New Antiretroviral Drugs

R.M. Gulick, MD, MPH
Professor of Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medical College
New York City

Newer ART Agents (partial list)

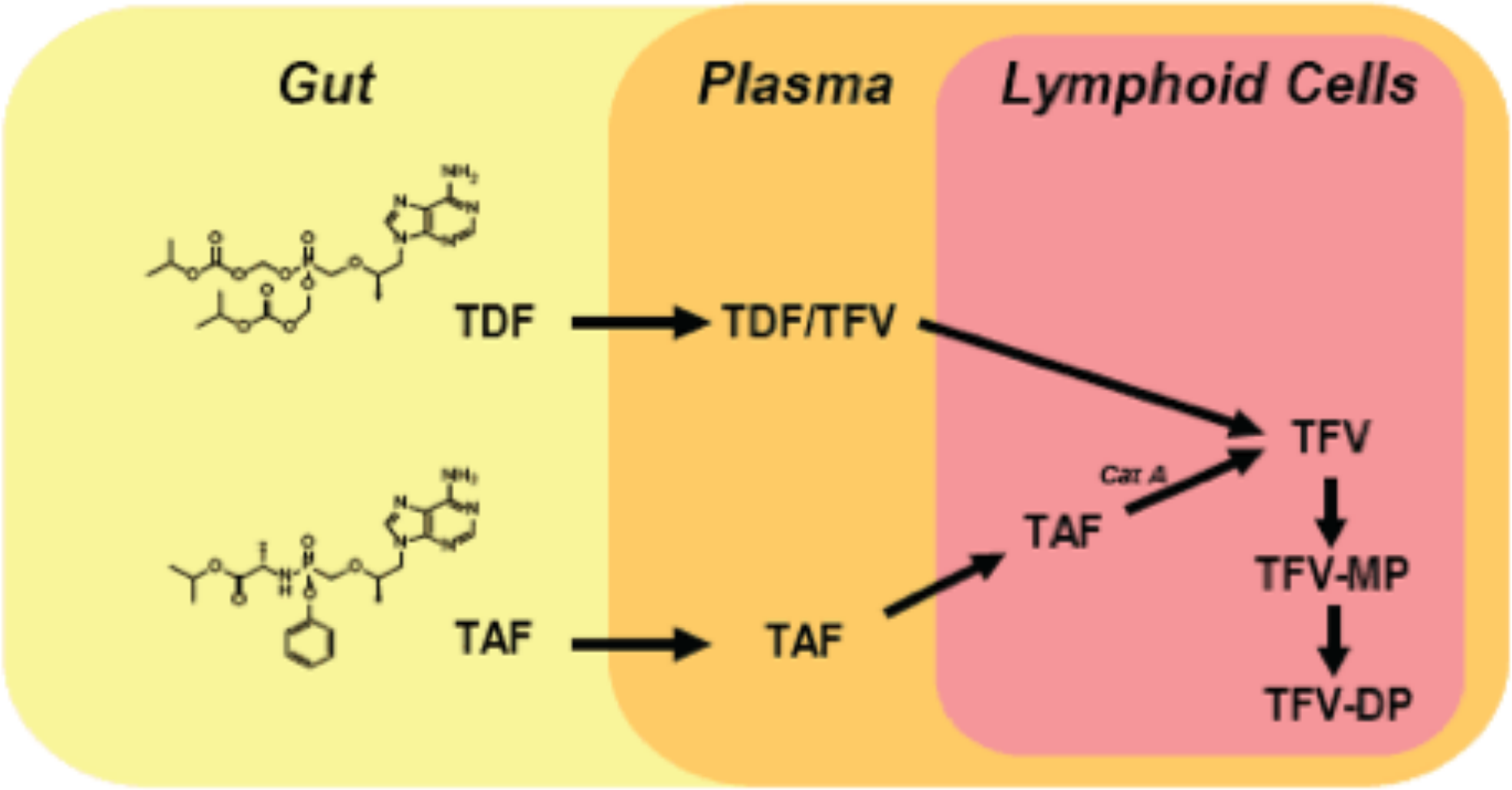
	NRTI	NNRTI	PI	Entry Inh	II	MI
Phase 3	TAF	doravirine		BMS-663068	cabotegravir	
Phase 2	apricitabine dexelvucitabine festinavir	BILR 355		cenicriviroc ibalizumab PF-232798	GS-9883	BMS-955176
Phase 1/2	elvucitabine		TMC 310911	HGS004		
Phase 1	CMX157	RDEA 806	CTP-298 CTP-518 PPL-100 SPI-256	SCH532706 VIR-576	BI 224436 INH-1001	GSK-2838232

NRTI

Needs:

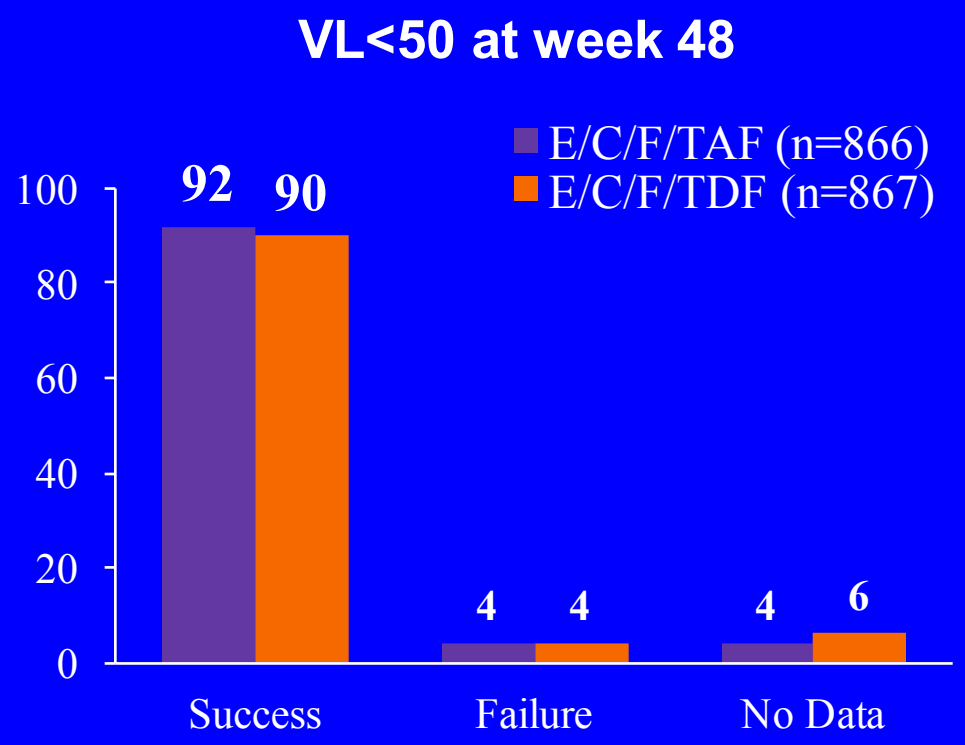
- Less long-term toxicity

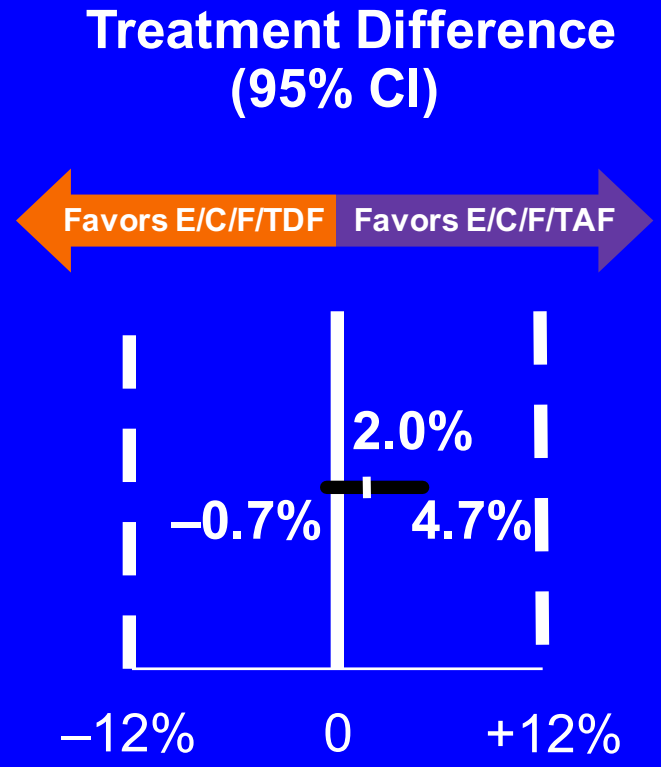
Drug Delivery: TDF vs. Tenofovir Alafenamide (TAF)



Phase 3 Studies: TDF vs. TAF + (/FTC/EVG/c)

Randomized, double-blind; 2-pill, once-daily regimen
Study population: Rx-naïve, VL ≥1000, eGFR ≥50 cc/min (N=1733)



