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BHIVA ‘Best of CROI’ Feedback Meetings

London | Birmingham

Haydock | Newcastle

Cardiff | Wakefield

Edinburgh

HIV testing Prevention and Cure

Dr Sarah Fidler

Imperial College London

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HIV testing Prevention and Cure

- Testing
  - Cascade of care / 90 90 90
- Prevention
  - Maraviroc prep
  - Dalpiverine ring
- Cure
- MTCT

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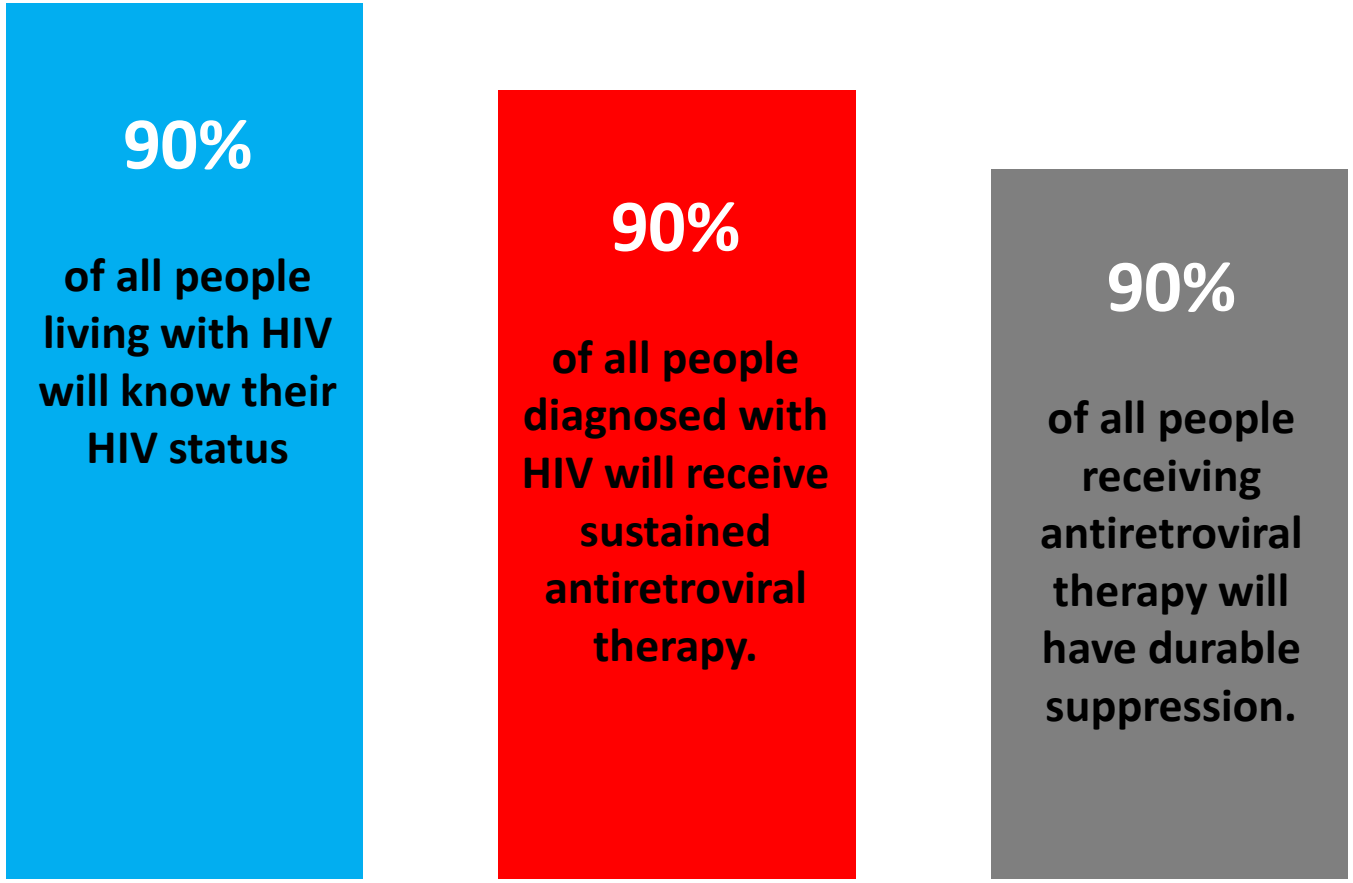
By 2020…UNAIDS and Partners



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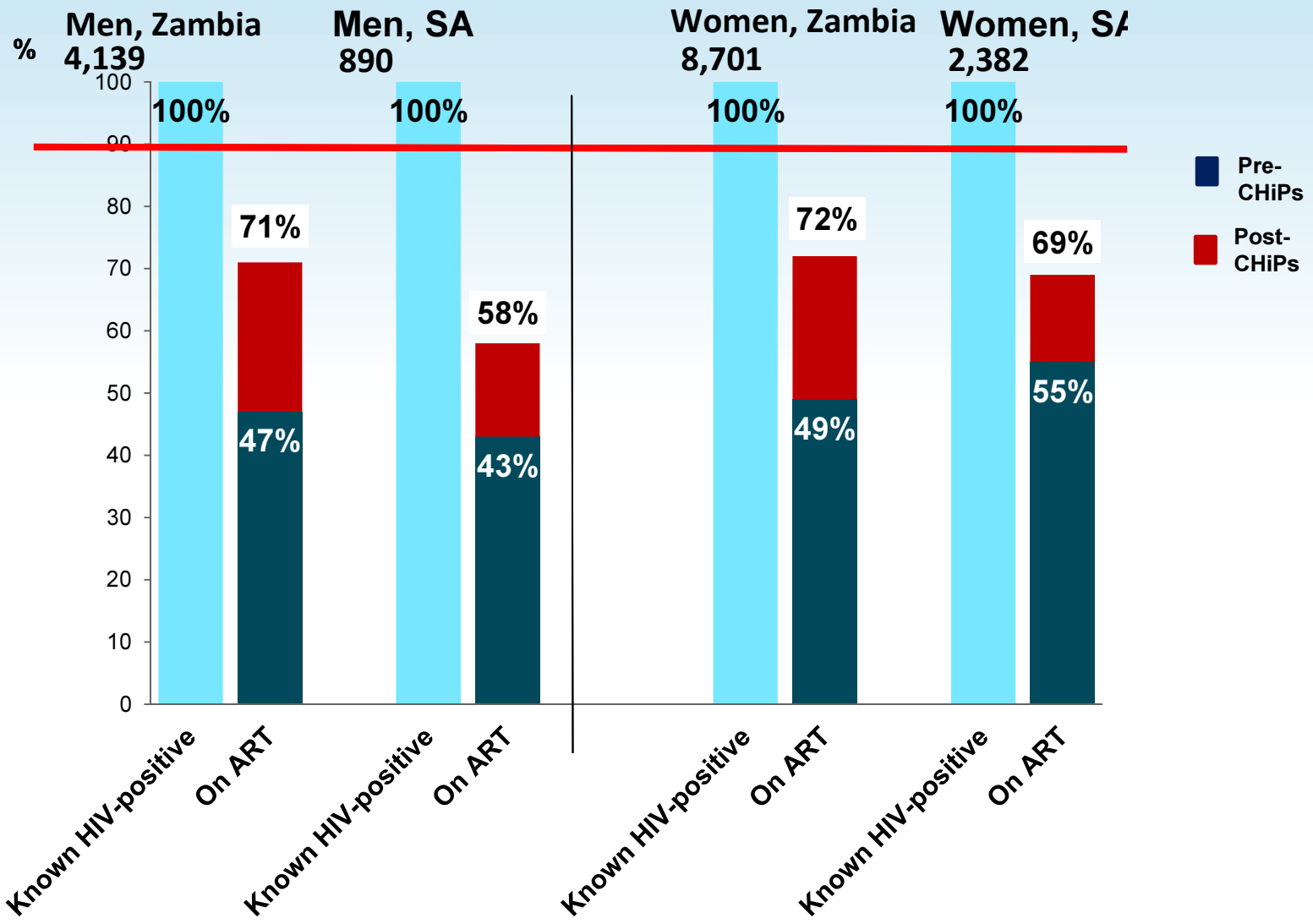
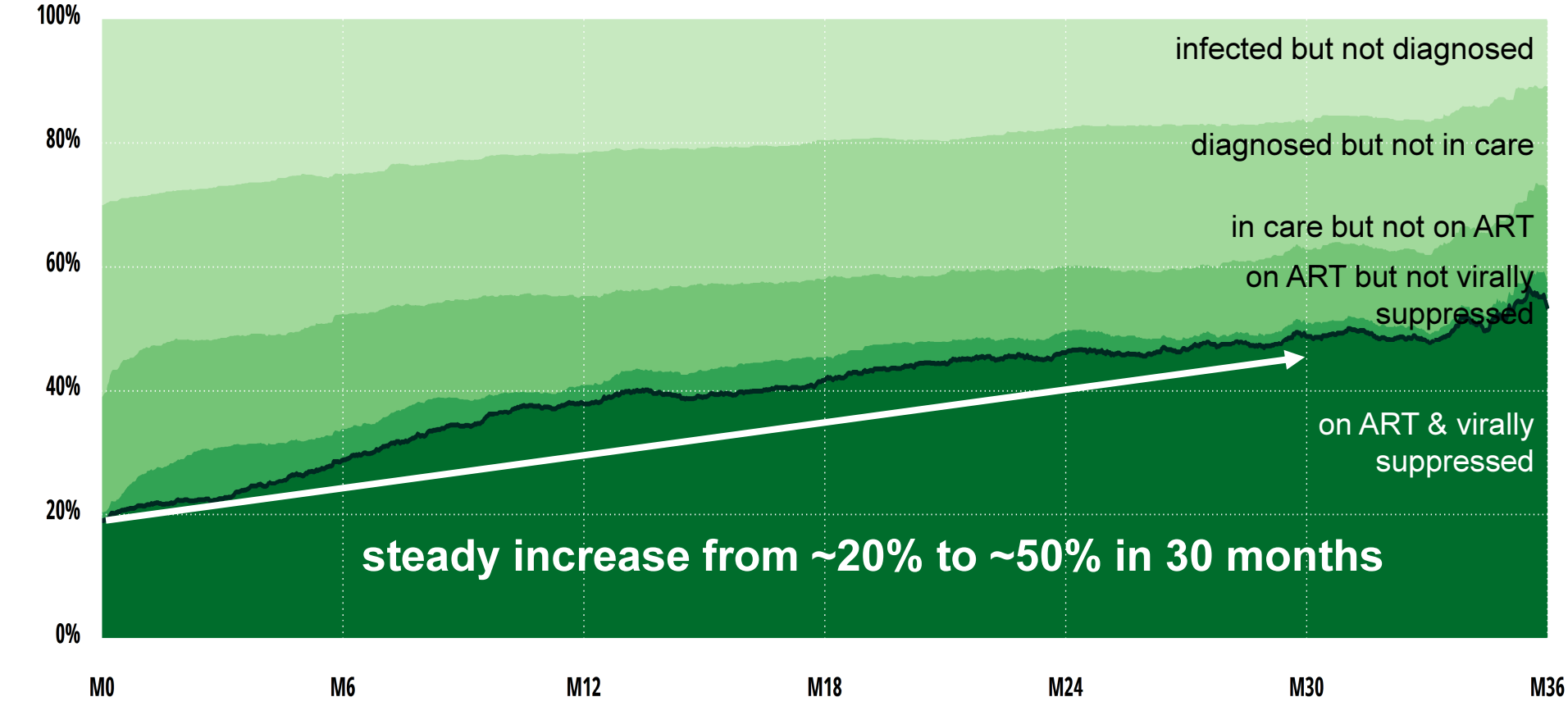
HIV Prevention Trials Network

