23rd CROI Report Back
AETC/Community Consortium

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Disclosures

I have no financial disclosures.

Outline

Part 1

- Initial ARV Therapy
  - New Agents in Development
- Switch Studies
- Novel agents in development

Part 2

- Cure Research Update
- A few other interesting abstracts

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MK-1439-007: Doravirine + TDF/FTC vs EFV + TDF/FTC In Treatment-Naive Pts

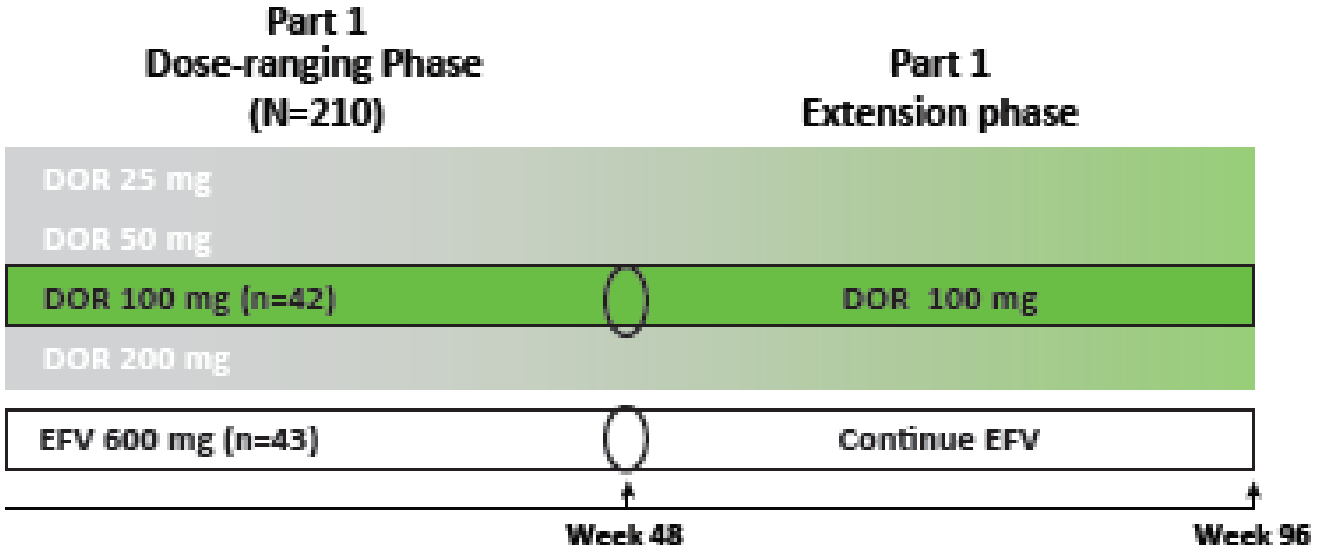
- Doravirine: investigational NNRTI with potent activity against common NNRTI resistance mutations, QD dosing, no PPI drug–drug interactions, improved CNS safety vs EFV in early studies
- Minimal pheno resistance to viruses with K103N, Y181C, G190A
- RPV and EFV resistant viruses are sensitive to DOR and vice versa

Gatell JM et al, CROI 2016, Abstract 470

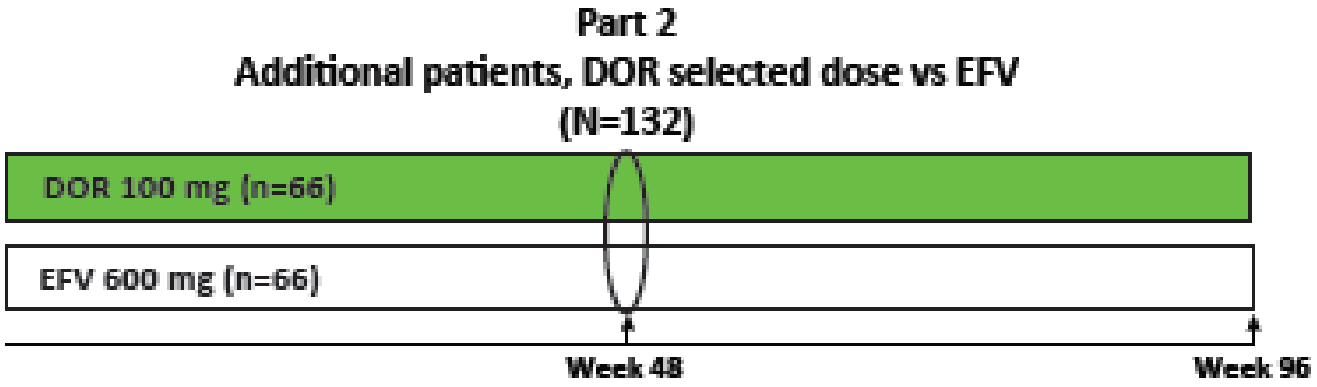
MK1439-007: Doravirine + TDF/FTC vs EFV + TDF/FTC In Treatment-Naive Pts

RCT, DB, dose-finding, 2-part study

Patients:
- HIV-1+ ART-naïve
- RNA ≥1,000 copies/mL
- CD4 ≥100 cells/µL
- Stratified by screening RNA (≤/>100,000 copies/mL)

