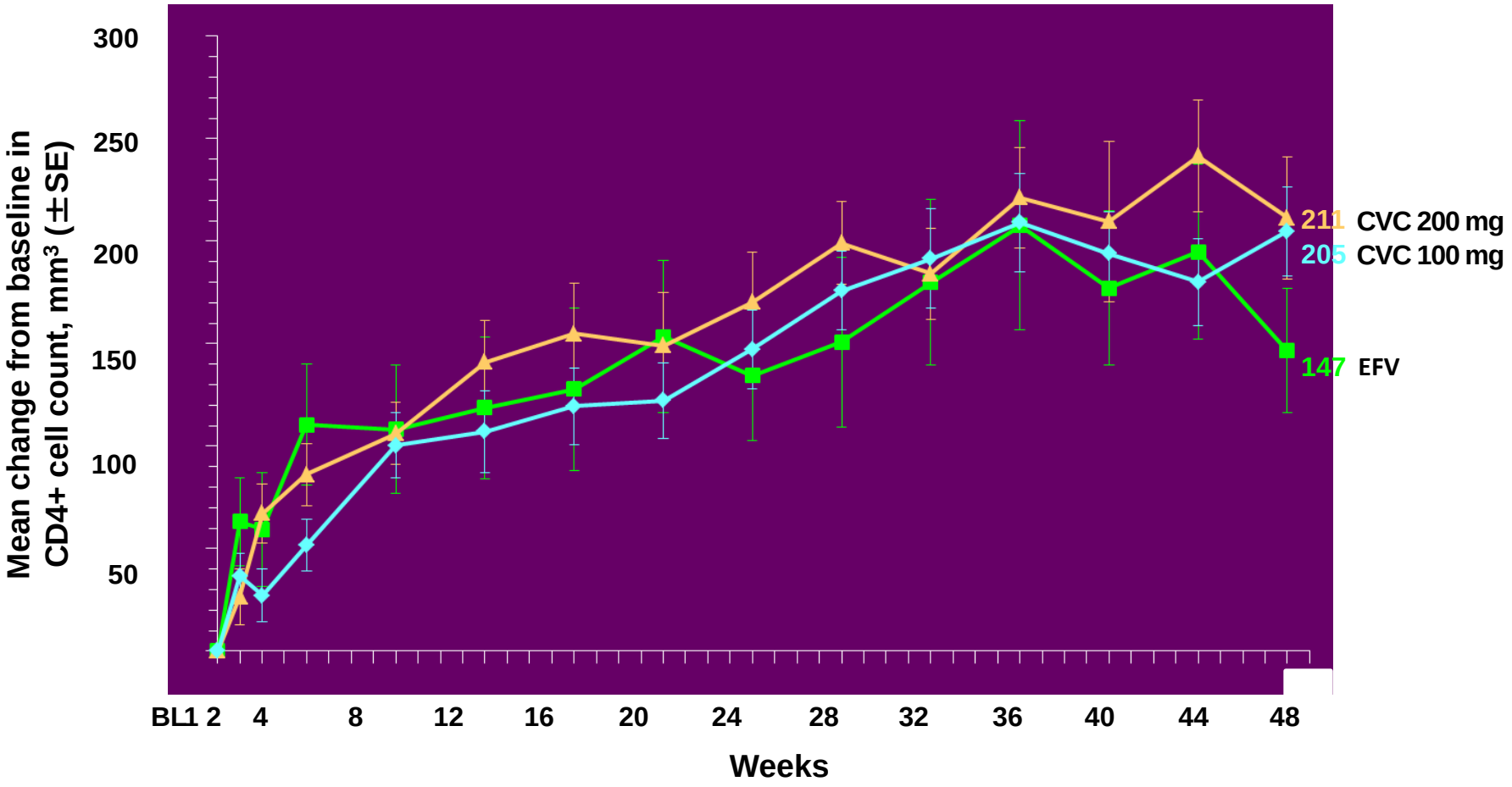
HIV-1 RNA <50 copies/mL (ITT-FDA Snapshot)



CVC 100 mg (N=59)	0	3	11	25	37	44	42	45	46	41	45	44	43	40
CVC 200 mg (N=56)	2	2	4	17	28	33	40	41	43	42	43	42	40	36
EFV (N=28)	0	4	5	12	16	18	19	20	20	19	19	19	18	14

