Community feedback: CROI 2015

Simon Collins
HIV i-Base
www.i-Base.info

Prevention and new drugs

- PrEP, prevention
- Drug interactions
- New ARVs
- UK case of remission

Slides compiled from 2015 BHIVA “Best of CROI” feedback meetings.

- CROI talks are all webcast
- BHIVA feedback is also webcast

Public Health England

PROUD

MRC Clinical Trials Unit

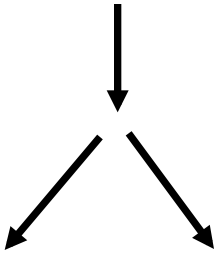
Pragmatic Open-Label Randomised Trial of Pre-Exposure Prophylaxis: the PROUD study

- To determine whether PrEP worked as well as iPrEx in this setting (44% reduction in HIV)
- Possibility that effectiveness might be less in real world

MRC | Medical Research Council

PROUD Pilot

MSM reporting UAI last/next 90 days



Truvada **NOW**

N= 267

Truvada **AFTER 12M**

N=256

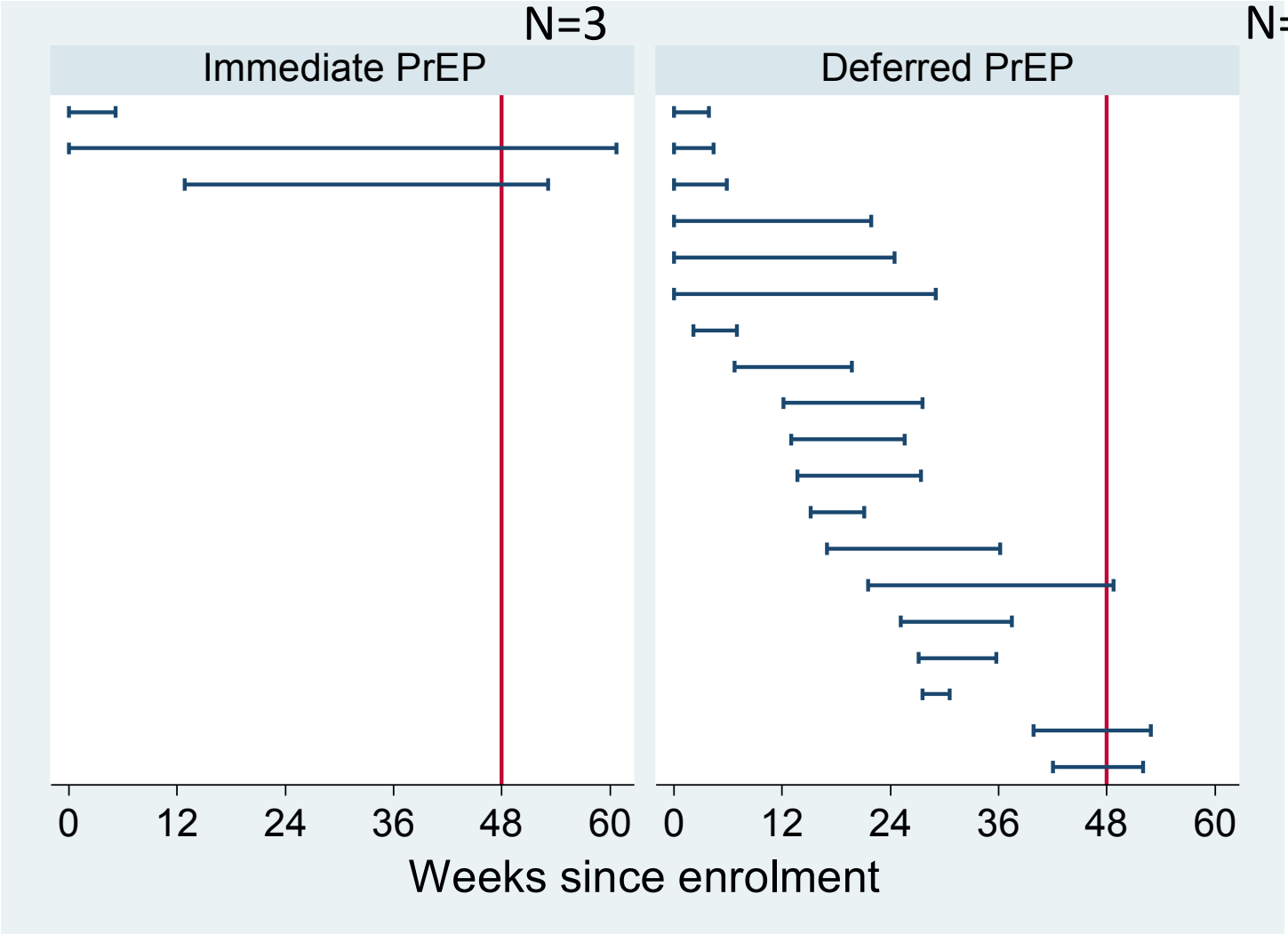
Follow **3 monthly** for up to 24 months

Main endpoints in Pilot: HIV infection in first 12 months

PROUD: Baseline demographics[1]

Characteristics		Immediate	Deferred
Age, median (IQR)		35 (30 – 43)	35 (29 – 42)
Ethnicity	White	80%	82%
Born UK	No	40%	40%
Education	University	59%	60%
Employment	Full-time	70%	73%
Sexuality	Gay	96%	94%
Current relationship	No	53%	55%
Recreational drug use	Yes	76%	64%

PROUD: new HIV infections



PROUD: HIV incidence rates

Group	No. of infections	Follow-up (PY)	Incidence (per 100 PY)	90% CI
Overall	22	453	4.9	3.4–6.8
Immediate	3	239	1.3	0.4–3.0
Deferred	19	214	**8.9**	6.0–12.7

Efficacy =86% (90% CI: 58 – 96%)
P value =0.0002

Rate Difference =7.6 (90% CI: 4.1 – 11.2)
Number Needed to Treat =13 (90% CI: 9 – 25)

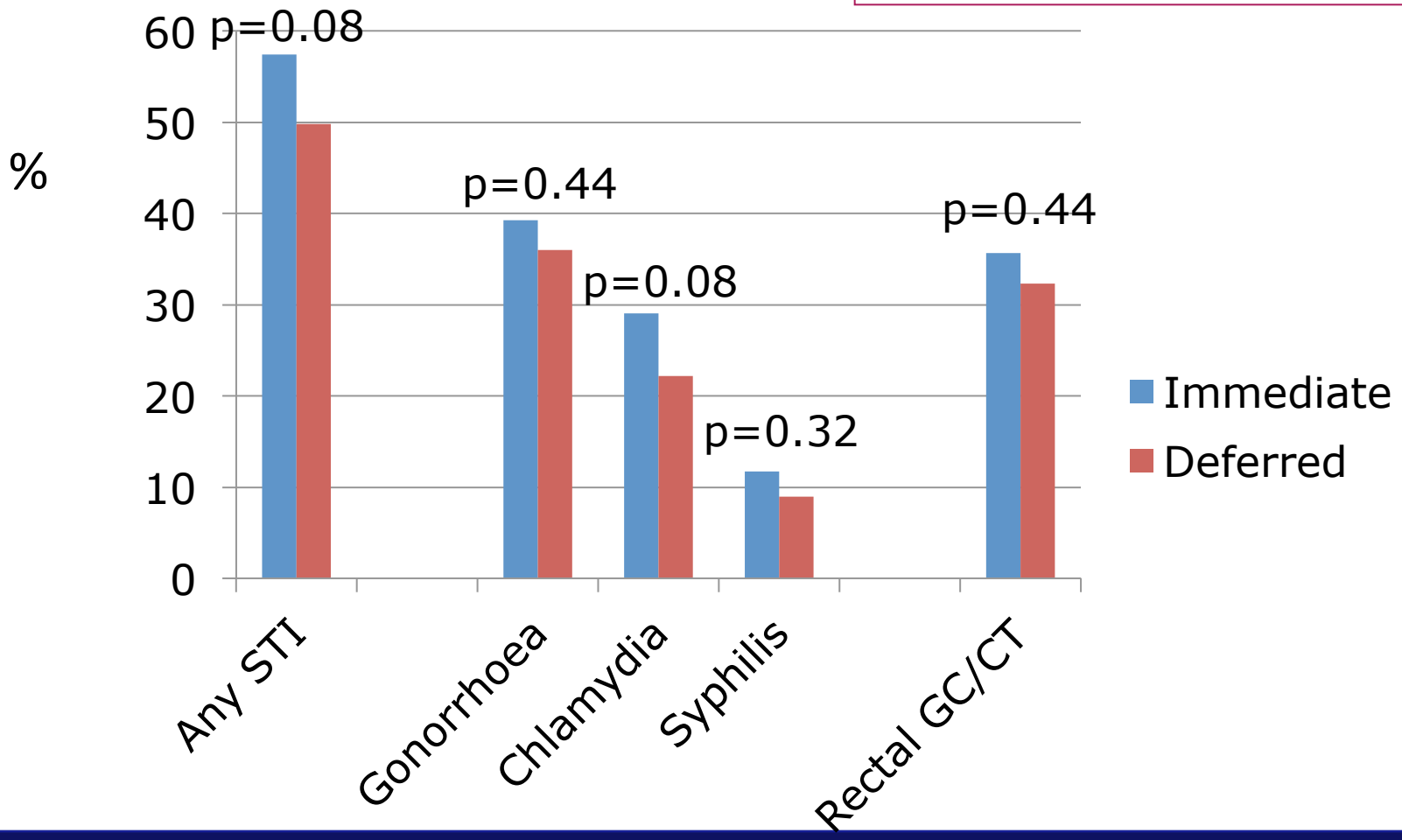
PROUD: Drug Resistance

- **3** of **6** individuals who were seroconverting as started truvada developed **M184V/I** mutations (as a mixture with wild type)

- **N=0 K65R**

PROUD: STIs

Caveat
Number of screens differed between the groups:
e.g. Rectal gonorrhoea/chlamydia 974 in the IMM group and 749 in the DEF



PROUD: conclusions

- HIV incidence was much higher than predicted
  - Despite extensive use of PEP in the deferred period
- Concerns about PrEP being less effective in the real world unfounded
- There was no difference in STIs, which were common in both groups
- Clinics were able to adapt routine practice to incorporate PrEP….JUST!

