Updates from ID Week 2022 on HIV, Monkeypox and Covid-19

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Current ART

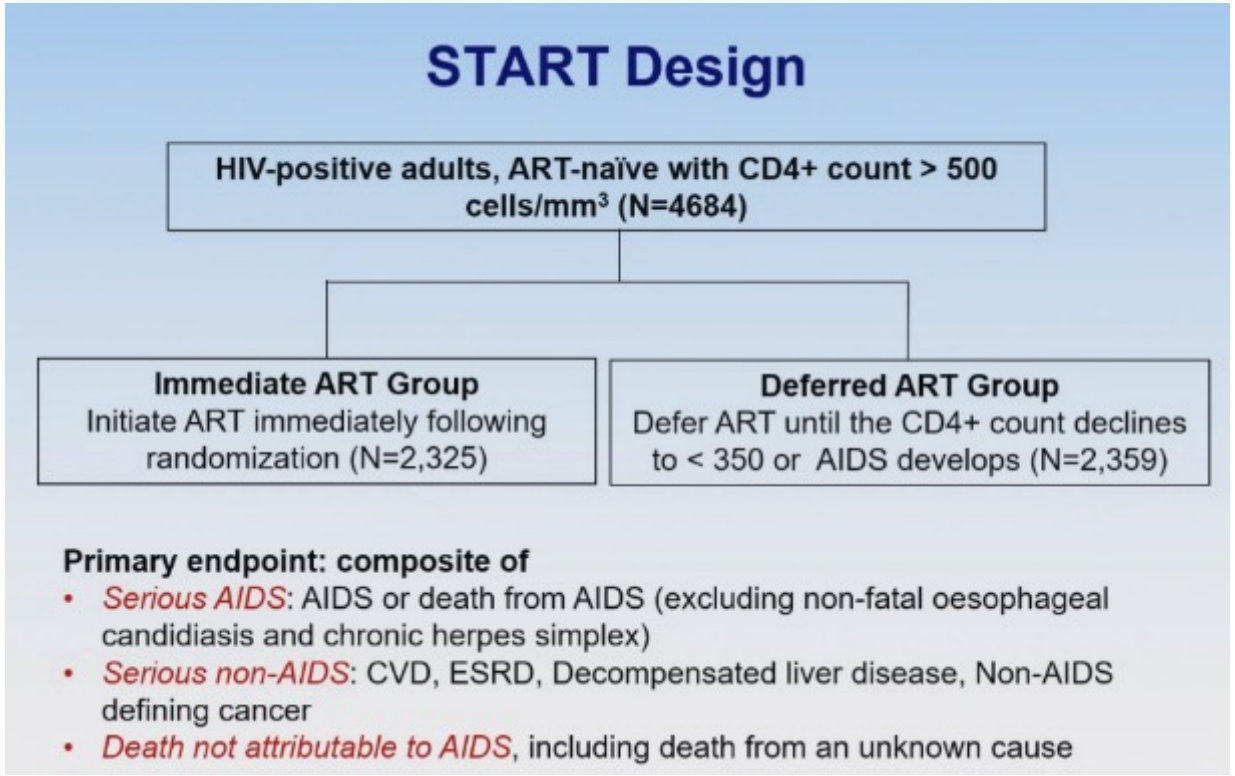
New ART

Coinfections

PrEP

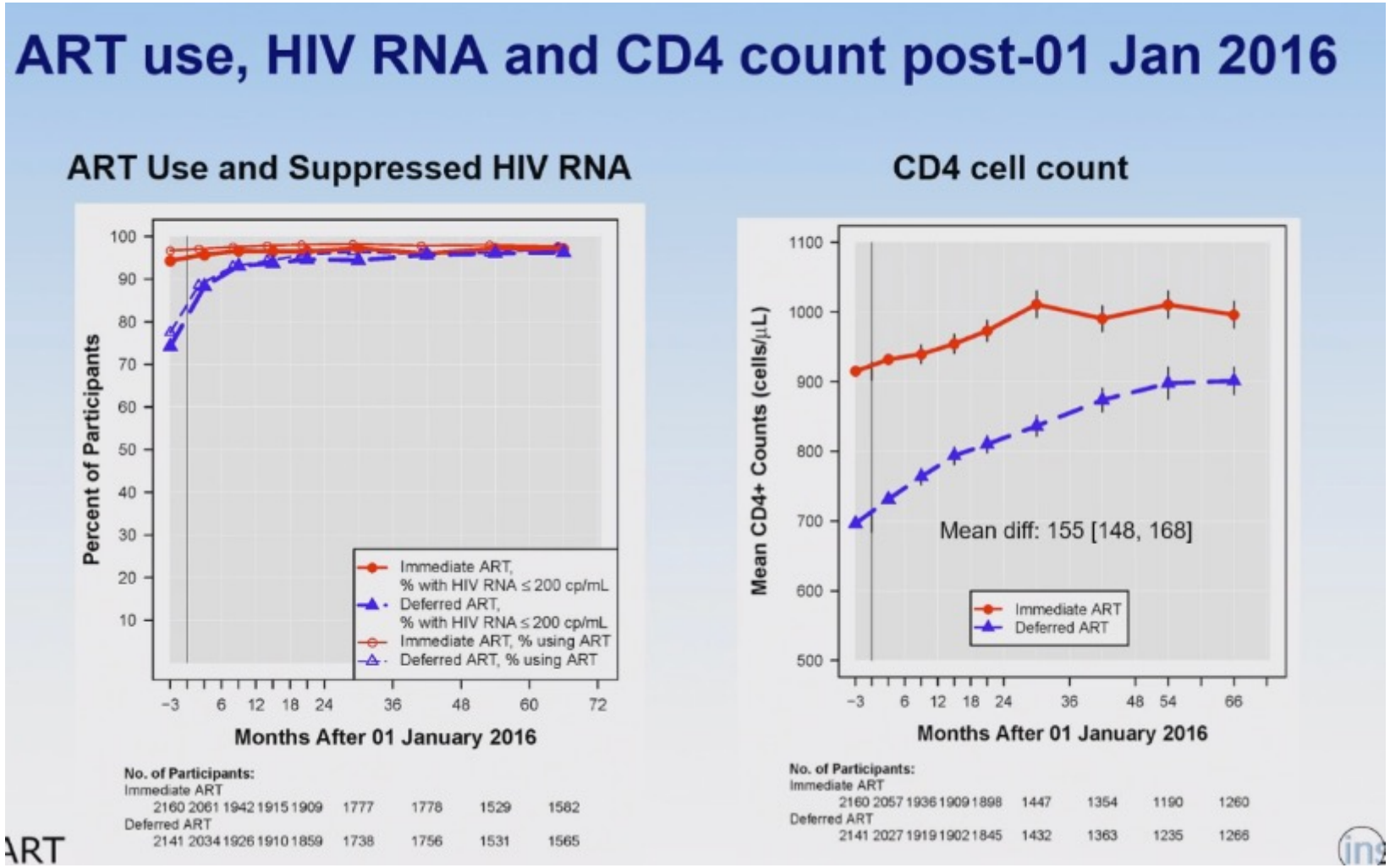
When to START? The Sooner, the Better

- START: randomized trial of immediate vs. delayed ART in PWH with CD4 count >500
- Primary results (previously published): early initiation of ART reduced AIDS and non-AIDS related complications
- Participants who were originally assigned to deferred ART group were all recommended to start ART.
- Median follow-up: about 9 years.



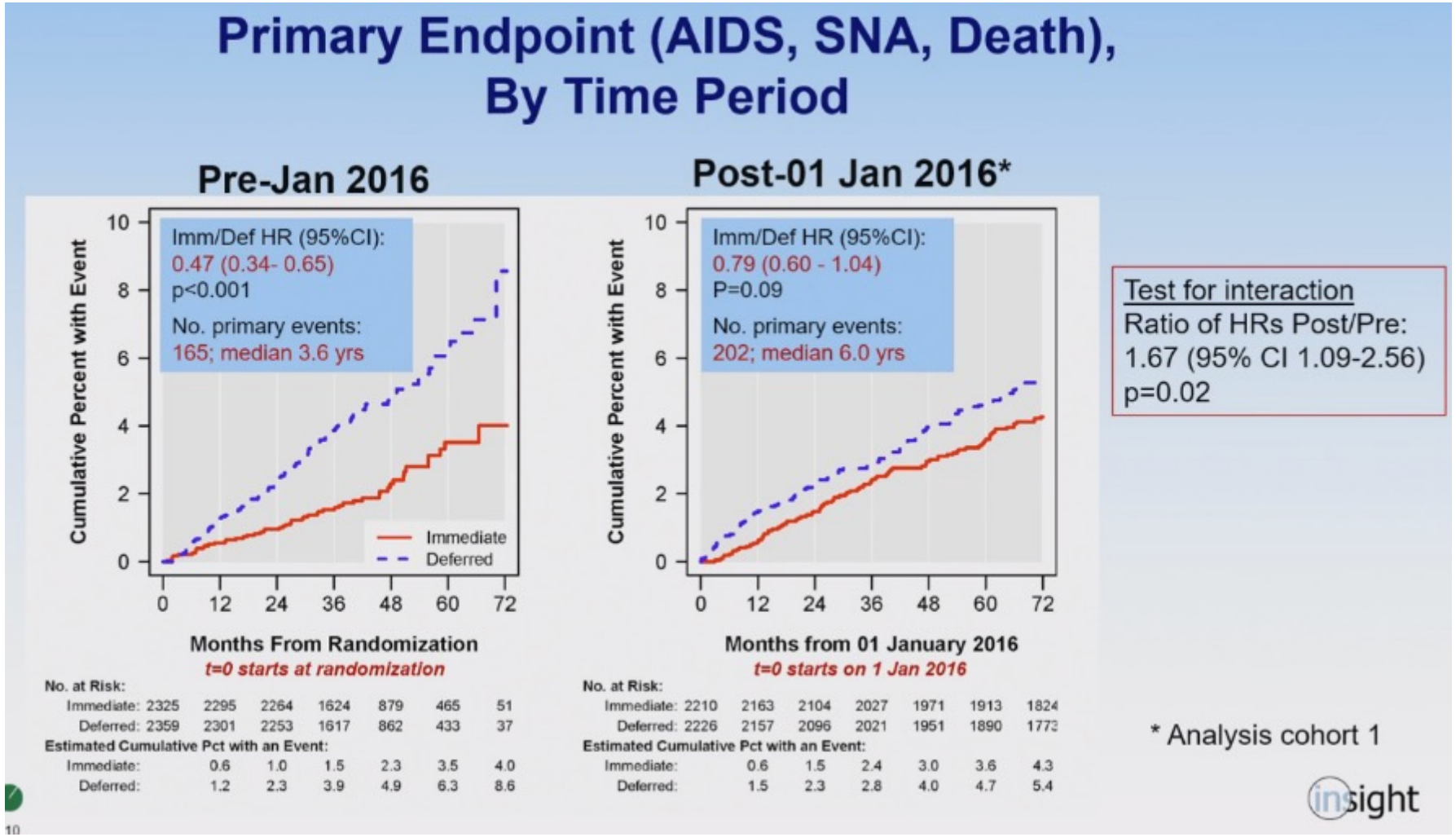
Babiker A, IDWeek 2022

Even after starting ART, CD4 counts remain lower in Delayed Group than in Early Group



Babiker A, IDWeek 2022

Risk of complications associated with delaying ART diminishes after ART is started, but some excess risk still persists



Babiker A, IDWeek 2022

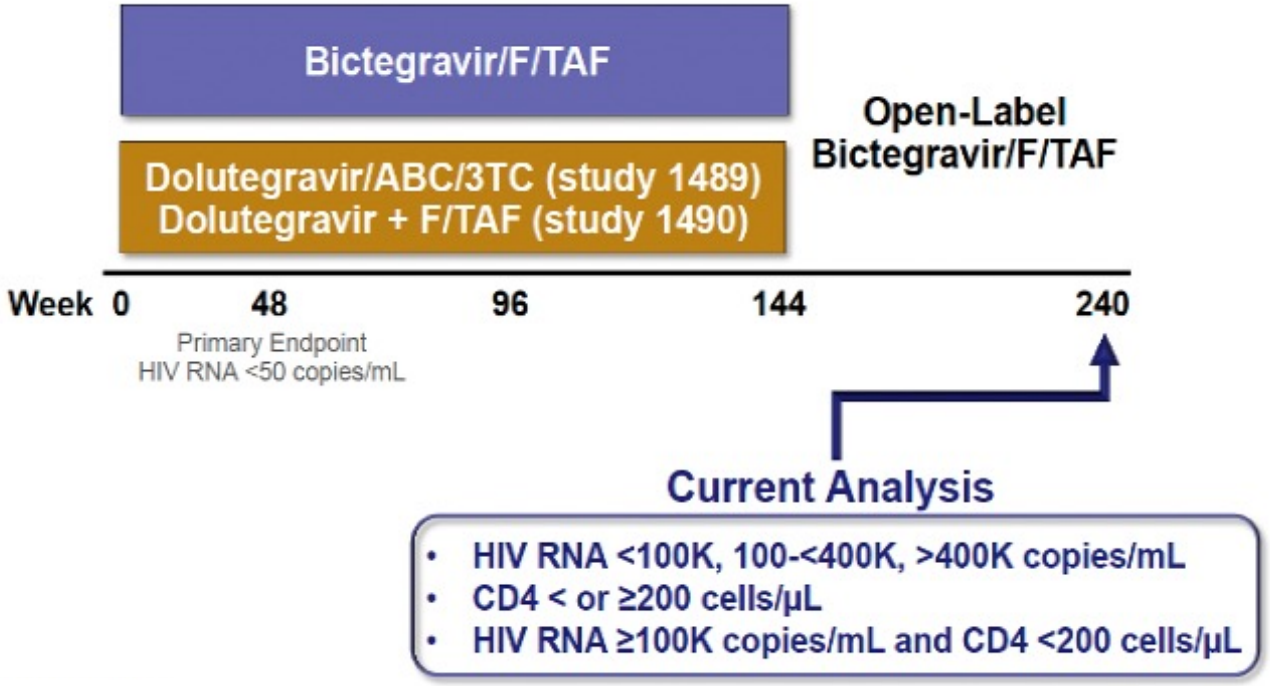
Implications: Need to Diagnose and Treat HIV Earlier

- Delayed ART initiation associated with higher rate of complications, perhaps related to immune dysregulation “legacy effect”
  - High levels of inflammation before ART correlate with high levels while on ART
- Even in high income countries, median CD4 cell count at ART initiation is <400; almost 20% have CD4 cell count <200
- We need to do better job of testing, diagnosing and treating all PWH.