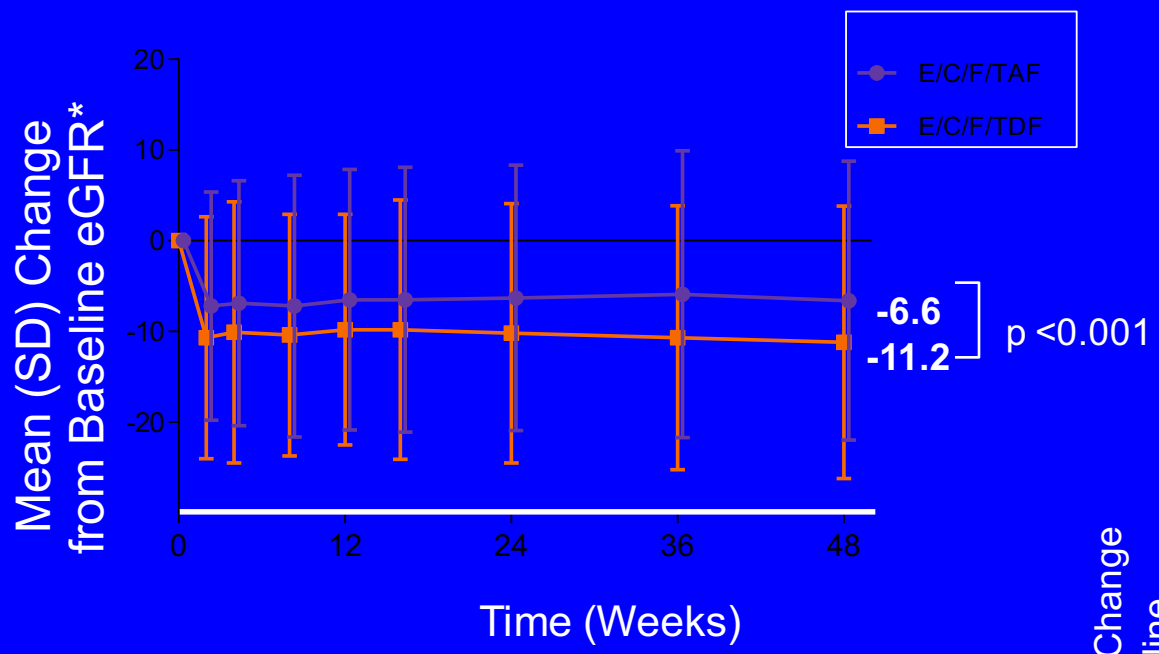


- E/C/F/TAF non-inferior to E/C/F/TDF at week 48
  - No difference by BL VL (above/below 100K or CD4 above/below 200)

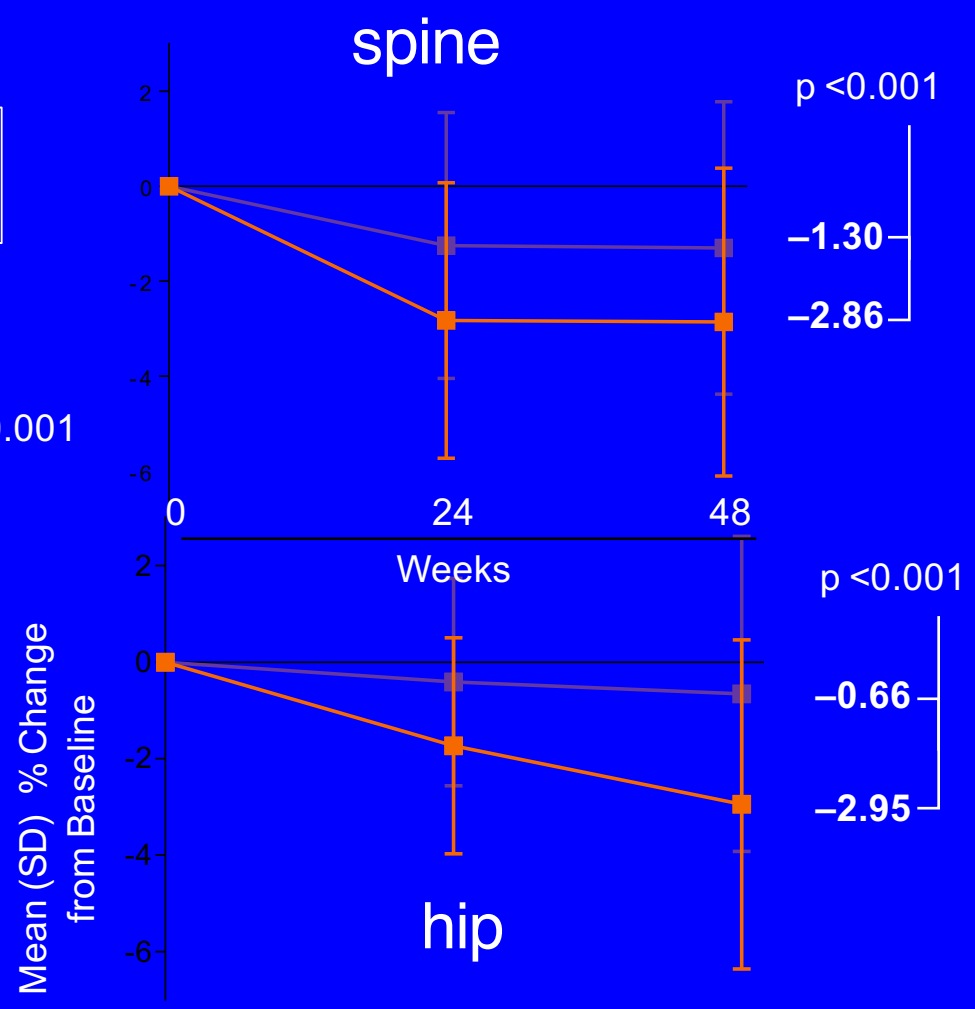
Sax Lancet 2015;385:2606-15

TAF Phase 3: Renal and Bone

Studies 104 and 111: Week 48 Combined Analysis



*Cockroft-Gault (mL/min).



Sax Lancet 2015;385:2606-15

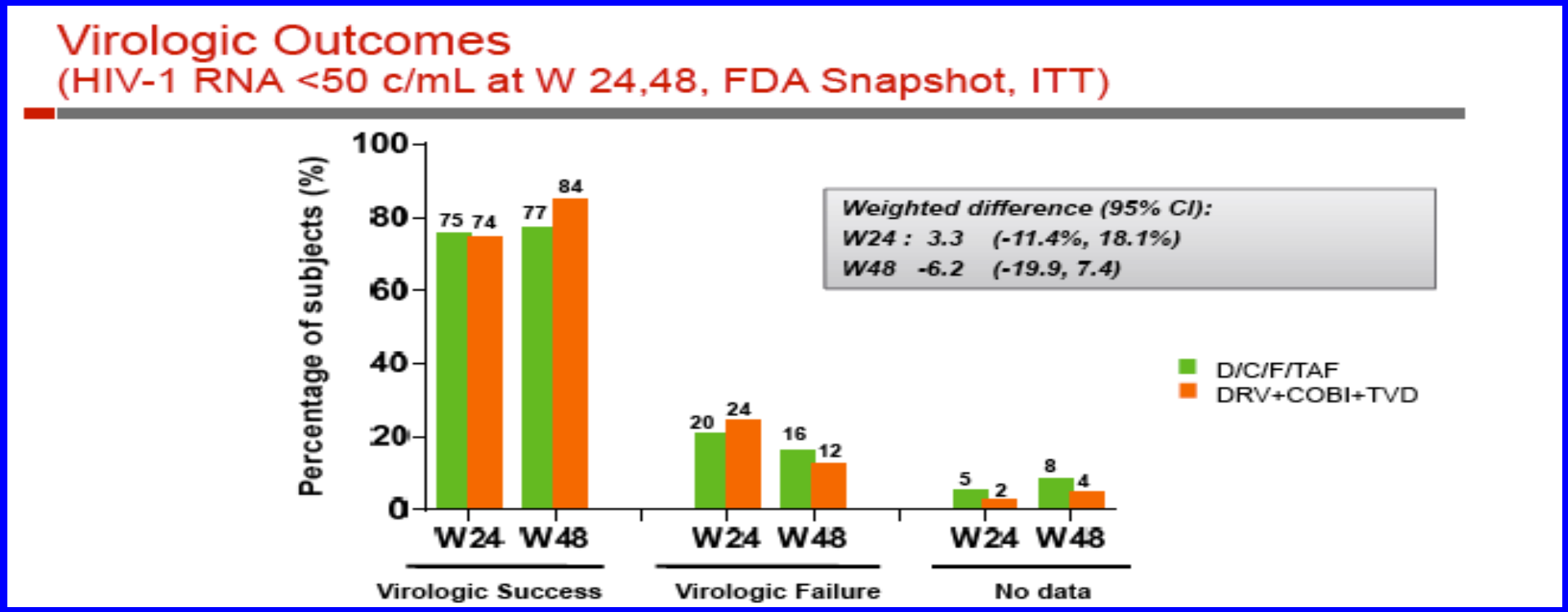
Phase 3: TAF/FTC vs. TDF/FTC + 3rd Drug

- Phase 3, randomized, placebo-controlled study
- Study pop: Suppressed on stable TDF/FTC-containing regimen X >6 months (N=663)
- Study treatment: continue TDF/FTC or change to TAF/FTC (2 doses, depending on 3rd drug)
- Results: VL <50 at week 48:
  TDF (93%) vs. TAF (94%), Δ=1.3% (95% CI -2.5, +5.1%)
  - safety, toxicity-related discontinuations "similar"
  - TAF significantly less median eGFR decrease (P<0.001)
  - TAF significantly less BMD loss (p<0.001)