On Demand PrEP with Oral TDF/FTC in MSM Results of the ANRS Ipergay Trial

Molina JM, Capitant C, Spire B, Pialoux G, Chidiac C, Charreau I, Tremblay C, Meyer L, Delfraissy JF, and the ANRS Ipergay Study Group

Hospital Saint-Louis and University of Paris 7, Inserm SC10-US019 Villejuif, Hospital Tenon, Paris, Hospital Croix-Rousse, Lyon, UMR912 SEAS Marseille, France, CHUM, Montreal, Canada and ANRS, Paris, France

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

www.ipergay.fr

Study Design

Double-Blinded Randomized Placebo-Controlled Trial

- HIV negative high risk MSM
- Condomless anal sex with ≥ 2 partners within 6 m

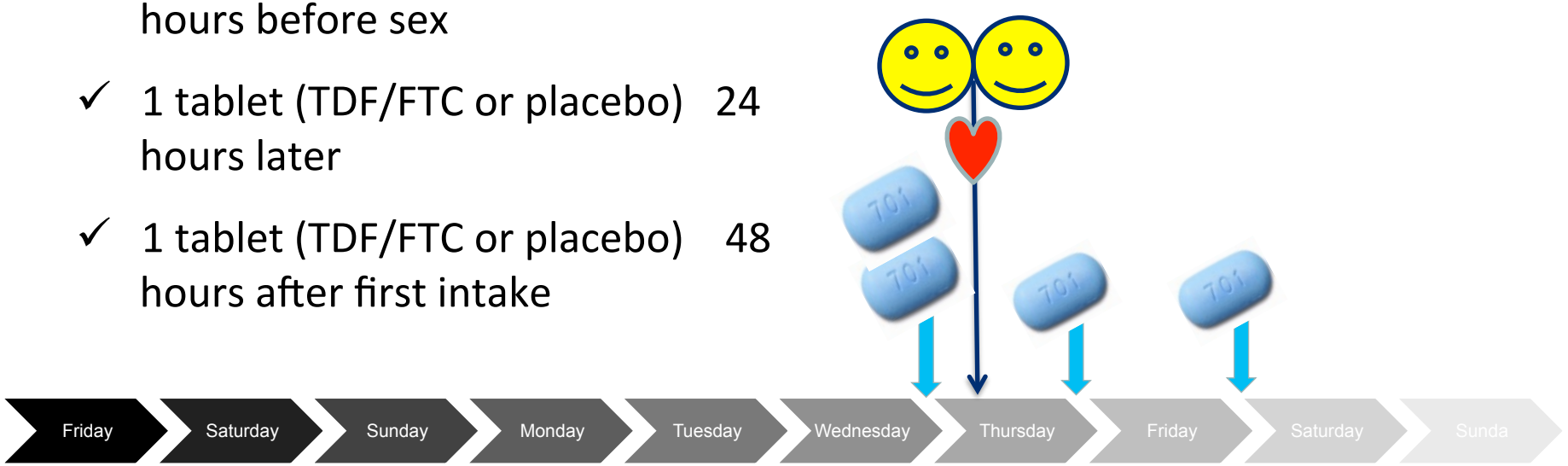
→ **TDF/FTC before and after sex** N=199

→ **Placebo before and after sex** N=201

- Follow-up visits: month 1, 2 and every two months thereafter

Ipergay : Event-Driven iPrEP

- ✓ 2 tablets (TDF/FTC or placebo) 2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo) 24 hours later
- ✓ 1 tablet (TDF/FTC or placebo) 48 hours after first intake



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Baseline Characteristics

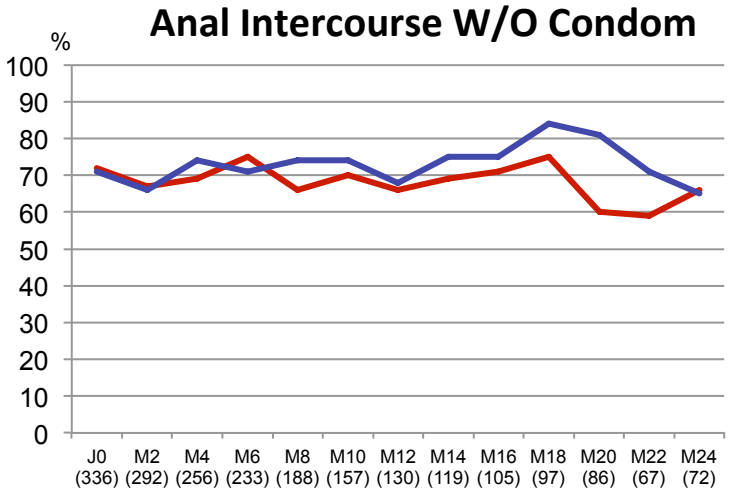
Characteristics (Median, IQR) or (n, %)	TDF/FTC n = 199	Placebo n = 201
Age (years)	35 (29-43)	34 (29-42)
White	190 (95)	184 (92)
Completed secondary education	178 (91)	177 (89)
Employed	167 (85)	167 (84)
Single	144 (77)	149 (81)
History of PEP use	56 (28)	73 (37)
Use of psychoactive drugs*	85 (44)	92 (48)
Circumcised	38 (19)	41 (20)
Infection with NG, CT or TP**	43 (22)	59 (29)
Nb sexual acts in prior 4 weeks	10 (6-18)	10 (5-15)
Nb sexual partners in prior 2 months	8 (5-17)	8 (5-16)

* in last 12 months: ecstasy, crack, cocaine, crystal, speed, GHB/GBL

** NG: Neisseria gonorrhoeae, CT: Chlamydia trachomatis, TP: Treponema pallidum

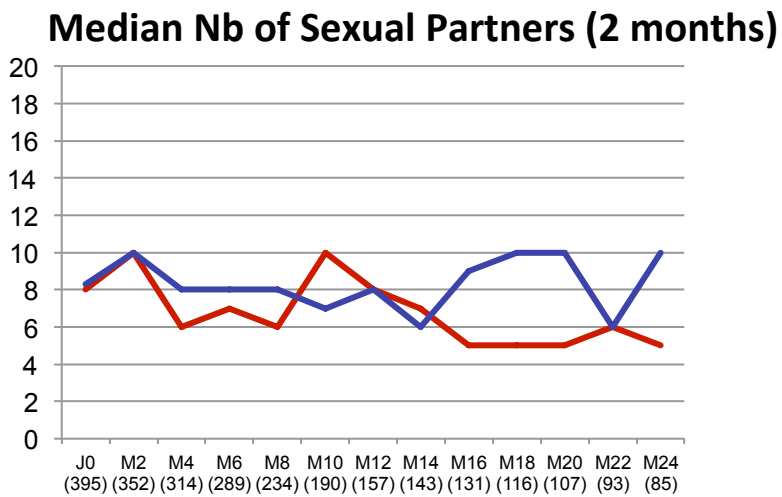
STI & Sexual Behavior

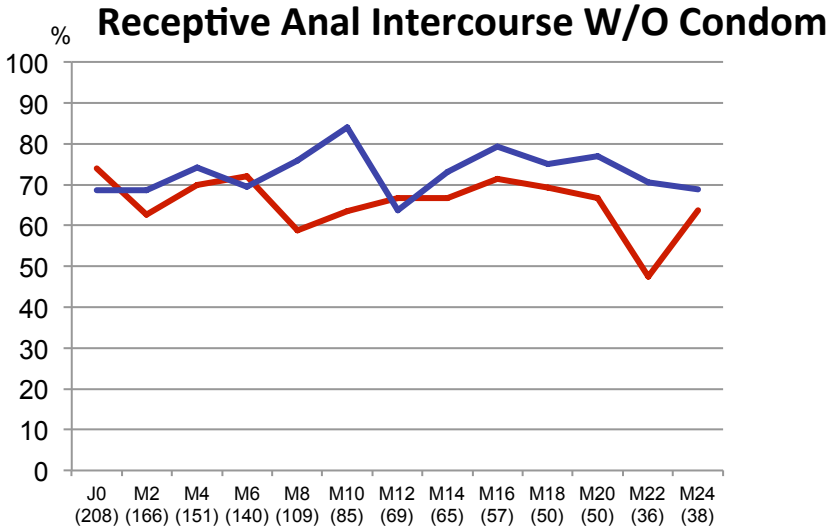
No difference between groups in any STI



TDF/FTC

Placebo





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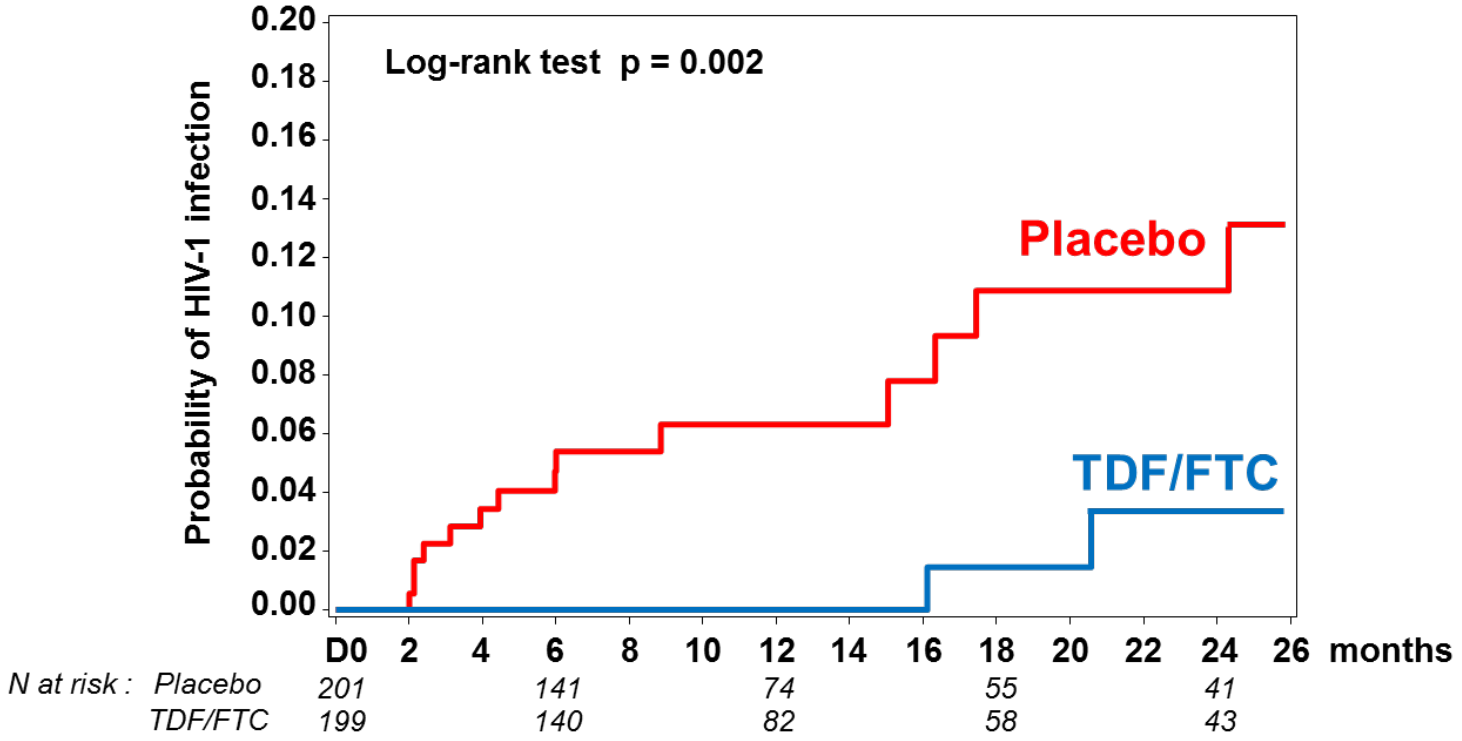
KM Estimates of Time to HIV-1 Infection (mITT Population)



Mean follow-up of 13 months: 16 subjects infected

14 in placebo arm (incidence: 6.6 per 100 PY), **2 in TDF/FTC arm** (incidence: 0.94 per 100 PY)

86% relative reduction in the incidence of HIV-1 (95% CI: 40-99, p=0.002)

NNT for one year to prevent one infection : 18

Adherence

- **PILL COUNT**
  - **Median number of pills/month (IQR):** 16 pills (10-23) in the placebo arm and 16 pills (12-24) in the TDF/FTC arm (p=0.84) ie 50% of daily
  - 20% took over 25 pills a month, i.e. the equivalent of almost daily
  - 20% less than four, i.e. less than one a week.
- **LAST SEX**
  - 43% used correct regime

ipergay
ANRS
Intervention Préventive de l'Exposition aux Risques avec et pour les Gays

Conclusions

- incidence of HIV-1 infection in placebo arm was higher than expected
- "On Demand" oral PrEP with TDF/FTC was very effective with a 86% (95% CI: 40-99) reduction in HIV-incidence
- Adherence was good
- Safety of "on demand" TDF/FTC was overall similar to placebo except for gastrointestinal AEs
- No evidence of risk compensation

Near elimination of HIV transmission in a demonstration project of PrEP and ART

Jared M. Baeten, Renee Heffron, Lara Kidoguchi, Nelly Mugo,
Elly Katabira, Elizabeth Bukusi, Stephen Asiimwe,
Jessica E. Haberer, Deborah Donnell, Connie Celum,
for the Partners Demonstration Project Team