Edwards JK et al, Ann Int Med, 2021; Lee JS et al, CID, 2020; IeDEA and COHERE Cohort Collaborations, CID, 2018; Gandhi RT, McMahon DK et al, PLoS Pathogens, 2017

Bictegravir/FTC/TAF in PWH With High Baseline HIV RNA and/or Low CD4 Count

- Many recent ART trials enrolled participants with high CD4 counts
- Less known about efficacy/safety of modern ART in PWH with low CD4 count and/or high baseline HIV RNAs
- ~600 adults received BIC/FTC/TAF in manufacturer-sponsored studies
  - 80 had baseline CD4 <200, 119 had VL >100,000

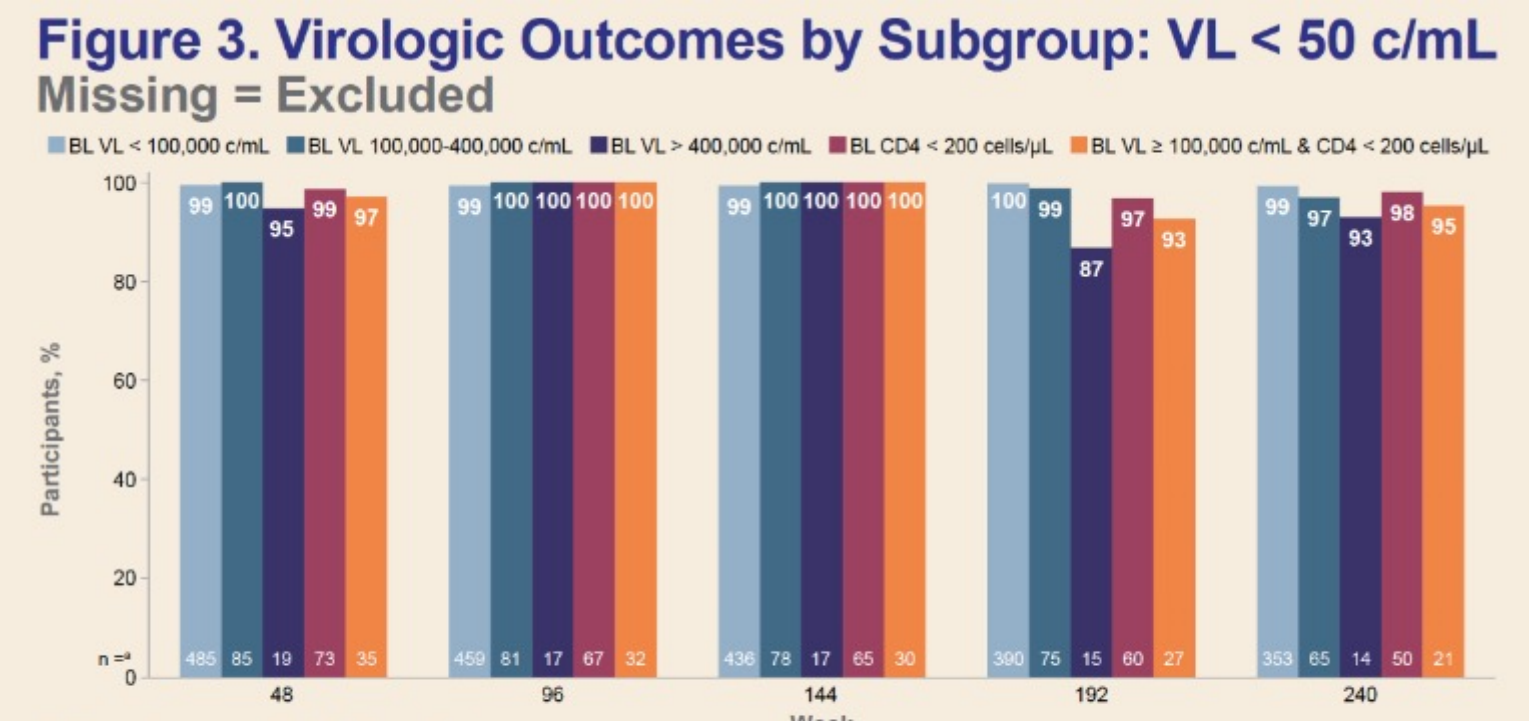


Ramgopal A, IDWeek 2022, Abstract 1251

Figure from Practice Point Communications

High rate of virologic suppression with Bictegravir/FTC/TAF in PWH With High Baseline HIV RNA and/or Low CD4 Count

- At 5 years of ART, among participants who remained in study, virologic suppression rates high for low baseline CD4 group and for high baseline HIV RNA group
- Greater median weight gain among those with low CD4 and/or HIV RNA at baseline

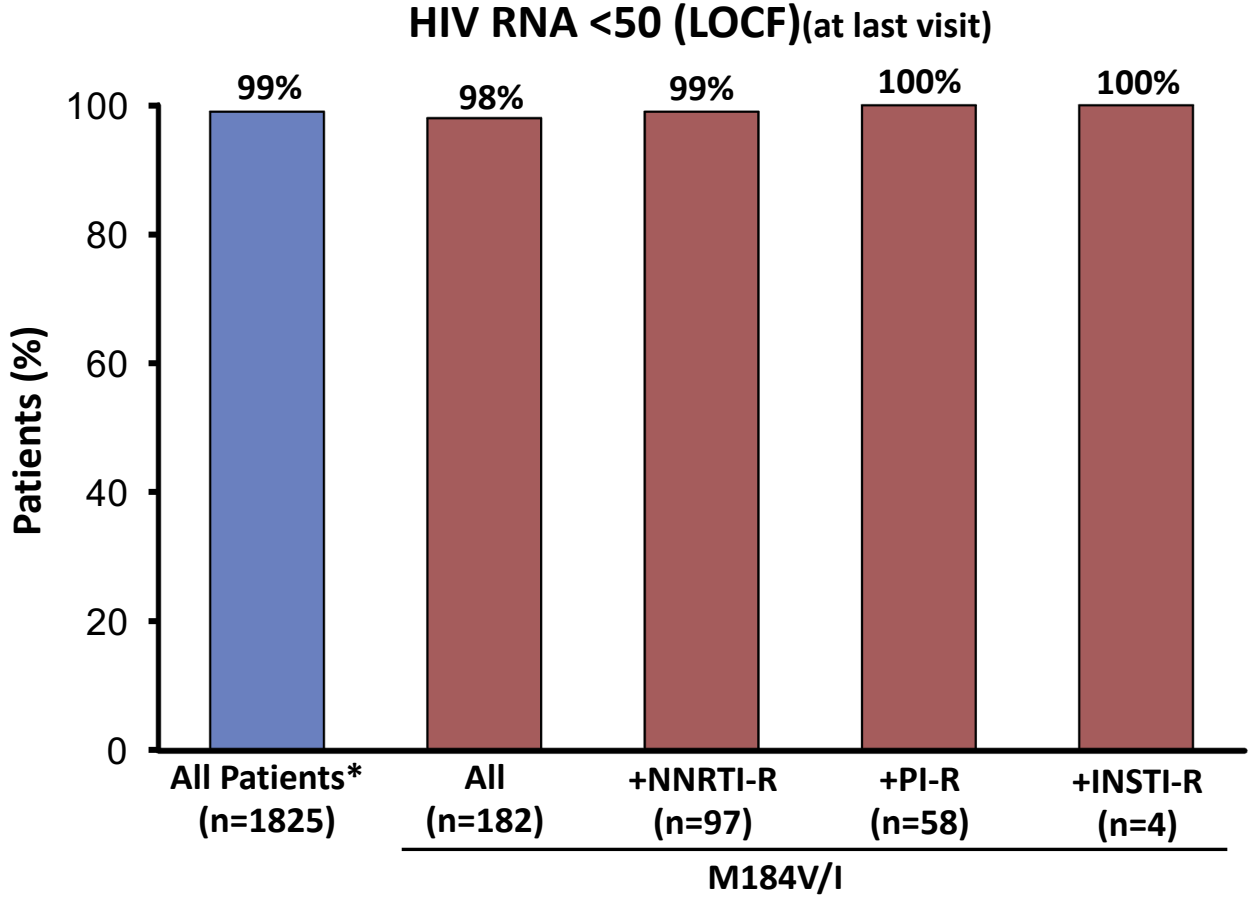


Ramgopal A, IDWeek 2022, Abstract 1251

What are the ART options for PWH who have drug resistance?

High Efficacy of Switching to Bictegravir/FTC/TAF with Suppressed HIV and pre-existing M184V/I

- Pooled data from 6 trials in which PWH and virologic suppression switched to B/F/TAF (n=1825 with baseline data)
- Preexisting M184V/I identified in 182 participants (10%)
- 98% of participants with pre-existing M184V/I maintained viral suppression



LOCF: last observation carried forward.
*Patients with baseline data.

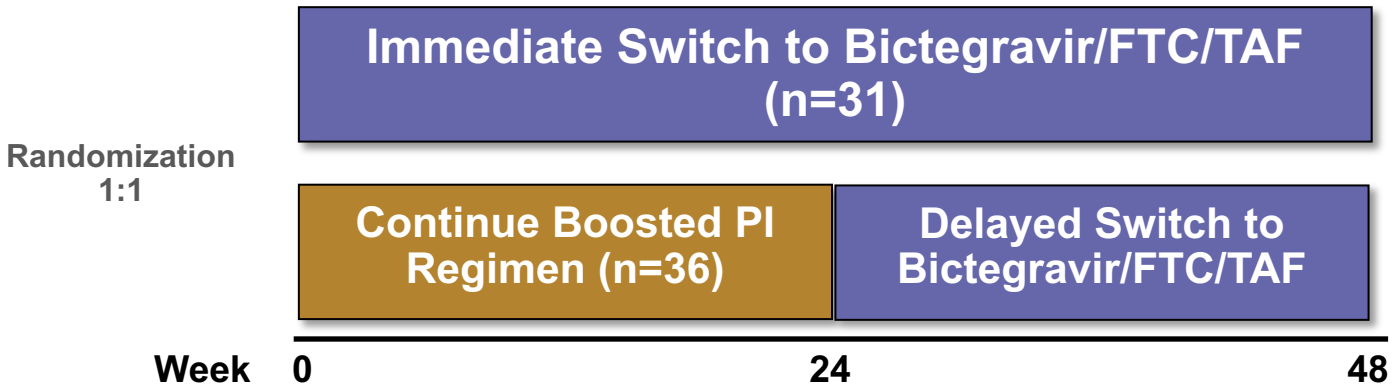
Sax PE, et al. *AIDS*. 2022 Figure from Practice Point Communications

PIBIK Study: Switch to Bictegravir/FTC/TAF From Boosted PI Regimens With Drug Resistance

Phase 4 (investigator initiated)

HIV RNA <50 on boosted PI regimen
Genotype:
- **M184V/I ± NRTI-associated mutation**
- **M184 V/I alone**
- **Up to 2 TAMs ± M184 V/I**
- **Any of the above ± NNRTI mutations**

No INSTI mutations



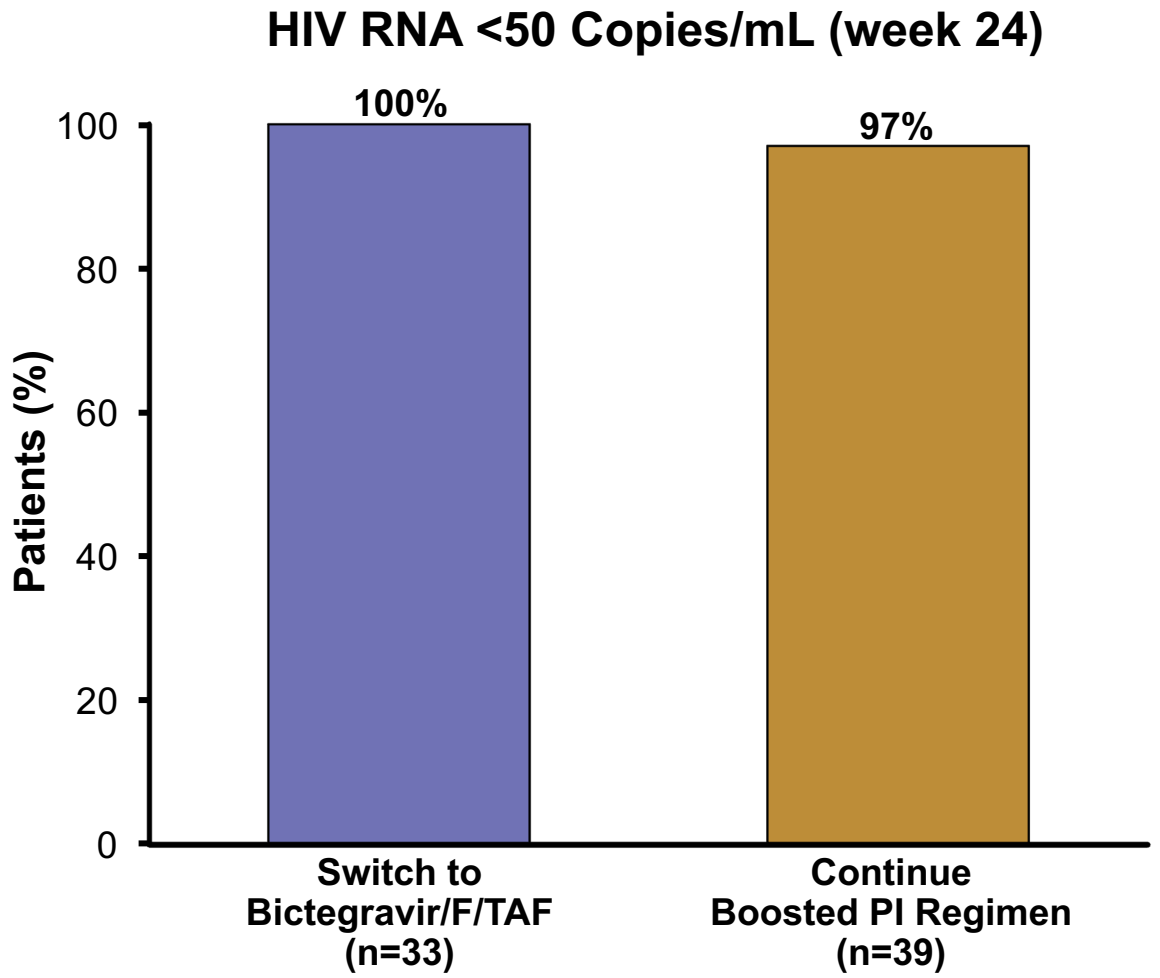
TAMs: thymidine analogue mutations.
Primary endpoint: HIV RNA <50 at week 24.
Baseline demographics:
Male: 89%.
- Median CD4 632 cells/μL.
- Boosted darunavir (81%) and atazanavir (19%).
- Genotype:
  - ≥2 NRTI (47%), M184 V/I only (26%).

Iwuji C, et al. *J Int AIDS Soc*. 2022;25(suppl 6):89-90. Abstract P089

Slide from Practice Point Communications

PIBIK Study: Outcomes Following Switch to Bictegravir/FTC/TAF

- Presence of limited NRTI resistance did not compromise virologic efficacy after switch to bictegravir/FTC/TAF in virologically suppressed adults on boosted PI regimens

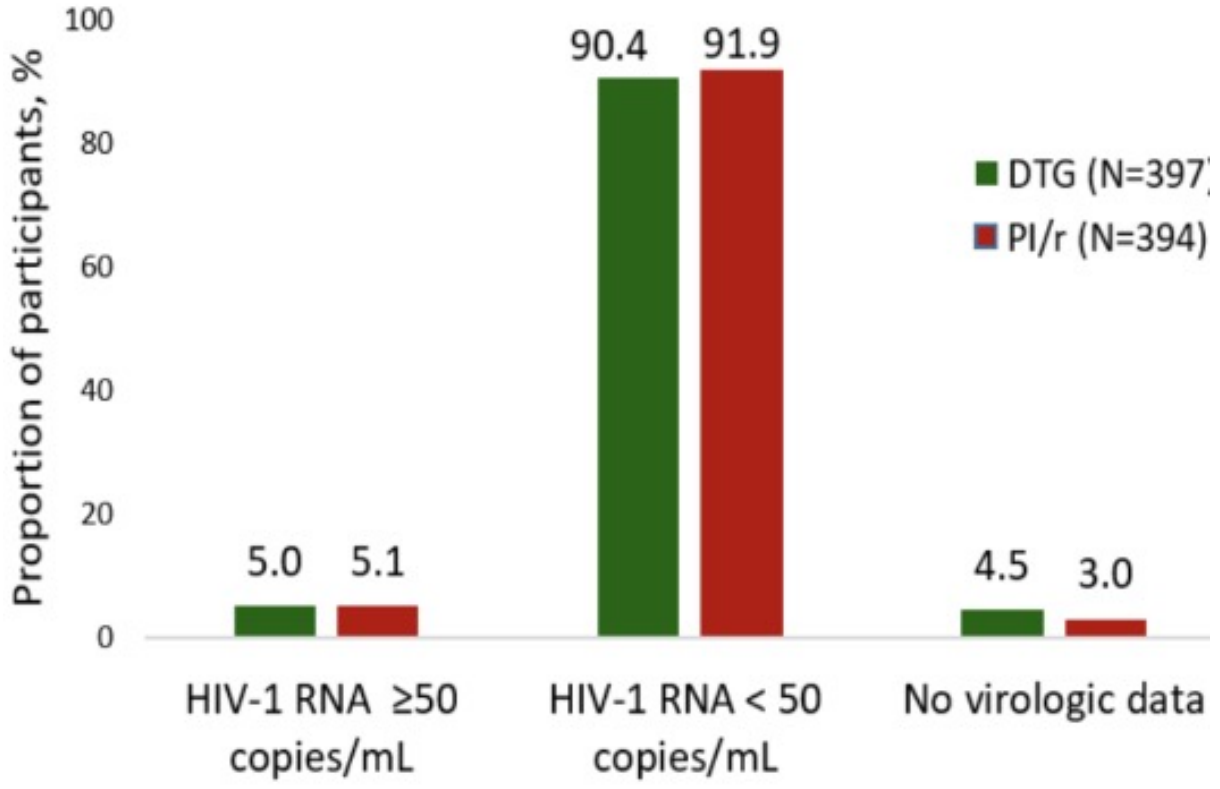


Iwuji C, et al. *J Int AIDS Soc*. 2022;25(suppl 6):89-90. Abstract P089

Slide from Practice Point Communications

2SD: Switching Treatment Experienced PWH from PI/r to DTG

- Randomized study in Kenya (n=795)
- Participants with viral suppression on second line ART with PI/r + 2 NRTIs randomized to switch to DTG + 2 NRTI or continue PI/r + 2 NRTI
- Prior drug resistance not assessed but anticipated to be common
- **High rate of virologic suppression in people switched to DTG + 2 NRTIs**
- **No treatment emergent INSTI or PI resistance**



