Southern African HIV Clinicians Society

3rd Biennial Conference

13 - 16 April 2016
Sandton Convention Centre
Johannesburg

Our Issues, Our Drugs, Our Patients

www.sahivsoc.org
www.sahivsoc2016.co.za

UNC SCHOOL OF MEDICINE

Antiretroviral Therapy Where we are and where we are going

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February 2016

Disclosures

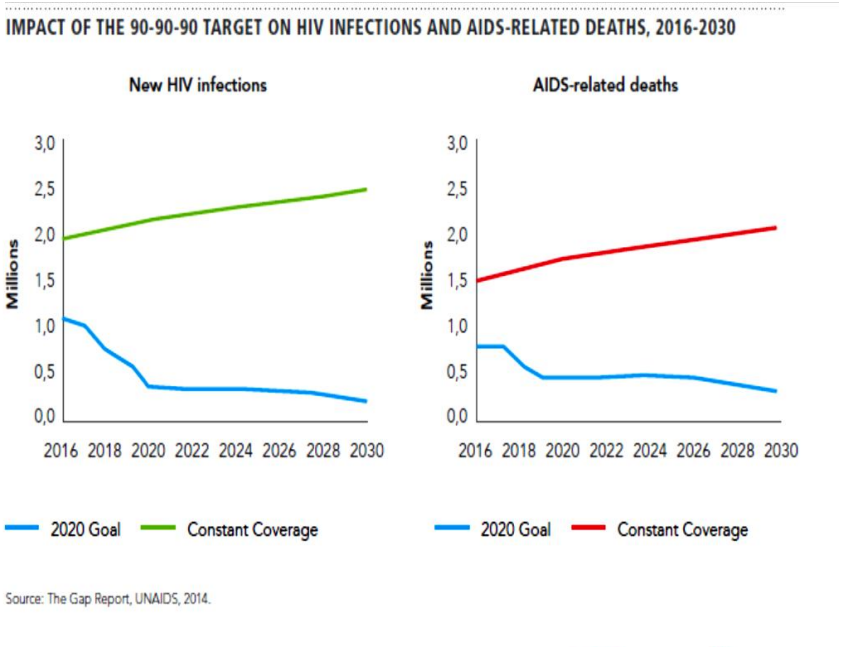
- Dr. Eron received research grants awarded to his institution from AbbVie, Janssen, and ViiV Healthcare, and has served as a consultant to AbbVie, Bristol-Myers Squibb, Gilead Sciences, Janssen, Merck, and ViiV Healthcare.

Goals of Antiretroviral Therapy

- Maintain or restore the health of people living with HIV-1 (PLWHIV) through suppression of HIV-1 replication
- Minimize or eliminate short and long-term adverse effects of the therapy
- Have therapies that are accessible to all PLWHIV
- Prevent transmission of HIV-1 to others via any route of exposure

We have big goals!

15.8 million PLWHIV on ART in 2015



CAN ANTIRETROVIRAL THERAPY HOLD UP ITS END OF THE BARGAIN – 90% SUPPRESSED?

The NEW ENGLAND JOURNAL of MEDICINE

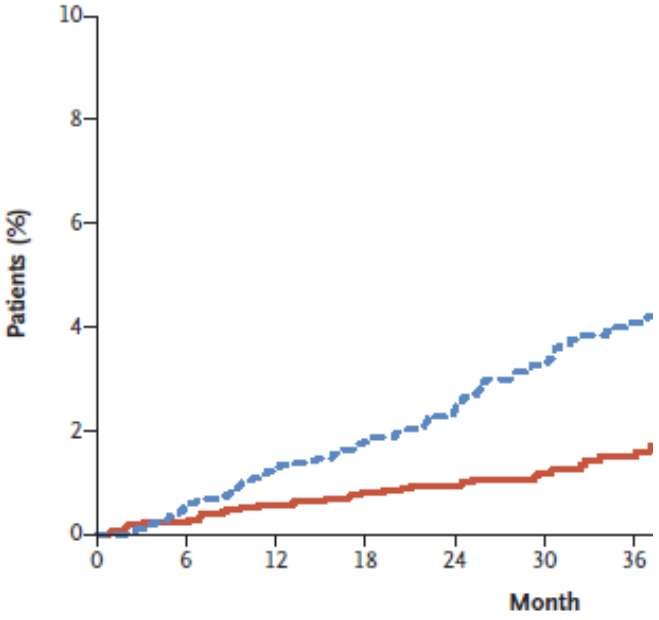
ORIGINAL ARTICLE

Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection

The INSIGHT START Study Group*

Published July 20, 2015
at NEJM.org

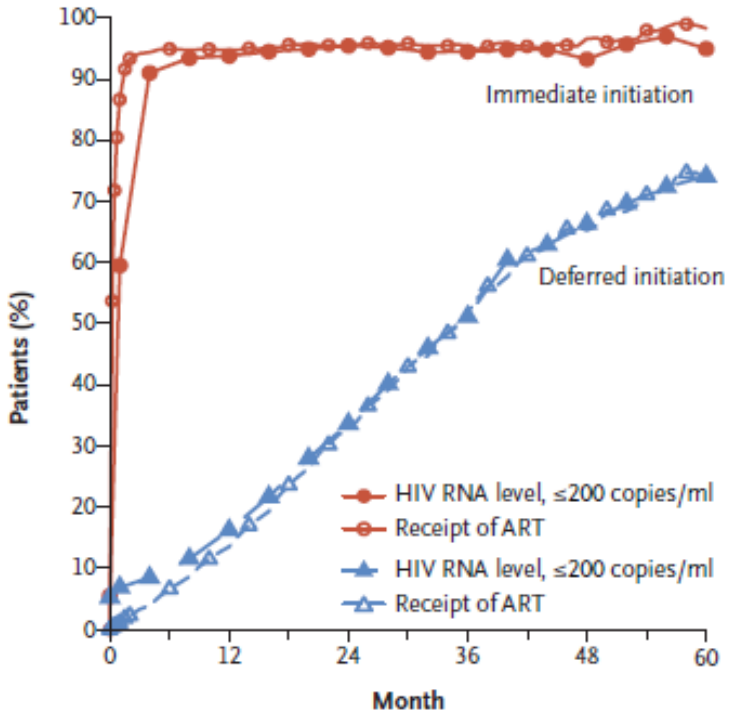
A Time to First Primary Event



No. at Risk							
Immediate initiation	2326	2302	2279	2163	1801	1437	1031
Deferred initiation	2359	2326	2281	2135	1803	1417	1021

Estimated Percentage						
Immediate initiation	0.2	0.6	0.8	0.9	1.2	1.5
Deferred initiation	0.5	1.2	1.8	2.4	3.3	4.1

A ART Use and HIV RNA Level



No. of Patients						
Immediate initiation	2326	2287	1809	1040	551	115
Deferred initiation	2359	2303	1837	1055	546	109

HPTN 052: Reduced Risk of Partner Infection

- ART offered to all index pts in delayed ART arm from May 2011 after interim results
  - 84% of pts in delayed ART arm had initiated ART at Yr 1 and 98% prior to study closure
- 8 linked HIV infections diagnosed after seropositive patient started ART
  - All occurred before or soon after initiation or after virologic failure
- No linked HIV transmissions observed when index participant stably suppressed on ART

	Overall (April 2005 - May 2015)	
Partner Infections, n (rate/100 PY)	**Early (4314 PY F/U)**	**Delayed (4180 PY F/U)**
All	19 (0.44)	59 (1.41)
Linked	3 (0.07)	43 (1.03)
Risk Reduction With Early ART, %		
All infections	69	--
Linked infections	93	--

Cohen MS, et al. IAS 2015. Abstract MOAC0101LB.

WHY IS ART SO SUCCESSFUL IN PATIENTS WHO HAVE ACCESS

Potent, Relatively simple (multiple single tablets regimens)

