21ª edición
POSTCROI
Una actualización de la "31st Conference on Retroviruses and Opportunistic Infections"

# 21ª Post-CROI 2024

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ScienHub

# COVID-19 e Infecciones Oportunistas en el CROI 2024


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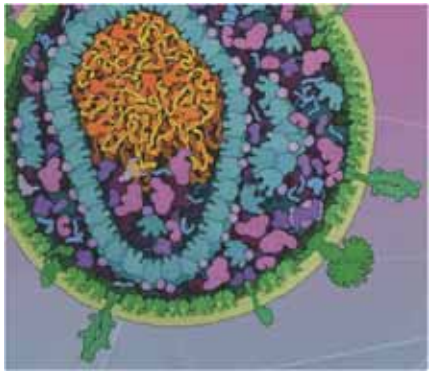
# Potential conflict of interest

**Dr. José M Miró has received honoraria for speaking or participating in Advisory Boards and/or research grants from the following Pharmaceutical Companies:**

**Abbvie**
**Angelini-Allergan**
**Bristol-Myers Squibb**
**Contrafect**
**Genentech**
**Gilead Sciencies**
**Jansen**
**Merck**
**Medtronic**
**Novartis**
**Pfizer**
**Roche**
**Theravance**
**ViiV Healthcare**

CROI 2024
Conference on Retroviruses and Opportunistic Infections
March 3-6 | Denver, Colorado

# COVID-19 & OIs Abstracts at CROI



## Statistics for Abstracts

| | |
|---|---|
| General Abstracts Submitted | 1682 |
| General Abstracts Accepted | 966 |
| Late-Breaking Abstracts Submitted | 220 |
| Late-Breaking Abstracts Accepted | 101 |
| Total Abstracts Accepted | 1067 |
| Ora Abstract Presentations | 111 |
| Themes Discussion Presentations | 54 |
| Poster Presentations | 956 |

## Accepted Abstracts for Emerging Infections or Specific Populations

| | |
|---|---|
| SARS-CoV-2 | 193 |
| Mpox | 33 |
| Adolescents | 137 |
| Men who have sex with men (MSM) | 220 |
| People Who Inject Drugs (PWID) | 84 |
| Transgender Men or Women | 84 |
| Women or girls | 259 |
| **Cryptococcal meningitis + Other mycosis** | **8** |


# COVID-19 & Opportunistic Infections (OIs) at CROI 2024

- **COVID-19 Clinical Pearls**
- COVID-19 Therapeutics
- Long COVID-19
- COVID-19 vaccination
- Cryptococcal meningitis
- Other mycosis

March 14th 2024

# Some Clinical Pearls

- COVID-19 Breakthrough Infections Among People With and Without HIV
- COVID-19 Breakthrough Infections between Natural Infection *vs.* Post-vaccination
- SARS-CoV-2 shedding in immunocompromised
- In-hospital mortality and SARS-CoV-2 Variants

# COVID-19 Breakthrough Infections Among People With and Without HIV

- This study aims to characterize and compare **breakthrough COVID-19 infections** (e.g., prevalence and disease severity) **between PWH and a propensity score matched (PSM) group of people without HIV (PWoH) and examine whether different immunity levels of PWH play a role in COVID-19 vaccine effectiveness.**
- Among a total of 2,144,415 participants, **8,335 were PWH** and 2,136,080 were PWoH before PSM.
- **No significant differences of severity of breakthrough infections** were observed between PWH and PWoH. After PSM, **HIV status was not associated with breakthrough infection in either the crude or adjusted models**. However, in the subgroup of individuals without any booster dose, PWH were more likely to experience a breakthrough infection than PWoH (aHR: 1.19; 95%CI: 1.03-1.39).

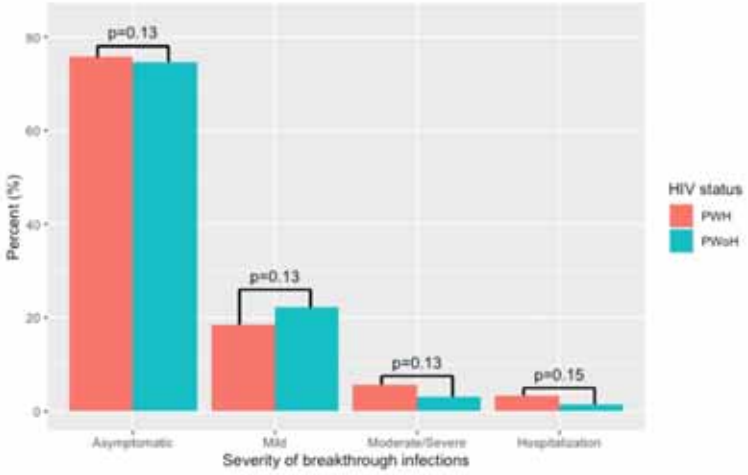



Figure 1 Severity of breakthrough infections between PWH and PWoH

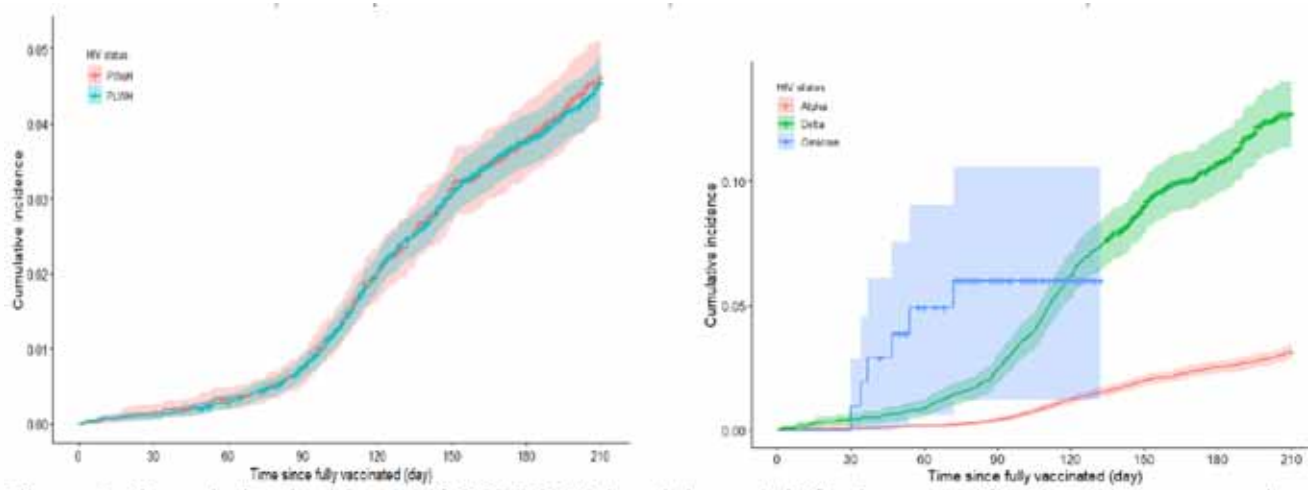



Figure 2 Cumulative incidence of COVID-19 breakthrough infections stratified by HIV status and different variants of concerns

- **This study do not support a broad conclusion that COVID-19 vaccine effectiveness is lower among PWH**, while **we did find that PWH had a higher risk of breakthrough infection** compared to PWoH if they did not receive a booster dose.

Yang X et al. CROI 2024, Denver, CO March 2-6 2024; P#397.

# COVID-19 Breakthrough Infections in Natural Infection *vs.* Vaccination

- Our aim was to determine the **incidence rate and rate of severe/critical COVID-19 disease among those with breakthrough infection after full vaccination compared with reinfection among unvaccinated persons**.
- Individuals with a first confirmed infection >14 days after 2 doses of Pfizer or Moderna vaccine were **matched 1:1 to individuals** with a second confirmed infection in unvaccinated individuals >14 days after the first infection.
- **Severe/critical disease, defined as hospitalization or death within 28 days of the index test positive date**.

## Results: Incidence of breakthrough infection or reinfection

| | Incidence rate/1000 person-days (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | N | Breakthrough infection among vaccinated | P-value (within group) | N | Reinfection among unvaccinated | P-value (within group) | P-value (with group) |
| **Overall** | 1,560 | 0.30 (0.29,0.32) | | 2,560 | 0.31 (0.30,0.32) | | 0.52 |

## Results: Incidence of hospitalization or death within 28 days

| | Incidence rate/1000 person-days (95% CI) | | | | | | |
|---|---|---|---|---|---|---|---|
| | N (Total 1,560) | After breakthrough infection among vaccinated | P-value (within group) | N (Total 2,560) | After reinfection among unvaccinated | P-value (within group) | P-value (with group) |
| **Overall** | 184 (11.8%) | 4.69 (4.06,5.42) | | 443 (17.3%) | 7.31 (6.66,8.03) | | <.0001 |

Butt AA et al. CROI 2024, Denver, CO March 2-6 2024; O#132.

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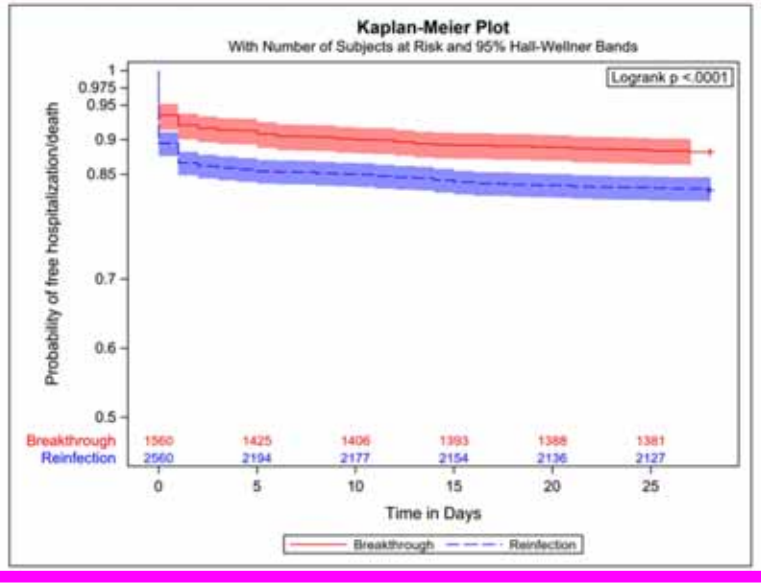
- **Severe/critical disease, defined as hospitalization or death within 28 days of the index test positive date**.

## Results: Probability of remaining free of hosp. or death




- Vaccinated, previously uninfected individuals and unvaccinated previously infected individuals have **similar level of protection against further infection**
- However, **the incidence of hospitalization/death is nearly twice as high after reinfection in the unvaccinated individuals** compared with breakthrough infection after vaccination

Butt AA et al. CROI 2024, Denver, CO March 2-6 2024; O#132.

# SARS-CoV-2 viral clearance and evolution varies by type and severity of immunodeficiency

- Despite vaccination and antiviral therapies, **immunocompromised individuals are at risk for prolonged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection**, but the immune defects that predispose an individual to persistent coronavirus disease 2019 (COVID-19) remain incompletely understood.
- The aim of this study was to perform a detailed viro-immunologic analyses of a prospective cohort of participants with COVID-19 from 5/2021 to 2/2023.

