18ª edición

POSTCROI 2021

Una actualización de la 28ª Conference on Retroviruses and Opportunistic Infections

virtual CROI 2021

Conference on Retroviruses and Opportunistic Infections

MARCH 6-10, 2021

CROI 2021: Top Ten for Clinicians

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Enfermedades Infecciosas

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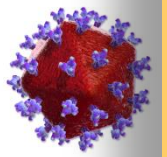
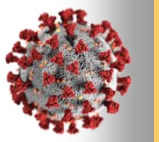
FUNDACIÓN LUCHA CONTRA EL SIDA Y LAS ENFERMEDADES INFECCIOSAS

FLS SCIENCE

Top Ten CROI 2021. Take homes.



1. Rifapentine & Moxifloxacin 4M (2HPZM+2HPM) beat classic 6M RHZE in pulmonary TB in PLWH.
2. Prévenir TDF/FTC PrEP: Daily = On demand.
3. NADIA: DRVr non-inferior to DTG in 2ND line (1ST salvage) in Africa.
4. Lenacavapir in salvage ART: record VL decay in HTE with MDR.
5. Islatravir multiple dosing possibilities for PrEP and ART… and new partner.
6. mRNA vaccines come to SHIV in macaques… with significant success.

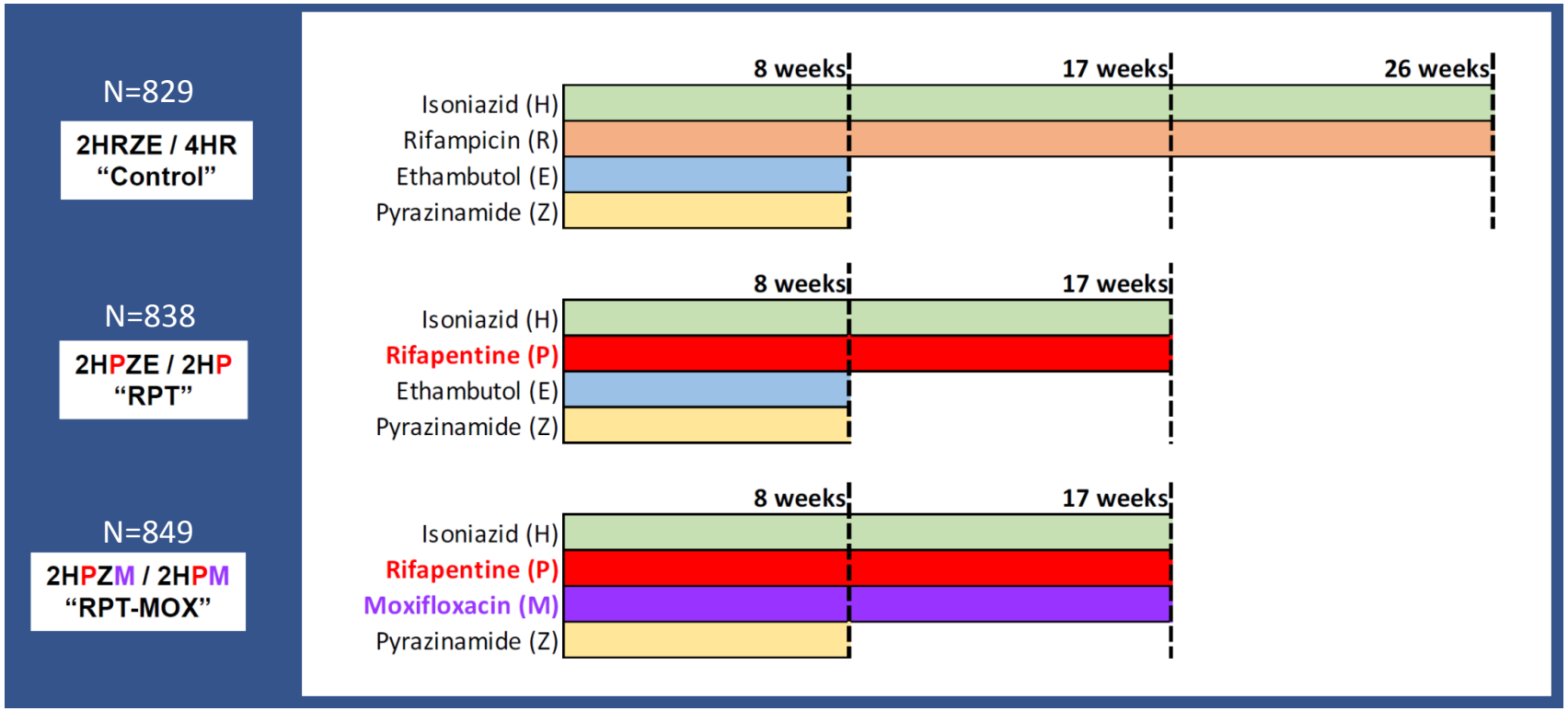


7. One dose mRNA vaccine sufficient in COVID-experienced.
8. Blaze-1: Bamlanivimab + etesivimab: significant improvement in mild-mod ambulatory COVID.
9. Bamlanivimab (& REG-2 cocktail) ↓ symptomatic COVID & faster viral clearance in PrEP/PEP.
10. Molnupiravir, oral: No culturable SARS-CoV-2 at 5 days.

Rifapentine +/– Moxifloxacin for Pulmonary TBC in PLWH (S31/A5349)

- Intl, randomized (1:1:1), phase 3, open-label, non-inferiority. HIV+ allowed if CD4 >100 cells, only EFV.
- Microbiol confirmed, *M. tuberculosis* susceptible. ITT-E, M≠F (lost to FU, pregnancy, violent, TB reinfection, deaths excluded).
- 2,516 randomized, 214 (8%) were HIV+ (median CD4+ 344 cells/mm^3; on EFV-based ART at enrollment 53%).
- 73% cavitary disease. Median BMI 19 kg/m^2.

Stratified by Site, HIV status, Presence of cavitary disease



AC Pettit. vCROI 2021; #130.

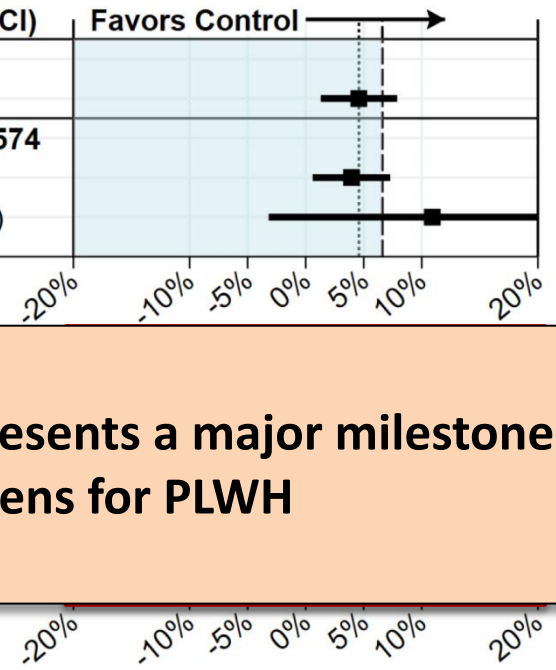
Rifapentine +/– Moxifloxacin for Pulmonary TBC in PLWH (S31/A5349)

Unfavourable outcomes (n(%)) **in <u>primary assessable analysis pop</u>: TB disease-free survival 12 months after randomization .**

- More people in the Control arm do not complete 95% of the TBC treatment.

Non-inferiority margin: 6.6%

	Rifapentine	Control	Unadj. diff. (95% CI)
Overall			
	107 (14.2%) / 752	70 (9.6%) / 726	4.6 (1.3, 7.9)
HIV Status			**Interaction p = 0.574**
Negative	90 (13.1%) / 687	61 (9.2%) / 666	3.9 (0.6, 7.3)
Positive	17 (26.2%) / 65	9 (15.3%) / 59	10.9 (-3.2, 25.0)



Rifapentine-Moxifloxacin (2HPZM/ 2HPM) regimen represents a major milestone in the pursuit of shorter TB treatment regimens for PLWH

HIV+ Safety Outcomes	Control	Rifapentine Moxifloxacin	Rifapentine	Total
Total safety population	70	72	71	213
Primary Safety Outcome (Grade 3-5 AEs on treatment)	**15 (21%)**	10 (14%)	12 (17%)	37 (17%)
SAEs during treatment	**7 (10%)**	2 (3%)	6 (8%)	15 (7%)
Deaths	2 (3%)	0 (0%)	**3 (4%)**	5 (2%)

AC Pettit. vCROI 2021; #130.