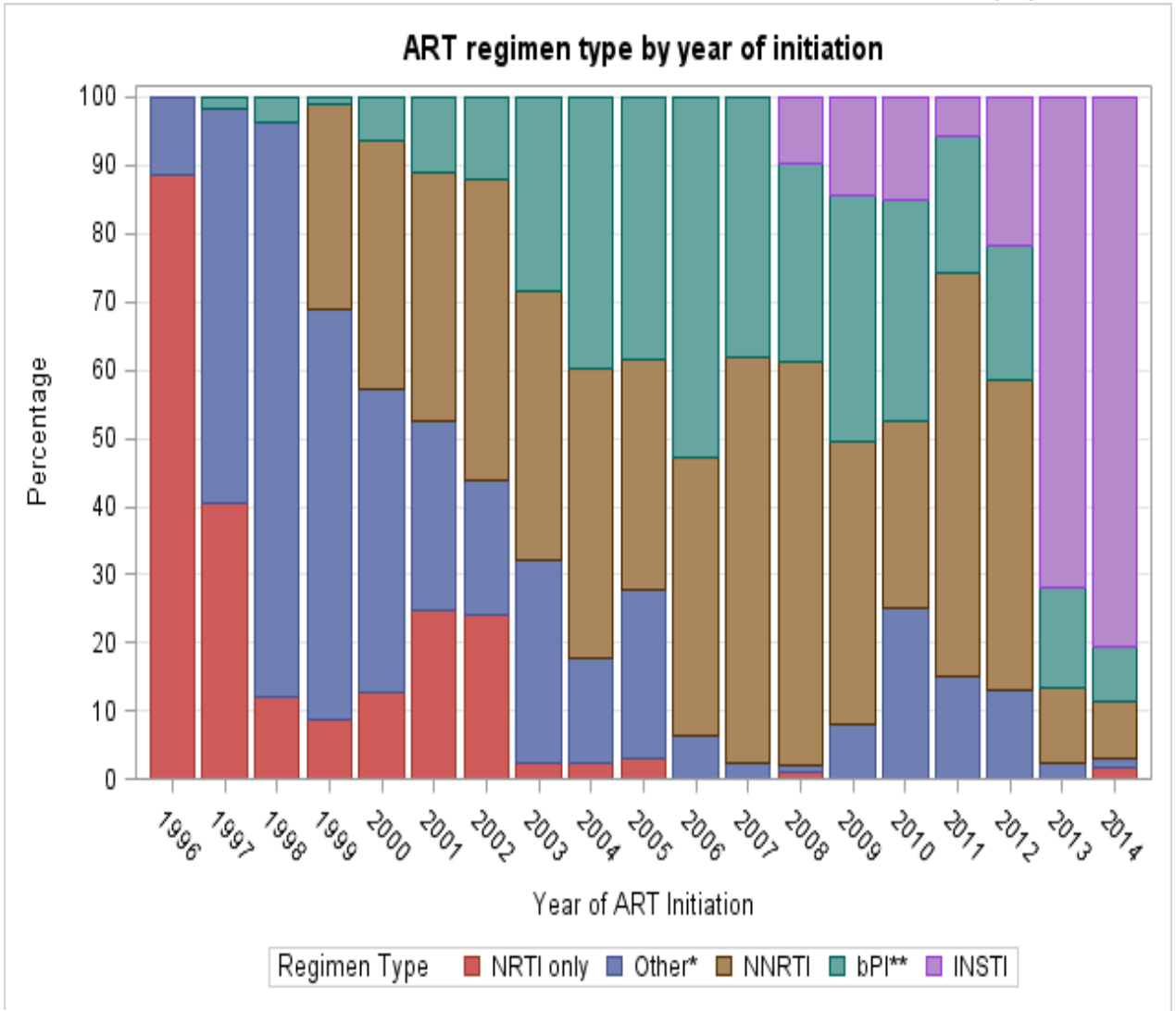
Favorable PK

Well tolerated

UCHCC: UNC
CFAR HIV
Clinical Cohort

Shift To Integrase Inhibitor-based Therapy

Initial Antiretroviral Therapy



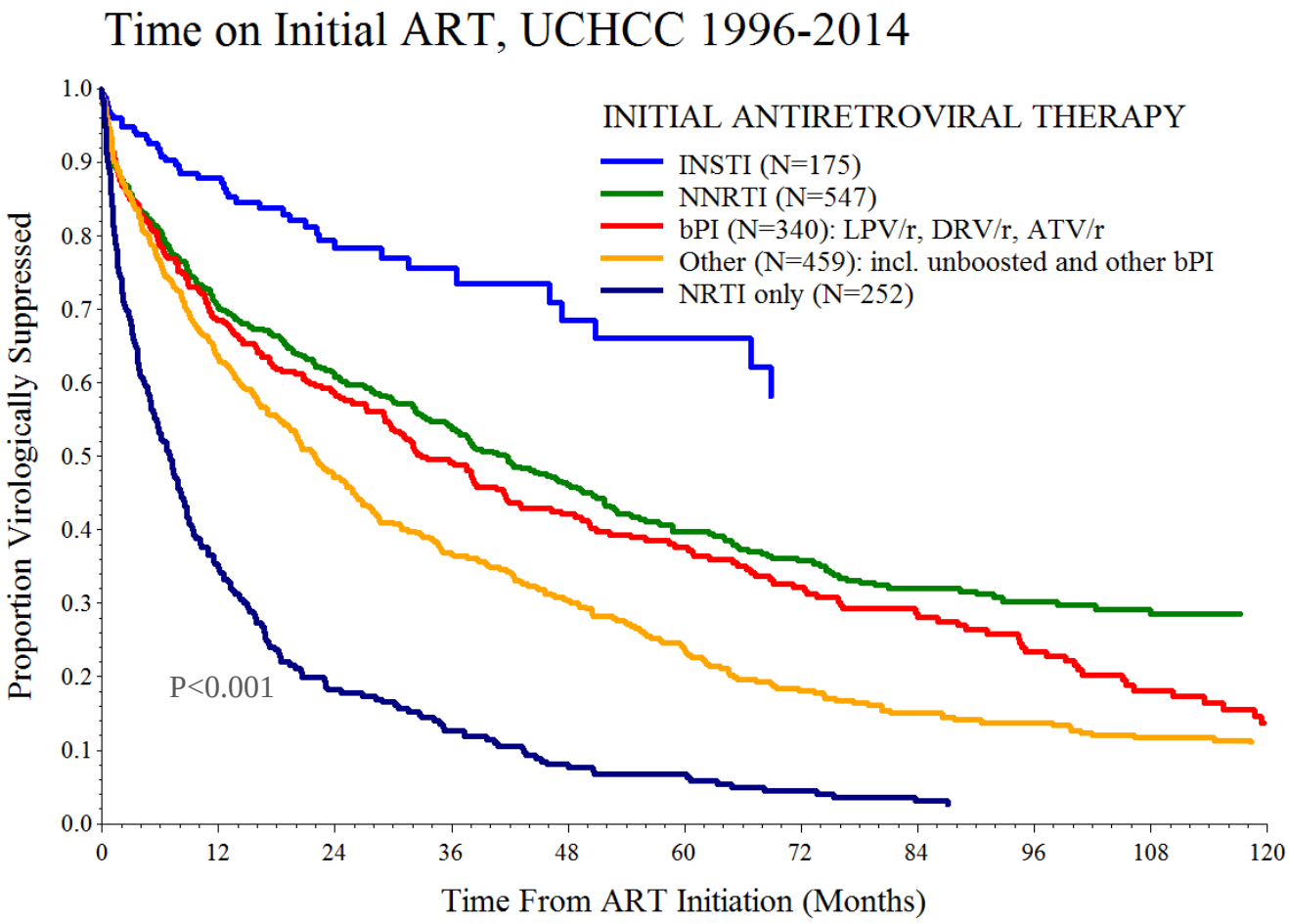
1,773 patients initiating ART between 1996 and 2014 in the UCHCC, follow-up through 2015

bPI = LPV/r, DRV/r or ATV/r therapy

Other = includes unboosted PI and other bPI combinations

Courtesy of Thibaut Davy and Sonia Napravnik

Persistence of Initial ART

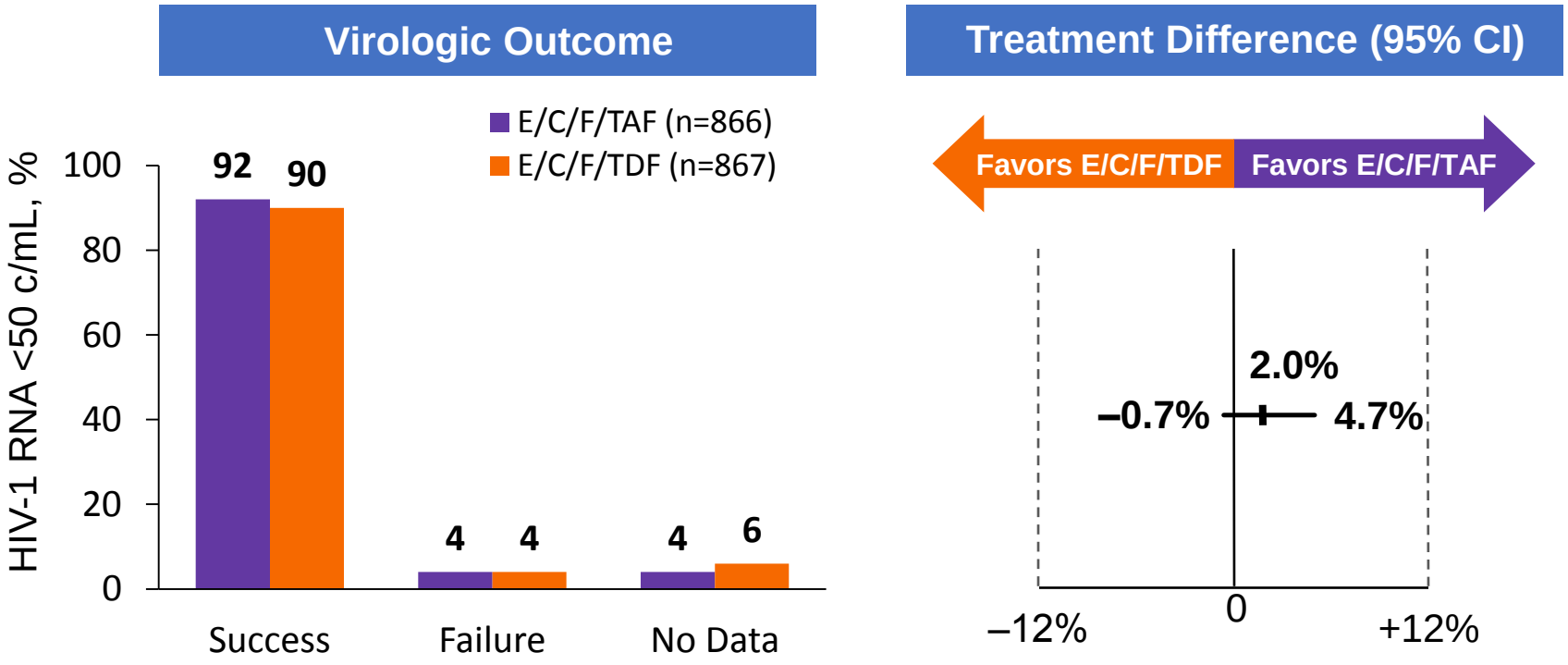


In CNICS cohort integrase inhibitor use was strongly associated with HIV RNA suppression in multivariate analysis see poster 1034 Simoni et al

Continued Improvement in Currently Available ART Classes

- Dolutegravir
  - Once daily, unboosted,
  - Limited drug interactions, high barrier to resistance
- Tenofovir alafenamide fumarate
  - Equal efficacy with TDF containing therapies, less bone toxicity and renal tubular effects
  - Smaller mg dosing (25 mg)
  - Use in renal dysfunction (CrCl down to 30 cc/min)
  - Activity against NRTI-resistant variants (?)
- Two drug therapy
  - Less expensive, fewer toxicities?

Elvitegravir/cobi/TAF/FTC vs. Elvitegravir/cobi/TDF/FTC Phase III treatment naïve study: 48 week results

