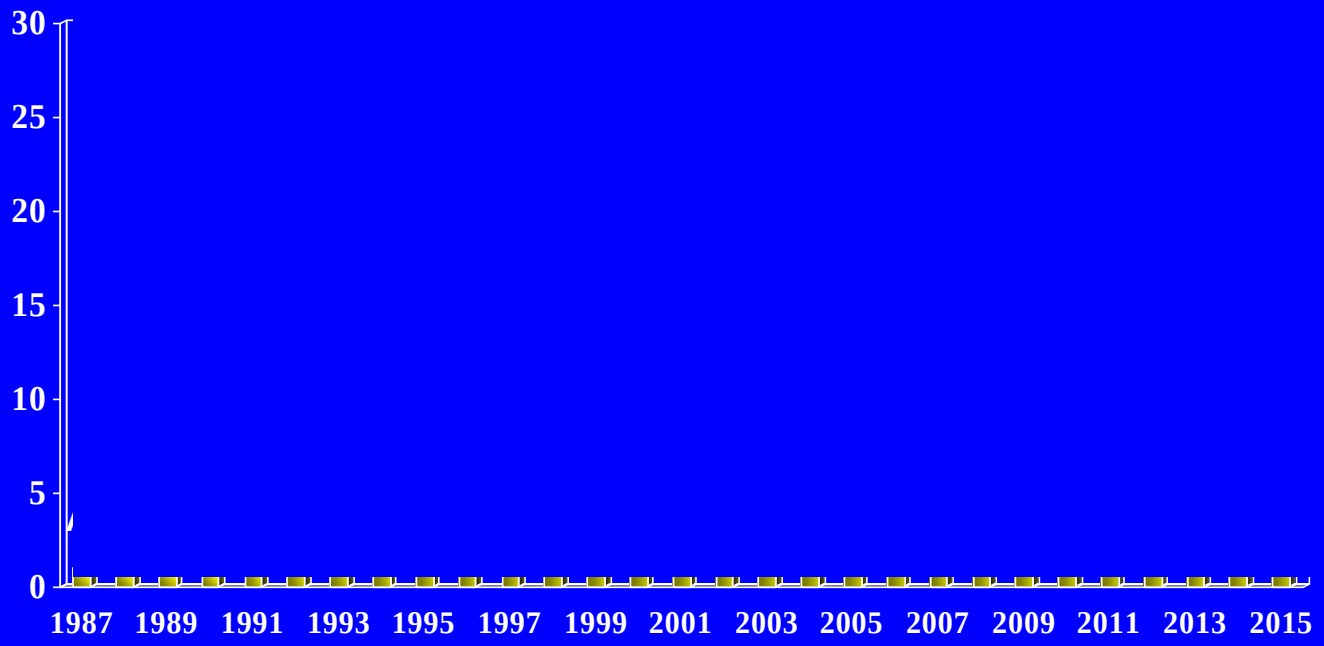
ART Progress: New Drugs

RM Gulick, MD, MPH
Rochelle Belfer Professor in Medicine
Chief, Division of Infectious Diseases
Weill Cornell Medicine

Antiretroviral Drug Approval: 1987 - 2017



Newer ART Agents (partial list)

	NRTI	NNRTI	PI	Entry Inh	II	MI
Phase 3		doravirine		albuvirtide fostemsavir ibalizumab PRO140	bictegravir cabotegravir	
Phase 2	apricitabine dexelvucitabine festinavir	BILR 355 elsulfavirine		cenicriviroc PF-232798		
Phase 1/2	elvucitabine		TMC 310911	HGS004 UB-421		
Phase 1	MK-8591 (EFdA) CMX157	RDEA 806	CTP-298 CTP-518 PPL-100 SPI-256	BMS-986197 SCH532706 VIR-576	BI 224436 INH-1001	GSK-2838232

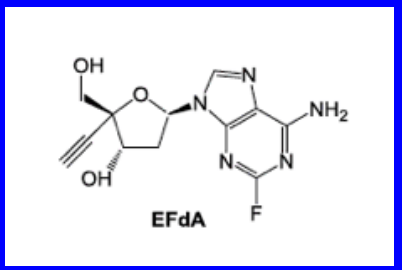
NRTI

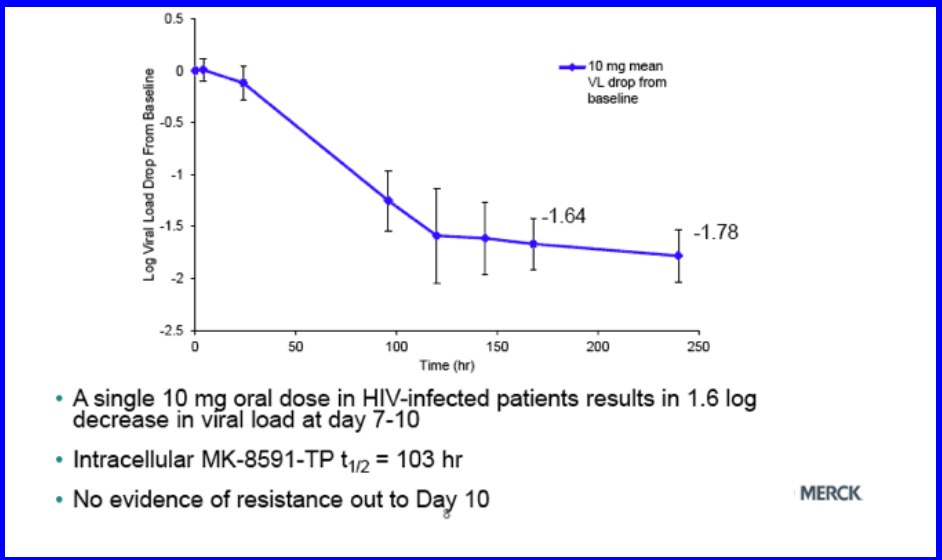
Needs:

- More convenient

MK-8591 (EFdA)

- 4’-ethynyl-2-fluoro-2’-deoxyadenosine; EFdA
- Nonobligate chain terminator
- Inhibits RT by preventing translocation (NRTTI)
- Potent antiviral activity (PBMC EC_{50} = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)
- Accumulates in LN, vagina, rectum (animals)
- Low-dose formulations

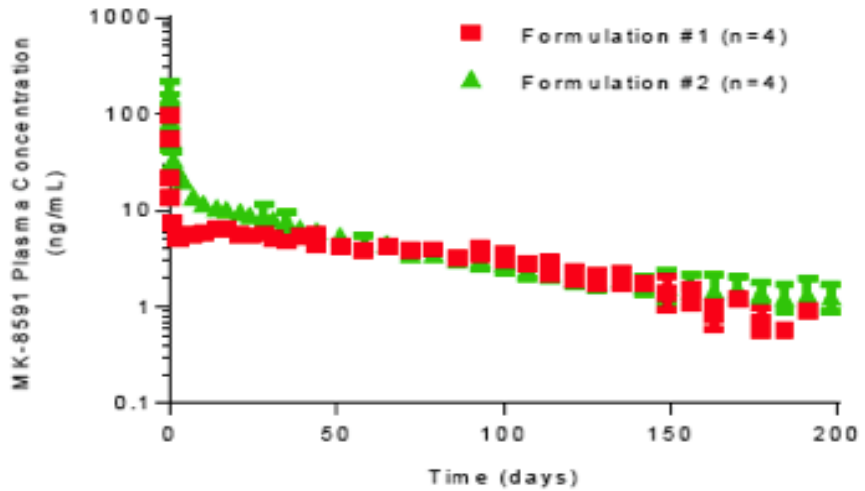




Grobler CROI 2016 #98
Friedman CROI 2016 #437LB
Grobler CROI 2017 #435

MK-8591 (EFdA)

MK-8591 Parenteral Formulations Release Effective Drug Levels for >180 days



- Low dose amenable to extended-duration parenteral formulation
- >180-day extended release from solid state formulations after a single injection in rat
- Data suggest the potential to provide coverage for durations up to 1 year

Grobler CROI 2016 #98
Friedman CROI 2016 #437LB
Grobler CROI 2017 #435

NNRTI

Needs:

- Less toxicity and better tolerability
- Active against NNRTI-resistant viruses
- Fewer drug interactions