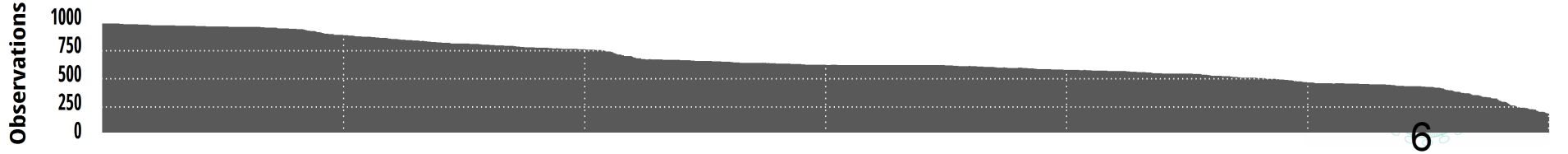
PopART HPTN 071

Second 90 Target: ART uptake, among those consenting to intervention



Position within the cascade per exposure time, TasP ANRS 12249 KZN S Africa





Getting to 90:90:90 Research studies and data from implementation science trials

Research studies	design	Primary endpoint	Population size	First 90 testing	Second 90 ART	Third 90 UD VL
HPTN071(Pop ART) Abstract 145	Community RCT arm A: combination prevention + UTT, arm B CP + ART guidelines and Arm C SOC	HIV incidence	Urban and peri-urban HIV prevalence 10-35% Population 1-1.2 million	89%	71%	n/a
SEARCH	Community RCT Uganda & Kenya 2 arms UTT vs SOC	HIV incidence	Rural Prevalence 10-25% Population 350 000	94%	90%	90%
TasP (ANRS 14429) Abstract 169LB	CRT 24 clusters South Africa KZN	HIV incidence	Rural	90%		50%
Bostwana BCPP Abstract 111	Community RCT Botswana UTT vs SOC	HIV incidence	Rural and urban	82%	86% BUT this is % ELIGIBLE for ART	95%

Challenges to achieve 90:90:90

- **Uptake of nearly 90% HIV testing** seems to be feasible and acceptable in a combination household based model with campaigns, HCF testing and opt out testing.
- **Linkage to care and ART initiation,** congested poorly functioning clinics, over burdened systems, lack of lab reagents and failure to deliver results. One study[1] showed offering same-day ART initiation to adult patients in South Africa increased uptake of ART by 36% and viral suppression by 26%.
- **Retention in care and viral suppression**: very variable, VL testing not routinely available in many settings, where in care good follow up , poor retention after option B+ in Malawi for pregnant women. Offer of community ART showed better uptake.[2]
  - Poor retention especially amongst young people and young women Malawi (stable patient community delivery of ART[3]
  - Individualized care pathways, for different patient needs S Africa[4]

1.RapIT (S Rosen)
2.Abstract 118 (Mugglin)
3 Abstract 122 (Grimsrud)
4 Abstract 121E Geng)

HIV testing Prevention and Cure

- Testing
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HPTN 069/ACTG A5305: Maraviroc Based PrEP in MSM Safety

	MVC (n=101)	MVC+FTC (n=106)	MVC+TDF (n=99)	TDF+FTC (n=100)	Total (N=406)
Diarrhea	2%	8%	7%	4%	5%
Nausea	0%	1%	4%	3%	2%
Vomiting	0%	0%	1%	1%	0.5%
Unintentional Weight Loss	0%	2%	2%	1%	1%
Increased Creatinine	0%	1%	0%	0%	0.25%

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Gulick R, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 103.

HPTN 069/ACTG A5305: Five Incident Infections

Demographics	Study Arm	Week Tested Positive	Tropism	Genotypic Resistance	Plasma Drug Conc. at Seroconversion Visit (ng/mL)
20, Black	MVC+TDF	4	R5	none	MVC=0† TFV=0
61, Asian	MVC	16	R5	none	MVC=145
21, Mixed	MVC	24	R5	none	MVC=0
35, White	MVC	32	R5	none	MVC=6.7
36, Black	MVC	48	R5	none	MVC=0.7

Gulick R, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 103.

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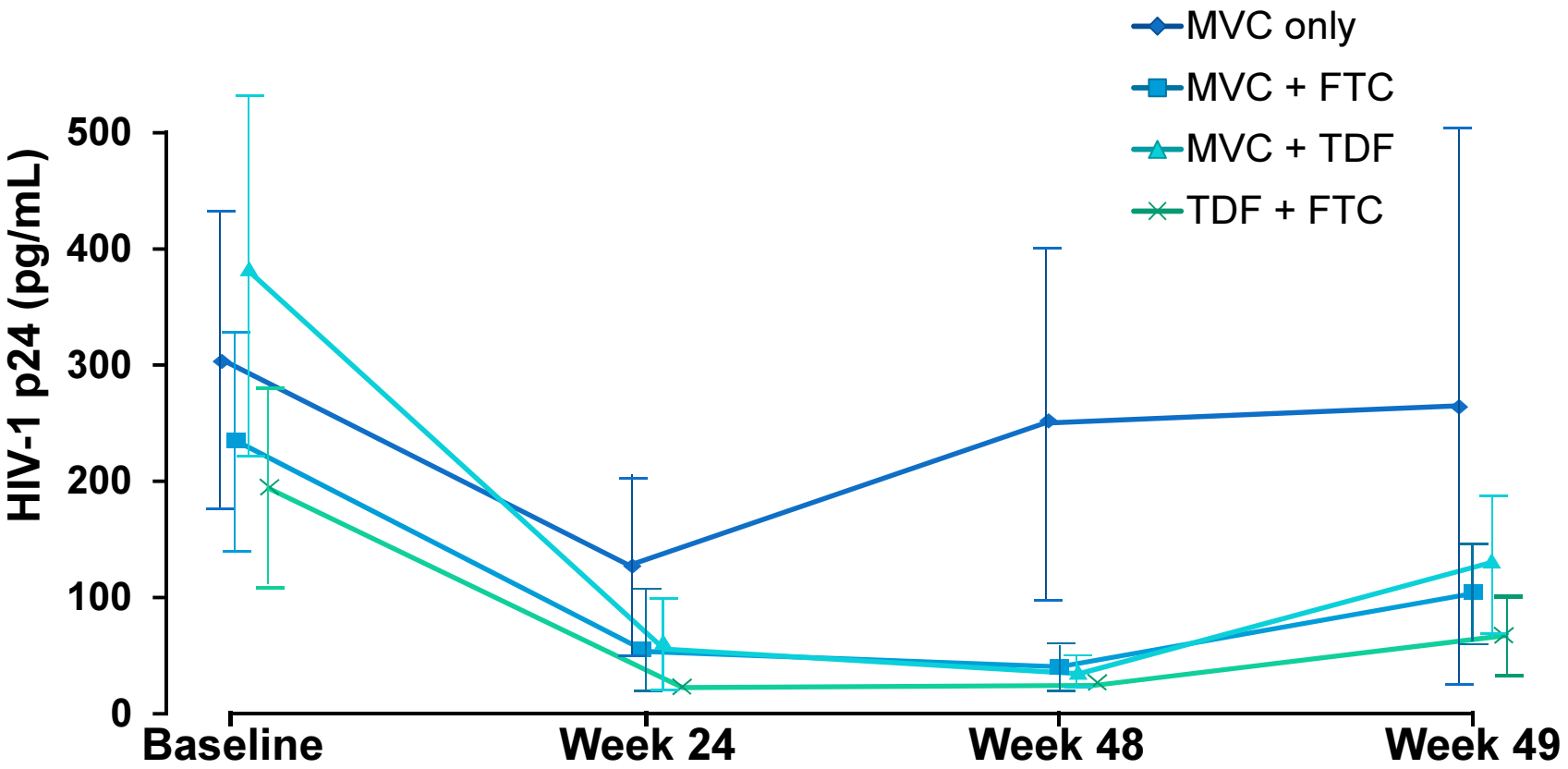
Maraviroc Less Effective at Inhibiting HIV Following Infection of Tissue Explants



McGowan I, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 104.