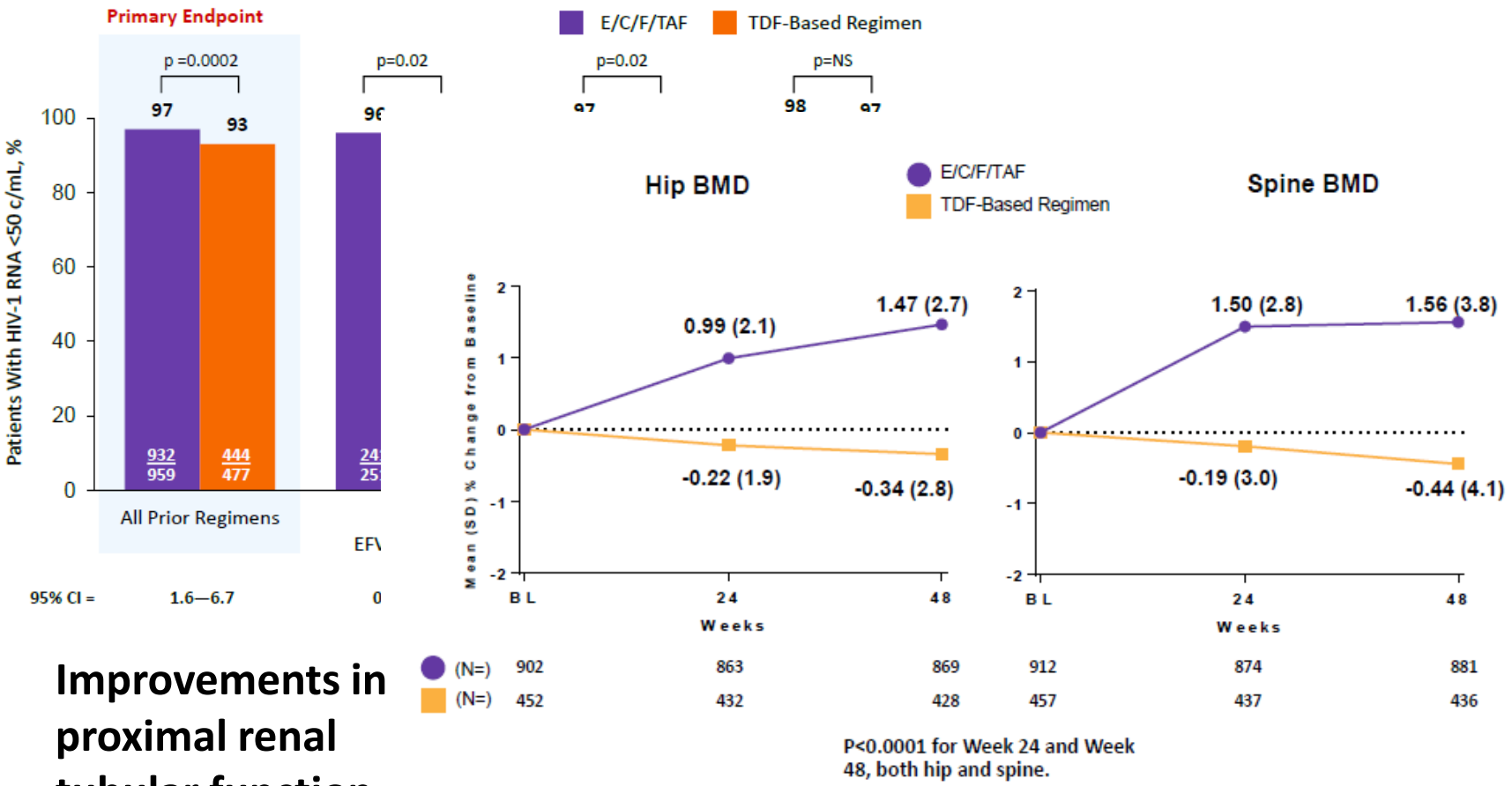


- E/C/F/TAF was non-inferior to E/C/F/TDF at Week 48 in each study
  - 93% E/C/F/TAF vs 92% E/C/F/TDF (Study 104)
  - 92% E/C/F/TAF vs 89% E/C/F/TDF (Study 111)

Sax P, Wohl D, et al Lancet 2015

ART to Decrease Long-term Toxicity

Switch from Tenofovir DF to Tenofovir alafenamide–containing therapy in patients with suppressed plasma HIV RNA levels.

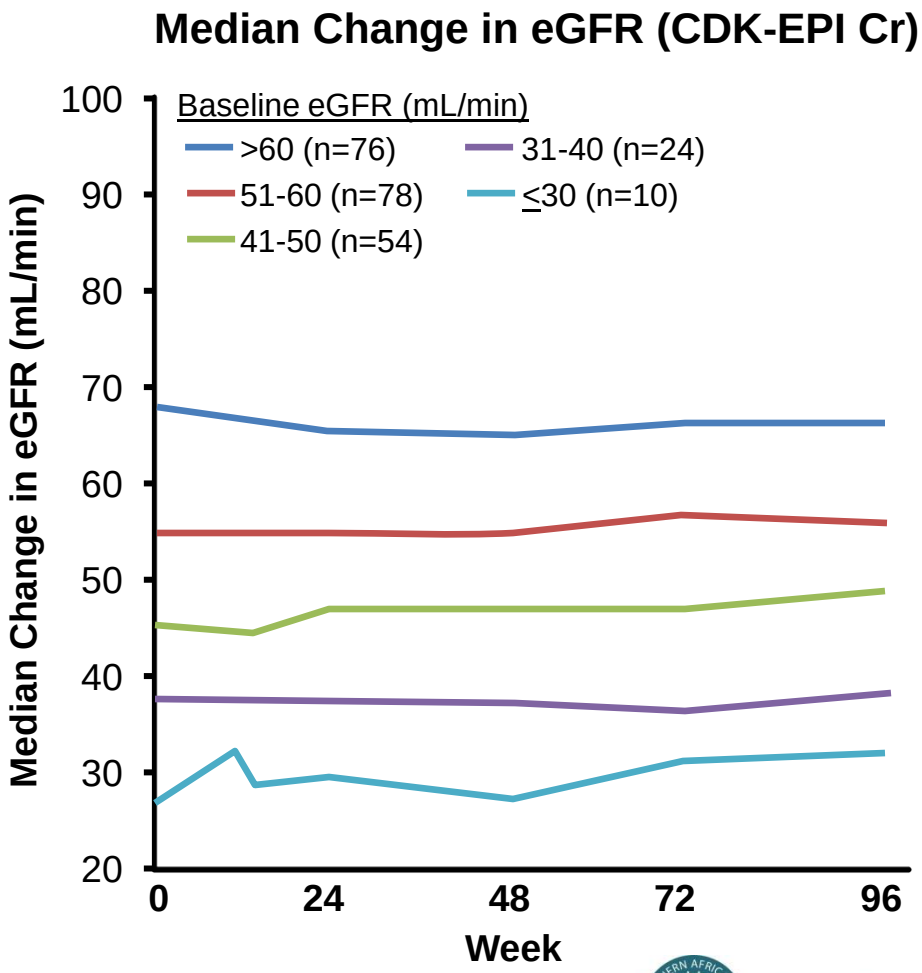


Improvements in proximal renal tubular function

Mills et al, ***Lancet Infect Dis*** **2016; 16: 43–52**

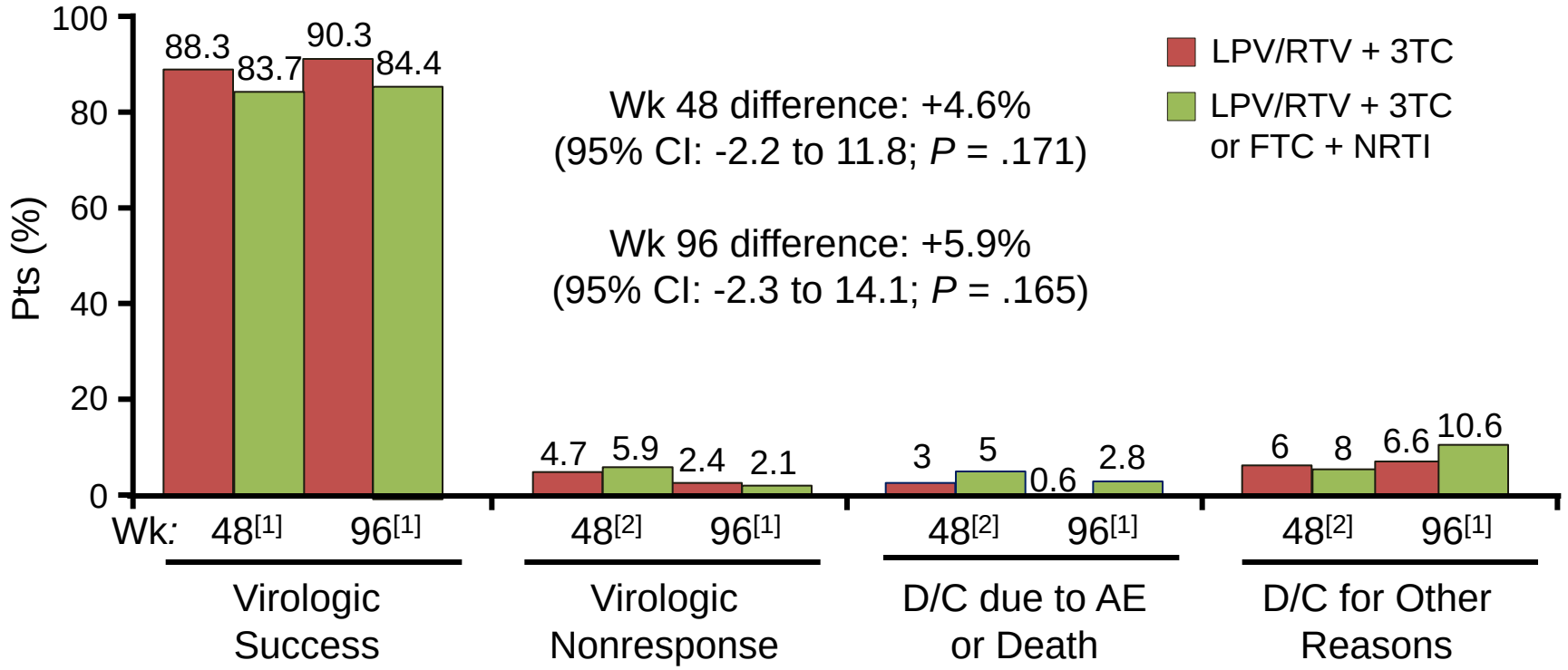
Study 112: Week 96 Changes After Switch to E/C/F/TAF in Patients With Renal Impairment

- Median eGFR change after E/C/F/TAF switch
  - CDK-EPI Cr: 1.0 mL/min (n=158)
  - CDK-EPI CysC: 3.9 mL/min (n=157)
- Significant improvements after E/C/F/TAF switch (*P*<0.05)
  - Proteinuria
  - Renal tubular function
  - Spine and hip bone mineral density
- Maintained HIV RNA <50 copies/mL: 88%
  - Virologic failure: 2% (5/242)
  - No virologic data: 10% (23/242)
- These 96-week data support the renal and bone safety of E/C/F/TAF in HIV patients with renal impairment (eGFR 30-69 mL/min)



GARDEL: Dual ART Noninferior to Triple ART in Tx-Naive Pts at Wks 48 and 96

- Phase III, international, open-label, randomized study



- Safety and tolerability also similar between treatment arms

1. Cahn P, et al. EACS 2015. Abstract 961. 2. Cahn P, et al. Lancet Infect Dis. 2014;14:572-80.

Two drug ART to Achieve and Maintain Suppression

Dolutegravir plus 3TC 24 week data

PADDLE Study

#	SCR	BSL	DAY 2	DAY 4	DAY 7	DAY 10	W.2	W.3	W.4	W.6	W.8	W.12	W.24
1	5.584	10.909	3.701	383	101	71	< 50	< 50	< 50	< 50	< 50	< 50	< 50
2	8.887	10.233	5.671	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
3	67.335	**151.569**	37.604	1.565	1.178	266	97	53	< 50	< 50	< 50	< 50	< 50
4	99.291	**148.370**	11.797	3.303	432	179	178	55	< 50	< 50	< 50	< 50	< 50
5	34.362	20.544	4.680	1.292	570	168	107	< 50	< 50	< 50	< 50	< 50	< 50
6	16.024	14.499	3.754	1.634	162	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
7	37.604	18.597	2.948	819	61	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
8	25.071	24.368	6.264	1.377	Not done	268	105	< 50	< 50	< 50	< 50	< 50	< 50
9	14.707	10.832	Not done	516	202	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
10	10.679	7.978	5.671	318	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
11	50.089	**273.676**	160.974	68.129	3.880	2.247	784	290	288	147	< 50	< 50	< 50
12	13.508	64.103	3.496	3.296	135	351	351	84	67	< 50	< 50	< 50	< 50
13	28.093	33.829	37.350	26.343	539	268	61	< 50	< 50	< 50	< 50	< 50	< 50
14	15.348	15.151	3.994	791	198	98	< 50	61	64	< 50	< 50	< 50	< 50
15	23.185	23.500	15.830	4.217	192	69	< 50	< 50	< 50	Not done	< 50	< 50	< 50
16	11.377	3.910	370	97	143	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50
17	39.100	25.828	11.879	1.970	460	147	52	< 50	< 50	< 50	< 50	< 50	< 50
18	60.771	73.069	31.170	2.174	692	358	156	< 50	< 50	< 50	< 50	< 50	< 50
19	82.803	**106.320**	35.517	2.902	897	352	168	76	< 50	< 50	< 50	< 50	< 50
20	5.190	7.368	3.433	147	56	< 50	< 50	< 50	< 50	< 50	< 50	< 50	< 50

From week 8 onwards all patients had pVL < 50 copies/mL

Figueroa et al (Pedro Cahn) 15th European AIDS Conference 2015

2016

Sued et al Poster 947

RESISTANT HIV-1 WILL ALWAYS BE WITH US

Four to eight decades of therapy!