Ombajo L et al, CROI 2022, Abstract 136

VISEND: Switching Therapy in Suppressed and Non-Suppressed PWH

- Randomized trial in Zambia
- Patients switching from NNRTI-based treatment (n=1201)
- Arm A: VL <1000: Randomized to TLD or TAFED
- Arm B: VL ≥1000
  - Randomized to TLD, TAFED, AZT/3TC/LPV/r or AZT/3TC/ATV/r

TLD: TDF/3TC/DTG; TAFED: TAF/3TC/DTG

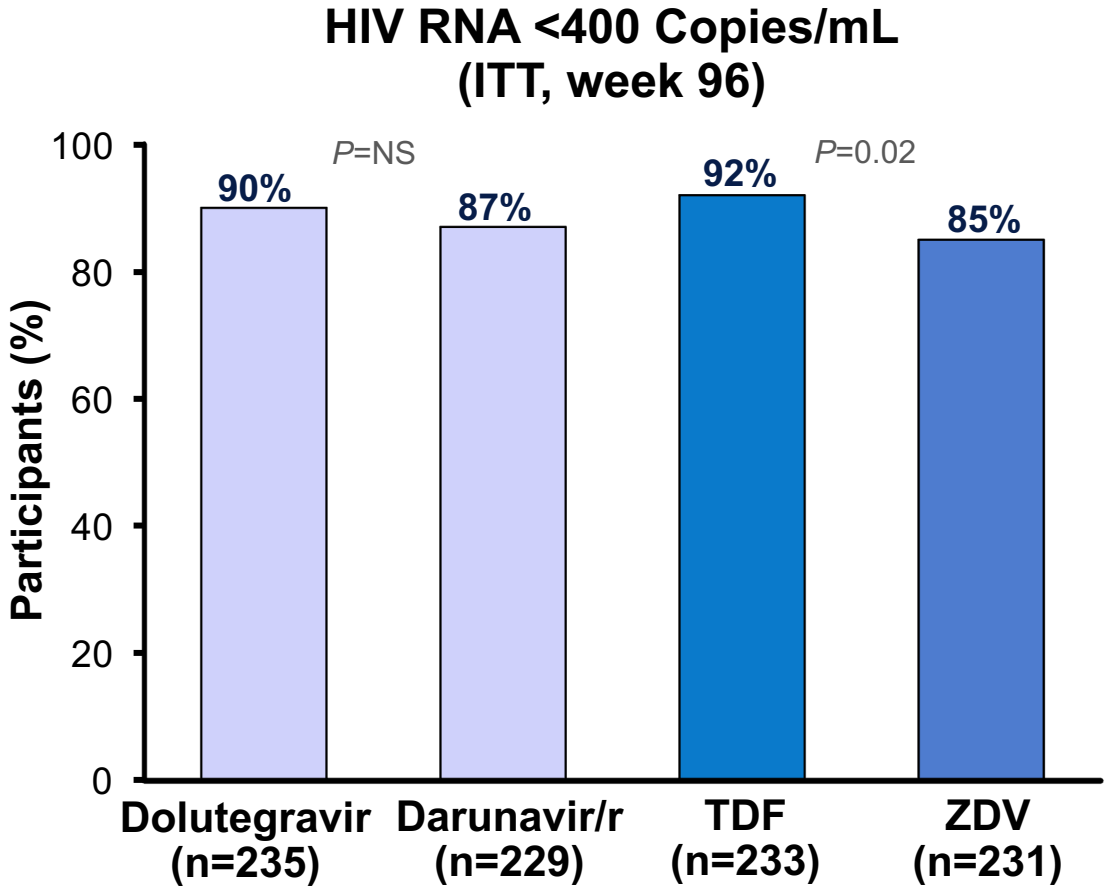
VL at Wk 48, %	DTG + TDF/3TC (n = 208)	DTG + TAF /3TC (n = 211)	ATV/r + 3TC/ZDV (n = 197)	LPV/r + 3TC/ZDV (n = 167)
ITT <50 c/mL	72	82	71	56
Per protocol <50 c/mL	82	89	78	68

- In PWH on NNRTI-based regimen with virologic non-suppression (VL≥1000), switching to DTG + tenofovir/3TC results in high rates of viral suppression

Mulenga L, CROI 2022, Abstract 135

NADIA: 2nd-Line ART after NNRTI Failure

- Participants with virologic failure on TDF/3TC/NNRTI (n=464)
- Randomized to switch to DTG or DRV/r with either TDF/3TC or AZT/3TC
- Study participants:
  - CD4 ≤200: 51%; VL ≥100,000: 28%
  - Resistance: K65R/N: 50%; M184V: 86%
- DTG + 2 NRTIs non-inferior to DRV/r + 2 NRTIs
  - High rate of suppression even when no NRTIs predicted to be active!
- Continuing TDF/3TC superior to switch to AZT/3TC
- 9 participants (4%) in DTG group developed resistance; no resistance in the DRV/r group



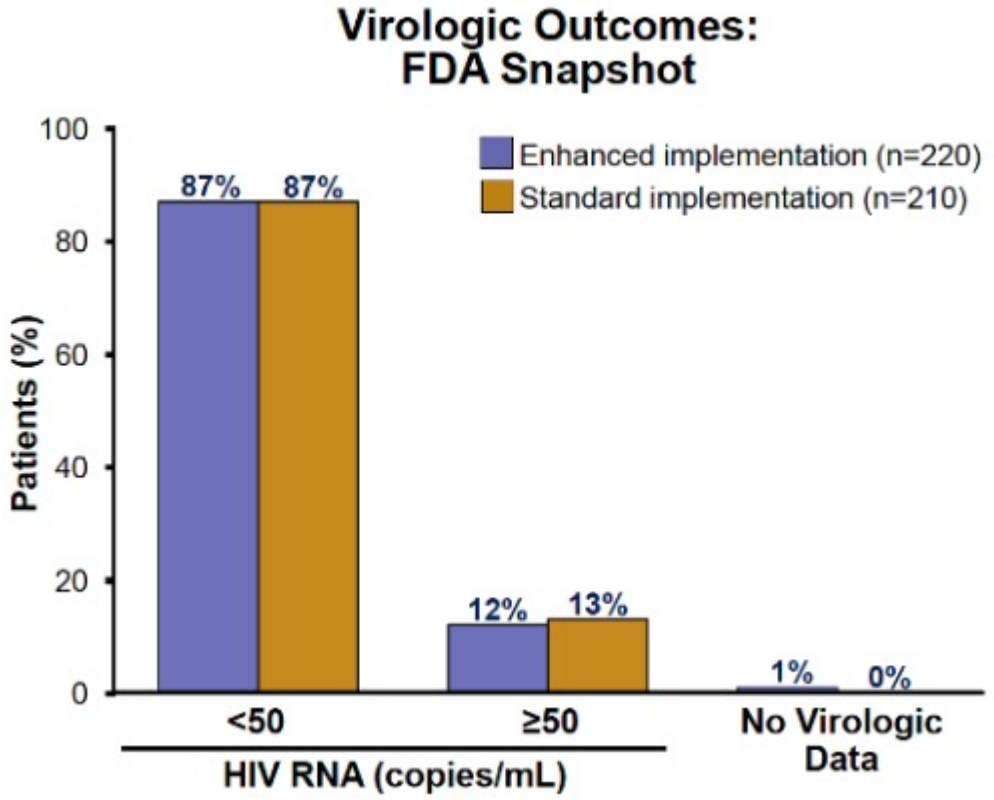
Paton N, Lancet, 2022

Lessons from Trials of Switching ART

- In treatment experienced patients with viral suppression, switching from PI/r to DTG maintains viral suppression even when resistance testing results not known
- In PWH who are virologically suppressed and have virus sensitive to INSTIs and PIs, switching to tenofovir/XTC + high barrier to resistance drug (DTG, BIC, DRV/r) likely to maintain suppression, even with pre-existing NRTI resistance
- In PWH with virologic failure with extensive NRTI resistance but INSTI and PI sensitivity, options include boosted DRV + 2 NRTI; DTG + boosted DRV; alternate: DTG + 2 NRTI (small risk of DTG resistance)

CARISEL: Long-acting Cabotegravir/Rilpivirine

- CAB/RPV approved in Jan 2021 for treatment of PWH who are virologically suppressed and do not have resistance to CAB or RPV
- CARISEL study evaluated implementation of CAB/RPV at clinics in Europe
- Sites randomized to standard implementation or enhanced implementation
- 430 participants enrolled and treated
  - At 1 year, 87% of participants maintained virologic suppression (similar across arms)



De Wit S, et al, IDWeek 2022, Abstract 1584

Figure from Practice Point Communications

LA Cabotegravir/Rilpivirine: Considerations

- Techniques proposed to minimize injection discomfort
  - slowing speed of injection,
  - ensuring that the medication reaches room temperature
  - having the patient relax their muscle prior to injection
- Clinics should develop systems to offer LA option to patients who prefer alternative to daily oral therapy.
- Need to know whether LA injectables improve HIV suppression rates in people who struggle to take daily antiretrovirals; studies ongoing.
- Need to develop LA drugs that can be self administered

De Wit S, et al, IDWeek 2022, Abstract 1584

CAB + RPV Long-Acting Injections: What's on the Horizon?

- Pharmacokinetic study in healthy patients **without HIV** (n=15) of CAB/RPV LA injections into the lateral thigh muscles

Figure 1. Study Design

*PK collection at pre-injection, 1 hr and 2 hr post-injection, on Days 2, 4, 5, 7/8, 10, 15, 17, and 22 post-injection, and at Weeks 4 (Day 28), 8, 12, 24, 36, and 52, and at withdrawal visit.
CAB, cabotegravir; LA, long-acting; PK, pharmacokinetics; RPV, rilpivirine.

- Plasma concentrations of both drugs higher than level anticipated to suppress HIV (based on protein adjusted-IC_{90})
- Subcutaneous injection of high concentration CAB also being evaluated

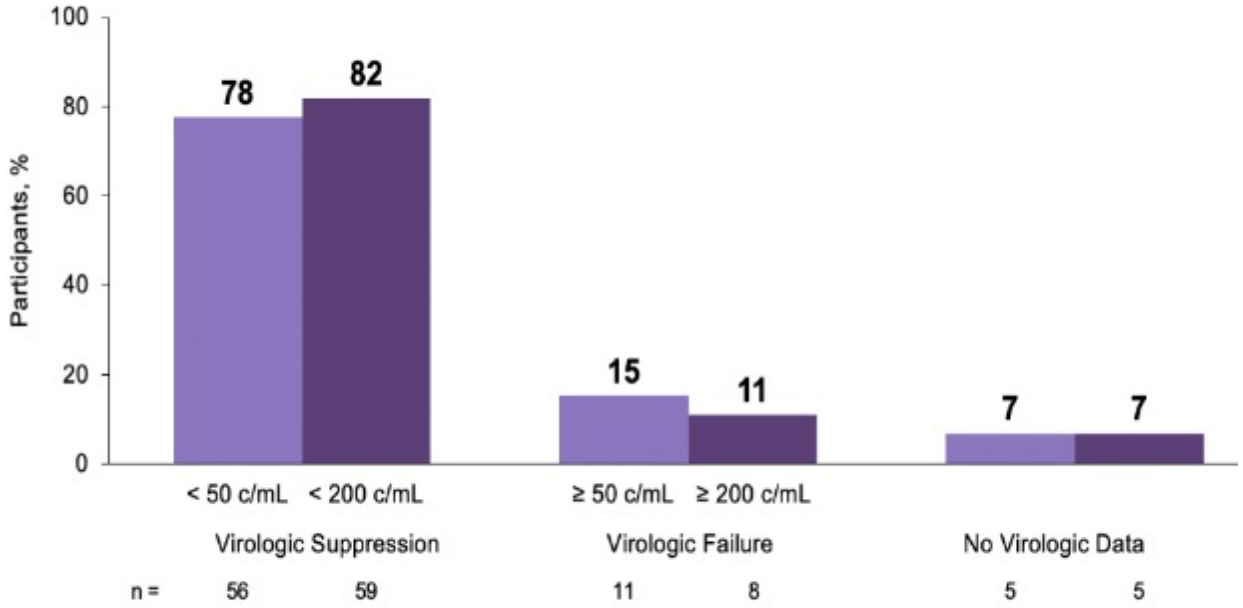
Han K et al, AIDS 2022, Abstract EPB176; Benn P, et al. AIDS 2022; Abst. PESUB24.

New ART

Lenacapavir (LEN) + Optimized Background Regimen (OBR) in People with Multi-drug Resistant HIV (CAPELLA)

- LEN: HIV capsid inhibitor; dosed every 6 m by subcutaneous injection
- In people with MDR HIV, LEN + OBR led to viral suppression in 82%
- Treatment emergent resistance in 9 participants (1 in 8): M66I most common
  - All had no other active drugs or incomplete adherence to OBR

Virologic suppression at wk 52



Ogbuagu O, et al. IDWeek 2022. Abstract 1585; Segal-Maurer S, NEJM, 2022

Lenacapavir Approval

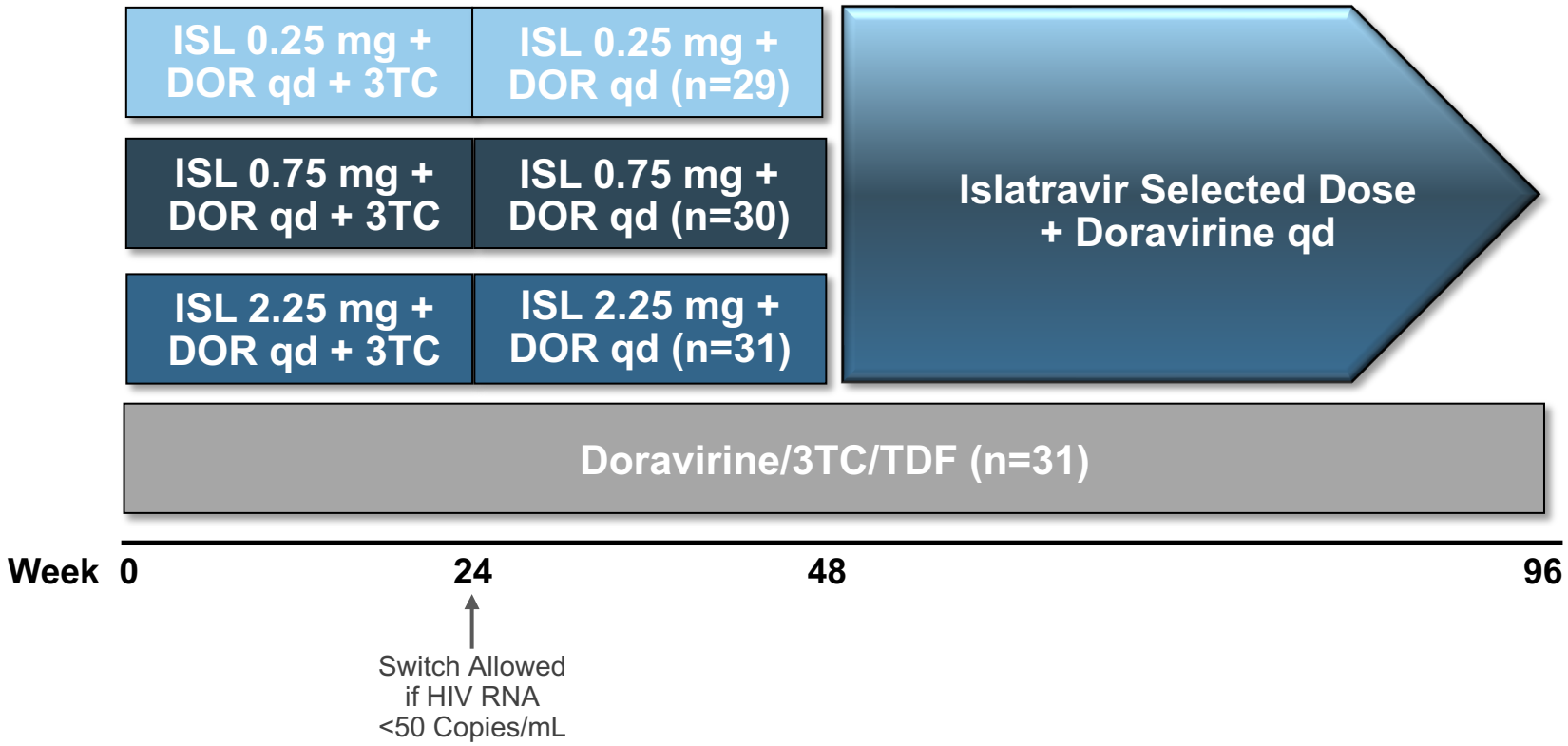
- European Medicines Agency and European Commission recently approved LEN for treatment in combination with other ART
- For use “in adults with multi-drug resistant HIV infection for whom it is otherwise not possible to construct a suppressive anti-viral regimen”

