CROI 2021: Updates on HIV Treatment & Prevention and SARS-CoV-2

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This activity is jointly provided by Physicians’ Research Network and the Medical Society of the State of New York.
virtual CROI 2021
March 6-10, 2021
Focus on Antivirals
Publications in last year
- HIV: 6600
- SARS-CoV-2: >64,000

Talks: 50% SARS-CoV-2-related content

1153 abstracts + 66 late breakers
- Acceptance rate: 56% regular and 24% late breakers
- 25% SARS-CoV-2-related
CROI 2021 – HIV Treatment
<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Regimen</th>
<th>Duration</th>
<th>Virologic response</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workowski</td>
<td>N=1274</td>
<td>TAF/FTC/BIC</td>
<td>4 years</td>
<td>&gt;98% VL &lt;50</td>
<td>Similar to DTG</td>
</tr>
<tr>
<td>GEMINI 1+2</td>
<td>N=1433</td>
<td>DTG+3TC</td>
<td>96 weeks</td>
<td>82% VL &lt;50</td>
<td>Non-inferior to TDF/FTC + DTG</td>
</tr>
<tr>
<td>Benson</td>
<td>N=741</td>
<td>DTG/3TC</td>
<td>96 weeks</td>
<td>&gt;99% VL &lt;50</td>
<td>Non-inferior to 3/4 drug regimens</td>
</tr>
<tr>
<td>ATLAS-2M</td>
<td>N=1045</td>
<td>CAB+RPV q8 weeks</td>
<td>96 weeks</td>
<td>&gt;90% VL &lt;50</td>
<td>Non-inferior to q4 weeks</td>
</tr>
</tbody>
</table>
ART: U.S. First Regimen Failures

CFAR Network of Integrated Clinical Systems
- 7 U.S. clinical cohorts, 2008-2018

Virologic failure (VL>200 after ≥24 wks)

Cohort (N=6810)
- 83% men, 40% Black, 40% White
- First regimen: 2 NRTI +
  - 37% EFV (81% EFV)
  - 33% INSTI (51% EVG, 31% DTG)
  - 21% PI/b (49% DRV, 43% ATV)

Results
- VF in 2010 (21%) by 2 years
  - ↑ VF in women, Blacks, lower CD4 at baseline
  - NNRTI + PI/b had 2.5X ↑ VF rate with switch than INSTI

Davy-Mendez CROI 2021 abstract
2nd-Line ART in U.S.: Cohort

CFAR Network of Integrated Clinical Systems

7 U.S. clinical cohorts, 2008-2018

Study population: on new anchor ART agent > 8 months after start in VL > 200 (N=705)

75% men, 23% women
54% B, 12% L, 31% W

1st regimen: 47% NNRTI, 29% PI

Results on 2nd regimens:
38% INSTI, 8% NNRTI, 24% PI
VF in 49% at 2 years

Davy-Mendez CROI 2021 abstract #94
ADIA: 2nd-Line ART in Sub-Saharan Africa

2 factorial, open-label, non-inferiority (Δ12%) study

Study population: Failing TDF/3TC/NNRTI with confirmed VL ≥ 1000; NRTI resistance information collected/blinded (N=464 at 7 sites)

61% women, 51% CD4 < 200, 28% VL ≥ 100,000

Study treatment: [TDF or ZDV]/3TC/[DRV/r or DTG]

Conclusion: For 2nd-Line, DTG non-inferior to DRV/r; TDF non-inferior to ZDV
CROI 2021 – HIV Treatment in Pregnancy
Antiretroviral Pregnancy Registry (APR) 20 years

APR started monitoring prenatal ARV use in 1989 to assess teratogenicity and congenital anomalies

Data from 70 countries; compared to general population

2 ARVs sufficient 1st trimester exposures to detect >2X ↑ + 11 sufficient to detect >1.5X ↑

Results: 21,599 evaluable pregnancies; 20,437 live births with ARV exposure; 580 congenital anomalies (2.8% prevalence)

