CROI 2021 Updates

ART Strategies in global settings

(and a little bit of COVID!)

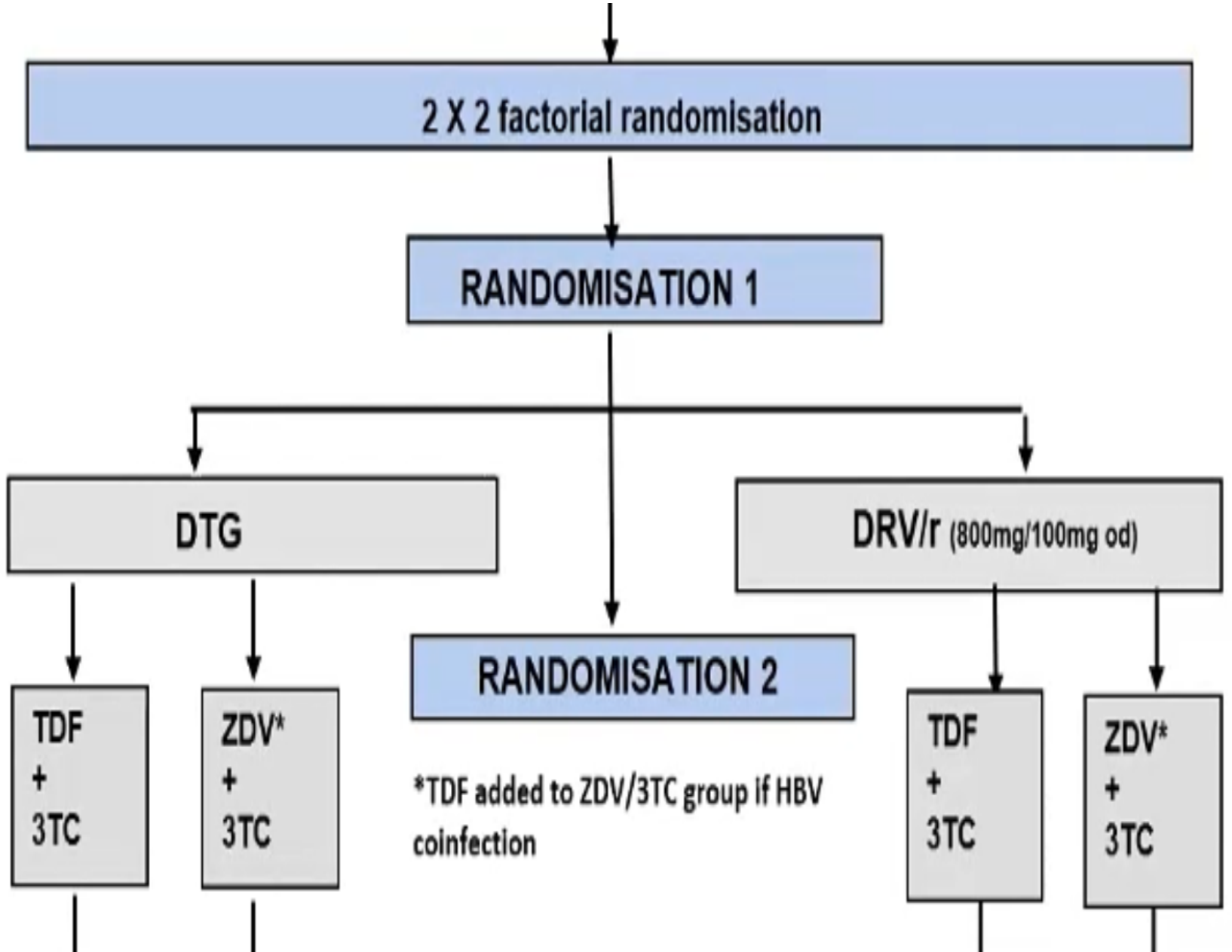
MASSACHUSETTS GENERAL HOSPITAL

Some slides/thoughts taken from Eric Darr (Practice point) and Paul Sax "*Really Rapid Review*"!

NADIA: DTG vs DRV and TDF vs ZDV as second line ART

- Resistance testing not typically available in resource-restricted settings

- At first-line NNRTI-based ART failure, WHO recommends
  - DTG
  - Empiric switch to ZDV (Public health approach)



Paton et al CROI 2021

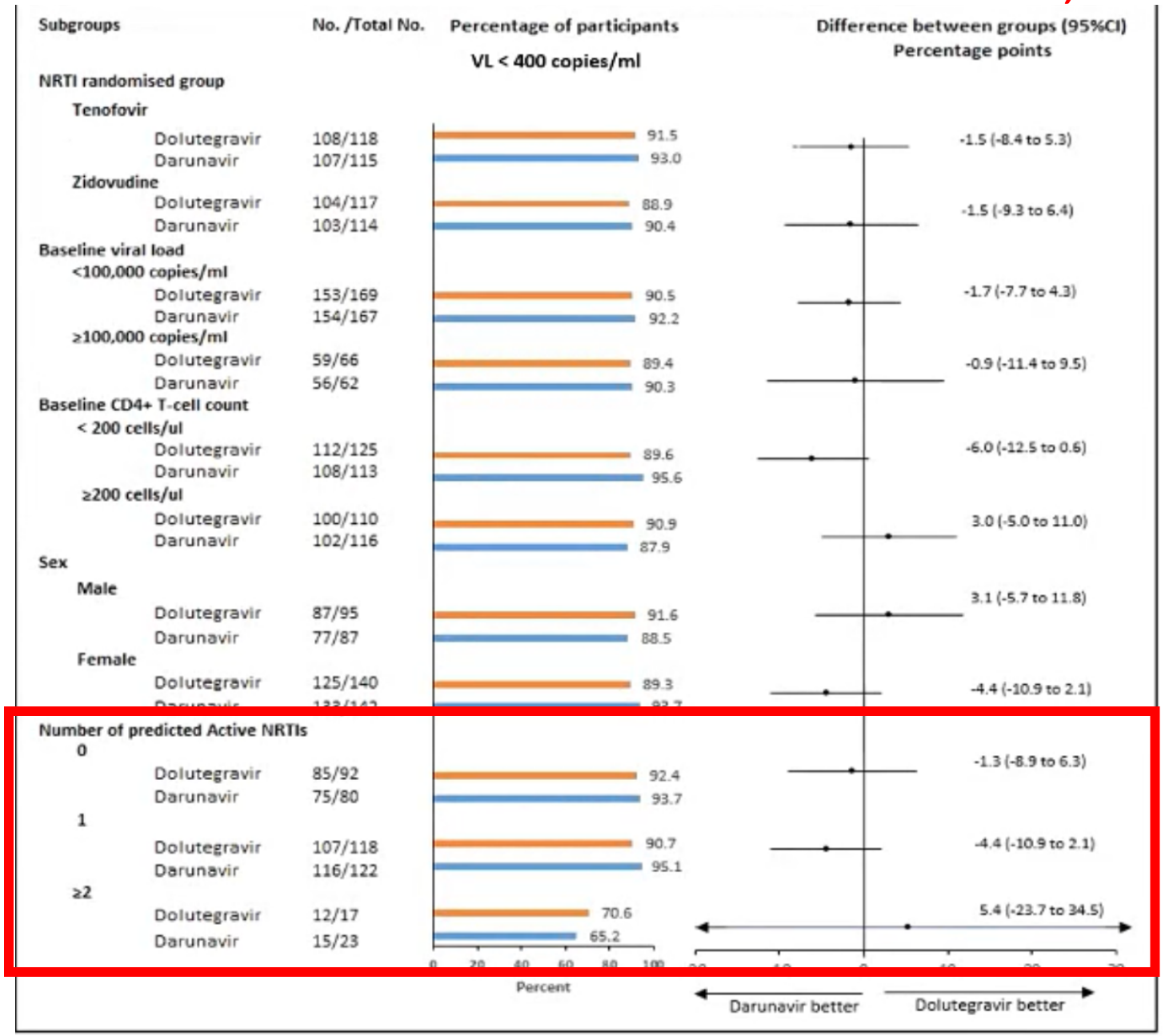
NADIA: DTG vs DRV and TDF vs ZDV as second line ART

Characteristic	Overall (N=464)
Female sex – no (%)	282 (60.8)
Median age (IQR) – yr	34 (28-41)
CD4+ lymphocyte count, Median (IQR) – per mm^3	194 (68-367)
< 50 per mm^3 – no (%)	93 (20.0)
50-199 per mm^3 – no (%)	145 (31.3)
200-349 per mm^3 – no (%)	99 (21.3)
> 350 per mm^3 – no (%)	127 (27.4)
HIV-1 viral load Median (IQR) – log_{10} copies/ml	4.4 (3.9-5.1)
<100,000	336 (72.4)
≥100,000	128 (27.6)
K65R/N present at baseline – no (%)	227 (50.2)
M184V/I present at baseline – no (%)	391 (86.5)
Int/high TDF resistance –no (%)	264 (58.5)
Int/high ZDV resistance – no (%)	83 (18.4)
Int/high 3TC resistance – no (%)	415 (92.0)

>95% completion rate!

Paton et al CROI 2021

NADIA: DTG vs DRV 90.2% vs 91.7%, non-inferior



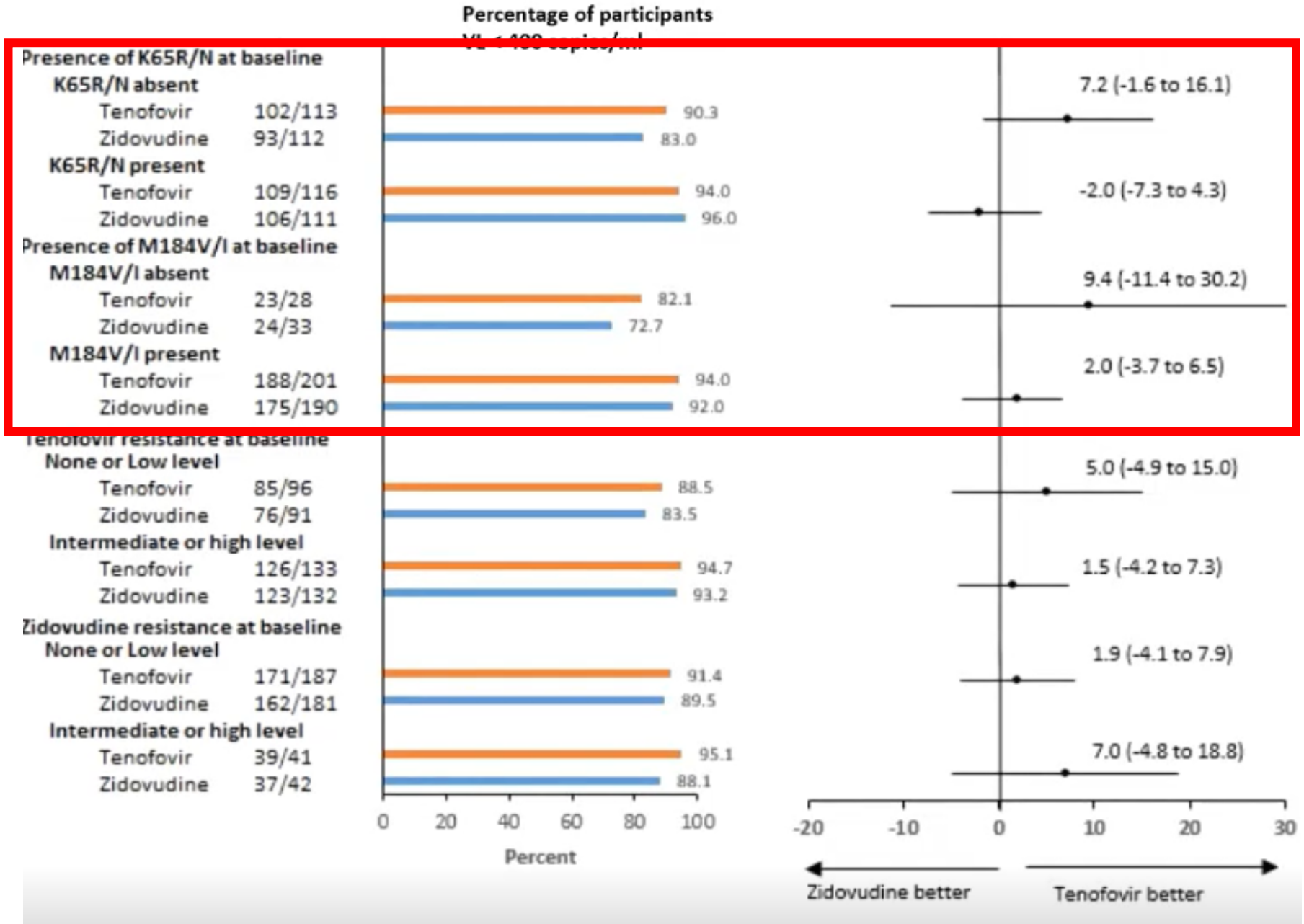
Resistance mutations:

4 in DTG arm

0 in DRV arm

Paton et al CROI 2021

NADIA: TDF vs ZDV 92.3% vs 89.6%, non-inferior



Paton et al CROI 2021

NADIA: Lessons

- Win for Public Health approach (yay!)

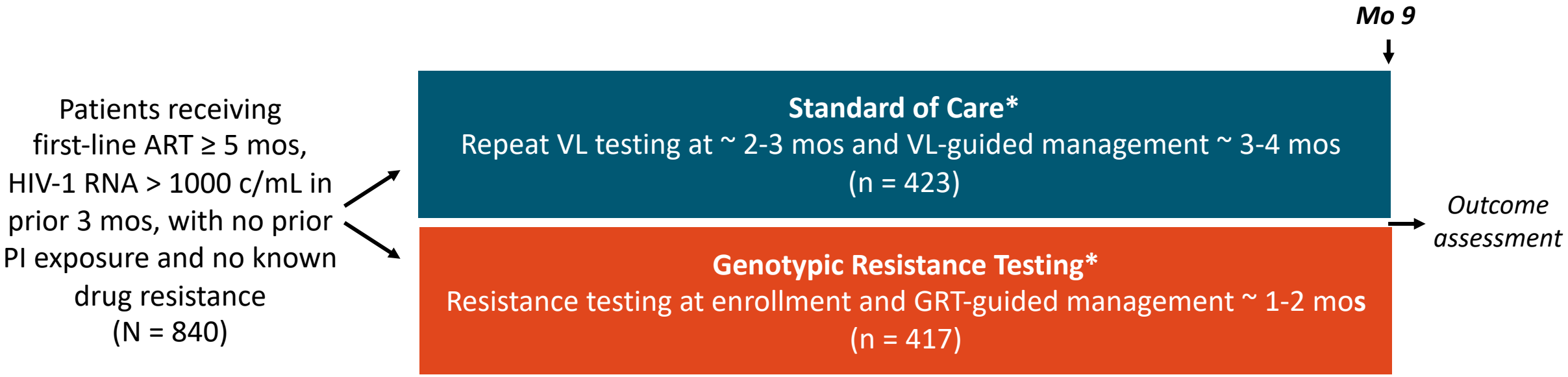
- DTG or DRV both excellent options in second line settings
- TDF/FTC (with either DRV or DTG) worked even in those with predicted resistance to TDF/XTC (K65R/M184V) !!
  - End of ZDV?
  - Re-calibrate NRTI mutations in presence of these powerful anchor agents?

