CROI 2022: Top Ten for Clinicians

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Enfermedades Infecciosas

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FUNDACIÓN LUCHA CONTRA EL SIDA Y LAS ENFERMEDADES INFECCIOSAS

FLS SCIENCE

948 Presentations
Abstract acceptance:
· **57%** overall
· **24%** for SARS-CoV-2

Oral presentations: 8 min!

CROI 2022: WHO ARE WE?

3333 registered attendees

86 countries represented

25% first-time CROI attendees

40% of registrants are from countries outside of the US

34% of accepted abstract presenting authors are from outside the US

Data as of February 12, 2022

Doing CROI summaries is a high-risk task…

TMP/SMX alone or + clindamycin or + caspofungin in mod/severe HIV/PJP

RCT, open-label, n=320

← Abstract as sent (**abstract book**) *vs* as presented (**poster**) →

Conclusion: Our results indicate that trimethoprim/sulfamethoxazole plus clindamycin or caspofungin may be more suitable for the management of HIV-positive patients with moderate to severe PCP compared with trimethoprim/sulfamethoxazole monotherapy.

Significantly higher rates of treatment response at week 4.

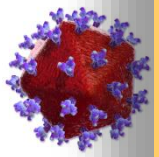
CONCLUSIONS

- Our results indicate that there are no significant statistical differences among the three studied treatment regimens in terms of antifungal effectiveness in HIV-infected patients with moderate to severe PCP. TMP-SMX monotherapy is a convenient, cheap, and effective therapeutic drug regimen to treat HIV-infected patients with moderate to severe PCP, and is an appropriate treatment strategy in resource-limited settings.

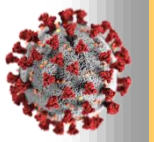
No significant differences of treatment response at week 4

Y Huang. CROI 2022, # 669.

Top Ten CROI 2022. Take homes.



1. ANCHOR RCT: Anal HSIL treatment halves cancer incidence.
2. TB-PRACTECAL RCT: New treatment for RIF-resistant pulmonary TBC, 24 w, all oral.
3. Innovative PrEP follow-up strategy: every 6 months.
4. IMPAACT 2010, new composite endpoint: DTG/FTC/TAF best trade-off for pregnant WLH.
5. LA ART currently has a HIV resistance cost.
6. ACTG 5324 (InMIND): DTG ± MVC intensification fails to improve NP performance.
7. Higher current risk MI in PWH vs PWoH, US

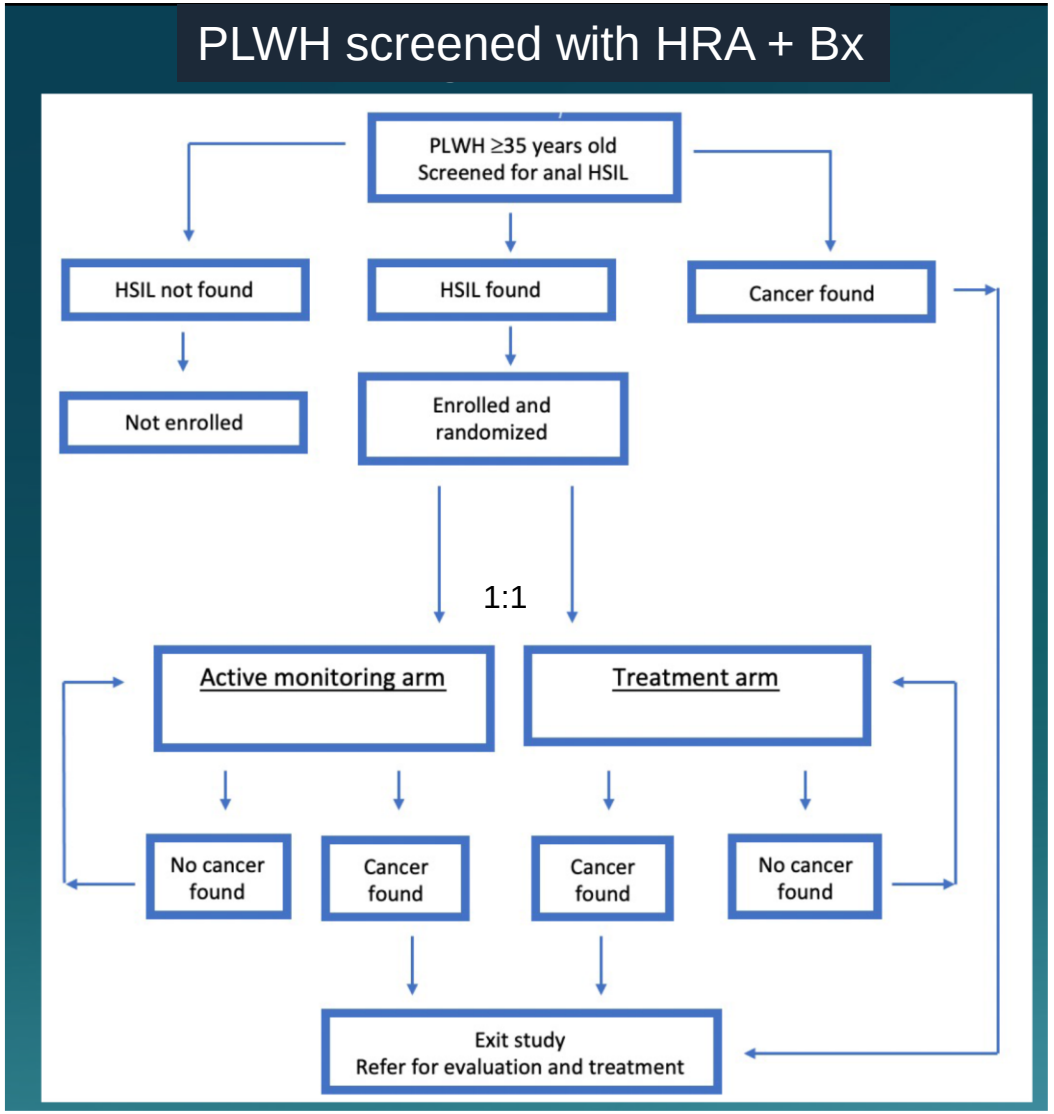


8. SARS-CoV-2 infectiousness with natural & breakthought infections.
9. COMET-TAIL: Sotrovimab IM non-inf to IV in high-risk outpatient-COVID.
10. COVID booster vaccination highly effective regardless of immune status.

ANCHOR: treatment of HSIL reduces anal cancer incidence

- Out of 10,723 PLWH, **52% had HSIL (!)**. 17 individuals (**0.16%, 160/100,000**) Dx with anal cancer at BL (x20 cervical cancer).

- Open-label RCT, randomization stratified by nadir CD4 and lesion size: **Immediate treatment of HSIL** vs follow-up.
- N=4446 PLWH, 50% with nadir CD4 <200 cells. Baseline CD4 604 cells.
- All patients perform HRA (+ Bx if indicated) every 6 months (plus cytology; every 3 months if concern with cancer), all biopsied annually.
- **Active arm**: Treatment at the investigator's discretion: electrocautery ablation (92.9%), 6% infrared coagulation. If Bx=HSIL re-Tx at 8 weeks.

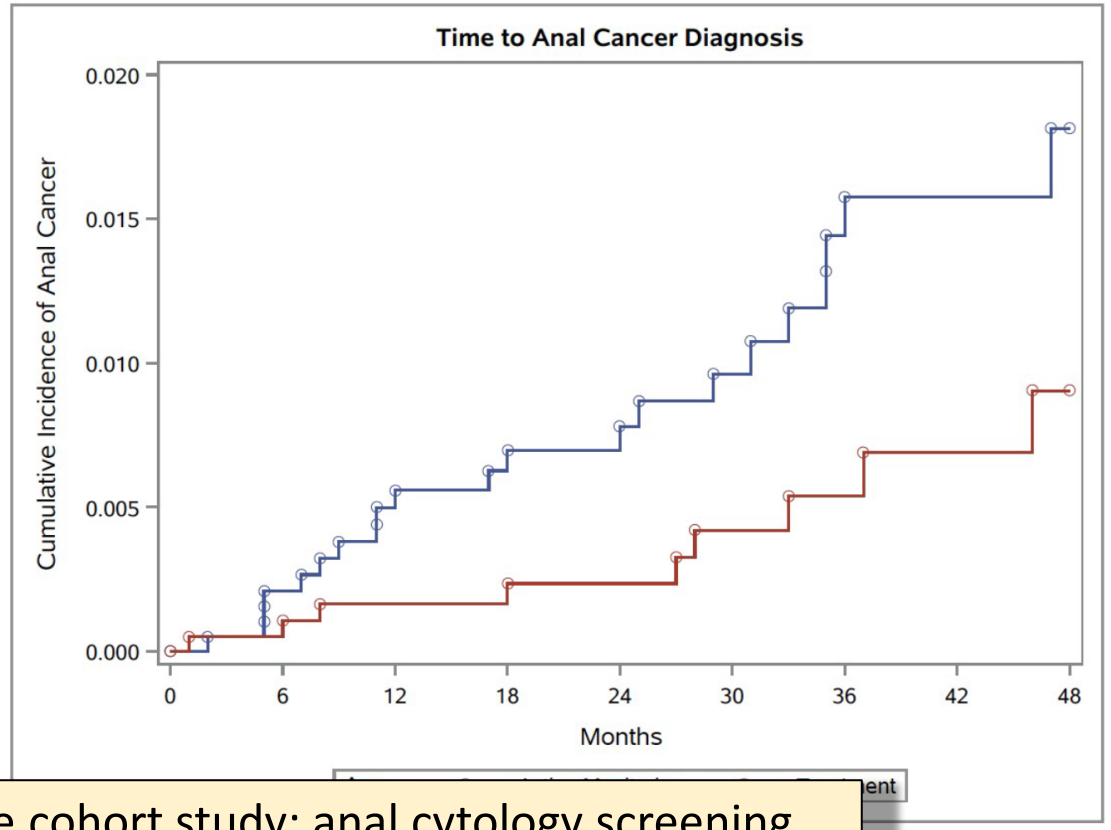


J Palefsky. vCROI 2022; #106.

ANCHOR: treatment of HSIL reduces anal cancer incidence

- **Median follow-up: 26 months.**
- **Cancer incidence**: 9 vs 21 cancers; treatment arm **173**/100,000 PY of follow-up, compared with **402**/100,000 PY in the AM arm; 57% reduction in anal cancer (95%CI 6% to 80%, P=.029)
- More study-related AEs.
- DSMB (predefined at 32 cancers) recommended stopping the study for efficacy (with 32 cancers): Recommendation made to treat all individuals in the monitoring arm

- **First RCT to show that treatment of anal HSIL reduces anal cancer incidence.**
  Many questions ahead, many subanalyses coming and how to implement this strategy?.



