Hot Topics: HIV/AIDS, COVID-19 and Monkeypox (MPX)

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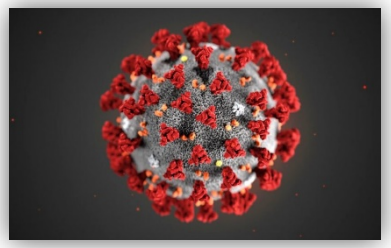
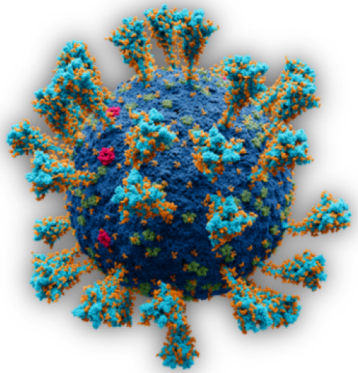
Disclosures: Consultant for Gilead, Merck, ViiV; Research support from Gilead and ViiV; Volunteer member of DHHS Antretroviral Treatment and NIH COVID-19 Guidelines Panels

Outline

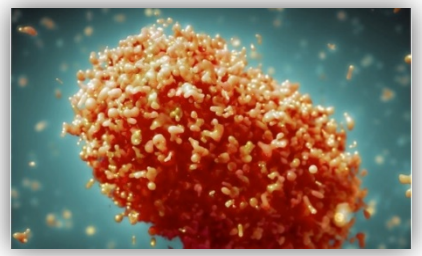
- HIV
  - Prevention
  - Treatment



- COVID-19
  - Epidemiology, and variants
  - Prevention
  - Treatment



- MPX
  - Epidemiology
  - Testing
  - Prevention
  - Treatment



HIV/AIDS:
Prevention and Treatment

Pre exposure Prophylaxis

MSM/TGW

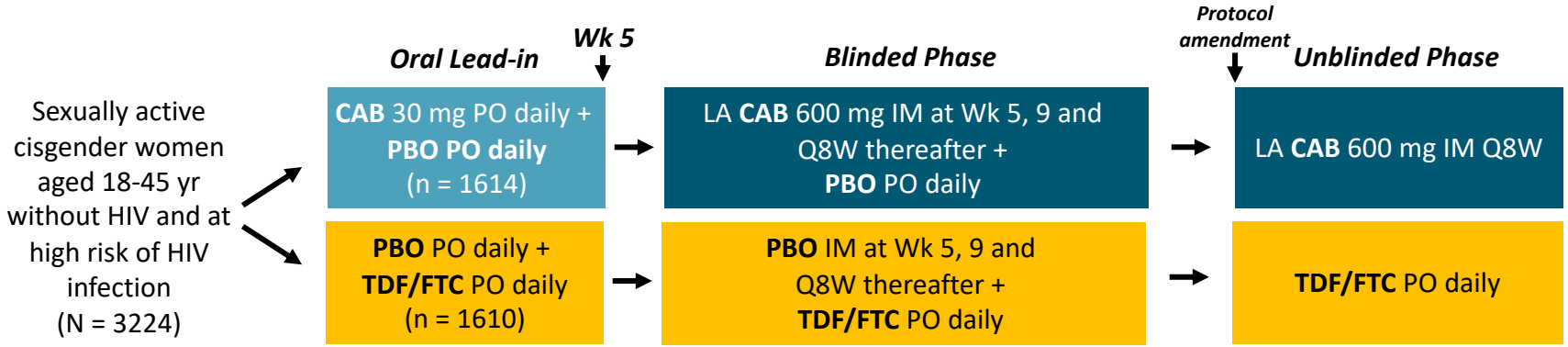
Tenofovir disoproxil fumarate/emtricitabine po qd
Tenoffovir disoproxil fumarate/emtricitabine po 2:1:1
Tenofovir alafenamide/emtricitabine po qd
Cabotegravir IM q8 weeks

Cis-Women

Tenofovir disoproxil fumarate/emtricitabine po qd
Cabotegravir IM q8 weeks

HPTN 084 Update: Study Design

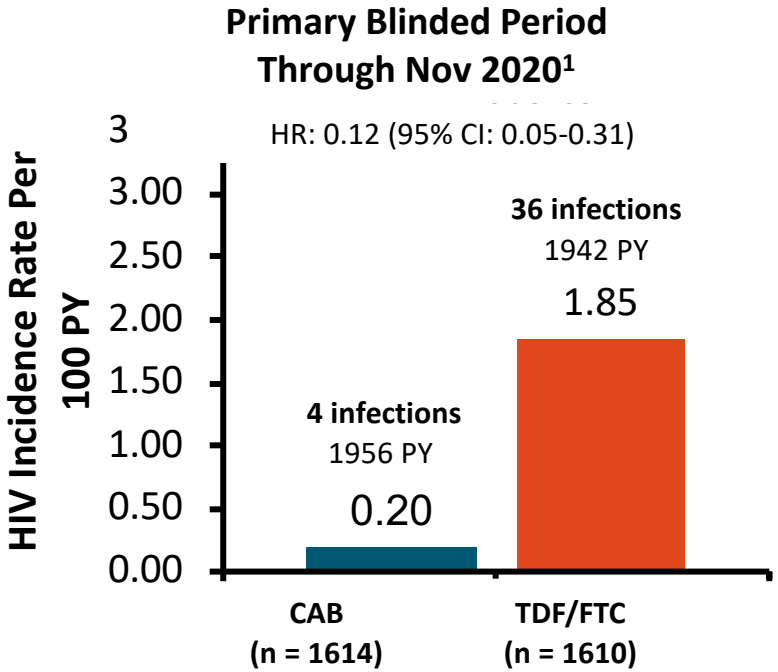
- International, randomized, double-blind phase III trial[1,2]

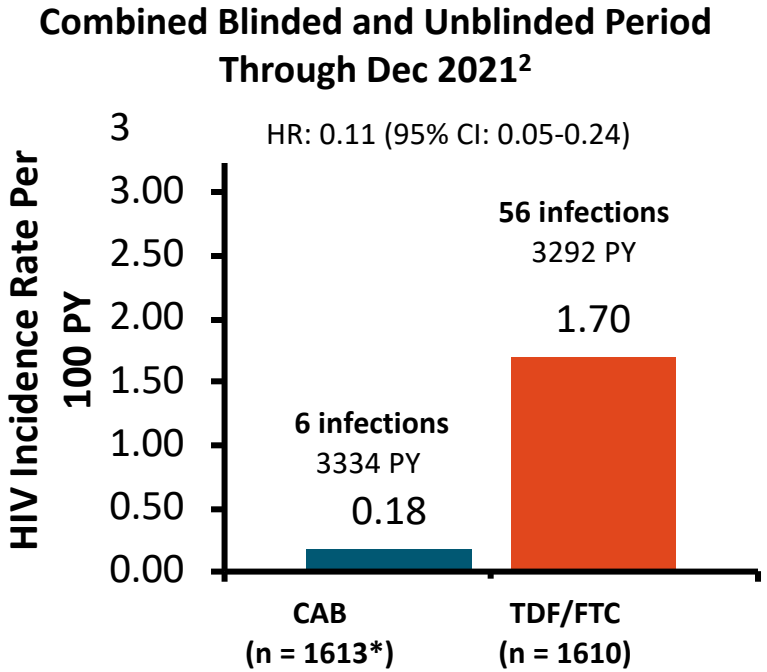


- Primary endpoints (blinded study): incident HIV infections (ITT), grade ≥2 AEs[1]
- Current analysis: incident HIV infections during 12-mo period following unblinding (11/5/2020 - 11/5/2021, detected through 12/31/2021); grade ≥2 AEs, ISRs, pregnancy incidence/outcomes during 12-mo unblinded phase; cumulative HIV incidence for primary blinded and 12-mo unblinded follow-up[2]

1. Delany-Moretlwe. Lancet. 2022;399:1779. 2. Delany-Moretlwe. AIDS 2022. Abstr OALBX0107.

HPTN 084 Update: HIV Incidence

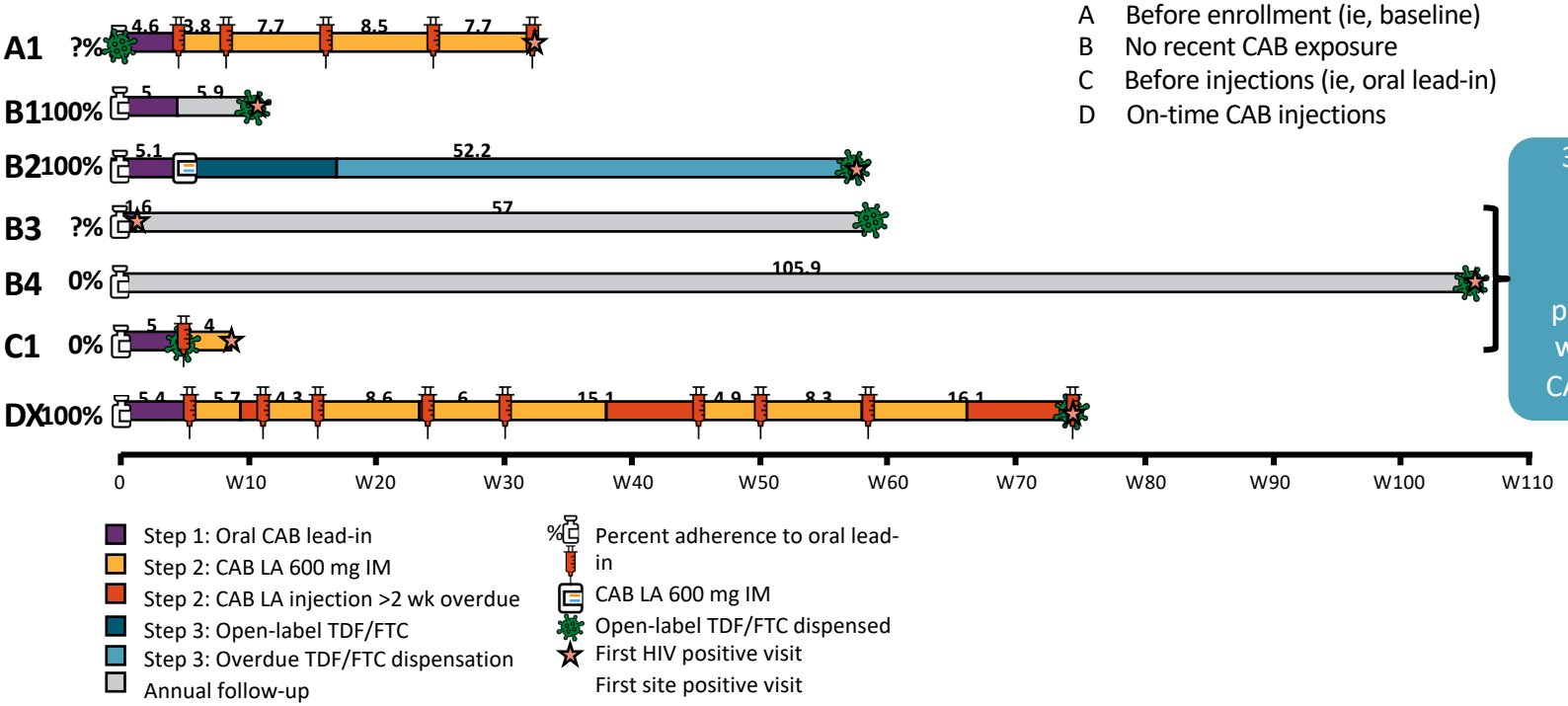




*Excludes 1 baseline infection from the blinded period.

1. Delany-Moretlwe. Lancet. 2022;399:1779. 2. Delany-Moretlwe. AIDS 2022. Abstr OALBX0107. Reproduced with

HPTN 084 Update: Cumulative HIV Infections



1. Delany-Moretlwe. Lancet. 2022;399:1779. 2. Delany-Moretlwe. AIDS 2022. Abstr OALBX0107

HPTN 084 Pregnancy Outcomes

Cumulative Pregnancy Outcomes, n	Total (n = 132)	CAB (n = 63)	TDF/FTC (n = 69)
Ongoing	57	23	34
Known pregnancy outcomes*			
▪ Live births	61	31	30
▪ Pregnancy loss			
– ≥37 wk	0	0	0
– 20-36 wk	3	1	2
– <20 wk†	13	9	4
Congenital anomalies	0	0	0

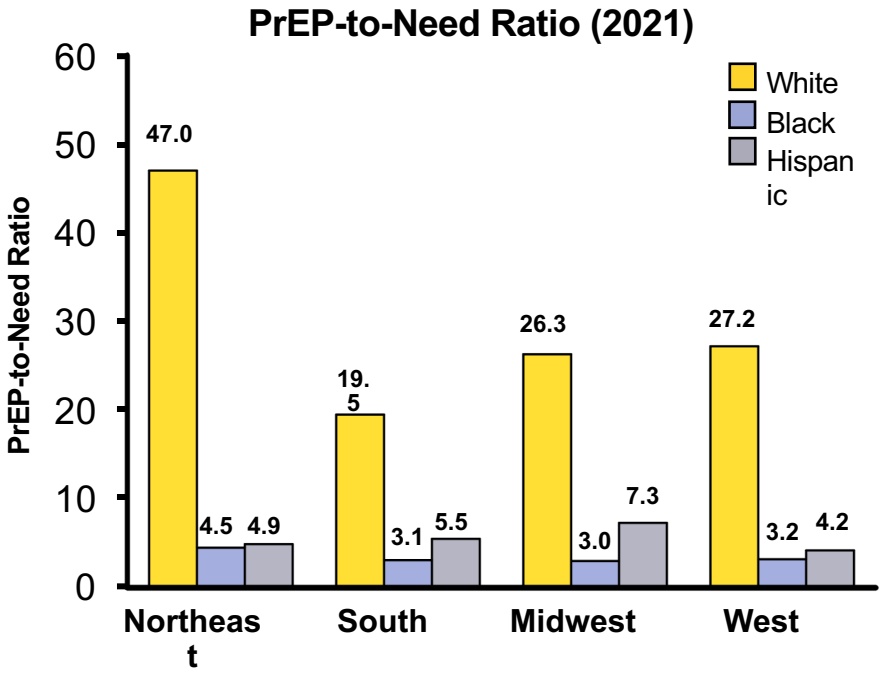
*Includes multiple births. †Includes ectopic pregnancies, elective and spontaneous abortion.

- Incidence of pregnancy increased between blinded and unblinded period
  - Overall: 1.3 vs 3.2 per 100 PY; CAB arm: 1.5 vs 2.6 per 100 PY; TDF/FTC arm: 1 vs 3.8 per 100 PY

Delany-Moretlwe. AIDS 2022. Abstr OALBX0107.

Trends in PrEP Use in the United States (2012-2021)

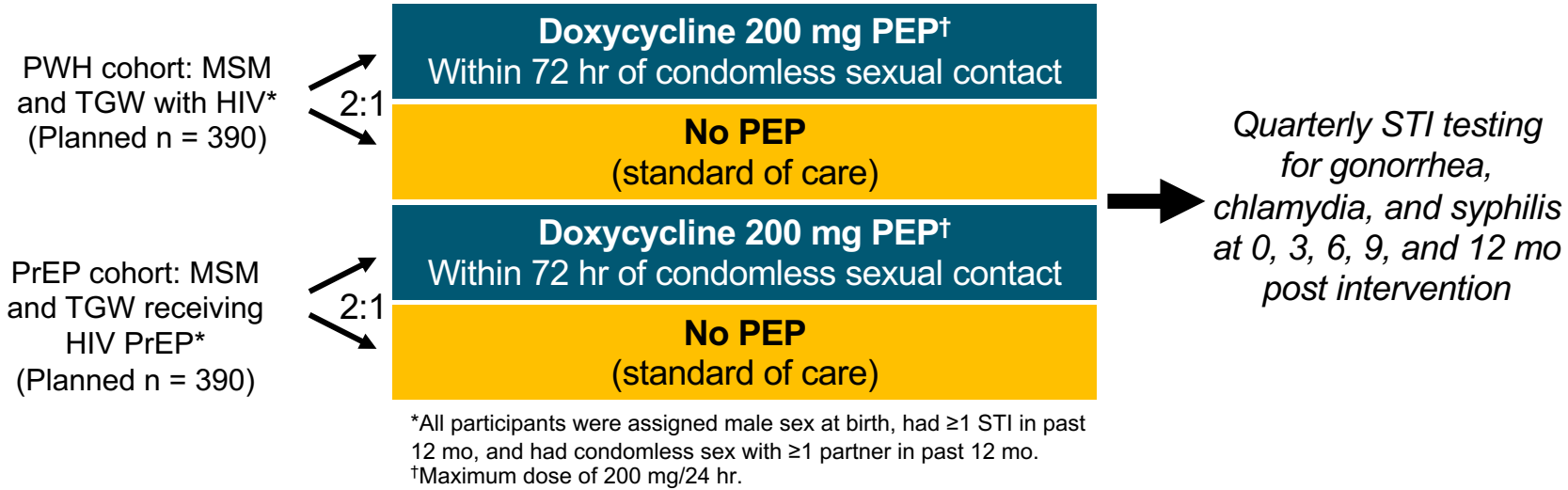
- PrEP-to-need ratio
  - Number of PrEP users divided by the number of new HIV diagnoses in that group in the same year
  - Equity metric, no “target” level
- US prevention programs in all regions have demonstrated larger gaps in PrEP-to-need ratios by race/ethnicity
  - Southern states lagged all other regions
- Better programs are needed to provide PrEP to communities and people at greatest risk for HIV infection



Sullivan P, et al. AIDS 2022. Abstract OALBX0104.

DoxyPEP: Study Design

- Randomized, open-label study conducted at HIV and STI clinics in San Francisco and Seattle

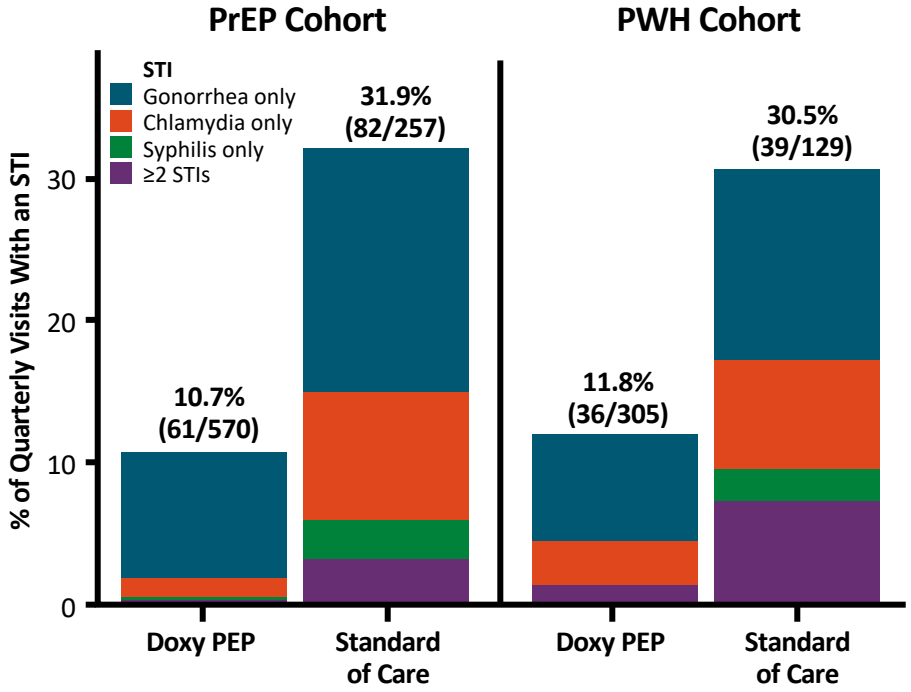


*All participants were assigned male sex at birth, had ≥1 STI in past 12 mo, and had condomless sex with ≥1 partner in past 12 mo.
†Maximum dose of 200 mg/24 hr.

- **Primary endpoint:** ≥1 incident STI (gonorrhea, chlamydia, or syphilis) during quarterly STI test
- **5/13/2022:** Enrollment stopped early per DSMB after interim analysis showed significant effectiveness in both cohorts

Luetkemeyer. AIDS 2022. Abstr OALBX0103.

DoxyPEP: Quarterly STI Incidence (Primary Endpoint)



Risk Reduction in STI Incidence per Quarter (95% CI)	Doxy PEP vs Standard of Care*
PrEP	0.34 (0.24-0.46)
PWH	0.38 (0.24-0.60)
Total	0.35 (0.27-0.46)

*All P <.0001

Luetkemeyer. AIDS 2022. Abstr OALBX0103.