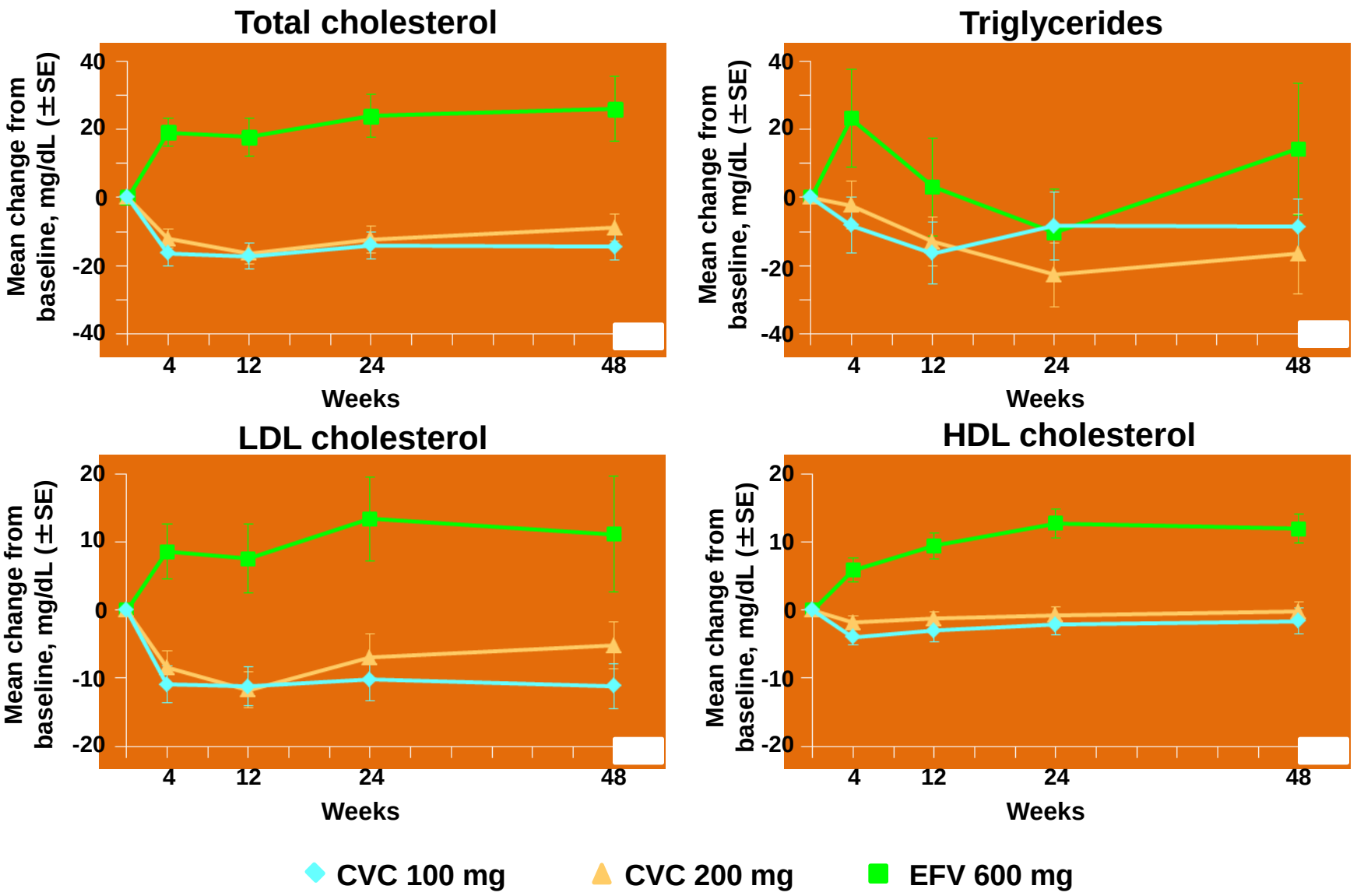
J Feinberg *et al, EACS* 2013

CD4+ Count Change from Baseline

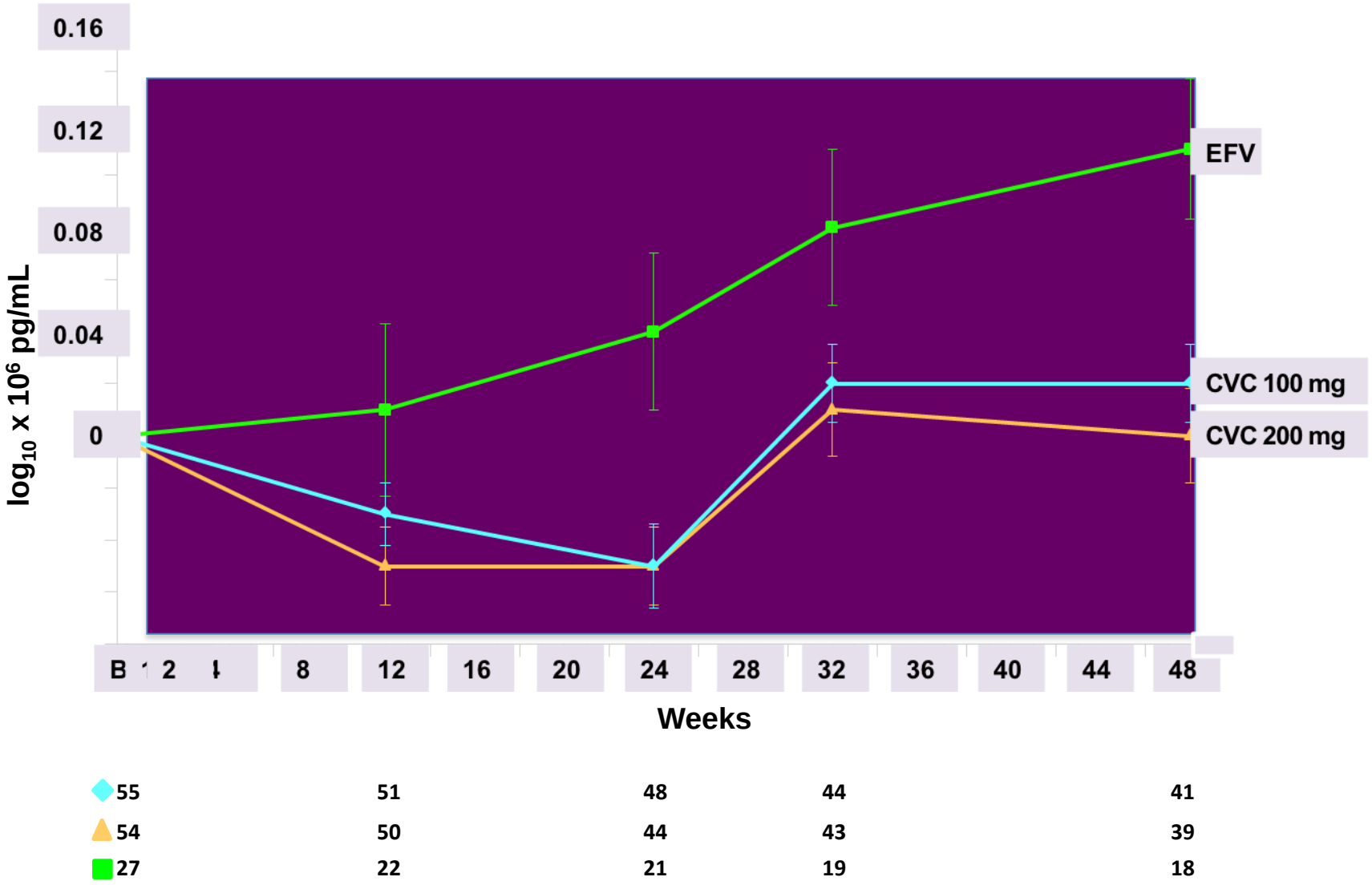


CVC 100 mg (N=59)	58	53	54	53	52	51	54	54	48	46	47	47	46	44	41
CVC 200 mg (N=56)	56	53	55	54	53	53	51	50	46	46	46	44	43	42	40
EFV (N=28)	28	25	26	24	23	22	21	22	21	21	19	21	21	20	17

