Le formulazioni a lento rilascio: razionali, studi in corso, nuovi studi

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Perché necessarie strategie terapeutiche differenti?

- Nonostante il sostanziale miglioramento in termini di morbosità e mortalità dell'infezione da HIV in seguito all'introduzione della cart, tuttavia la terapia orale a lungo termine presenta delle limitazioni
- I regimi attuali sono molto potenti e generalmente ben tollerati
- Gli elevati livelli di risposta virologica in chi inizia una cART (>90%) devono essere mantenuti nel tempo e questo è strettamente correlato ai livelli di aderenza alla terapia stessa
- Le tossicità a lungo termine, le interazioni farmacologiche, i costi e le limitate opzioni teraputiche per i pazienti che falliscono, possono limitare l'efficaca del trattamento stesso.
- In assenza di trattamento eradicante, i farmaci antiretrovirali devono essere assunti per tutta la vita per mantenere la soppressione virologica.

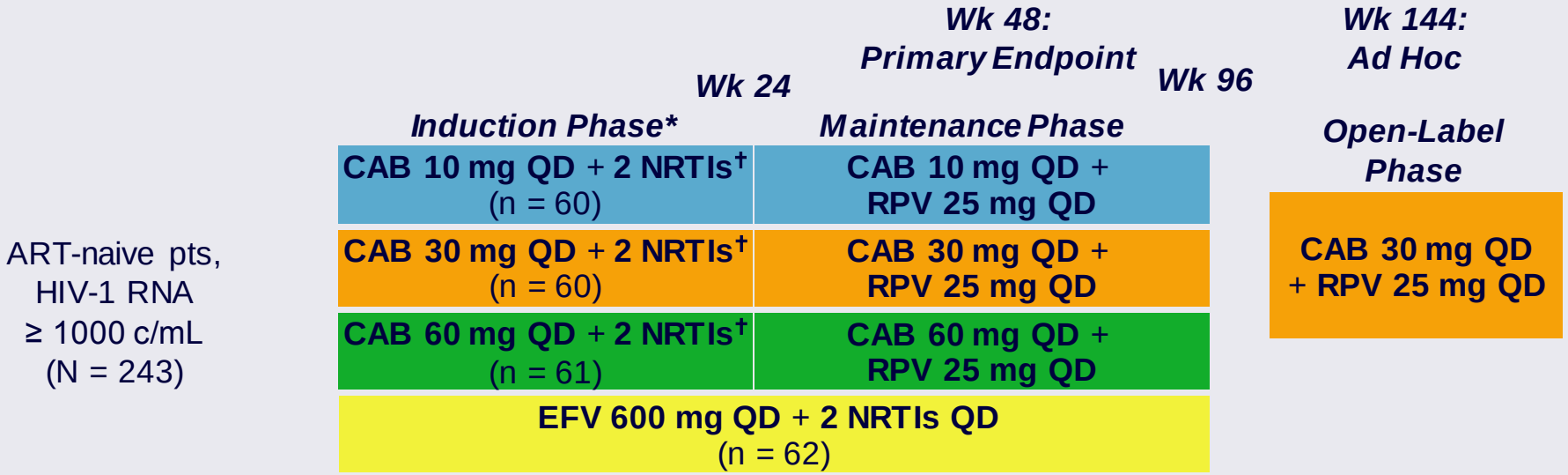
Rusconi et al, New Microbiol 2017

Ruolo dei farmaci antiretrovirali a lento rilascio: dove siamo

- Trattamento
- Prevenzione
- Prospettiva dei pazienti

LATTE: Efficacy, Safety of Dual Oral Cabotegravir + RPV Maintenance

- Dose-ranging, randomized phase IIb study
  - Primary endpoint: HIV-1 RNA < 50 c/mL at Wk 48
  - At Wk 96: 76% of pts receiving CAB + RPV had HIV-1 RNA < 50 copies/mL



*Pts with HIV-1 RNA < 50 c/mL at Wk 24 continued to maintenance phase.
†FTC/TDF or ABC/3TC.

Margolis DA, et al. CROI 2015. Abstract 554LB. Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-1155.

LATTE: Viral Suppression Thru Wk 144 With Dual Oral CAB + RPV Maintenance

- Ad hoc analysis through Wk 144 of open-label phase
- Serious AEs: 9%; d/c for AEs: 3%
- PDVF in 9 pts (ITT-E)
  - 6 during induction/maintenance
  - 3 during open-label (Wks 96-144)
    - 2 of 3 had emergent mutations: n = 1 with V151V/I (IN); n = 1 with K101E + M230M/L (NNRTI)
- 1 pt without PDVF developed E138K + V108V/I (NNRTI)

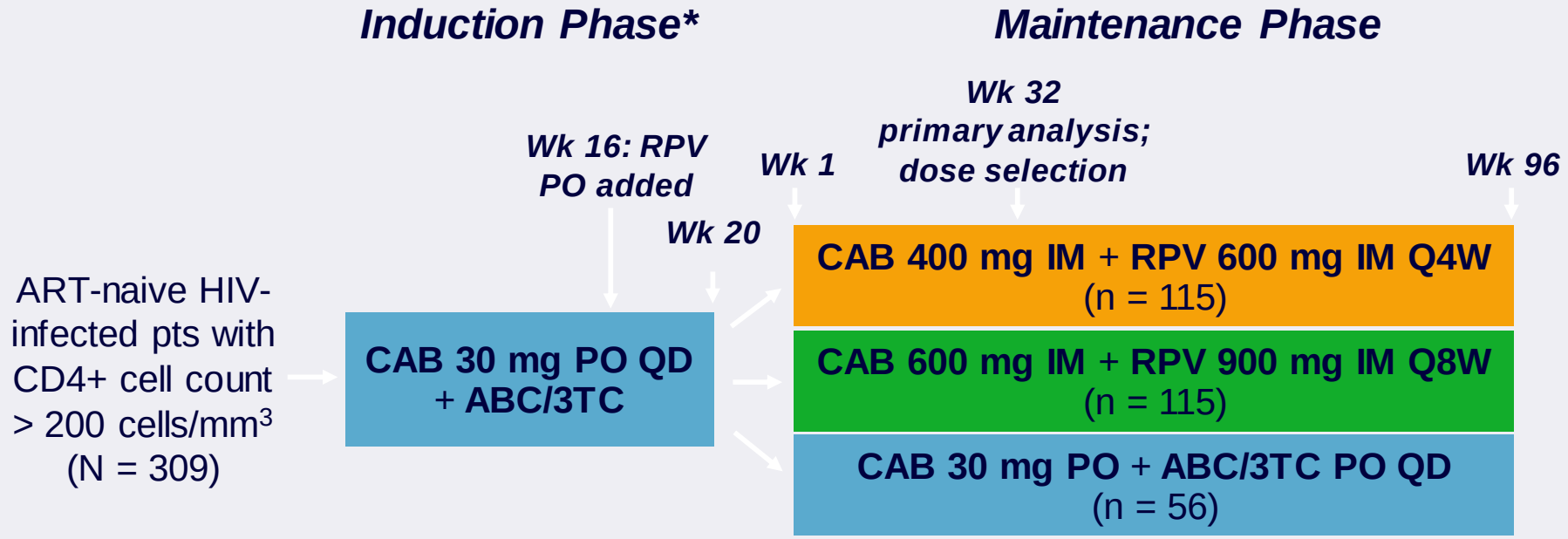
Treatment Outcomes at Wk 144 (Snapshot), n (%)	CAB Subtotal* (ITT-E) (n = 181)	CAB Subtotal* (ITT-ME) (n = 160)
HIV-1 RNA < 50 c/mL	122 (67)	122 (76)
HIV-1 RNA ≥ 50 c/mL ▪Previous change in ART	18 (10) 3 (2)	13 (8) 2 (1)
No virologic data in window ▪D/c for AE or death ▪D/c for other reasons ▪On study with missing data in window	41 (23) 8 (4) 27 (15) 6 (3)	25 (16) 4 (3) 15 (9) 6 (4)
PDVF	9 (5)	6 (4)

*CAB 10 mg + CAB 30 mg + CAB 60 mg.

Margolis DA, et al. CROI 2017. Abstract 442. Margolis DA, et al. CROI 2015. Abstract 554LB. Margolis DA, et al. Lancet Infect Dis. 2015;15:1145-1155.