Gilead Press Release 9/2/15

Phase 2: TDF vs TAF + (/FTC/DRV/r)

- Randomized, placebo-controlled; 2-pill, once-daily regimen
- Study population: Rx-naïve, VL ≥5000, CD4>50, eGFR >70 cc/min (N=150)



TAF associated with less changes in renal markers, bone mineral density

Mills JAIDS 2015;69:439-445

Tenofovir alafenamide (TAF)

- Based on drug-drug interactions studies, 2 doses:
  - TAF 10 mg (with boosted PIs); 25 mg (with NNRTIs/IIs)
    Lawson ICAAC 2014 #H-1012
- Switch to TAF improved renal markers and BMD
  - 1386 pts on TDF with CrCL >50 Mills IAS 2015 #TUAB0102
  - 242 pts on TDF (65%) or not (35%) with eGFR 30-69
    Gupta IAS 2015 #TUAB0103
- Co-formulations
  - TAF/FTC/EVG/c: **FDA approved 11/5/15!**; under EMA rvw
  - TAF/FTC: FDA target action date: 4/7/16; under EMA rvw
  - TAF/FTC/RPV: submitted to FDA: 7/1/15; under EMA rvw
  - TAF/FTC/DRV/c: in phase 3 clinical trials

NNRTI

needs:

- Less toxicity and better tolerability
- Active against resistant viral strains
- Fewer drug interactions

doravirine (DOR)

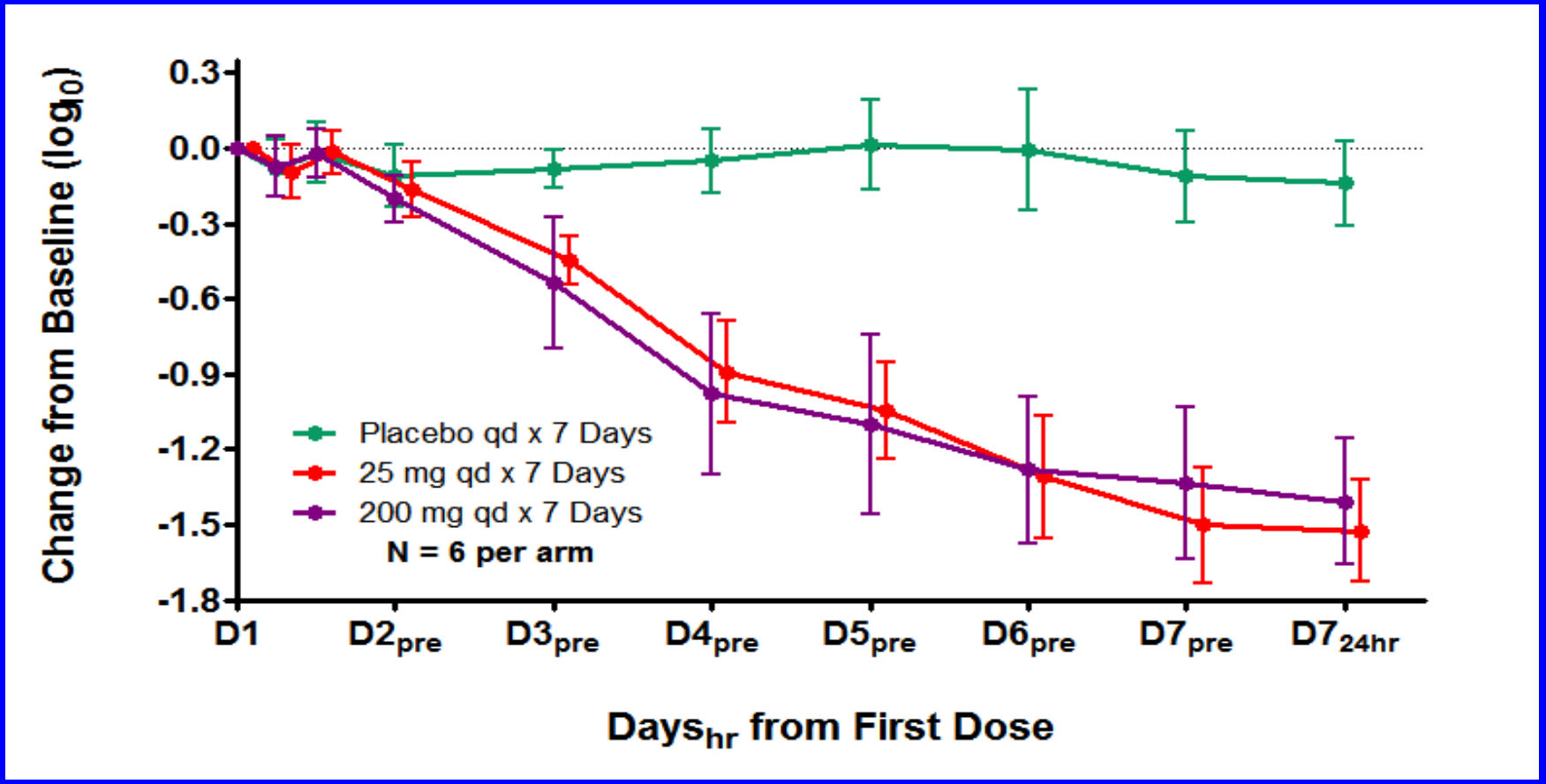
- Investigational NNRTI
- Pre-clinical — Lai AAC 2014;58:1652-1663
  - –Potent at low miligram dose
  - –Not a CYP450 inhibitor or inducer
  - –Metabolized by CYP3A4
  - –Active in vitro against viral strains with K103N, Y181C, G190A, E101K, E138K or K103N/Y181C

- Clinical — Anderson Antivir Ther 2015;20:397-405
  - –Multiple doses in 40 HIV- men X 10d:
    - no rash/CNS events (except HA)
    - PK supportive of once-daily dosing

doravirine (DOR): Phase Ib

Double-blind, randomized, placebo-controlled

Study population: HIV+, treatment-naïve (N=18)



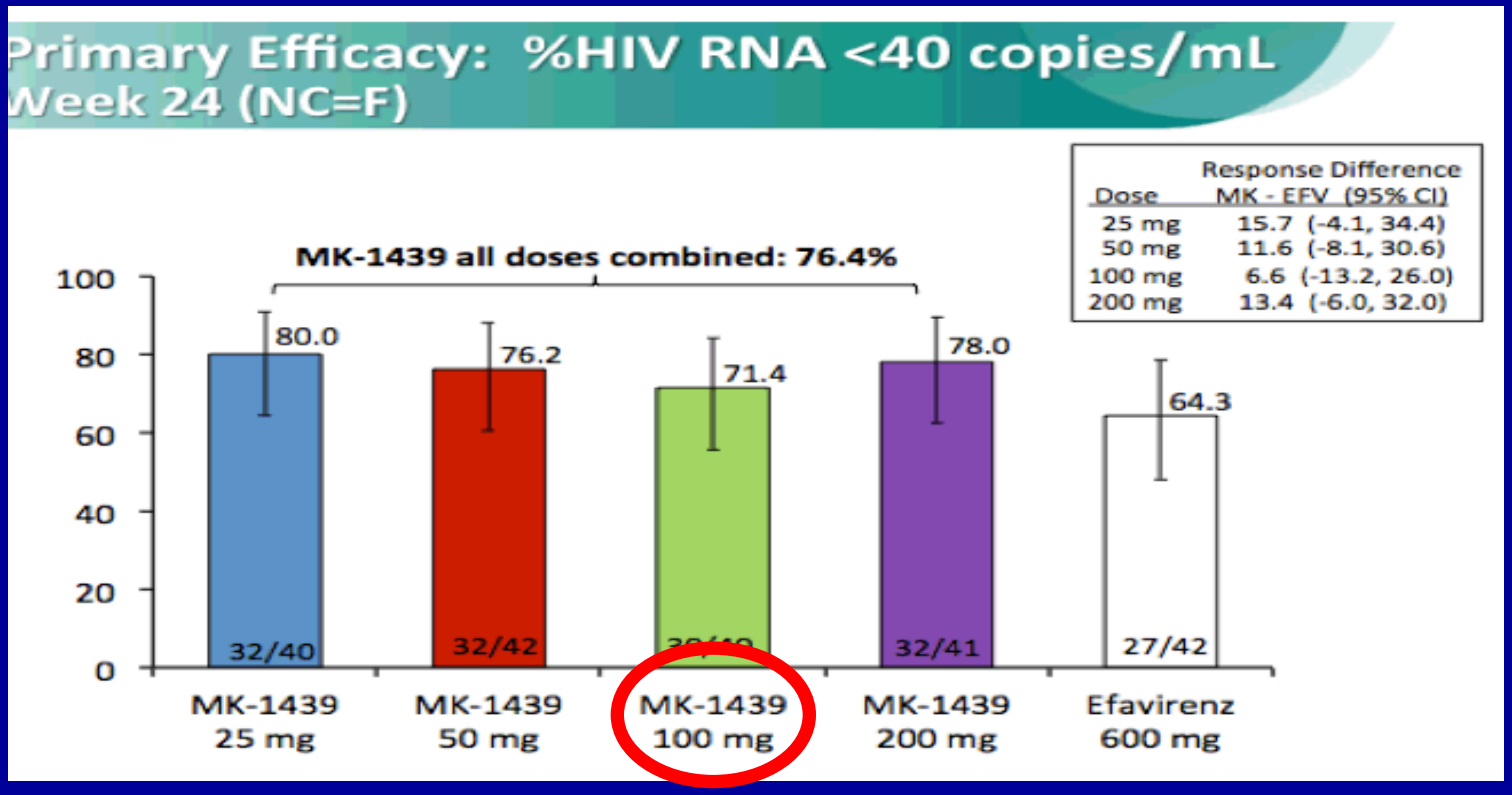
Schurmann AIDS 2015 (epub 9/13/15)