3 ARVs with modest ↑ in prevalence: ddI and NFV (both 2.9%), TAF (4.4%)

95% CI within upper bound of 1-2 population registries

No parent or congenital anomalies

Conclusion: No significant difference in congenital anomalies with ARVs compared to general population; ongoing monitoring continues
IMPAACT 2010 (VESTED)

Phase III safety and efficacy study of:
- TAF/FTC + DTG
- TDF/FTC + DTG
- TDF/FTC/EFV

Study population: ART-naive women in 9 countries initiating ART during pregnancy at 14-28 weeks gestation) (N=643)

Primary outcomes:
- VL <200 (non-inferiority -Δ10%)
- Pregnancy outcomes

Who was in VESTED?
- 26-27 yo
- Enrolled in Africa: 86-89%
- Median gestational age: 21-22 wk
AACT 2010: Results through 50 Weeks Postpartum

VL <200: 96% in all 3 treatment arms

- Regimen stops ↑ with EFV due to VF/drug resistance and ↑ with DTG due to fertility choices

No differences in maternal or infant grade ≥3 adverse events

Neonatal death higher with EFV (6.9%) vs. TAF/FTC + DTG (1.0%, p <0.001) or TDF/FTC + DTG (2.0%, p=0.008)

Conclusions:

- Similar virologic outcomes, but more VF on EFV
- Infant mortality ↑ with EFV

Chinula CROI 2021 Abstract #177
MPAAACT 2010: Antepartum Weight Gain

Lower weight gain during pregnancy associated with adverse pregnancy outcomes (HR 1.4).

No associations with higher weight gain.

Average weekly weight gains

Conclusions:

- Low (but not high) weight gain associated with adverse outcomes
- Weight gain: TAF/FTC + DTG > TDF/FTC + DTG > TDF/FTC/EFV
CROI 2021 – HIV Prevention
Daily vs. On-Demand TDF/FTC PrEP in France

ANRS Prevenir Prospective Cohort Study

Study population: high-risk MSM (N=3067 at 22 sites in Paris region; 44% PrEP naïve)

Study treatment: Choice of daily or on-demand TDF/FTC

Results (median f/u ~2 years):

- Median sex partners over past 3 months: 10
- 50% daily; 50% on-demand; 20% condom use
- 19 (0.6%) discontinued for PrEP-related adverse events
- New HIV infections: 3 (daily) and 3 (on-demand) – ALL stopped PrEP prior
- Overall HIV incidence 0.11/100 pt-years
- Overall bacterial STI incidence 73/100 pt-years (32/100 pt-yrs during COVID-19 lockdown)

Conclusion:

- HIV incidence low with PrEP (daily or on-demand)
- High incidence of bacterial STIs

Molina CROI 2021 abstract #148
PTN 083:
PrEP with IM CAB vs. TDF/FTC

Phase 2b/3 randomized, double-blinded HIV PrEP international study

Study pop: High-risk adult MSM/TGW (N=4570)
67% <30 yo; 12% TGW; 50% Black in U.S.

Study reg: CAB oral (5 wks) → IM q2 mos vs. TDF/FTC po daily
DSMB stopped study early!

Results:
New HIV infections:
- 13 (CAB) vs. 39 (TDF/FTC)

HIV incidence rates (/100 pt yrs):
- 0.41 (CAB) vs. 1.22 (TDF/FTC)

Safety:
- ISR 81% (CAB) vs. 31% (placebo)
- 2% of CAB participants d/c

Conclusion: CAB non-inferior and superior!

Landovitz IAS 2020 #OAXLBO
13 Incident HIV Infections

**Cabotegravir**

- **Infection prior to CAB start**
- **Infection after prolonged missed CAB**
- **Infection during oral lead-in phase**
- **Infection despite continuous, on-time CAB injections**

- **5 with INSTI resistance mutations, including Q148R/K, R263K**

**Step 1:** Oral CAB lead-in
**Step 2:** CAB LA 600 mg IM
**Step 2:** CAB LA injection > 2 week overdue
**Step 3:** Open-label TDF/FTC
**Step 3:** Overdue TDF/FTC dispensation

- **First site positive HIV test**
- **Awaiting HIV back-testing**

Landovitz CROI 2021 #LB153
## HIV PrEP with Cabotegravir LA vs. oral TDF/FTC in African Women