Fasting Lipid Changes from Baseline

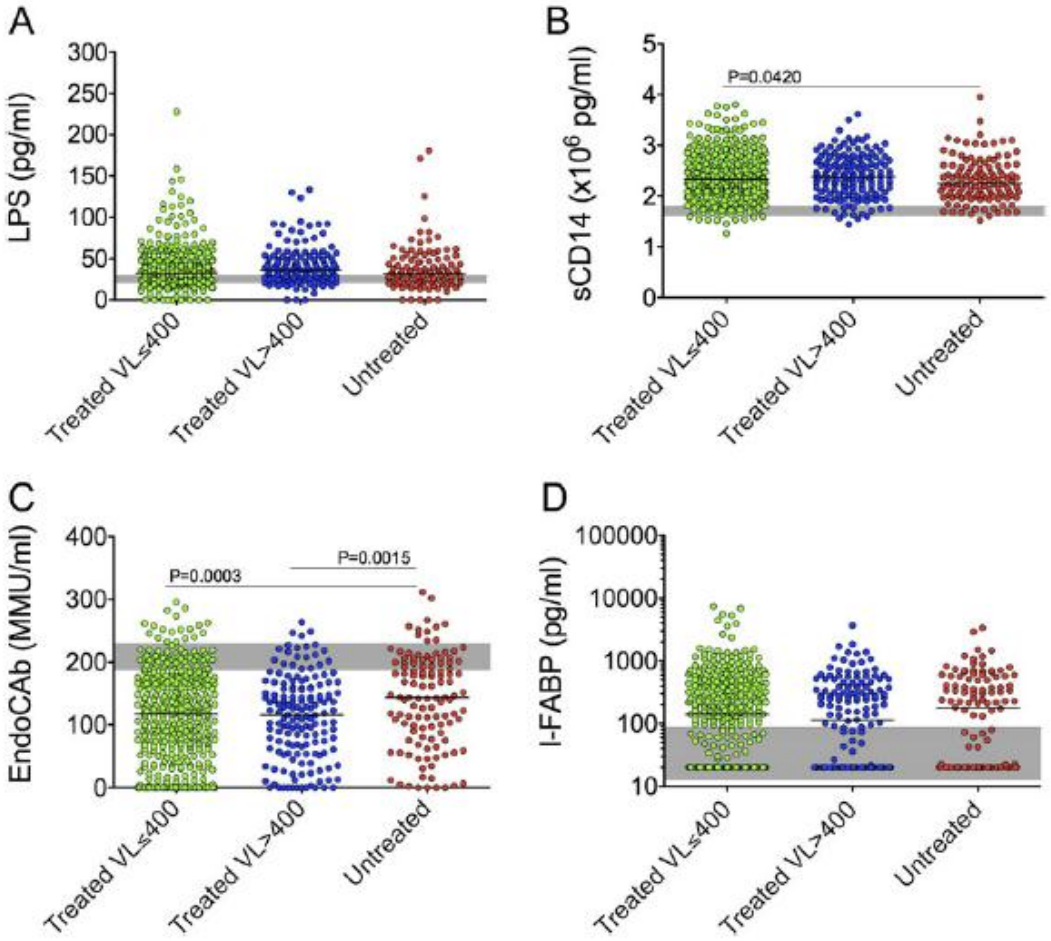


Changes from Baseline in sCD14



Plasma Levels of Soluble CD14 Independently Predict Mortality in HIV Infection

The Journal of Infectious Diseases 2011;203:780–790



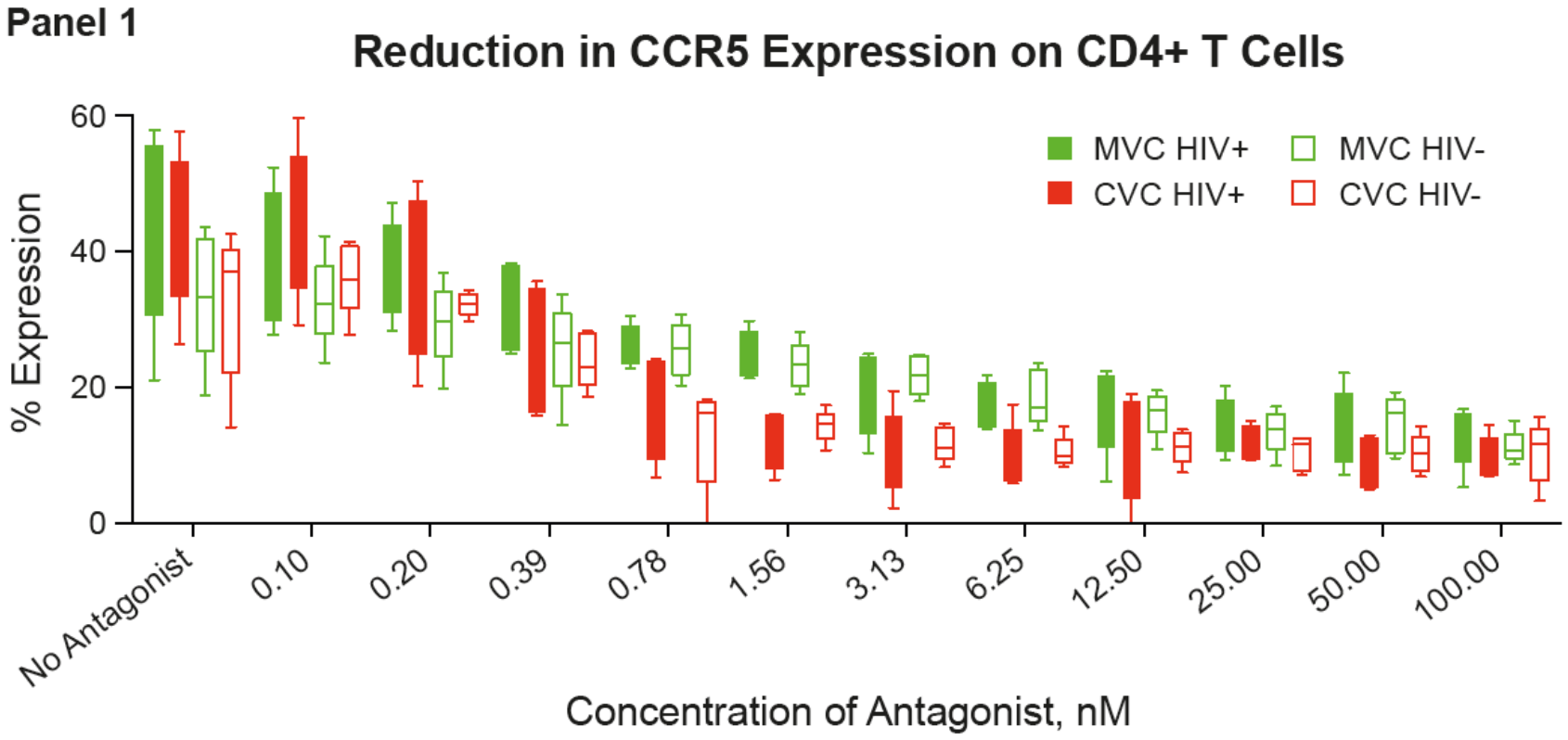
RISCHIO di Morte e sCD14:

6 volte maggiore per
pz nel quartile superiore
rispetto al quartile inferiore
($p<0.01$)

Cenicriviroc Achieves High CCR5 Receptor Occupancy at Low Nanomolar Concentrations

Emilie Jalbert1, Mary Margaret Byron1, Cecilia M. Shikuma1, Helen Jenkins2, Eric Lefebvre2, Jason D. Barbour1*

21st CROI 1. Hawaii Center for AIDS, John A. Burns School of Medicine, University of Hawaii Manoa, Honolulu, Hawaii, 2. Tobira Therapeutics, Inc., South San Francisco, California