Antiretroviral Guidelines: First-line Therapy

DHHS (1/2022) Recommended for Most People With HIV
Bictegravir/Emtricitabine/Tenofovir alafenamide
Dolutegravir/Abacavir/Lamivudine*
Dolutegravir + Emtricitabine/Tenofovir alafenamide (or disoproxil fumarate)
Dolutegravir/Lamivudine†

*Only for persons HLA-B*5701 negative and without chronic HBV coinfection.
†Not for persons with pre-treatment HIV RNA >500K copies/mL or known to have active HBV coinfection, or no genotype available

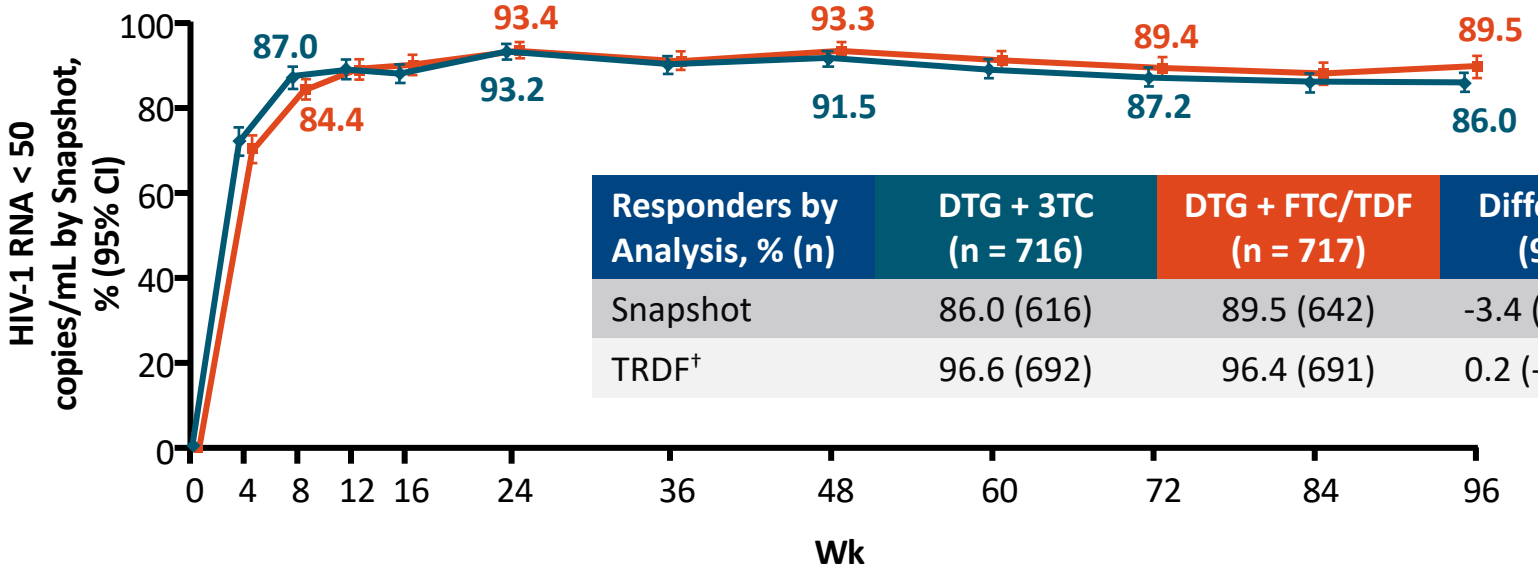
IAS-USA (10/2020) Recommended Initial Regimens
Bictegravir/Emtricitabine/Tenofovir alafenamide
Dolutegravir + Emtricitabine/Tenofovir alafenamide (or disoproxil fumarate), or Lamivudine + Tenofovir disoproxil fumarate
Dolutegravir/Lamivudine*

*Not recommended for rapid start because baseline laboratory evaluation results must be reviewed before initiation. Also not recommended for patients with chronic HBV or HIV RNA level >500K copies/mL.
Close monitoring for adherence and virological response is needed.
Not recommended for patients being treated for an active opportunistic infection.

DHHS. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Revision January 20, 2022.
Saag MS, et al. JAMA. 2020;324:1651-1669.

GEMINI-1 and -2: Virologic Response at Wk 96

- DTG + 3TC met Snapshot criteria for **noninferior efficacy** vs DTG + FTC/TDF at Wk 96

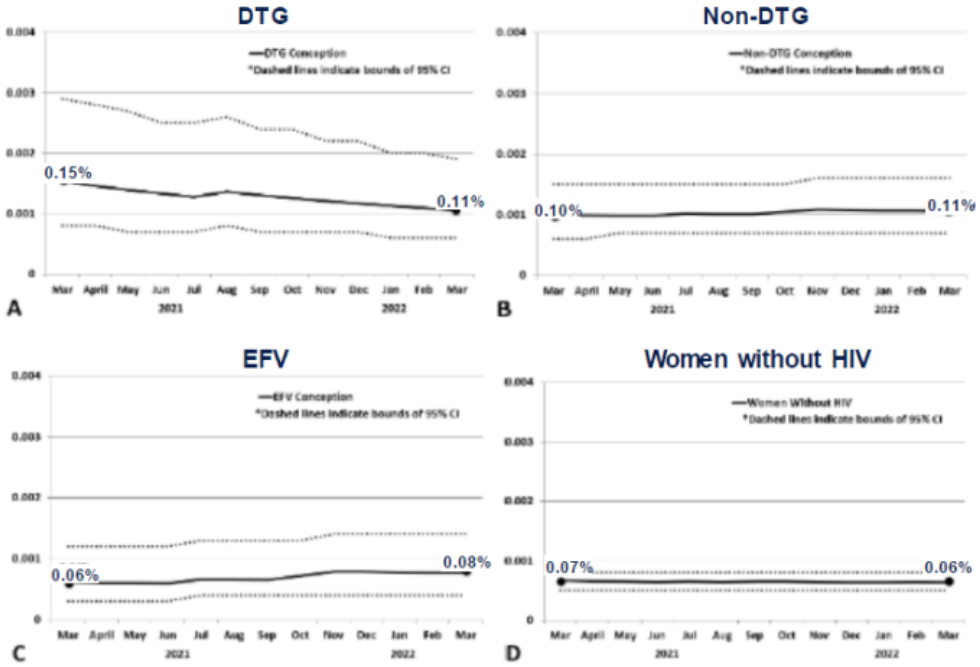


Responders by Analysis, % (n)	DTG + 3TC (n = 716)	DTG + FTC/TDF (n = 717)	Difference, % (95% CI)
Snapshot	86.0 (616)	89.5 (642)	-3.4 (-6.7 to 0)*
TRDF†	96.6 (692)	96.4 (691)	0.2 (-1.8 to 2.2)

*Adjusted for baseline HIV-1 RNA, baseline CD4+ cell count, and study.
†Accounts for CVW, withdrawal for lack of efficacy or treatment-related AE, and participants meeting protocol-defined stopping criteria.

Cahn. IAS 2019. Abstr WEAB0404LB.

TSEPAMO: Update on Neural Tube Defects



- Prevalence of NTDs has decreased over time from 0.94% (n=426) in May 2018
- Current analysis up to March 2022 reports 10 NTDs out of 9460 pregnancies exposed to DTG at conception: prevalence rate of 0.11% (95% CI, 0.06-0.19) compared with 0.11% (95% CI, 0.07-0.16) for non-DTG ART exposures

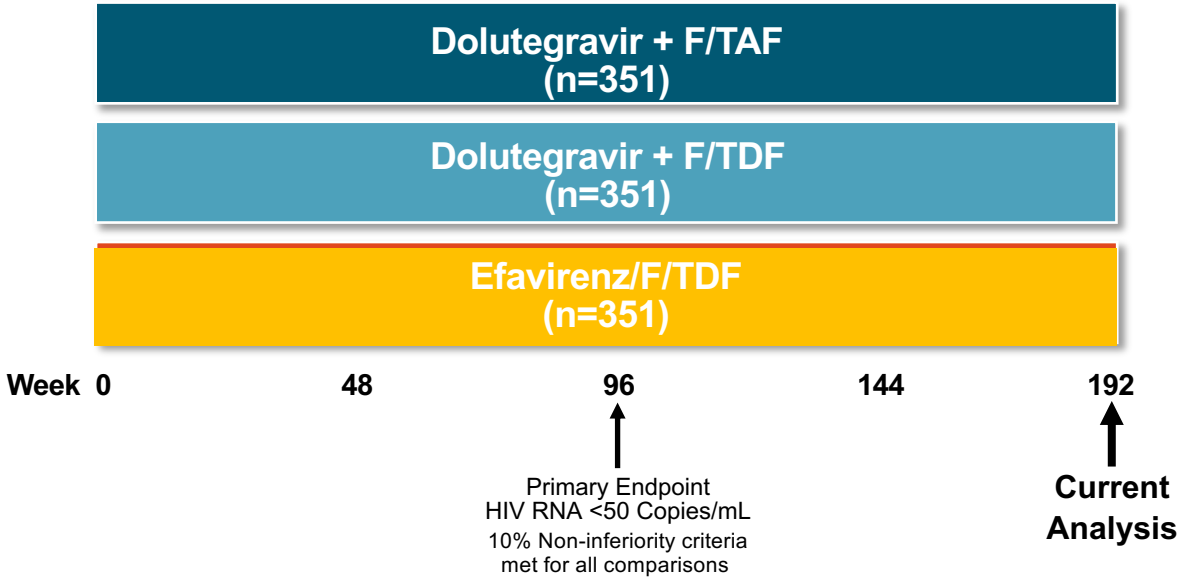
Trends in NTD Prevalence (95% CI) With (A) DTG, (B) Non-DTG ART, and (C) EFV Exposure at Conception and (D) in Women Without HIV, March 2021 to March 2022

Zash et al. AIDS 2022; Virtual and Montreal, Canada. Poster PELBB02.

ADVANCE: First-line DTG/FTC/TAF vs DTG/FTC/TDF vs EFV/FTC/TDF

Phase 3 (South Africa)

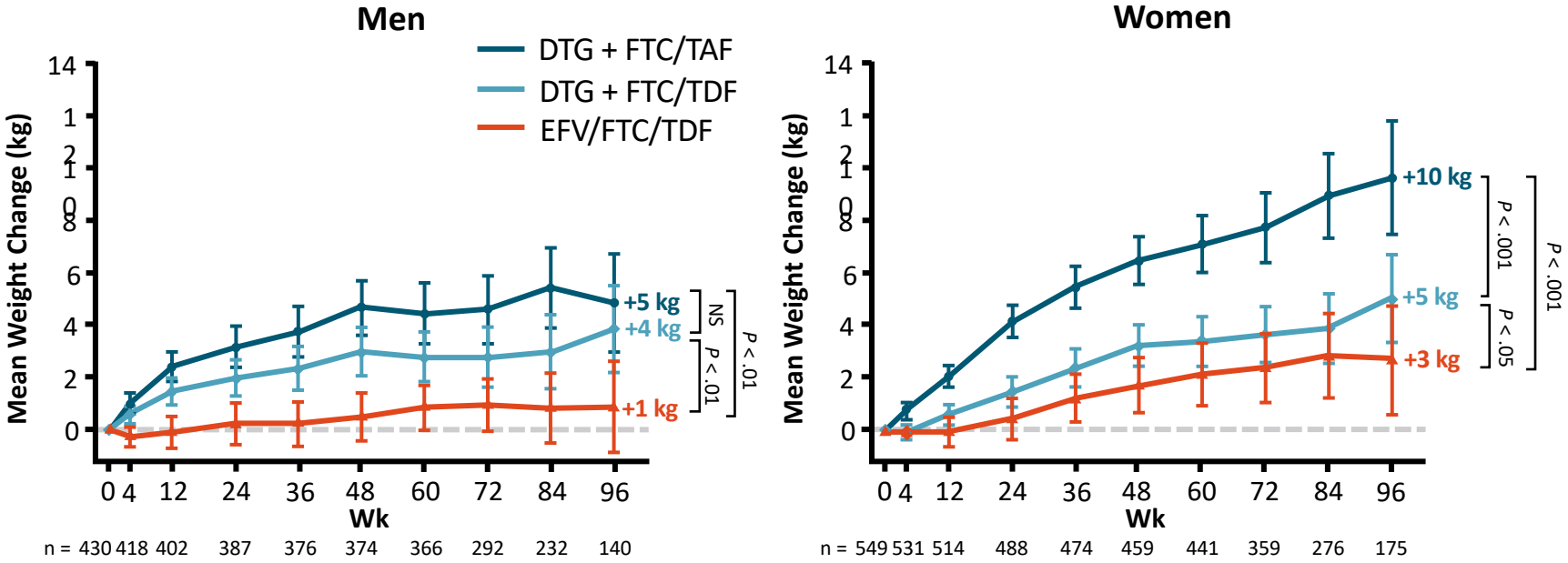
Open-label
Treatment-naïve
HIV RNA ≥500 copies/mL
No TB or pregnancy
No baseline genotyping



Venter. NEJM. 2019; Venter AIDS 2022, Abst PELBB01

ADVANCE: Mean Change in Weight to Wk 96 by Sex

- Significantly greater weight increase* with DTG vs EFV, with TAF vs TDF; plateauing in weight gain after Wk 48 observed in men but not in women



Hill. IAS 2019. Abstr MOAX0102LB.

*Wilcoxon rank-sum comparison at Wk 96.

ADVANCE Study: Results at Week 192

- HIV RNA <50 copies/mL (ITT)
  - DTG-based ART superior to EFV ART
- DTG + F/TAF (versus DTG + F/TDF)
  - Greater weight gain, clinical obesity, and risk of metabolic syndrome (*P*<0.001)
- Predictors of obesity (*P*≤0.001)
  - Dolutegravir + F/TAF (ref: efavirenz/F/TDF): HR 3.28 (95% CI: 2.10-5.14)
  - Baseline BMI: HR 1.82 (95% CI: 1.68-1.98)
  - Female: HR 2.14 (95% CI: 1.38-3.32)
  - Baseline HIV RNA: HR 1.97 (95% CI: 1.58-2.46)

Outcomes at Week 192

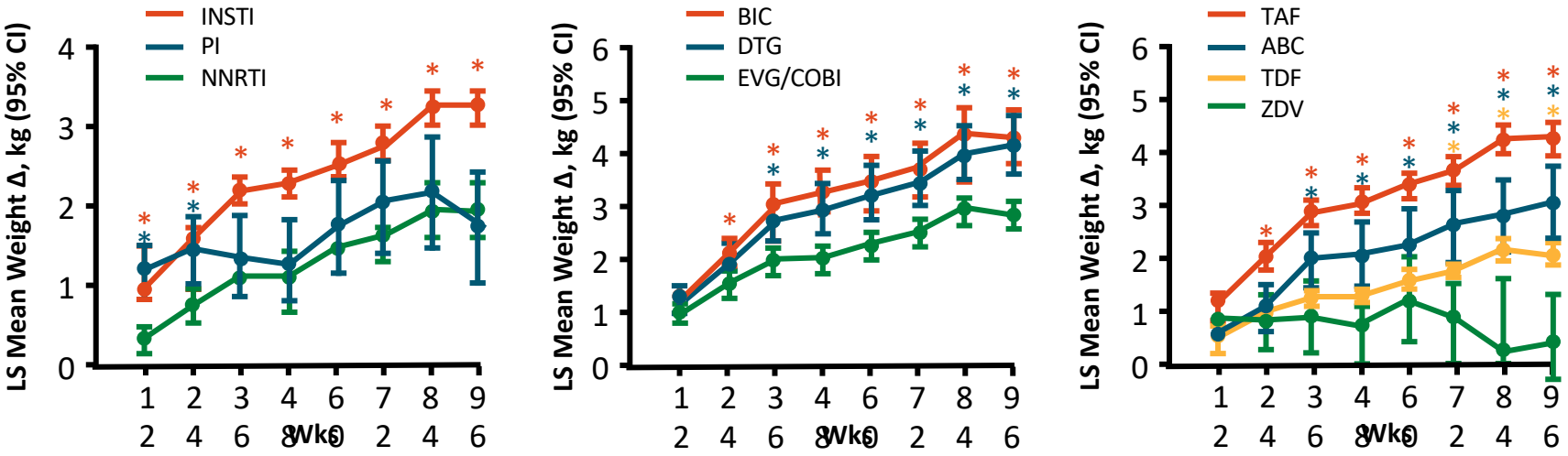
	DTG + F/TAF (n=351)	DTG + F/TDF (n=351)	EFV/ F/TDF (n=351)
HIV RNA <50 copies/mL (%)			
ITT	62	58	50
On treatment	96	98	99
Weight gain (kg)			
Overall	8.9	5.8	3.3
Women/men	10.0/7.5	6.5/5.0	5.0/2.0
Obesity (BMI ≥30 kg/m^2) (%)			
Overall	29	21	15
Women/men	43/10	27/10	20/2
Metabolic syndrome (%)			
Overall	15	10	7
Women/men	20/7	12/6	10/3

Observed analysis: weight gain, obesity, treatment-emergent metabolic syndrome.

Venter WD, et al. AIDS 2022. Abstract PELBB01.

Multivariate Analysis of Weight Gain Following ART Initiation

- Pooled analysis of weight gain across 8 randomized phase III clinical trials of first-line ART initiation occurring in 2003-2015 (N = 5680)



*Color-coded to match respective comparators, denoting $P \leq .05$ vs NNRTI (first panel), EVG/COBI (second panel), or ZDV (last panel).

Sax. Clin Infect Dis. 2019;[Epub].

Factors to consider when addressing potential weight gain associated with starting ART

- Weight gain occurs in most people starting ART
- Weight gain is potentially greater with 2nd generation INSTIs and TAF
- Weight gain potentially attenuated with EFV and TDF
- There are clear clinical advantages to starting 2nd generation INSTIs over alternative agents and they remain preferred options for most
- The mechanism behind differences in weight gain by ARVs remain poorly understood
- There is no definitive strategy for managing excessive weight gain that may be mediated by select ARVs

Optimization/Simplification of Therapy: Applies to those virologically suppressed

Why

- Simplify regimen (pill number and frequency)
- Tolerability
- Comorbidity
- Drug–drug and drug–food interactions
- Pregnancy
- Cost

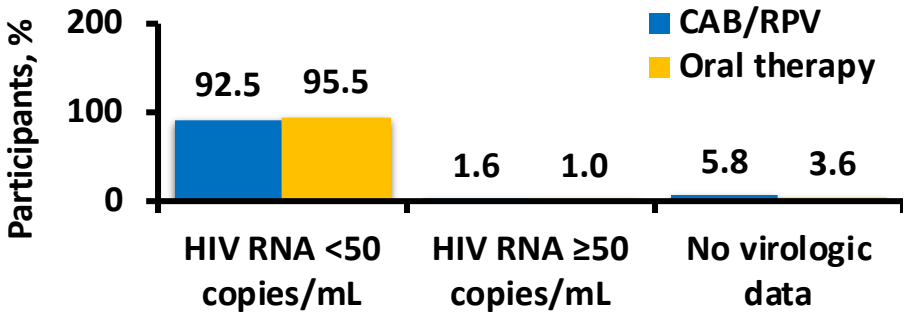
How

- Maintain viral suppression to avoid resistance
- Need to consider
  - Previous ART
  - Previous resistance
  - Likelihood of adherence
  - Drug–drug or drug–food interactions
  - Comorbid conditions

DHHS guidelines. September 2022.