CROI 2015, Seattle

PARTNERS DEMONSTRATION PROJECT

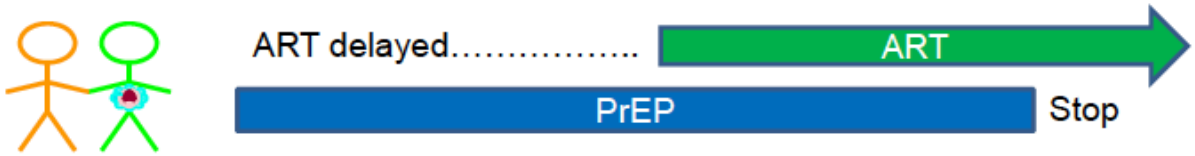
New Partners PreP cohort

- Enrolled HIV serodiscordant couples not on ART or PrEP who scored high on 'risk score'
  - Young, sex
- TASP and PreP offered to couples

PrEP as a bridge to ART

- For couples initiating ART at enrollment, PrEP is offered through 6 months, then stopped:

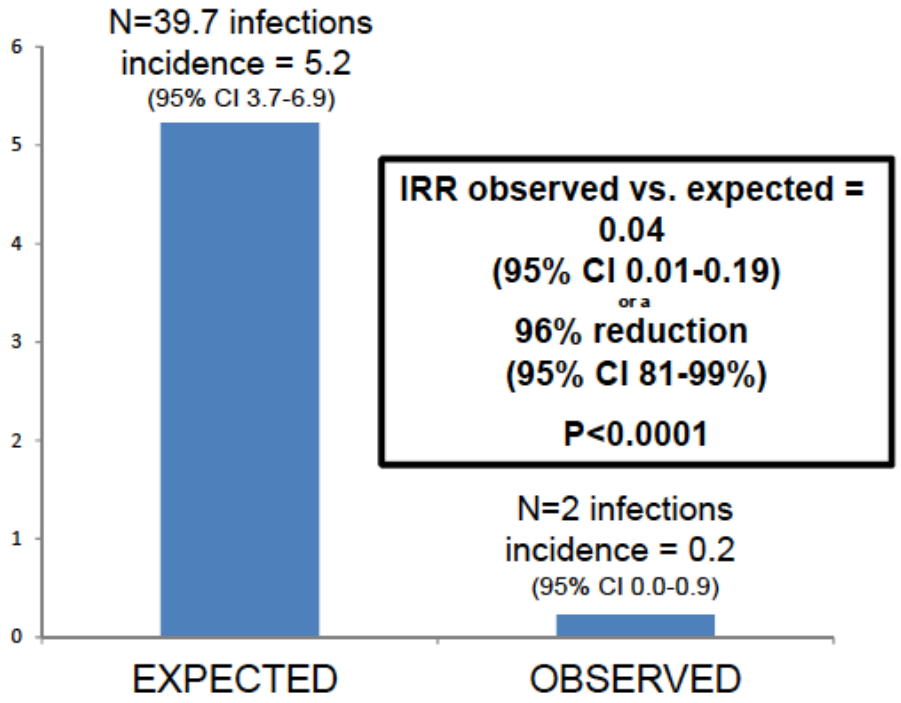
- For couples in which the infected partner delays or declines ART, PrEP is continued until 6 months after ART initiation:



N=2 transmissions: both not on TASP or Prep (Expected annual HIV incidence 5.2%)

HIV incidence

- The observed incidence is a **96% reduction** compared to expected, a result that was highly statistically significant



1st study showing low incidence in extra marital infections

FACTS
Follow-on African Consortium for Tenofovir Studies

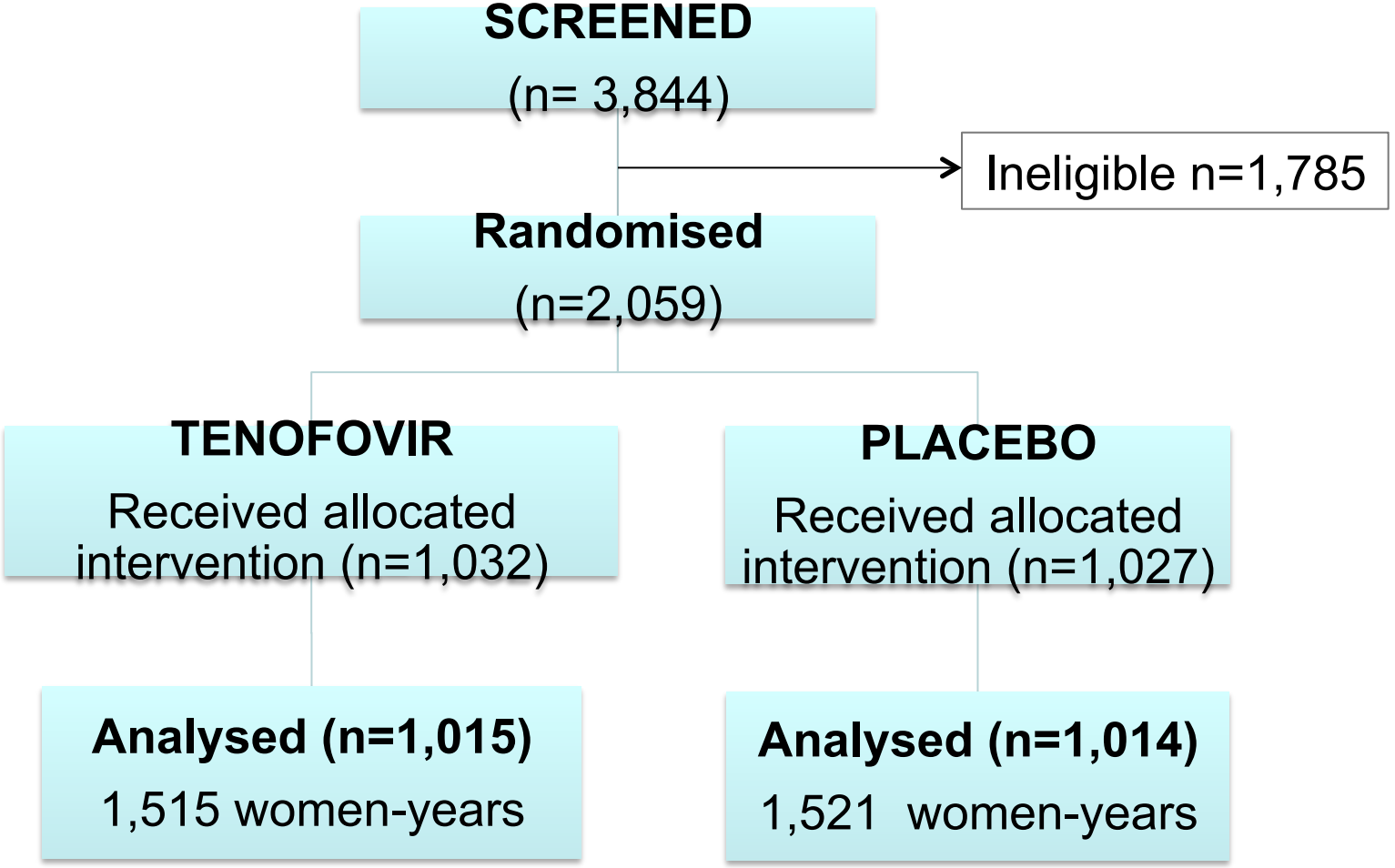
FACTS 001: a multi-centred phase III randomised, double-blind, placebo-controlled trial of pericoital tenofovir 1% gel for HIV prevention in women

Helen Rees, Sinead Delany-Moretlwe, Carl Lombard, Deborah Baron, Ravindre Panchia, Landon Myer, Jill Schwartz, Gustavo Doncel, Glenda Gray on behalf of the FACTS 001 study group

FACTS 001: Primary Objective

To evaluate the safety and **effectiveness of pericoital tenofovir (TFV) 1% gel** applied intravaginally in preventing HIV-1 infection in women.

FACTS 001: RCT



>90% attended scheduled exit visit

FACTS 001: Baseline characteristics

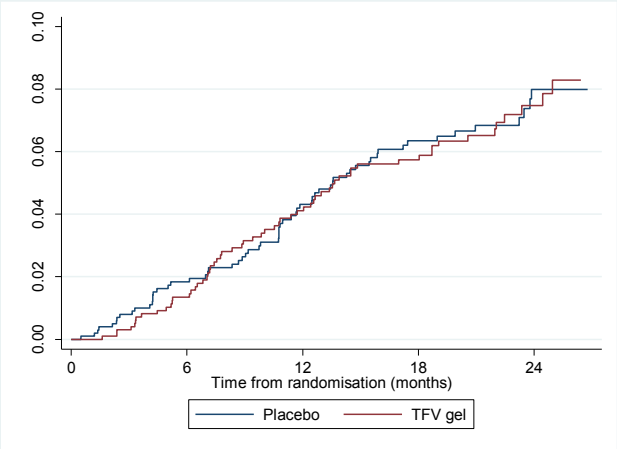
	TFV gel N= 1015 % or median (IQR)	Placebo gel N=1014 % or median (IQR)
Mean Age (years)	23 (20 – 25)	23 (20 – 25)
<25 years	71%	70%
Single	89%	89%
Living with parents/siblings	61%	63%
Secondary education or higher	56%	56%
Anal sex *	1%	1%
Consistent condom use*	35%	32%
Perceived HIV risk > than usual*	18%	17%
Median no. of sex partners*	1 (1- 1)	1 (1- 1)
HSV-2 seroprevalence	43%	40%

** in the past 28 days*

FACTS 001: No difference in HIV incidence between TFV gel vs placebo

	TFV gel	Placebo gel
Person-years	1515	1521
Protocol-specified HIV endpoints	61	62
HIV incidence per 100 p-y (95% CI)	4.0 (3.1-5.2)	4.0 (3.1-5.2)

Incidence Rate Ratio (IRR) 1.0; 95% CI: 0.7-1.4 *



*stratified by site

FACTS 001: Case-cohort sample of Tenofovir detection in CVL

- 56 HIV cases, 158 controls (n=214)

Percent of ***samples*** with any TFV detected*	64%
Percent of ***women*** with:	
TFV never detected at quarterly visits	13%

FACTS 001: Tenofovir detection and HIV incidence

TFV exposure	Adjusted Hazard Ratio (95% CI)	Protection (%)	P-value
TFV detected in samples from women who reported sex in 10 days preceding CVL	0.48 (0.23 - 0.97)	52	0.04

FACTS 001: Conclusion

- Pericoital vaginal TFV 1% gel was safe, but not effective in preventing HIV acquisition

- Effectiveness limited by adherence

Levonorgestrel Implant + EFV-Based ART: Unintended Pregnancies and PK Data

- Kimberly K. Scarsi
- *University of Nebraska Medical Center, Omaha, NE, United States*

Implanon- Levonorgestrel implant

- Failure rate <1%
- Long acting: 4-5yr
- Metabolized by cyp P450 3A4
- Constant drug exposure but slow decline
  - Need 180mcg/day levels to prevent pregnancy

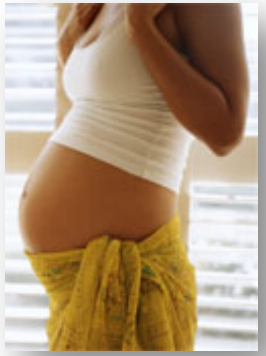
- Non randomized open label parallel group pk study in Uganda
  - EFZ group: HIV implant + starting EFZ based regime
  - Controls: HIV + implant only
- 48 weeks
  - Drug levels & PT every 3-,months

Results

- 20 women in each group
- PK : Comparing EFZ and control group
  - ~50% lower [LVG] at each time point
  - Over 45-57% LVG reduction in EFZ group AUC
- Pregnancy outcomes:
  - 3/20 pregnancies in EFZ
  - 0 in control
- No controls had LVG <300mcg
- All 3 pregnancies were in LVG 200-300mcg

Summary

- Reduced efficacy of sub dermal implants in women on EFZ
  - EFZ and subdermal use is increasing exponentially in africa
- Threshold of 150 mcg insufficient in HIV population study group
- Need more data on interactions with other ART