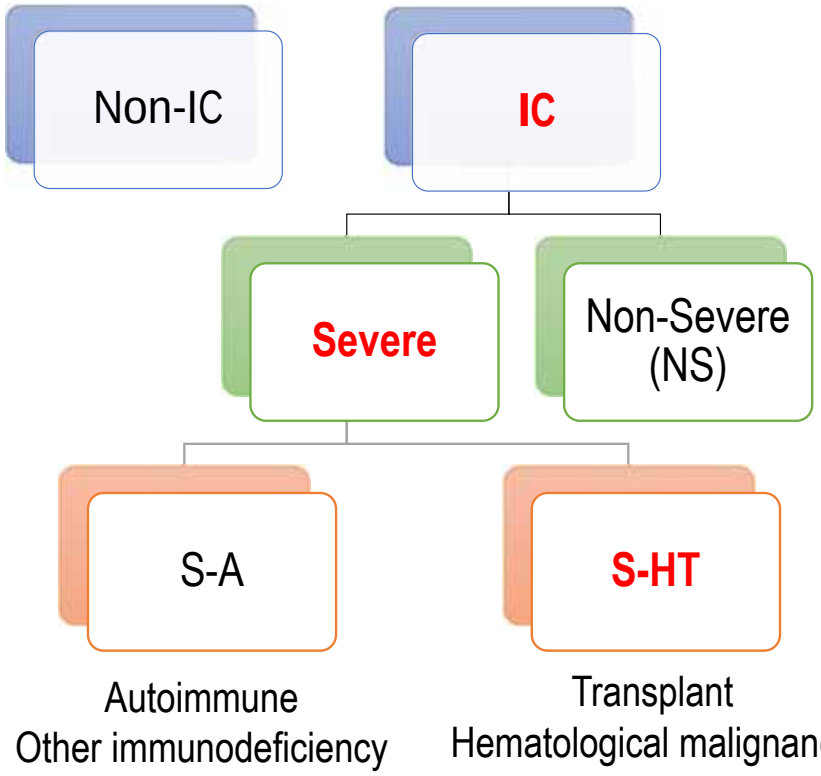
## Methods

- Self-collected anterior nasal swab: Collected 3x/week for first 2 weeks and then weekly until negative. Subgroup of participants consented to blood draws.
- Quantitative SARS-CoV-2 viral load
- SARS-CoV-2 viral culture: Vero-E6 cell-based culture system
- Sequencing: spike gene
- Neutralization: Pseudovirus assay (Half-maximal inhibitory concentration, IC50)
- Binding antibody assay: binding antibody to Nucleocapsid T cell function: overlapping spike peptide pools.
- Effector: ELISpot assay
- Proliferation: CFSE or CellTrace Far Red (CTFR) proliferation assays

Li Y et al. Sci Transl Med. Jan 24 2024;16(731):eadk1599; and, CROI 2024, Denver, CO March 2-6 2024; O#134.

# SARS-CoV-2 viral clearance and evolution varies by type and severity of immunodeficiency

## Definition of immunocompromise (IC)

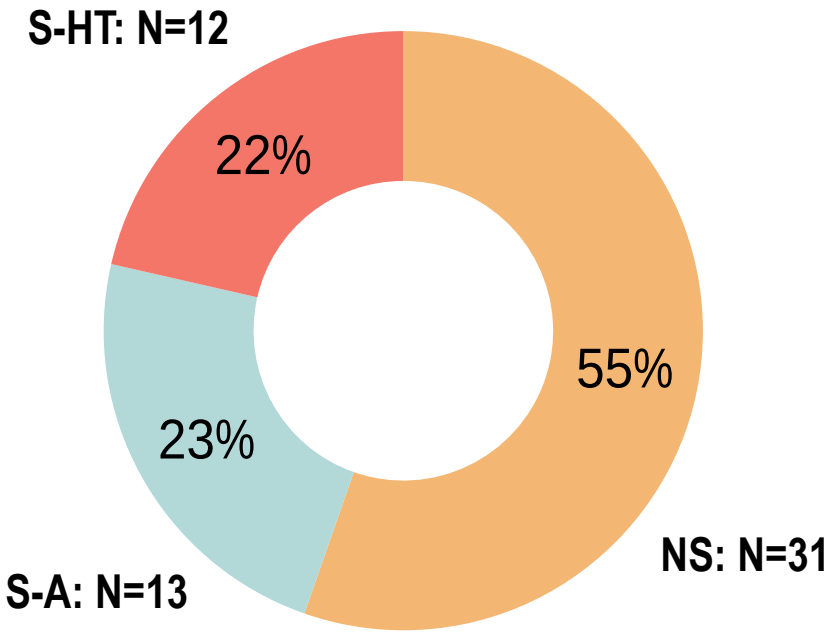



| | |
|---|---|
| **NS** | • Autoimmune diseases, receiving immunosuppressants (not targeting B/plasma)<br>• Solid malignant tumor<br>• Corticosteroid use (~Prednisone >20mg/d for ≥14 consecutive days within 30 days before entry)<br>• HIV (CD4 cell count <200 cells/$mm^3$ ) |
| **S-A** | • Autoimmune diseases on B cell/plasma cell targeted therapy<br>• Congenital or late onset B cell deficiency |
| **S-HT** | • Solid organ transplant (SOT)<br>• Hematopoietic stem cell transplant<br>• Lymphoma, leukemia<br>• Immune-Related Adverse Event on multiple immunosuppressants targeting different pathways |

Li Y et al. Sci Transl Med. Jan 24 2024;16(731):eadk1599; and, CROI 2024, Denver, CO March 2-6 2024; O#134.

# SARS-CoV-2 viral clearance and evolution varies by type and severity of immunodeficiency

| Demographics | IC (N=56) | Non-IC (N=184) |
|---|---|---|
| Sex, n (%) | | |
| Female | 32 (57) | 126 (69) |
| Male | 24 (43) | 58 (32) |
| Age | 55 (45, 67) | 46 (33, 59) |
| **Number of vaccinations** | **3 (3-4)** | **3 (2-3)** |
| mAb, n (%) | 24 (43) | 10 (5) |
| Antiviral, n (%) | 39 (70) | 57 (31) |
| Symptom duration | 5 (4, 7) | 4 (3, 6) |

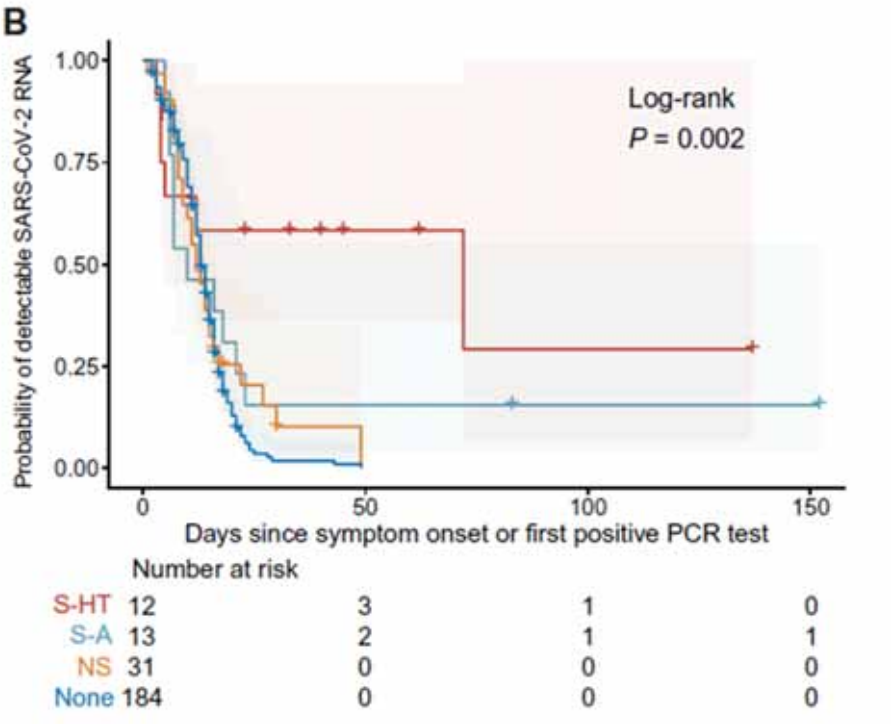



For continuous variables, median and first-third quartiles are shown
mAb: choices of SARS-CoV-2 targeting mAb per treating clinicians, active against contemporary variants

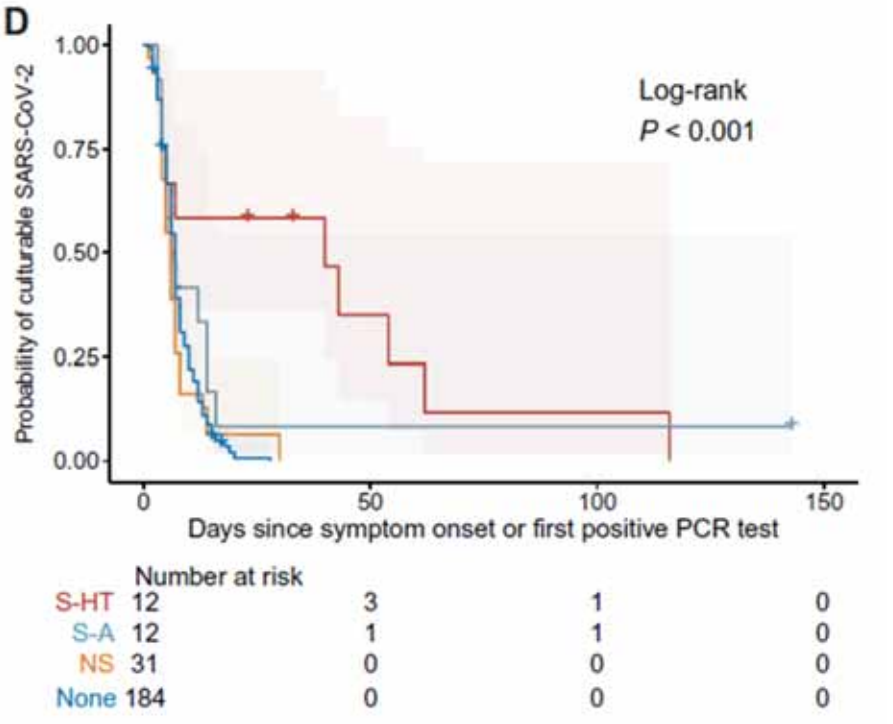
Li Y et al. Sci Transl Med. Jan 24 2024;16(731):eadk1599; and, CROI 2024, Denver, CO March 2-6 2024; O#134.

