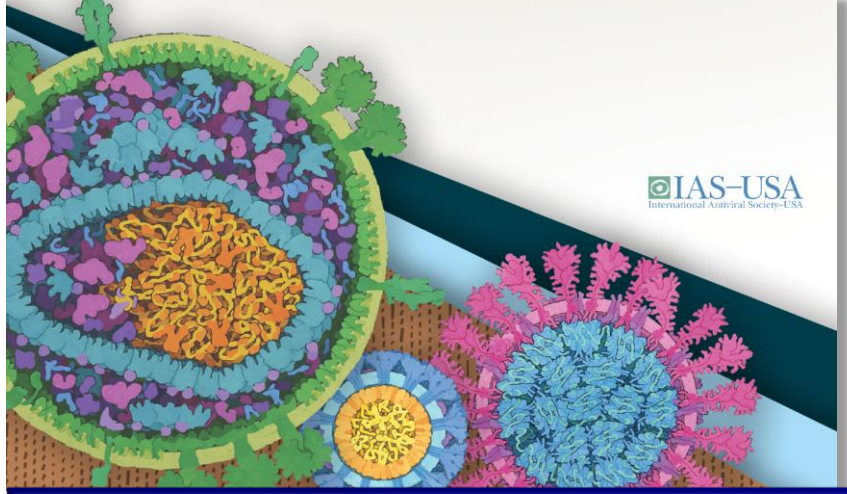


CROI 2023: 18TH Top Ten for Clinicians

Josep M Llibre, MD, PhD

Malalties Infeccioses, Fundació Lluita contra les Infeccions

Hospital Universitari Germans Trias, Badalona, Barcelona

@DrBike7

FLS SCIENCE

Top Ten CROI 2023. Take homes.

1. **TRUNCATE-TB: 8-week TB Tx?... Not yet.**

TRUNCATE-TB: Trial Regimens (Rif sensitive TB, mild-moderate)

8w: ±Extension (to 12weeks) if persistent clinical disease (symptoms and + smear)

Standard Treatment	24w	Rifampicin 10mg/kg	Isoniazid	Pyrazinamide (first 8w)	Ethambutol (first 8w)	
hRIF-LZD	8w	↑ Rifampicin 20-35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg
hRIF-CFZ	8w	↑ Rifampicin 35 mg/kg	Isoniazid	Pyrazinamide	Ethambutol	Clofazimine 200mg
RPT-LZD	8w	Rifapentine 1200mg	Isoniazid	Pyrazinamide	Levofloxacin 1000mg	Linezolid 600mg
BDQ-LZD	8w	Bedaquiline 400/200mg	Isoniazid	Pyrazinamide	Ethambutol	Linezolid 600mg

N Paton. CROI 2023, #113. NEJM 2023; DOI:10.1056/NEJMoa2212537

TRUNCATE-TB: Outcomes: treatment failure, relapse or death w96 (vs death, ongoing treatment, or active disease at week 96, main analysis, non-inf proven BDQ/LZD)

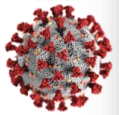
	24 weeks Standard Rx (N=181)	**8 weeks hRIF/LZD (N=184)**	**8 weeks BDQ/LZD (N=189)**
Unfavourable outcome – no (%)	7 (3.9%)	46 (25.0%)	26 (13.8%)
Treatment failure at switch to standard Rx	0 (0.0)	0 (0.0)	1 (0.5)
Treatment failure at end of treatment	0 (0.0)	0 (0.0)	1 (0.5)
Confirmed relapse	4 (2.2)	39 (21.2)	20 (10.6)
Un-confirmed relapse	0 (0.0)	0 (0.0)	3 (1.6)
Death by W96, possible TB-related cause	2 (1.1)	5 (2.7)	0 (0.0)
Did not attend W96, lacks cure at last attended visit	1 (0.6)	2 (1.1)	1 (0.5)
Unassessable outcome	6 (3.3)	29 (15.8)	16 (8.5)

SimpliciTB: 4BPaMZ did not meet non-inf vs standard 2RHZE/4RH in drug-sensitive TB: Faster time to culture negative, but high D/C due to toxicity.

M Cevik. CROI 2023; #109

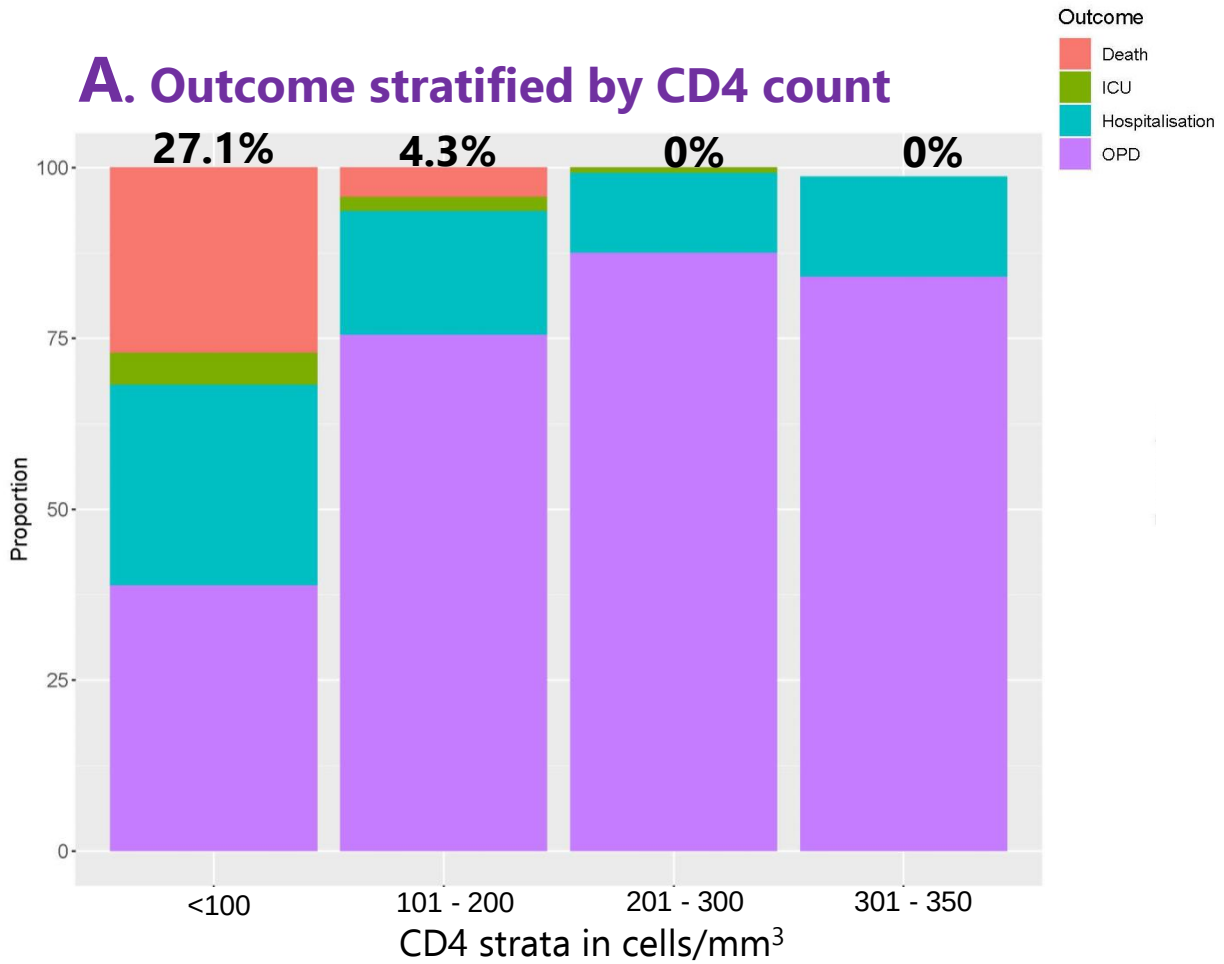
N Paton. CROI 2023, #113. NEJM 2023; DOI:10.1056/NEJMoa2212537

Top Ten CROI 2023. Take homes.