- US FDA accepted NDA for lenacapavir June 27, 2022. Decision expected by December 27, 2022

https://www.gilead.com/news-and-press/press-room/press-releases/2022/8/gilead-announces-first-global-regulatory-approval-of-sunlenca-lenacapavir-the-only-twiceyearly-hiv-treatment-option

Lymphocyte Changes With Islatravir + Doravirine

- Islatravir: Nucleoside RT translocation inhibitor (NRTTI)
- Studies placed on hold in 2021 because of dose dependent lymphopenia, decline in CD4 cell count
- Phase 2b dose ranging study in treatment-naïve PWH



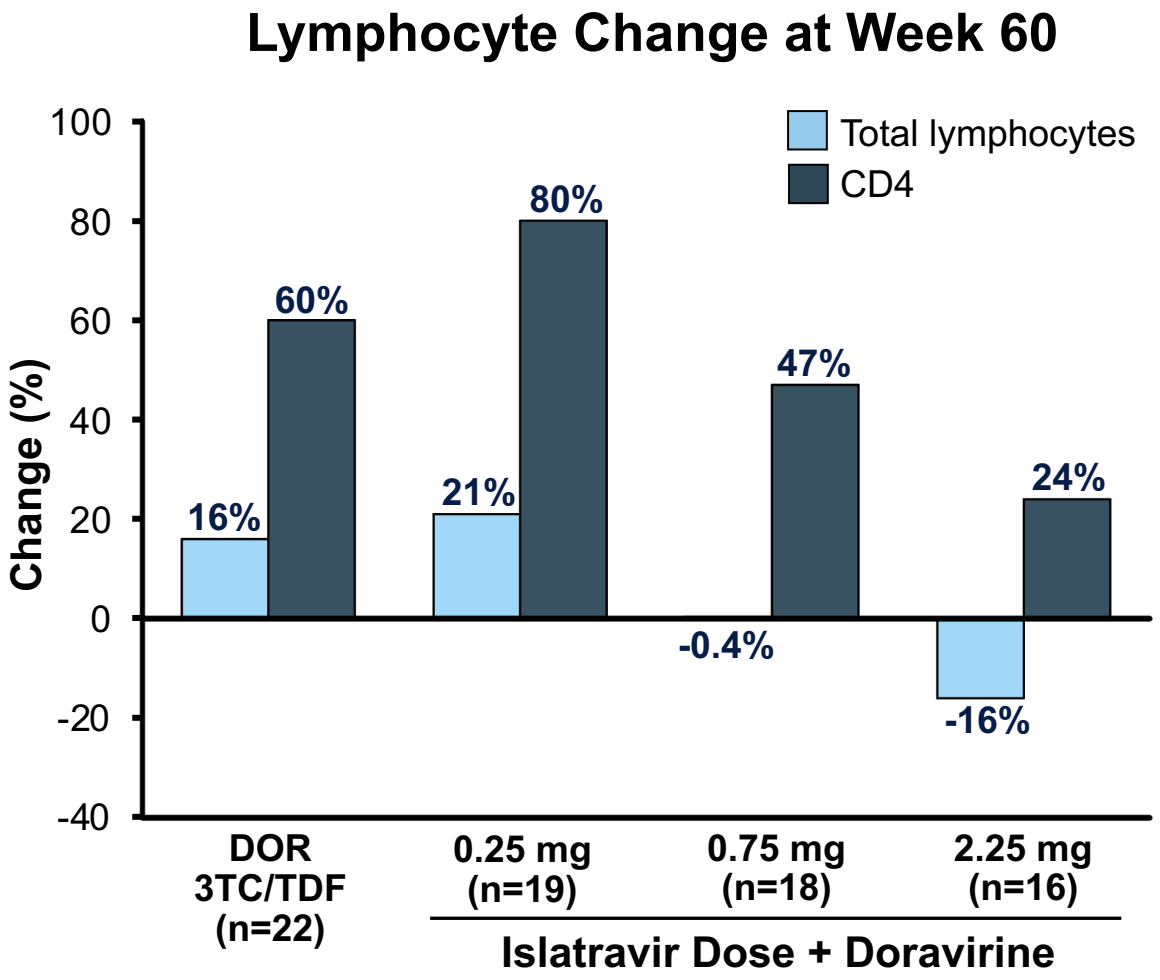
ISL: islatravir; DOR: doravirine.

Correl T, et al. *J Int AIDS Soc*. 2022;25(suppl 6):23. Abstract O46.

Slide adapted from Practice Point Communications

Lymphocyte Changes With Islatravir + Doravirine

- Exposure-related decreases in total lymphocytes, CD4 cell counts, and B-cell counts observed with islatravir doses ≥0.75 mg
- Islatravir 0.25 mg + doravirine and doravirine + 3TC/TDF
  - Comparable increases in total lymphocytes and CD4 counts



Correl T, et al. *J Int AIDS Soc*. 2022;25(suppl 6):23. Abstract O46.
Slide adapted from Practice Point Communications

Islatravir: Clinical Trial Updates

- In Sept 2022, FDA granted permission for resumed testing with lower dose of islatravir

Indication	Current status *(October 2022)*	
PrEP *(all patients)*	**All studies discontinued**	
Treatment *treatment-naïve patients*	**Doravirine/ islatravir**	• Once-daily oral combination • New Phase 3 study with a lower dose of islatravir
Treatment *virally suppressed patients*	**Doravirine/ islatravir**	• Once-daily oral combination • Two new Phase 3 studies with a lower dose of islatravir
	Islatravir + lenacapavir	• Once-weekly oral treatment • Phase 2 study to resume with a lower dose of islatravir

PRIME Education, LLC. 2022

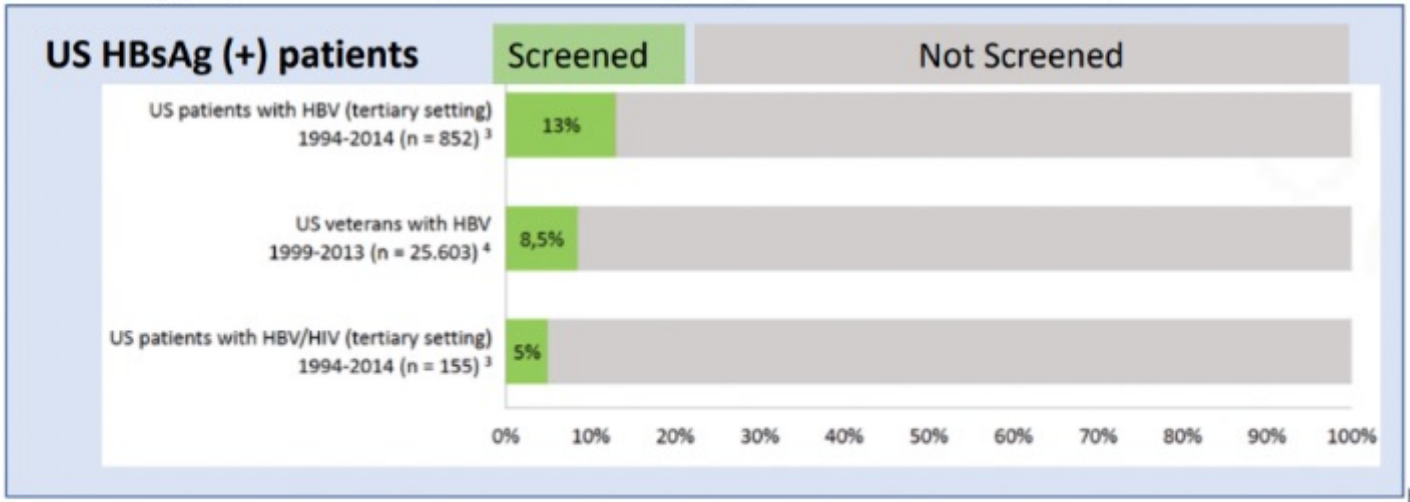
Coinfections

Hepatitis Delta (HDV)

- Most severe form of viral hepatitis
- Occurs as superinfection or coinfection with HBV
  - Superinfection ↑↑ risk of cirrhosis & liver failure
- Despite guidance to screen many (AASLD) or all (EASL) HBsAg(+) for HDV, screening uptake has been poor

5 -10% of people living with hepatitis B are co-infected with hepatitis D.

15-20 million people worldwide



AASLD HDV Screening Guidelines for HBsAg (+)

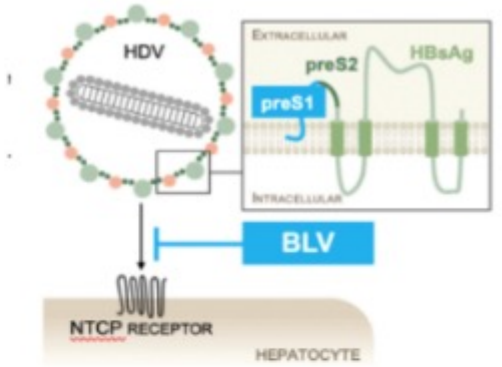
- HIV Coinfection
- Men who have sex with men
- People who inject drugs
- From HDV endemic countries

- Interferon: poorly tolerated, limited response

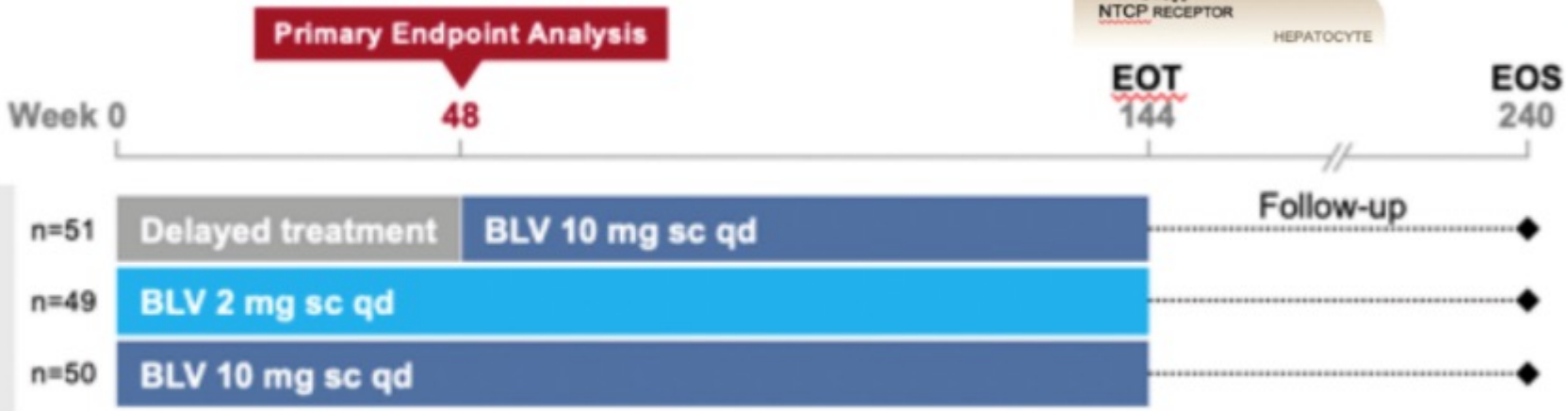
https://www.cdc.gov/hepatitis/hdv/hdvfaq.htm
EASL 2017 HBV Guidelines, AASLD 2018 HBV Guidelines
Safaie *Virus Res* 2018, Kushner *J Hep* 2015
https://www.hepb.org/assets/Uploads/Copy-of-HDV-FACT-SHEET.png

Slide from Dr. Annie Luetkemeyer, IDWeek 2022

Bulevirtide: HDV entry inhibitor



MYR 301 Study



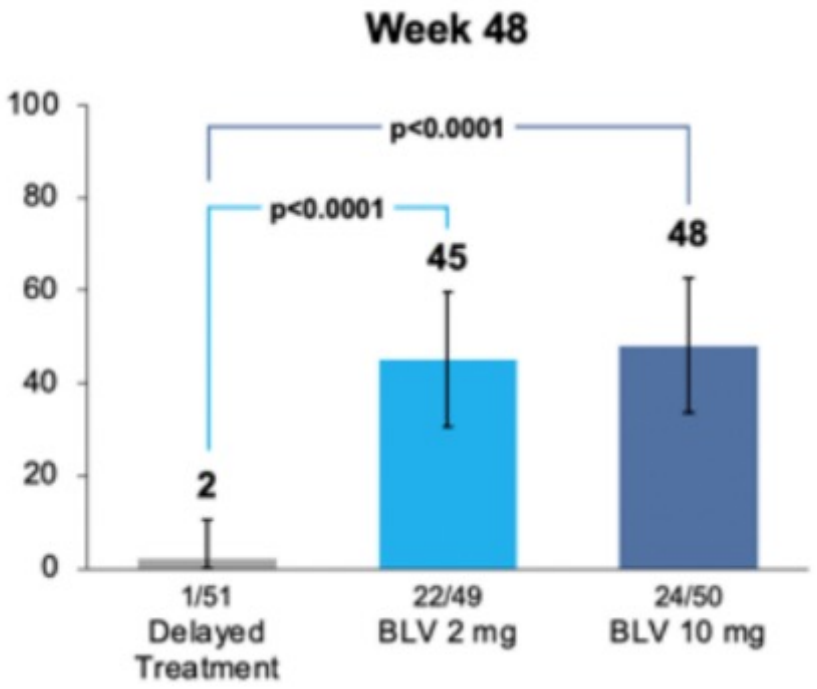
Key Inclusion Criteria
CHD without or with cirrhosis and CPT ≤7
ALT >1x–<10x ULN
Platelets ≥60.000 cells/mm^3
Controlled HIV coinfection allowed

Study Population
- 48% with cirrhosis
- HDV RNA, mean ≈ 5 $\log_{10}$ IU
- HBV DNA: mean ≈ 1 $\log_{10}$ IU
- 54-63% taking HBV active NRTIs

Wedemeyer EASL 2022

Slide from Dr. Annie Luetkemeyer, IDWeek 2022

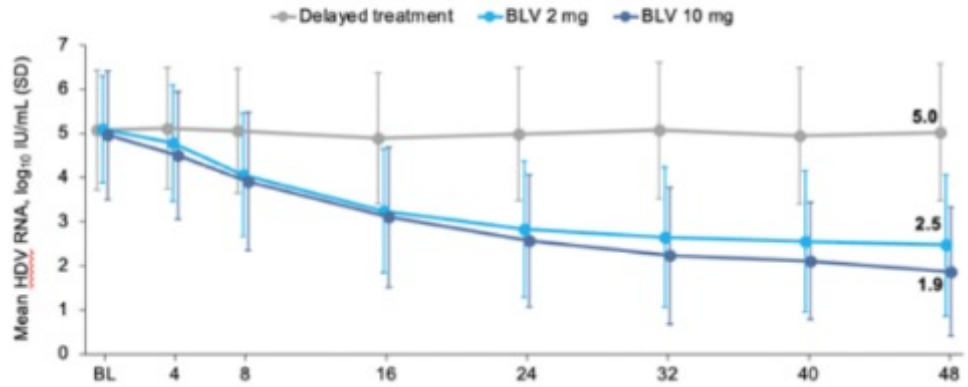
1^0 Endpoint: Virologic response & ALT normalization



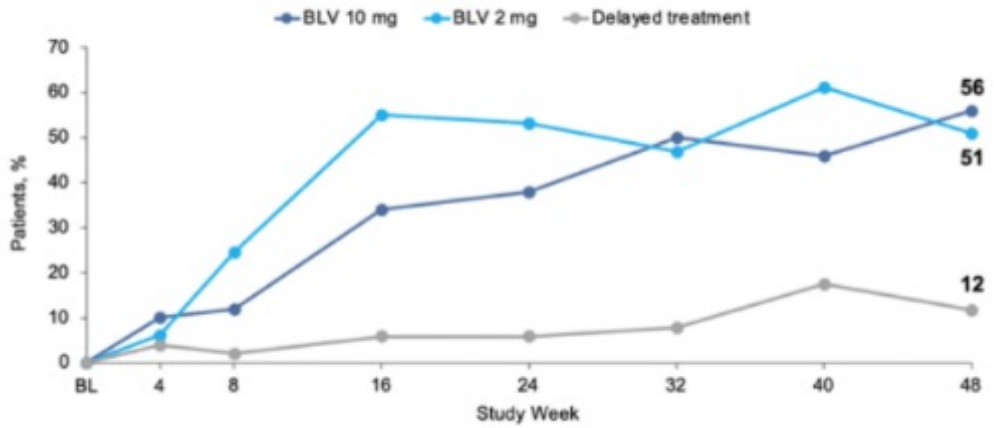
- Improved liver stiffness by elastography
- Generally safe and well tolerated
- Some injection site reactions