PROMISE
IMPAACT 1077
Promoting Maternal and Infant Survival Everywhere

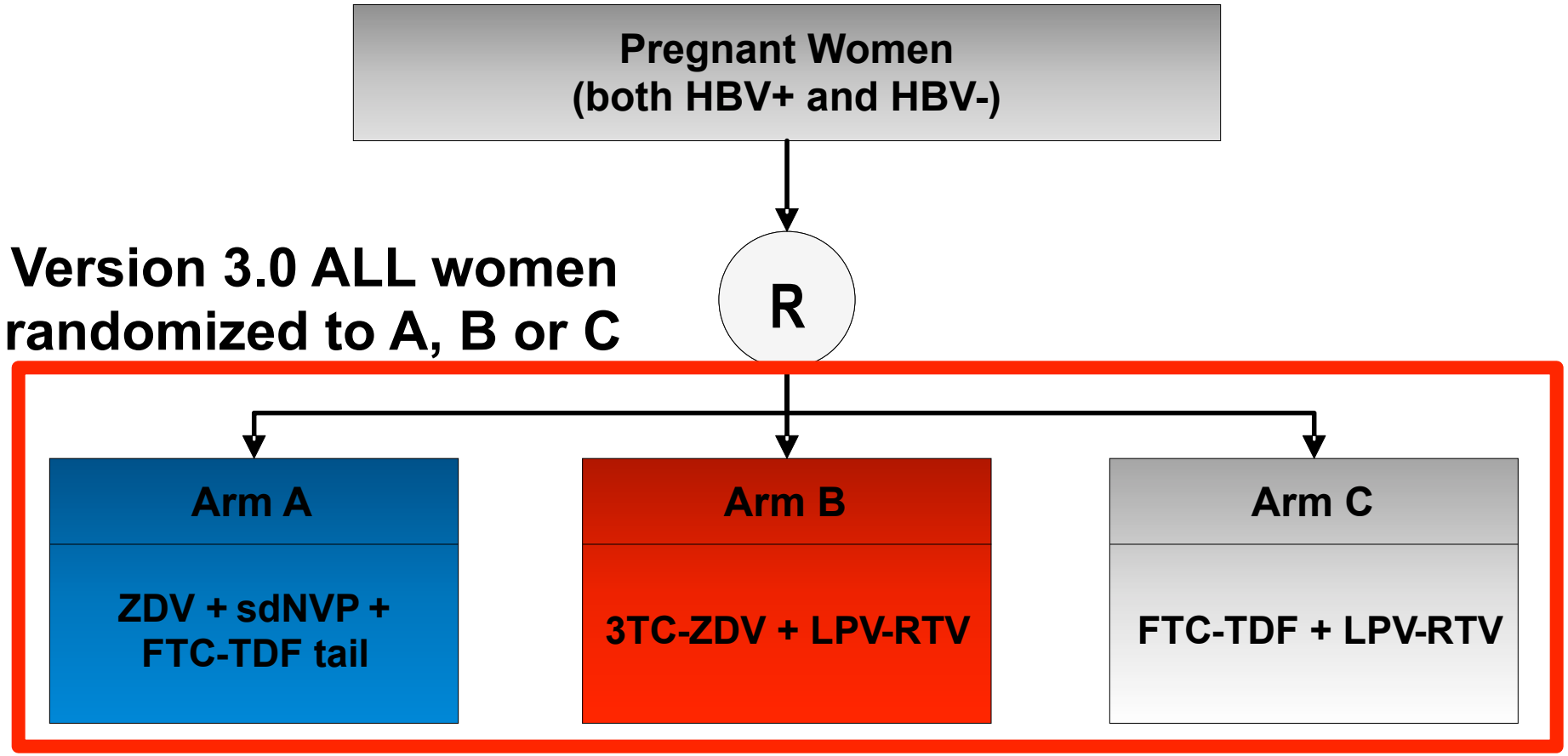
PROMISE: Efficacy and Safety of Two Strategies to Prevent Perinatal HIV Transmission

MG Fowler, M Qin, S Fiscus, JS Currier, P Flynn, J McIntyre, T Chipato, B Makanani, FE Martinson, R Browning, DE Shapiro, and LM Mofenson for The IMPAACT PROMISE 1077BF/1077FF Team

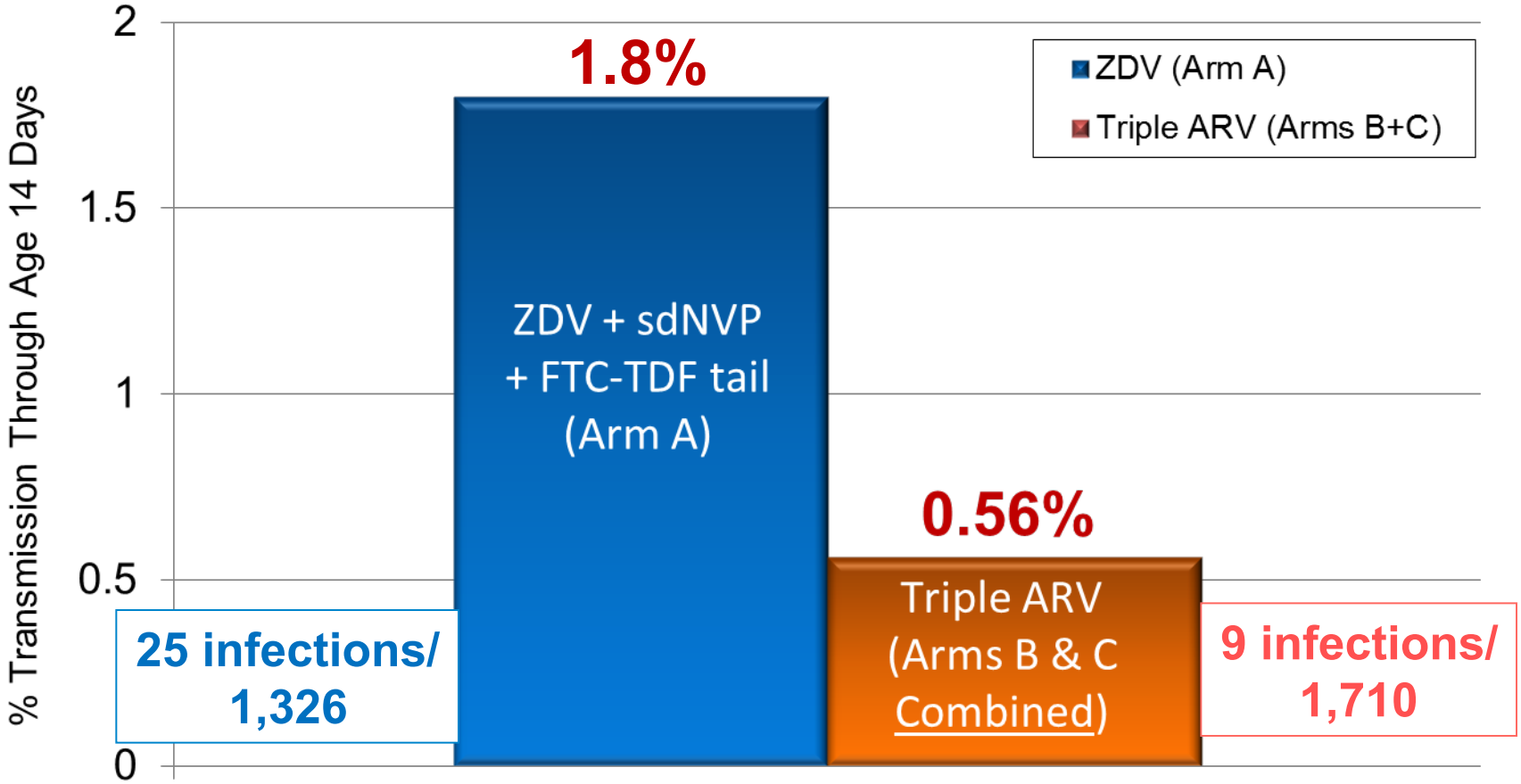
NIH
National Institutes of Health

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Antepartum Component
Maternal Randomization (Version 3)



MTCT Through Age 14 Days Significantly Lower in Triple ARV Arms



Difference in MTCT Risk (Repeated Confidence Interval): -1.28% (95% CI -2.11%, -0.44%)

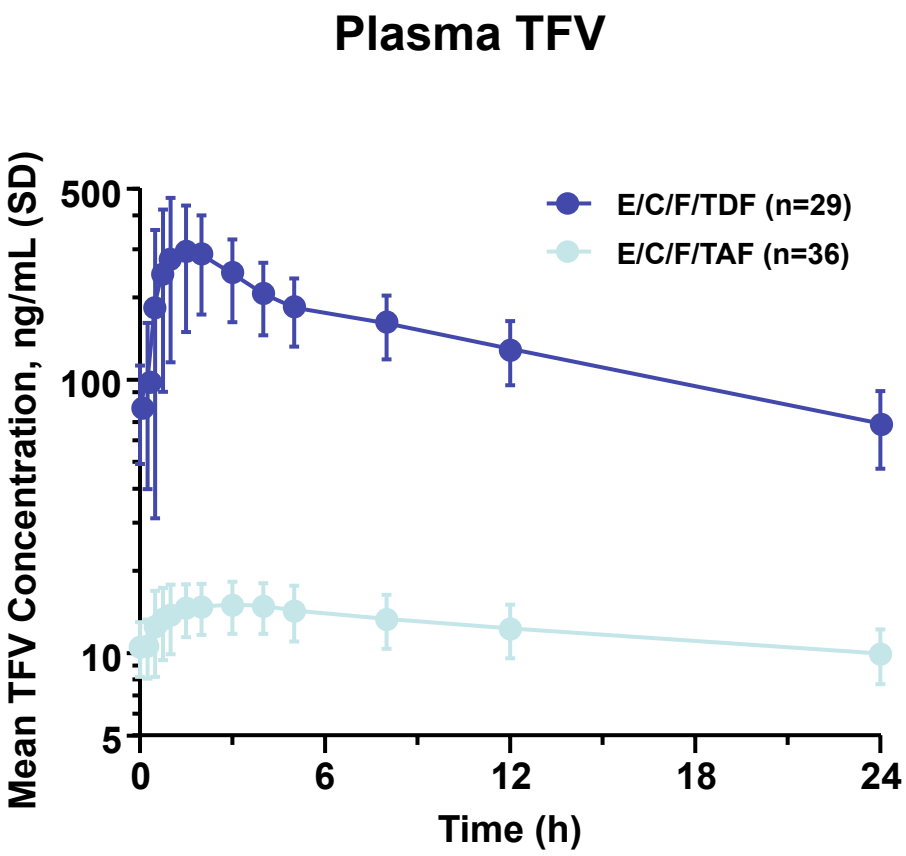
Conclusions

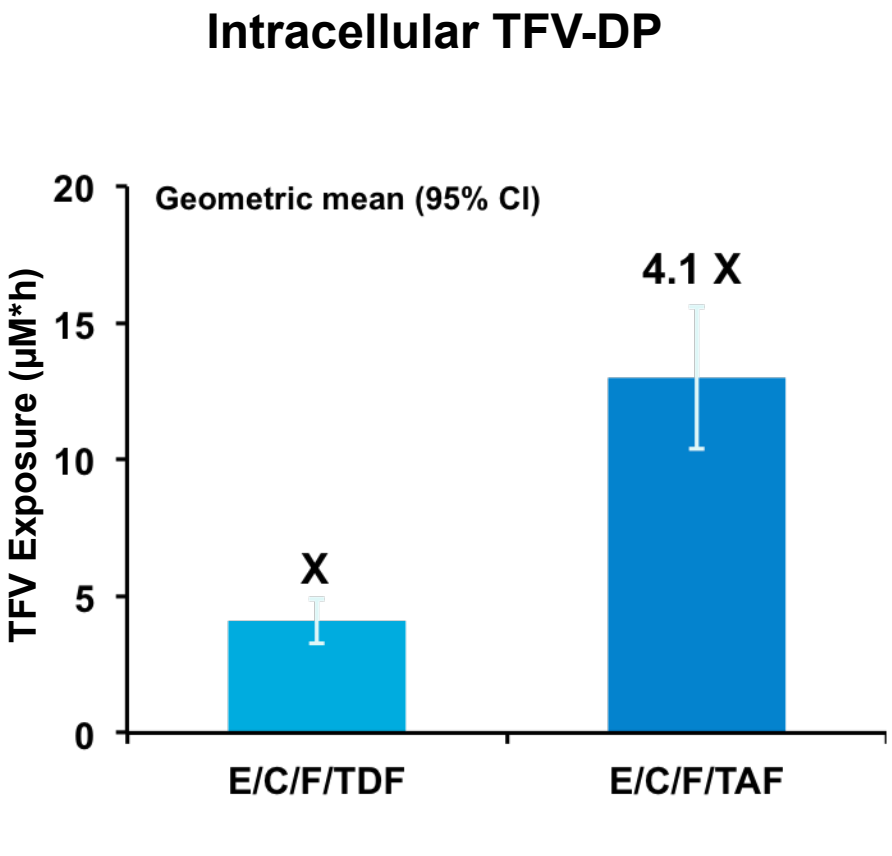
- results support the 2013 WHO recommendations for use of triple maternal ARV regimens in pregnancy to achieve the lowest risk of transmission.
- triple ARV regimens were associated with higher risk of moderate but not severe adverse maternal and pregnancy outcomes including preterm birth and low birth weight,
- The difference in risk of early infant deaths in the FTC-TDF triple ARV arm compared to the 3TC-ZDV triple ARV arm was unanticipated and requires further investigation.