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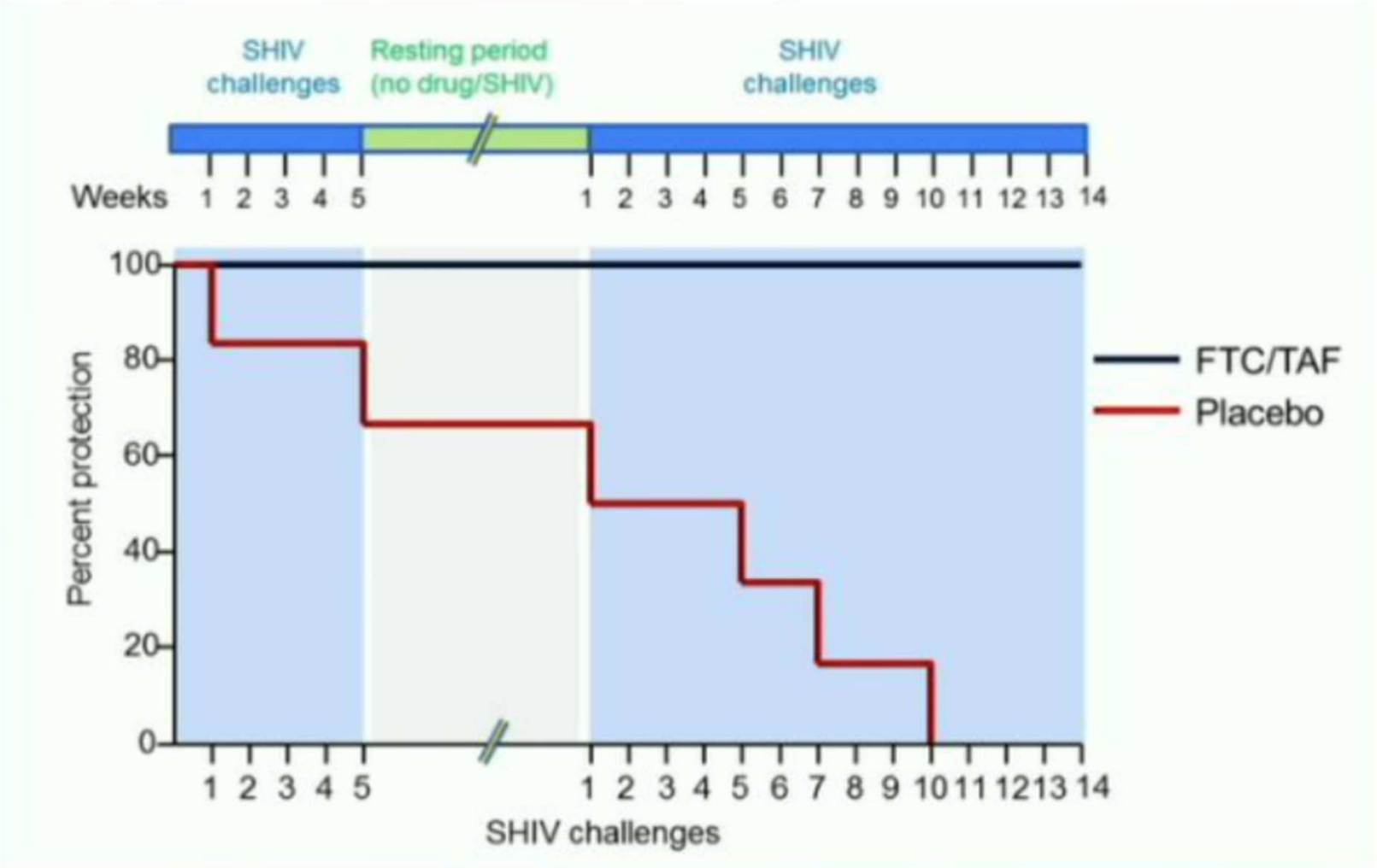
Prophylactic efficacyof FTC/TAF against rectal SHIV infection



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ASPIRE Study:
Phase III Trial of Dapivirine Vaginal Ring

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Baeten J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 109LB.

ASPIRE Study:
Primary HIV-1 effectiveness ITT (15 sites)

	Dapivirine	Placebo
# HIV-1 infections	**71**	**97**
HIV-1 incidence (Per 100 person-years)	**3.3**	**4.5**
HIV-1 Protection Effectiveness (95% CI) [p-value]	**27% (1, 46) [0.046]**	

Baeten J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 109LB.

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ASPIRE: Phase III Trial of Dapivirine Vaginal Ring Efficacy by Age

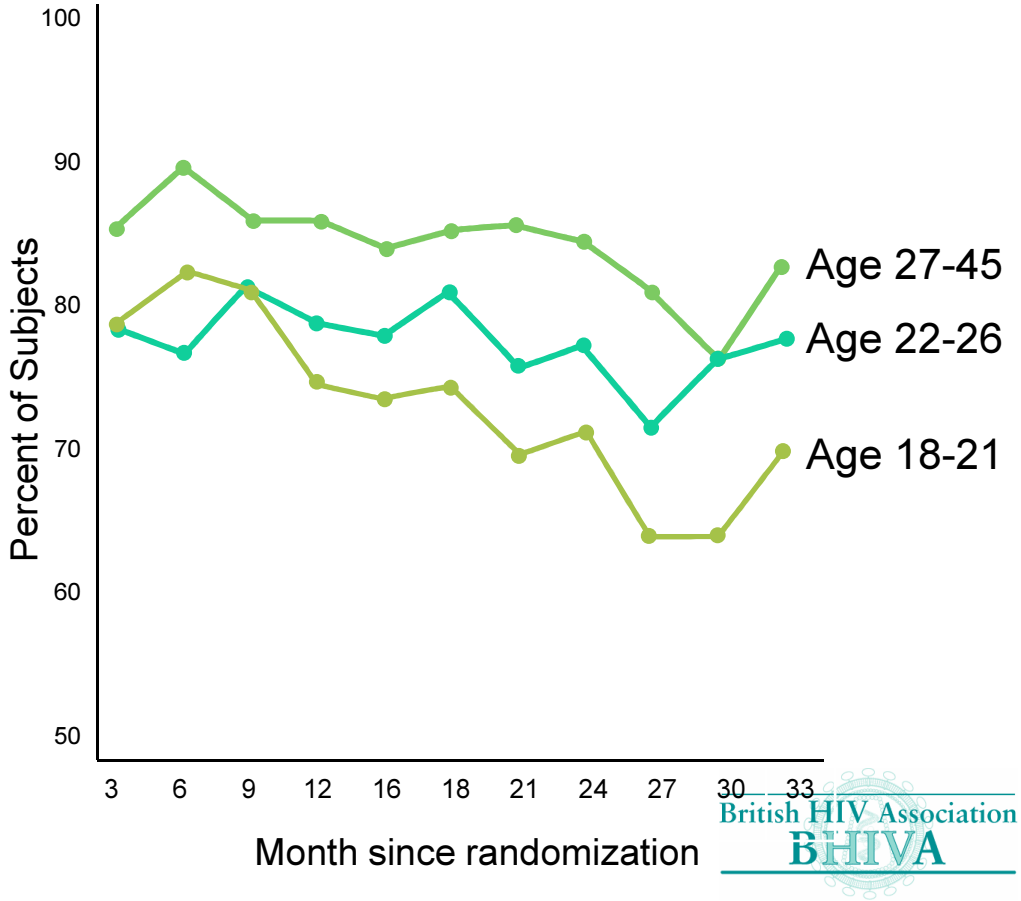
Efficacy

Age 18 – 21
-27% (-133, 31)
Placebo incidence – 5.4%/y

Age 22 – 26
+56% (19, 76)
Placebo incidence – 6.1%/y

Age 27 – 45
+51% (8, 74)
Placebo incidence – 3.0%/y

Adherence by Plasma Drug Concentration and Concentration in Returned Ring



Baeten J, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 109LB.

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IPM027 Study:
Phase III Trial of Dapivirine Vaginal Ring

Variable	Dapivirine (N = 1300)	Placebo (N = 650)
Number of confirmed seroconversions	77 (5.9%)	56 (8.6%)
Total person years of follow-up (years)	1888	917
HIV-1 seroconversion rate (per 100 person-years)	4.1	6.1
% reduction in HIV-1 seroconversion (95% CI) [p-value]	31% [0.9%, 51.5%) [0.040]	

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Nel A, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 110LB.

IPM027 Study: Efficacy by Residual Drug Level

Cut-off ring residual level (mg)	Adherent vs. Non-adherent	
	% Reduction in HIV-1 seroconversion	95% CI
20	65%	21% to 84%
21	44%	7% to 67%
22	36%	-8% to 62%
23.5	22%	-40% to 56%

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Nel A, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 110LB.