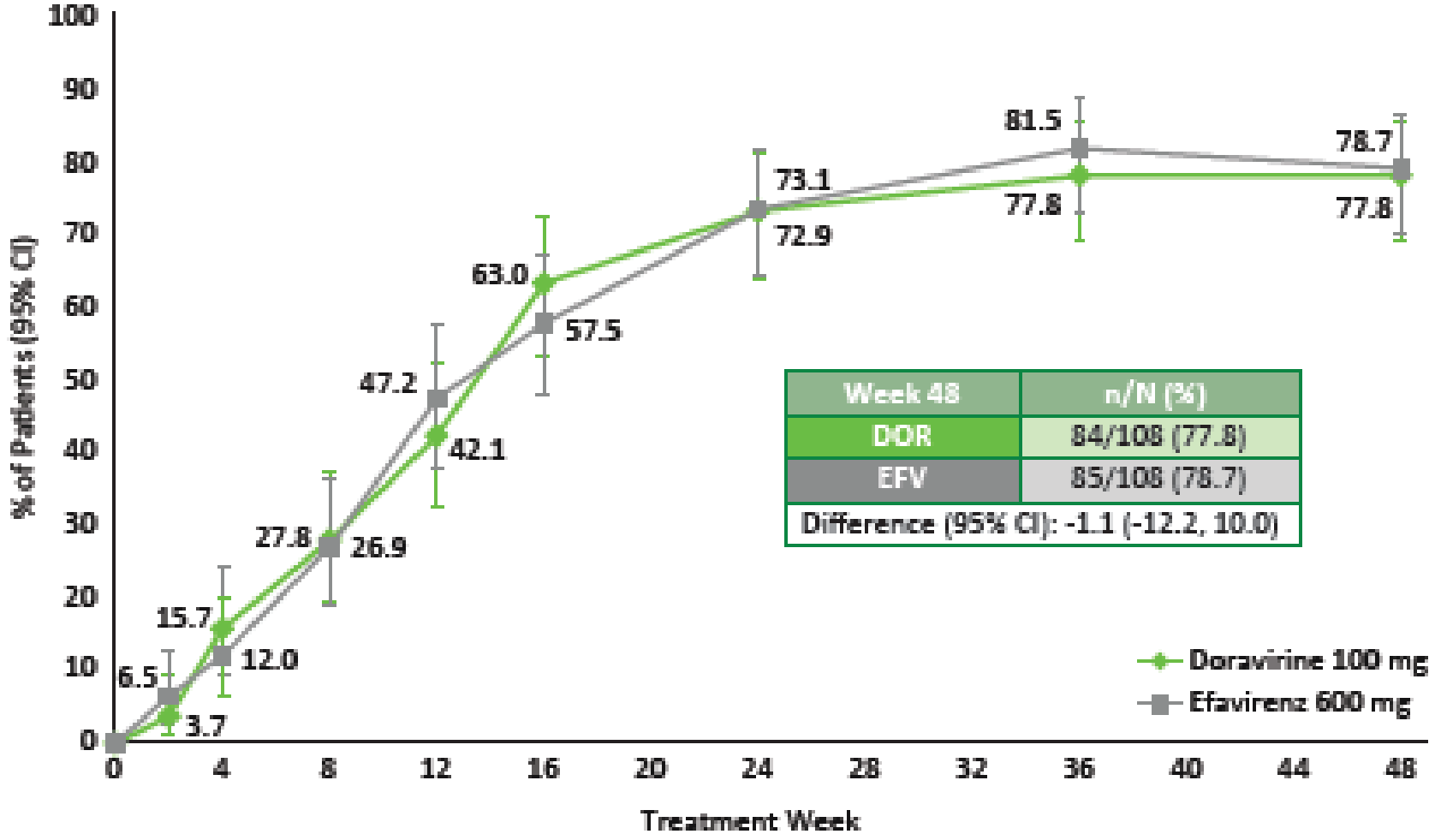


Part 2 began after dose selection based on Part 1 Week 24 results.



Gatell JM et al, CROI 2016, Abstract 470

Primary Endpoint: HIV RNA < 40 (ITT)



Gatell JM et al, CROI 2016, Abstract 470

MK-1439-007: Clinical Adverse Events

Clinical Adverse Events (%)			
	DOR 100 mg (N=108)	EFV 600 mg (N=108)	Difference [DOR – EFV] (95% CI)
One or more adverse events (AE)	**87.0**	**88.9**	**-1.9 (-10.9, 7.1)**
Serious AE†	6.5	8.3	-1.9 (-9.5, 5.6)
Death	0	0	
Discontinued due to AE	2.8	5.6	-2.8 (-9.2, 3.0)
Drug-related‡ AE	31.5	56.5	-25.0 (-37.3, -11.8)
Diarrhea	0.9	6.5	—
Nausea	7.4	5.6	—
Dizziness	6.5	25.9	—
Headache	2.8	5.6	—
Abnormal dreams	5.6	14.8	—
Insomnia	6.5	2.8	—
Nightmares	5.6	8.3	—
Sleep disorder	4.6	6.5	—

Gatell JM et al, CROI 2016, Abstract 470

MK1439-007: Conclusions

In ART-naïve subjects with HIV-1 infection, doravirine 100 mg QD in combination with TDF/FTC:

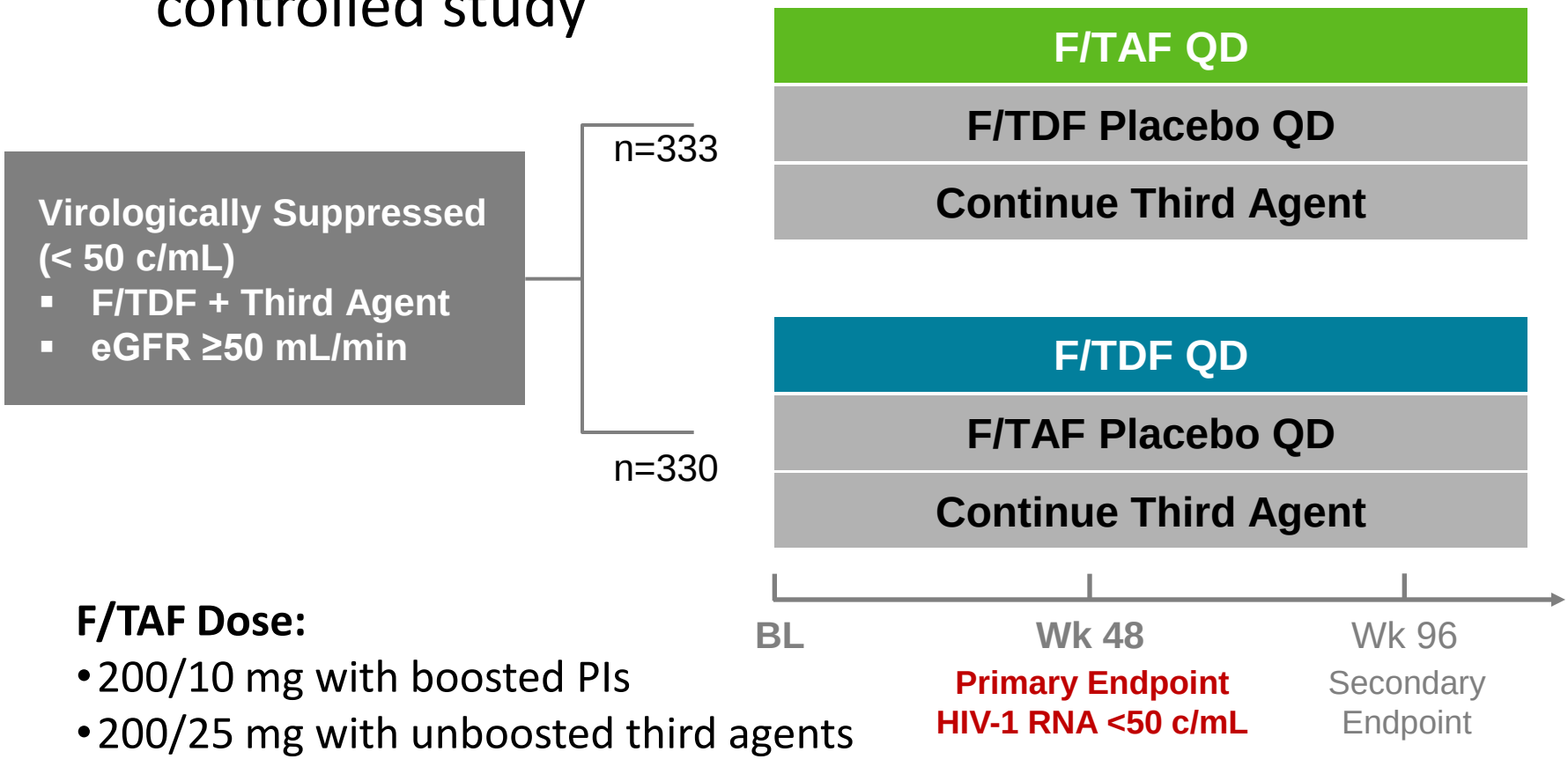
- Demonstrates antiretroviral activity and immunological effect similar to efavirenz with TDF/FTC at Week 48
- Is safe and generally well tolerated through Week 48
  - Drug-related AEs were significantly less common in the DOR group (31.5%) vs the EFV group (56.5%)

Phase 3 trials of doravirine 100 mg QD are currently ongoing.