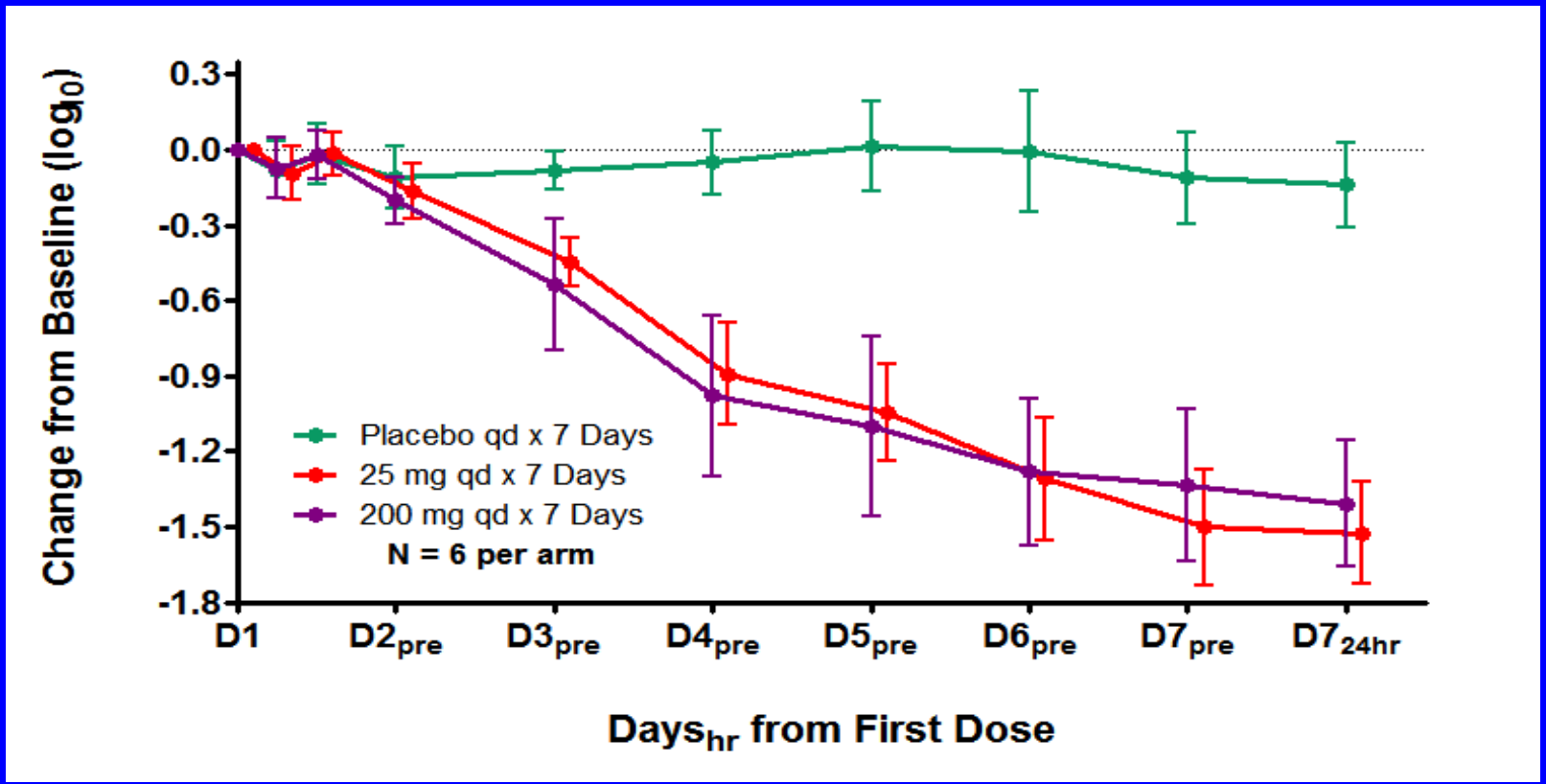
Doravirine (DOR; MK-1439)

- Investigational NNRTI
- Preclinical
  - –Potent at low-milligram dose
  - –Metabolized by CYP3A4; not a CYP450 inhibitor or inducer
  - –Active in vitro against viral strains with:
    - •K103N
    - •Y181C
    - •G190A
    - •E101K
    - •E138K
    - •K103N/Y181C

Lai AAC 2014;58:1652-1663

Doravirine (DOR): Phase Ib

Double-blind, randomized, placebo-controlled
Study population: HIV+, treatment-naïve (N = 18)