Overview of efficacy results for ASPIRE and The Ring Study

	Aspire	The Ring Study
Overall	37%*	31%
18-21 years old	No protection	15%
>21 years old	56%	38%

* Excluding two non-adherent sites

§ >25 years old: 61% efficacy

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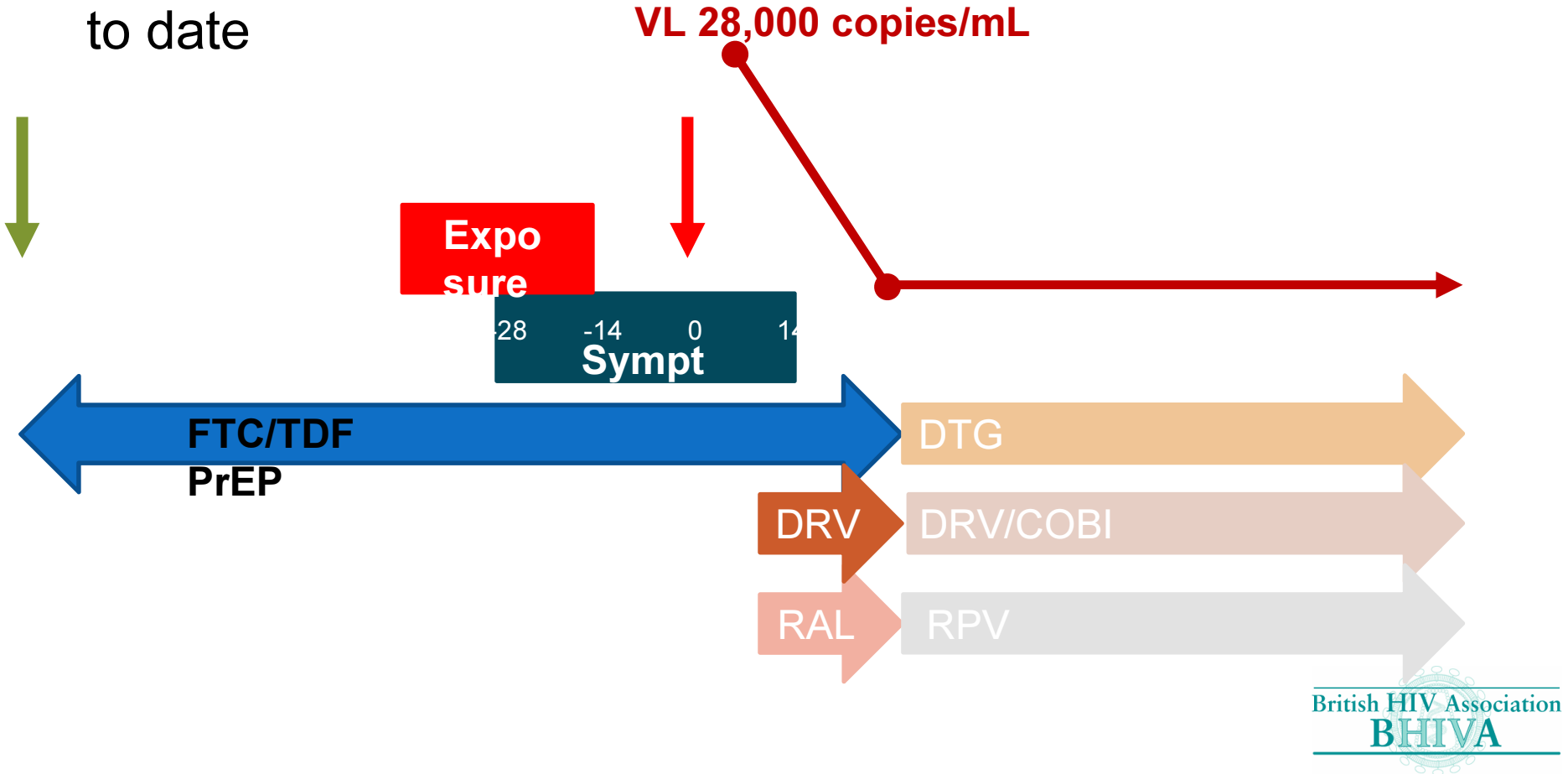
Prep failure due to infection with multi drug resistant virus

- ART regimen optimized, and viral load remains undetectable to date



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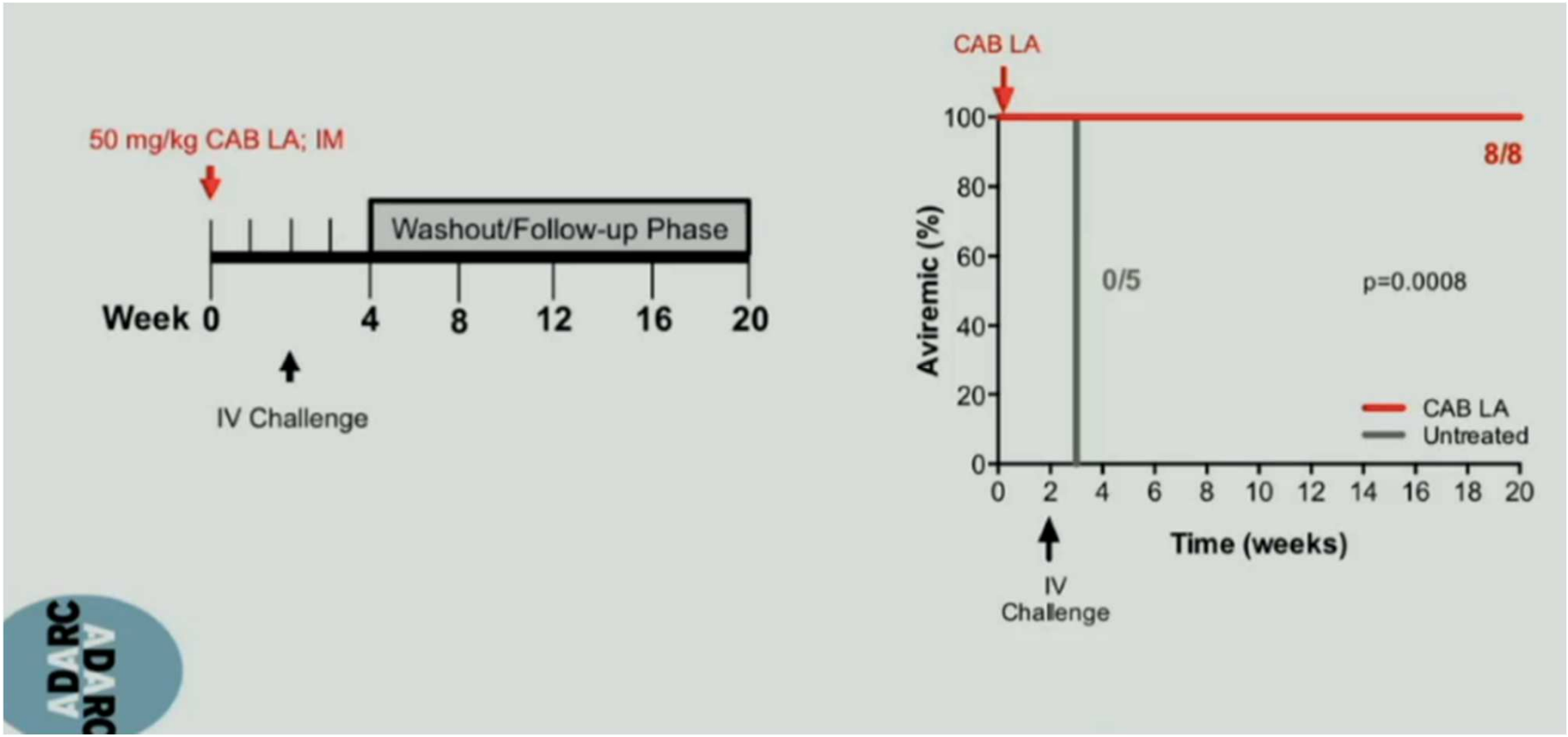
Determine if a Single 50 mg/kg CAB LA Dose Provide Sustained CAB Plasma Levels for Protection against IV Challenge



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The Perils of LA PrEP

- Safety
- Acceptability
- Adherence
- Pharmacokinetics
- Resistance
- Operational complexity