Gatell JM et al, CROI 2016, Abstract 470

Study Design

- Randomized, double-blind, double-dummy, active-controlled study



F/TAF Dose:

- 200/10 mg with boosted PIs
- 200/25 mg with unboosted third agents

Gallant J, et al. CROI 2016. Abstract 29

Baseline Characteristics

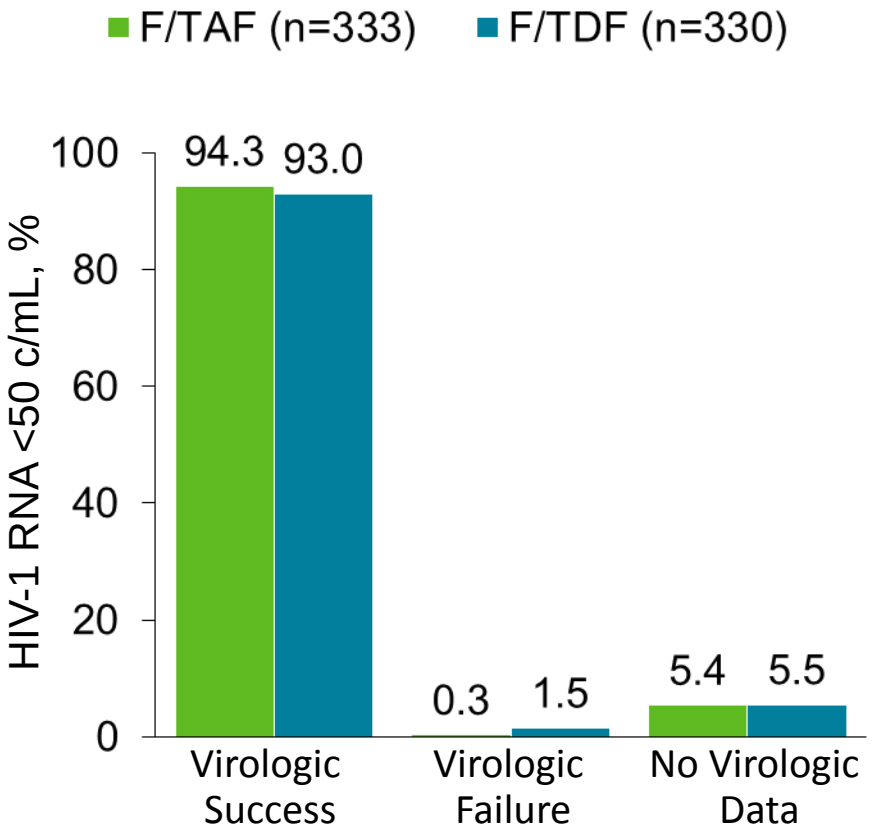
	F/TAF n=333	F/TDF n=330
Median age (range), years	48 (22, 78)	49 (22, 79)
Female, n (%)	48 (14)	54 (16)
Race, n (%)		
White	244 (73)	253 (77)
Black or African descent	69 (21)	67 (20)
Other	20 (6)	10 (3)
Hispanic/Latino ethnicity, n (%)	48 (14)	78 (24)
Median CD4 count, cells/mm^3	663	624
<200 cells/mm^3, n (%)	5 (2)	4 (1)
Median eGFR*, mL/min	99	100
Use of third agent, n (%)		
Boosted PI	155 (47)	150 (45)
Unboosted third agents	178 (53)	180 (55)

*eGFR calculated with Cockcroft-Gault equation

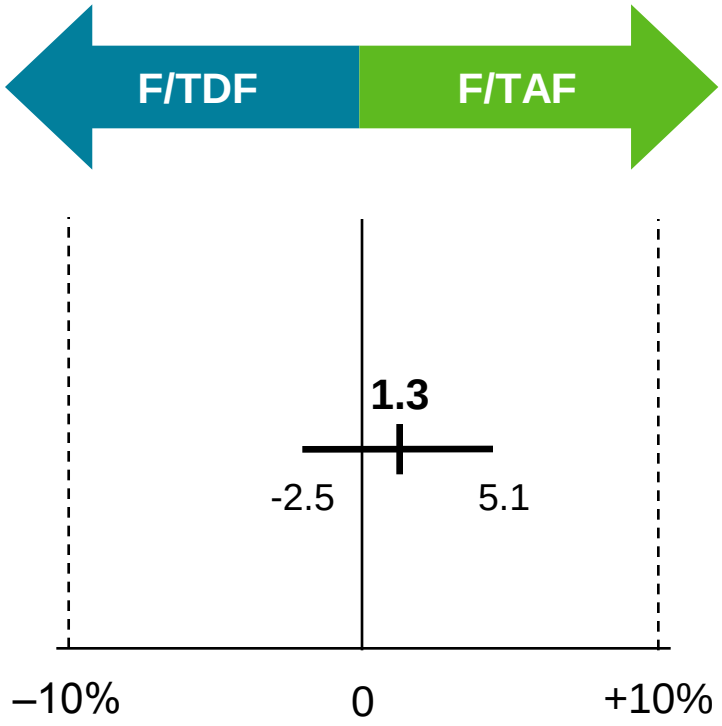
Gallant J, et al. CROI 2016. Abstract 29

Efficacy at Week 48 (Snapshot)