1. TRUNCATE-TB: 8-week TB Tx?... Not yet.
2. Severe necrotising MPOX in PWH with low CD4 counts
3. TOGETHER: Peg IFN λ in outpatient early “high-risk” COVID

MPOX outcome PWH stratified by CD4 count and VL



Legend: % mortality rate

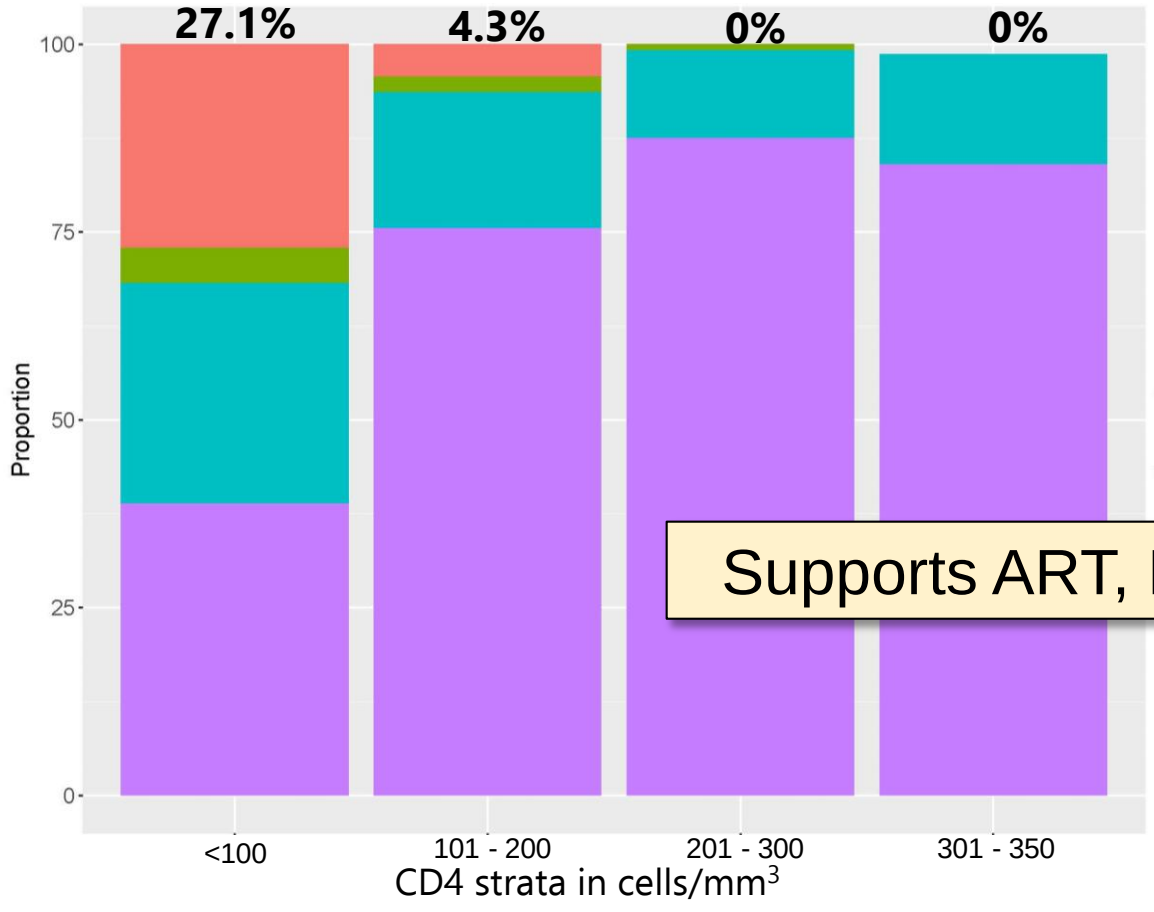
- **N=382** PWH (96% ♂) with CD4 <350 or CDC C.
- Multi-country (19) cohort. 91% diagnosed with HIV.
- **32% diagnosed but not on ART.**
- 7.2% vaccinated against MPOX.
- **Skin rush 96%, but anal lesions only 33%.**
- 8% concurrent OI (26% of those <100 CD4).
- All severe complications more common with low CD4.
- **IRIS 25%** (suspected), median 14 days.
- **0 deaths with CD4 >200 cells, or VL <200 c/mL, or MPOX vaccinated.**

- Should Disseminated severe MPOX disease **be classified as a new AIDS-defining OI?.**

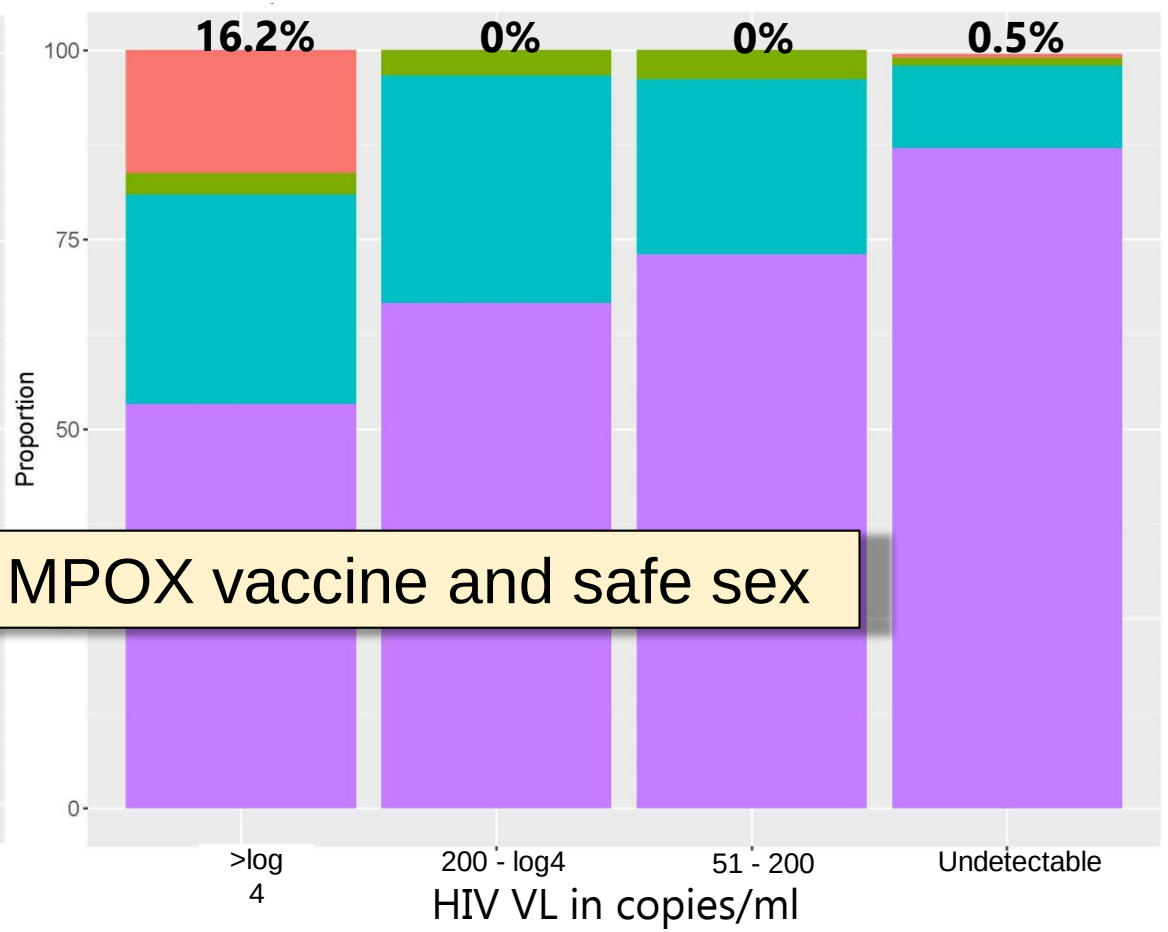
C Orkin. CROI 2023; #173. O Mitja. Lancet 2023; https://doi.org/10.1016/ S0140-6736(23)00273-8