Wedemeyer EASL 2022

HDV RNA Decline Over 48 Weeks



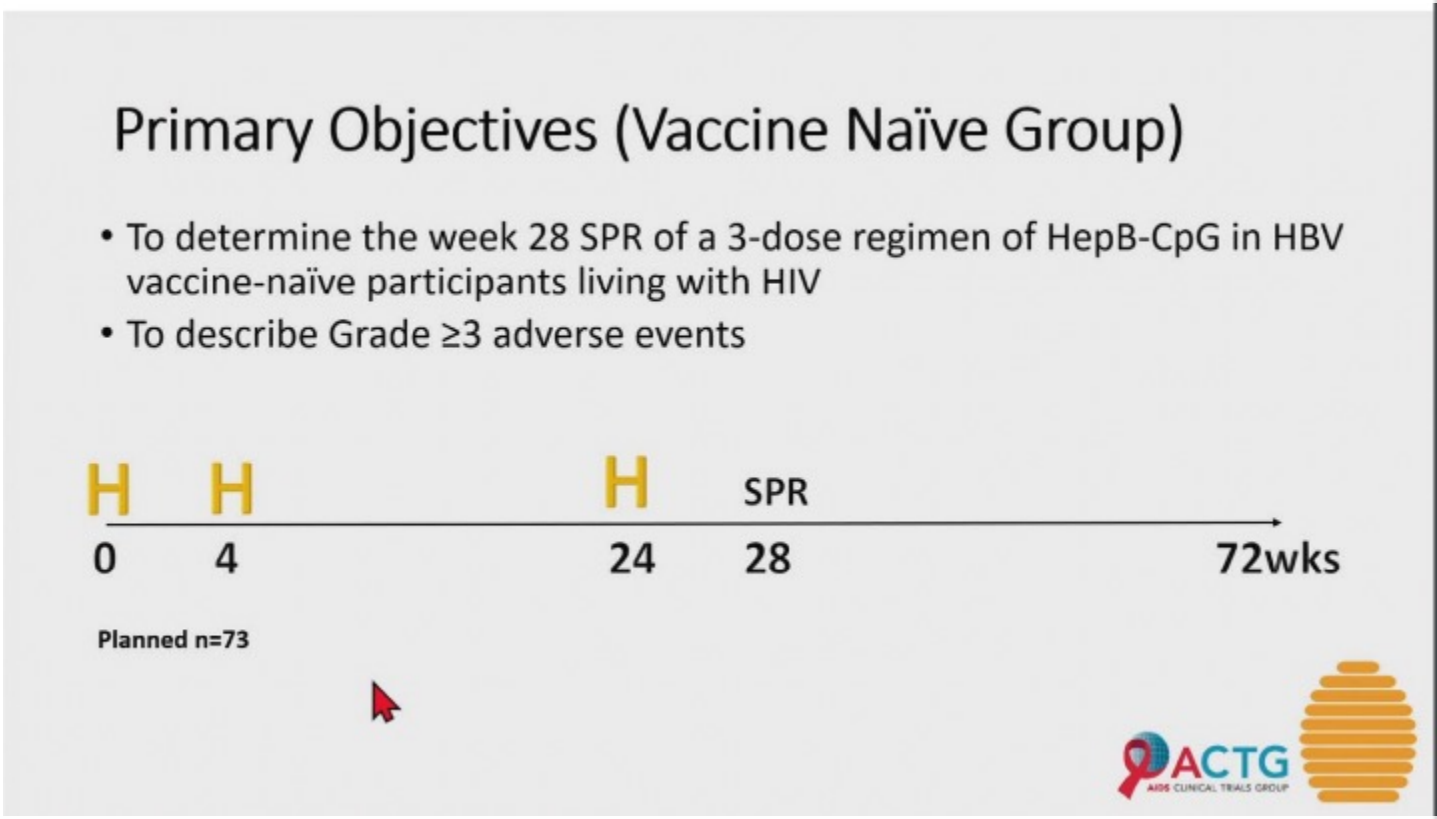
ALT Normalization Over 48 Weeks



Slide from Dr. Annie Luetkemeyer, IDWeek 2022

HepB-CpG Vaccine in PWH without prior HBV Vaccination

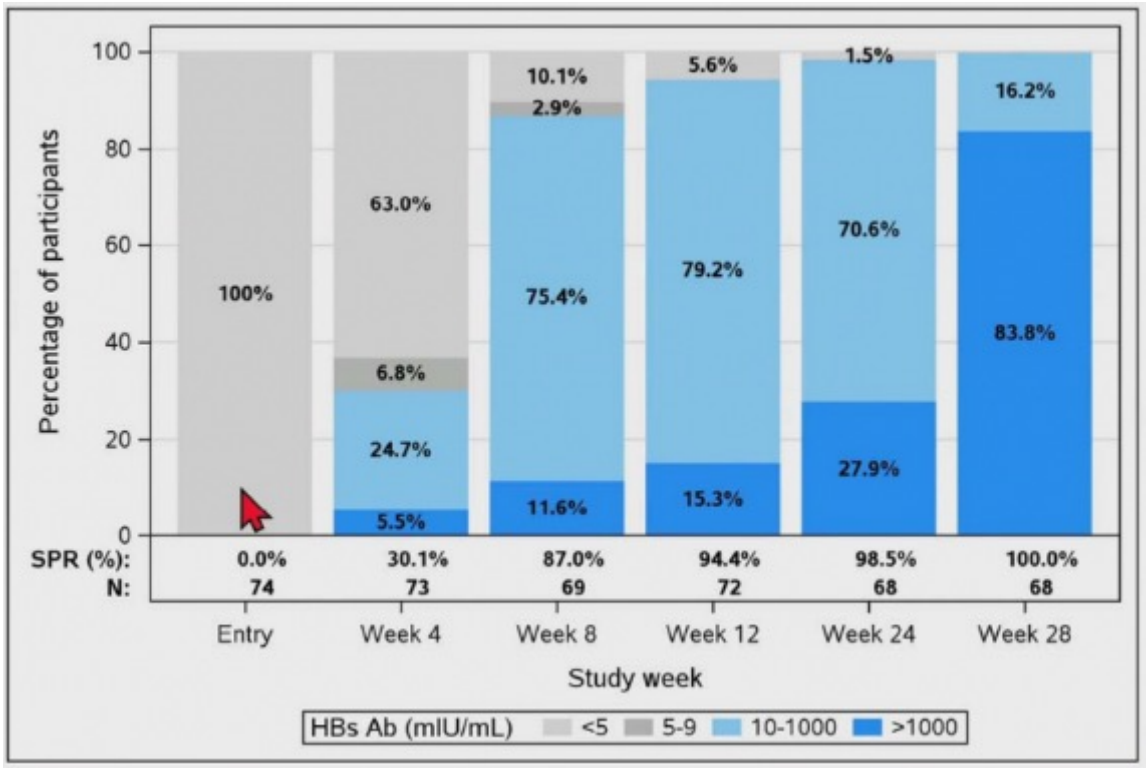
- Substantial proportion of PWH who receive conventional HBV vaccine do not achieve seroprotective levels of antibody to hepatitis B surface antigen
- New hepatitis B vaccine adjuvanted with CPG (TLR-9 agonist) recently approved as 2-dose vaccine for most adults. Limited data in PWH
- ACTG evaluated this vaccine in 74 PWH who had not previously been vaccinated



Marks K, et al. IDWeek 2022. Abstract LB749

HepB-CpG Vaccine in PWH without prior HBV Vaccination

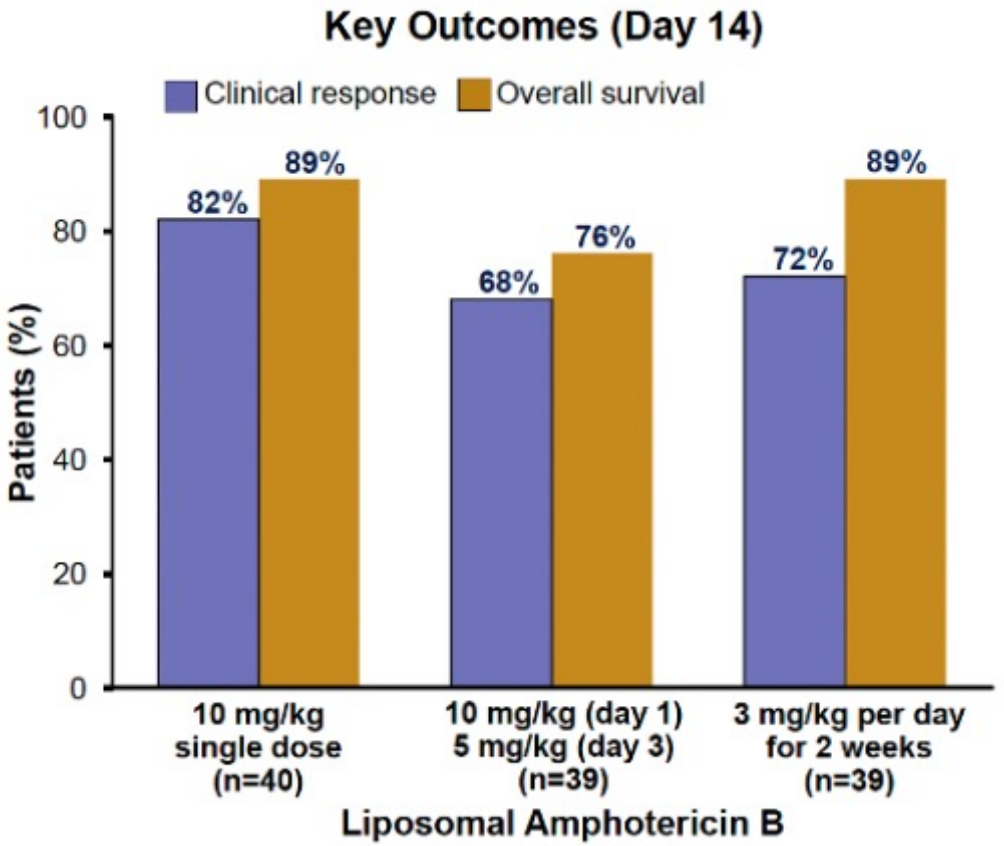
- Participants were on ART. Median CD4 cell count 625, >95% had suppressed VL
- 98.5 % achieved seroprotective response (SPR) after 2 doses; 100% achieved SPR after 3 doses
- Supports use of HepB CPG vaccine in PWH who have on ART with high CD4 counts, suppressed HIV RNA.
- Upcoming data with this vaccine in PWH who are previous vaccine non-responders



Marks K, et al. IDWeek 2022. Abstract LB749

Single High-dose Liposomal Amphotericin B in Histoplasmosis

- ~120 patients with advanced HIV (median CD4 count 25) and disseminated histoplasmosis in Brazil randomized to receive induction therapy with single high dose of L-AmB, two doses of L-AmB, or 2 weeks of L-AmB
- Oral intraconazole started on day L-AmB finished
- Rate of clinical response at day 14 and overall survival similar in all three groups
- Confirmatory phase 3 trial is needed and planned



Pasqualotto A, IDWeek 2022, Abstract LB2303

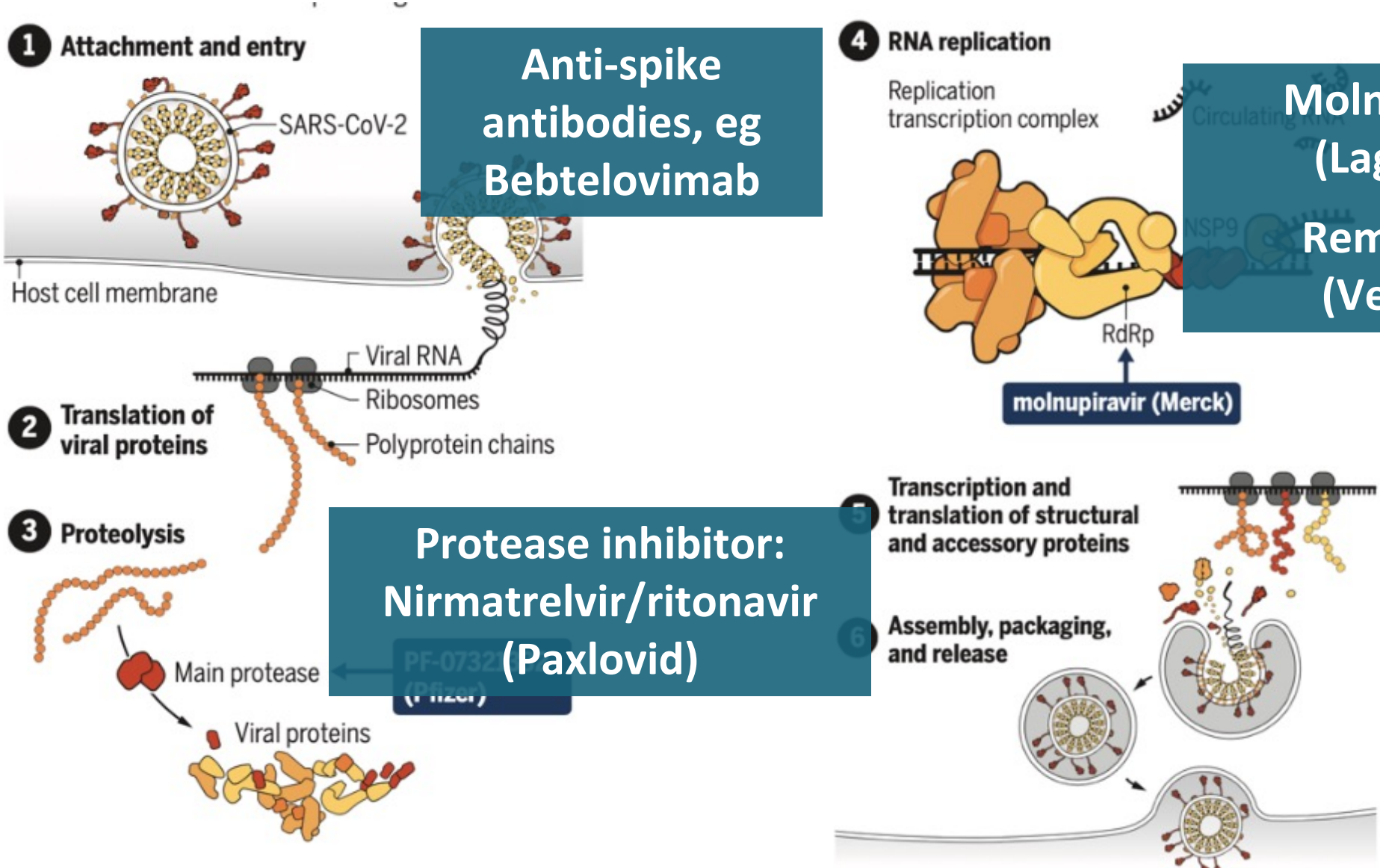
Slide adapted from Practice Point Communications

Factors for COVID-19 and Severe Outcomes in PWH

- Retrospective cohort study: Compared PWH who tested positive for COVID to those who tested negative for COVID between Jan 2020 and Jan 2022
- Testing positive for COVID-19 associated with younger age, living in US South and being uninsured.
  - Hispanic Whites and African Americans: higher odds of testing + for COVID than non-Hispanic Whites.
- Low CD4 cell count, detectable HIV RNA associated with death
- Implications:
  - Need to address social determinants of health in patients with HIV at higher risk of COVID and ensure PWH are effectively treated with ART.
  - Need to continue to recommend vaccinations and boosters in PWH
  - Need to continue to test people with suspected COVID and offer treatment to high-risk people who are infected.