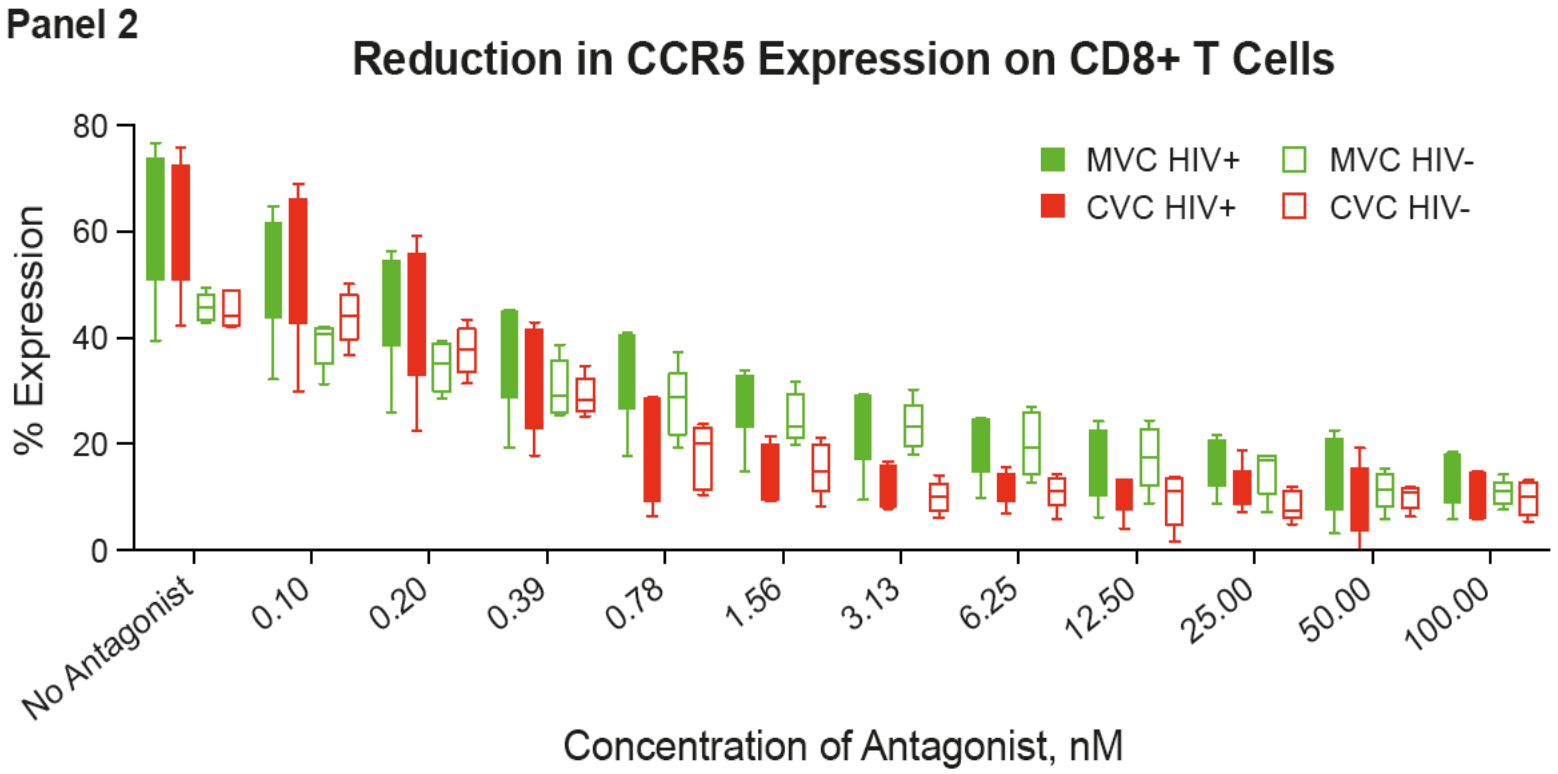


@ CROI 2014

Cenicriviroc Achieves High CCR5 Receptor Occupancy at Low Nanomolar Concentrations

Emilie Jalbert1, Mary Margaret Byron1, Cecilia M. Shikuma1, Helen Jenkins2, Eric Lefebvre2, Jason D. Barbour1*

21st CROI 1. Hawaii Center for AIDS, John A. Burns School of Medicine, University of Hawaii Manoa, Honolulu, Hawaii, 2. Tobira Therapeutics, Inc., South San Francisco, California