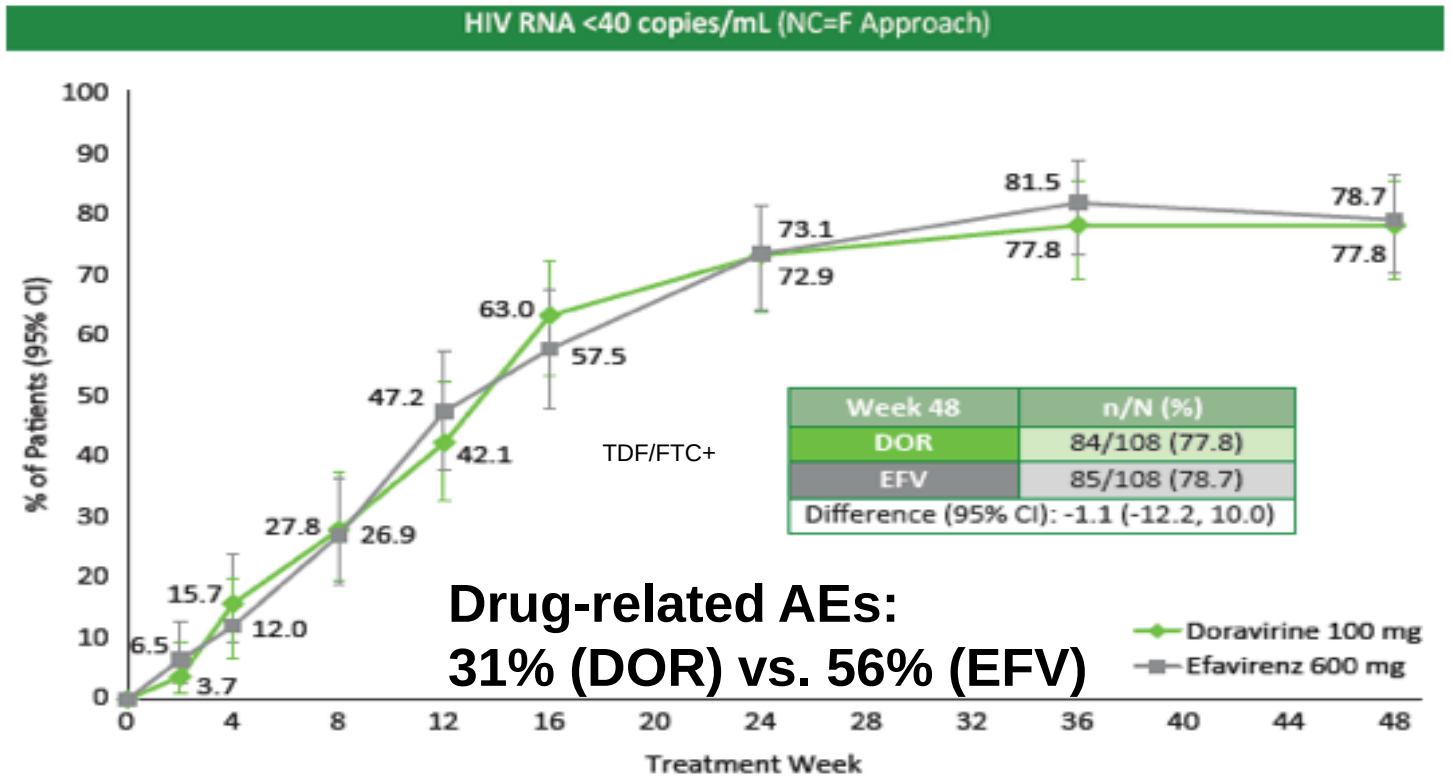


Schurmann AIDS 2016;30:57-63

Doravirine (DOR) – Phase 2

Randomized, double-blind, 2-part study

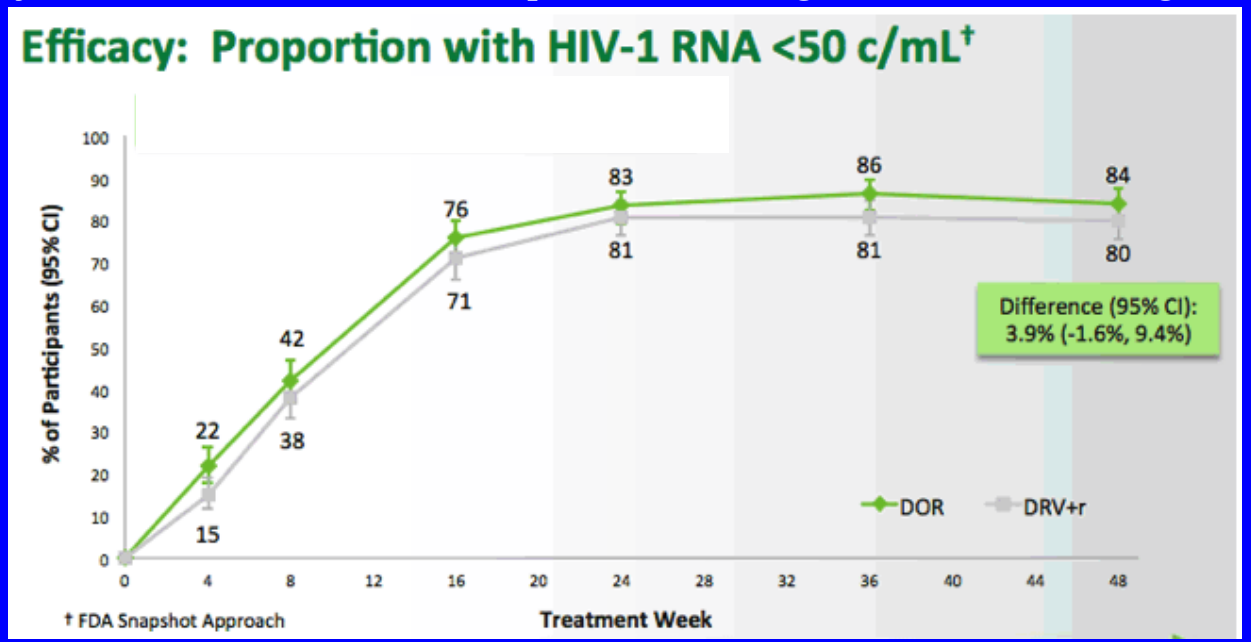
Study population: Rx-naïve participants, VL ≥1000, CD4 ≥100 (N = 216)



Gatell JIAS 2016;17:19532

Doravirine (DOR) – Phase 3

Phase 3, multicenter, double-blind, placebo-controlled randomized study
Study population: Rx-naïve, VL ≥1000, no GT resistance to study drugs (N = 769)
Study treatment: 2 NRTIs + [DOR 100 mg vs. DRV 800 mg/RTV 100 mg]



Pts with protocol-defined VF: DOR 19 (5%) vs DRV/r 24 (6%) → NO drug resistance
Discontinued due to AE: DOR 2% vs DRV/r 3%
most common: diarrhea DOR 14% vs DRV/r 22%; nausea DOR 11% vs DRV/r 12%
lipids decreased with DOR (chol -1, triglyc -3 mg/dL), increased with DRV/r (chol +18, triglyc +22)

Molina/Squires CROI 2017 #45LB

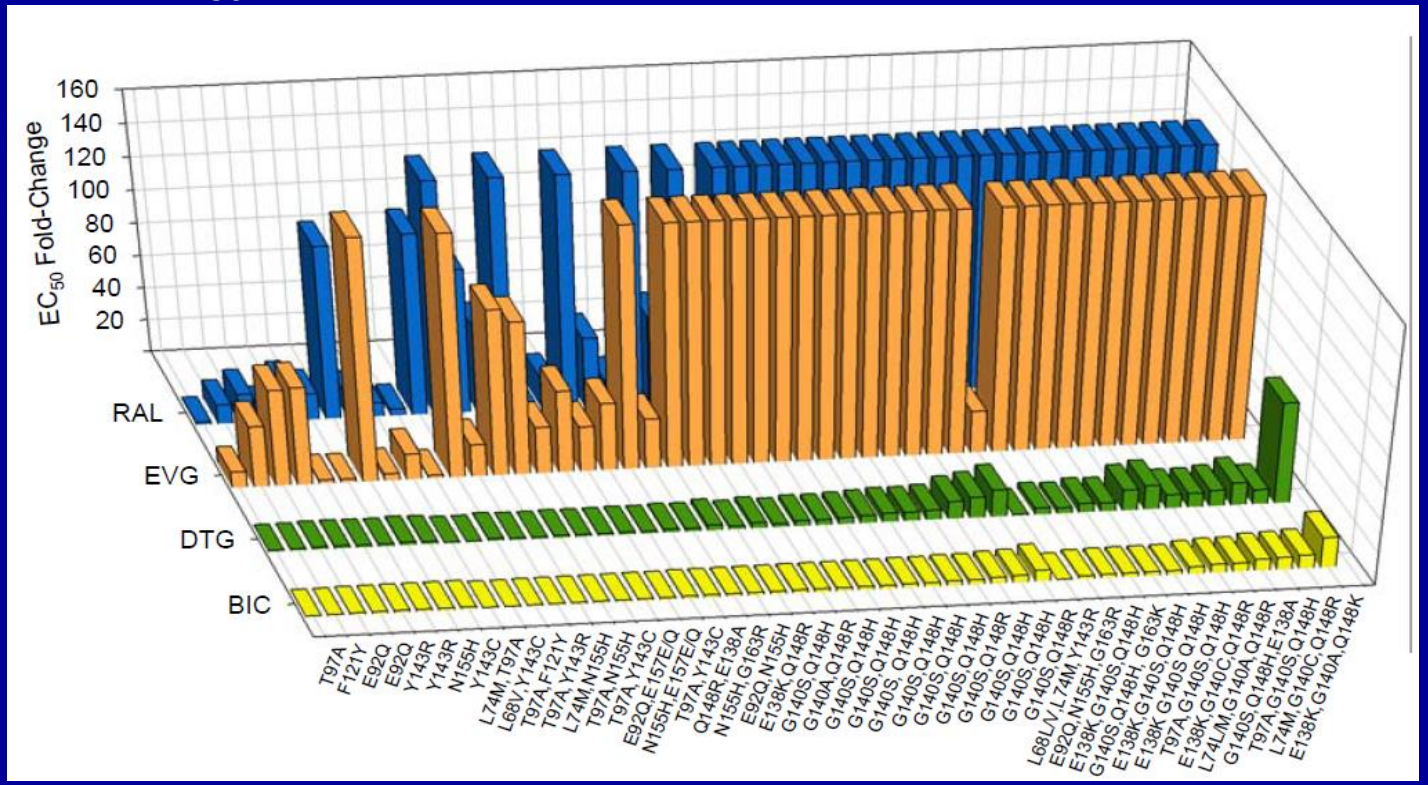
INSTI

Needs:

- Active against INSTI-resistant virus
- More convenient

Bictegravir (GS-9883): In vitro

- In vitro EC_{50} 0.75 nM against wt clinical isolates of HIV-1 and -2



- $T_{1/2}$ 18 hours (once-daily); no PK boosting required

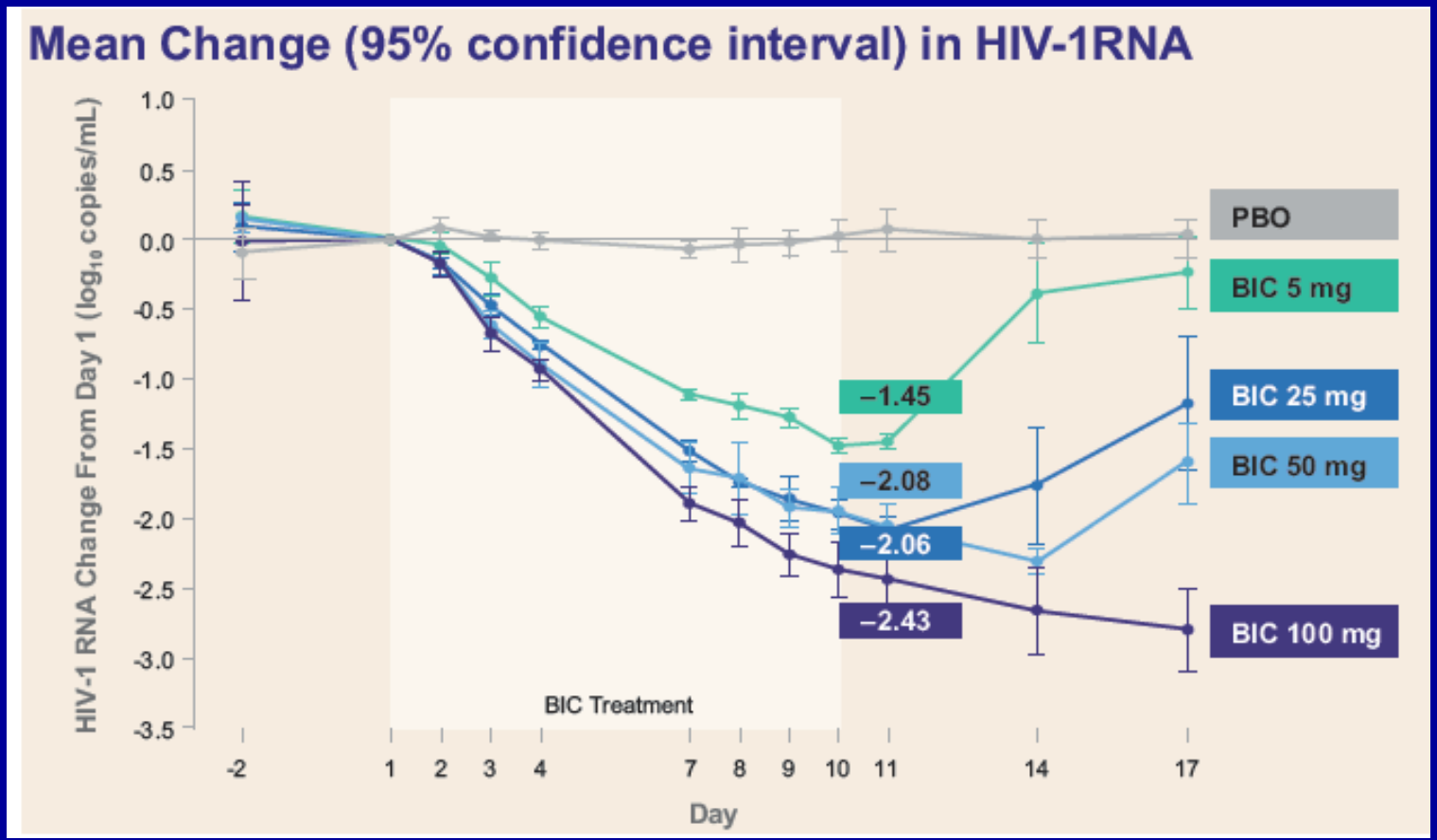
Tsiang Antimicrob Agents Chemo 2016;60:7086-7097

- No inhibition or induction of CYP3A4 or UGT -- low potential for drug interactions

Zhang/Custodio CROI 2017 #40

Bictegravir (GS-9883): Phase 1

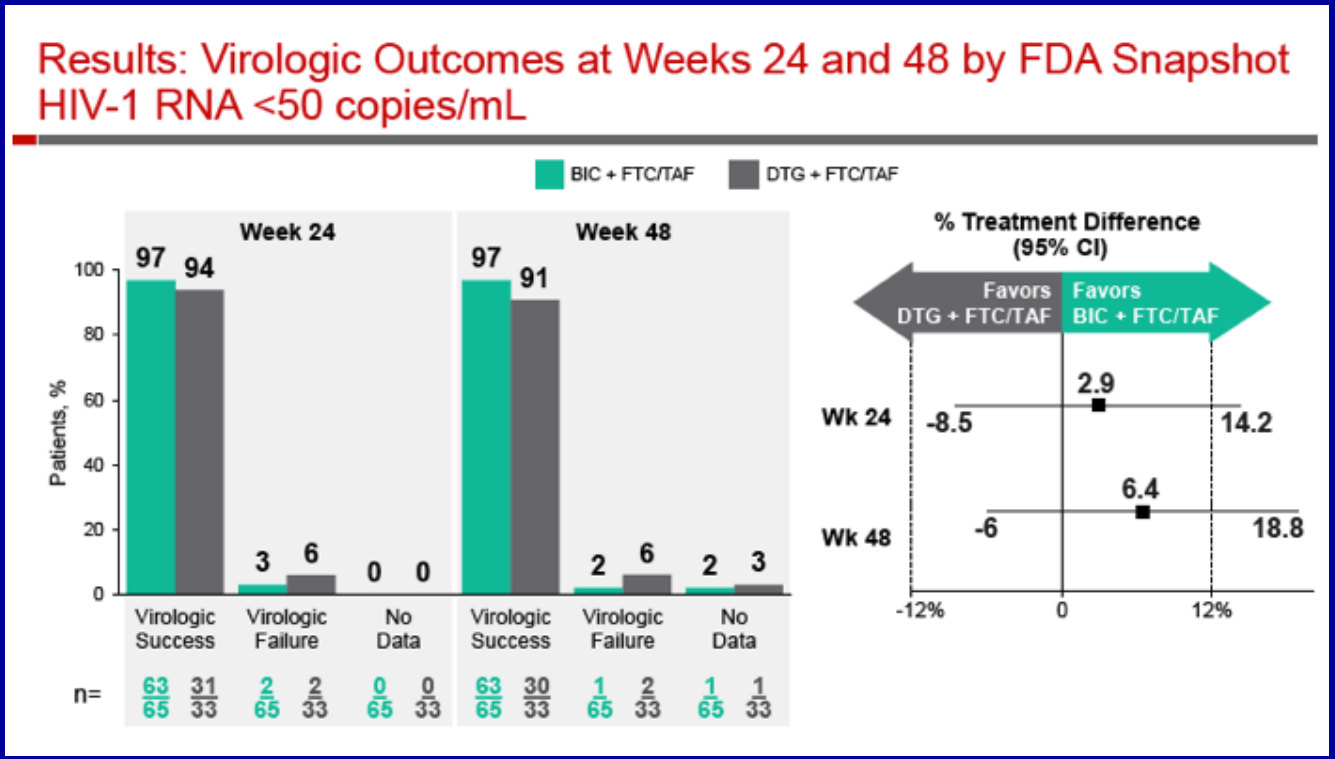
- Study population: HIV+, naïve/off ART X ≥12 wks, no prior INSTI, VL 10K-400K, CD4 >200 (N = 20)



Gallant, ASM Microbe 2016, abstract #415

Bictegravir (GS-9883): Phase 2

- Study population: Rx-naïve, VL ≥1000, CD4 ≥200, HBV/HCV-neg (N=98)
- Study rx: TAF/FTC + [BIC or DTG] (2:1 randomization)



Adverse events and lab abnormalities similar; no drug resistance detected

- Phase 3 studies in progress: TAF/FTC/BIC

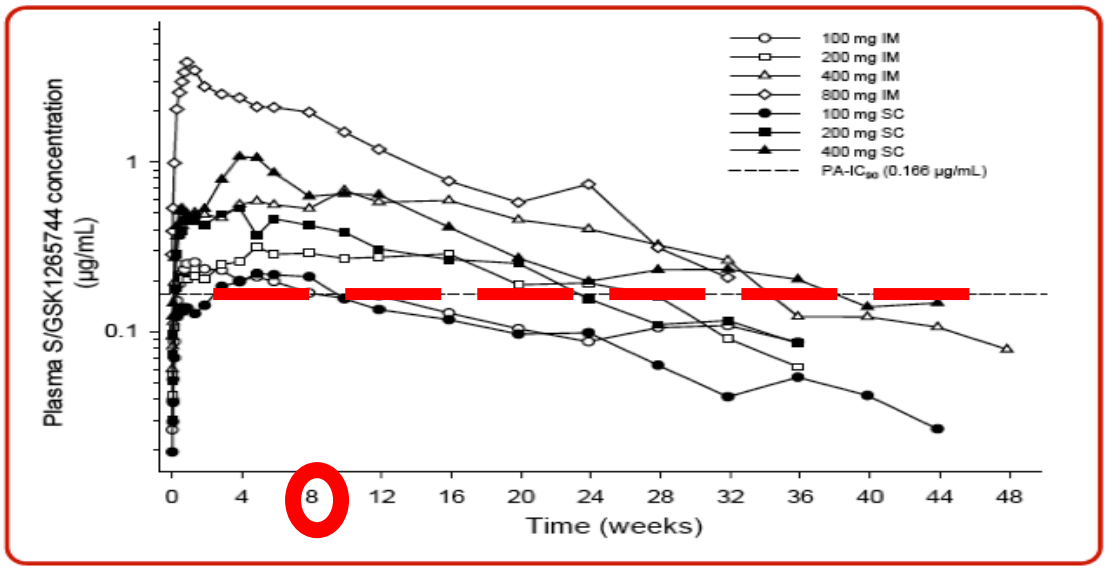
Sax CROI 2017 #41

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
- Nanotechnology formulation; SC + IM injections
- $T_{½}$ 21-50 days!
- Supports monthly or quarterly dosing
- Safety: ISR (all mild) nodules with SC dosing