Doravirine: Phase 2b Dose Finding (Part 1)

- Randomized: TDF/FTC + 4 doses of DOR vs. EFV

Results:

VL <40



Morales-Ramirez CROI 2014 #92LB

Non-CNS tox 48 wk

DOR vs. EFV

- nausea (8% vs. 2%)
- fatigue (7% vs. 5%)
- diarrhea (5% vs. 10%)

wk 48: 73% 72% 76% 83% 71%

Gatell Glasgow 2014 #O434

Doravirine: Phase 2b (Part 2)

- Randomized: TDF/FTC + DOR 100 mg vs. EFV (N=132)
- Results (combining parts 1 and 2; N=216):
  - CNS Toxicity (48 wks)
    - overall (DOR 22% vs. EFV 44%; $p<0.001$)
      - dizziness (DOR 9% vs. EFV 28%)
      - insomnia (DOR 6% vs. EFV 3%)
      - abnormal dreams (DOR 6% vs. EFV 17%)
      - nightmares (DOR 6% vs. EFV 8%)

Gatell Glasgow 2014 #O434

- Significant interaction with rifampin (↓DOR >57%)

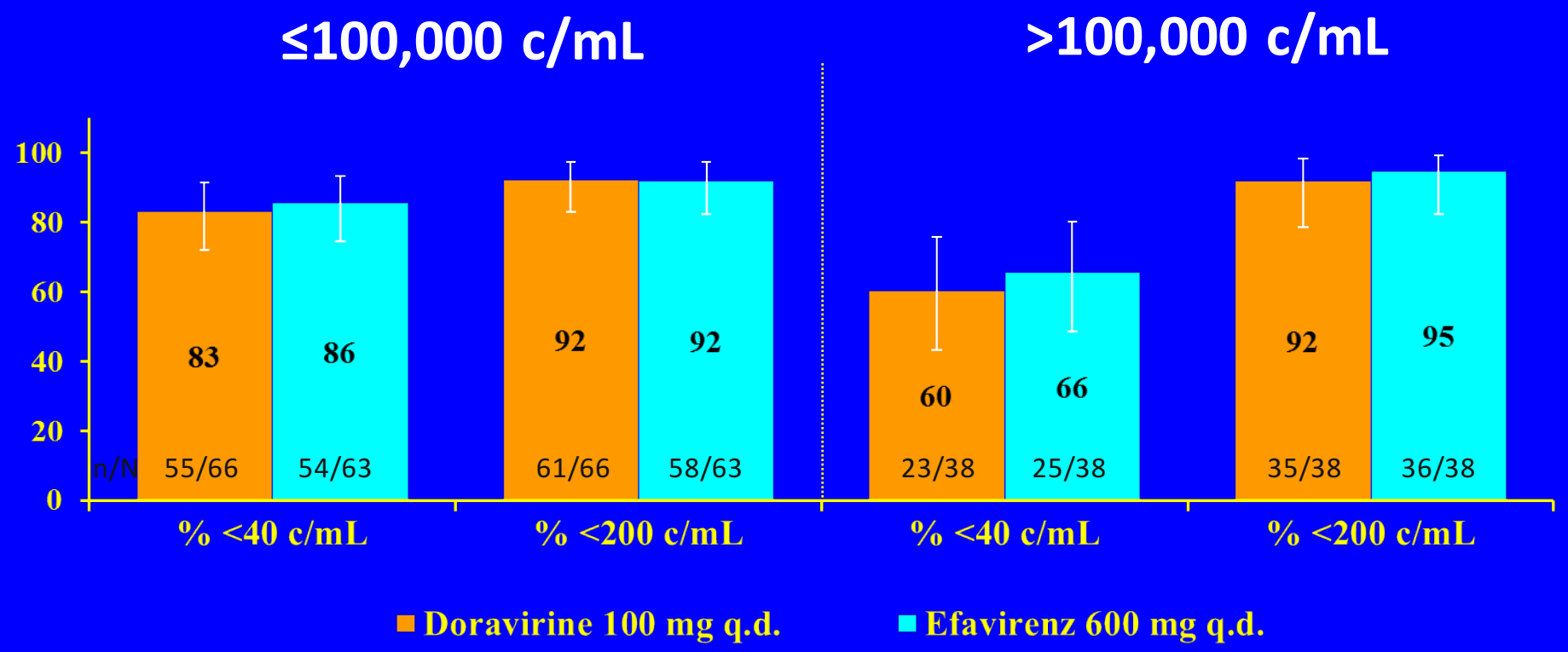
Judge CROI 2015 #521

DOR Phase 2: Study 007

Study population: Treatment-naïve, VL≥1000, CD4≥100 (N=216)

Study regimen: TDF/FTC + **DOR** or **EFV**

Results: VL <40 at 24 weeks: 74% (DOR) vs. 73% (EFV)



Patients with ≥1 CNS event: 27% (DOR) vs. 46% (EFV)

*Excludes: Patients who discontinued due to non-treatment related reasons but with last RNA <40 c/mL, or due to AE, or who lack data in week 24 window.

Gatell IAS 2015 #TUAB0104

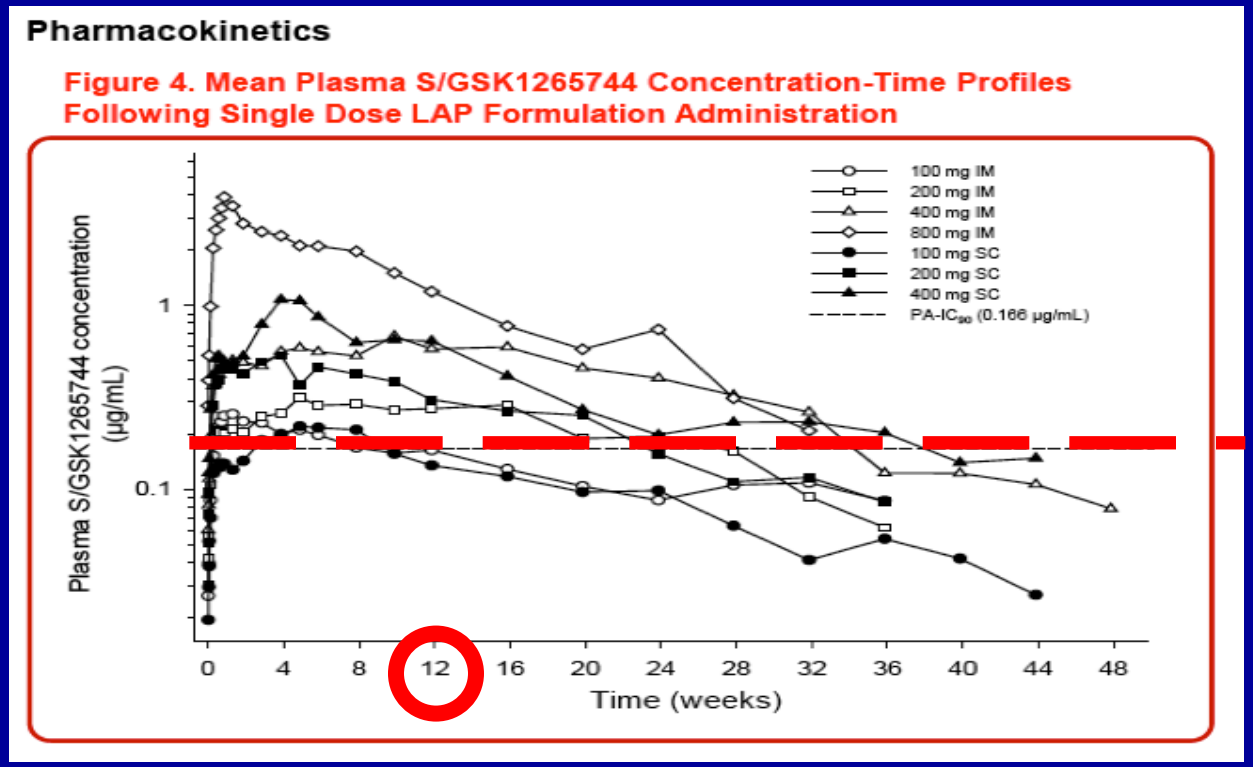
INSTI

needs:

- less frequent dosing

Cabotegravir (CAB)

- Integrase inhibitor similar to DTG; similar resistance
- Potent in HIV+ individuals (5, 10, 30, 60 mg oral)
  Margolis EACS 2013; Spreen HIV Clin Trials 2013;14:192
- Nanotechology formulation; SC + IM injections
- T ½ 21-50 days!
- Supports monthly or quarterly dosing
- Safety: ISR (all mild) and nodules with SC dosing