- 4 people with DTG resistance

Also see Keiser et al: Public-Health and Individual Approaches to Antiretroviral Therapy: Township South Africa and Switzerland Compared. PLOS Medicine 5(9): e195 2008

REVAMP: genotypic resistance testing–guided vs Std of care

- Randomized, open-label, pragmatic study at 5 publicly operated clinics in Uganda and South Africa



*All patients received routine clinical care per clinic protocols.

- Primary endpoints: HIV-1 RNA < 200 copies/mL at Mo 9 following enrollment; lost to follow-up or death attributed to treatment failure
- Secondary endpoints: undetectable HIV-1 RNA; HIV-1 RNA suppression on initial therapy; acquired resistance; lost to follow-up; 9-month cumulative mortality

Siedner. CROI 2021. Abstr 95.

Slide credit: clinicaloptions.com

REVAMP: Primary and Secondary Endpoints at Mo 9

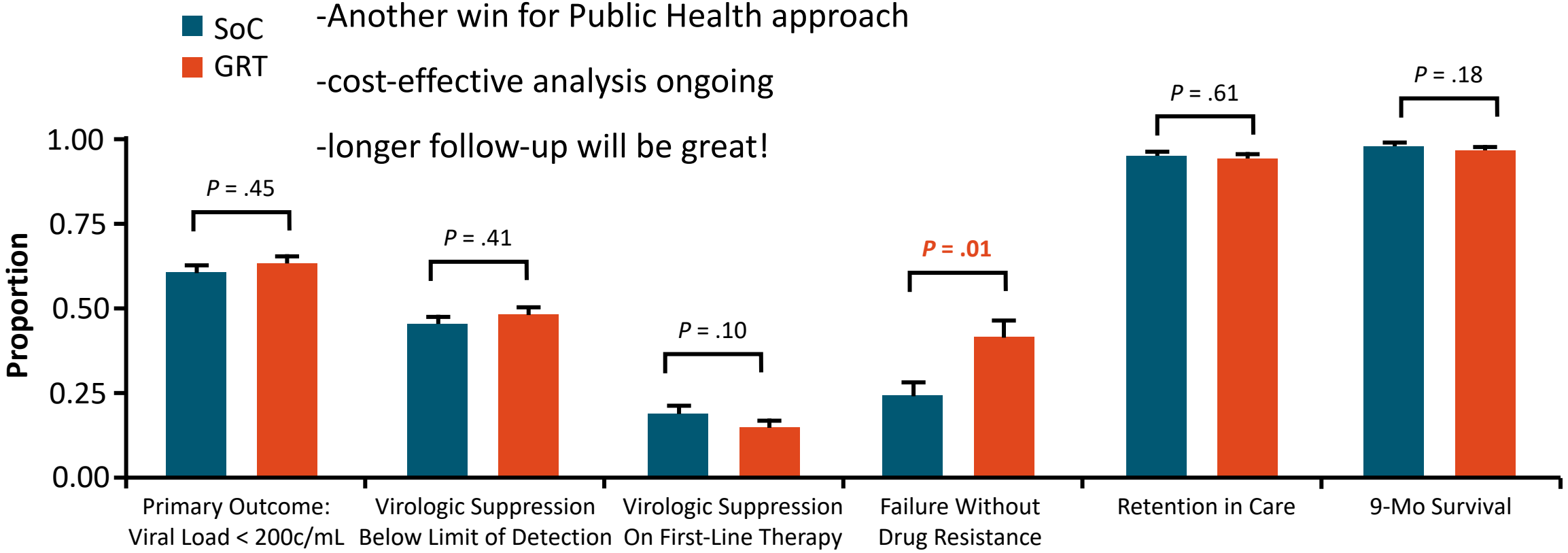
Lessons

-Can we do without routine resistance testing in these settings (only do for surveillance purposes in select samples?)

-Another win for Public Health approach

-cost-effective analysis ongoing

-longer follow-up will be great!



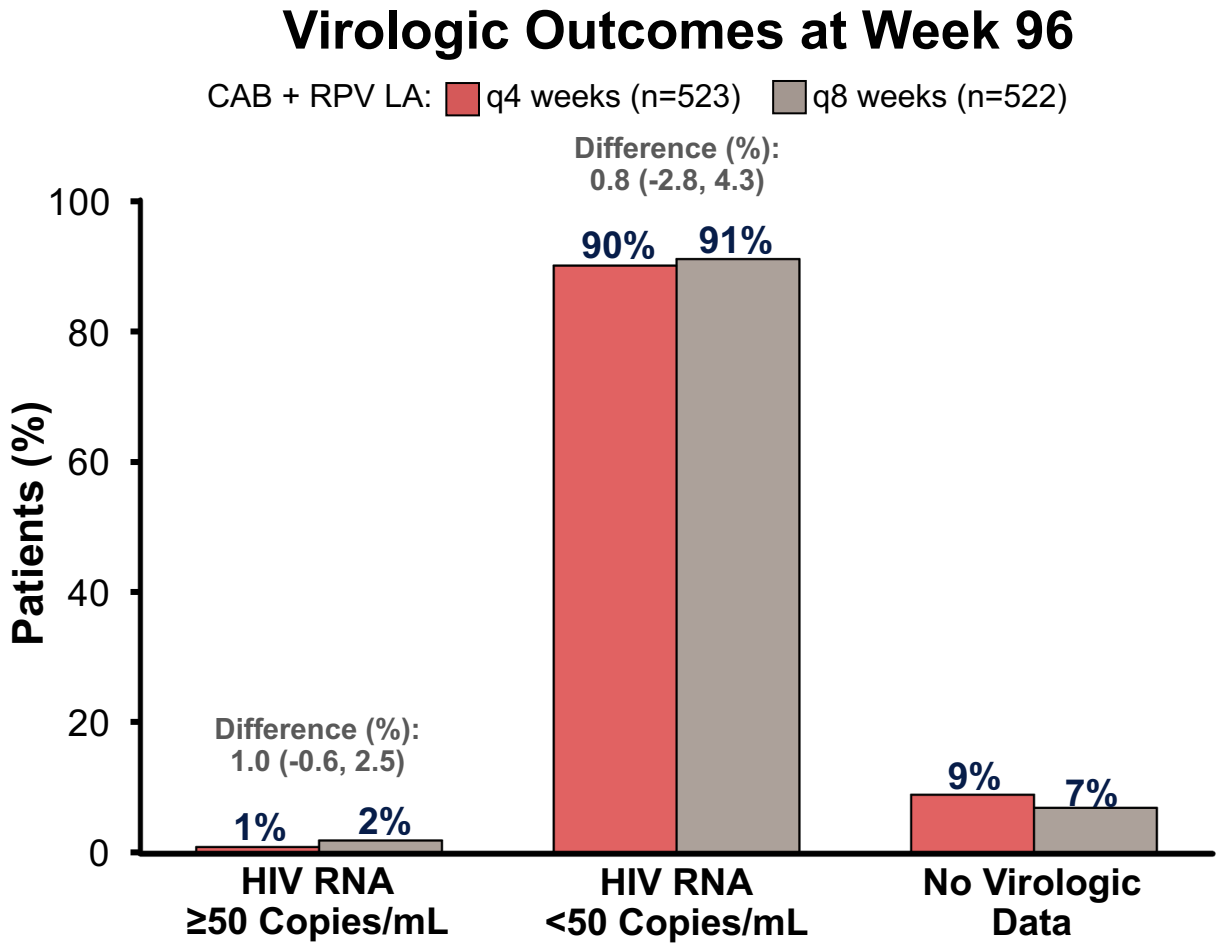
Siedner. CROI 2021. Abstr 95.

Slide credit: clinicaloptions.com

ATLAS-2M Study 96 weeks: Q4 Versus Q8 Weekly Dosing of Cabotegravir + Rilpivirine LA as Maintenance Therapy

- Cabotegravir + rilpivirine LA q8 weeks was non-inferior to q4 weeks at week 96
  - Similar virologic non-response
  - Similar rates of virologic suppression maintained
- Confirmed virologic failure rate
  - q4 versus q8 weeks: 1% versus 2%
  - All confirmed virologic failures (n=11) retained phenotypic sensitivity to dolutegravir
  - Confirmed virologic failures with rilpivirine RAMs
    - q8 versus q4 weeks: 7/9 versus 1/2
- No new safety signals

-Q8 weeks definitely easier than Q4 weeks
-Implementation challenges remain
-Which patients most likely to benefit? Lifestyle choice?



Jaeger H, et al. *v*CROI 2021. Abstract 401.

ATLAS-2M Study: simulations of effect of missed visits

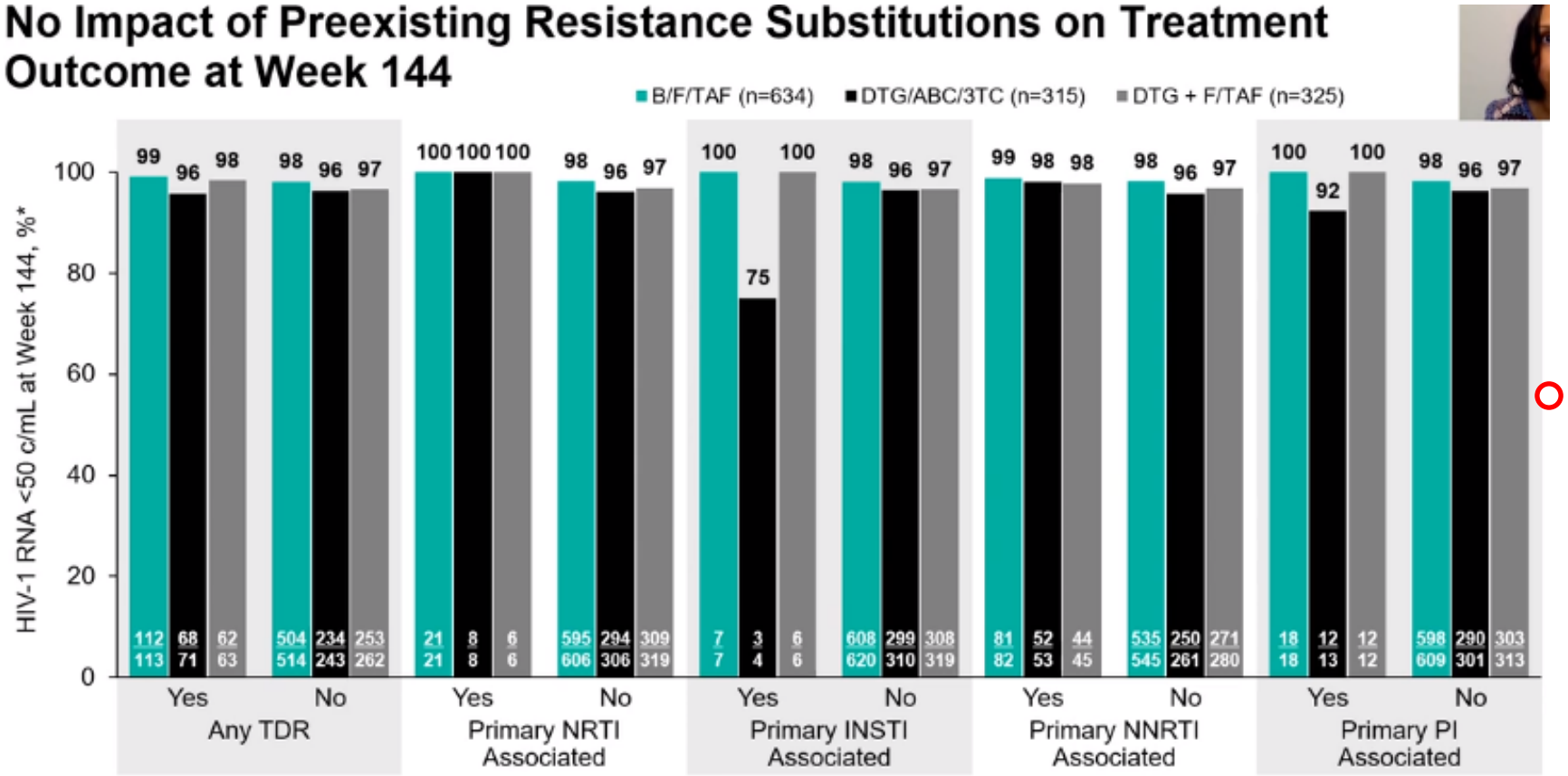
Conclusions

- Adherence to the dosing schedule of Q2M regimen is strongly recommended.
- CAB injection delays of up to 1 week were predicted to have minimal impact, but longer delays have a greater impact, particularly for the 2nd injection.
- CAB oral bridging was predicted to provide therapeutic and safe exposure for planned interruptions in CAB LA IM injection.
- Regardless of oral bridging, CAB simulations support:
  - ≤2 months between the 1st and 2nd injections or ≤3 months between subsequent injections (i.e., injection is delayed by ≤1 month): resume 3 mL injections Q2M as soon as possible.
  - >2 months between the 1st and 2nd injections or >3 months between subsequent injections (i.e., injection is delayed by >1 month): re-initiate the Q2M regimen beginning with an initiation injection of 3 mL followed by a 2nd injection of 3 mL one month later and injections of 3 mL Q2M thereafter.
- Guidance for resuming CAB LA injections following injection delays and CAB oral bridging is aligned with RPV as part of a complete HIV treatment regimen.