Pharmacokinetics

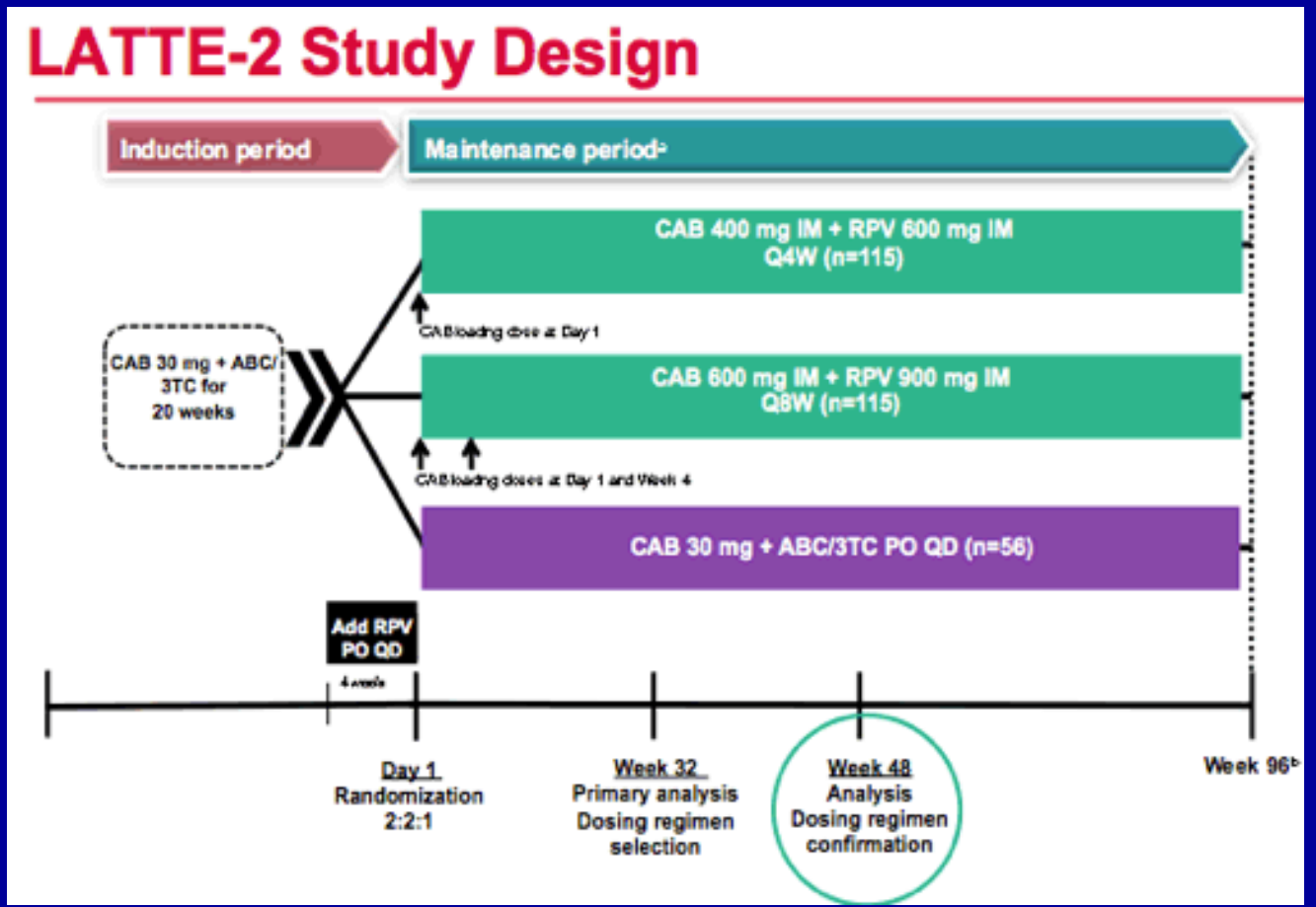
Figure 4. Mean Plasma S/GSK1265744 Concentration-Time Profiles Following Single Dose LAP Formulation Administration



Spreen JAIDS 2014;67:481

LATTE-2: CAB + RPV IM Maintenance

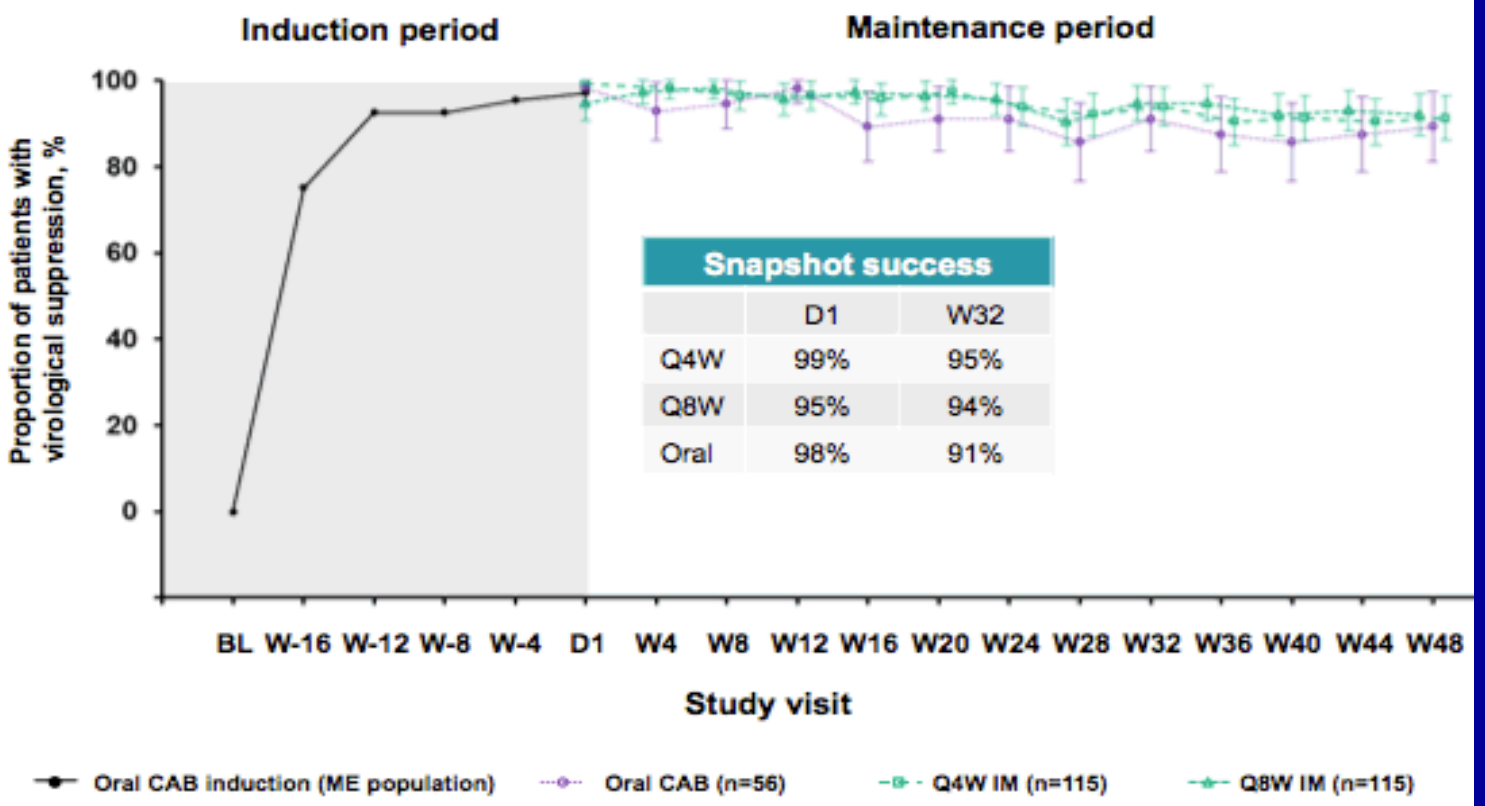
Phase 2b multicenter, parallel group, open-label study
Study population: Rx-naïve individuals (N = 309)