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, Lancet 2017

LATTE-2: baseline characteristics of patients

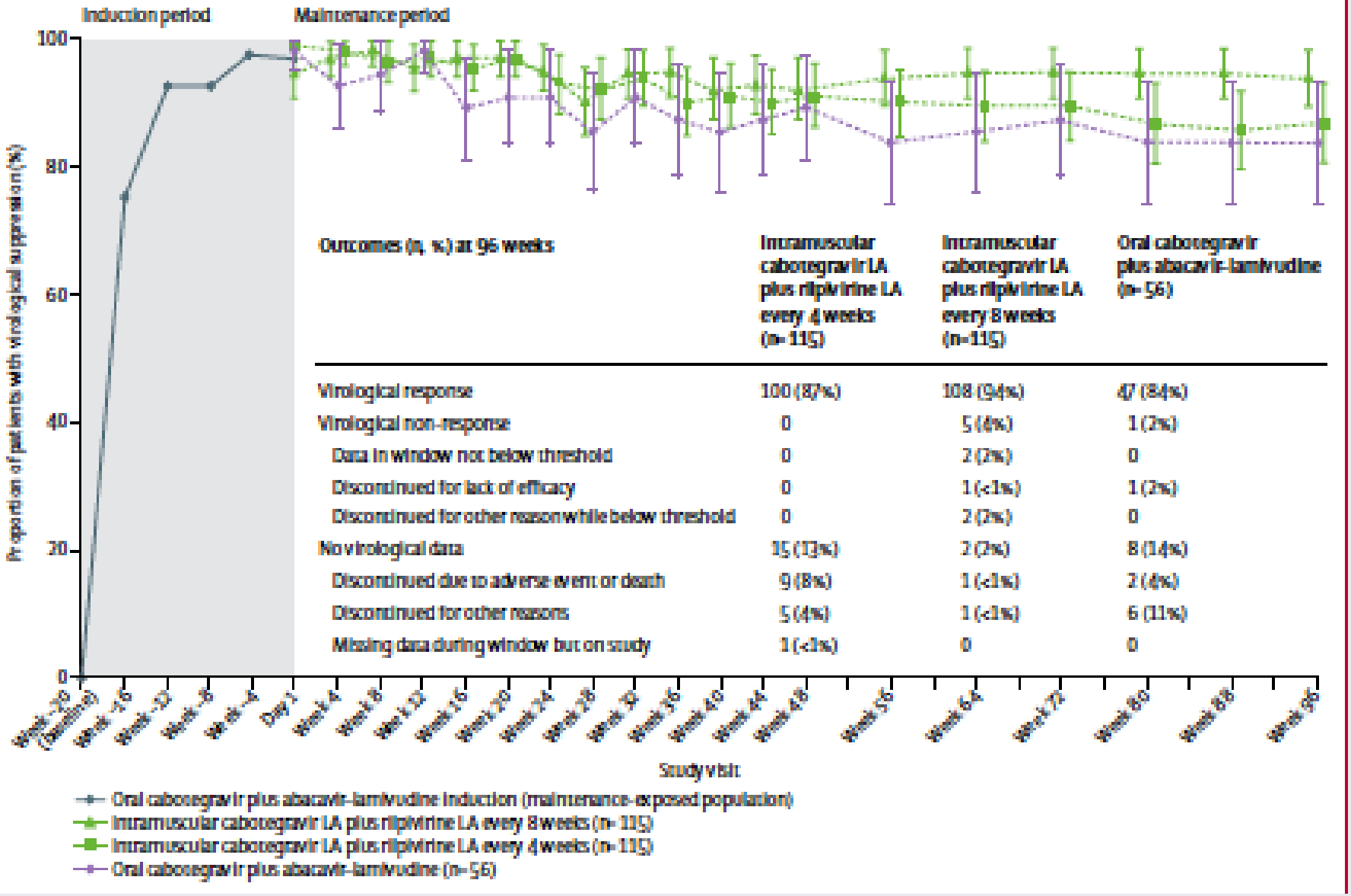
	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir–lamivudine (n=56)	Total (n=286)
Age (years; range)	36 (19–62)	35 (20–64)	35 (19–57)	35 (19–64)
Sex				
Male	109 (95%)	107 (93%)	46 (82%)	262 (92%)
Female	6 (5%)	8 (7%)	10 (18%)	24 (8%)
Ethnic origin				
White	94 (82%)	93 (81%)	39 (70%)	226 (79%)
African American or African heritage	12 (10%)	17 (15%)	15 (27%)	44 (15%)
Other	9 (8%)	5 (4%)	2 (4%)	16 (6%)
Baseline HIV-1 RNA				
Log_{10} copies per mL	4·46 (4·00–4·97)	4·42 (4·05–4·80)	4·29 (4·01–4·74)	4·39 (4·03–4·83)
≥100 000 copies per mL	28 (24%)	16 (14%)	7 (12%)	51 (18%)
Baseline CD4+ cell count (cells per mm^3)	499 (359–624)	449 (343–618)	518 (417–630)	489 (359–624)
Hepatitis C co-infection	5 (4%)	3 (3%)	2 (4%)	10 (3%)
NRTI during induction				
Abacavir–lamivudine	107 (93%)	107 (93%)	53 (95%)	267 (93%)
Tenofovir–emtricitabine	8 (7%)	8 (7%)	3 (5%)	19 (7%)

Data are median (IQR) or n (%) unless stated otherwise. LA=long-acting. NRTI=nucleoside reverse transcriptase inhibitor.

Table 1: Baseline demographics and disease characteristics (maintenance-exposed population)

Margolis, Lancet 2017

Virological response at week 96

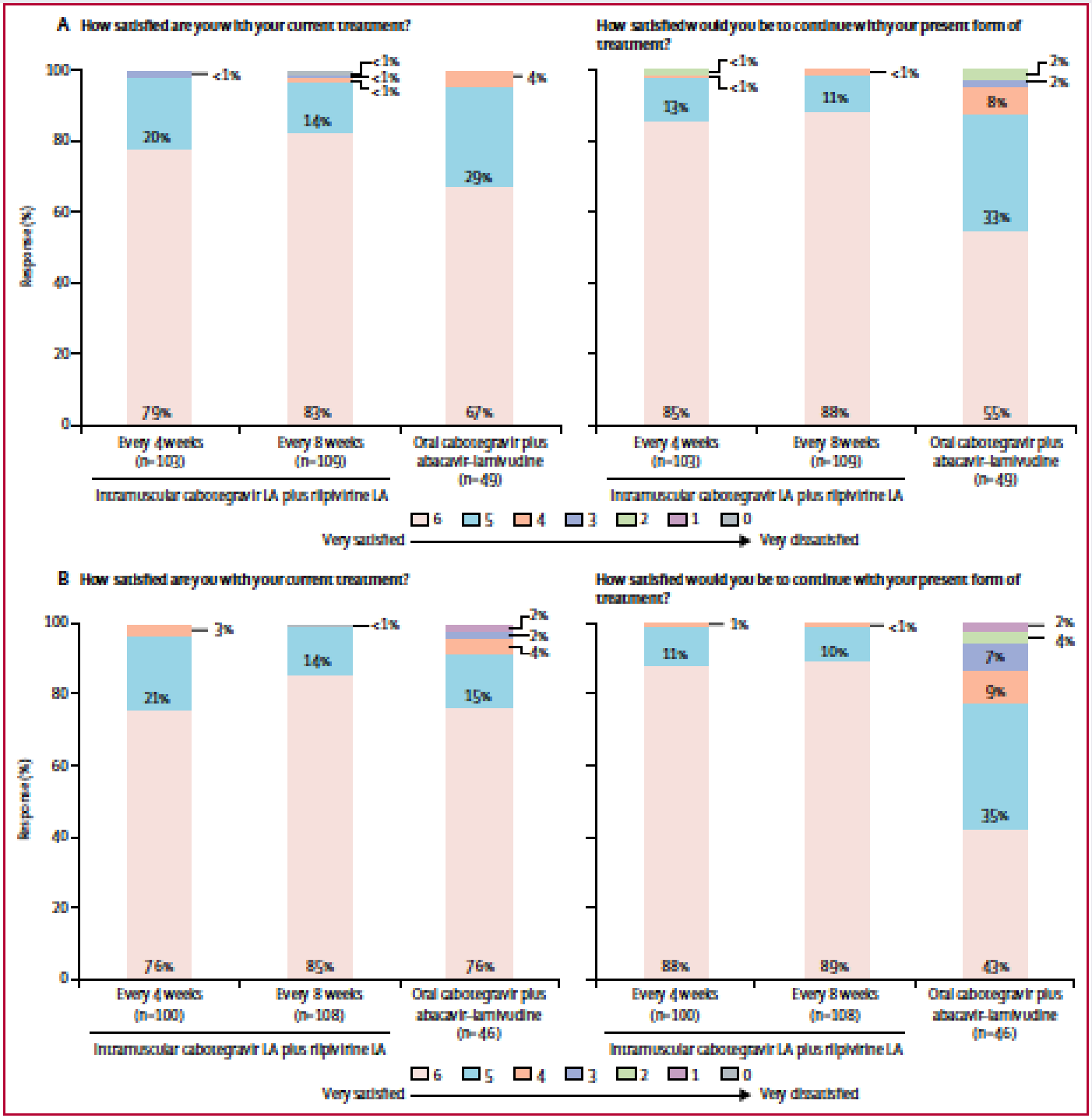


Outcomes (n, %) at 96 weeks	Intramuscular cabotegravir LA plus rilpivirine LA every 4 weeks (n=115)	Intramuscular cabotegravir LA plus rilpivirine LA every 8 weeks (n=115)	Oral cabotegravir plus abacavir-lamivudine (n=56)
Virological response	100 (87%)	108 (94%)	47 (84%)
Virological non-response	0	5 (4%)	1 (2%)
Data in window not below threshold	0	2 (2%)	0
Discontinued for lack of efficacy	0	1 (<1%)	1 (2%)
Discontinued for other reason while below threshold	0	2 (2%)	0
No virological data	15 (13%)	2 (2%)	8 (14%)
Discontinued due to adverse event or death	9 (8%)	1 (<1%)	2 (4%)
Discontinued for other reasons	5 (4%)	1 (<1%)	6 (11%)
Missing data during window but on study	1 (<1%)	0	0

Side effects

Treatment-related adverse events*						
Any event	113 (98%)	10 (9%)	110 (96%)	10 (9%)	21 (38%)	1 (2%)
Injection-site pain	112 (97%)	6 (5%)	109 (95%)	8 (7%)	0	0
Injection-site nodule	35 (30%)	1 (<1%)	29 (25%)	1 (<1%)	0	0
Injection-site swelling	34 (30%)	0	29 (25%)	1 (<1%)	0	0
Injection-site pruritus	33 (29%)	0	24 (21%)	0	0	0
Injection-site induration	25 (22%)	0	28 (24%)	1 (<1%)	0	0
Injection-site warmth	21 (18%)	0	22 (19%)	1 (<1%)	0	0
Injection-site bruising	14 (12%)	0	19 (17%)	0	0	0
Injection-site erythema	19 (17%)	0	12 (10%)	1 (<1%)	0	0