# Individuals with hematologic malignancy or transplant had prolonged SARS-CoV-2 viral shedding (median 40 days)

**Upper respiratory RNA viral clearance**

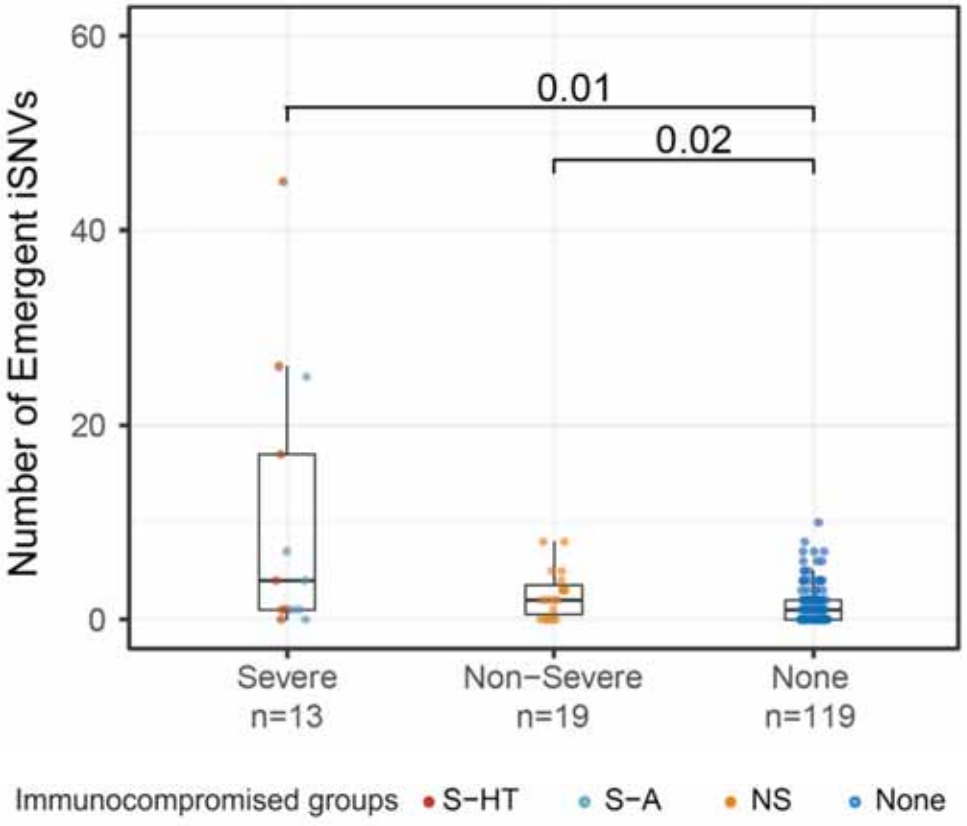


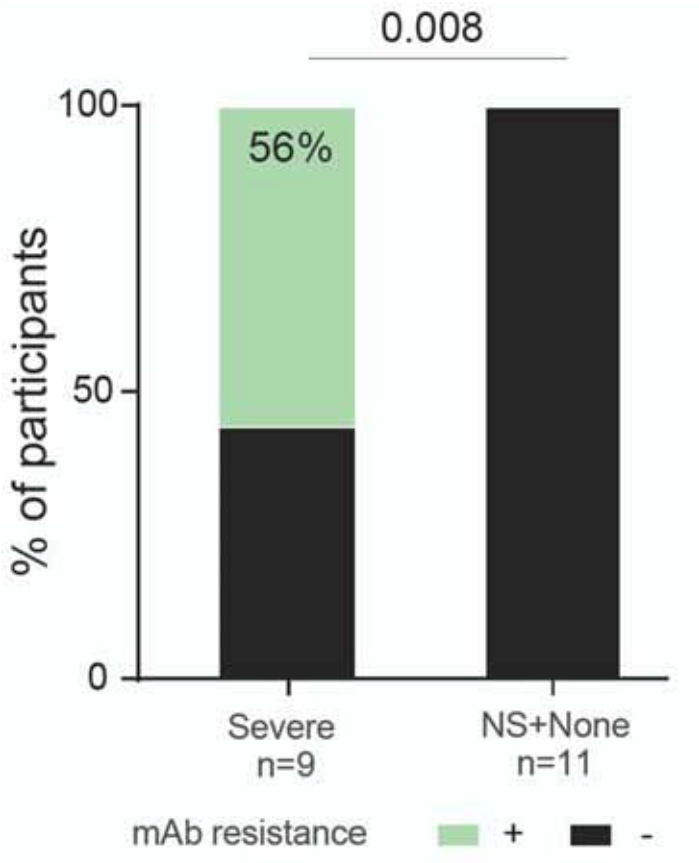

**Upper respiratory culturable viral clearance**




Li Y et al. Sci Transl Med. Jan 24 2024;16(731):eadk1599; and, CROI 2024, Denver, CO March 2-6 2024; O#134.

# Severe immunocompromise is associated with emerging SARS-CoV-2 antiviral polymorphisms and mAb resistance

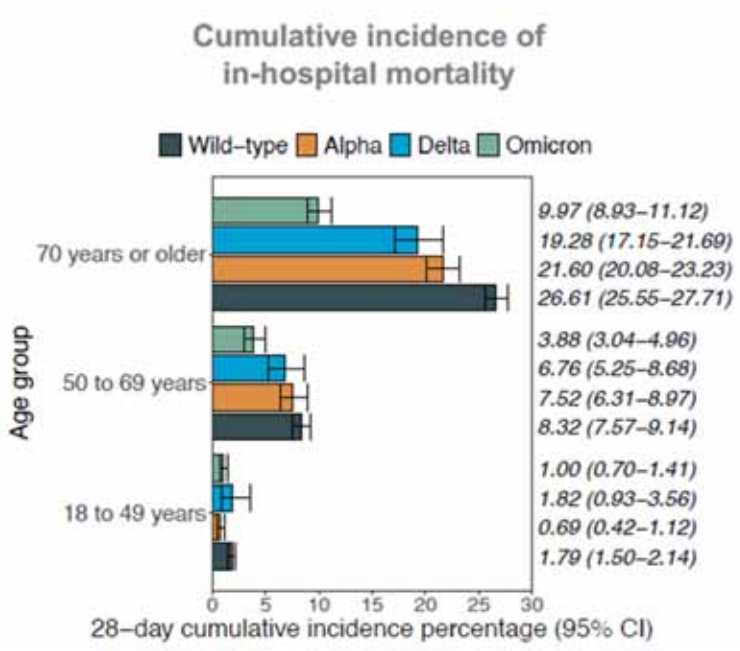


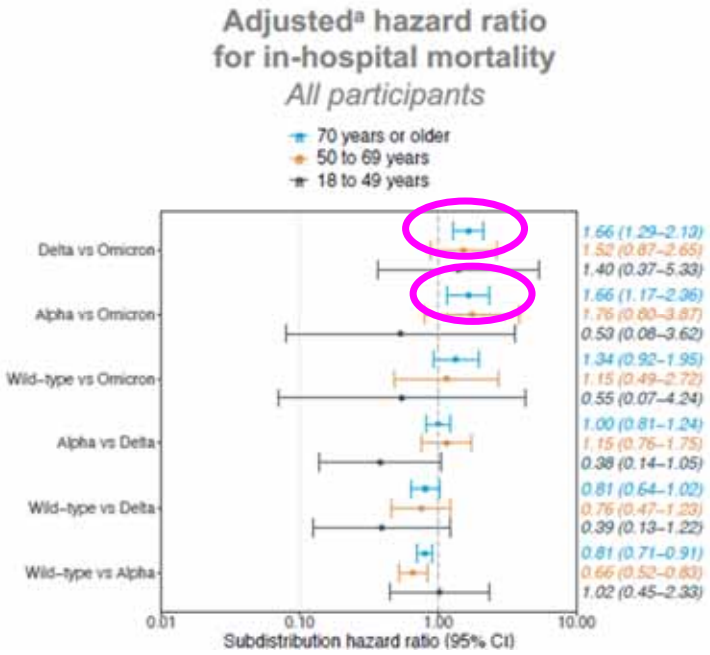



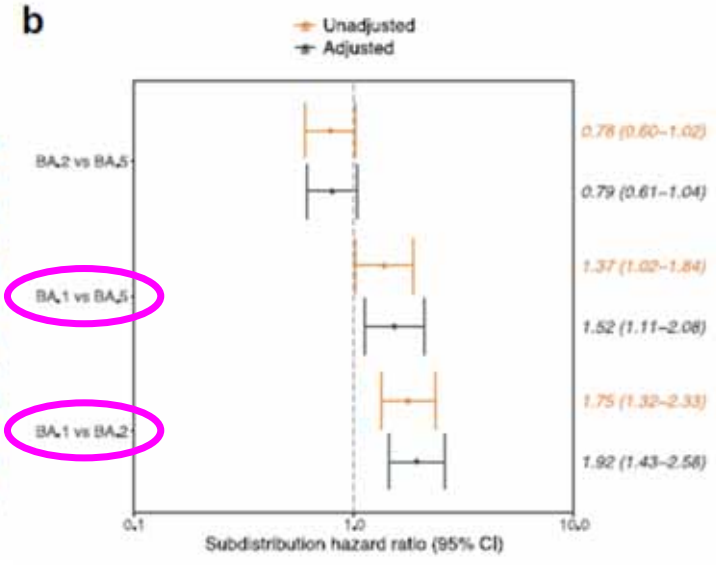

Li Y et al. Sci Transl Med. Jan 24 2024;16(731):eadk1599; and, CROI 2024, Denver, CO March 2-6 2024; O#134.

# In-hospital mortality and SARS-CoV-2 Variants

- We compared **28-day in-hospital mortality** in adults hospitalized with COVID-19 caused by **Wild-type, Alpha, Delta, or Omicron variants**.
- **EuCARE Multinational cohort study** included adult patients hospitalized with COVID-19 10 centers in 9 countries: Germany, Italy, Kenya, Lithuania, Mexico, Poland, Portugal, Sweden, and United Kingdom from **February 2020 to October 2022**.




- Cumulative incidence of **28-day in-hospital mortality decreased** throughout the study period, particularly during the **Omicron period**.
- **Among participants >70 years**, **Alpha and Delta had an increased risk of in-hospital mortality** vs. Omicron. **Omicron BA.1 carried a higher risk of death** vs. BA.2 and BA.5 variants. **Viral evolution shows that the virus has lost pathogenicity and the clinical forms are less severe**.

Hedberg P et al. The Lancet Regional Health - Europe. Feb 2 2024; 38:100855, and CROI 2024, Denver, CO March 2-6 2024; P#863.


# COVID-19 & Opportunistic Infections (OIs) at CROI 2024

- COVID-19 Clinical Pearls
- **COVID-19 Therapeutics**
- Long COVID-19
- COVID-19 vaccination
- Cryptococcal meningitis
- Other mycosis

March 14th 2024

# New Antivirals against SARS-CoV-2

## RNA-dependent RNA polymerase (RdRp) inhibitors

### Chain terminators

- Remdesivir, IV
- Mindeudesivir, oral
- Obeldesvir, oral

### RNA mutagenesis (G/A and C/U)*

- MolnupiravIr, oral

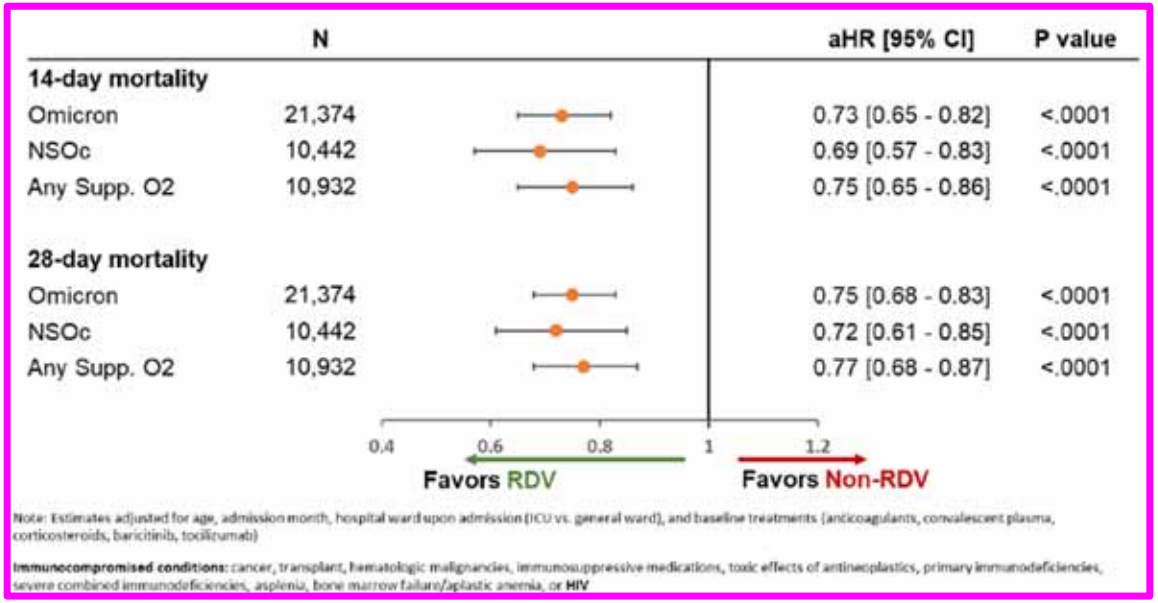
## 3Cl Protease inhibidors

- Nirmatrelvir/ritonavir
- Ensitrelvir
- Simnotrelvir/ritonavir

*Kabinger F et al. Nat Struct Mol Biol. 2021; 28:740-746.

# Remdesivir Reduces Mortality in Immunocompromised Patients Hospitalized for COVID-19 During Omicron

- The objective of this study was to compare **inpatient all-cause mortality** in patients who were administered **Remdesivir (RDV) in the first two days of hospitalization** vs. those not administered RDV during **Omicron predominant era** (Dec 2021–Apr 2023)
- After applying inclusion/exclusion criteria, 26,770 patients were included in the analysis: **15,257 patients were treated with RDV** in the first two days of hospitalization and **11,513 patients were not treated with RDV**.
- **Comorbidities**: Obesity (26%), COPD (40%), Cardiovascular disease (88%), Diabetes mellitus (38%), Renal disease (32%), and **Cancer (42%).**
- **Primary End Points**: **14-day and 28-day all-cause inpatient mortality** (defined as a discharge status of "expired" or "hospice").