2019: A PS-adjusted prospective cohort study: anal cytology screening reduces anal cancer incidence (HR 0.17; 95% CI, 0.03–0.86).

Boris Revollo. Clinical Infectious Diseases 2020;71(2):390–9

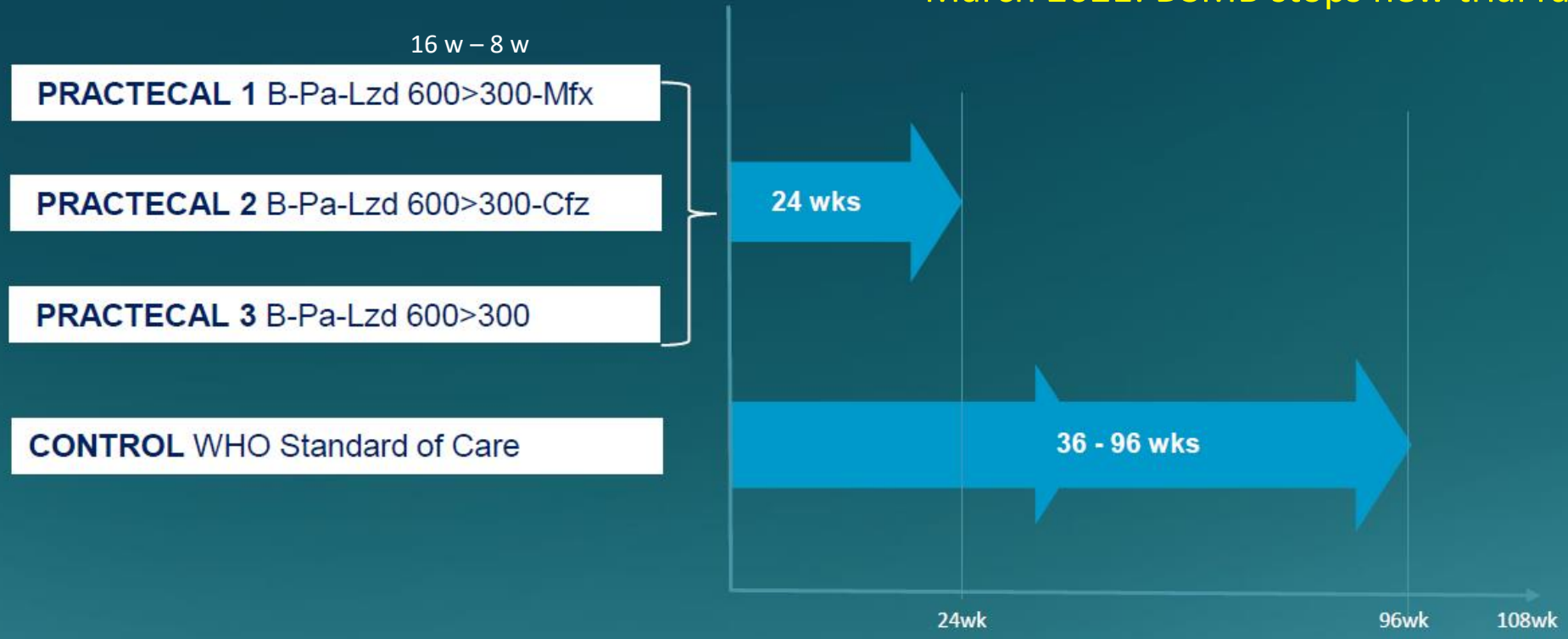
J Palefsky. vCROI 2022; #106.

BT Nyang'wa. vCROI 2022, #79.

Trial design Stage 1

A randomised, controlled, open-label, phase II-III trial to evaluate the safety and efficacy of drug regimens containing bedaquiline and pretomanid for the treatment of patients with pulmonary rifampicin-resistant tuberculosis (22% PLWH; quinolone resistant ≈30%)

March 2021: DSMB stops new trial randomisation



B - bedaquiline, Pa – pretomanid, Lzd - linezolid, Mfx – moxifloxacin, Cfz - clofazimine

Primary efficacy outcome (mITT)

Excluding participants who had sputum culture negative and/or rifampicin sensitive at inclusion.

	Practecal arm-2 BPaLC	Practecal arm-3 BPaL
Number in mITT population 2	64	60
(Tx failure or D/C, death, recurrence, los		
Number with no unfavourable outcome	52 (81.3%)	46 (76.7%)
Number with an unfavourable outcome	12 (18.8%)	14 (23.3%)
Risk difference (one-sided 98.3% confi	-29.7% (-∞ to -13.1%)	-25.2% (-∞ to -7.7%)
Non-inferiority p-value (non-inferiority	p<0.0001	p<0.0001
Superiority p-value	p<0.0001	p = 0.001
Risk ratio (one-side	0.71)	0.48 (-∞ to 0.85)
Deaths		0 (0%)
Early discontinuatic		8 (13.3%)
Adherence issu		2
Adverse event		5
Not meeting inc		1
Withdrew cons		0
Other		0
Treatment failure		0 (0%)
Lost to follow-up at		3 (5.0%)
Recurrence		3 (5.0%)

BPaLM 6 months:

- Superior to SOC
- Shorter (6 months)
- Safer
- Easier (lower pill count)

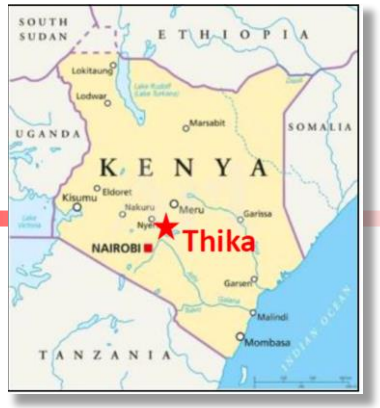
(not powered to compare among the 3 BPaL strategies)

Current standard of care

PRACTECAL Arm-1 (BPaLM)

Safe: Significantly lower number of Grade 3 or SAE

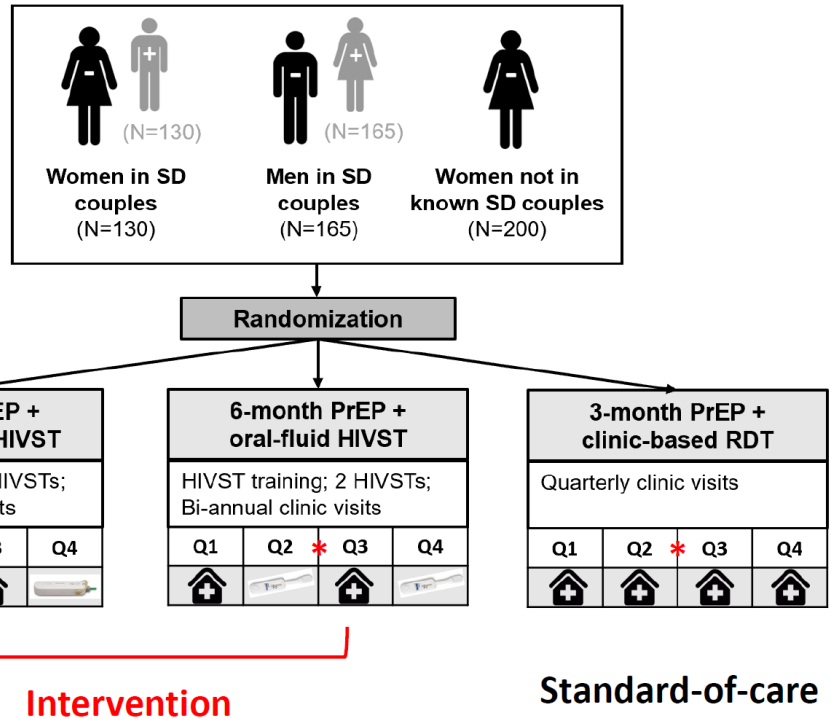
PrEP dispensing every 6 months with HIVST effective in serodifferent HTSX couples: a RCT.



- Barriers to PrEP implementation/3 months: costs, time spent at the visit, distance to the center.
- Innovative model: HIV Self testing and medication for 6 months.

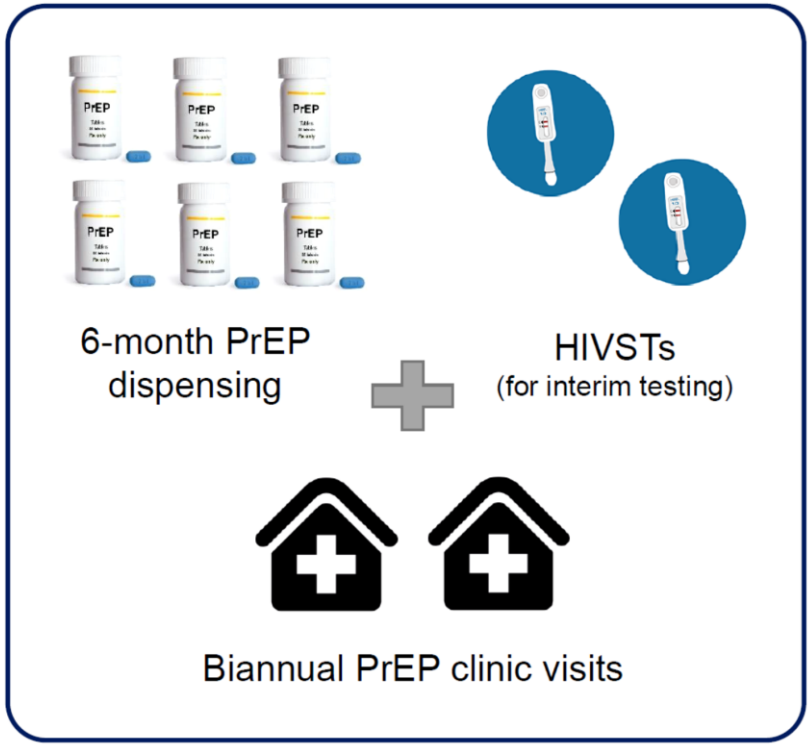
Inclusion criteria:

- ≥18 years
- Using PrEP 1 month



primary outcome measurement

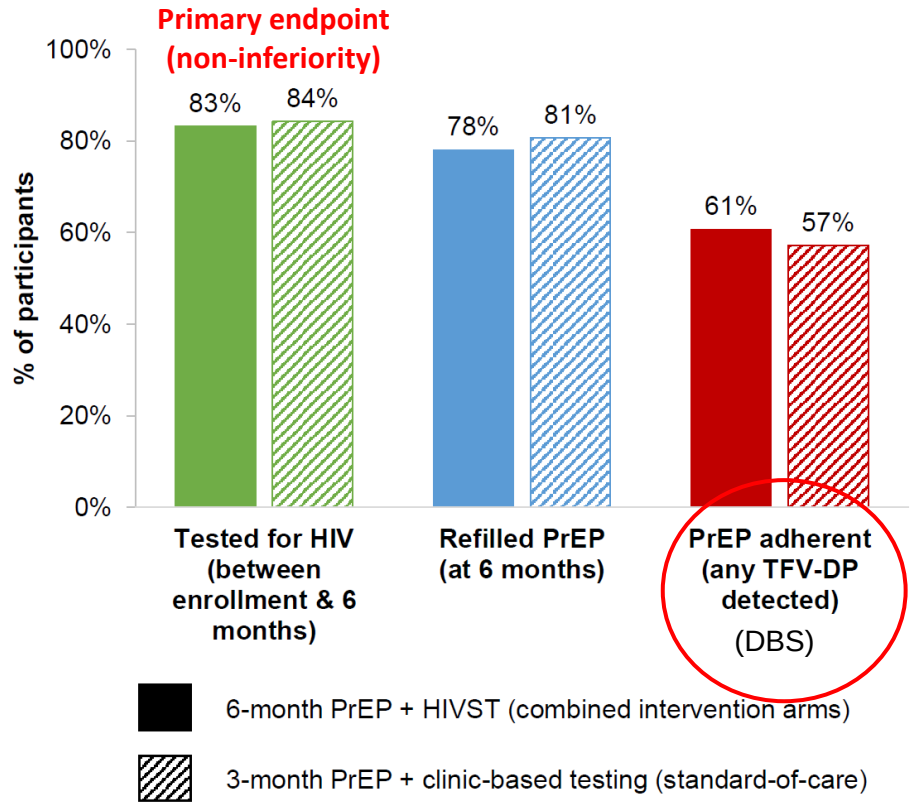
The intervention:

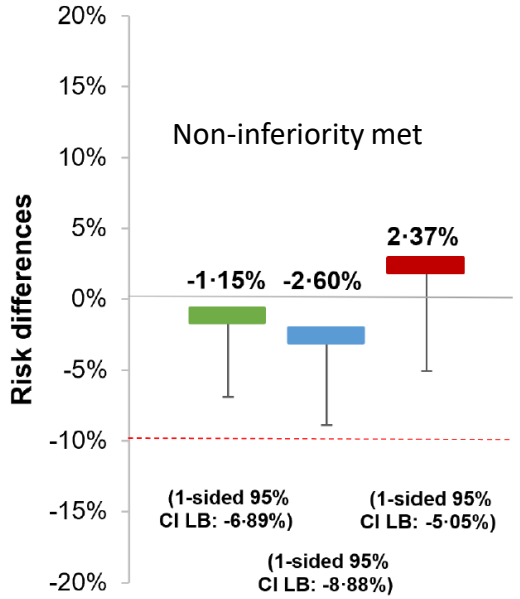


K Ngure. vCROI 2022; #146.

PrEP dispensing every 6 months with HIVST effective in serodifferent HTSX couples: a RCT.

Primary endpoint: All participants (n=495) at 6 months, both interventions together vs SOC

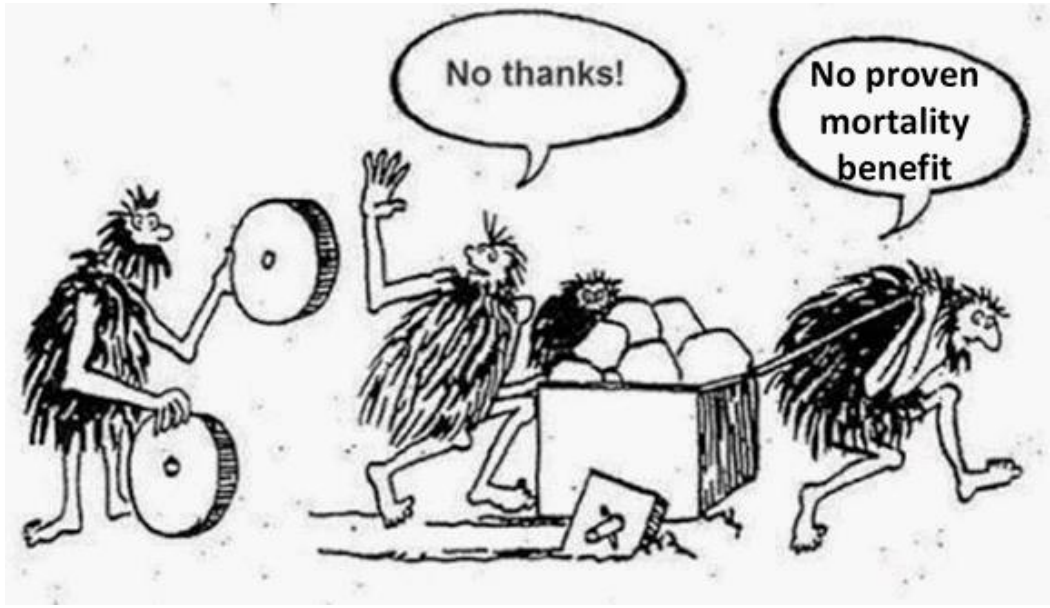


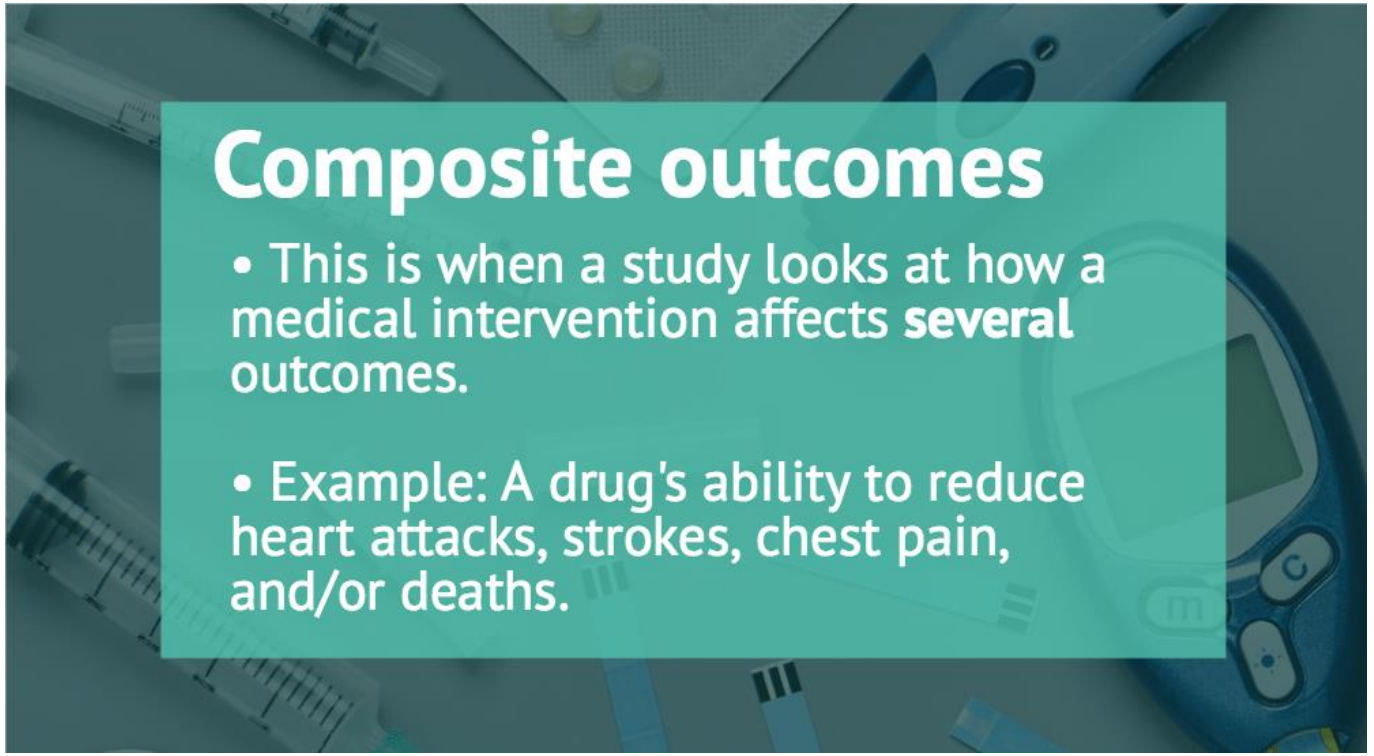


Six-month PrEP dispensing with HIVST for interim testing at three months reduced the number of PrEP clinic visits in half **without compromising HIV testing, retention, or adherence** at six months.
<u>Caveat:</u> Extrapolation to MSM in developed countries would need STI testing (and syphilis)