New drugs

- TAF
- Bevirimat
- Carbotegravir/rilpivirine (LATTE)
- DTG week 96 comparison

Tenofovir Alafenamide (TAF): Plasma & Cell pK





Sax P, et al. 22nd CROI, Seattle, WA, February 23-26, 2015. Abst. 143LB.

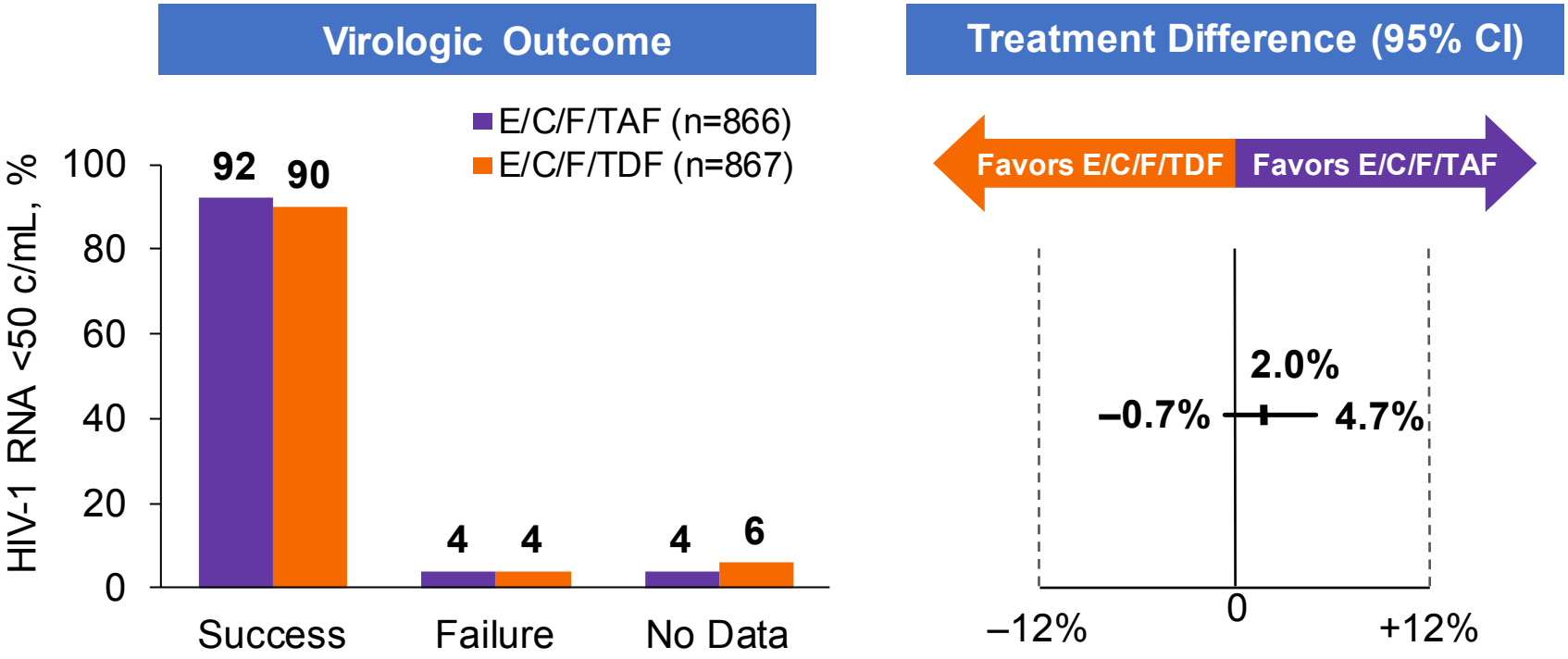
TAF vs. TDF: Baseline Characteristics

	E/C/F/TAF n=866	E/C/F/TDF n=867
Median age, years	33	35
Sex, %		
Female	15	15
Race/ethnicity, %		
Black or African descent	26	25
Hispanic/Latino ethnicity	19	19
Median HIV-1 RNA, $\log_{10}$ c/mL	4.58	4.58
% with HIV-1 RNA >100,000 c/mL	23	23
Median CD4 count, cells/μL	404	406
% with CD4 count <200	13	14
Median estimated GFR*, mL/min	117	114

*Cockcroft-Gault.

Wohl D, et al. 22nd CROI, Seattle, WA, February 23–26, 2015. Abst. 113LB.

TAF vs. TDF: Virologic 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)

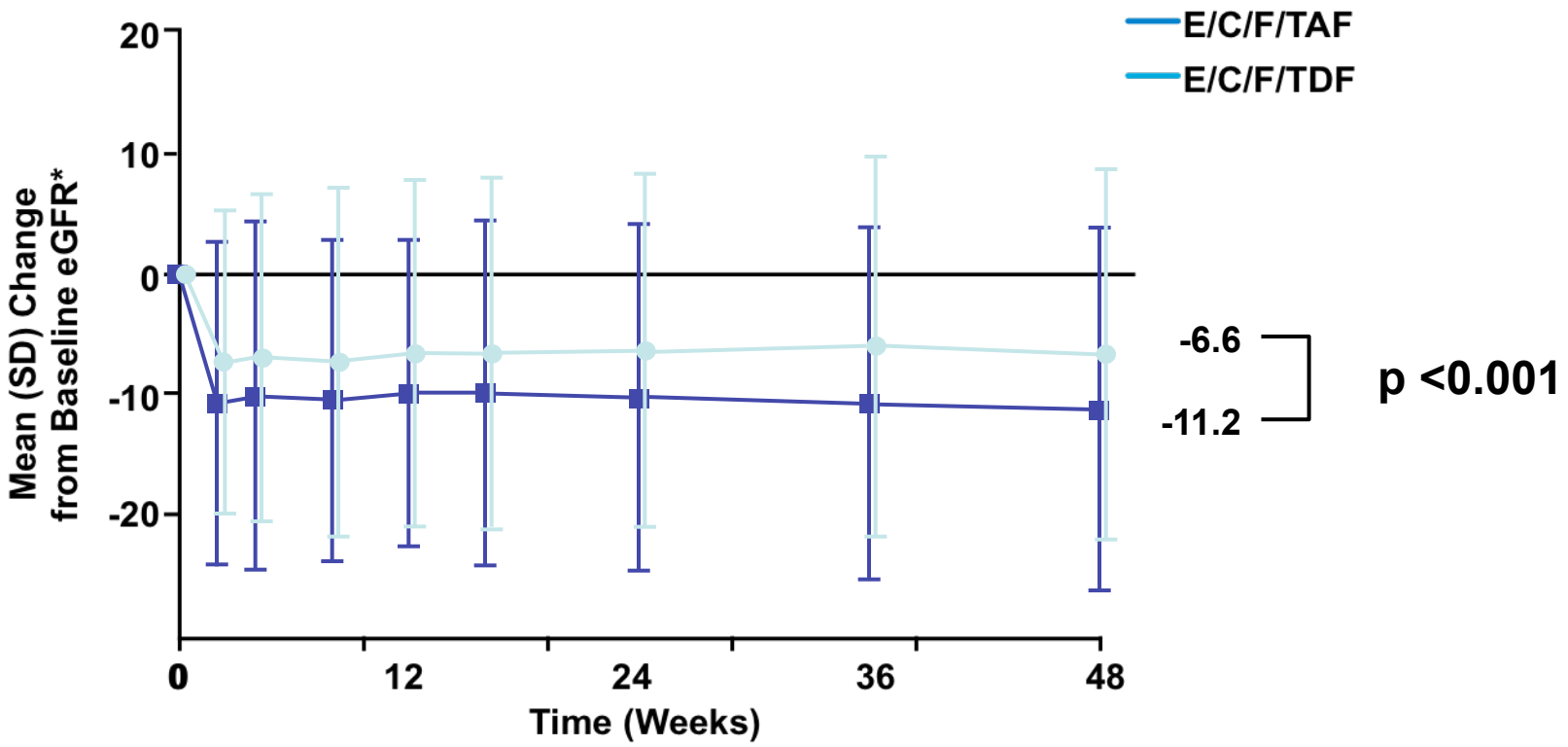
Wohl D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 113LB.

High and similar response rates, irrespective of age, sex, race, HIV-1 RNA, and CD4 cell count

TAF vs TDF: Adverse Events

	E/C/F/TAF n=866	E/C/F/TDF n=867
% (n) Discontinuations	**0.9% (8)**	**1.5% (13)**
AEs in ≥5% of patients, %		
Diarrhea	17	19
Nausea	15	17
Headache	14	13
Upper respiratory tract infection	11	13
Nasopharyngitis	9	9
Fatigue	8	8
Cough	8	7
Vomiting	7	6
Arthralgia	7	5
Back pain	7	7