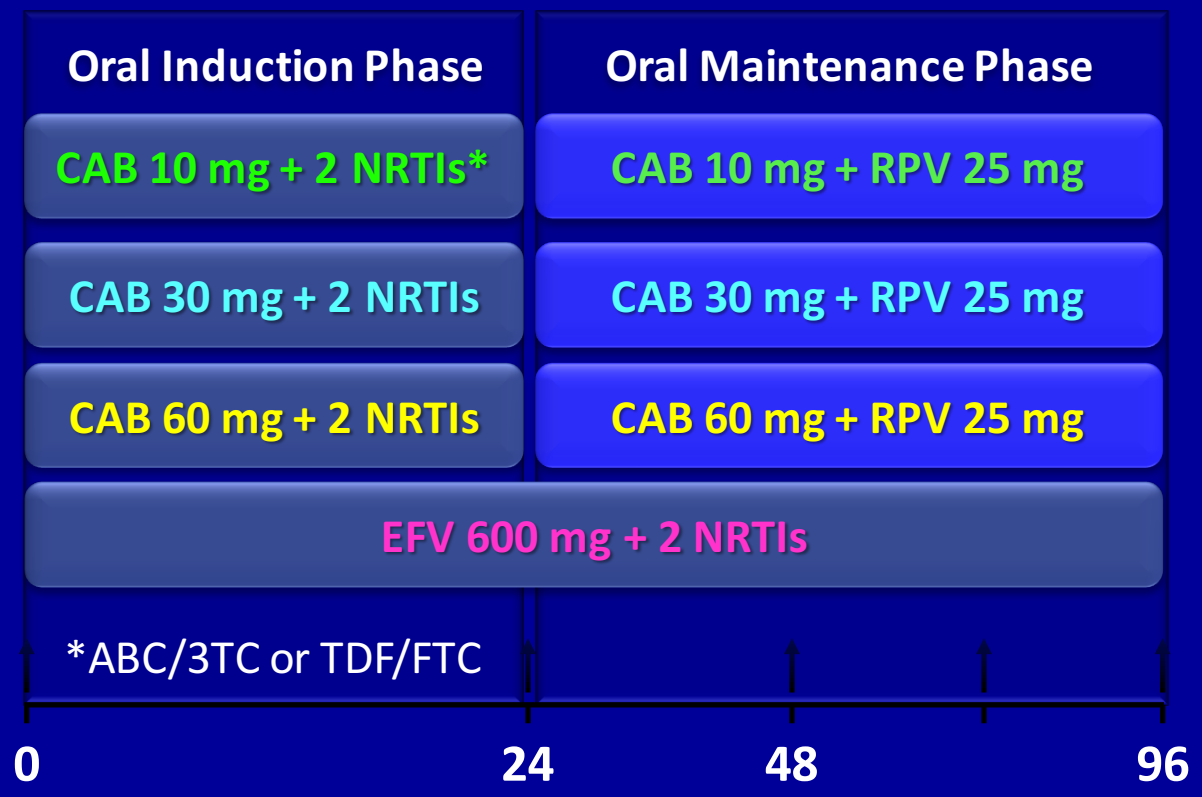
- treatment + prevention

Spreen JAIDS 2014;67:481

LATTE 1: CAB and RPV Oral Maintenance

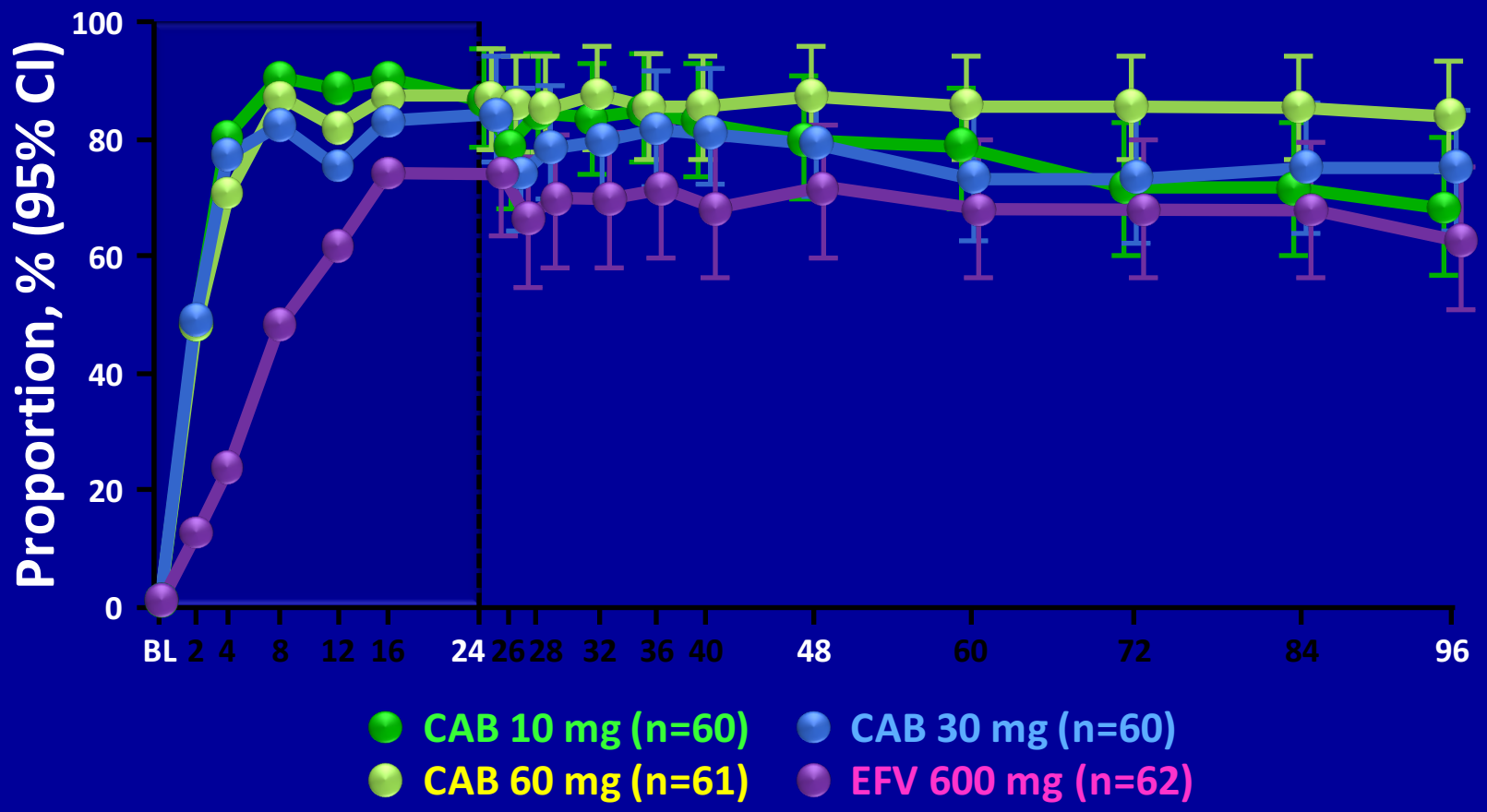
Study Design

- HIV ART-naïve
- VL ≥1000 c/mL
- CD4 ≥ 200 cells/mm^3
- 1:1:1:1
- Randomization Stratified by VL and NRTI
- Blinded to CAB dose
- N=243



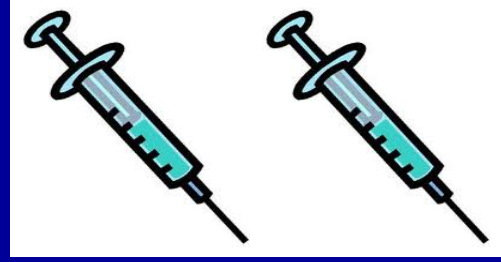
Margolis Lancet ID 2015 (epub 7/17/15)

LATTE 1: CAB and RPV Oral Maintenance



Margolis Lancet ID 2015 (epub 7/17/15)

LATTE 2: CAB LAP + RPV-LA as Maintenance Therapy



Phase 2b open-label 96-wk study in rx-naïve (N=309)

Start with CAB oral + 2 NRTIs; 93% suppressed and randomized 2:2:1 to: CAB LAP + RPV-LA q4 weeks, q8 weeks or continue oral CAB + 2 NRTIs

Results: At 32 weeks of maintenance (primary endpoint):

HIV RNA <50: 94% (4 wks), 95% (8 wks), 91% (oral)

AEs→withdrawal: 5% (4 wks), 2% (8 wks), 2% (oral)