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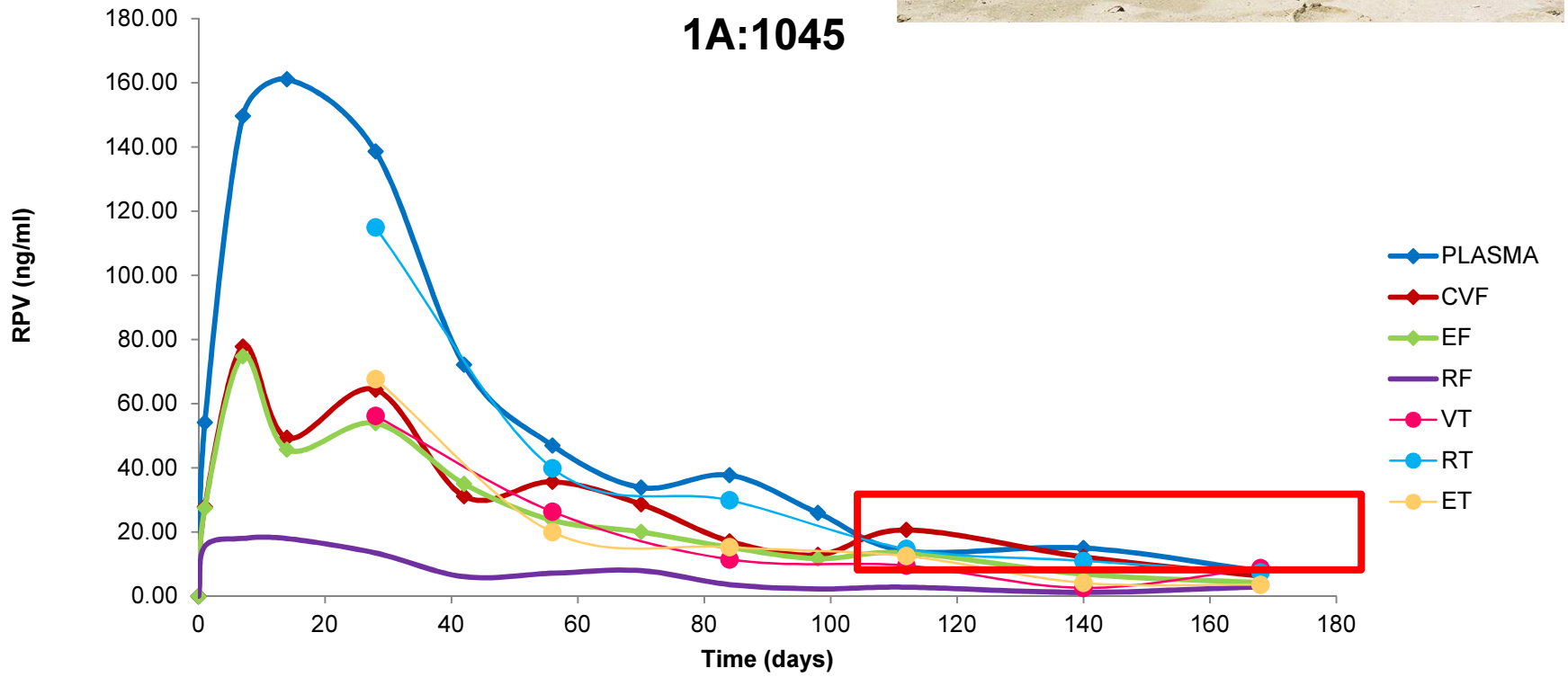
The PK Tail



Female participant receiving a single 1200 mg dose of rilpivirine

?

Summary

Maraviroc for HIV Prevention

- The number of incident infections in HPTN 069/ACTG A5305 and the low tissue levels suggest that maraviroc will not be effective for PrEP if used as monotherapy

Vaginal Dapivirine Ring

- Rate of protection was disappointing
- Rate of sub-optimal adherence higher than expected
- Are there any biological differences that explain the poorer rate of protection in the younger women?

Long-acting injectables for prevention

- Maybe effective and much better accepted but the PK tail could be a real challenge

HIV testing Prevention and Cure

- Testing
  - Cascade of care / 90 90 90
  - Partner notification stratergies
- Prevention
  - Maraviroc prep
  - Depo prep
  - Dalpiverine ring
- Cure
- MCTC

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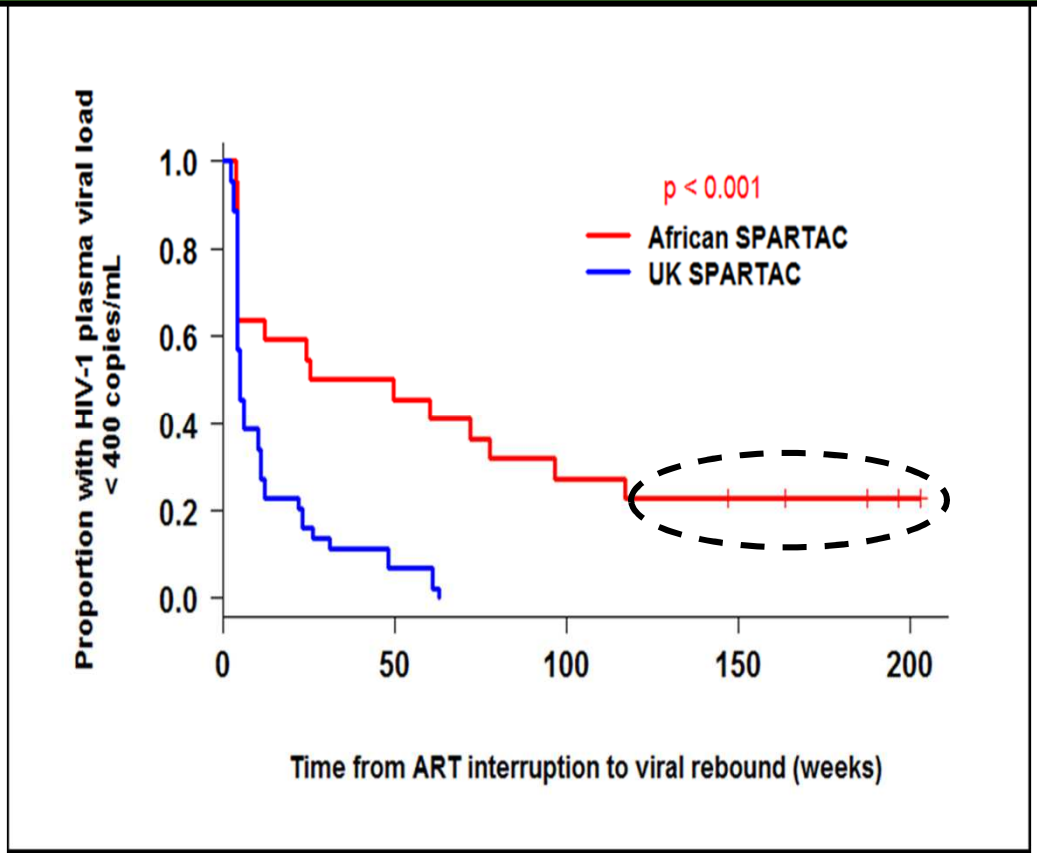
Viral rebound in African SPARTAC *versus* UK SPARTAC



5 / 22 !!!

African (n=22) and UK SPARTAC (n=44) participants undertaking TI after 48 weeks of ART

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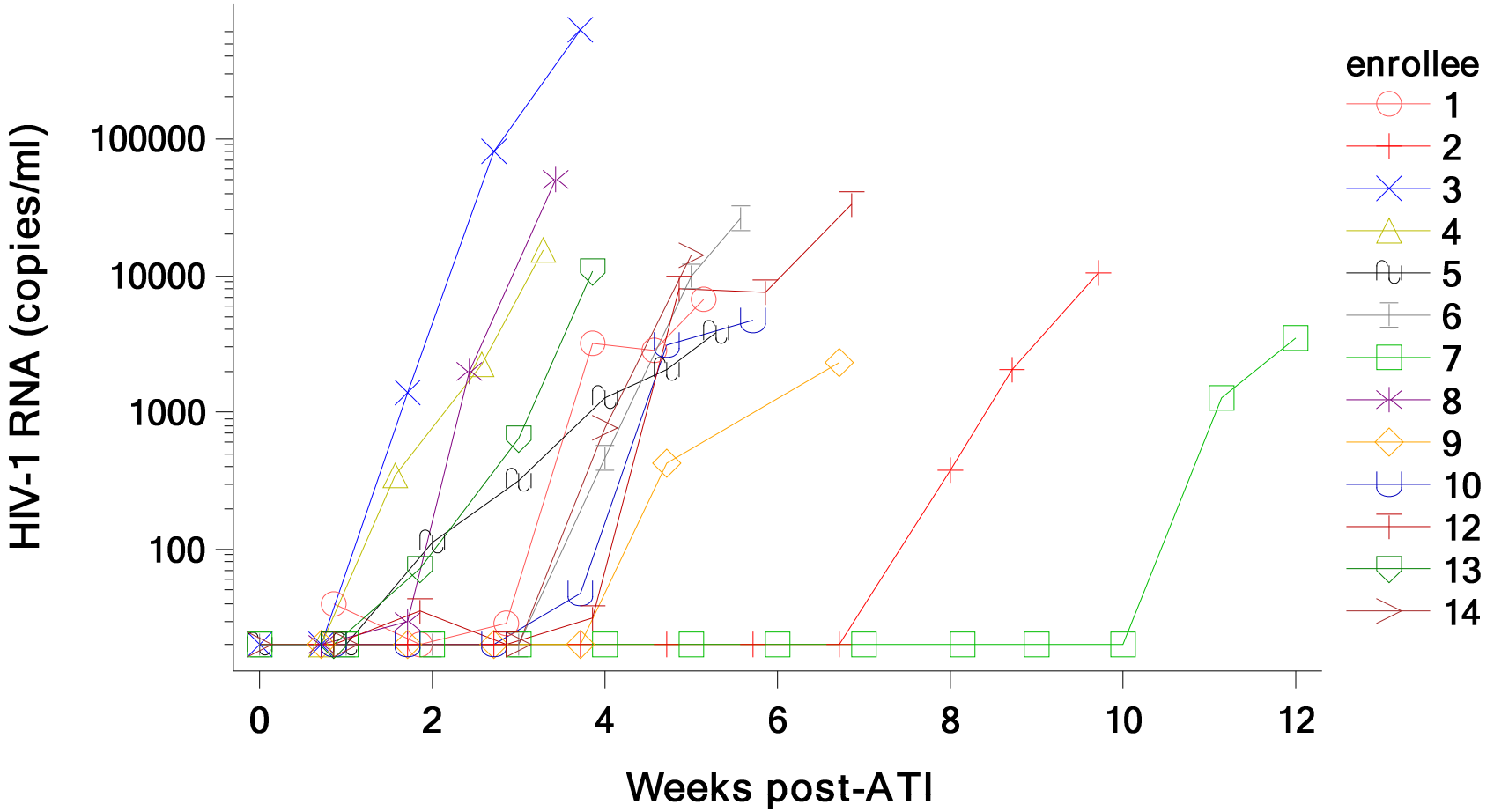
Treatment interruption studies and post-treatment control (PTC)