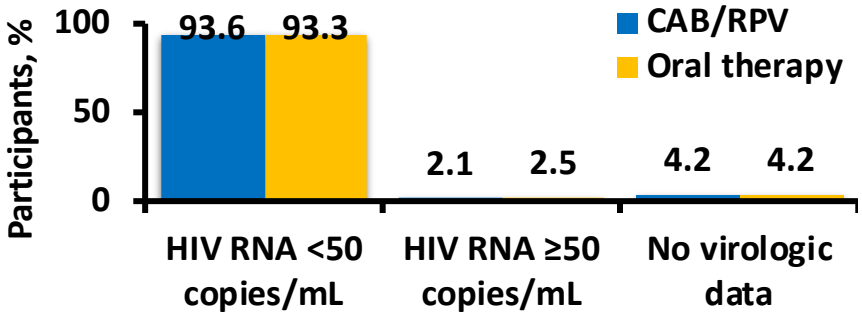
Long-Acting CAB/RPV vs Oral ART in Treatment-Experienced and Treatment-Naïve Patients

ATLAS: LA CAB/RPV is noninferior to oral ART at 48 weeks in treatment-experienced patients[1]



Injection site reactions were seen in 81% of CAB/RPV group and decreased to 11% at week 48

FLAIR: LA CAB/RPV is noninferior to oral ART at 48 weeks in treatment-naïve patients[2]

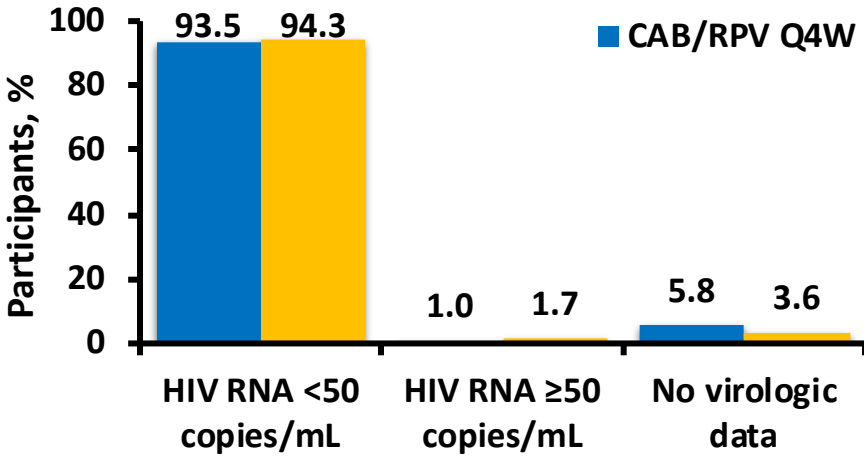


Injection site reactions were seen in 86% of CAB/RPV group and decreased to 20% at week 48

1. Swindells S, et al. *N Engl J Med*. 2020;382(12):1112-1123; 2. Orkin C, et al. *N Engl J Med*. 2020;382(12):1124-1135.

Long-Acting CAB/RPV Q4W vs Q8W
ATLAS-2M (Wk 48)

CAB/RPV Q8W noninferior to Q4W



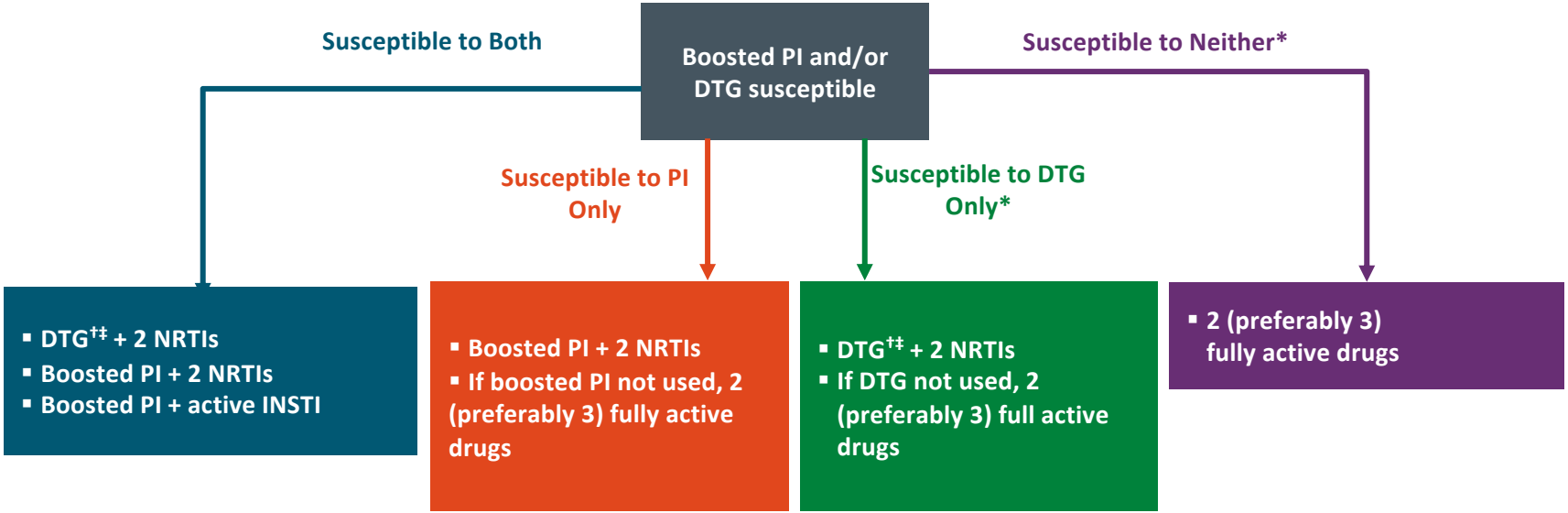
- Injection site reactions were rated as mild-to-moderate by 98% of participants experiencing them
  - Median duration of 3 days

Only indicated for those virologically suppressed
Limited data in those with concern for or actual poor adherence with visits or therapy

Overton ET, et al. *Infect Chemother.* 2020;52(suppl):S378-S379.

Managing Antiretroviral Failure

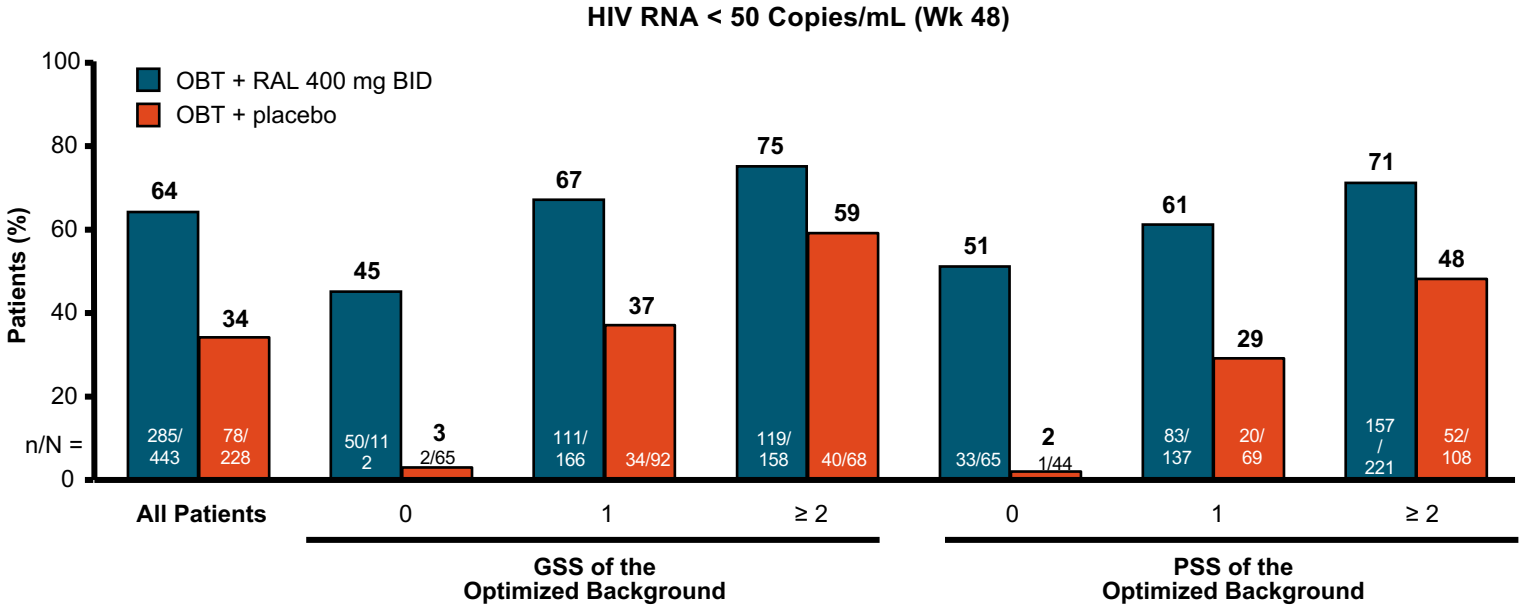
Management of ARV Failure: Second Line and Beyond



*Rare in patients never exposed to unboosted PIs (eg, NFV, DHHS alternative since 2003 and not recommended since 2008).
†If INSTI naive or experienced with no resistance (limited data in patients with resistance to RAL or EVG but susceptibility to DTG).
‡Data limited to DTG, but similar results might be seen with BIC.

Adapted from DHHS ART Guidelines. January 2022.

BENCHMRK: Management of Treatment-Experienced



Cooper. NEJM. 2008;359:355.

Ibalizumab: Virologic Outcomes (Wk 96)

- TMB-311: patients enrolled in US and Puerto Rico who completed 25 wks in TMB-301 continued ibalizumab 800 mg Q2W for up to 96 wks

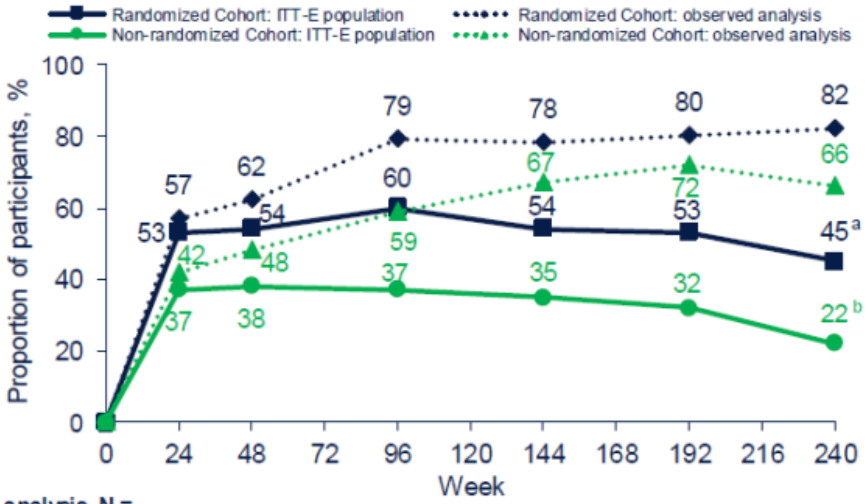
Virologic Outcome	Day 14[1] (N = 40)	Wk 25[1] (N = 40)	Wk 48[2,3] (N = 27)	Wk 96[4] (N = 27)
≥ 0.5 log_{10} HIV-1 RNA decrease, %	83*†	63	NR	NR
≥ 1.0 log_{10} HIV-1 RNA decrease, %	60	55	67	NR
Mean log_{10} HIV-1 RNA decrease	1.1	1.6	2.1	NR
Median log_{10} HIV-1 RNA decrease	NR	2.5	2.8	2.8
HIV-1 RNA < 50 copies/mL, %	NR	43	59	56
HIV-1 RNA < 200 copies/mL, %	NR	50	63	NR

1. Emu. NEJM. 2018;379:645. 2. Emu. IDSA 2017. Abstr 1686. 3. Emu. HIV Glasgow 2018. Abstr O345.
4. Emu. CROI 2019. Abstr 485. 5. DeJesus. HIV Glasgow 2018. Abstr P064.

Fostemsavir: Virologic Outcomes (Wk 240)

- In the Randomized Cohort, virologic response rates (HIV-1 RNA <40 c/mL) generally remained consistent through Week 240
  - Reduced virologic response rates by Snapshot at Week 192 and beyond were partially confounded by missing data due to COVID-19: at Week 240, 19 (7%) participants in the Randomized Cohort and 5 (5%) in the Non-randomized Cohort were counted as virologic failures for this reason

HIV-1 RNA <40 c/mL Through Week 240 by Snapshot Analysis (ITT-E) and Observed Analysis

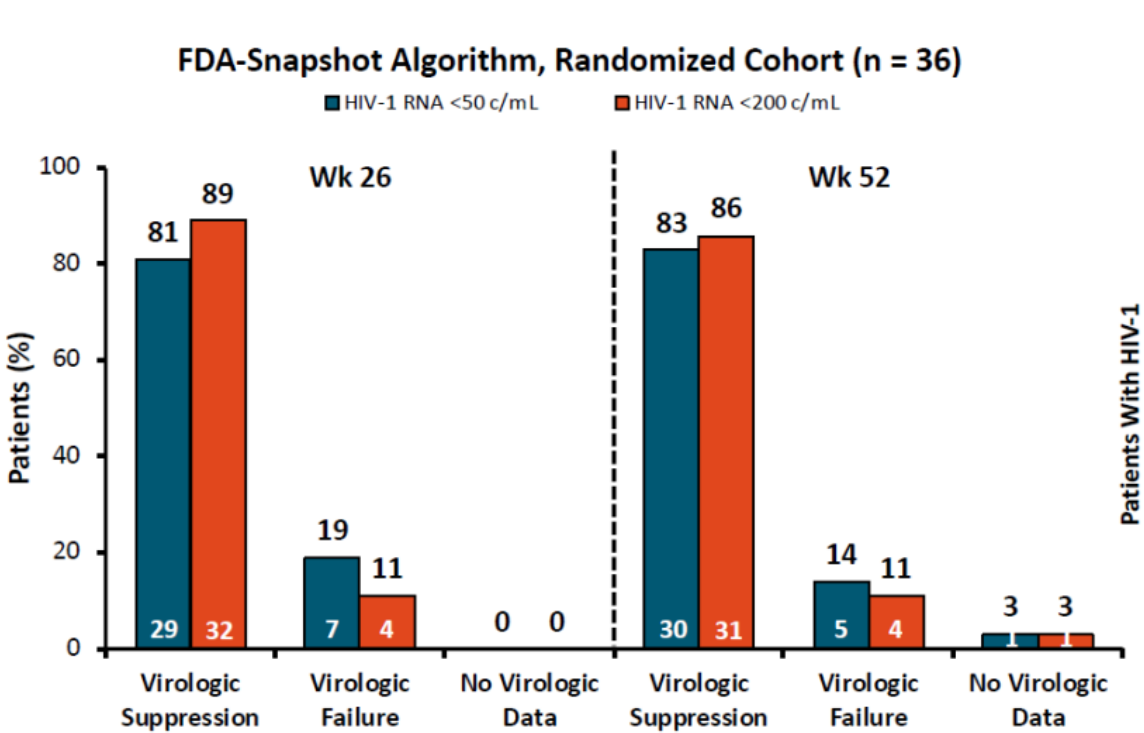


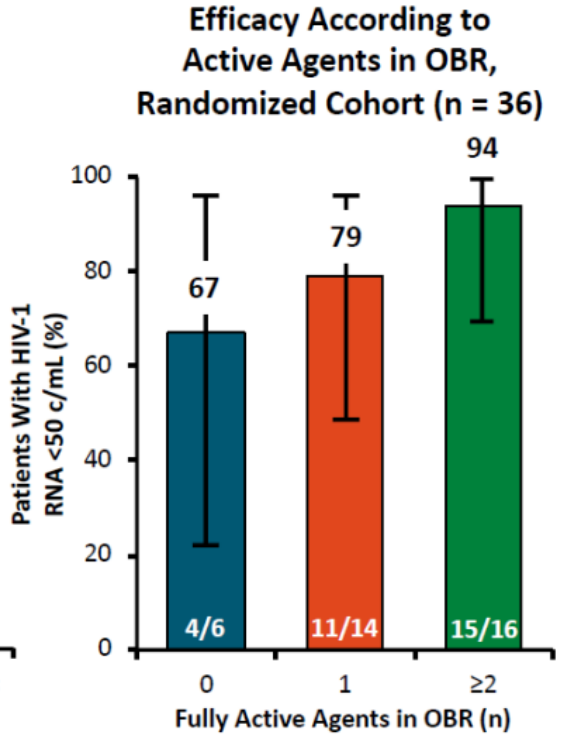
Observed analysis, N =						
Randomized Cohort	247	233	214	206	195	164
Non-randomized Cohort	89	83	66	57	50	35

ITT-E participants without an HIV-1 RNA value at the relevant time point or those who changed OBT due to lack of efficacy up to each time point counted as failures.

[a]ITT-E population, N=267. [b]ITT-E population, N=92.

Lenacapavir: CAPELLA virologic outcomes (Wk 52)

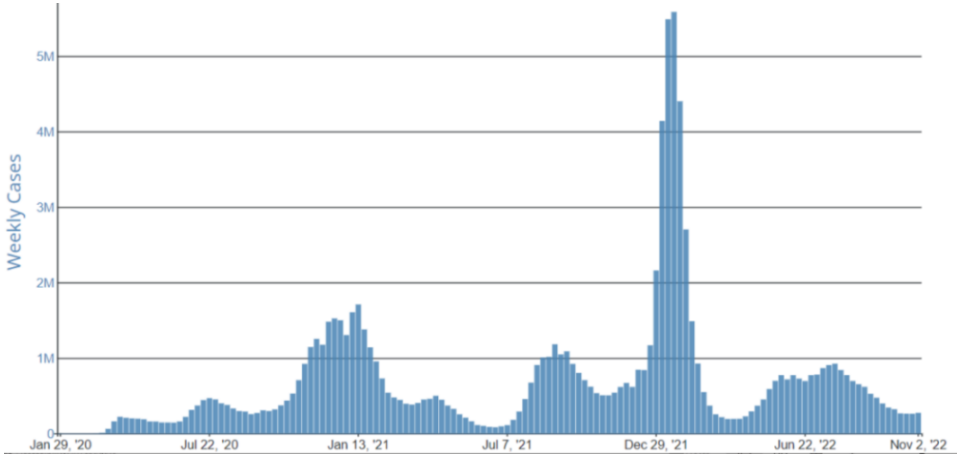




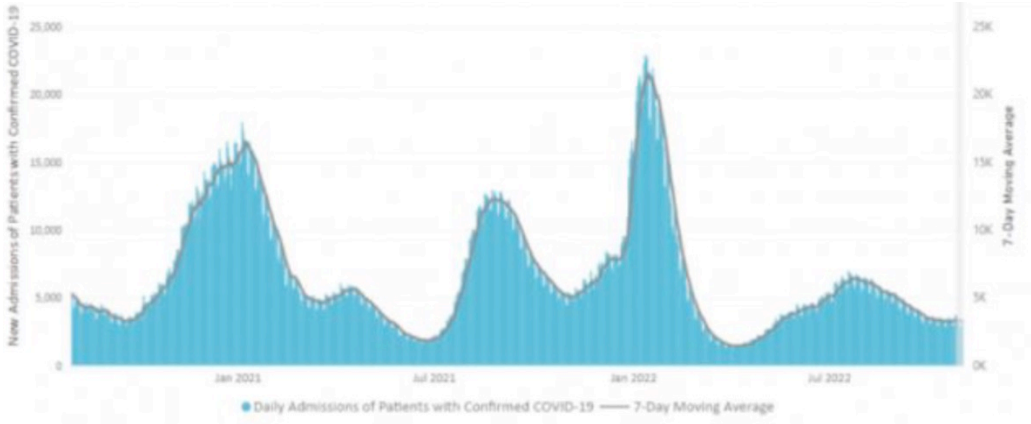
Ogbuagu. CROI 2022. Abstr 491.