Patients' satisfaction



Additional Investigational Agents Reported at CROI 2017: Preclinical and Phase I

Agent	MoA or Formulation	Phase	Dosing/ Administration	Implications
GS-CA1[1]	HIV capsid inhibitor	Pre-clinical	Extended release, suitable for SC of solid depot formulation	▪ Potent ART with orthoganol resistance profile to existing ART; potential for long-acting formulation due to low aqueous solubility, high stability
GS-9131[2]	NRTI	Pre-clinical	Potential for once daily dosing	▪ Potent ART active against NRTI RAMs K65R, L74V, M184V alone or in combination; minimal loss of susceptibility with 4 or more TAMs
MK-8591[3]	Nucleoside Reverse Transcriptase **Translocation** Inhibitor (NRTTI)	I	10 mg QW PO; potential for extended duration	▪ Comparable MK-8591 levels in animal rectal, vaginal tissue to TDF levels in tissues of human subjects highlights potential prophylaxis utility
GS-PI1[4]	PI	Pre-clinical	Potential for unboosted, QD dosing	▪ Potent ART with high barrier to resistance, including < 2-fold loss in potency against major PI RAMs, and 10-fold to 40-fold longer in vivo half life vs ATV or DRV
NANO-EFV, NANO-LPV[5]	Oral, lower dose SDN	I	nEFV: 50 mg QD, 21 d nLPV/RTV: 200/100 mg BID, 7 d	▪ Enhanced oral bioavailability suggests can reduce EFV, LPV dose by ~ 50% while maintaining PK

1. Tse WC, et al. CROI 2017. Abstract 38. 2. White KL, et al. CROI 2017. Abstract 436. 3. Grobler J, et al. CROI 2017. Abstract 435. 4. Link JO, et al. CROI 2017. Abstract 433. 5. Owen A, et al. CROI 2017. Abstract 39.

Additional Investigational Agents Reported at CROI 2017: Phase II

Agent	MoA or Formulation	Phase	Dosing/ Administration	Implications
TMC278 LA[1]	LA injectable RPV (IM)	II	1200 mg IM Q8W	▪ Potential as injectable, long-acting PrEP
Elsulfavirine[2]	Prodrug of new NNRTI VM1500A	IIb	Combined therapy: 20 mg elsulfavirine + FTC/TDF PO QD	▪ Less toxic alternative to EFV for initial ART
UB-421[3]	Anti-CD4 receptor mAb	II	10 mg/kg QW IV or 25 mg/kg Q2W IV	▪ Possible ART alternative for maintenance therapy in virologically suppressed pts

1. Bekker L-G, et al. CROI 2017. Abstract 421LB. 2. Murphy R, et al. CROI 2017. Abstract 452LB. 3. Wang C-Y, et al. CROI 2017. Abstract 450LB.

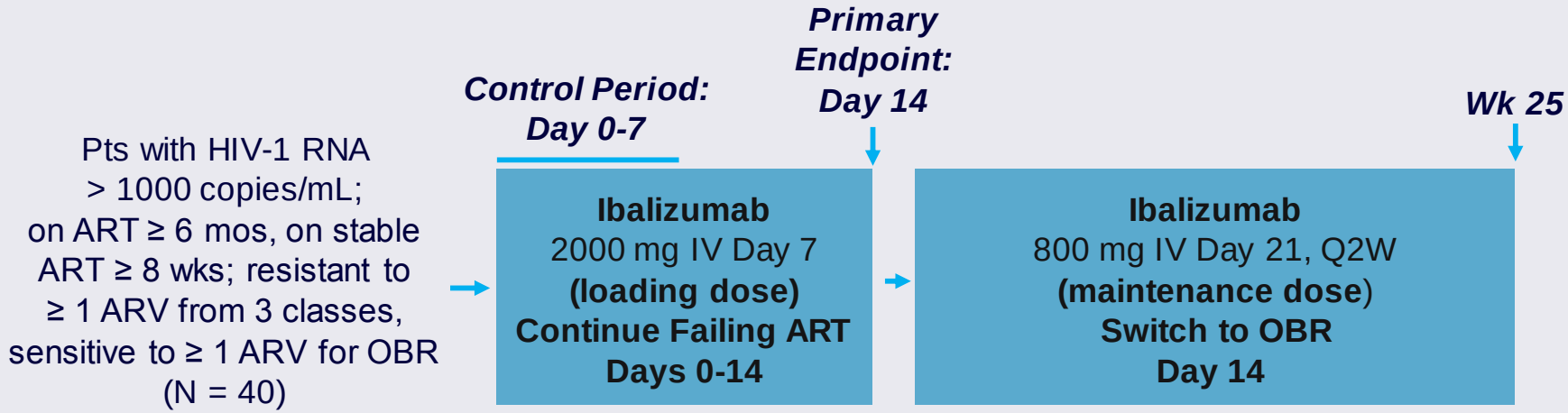
CD01 Extension: Long-term, Maintenance PRO 140 Monotherapy Following Initial ART

- PRO 140: humanized IgG4 CCR5 mAb
- Single-arm, open-label phase IIb extension study (N = 16)[1]
  - In initial study, pts stable on initial ART switched to maintenance PRO 140 monotherapy 350 mg SC/wk (N = 42)
  - 17 pts with maintained viral suppression for 13 wks trained to self administer wkly PRO 140 SC and offered continued monotherapy in extension study: N = 16 enrolled in extension
- CD4+ cell counts stable through study
- No anti-PRO 140 Abs detected
- Wkly PRO 140 maintenance SC injection generally well tolerated
  - No drug-related severe AEs or d/c for AEs
  - Infrequent, mild, transient injection-site reactions in < 10% of pts
- HIV-1 RNA < 40 copies/mL maintained in majority of pts
  - > 40 wks: 13/16 pts (81.3%)
  - > 2 yrs: 10/16 pts (62.5%)
  - 1 pt d/c (relocation); 5 pts had VF
- Ongoing phase IIb/III studies of PRO 140 monotherapy[2] and in combination with ART[3]

1. Lalezari J, et al. CROI 2017. Abstract 437. 2. ClinicalTrials.gov. NCT02859961. 3. ClinicalTrials.gov. NCT02483078.

TMB-301: Long-Acting Ibalizumab for Pretreated Multidrug-Resistant HIV

- Ibalizumab: humanized mAb to conformational epitope on CD4 receptor that blocks postattachment HIV entry into CD4+ T-cells without altering normal cell function
- Single-arm, open-label phase III trial
  - Primary endpoint: ≥ 0.5 $\log_{10}$ HIV-1 RNA decrease at Day 14



- 53% with resistance to all drugs from ≥ 3 classes; 68% with INSTI resistance

Lewis S, et al. CROI 2017. Abstract 449LB.

Efficacy, Safety of Ibalizumab Through 24 Wks

- Primary endpoint: 83% with ≥ 0.5 log_{10} HIV-1 RNA decrease at Day 14 vs 3% at end of control period (*P* < .0001)
  - 60% with ≥ 1.0 log_{10} HIV-1 RNA decrease
  - Mean decrease by Day 14: 1.1 log_{10}

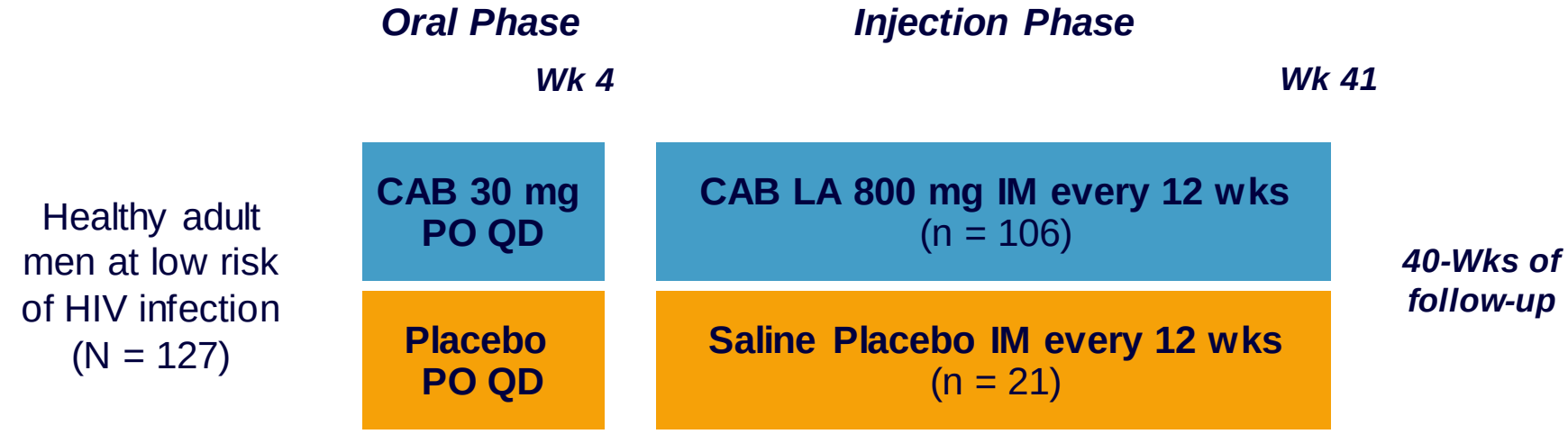
Wk 24 Virologic Outcome	Ibalizumab + OBR
≥ 1.0 log_{10} HIV-1 RNA decrease, %	55
≥ 2.0 log_{10} HIV-1 RNA decrease, %	48
HIV-1 RNA < 50 copies/mL, %	43
HIV-1 RNA < 200 copies/mL, %	50
Mean HIV-1 RNA decrease from baseline, log_{10}	1.6

- 9 pts reported 17 serious AEs
  - 1 drug-related serious AE (IRIS) resulted in discontinuation
- 9 other pts discontinued
  - Death (n = 4; liver failure, Kaposi sarcoma; end-stage AIDS, lymphoma)
  - Consent withdrawal (n = 3)
  - Lost to follow-up (n = 2)
- No cases of anti-ibalizumab antibodies

Lewis S, et al. CROI 2017. Abstract 449LB.