Study Design

http://prevenir.anrs.fr/

Open-Label Prospective Cohort Study in the Paris Region

n = 3,067
MSM 98.5%
Chemsex use 14%

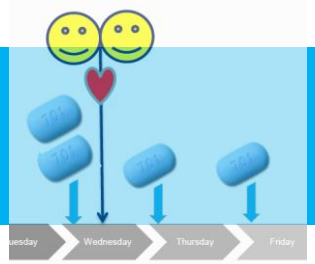
- **HIV-negative high risk adults**
- **Inconsistent Condom use**
- **eGFR ≥ 50 mL/mn**
- **HbsAg negative if On Demand**

May 3rd 2017

September 30, 2020

TDF/FTC
Daily

~50% each along the study period



TDF/FTC
On Demand

- **Participants opted for either Daily or On Demand PrEP and could switch regimen**
- Follow-up every 3 months with 4th Gen ELISA HIV test and plasma creatinine
- STI screening at physician's discretion (Guidelines recommend every 3 months in MSM)
- Condoms, gels, risk reduction and adherence counseling, Q on sexual behavior

JM Molina. CROI 2021; #148

HIV Incidence

Global HIV Incidence: 0.11/100 PY (95% CI: 0.04-0.23) (6 cases; all them PrEP stopped. 1/6 M184V)

Mean Follow-up of 22.1 months and 5633 Person-Years

Rate of study discontinuation: 14.4/100 PY

Treat	IRR (95%CI)
TDF/FTC Daily	
TDF/FTC On D	**0.99** (0.13-7.38)

High and identical efficacy of daily and on-demand PrEP.
Good safety profile with both dosing regimens.
High retention rate.
High rate of bacterial STIs, watch out hep C.

- Any STD
- 43 cases
- Lower dru

toxicity.

RCT (n=52) with Doxycycline 100 mg/daily x 48 weeks in HIVneg MSM with prior syphilis demonstrates: 82% reduction in STIs with no *Chlamydia* (p=0.001) and Syphilis (p=0.98). No impact on gonorrea.
DISCO Multicenter study (n=500) ongoing.

T Grennan, CROI 2021, #709

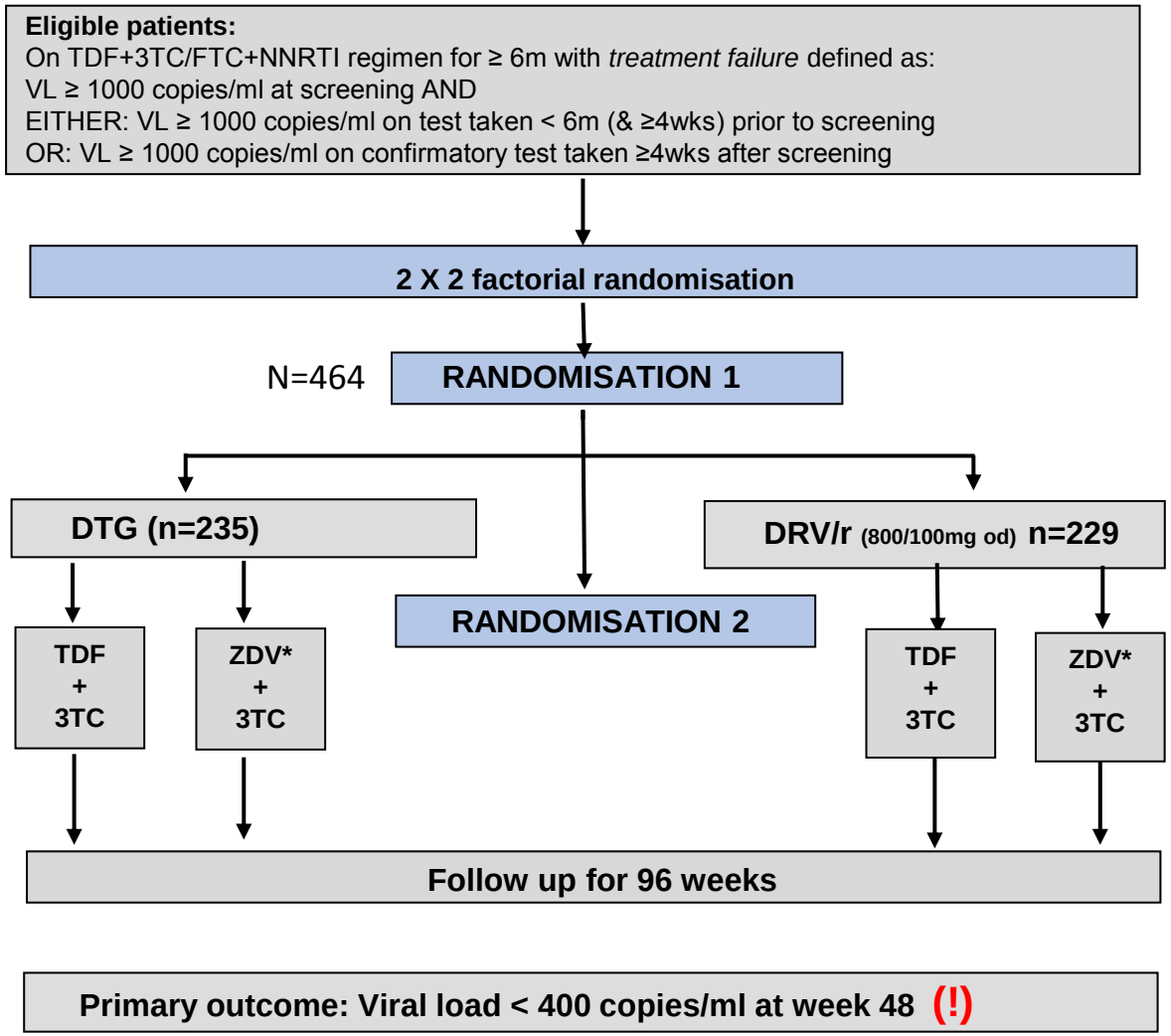
JM Molina. CROI 2021; #148

Oral Abstract-02

HIV TREATMENT AND PREVENTION: NEW OPPORTUNITIES TO OPTIMIZE DRUG DOSING, ADHERENCE, AND ANTIRETROVIRAL THERAPY

11:15 AM - 1:15 PM EST

NADIA Trial: DRV/r vs DTG and TDF vs ZDV in 1ST salvage (2ND Line) in Africa.



- 7 sites in Uganda, Kenya, Zimbabwe (July-Dec 2019).
- HIV VL and CD4 monitoring at 24 and 48 weeks.
- Batched GRT on stored BL samples (results blinded).
- ITT; δ for non-inf: 12%.

- Died prior to week 48: 5 (1.1%), Lost-to-FU: 1 (0.2%).
- Scheduled visits attended: > 99%.

- Median CD4 194 cells/mm^3, VL >100.000 28%.
- M184V/I 86%; K65R/N 50%.

N Paton. CROI 2021, #94.

NADIA Trial: DRV/r vs DTG and TDF vs ZDV in 1ST salvage (2ND Line) in Africa.

Efficacy outcomes (VL < 50 c/mL, ITT; secondary outcome):

DTG vs DRV/r: 80.9% vs 79.5% (1.4; 95%CI -5.9 to 8.6). **Non-inf confirmed** (δ 12%).

- With CD4 <200 cells: 89.6% vs 95.6% (-6.0; -12.5, +0.6).
- No active (0) NRTIs: 92.4% vs 93.7%.
- D/C due to AEs: 0.9% vs 1.3%.
- VL rebound ≥ 1000 c/ml (confirmed) with ≥1 major DRM: 4 DTG (1.7%; 1 intermediate, 3 high-level) vs 0 DRV/r.

TDF vs ZDV: 80.7%

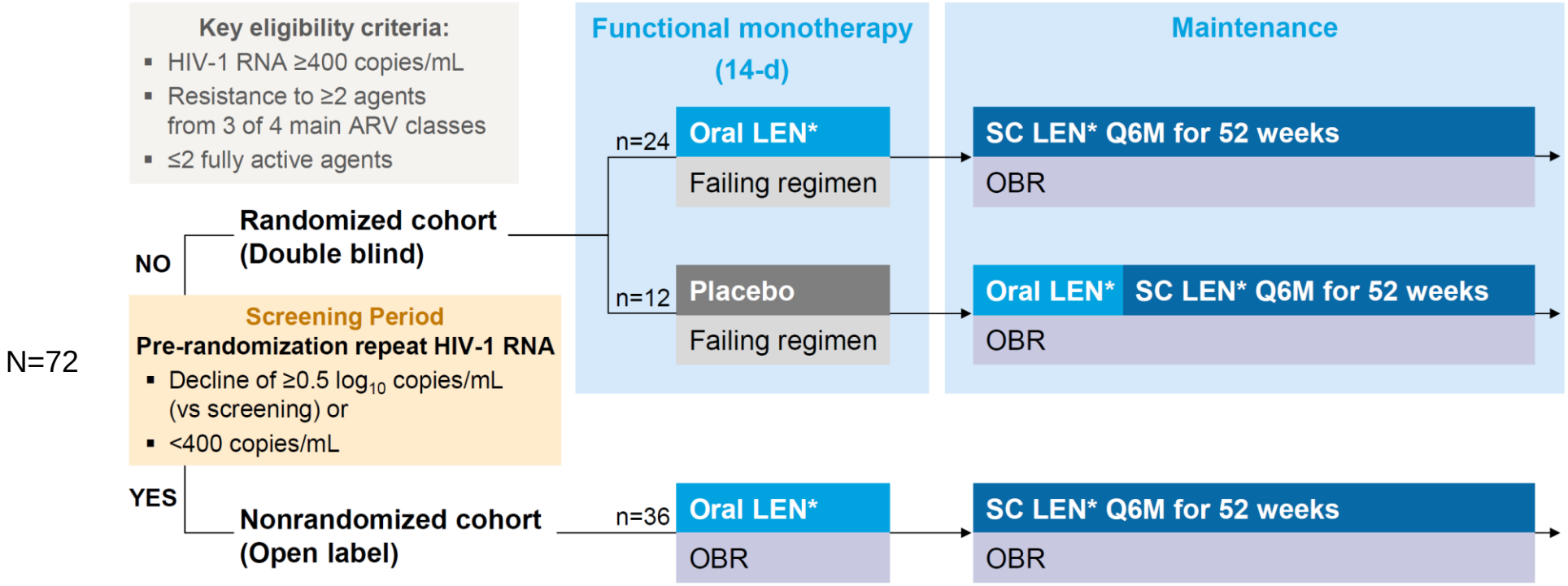
- With K65R/N pre
- With M184V/I: 9

DTG was <u>not</u> superior to DRV/r in efficacy or safety in 2ND line.
DTG resistance (2%) can occur, usually high-level.
TDF/3TC is non-inferior to switching to ZDV/3TC.
High rates of VS will all strategies

N Paton. CROI 2021, #94.