COVID-19:
Prevention and Treatment

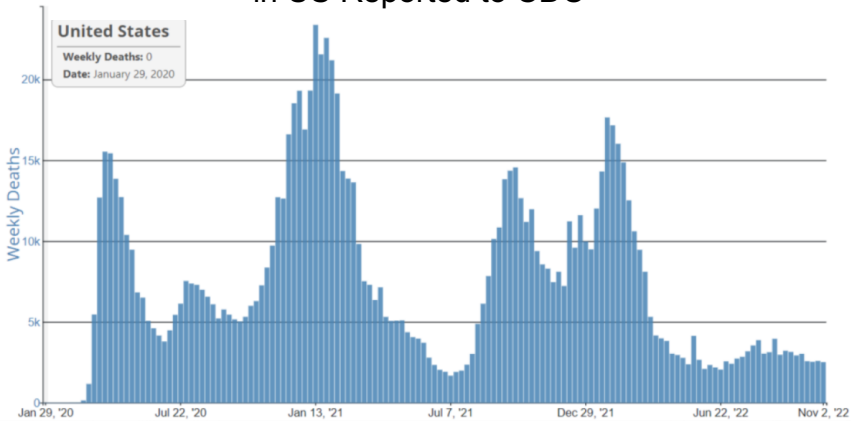
Weekly Trends in COVID-19 Cases in U.S> Reported to CDC



Daily Admissions with COVID-19- 7 Day Morning Average

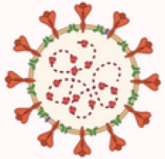


Weekly Trends in Number of COVID-19 Deaths in US Reported to CDC



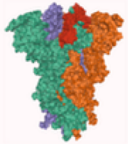
a. Inactivated vaccines

Inactivated vaccines contain SARS-CoV-2 viruses that are chemically inactivated



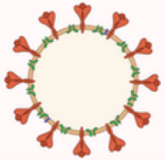
b. Recombinant proteins vaccines

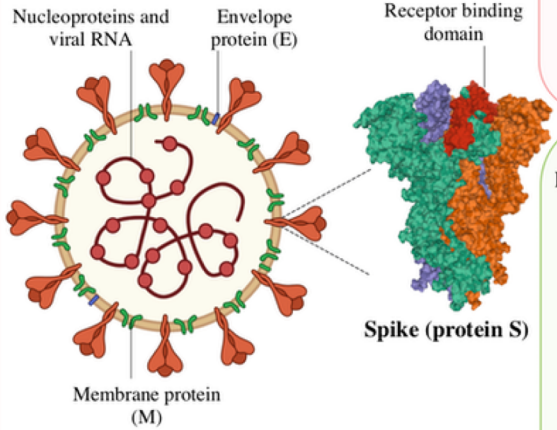
Vaccines composed of recombinant spikes



Vaccines composed of receptor binding domain

Virus-like particles are devoid of genetic material but display spikes, M and E proteins on their surface

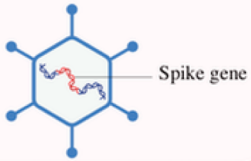




SARS-CoV-2

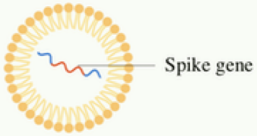
c. Viral vector vaccines

Viral vector vaccines contain another virus modified to express S protein



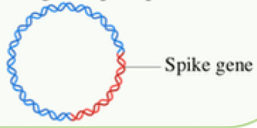
d. RNA vaccines

RNA vaccines consist of RNA packed in lipid nanoparticles

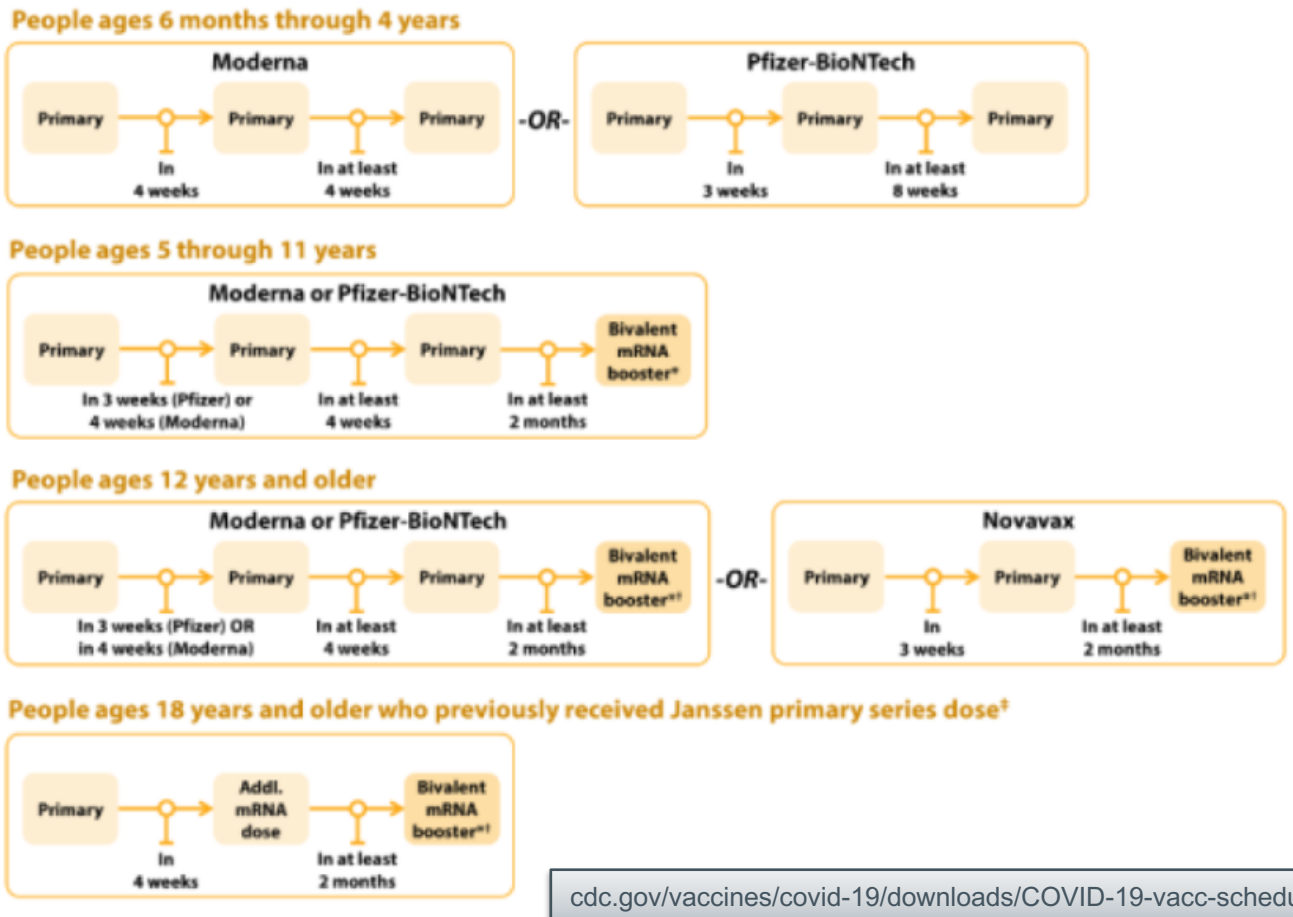


e. DNA vaccines

DNA vaccines contain a circular DNA encoding the spike protein



COVID-19 Vaccination Schedule Infographic for People who are Moderately or Severely Immunocompromised

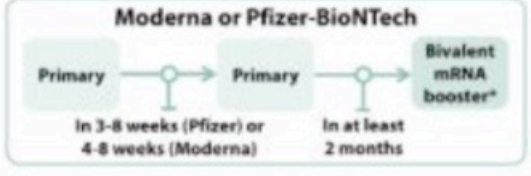


cdc.gov/vaccines/covid-19/downloads/COVID-19-vacc-schedule-at-a-glance-508.pdf

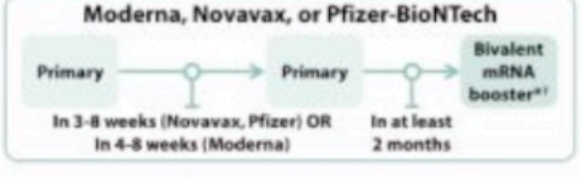
COVID-19 Vaccination Schedule Infographic for People who are NOT Moderately or Severely Immunocompromised

People ages 6 months through 4 years

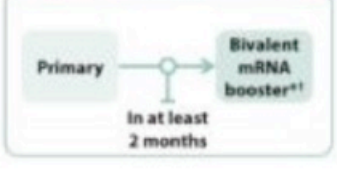
People ages 5 through 11 years



People ages 12 years and older



People ages 18 years and older who previously received Janssen primary series dose‡



cdc.gov/vaccines/covid-19/downloads/COVID-19-vacc-schedule-at-a-glance-508.pdf

Current (Monovalent) COVID-19 vaccines

50µg  Moderna COVID-19 vaccine

50µg of spike protein from
'ancestral' ('original') SARS-CoV-2

30µg  Pfizer-BioNTech COVID-19 vaccine

30µg of spike protein from
'ancestral' ('original') SARS-CoV-2

Updated (Bivalent) COVID-19 vaccines

50µg  Moderna COVID-19 vaccine

25µg of spike protein from
'ancestral' ('original') SARS-CoV-2

25µg of spike protein from
Omicron (BA.4/BA.5) SARS-CoV-2

30µg  Pfizer-BioNTech COVID-19 vaccine

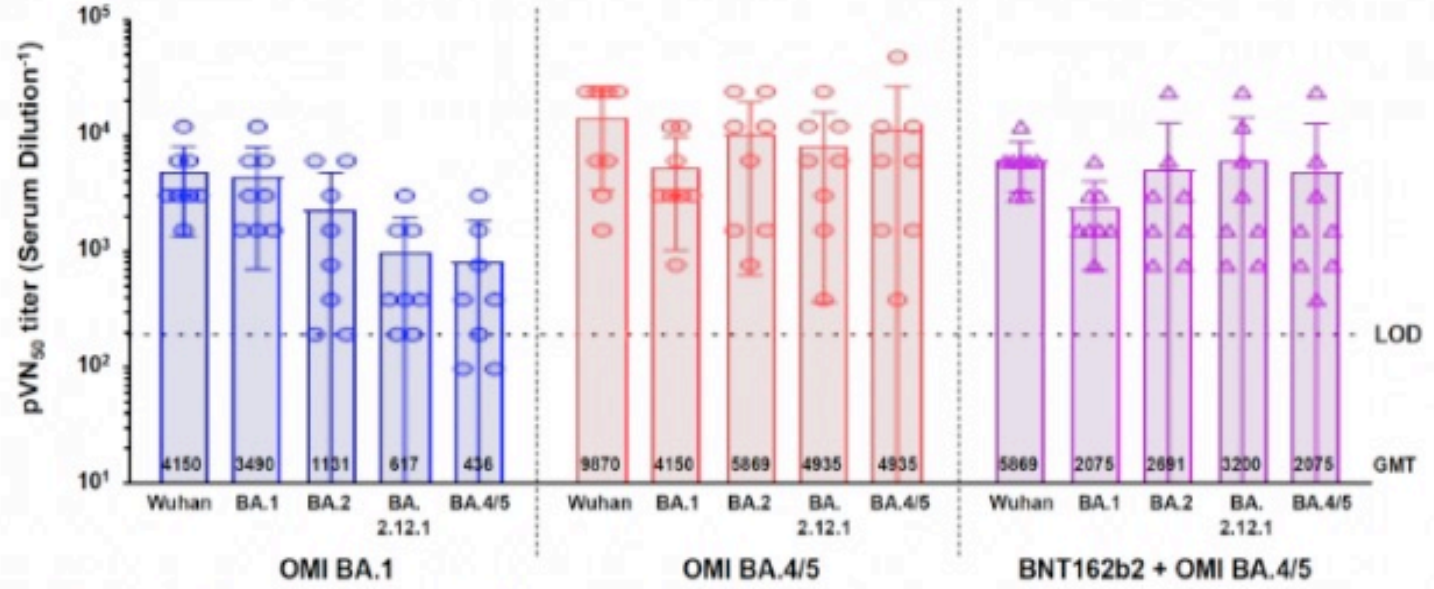
15µg of spike protein from
'ancestral' ('original') SARS-CoV-2

15µg of spike protein from
Omicron (BA.4/BA.5) SARS-CoV-2

Bivalent vaccines have the **same** total antigen amount as monovalent vaccines

Omicron BA.4/5 Monovalent and Bivalent Boosters in Mice Substantially Increase Omicron Neutralization Responses to all Omicron Variants Including BA.4/5 and Reference Strain

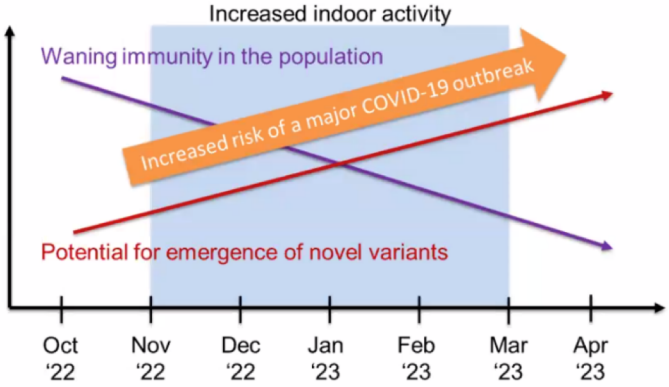
Compared to Monovalent OMI BA.1, BA.4/5 neutralizing titers increase by ~11.3 fold [mono BA.4/5] or ~4.8 fold (bivalent BA.4/5)



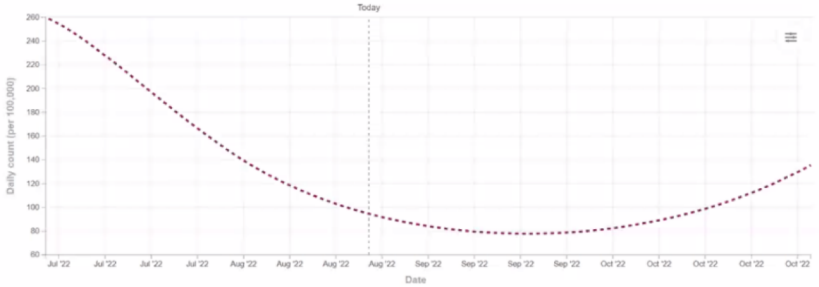
=8 mice Balb/c mice. Mice preimmunized with 2 doses of BNT162b2; boosters given at day 104
seudovirus neutralization assay; LOD, Limit of Detection

Fall 2022 Predictive Modeling

Potential evolution of COVID-19



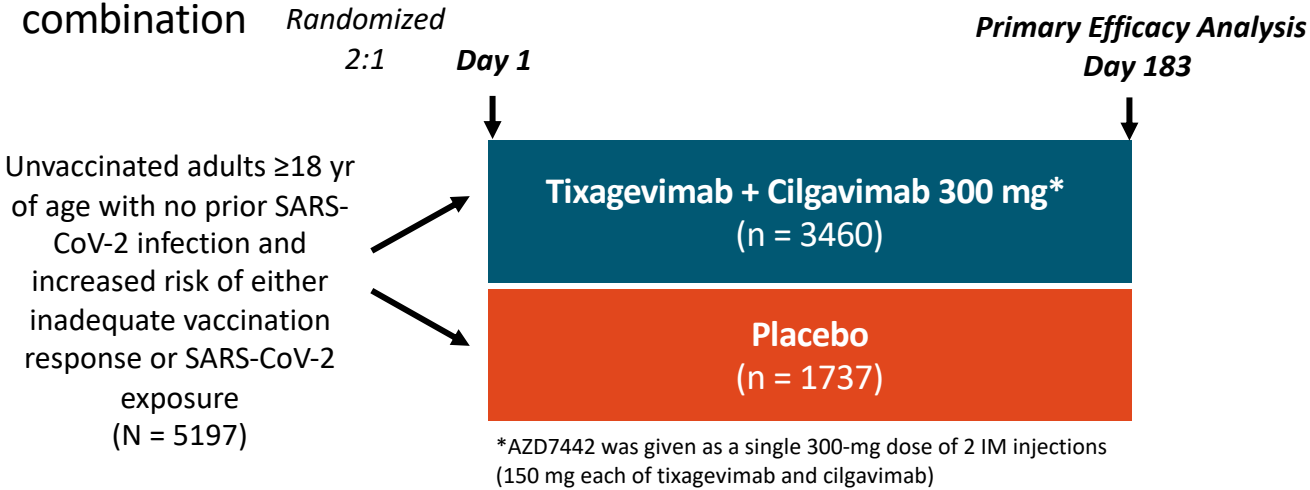
Modelers predicting next peak in late November



https://covid19.healthdata.org/united-states-of-america?view=infections-testing&tab=trend&test=infections

PROVENT: Tixagevimab + Cilgavimab as PrEP of COVID-19

- Randomized, double-blind, placebo-controlled phase III study of long-acting mAb combination



Outcome	Tixagevimab + Cilgavimab (n = 3441)	Placebo (n = 1731)	Relative Risk Reduction, % (95% CI)	*P* Value
First SARS-CoV-2 RT-PCR–positive **symptomatic illness,*** n (%)	8 (0.2)	17 (1.0)	**77** (46.1-90.0)	<.001

Levin. IDWeek 2021. Abstr LB5.

Tixagevimab + Cilgavimab Emergency Use Authorization for PrEP

*. . . for **pre-exposure prophylaxis of COVID-19** in patients ≥12 yr of age weighing ≥40 kg who are not currently infected with SARS-CoV-2 and who have moderate to severe immune compromise and/or for whom COVID-19 vaccination is not recommended*

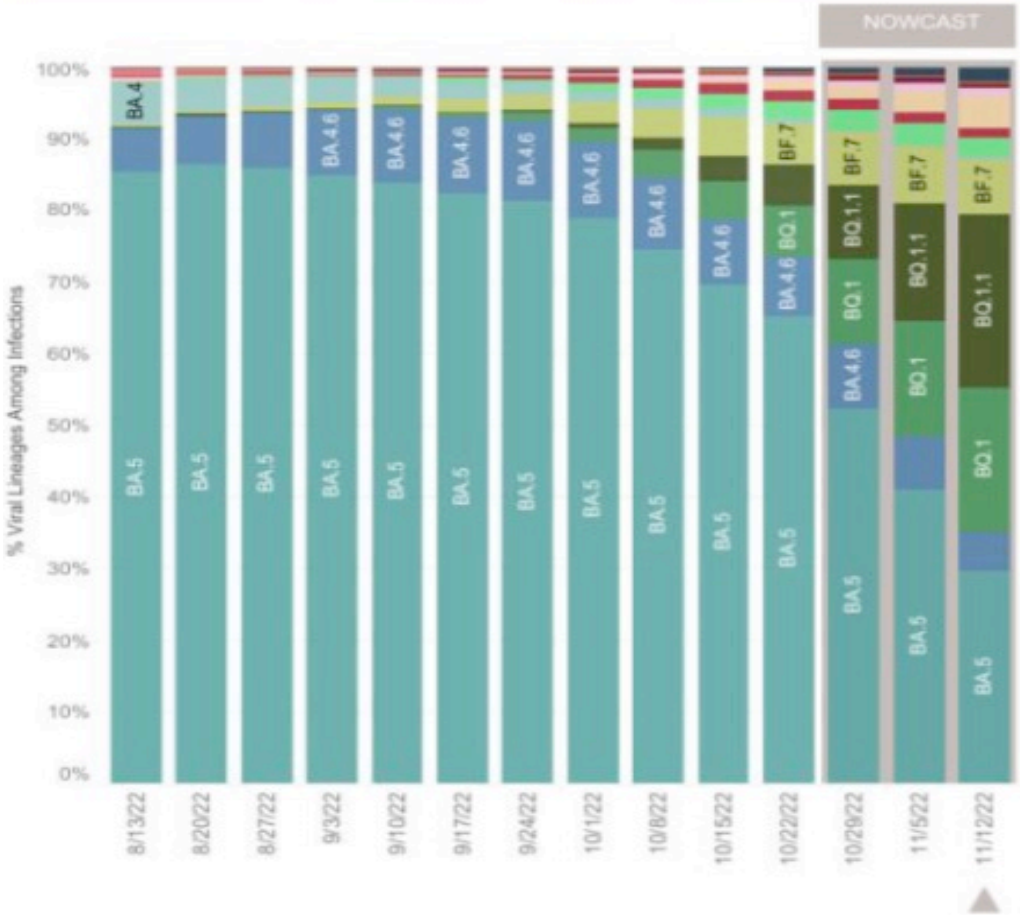
- EUA was updated in June 2022 to modify the initial dose and repeat dosing recommendations

Tixagevimab + Cilgavimab Neutralization Data for SARS-CoV-2 Variants

Lineage With Spike Protein Substitution	WHO Nomenclature	Fold Reduction in Susceptibility (Pseudotyped VLPs)	Fold Reduction in Susceptibility (Authentic Virus)
B.1.617.2	Delta	No change	No change
AY.1/AY.2	Delta [+K417N]	No change	No change
BA.1	Omicron (BA.1)	132- to 183-fold	12- to 30-fold
BA.1.1	Omicron (BA.1) [+R346K]	424-fold	176-fold
BA.2	Omicron (BA.2)	No change	5.4-fold

FDA. Fact sheet for healthcare providers: Emergency Use Authorization for tixagevimab co-packaged with cilgavimab.