Virologic Outcome

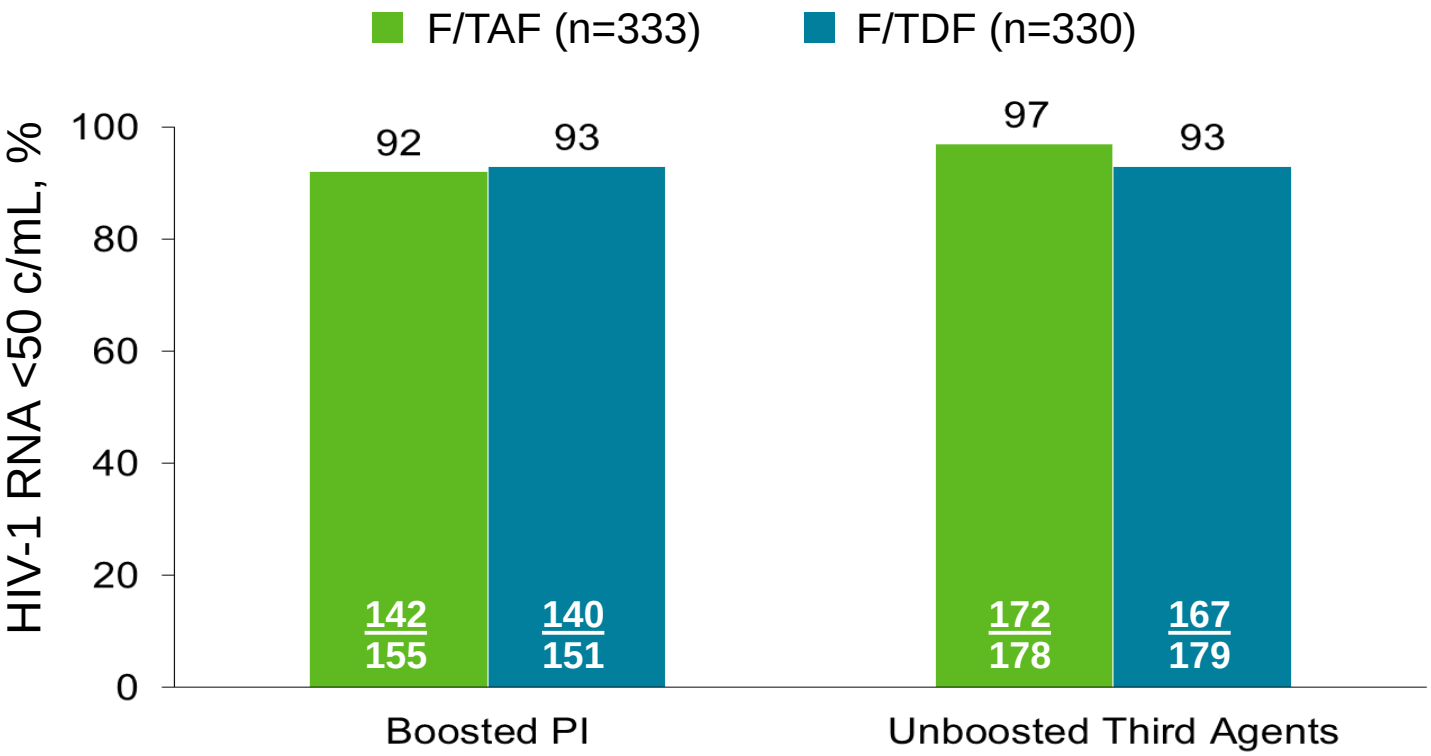


Treatment Difference (95% CI)



Gallant J, et al. CROI 2016. Abstract 29

Virologic Success by Third Agent



n, (%)	Tested for Resistance*	Resistance	Mutation
F/TAF	2	1 (0.3%)	M184V
F/TDF	1	--	

*Confirmed HIV-1 RNA ≥50 c/mL at any visit or unconfirmed >400 c/mL at endpoint or discontinuation

Gallant J, et al. CROI 2016. Boston, MA. #29

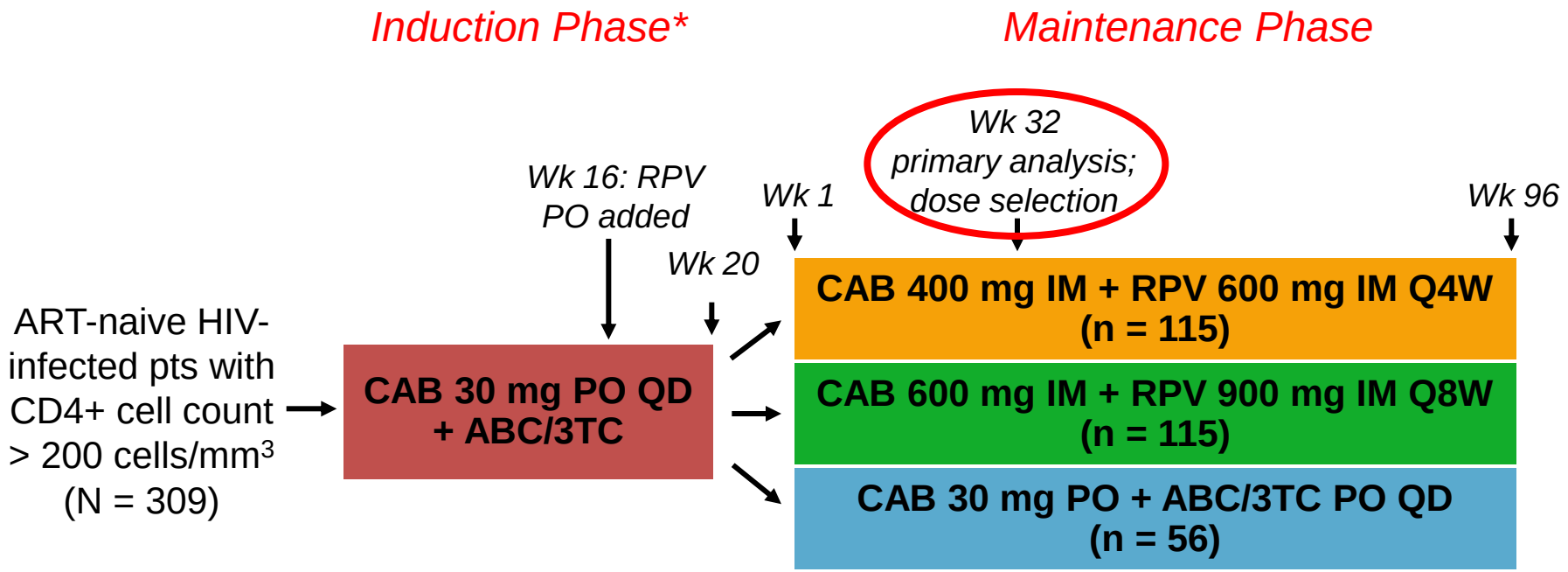
Study 1089: Other findings

- Similar AE rates and discontinuations in both arms
- EGFR improved greater with TAF than with TDF (8.4 vs 2.8 mg/min)
- Four renal biomarkers improved with TAF vs worsening for TDF
- Spine and hip BMD improved with TAF vs remaining unchanged with TDF
- Increased BMD >3% greater in TAF arm than TDF arm (30% vs 17%)
- LDL rose more in TAF arm than in TDF arm

Gallant J, et al. CROI 2016. Abstract 29

LATTE-2: Cabotegravir IM + Rilpivirine IM for Long-Acting Maintenance ART

- **Multicenter, open-label phase IIb study**
  - **Primary endpoints: HIV-1 RNA < 50 c/mL by FDA snapshot, PDVF, and safety at maintenance Wk 32**