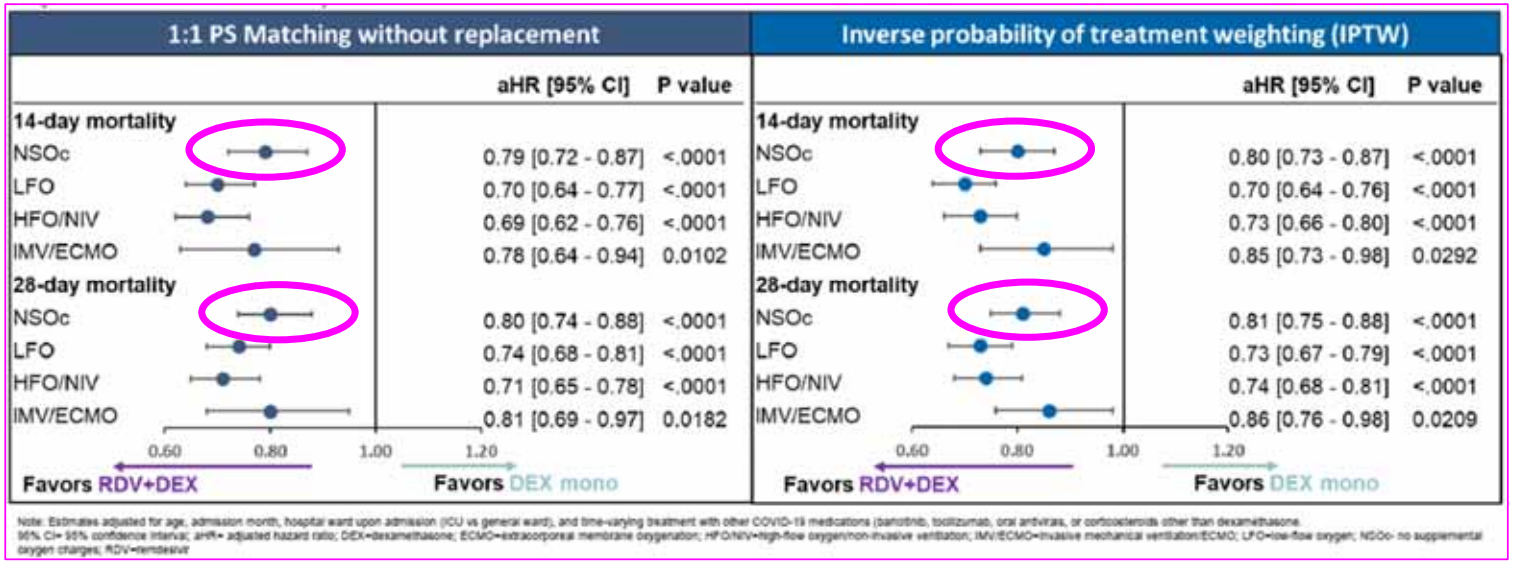



- **Remdesivir Reduces Mortality in Immunocompromised Patients** Hospitalized for COVID-19 During Omicron

Mozaffari E. et al. CROI 2024, Denver, CO March 2-6 2024; P#664.

# Remdesivir + Dexamethasone vs. Dexamethasone for the Treatment of non-Severe Hospitalized COVID-19: Real-world Study in the USA

- **NIH and WHO treatment guidelines recommend against the use of dexamethasone for COVID-19 patients who do not require supplemental oxygen.**
- The objective of this study was to assess the effectiveness of **Remdesivir (RDV) plus Dexamethasone (DEX)** compared to **DEX monotherapy** given in the **first 2 days of admission in 280,114 patients hospitalized for COVID-19** during the Omicron period using a large real-world data base in the United States.
- **44% of patients did not need supplemental oxygen charges (NSOC)**.
- **Primary End Points**: **14-day and 28-day all-cause inpatient mortality**.

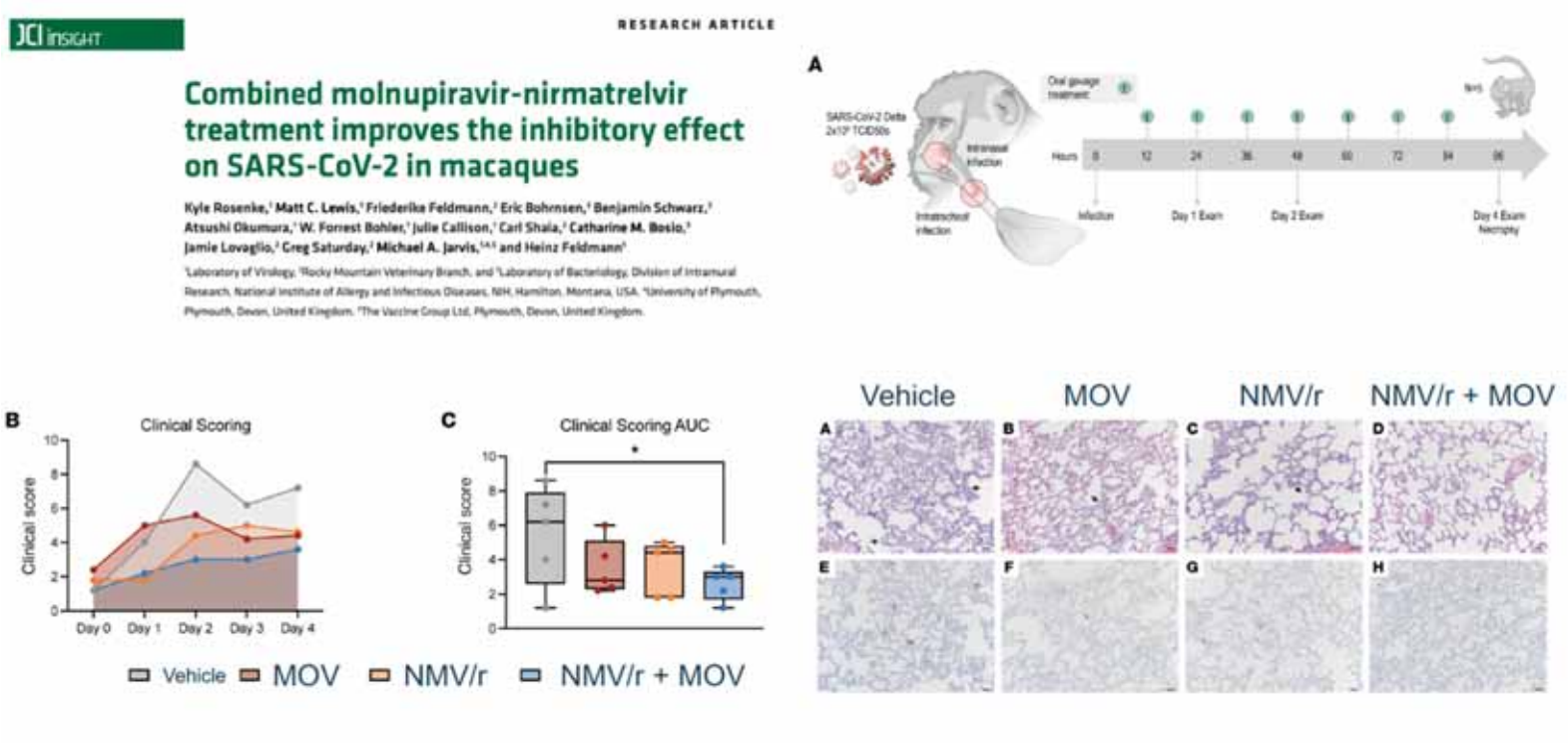



- The effectiveness of **RDV+DEX in reducing mortality compared to DEX monotherapy was confirmed across all levels of baseline supplemental oxygen requirements** through PS matching and IPTW methods.

Mozaffari E. et al. CROI 2024, Denver, CO March 2-6 2024; P#665.

# Molnupiravir Does Not Increase 3CLpro Resistance Mutations When Co-Administered With Nirmatrelvir/ritonavir

- In a previous study, **we compared the antiviral effect of MOV or NMV/r alone, or the co-administration of both in a SARS-CoV-2 macaque model**.
- **We showed an additive effect of the two antivirals on several markers of disease**.



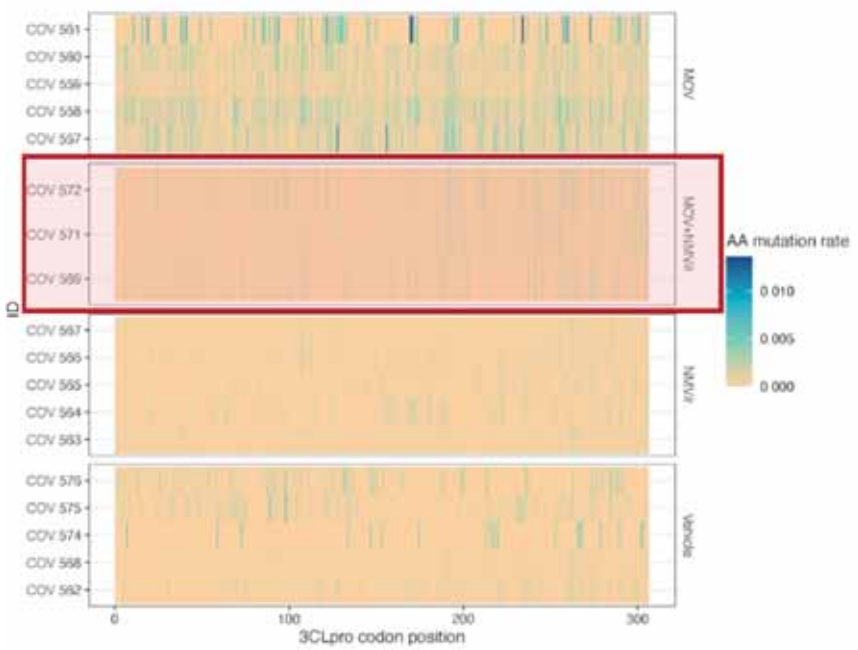

- In this follow-up study, **we investigated the mutation profiles of SARS-CoV-2 in samples collected in the animal model study**.

Rosenke K et al. JCI Insight. 2023 Feb 22; 8:e166485; Zhou S et al. CROI 2024, Denver, CO March 2-6 2024; O#136.

# Molnupiravir Does Not Increase 3CLpro Resistance Mutations When Co-Administered With Nirmatrelvir/ritonavir

- In this study **we investigated the mutation profiles of SARS-CoV-2 in samples collected in the animal model study**.

**No Mutation Hot Spot on 3CLpro**




**MOV increased NMR resistance mutations due to C-to-U mutation, but these mutations were NOT further enriched in dual therapy through further selection**

| | | C>U | C>U | | | | C>U | C>U | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Mutation** | | **T21I** | **L50F** | **E166A** | **E166V** | **L167F** | **A173V** | **P252L** | **T304I** | **Group** |
| *$EC_{50}$ value fold-change* | | *1.1-4.6* | *1.5-4.2* | *3.3* | *25-288* | *ND* | *0.9-1.7* | *2.9* | *1.4-5.5* | |
| *COV 557* | | 4.6 | 18.6 | | | | 14.7 | | | |
| *COV 558* | | 8.2 | 9.9 | | | 1.1 | 21.6 | 4.6 | | |
| *COV 559* | | | 14.0 | | | | 12.0 | 12.0 | | MOV |
| *COV 560* | | 9.9 | 6.0 | | | | 14.7 | 7.4 | | |
| *COV 561* | | | | | | | 34.0 | | | |
| *COV 563* | | 3.8 | 2.6 | | | | 2.5 | 0.8 | | |
| *COV 564* | | 10.3 | | | | | | 7.3 | | |
| *COV 565* | | | | | 2.4 | | 2.4 | | | NMV/r |
| *COV 566* | | 2.0 | 7.9 | | 1.2 | | 4.8 | 3.6 | | |
| *COV 567* | | 2.8 | 3.5 | 0.5 | | 0.5 | 2.1 | 0.5 | | |
| *COV 569* | | | 11.6 | | | | 8.3 | | | |
| *COV 571* | | | | | | | 2.0 | | | MOV+NMV/r |
| *COV 572* | | 6.7 | 3.3 | | | | 2.4 | 4.9 | | |
| *COV 562* | | | 6.7 | | | | 4.5 | | | |
| *COV 568* | | 3.1 | 0.5 | | | | | 1.3 | | |
| *COV 574* | | | | | | | | | | Vehicle |
| *COV 575* | | | | | | | | | | |
| *COV 576* | | | 8.5 | | | | | | | |

Highlighted mutations: FDR-adjusted p value < 0.05

- **NMV/r reduces MOV-induced mutagenicity of SARS-CoV-2 when co-administered**.
- **MOV does not increase 3CLpro resistance mutations** (against NMV/r) when co-administrated.