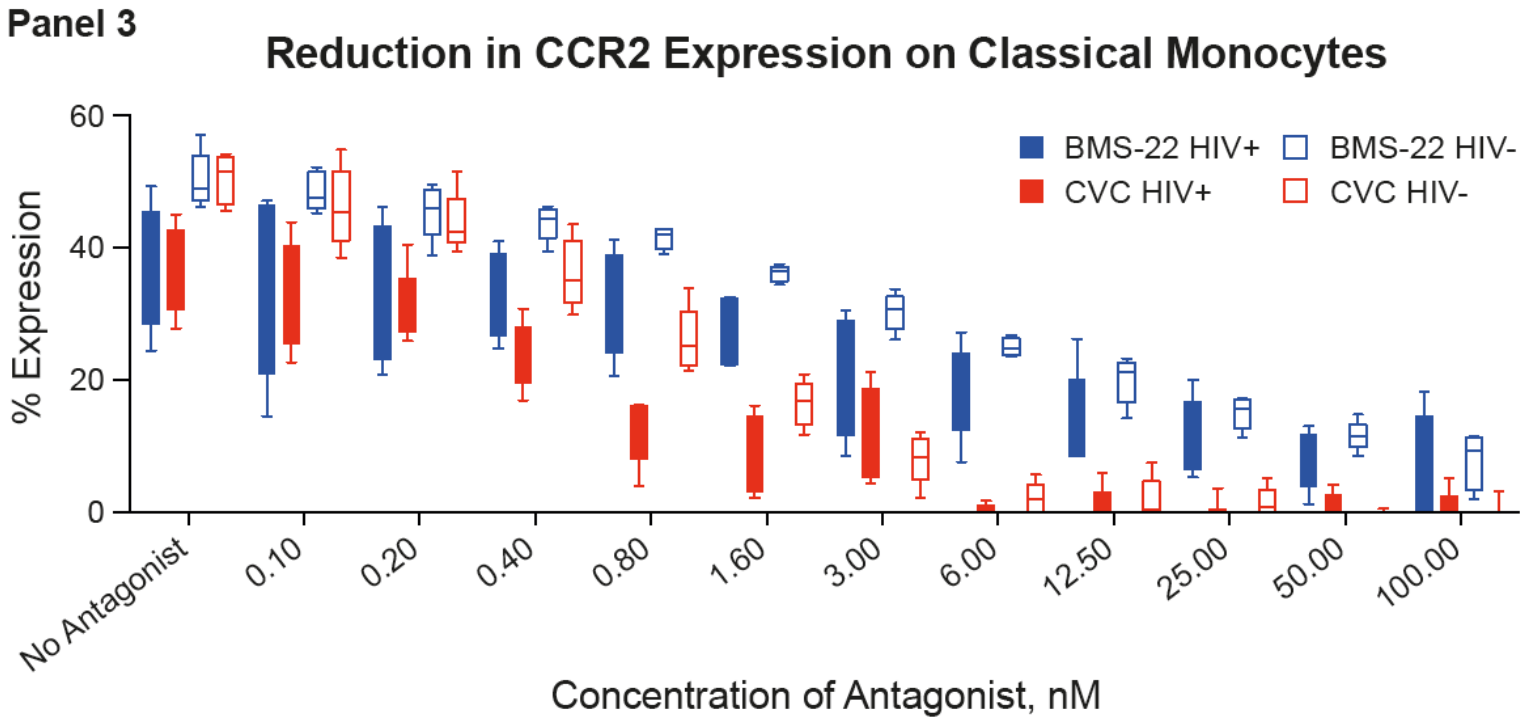


@ CROI 2014

Cenicriviroc Achieves High CCR5 Receptor Occupancy at Low Nanomolar Concentrations

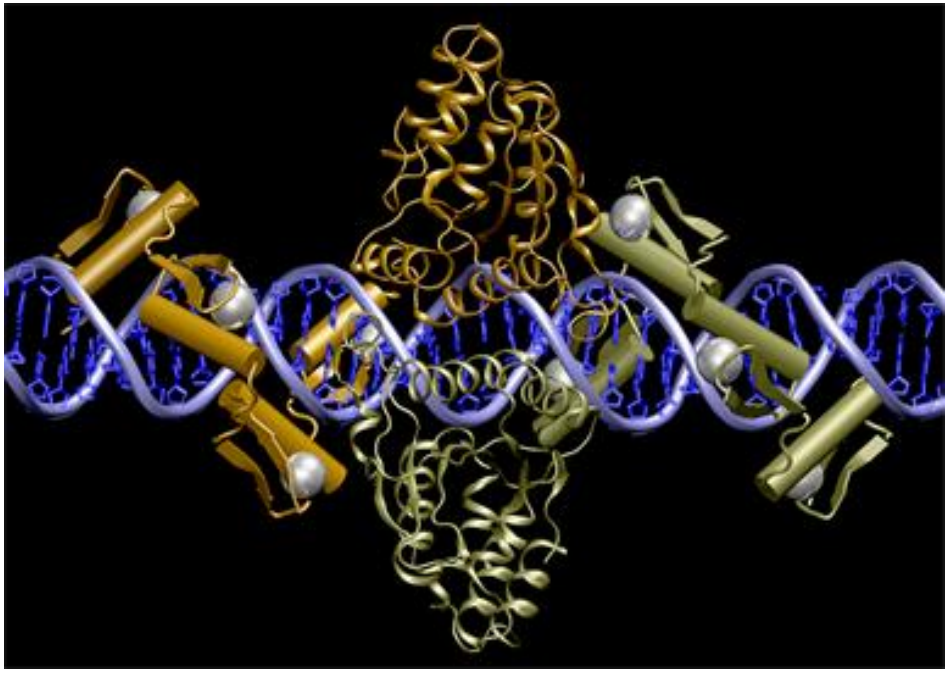
Emilie Jalbert1, Mary Margaret Byron1, Cecilia M. Shikuma1, Helen Jenkins2, Eric Lefebvre2, Jason D. Barbour1*

21st CROI 1. Hawaii Center for AIDS, John A. Burns School of Medicine, University of Hawaii Manoa, Honolulu, Hawaii, 2. Tobira Therapeutics, Inc., South San Francisco, California



@ CROI 2014

A Novel Approach to HIV Therapy: Successful and Persistent Engraftment of ZFN-Modified CCR5-Disrupted Autologous CD4 T-cells (SB-728-T) in Aviremic HIV-infected Subjects on HAART



Lalezari J, et al. CROI, February 27 – March 2, 2011. Abstract 46

CCR5 gene therapy – recent progress

CONCEPT

To **produce reservoir of cells resistant** to HIV infection.