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>CAB LA</th>
<th>TDF/FTC</th>
<th>Hazard Ratio (95% CI) for CAB v TDF/FTC</th>
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</thead>
<tbody>
<tr>
<td>Total Participants Enrolled</td>
<td>3223</td>
<td>1613</td>
<td>1610</td>
<td></td>
</tr>
<tr>
<td>HIV Events</td>
<td>38</td>
<td>4</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>Person-Years</td>
<td>3808</td>
<td>1912</td>
<td>1896</td>
<td>DSMB stopped study</td>
</tr>
<tr>
<td>Incidence Rate</td>
<td>1</td>
<td>0.21</td>
<td>1.79</td>
<td>0.11 (0.04, 0.41)</td>
</tr>
<tr>
<td>95% CI for Incidence rate</td>
<td>[0.71, 1.37]</td>
<td>[0.06, 0.54]</td>
<td>[1.24, 2.51]</td>
<td></td>
</tr>
</tbody>
</table>
CROI 2021 – New HIV Drugs for Treatment and Prevention
Ilatravir (ISL)

4'-ethynyl-2-fluoro-2’-deoxyadenosine; MK-8591; EFdA

DNA chain terminator

Inhibits RT by preventing translocation (RTTI)

Half-life = 50-60 hours in plasma

Potent antiviral activity (PBMC EC50 = 0.2 nM) with broad coverage (HIV-1, HIV-2, MDR strains)

Low-dose and parenteral formulations

Phase 1b: single oral dose

Infrequent dosing for treatment/prevention

Schurmann Lancet HIV 2020;7:e164-e172
ISL -- Prevention

A Phase 2a randomized, double-blind, placebo-controlled, multicenter pharmacokinetic study of monthly ISL for HIV prevention.

Study population: low-risk adults (n=171); 68% women, 71% white.

Study intervention: oral ISL 60 mg, ISL 120 mg, placebo dosed monthly.

Results:
- Interim PK analysis
- Tissue subset PK (rectal, cerv, vag): sustained, adequate distribution
- Generally well-tolerated

Conclusions:
- Target thresholds achieved
- Phase 3 dose: 60 mg monthly

Hillier R4P 2021 abstract #OA4.05LB
Patel CROI 2021 abstract #87
Istratvir (ISL): Next Generation Implant

Study Design: double-blind, placebo-controlled, multi-site

Study Population: HIV-, low-risk adults (8 ISL + 4 placebo/dosing group)

Study intervention: implant

48, 56 mg ISL, subdermal, upper arm, non-dominant side, in place X 12 weeks

Intracellular ISL-TP PK threshold of 0.05 pmol/10^6 cells maintained throughout placement for two highest doses

56 mg implant ISL-TP concentrations comparable to 62 mg from previous study

Half-life after removal of implant similar to half-life of orally dosed ISL (t_{1/2} for 56 mg is ~198 hr)

56 mg implant projected to lead to concentrations above threshold for 52 weeks

Matthews CROI 2021 abstract #88
MK-8507: Investigational NNRTI

- Potent in vitro (IC50 ~50nM)
- Activity in vitro against common NNRTI-resistant variants
- Pharmacokinetics support once-weekly oral dosing

Phase 1 study (N=18)
- HIV+ rx-naïve, VL>10,000, CD4 >200, no NNRTI mutations, no HBV/HCV
- Single doses tested: 40, 80, 600 mg

Results:
- Generally well-tolerated
- 1 pt with F227C (uncommon NNRTI mutation)

Conclusion: Supports weekly combination rx studies
MK-8507: Investigational NNRTI

Viral resistance studies

**MK-8507** IC₅₀ 51 nM against wild-type virus across subtypes
- Additive antiviral activity with other ARV, including ISL
- V106A was primary mutation with subtype B
- V106M was primary mutation with subtypes A and C
- <5 fold ↓ against K103N, K181C, G190A
- Similar to doravirine