Margolis IAS 2016 #THAB02LB

LATTE-2: Virologic Suppression

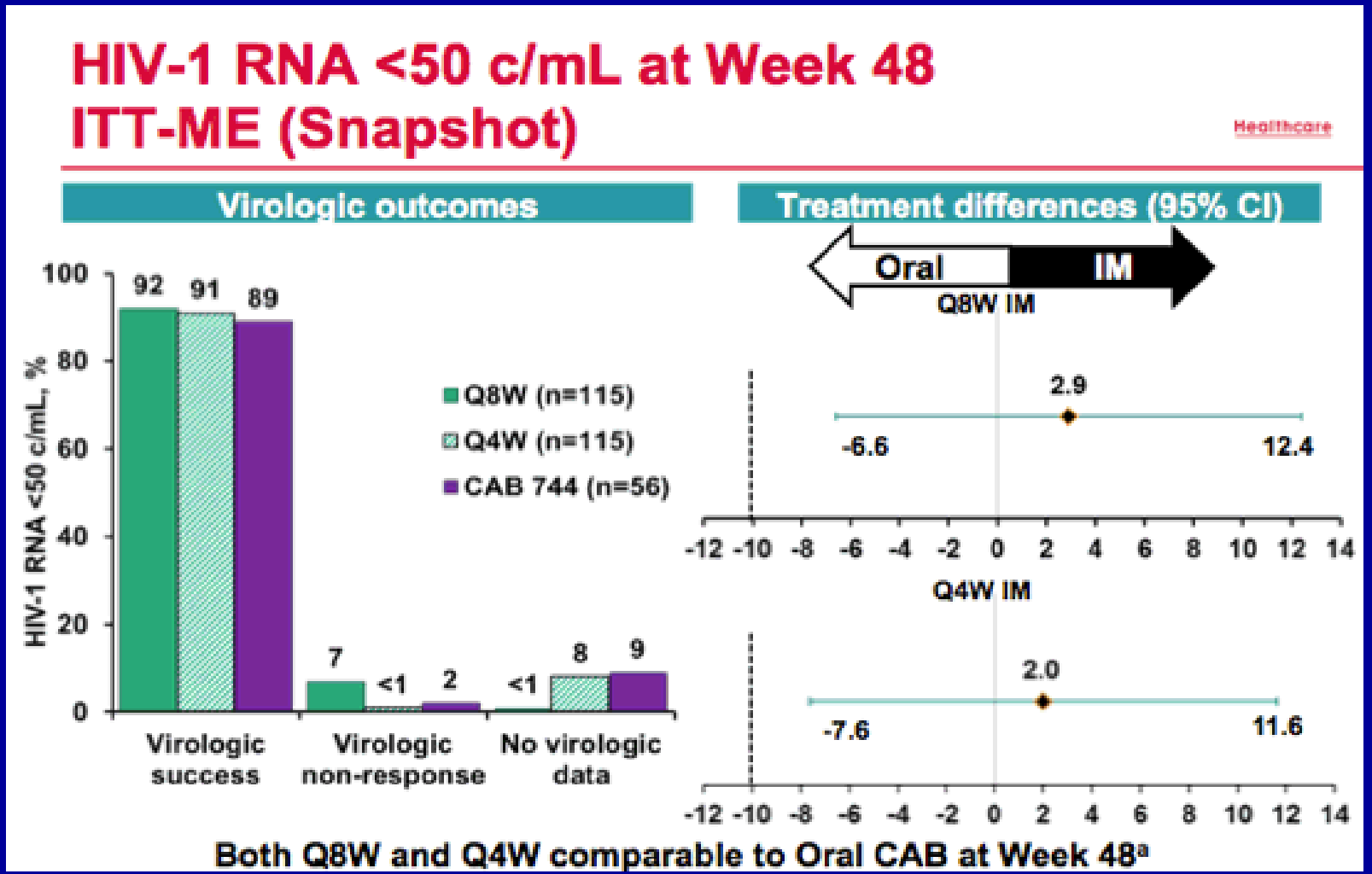
LATTE-2 Week 48 Results: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)



Snapshot success		
	D1	W32
Q4W	99%	95%
Q8W	95%	94%
Oral	98%	91%

Margolis IAS 2016 #THAB02LB

LATTE-2: Efficacy



Margolis IAS 2016 #THAB02LB

LATTE-2: Injection Site Reactions

	Q8W IM (n=115)	Q4W IM (n=115)	IM subtotal (N=230)
Number of injections	1623	2663	4286
Number of ISRs (events/injection)	1054 (0.65)	1228 (0.46)	2282 (0.53)
Grades			
Grade 1	839 (80%)	1021 (83%)	1860 (82%)
Grade 2	202 (19%)	197 (16%)	399 (17%)
Grade 3	12 (1%)	10 (<1%)	22 (<1%)
Grade 4	0	0	0
Duration, days			
≤7	943 (89%)	1121 (91%)	2064 (90%)
Median	3.0	3.0	3.0

- Most common ISR events overall were pain (67%), swelling (7%), and nodules (6%)
- Number of subjects reporting ISRs decreased over time, from 86% (Day 1) to 33% (Week 32)[a]
- 2/230 subjects (1%) withdrew as a result of injection reactions (Q8W)