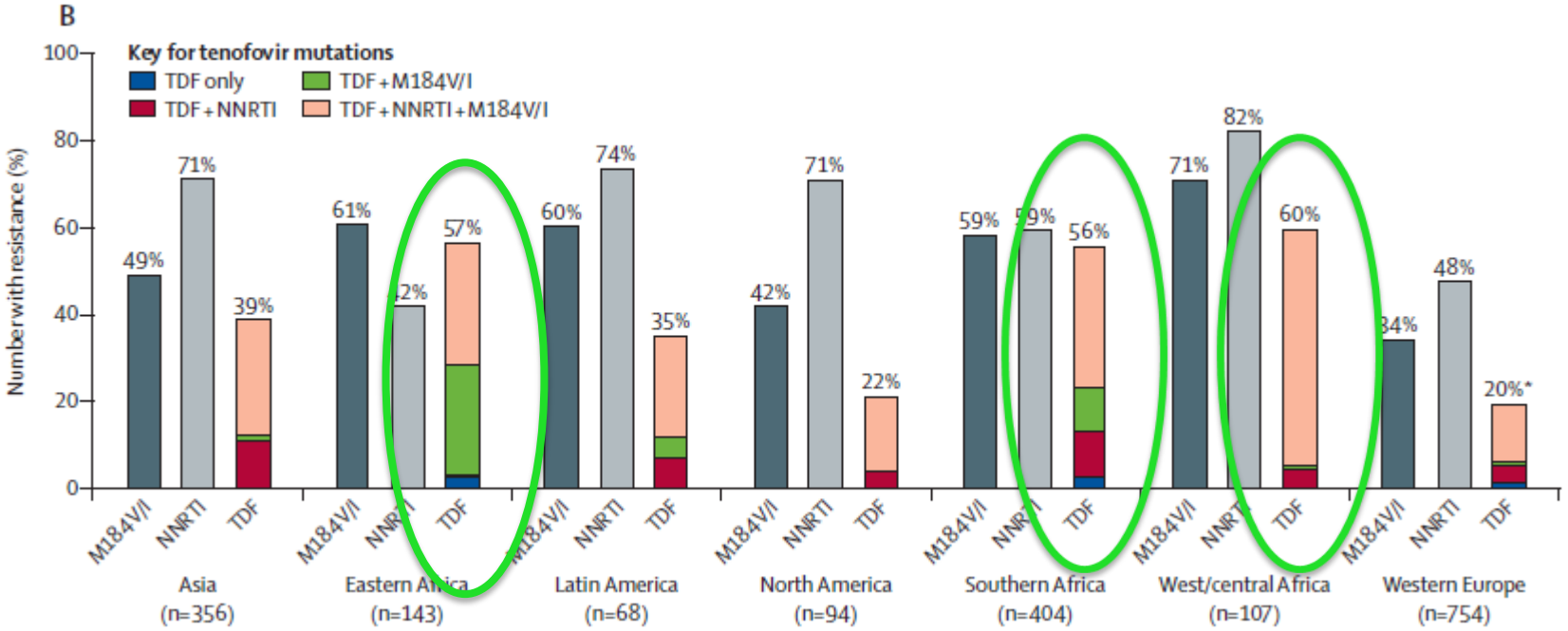
Previous exposure to suboptimal treatment developed world

Limited monitoring of virologic response world-wide

Transmitted drug resistance

Resistance in Developing World

- Second-line study: NNRTI/NRTI first line virologic failure – 15 countries – majority of participants from Africa or Asia
  - Baseline resistance - 492 participant samples



Boyd, M et al *Lancet* 2013; 381: 2091–99

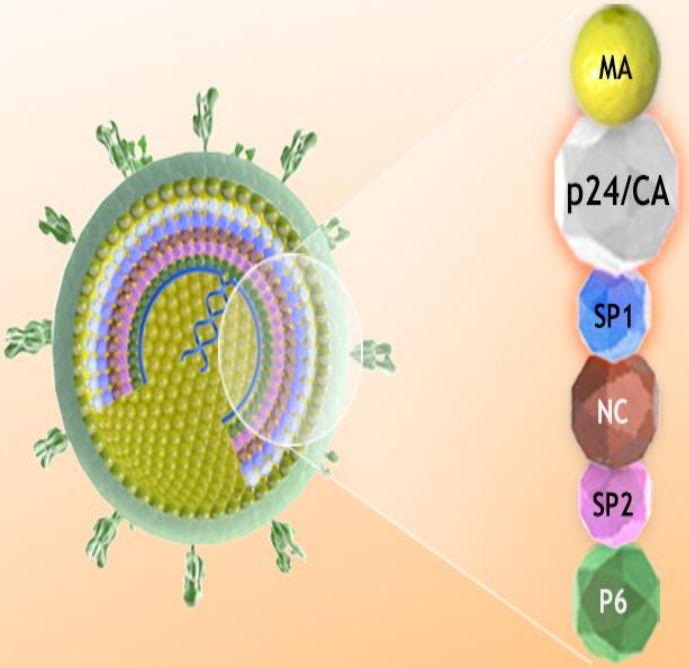
The TenoRes Study Group ***Lancet Infect Dis*** **2016**
Published **Online** January 28, 2015 – **Abstract 503**

New Agents for Resistant HIV-1

- Integrase Inhibitors
  - Dolutegravir (approved)
  - GS-9883 (Phase III)
- N(t)RTI
  - TAF (approved)
  - EFdA (4'-ethynyl-2-fluoro-2'-deoxyadenosine)(Phase I-II)
- NNRTI
  - Doravirine (Phase III)
- Maturation Inhibitors
  - BMS 955176 (Phase II)
- Attachment inhibitors
  - BMS 663068 -> 626529 (Phase III)
- Broadly neutralizing monoclonal antibodies

New Targets: e.g. LEDGF, combination entry, additional maturation sites, HIV-1 RNA processing

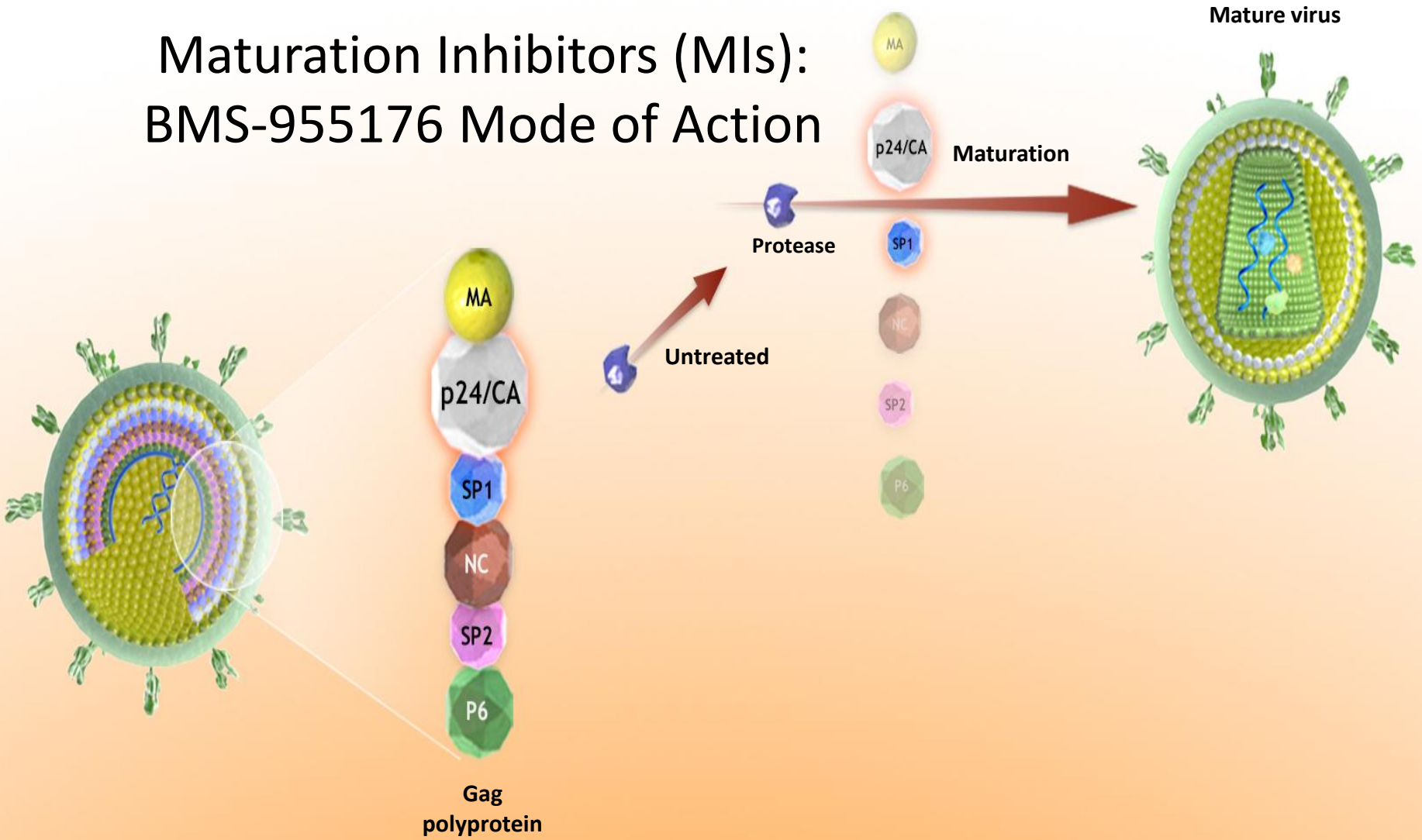
Maturation Inhibitors (MIs): BMS-955176 Mode of Action