Lenacapavir in Phase 2/3 in Heavily ART-experienced PMW

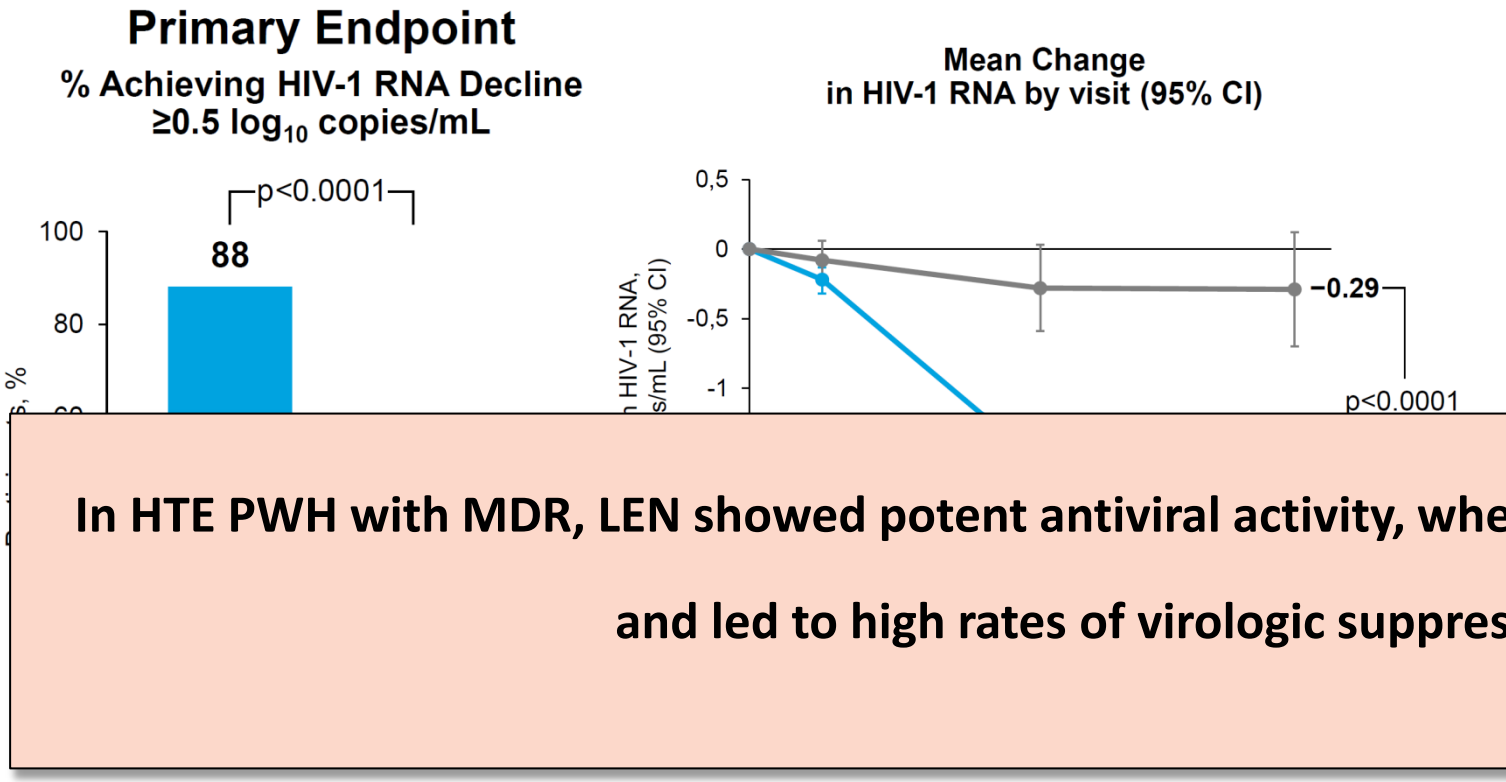
- First-in-class HIV capsid inhibitor, multi-site MOA, highly potent (nano-molar, EC_{50}=50 pM) and long-acting.
- No cross-resistance and no observed pre-existing resistance.
- Single SC doses maintained target concentrations for 26 weeks, supporting its use once every 6 months.
  Median CD4 150 cells, VL >75.000 c/mL 28%.



*Oral LEN administered as 600 mg on Days 1 and 2, 300 mg on Day 8; SC LEN administered as 927 mg (2 x 1.5 mL) in the abdomen on Day 15.
OBR, optimized background regimen (investigational agents, such as fostemsavir, were allowed; ATV, ATV/co, ATV/r, EFV, ETV, NVP, TPV were not allowed).

S Segal-Maurer. CROI 2021. #127.

Lenacapavir in Phase 2/3 in Heavily ART-experienced PMW



VL decline of some comparators
(log_{10} copies/mL)

LEN SC[1]	IBA[2]	FTV[3]	DTG[4]
-2.3	1.1	0.79	1.43

In HTE PWH with MDR, LEN showed potent antiviral activity, when added to a failing regimen and led to high rates of virologic suppression

- 73% VL<50 c/mL at week 26 (ITT M=F), CD4 increase +72 cells/mm^3.
- 2 CVF with LEN DRMs (M66I, and M66I + N74D) with high level LEN resistance.
- No safety issues. No SAEs related to study drug or leading to study drug discontinuation.
- ISRs common (46%), mostly grade 1.

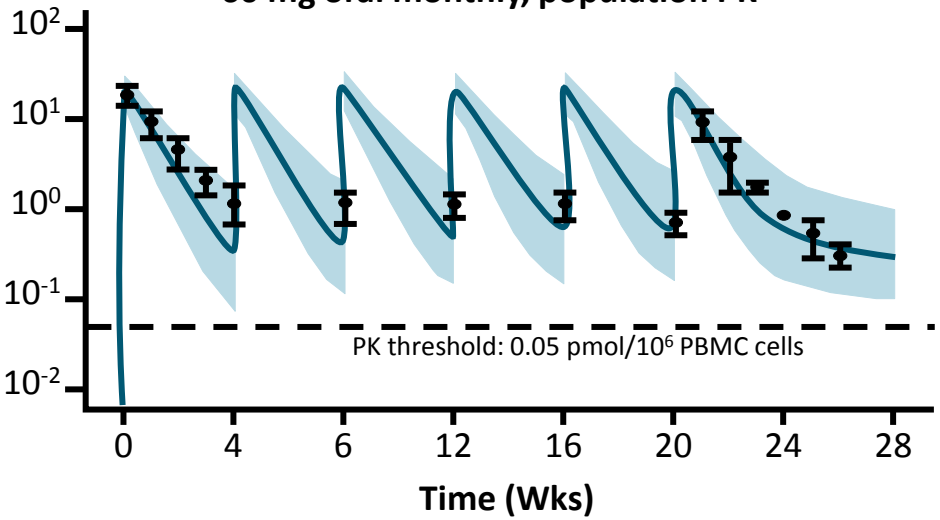
S Segal-Maurer. CROI 2021. #127.

1. Daar E, et al. CROI 2020, #769. 2. B Emu. N Engl J Med 2018;379:645-54. 3. M Kozal. N Engl J Med 2020;382:1232-43. 4. A Castagna. JID 2014;210:354–62

Islatravir LA, multiple dosing possibilities for PrEP and ART

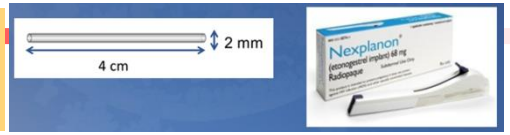
- First-in-class nucleoside transcriptase translocation inhibitor.
- Intracellular $t_{1/2}$ of ISL-TP: 190 hours (8 days).
- High potency, amenable for LA formulations.