Margolis CROI 2016 #31LB

HPTN 083: PrEP with TDF/FTC oral vs CAB IM

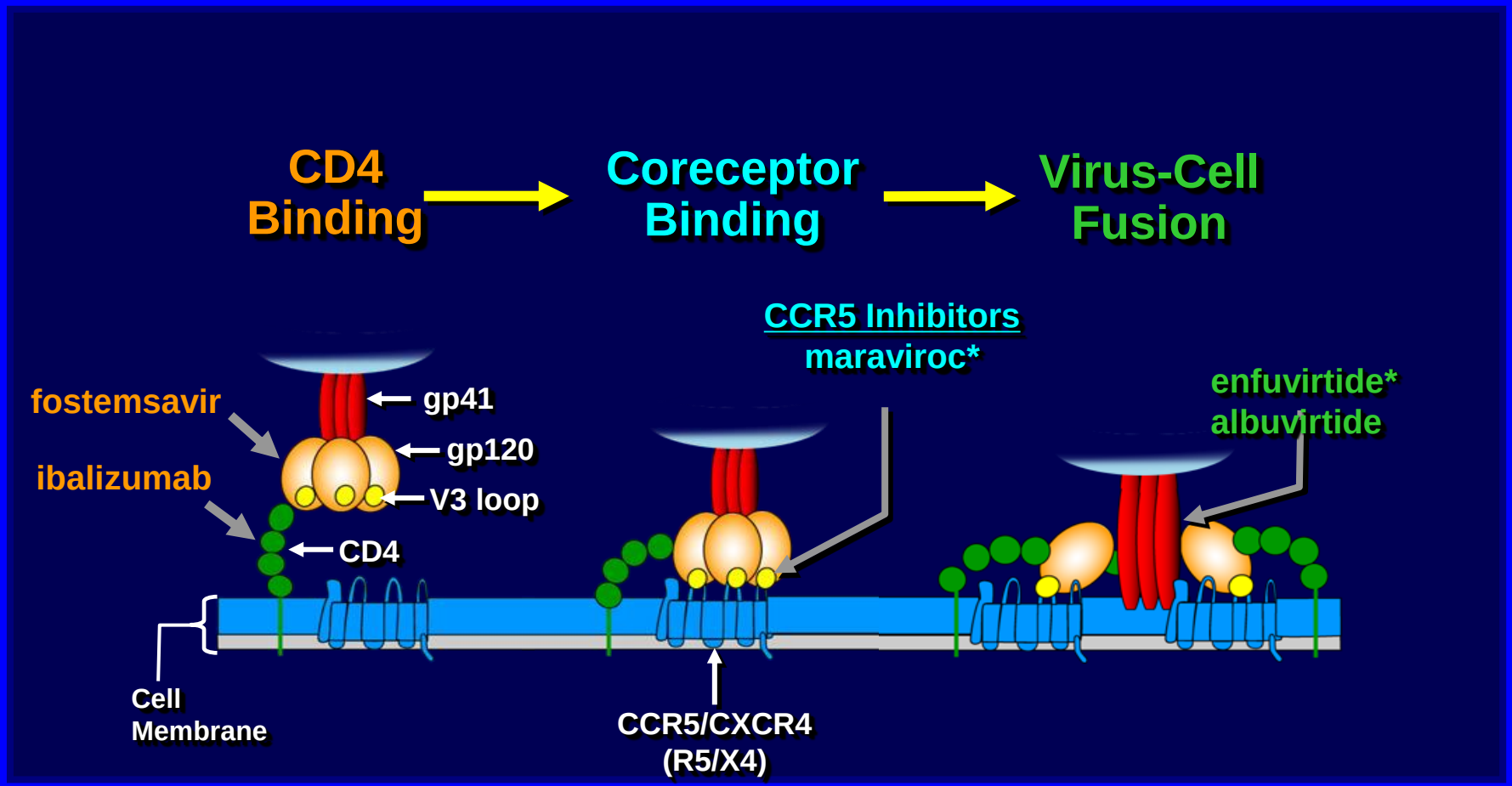
- Study population: Adult MSM and TGW, at high-risk for HIV acquisition (N = 4500)
  - High risk
    - Any non-condom receptive anal intercourse (RAI)
    - >5 partners
    - Stimulant drug use
    - Rectal or urethral STI in past 6 months
- Study regimen: TDF/FTC daily oral vs CAB q2-month injections
  - Double-blind, double-dummy design
- Design: noninferiority, efficacy study
- NY area: Weill Cornell Chelsea, Rutgers, Harlem, NY Blood Center, Bronx -- First participant enrolled 12/16!

Entry Inhibitors

Needs:

- Novel mechanism of action
- More convenient dosing

HIV Entry Inhibitors



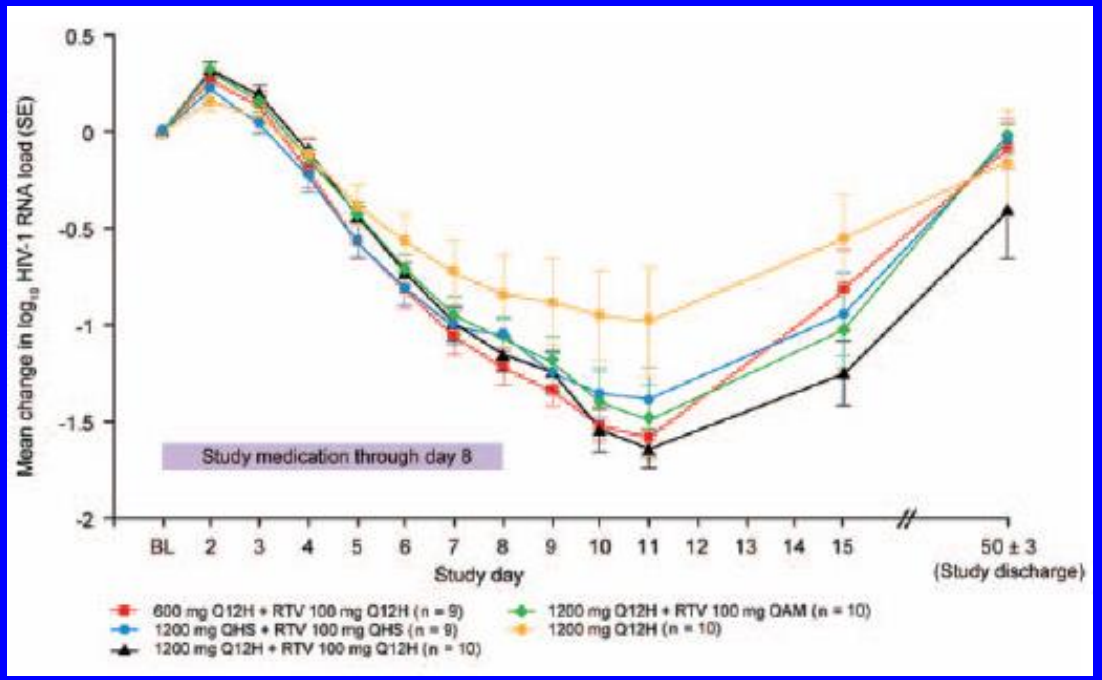
* = FDA approved

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

Fostemsavir: Oral HIV Attachment Inhibitor

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

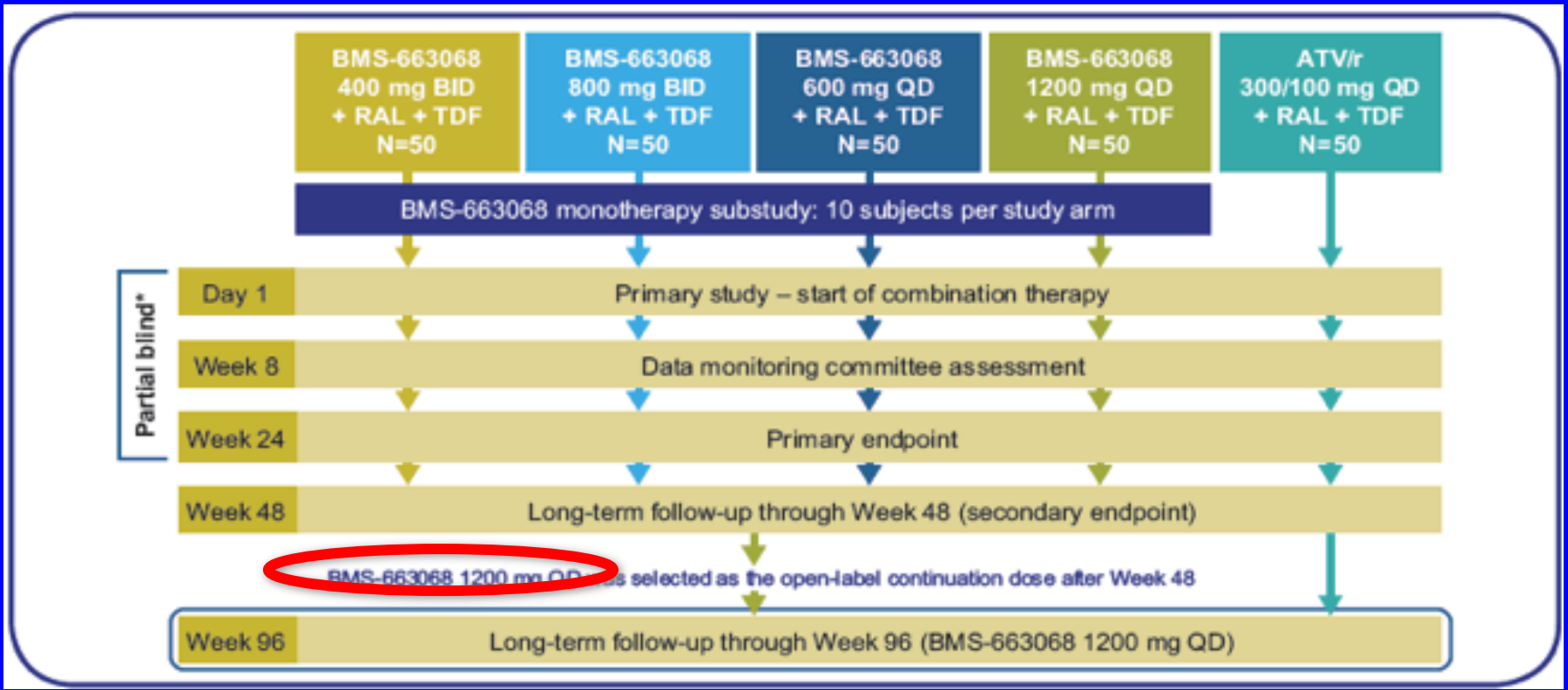
- Prodrug of **temsavir**
- Inhibits CD4 binding by binding to gp120
- PK suggest QD or BID dosing without boosting
- ↓ baseline susceptibility in 12% of pts due to envelope polymorphisms; screened by baseline IC_{50}