Pharmacokinetics
- T₁/₂ ~ 70 hours → weekly dosing
- Modeling supports oral ISL 20 mg + MK-8507 (100, 200 or 400 mg) wkly dosing
  - phase 2b study
HIV Capsid Inhibitor: Lenacapavir (LEN)

LEN (EC50=50 pM)

Capsid disassembly and nuclear transport

Virus production

Capsid assembly

EC50, half maximal effective concentration.
Capsid Inhibitor: Lenacapavir (LEN)

- Potent antiretroviral activity: EC$_{50}$ 140 pM in PBMC
- Active across all tested subtypes
- Resistant variants in vitro have low fitness
- Clearance and solubility → long $1/2$ life: 30-43 days
- Oral and SC formulations
- Phase 1 in HIV- and HIV+ pts
- Max VL ↓ 2.2 log cps/ml at day 10
- New sustained-delivery formulation:
  - Phase 1 in 30 HIV- pts
  - 3 SC doses (10/group)
- Phase 2/3 studies

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**Graphs:**
- Mean LEN Single-Dose Plasma Concentration-Time Profiles
- Clearance and solubility graph
LEN Resistance

LEN has similar activity against all HIV-1 subtypes

*In vitro* resistance arises at 6 amino acids at the LEN binding site to capsid:
- L56I, M66I, Q67H, K70N, K74S/D, T107N

Resistance correlated with low replication capacity (except Q67H)

Pre-existing LEN mutations not found in 1500 HIV clinical isolates

LEN-resistant isolates are susceptible to HIV PIs

LEN has activity against HIV-2 (20X↓ than HIV-1)

Callebaut CROI 2021 abstract #128
CAPELLA: LEN in Heavily Treatment-Experienced Pts

Phase 2/3 randomized, double-blind, placebo-controlled study

Study population: Pts with MDR HIV (resistant to ≥2 drugs and 3 of 4 classes and confirmed VL >400 and ≤2 fully active agents); (randomized n=36; non-randomized

Study treatment:

Randomized cohort (2:1): continue ART + LEN 600mg d1+2, 300 mg d8 (or placebo), the optimized ART regimen + LEN 927 mg IM abdomen d15

Results: 1° endpoint: % with 0.5 log VL ↓: 88% (LEN) vs. 17% (pbo) (p<0.001)

Δ log VL

% VL <50

Generally safe/well-tolerated; 2 developed capsid resistance mutations (M66I)

Conclusion: clinically relevant VL ↓

Segal-Maurer CROI 2021 abstract #127
HIV Maturation Inhibitors (MI)
HIV Maturation Inhibitors

**bevirimat** – phase 2
- ~50% of rx-experienced pts had no response due to gp120 polymorphisms
  McCallister 2008 XVII HIV Drug Resistance Conference

**GSK 3532795/BMS-955176** – phase 2b
- TDF/FTC + ‘795: 76-83% <40 cps/ml
- GI intolerance

**GSK 2838232** – phase 2a
- ‘232 + cobicistat: up to ↓1.7 log cps/ml at 10 days
- need for boosting
  DeJesus CID 2020;71:1255-1262

**GSK 3640254** – phase 1 in HIV-
- once-daily; no drug interactions with TAF/FTC, DTG, or ethinyl estradiol/levonorgestrel
  Pene Dumitrescu Intnatl Workshop on Clin Pharm 2020 #13
GSK 3640254: Proof of Concept

Phase 2a double-blind, randomized, placebo-controlled adaptive study

Study population: Rx-naïve PLWH (N-34)

Study rx: GSK 254 vs. placebo; Part 1 (10 days); Part 2 (7 days)

Results: 1° endpoint – max Δ in VL

Resistance: Part 1 -- 4/6 pts with mutations, 1 with phenotypic resistance

No safety/tolerability concerns

Conclusion: +antiretroviral dose response; supports phase IIb study

Spinner CROI 2021 abstract #
CROI 2021 – HIV and COVID-19
U.S. PLWH and COVID-19 (1)

Retrospective cohort analysis
Adults that underwent SARS-CoV-2 testing after 1/1/20

U.S. National COVID Cohort Collaborative (N3C) – 34 institutions

Results
2.1 million people: 14% COVID-19+; 12% PLWH (→ 12% COVID-19+)