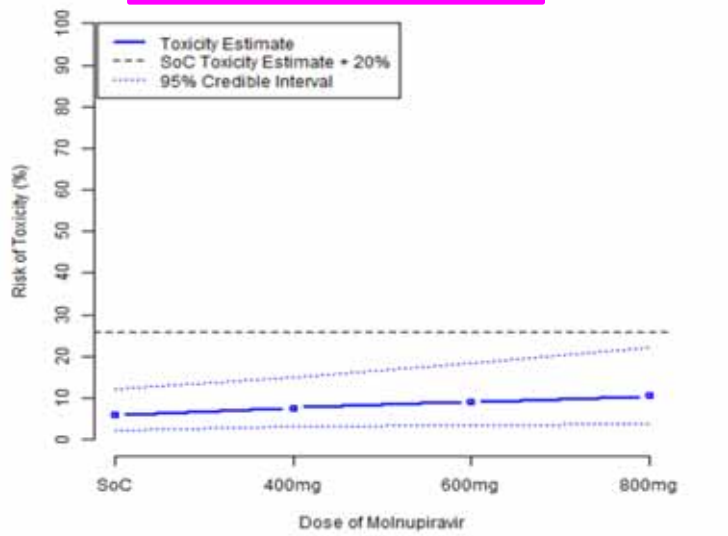
→ **Supports the use of combination therapy**

Zhou S et al. CROI 2024, Denver, CO March 2-6 2024; O#136.

# AGILE CST-8 Phase I Trial of Combined Nirmatrelvir/r and Molnupiravir for Mild-Moderate COVID-19

- AGILE-CST-8 is a **phase I, adaptive, dose de-escalation study of combination nirmatrelvir/ritonavir plus molnupiravir**
- Multicenter, open-label, randomized, dose de-escalation Bayesian adaptive design.
- Adults (≥18years) with a positive lateral flow test, **within 5 days of mild to moderate symptoms of COVID-19 were randomized (2:1, cohorts of 6) to drug combination or standard of care (SoC).** Participants were randomized to receive NMVr (300mg/100mg bd) plus MOL (800mg bd) orally or SoC for 5 days.
- The **primary endpoint was dose-limiting toxicities (DLT**; **AEs ≥ grade 3** [CTCAE v5]) up to day 11.

**Dose-toxicity Model (D11)**




| Table 1 Overall toxicity summary | Combination (n=16) | SoC (n=8) |
|---|---|---|
| **Number with at least one AE – n (%)** | **14 (87.5%)** | **5 (62.5%)** |
| Blood and lymphatic system | 1 (6.3%) | 0 (0.0%) |
| Cardiac | 1 (6.3%) | 0 (0.0%) |
| | | 0 (0.0%) |
| | | 1 (12.5%) |
| Ge | | 0 (0.0%) |
| | | 1 (12.5%) |
| | | 1 (12.5%) |
| | | 0 (0.0%) |
| | | 0 (0.0%) |
| | | 0 (0.0%) |
| | | 1 (12.5%) |
| Reproductive system and breast disorders | 1 (6.3%) | 0 (0.0%) |
| Respiratory, thoracic and mediastinal disorders | 2 (12.5%) | 3 (37.5%) |
| Skin and subcutaneous tissue disorders | 1 (6.3%) | 0 (0.0%) |
| Vascular disorders | 1 (6.3%) | 0 (0.0%) |
| Unclassified (altered taste, dry mouth, brain fog, loose stools, headache) | 4 (25.0%) | 1 (12.5%) |

**No DLTs or AE of grade 3 or above were observed through D29**

- This first report of **the combination nirmatrelvir/ritonavir with molnupiravir confirms safety and tolerability** at full doses in adults.
- The recommended **Phase II dose is nirmatrelvir/ritonavir 300mg/100mg bd plus molnupiravir (800mg bd) for 5 days.**
- The clinical and virological benefit of this combination should be tested in larger Phase II studies.

Khoo S et al. CROI 2024, Denver, CO March 2-6 2024; P#668.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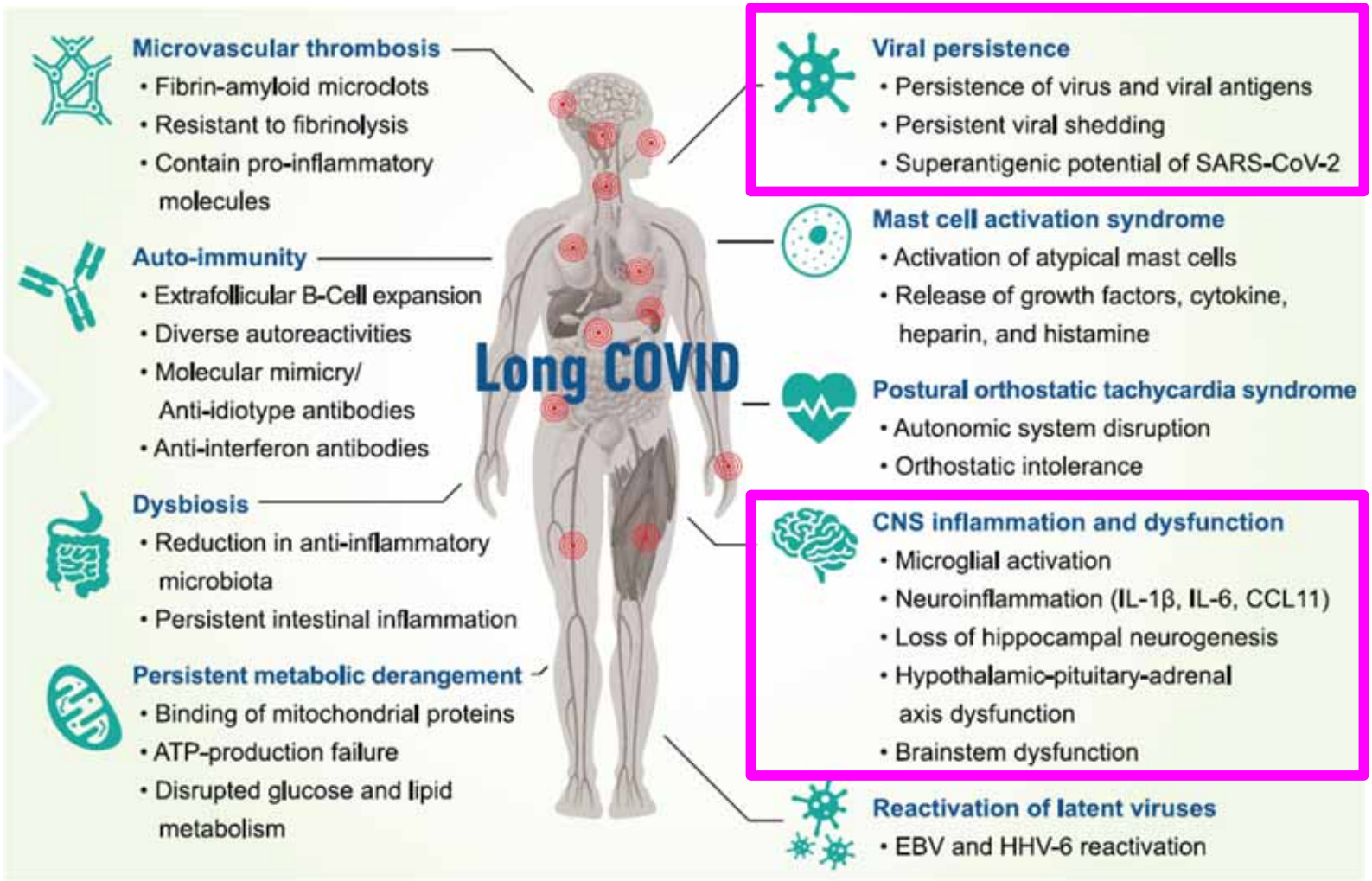
March 14th 2024

# Potential biological mechanisms for development of Long COVID

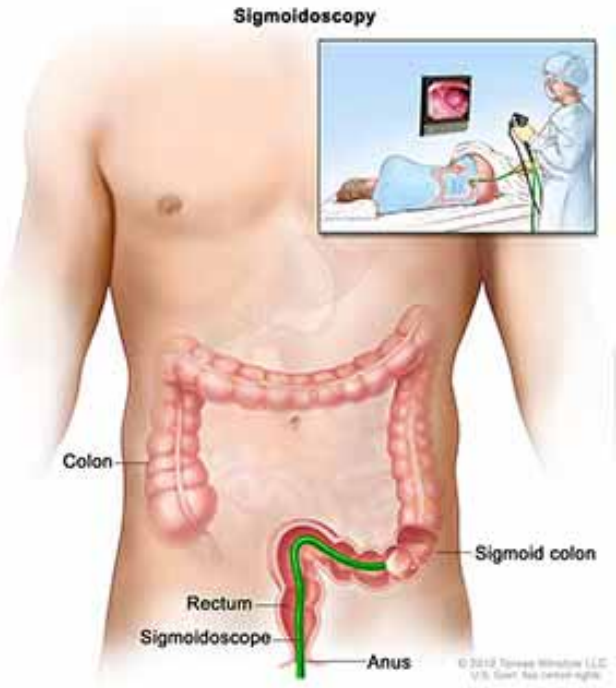



**Poster Sessions**
**B4; C4; E3; E4; M1**

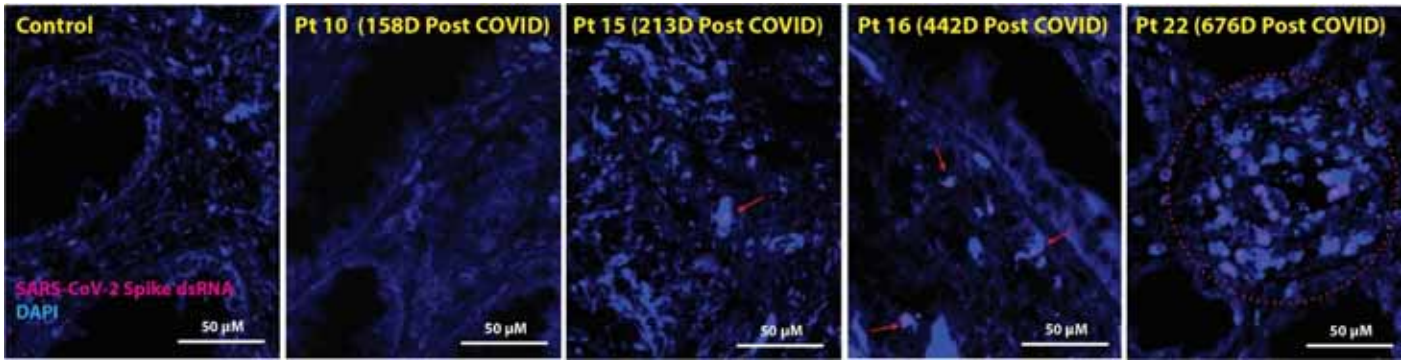
Perumal R et al. iScience. 2023 Jun 16;26(6):106935; Antar A. CROI 2024, Denver, CO March 2-6 2024; O#137.

# Antigen Persistence in the Post-acute Phase of SARS-CoV-2 Infection

- We assessed **viral persistence assessing SARS-CoV-2 spike RNA** *in situ* **in rectal tissue** obtained via flexible sigmoidoscopy in 5 immunocompetent individuals between 90 and 676 days post-COVID (without reinfection), with H&E and immunohistochemical visualization of CD3 and CD68 to localize viral RNA signals within tissue regions and immune cell types.