CAB: cabotegravir; IM: intramuscular; LA: long-acting; PrEP: pre-exposure prophylaxis; Q2M: once every 2 months.

Han et al. CROI 2021; Virtual. Abstract # 1327.

HIV WITH TRANSMITTED DRUG RESISTANCE IS DURABLY SUPPRESSED BY B/F/TAF AT WEEK 144



More argument against routine baseline resistance testing?

- >99% of B/F/TAF participants with preexisting resistance substitutions had virologic suppression at Week 144 or last visit

*LOCF outcome analysis did not include 7 B/F/TAF participants and 1 DTG/ABC/3TC participant who had no on-treatment postbaseline HIV-1 RNA data; 1 of these B/F/TAF participants had a primary PI-associated resistance substitution.

Also see Hyle E CID 2020 on cost-effectiveness of routine resistance testing (it was not!)

M184 and switch to DTG/3TC? Observational study

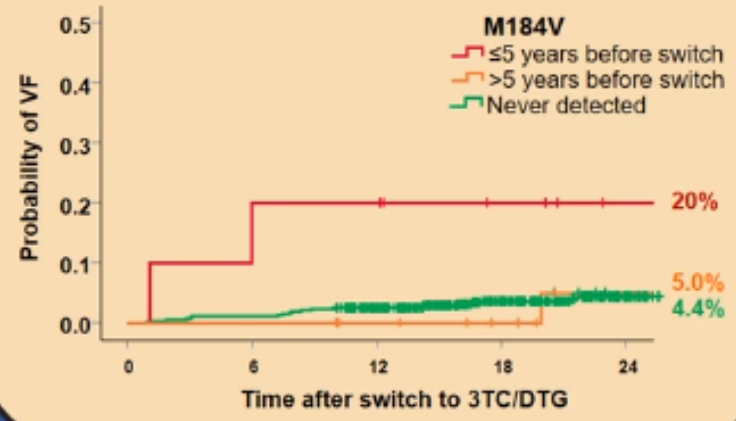
Probability of VF after 3TC/DTG switch

Overall probability at 1 year: 2.8%
Overall probability at 2 years: 4.8%

No significant difference in the probability of VF was found according to the presence/absence of M184V (1 yr: 5.4% vs 2.6%; 2 yrs: 9.2% vs 4.4%; p=0.345).

A significant higher probability of VF was found in individuals with M184V detected ≤5 yrs before switch compared to those with M184V detected >5 yrs and those without M184V (Figure).

Kaplan-Meier estimates of VF according to M184V absence/presence and its time of last detection



Factors associated with VF after 3TC/DTG switch

Cox regression analysis confirmed that past M184V influenced VF only in the context of a more "recent" (<5 years) detection. Other factors associated with VF were risk factor, zenith viremia and previous resistance to at least 3 classes.

Factors significantly associated with virological failure at uni-multivariable Cox regression analyses

Variables	Hazard ratio (HR, 95% C.I.) to experience VF			
	Crude HR	P value	Adjusted HR	P value
Risk factor, n (%)				
Homosexual	1		1	
Heterosexual	**4.8 (1.8-13.1)**	**0.002**	**3.8 (1.1-13.3)**	**0.034**
Drug abuse	2.2 (0.5-9.1)	0.290	0.9 (0.1-5.4)	0.886
Sexual	2.2 (0.3-18.6)	0.479	2.3 (0.3-21.2)	0.458
Viremia Zenit (copies/mL), n (%)				
<100,000	1		1	
100,000-500,000	2.8 (0.9-8.1)	0.063	3.3 (1.0-11.1)	0.050
>500,000	**4.1 (1.4-12.0)**	**0.010**	**3.6 (1.1-12.0)**	**0.041**
Cumulative class resistance before switch, n (%)				
None	1		1	
1	1.6 (0.6-4.4)	0.366	1.3 (0.4-3.9)	0.635
2	3 (0.8-10.3)	0.089	5.1 (0.9-28-6)	0.065
≥3	**7.1 (2-24.7)**	**0.002**	**23.0 (3.1-168.5)**	**0.002**
Past M184V according to detection time, n (%)				
Never detected	1		1	
Detected ≤5 years before switch	**5.6 (1.3-23.7)**	**0.020**	1.9 (0.3-14.6)	0.518
Detected >5 years before switch	0.7 (0.1-5.6)	0.778	**0.1 (0.0-1.2)**	**0.040**

No emergent DTG or NRTI resistance

But why did they switch??

Santoro et al CROI 2021

Notable symposium: Jose Arribas **TRIPLE DRUG ART, DUAL ART, OR JUST ART?**

Two drug regimens

- One RTI adds antiviral activity and genetic barrier to a bPI or DTG (as opposed to say MVC)
- 3TC adds antiviral activity even in those with M184 history

RISK/BENEFIT RATIO DUAL Vs TRIPLE

EFFICACY

- So far triple regimens have not proven an efficacy benefit in comparison with DTG/3TC or DTG+RPV

RESISTANCE

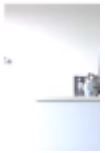
- Compared to triple drug ART risk of emergent resistance appears minimal although is not 0 and appears larger for DTG+RPV in switch[1] (1.1% @ 148 wk) than for DTG+3TC in naïve[2] (0.13% @ 144 wk) or DTG/3TC in switch[3] (0% @ 96wk)

COST

- Pharmacoeconomically DTG/3TC is a dominant strategy[4]

UNKNOWNS

- Advanced disease
- Test and treat
- Pregnancy
- TB
- Long term weight impact



COVID-19 Hospitalizations Among Persons With HIV or Solid Organ Transplant

- National COVID Cohort Collaborative 39 centers; 2020-2021)
  - Adults who had COVID-19 (n=509,092)
- Primary outcomes
  - Hospitalization and mechanical ventilation
- Persons with HIV and solid organ transplant recipients
  - More likely to be hospitalized and require mechanical ventilation during hospitalization
  - Increased hospitalization risk was driven mostly by the high burden of comorbidities in both groups

Adjusted Odds Ratios for Hospitalization or Mechanical Ventilation

	Hospitalization (95% CI)	Mechanical Ventilation (95% CI)
HIV negative/no SOT (reference: n=501,416)	1.0	1.0
HIV positive/no SOT (n=2932)	1.32* (1.22, 1.43)	1.86* (1.56, 2.22)
SOT/HIV negative (n=4633)	1.69* (1.58, 1.81)	1.96* (1.74, 2.12)
HIV positive/SOT (n=111)	1.65† (1.06, 2.56)	3.73* (2.08, 6.67)

Adjusted for demographics, study site, and comorbidities (severe liver disease, diabetes, cancer, kidney disease, and total comorbidities [0, 1, 2, ≥3]).
SOT: solid organ transplant.
*P<0.01 and †P<0.05.

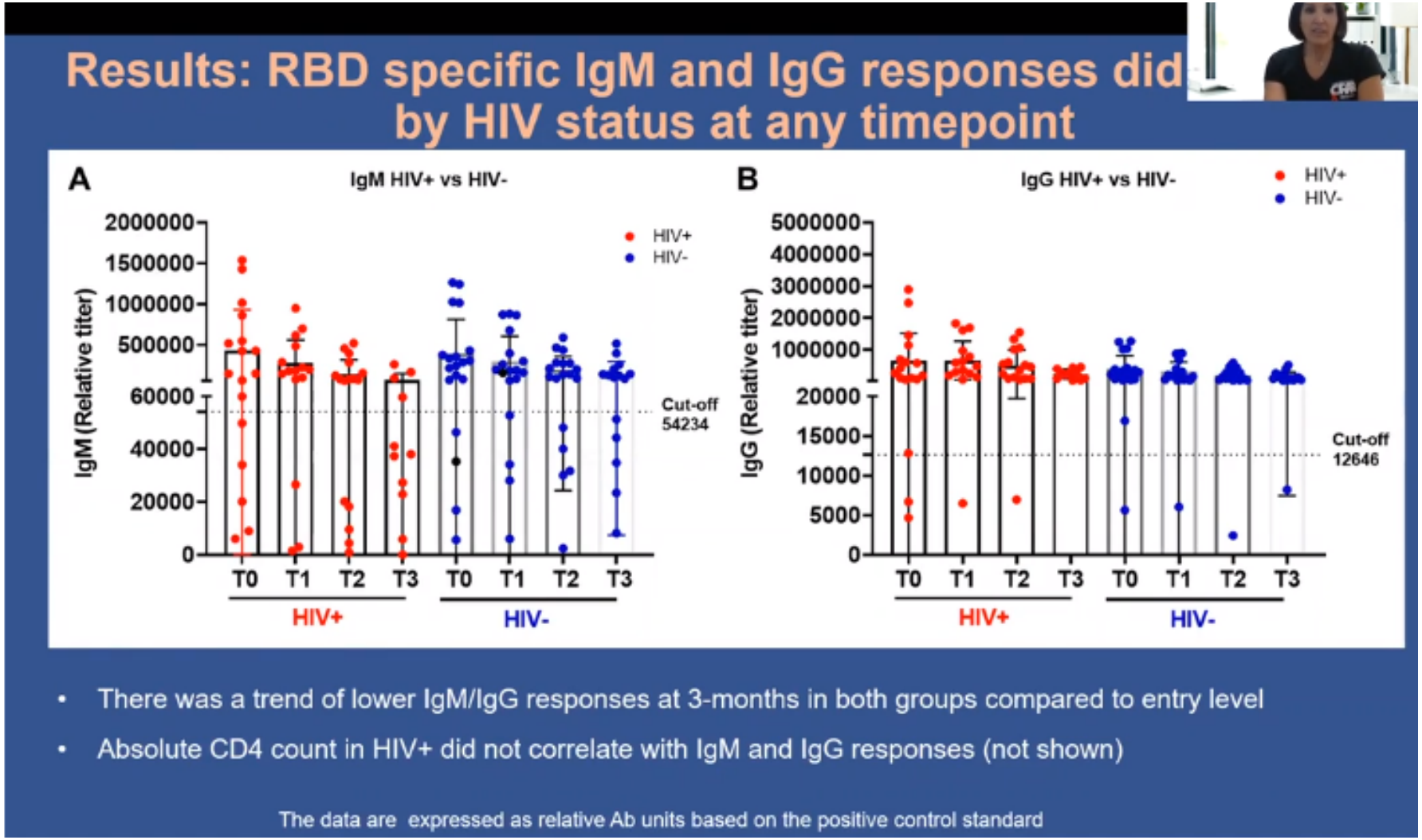
Note: large but still select sample; higher than expected rate of hospitalization overall; no data on ART/VL

HIV not recognized as a co-morbidity for vaccine prioritization in many places yet- perhaps it should be!

COVID-19 positive: RT-PCR (>99%) or antigen positive (<1%).

Sun J, et al. *v*CROI 2021. Abstract 103.

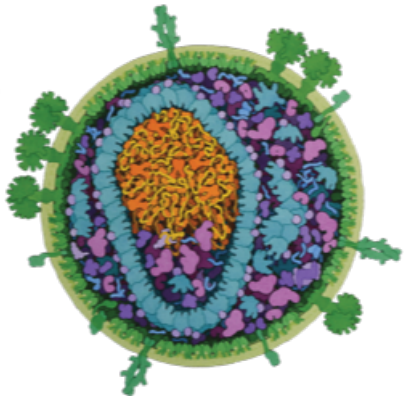
Antibody response after infection in HIV+ve on ART



RBD= spike receptor binding protein

CROI 2021 Update

virtual



CROI
Conference on Retroviruses and Opportunistic Infections

Raj Gandhi, MD
Massachusetts General Hospital
Harvard Medical School

Thanks to Efe Airewele and Dr. Mike Dougan with assistance with slides

Outline

- Novel ART
- ART during pregnancy
- COVID-19 Treatment and Prevention

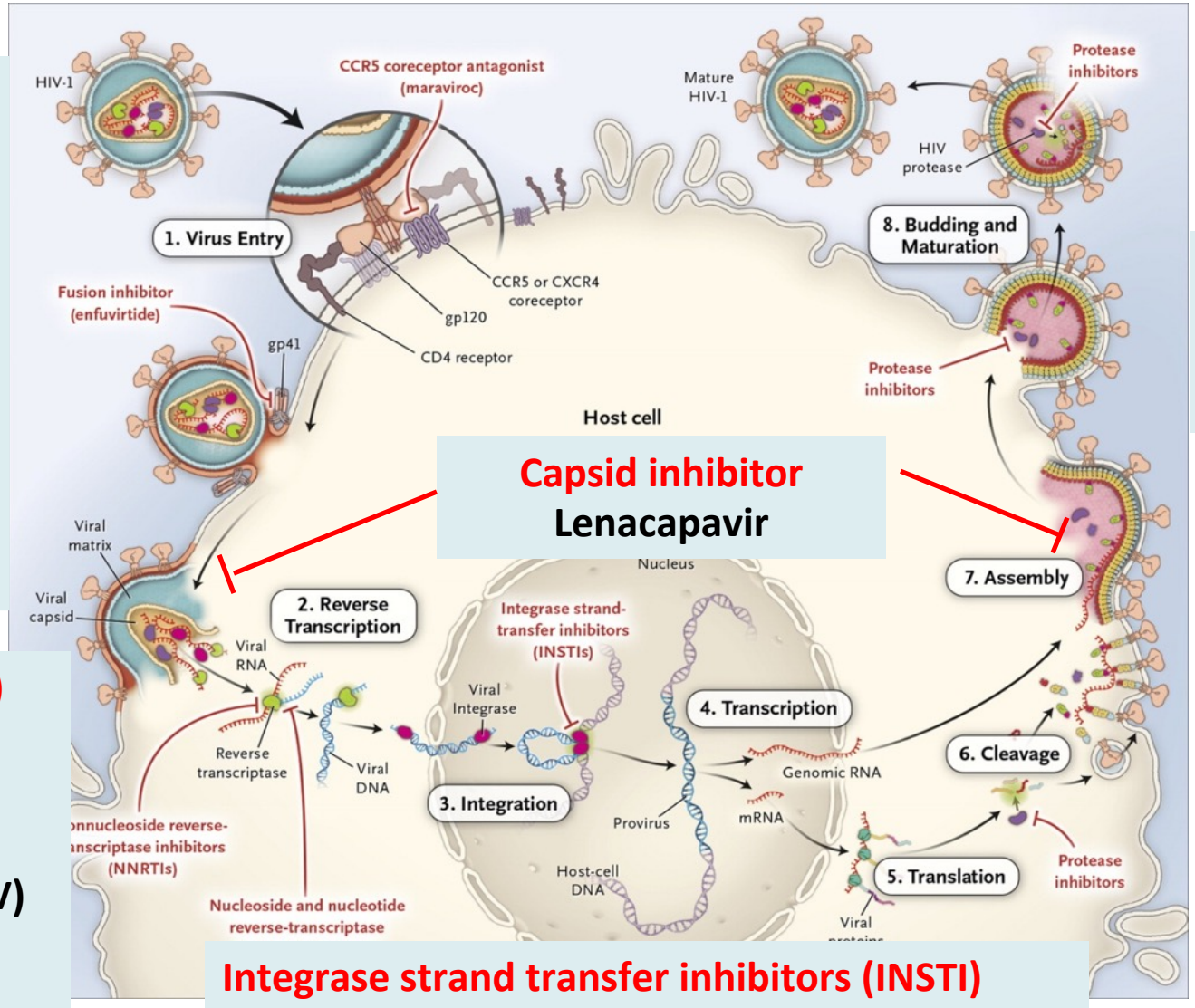
New Drugs in Development

Entry inhibitors:

- **Attachment inhibitor:**
  - **Fostemsavir**
  - **UB-421**
- **CCR5 Antagonist:**
  - **Leronlimab**
- **Fusion Inh.: Albuvirtide**
- **Multisite: Combinectin**
- **Broadly neutralizing Abs**

Reverse Transcriptase Inh. (RTI)

- **Nucleoside RTI (NRTIs)**
- **Nonnucleoside RTI (NNRTIs)**
  - **Long-acting rilpivirine (RPV)**
  - **MK-8507**
- **Nucleoside RT translocation inhibitor: Islatravir**



Capsid inhibitor
Lenacapavir

Integrase strand transfer inhibitors (INSTI)
Long-acting cabotegravir (CAB)

Maturation inhibitor

GSK3640254 (non-boosted)

Gandhi M, Gandhi RT. NEJM 2014;371:248-259.

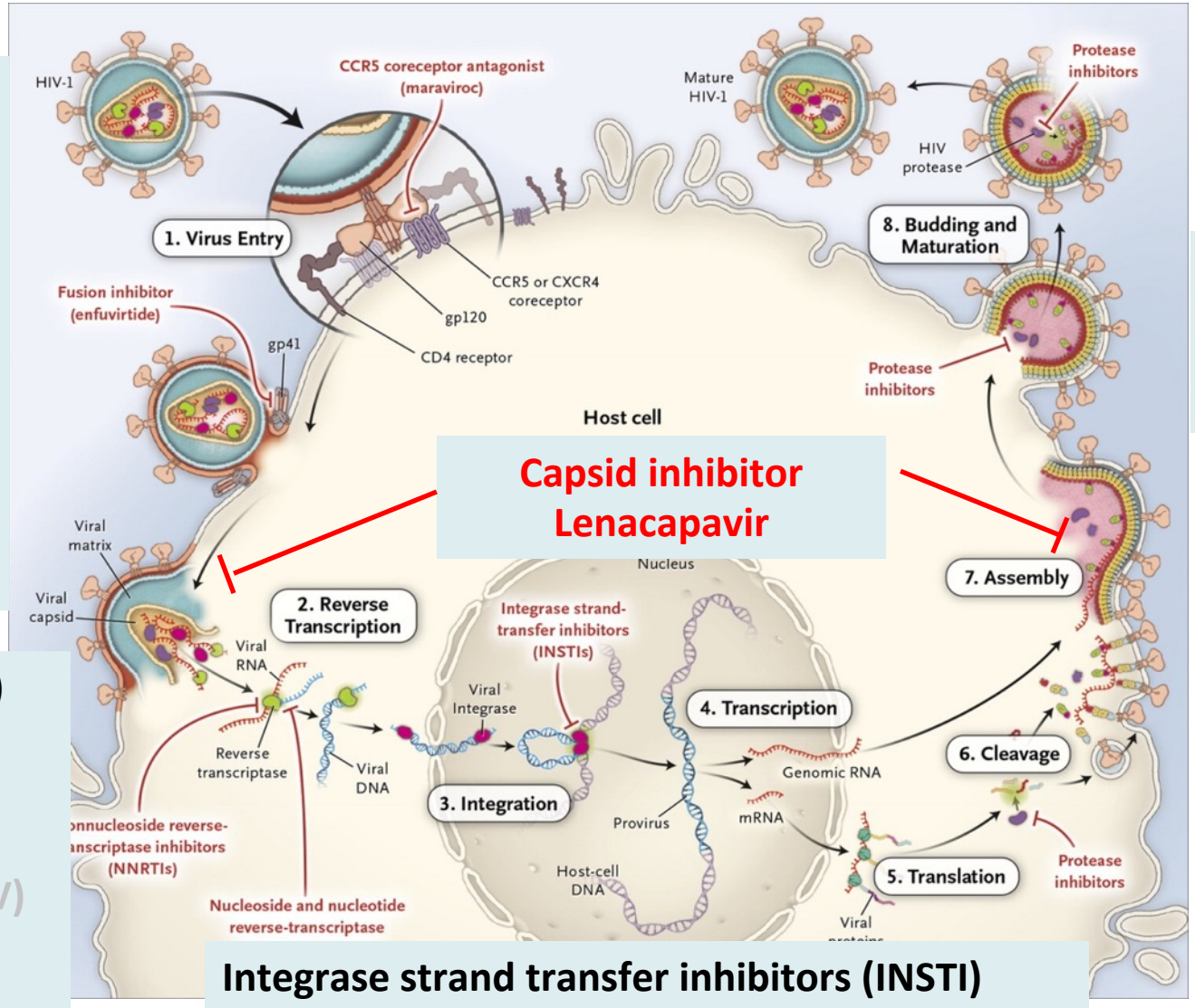
New Drugs in Development

Entry inhibitors:

- Attachment inhibitor:
  - Fostemsavir
  - UB-421
- CCR5 Antagonist:
  - Leronlimab
- Fusion Inh.: Albuvirtide
- Multisite: Combinectin
- Broadly neutralizing Abs

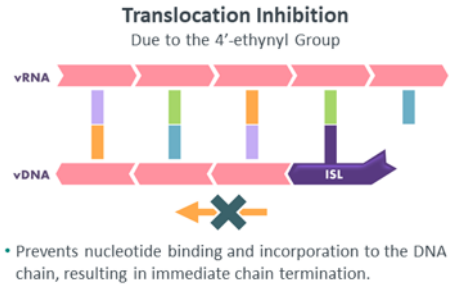
Reverse Transcriptase Inh. (RTI)

- **Nucleoside RTI (NRTIs)**
- **Nonnucleoside RTI (NNRTIs)**
  - Long-acting rilpivirine (RPV)
  - MK-8507
- **Nucleoside RT translocation inhibitor: Islatravir**

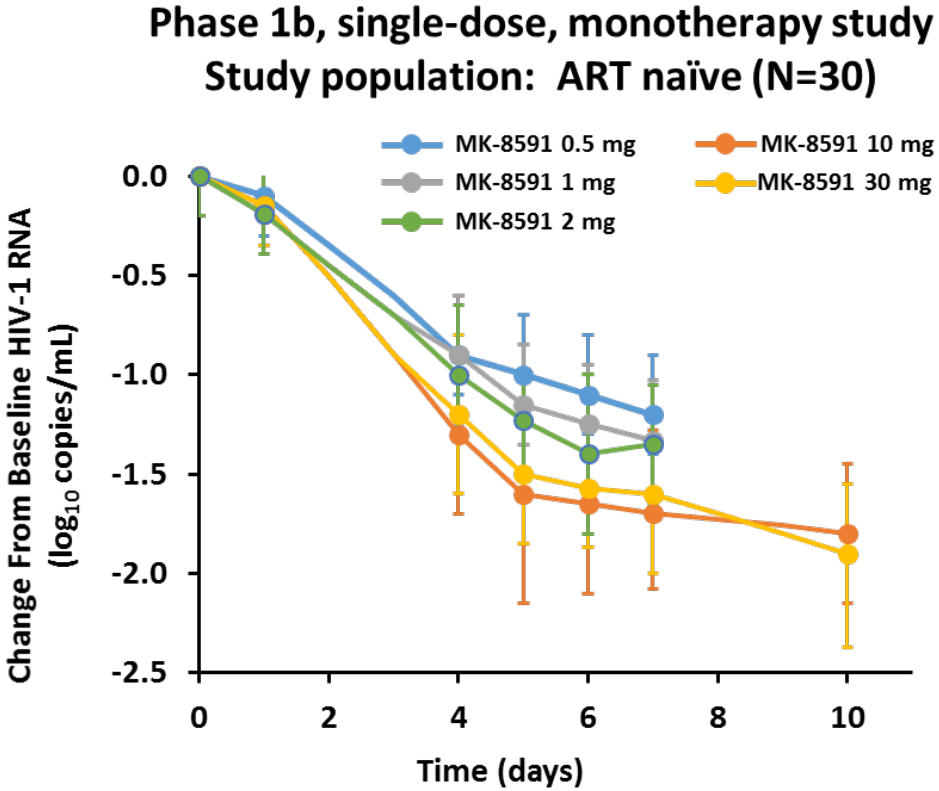


Gandhi M, Gandhi RT. NEJM 2014;371:248-259.

Islatravir (MK-8591)



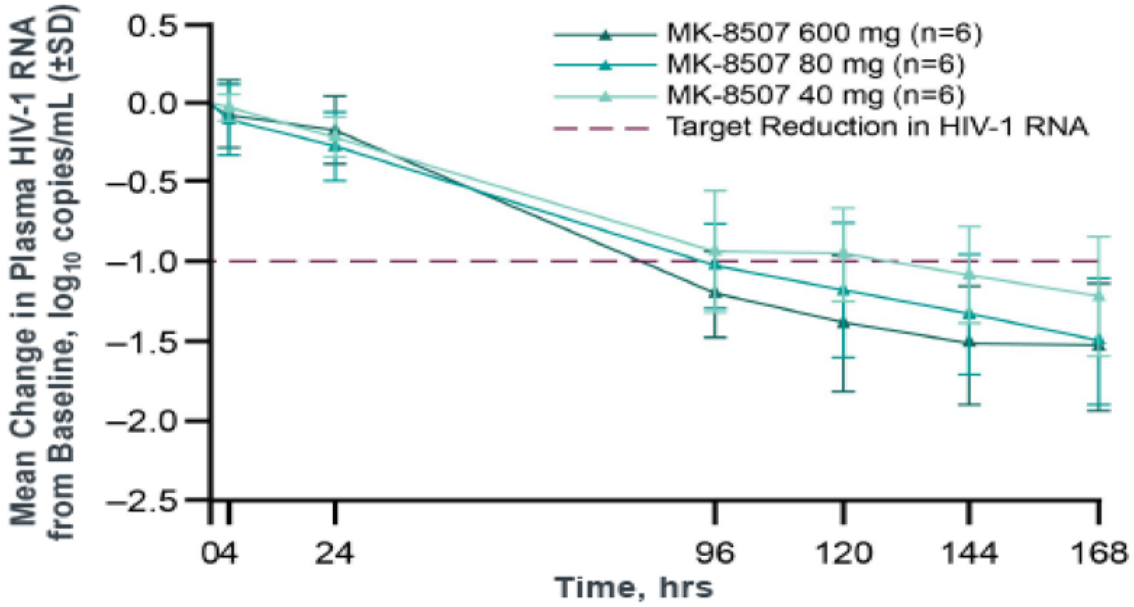
- Nucleoside RT translocation inhibitor (NRTTI)
- Long intracellular half-life (78-120 h): potential for once daily, once weekly or less frequent dosing
- Phase 3 trials: evaluating ISL/DOR (0.75 mg/100 mg) daily for:
  - Switch[1,2]
  - People with multi-drug resistance[3]
  - Treatment naïve participants[4]



Schurmann et al, Lancet HIV, 2020; [1]NCT04223791; [2]NCT04223778; [3]NCT04233216; [4]NCT04233879; [5]Markowitz M, CROI 2020, #89LB; [6]NCT04003103; [7]Matthews R, IAS 2019, TUAC0401LB

MK-8507: Investigational NNRTI

- High antiviral potency, including against virus with K103N, Y181C, G190A (similar resistance profile as doravirine)
- PK supports once weekly dosing (mean terminal half-life: 56-69 hr)
- Single oral dose in people with HIV (n=18): all doses reduced VL >1 log
  - 1 patient developed F227C mutation
- Phase 2b switch trial: ISL/MK-8507 wkly