Gag polyprotein

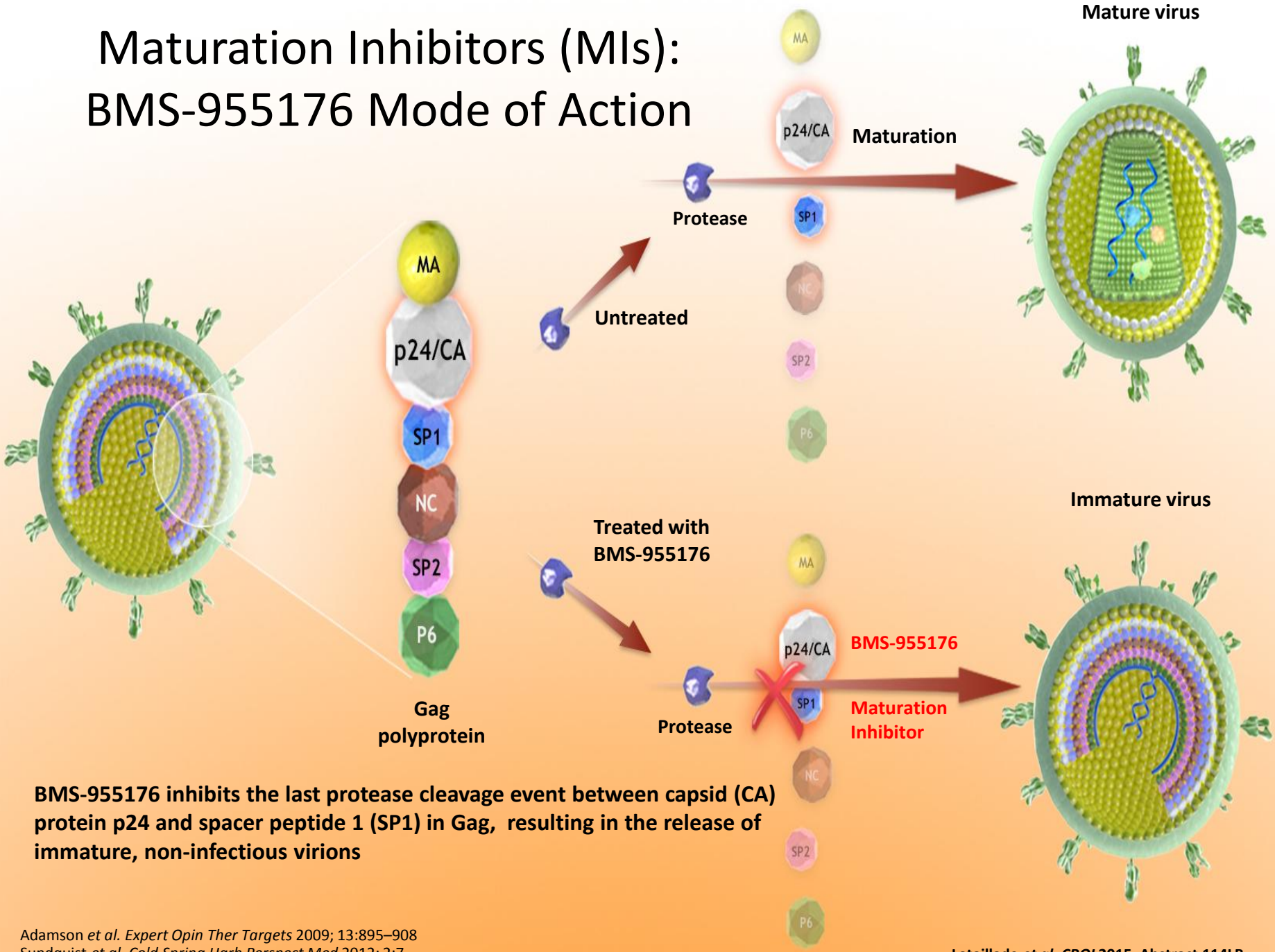
Lataillade *et al. CROI* 2015, Abstract 114LB

Maturation Inhibitors (MIs): BMS-955176 Mode of Action



Lataillade *et al. CROI* 2015, Abstract 114LB

Maturation Inhibitors (MIs): BMS-955176 Mode of Action

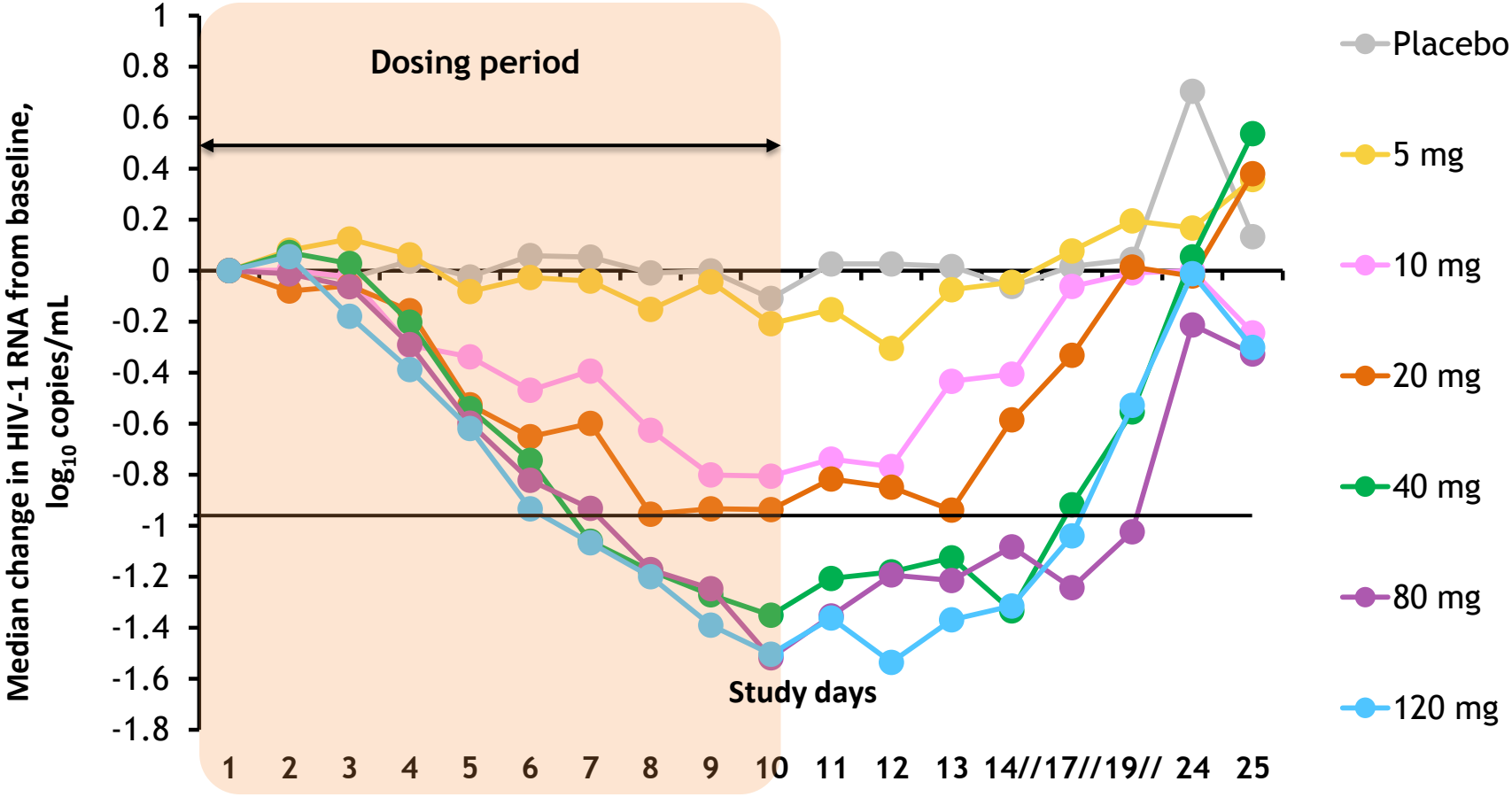


- **BMS-955176 inhibits the last protease cleavage event between capsid (CA) protein p24 and spacer peptide 1 (SP1) in Gag, resulting in the release of immature, non-infectious virions**

Adamson *et al. Expert Opin Ther Targets* 2009; 13:895–908
Sundquist *et al. Cold Spring Harb Perspect Med* 2012; 2:7.

Lataillade *et al. CROI* 2015, Abstract 114LB

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

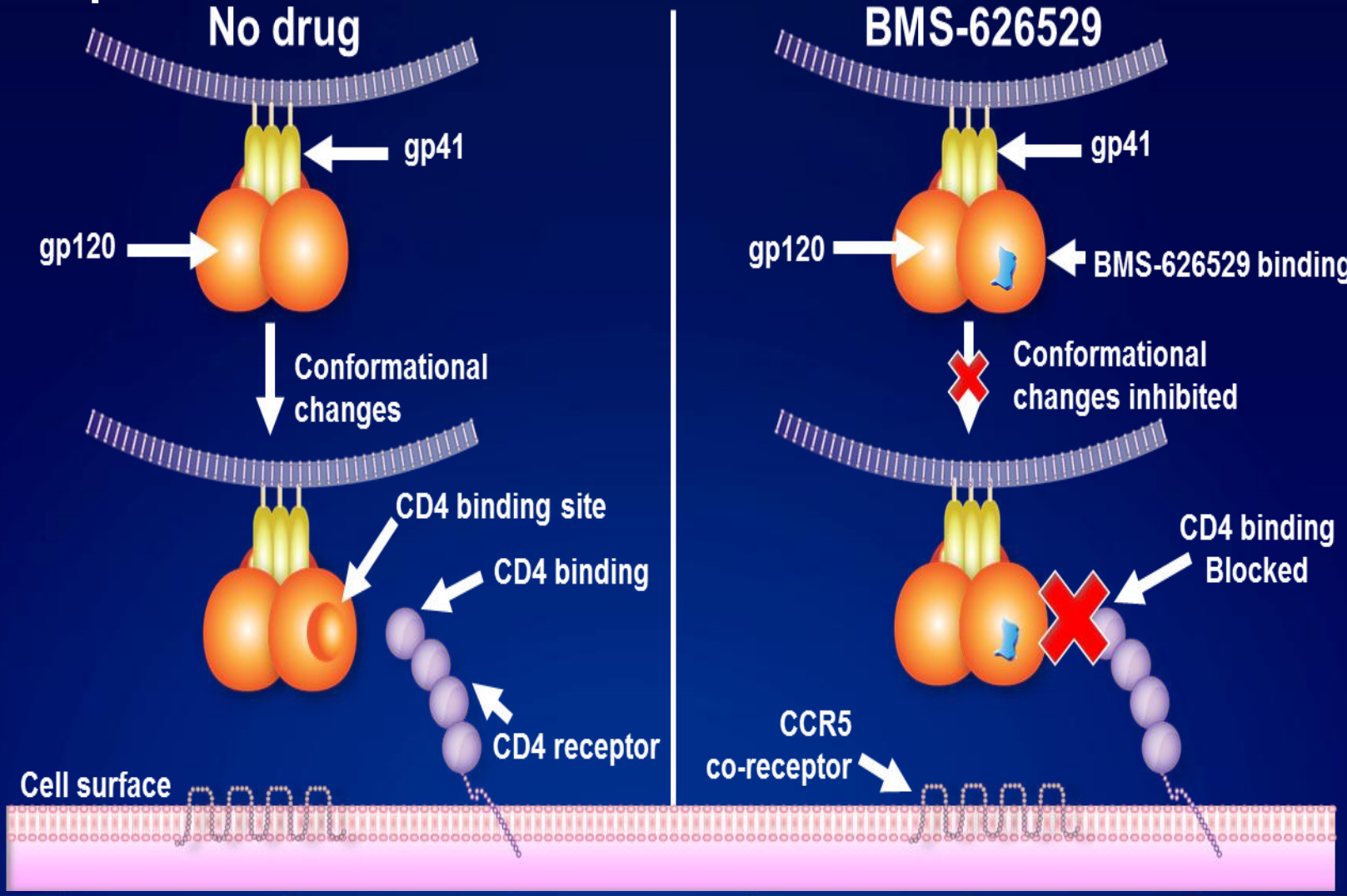


- Median change in HIV-1 RNA from baseline to Day 11 reached ~-1.4 $\log_{10}$ c/mL