United States: 8/7/2022 – 11/12/2022

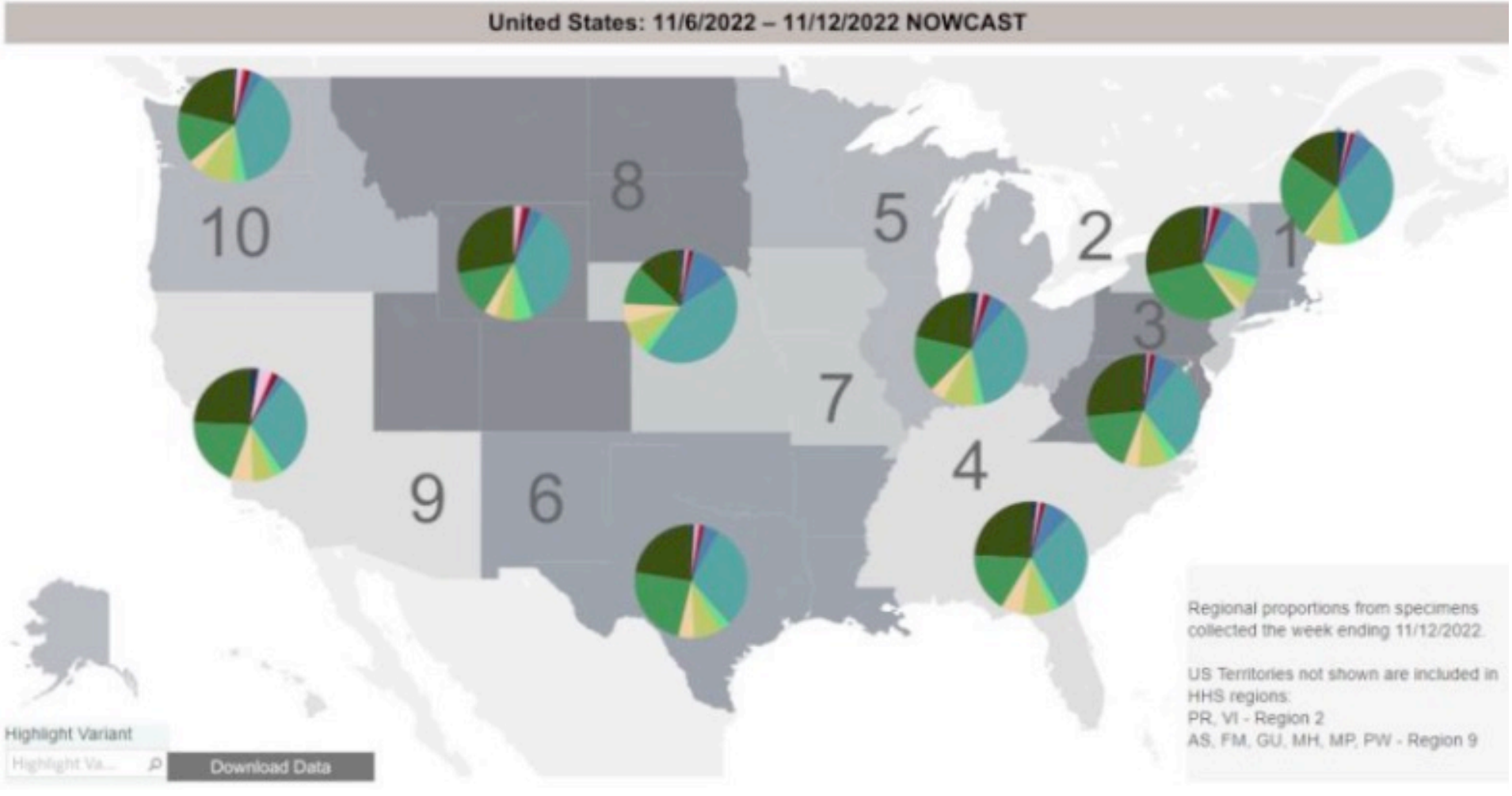


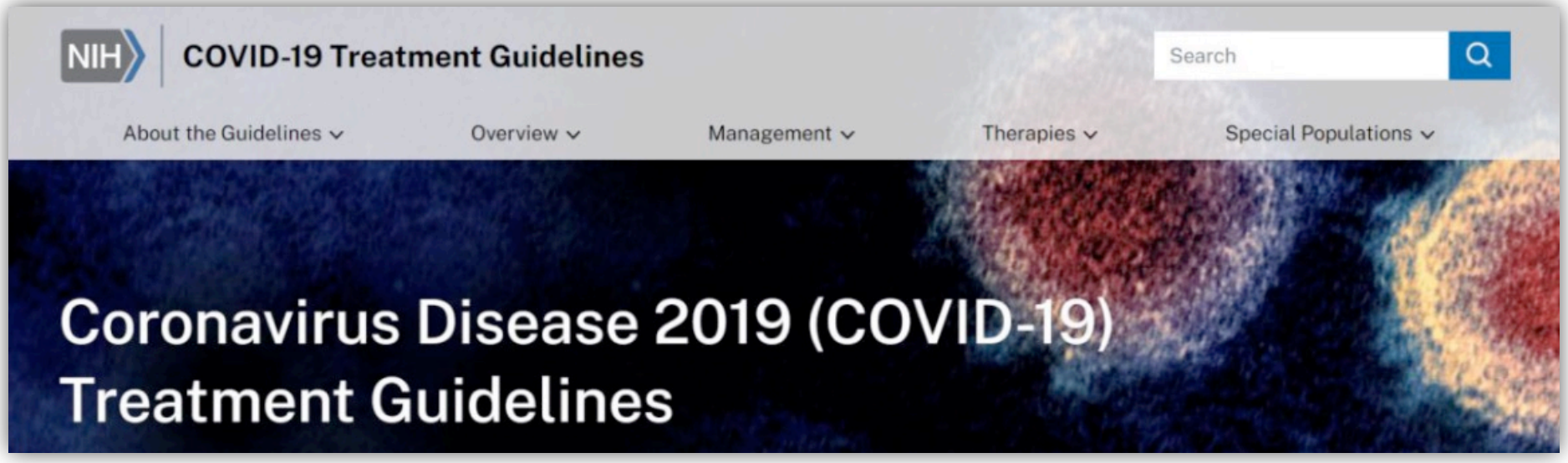
United States: 11/6/2022 – 11/12/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	29.7%	27.2-32.3%
	BQ.1.1	VOC	24.1%	21.3-27.3%
	BQ.1	VOC	20.1%	17.2-23.4%
	BF.7	VOC	7.8%	6.8-9.0%
	BA.4.6	VOC	5.5%	5.0-6.2%
	BN.1	VOC	4.3%	3.0-6.2%
	BA.5.2.6	VOC	2.9%	2.5-3.4%
	BA.2	VOC	1.3%	0.8-1.9%
	BA.2.75	VOC	1.2%	1.0-1.5%
	BA.2.75.2	VOC	0.9%	0.6-1.2%
	BA.4	VOC	0.1%	0.1-0.1%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		2.0%	1.1-3.3%

>55% TIX-CIL Resistant


United States: 11/6/2022 – 11/12/2022 NOWCAST
10
8
5
2
1
3
7
4
9
6
Regional proportions from specimens collected the week ending 11/12/2022.
US Territories not shown are included in HHS regions:
PR, VI - Region 2
AS, FM, GU, MH, MP, PW - Region 9
Highlight Variant
Highlight Va...
Download Data



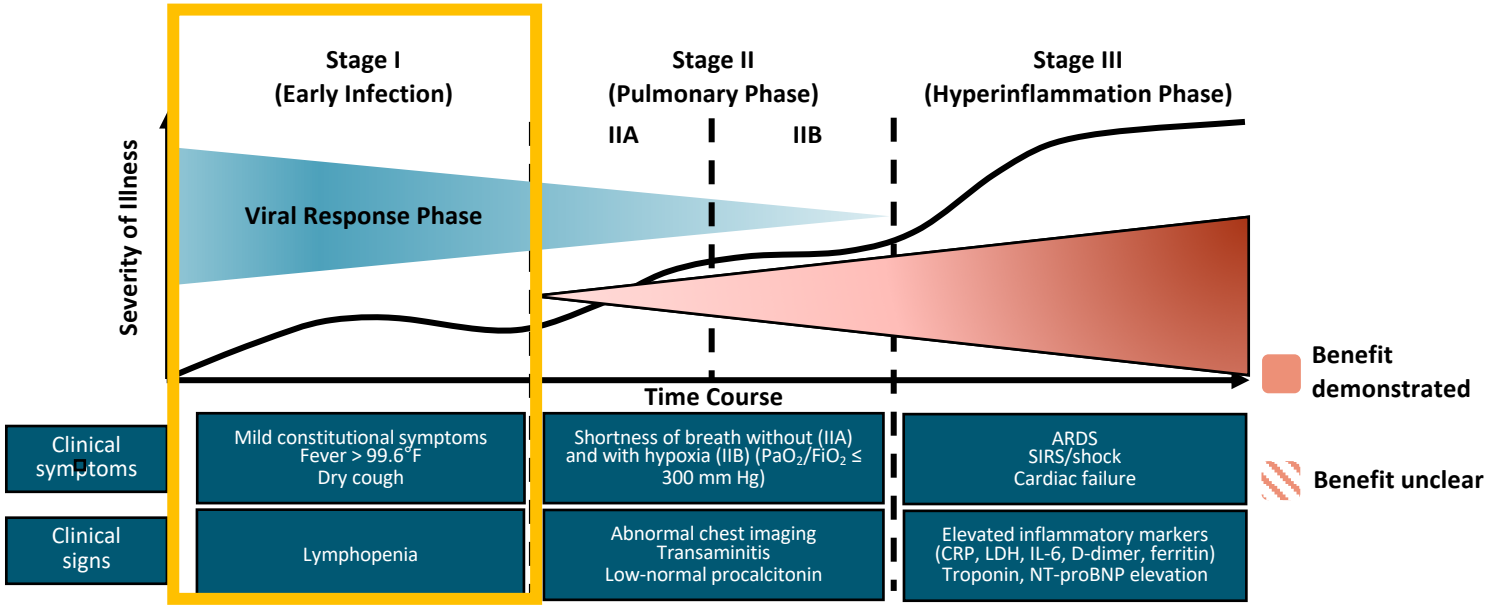
https://www.covid19treatmentguidelines.nih.gov/

For Pre-Exposure Prophylaxis

- The COVID-19 Treatment Guidelines Panel (the Panel) recommends that all patients who are eligible to receive tixagevimab plus cilgavimab (Evusheld) as pre-exposure prophylaxis (PrEP) should receive bivalent COVID-19 vaccines unless the use of these vaccines is contraindicated due to a history of severe adverse reactions to a COVID-19 vaccine or any of its components **(AIII)**.
- The prevalence of Omicron subvariants that are resistant to tixagevimab plus cilgavimab is rapidly increasing. The proportion of SARS-CoV-2 infections caused by these subvariants is currently estimated to exceed 45% in all regions in the United States.
- Tixagevimab plus cilgavimab is the only agent authorized by the Food and Drug Administration for use as COVID-19 PrEP in people who are not expected to mount an adequate immune response to COVID-19 vaccination or those with contraindications for COVID-19 vaccines.
  - In the absence of an alternative option for PrEP, the Panel continues to recommend the use of **tixagevimab plus cilgavimab** as PrEP for eligible individuals **(BIIb)**. See Prevention of SARS-CoV-2 Infection for more information.
  - Given the increasing prevalence of these resistant SARS-CoV-2 subvariants, the decision to administer tixagevimab plus cilgavimab to a given patient should be based on the regional prevalence of the resistant subvariants, the individual patient's risks, the available resources, and logistics.
  - Individuals who receive tixagevimab plus cilgavimab as PrEP should continue to take precautions to avoid exposure to SARS-CoV-2. If they experience signs and symptoms consistent with COVID-19, they should be tested for SARS-CoV-2 infection and, if infected, promptly seek medical attention and treatment, if appropriate.

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-omicron-subvariants/

COVID-19 Therapies Predicted to Provide Benefit at Different Stages

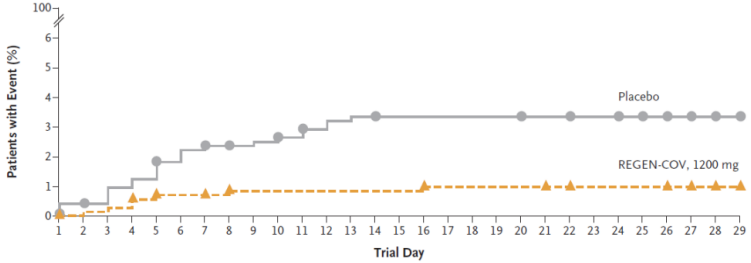


Siddiqi. J Heart Lung Transplant. 2020;39:405.

REGEN-COV Antibody Combination and Out[illegible] in Outpatients with Covid-19

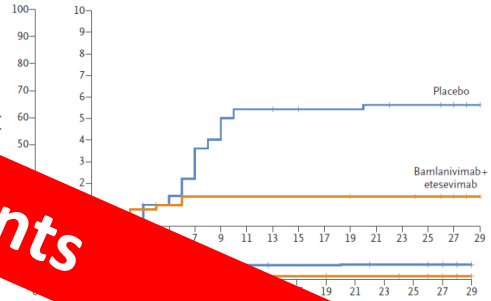
DOI: 10.1056/NEJMoa2108163

A Covid-19–Related Hospitalization or Death from Any Cause — Amended Phase 3 Trial



Bamlanivimab plus Etesevimab [illegible] or Moderate Covid-19

DOI: 10.1056/NEJMoa2102685



Victim of Variants

JAMA | Original Investigation

Effect of Sotrovimab on Hospitalization or Death Among High-risk Patients With Mild to Moderate COVID-19

A Randomized Clinical Trial

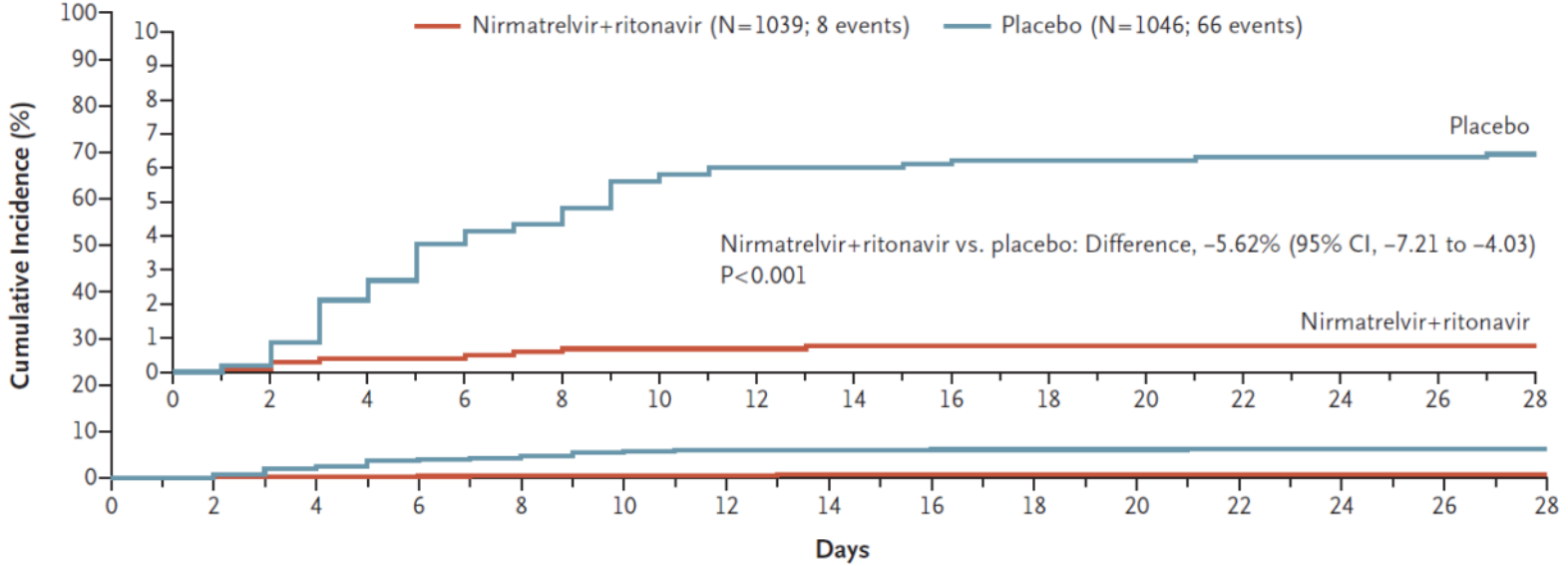
JAMA. 2022;327(13):1236-1246. doi:10.1001/jama.2022.2832

Table 2. Primary and Secondary Efficacy Outcomes for the As-Randomized Population[a]

	Sotrovimab (n = 528)	Placebo (n = 529)	Absolute difference (95% CI), %[b]	Adjusted relative risk (95% CI)	*P* value[c]
Primary efficacy outcome, No. (%)[d]					
All-cause hospitalization lasting >24 h for acute illness management or death due to any cause through 29 d	6 (1)	30 (6)	-4.53 (-6.70 to -2.37)	0.21 (0.09 to 0.50)[e]	<.001
Components of the primary outcome, No. (%)					
All-cause hospitalization lasting >24 h for acute illness management	6 (1)	29 (5)			
Death due to any cause	0	2 (<1)[f]			

Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19

B **Covid-19–Related Hospitalization or Death from Any Cause through Day 28 among Patients Treated ≤5 Days after Symptom Onset**

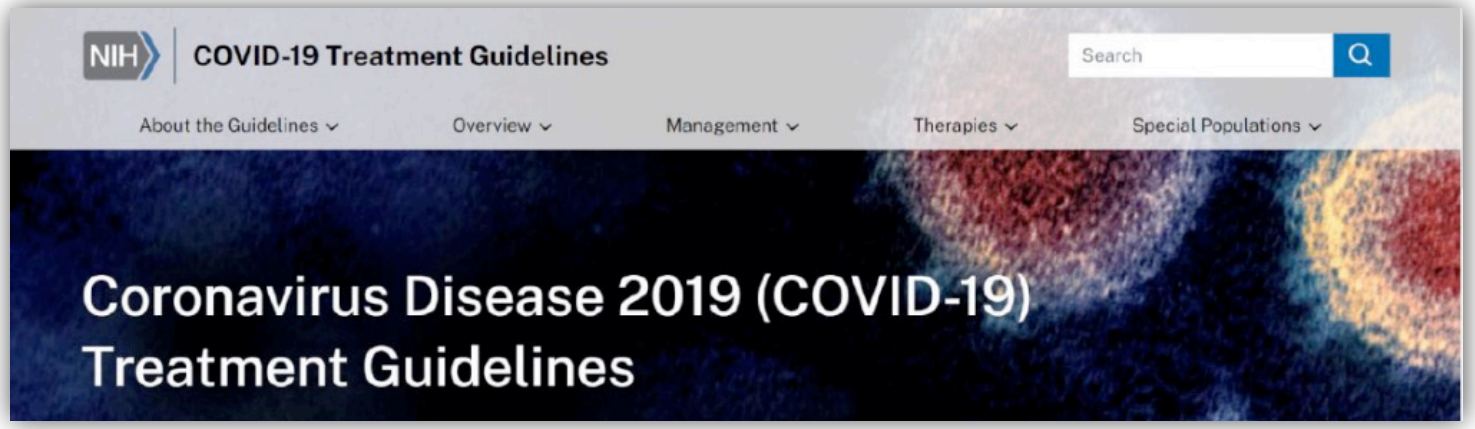


No. at Risk

NMV-r	1039	1034	1023	1013	1007	1004	1002	1000	997	995	993	993	993	993	992
Placebo	1046	1042	1015	990	977	963	959	959	955	953	951	948	948	948	945

DOI: 10.1056/NEJMoa2118542

Nirmatrelvir plus Ritonavir Drug-Drug Interactions



https://covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/paxlovid-drug-drug-interactions/

https://covid19-druginteractions.org/checker

Medications Without Clinically Relevant Interactions

These commonly prescribed medications may be coadministered without dose adjustment and without increased monitoring.[a] This list is not inclusive of all noninteracting medications within each drug category.

Acid reducing agents

- Famotidine
- Omeprazole
- Pantoprazole

Allergy medications

- Cetirizine
- Diphenhydramine
- Loratadine

Anti-infective agents

- Azithromycin
- Hydroxychloroquine

Cardiovascular agents

- Aspirin
- Atenolol
- Carvedilol
- Furosemide
- Hydrochlorothiazide
- Irbesartan
- Isosorbide Dinitrate
- Lisinopril
- Losartan
- Metoprolol
- Prasugrel

Diabetes medications

- Empagliflozin
- Insulin
- Metformin
- Pioglitazone

Immunosuppressants

- Methotrexate
- Mycophenolate
- Prednisone

Lipid-modifying agents

- Ezetimibe
- Pitavastatin
- Pravastatin

Neuropsychiatric agents

- Amitriptyline
- Bupropion
- Citalopram
- Duloxetine
- Escitalopram
- Fluoxetine
- Gabapentin
- Lorazepam
- Nortriptyline
- Olanzapine
- Paroxetine
- Sertraline

Pain medications

- Acetaminophen
- Aspirin
- Codeine
- Ibuprofen
- Naproxen

Respiratory medications

- Corticosteroids (inhaled)
- Formoterol
- Montelukast

Miscellaneous

- Allopurinol
- Contraceptives (oral)[b]
- Donepezil
- Enoxaparin
- Finasteride
- Levothyroxine
- Ondansetron

Continue Concomitant Medication and Monitor for Adverse Effects

Pre-emptive dose adjustment is not required but may be considered. Educate patients on potential adverse effects. Consult the Liverpool COVID-19 Drug Interactions website or the Ontario COVID-19 Science Advisory Table for monitoring guidance and dose adjustment information if needed.[i]

Temporarily Withhold Concomitant Medication, If Clinically Appropriate

Withhold these medications during ritonavir-boosted nirmatrelvir treatment and for at least 2–3 days after treatment completion. They may need to be withheld for longer if the patient is elderly or the medication has a long half-life. If withholding is not clinically appropriate, use an alternative concomitant medication or COVID-19 therapy.