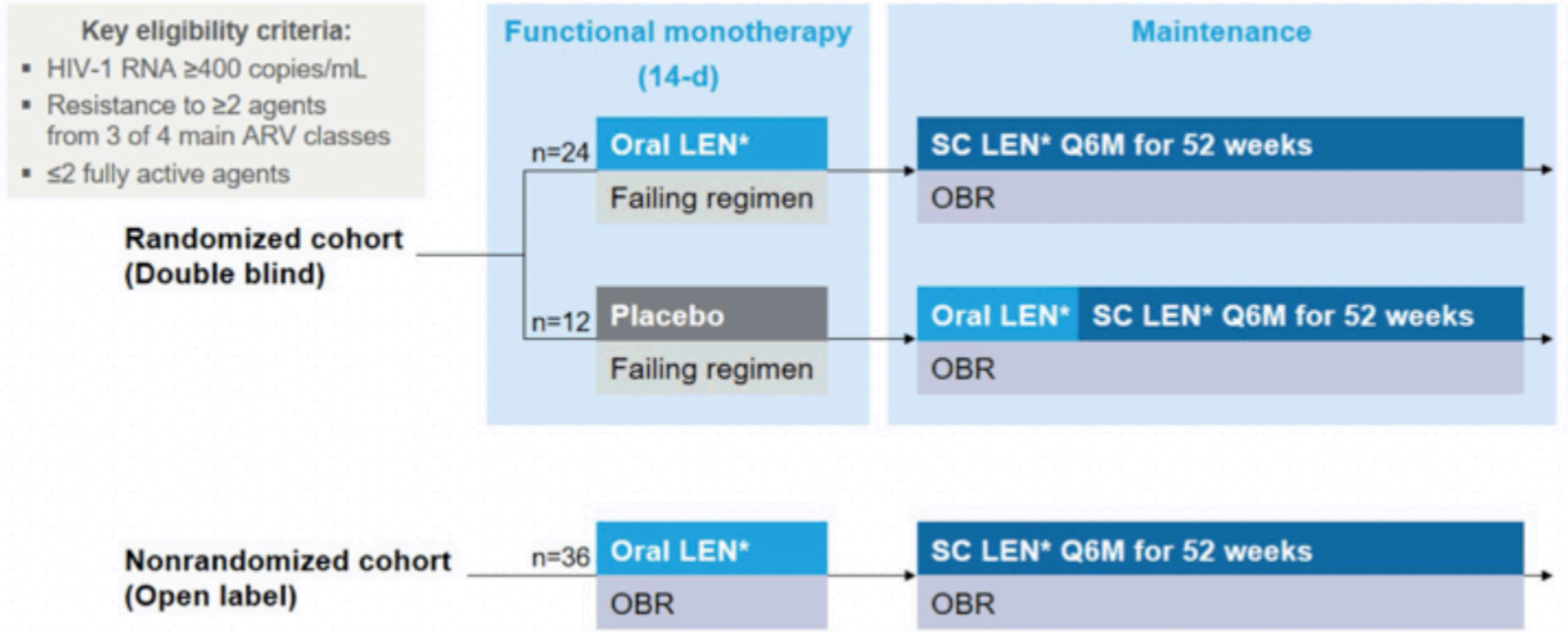


Ankrom W et al, HIV Glasgow, 2020; https://clinicaltrials.gov/ct2/show/NCT04564547?term=MK+8507&draw=2&rank=2
Diamond, T et al., CROI 2021, #129

Lenacapavir (LEN)

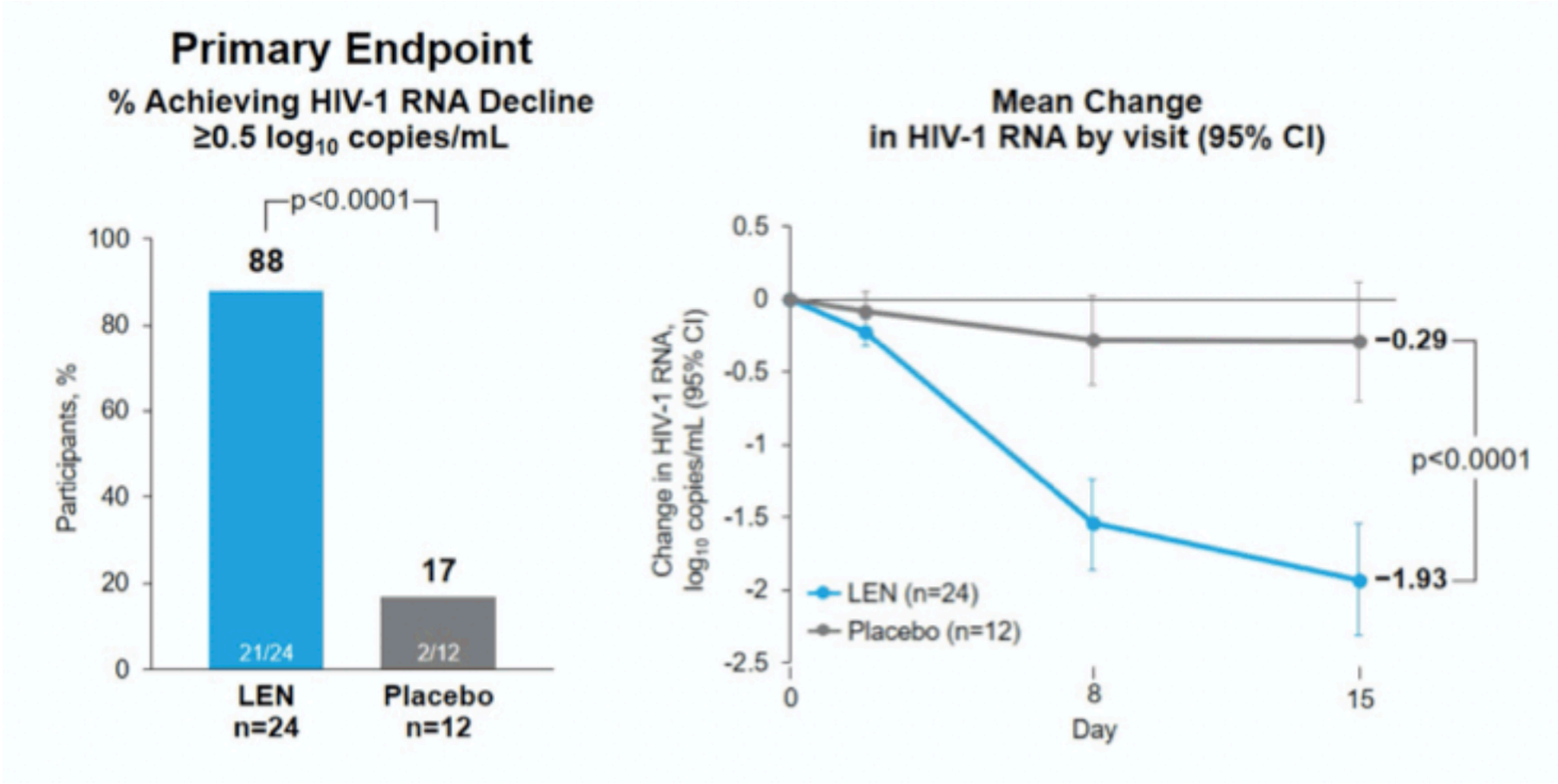
- Investigational capsid inhibitor. Oral formulation: median half-life 11-13 d; subcutaneous injection: every 6 months

CAPELLA: LEN in People with Multi-Drug Resistant HIV



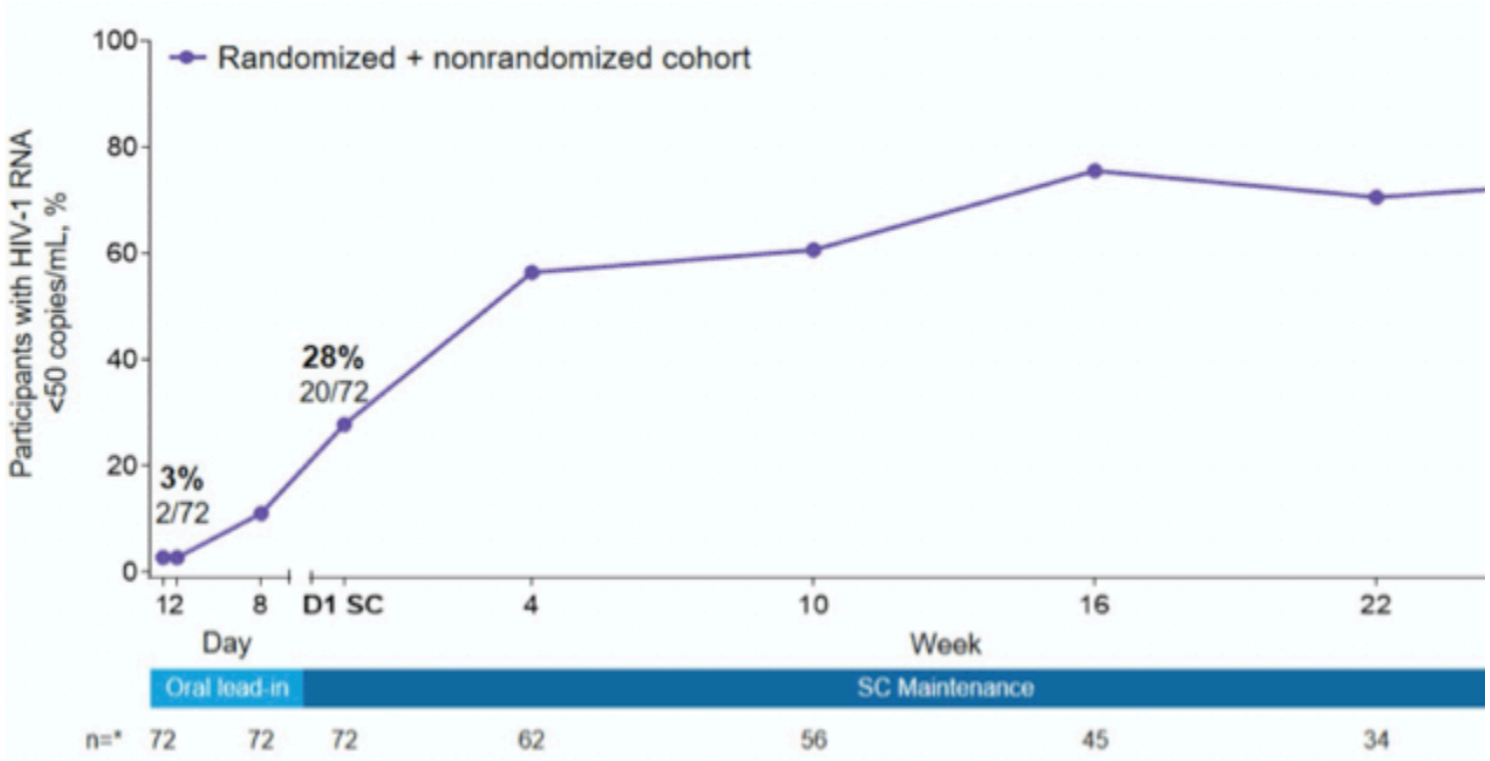
Segal-Maurer S et al, CROI 2021, #127

LEN: Antiviral Activity During Functional Monotherapy



Segal-Maurer S et al, CROI 2021, #127

HIV RNA <50 in Participants Receiving SC LEN



- 2 participants developed emergent capsid mutations (M66I +/- N74D) conferring high level LEN resistance (may affect replication capacity)
  - Both re-suppressed
- Injection site reactions: 46%
  - Pain: median duration 4 d
  - Erythema, swelling: 6-11 d
  - Nodules (grade 1) in 18%: few months

Segal-Maurer S et al, CROI 2021, #127

How do the long-acting drugs stack up?

PARTNERS WANTED!!!

Drug	Route	Dosing Interval	Long-acting Partner
Cabotegravir/rilpivirine	IM	Monthly/	
Islatravir (NRTTI)	PO/ Implant?	Daily; possil long	
GS-6207 (Capsid inhibitor)	SC/PO	Possibly ever	
Albuvirtide (fusion inh) + 3BNC117 (bNAb)	IV/IV	Being tested 4 we	
Ibalizumab	IV	Every	
UB-421	IV (SC?)	Every 2 wk	SAMS?
Leronlimab	SC	Every 1 wk	SAMS?
Broadly neutralizing Ab	IV (SC?)	?	?

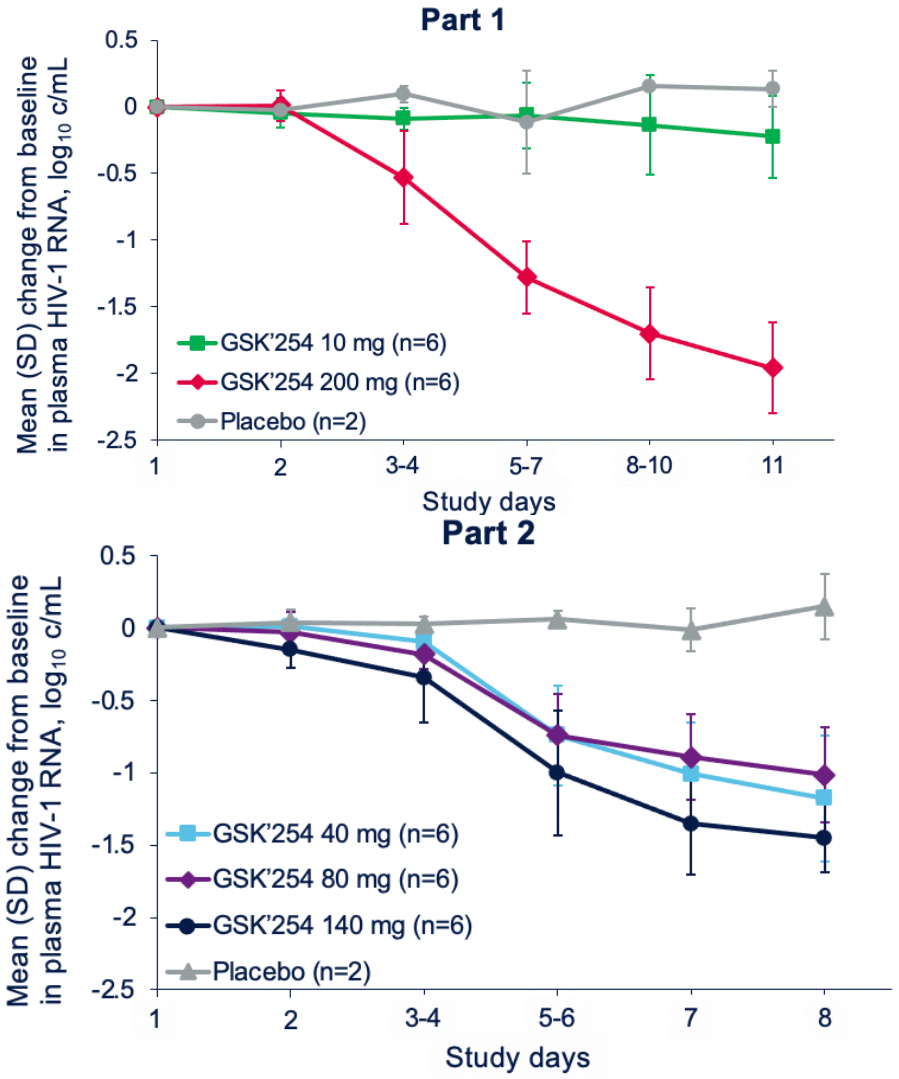
Gilead and Merck Announce Agreement to Jointly Develop and Commercialize Long-Acting, Investigational Treatment Combinations of Lenacapavir and Islatravir in HIV

March 15, 2021 6:45 am EST

SAMS: single agent maintenance of suppression

Maturation Inhibitor: GSK3640254 (GSK ‘254)