PLWH with COVID-19
- Significantly more likely to be >45 years old, men, treated on an outpatient basis
- Significantly more likely to be Black or Latino and less likely to be White than PLWH without COVID-19

Conclusions
Blacks/Latinos disproportionately affected by COVID-19, including PLWH

HIV+ with COVID
HIV- with COVID
HIV+ w/o COVID

Islam CROI 2021 abstract
S. PLWH and COVID-19 (2)

• Retrospective cohort analysis
  Adults with confirmed SARS-CoV-2 1/20-12/20
  TriNetX – 44 institutions

Results
297194 confirmed COVID-19 cases
1638 (0.6%) were PLWH, >83% on ART, 48% VL <20
  • More commonly younger (p<0.001), men (p<0.001), African American/Latino (p<0.001), cardiovascular disease (p<0.001) and other comorbidities
  • More symptomatic at presentation; more use of healthcare services
  • ↑ odds of hospitalization (OR 1.26, p=0.02)
  • ↑ odds of ICU/mechanical ventilation (2.4% vs. 1.6%, OR 1.32, p=0.003)
  • mortality at 30 days 2.9% vs. 2.3%, p=0.12

Conclusions
PLWH more underlying risk factors, symptom severity, ↑ odds of hospitalization/mechanical ventilation vs. controls
COVID-19 Hospitalizations Among Persons With HIV or Solid Organ Transplant

National COVID Cohort Collaborative

Adults who had COVID-19 (n=509,092)

Primary outcomes

Hospitalization and mechanical ventilation (overall 26%)

Persons with HIV and solid organ transplant recipients

More likely to be hospitalized and require mechanical ventilation during hospitalization

Increased hospitalization risk driven mostly by the high burden of comorbidities in both groups

Adjusted Odds Ratios for Hospitalization or Mechanical Ventilation

<table>
<thead>
<tr>
<th></th>
<th>Hospitalization (95% CI)</th>
<th>Mechanical Ventilation (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV negative/no SOT</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>(reference: n=501,416)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive/no SOT</td>
<td>1.32* (1.22, 1.43)</td>
<td>1.86* (1.74, 2.00)</td>
</tr>
<tr>
<td>(n=2932)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SOT/HIV negative</td>
<td>1.69* (1.58, 1.81)</td>
<td>1.96* (1.74, 2.22)</td>
</tr>
<tr>
<td>(n=4633)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV positive/SOT</td>
<td>1.65† (1.06, 2.56)</td>
<td>3.73* (2.08, 6.67)</td>
</tr>
<tr>
<td>(n=111)</td>
<td></td>
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</tr>
</tbody>
</table>

Adjusted for demographics, study site, and comorbidities (severe liver disease, diabetes, cancer, kidney disease, and total comorbidities [0, 1, 2, ≥3]).

SOT: solid organ transplant.

*P<0.01 and †P<0.05.

COVID-19 positive: RT-PCR (>99%) or antigen positive (<1%).
CROI 2021 – COVID-19 Treatment
COVID-19 Treatment: Antivirals
Life Cycle of SARS-CoV-2

1. Attachment
2. Fusion + Endocytosis
3. Transcription
4. Uncoating
5. Assembly
6. Release

Inhibitors:
- Fusion inhibitors
- Protease inhibitors
- Polymerase inhibitors
- Nuclear export inhibitors

Molnupiravir

• Oral direct-acting antiviral inhibitor of replication of SARS CoV-2: cytosine analogue → introduces mutations → viral error catastrophe

• In vitro assay: not mutagenic or genotoxic in mammals

• Phase 2a randomized trial in patients with symptomatic SARS CoV-2 infection (confirmed within 4 days of enrollment)

Molnupiravir or placebo twice daily

• Results: N=202 treated participants with evaluable swabs; 78 (45)% with positive baseline culture

Figure 1. Proportion of overall participants with positive culture by RT-PCR (for participants positive at baseline)
COVID-19 Treatment: Antibodies

Abraham Nature Reviews Immunology 2020;20:401-403
Title: Convalescent Plasma (CP) for COVID-19