Protected cells would proliferate while susceptible cells would be infected with HIV and die

6 HIV+ participants on ARV with undetectable viral load (< 50 copies/ml) and CD4+ T-cell counts 200–500 cells/mm^3

↓ **T cells harvested by apheresis**

Cell treatment with zinc finger nuclease/adenovirus vector to disrupt the CCR5 gene

↓ **CCR5-deleted cells infused back into original patient**

5/6 had significant and sustained increases in CD4+ cells of around 200 cells/mm^3 on average

5/6 had normalization of the CD4/CD8+ T-cell ratio

↓ 90 days post therapy

7% of peripheral blood CD4 cells had CCR5 deletion. Biopsies revealed that the altered cells were distributed to the gut lining

1. Lalezari J, *et al. CROI*, Boston, Feb–Mar 2011; Abstract 46

SangamoPhase I Study (SB-728-T): Background and Rationale

- CCR5 is the major co-receptor for HIV entry
- CCR5 delta-32 mutation produces a nonfunctional form of the protein

-Homozygotes are resistant to HIV infection

-Heterozygotes have slower disease progression

- The “Berlin Patient” is HIV-free w/o HAART for 3.5 years following hematopoietic stem cell transplant (HSC) from an allogeneic, HLA matched, CCR5 delta-32 donor.
- Zinc Finger Nuclease (ZFN) technology enables precise genetic modification of CCR5 resulting in elimination of receptor expression.
- The therapeutic potential of CCR5 modification as seen in the natural mutation can be extended with ZFN modification of autologousCD4+ T cells in HIV subjects.

Lalezari J, et al. CROI, February 27 – March 2, 2011. Abstract 46

SangamoSB-728-0902

Summary

- **SB-728-T can be manufactured at doses of 10-30 billion cells from a single apheresis with a CCR5 disruption frequency of ~25%**
- **SB-728-T treatment is well-tolerated**
- Minor reversible infusion-related symptoms
- **Improved and sustained increase in total CD4+T-cell counts seen in 5/6 subjects**
- **Normalization of CD4:CD8 ratios seen in 3/5 subjects**
- **ZFN-modified T-cells engraft, expand, and persist in peripheral blood**
- ZFN-modified CD4+ T-cells detected at frequencies up to 7-fold higher (median 2.9) than predicted input on day 14
- Expansion of ZFN-modified T cells in PBMC may be due to cell proliferation and/or altered distribution
- **ZFN-modified T-cells engraft and persist in rectal mucosa**
- Engraftment and persistence of ZFN-modified T cells in rectal mucosa demonstrated normal homing to this important tissue

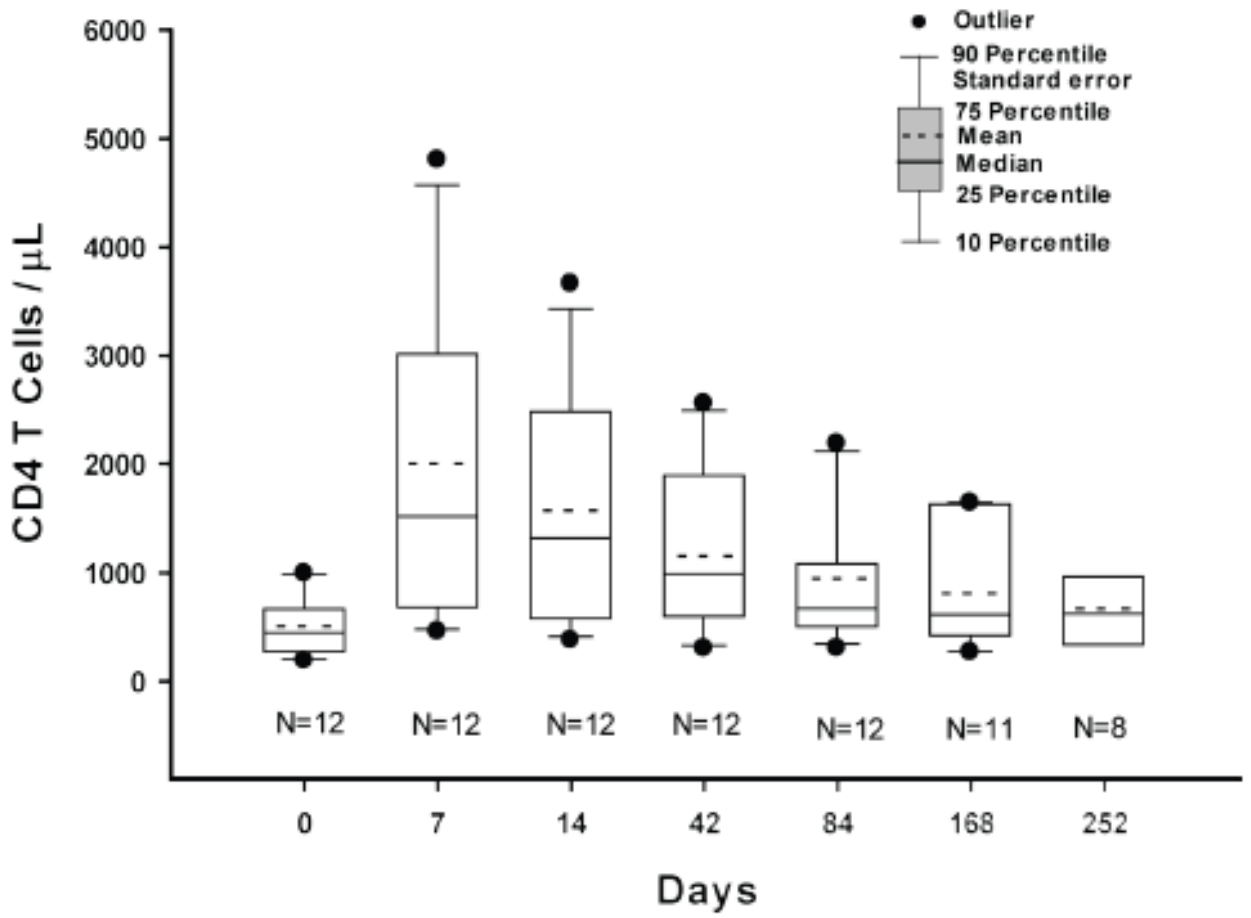
Lalezari J, et al. CROI, February 27 – March 2, 2011. Abstract 46