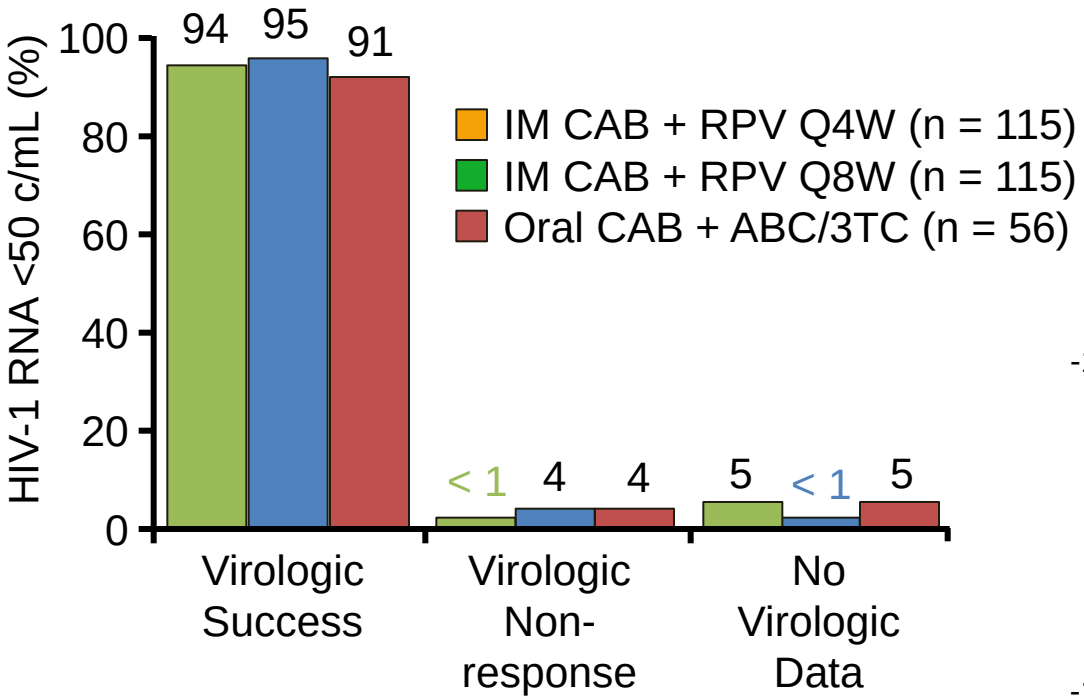


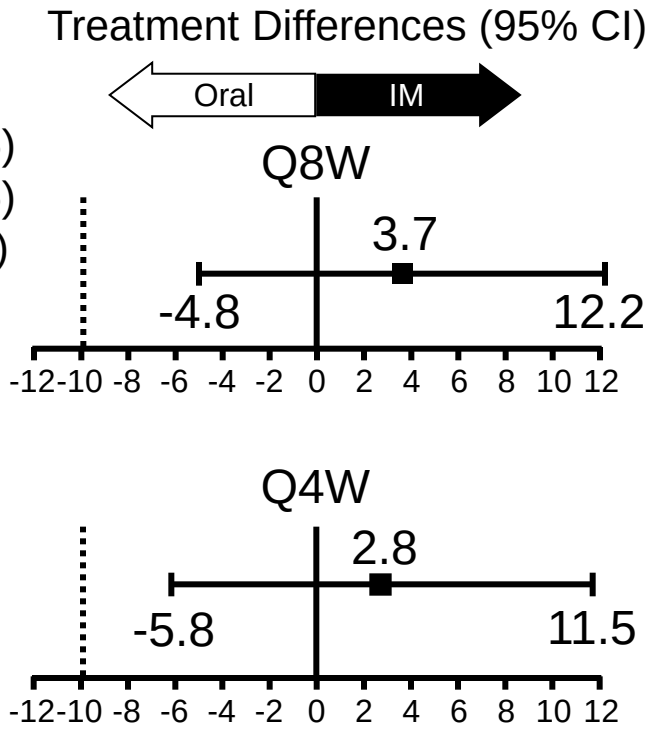
*Pts with HIV-1 RNA < 50 c/mL from Wk 16 to Wk 20 continued to maintenance phase. 6 pts discontinued for AEs or death in induction analysis.

Margolis DA et al, CROI 2016, Abstract 31LB

LATTE-2: Maintenance Wk 32 Virologic Efficacy (ITT-Maintenance Exposed)

- Virologic efficacy of Q4W and Q8W IM regimens similar to oral regimen
- No INSTI, NNRTI, or NRTI resistance mutations detected