MPOX outcome PWH stratified by CD4 count and VL

A. Outcome stratified by CD4 count



B. Outcome stratified by HIV Viral Load



Supports ART, MPOX vaccine and safe sex

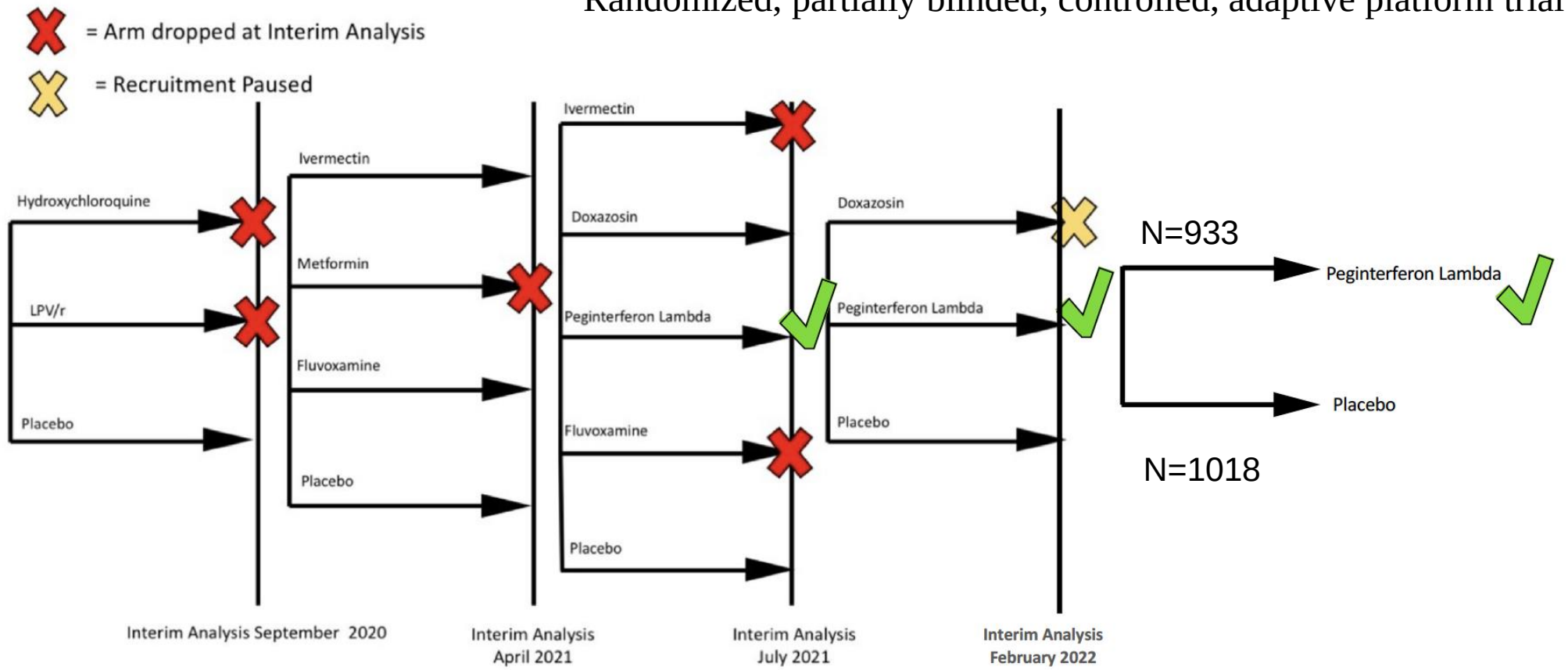
Legend: % mortality rate

Mortality CD4 <100	
VL <50	**VL > 4 log**
7%	**29.7%**

C Orkin. CROI 2023; #173. O Mitja. Lancet 2023; https://doi.org/10

together • COVID-19 : Intervention Timelines

Randomized, partially blinded, controlled, adaptive platform trial



- Peg IFN Lambda (single sc injection, 180 µg) vs placebo
- Early (<7 days) COVID in “high risk” (only 75%) individuals. 83% vaccinated, 41% Omicron.
- Primary composite outcome: hospitalization or emergency department visit within 28 days

JS Glenn CROI 2023; #167. G Reis. N Engl J Med 2023;388:518-28. DOI: 10.1056/NEJMoa2209760

TOGETHER: Peg IFN Lambda in early “high-risk” COVID

- AEs comparable to placebo.
- Significantly greater VL reduction,

  und. VL at day 7: 50.5% vs 33%.

Risk	# Days of Symptoms Before Treatment	Risk Reduction (95% BCI)	Probability of Superiority*
COVID-19-Related Hospitalization or ER retention	≤ 7 days	51% (24 - 70%)	>99.9%
	≤ 3 days	58% (21 - 80%)	99.6%

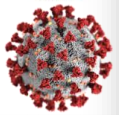
2.7% vs 5.6%

- **1ST major study in vaccinated early COVID with all variants**.
- **Feasible alternative** to Nirmatrelvir/r, REM IV or Molnupiravir (bNAbs inactive). No drug interactions, one dose and done.
- A study in “any” early viral respiratory tract infections?

- Driven by hospitalizations (74%)
- Deaths: 0.1% vs 0.4% (p=NS)
- Efficacy in unvaccinated: HR 0.11, 95%CI: 0.01-0.75

JS Glenn CROI 2023; #167. G Reis. N Engl J Med 2023;388:518-28. DOI: 10.1056/NEJMoa2209760

Top Ten CROI 2023. Take homes.



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4. DOXYVAC: PEP with Doxy and Meningo vaccine reduce STIs.
5. Good Doxy PK concentrations in genital tract (♂ ♀)

Oral Abstract Session-03 HIV AND STI PREVENTION: NEW TOOLS AND APPROACHES

Flex C (Level 2) 10:00 AM - 12:00 PM

118 *10:05*
MUCOSAL PHARMACOLOGY OF DOXYCYCLINE FOR BACTERIAL STI PREVENTION IN MEN AND WOMEN
Richard Haaland, Jeffrey Fountain, Chuong Dinh, Tiancheng Edwards, Amy Martin, Deborah Omoyege, Christopher Conway-Washington, Colleen Kelley, Walid Heneine

119 *10:13*
ANRS 174 DOXYVAC: AN OPEN-LABEL RANDOMIZED TRIAL TO PREVENT STIs IN MSM ON PrEP
Jean-Michel Molina, Beatrice Bercot, Lambert Assoumou, Algarte-Genin Michele, Emma Rubenstein, Gilles Pialoux, Christine Katlama, Laure Surgers, Cecile Bebear, Nicolas Dupin, Jean-Paul Viard, Juliette Pavie, Claudine Duvivier, Jade Ghosn, Dominique Costagliola
Research Group: ANRS 174 Doxyvac Group

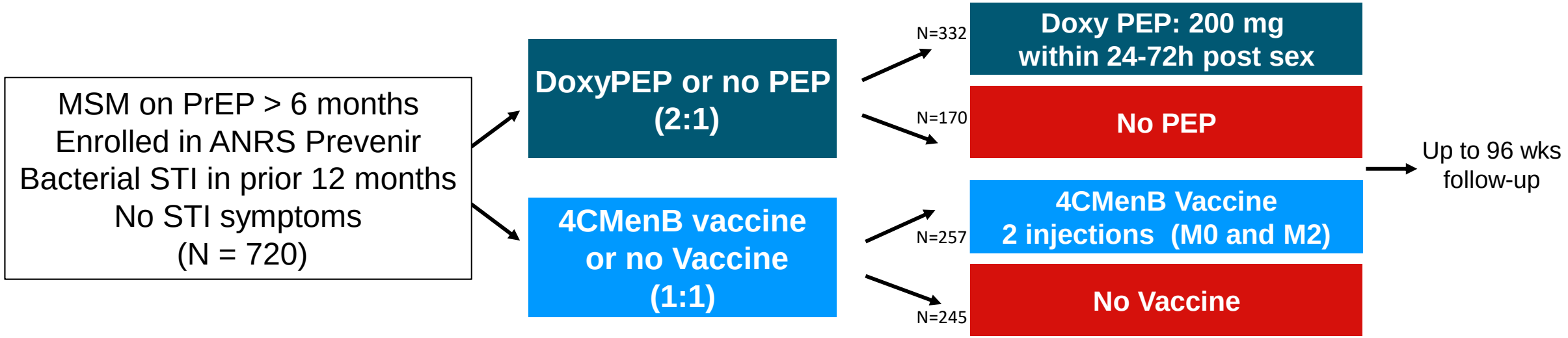
120 *10:21*
DOXYPEP & ANTIMICROBIAL RESISTANCE IN *N. GONORRHOEAE,* COMMENSAL NEISSERIA & *S. AUREUS*
Anne F. Luetkemeyer, Deborah Donnell, Julia C. Dombrowski, Stephanie Cohen, Cole Grabow, Clare Brown, Cheryl Malinksi, Sharon K. Martens, Alison Cohee, Veronica Viar, Phong Pham, Susan P. Buchbinder, Diane V. Havlir, Connie Celum, Olusegun O. Soge
Research Group: ANRS 174 Doxyvac Group