study	design	No	ART length	outcome	findings
Abstract 332 ULTRASTOP	Early chronic treated patents with ultra-low reservoirs ultralow HIV-DNA (<66 cp/106 PBMC).	10	n/a	Viral rebound >400 copies/ml after TI Or CD4 < 400 after TI	**10% PTC** 1 individual VL < 20 up to week 56 after TI 9/10 rebounded between weeks 2-12 Virus rebounds from transitional memory CD4 T-cell population
Abstract 346	Analysis of 6 ACTG TI studies	235		confirmed VL rebound ≥200 HIV RNA copies/mL and VL set point (mean log10 VL during ATI weeks 12-16)	Pre-ART VL and VL set point were correlated with time to VL rebound (CHI higher than PHI) **PTC 10%**
Spartac Abstract 87	Acute HIV infection RCT to ART48 vs no immediate ART	91 African women	48 weeks or none	Time to VL rebound and total HIV DNA	**PTC 5/22 (22.7%)** Africans maintained VL<400 copies/ml over a median 188 weeks follow-up (range 147-203) much longer than UK MSM cohort
Abstract 347	Review of 8 ACTG TI studies	497		VL < 400 for > 24 weeks	**PTC 16/497 3.2%** More common in early treated group vs chronic

Results: Viral rebound



- Majority of participants rebounded by week 5
  - 2 participants with delayed rebound at 8, 11 weeks
- Time to rebound not associated with VRC01 level, age, nadir or entry CD4 ct, time on ART

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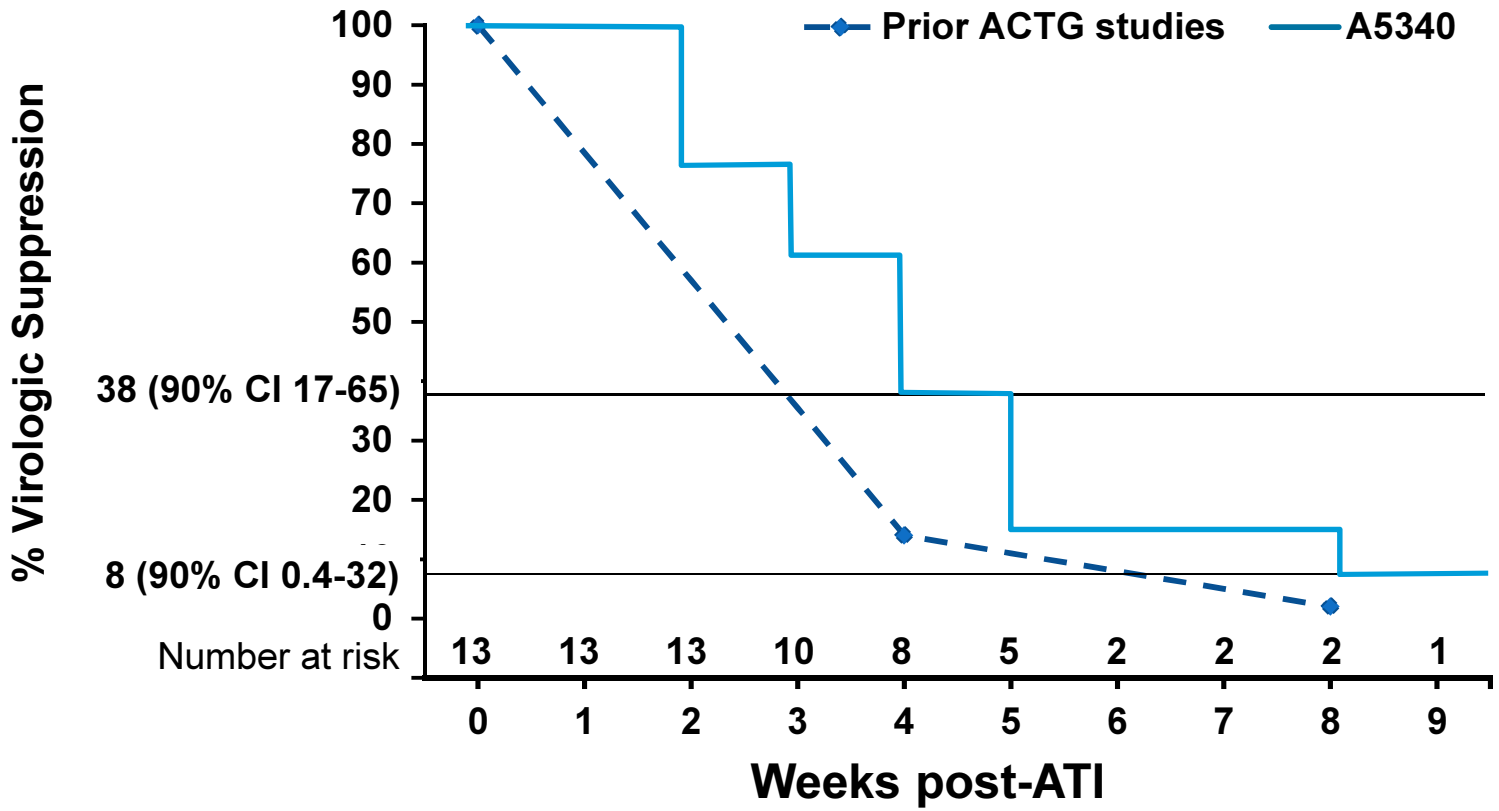
ACTG A5340

ACTG 5340: Time to Rebound in Viral Load After Infusions with VRC01



- 38% vs. 13% suppression at 4 weeks, p=0.04
- 8% vs. 3% suppression at 8 weeks, p=0.44
  - compared to historical controls on non-NNRTI regimens undergoing ATI in ACTG studies

Bar K, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 32LB.

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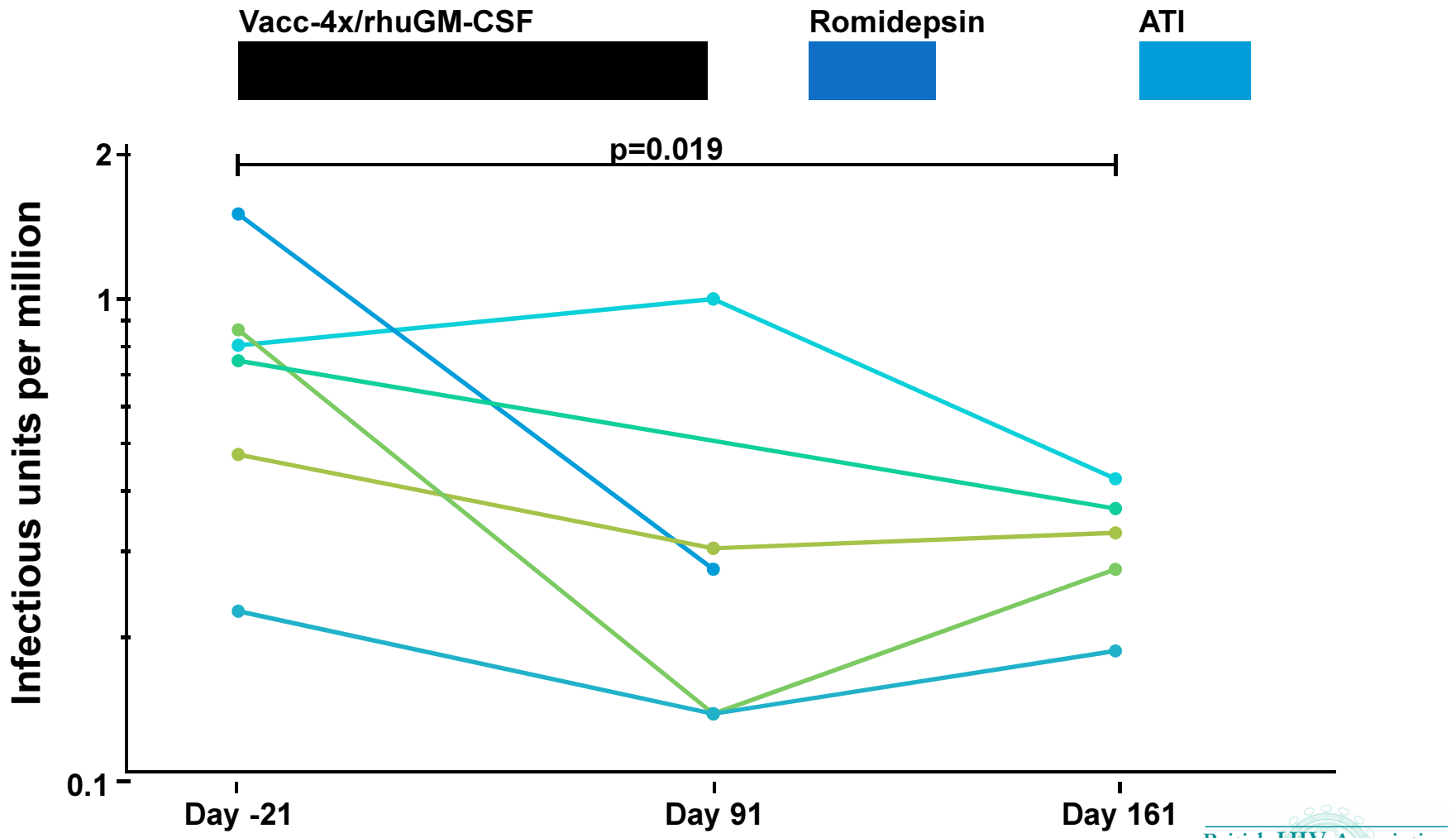
Decrease in Latent Reservoir Following Therapeutic Vaccination and Romidepsin



Leth S, et al. 23rd CROI; Boston, MA; February 22-25, 2016. Abst. 26LB.