Margolis DA et al, CROI 2016, Abstract 31LB

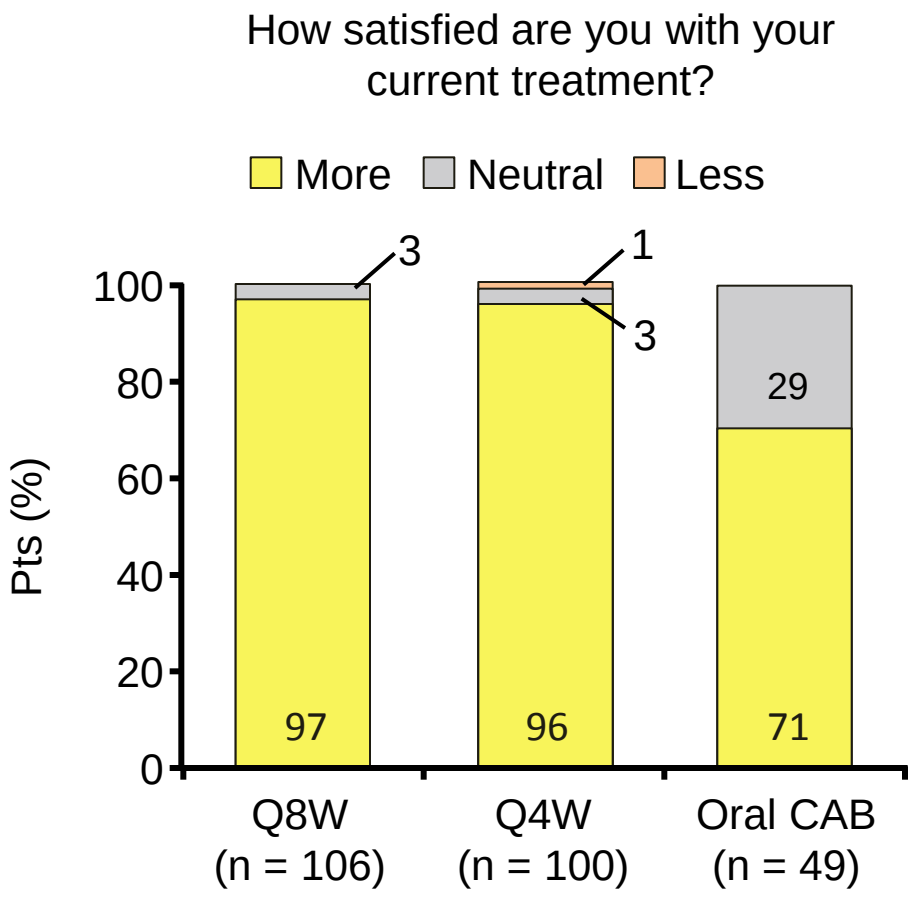
LATTE-2: Safety data through wk 32

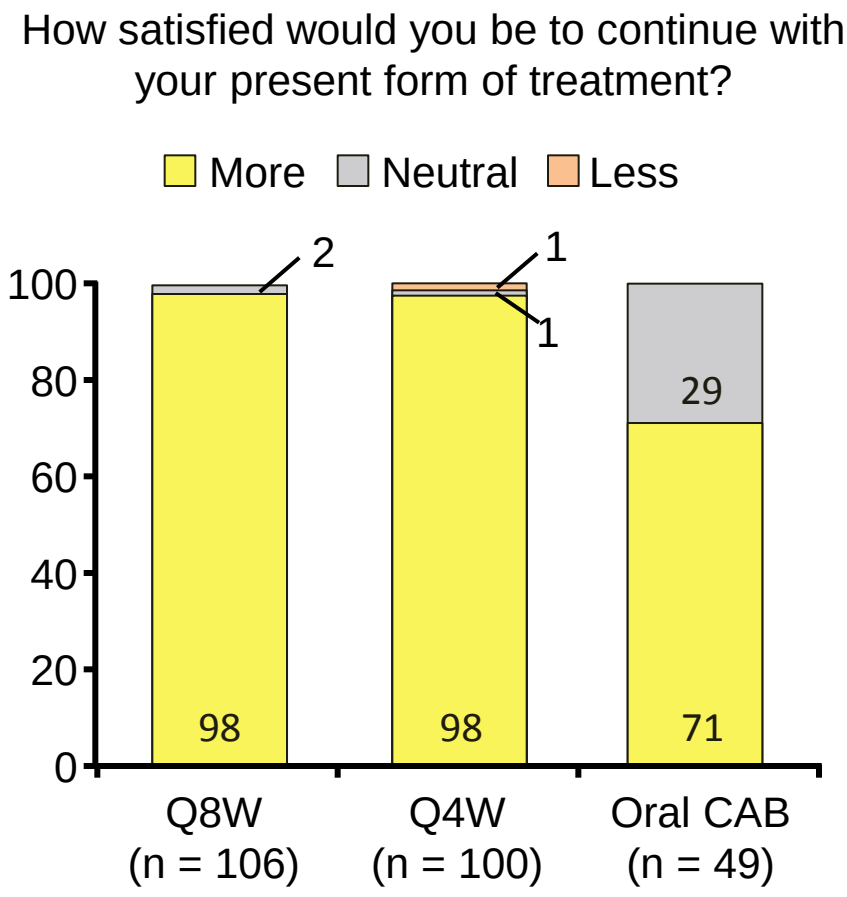
- Most frequent ISRs were pain (67%), swelling (7%), and nodules (6%)
  - ISR events/injection: 0.53
  - 99% of ISRs grade 1/2; none grade 4
  - Proportion of pts reporting ISRs decreased with time from 86% on Day 1 to 33% at Wk 32; 1% of pts withdrew for ISRs

AEs, %	Pooled CAB + RPV IM Arms (n = 230)	Oral CAB + ABC/3TC (n = 56)
Drug-related grade 3/4 AEs (excluding ISRs)	3	0
Serious AEs	6	5
AEs leading to withdrawal	3	2

Margolis DA et al, CROI 2016, Abstract 31LB

LATTE-2: Wk 32 Pt Satisfaction With Maintenance Therapy vs Oral Induction





Margolis DA, et al. CROI 2016. Abstract 31LB.
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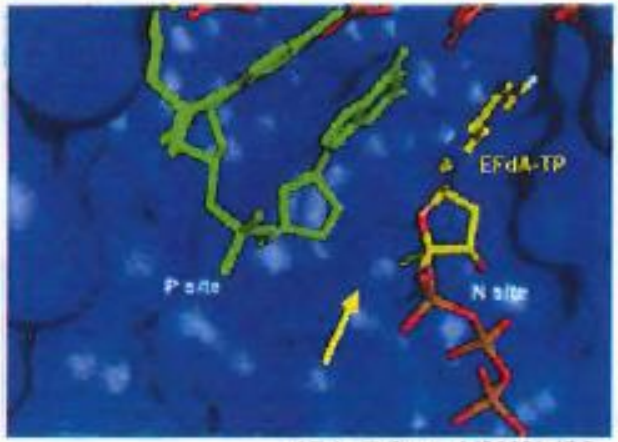
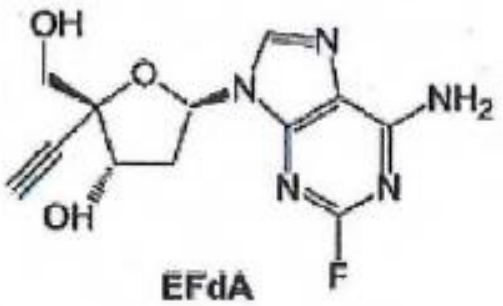
Margolis DA et al, CROI 2016, Abstract 31LB

MK-8591, EFdA: A Novel Nucleoside with a Unique Mechanism of Action



Michailidis et al (2009) JBC



EFdA

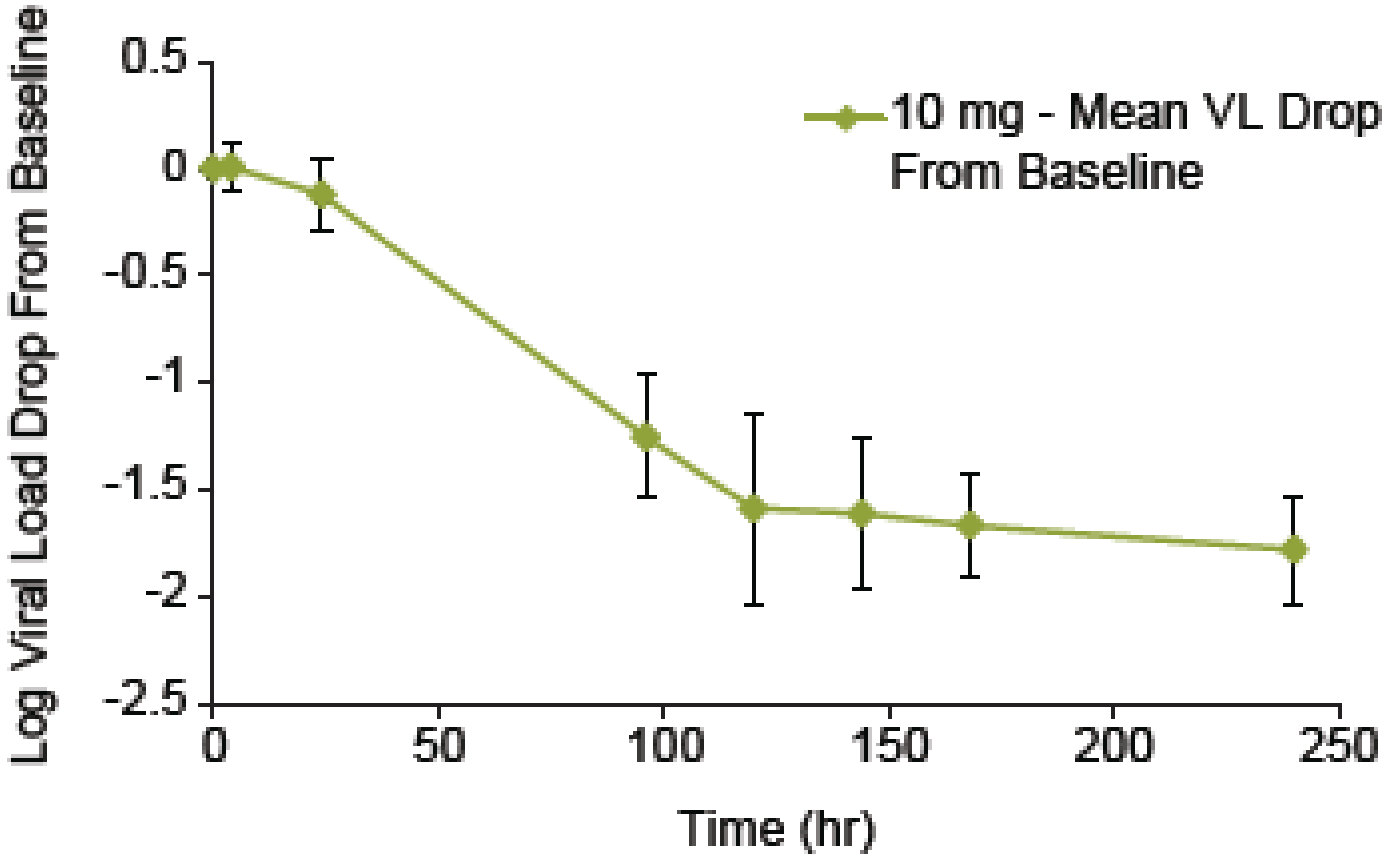
- MK-8591 (4'-ethynyl-2-fluoro-2'-deoxyadenosine; EFdA) licensed from Yamasa
- Virologic profile and mechanism of action is extensively described in the literature (Mitsuya, Sarafianos, Parniak)
  - Non-obligate chain terminator
  - Inhibits reverse transcriptase by preventing translocation
  - Potent antiviral activity (PBMC EC_{50} = 0.2 nM) with broad subtype and mutant coverage (HIV-1, HIV-2, MDR strains)