121 *10:29* LB
DOXYCYCLINE POSTEXPOSURE PROPHYLAXIS FOR PREVENTION OF STIs AMONG CISGENDER WOMEN
Jenell Stewart, Kevin Oware, Deborah Donnell, Lauren R. Violette, Josephine Odoyo, Caitlin W. Scoville, Olusegun O. Soge, Victor Omollo, Felix Mogaka, Fredricka A. Sesay, R. Scott McClelland, Elizabeth A. Bukusi, Jared M. Baeten
Research Group: the dPEP Kenya Study Team

122 *11:00* LB
POTENTIAL IMPACT AND EFFICIENCY OF DOXY-PEP AMONG PEOPLE WITH OR AT RISK OF HIV
Michael W. Traeger, Kenneth H. Mayer, Douglas S. Krakower, Sy Gitin, Samuel Jenness, Julia L. Marcus

ANRS 174 DOXYVAC. Study Design

- Multicenter, 2 x 2 factorial randomized, open-label, superiority, phase III trial (NCT04597424)

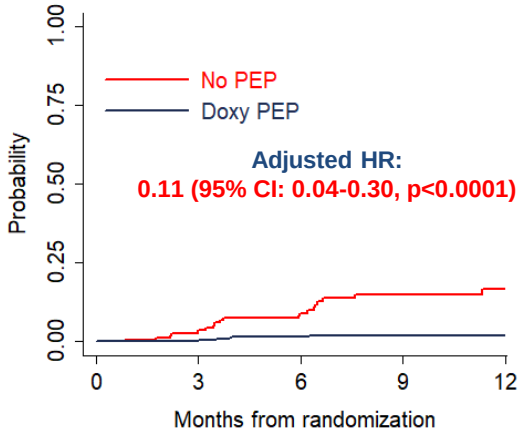


- Primary efficacy end-points: impact of DoxyPEP on time to a first episode of syphilis or chlamydia and impact of the 4CMenB vaccine on time to a first episode of *N. gonorrhoae* infection.
- September 2, 2022: **DSMB requested unblinded analysis** to offer Doxy PEP and 4CMenB vaccine to all.

JM Molina. CROI 2023; #119.

Doxycycline PEP. Time Time to First STI

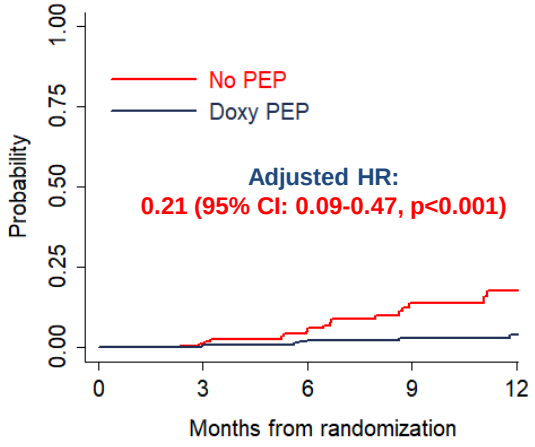
CT



at risk					
No PEP	170	139	105	58	30
Doxy PEP	332	274	223	147	86

26 subjects infected
21 in No PEP arm (incidence: 19.3/100 PY),
5 in Doxy PEP arm (incidence: 2.1/100 PY)

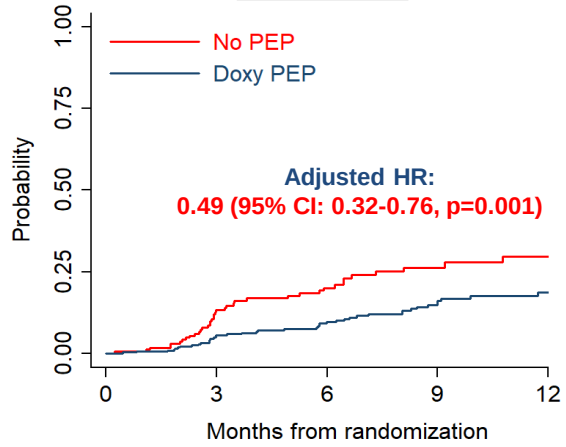
Syphilis



at risk					
No PEP	170	142	109	56	27
Doxy PEP	332	272	224	147	85

26 subjects infected
18 in No PEP arm (incidence: 16.3/100 PY),
8 in Doxy PEP arm (incidence: 3.4/100 PY)

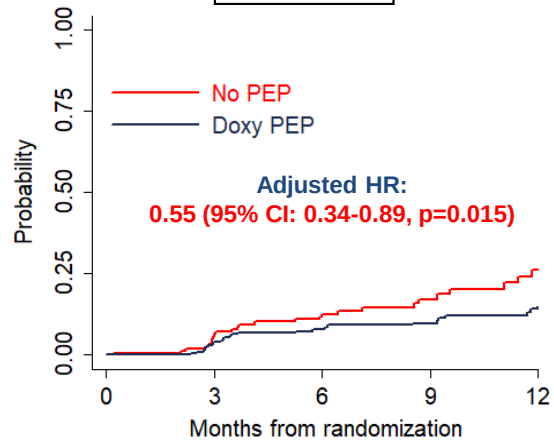
GC



at risk					
No PEP	170	125	90	47	20
Doxy PEP	332	259	201	128	66

84 subjects infected
40 in No PEP arm (incidence: 41.3/100 PY),
44 in Doxy PEP arm (incidence: 20.5/100 PY)