ÉCLAIR: Cabotegravir LA in HIV-Negative Men at Low Risk for HIV Infection

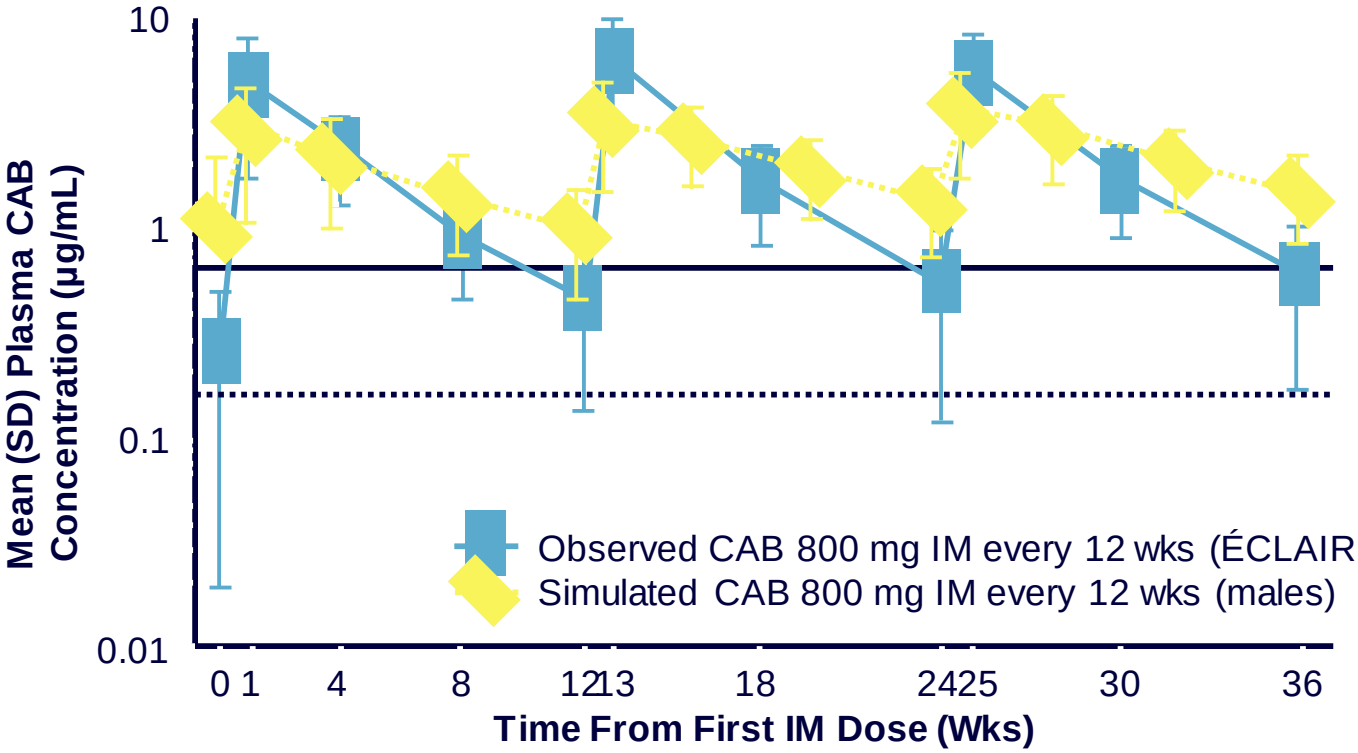
- Cabotegravir: potent INSTI formulated as oral tablet and for LA IM injection
- Randomized, double-blind phase IIa trial
  - Primary endpoint: safety, tolerability of CAB LA IM injections
  - 2 HIV seroconversions, none during CAB LA dosing period



Markowitz M, et al, Lancet HIV 2017

ÉCLAIR: Predicted vs Observed Cabotegravir LA Pharmacokinetics

- Peak CAB LA exposure higher and trough exposure lower than predicted because of more rapid absorption and release after injection
  - ~ 70% of pts had C_{trough} < 4 x protein-binding adjusted IC_{90}; every-8-wk dosing now under investigation



Geometric mean C_{trough} with 10 mg PO QD: 1.35 µg/mL (LATTE)

4 x Protein-binding adjusted IC_{90}: 0.664 µg/mL

Protein-binding adjusted IC_{90}: 0.166 µg/mL

Markowitz M, et al. CROI 2016. Abstract 106. Reproduced with permission.

ÉCLAIR: Injection Safety and Pain Outcomes

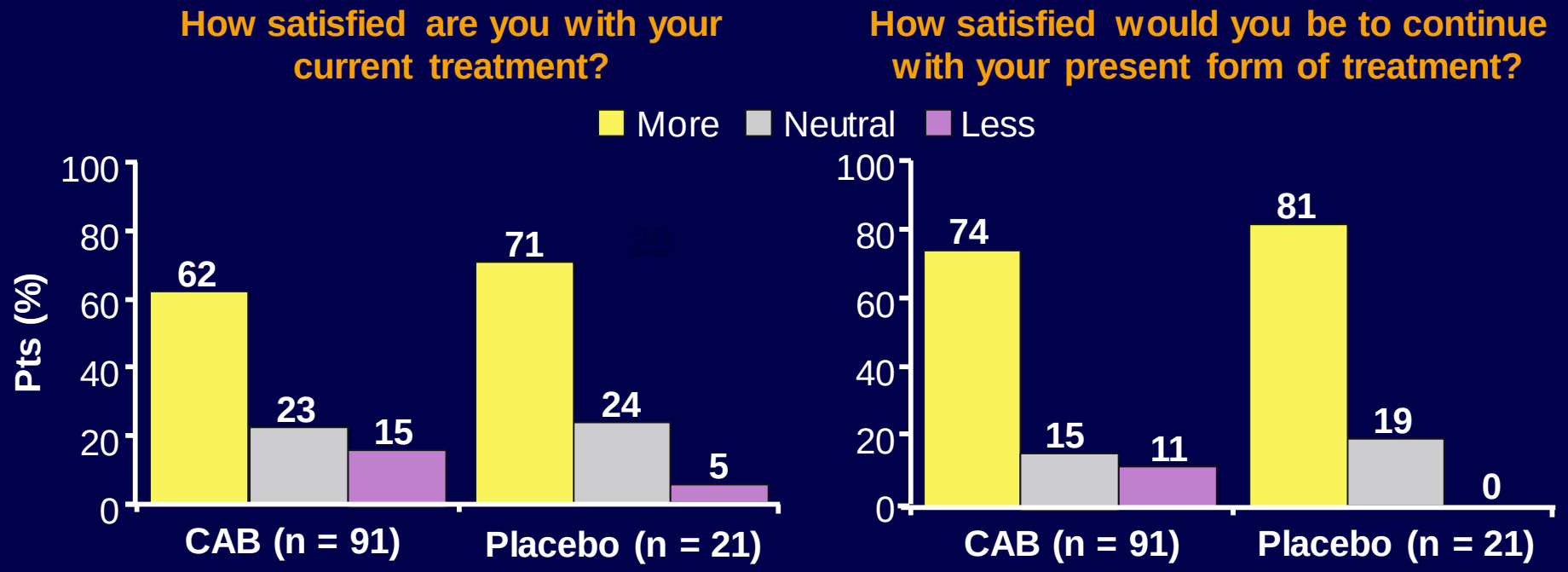
- ISR events occurred in 93% of pts with IM CAB vs 57% with placebo
- No discontinuations for AEs during inj. phase; however, 4 pts who withdrew consent noted inj. tolerability as reason
- On 0 (none of time) to 6 (all of time) pain/discomfort scale assessed at Wk 30, 6% of pts in CAB arm reported pain/ discomfort all of the time
  - 21% of pts in CAB arm reported being dissatisfied with study medication AEs

ISR Event	CAB (n = 94)		Placebo (n = 21)	
	Events, %	Mean Duration, Days	Events, %	Mean Duration, Days
Pain	92	5.4	27	2.0
▪ Gr 1	45		26	
▪ Gr 2	37		2	
▪ Gr 3	10		0	
Pruritus	10	2.5	6	1.8
Swelling	8	3.8	0	
Nodule/ bump	8	9.7	0	
Warmth	7	3.2	0	
Bruising	6	3.3	2	2.0
Induration	6	4.3	0	

Markowitz M, et al. Lancet HIV 2017

ÉCLAIR: Patient Satisfaction With IM Therapy vs Oral Phase

- Pt satisfaction assessed by questionnaire at Wk 18 of IM treatment; asked pts to compare satisfaction of current IM vs past oral therapy[1]



- In separate macaque study, CAB LA conferred 88% protection (21/24 animals) against IV exposure to SIVmac251; results may be relevant to humans who inject drugs[2]