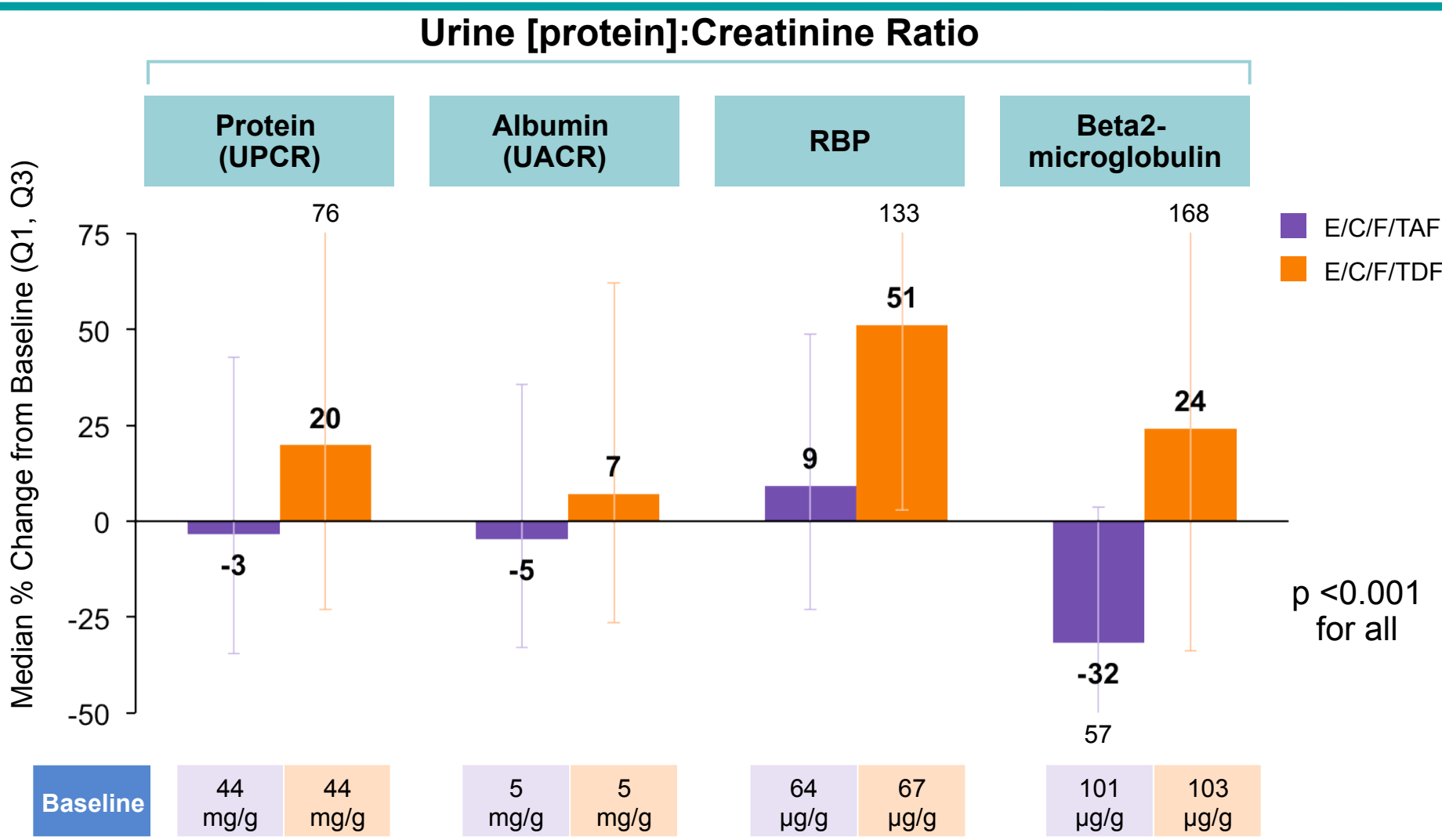
TAF vs. TDF: Effect on eGFR



	n (%)	E/C/F/TAF n=866	E/C/F/TDF n=867
Events	Renal adverse events leading to discontinuation	0	4 (0.5)
	Tubulopathy/Fanconi syndrome	0	0

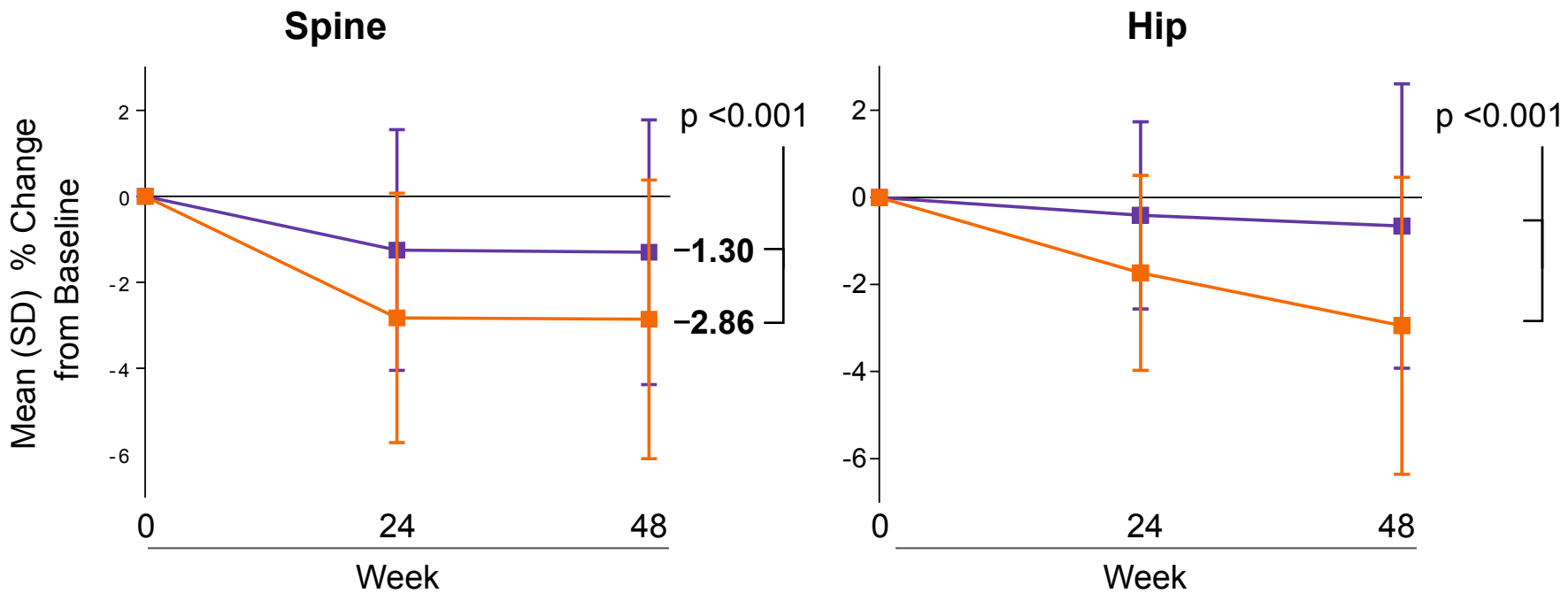
Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.

TAF vs. TDF: Quantitative Proteinuria



Sax P, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 143LB.

TAF vs. TDF: Spine and Hip BMD



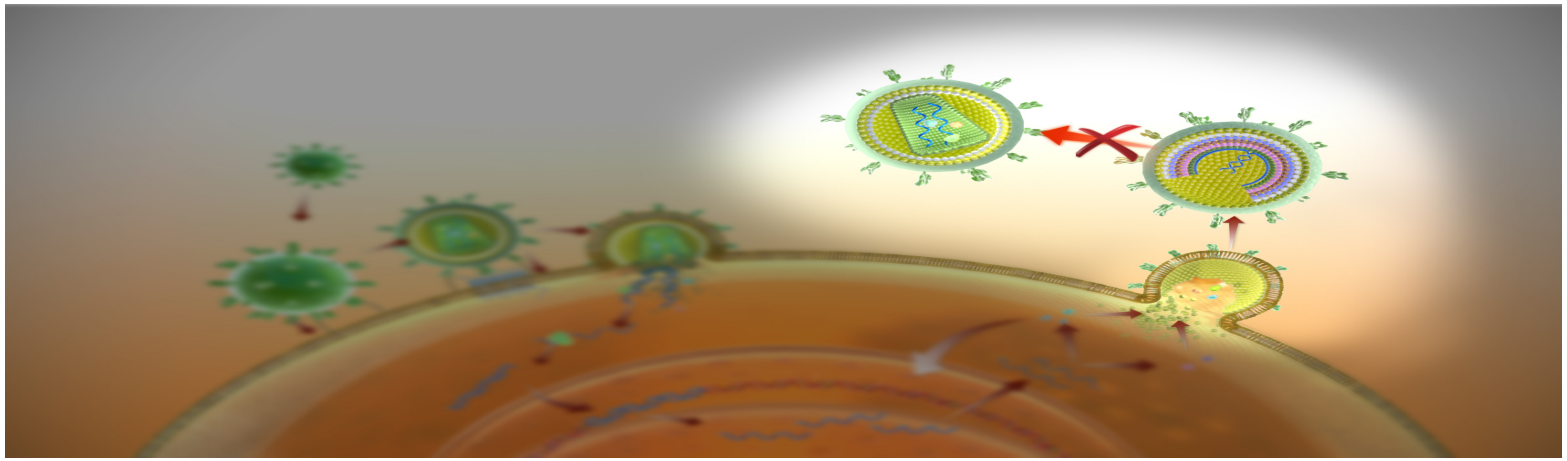
	Spine			Hip		
E/C/F/TAF, n	845	797	784	836	789	780
E/C/F/TDF, n	850	816	773	848	815	767

Sax P, et al. 22nd CROI, Seattle, WA, February 23-26, 2015. Abst. 143LB.

BMS-955176: Antiviral Activity and Safety of a Second-Generation HIV-1 Maturation Inhibitor

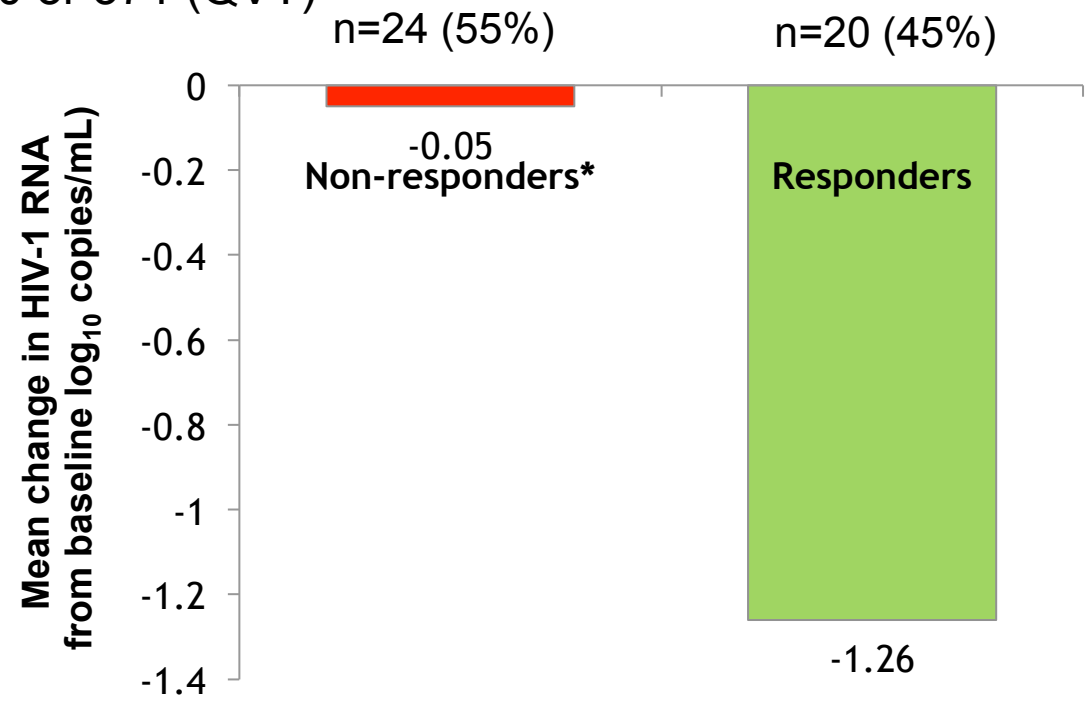
Carey Hwang[1], Dirk Schürmann[2], Christian Sobotha[2], Heather Sevinsky[1], Palanikumar Ravindran[1], Hong Xiao[1], Neelanjana Ray[1], Mark Krystal[3], Ira Dicker[3] and Max Lataillade[3], for the BMS HIV Development Team

[1] Bristol-Myers Squibb, Research and Development, Princeton, NJ, USA
[2] Charité Research Organisation GmbH, Charitéplatz 1, 10117 Berlin, Germany
[3] Bristol-Myers Squibb, Research and Development, Wallingford, CT, USA



Clinical Proof of Concept Demonstrated by 1st-Generation MI, Bevirimat[1]