MG



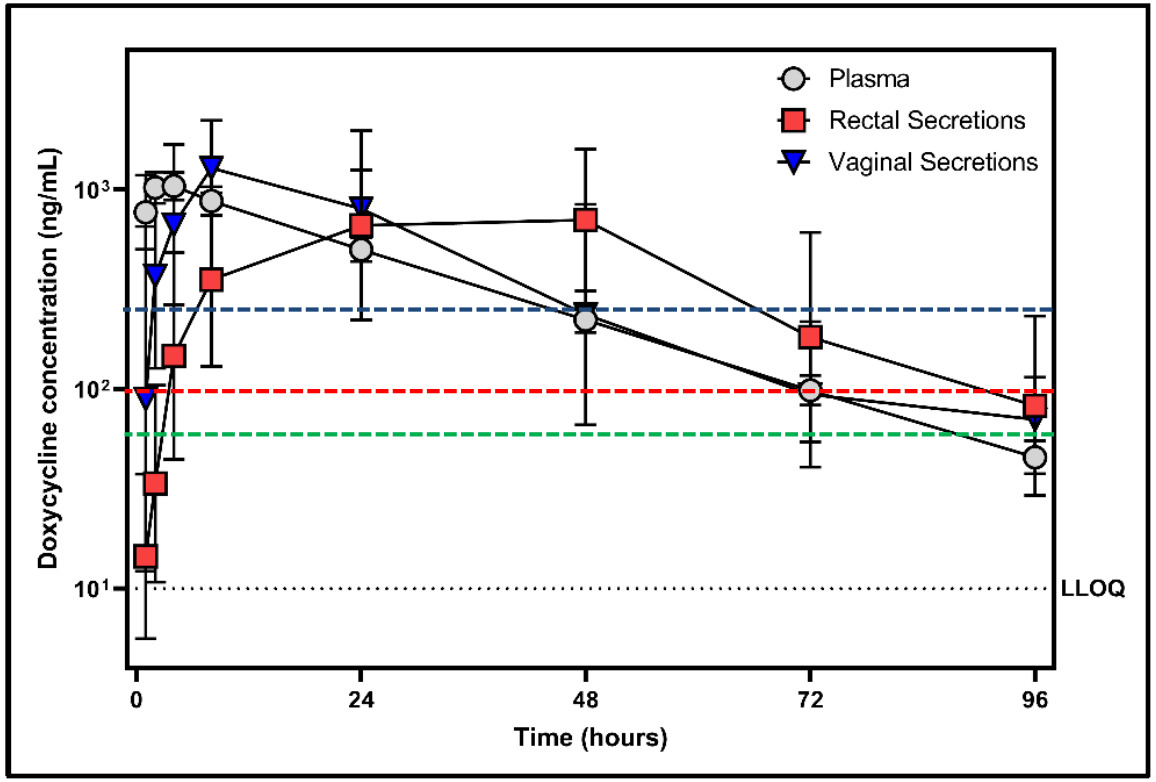
at risk					
No PEP	170	148	110	67	38
Doxy PEP	332	298	234	157	89

68 subjects infected
31 in No PEP arm (incidence: 29.4/100 PY),
37 in Doxy PEP arm (incidence: 16.8/100 PY)

- No clear impact on GC or CT resistance (limited number; monitor)
- **4CMenB Vaccine effect: Adjusted HR: 0.49 (95% CI: 0.27-0.88, p=0.016)**

JM Molina. CROI 2023; #119.

Good doxycicline PK in genital tract (worse *N gonorrhoeae*)



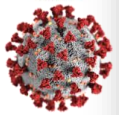
C trachomatis MIC_{90}= 64 ng/mL
T pallidum MIC_{90}= 100 ng/mL
N gonorrhoeae MIC = 250 ng/mL

- Good distribution of Doxy in genital tract ♂>♀.
- Remain > 4x *T pallidum* or *C Tracomatis* MIC up to 2 days after dose.
- Remain > 4x *N gonorrhoeae* MIC for < than 12 hours

	C_{24} (ng/g or ng/mL) [95% CI]	Fold above MIC		
		C trachomatis	***T pallidum***	***N gonorrhoeae***
Rectal Tissue	616 [495 – 766]	9x	6x	2x
Vaginal Tissue	301 [130 – 698]	4x	3x	1x
Cervical Tissue	430 [220 – 840]	6x	4x	1x
Urethral Secretions	1166 [598 – 2394]	18x	11x	4x

R Haaland. CROI 2023; #118

Top Ten CROI 2023. Take homes.



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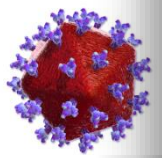
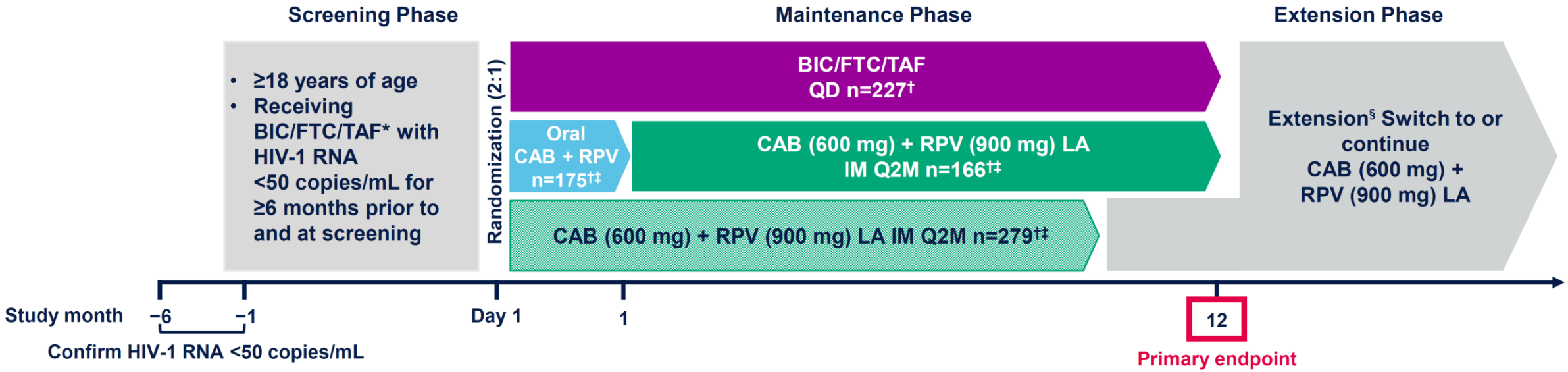


6. SOLAR: CAB + RPV LA non-inf to BIC/F/TAF in switch… with caveats
7. Low LA CAB RPV trough concentrations Q8W: clinical implications?
8. D2EFT: DTG + DRV/c superior to DRV/r + 2 NRTIs in 1ST line NNRTI VF
9. ENV DRMs confer high-level resistance to INSTIs without IN DRMs
10. Ultra-LA ISL implants fully protect NHP against SHIV: feasible!

SOLAR Study Design

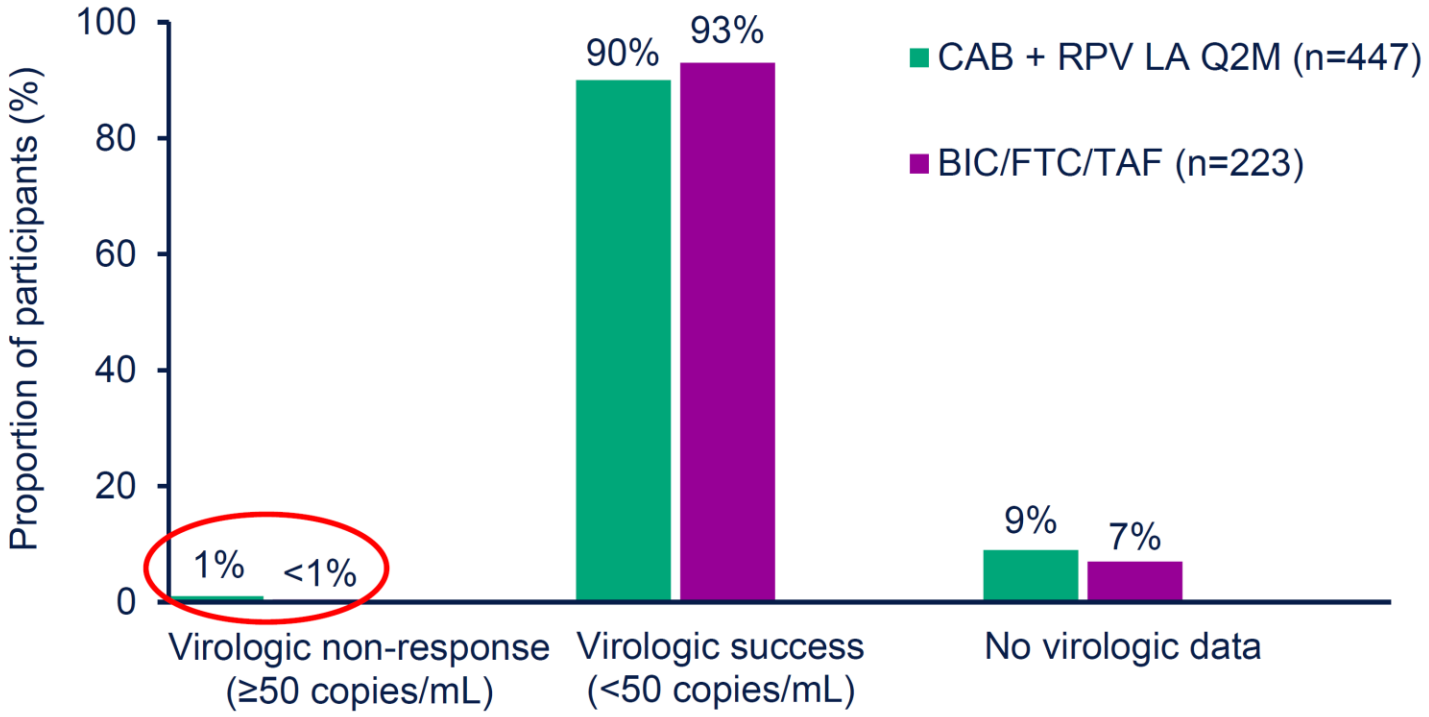
Phase 3b, Randomized (2:1), Open-Label, Active-Controlled, Multicenter, Parallel-Group, Noninferiority Study