## Spike RNA on Gut Biopsy Up to 2 Years Post-COVID



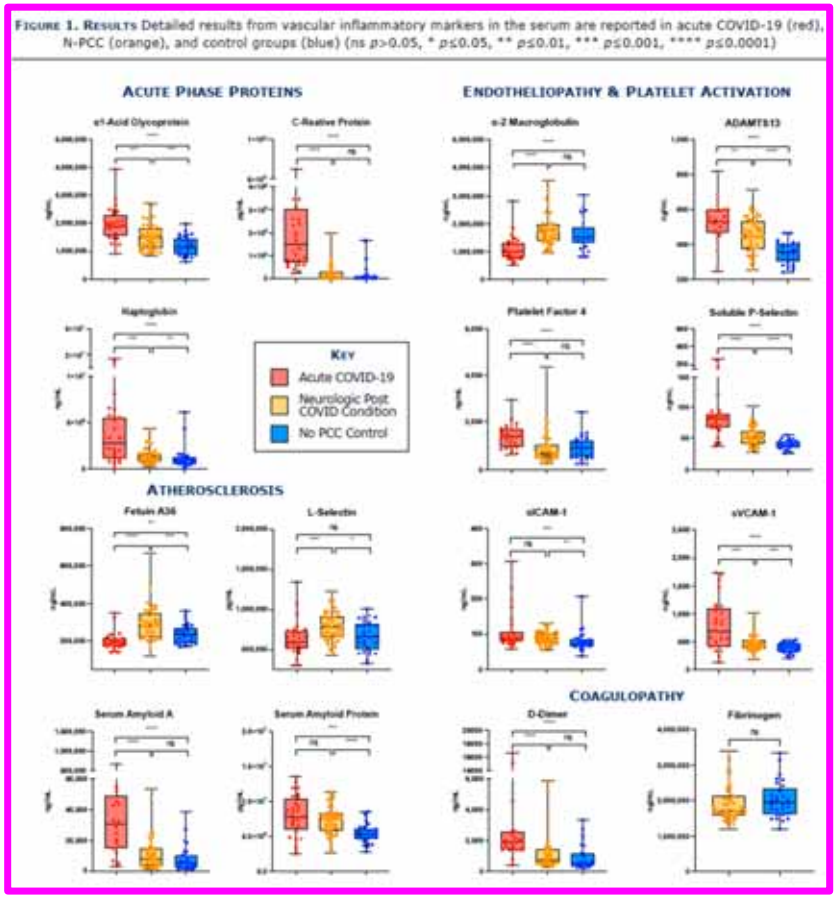

Sense and antisense probes. In situ hybridization of double-stranded RNA in rectosigmoid tissue. Should only be made during active viral life cycling and progression through replication

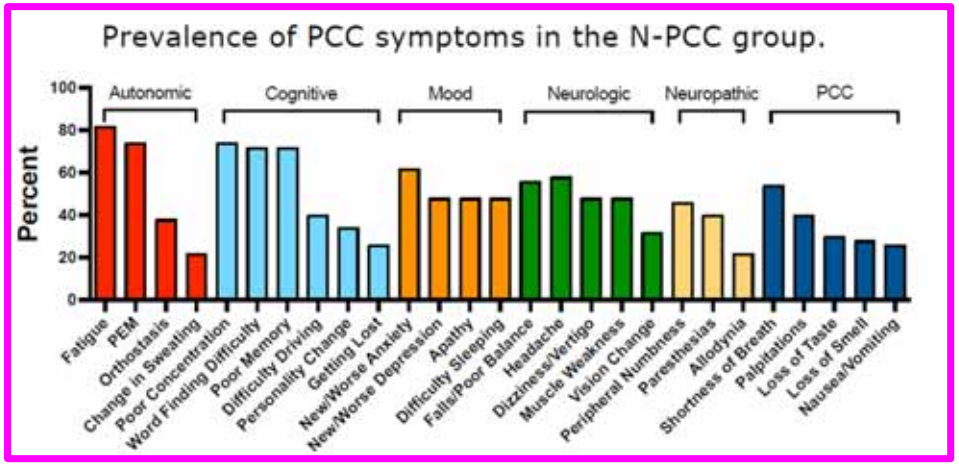
- Our findings provide strong evidence that **SARS-CoV-2 antigens can persist beyond the period of acute illness during several months**.
- Work to determine if persistent antigen contributes to post-acute sequelae such as Long COVID is needed.

Peluso M et al. CROI 2024, Denver, CO March 2-6 2024; O#138.

# Vascular Inflammation in Neuropsychiatric Post-Acute Sequelae of COVID-19 (N-PCC)

- It is unknown if vascular inflammation persists in individuals with **neuropsychiatric Post-COVID-19 Conditions** (N-PCC).
- We investigated for **vascular inflammation in plasma samples** in 3 groups of patients: **acute COVID-19 (N=28)**, **N-PCC (N=50)**, and **post-COVID-19 controls with no PCC (N=29)**.




- In individuals with **neuropsychiatric Post-COVID-19 Conditions (N-PCC)**, we report persistent **elevation of markers related to leukocyte adhesion to the endothelium, endothelial dysfunction, vascular calcification, and vascular remodeling**.
- There is **no evidence of an ongoing coagulopathy**.
- Further studies will **longitudinally investigate endothelial adhesion and dysfunction** in individuals with N-PCC.

McAlpine L et al. et al. CROI 2024, Denver, CO March 2-6 2024; O#568.

# Long COVID Between People With and Without HIV in USA (I)

- We aim to evaluate the effect of HIV on **Post-COVID Conditions (PCC) incidence** among **PWH compared with people without HIV (PWoH)** within Kaiser Permanente Mid-Atlantic States (KPMAS), an integrated closed healthcare system with high ascertainment of member COVID-19 testing, between 2020-2022.

**Matched cohort demographics and relative risk estimate**

| Variables | | PWH n(%); N=749 | PWOH n(%); N=2,236 |
|---|---|---|---|
| Matching Ratio | 1:3; 1:2; 1:1 (n only) | 740; 7; 2 | 2,220; 14; 2 |
| Sex | Female; Male | 270 (36.1%); 479 (64.0%) | 804 (36.0%); 1,432 (64.0%) |
| Vaccine Status at Index Date | Vaccinated | 296 (39.5%) | 882 (39.4%) |
| Race/Ethnicity | Non-Hispanic Black | 600 (80.11%) | 1,794 (80.23%) |
| | Hispanic | 67 (8.95%) | 201 (8.99%) |
| Age at Index [Median years (IQR)] | | 47.7 (27.4, 68.0) | 47.4 (27.4, 67.4) |
| Variant Time Periods | Alpha (1/1/2020-12/31/2020) | 262 (35.0%) | 782 (35.0%) |
| | Delta (1/1/2021-10/1/2021) | 170 (22.7%) | 505 (22.6%) |
| | Omicron (10/2/2021-1/31/2022) | 317 (42.3%) | 949 (42.4%) |
| Outcome | Met Incident PCC Criteria | 166 (22.2%) | 416 (18.6%) |
| Relative Risk of PCC PWH to PWoH | | 1.19 [1.01,1.40] | |

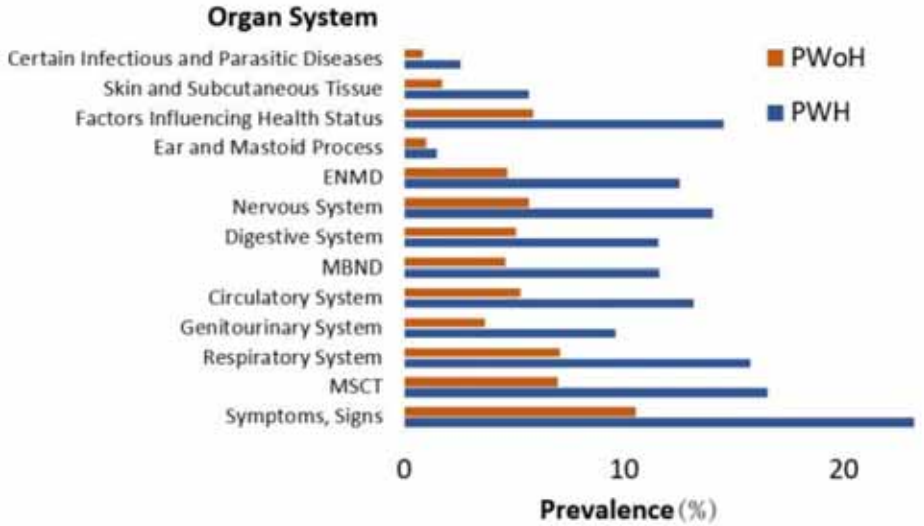
- Risk of incident **Post-COVID Conditions is 19% higher among PWH** compared to people without HIV of similar age, race, sex, and vaccination status prior to COVID

Horberg MA et al. CROI 2024, Denver, CO March 2-6 2024; O#844.

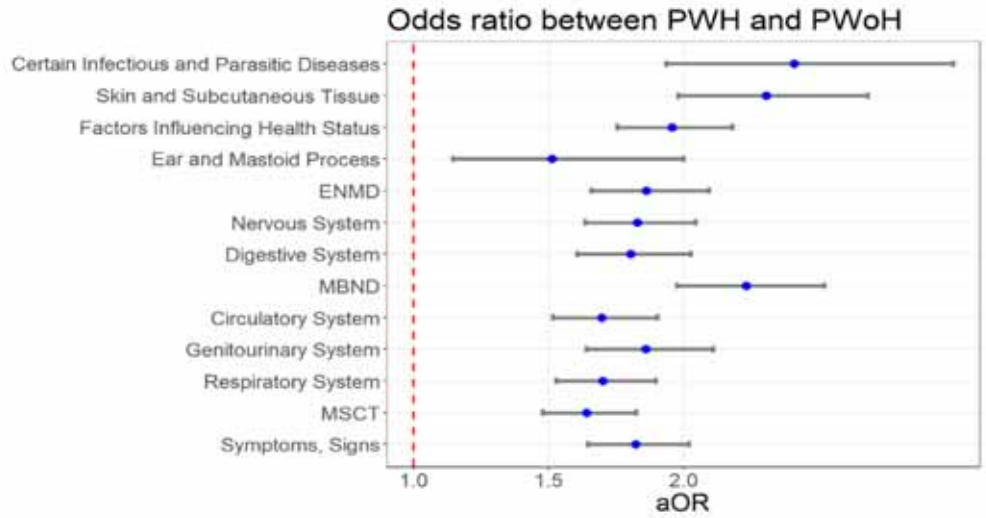
# Long COVID Between People With and Without HIV in USA (II)

- This **study** aims to characterize and compare the risks of a panel of **post-acute sequelae of COVID-19 (PASC) between PWH in South Carolina, USA during 2020-20222**.
- Among 1,351,489 COVID-19 positive individuals, **3,485 were PWH and 1,348,004 were PWoH**. The **prevalence of any long COVID condition was 59% and 34% for PWH and non-PWH, respectively.** The top manifestations of long COVID are similar between PWH and PWoH, yet PWH had a persistently higher prevalence of PASC by organ system than PWoH.

**Comparison of the prevalence of long COVID by organ system between PWH and PWoH**




**Estimated odds ratio for Long COVID sequelae by organ system between PWH and PWoH**



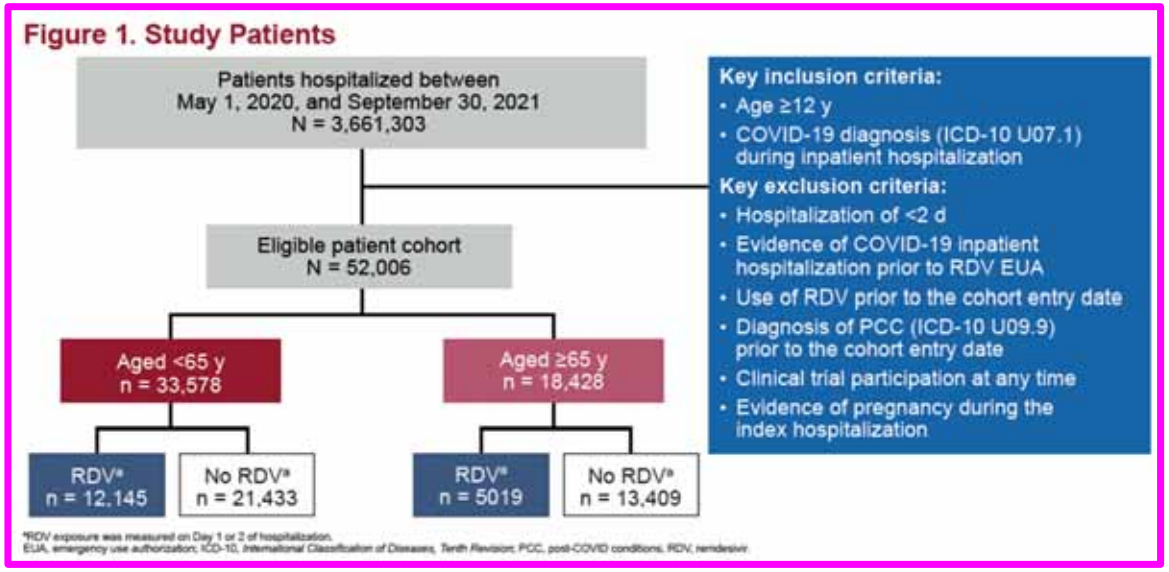

Note: "ENMD": Endocrine, Nutritional and Metabolic Diseases; "MBND": Mental, Behavioral and Neurodevelopmental Disorders; "MSCT": Musculoskeletal System and Connective Issue; "Symptoms, signs": Symptoms, Signs and Abnormal Clinical and Laboratory Findings, Not Elsewhere Classified.