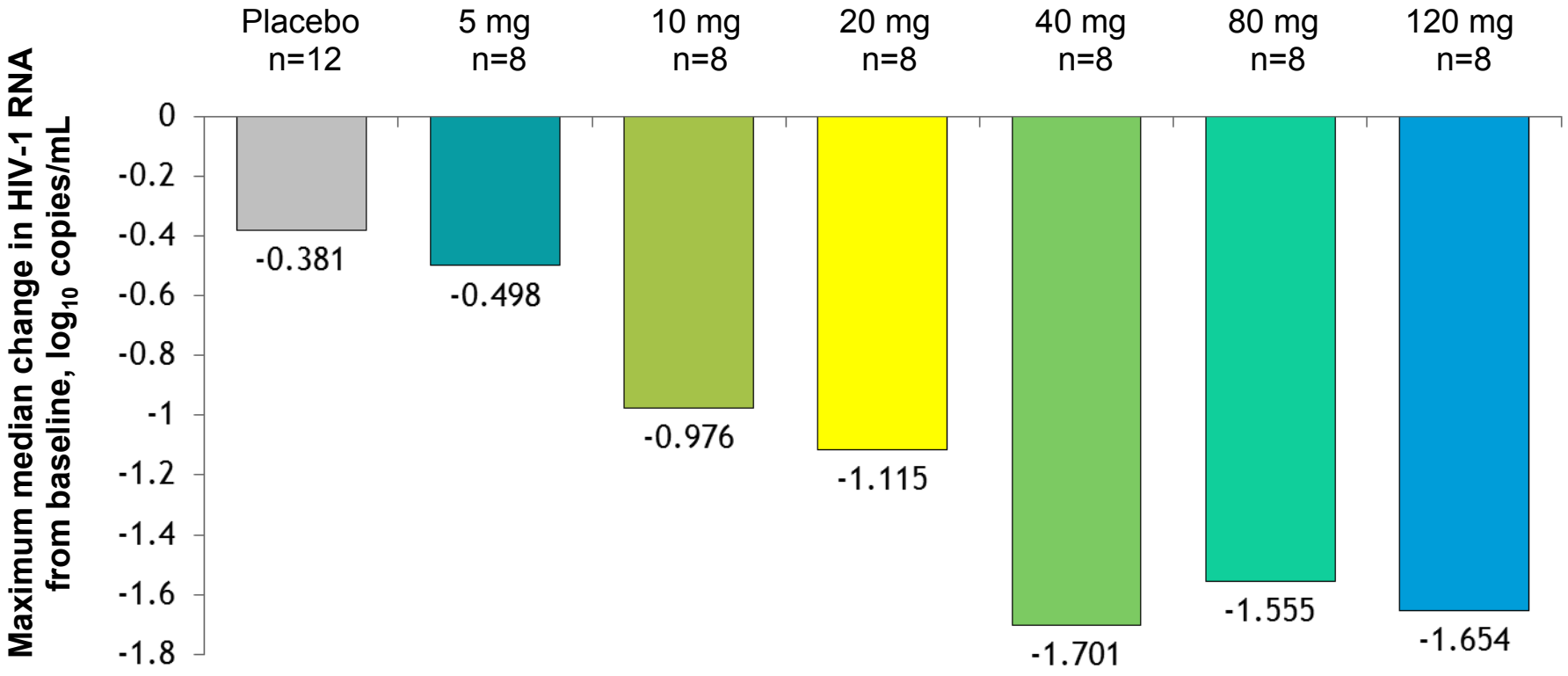
- Phase 2b bevirimat study in heavily treatment-experienced patients
- Non-response was associated with baseline Gag polymorphisms at positions 369, 370 or 371 (QVT)



*Non-responders were defined as subjects with a viral load reduction of <0.5 c/mL

1. McCallister et al. *Antivir Ther* 2008; 13:A10.

BMS-955176: Phase II Trial

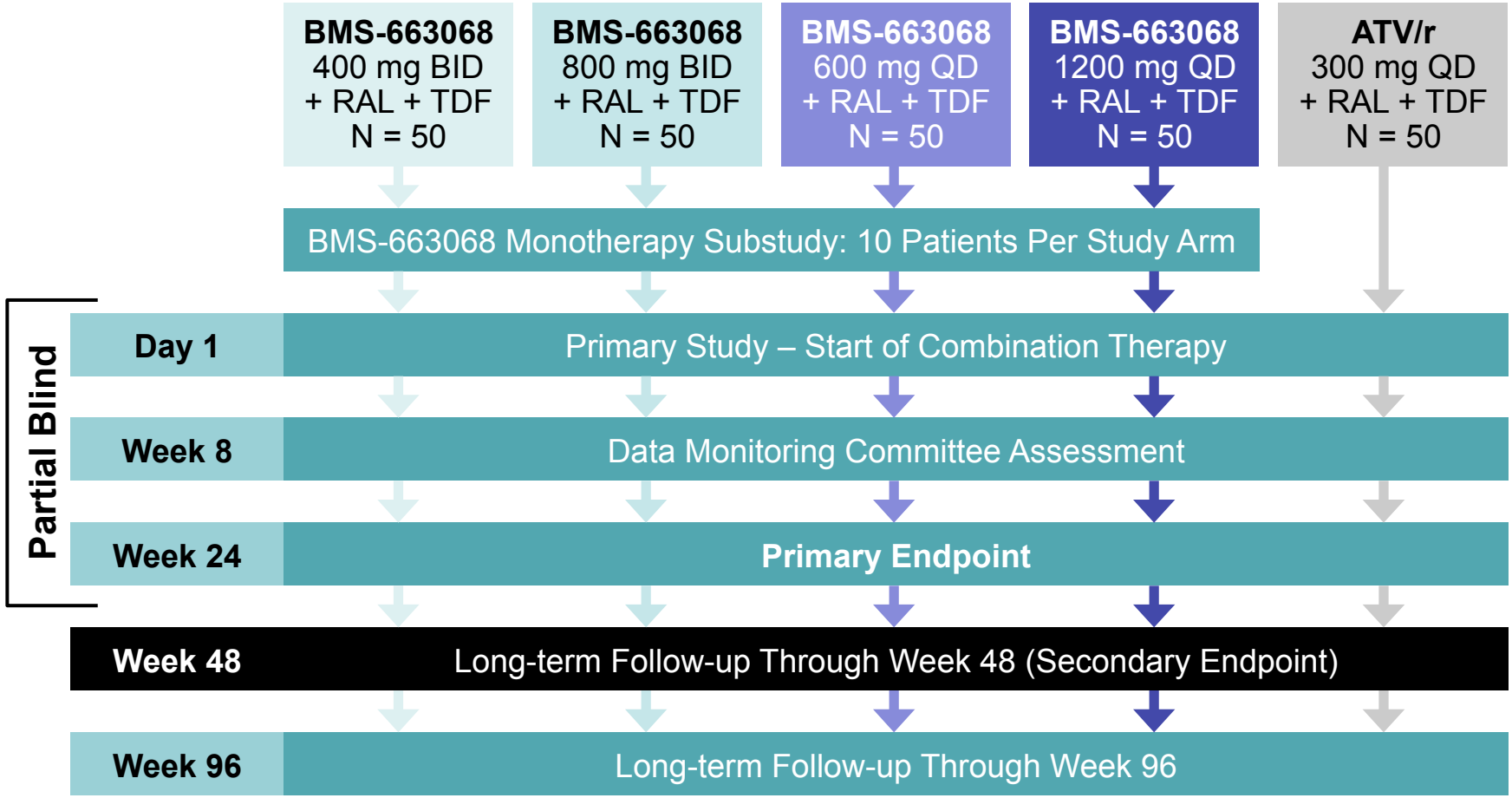


BMS-955176, a 2nd generation maturation inhibitor, demonstrated similar antiviral activity against both wild-type HIV-1 and HIV-1 with Gag polymorphisms not responsive to a 1st-generation MI

Hwang C, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 114KLB.

Attachment Inhibitor BMS-663068: Design

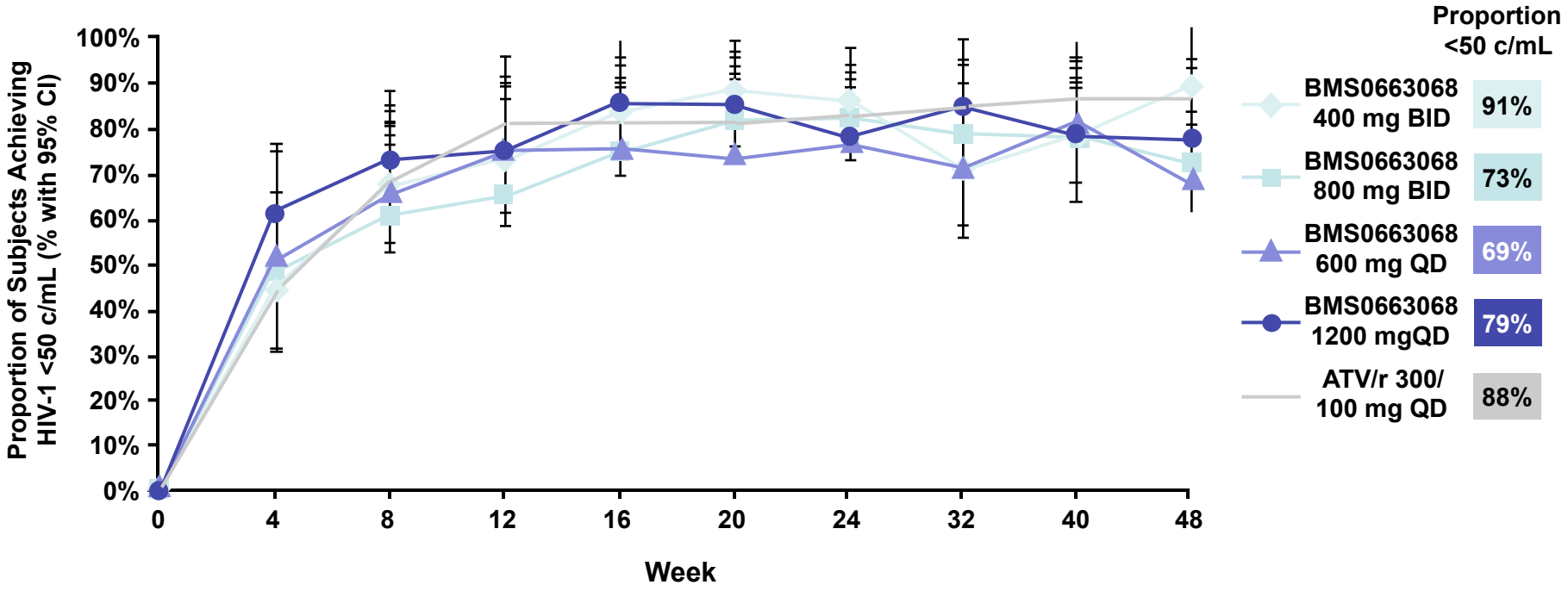
Treatment experienced patients, sensitive to all study drugs



Thompson M, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 545.