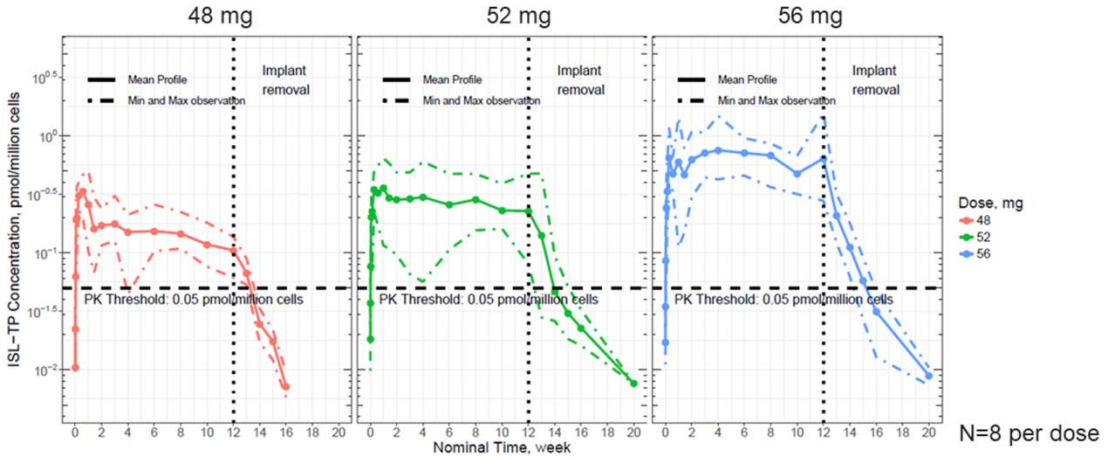
60 mg oral monthly, population PK



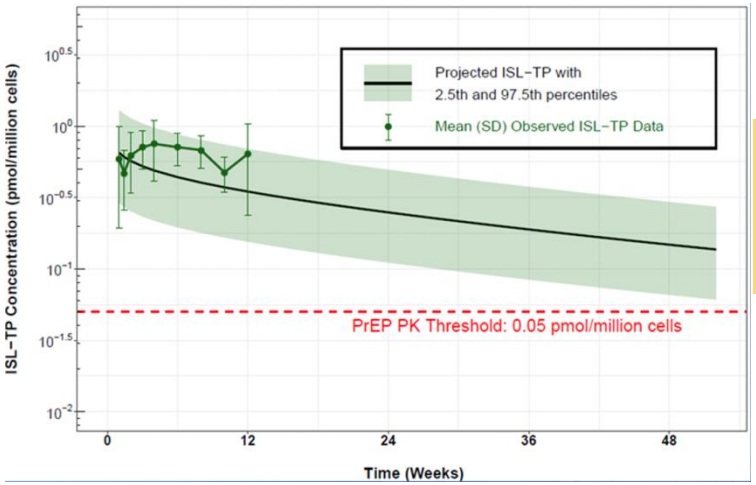
- Predicted IQ >17
- IQ>5 associated with antiviral efficacy against wt and M184V HIV in PrEP
- Adequate tissue distribution (rectal, cervical, vaginal).
- Dose selected for phase 3 studies: 60 mg oral monthly:
- IMPOWER-022 (Women) and 023 (MSM) vs TDF/TAF.

Next generation radiopaque implants.
Implanted in non-dominant upper arm.





56 mg reformulated implant projected to release adequate ISL-TP for >52 weeks

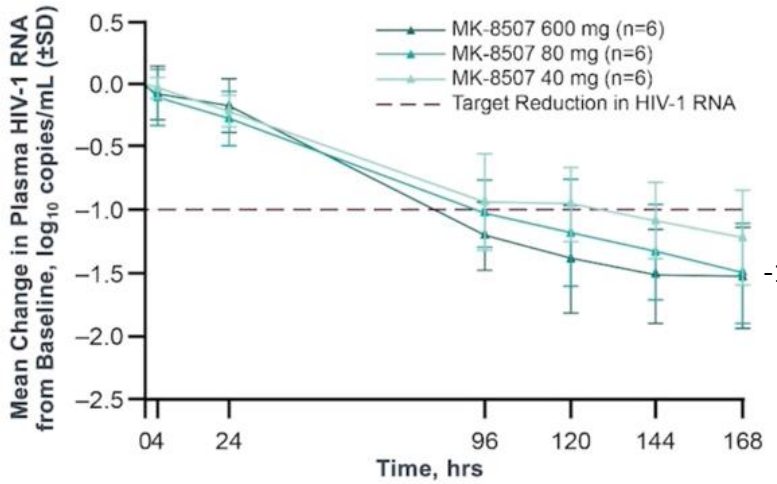


Potential for once-yearly SC PrEP

M Patel. CROI 2021, #87. RP Mattews. CROI 2021, #88.

LECTURAS HOLA.com DIEZ MINUTOS

Se presenta en sociedad la pareja de Islatravir: MK-8507 (NNRTI). $T_{1/2}$ 70 hours (3 days).

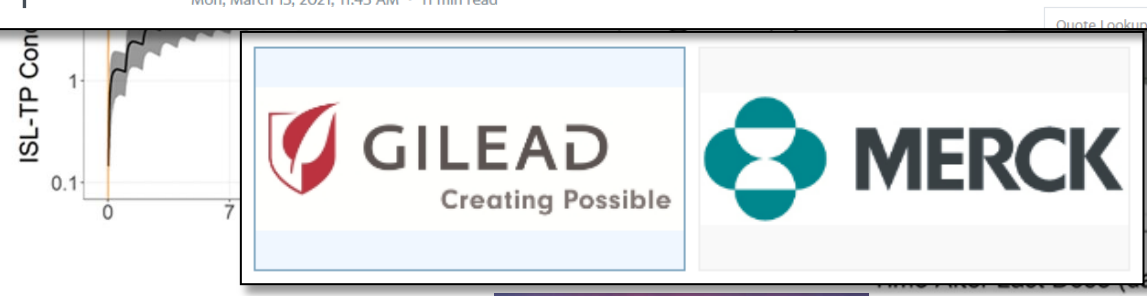


-1.5 log

businesswire

Gilead and Merck Announce Agreement to Jointly Develop and Commercialize Long-Acting, Investigational Treatment Combinations of Lenacapavir and Islatravir in HIV

Mon, March 15, 2021, 11:45 AM · 11 min read



80 mg MK-8507 QW ~~probably~~ taken forward + 20 mg QW ISL.

TL Diamond. CROI 2021, # 129. B Kandala. CROI 2021, #376

Moderna/NIH/Bill&Melinda Gates

An Env/Gag VLP mRNA vaccine induced significant protection from SHIV infection

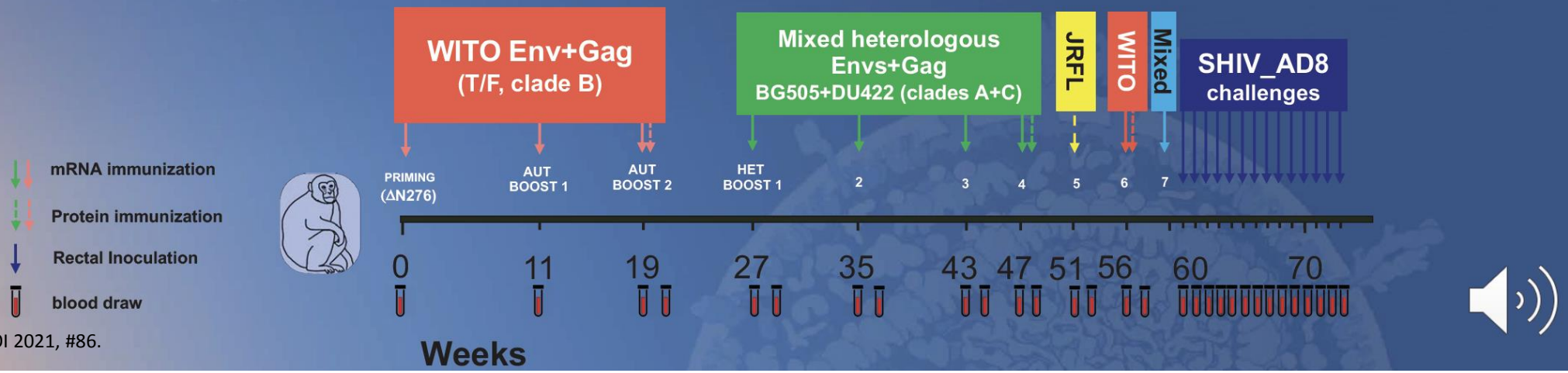
Design of the Study

Animals: Rhesus macaques (*M. mulatta*), juvenile males

Immunogens: mRNA (HIV-1 Env, SIV Gag), 200-400 μg/animal by IM injection

Study groups:
- **Arm 1 (n=3):** Clade-B priming (WITO Env+Gag), clades A+C boosts (BG505+DU422+Gag) + final protein boosts (SOSIP.664 trimers)
- **Arm 2 (n=4):** Clade-B priming (WITO+Gag), clades A+C boosts (BG505+DU422+Gag)
- **Arm 3 (n=7):** Naïve controls (added at challenge phase)

Challenge: *In vivo*-titrated SHIV-AD8, 13 weekly low-dose 10 $TCID_{50}$ by rectal inoculation

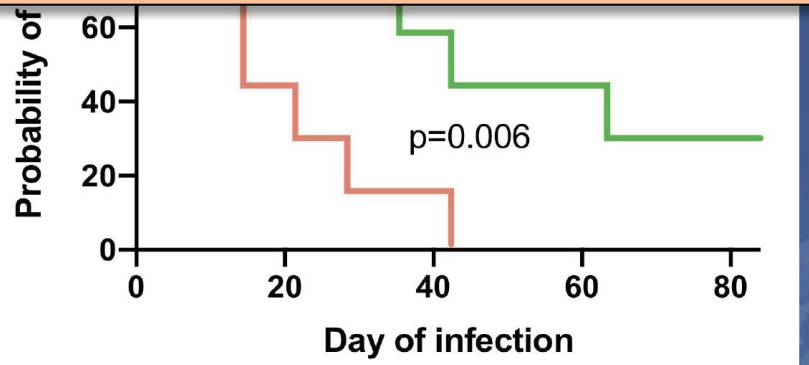


P Zhang. CROI 2021, #86.