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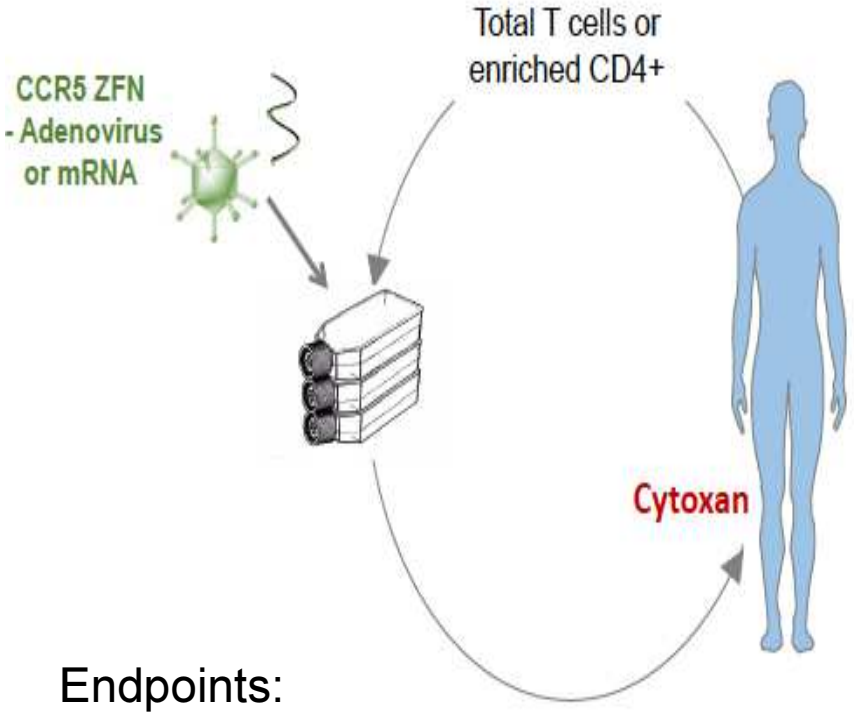
Gene therapy approaches for HIV cure:

- Integrating gene transfer vectors: retroviral and lentiviral
- Adoptive T cell therapy
- Autologous HSC transplants in cancer patients
- Autologous HSC transplants in non-cancer patients (non-myeloablative conditioning)
- Targeted nucleases (Zinc Finger Nucleases, TALENs, CRISPR/Cas9) -more precise gene therapy

Paula Cannon plenary & R. Sekaly abstract #358LB

ZFN-treated T cells – SB-728-T:
5 trials, completed or ongoing



Endpoints:
Safety
CD4 counts
HIV reservoir measures
CCR5 editing

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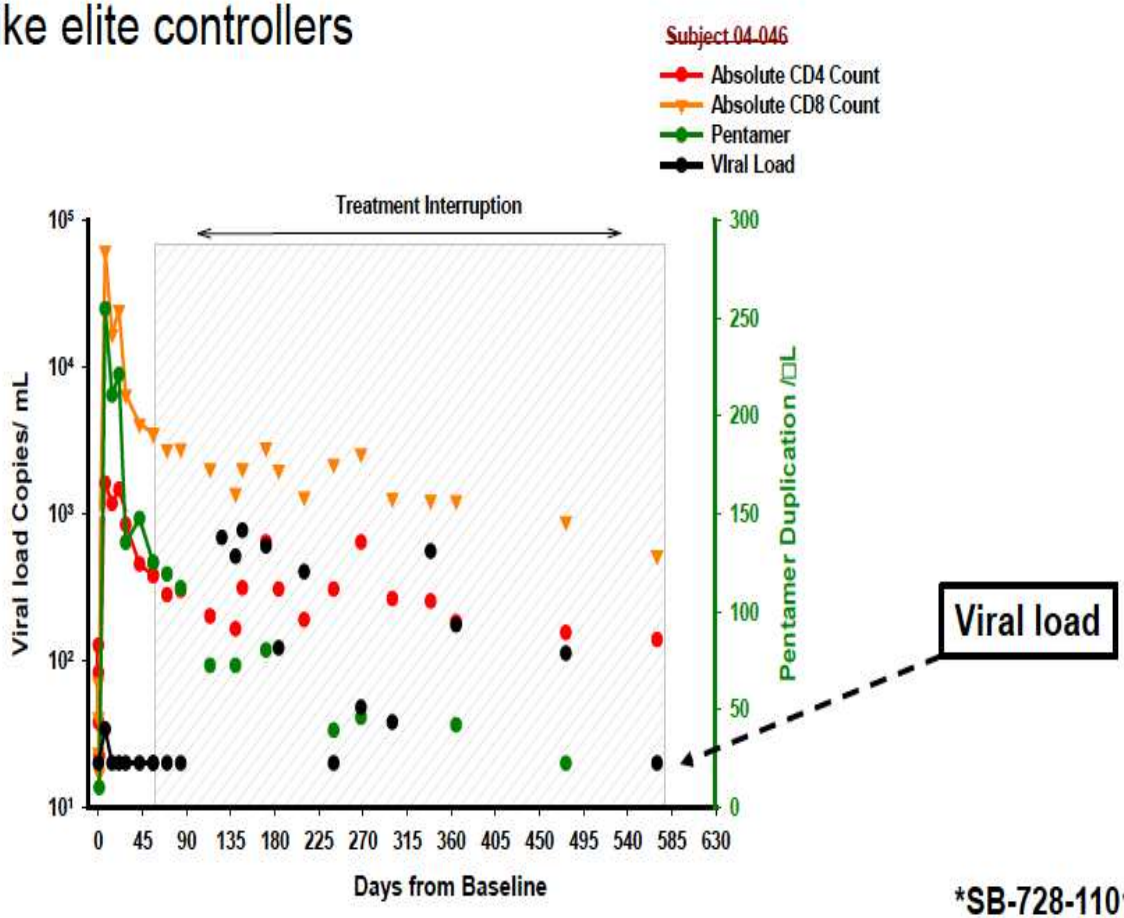
Virological control after ART interruption

- 6/9 individuals controlled HIV after TI (2 <1,000, 4 <10,000 copies/ml)*
- They look like elite controllers



SB-728-1101, cohorts 3, 5, 3

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Treatment interruption studies after intervention

Study	Intervention/study design	No participants	Years on ART	Outcome	Time to VL rebound
ACTG5340 Abstract 32LB	VCR01 antibody 40mg/kg every 3 weeks for 3 infusions	14	4.7	All rebounded after TI	>200 copies 8 weeks max
Abstract 311LB	Suppressed VL > 3 years CD4 > 450 Infusion of VRC01 (40mg/kg) 3 days prior to and 14 and 28 days following interruption of ART	10	Median 10.6 years	Viral rebound after TI	9/10 subjects experienced plasma viral rebound (>40 copies/ml) between 11-54 days (median 39) Despite adequate levels of antibody in serum
Abstract 26LB	Single arm 6 x Vacc 4x + GMCSF adjuvant then 3 x 5mg/m2 weekly Romidepsin infusion	20 17 completed	-	Data on 6/17 showed reduction in total DNA by 36% IUMP 40% All rebounded after TI	>50 copies 14 days
Abstract 358LB	CD4 > 500 preconditioned with 0.1-2.0 g/m2 of Cytoxan prior to infusion of SB-728-T then TI	18	-	VL < 10,000 after TI	6/9 treated participants maintained VL control below threshold 10,000 up to 14-24 months

Treatment interruption studies and post-treatment control (PTC)

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Summary of Cure research intervention studies

- ART alone is VERY unlikely to confer cure or even PTC (except if ART started in acute infection)
- Intervention studies with disappointing results: VRC01 antibody, Vax4,GMCSF Romidespin, Anti-PD-L1, all patients interrupting ART after intervention had VL rebound (rapidly within 4-8 weeks)
- Gene therapy looks promising…
- Where are the reservoirs, what cells, what sanctuary sites, how to measure reservoir with clinical meaning?