See Abstract 425, 464

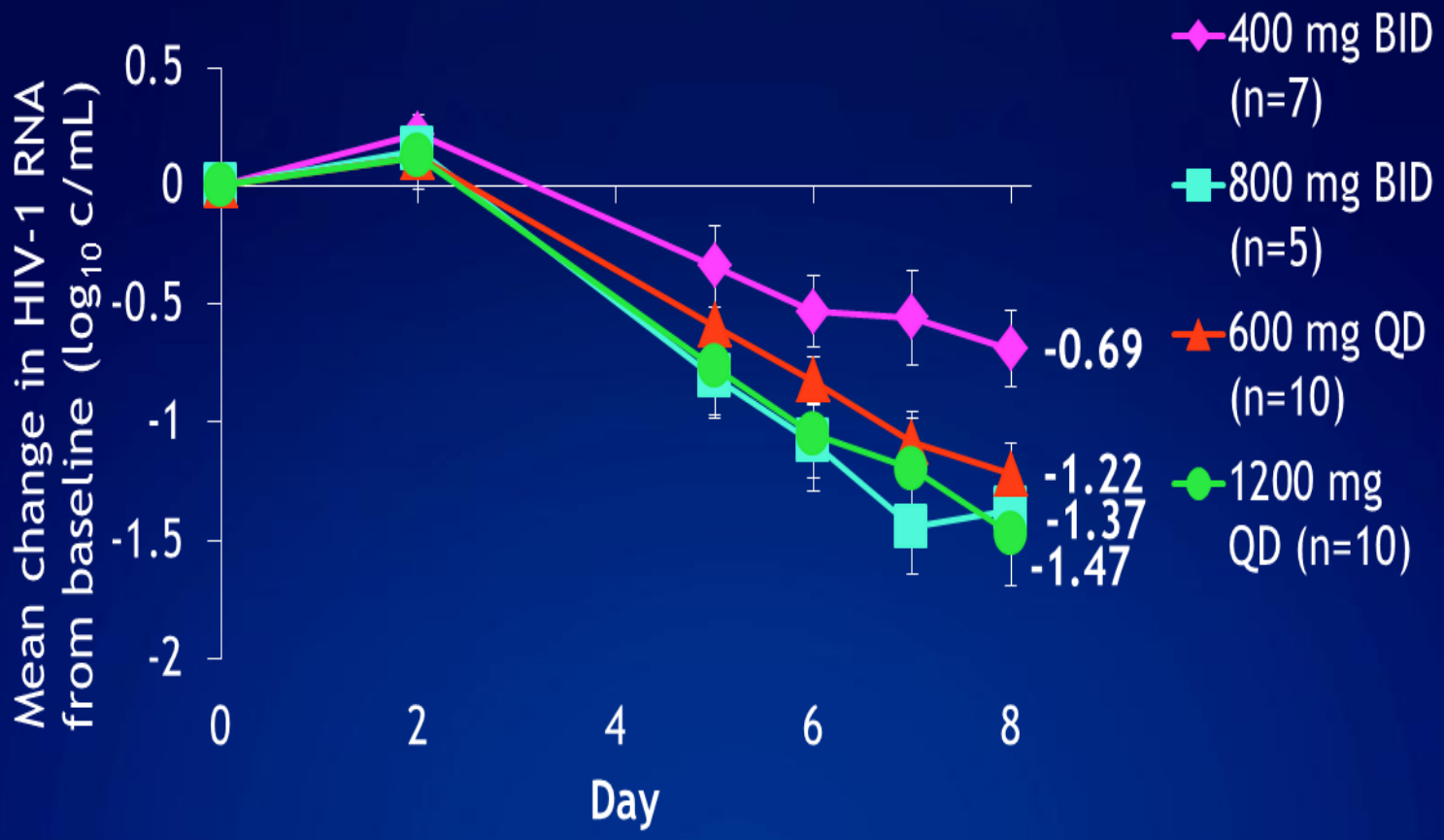
Lataillade *et al. CROI* 2015, Abstract 114LB

BMS-626529 Attachment Inhibitor: Proposed Mechanism of Action



1. Langley DL et al. Manuscript in development.

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



*Error bars represent standard error of the mean.

Abstract 472

Lalezari et al CROI 2014 abstract 86

Bristol-Myers Squibb

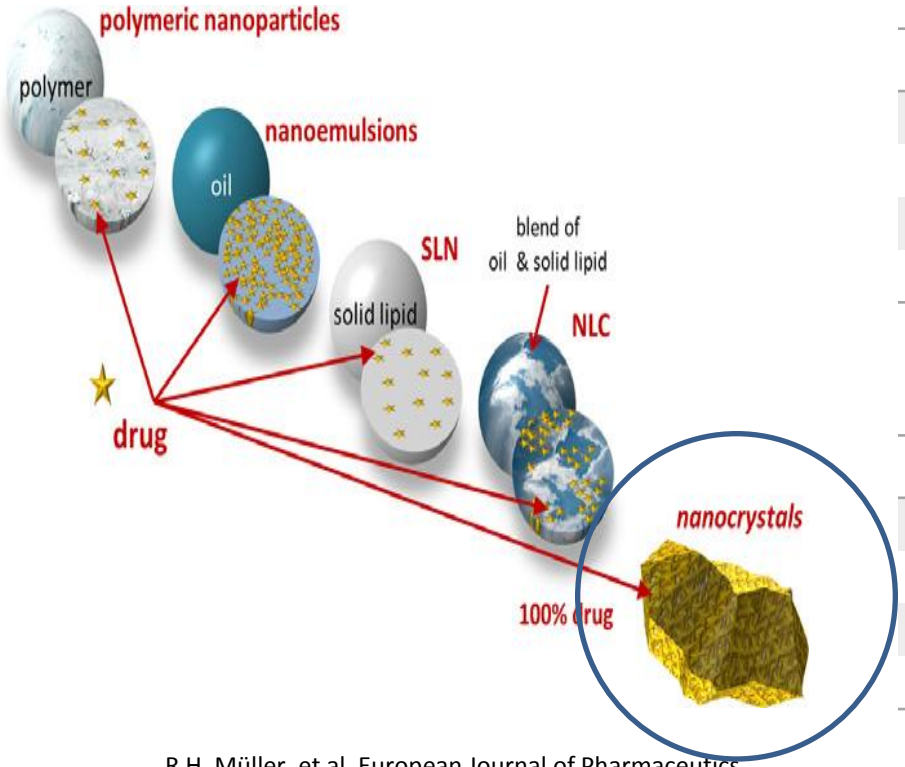
Maintaining therapy for Life in all PLWHIV

- Adherence
  - Hard to reach populations, substance use, depression, children, adolescents …….
- Life Chaos
  - Travel, dislocation for work or safety, surgery, drug interactions, pill fatigue, patient preference ……

Long acting antiretroviral Therapy!

Cabotegravir LA and Rilpivirine LA Nanosuspensions

- Drug nanocrystal suspended in liquid = nanosuspension
- Nanomilled to increase surface area and drug dissolution rate
- Allows ~100% drug loading vs. matrix approaches for lower inj. volumes



R H. Müller, et al. European Journal of Pharmaceutics and Biopharmaceutics 78 (2011) 1-9

GSK744 200mg/mL

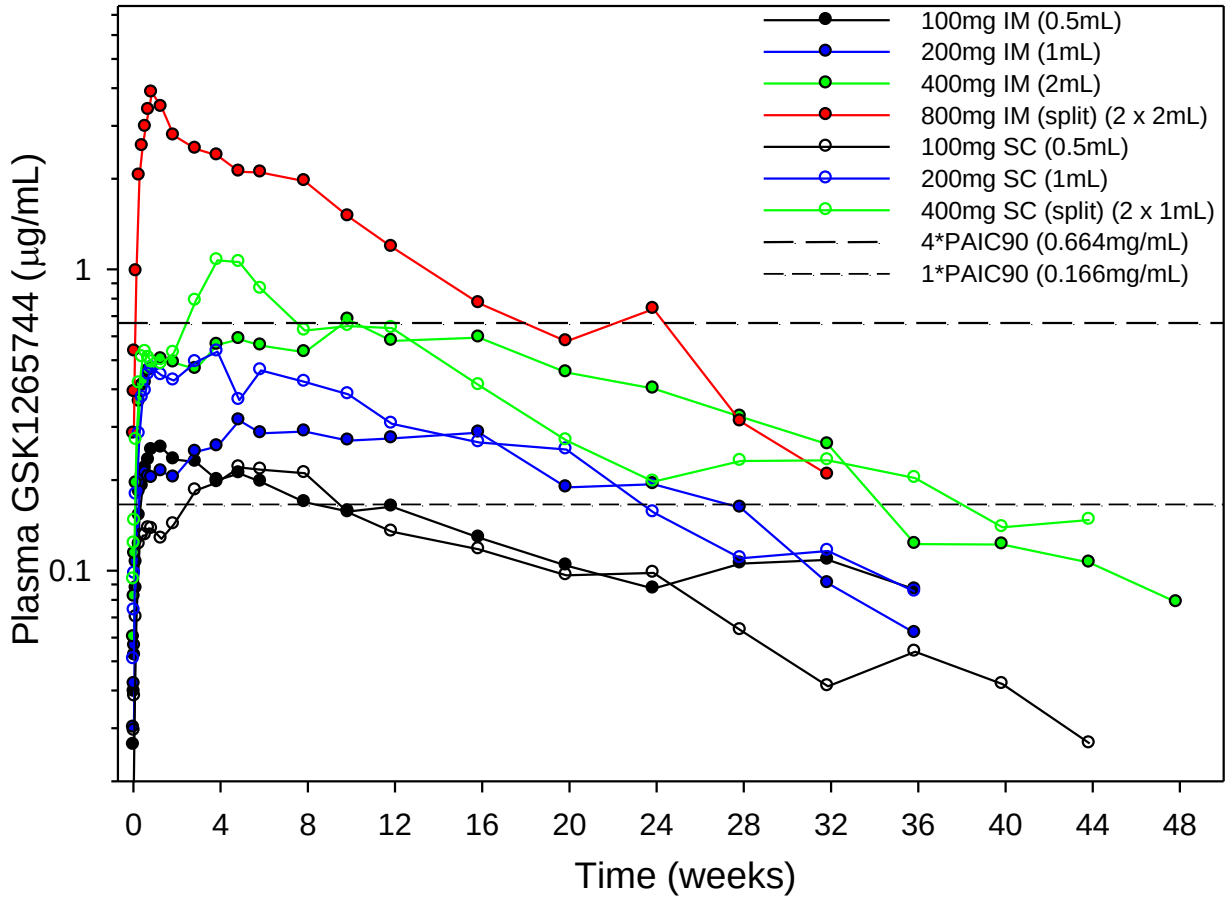
Component	Function
GSK1265744 (d50 ~200 nm)	Active
Mannitol	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

TMC278 300mg/mL

Component	Function
TMC278 (d50 ~200 nm)	Active
Glucose	Tonicity agent
Surfactant System	Wetting/Stabilizer
Water for Injection	Solvent

Spreen et al. IAS 2013; Kuala Lumpur. Abstract WEAB0103.