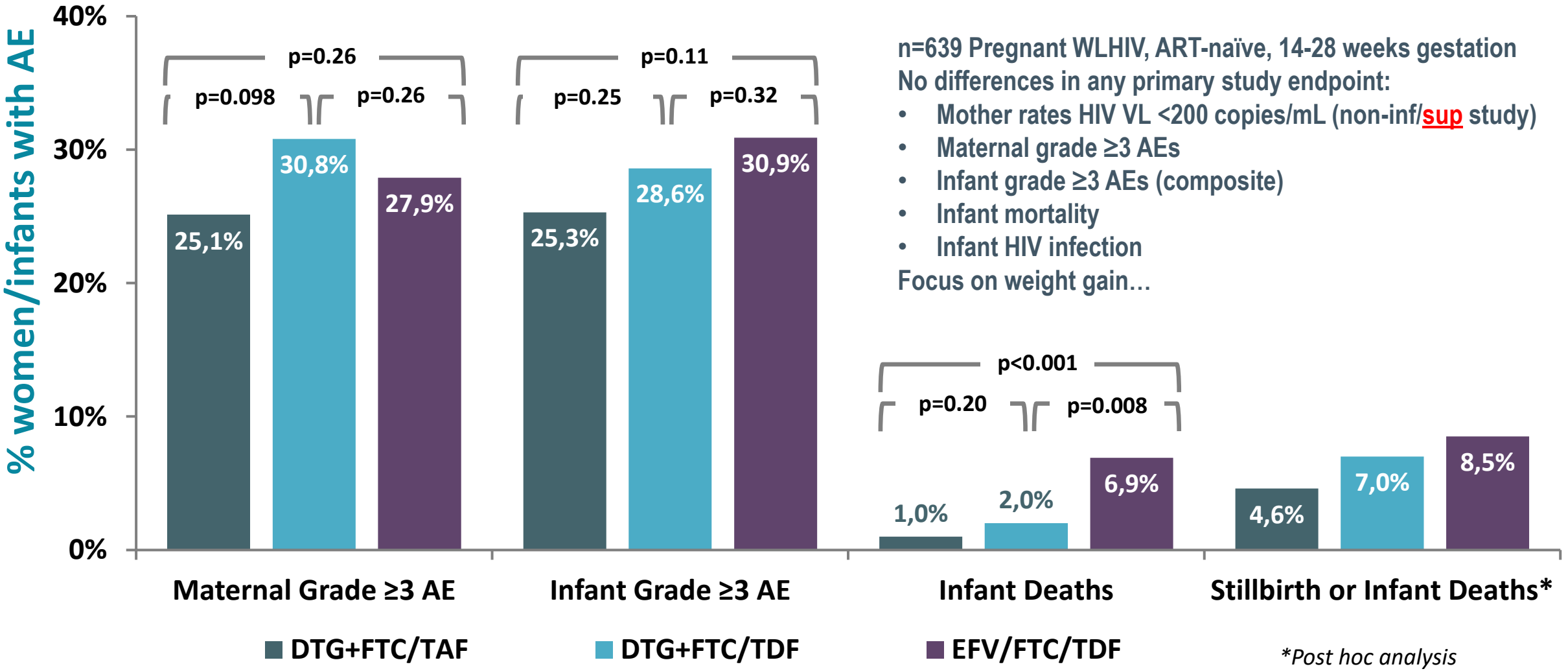
K Ngure. vCROI 2022; #146.

Choose the right study endpoint…





IMPAACT 2010. Primary endpoint: Maternal and Infant AEs Grade ≥3 Through 50 Weeks Postpartum. No significant differences



n=639 Pregnant WLHIV, ART-naïve, 14-28 weeks gestation

No differences in any primary study endpoint:

- Mother rates HIV VL <200 copies/mL (non-inf/sup study)
- Maternal grade ≥3 AEs
- Infant grade ≥3 AEs (composite)
- Infant mortality
- Infant HIV infection

Focus on weight gain…

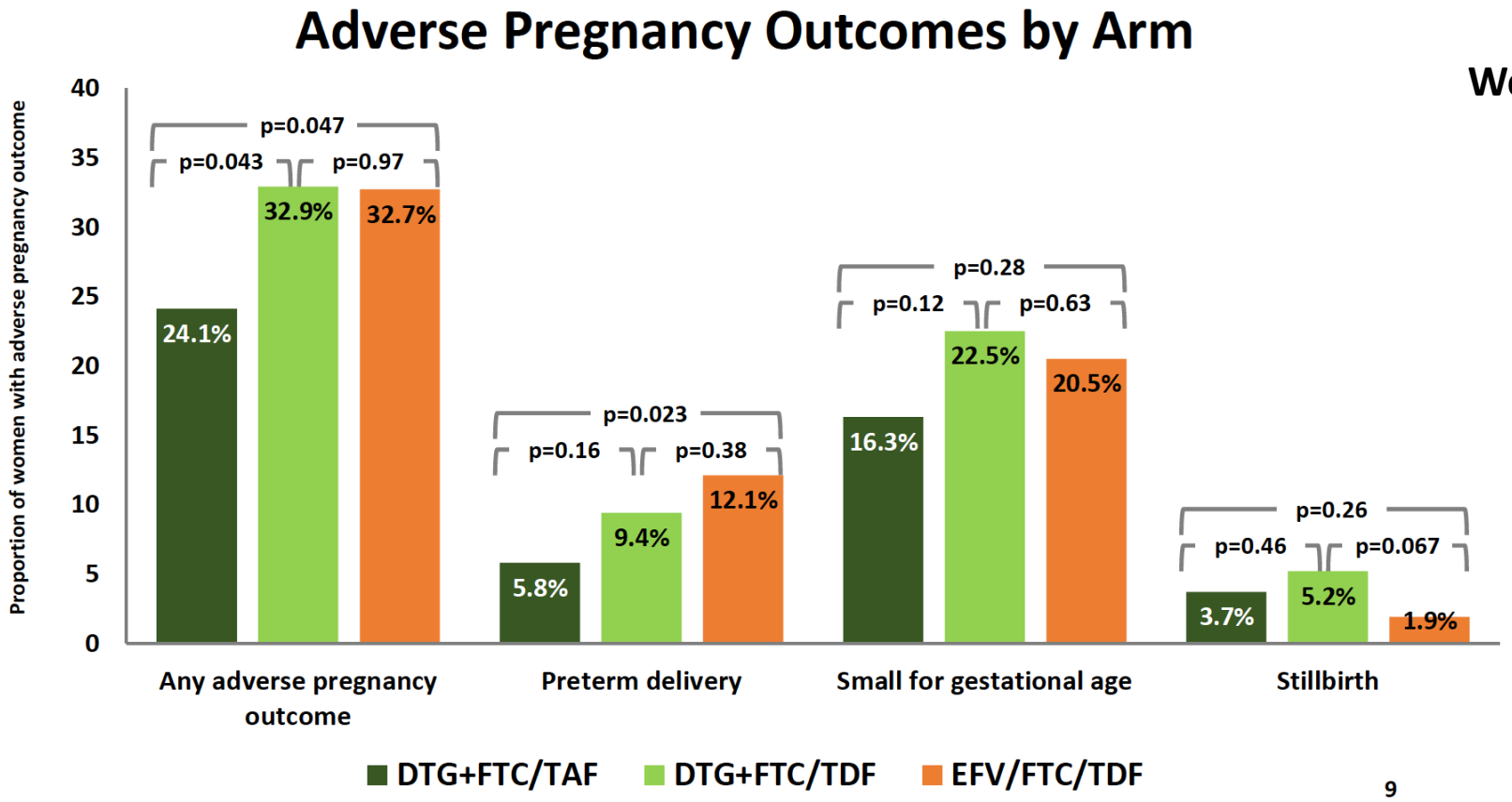
*Post hoc analysis

L Chinula. vCROI 2021; #177

IMPAACT 2010. n=639 Pregnant WLHIV, ART-naïve, 14-28 weeks gestation

Primary virological endpoint: Superiority VL < 200 c/mL at delivery DTG vs EFV: 97.5% vs 91% (dif 6.5%; 2.0%, 10.7%)

Primary safety endpoint:



Weight gain…

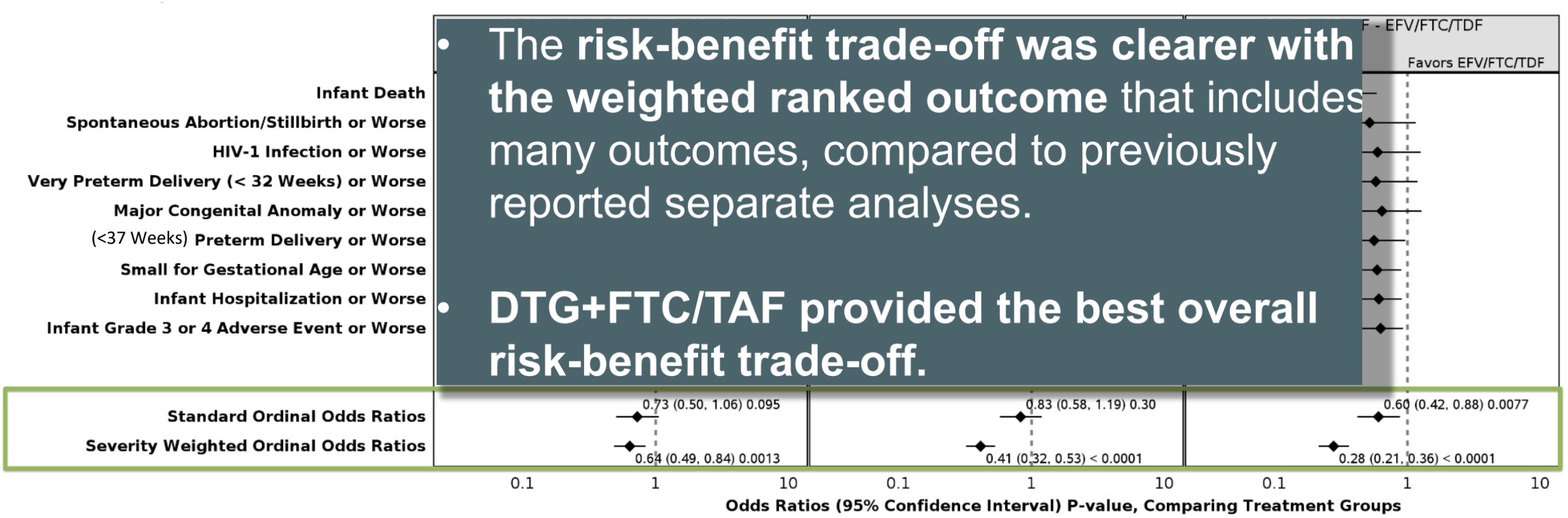
Notes: stillbirth was post-hoc analysis; and no spontaneous abortions occurred

L Chinula. vCROI 2020, Boston, US; #LB130

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

IMPAACT 2010. Composite endpoint (ad hoc) grouping all 9 mother-infant adverse outcomes

- **Ordinal logistic regression** was used to compare the odds of a more severe outcome across arms.
- **Weights to account for severity outcome** according to the study team's belief of their relative severity.