93% of injection participants reported ISR

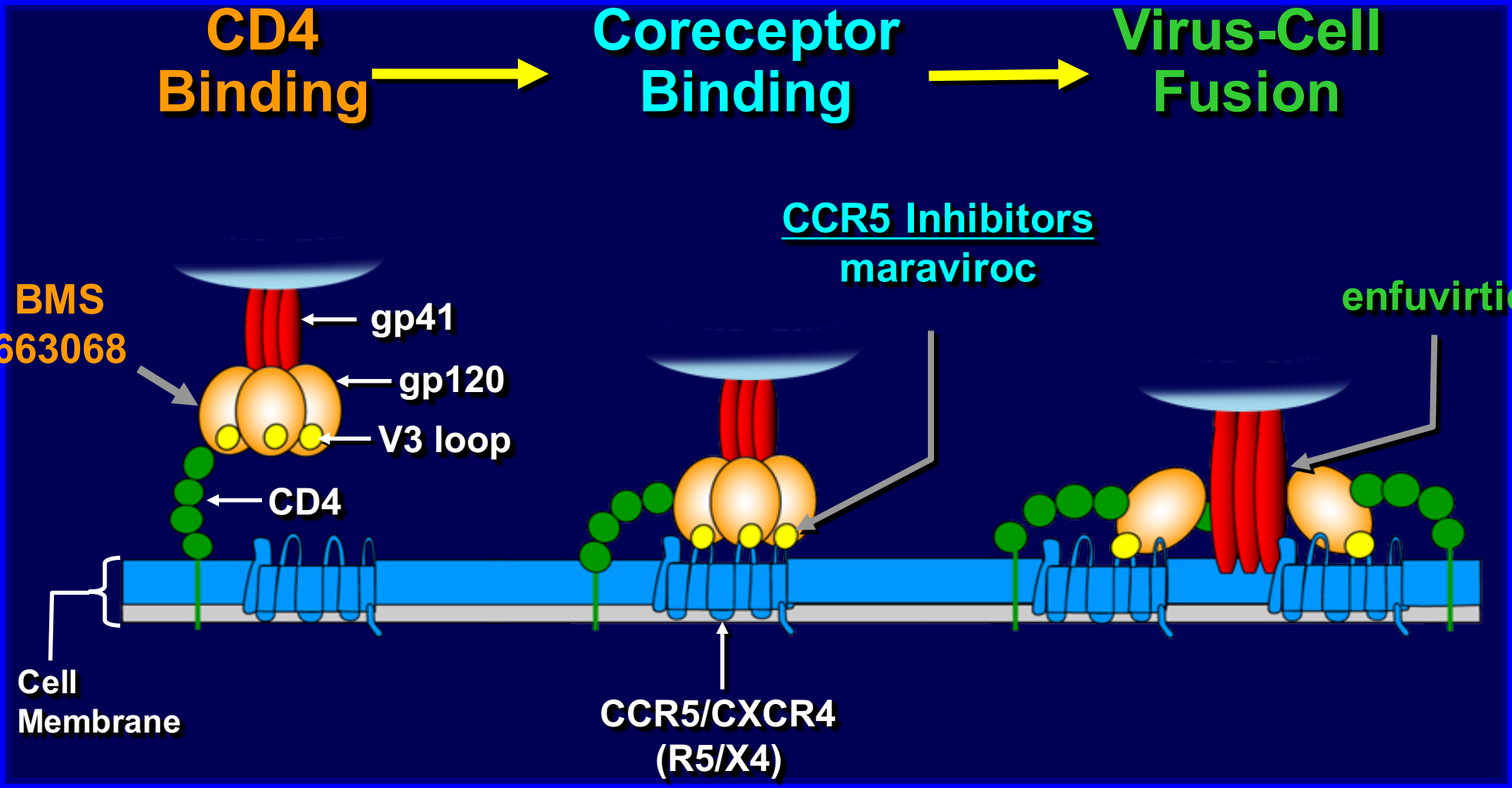
Janssen and ViiV Press Releases 11/3/15

CD4 Attachment Inhibitor

needs:

- novel mechanism of action

HIV Entry Inhibitors

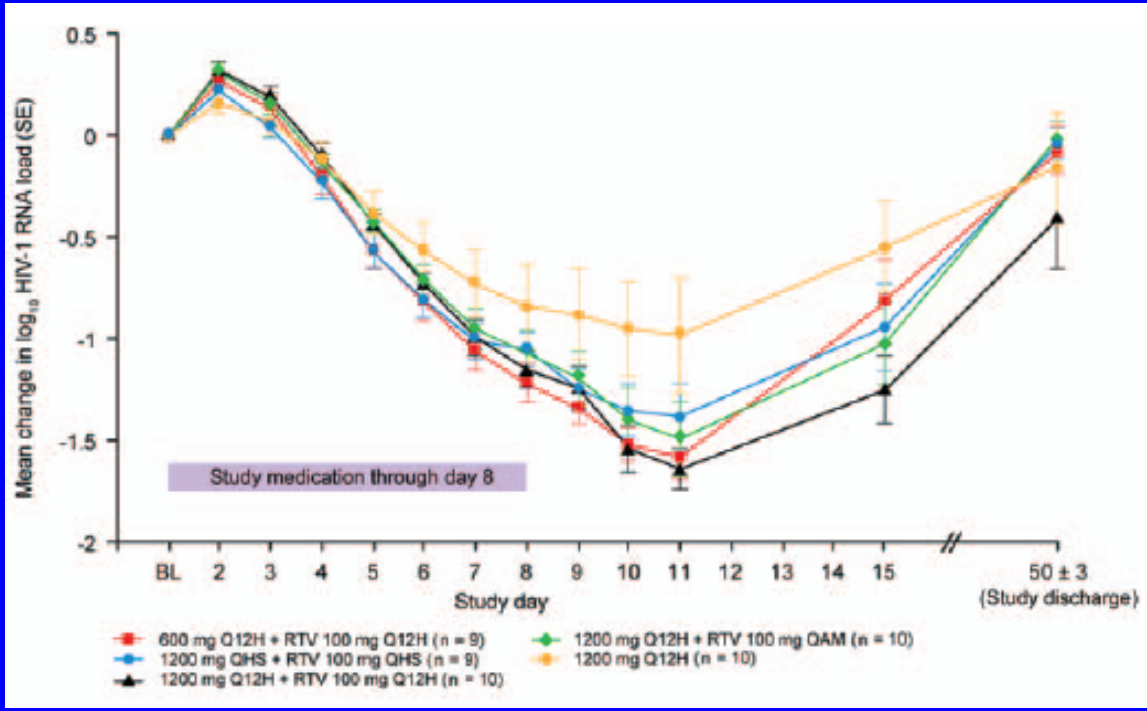


Adapted from Moore JP, *PNAS* 2003;100:10598-10602.

BMS-663068: Oral HIV Attachment Inhibitor

Study pop: CD4 ≥200, VL ≥5000 off ART X ≥8 wks or ART-naive (N=50)

- Prodrug of **BMS-626529**
- Inhibits CD4 binding by binding to gp120
- PK suggest QD or BID dosing without boosting
- ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms; screened by baseline IC_{50}



Nettles JID 2012;206:1002

- **M426L** substitution correlated with resistance (↑IC50 and poor VR); no selection of M426L day 1 to 8

Zhou JAC 2014;69:573

BMS-663068: Phase 2b -- 24 weeks

- Randomized, partially blinded (to 068 dose)
- Rx-experienced pts (≥1 wk on ≥1 ART) with IC50<100nM for '529 (N=251)
- Randomized to TDF + RAL +
  - 1 of 4 doses of 068 [400 or 800 bid or 600 or 1200 qd] or ATV/r
- Results:
  - 8d monotherapy: up to 1.5 log ↓ with 1200 mg qd
  - Wk 24 VL <50
    - 068 69-80% vs. ATV/r 75%; no difference by BL VL/CD4
  - 068: no SAE or rx d/c

Lalezari Lancet HIV 2015;2:e427-37

BMS-663068: Phase 2b -- 48 weeks

- Results:
  - Wk 48 VL <50
    - 068 61-82% vs. ATV/r 71%

Thompson CROI 2015 #545

  - Safety

	BMS-663068 + TDF + RAL				ATV/r + TDF + RAL
Total number of subjects, n (%)	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
SAEs	3 (6.0)	5 (10.2)	4 (7.8)	3 (6.0)	5 (9.8)
Grade 2-4 related clinical AEs	4 (8.0)	4 (8.2)	3 (5.9)	6 (12.0)	15 (29.4)
AEs leading to discontinuation	1 (2.0)	2 (4.1)	0	2 (4.0)	2 (3.9)