Hanna JJ et al, IDWeek 2022, Abstract 2357

SARS CoV-2 Antivirals



Anti-spike antibodies, eg Bebtelovimab

Molnupiravir (Lagevrio)

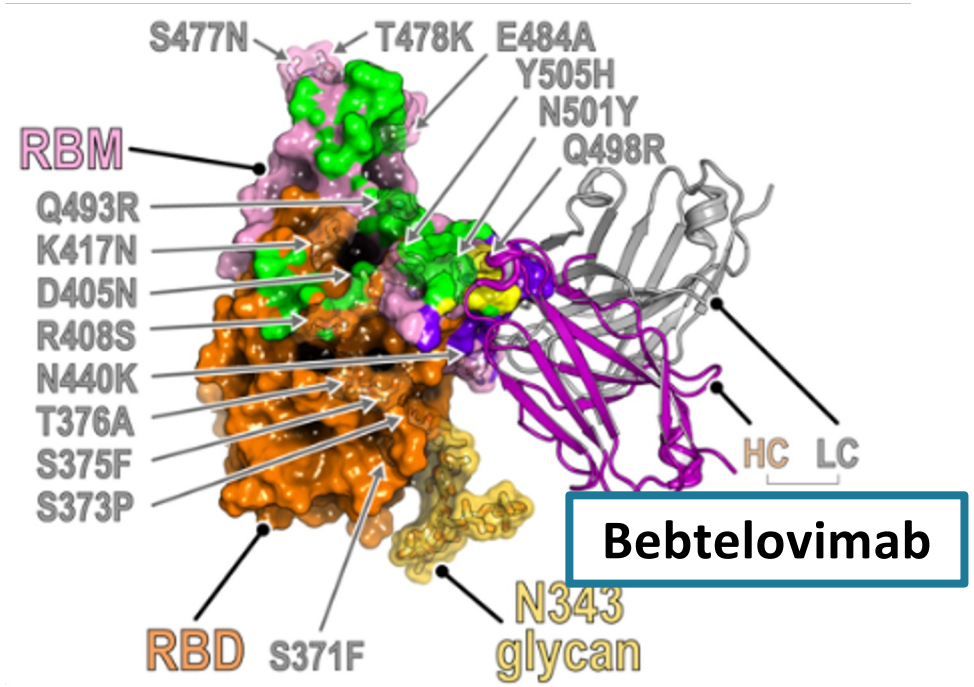
Remdesivir (Veklury)

Protease inhibitor: Nirmatrelvir/ritonavir (Paxlovid)

Modified from https://www.science.org/doi/epdf/10.1126/science.acx9605

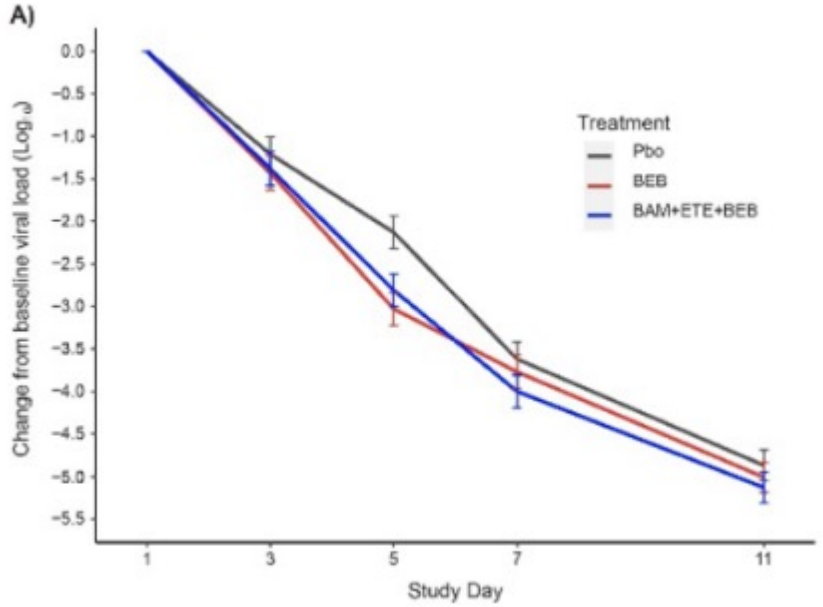
Phase 2 Clinical Trial Data for Bebtelovimab

Spike Protein



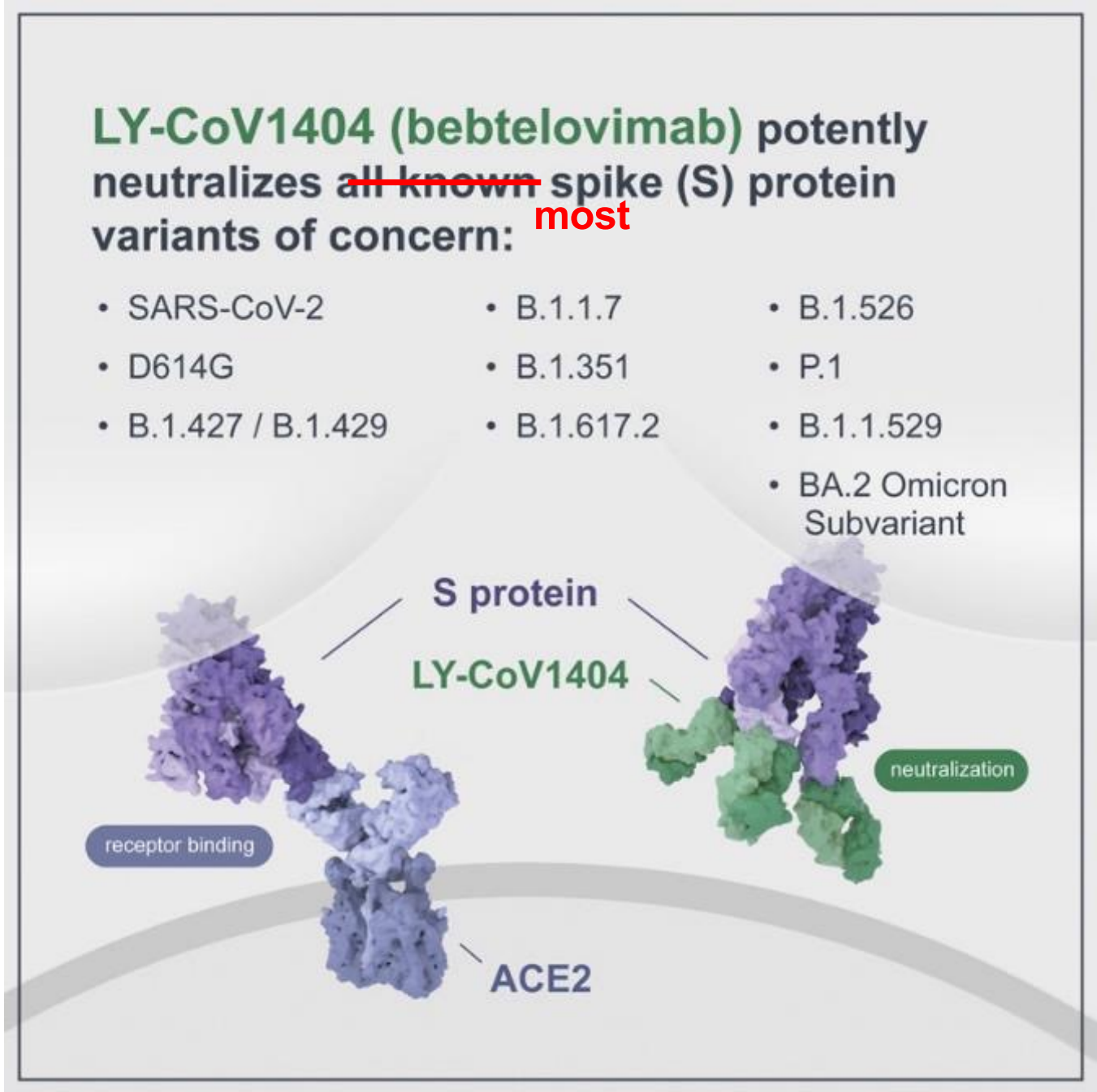
Bebtelovimab

Change from baseline in SARS CoV-2 Viral Load



Low risk participants	BEB N=125	BEB+BAM+ ETE (n=127)	Placebo (n=126)
Symptom resolution, median days (95% CI)	6 (5,7)	7 (6, 8)	8 (7, 9)
COVID-19 Hospitalization/Death	2/125 (1.6%)	3/127 (2.4%)	2/128 (1.6%)

Iketani S et al, Nature, 2022;
doi: https://doi.org/10.1101/2022.02.07.479306
https://twitter.com/abrahamlabhms
Westendorf, bioRxiv 2022
Dougan, medRxiv, 2022



- Bebtelovimab active in vitro against BA.1-5.

- New variants (BQ.1, BQ.1.1) may be resistant to bebtelovimab

Modified from slide from Dr. Arthur Kim

Iketani Nature 2022; Arora Cell Host Microbe 2022; Dougan medRxiV 2022; NIH Treatment Guidelines; Westendorf Cell Rep 2022

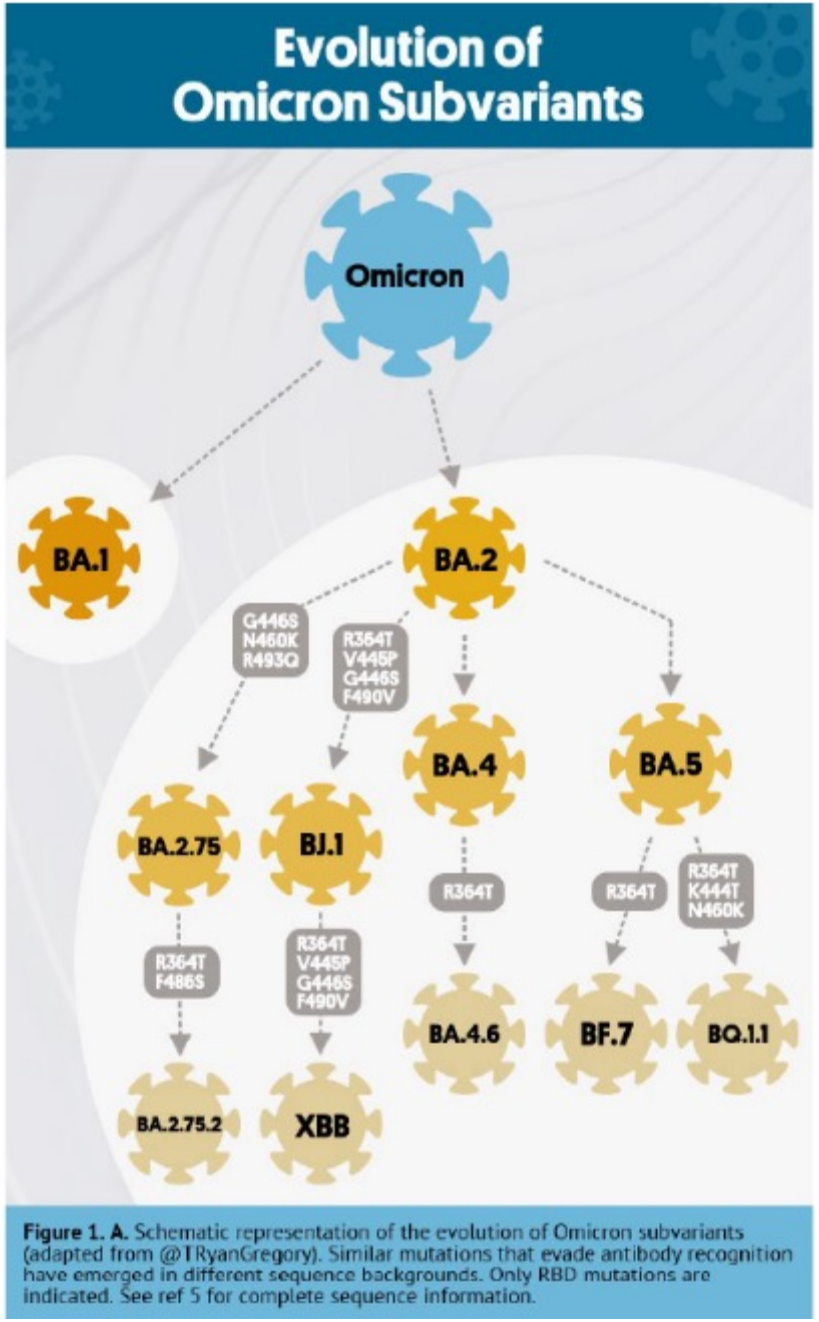


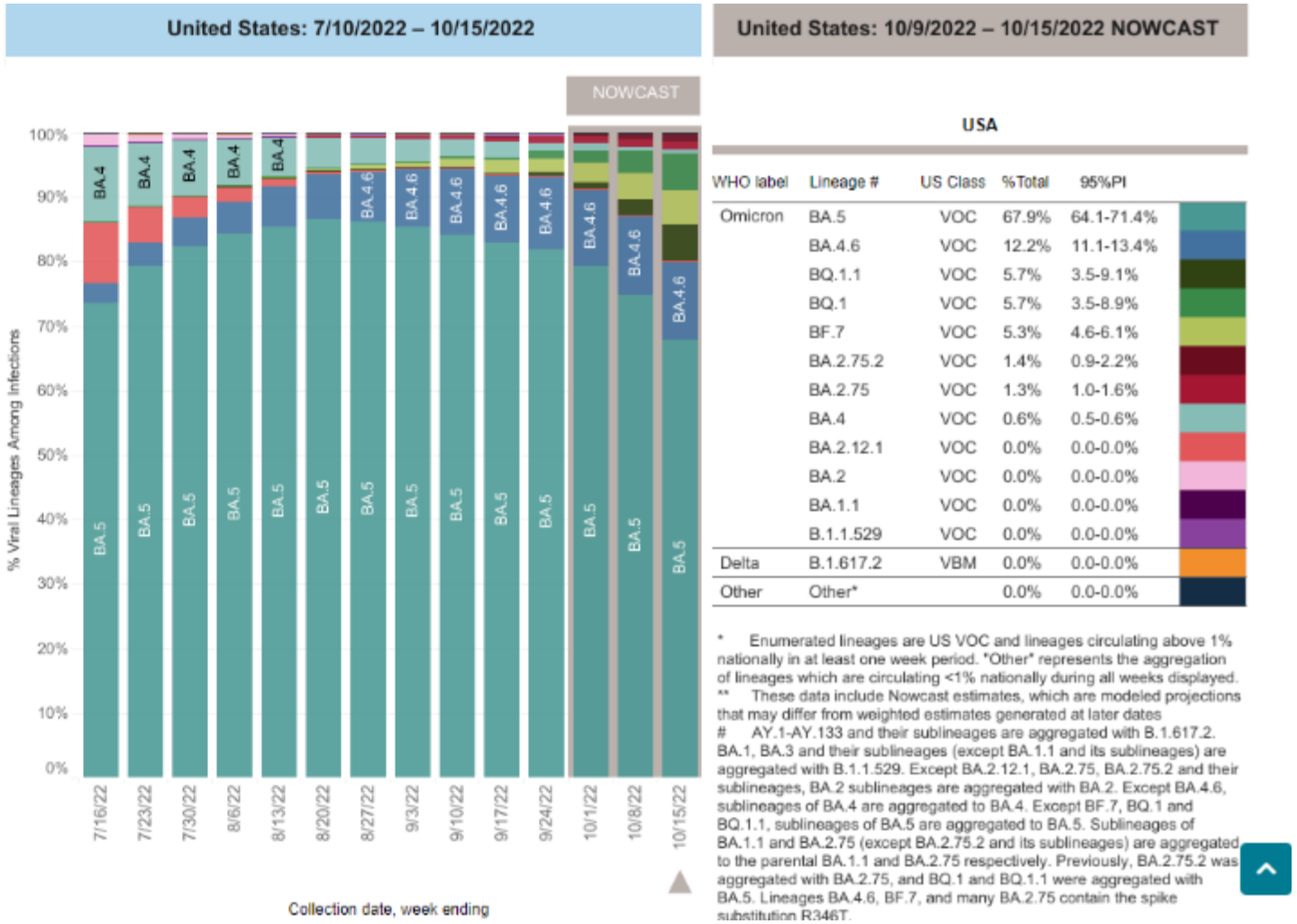
Figure 1. A. Schematic representation of the evolution of Omicron subvariants (adapted from @TRyanGregory). Similar mutations that evade antibody recognition have emerged in different sequence backgrounds. Only RBD mutations are indicated. See ref 5 for complete sequence information.