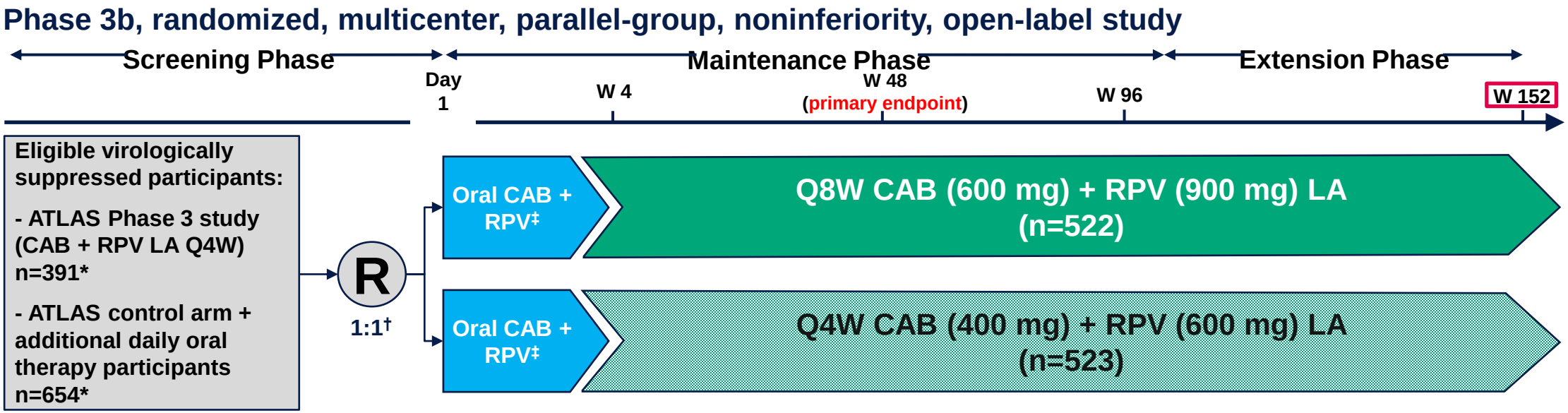


- The **risk-benefit trade-off was clearer with the weighted ranked outcome** that includes many outcomes, compared to previously reported separate analyses.
- **DTG+FTC/TAF provided the best overall risk-benefit trade-off.**

S Brummel. vCROI 2022; #679.

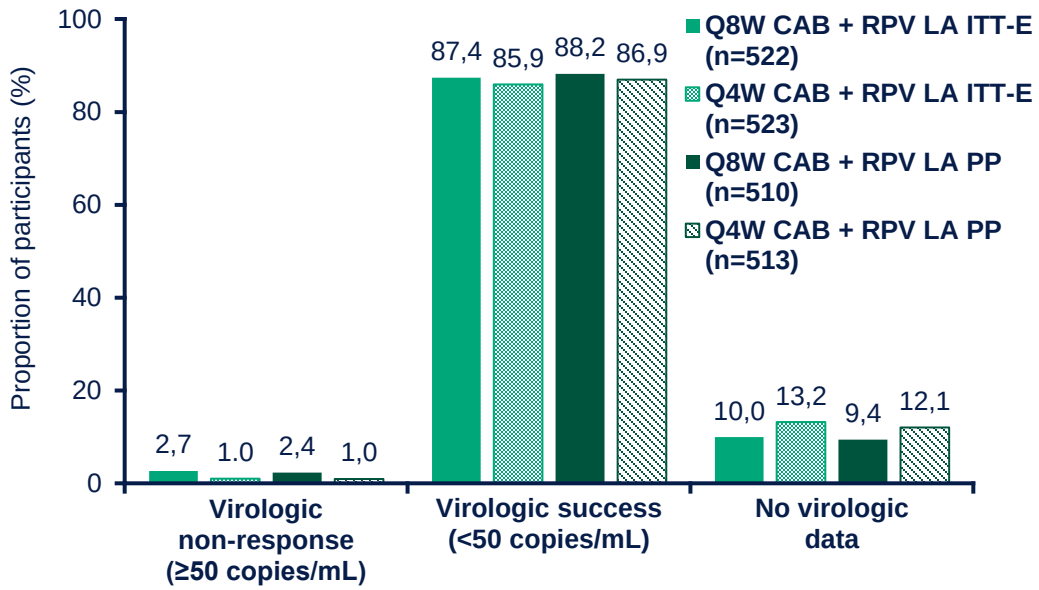
IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

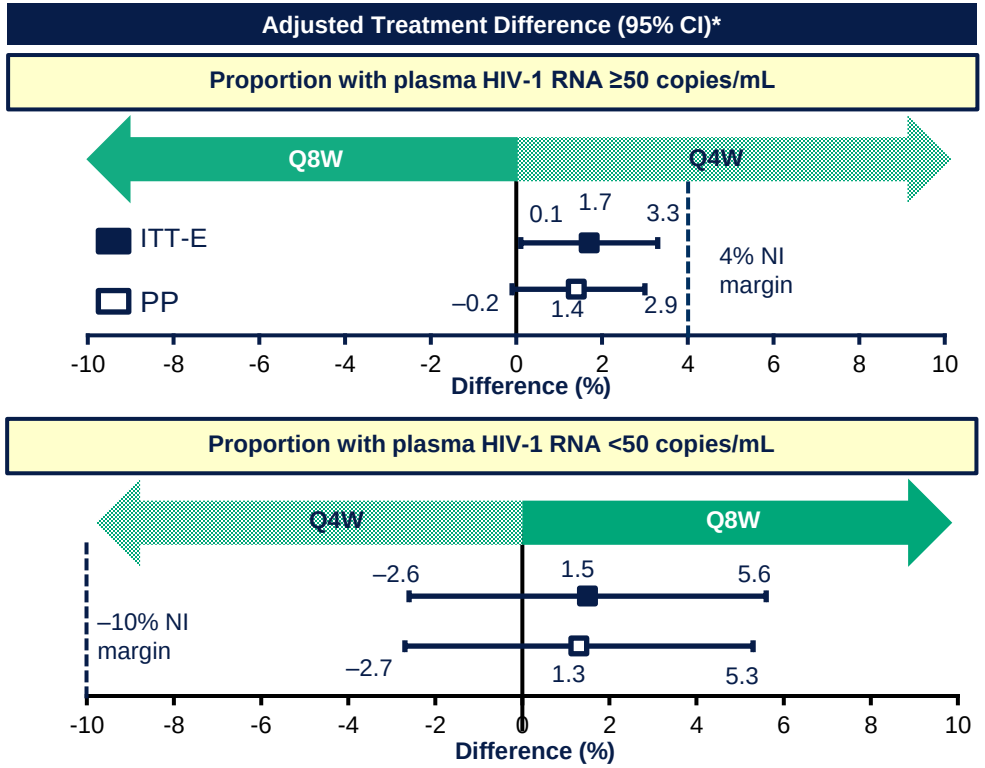
ATLAS-2M Study Design



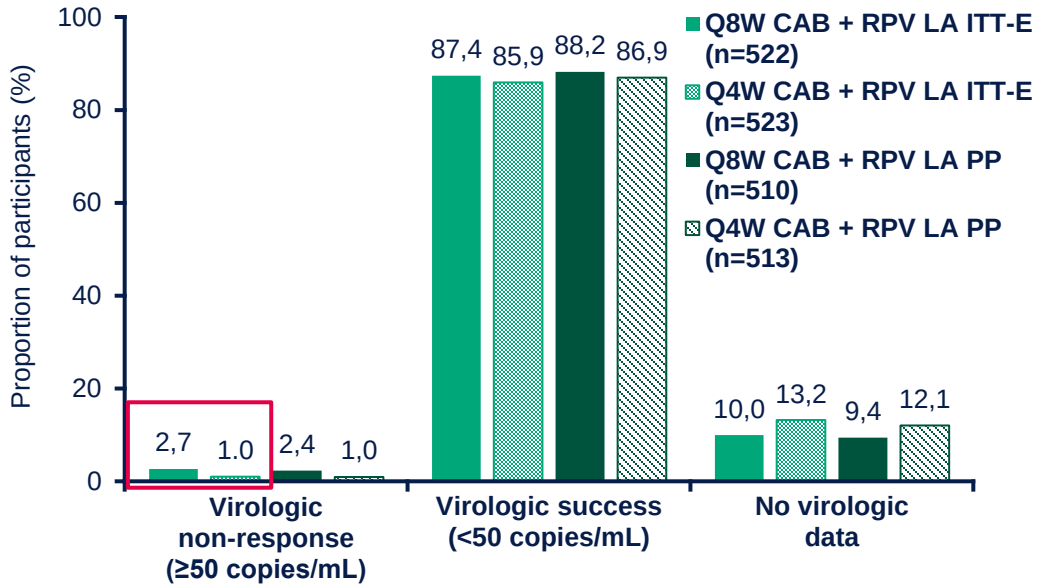
- Primary endpoint: HIV-1 RNA ≥50 c/mL at Wk 48 by FDA snapshot in ITT-E
- Secondary/other Wk 152 endpoints: plasma HIV-1 RNA ≥50 or <50 c/mL at Wk 152 by FDA snapshot in ITT-E, CVF incidence, viral resistance in patients with CVF, safety and tolerability, treatment satisfaction

Virologic Outcomes at Week 152





Virologic Outcomes at Week 152

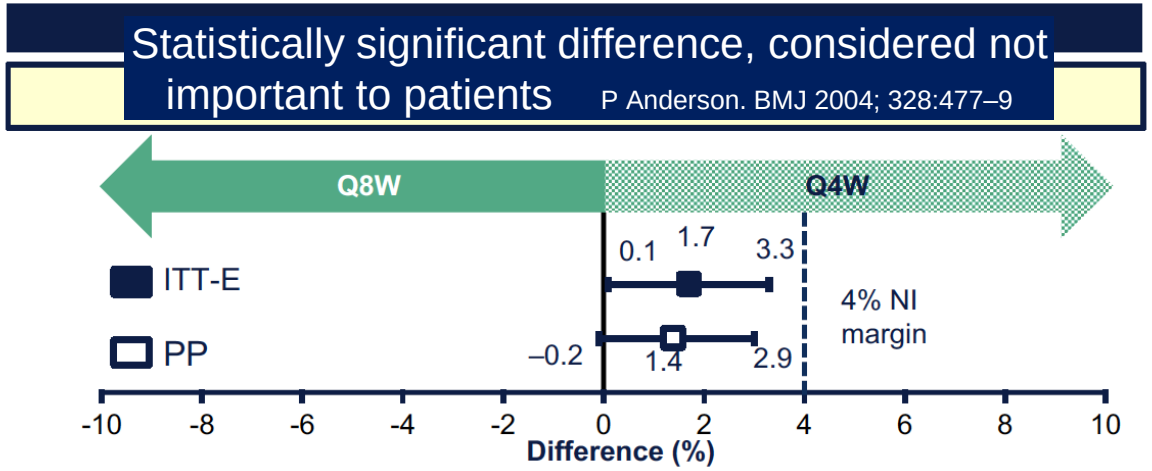


Through Wk 152, 13 participants had CVF:

- Q8W, n = 11 (+1)◆ (2,6%/2.8%)*
- Q4W, n = 2 (0,5%)*

* Participants reaching week 152 (excluding D/C for "other reasons" or AE/death

◆ An additional participant had a non-protocol-defined virologic failure at Week 48 (Q8W)



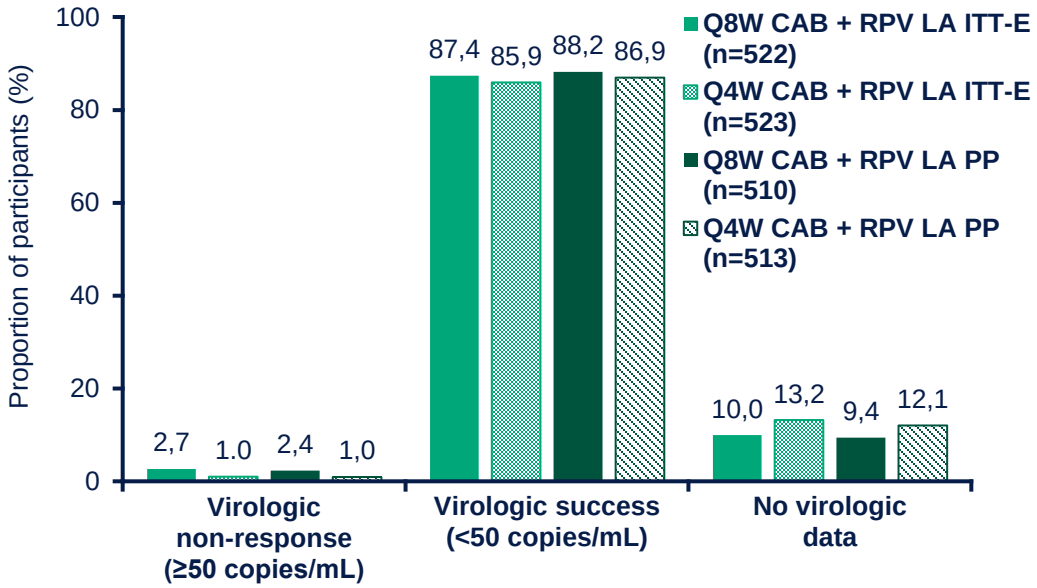
2 additional participants (both male, BMI <30 kg/m^2) in Q8W arm met CVF criteria after Wk 96 (Wk 112, 120).

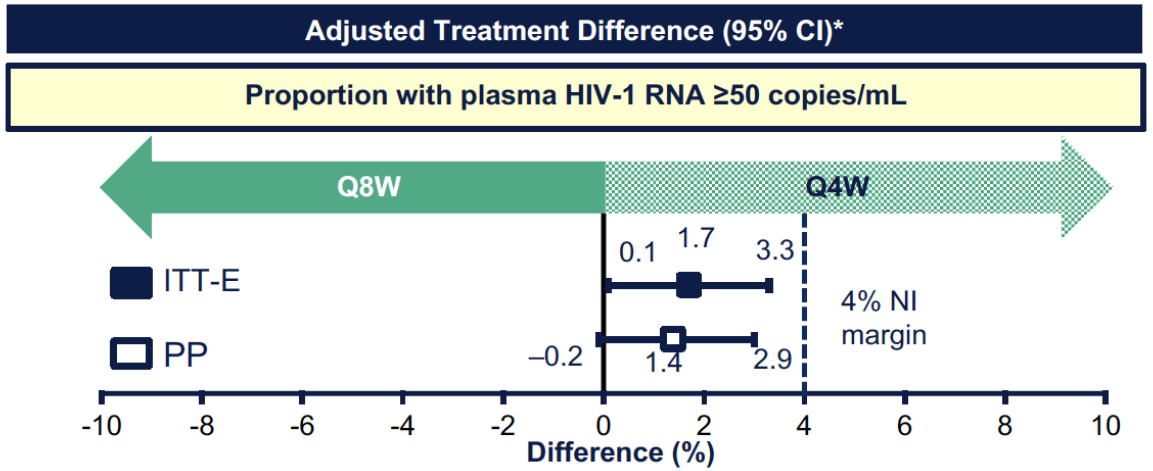
- At BL, neither had RAMs; participant with A6 subtype had L74I integrase polymorphism.
- None with injection >7 days late.

Country	Baseline	At Failure		
	HIV-1 Subtype	HIV-1 RNA (c/mL)	RPV RAMs	INI RAMs
Germany	B	24,221	E138A+ M230M/L	Q148R
Russia	A6*	59,467	E138A+ Y181Y/C	Q148R

Overton et al. CROI 2022; Virtual. Poster 479.

Virologic Outcomes at Week 152





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Most CVF:

- In the first 48 weeks.
- Have high-level NNRTI and INSTI resistance.
- Have plasma CAB and RPV plasma conc. within the range.
- Only 50% have ≥2 baseline factors (proviral RPV RAMs, HIV-1 subtype A6/A1, BMI ≥30 kg/m^2), which have been reported to be associated with increased risk of failure.
- L74I has greater *in vitro* fitness but does not explain the resistance pathway by itself **
- Nearly all CVF achieved viral resuppression on a bDRV regimen.

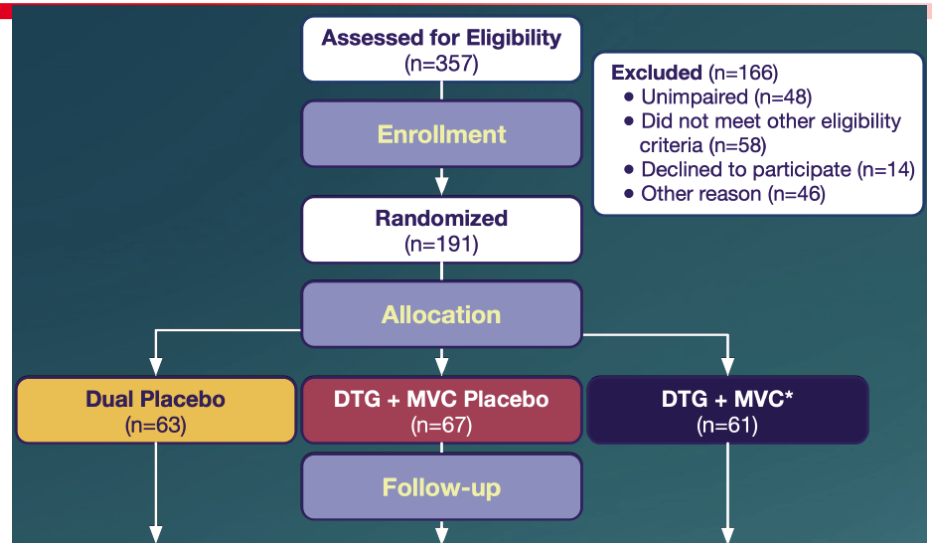
Overton et al. CROI 2022; Virtual. Poster 479.