MERCK

Unique mechanism: RT translocation inhibitor

Grobler JA et al, CROI 2016, Abstract 98

MK-8591: Time vs Log_{10} Viral Load Reduction (N=6)

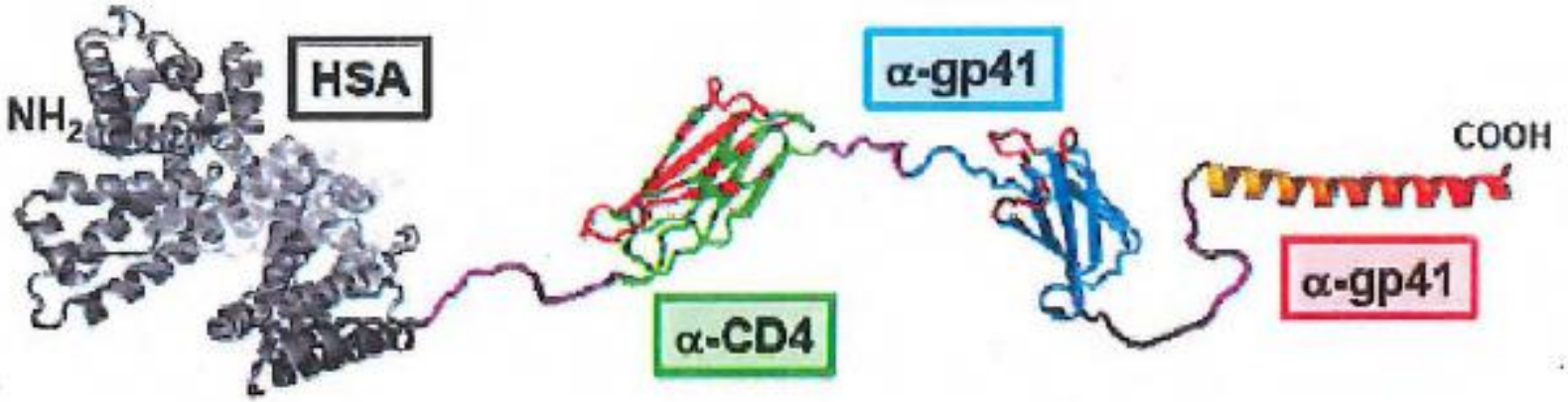


- No NRTI related resistance mutations were identified predose or postdose in any patient

Friedman E et al., CROI 2016, Abstract 437 LB

HIV Combinectin BMS-986197:

A long-acting inhibitor with multiple modes of action

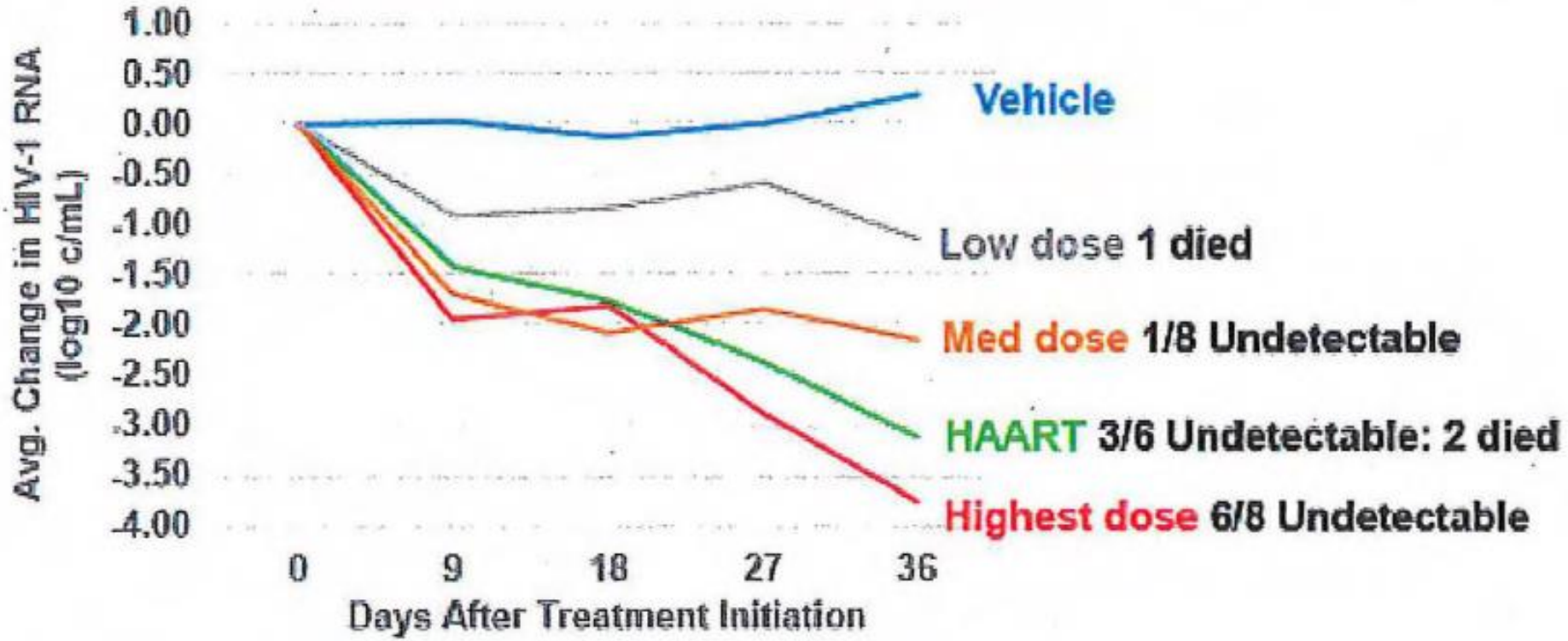


Mark Krystal, David Wensel, Yongnian Sun, Jonathan Davis, Zhufang Li, Thomas McDonagh, Sharon Zhang, Matt Soars, Mark Cockett