- Inhibits last protease cleavage event between capsid and gag –> immature, non-infectious virus
- Phase 2a study in treatment naïve adults
- Resistance emerged in participants receiving 10 d monotherapy (part 1)
- Protocol changed to 7 d monotherapy (part 2): no resistance
- Ongoing phase 2b study of GSK ‘254 with 2 NRTI in treatment naïve adults

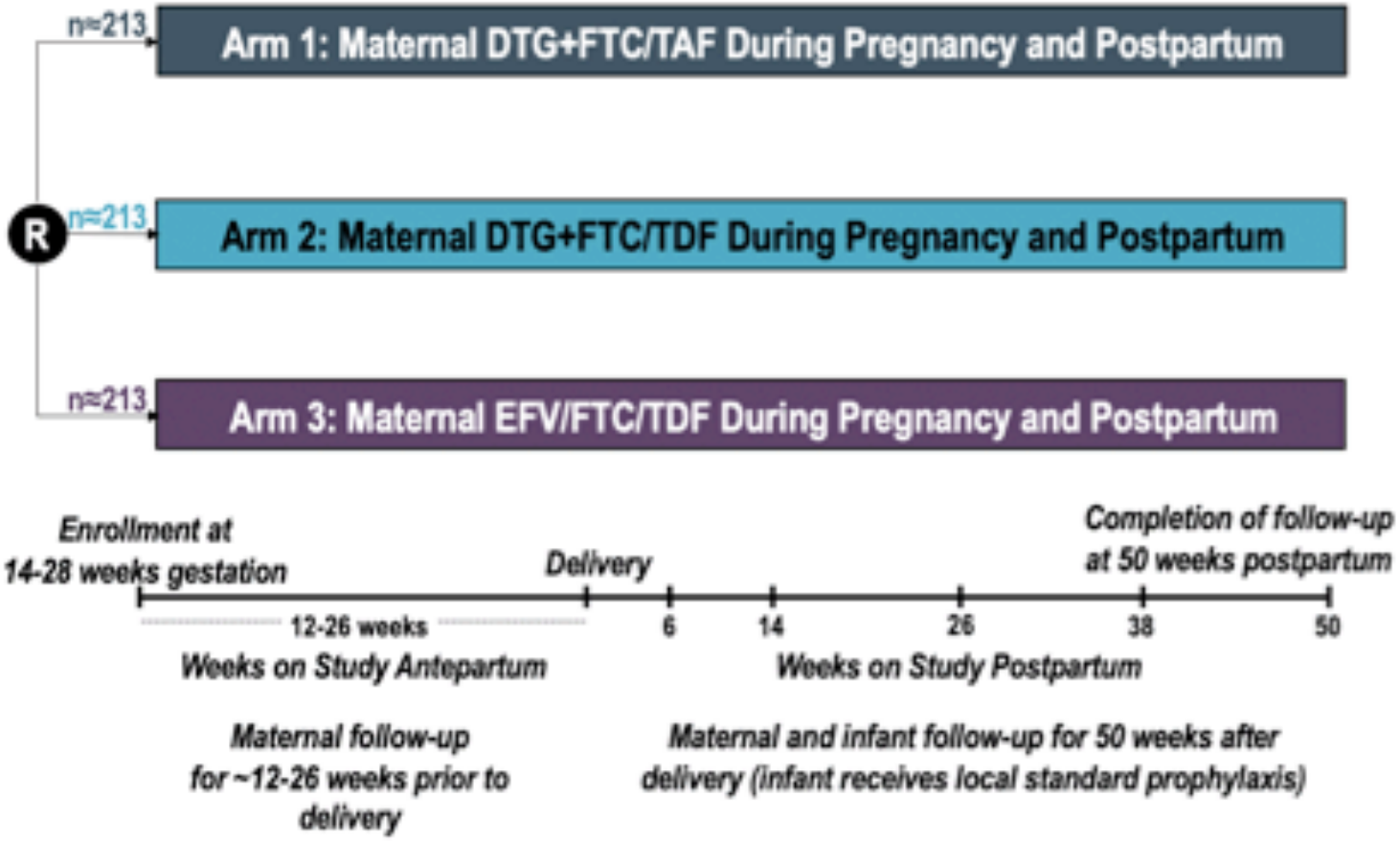


Spinner C et al, CROI 2021, #126

ART During Pregnancy

IMPAACT 2010 (VESTED)

- Phase III trial: safety and efficacy of DTG + FTC/TAF vs DTG + FTC/TDF vs EFV/FTC/TDF in ART-naive women initiating ART during pregnancy (14-28 wks gestation)



Who was in VESTED?
- Age: 26-27 yo
- Enrolled in Africa: 86-89%
- Median gestational age: 21-22 wk

Chinua. CROI 2021; #177

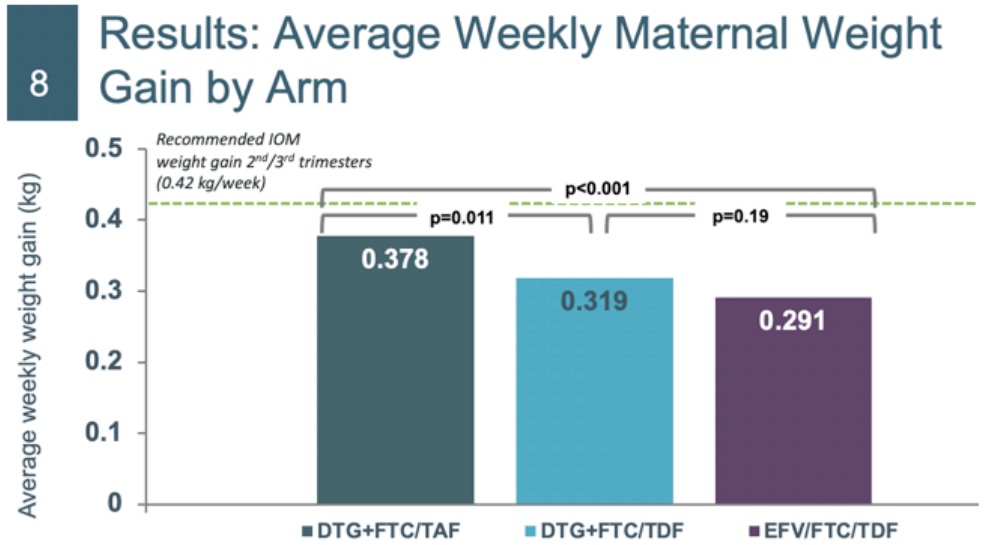
IMPAACT 2010: Results through Delivery

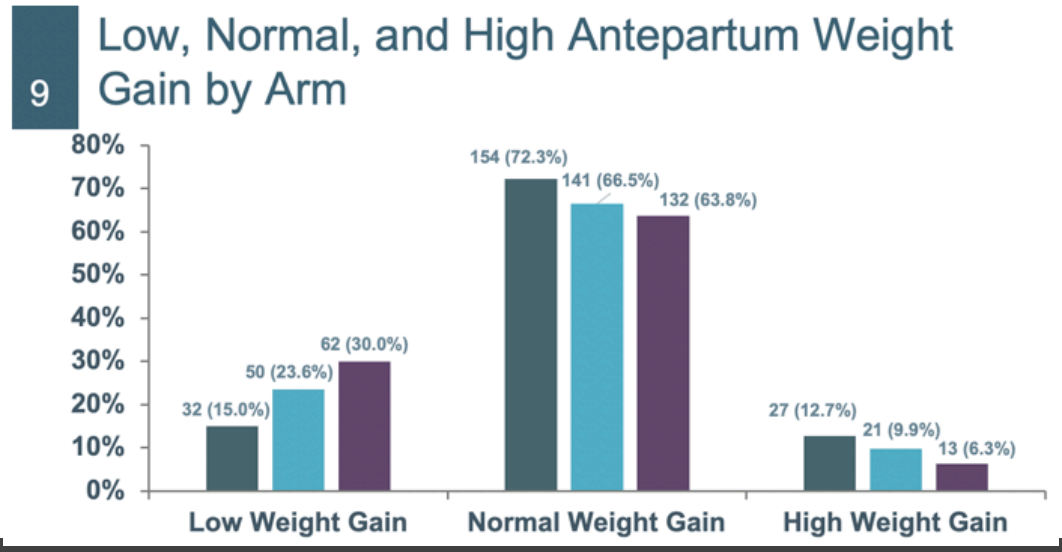
- Virologic efficacy of DTG-based ART at delivery superior to that of EFV/FTC/TDF (97.5% vs. 91%, p=0.005)
- Time to viral suppression shorter with DTG-based ART (*P* < .001)
- Adverse pregnancy outcomes significantly less frequent with DTG + FTC/TAF (24.1%) vs DTG + FTC/TDF (32.9%) and EFV/FTC/TDF (32.7%)
- Neonatal death significantly less frequent with DTG + FTC/TAF vs EFV/FTC/TDF (P = .019)

Chinua. CROI 2020. Abstr 130LB. NCT03048422.

IMPAACT 2010: Antepartum Weight Gain

- Both insufficient and excessive weight gain during pregnancy associated with adverse pregnancy outcomes
- Average weekly weight gain: DTG + TAF/FTC > EFV + TDF/FTC
- Significant association between higher average weekly weight gain and lower risk of adverse pregnancy outcome (HR 0.5, p=0.04)





Hoffman RM et al, CROI 2021. Abstr 13

What to Start in Pregnancy: DHHS Guidelines Feb 10, 2021

Two NRTIs

Abacavir/3TC

or

TDF/FTC or TDF/3TC

TAF/FTC – alternative NRTI

Plus

Bictegravir (insufficient data)
Elvitegravir/cobi (PK concerns)
DRV/cobi (PK concerns)
ATV/cobi (PK concerns)
DOR (insufficient data)
Fostemsavir (insufficient data)

Integrase inhibitor:

Raltegravir (twice daily) or

Dolutegravir (*Preferred ARV throughout pregnancy and for those who are trying to conceive*)

or

Protease inhibitor:

Darunavir/ritonavir (twice daily) or

Atazanavir/ritonavir

https://clinicalinfo.hiv.gov/en/guidelines/perinatal/whats-new-guidelines

COVID-19 Advances

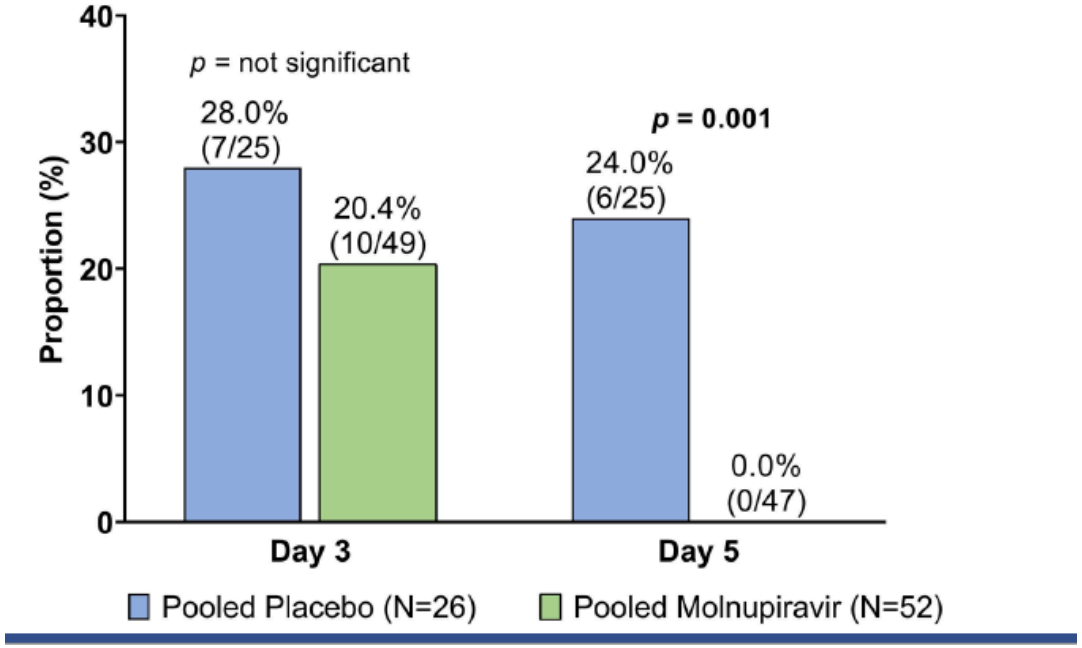
- Molnupiravir
- Monoclonal antibodies for treatment and prevention
- SARS CoV-2 variants and implications for vaccines

Molnupiravir

- Oral inhibitor of replication of SARS CoV-2: viral error catastrophe
- Big Blue assay: not mutagenic or genotoxic in mammals
- Phase 2a randomized trial in outpatients with symptomatic SARS CoV-2 infection (confirmed within 4 days of enrollment)
- Molnupiravir or placebo twice daily