1. Markowitz M, et al. Lancet HIV 2017

HPTN
HIV Prevention
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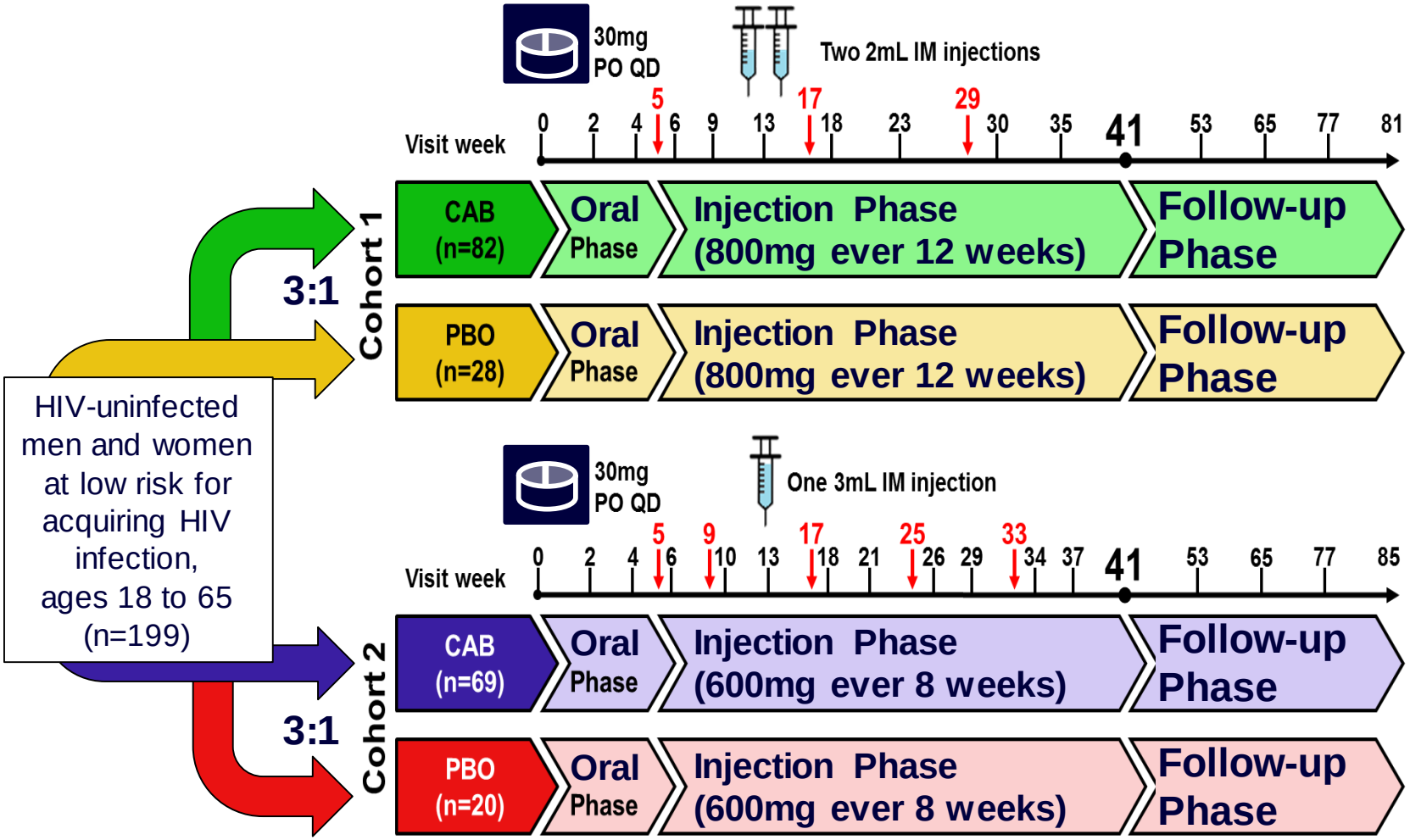
HPTN 077

Safety, Tolerability, and Pharmacokinetics of Long-Acting Injectable Cabotegravir in Low-Risk HIV-uninfected Women and Men

- **Aims:** To evaluate the safety, tolerability, pharmacokinetics and acceptability of CAB LA
- **Design:** Multi-site, double-blind, randomized (3:1) placebo-controlled
- **Sample Size:** 199 HIV-uninfected males and females at low risk for HIV infection, age18-65, at 8 sites in Brazil, South Africa, Malawi and the US
- **Primary Endpoint:** Week 41
- **Study Status**: Ongoing, Follow-up Phase, Complete July-August 2018

HPTN 077 Study Design



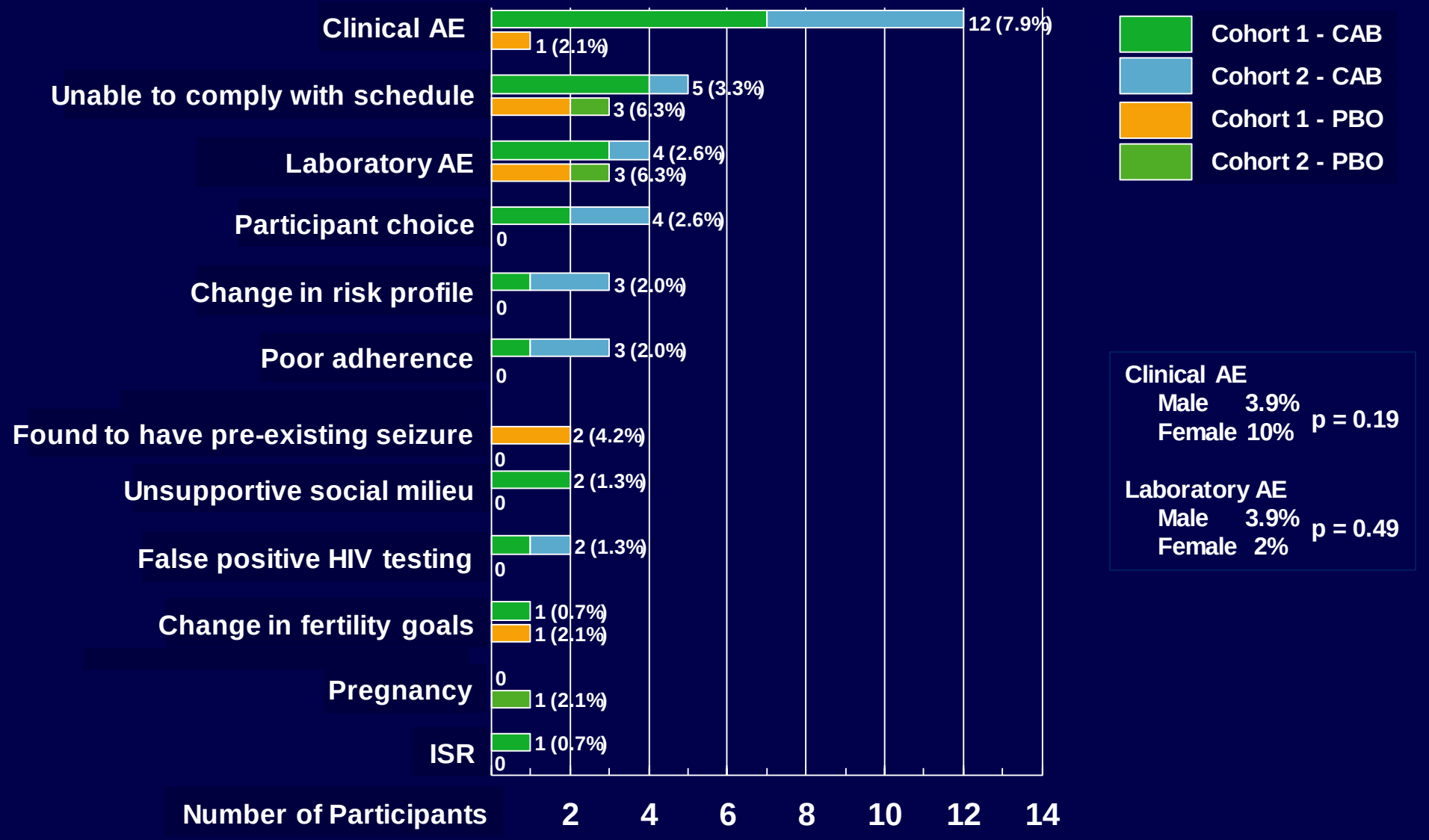
Demographics

	Overall	Cohort 1	Cohort 2
Age, median (IQR)	31 (24, 40)	33 (25, 42)	31 (24,37)
BMI, median (IQR)	27(23, 32)	27(24, 32)	26(23, 33)
Sex at birth and Region, n (%)*			
Female	132 (66)	72 (65)	60(67)
United States	57 (29)	32 (29)	25 (28)
Brazil	24 (12)	11 (10)	13 (15)
Sub-Saharan Africa	52 (26)	29 (26)	22 (25)
Male	67 (34)	38 (35)	29 (33)
United States	49 (25)	31 (28)	18 (20)
Brazil	10 (5)	5 (5)	5 (6)
Sub-Saharan Africa	8 (4)	2 (2)	6 (7)
Race/Ethnicity, n (%)			
Non-Hispanic White	54 (27)	36 (33)	18 (20)
Non-Hispanic Black	82 (41)	42 (38)	40 (45)
Hispanic/Latino	47 (24)	24 (22)	23 (26)
Asian	5 (3)	1 (1)	4 (4)
Mixed/Other	11 (6)	7 (6)	4 (4)

*Includes 6 trans men and 1 trans woman

Study Product Discontinuation by Cohort and Arm (Oral and Inj Phase)

n=199 (CAB 151, PBO 48)