Mean Plasma cabotegravir Concentration-Time Profiles Following Single 100-800 mg LAP Doses (200mg/mL nanosuspension)

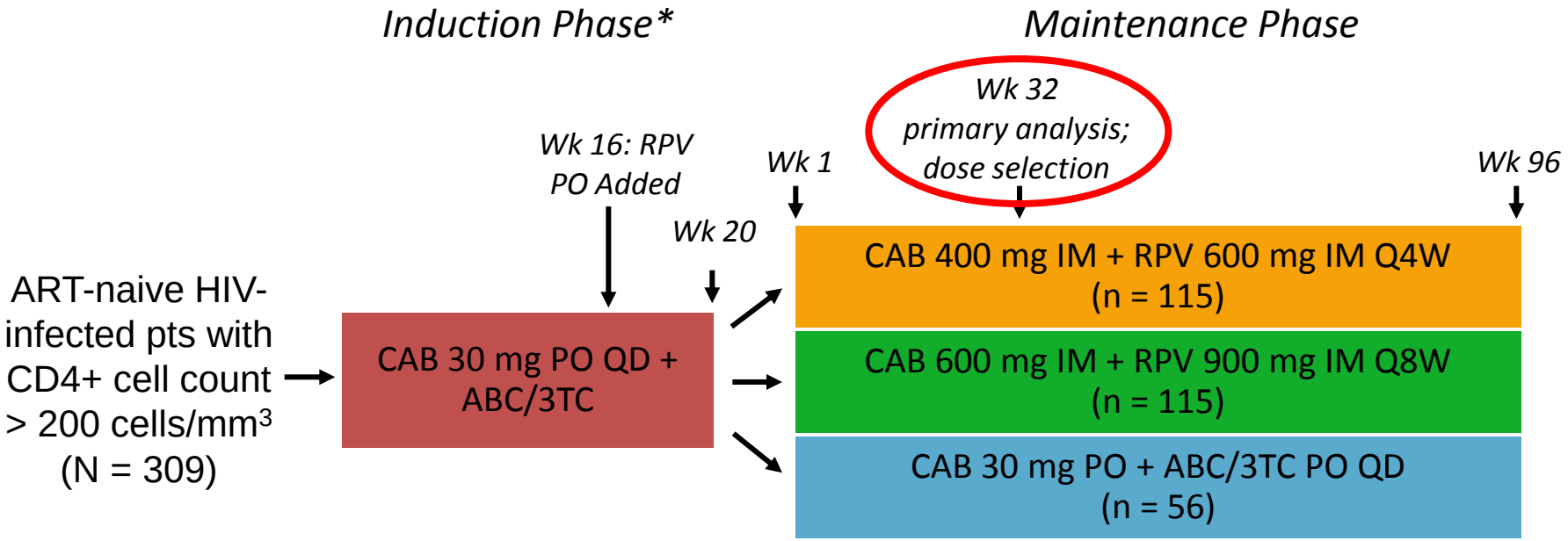


Differences observed between split and unsplit dosing

Spreen et al. IAC 2012; Washington, DC. Abstract TUPE040.

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. In snapshot induction analysis, 14 pts had virologic nonresponse and 13 pts had no virologic data in window, including 6 pts who discontinued for AEs or death and 7 pts who discontinued for other reasons.

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

Slide credit: clinicaloptions.com

Two Drug ART Maintains Suppression

Latte: Cabotegravir (InSTI) + rilpivirine maintenance vs. EFV-based therapy

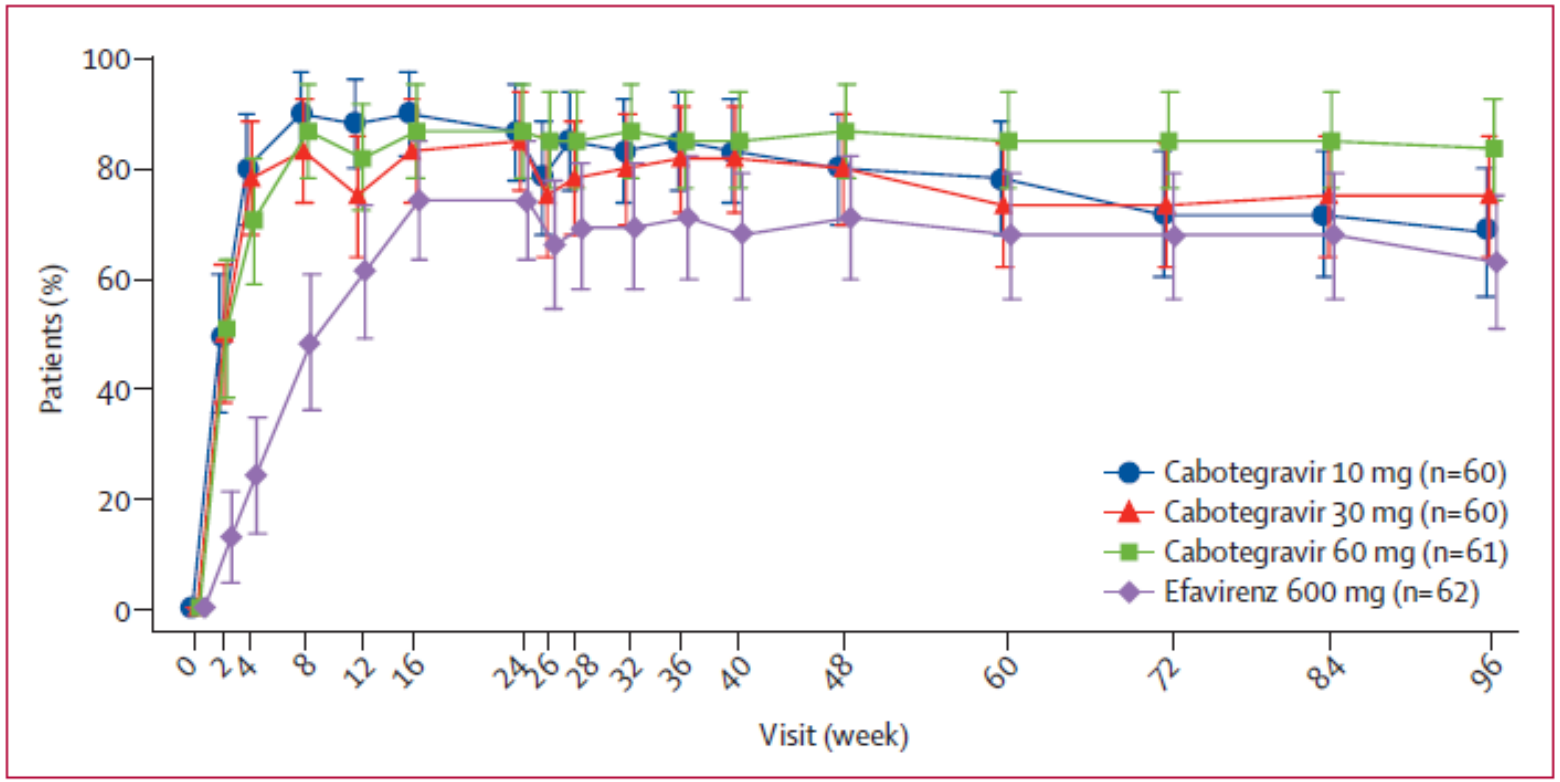
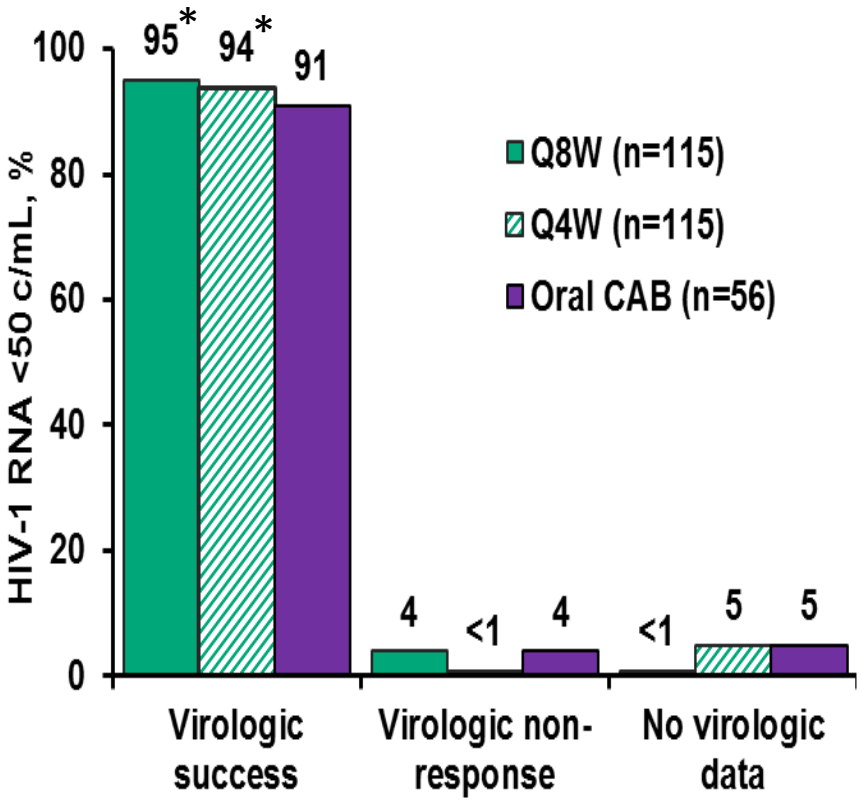


Figure 2: **Proportion of patients with HIV-1 RNA concentration of less than 50 copies per mL by visit in the intention-to-treat exposed population**
Error bars indicate 95% CI.