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BHIVA 'Best of CROI' Working Party 2016

- Dr Jasmini Alagaratnam
- Prof Brian Angus
- Dr David Asboe
- Dr Sanjay Bhagani
- Dr Daniel Bradshaw
- Dr Kate Childs
- Dr Duncan Churchill
- Dr Amanda Clarke
- Dr Paul Collini
- Mr Simon Collins
- Prof Satyajit Das
- Dr Annemiek de Ruiter
- Prof David Dockrell
- Prof Lucy Dorrell
- Dr Ellen Dwyer
- Dr Sarah Fidler
- Dr Julie Fox
- Dr Andrew Freedman
- Dr David Hawkins
- Prof Saye Khoo
- Prof Clifford Leen
- Prof Derek Macallan
- Dr Achyuta Nori
- Dr Ed Ong
- Dr Chloe Orkin
- Dr Adrian Palfreeman
- Dr Brendan Payne
- Dr Frank Post
- Dr Iain Reeves
- Dr Jonathan Underwood
- Dr Ed Wilkins
- Dr Jaime Vera

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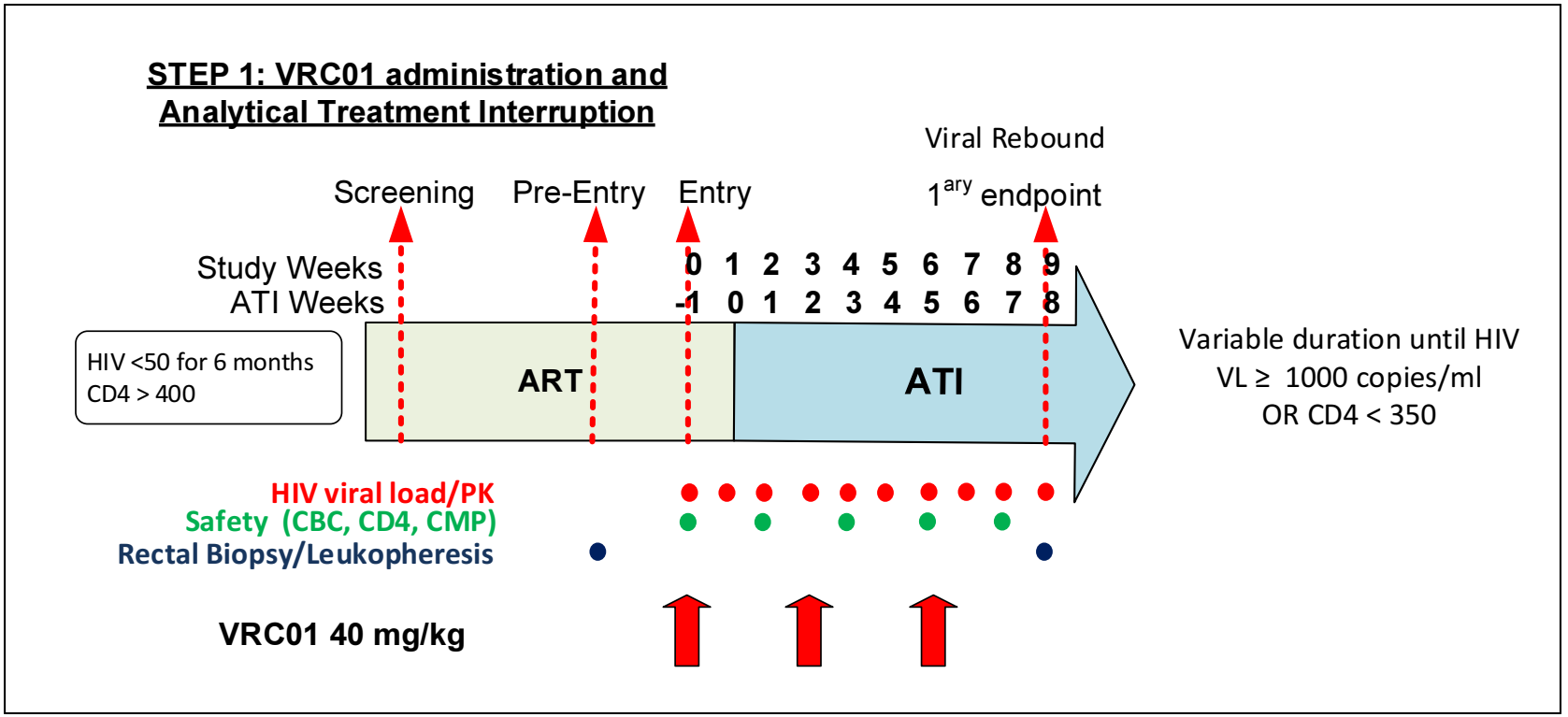
Study Design



- **Participants:**
  - Chronically infected, on ART with VL<50 copies/ml for > 6 months
  - CD4 count > 400 cells/ml, nadir CD4 > 200 cells/ml
  - INSTI or PI-based regimen
- **Power:** 13 evaluable participants 90% power to detect 40% increase in suppression at week 8

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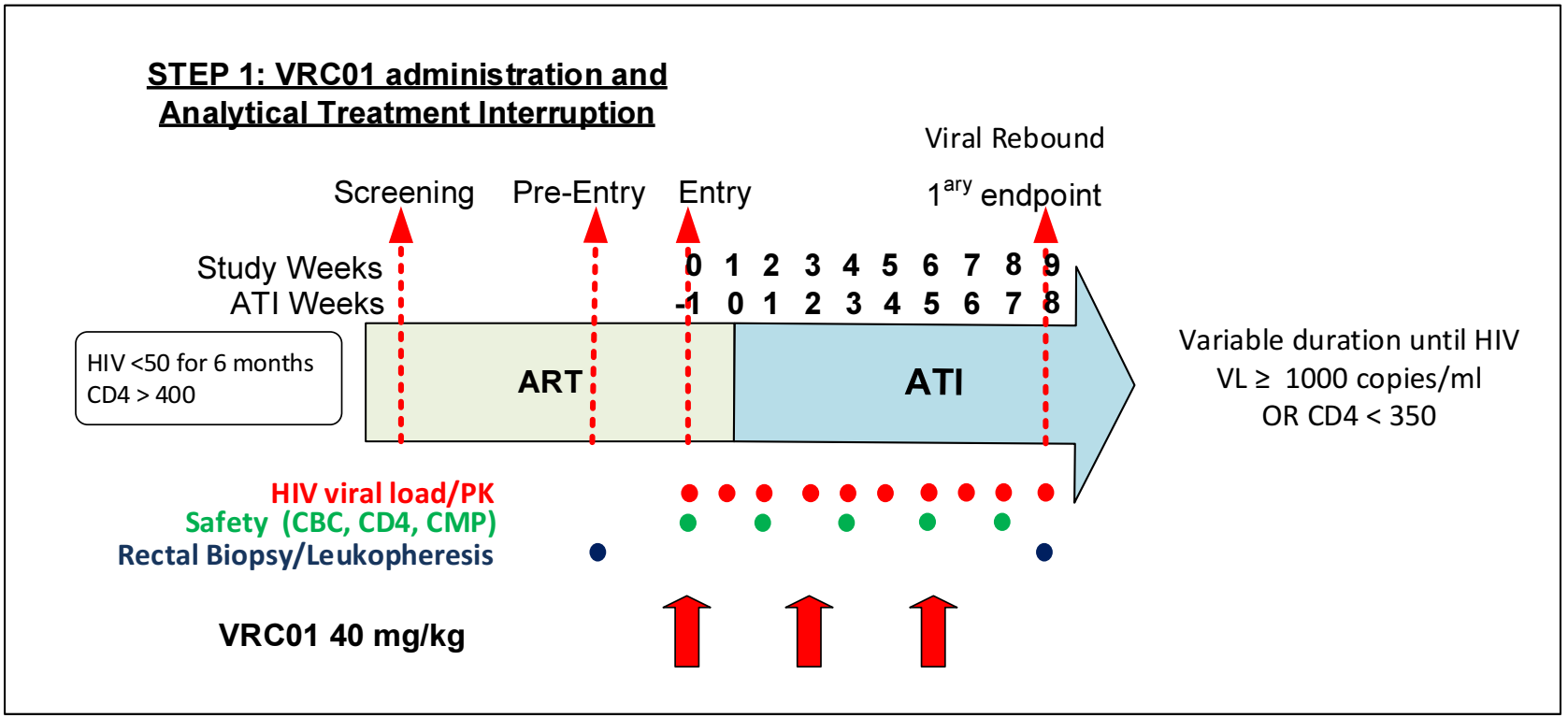
Study Design



Intervention:

- 40 mg/kg IV VRC01 every 3 weeks
  - PK modeling suggested plasma levels >50 ug/ml x 10 wks
- ATI 1 week after VRC01 initiation
- Weekly monitoring for viral rebound, ART reinitiation upon confirmation

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ACTG A5340

Results: Study Population

- 14 participants enrolled at 2 clinical sites
  - 13 evaluable. 1 participant stopped ART before the infusion.
- Demographics:
  - 100% male
  - Median age 38, range 27-52 years
  - 50% African American (n=7), 50% Caucasian (n=7)
    - 14% Latino (n=2)
- HIV clinical data:
  - Median CD4 count: 896 cells/μL (range 470-1,586)
  - Median 4.7 years on ART (range 2.7-14.5)
  - 71% INSTI, 29% PI-based regimens

Why did high concentrations of VRC01 fail to suppress rebound viremia?

- ***Suboptimal antiviral effect?***
  - Evidence of selection
  - A5340 participant who stopped ART early had 2 log drop in plasma viremia (50,000→500 c/ml)
    - Similar to VRC601: 1.1-1.8 log drop in viremics
- ***Neutralization resistance to VRC01?***
  - Pre-existent and/or rapidly acquired resistance likely relevant to VRC01 efficacy
- ***Different activity of VRC01 in vivo?***
  - *In vitro* neutralization measures not predictive of full range of antiviral activity needed to inhibit virus *in vivo*

Lynch Sci Transl Med 2016; Trkola PLoS Pathog 2015