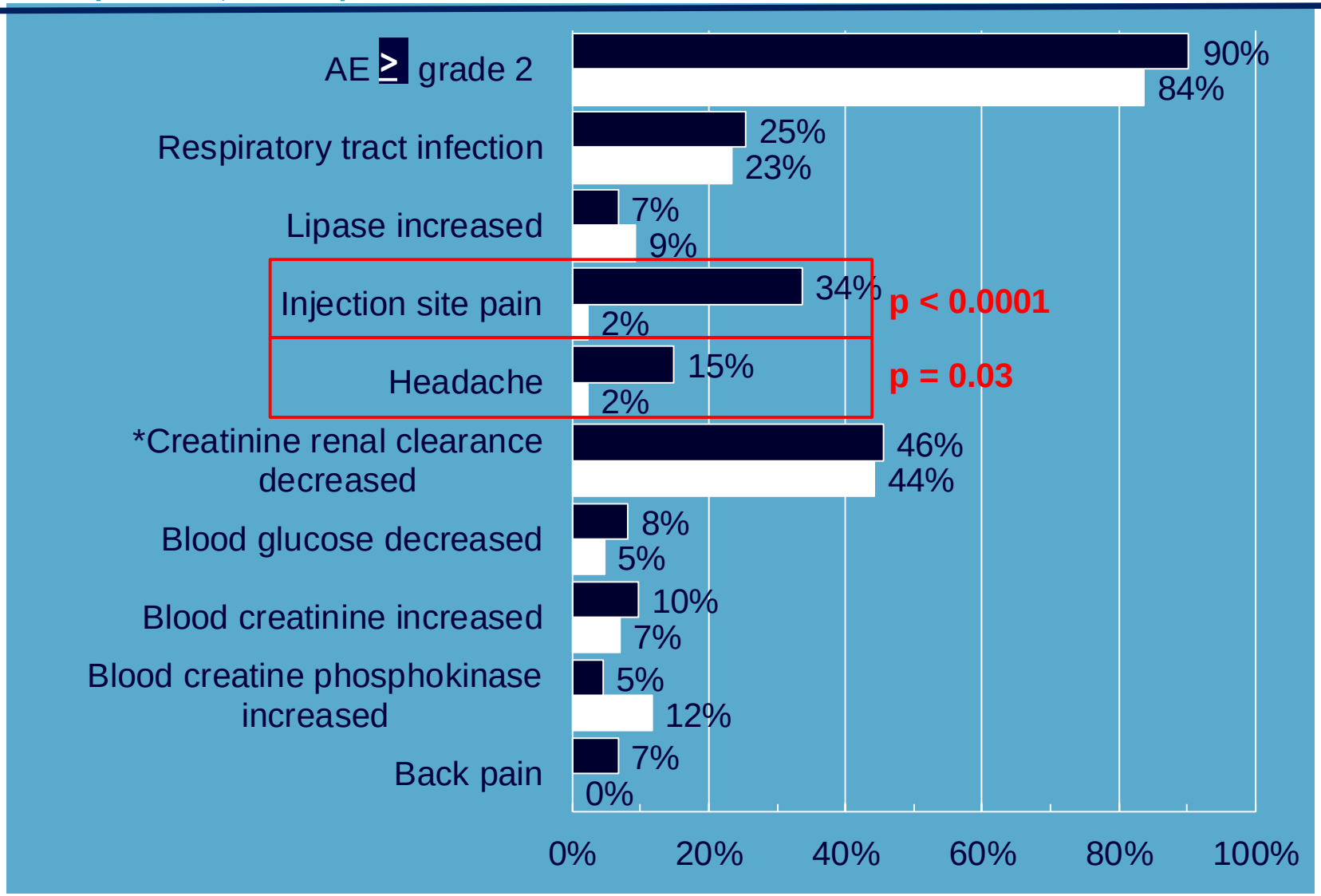


Clinical AE
Male 3.9%
Female 10%
p = 0.19

Laboratory AE
Male 3.9%
Female 2%
p = 0.49

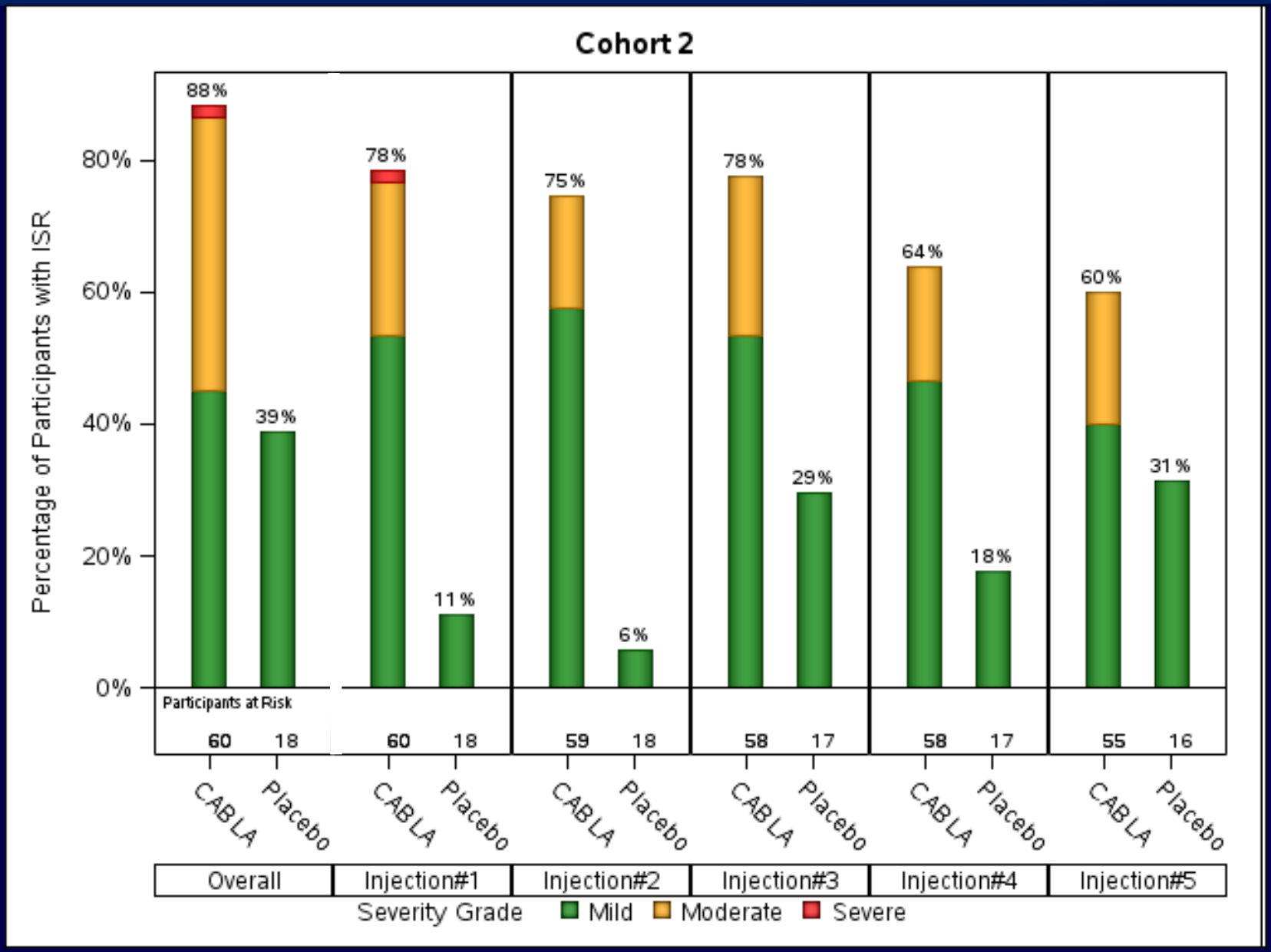
Grade 2 or Higher AE's Experienced by >5% of Any Arm During Injection Phase

n=177 (CAB 134, PBO 43)

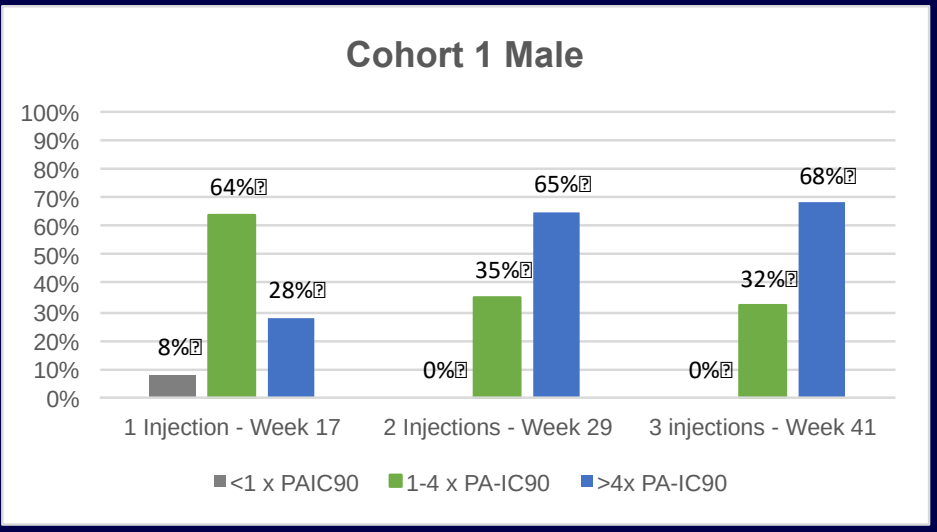


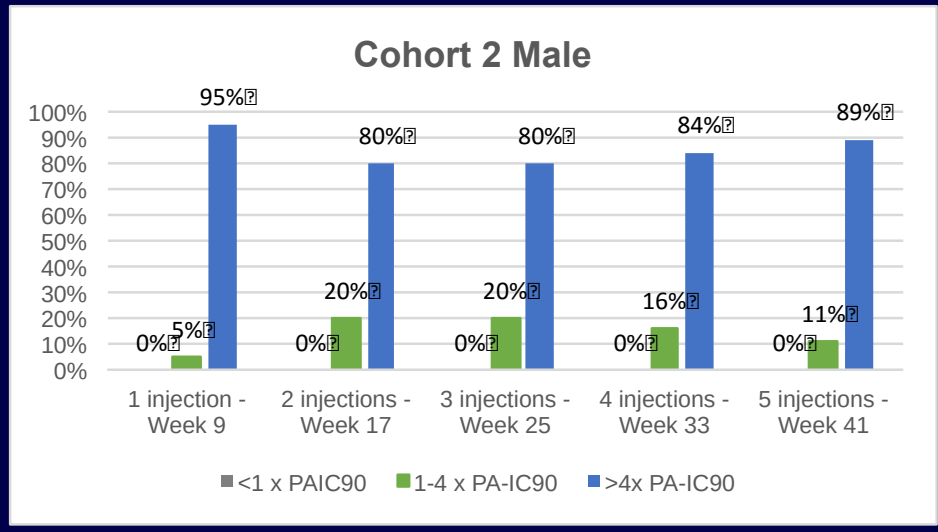
* Grade 2: < 90 to 60 ml/min or 10 to < 30% decrease from participant's baseline.
Grade 3: < 60 to 30 ml/min or 30 to < 50% decrease from participant's baseline.