Retrospective cohorts suggested benefit

Expanded Access Program (hospitalized COVID-19)

  transfusion reactions <1%; 7-day mortality 13%

Randomized controlled clinical trials:

Agarwal BMJ (epub 10/22/20) (N=464; India): no Δ in severe disease/mortality

Simonovich NEJM (epub 12/24/20) (N=344, Argentina): no clinical benefit

Libster NEJM (epub 1/6/21) (N=160 ≥65 yo, mild disease; Argentina):
  48% ↓ in severe respiratory disease

RECOVERY (Horby MedRxiv 3/10/21) (N=11,558; UK): no Δ in clinical/survival

Jordans (CROI 2021 abstract #124) (N=87 severe disease; Netherlands): no Δ in clinical/survival; 79% of participants had potent neutralizing Ab at baseline with comparable titers to CP – stopped for futility
AZE-1: BAM + ETE for Outpatient Rx of COVID

Phase 3, randomized, double-blind, placebo-controlled study

**Study population:** ≥12 years old + 1 risk factor for severe COVID-19 (including age >65 and comorbidities) with mild-moderate COVID-19 within 3 days of symptoms (N=1035)

**Study treatment:** [bamlanivimab 2800 mg + etesevimab 2800 mg] or placebo – single IV infusion

**Primary endpoint:** COVID-related hospitalization or any-cause death by day 29

**Secondary endpoints:** change in viral load, symptom resolution
The Panel **recommends** the use of bamlanivimab 700 mg plus etesevimab 1,400 mg for the treatment of outpatients with mild to moderate COVID-19 who are at high risk of clinical progression as defined by the EUA criteria (BIIa).

Treatment should be started as soon as possible after the patient has received a positive result on a SARS-CoV-2 antigen or nucleic acid amplification test and within 10 days of symptom onset.

Laboratory studies suggest that BAM and ETE have activity against the SARS-CoV-2 B.1.1.7 variant but have markedly reduced activity against the B.1.351 variant. Ongoing **population-based genomic surveillance** of the types and frequencies of circulating SARS-CoV-2 variants will be important in defining the utility of bamlanivimab plus etesevimab in the future.

The Panel **recommends against** the use of BAM+ ETE for patients who are hospitalized because of COVID-19, except in a clinical trial.
### Table 3: Pseudovirus Neutralization Data for SARS-CoV-2 Variant Substitutions with Bamlanivimab and Etesevimab Together (1:2 Molar Ratio)

<table>
<thead>
<tr>
<th>Lineage with Spike Protein Substitution</th>
<th>Key Substitutions Tested&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Fold Reduction in Susceptibility&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>B.1.1.7 (UK origin)</td>
<td>N501Y</td>
<td>no change&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>B.1.351 (South Africa origin)</td>
<td>K417N + E484K + N501Y</td>
<td>&gt;45&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>P.1 (Brazil origin)</td>
<td>K417T + E484K + N501Y</td>
<td>&gt;511&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>B.1.427/B.1.429 (California origin)</td>
<td>L452R</td>
<td>7.4</td>
</tr>
<tr>
<td>B.1.526 (New York origin)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>E484K</td>
<td>17</td>
</tr>
</tbody>
</table>

<sup>a</sup> For variants with more than one substitution of concern, only the one(s) with the greatest impact on activity is(are) listed.

<sup>b</sup> No change: <5-fold reduction in susceptibility.

<sup>c</sup> No activity observed at the highest concentration tested. Bamlanivimab and etesevimab together are unlikely to be active against variants from this lineage.

<sup>d</sup> Not all isolates of the New York lineage harbor the E484K substitution (as of February 2021).

It is not known how pseudovirus data correlate with clinical outcomes. Given the similarities between the substitutions in B.1.351 and P.1, it is unlikely that bamlanivimab and etesevimab together will be active against these variants.