Bristol-Myers Squibb, Research and Development, Wallingford, CT and Waltham. MA

Krystal M et al, CROI 2016, Abstract 97

Efficacy of BMS-986197 at Day 36



- Dose dependent decrease in viral load
- Efficacy at highest dose of '197 similar to HAART
- Study is continuing for an additional 27 days

Krystal M et al, CROI 2016, Abstract 97

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"Kick and Kill" Strategy to Eliminate Reservoirs of Latent HIV

KICK

Activate expression of HIV

KILL

Kills cells expressing HIV proteins

Latency Reversal Agents

HDACis

PKC agonists

TLR7 agonists

PROTECT

cART

Latent reservoir elimination

Latent reservoir (rCD4 T cells)

Killing Strategies

Therapeutic vaccines

Anti-Env antibodies

Anti-PD-L1

Immune effector cells

CD8 cells

NK cells

MΦs

Reduc Study: Vacc 4x + GMCSF (kill) & HDAC romidepsin (kick)

- 20 HIV+ pts, well controlled, received 6 sequential IM doses of Vacc 4x vaccine (4 gag epitopes) + GMCSF (adjuvant) followed by romedepsin IV infusions weekly x 3
- Romidepsin previously approved for T cell lymphoma
- Results: 8/20 measureable HIV RNA; median HIV DNA reduction 40%; no reduction integrated HIV DNA

S Leth et al, CROI 2016, Abstract 26 LB

Antilatency agent: αPD1-L1 (BMS-936559)

Background:

- PD1 receptor upregulated in T cells that are exhausted
- αPD1-L1 and αPD1-L2 restore T cell function in vitro
- CD4+ latently infected cells express PD1
- αPD1 decreases viral latency in vitro
- BMS agent caused retinal toxicity in animal studies

Eron J et al., CROI 2016, Abstract 25

BMS-936559: pilot study

Results:

- Administered IV (0.3 mg/kg) to 6 HIV + patients on suppressive ARV vs placebo in 2 patients
- 2/6 recipients developed increased gag-specific CD8 T cell responses
- 1 recipient with 30 fold reduction cell-associated HIV RNA/DNA ratio
- One patient developed autoimmune hypophysitis (adrenal, gonadal insufficiency) 9 months post infusion
- Future studies with related agent (pembrolizumab) in HIV + patients with malignancy planned

Eron J et al., CROI 2016, Abstract 25

ACTG 5340: VRC-01 Broadly Neutralizing Antibody (bnAb)

- Targets CD4 binding site

Study design:

  - 40 mg/kg IV q3w x 3 doses in 14 pts in PI-or INI based ART suppressed x 6 mos
  - d/c ARVs one week after first infusion

Results:

  - Modest delay virologic rebound in recipients (38% remained suppressed at week 4 after rx vs 13% in prior studies of treatment interruption); no difference at week 8

- ?role for combination bnAbs in future?

Bar K et al., CROI 2016, Abstract 32LB

TLR-7 Agonists GS986 and GS9620

Background:

- TLR-7 increases antigen presentation, enhances activity of NK cells, B cells, CD4 and CD8 T cells

Study design:

- 11 macaques infected with SIV and treated with TDF/FTC/DOL 65 days after infection
- Multiple doses GS6 and GS9620 given SC q 2w x 5 – 6 mos while receiving ARVs

Results:

- Induces transient SIV viremia
- decreased proviral DNA in PBMCs, colon, LN bx
- ART discontinued and 2/9 macaques remain SIV RNA negative after 3 – 4 months
- Planned Phase 1b trial for HIV+ patients

Whitney JB et al, CROI 2016, Abstract 95LB

Second Berlin Patient (from Dusseldorf)?

- 41 yo man with HIV (HIV RNA suppressed) underwent induction chemo 1/11 then allogeneic SCT 2/13 for relapse from CCR5Δ32 homozygote
- Proviral DNA 29K at baseline, R5 virus
- After SCT, multiple neg proviral DNA results from PBMC, rectal bx, BM bx, in 2 labs up to 2 years

Kobbe G et al, CROI 2016, Abstract 364

Paroxitene + fluconazole for HAND?

Background:

- HAND increases CNS inflammation, macrophage activation, oxidative stress
- PRX and FLUC neuroprotective in macaques

Study Design – single center study from Johns Hopkins:

- 45 patients with HIV on stable ARVs with low baseline NC function randomized to 4 treatment arms: PRX 20 mg qd; FLUC 100 mg q12; PRX + FLUC; placebo
- Analysis of 24 patients with >90% adherence after 6 mos

Results:

- Improved NC scores on 8 neuropsych tests in PRX vs non PRX arms

Sacktor N et al., CROI 2016, Abstract 146

ACTG 5298:
Phase 3 RCT Quadrivalent HPV Vaccine

- HIV positive; age > 27
- N = 575, 82% male, 18% women, mean CD4 602, HIV PCR < 50 in 83%
- Baseline anal and oral HPV, cytology, HRA
- Intervention: vaccine vs placebo week 0, 8, 24
- Measurements: q6mos anal HPV, cytology, oral HPV
- Primary endpoint: persistent anal HPV

Wilkin TJ et al, CROI 2016, Abstract 161

ACTG 5298:
Phase 3 RCT Quadrivalent HPV Vaccine

- Results: DSMB terminated trial for futility 9/3/2015, median 2.6 years f/u
- No reduction in persistent anal HPV and HSIL
- Trend for reduction in persistent oral HPV in treatment arm
- Vaccine was safe and highly immunogenic
- Low infection rates and low persistence rates may explain negative results

Wilkin TJ et al, CROI 2016, Abstract 161

Persistent anal HPV infection and HSIL

Outcome	4vHPV (n)	Placebo (n)	HR (95.1% CI)
Persistent anal HPV, or single detection at last visit[1]	26	33	0.75 (0.45, 1.26)
Persistent anal HPV[1]	13	17	0.73 (0.36, 1.52)
Anal HSIL Wk 52 or later (histology)[2]	46	45	1.0 (0.69-1.44)

[1]Cox proportional hazards model [2]Mantel-Haenszel relative risk estimate adjusting for both stratification factors (sex and HSIL at baseline).

ACTG

Wilkin TJ et al, CROI 2016, Abstract 161

Persistent oral HPV infection

Outcome	4vHPV (n)	Placebo (n)	HR (95.1% CI)
Persistent oral HPV, or single detection at last visit	7	10	0.68 (0.26, 1.80)
Persistent oral HPV	1	8	0.12 (0.02, 0.98), *P*=.019

Wilkin TJ et al, CROI 2016, Abstract 161

Thank you

- Claire Rappoport
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- Clinical care options
- www.natap.org