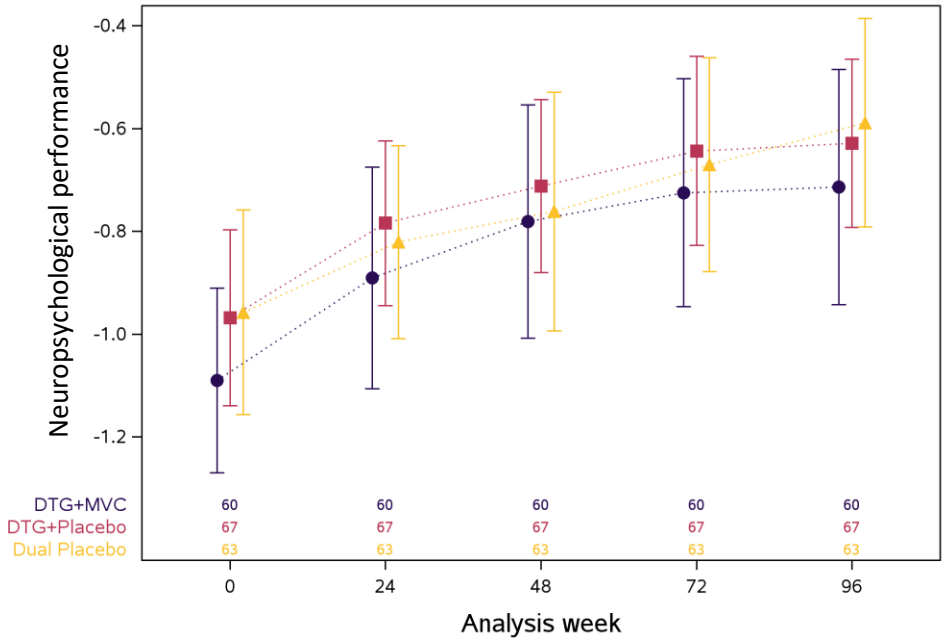
**ZX Hu. vCROI 2022; #506

ACTG 5324 (InMIND Trial): no benefit in NP performance

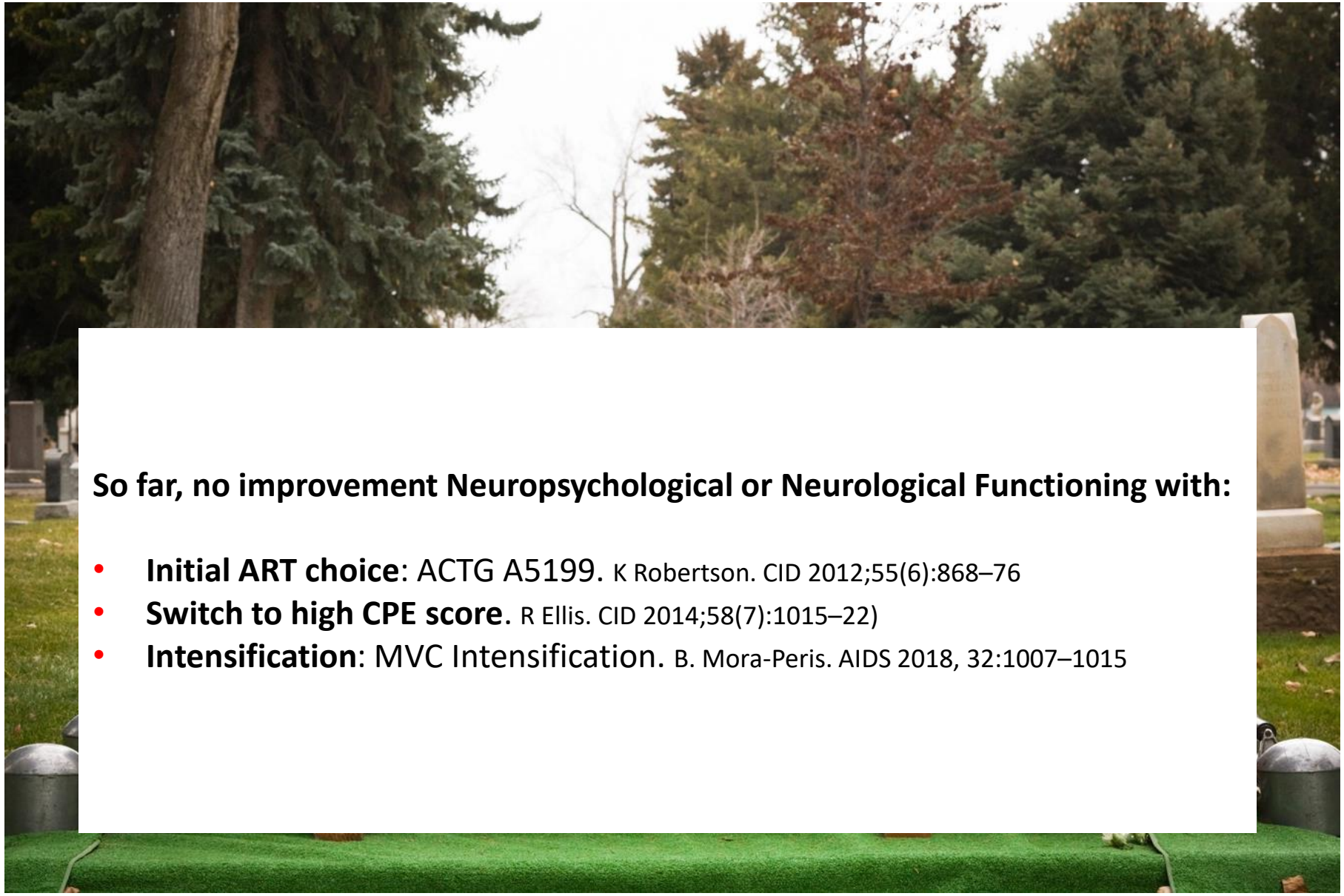
- 14 US and 11 Intl sites. Double-blind, pbo controlled, RCT.
- **191 PLWH with HIV RNA < 50 c/mL** and **unexplained lower performance in 2 domains** in 2 NP tests enrolled.
- More drug-related AEs DTG+MVC > DTG > Pbo.
- DTG + MVC (but not DTG) greater increases in CD4+ and CD8+ T-cells over time.
- Z-score and depression scores improved over time similarly in all 3 groups.

- **DTG ± MVC ART intensification FAILED to improve (NP) performance or depresion in PWH on suppressive ART with cognitive impairment.**





S Letendre. vCROI 2022; #133.



So far, no improvement Neuropsychological or Neurological Functioning with:

- **Initial ART choice**: ACTG A5199. K Robertson. CID 2012;55(6):868–76
- **Switch to high CPE score**. R Ellis. CID 2014;58(7):1015–22)
- **Intensification**: MVC Intensification. B. Mora-Peris. AIDS 2018, 32:1007–1015

Oral Abstract Session-3 MALIGNANCIES AND COMORBIDITIES: AN INCREASING BURDEN

9:45 AM MT - 11:45 AM MT

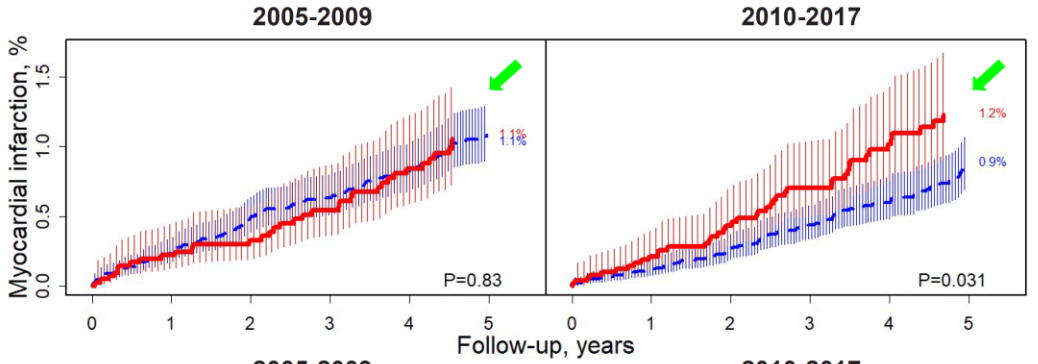
Higher risk MI in PWH vs PWoH (2010-2017)… but not before

- PS-matched Cohort 3:1 PWH (n=9401) vs PWoH (n=29418), with no history of CVD. Kaiser Permanente Northern California (KPNC) and Mass General Brigham, Boston (Partners).
- Follow-up until MI, death, loss-to-FU, 5 years after baseline, or administrative end of follow-up (2020).

RESULTS

- Despite higher CD4, use of INSTI and rates of virol suppression: **60% higher risk MI in PWH for years 2010-2017** (but not in 2005-2009).
- **Results appear to be driven by decrease in MI risk for PWoH, that was not seen for PWH** (maintain similar rates).
- Similar results in 3 sensitivity analyses.

Cumulative incidence of MI similar by HIV status in 2005-2009 but higher for PWH compared with PWoH in 2010-2017



2005-2009

HIV Status	KPNC PWH	KPNC PWoH	Partners PWH	Partners PWoH	Overall PWH	Overall PWoH
N	3,584	10,740	696	3,319	4,280	14,059
MI events	33	105	2	12	35	117
MI rate*	0.24	0.25	0.08	0.10	0.21	0.22

* per 100 person-years

2010-2017

HIV Status	KPNC PWH	KPNC PWoH	Partners PWH	Partners PWoH	Overall PWH	Overall PWoH
N	4,615	13,857	506	1,502	5,121	15,359
MI events	39	81	4	6	43	87
MI rate*	0.25	0.17	0.22	0.12	0.25	0.16

* per 100 person-years

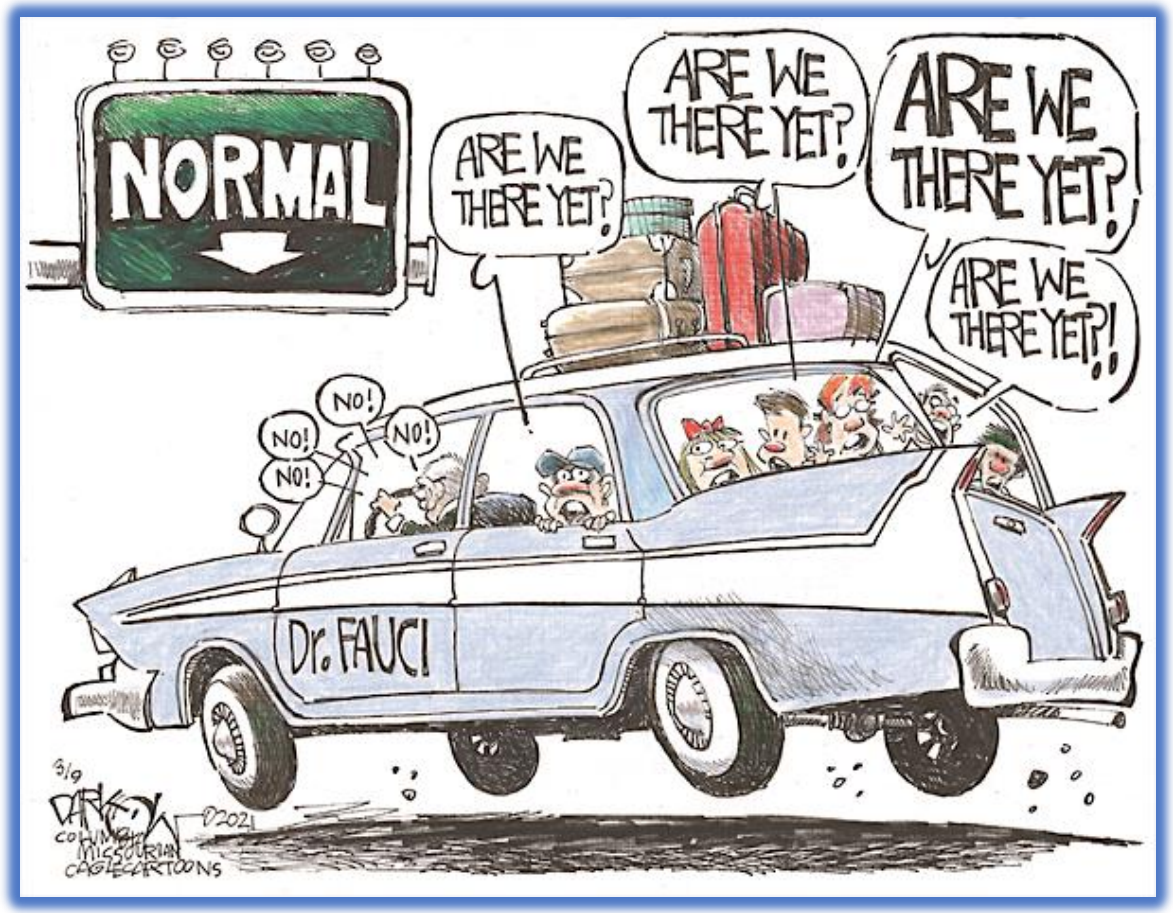
Adjusted* HRs for MI by HIV Status (PWoH reference), and stratified by Calendar era and Cohort

	KPNC		Partners		Overall	
Era	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
2005-2009	1.0 (0.7, 1.5)	0.90	1.2 (0.3, 5.8)	0.82	1.1 (0.8, 1.5)	0.61
2010-2017	1.6 (1.1, 2.4)	0.02	2.1 (0.6, 7.5)	0.28	1.6 (1.1, 2.4)	0.007

*Stepwise adjusted models considering demographics

P-interaction (Era*HIV)=0.12

MJ Silverberg. vCROI 2022; #39.