From BA.5: BQ.1, BQ.1.1, BF.7

From BA.2: BA.2.75.2

From BA.4: BA.4.6

New Omicron variants resistant to bebtelovimab



United States: 10/9/2022 – 10/15/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	67.9%	64.1-71.4%
	BA.4.6	VOC	12.2%	11.1-13.4%
	BQ.1.1	VOC	5.7%	3.5-9.1%
	BQ.1	VOC	5.7%	3.5-8.9%
	BF.7	VOC	5.3%	4.6-6.1%
	BA.2.75.2	VOC	1.4%	0.9-2.2%
	BA.2.75	VOC	1.3%	1.0-1.6%
	BA.4	VOC	0.6%	0.5-0.6%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
	BA.2	VOC	0.0%	0.0-0.0%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		0.0%	0.0-0.0%

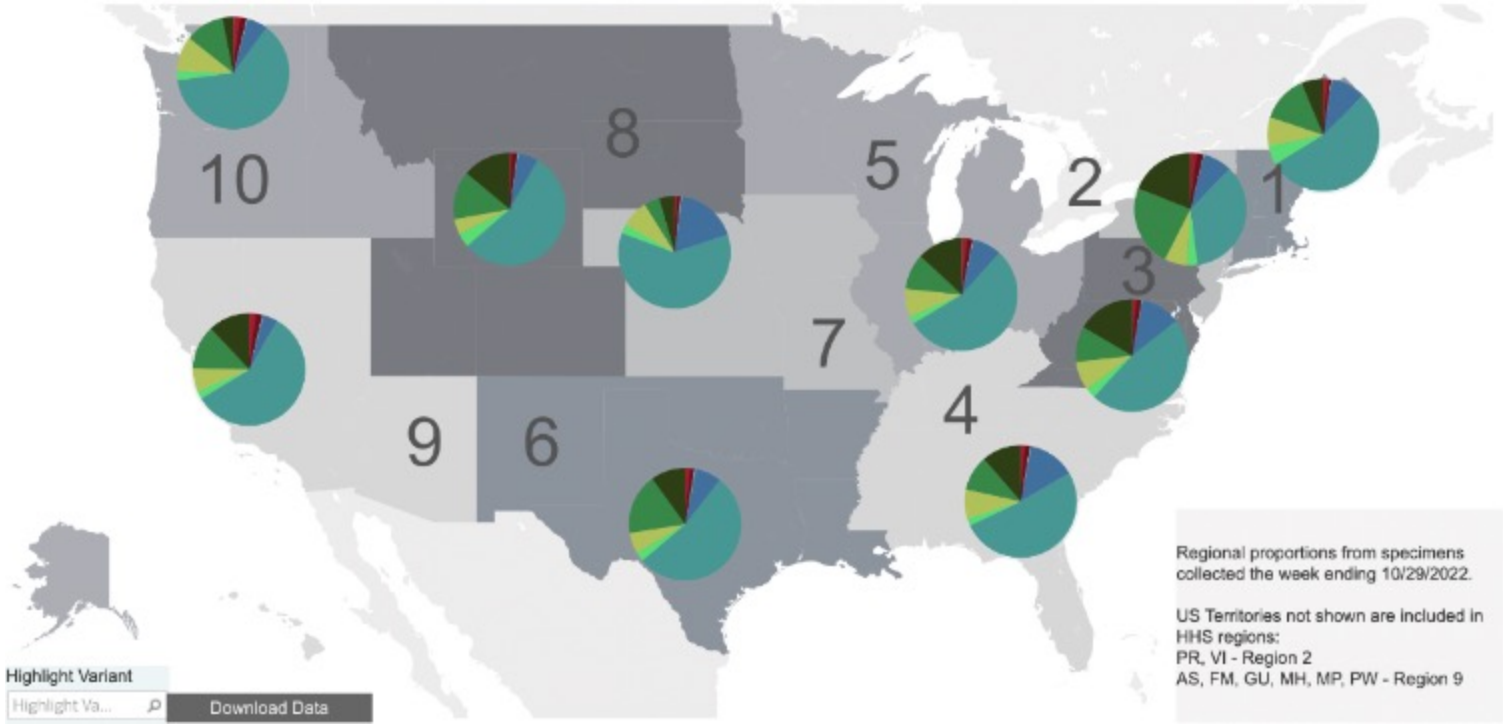
* Enumerated lineages are US VOC and lineages circulating above 1% nationally in at least one week period. "Other" represents the aggregation of lineages which are circulating <1% nationally during all weeks displayed.
** These data include Nowcast estimates, which are modeled projections that may differ from weighted estimates generated at later dates
# AY.1-AY.133 and their sublineages are aggregated with B.1.617.2. BA.1, BA.3 and their sublineages (except BA.1.1 and its sublineages) are aggregated with B.1.1.529. Except BA.2.12.1, BA.2.75, BA.2.75.2 and their sublineages, BA.2 sublineages are aggregated with BA.2. Except BA.4.6, sublineages of BA.4 are aggregated to BA.4. Except BF.7, BQ.1 and BQ.1.1, sublineages of BA.5 are aggregated to BA.5. Sublineages of BA.1.1 and BA.2.75 (except BA.2.75.2 and its sublineages) are aggregated to the parental BA.1.1 and BA.2.75 respectively. Previously, BA.2.75.2 was aggregated with BA.2.75, and BQ.1 and BQ.1.1 were aggregated with BA.5. Lineages BA.4.6, BF.7, and many BA.2.75 contain the spike substitution R346T.

Modified from slide by Dr Jon Li

Oct 14: BQ.1, BQ.1.1: about 11% of US isolates – will update

Omicron	Beb
BA.5	✓
BA.4.6	✓
BA.2.75.2	✓
BQ.1, 1.1	✗
XBB	✗

CDC Nowcast (10/29/2022)/ -- Will update



WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	49.6%	45.3-53.9%
	BQ.1	VOC	14.0%	11.2-17.5%
	BQ.1.1	VOC	13.1%	9.8-17.3%
	BA.4.6	VOC	9.6%	8.6-10.7%
	BF.7	VOC	7.5%	6.6-8.5%
	BA.5.2.6	VOC	2.8%	2.3-3.5%
	BA.2.75	VOC	1.8%	1.5-2.2%
	BA.2.75.2	VOC	1.2%	0.9-1.6%
	BA.4	VOC	0.2%	0.2-0.3%

Variants	All Regions	Region 1	Region 2	Region 3	Region 4	Region 5	Region 6	Region 7	Region 8	Region 9	Region 10
BA.4.6	9.6%	10.2%	8.4%	11.4%	13.6%	8.3%	7.5%	17.8%	5.8%	4.3%	5.9%
BQ.1	14.0%	13.6%	23.5%	10.2%	10.2%	10.3%	17.5%	4.5%	13.9%	12.6%	11.2%
BQ.1.1	13.1%	6.4%	19.0%	16.6%	11.4%	13.1%	10.0%	4.4%	13.9%	12.0%	3.1%
total	36.7%	30.2%	50.9%	38.2%	35.2%	31.7%	35.0%	26.7%	33.6%	28.9%	20.2%

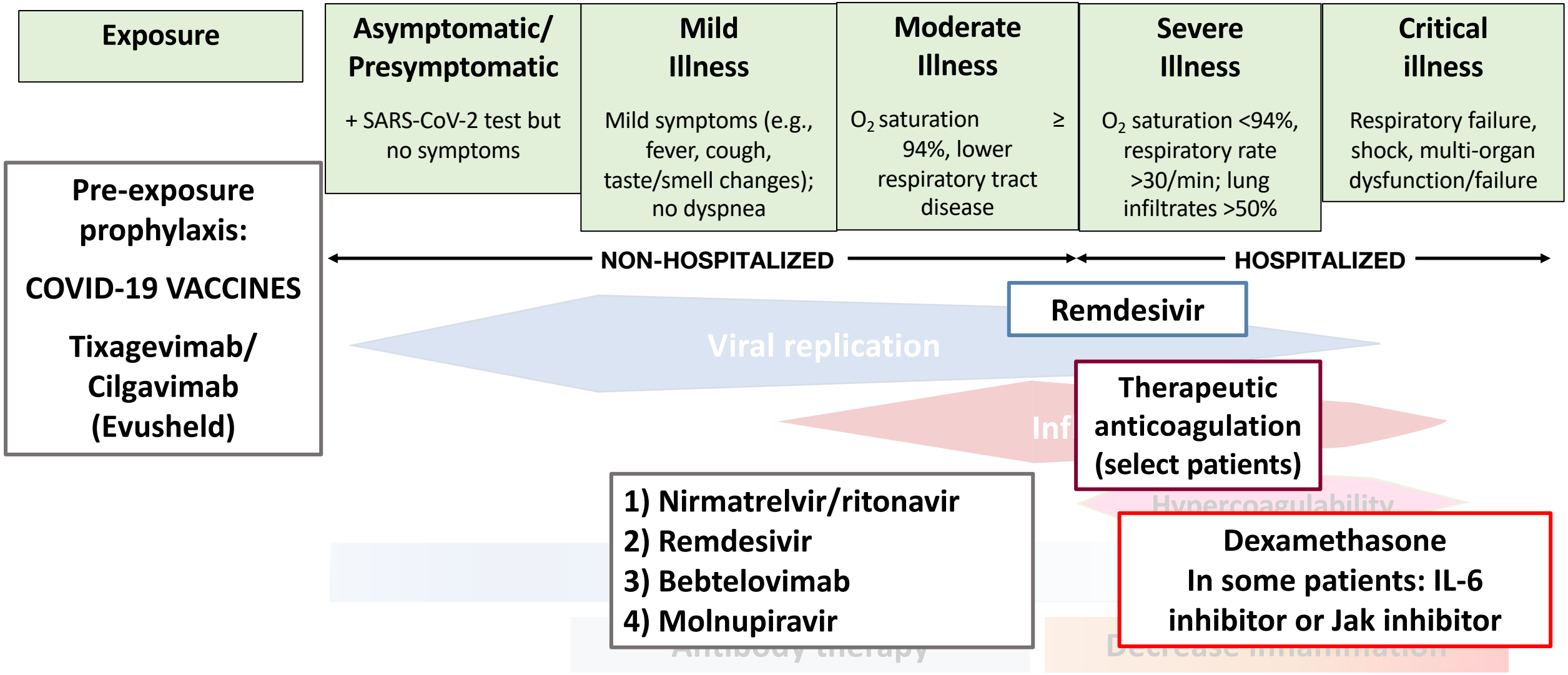
Table adapted from Alice Pau. https://covid.cdc.gov/covid-data-tracker/#variant-proportions

Small molecule antivirals anticipated to be active against new variants

	1) Nirmatrelvir/r	2) Remdesivir	3) Molnupiravir
Efficacy (prevention hospitalization or death)	• **Relative risk reduction: 88%** • Absolute risk: 6.3%→0.8% • NNT: 18	• **Relative risk reduction: 87%** • Absolute risk: 5.3%→0.7% • NNT: 22	• **Relative risk reduction: 30%** • Absolute risk: 9.7%→6.8% • NNT: 35
Pros	• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy	• Highly efficacious • Studied in pregnancy • Few/no drug interactions	• Oral regimen • Not anticipated to have drug interactions
Cons	• Drug drug interactions	• Requires IV infusion on 3 consecutive days	• Low efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

Modified from Table in Gandhi RT, Malani P, del Rio C, JAMA, Jan 14, 2022

Treatment Across the COVID-19 Spectrum



Gandhi RT, CID, 2020; Gandhi RT, Lynch J, del Rio C. NEJM 2020

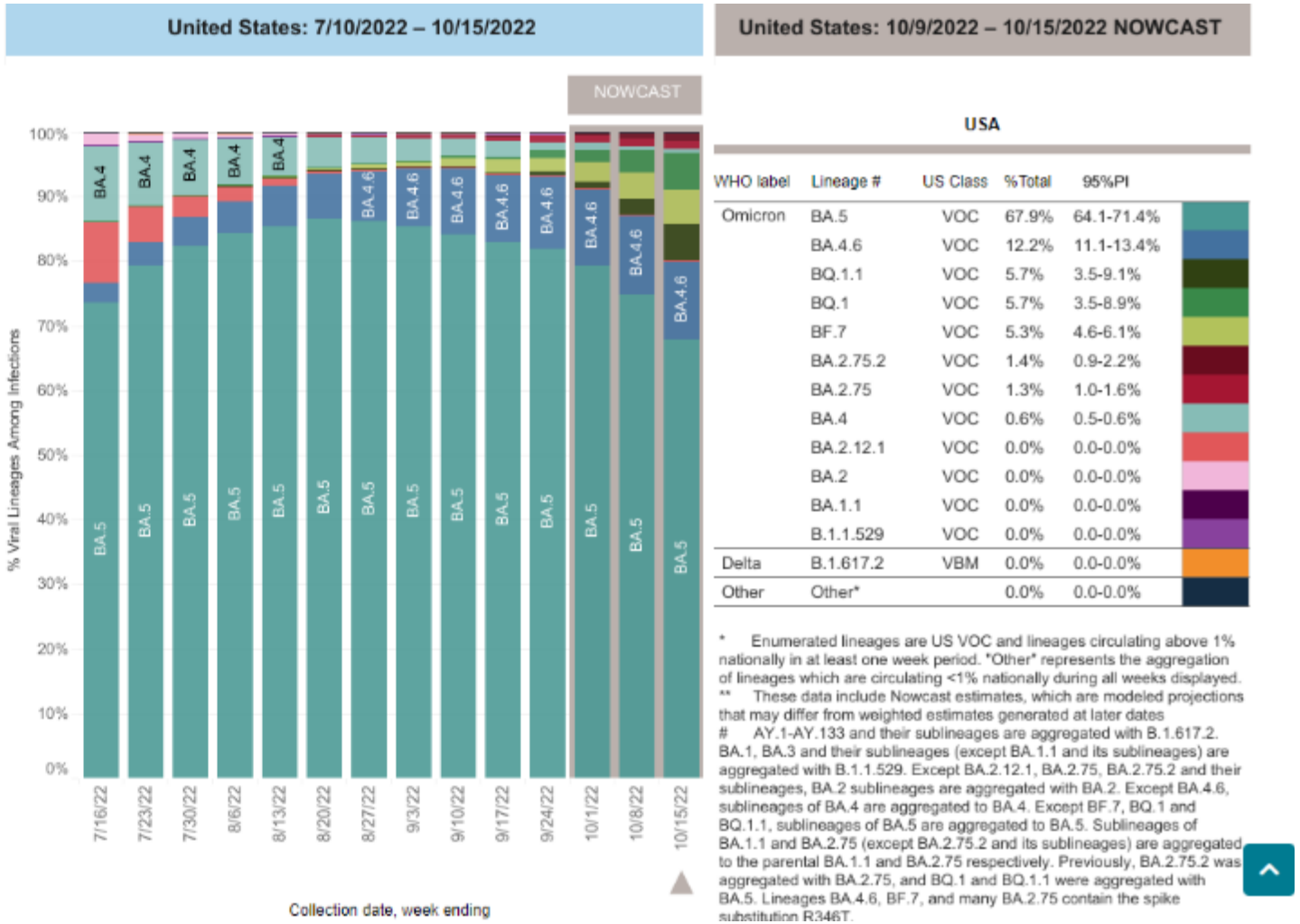
Tixagevimab/cilgavimab for COVID-19 Pre-Exposure Prophylaxis

- **FDA Emergency Use Authorization**:
  - Who have moderate to severe immune compromise due to medical condition or receipt of immunosuppressive medications or treatments
- Includes advanced or untreated HIV: CD4 <200, history of AIDS defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV
- Wait 2 weeks *after* vaccination to administer tixagevimab/cilgavimab

https://www.fda.gov/media/154701/download

New Omicron variants resistant to tixagevimab/cilgavimab

Oct 14: BQ.1, BQ.1.1, BA.4.6, BF.7 and BA.2.75.2: about 30% of US isolates – will update



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Omicron	Tixa/cil
BA.5	✓
BA.4.6	✗
BA.2.75.2	✗
BQ.1, 1.1	✗
XBB	✗

Modified from slide by Dr Jon Li

Conclusions

- In regions where majority of circulating variants anticipated to be resistant, bebtelovimab is no longer reliable option for treating high-risk non-hospitalized patients with mild-to-moderate COVID-19
- Small molecule antivirals (nirmatrelvir/ritonavir, remdesivir, molnupiravir) anticipated to still be active
- Immunocompromised individuals who receive tixagivimab/cilgavimab for pre-exposure prophylaxis should be counseled to continue measures to avoid infection (including staying up to date with vaccination) and to seek testing and treatment if symptoms of COVID-19 develop

Rebound after NMV/r: What We Know So Far (1)

- Clinical improvement with negative antigen/PCR -> relapse of URI symptoms 4 to 10 days after completing NMV/r, sometimes with antigen positivity – usually mild; typically resolves without further treatment
- **How often?**
  - PCR rebounds reported in ~2% of EPIC-HR trial of NMV/r; equal in placebo and treated groups
  - TriNetX (EHRs) - suggest ~3.5% within 7 days

Modified from slide from Dr. Arthur Kim

Charness NEJM Sept 15, 2022; Wang Preprint 2022

Rebound after NMV/r: What We Know So Far (2)

- **Transmission?**
  - Series of 10 patients, all fully vaccinated with booster, putative transmission in 2 instances
  - MGH series, 7 patients – rebound SARS-CoV-2 levels similar to pre-treatment values; 3 of 7 patients were culture positive during rebound

- **Why?**
  - Early reports: no decrements in antibody levels or adaptive immunity
  - Thus far, no resistance detected before or after NMV/r
  - Rebound may occur even without NMV/r; not known if incidence different

Modified from slide from Dr. Arthur Kim

Charness NEJM 2022; Epling, CID 2022; Boucau CID 2022; Carlin. Clin Infect Dis. 2022;[Epub]; Deo R et al, medRxiv, 2022; Callaway E, Nature, 2022