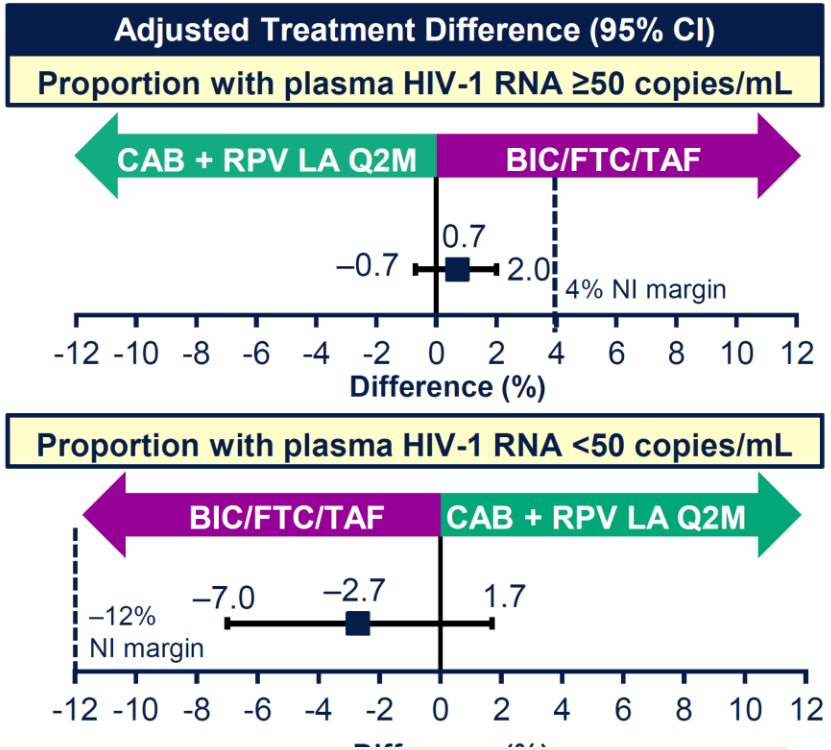


*A single prior INI regimen is allowed if BIC/FTC/TAF is a second-line regimen 6 months prior to screening. Any prior change in regimen, defined as a change of a single drug or multiple drugs simultaneously, must have occurred due to tolerability/safety, access to medications, or convenience/simplification, and must not have been done for treatment failure (HIV-1 RNA ≥400 copies/mL).
†n values are based on the safety population.
‡Participants randomized to the LA arm were offered an optional OLI; the decision was determined by the participants following informed consent discussions with the investigator.
§The extension phase will continue study treatment until CAB LA and RPV LA are either locally approved and commercially available, the participant no longer derives clinical benefit, the participant meets a protocol-defined reason for discontinuation, or until development of either CAB LA or RPV LA is terminated. Visits will continue to occur Q2M.
IM, intramuscular; LA, long-acting; OD, once daily; OLI, oral lead-in; Q2M, every 2 months.

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

Virologic Outcomes at Month 12 (mITT-E Population)





Drug-related A /F/TAF): 20% vs 0.9% (excluding ISR), p<0.001

≥3 AE drug-related: 8% vs 0% (6,5% ISR, 1.5% non-ISR), p <0.001

ading to withdrawal: 4.5% vs 0% (2.5% ISR, 2.0 non-ISR), p=0.001

No differences ir composition measurements (#146)

0.7% vs 1.5% in ATLAS-2M*

Confirmed VF: 3 (0.7%) vs 0, all selected resistance: 3/3 NNRTI DRMs, 2/3 IN DRMs (1 failed IN amplification). Months 3, 6, 11. None high BMI (1 BMI 30.5), no subtype A (one AE), no archived NNRTI DRMs at baseline; 1/3 IN G140G/R at baseline.

* ET Overton. Lancet 2020; 396: 1994–2005

Ramgopal et al. CROI 2023; Virtual and Seattle, WA. Oral presentation 191.

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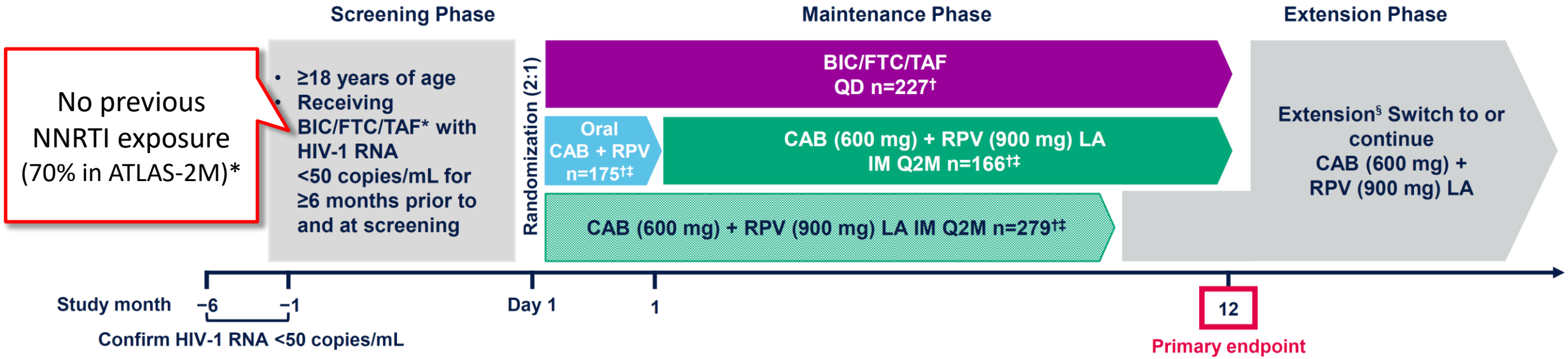
Phase 3b, Randomized (2:1), Open-Label, Active-Controlled, Multicenter, Parallel-Group, Noninferiority Study



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CAB RPV LA Q8w Trough concentrations

Drug trough concentrations		At 1 month (n=58)	At 3 months (n=56)
CAB	**Trough < 1120 ng/mL**, n (%)	**35 (60)**	**43 (77)**
	Median trough, ng/mL (IQR)	**976 (706 – 1434)**	**701 (440 – 1087)**
	No lead-in (n=42)	*951 (681 – 1196)*	*625 (397 – 880)*
	Lead-in (n=16)	*1213 (908 – 1479)*	*1103 (689 – 1246)*
RPV	**Trough < 32 ng/mL**, n (%)	**16 (28)**	**15 (27)**
	Median trough, ng/mL (IQR)	**48 (29 – 66)**	**43 (32 – 55)**
	No oral rilpivirine before switch (n=25)	*47 (35 – 68)*	*44 (30 – 58)*
	Oral rilpivirine before switch (n=33)	*49 (29 – 62)*	*43 (32 – 53)*