NORMAL
ARE WE THERE YET?
ARE WE THERE YET?
ARE WE THERE YET?
ARE WE THERE YET?!
NO!
NO!
NO!
NO!
Dr. FAUCI
©2021

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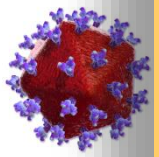

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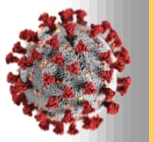


8. **SARS-CoV-2 infectiousness with natural & breakthought infections.**
9. **COMET-TAIL: Sotrovimab IM non-inf to IV in high-risk outpatient-COVID.**
10. **COVID booster vaccination highly effective regardless of immune status.**

Infectiousness of breakthrough infections after vaccination and natural infection

- Qatar's National DB
- SARS-CoV-2 PCR-Ct.

Pairwise comparison in 4 matched cohorts:

Hierarchy in infectiousness

1. Primary infections in unvaccinated
2. BNT162b2 (Pfizer-BioNTech) breakthrough infections
3. mRNA-1273 (Moderna) breakthrough infections
4. Reinfections in unvaccinated

Breakthrough infections are ≤50% infectious than primary infections in unvaccinated individuals.

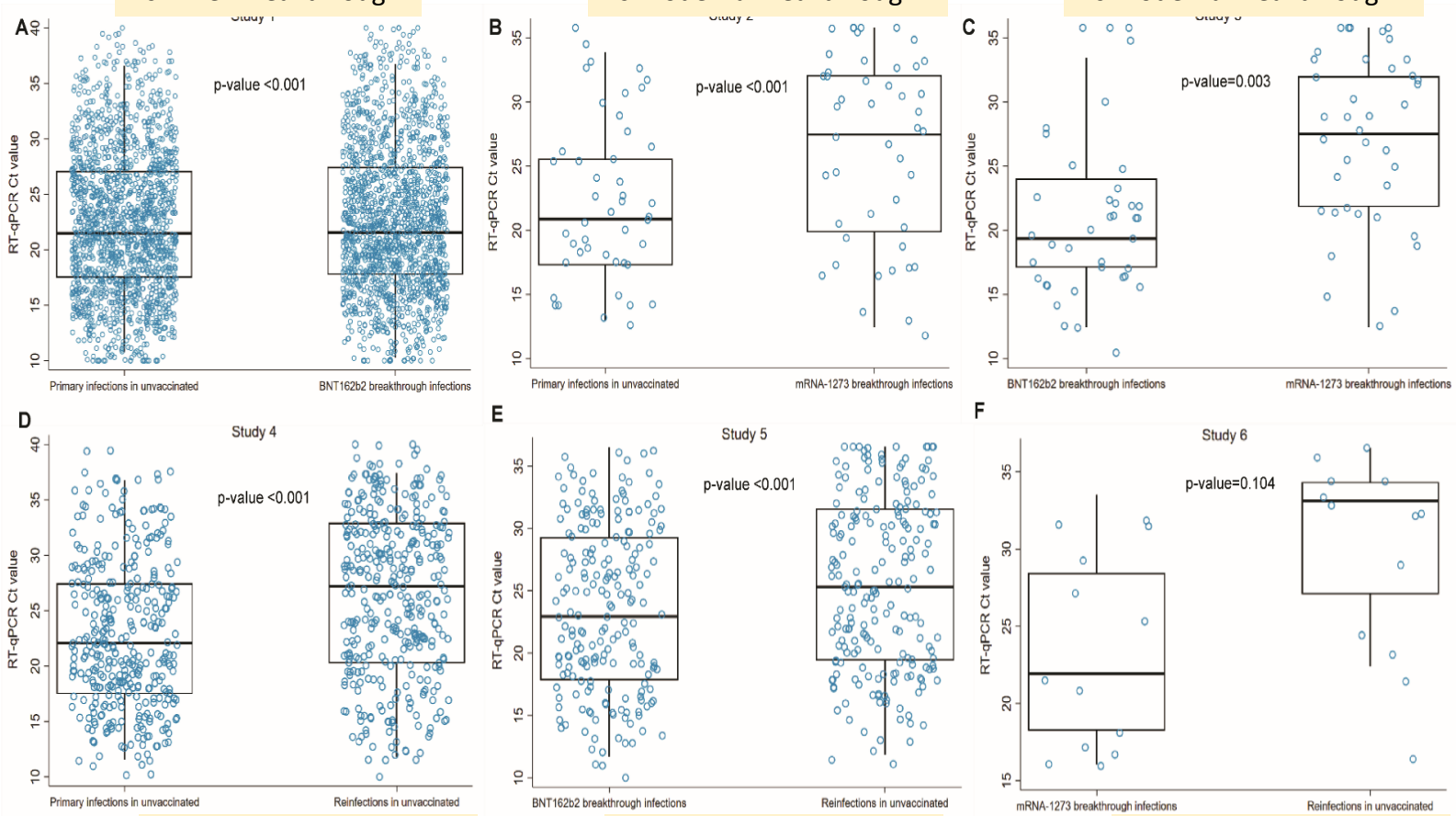
(limitation: Not Omicron era)

+ Infectiousness -

Primary unvaccinated vs Pfizer Breakthrough

Primary unvaccinated vs Moderna Breakthrough

Pfizer breakthrough vs Moderna Breakthrough



Primary unvaccinated vs Reinfection vaccinated

Pfizer breakthrough vs Reinfection vaccinated

Moderna breakthrough vs Reinfection vaccinated

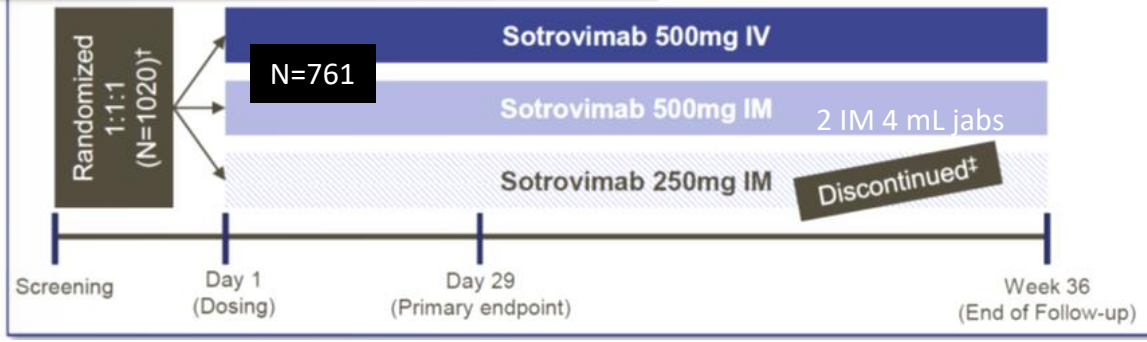
LJ Abu-Raddad. vCROI 2022;

Sotrovimab IM non-inf to IV in mild-mod outpatient COVID

Omicron BA.2
- Sotrovimab: FC: 26 ….
- Bebtelovimab: No change
- Evusheld℞: FC: 5.4 - 176…

- Pan-sarbecovirus IgG monoclonal Ab that tightly binds a highly conserved epitope of the SA… protein outside the ACE2 receptor-binding motif (potentially good for new VOC); ≈ bebtelov… CoV1404).
- The parental form of sotrovimab, S309, was isolated from a patient with SARS-CoV-1.

STUDY DESIGN[1]



Patient Population:
- Positive for COVID-19 with symptoms ≤7 days
- Aged ≥12–54 years with at least one of the following comorbidities:
  - Diabetes, obesity, CKD, sickle-cell disease, congenital heart disease, neurodevelopmental disorders, chronic lung disease, immunosuppression or chronic liver disease
- Aged ≥55 years, irrespective of comorbidities
- Enrollment occurred from June to August 2021, coinciding with a surge of the Delta variant

- Risk factors: Obesity 63%, Age ≥55 years 43%, COLD 17%; ≥2 factors 13% (no Omicron era, limited δ).
- **Primary endpoint**:
  - Proportion of participants hospitalized >24 hours or dead due to any cause through Day 29: **IV 1.3% vs IM 2.7%; adjusted risk difference 1.07 (95%CI: -1.25, 3.39); predefined 3.5%.**
  - Deaths 0 vs 2.
  - Well tolerated, no toxicity issues.
- Seropositive pa…

CROI #103: "*Treatment with sotrovimab reduced progression to severe COVID-19, regardless of serostatus*"…

- Primary endpoint relative RR 0.16 (0.06, 0.45) in seronegative and RR 0.49 (0.09, 2.64) in seropositive.

AE Shapiro. vCROI 2022; #102. A Gupta. vCROI 2022; #103.

COVID Booster vaccination effectiveness in people w/ and w/o immune dysfunction

- US Natl Collab Cohort (NIH). **784,555 fully vaccinated** (2 mRNA [97%] or 1 J&J). **Booster: 174,042 vs non-booster 614,750**.
- Immune dysfunction: HIV infection, solid organ or bone marrow transplant, autoimmune disease, and cancer.
- PS matched Cox regression models; MV logistic regression models.
- **Includes delta and omicron eras**.

Booster effectiveness, breakthrough events.
Without immune dysfunction / With immune dysfunction

Months since full vaccination	Hazard Ratio (95% CI)	P-value	Booster vaccine efficacy	Hazard Ratio (95% CI)	P-value	Booster vaccine efficacy
≤5	0.33 (0.22, 0.52)	<0.001	70.5%	0.84 (0.67, 1.04)	0.11	29.9%
6	0.27 (0.19, 0.40)	<0.001	73.6%	0.60 (0.47, 0.75)	<0.001	40.5%
7	0.23 (0.19, 0.27)	<0.001	77.4%	0.39 (0.32, 0.47)	<0.001	60.2%
8	0.36 (0.32, 0.41)	<0.001	62.5%	0.38 (0.31, 0.46)	<0.001	60.1%
9	0.45 (0.40, 0.51)	<0.001	52.1%	0.56 (0.42, 0.75)	<0.001	39.5%

J Sun. vCROI 2022; #48. J Sun. JAMA Intern Med. doi:10.1001/jamainternmed.2021.7024

COVID Booster vaccination effectiveness in people w/ and w/o immune dysfunction

Risk of COVID-19 Related Outcomes by Booster Vaccine Status

	Patients without immune dysfunction		Patients with immune dysfunction	
	Odds Ratio (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Hospitalization	0.13 (0.12, 0.15)	<0.001	0.21 (0.19, 0.23)	<0.001
Invasive ventilation	0.09 (0.05, 0.19)	<0.001	0.25 (0.18, 0.34)	<0.001
Death	0.13 (0.06, 0.30)	<0.001	0.17 (0.11, 0.27)	<0.001

J Sun. vCROI 2022; #48. J Sun. JAMA Intern Med. doi:10.1001/jamainternmed.2021.7024