What About Rebound? Should therapy duration be extended? My Take

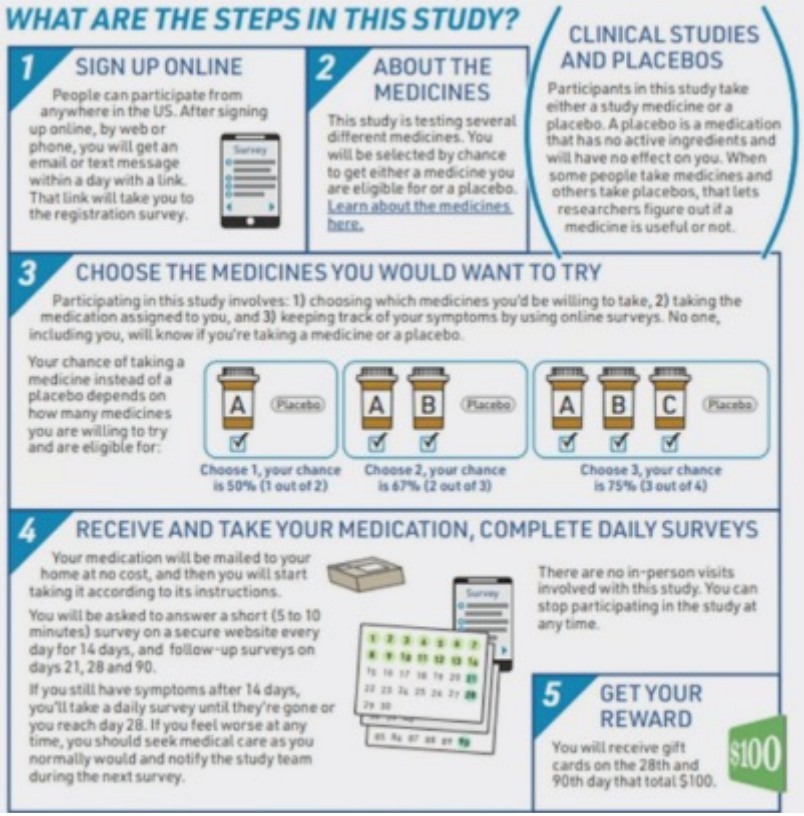
- I counsel patients that rebound may occur, but it will not be severe; therefore, I do not suggest avoiding therapy because of potential for rebound
- In patients who have symptomatic rebound and whose antigen test turns positive again, I reset isolation clock
- I generally do not extend duration of therapy or re-treat, but this is an important area for future study

ACTIV-6

a decentralized, placebo-controlled, randomized, platform clinical trial

Study Design

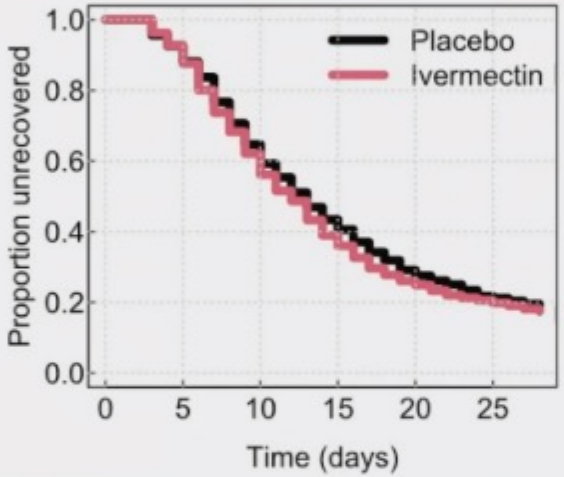
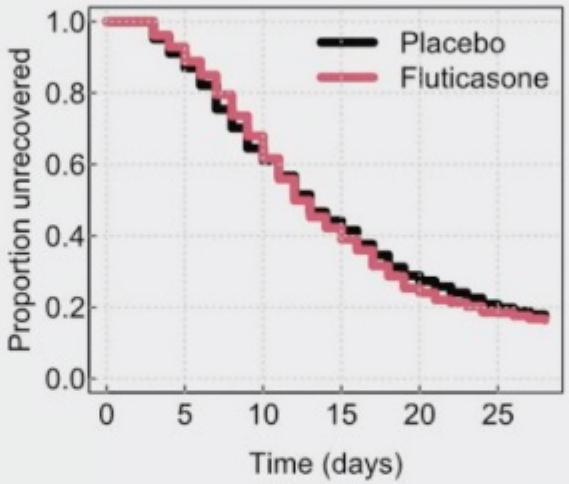
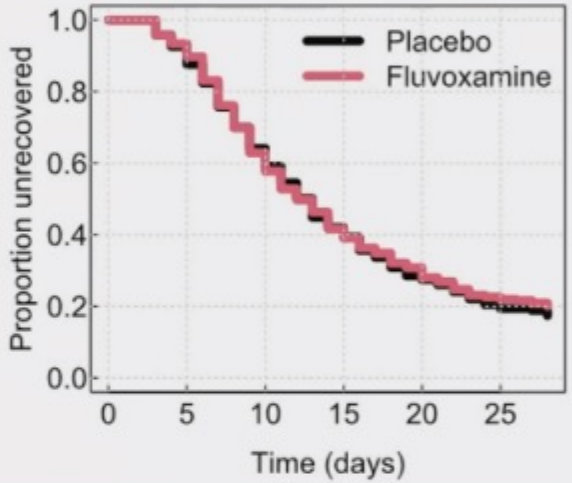
- Direct-to-participant
- All participants assigned to a site
- Symptom reporting daily
- COVID-19 outcome reporting
- Remote visits
- Continuous safety assessments
- 5 active arms to date



McCarthy MW. Fluvoxamine for outpatient treatment of COVID-19: IDWeek 2022, Abstract LB1528A.
Boulware DR. Inhaled fluticasone for outpatient treatment of COVID-19. IDWeek 2022, Abstract LB1528B.
Naggie S. Ivermectin for treatment of mild-to-moderate COVID-19 in the outpatient setting. IDWeek 2022, Abstract LB1528C.

Primary Endpoint: Time to Sustained Recovery

Among participants that did not die during follow-up, recovery was defined as **three consecutive days without COVID-19** symptoms, as affirmatively reported by the study participant. Time to recovery was administratively censored at 28 days.

	IVERMECTIN 400 µg/kg	FLUTICASONE	FLUVOXAMINE 50 mg
Kaplan-Meier			
HR (95% CrI) P(HR>1)	1.07 (0.96, 1.17) 0.91	1.01 (0.91, 1.12) 0.56	0.96 (0.87, 1.07) 0.22
Median time (IQR), active vs placebo	12 (11-13) vs 13 (12-14)	11 (10.9-11.2) vs 11.5 (11.3-11.6)	12 (11-14) vs 13 (12-13)

ACTIV-6

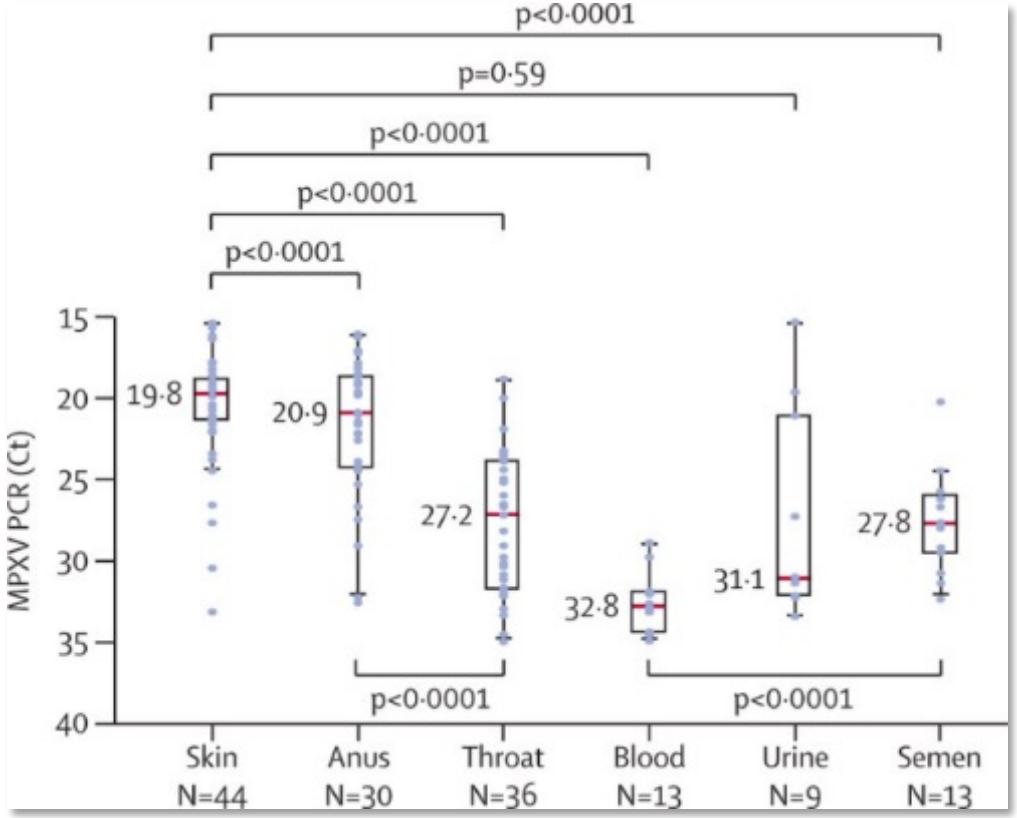
The NEW ENGLAND JOURNAL of MEDICINE

Time to Stop Using Ineffective Covid-19 Drugs

Salim S. Abdool Karim, M.B., Ch.B., Ph.D., and Nikita Devnarain, Ph.D.

Transmission of Monkeypox Virus (MPXV)

MPXV viral loads



Samples collected from 50 men (Palich et al)

- Main mode of transmission= sexual contact
  - Majority MSM, but heterosexual and non-sexual contact documented
- Small number of transmissions through needle sticks, skin piercing, tattooing
- Asymptomatic infections documented, but asymptomatic transmission not definitive
- Skin and anal lesions contain highest concentration of virus
- Risk of infection through fomites considered low

Palich R et al, Lancet Inf Dis, 2022
https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html

MPXV in Human Samples and Implications for Transmission

Exposure Source	*MPXV* DNA detected by PCR	Replication-competent virus detected/isolated	Epidemiologically supported source of infection
Skin	Yes	Yes	Yes
Oropharynx and saliva	Yes	Yes	Yes
Anorectum	Yes	Yes	Yes
Semen	Yes	Yes	Insufficient data
Urine/urethra	Yes	Yes	Insufficient data
Conjunctiva or ocular fluid	Yes	Yes	Insufficient data
Blood/plasma/serum	Yes	Insufficient data	Insufficient data
Feces	Yes	Insufficient data	Insufficient data
Vaginal fluid	Insufficient data	Insufficient data	Insufficient data
Breastmilk	Insufficient data	Insufficient data	Insufficient data
Contaminated sharp	Insufficient data	Insufficient data	Yes

MPXV detectable in many samples, but not all replication-competent or source of infection

https://www.cdc.gov/poxvirus/monkeypox/about/science-behind-transmission.html

No sustained transmission outside of MSM networks

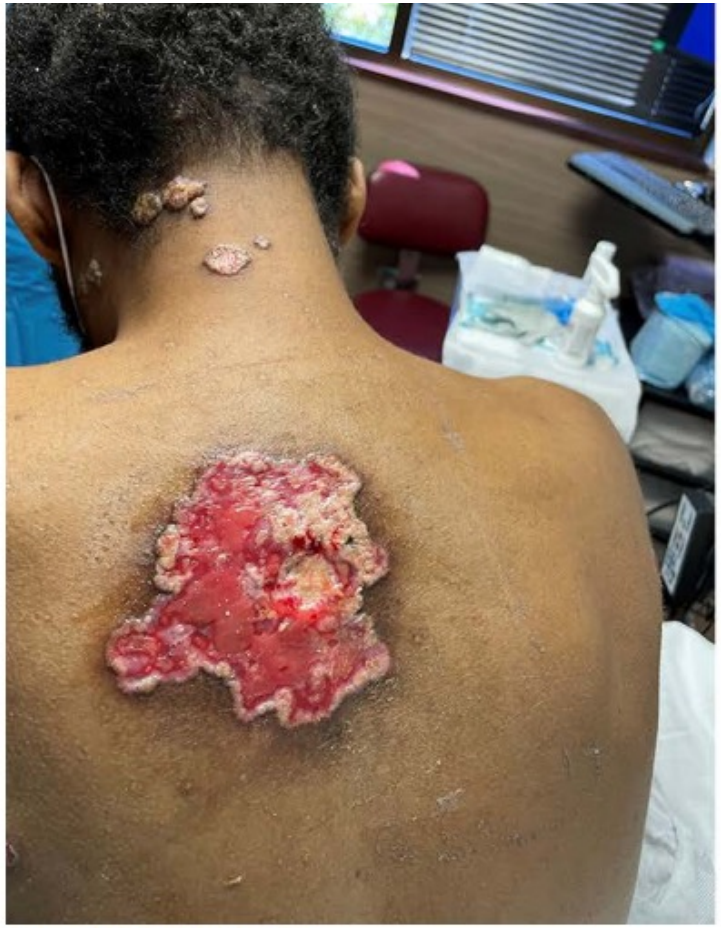
- Correctional facilities: Investigation at Cook County, Illinois jail
  - No secondary cases; virus DNA (but no viable virus) detected on one surface
- Healthcare personnel presumably due to work exposure: 3 cases
  - Sharps injuries while attempting to unroof lesions. Localized, self-limited infections
  - Lesions should be vigorously swabbed; unroofing discouraged
- People experiencing homelessness
  - Cases identified, including severe cases
  - Anecdotally may be mostly in people experiencing unsheltered homelessness
  - Vigilance needed
- Daycare settings and schools: No known secondary cases
- Reverse zoonoses to animals: Uncertainty about reported cases

Agam Rao, MD (CDC), ID Week 2022

Severe Monkeypox in People with Advanced HIV

- 27,884 MPX cases confirmed and probable in the US (through Oct 21, 2022)
- Majority of cases in MSM; PWH and racial/ethnic minorities disproportionately affected
- CDC consultation provided for 57 hospitalized patients:
  - 47 (82%) had HIV infection, 4 (9%) on ART before MPX infection; CD4 count <50 in 72%
  - 95% male; 68% non-Hispanic Black, 23% experiencing homelessness
  - 93% received tecovirimat
  - 12 (21%) died; MPX cause or contributing factor in 5 deaths; additional 6 deaths under investigation
- Emphasizes importance of testing people with MPXV infection for HIV and importance of diagnosing and treating all PWH

https://www.cdc.gov/mmwr/volumes/71/wr/mm7144e1.htm



Photos/Alexandra Dretler
* Patient has consented to the publication of these photographs.

https://www.cdc.gov/mmwr/volumes/71/wr/mm7144e1.htm

- AIDS Clinical Trials Group study A5418
- Opportunity for persons with minimal or mild disease to access treatment and participate in research
  - >65 clinical centers enrolling (1st enrollee September 12, 2022)
  - Fully remote option under development
- Randomized 2:1 to receive drug-vs-placebo for 14 days
  - If evidence of disease progression after 5 days, can receive tecovirimat
- People who are at higher risk for severe disease because of their age or their medical history will be assigned to receive open-label tecovirimat for 14 days

Source: https://actgnetwork.org/studies/a5418-study-of-tecovirimat-for-human-monkeypox-virus-stomp/

PrEP

Awareness and Interest in PrEP Options Among Cisgender Women in US

- Women account for 20% of new HIV diagnoses but only 8% of PrEP users
- Almost 1000 sexually active women without HIV surveyed about awareness and interest in PrEP in 2021
- 7 in 10 had heard of PrEP but only about 1 in 3 had talked to HCP about PrEP

Interim Results of Survey

	Respondents (%)
Sexual behavior (n=732)	
Condom use all of the time	16
Exchanged sex for money	19
STI diagnosis in past 2 years	9
PrEP awareness (n=961)	
Heard of PrEP	71
Talked to health care professional	37
PrEP use (n=961)	
Currently taking PrEP	9
Ever taken PrEP	20
Long-acting PrEP (n=61)	
Heard of long-acting PrEP	50
Expressed interest in taking	66

Poteat T, et al. IDWeek 2022. Abstract 795. Table from Practice Point Communications

PrEP: Where We Are Now

- More than decade since PrEP was shown to be effective in preventing HIV, most women have never spoken to a health care provider about it.
- In 2021, CDC revised PrEP guidelines to recommend that “all sexually active adult and adolescent patients should receive information about PrEP.”
- Information about PrEP needs to be fully integrated into primary care and discussed with all sexually active women and men

Summary

- Diagnosing and treating HIV as soon as possible remains a high priority
- Current antiretroviral options work well, even in people with high HIV RNA, low CD4 counts
- For patients who are virologically suppressed, many options to simplify therapy, including long-acting injectable CAB/RPV; more data needed on CAB/RPV in people who are viremic
- In people with NRTI resistance, combining a drug with high barrier to resistance (DRV/r, DTG, BIC) with tenofovir/FTC or 3TC likely to achieve or maintain viral suppression
- Lenacapavir for treatment of multi-drug resistant HIV may be approved soon
- Coinfections, including viral hepatitis, COVID-19 and monkeypox virus, pose new challenges and opportunities
- Need to expand PrEP access and integrate its use into primary care

Thank You for Your Attendance!

Please visit us at:

www.prn.org