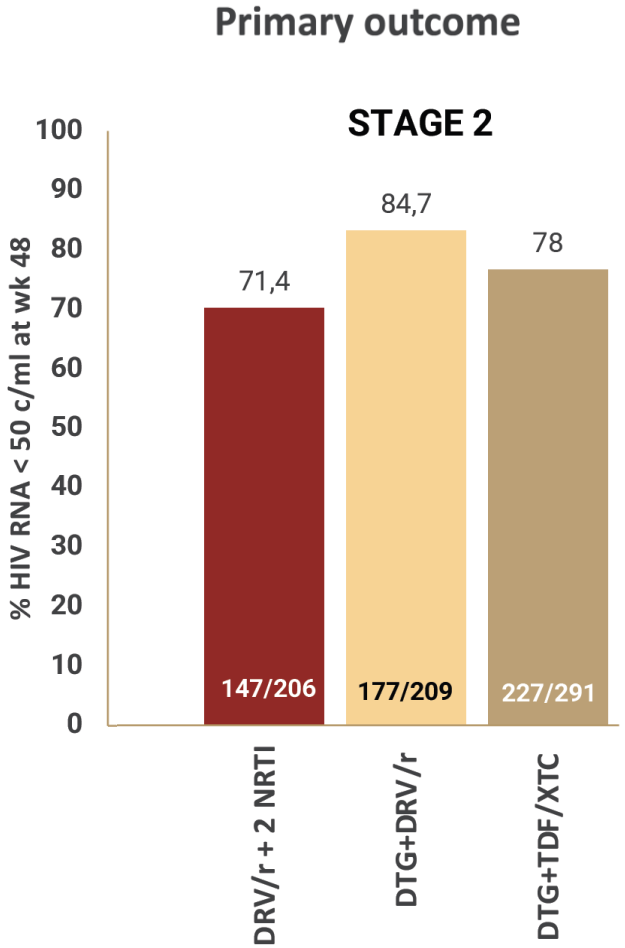
- Thresholds: 1st quartiles in FLAIR/ATLAS/ATLAS-2M pooled population[1]: CAB 1120 ng/mL, RPV 32 ng/mL
- Protein-adjusted 90% inhibitory concentrations ($PAIC_{90}$)[2]:
  - $PAIC_{90}$: CAB 166 ng/mL, RPV 12 ng/mL
  - $4xPAIC_{90}$: CAB 664 ng/mL, RPV 48 ng/mL

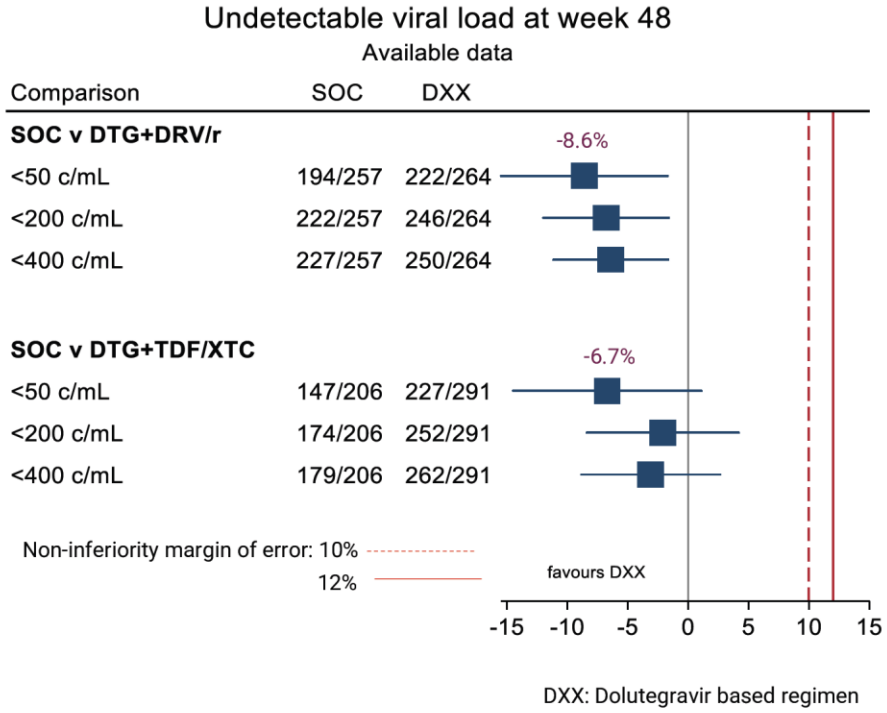
- **High intra- and inter-individual variability**
- **1 patient with VF at M1** and C_t CAB = 701 ng/mL, C_t RPV = 28 ng/mL (subtype AG, BMI 29.4)
- No oral lead-in and high BMI associated with low trough concentrations

[1]Cutrell et al, AIDS, 2021, [2]Margolis et al, LATTE, Lancet Infect. Dis., 2015

D2EFT: DTG + DRV/R in 1ST ART VF with NNRTI, 48 weeks

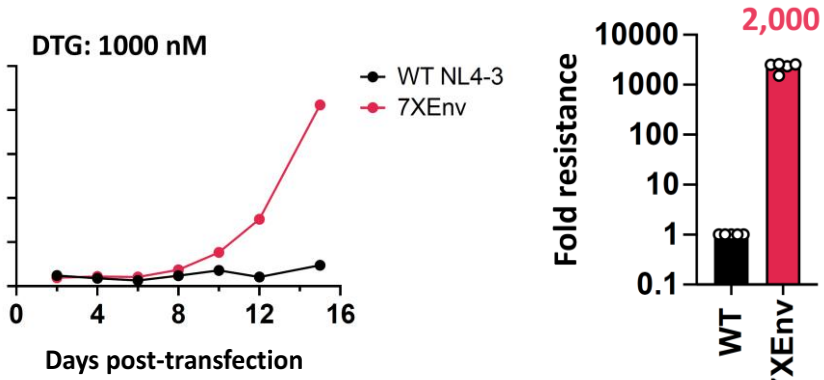
- Non-inf: ɗ 12%.
- VF 1ST NNRTI+2 NRTIs (83% EFV)
- n=831 (14 countries).
- Median CD4 206 cells
- 3 arms: DTG/DRV/r (272)
  DRV/r + 2 NRTIs (SOC, 263)
  DTG + TDF/XTC (296) New
- NRTIs with DRV/r:
  - 76% ZDV/3TC, 19% TDF/XTC
- Both DTG arms: greater CD4 ↑
  greater weight gain
- vs SOC: DTG + 2 NRTIs non-inf
  DTG + DRV/r superior

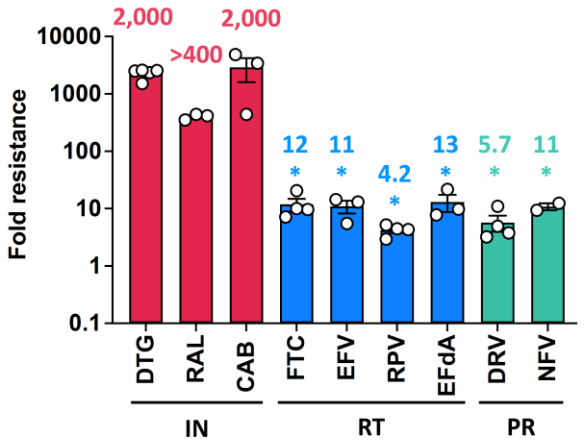




Gail Mattews. CROI 2023; #198.