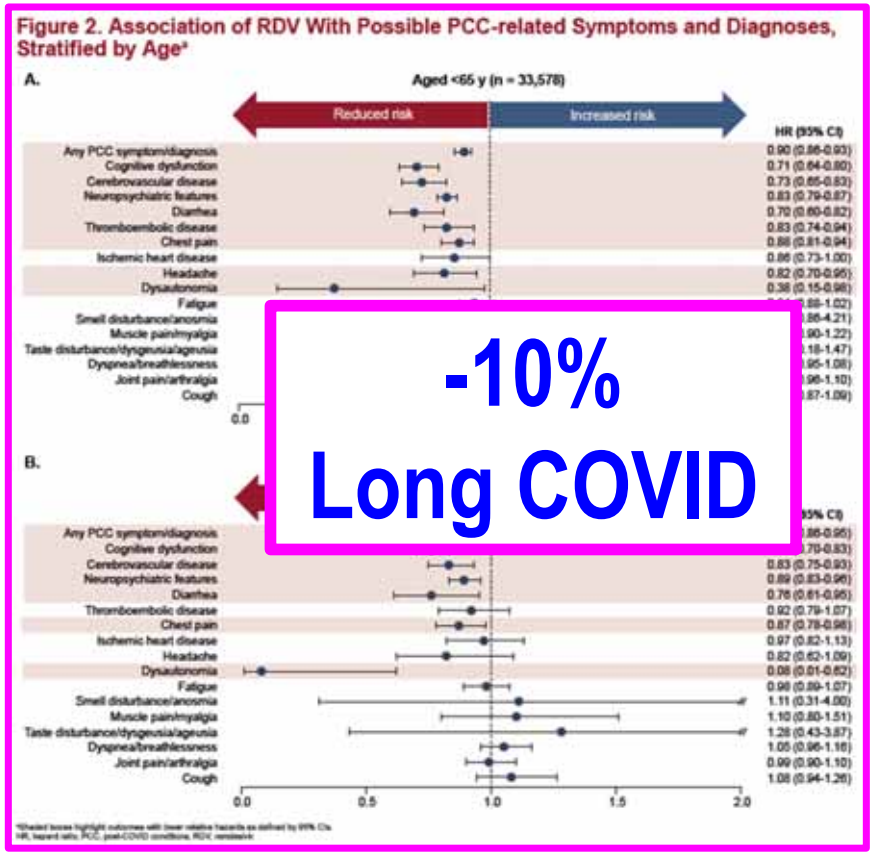
- Despite similar common long COVID manifestations, **PWH appeared to have a higher prevalence and risk of a variety of long COVID outcomes**, particularly for **Circulatory Disease and Mental and Behavioral Disorders/conditions.**

Yang X et al. CROI 2024, Denver, CO March 2-6 2024; O#848.

# Remdesivir reduced 10% Long COVID in Hospitalized Patients in USA

- To assess the effect of **RDV treatment during acute COVID-19 illness on the incidence of PCC-related symptoms and diagnoses in patients aged <65 and ≥65 years hospitalized with COVID-19 in the United States.**




- **Remdesivir treatment** during the first 2 days of hospitalization (vs no RDV treatment during the first 2 days of hospitalization) was associated with **lower relative hazards for any PCC symptom/diagnosis in patients aged <65 years** (HR, 0.90 [0.86-0.93] **and in patients aged ≥65 years** (HR, 0.90 [0.86-0.95])

Berry M et al. CROI 2024, Denver, CO March 2-6 2024; O#657.


# COVID-19 & Opportunistic Infections (OIs) at CROI 2024

- COVID-19 Clinical Pearls
- COVID-19 Therapeutics
- Long COVID-19
- **COVID-19 vaccination**
- Cryptococcal meningitis
- Other mycosis
- and nothing more!

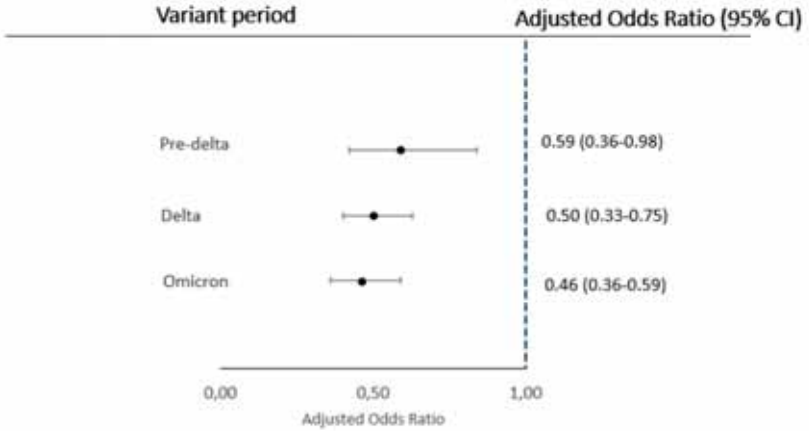
March 14th 2024

# Vaccine Effectiveness Against COVID In-Hospital Mortality by HIV Status Across SARS-CoV-2 Variants

- We assessed the **impact of COVID-19 vaccine in reducing in-hospital mortality among PLHIV relative to HIV negative population** during the different **SARS-CoV-2 variant waves**.
- We analyzed individual-level data from the WHO Global Clinic Platform comprising **159,82 patients hospitalized with information on COVID-19 vaccine** from 43 countries. **This included 10,147 (6.4%) data on PLHIV**. **Most cases came from South Africa.**

https://www.who.int/teams/health-care-readiness/covid-19/data-platform

## Impact of vaccination on in-hospital mortality among PLHIV across pre-delta, delta and omicron variant periods




Vaccinated PLHIV had a 40-64% reduction in in-hospital deaths compared to the unvaccinated across the three variant waves

Inzaule S et al. CROI 2024, Denver, CO March 2-6 2024; O#199.

# Vaccine Effectiveness Against COVID In-Hospital Mortality by HIV Status Across SARS-CoV-2 Variants

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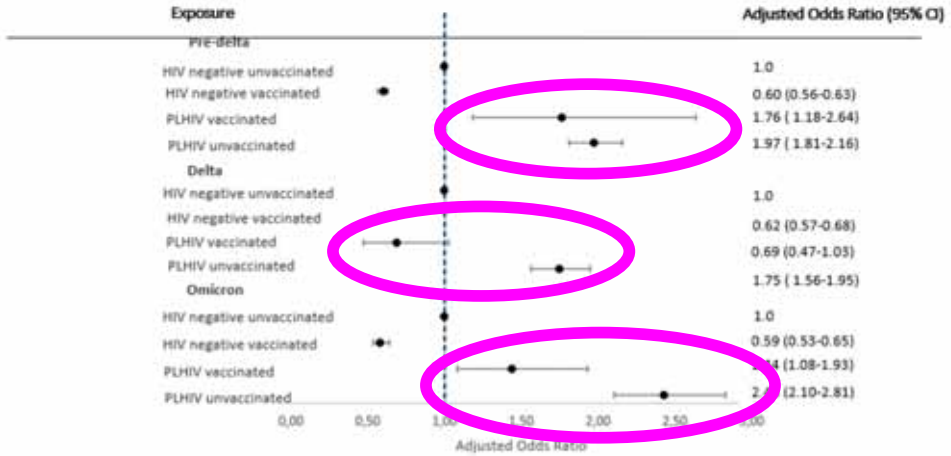
## Impact of vaccination on in-hospital mortality by HIV status across pre-delta, delta and omicron variant periods




Compared to the unvaccinated HIV negative group, vaccinated HIV negative persons had 38-41% reduction in in-hospital deaths across the variant waves but mortality risk remained higher among PLHIV especially in the unvaccinated

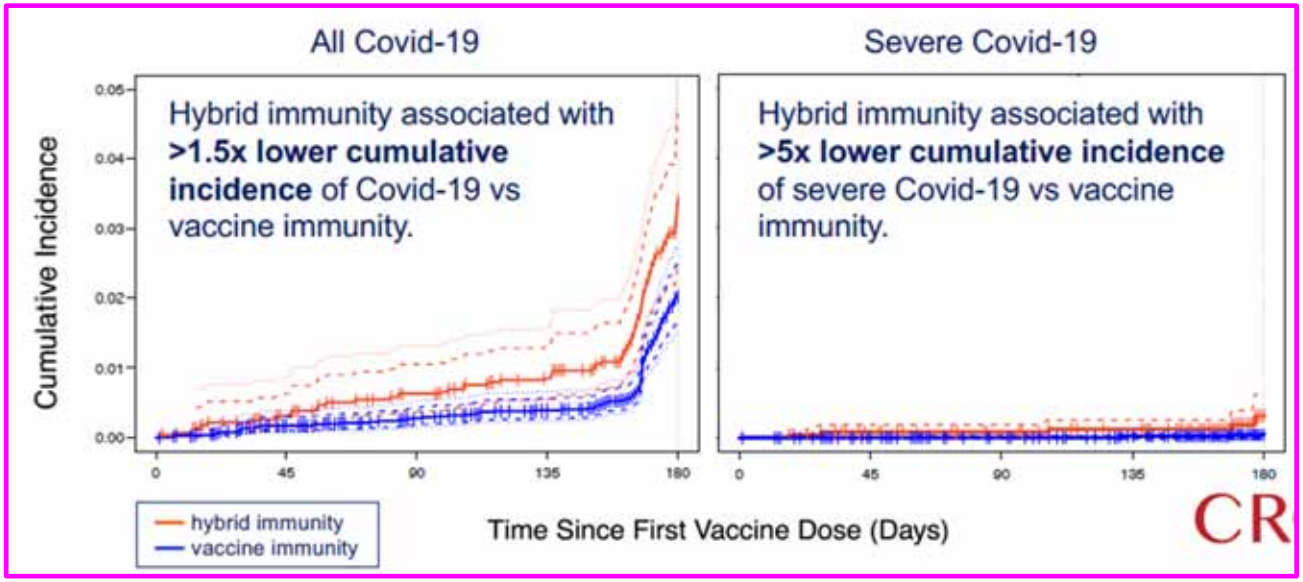
*Mortality rates during pre-delta, delta and omicron variants*
Unvaccinated HIV neg-20%, 19%, 8.4%
Vaccinated HIV neg-16%, 15%, 8.2%
unvaccinated PLHIV-30%, 25%, 19%
Vaccinated PLHIV -21%, 18%, 15%

- Overall COVID-19 vaccination was associated with **40-64% reduction in risk of death among hospitalized PLHIV compared to the unvaccinated** across the different SARS-CoV-2 variant waves. However, **mortality was higher than that of the vaccinated HIV-negative population**.

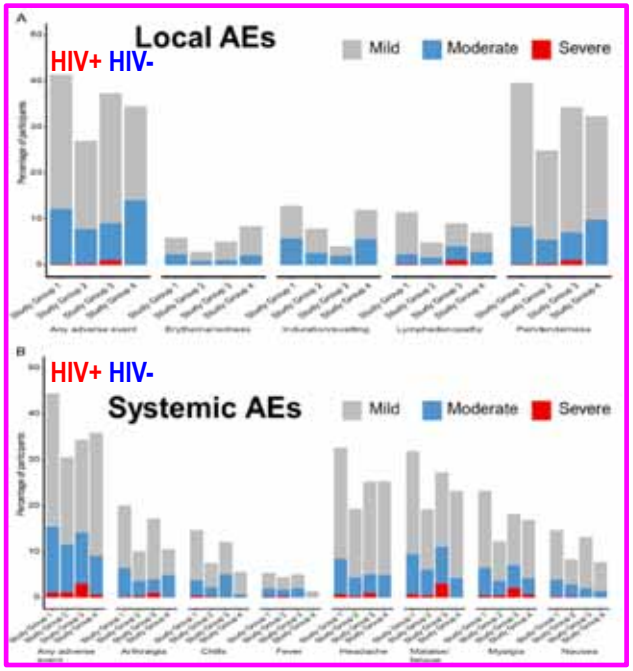
Inzaule S et al. CROI 2024, Denver, CO March 2-6 2024; O#199.