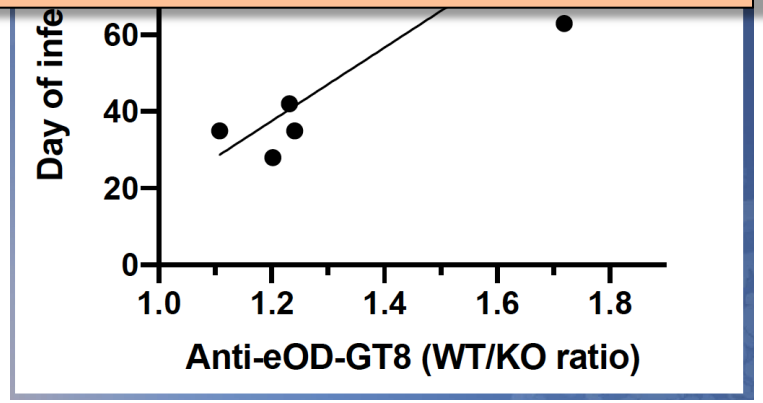
An Env/Gag VLP mRNA vaccine induced significant protection from SHIV infection

- Lipid nanoparticles that include small lengths of a nucleic acid that deliver instructions for making proteins.
- mRNA vaccines allow sustained *in vivo* expression of native endogenous proteins (identical to real-life infection) with no distracting epitopes.
- Early and strong induction of neutralizing Abs.

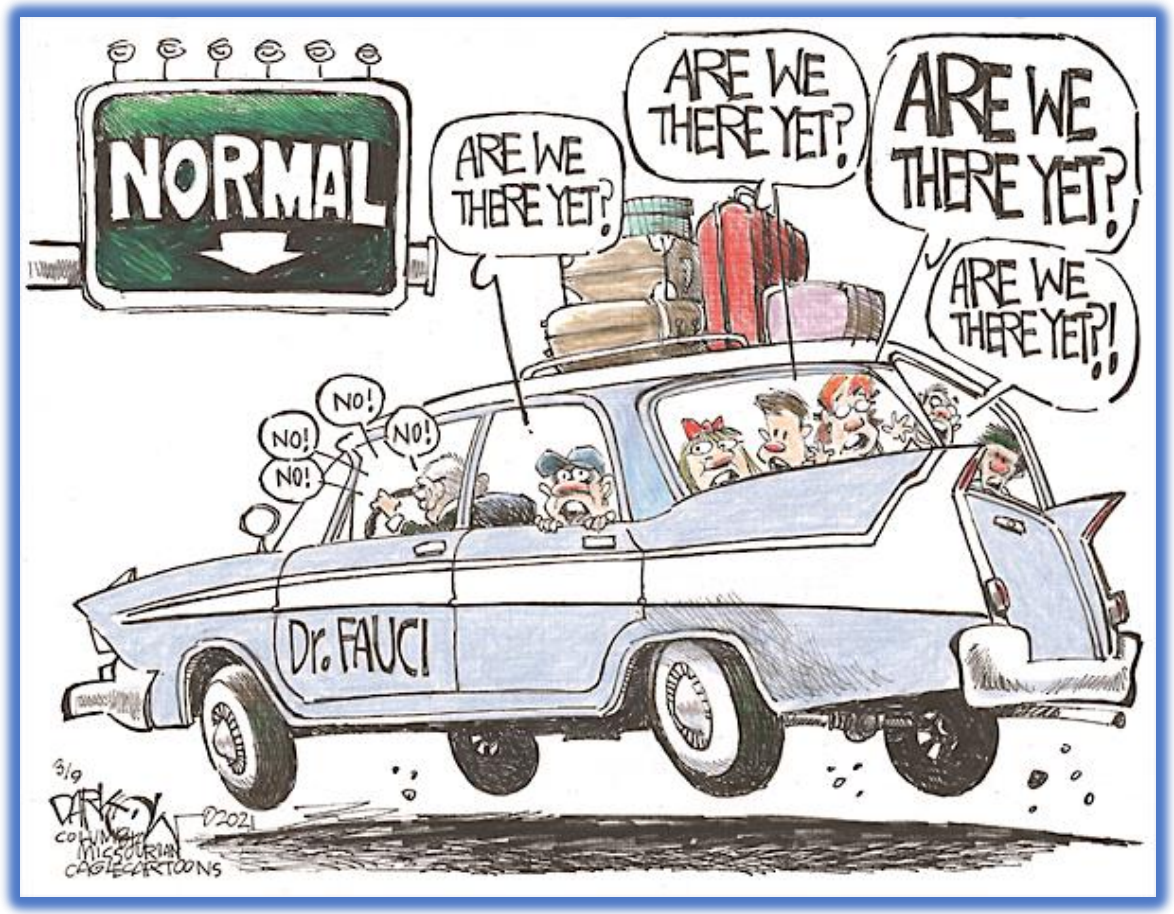
An Env/Gag VLP mRNA vaccine induced significant (but partial) protection from infection with a difficult-to-neutralize heterologous SHIV in macaques.



	ratio	lower	upper	risk reduction	lower	upper
All vaccinated vs. Control	0.15	0.03	0.78	85%	22%	97%
mRNA+ Protein vs. Controls	0.12	0.01	1.07	88%	1%	99%
mRNA only vs. Controls	0.24	0.04	1.31	76%	1%	96%



P Zhang. CROI 2021, #86.


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

Top Ten CROI 2021. Take homes.

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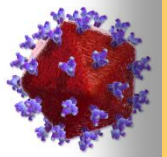

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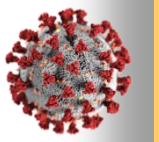


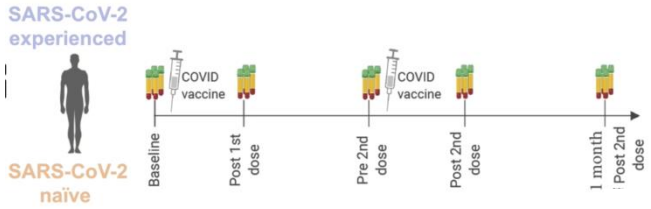
7. **One dose mRNA vaccine sufficient in COVID-experienced.**
8. **Blaze-1: Bamlanivimab + etesivimab: significant improvement in mild-mod ambulatory COVID.**
9. **Bamlanivimab (& REG-2 cocktail) ↓ symptomatic COVID & faster viral clearance in PrEP/PEP.**
10. **Molnupiravir, oral: No culturable SARS-CoV-2 at 5 days.**

One dose of mRNA vaccine sufficient in COVID-experienced (Pfizer/BNT). HCWs

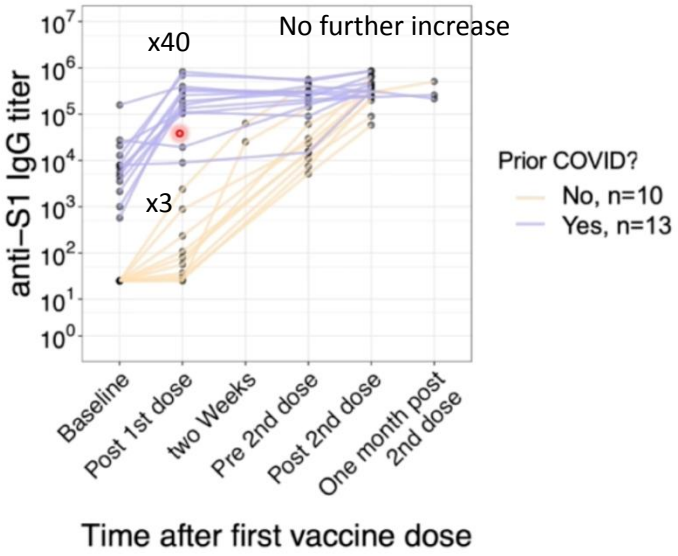
- Large scale RCTs excluded subjects with prior diagnosis of COVID.
- The magnitude, quality and durability of response to vaccination is unknown in subjects with prior SARS-CoV-2 infection.