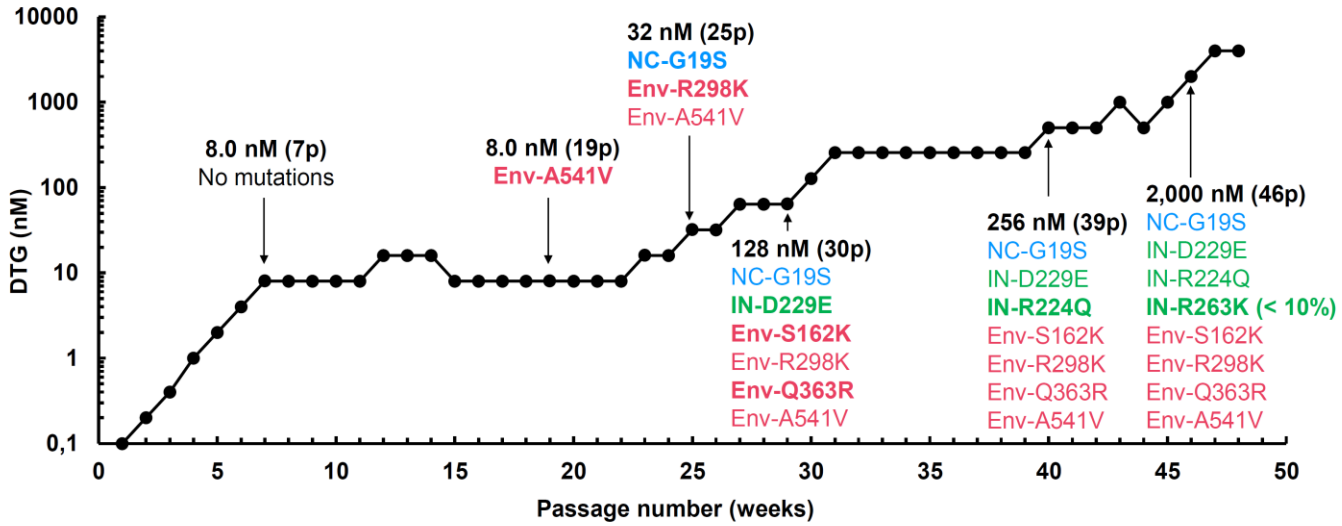
ENV DRMs confer high-level resistance to INSTIs in the absence of IN DRMs





Heavily Mutated Env Confers High-level Resistance to INSTIs and Broadly but Modestly Reduces Sensitivity to Other Classes of ARVs

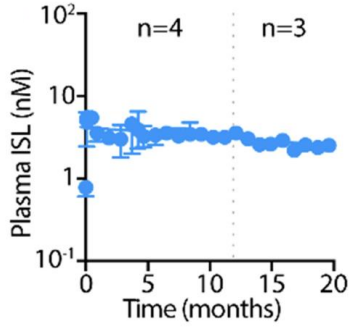
Long-Term Passaging of the NL4-3 Strain in the Presence of DTG

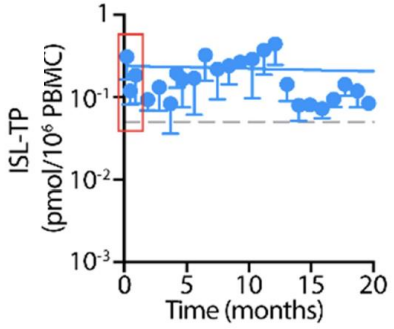


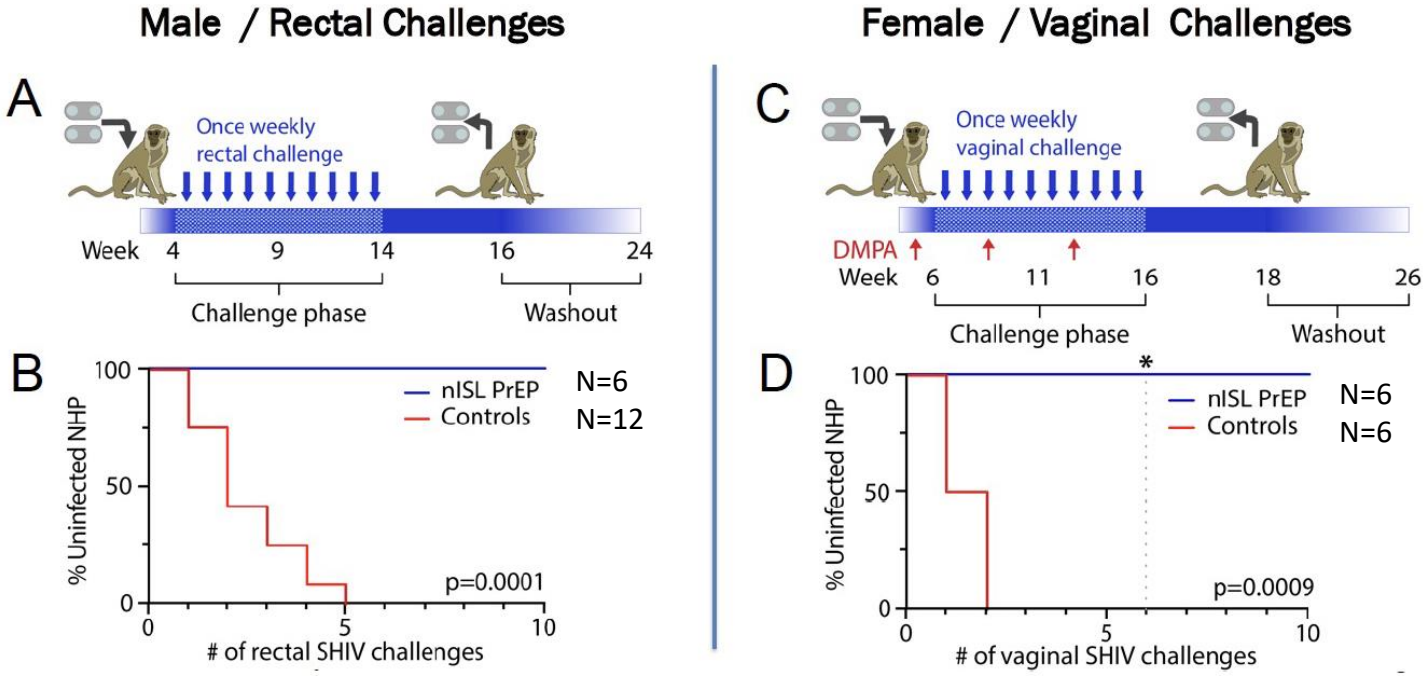
- NL4-3 sequentially acquired mutations in Env, Gag-NC and IN-coding regions.
- The selected IN mutations do not confer resistance to INSTIs.

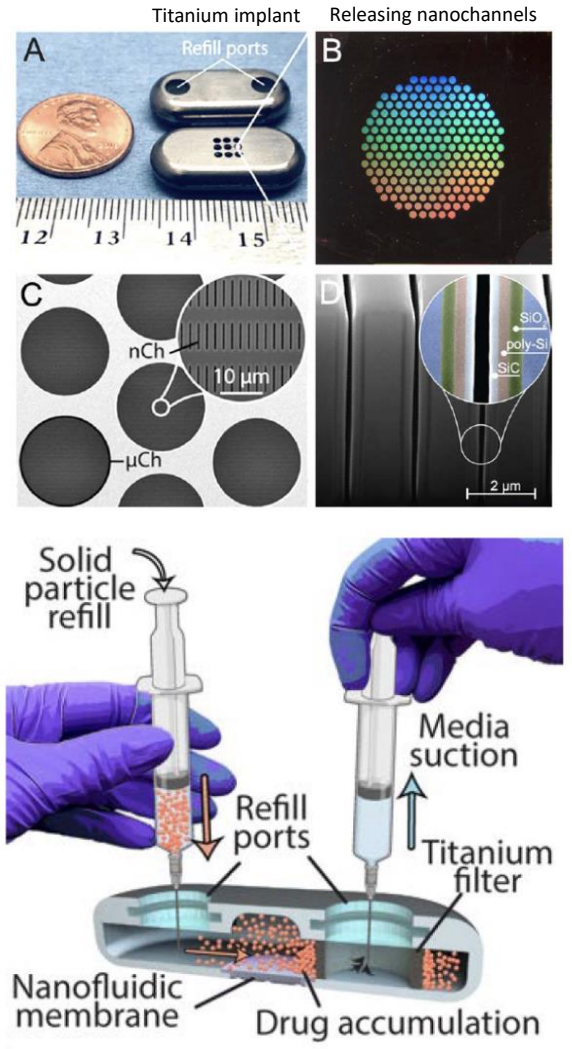
Y Hikichi. CROI 2023, #103.

Ultra LA refillable ISL implants protect 100% NHP against SHIV









A Grattoni. CROI 2023; #165. FP Pons-Faudoa. BioRxiv 2022; doi: https://doi.org/10.1101/2022.12.15.520646

Moltes gràcies