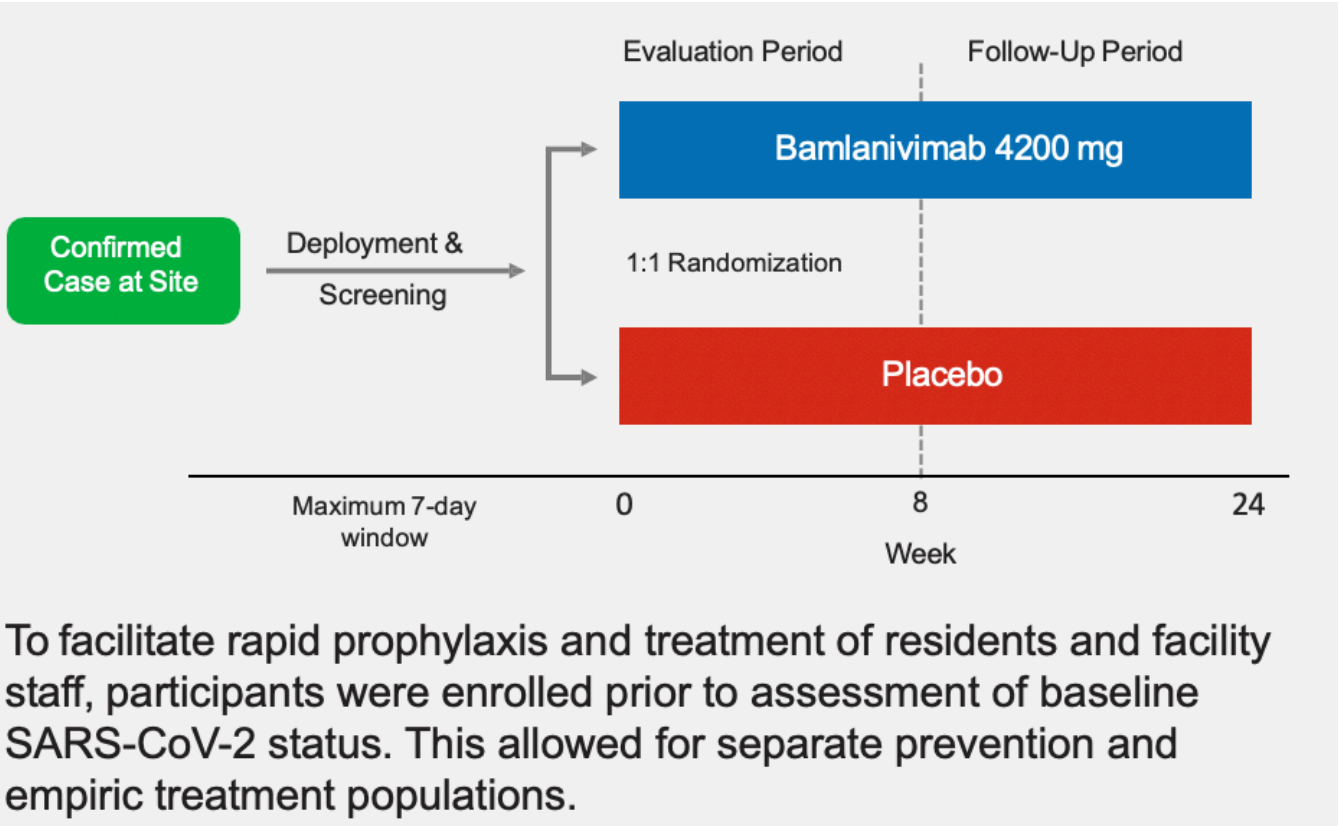
- N=202 treated participants; 182 with evaluable swabs; 43% positive baseline Cx

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



Painter W et al, CROI 2021, #777

Bamlanivimab for Prevention: BLAZE-2

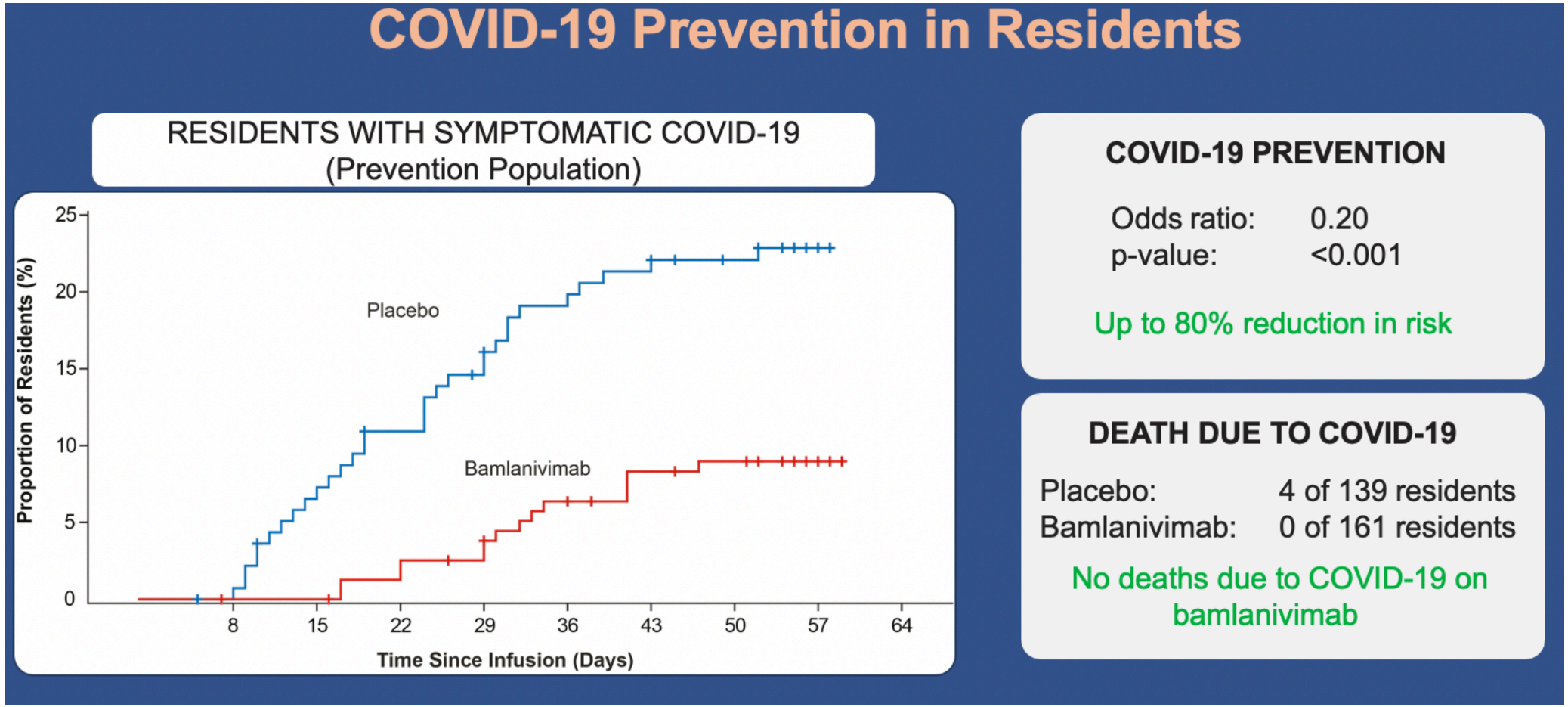


To facilitate rapid prophylaxis and treatment of residents and facility staff, participants were enrolled prior to assessment of baseline SARS-CoV-2 status. This allowed for separate prevention and empiric treatment populations.

- Ongoing Phase 3 randomized trial among residents and staff of long-term care facilities
- Analyzed data in participants who were negative at baseline for SARS CoV-2 by PCR and serology
- Key sub-populations:
  - Residents
  - High risk participants (all residents and high risk staff)

Cohen M et al, CROI 2021, #121

Bamlanivimab for Prevention: BLAZE-2

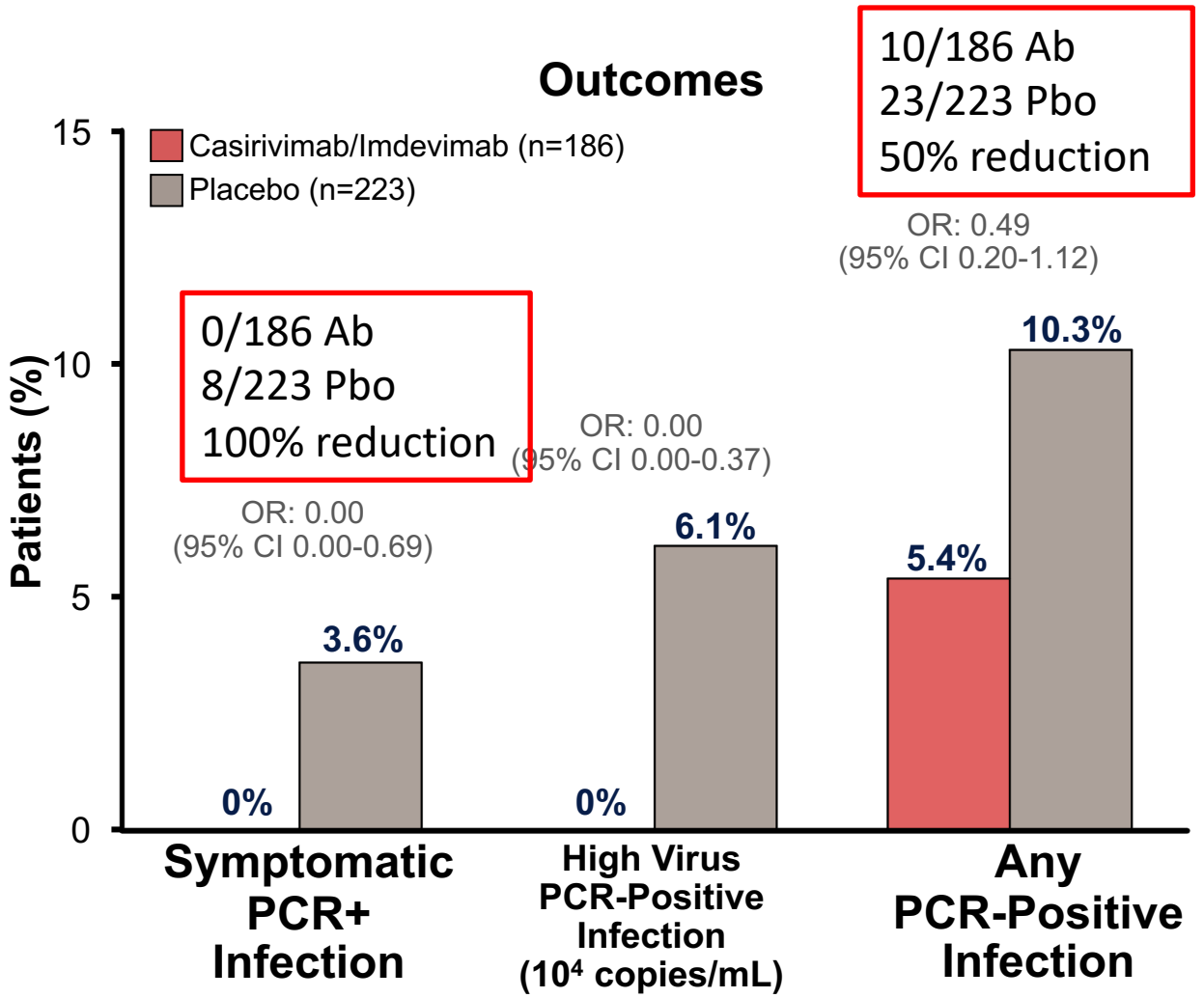


- Symptomatic COVID-19 in high-risk participants: 72% reduction
- Detection of SARS CoV-2 by PCR in residents: 76% reduction

Cohen M et al, CROI 2021, #121

Casirivimab/Imdevimab for Prevention

- Interim analysis of ongoing phase 3 trial: casiribivimab/imdevimab (600/600 mg sc) vs. placebo in asymptomatic participants within 96 h of household member testing positive
- 100-fold higher peak VL in placebo recipients
- VL >10,000: 13/21 (placebo) vs. 0/9 (Abs)
- Duration of PCR positivity shorter in antibody group



O'Brien MP, et al. *v*CROI 2021. Abstract 123LB.

Bamlanivimab/Etesevimab for Treatment: BLAZE-1

- Outpatients with mild to moderate COVID-19 within 3 d of first positive test; 1 or more risk factors for developing severe COVID-19
- Single iv infusion of bamlanivimab 2800 mg + etesevimab 2800 mg or placebo

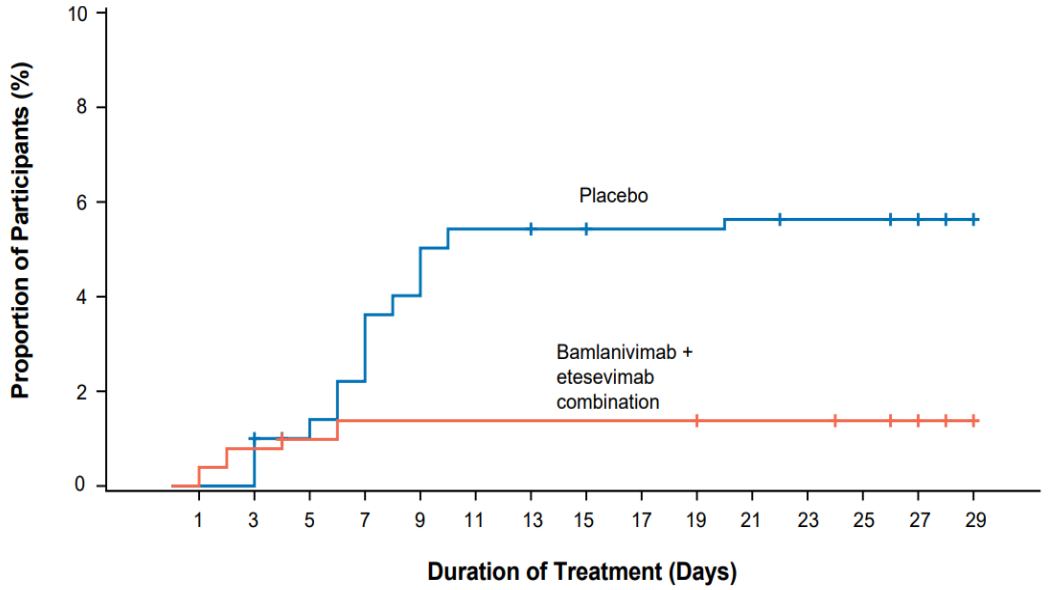
	Placebo (N=517)	Bamlanivimab 2800 mg + Etesevimab 2800 mg (N=518)
Female†	50%	54%
Hispanic or Latino	30%	29%
Black or African American	8%	9%
Age (median)	56	57
Age ≥ 65	30%	32%
Body-mass index (mean)	33	34
Mild COVID-19	78%	77%
Moderate COVID-19	22%	23%
Duration of symptoms (days, mean)	4.2	4.1

Dougan M et al, CROI 2021, #122

Bamlanivimab/Etesevimab for Treatment: BLAZE-1

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 in COVID-19 hospitalization or any-cause death by d 29