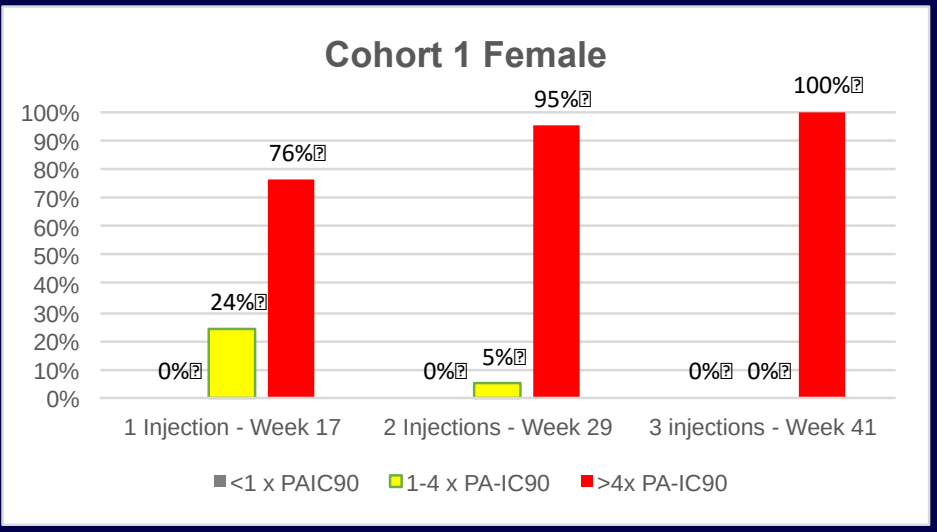
Percentage of Participants with ISR

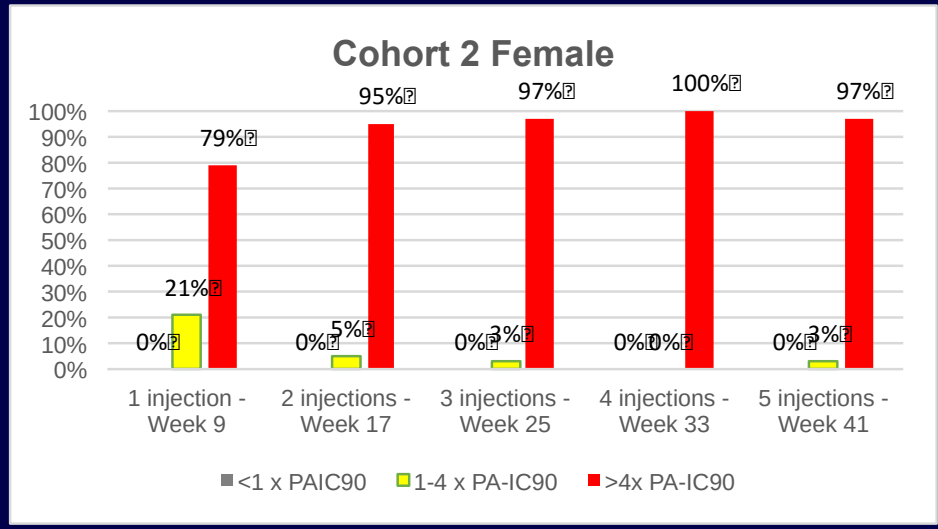


Pharmacokinetic thresholds by cohort and sex

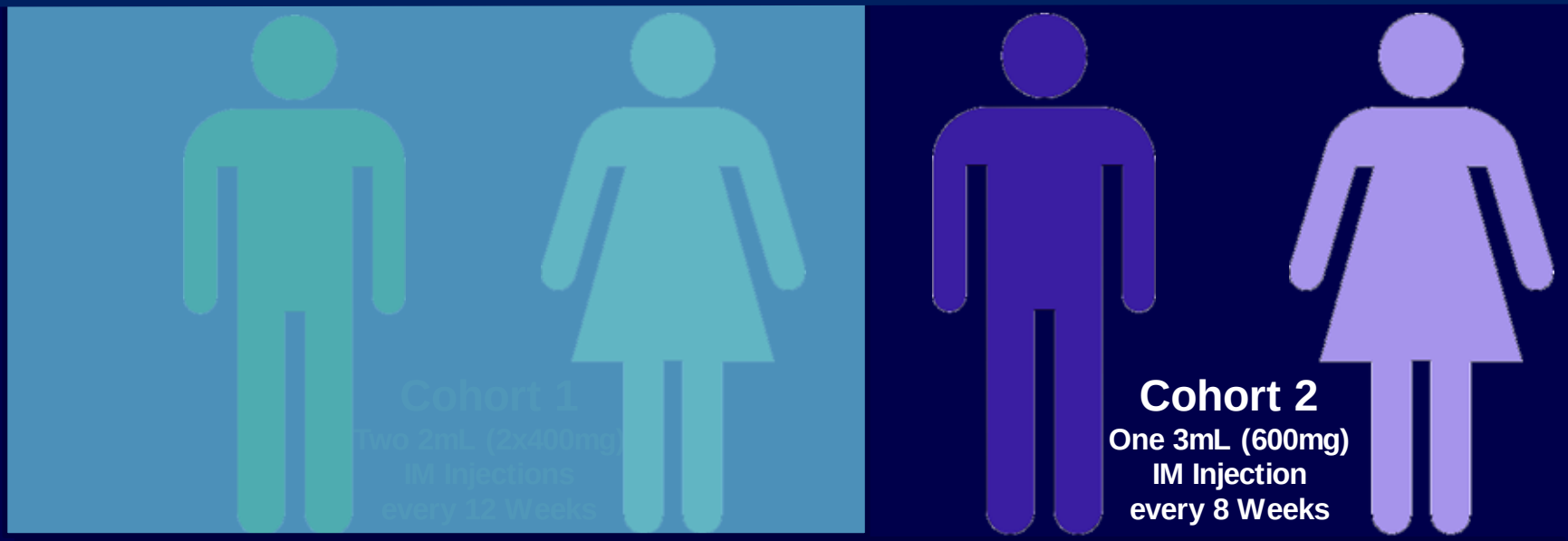








Cohort 2 Participants Consistently met Pharmacokinetic Targets



Median Steady State Trough:	~1.35 ug/mL
% > 1X PA-IC90:	≥95%
% > 4X PA-IC90:	≥80%

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Summary

- CAB LA was well tolerated at doses of 800 mg (2 x 2mL) and 600 mg (1 x 3mL) in HIV-uninfected low-risk males and females
- Injection Site Reactions were frequent but generally mild; only 1 (0.75%) participant discontinued for injection-related AE
- 600 mg IM Q8W (after 4 week loading dose) consistently met prespecified PK targets for both sexes and is being evaluated in Phase 3 efficacy studies in at-risk individuals.

IAS2017
9TH IAS CONFERENCE ON HIV SCIENCE
PARIS, FRANCE | 23-26 JULY 2017

Weekly Oral MK-8591 Protects Male Rhesus Macaques against Repeated Low Dose Intrarectal Challenge with SHIV109CP3

Martin Markowitz MD
Aaron Diamond AIDS Research Center
An affiliate of the Rockefeller University
New York, New York
USA

ADARC

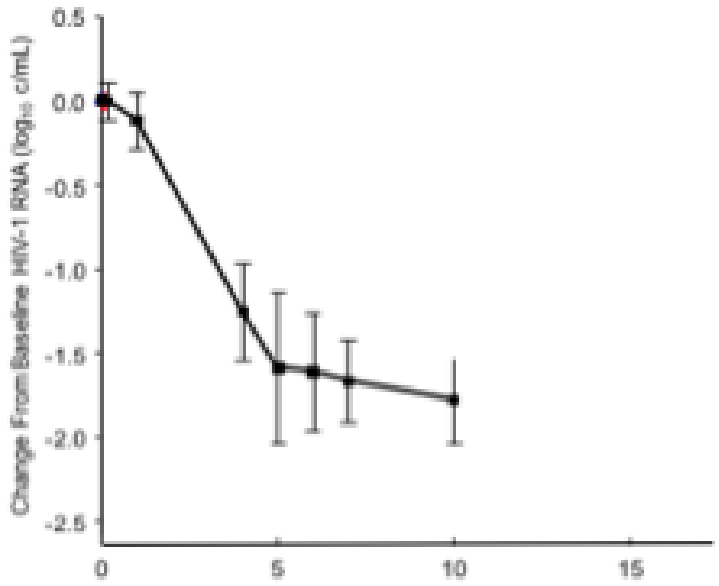
#IAS2017 | @IAS_Conference

MK-8591
(4'-Ethynyl-2-Fluoro-2'-Deoxyadenosine, EFdA)