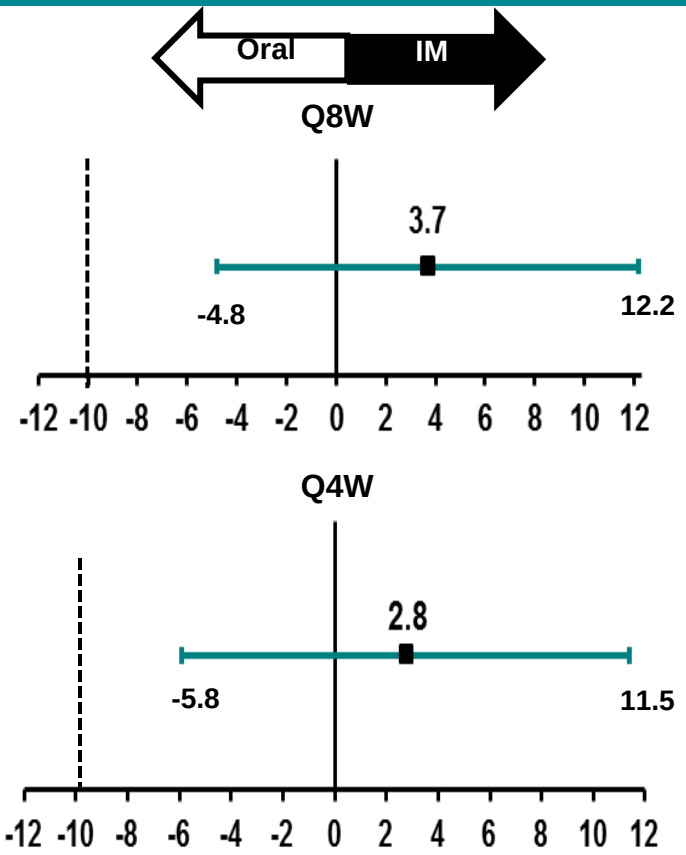
Margolis DA, et al Lancet Infect Dis 15;1145 2015

LATTE-2 Week 32 Primary Endpoint: HIV-1 RNA <50 c/mL by Snapshot (ITT-ME)

Virologic outcomes



Treatment differences (95% CI)



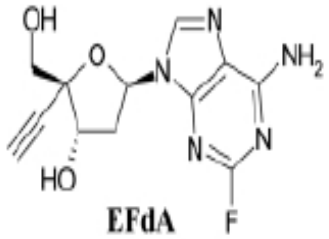
Both Q8W and Q4W comparable/non-inferior to oral CAB at Week 32

*Met pre-specified threshold for concluding IM regimen is comparable to oral regimen (Bayesian posterior probability >90% that true IM response rate is no worse than -10% compared with the oral regimen).

Margolis et al. CROI 2016; Boston, MA. Abstract 31LB.

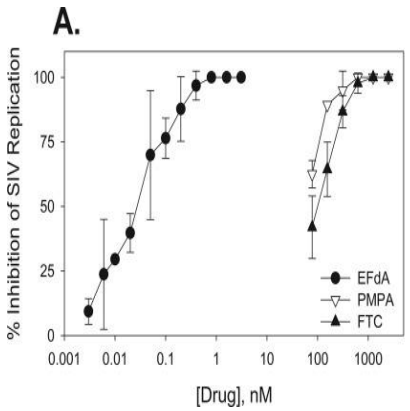
4’-ethynyl-2-fluoro-2’-deoxyadenosine (EFdA) MK8591

- EFdA (MK-8591) is a nucleoside reverse transcriptase translocation inhibitor (NRTTI)



EFdA

- Sub-nanomolar potency in vitro[1] and prolonged suppression of SIV in macaque model[2]



B.

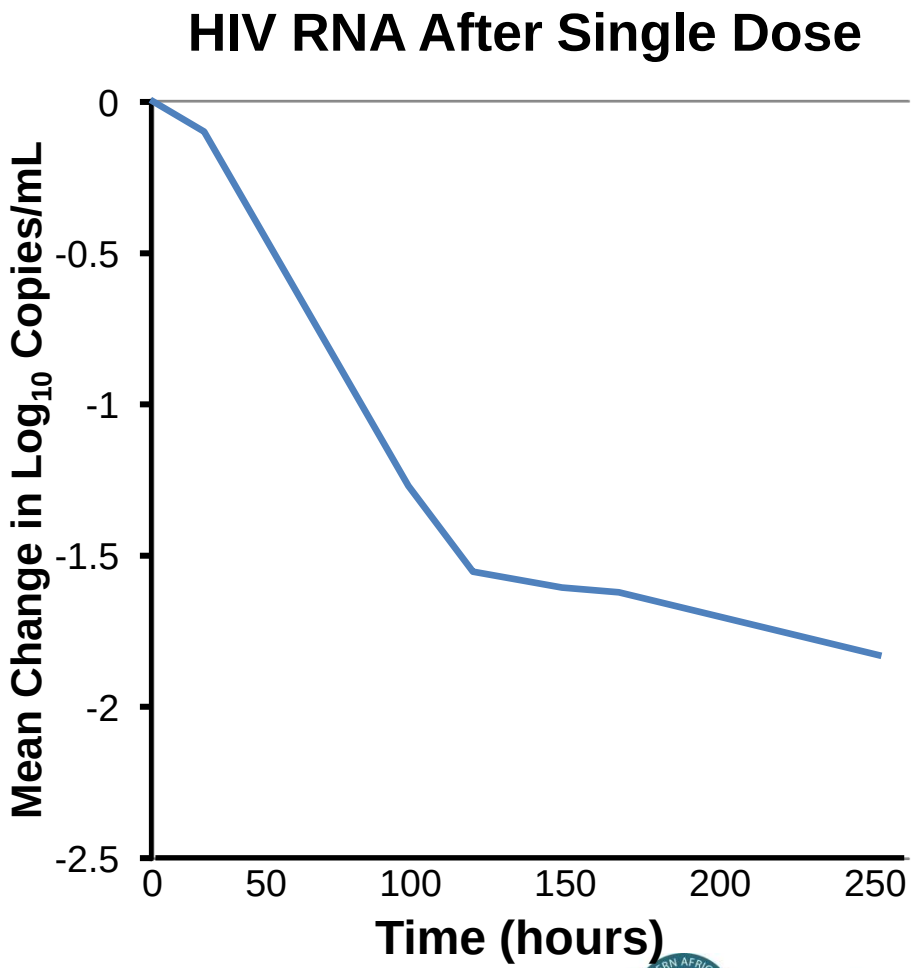
	EC_{50} (nM)	EC_{95} (nM)
EFdA	0.04 +/- 0.01	0.4
PMPA	67.5 +/- 6.5	240
FTC	108.6 +/- 9.2	580

- Prolonged persistence of triphosphate form in PBMC and macrophage
- Potential for once weekly dosing **(Friedman et al Abstract 437LB)**
- Long-acting formulations under development **(Grobler et al Abstract 98)**

[1]Michailidis et al J Biol Chem 284: 35681-91; 2009 [2]Murphey-Corb et al AAC 56:4707-12; 2012

MK-8591: Reduction in HIV RNA for at Least 10 Days After Single Oral Dose

- Open-label study (n=6)
  - Treatment-naïve males
  - CD4 >500 cells/mm^3
- MK-8591 (NRTI)
  - Single, 10-mg oral dose
- Intracellular MK-8591-TP in PBMC
  - T1/2 (geometric mean): 103 hours
- No evidence of resistance out to day 10
- HIV RNA reduction (log_{10} copies/mL)
  - Day 7: 1.67
  - Day 10: 1.78
- Generally well tolerated



TP: triphosphate.

Friedman E, et al. 23rd CROI. Boston, 2016. Abstract 437LB.

BROADLY NEUTRALIZING ANTIBODIES

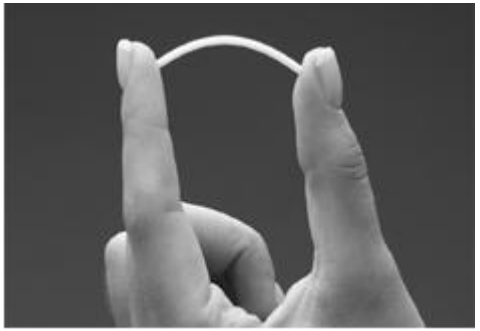
Can they be harnessed as therapy?

Broadly Neutralizing Antibodies as Therapy

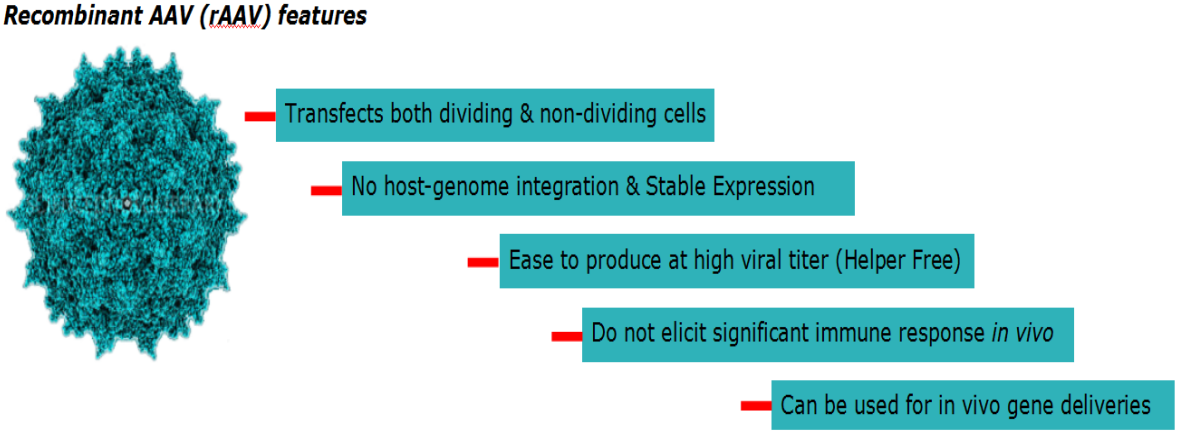
- Can they be used successfully as therapy?
  - Single antibodies lack needed breadth[refs]
  - Combinations of antibodies with differing targets
    - Anti-CD4 binding plus anti-V3 or V2 plus others?
  - Modifiable to increase half-life
  - Bispecific antibodies
  - Antibody-like inhibitors (e.g. eCD4-Ig)
  - In combination with long-acting antiretrovirals?
- But…
  - Cumbersome delivery, increasing potency = decreasing dose
  - Virus escape – frequency of monitoring
  - Anti-idiotype or other inhibitory antibodies
  - Advantages over antiretrovirals – other than being sexy?

Antiretroviral Therapy: The Next Generation?

- Implantable (and removable) combination antiretrovirals



- Vectored delivery of combinations of antibody-based therapy or protein based therapy



Antiretroviral Therapy: The Future

HIV-1 discovered

1983

ZDV monotherapy

1987

ZDV/3TC

1995

Triple Drug Therapy

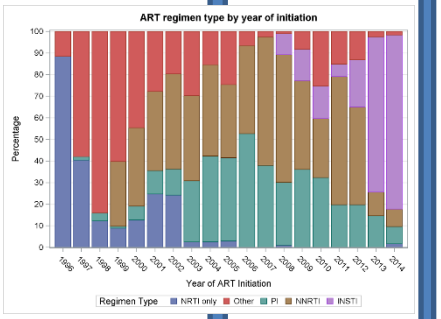
1996

Single Tablet Regimens

2006

The Integrase Era

2012-13



Long Acting Injectable?

2017

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2020

2016

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