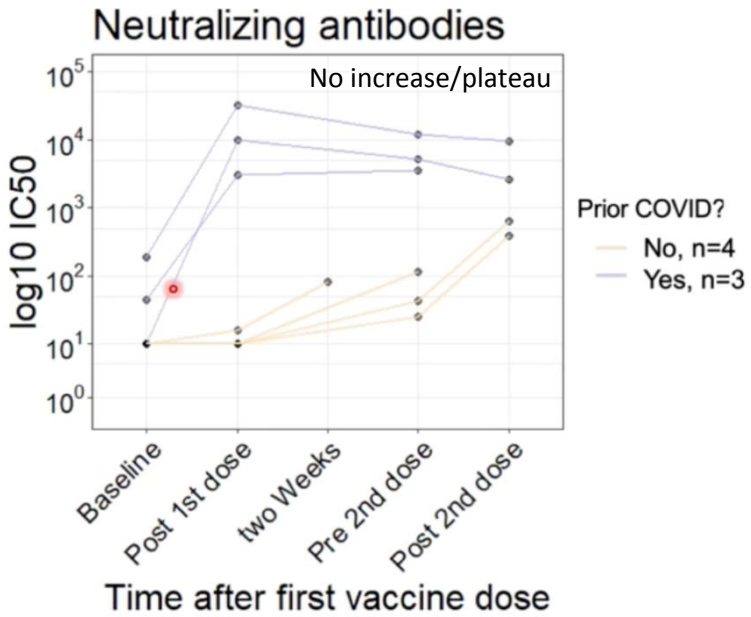
N=13
median time 8 months

N=20

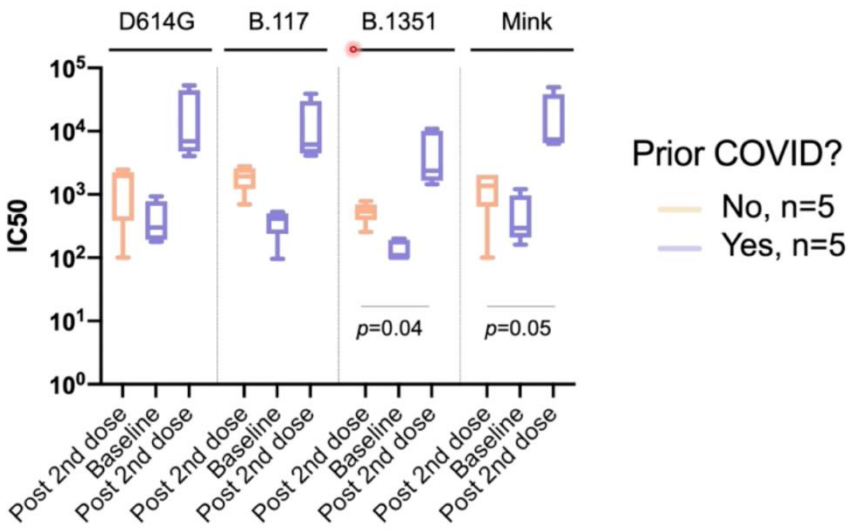


ELISA for anti-S1 IgG antibodies





Neutralizing titers against new variants



MI Samanovic-Golden. CROI 2021, #119.

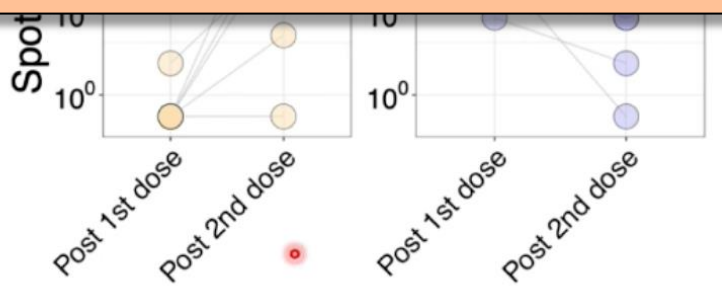
One dose of mRNA vaccine sufficient in COVID-experienced (Pfizer/BNT). HCWs

Cellular immune response: antigen-specific B-cell responses (ELISpot Assay).

More S1 antigen-specific Spot cells with 2ND dose in naives, but no increase (or decrease) in experienced.

A single dose of mRNA vaccine in SARS-CoV-2 experienced subjects induced similar or higher Ab responses (total, neutralizing and avidity) than 2 doses in SARS-CoV-2 naive subjects.
Titers were not boosted by second dose.
Cellular iummune responses after one dose showed a similar pattern.

Post vaccine dose 1
Post vaccine dose 2



MI Samanovic-Golden. CROI 2021, #119.

ELI-Lilly/NIAID/AbCellera (BLAZE-1)

Bamlanivimab + etesivimab in high-risk ambulatory COVID-19

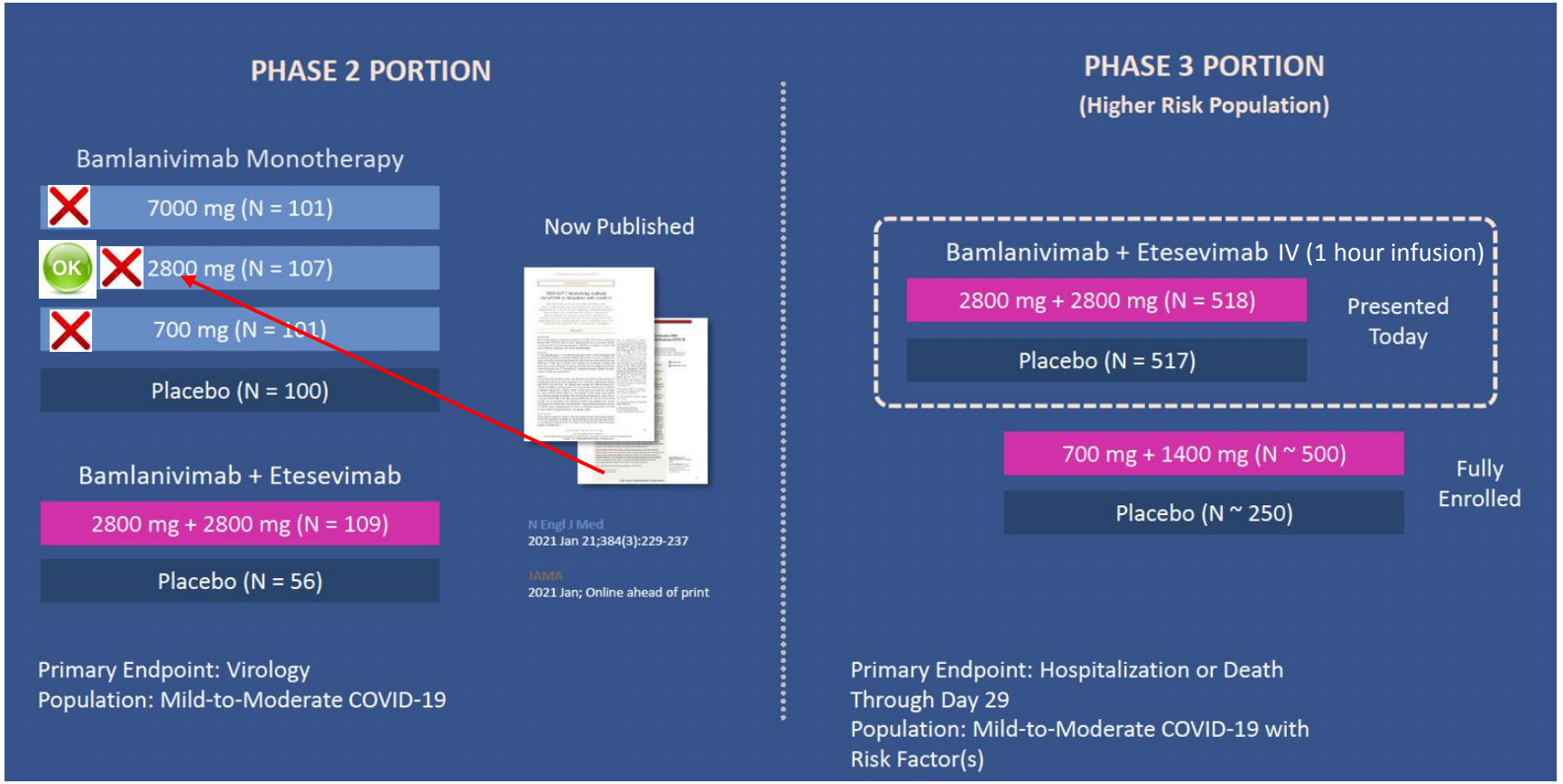
- Fully human nmAb IgG1, binds to SARS-CoV-2 RBD (Spike).
- N=1035 Mild (77%)-mod (23%) COVID-19 <3 days of RT-PCR+ and ≥1 comorbidity. Median duration of symptoms: 4 days.

VL decay vs pbo:

P = 0.70

P = 0.02

P = 0.38



M Dougan. CROI 2021, #122.