- Potent and long acting nucleoside reverse transcriptase **translocation** inhibitor (NRTTI)
- Multiple mechanisms of action
  - Immediate chain termination by inhibition of primer translocation
  - Delayed chain termination which prevents nucleotide excision (a significant mechanism of NRTI drug resistance) from occurring
- MK-8591-TP concentrates in both rectal and cervical tissue

Michailidis et al 2009, 2014 J Biol Chem
Grobler et al 2017 CROI, Seattle, WA

Single Once-Weekly 10mg Dose of MK-8591 in 6 HIV-1- infected individuals



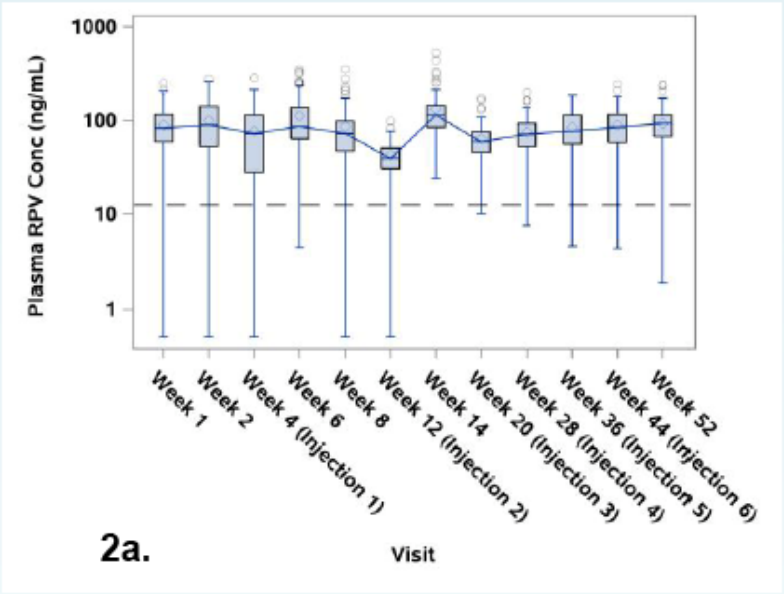
C168hr (7d) of MK-8591-TP=0.983 pmol/10^6 cells

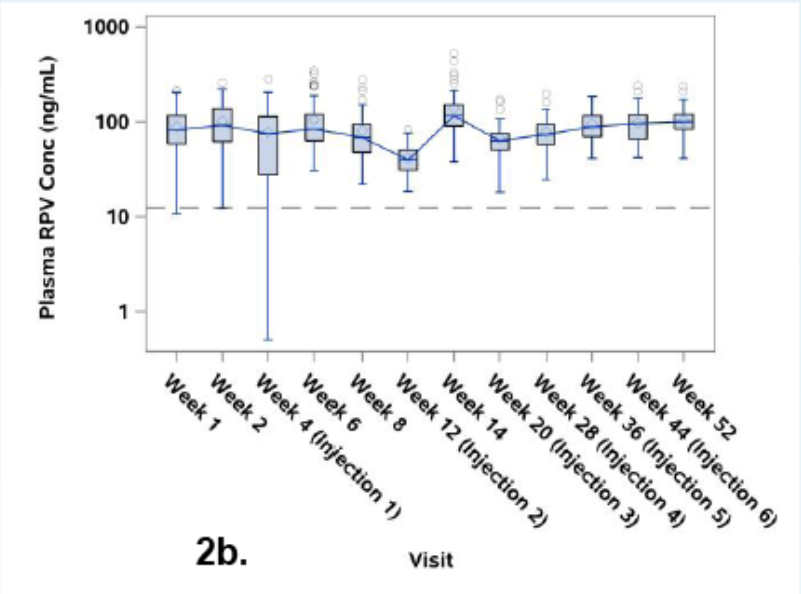
*Matthews et al., "Single doses as low as 0.5 mg of the novel NRTTI MK-8591 suppress HIV for at least seven days" at Late Breaker Poster Discussion, Tuesday, 25 July, 13:00-14:00, Havana Amphitheater

Friedman et al 2016 CROI, Boston, MA
Grobler et al 2016. CROI, Boston, MA

Phase II Safety and Acceptability of an Investigational Injectable Product, TMC278 LA, for Pre Exposure Prophylaxis (PrEP): HTPN 076

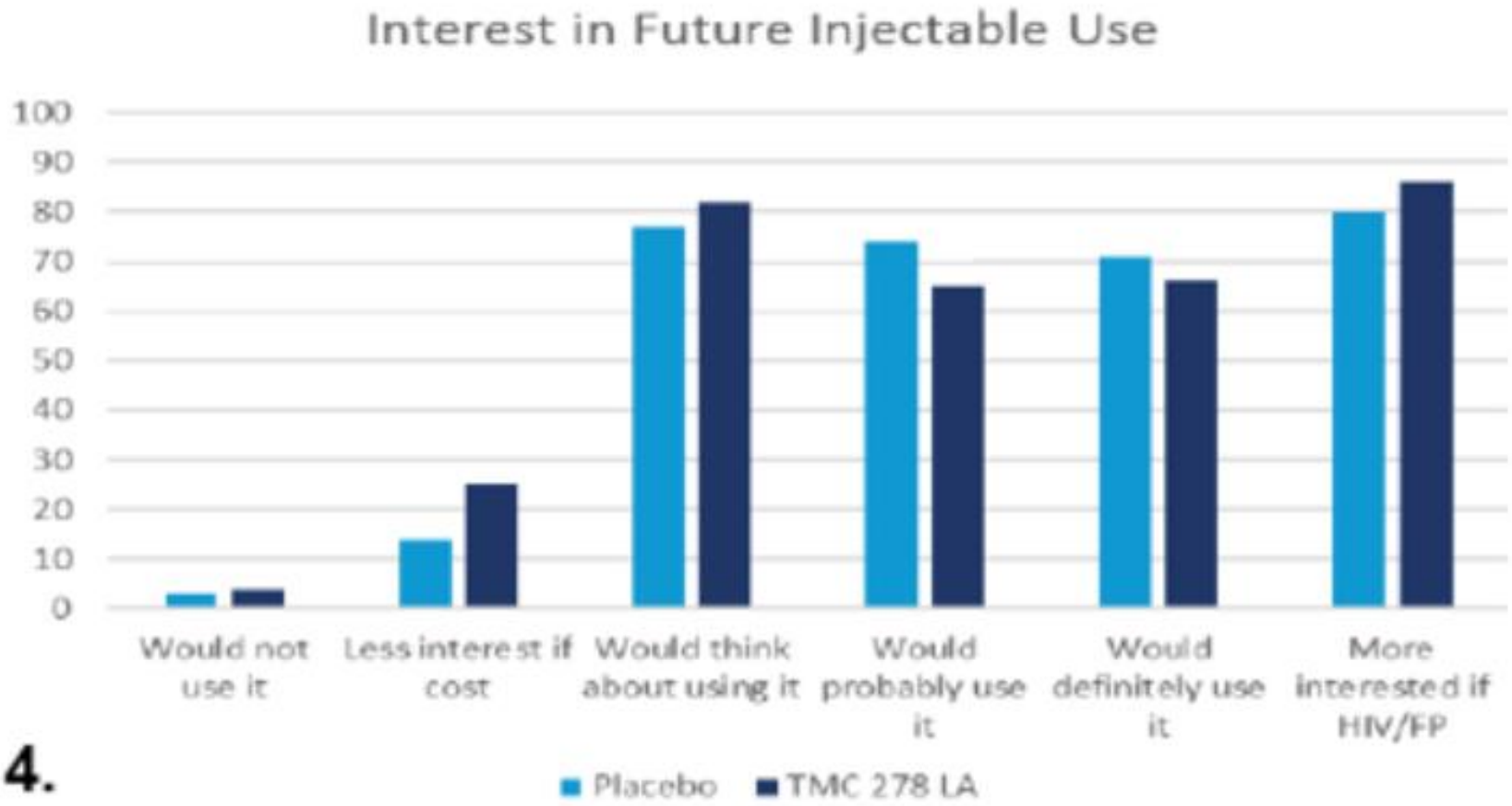
FIGURE 2. Rilpivirine Concentration in Active Arm Participants (a) Receiving at Least One Injection (N=80) and (b) Receiving all Six Injections (N=64).*





The solid line connects the median concentration over time.
The dashed line is the PA-IC_{90} for RPV (=12.5 ng/mL).

FIGURE 4. Percentage of Participants Interested in Future Injectable PrEP Use.



4.

ACCEPTABILITY DATA

- The majority of participants liked that the injectable was:
  - Easier to use (>80%)
  - Potential to provide longer-term protection (>73%)

- Some participants disliked that the injectable was:
  - Painful (~30%)
  - Had side effects (31-37%)

- Acceptability did not differ by arm. At the last injection visit 68% of women strongly agreed that they would definitely use and 80% that they would think about using a PrEP injectable in the future.
  - At the last injection visit, only 4% of participants “strongly agreed” that they would NOT use an injectable PrEP agent if it were available.

- Participants reported strongest interest in future use of an injectable that prevented both HIV and pregnancy.

Di cosa c'è ancora bisogno?

A livello di ricerca clinica:

- No fase di induzione orale
- farmacocinetica CNS
- Farmacocinetica compartimento genitale
- IM vs sc
- Siti di iniezione alternativi

A livello organizzativo:

- Ruolo dell'ospedale
- Ruolo del medico/IP/altro…
- Ruolo della community
- integrazione tempi di visita/tempi di refill

Grazie per l’attenzione!!