FDA EUA Fact Sheet
COVID-19 Prevention: Antibodies

Abraham Nature Reviews Immunology 2020;20:401-403
Monoclonal Antibodies for Prevention: Bamlanivimab (BLAZE-2)

Phase 3 trial: bamlanivimab (4200 mg) vs. placebo

Staff and residents in long-term care facilities with ≥1 confirmed case of SARS-CoV-2 ≤7 days prior to randomization

N=966 SARS-CoV-2 negative at baseline: 299 residents, 667 staff

Results (by day 57):
- 80%↓ sx COVID (residents)
- 5 COVID-related deaths (all in placebo group)
- Adverse events “well-balanced”

OR 0.20, CI 0.08, 0.49, P<0.001
Casirivimab/Imdevimab (C/I) for Prevention

Ongoing phase 3 trial in household contacts of SARS-CoV-2

Study Rx: Participants randomized to C/I (1200 mg, sc) or placebo

Interim analysis (n=409 evaluable individuals)

Results

Infection

Symptomatic: 8/223 placebo vs. 0/186 C/I (OR 0.00; 95% CI 0.0, 0.69 -- “100% prevention”)

Symptomatic + asymptomatic infection: 23/223 placebo vs. 10/186 C/I (48%; OR 0.49 95% CI 0.20, 1.12)

Clinical: total symptomatic weeks 21 (placebo) vs. 0 (C/I)

Virologic

Placebo group on average had >100-fold ↑ peak viral load vs. C/I

Viral shedding:

• ~40% lasted 3-4 weeks (placebo) vs. < 1 week (C/I)

Virus level >10,000 copies/mL: 13/21 (62%) placebo vs. 0/9 (0%) CI

O’Brien CROI 2021 abstract #123
<table>
<thead>
<tr>
<th>Form</th>
<th>Developer</th>
<th>Phase 1/2</th>
<th>Phase 2/3</th>
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<tbody>
<tr>
<td>mRNA</td>
<td>Moderna</td>
<td>Enrolled</td>
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<td>Protein subunit</td>
<td>Novavax</td>
<td>Enrolled</td>
<td>Enrolled</td>
</tr>
<tr>
<td></td>
<td>GSK Sanofi</td>
<td>Ongoing</td>
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</tbody>
</table>
## COVID-19 Vaccines: Phase 3 Results

### TOP-LINE ANALYSIS

(FDA EUA Briefing Document 2/26/21)

<table>
<thead>
<tr>
<th>Vaccine (reference)</th>
<th>Sample size</th>
<th># of new COVID-19 infections at 14 days</th>
<th>Efficacy</th>
<th># of severe COVID-19 infections</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=39,321</td>
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<td></td>
<td>561 total</td>
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<td></td>
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<td>348 placebo</td>
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<td>116 vaccine</td>
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<td>67%</td>
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<td></td>
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<td>↓ hospitalizations + death</td>
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<td>65%</td>
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<td></td>
<td></td>
<td>↓ non-fatal serious adverse events (0.4% in each)</td>
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<td></td>
<td>52%</td>
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<td></td>
<td></td>
<td>1 hypersensitivity reaction (non-anaphylaxis) in vaccine group</td>
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<td></td>
<td>No adverse events leading to study d/c</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No study-related deaths</td>
<td></td>
</tr>
</tbody>
</table>

*generally well tolerated; injection site pain 49%, HA 39%, fatigue 38%, myalgia 33% predominantly mild-moderate, > in <59 years old; most resolved in 1-2 days*

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Additional notes:

- **N=39,321**
- **41%** Latin America
- **47%** U.S.
- **13%** South Africa
- **44%** women; **17%** Black, **45%** Latino, **62%** White
- **40%** comorbidities
- **561** total:
  - **348** placebo
  - **116** vaccine
- **67%** efficacy
  - **74%** US, **65%** Latin America, **52%** S. Africa
  - **85%** ↓ hospitalizations + death
- **60** non-fatal serious adverse events (0.4% in each)
- **1** hypersensitivity reaction (non-anaphylaxis) in vaccine group
- **No adverse events leading to study d/c**
- **No study-related deaths**
Thanks to:
Weill Cornell Division of ID
Weill Cornell Department of Medicine
Charlie Flexner + Raj Gandhi for slides
rgulick@med.cornell.edu
Thank You for Your Attendance!

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