BMS-663068: Results

Treatment experienced patients, sensitive to all study drugs

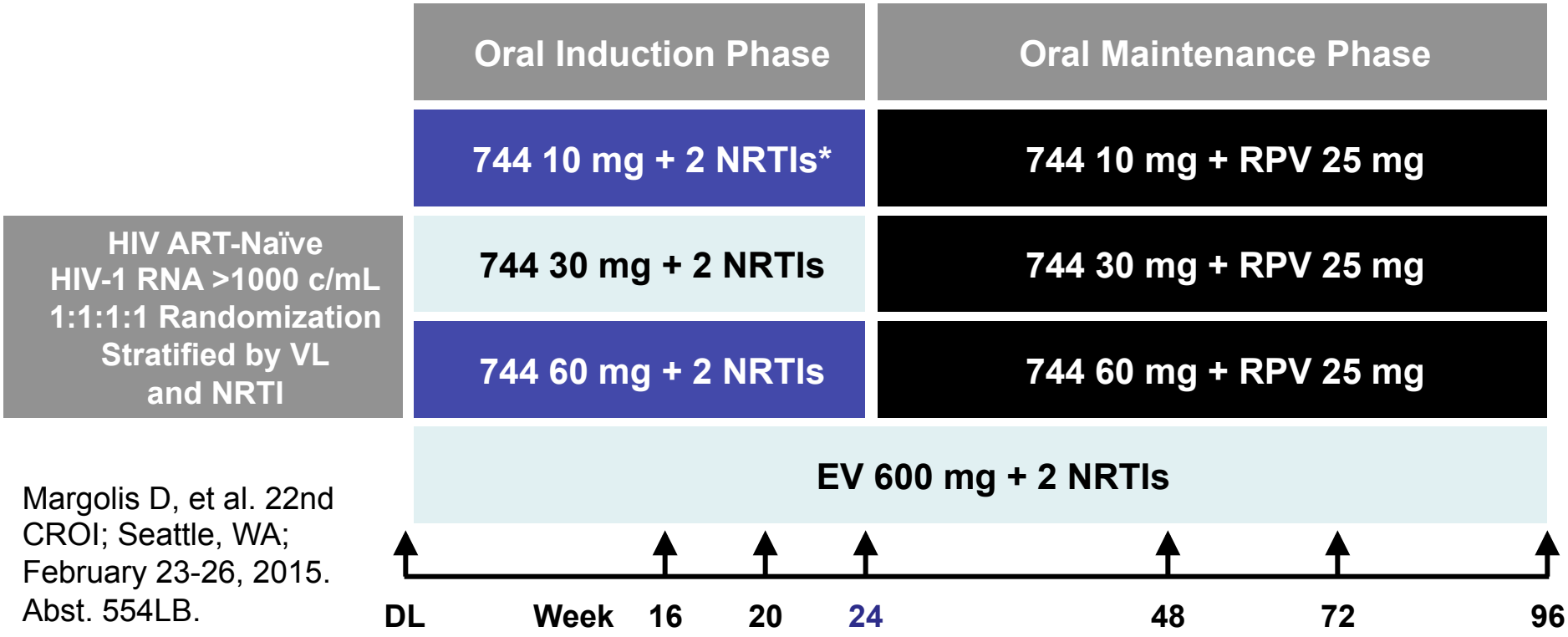


On Treatment Analysis

Thompson M, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 545.

Latte 96 week: cabotegravir and rilipvirine as two-drug oral maintenance therapy

- Phase IIb, randomized, multicenter, partially blind, dose-ranging study
- Patients on 744 + NRTI: If week 20 VL <50 c/mL – simplify to 744/RPV at week 24
- Following Week 96, subjects on the CAB arms transition into the Open-Label Phase. Subjects on the EFV arm are withdrawn from the study at Week 96.



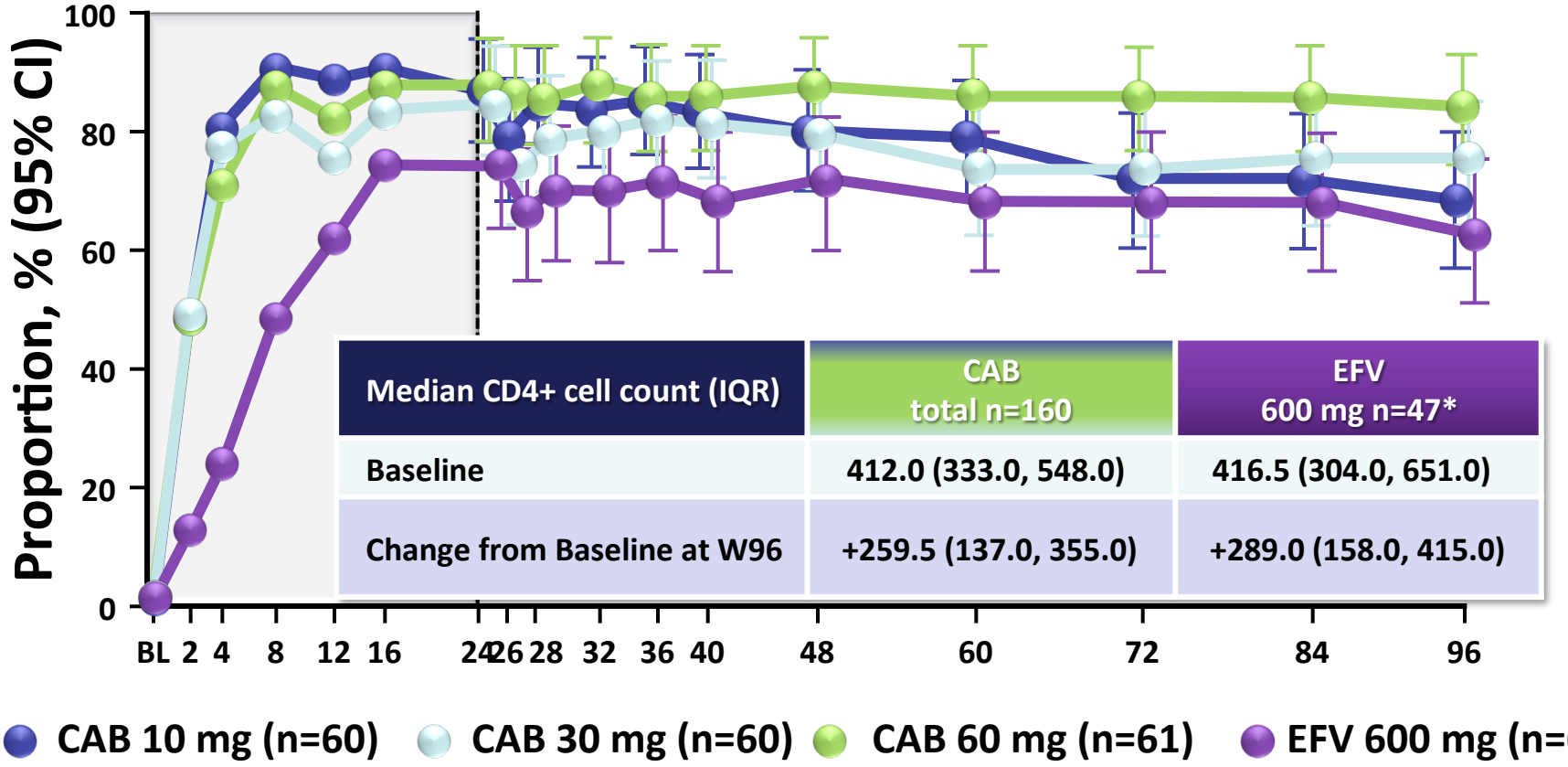
Margolis D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 554LB.

LATTE: Baseline Characteristics

Margolis D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 554LB.		744 10 mg n=60	744 30 mg n=60	744 60 mg n=61	EFV 600 mg n=62
Age	Median (y)	32.0	32.5	36.0	32.5
Gender	Male	95%	97%	93%	98%
Race	White	62%	65%	59%	63%
	African American/African	35%	28%	30%	32%
Ethnicity	Hispanic/Latino	15%	27%	23%	19%
Baseline HIV-1 RNA	Median (log_{10} c/mL)	4.281	4.178	4.349	4.343
	>100,000 c/mL	13%	12%	20%	13%
Baseline CD4+	Median (cells/mm^3)	415.0	404.0	420.0	416.5
	<200 cells/mm^3	3%	7%	3%	2%
Hepatitis coinfection	HCV	0	5 (8%)	4 (7%)	1 (2%)
Investigator-selected dual NRTIs at Day 1	TDF/FTC	37 (62%)	37 (62%)	37 (61%)	38 (61%)
	ABC/3TC	23 (38%)	23 (38%)	24 (39%)	24 (39%)

cabotegravir and rilpivirine as Two-Drug Oral Maintenance Therapy: LATTE Week 96 results

Figure 2. Virologic Success: HIV-1 RNA <50 c/mL by FDA Snapshot (ITT-E)



Median CD4+ cell count (IQR)	CAB total n=160	EFV 600 mg n=47*
Baseline	412.0 (333.0, 548.0)	416.5 (304.0, 651.0)
Change from Baseline at W96	+259.5 (137.0, 355.0)	+289.0 (158.0, 415.0)

LATTE: HIV-1 RNA <50 c/mL

Week 96 Treatment Outcomes

Outcome at Week 96	CAB 10 mg	CAB 30 mg	CAB 60 mg	CAB Total	EFV 600 mg
% <50 c/mL at W96 Snapshot (ITT-E)	**41/60 (68%)**	**45/60 (75%)**	**51/61 (84%)**	**137/181 (76%)**	**39/62 (63%)**
Protocol-defined Virologic Failure	3 (5%)	2 (3%)	1 (2%)	6 (3%)	6 (10%)
Failure – Adverse Event	1 (2%)	1 (2%)	4 (7%)	6 (3%)	9 (15%)
Failure – HIV-1 RNA ≥50 c/mL	5 (8%)	1 (2%)	2 (3%)	8 (4%)	2 (3%)
Failure - Other[+] Reasons while ≥50 c/mL	2 (3%)	2 (3%)	1 (2%)	5 (3%)	3 (5%)
Failure - Other[+] Reasons while <50 c/mL	8 (13%)	9 (15%)	2 (3%)	19 (10%)	3 (5%)
% <50 c/mL at W96 Snapshot (ITT-ME)	**41/52 (79%)**	**45/53 (85%)**	**51/55 (93%)**	**137/160 (86%)**	**39/47* (83%)**
Protocol-defined virologic failure	2 (4%)	1 (2%)	0	3 (2%)	2 (4%)
Failure – Adverse Event	1 (2%)	0	1 (2%)	2 (1%)	2 (4%)
Failure – HIV-1 RNA ≥50 c/mL	4 (8%)	1 (2%)	1 (2%)	6 (4%)	2 (4%)
Failure - Other[+] Reasons while ≥50 c/mL	1 (2%)	1 (2%)	1 (2%)	3 (2%)	0
Failure - Other[+] Reasons while <50 c/mL	3 (6%)	5 (9%)	1 (2%)	9 (6%)	2 (4%)

Margolis D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 554LB.

LATTE: Adverse Events

	CAB 10 mg n=60	CAB 30 mg n=60	CAB 60 mg n=61	EFV 600 mg n=62
Grade 2-4 Drug-related Events (>3% Any Arm)	**5 (8%)**	**8 (13%)**	**13 (21%)**	**12 (19%)**
Insomnia	1 (2%)	2 (3%)	0	4 (6%)
Depression	0	0	2 (3%)	0
Nausea	0	2 (3%)	3 (5%)	1 (2%)
Fatigue	0	2 (3%)	1 (2%)	1 (2%)
Headache	1 (2%)	1 (2%)	3 (5%)	0
Rash Macular	0	0	0	3 (5%)
% <50 c/mL at W96 Snapshot (ITT-ME)	**1 (2%)**	**2 (3%)**	**3 (5%)**	**2 (3%)**
Serious AEs	**7 (12%)**	**5 (8%)**	**7 (11%)**	**4 (6%)***
Serious AEs (W24+)	**5 (8%)**	**5 (8%)**	**5 (8%)**	**2 (3%)**
AEs Leading to Withdrawal (>1 Subject)	**1 (2%)**	**2 (3%)**	**4 (7%)**	**9 (15%)**
Dizziness	0	0	0	2 (4%)
ALT Increased	0	0	2 (3%)**	0

Abstract 554LB, David A Margolis

LATTE: Adverse Events

	CAB 10 mg n=60	CAB 30 mg n=60	CAB 60 mg n=61	EFV 600 mg n=62
Grade 1-4 ALT Abnormalities	**8 (13%)**	**12 (20%)**	**17 (28%)**	**13 (21%)**
Select Grade 3-4 Laboratory Abnormalities				
Creatine Phosphokinase (CPK)	7 (12%)	7 (12%)	5 (8%)	9 (15%)
Alanine Aminotransferase (ALT)	0	1 (2%)	2 (3%)**	1 (2%)
Lipase	3 (5%)	2 (3%)	6 (10%)	1 (2%)
Total Bilirubin	0	0	0	0
Total Neutrophils	1 (2%)	1 (2%)	2 (3%)	2 (3%)
Creatinine	0	0	0	0

Margolis D, et al. 22nd CROI; Seattle, WA; February 23-26, 2015. Abst. 554LB.

Thanks to researchers for use of slides and BHIVA compilation from 2015 BHIVA “Best of CROI” feedback meetings.

Four talks are web cast at:

www.bhiva.org

Original selections led by Julie Fox for prevention studies and Frank Post for ARVs.