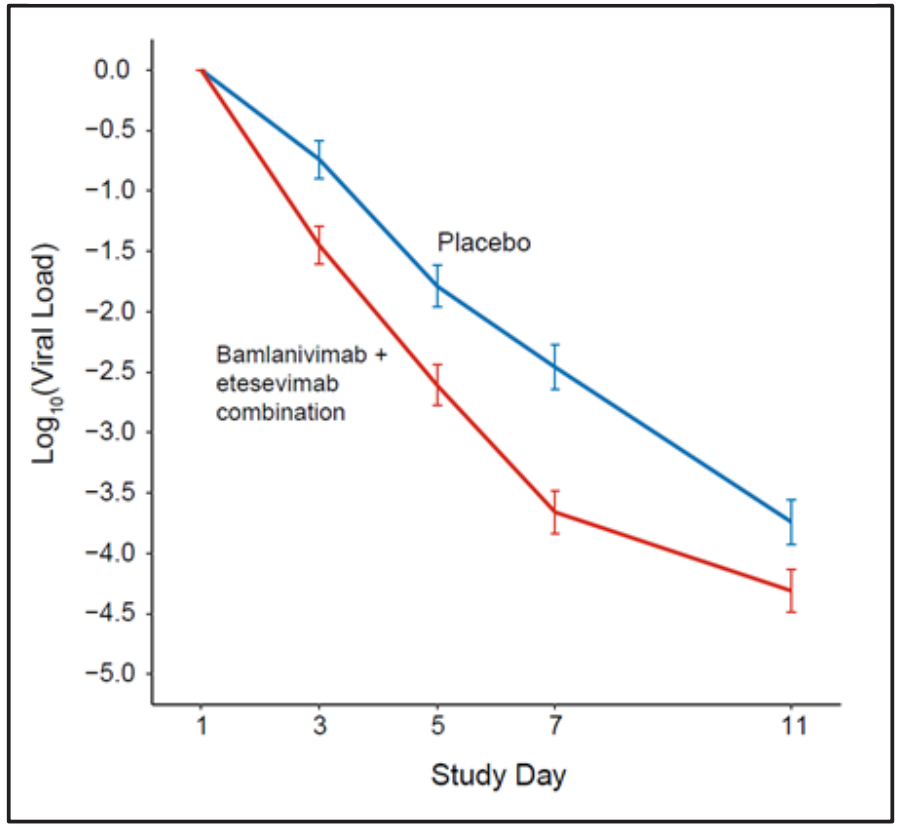
ANY-CAUSE DEATHS

Treatment	N	Events	Rate
Placebo	517	10†	1.9%
Bamlanivimab 2800 mg + Etesevimab 2800 mg	518	0	0%

Dougan M et al, CROI 2021, #122

Bamlanivimab/Etesevimab for Treatment: Effect on VL

VIRAL LOAD CHANGE FROM BASELINE



MEAN VIRAL LOAD

	Placebo	Bamlanivimab + Etesevimab	*p*
Day 1	6.52	6.51	-
Day 3	5.74	5.04	<0.001
Day 5	4.68	3.85	<0.001
Day 7	4.05	2.87	<0.001
Day 11	2.69	2.21	<0.001

Dougan M et al, CROI 2021, #122

Casirivimab/Imdevimab Phase III Results

- Outpatients with mild-moderate COVID randomized to placebo or casi./imdevimab (1200 mg or 2400 mg)
- Modified full analysis set
  - +PCR at enrollment
  - >=1 risk factor for severe COVID-19
- Risk factors:
  - Median age 50 years
  - Obesity (≈58%); CVD, inc. HTN (≈36%)
  - Immunosuppressed ≈2.5-3.4%
- Median days of symptoms: ≈3

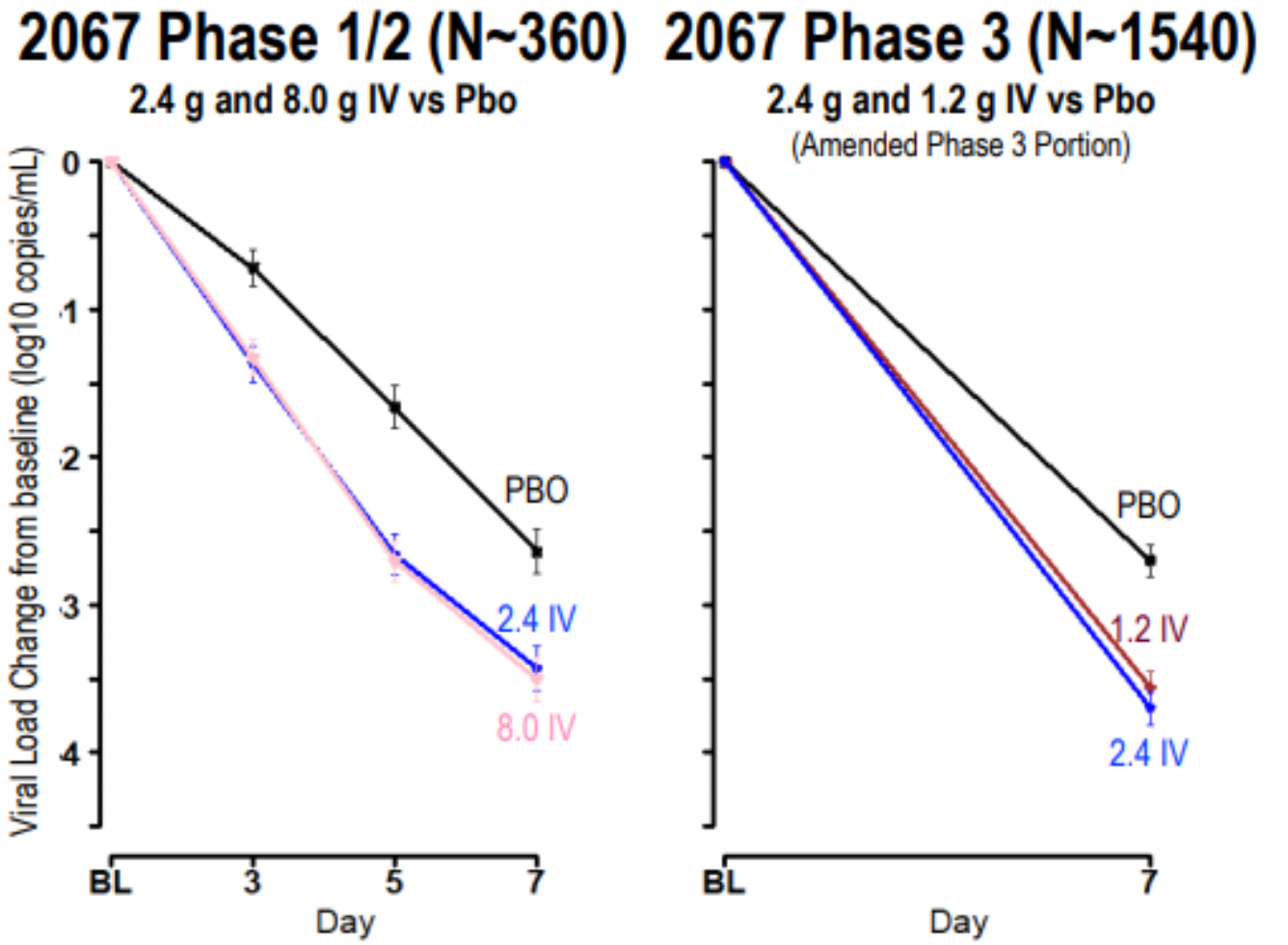
1200 mg: COVID-19-related Hospitalization/Death by d 29				
	N	Events	Proportion	Risk Reduction
Placebo	748	24	3.2%	70% (p=0.0024)
1200 mg	736	7	1%	

2400 mg: COVID-19-related Hospitalization/Death by d 29				
	N	Events	Proportion	Risk Reduction
Placebo	1341	62	4.6%	71% (p<0.0001)
2,400 mg	1355	18	1.3%	

- Deaths
  - Placebo: 5 out of 1843
  - 1200 mg antibody: 1 out of 827
  - 2400 mg antibody: 1 out of 1849

https://investor.regeneron.com/static-files/6ab24e8d-9733-4d91-8511-76e56b540723

Change from Baseline in Viral Load



https://investor.regeneron.com/static-files/6ab24e8d-9733-4d91-8511-76e56b540723

What about SARS-CoV-2 variants?

Variants and Anti-SARS-CoV-2 Antibodies: In Vitro Studies

- B.1.1.7
  - Susceptible to bam/ete, casi/imdev.
- B.1.351, P.1
  - 484K: marked reduction in susceptibility to bam/ete, bam
  - K417N and E484K: reduce casi activity; casi/imdev appears to retain activity
- B1.429/B.1.427 (20C/CAL.20C)
  - L452R: marked reduction in susceptibility to bam; modest reduction in susceptibility to bam/ete
- B.1.526
  - Sometimes has E484K: marked reduction in susceptibility to bam; decrease in susceptibility to bam/ete; may reduce casi activity; casi/imd retain susceptibility

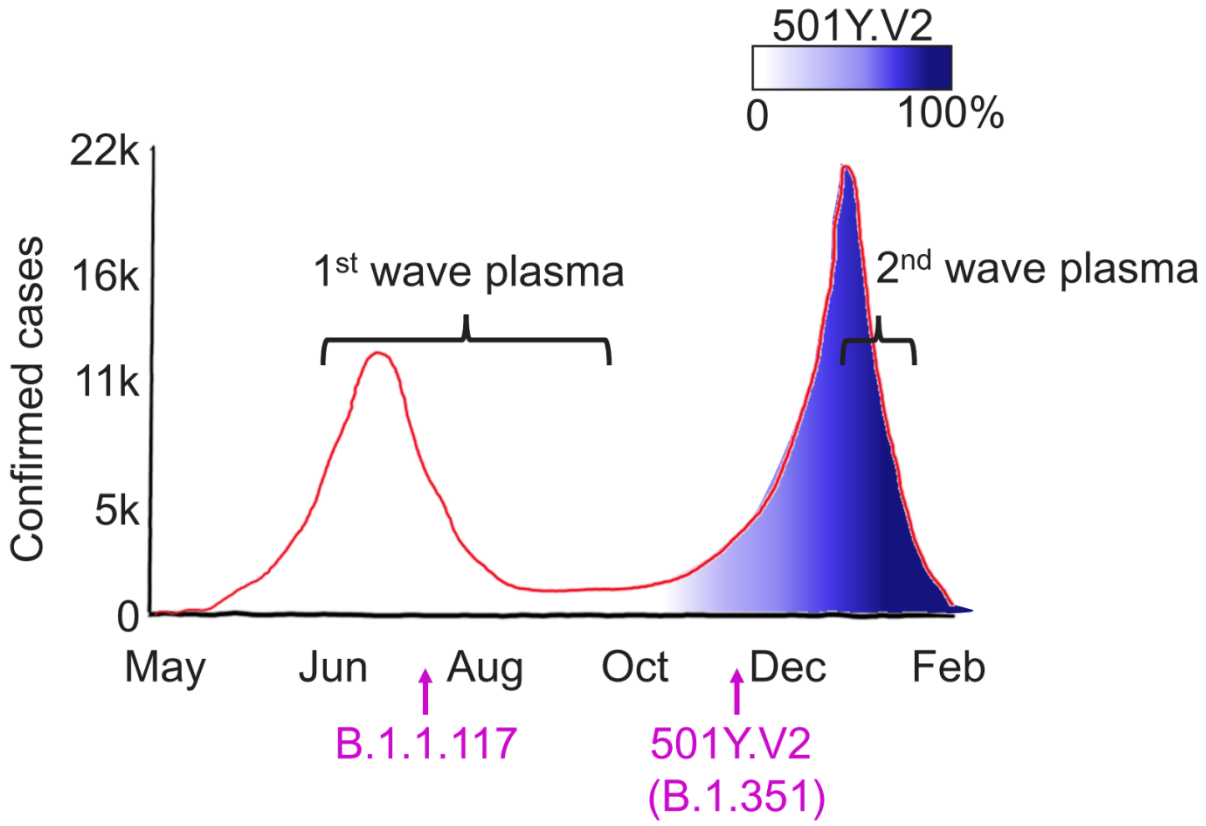
Clinical impact of in vitro susceptibilities unknown

On the horizon: VIR-7871 (GSK4182136)

- Anti-SARS CoV-2 mAb: targets conserved epitope of spike
  - In vitro, neutralizes wild-type SARS CoV-2 as well as pseudotyped viruses encoding spike protein from B.1.1.7, B.1.351, P.1
- Phase 3 COMET ICE trial (n=583)
  - Outpatients with mild to moderate COVID at high risk of hospitalization
  - VIR-7831 vs. placebo
  - 85% reduction in hospitalization or death with VIR-7871 compared to placebo (additional details not yet available)
- EUA application submitted March 26, 2021
- Bamlanivimab + VIR-7871 associated with greater reduction in SARS CoV-2 level than placebo in low-risk adults

https://www.biorxiv.org/content/10.1101/2021.03.09.434607v1; https://www.gsk.com/en-gb/media/press-releases/gsk-and-vir-biotechnology-announce-submission-of-emergency-use-authorization-request-to-fda-for-vir-7831-for-the-early-treatment-of-covid-19/. https://investor.lilly.com/news-releases/news-release-details/lilly-vir-biotechnology-and-gsk-announce-positive-topline-data

SARS CoV-2 Variants



- Does 501Y.V2 variant escape neutralizing antibody response elicited by natural infection with earlier variants?
- Does antibody response elicited by 501Y.V2 neutralize earlier variant?

Cele S … Sigal A, CROI 2021, #263

SARS CoV-2 Variants

Plasma $PRNT_{50}$

	1st wave	501Y.V2	Fold change HM/HT
1st wave	344.0 (275.4-458.0)	149.7 (132.1-172.8)	2.3
501Y.V2	41.1 (32.7-55.50)	619.7 (517.8-771.5)	15.1
Fold change HM/HT	8.4	4.1	

1st wave plasma neutralizes 1st wave virus but less effective at neutralizing 501Y.V2

2nd wave plasma neutralizes 501Y.V2 and 1st wave virus

Suggests vaccine based on 501Y.V2 or similar sequences may retain activity against other SARS CoV-2 lineages

Cele S … Sigal A, CROI 2021, #263

Summary

- Novel ART: islatravir (NRTTI), MK-8507 (weekly NNRTI); lenacapavir (capsid inhibitor), GSK ‘254 (maturation inhibitor)
- Growing prospects for long-acting ART
- New data supporting safety and efficacy of DTG + TAF/FTC during pregnancy; DHHS guidelines updated
- COVID-19 advances: molnupiravir (phase 2 promising; in phase 3); monoclonal antibodies – keep an eye on variants