Prescribe Alternative COVID-19 Therapy

For these medications, management strategies are not possible or feasible, or the risks outweigh the potential benefits.

Anticonvulsants

- Carbamazepine
- Phenobarbital
- Phenytoin
- Primidone

Anti-infective agents

- Glecaprevir/pibrentasvir
- Rifampin
- Rifapentine

Cardiovascular agents

- Amiodarone
- Clopidogrel[a,b]
- Disopyramide
- Dofetilide
- Dronedarone
- Eplerenone
- Flecainide
- Ivabradine

Pain medications

- Meperidine (pethidine)

Pulmonary hypertension medications

- Sildenafil
- Tadalafil
- Vardenafil

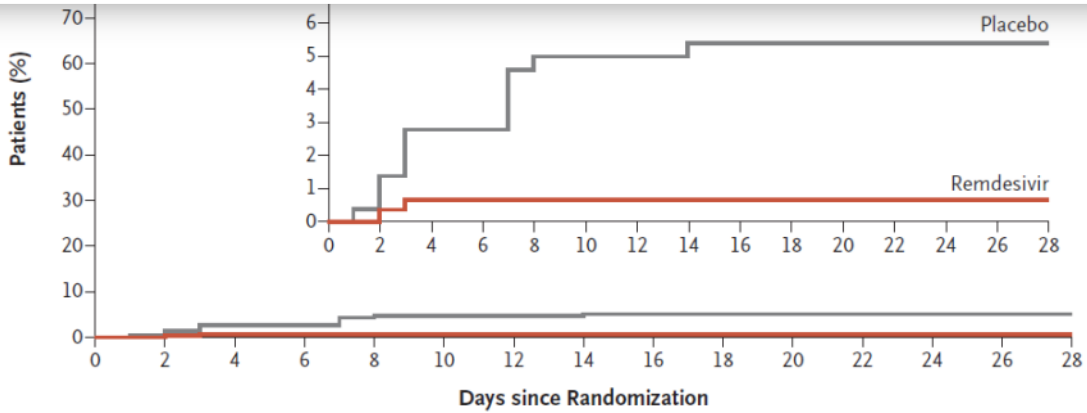
Miscellaneous

- Bosentan

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

R.L. Gottlieb, C.E. Vaca, R. Paredes, J. Mera, B.J. Webb, G. Perez, G. Oguchi, P. Ryan, B.U. Nielsen, M. Brown, A. Hidalgo, Y. Sachdeva, S. Mittal, O. Osiyemi, J. Skarbinski, K. Juneja, R.H. Hyland, A. Osinusi, S. Chen, G. Camus, M. Abdelghany, S. Davies, N. Behenna-Renton, F. Duff, F.M. Marty,* M.J. Katz, A.A. Ginde, S.M. Brown, J.T. Schiffer, and J.A. Hill, for the GS-US-540-9012

End Point	Remdesivir (N=279)	Placebo (N=283)	Hazard Ratio (95% CI)	P Value
Primary efficacy end point				
Covid-19–related hospitalization or death from any cause by day 28 — no. (%)†	2 (0.7)	15 (5.3)	0.13 (0.03 to 0.59)	0.008

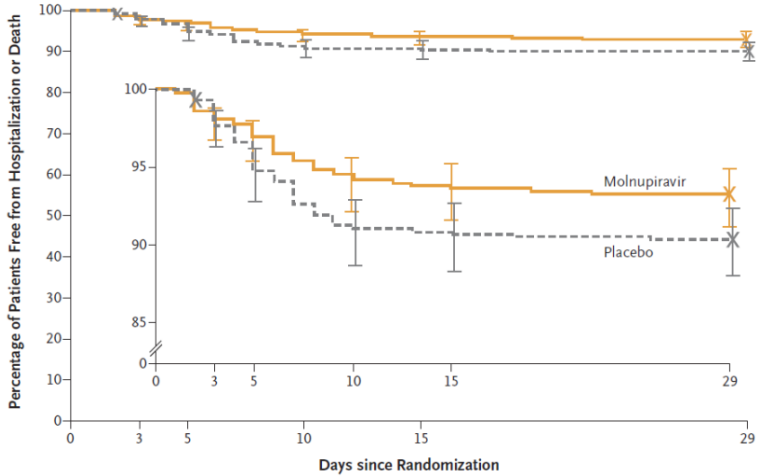


DOI: 10.1056/NEJMoa2116846

ESTABLISHED IN 1812 FEBRUARY 10, 2022 VOL. 386 NO. 6

Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients

A. Jayk Bernal, M.M. Gomes da Silva, D.B. Musungaie, E. Kovalchuk, A. Gonzalez, V. Delos Reyes, A. Martín-Quirós, Y. Caraco, A. Williams-Diaz, M.L. Brown, J. Du, A. Pedley, C. Assaid, J. Strizki, J.A. Grobler, H.H. Shamsuddin, R. Tipping, H. Wan, A. Paschke, J.R. Butterton, M.G. Johnson, and C. De Anda, for the MOVe-OUT Study Group*



No. at Risk						
Molnupiravir	709	699	693	670	665	661
Placebo	699	693	674	637	634	631
No. of Events						
Molnupiravir	10	6	23	5	4	0
Placebo	5	19	37	3	3	0

N Engl J Med 2022;386:509-20.
DOI: 10.1056/NEJMoa2116044

FACT SHEET FOR HEALTHCARE PROVIDERS: EMERGENCY USE AUTHORIZATION FOR BEBTELOVIMAB

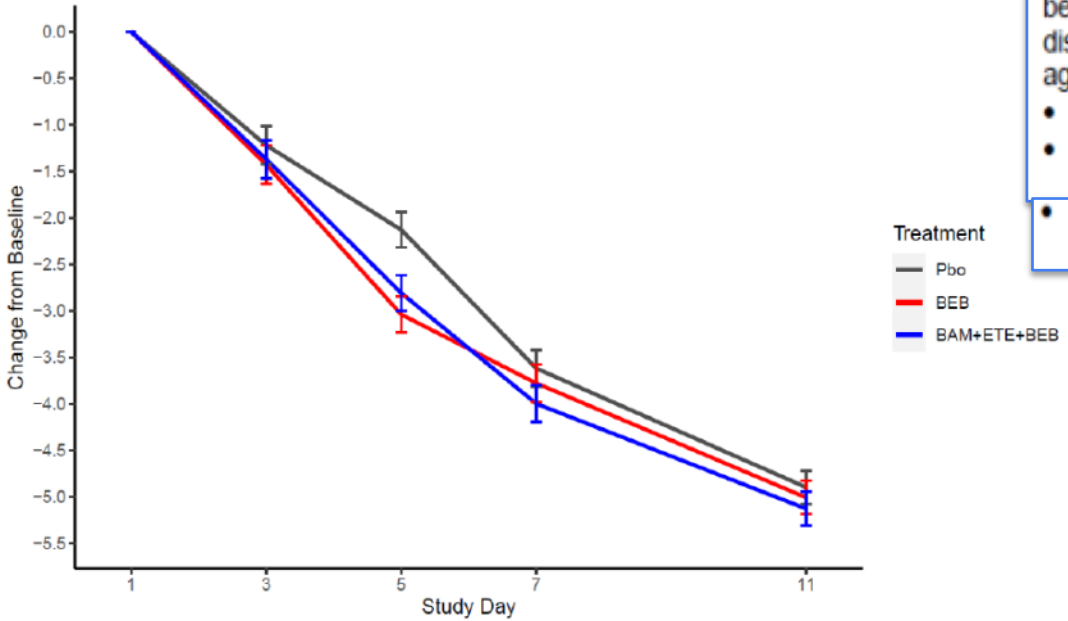


Figure 1: SARS-CoV-2 Viral Load Change from Baseline (Mean ± SE) by Visit from the Placebo-Controlled Portion of BLAZE-4 in Low Risk Adults (700 mg bamlanivimab, 1,400 mg etesevimab, 175 mg bebtelovimab together and 175 mg bebtelovimab alone).

----------**EMERGENCY USE AUTHORIZATION**----------

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) for the emergency use of bebtelovimab for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults and pediatric patients (12 years of age and older weighing at least 40 kg):

- with positive results of direct SARS-CoV-2 viral testing, **and**
- who are at high risk for progression to severe COVID-19, including hospitalization or death, **and**
- for whom alternative COVID-19 treatment options approved or authorized by FDA are not accessible or clinically appropriate.

Efficacy of BEB and Nirmatrelvir + RTV Against BA.2

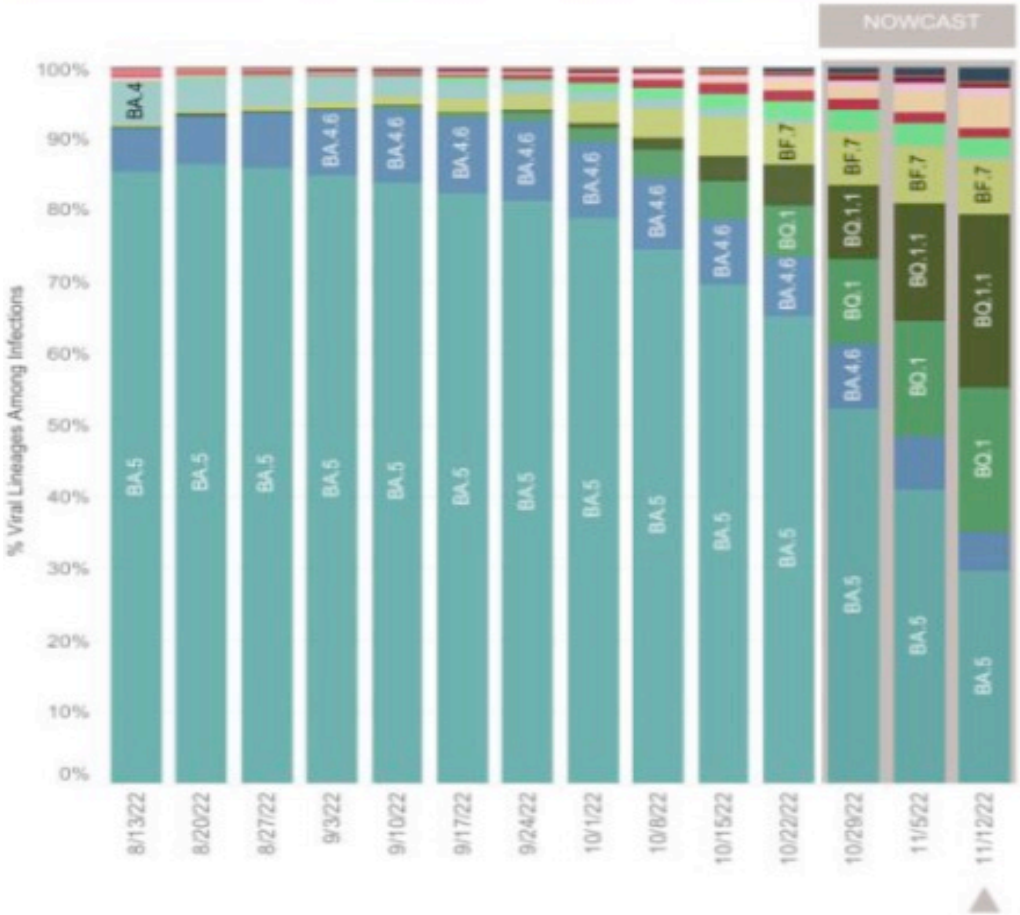
Mayo Clinic Experience

- Patients receiving BEB were older and had a higher number of comorbid conditions
  - CVD, lung disease, kidney disease, rheumatologic disease, cancer, and immunocompromised status
- Patients receiving nirmatrelvir + RTV had a higher median BMI and proportion of T2D

Outcome	BEB (n=2833), %	Nirmatrelvir + RTV (n=774), %
Severe outcome[a]	1.4	1.2
ICU admission	0.5	0.3
Death	0.2	0

[a]Severe outcome is defined according to World Health Organization classification of 4 (hospitalization and oxygen supplementation) or higher (including death).
N=3607 adults at high risk for progression to severe COVID-19 who attended Mayo Clinic received either BEB (n=2833) or nirmatrelvir + ritonavir (n=774).
BMI, body mass index.
Razonable R, et al. *J Infect Dis*. 2022. [Epub ahead of print].

United States: 8/7/2022 – 11/12/2022

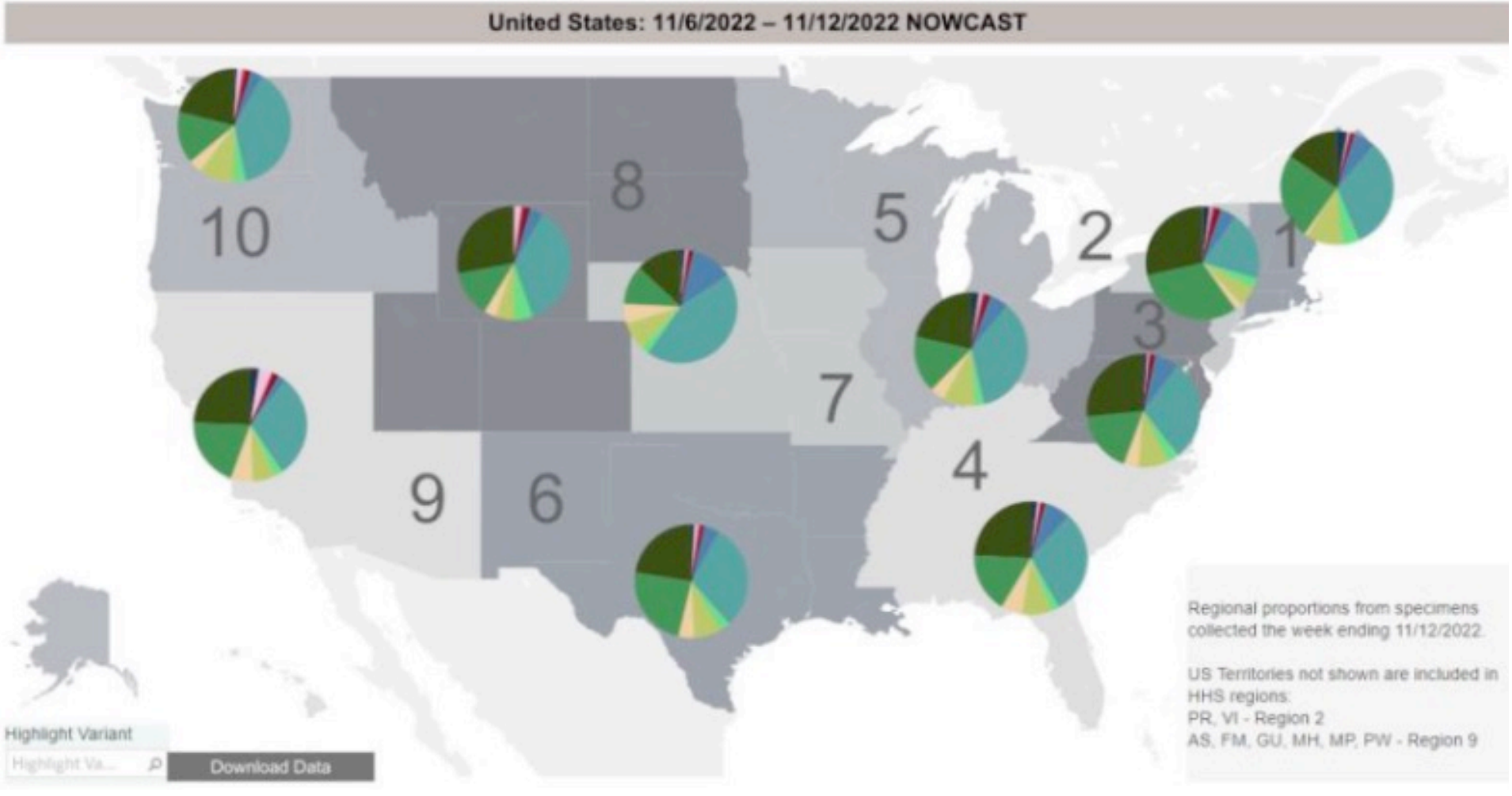


United States: 11/6/2022 – 11/12/2022 NOWCAST

USA

WHO label	Lineage #	US Class	%Total	95%PI
Omicron	BA.5	VOC	29.7%	27.2-32.3%
	BQ.1.1	VOC	24.1%	21.3-27.3%
	BQ.1	VOC	20.1%	17.2-23.4%
	BF.7	VOC	7.8%	6.8-9.0%
	BA.4.6	VOC	5.5%	5.0-6.2%
	BN.1	VOC	4.3%	3.0-6.2%
	BA.5.2.6	VOC	2.9%	2.5-3.4%
	BA.2	VOC	1.3%	0.8-1.9%
	BA.2.75	VOC	1.2%	1.0-1.5%
	BA.2.75.2	VOC	0.9%	0.6-1.2%
	BA.4	VOC	0.1%	0.1-0.1%
	BA.1.1	VOC	0.0%	0.0-0.0%
	B.1.1.529	VOC	0.0%	0.0-0.0%
	BA.2.12.1	VOC	0.0%	0.0-0.0%
Delta	B.1.617.2	VBM	0.0%	0.0-0.0%
Other	Other*		2.0%	1.1-3.3%

~45% BEB Resistant


United States: 11/6/2022 – 11/12/2022 NOWCAST
10
8
5
2
1
3
7
4
9
6
Regional proportions from specimens collected the week ending 11/12/2022.
US Territories not shown are included in HHS regions:
PR, VI - Region 2
AS, FM, GU, MH, MP, PW - Region 9
Highlight Variant
Highlight Va...
Download Data

For Treatment of Mild to Moderate COVID-19 in Nonhospitalized Adults Who Are at High Risk of Progressing to Severe COVID-19

- The Panel has recommended bebtelovimab as an alternative treatment for COVID-19 when neither of the preferred treatments (ritonavir-boosted nirmatrelvir [Paxlovid] or remdesivir) are available, feasible to use, or clinically appropriate. However, when resistant Omicron subvariants (e.g., BQ.1, BQ.1.1) represent the majority[a] of infections in the region,[b,c] clinicians cannot rely on bebtelovimab to be effective for the treatment of COVID-19. Ritonavir-boosted nirmatrelvir, remdesivir, and molnupiravir are expected to be active against these resistant subvariants.
- The Panel continues to recommend the following anti-SARS-CoV-2 therapies as preferred treatments for COVID-19. These drugs are listed in order of preference:
  - **Ritonavir-boosted nirmatrelvir (Paxlovid) (AIIa)**
  - **Remdesivir (BIIa)**
- The following alternative therapies should be used **ONLY** when neither of the preferred therapies are available, feasible to use, or clinically appropriate. These drugs are listed in alphabetical order:
  - **Bebtelovimab**, but **ONLY** when the majority[a] of circulating Omicron subvariants in the region[b,c] are susceptible **(CIII)**
  - **Molnupiravir (CIIa)**

[a] The Panel acknowledges that the Centers for Disease Control and Prevention's (CDC) prevalence reports for SARS-CoV-2 subvariants are only estimates and that there is currently no definitive prevalence threshold for resistant subvariants that determines when the use of bebtelovimab for the treatment of COVID-19 will be ineffective. When the majority (>50%) of isolates in a region are likely to be resistant, the ongoing use of bebtelovimab may no longer be justified.