Clotet EACS 2015

BMS-663068: PK and Current Status

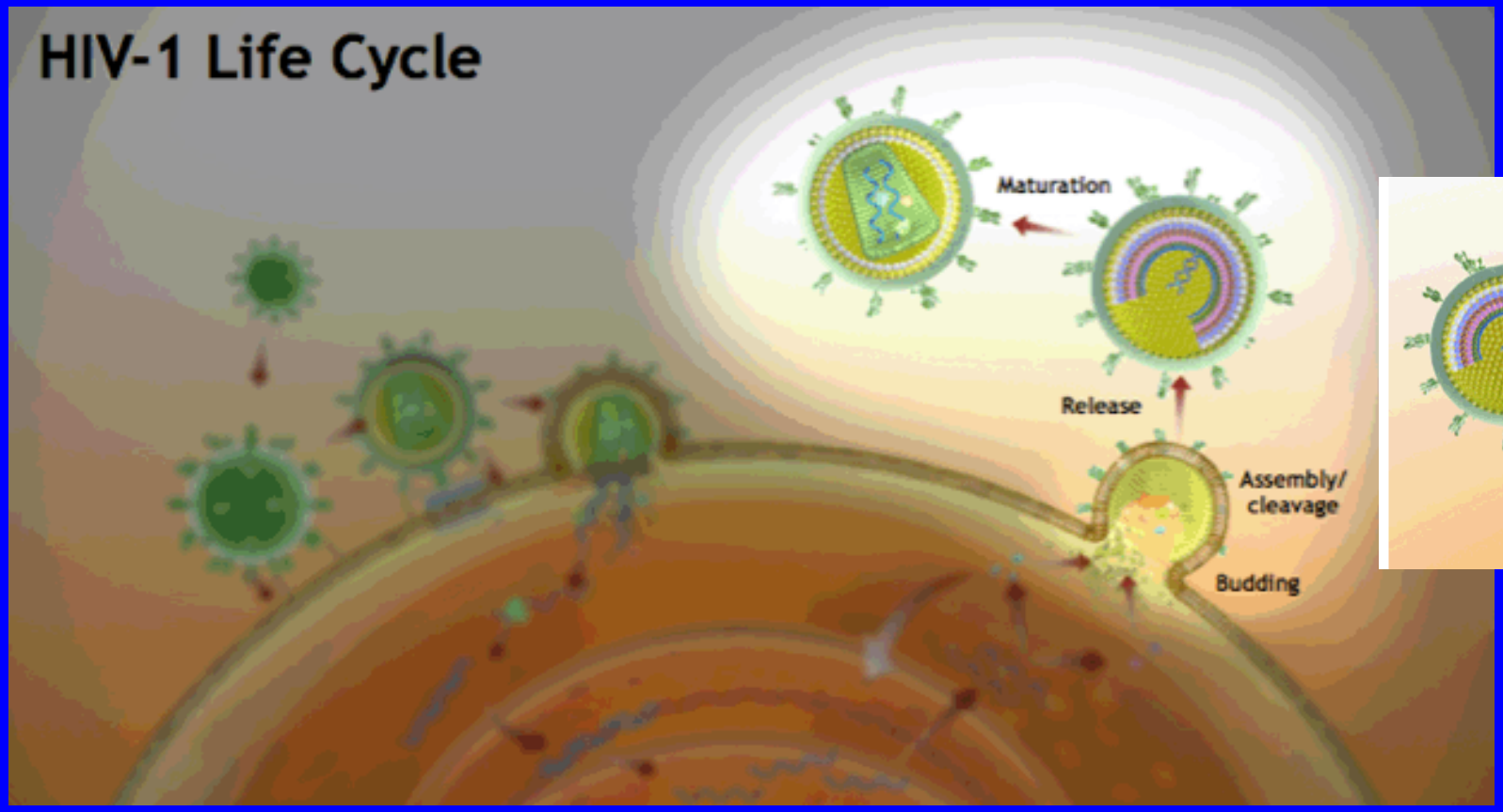
- No PK Interactions with ATV or ATV/r Zhu CROI 2013 #534
- No PK Interactions with DRV/r or DRV/r + ETR (ETR alone ↓663068) Landry CROI 2015 #523

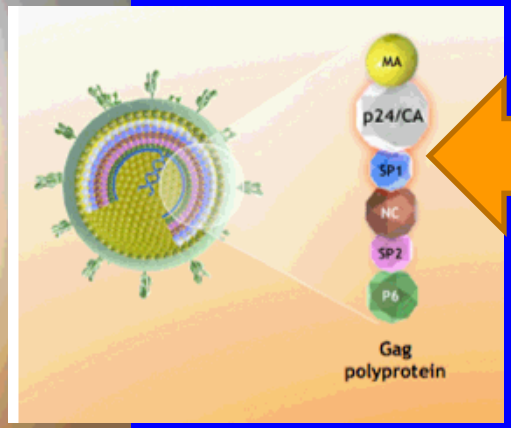
- FDA "breakthrough" designation 7/15
- Currently in Phase 3 in heavily treatment-experienced patients

Maturation Inhibitor

needs:

- novel mechanism of action
- no baseline polymorphisms that confer resistance



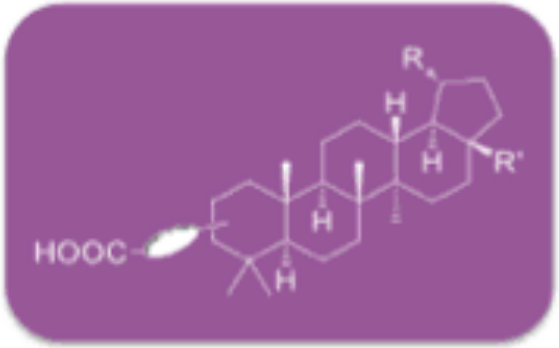


Lataillade CROI 2015 #114LB

BMS-955176: Profile of a Second-Generation MI

- Binds tightly and reversibly to HIV-1 Gag[1]
- Greater potency and coverage of Gag polymorphs compared with first-generation MI[1]
- Low serum binding[1]
- Low-dose prediction with half-life supportive of once-daily dosing
- No significant safety issues identified in early clinical studies

Core structure of BMS-955176



Broad Polymorphic Coverage of BMS-955176

Virus (HIV-1 NL_{4-3})	Subtype B, % LANL database†	EC_{50}, nM		Fold change in EC_{50} v.s. WT	
		BVM	BMS-176	BVM	BMS-176
WT (NL_{4-3})	51	10	2	-	-
WT + serum*	-	1300	10	130	5.0
V362I	12	74	4	7.4	2.2
Q369H	2.4	8	2	0.8	1.0
V370A	15	552	3	55	1.4
V370M	5	111	3	11	1.5
ΔV370‡	0.6	>4000	13	>400	6.8
ΔV370/T371A‡	1.9	>4000	7	>400	3.5
T371A	5	10	3	1.0	1.5
ΔT371	3	77	5	7.7	2.5

SDMs in NL4-3 background (subtype B)

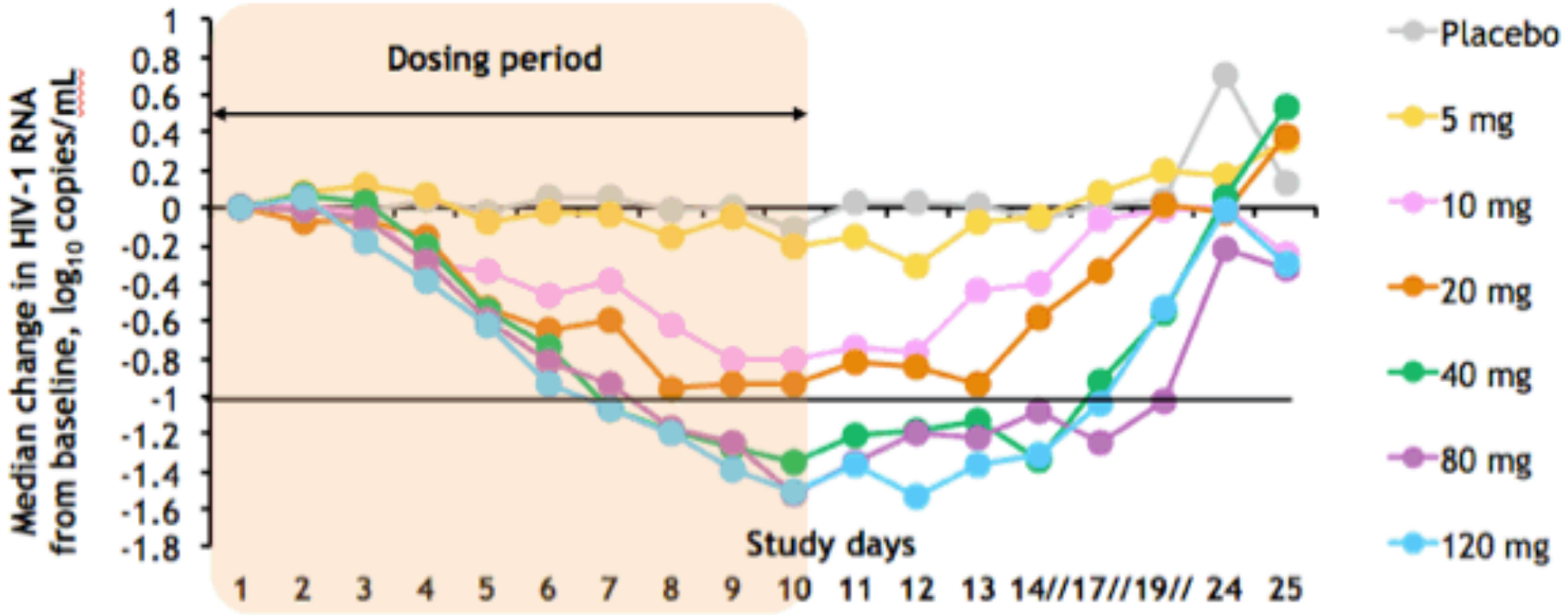
1. Lin *et al.* Maturation Inhibitor Mechanistic Studies - Differential Inhibition of Gag Polymorphs. Poster 539, Session P-11 (February 25, 2:30-4:00 pm PST);
*Assay conducted in the presence of 40% human serum + 27 mg/mL human serum albumin; ‡Surrogate genotypes for subtype C; †Percentage of subtype B isolates in the Los Alamos database (2010). BVM, Bevirimat; SDM, site directed mutant; WT, wild-type.