ELI-Lilly/NIAID/AbCellera

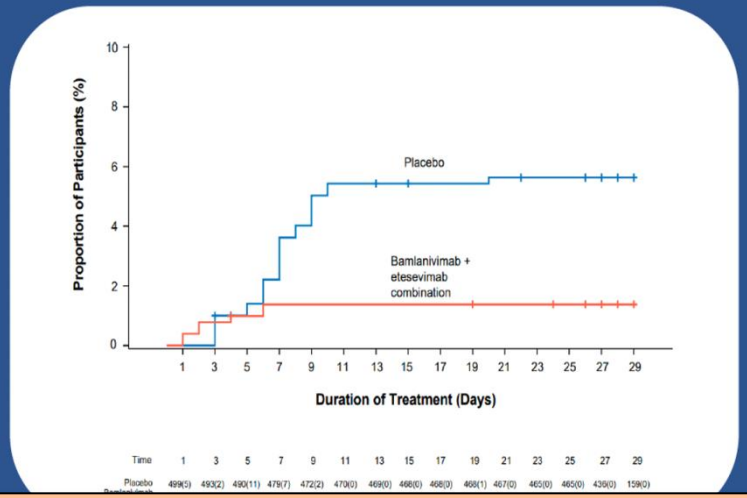
Bamlanivimab + etesivimab in high-risk ambulatory COVID-19

BLAZE-1 PHASE 3: PRIMARY ENDPOINT

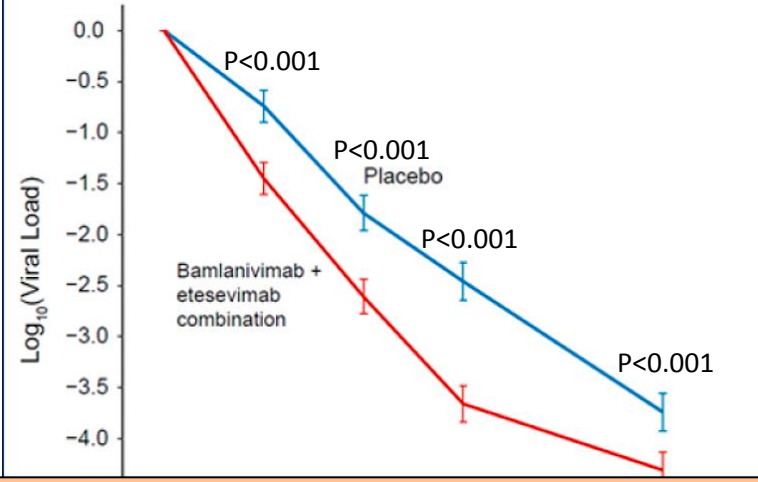
COVID-19 RELATED HOSPITALIZATION OR ANY-CAUSE DEATH BY DAY 29

Treatment	N	Events	Rate	*p*
Placebo	517	36	7.0%	-
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	11	2.1%	0.0004

70% reduction vs. placebo



VIRAL LOAD CHANGE FROM BASELINE



BLAZE-1 confirms 70% reduction in hospitalization, significantly faster viral load decrease and symptom ressolution in ambulatory mild-mod COVID with bamlanivimab + etesivimab.
No deaths (1.9% v 0)

M Dougan. CROI 2021, #122.

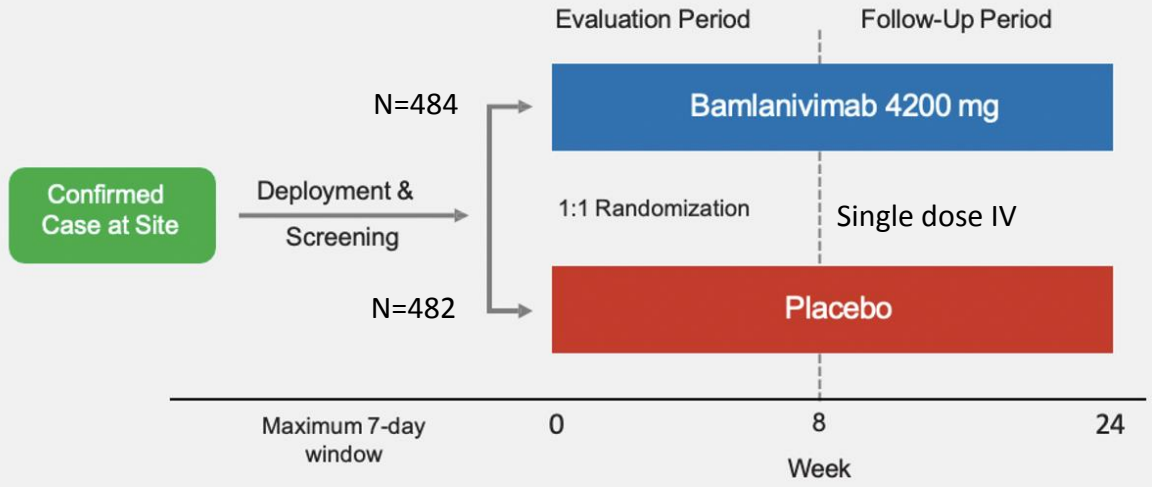
BLAZE-2: Bamlanivimab in nursing-home settings reporting at least 1 COVID case.

- PREVENTION POPULATION: 966 participants negative at BL for SARS-CoV-2 RT-PCR and serology (666 staff, 300 residents).
- Median age 52 y (residents 76 y). High-risk: 59% and 100.
- Primary endpoint: ≥mild COVID within 8 weeks.

In US nursing home residents: 5% of cases, 37% of deaths.

Study Design

1175 participants dosed, 966 (82.2%) comprised the prevention population



To facilitate rapid prophylaxis and treatment of residents and facility staff, participants were enrolled prior to assessment of baseline SARS-CoV-2 status. This allowed for separate prevention and empiric treatment populations.

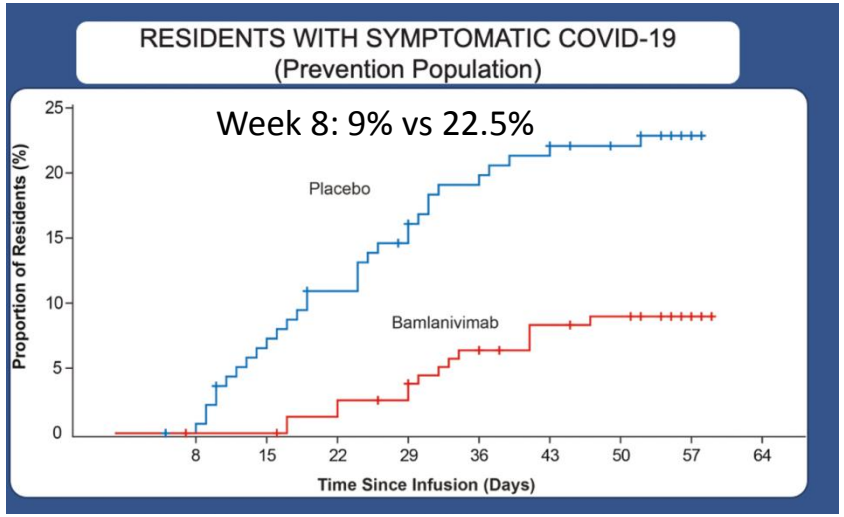
Mobile Research Units

M Cohen. CROI 2021, #121

BLAZE-2: Bamlanivimab in nursing-home settings reporting at least 1 COVID case.

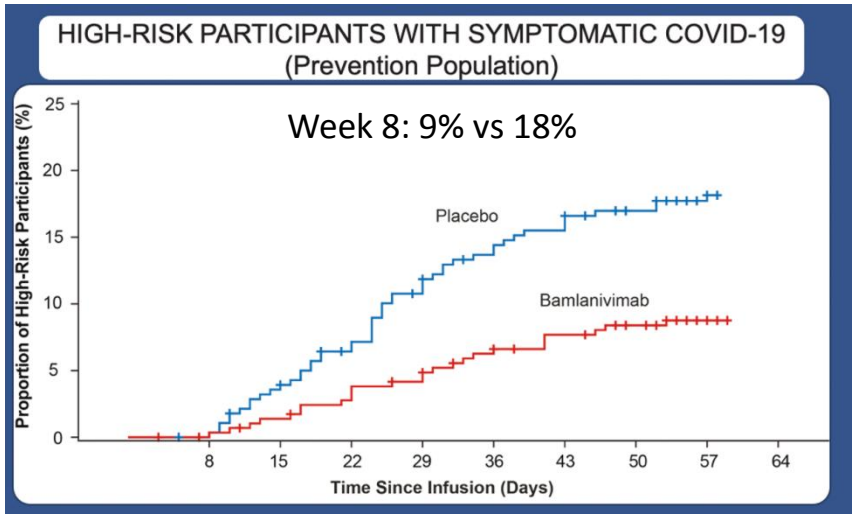
Nasal swabs were collected at baseline and weekly through day 57