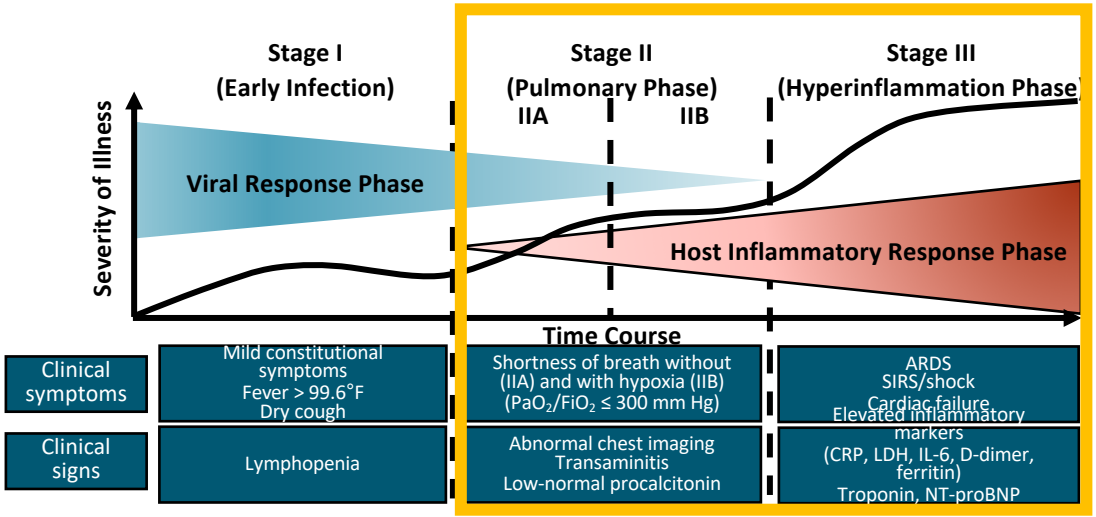
[b] See the CDC COVID Data Tracker for regular updates on the regional proportions of SARS-CoV-2 variants in the United States.

[c] Clinicians should also consider a patient's recent travel (i.e., where the patient is thought to have acquired SARS-CoV-2 infection) when reviewing regional proportions of SARS-CoV-2 variants to guide treatment.

https://www.covid19treatmentguidelines.nih.gov/therapies/statement-on-omicron-subvariants/

Drug	Dosing	Duration	Time from Symptom Onset	Specific issues
Nirmatrelvir (N) + ritonavir (RTV)	eGFR ≥60mL/min: N- 300 mg with RTV- 100 gm po bid eGFR ≥30 to <60 mL/min N- 150 mg with RTV-100 mg po bid	5 days	≤5 days	• DDIs • Not recommended with Child-Pugh Class C • All data in vaccinated
Remdesivir (RDV)	RDV 200 mg IV F/B 100 mg IV daily	Day 1 Day 2, 3	≤ 7 days	• Infusion over 30-120 min • Infusions over 3 consecutive days
Bebtelovimab (BEB)	BEB 175 mg IV	Day 1	≤ 7 days	• Administer ≥30 seconds • No clinical endpoint data
Molnupiravir (MOL)	MOL 800 mg po bid	5 days	≤5 days	• Potentially less efficacious than other options • Safety concerns

COVID-19 Therapies Predicted to Provide Benefit at Different Stages



- Remdesivir
- Corticosteroids
- Tocilizumab
- Baricitinab
- Anticoagulation

Siddiqi. J Heart Lung Transplant. 2020;39:405.

RECOVER
Researching COVID to Enhance Recovery

Home | Help Us Recruit for RECOVER Studies

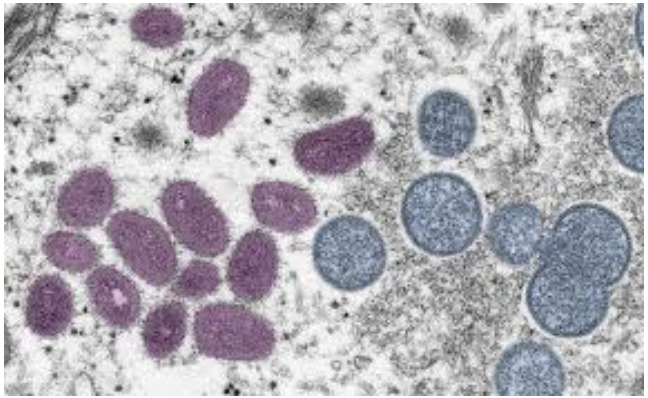
Ask to Join RECOVER Studies

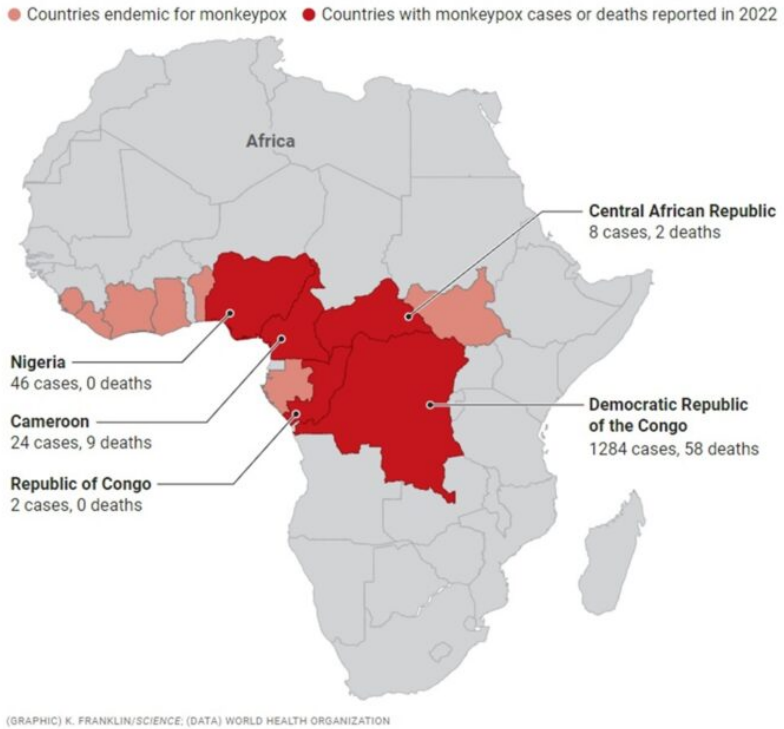
RECOVER is a research project that aims to learn about the long-term health effects of COVID. To understand COVID, we need to include many people in **RECOVER** studies. You can participate whether you have COVID now, had COVID before, or never had COVID.

We need to learn how COVID affects all people, and that means adults, including pregnant people, and children from every walk of life and across the country.

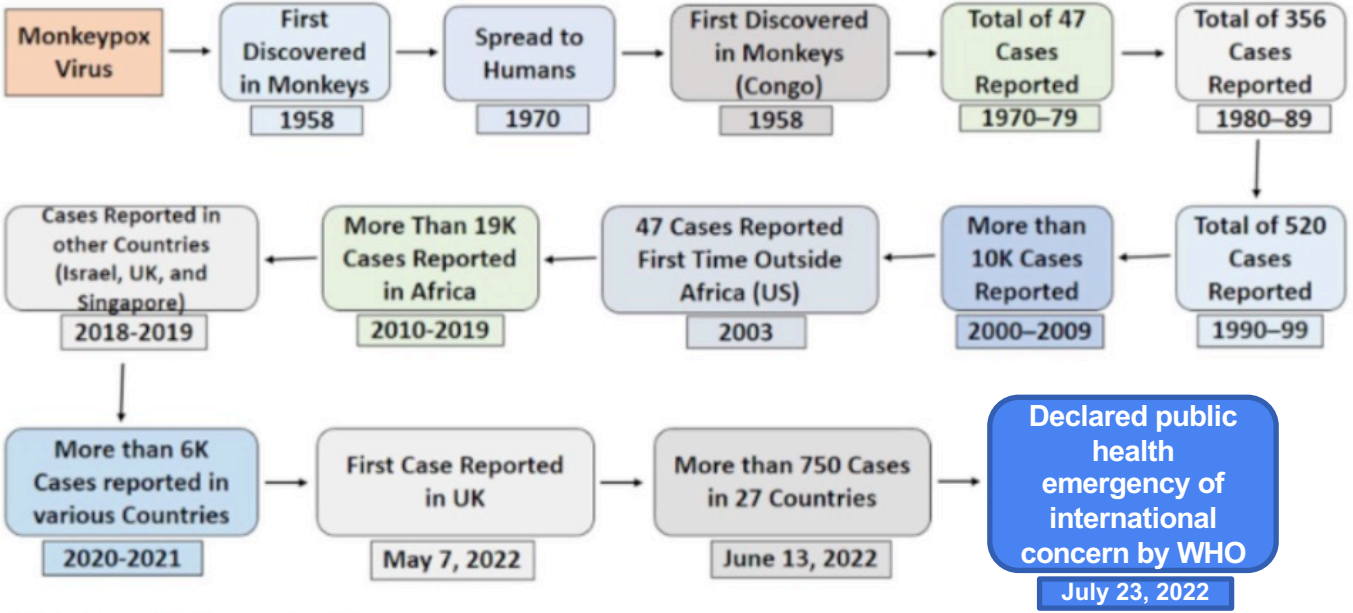
MPX:
Epidemiology, Testing, Prevention and Treatment

Monkeypox (MPX)



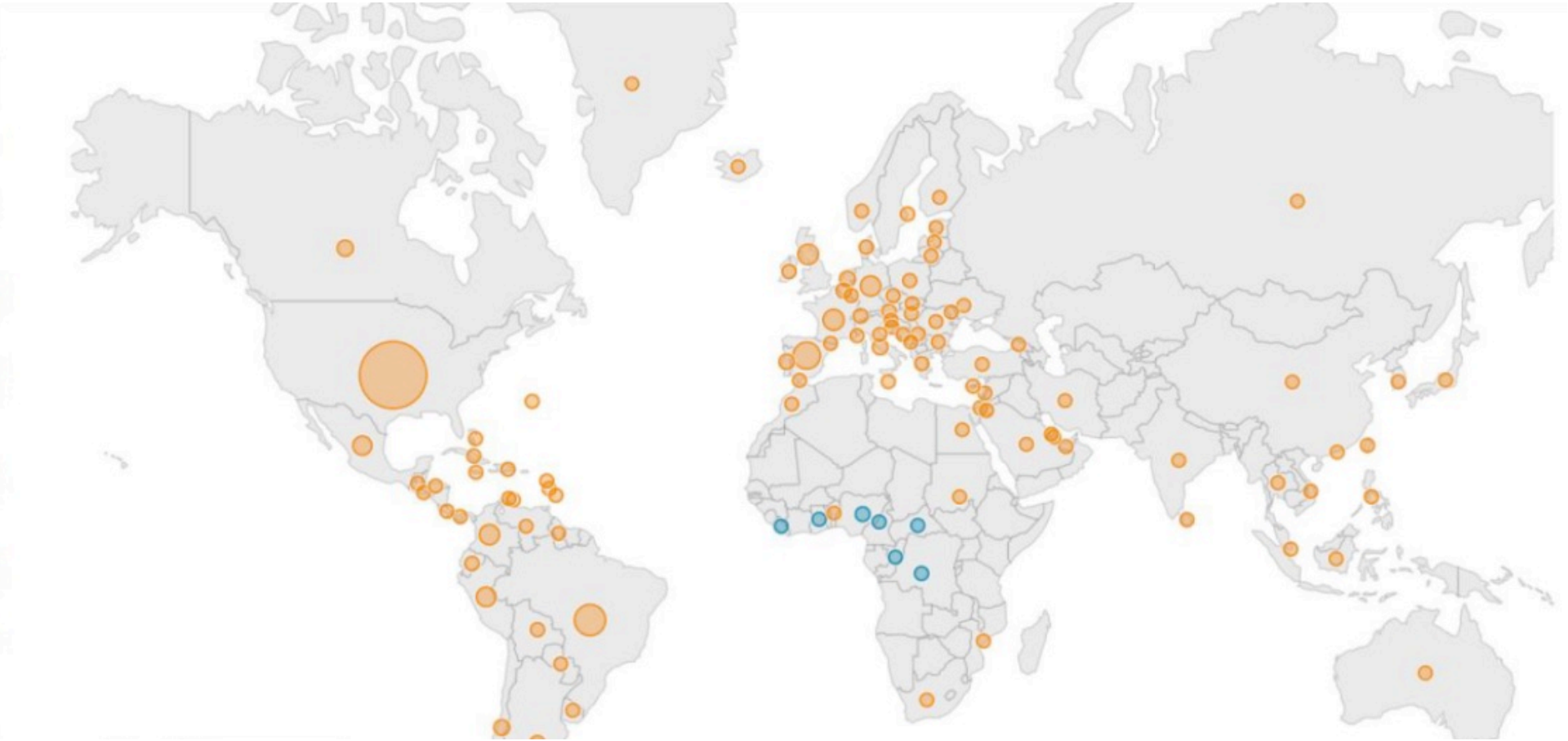


Monkeypox Timeline

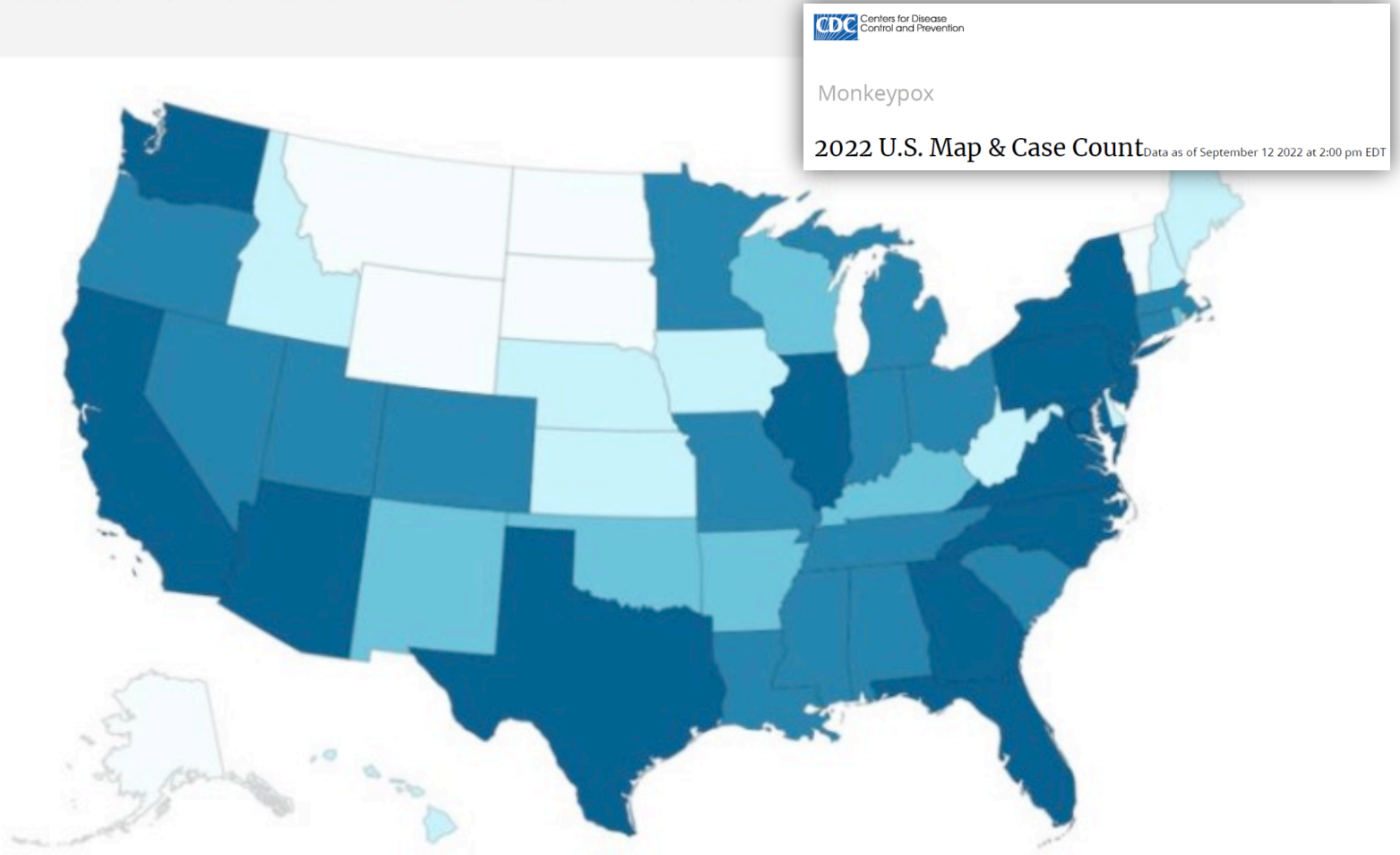


i. 1. Timeline of Monkeypox virus infection.

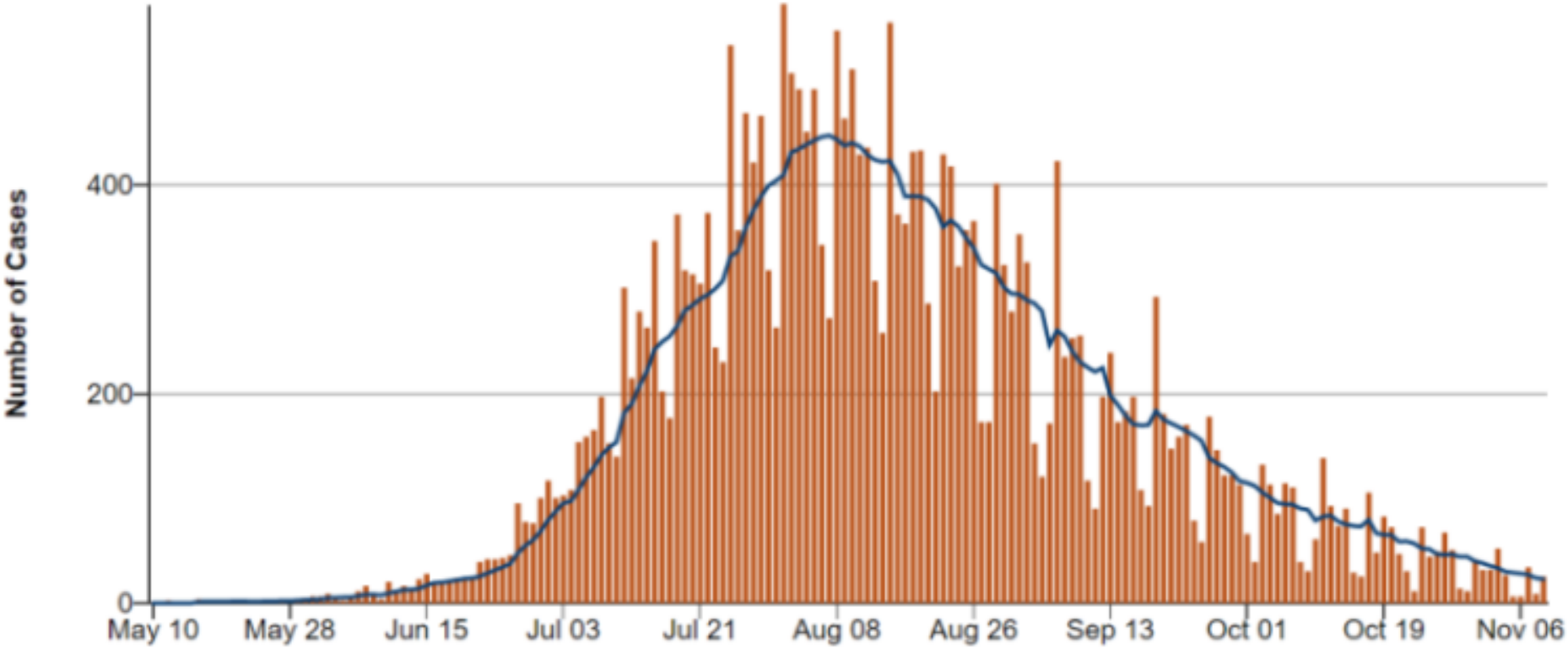
Anwar F, Waris A. New Microbe and New Infect 2022;48:101004
https://www.cdc.gov/poxvirus/monkeypox/response/2022/world-map.html