Nettles JID 2012;206:1002

Fostemsavir: Phase 2b

Phase 2b, randomized, controlled, partially blinded (to '068 dose)
Study pop: Rx-experienced (≥1 wk on ≥1 ART); IC_{50} <100 nM for '529 (N = 254)



Lalezari Lancet HIV 2015;2:e427-37
Thompson Antivir Ther (epub 12/16)

Fostemsavir: Phase 2b Efficacy

- Week 48 VL <50:
  - MITT: 61-82% (fostemsavir) vs 71% (ATV/r)
  - Observed: 77-95% (fostemsavir) vs 88% (ATV/r)

Table 2: Proportion of subjects achieving HIV-1 RNA <50 c/mL (Week 96 Snapshot): mITT analysis

Parameter, n (%)	BMS-663068 + TDF + RAL 1200 mg QD* N=200	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
HIV-1 RNA <50 c/mL	122 (61%)	27 (53%)
HIV-1 RNA ≥ 50 c/mL	14 (7%)	3 (6%)
Reasons for not achieving HIV-1 RNA <50 c/mL	64 (32%)	21 (41%)
Discontinued due to lack of efficacy	21 (10.5%)	3 (6%)
Discontinued due to other reasons	24 (12%)	6 (12%)
No virologic data at Week 96		
Discontinued due to AEs	6 (3%)	5 (10%)
Discontinued for other reasons	13 (6.5%)	7 (14%)

DeJesus CROI 2016 #472
Thompson Antivir Ther (epub 12/16)

Fostemsavir: Phase 2b Safety

Parameter, number of subjects (%)	BMS-663068 + TDF + RAL 1200 mg QD§ N=200	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
SAEs†	24 (12%)	7 (14%)
AEs leading to discontinuation‡	5 (2.5%)	5 (10%)
Grade 2–4-related clinical AEs		
Total subjects with an event	17 (8.5%)	19 (37%)
Present in ≥2 subjects		
Hyperbilirubinemia	0	6 (12%)
Blood bilirubin increased	0	3 (6%)
Abdominal pain	1 (0.5%)	2 (4%)
Jaundice	0	2 (4%)
Nausea	0	2 (4%)
Headache	1 (0.5%)	2 (4%)

Table 5: Select Grade 3–4 laboratory abnormalities (≥2 subjects)

Parameter, number of subjects (%)	BMS-663068 + TDF + RAL 1200 mg QD* N=200	ATV/r + TDF + RAL 300 mg/100 mg QD N=51
Neutropenia	6 (3%)	1 (2%)
Alanine aminotransferase	2 (1%)	3 (6%)
Aspartate aminotransferase	4 (2%)	3 (6%)
Total bilirubin	0	31 (62%)
Creatinine kinase	6 (3%)	0
Glucose fasting serum	2 (1%)	0
Uric acid	3 (2%)	0

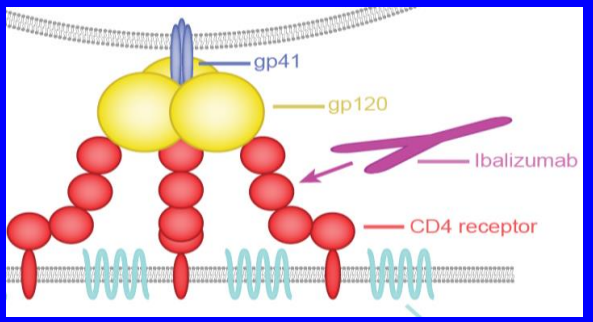
Thompson Antivir Ther (epub 12/16)

FDA “Breakthrough Status” 7/15

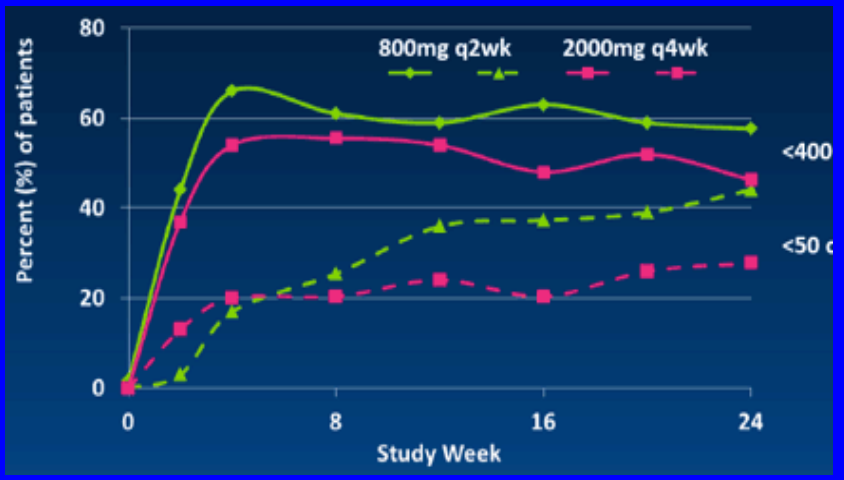
Phase 3 in treatment-experienced enrolled

Ibalizumab: HIV Entry Inhibitor

- Monoclonal antibody; IV, SC
- Binds to CD4 receptor
- Dosing every 1-4 weeks
- Phase 1a Kuritzkes JID 2004;189:286
- Phase 1b Jacobson AAC 2009;53:450
- Phase 2a Norris IAS 2006 #TuPE0058
- Phase 2b Khanlou IDSA 2011 #LB9

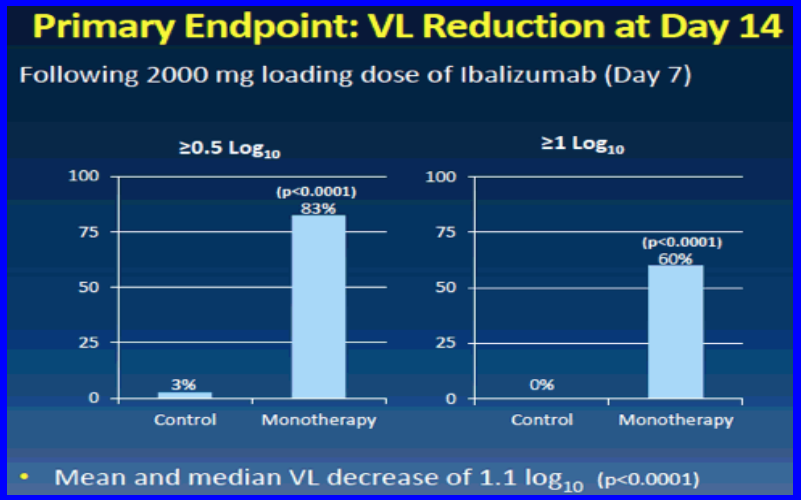


Rx-experienced; 3-class resistance (N = 113)



Ibalizumab: HIV Entry Inhibitor

- Phase 3
  - Study population: VL>1000, on ART >6 months, 3-class resistance, ≥1 sensitive drug (N = 40)
  - Study treatment: continue ART, +ibalizumab 800 mg day 7, +OBR day 14, +ibalizumab day 21 and q 2 wks →24 wks



Lalezari IDWeek 2016 #LB6

Efficacy at Week 24

- Mean viral load decrease of 1.6 log_{10} from Baseline
- 55% and 48% of patients with a ≥1 and ≥2 log_{10} reduction, respectively
- Undetectable viral load in 43% of patients; 50% with <200 copies

Lewis CROI 2017 #449LB

- FDA: orphan drug; breakthrough designation

Acknowledgments

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

- The patient volunteers!

HIV Management
Hepatitis Management

THE NEW YORK COURSE