OR 0.20, p<0.001; deaths 4 pbo vs 4 BAM



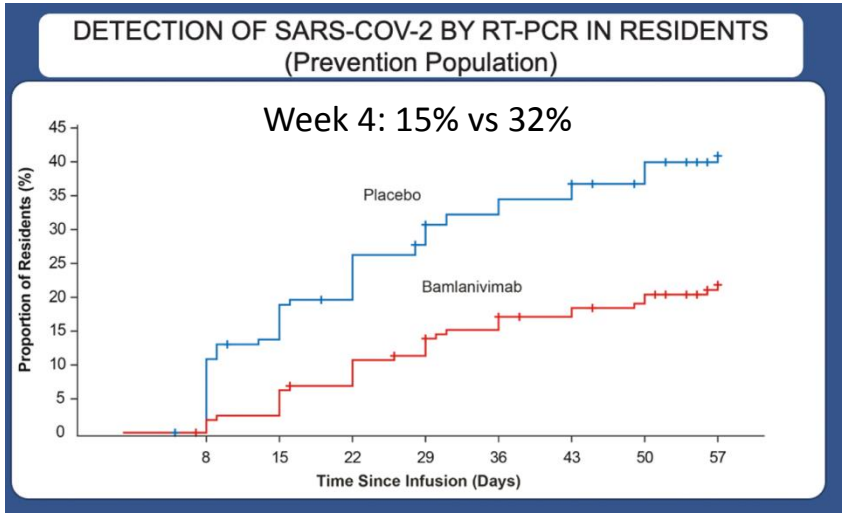
80% reduction in risk, no deaths

OR 0.28, p<0.001

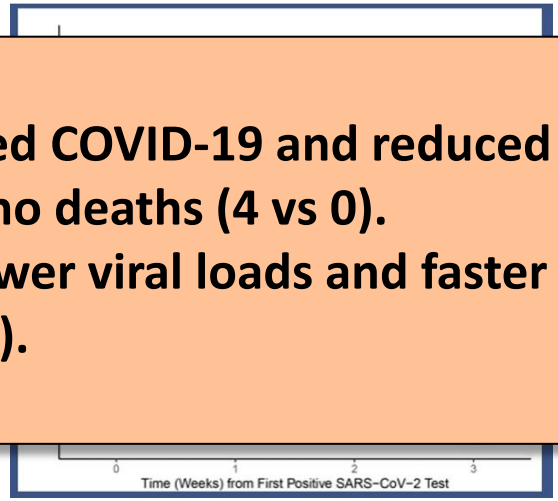


72% reduction in risk

OR 0.24, p<0.001



76% reduction in risk



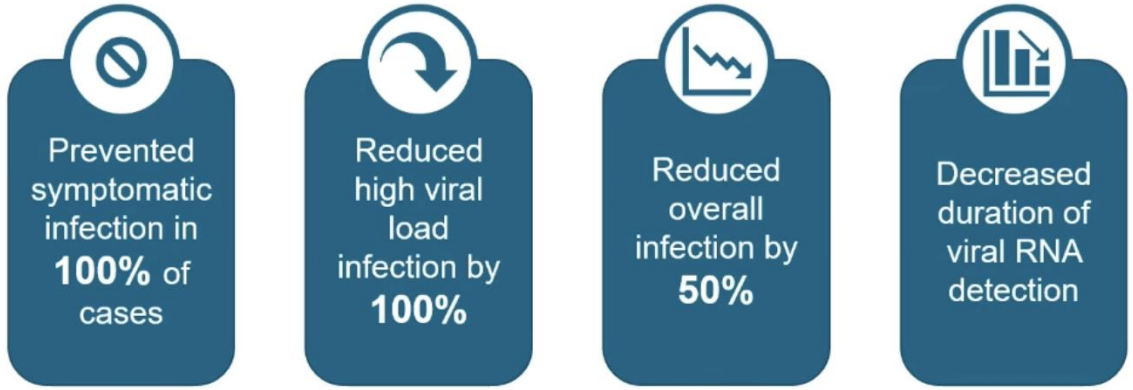
A single mAb (Bamlanivimab) PrEP significantly prevented COVID-19 and reduced progression in nursing facilities by 72-80%, with no deaths (4 vs 0).
Those who acquired COVID-19 with bamlanivimb had lower viral loads and faster viral clearance (spread reduction).

M Cohen. CROI 2021, #121

mAbs for COVID-19 prevention in household contacts

Similar results with phase 3 Casirivimab + Imdevimab mAb (REGEN-CoV cocktail, SC) in COVID PrEP in 409 household contacts (interim analysis): no symptomatic COVID and 50% reduction in PCR+ (low rates overall), strong impact on SARS-CoV-2 VLs.
(REGN-COV2)

- Passive immunization with a subcutaneous dose of the REGEN-COV antibody cocktail:



MP O'Brien. CROI 2021, #123.

Declaraciones polémicas

Trump promete distribuir gratis un tratamiento experimental contra el covid

Pittsburgh (Pensilvania)
08 de octubre del 2020. 10:39

El presidente afirma que haber pasado la enfermedad es "una bendición de Dios"

En un vídeo colgado en las redes, se compromete a poner a disposición de todos los estadounidenses y de forma gratuita el Regeneron

Molnupiravir: Time to clearance of infectious SARS-COV-2. Phase 2 (dose-finding)

1ST specific SARS-CoV-2 antiviral

- Broad range *in-vitro* activity against all CoVs including SARS-CoV-2 REM-resistant mutants.
- Potent ribonucleoside analog: induces viral error catastrophe (Emory → Ridgeback → MSD).
- Activity proven in mouse and ferret models for Tx and PrEP with SARS-CoV-2.
- Favourable PK: ORAL. Safe in humans in phase 1.
- N=200 ambulatory symptomatic COVID <7 days.
- NP swabs collected at 3,5,7,14,28 days.
- Molnupiravir 200, 400 or 800 mg BIG x 5 d.

Of 182 subjects with evaluable swabs, 78 (43%) had positive baseline cultures.

- **No culturable SARS-CoV-2 at 5 days with any dose** (n=47): 200 mg (n=11), 400 mg (n=15) or 800 mg (n=26=).
- **SAFE** (author comment).
- Phase 3 studies underway

Figure 1. Proportion of overall participants with positive viral culture by RT-PCR (for participants positive at baseline)

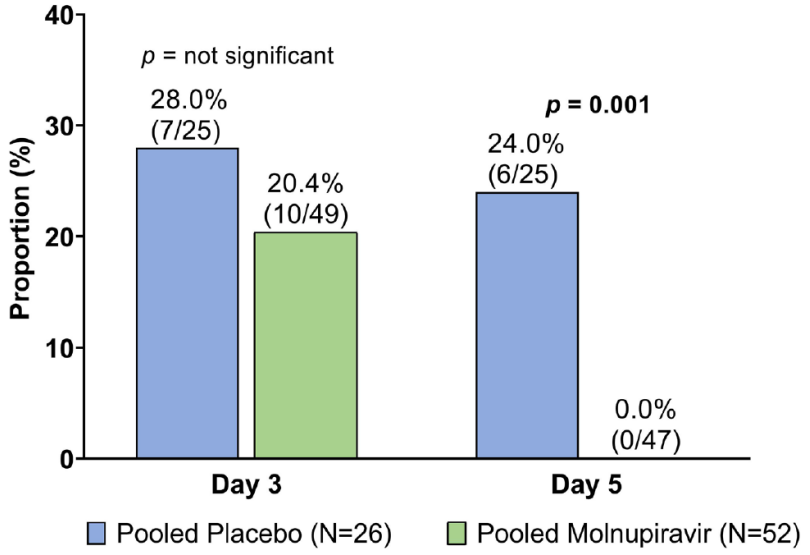
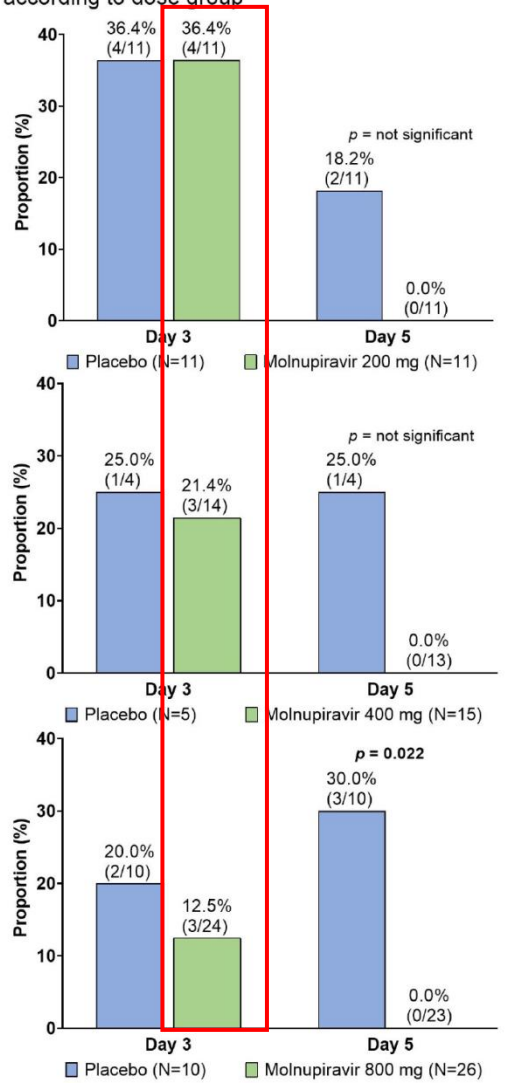


Figure 2. Proportion of participants with positive viral culture by RT-PCR (for participants positive at baseline) according to dose group



WP Painter. CROI 2021, #777.

¡MUCHAS GRACIAS!

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