28,881 Total confirmed monkeypox/orthopoxvirus cases

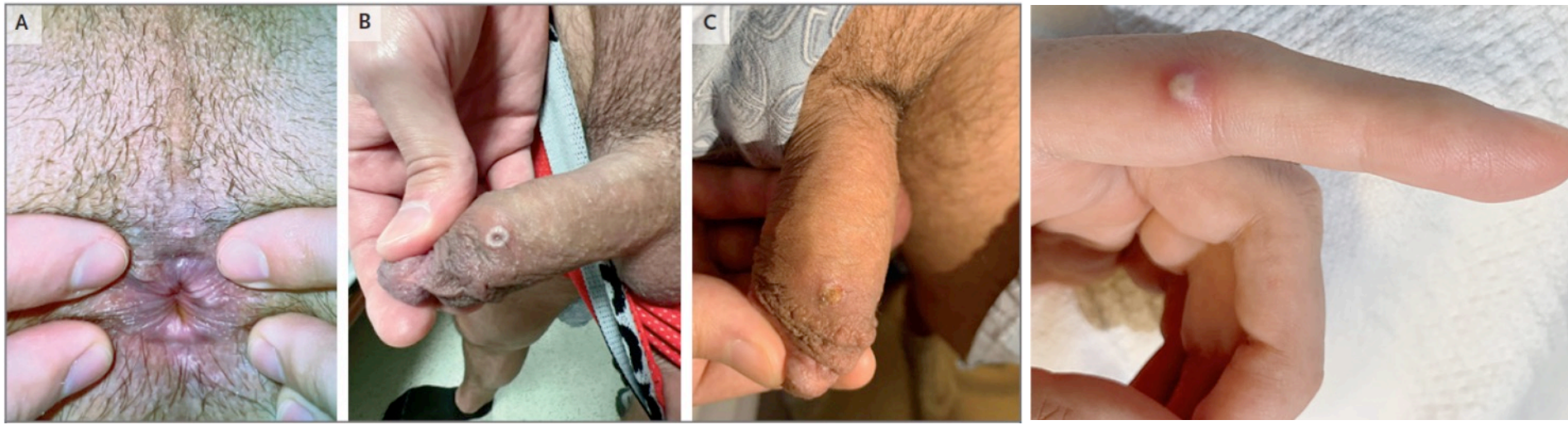


Daily Monkeypox Cases Reported and 7 Day Daily Average

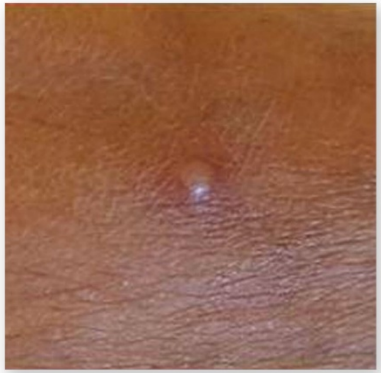


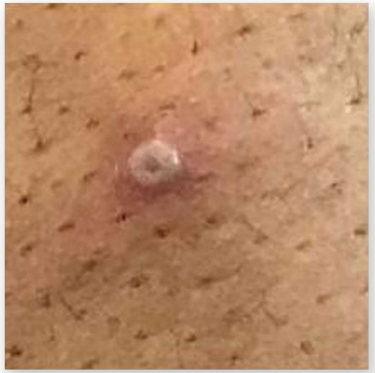
Case 24-2022: A 31-Year-Old Man with Perianal and Penile Ulcers, Rectal Pain, and Rash

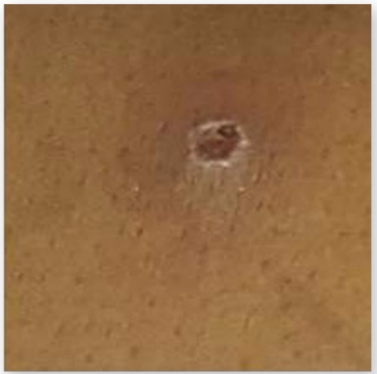
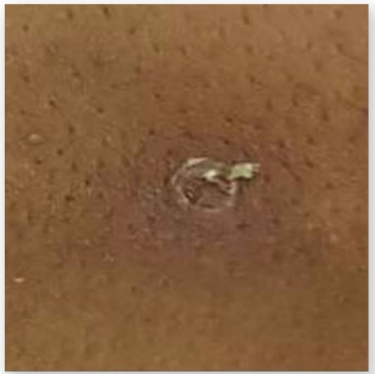
Nesli Basgoz, M.D., Catherine M. Brown, D.V.M., M.P.H., Sandra C. Smole, Ph.D., H.C.L.D. (A.B.B.), Lawrence C. Madoff, M.D., Paul D. Biddinger, M.D., Joshua J. Baugh, M.D., M.P.P., M.H.C.M., and Erica S. Shenoy, M.D., Ph.D.

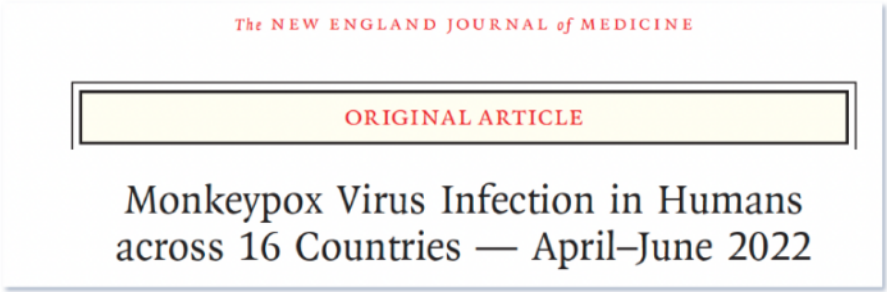


NEJM 2022; 387:547-56





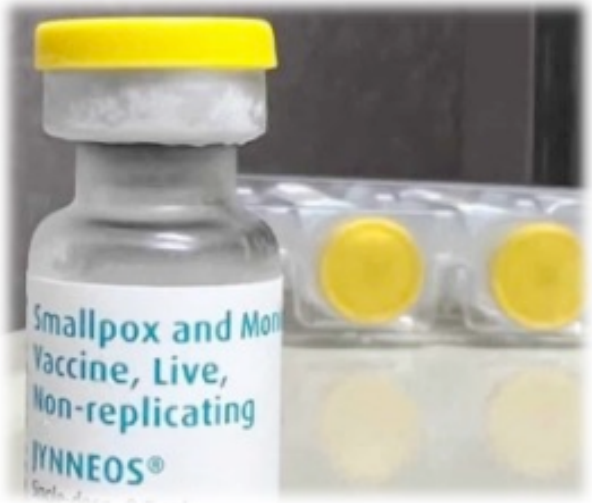


- N=528
  - 99% men
  - 98% MSM
  - 41% HIV+
  - 29% with an STI (GC, Chl, Syph)
  - 28% recent foreign travel
  - **9% with reported prior Smallpox vax**
  - Median intimate partner #/3m = 3
- Presentation
  - 95% Skin lesion (68% anogenital)
  - 62% Fever
  - 56% LAN
  - 21% Pharyngitis
  - 14% Proctitis

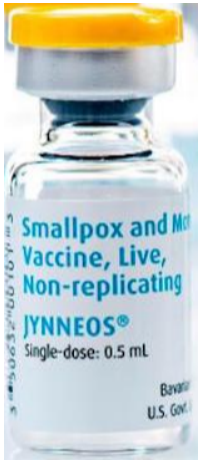
Differential diagnosis

- Herpes zoster (shingles)
- Herpes simplex
- Scabies
- Syphilis
- Chancroid
- LGV
- Allergic reaction

Addressing MPX Outbreak

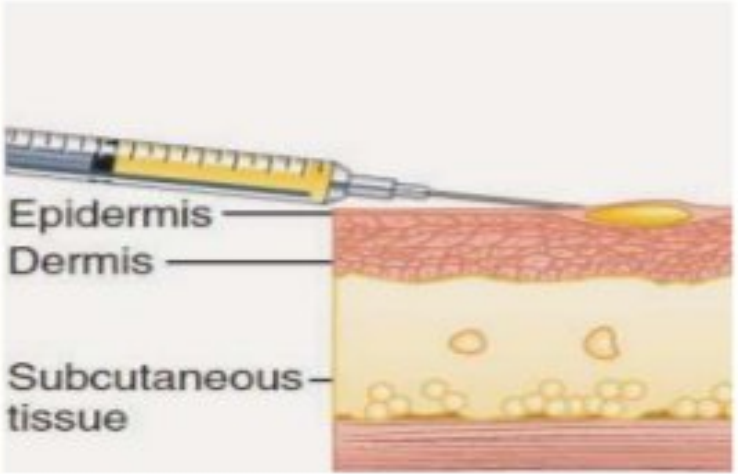


- The MVA-BN vaccine is called Imvanex (in Europe), Jynneos (in USA) and Imvamune (in Canada)
- All the same vaccine manufactured by Bavarian Nordic
- Live non-replicating Modified Vaccinia Ankara approved for smallpox and Monkeypox
- **No human efficacy data**



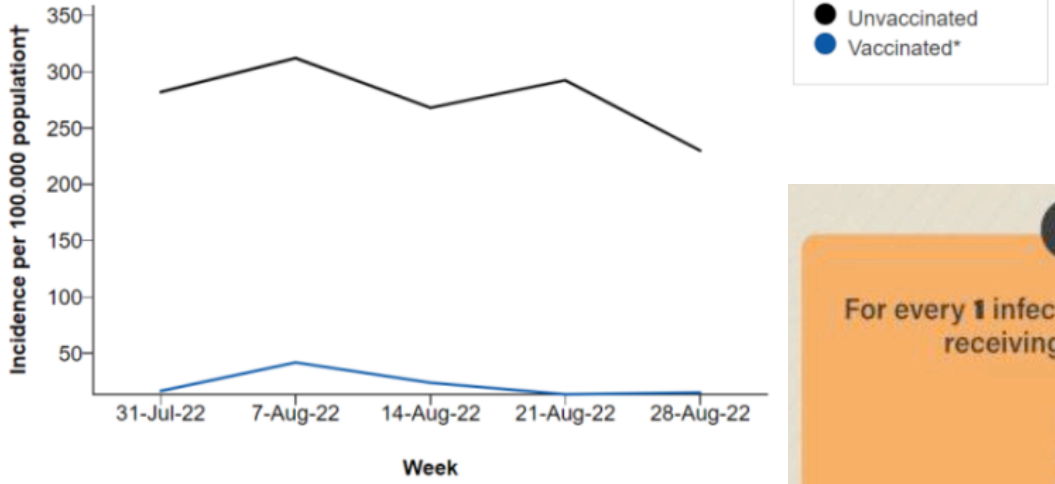
FDA NEWS RELEASE
Monkeypox Update: FDA Authorizes Emergency Use of JYNNEOS Vaccine to Increase Vaccine Supply

August 09, 2022



Rates of Monkeypox Cases by 1st Dose Vaccination Status

July 31, 2022 – September 3, 2022 (32 U.S. jurisdictions)



Health Services
LOS ANGELES COUNTY

Expected Practices

Specialty: ID Workgroup, Microbiology Workgroup, CORE P&T

Subject: Guidance for prevention, diagnosis, and treatment of Monkeypox disease

1) Pre-Exposure Prophylaxis (PrEP) use of vaccination
After risk-benefit discussion, certain high-risk individuals can be offered pre-exposure vaccination with JYNNEOS™ vaccine. These groups are likely to change and so routine review of the DPH and CDC groups is recommended to providers who treat the highest risk groups. The list of eligible patients for vaccine can be found at:

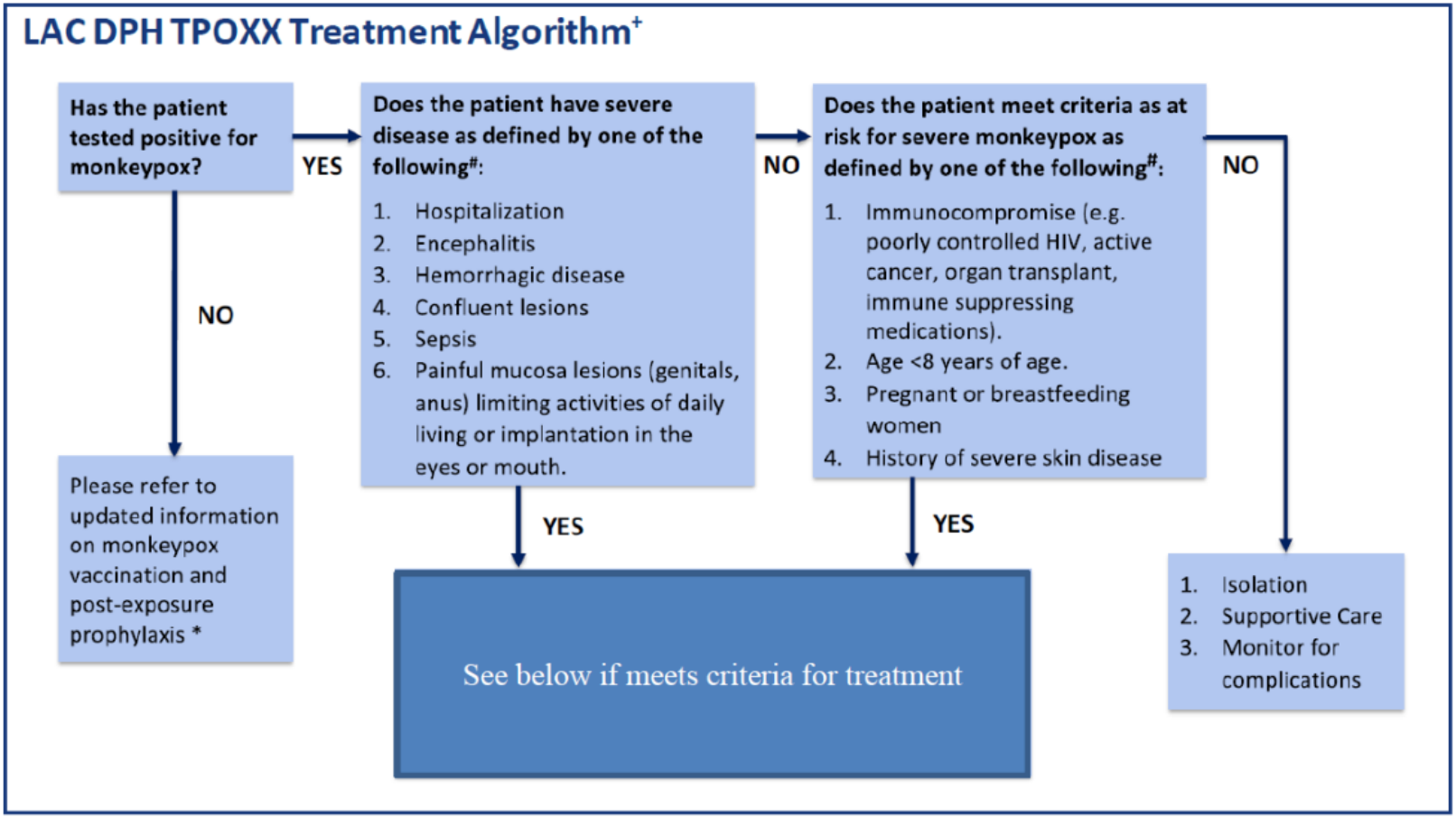
http://publichealth.lacounty.gov/media/monkeypox/

2) Post-Exposure Prophylaxis (PEP) use of vaccination
After risk-benefit discussion, vaccination of individuals within 4 days of a high-risk exposure may reduce the risk of developing monkeypox disease. If given 4-14 days after exposure, vaccination may reduce the symptoms but may not completely prevent infection.

- Treatment
  - Tecovirimat PO and IV (14-day course)
  - FDA approved for smallpox based on animal rule
  - No human studies of efficacy for smallpox or MPX
  - Available via compassionate use (IND) from National Strategic Stockpile

Inhibits activity of orthopoxvirus VP37 protein (encoded by all orthopoxvirus) and blocks interaction with cellular Rab9 GTPase and TIP47, preventing the formation of egress-competent enveloped virions

Safety and efficacy data are lacking for HMPXV



Further information regarding treatment can be found at: **Guidance for the Treatment of Monkeypox-Tecovirimat**

Tecovirimat Oral Dosing:

Dosage adjustments for oral formulation:

Renal Impairment: no dosage adjustment necessary (including patients with ESRD requiring HD)

Hepatic Impairment: no dosage adjustment necessary

Pediatric and adult patients weighing 13 kg or more:

1) 13 kg to less than 25 kg: 200 mg (1 capsule) of TPOXX every 12 hours for 14 days
2) 25 kg to less than 40 kg: 400 mg (2 capsules) of TPOXX every 12 hours for 14 days
3) 40 kg to less than 120 kg: 600 mg (3 capsules) of TPOXX every 12 hours for 14 days
4) 120 kg and above: 600 mg (3 capsules) of TPOXX every 8 hours for 14 days

Administration: Oral formulation should be given within 30 minutes after a full meal containing moderate or high fat (about 25 g of fat). Drug absorption of oral formulation is dependent on adequate concurrent intake of a full, fatty meal.

For small children and patients who cannot swallow capsules, capsules may be opened and entire contents mixed with 30 mL of liquid (e.g. milk, chocolate milk) or soft food (e.g. applesauce, yogurt); powder may not dissolve completely. Administer entire mixture within 30 minutes after preparation.

Tecovirimat Intravenous Dosing:

Dosage adjustments for intravenous formulation:

Renal Impairment:

CrCl <30 mL/minute: Use is contraindicated (cyclodextrin accumulation)

CrCl ≥30 mL/minute: No dosage adjustment necessary

Dosage:

1) Not indicated for those <3 kg in weight
2) 3 kg to less than 35 kg: 6 mg/kg every 12 hours by IV infusion over 6 hours for up to 14 days
3) 35 kg to less than 120 kg: 200 mg every 12 hours by IV infusion over 6 hours for up to 14 days
4) 120 kg and above: 300 mg every 12 hours by IV infusion over 6 hours for up to 14 days

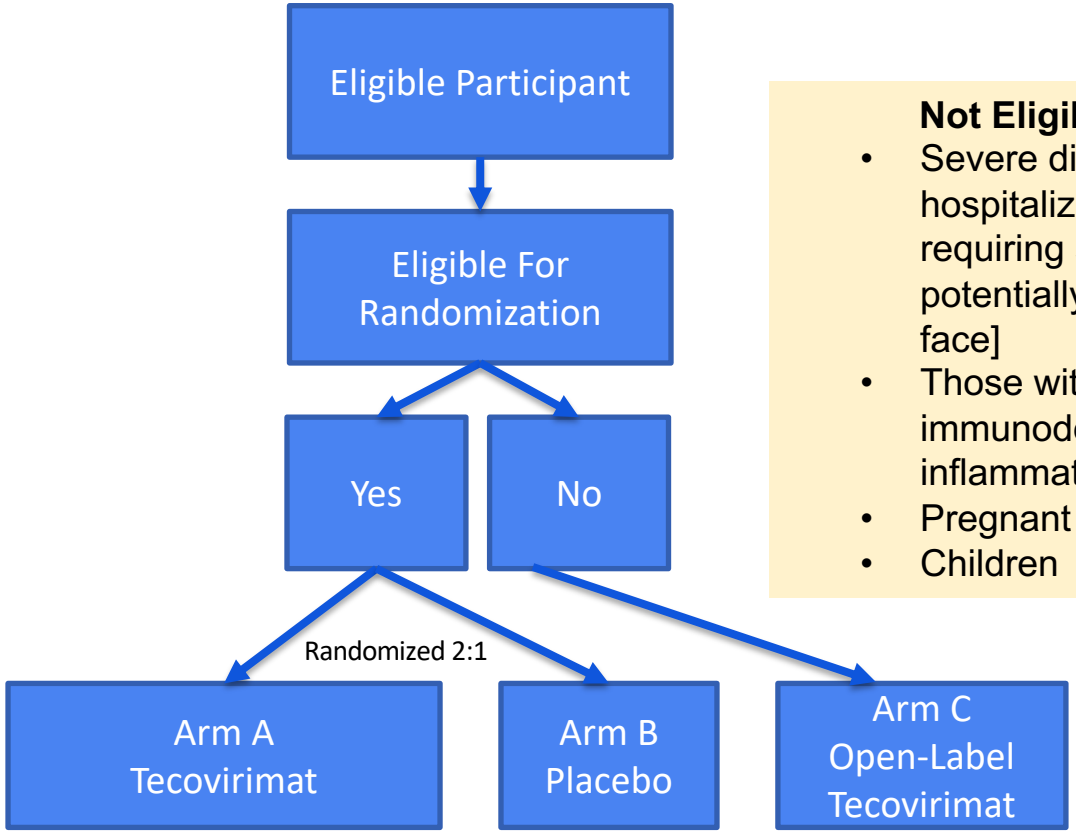
A5418

A Randomized, Placebo-Controlled, Double-Blinded Trial of the Safety and Efficacy of Tecovirimat for the Treatment of Persons with Human Monkeypox Virus Disease

Study of Tecovirimat for Human Monkeypox Virus (STOMP)

SPONSOR: NIH/AIDS CLINICAL TRIALS GROUP

ACTG
AIDS CLINICAL TRIALS GROUP



Not Eligible for Randomization

- Severe disease [e.g., ocular, hospitalization, deep lesions requiring surgical intervention, potentially disfiguring lesions on the face]
- Those with severe immunodeficiency, Severe inflammatory skin conditions
- Pregnant and breastfeeding people
- Children

ACTG
AIDS CLINICAL TRIALS GROUP

Conclusions

- Major advances have been made in HIV PrEP and Treatment
- STI PEP represents a potentially important strategy to compliment PrEP and HIV U=U
- COVID-19 pandemic continues with major advances in vaccine strategies and treatment; however, emerging variants has limited PrEP and treatment
- Monkeypox spread in U.S. continues, although marked reduction in cases associated with changes in behavior, natural infection and vaccine strategies

Thank You!!

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