P Tebas et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N Engl J Med 2014 Mar 6;370(10):901-10

Methods

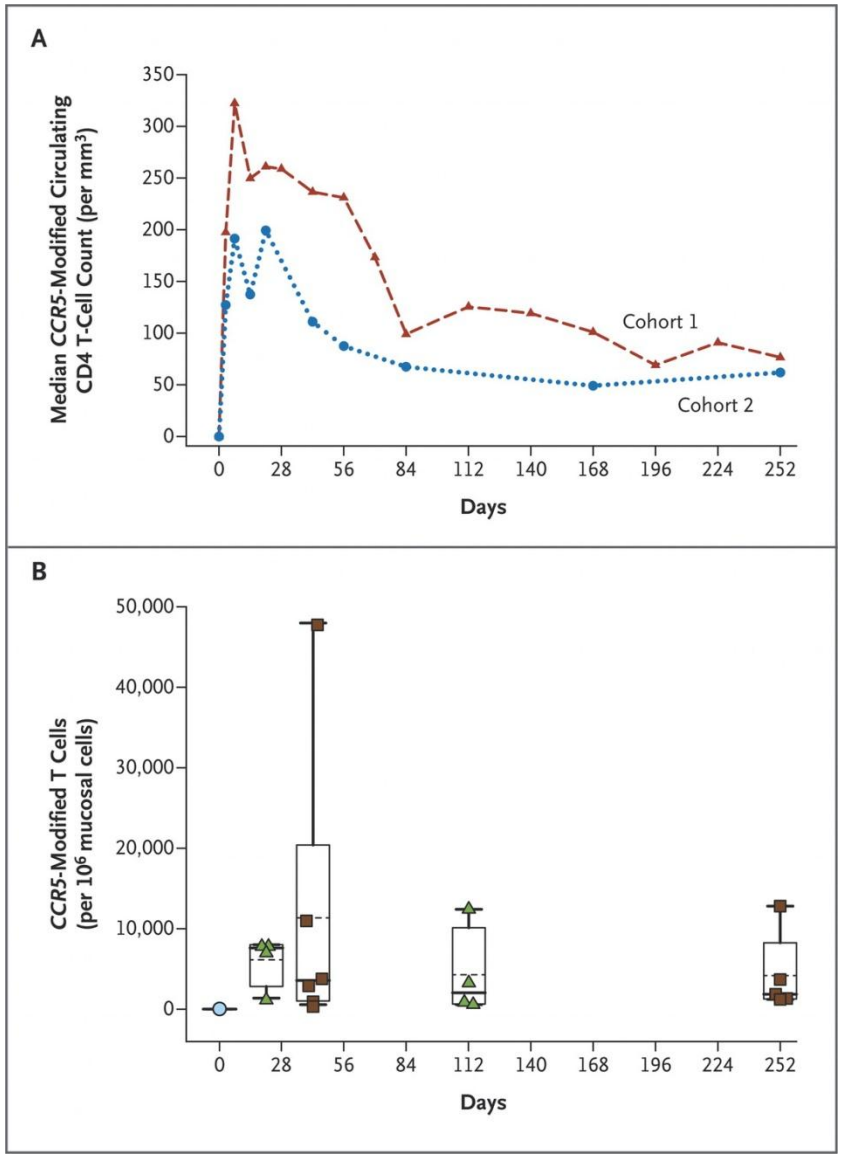
We enrolled 12 patients in an open-label, nonrandomized, uncontrolled study of a single dose of ZFN-modified autologous CD4 T cells. The patients had chronic aviremic HIV infection while they were receiving highly active antiretroviral therapy. **Six of them underwent an interruption in antiretroviral treatment 4 weeks after the infusion** of 10 billion autologous CD4 T cells, 11 to 28% of which were genetically modified with the ZFN. The primary outcome was safety as assessed by treatment-related adverse events. Secondary outcomes included measures of immune reconstitution and HIV resistance.

Change in CD4+ cell counts



P Tebas et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N Engl J Med 2014 Mar 6;370(10):901-10.

CCR5-Modified CD4 T Cells in the Circulation and Mucosal Tissues



P Tebas et al. Gene editing of CCR5 in autologous CD4 T cells of persons infected with HIV. N Engl J Med 2014 Mar 6;370(10):901-10.

Conclusioni

- E’ necessario ricercare vie alternative per rinnovare/restaurare il sistema immune che resta “azzoppato” nonostante anni di successo virologico grazie alla HAART, e questo si configura nel filone della cura funzionale o sterilizzatrice.
- Gli agenti terapeutici che agiscono a livello dell’entrata di HIV nella cellula suscettibile all’infezione, sia bloccando un co-recettore che bloccando una proteina dell’envelope, possono essere i candidati ideali, naturalmente all’interno di una combinazione terapeutica.
- CVC ora, MCV prima, agiscono non solo contro HIV ma anche, e sopratutto, modulando il sistema immune, con il caveat che l’**inibizione del CCR5**, tra le altre cose, è tanto più efficace tanto più precocemente viene instaurata, *e.g.* in PHI.
- La terapia genica è molto affascinante dal pdv scientifico, resta da stabilire quanto praticabile possa essere.