Lataillade CROI 2015 #114LB

Phase 2a, Part A

BMS-955176: Median Change in HIV-1 RNA over Time

Study population: ART naïve or experienced, VL ≥5000, CD4 ≥200 (N=60)



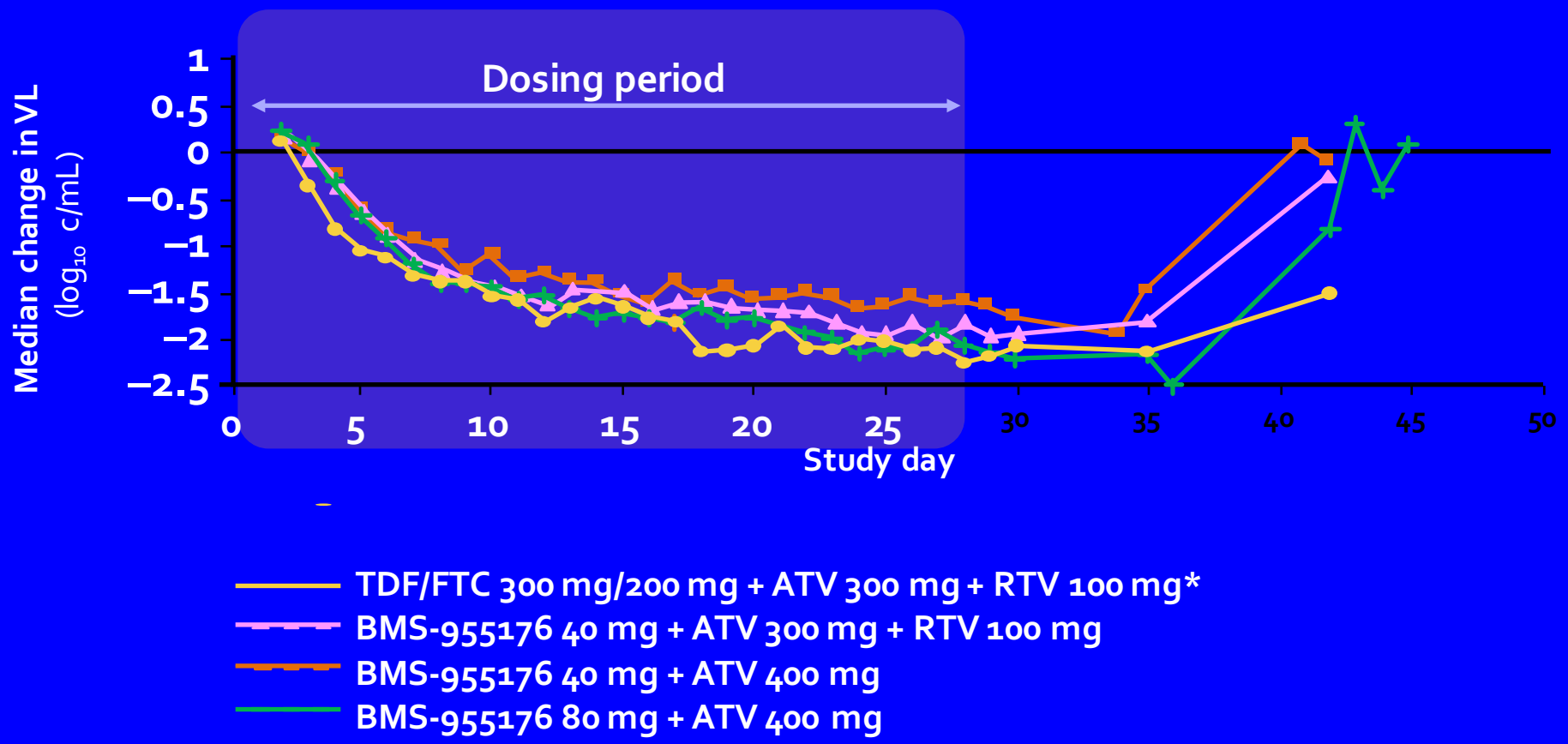
- Median change in HIV-1 RNA from baseline to Day 11 reached --1.4 log_{10} c/mL

- No serious adverse events, grade 3/4 events, no d/c due to adverse events

Lataillade CROI 2015 #114LB

BMS-955176: Phase 2a (Part B)

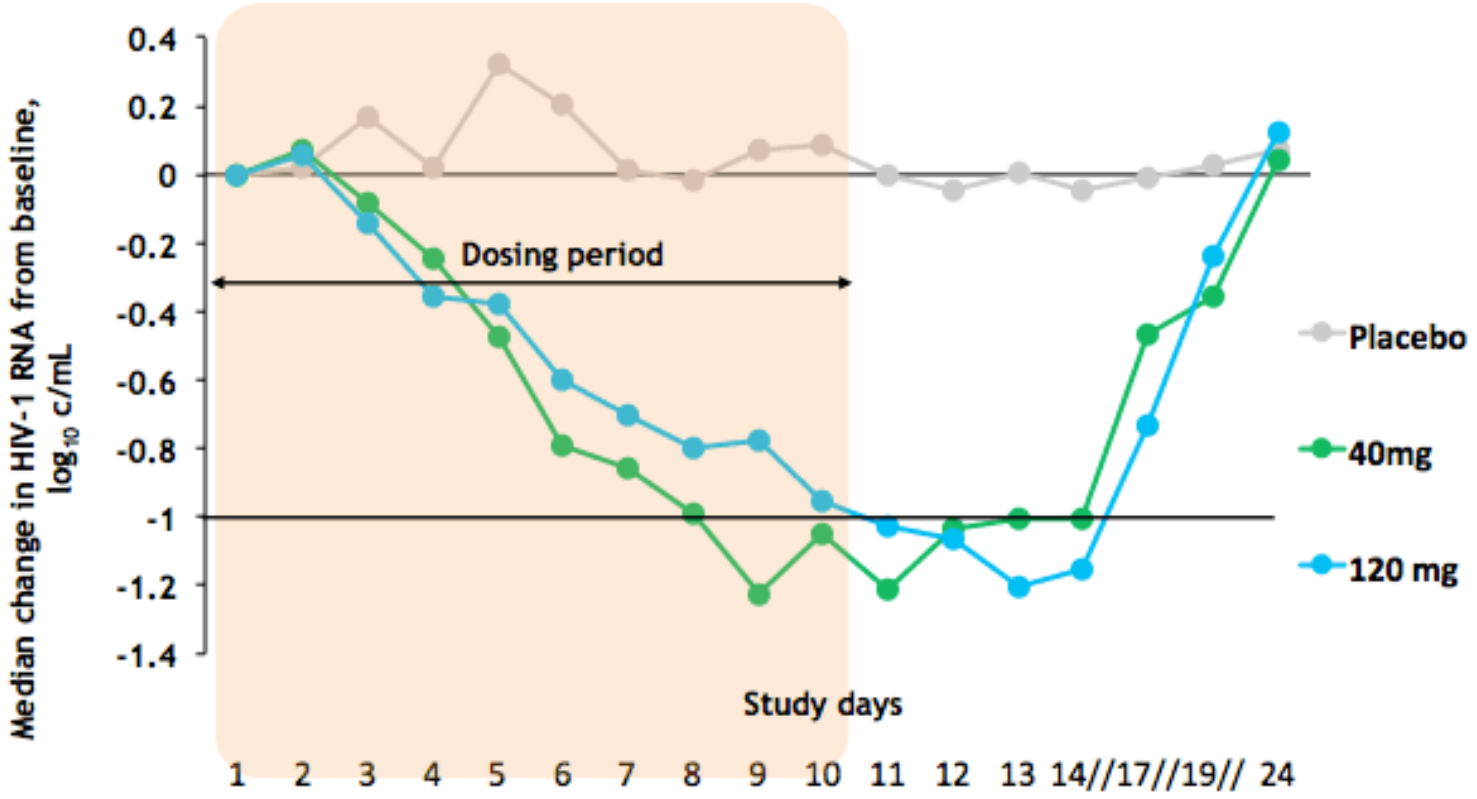
Study population: Subtype B, Rx-naïve, VL≥5000, CD4≥200 (N=28)



Hwang IAS 2015 #TUAB0106LB

BMS-955176: Median Change in HIV-1 RNA Over Time (Part C, Subtype C)

Study population: ART naïve or experienced, VL ≥5000, CD4 ≥200 (N=19)



All doses were QD.

Hwang EACS 2015 PS 10/5

BMS-955176: Safety Summary

- Part A and C (10d monotherapy, dose escalation)
  - No deaths, AE requiring discontinuation, serious AE, grade 3-4 clinical AE
  - 1 grade 3 neutropenia (transient) at 120 mg dose

- Part B (28d in combination with ATV)
  - No deaths, AE requiring discontinuation, serious AE
  - 1 neutropenia; 10 increased total bilirubin

Acknowledgments

- Cornell HIV Clinical Trials Unit (CCTU)
- Division of Infectious Diseases
- Weill Cornell Medical College
- AIDS Clinical Trials Group (ACTG)
- HIV Prevention Trials Network (HPTN)
- Division of AIDS, NIAID, NIH

- The patient volunteers!