# Efficacy and Safety Outcomes in a Trial of COVID-19 mRNA Vaccine Among People With HIV (PLHIV) in Sub-Saharan Africa

- The CoVPN 3008 (Ubuntu) trial, a large study of the **mRNA-1273 COVID-19 vaccine in 14,001 participants (11,681 PLHIV) in East and Southern Africa**, provided a unique opportunity to prospectively study the efficacy and safety outcomes after vaccination in PWH, people with prior SARS-CoV-2 infection, and pregnant persons.
- **CD4>200 cells/mm3 in 93%; Plasma HIV VL<50 copies/mL, 81.5%. No ART 15%.**
- **358 Covid-19 cases, including 15 severe cases and one ICU admission. No Covid-19 related deaths**.




**Percentage of Safety Subset participants who had a solicited local (A) or systemic (B) adverse event within 7 days after vaccination**




- **Hybrid immunity was associated with an over 40% reduction in risk of Covid-19 and over 70% reduction in risk of severe Covid-19** compared to vaccine-only immunity **in the first 6 months after vaccinations** in a diverse population of PLWH (e.g., uncontrolled HIV, low CD4 count, pregnant).
- The study provides additional evidence that mRNA vaccines are **safe and well tolerated, including in PWH** and those with prior SARS-CoV-2 infection.

Tapley A et al. CROI 2024, Denver, CO March 2-6 2024; O#133; Hendricks S et al. CROI 2024, Denver, CO March 2-6 2024; P#1212.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March 14th 2024

# Daily Liposomal Amphotericin with 5FC in Cryptococcal Meningitis in PWH

- We aimed to compare the quantitative **antifungal activity and mortality** between **daily amphotericin B deoxycholate and daily liposomal amphotericin B** among persons with HIV-related cryptococcal meningitis receiving adjunctive flucytosine 100mg/kg/day. After 7 days, all received fluconazole 1200mg/d through 2 weeks, then 800mg/d through 10 weeks. **This regimen as recommended in IDSA and US HHS guidelines** is appropriate, **despite never being tested in a clinical trial**.

**FIGURE 1:** CSF Early Fungicidal Activity (EFA) measured by Quantitative CSF Culture change over time. Each line is a participant's cultures.

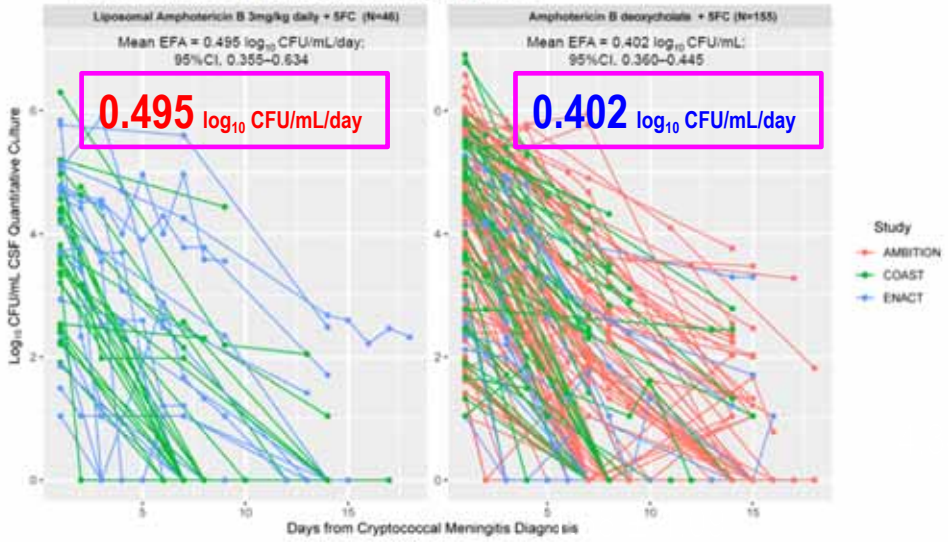
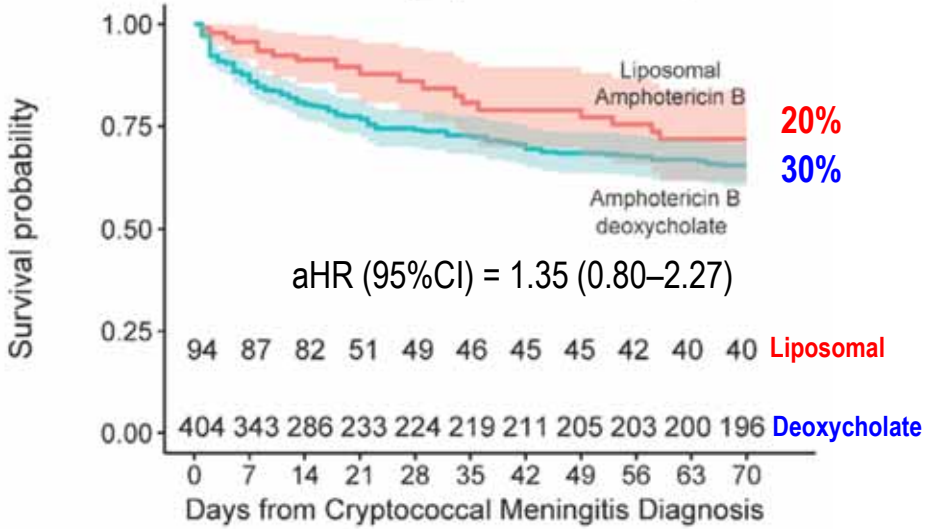



**FIGURE 2:** 10-week survival in HIV-related cryptococcal meningitis between daily 3mg/kg liposomal amphotericin B + 5FC for 7 days vs amphotericin B deoxycholate 0.7-1.0 mg/kg + 5FC for 7 days.




- Daily **liposomal amphotericin B** 3 mg/kg induction therapy with 5FC demonstrated **similar CSF fungal clearance and 10-week mortality** compared to **amphotericin B deoxycholate** with 5FC for the treatment of HIV-associated cryptococcal meningitis.

Boulware D et al. CROI 2024, Denver, CO March 2-6 2024; P#888.

# Semi-quantitative Cryptococcal Antigen (CrAg) is a Prognostic Factor of Mortality in HIV-related Cryptococcal Meningitis (HIV-CM)

- To study the **prognostic accuracy of Cryptococcal antigen** (**CrAgSQ IMMY, Norman, OK, USA**) in **796 patients with HIV-CM (AMBITION Phase 3 RCT in Africa)**
- **Frozen pretreatment CSF and/or plasma** were thawed and tested using CrAgSQ as per the manufacturer's instructions yielding **scores of 0 to 5+**

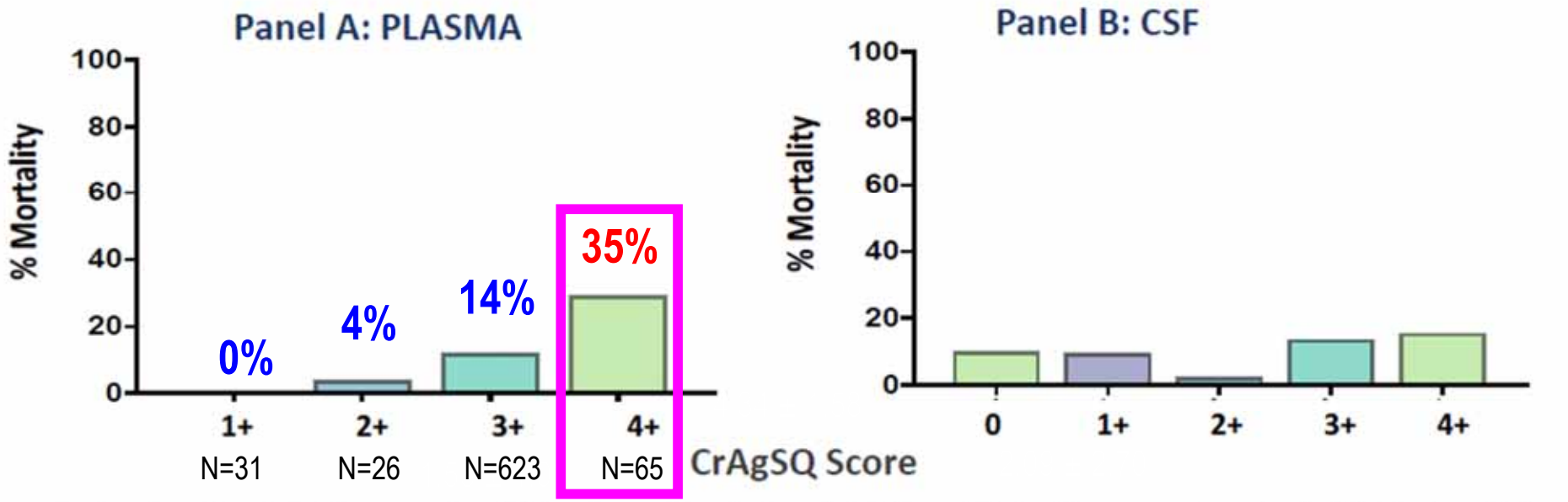



**Figure 1.** Depicts baseline CrAgSQ scores (x-axis) in plasma (**Panel A**) and CSF (**Panel B**) for the proportion of individuals who died within 2-weeks of initiating antifungal therapy (y-axis). **Mortality risk increased with increasing plasma SQ score (Panel A) (p for trend <0.001),** plasma SQ score could potentially identify individuals who are at risk of dying within 2-weeks.

Boyd FK et al. CROI 2024, Denver, CO March 2-6 2024; P#893.

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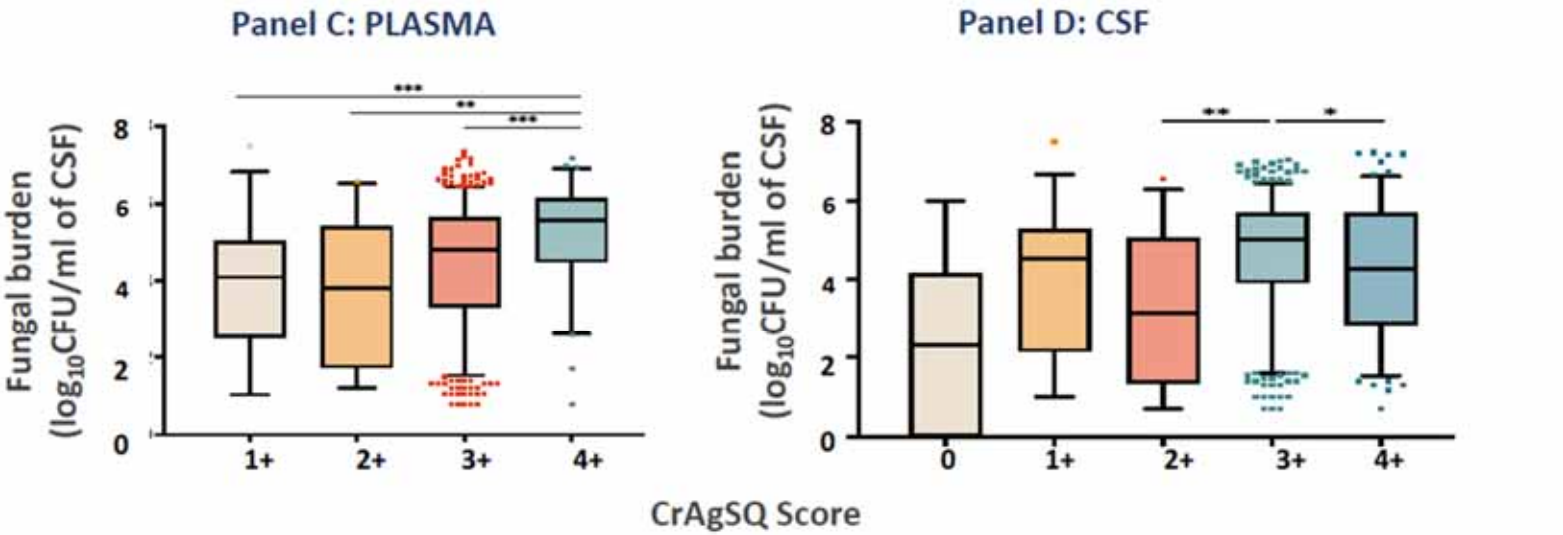


**Figure 2.** Baseline CSF cryptococcal burden determined by quantitative fungal culture (QFC) (i.e. colony forming units (CFU) per ml of CSF). $Log_{10}$ QFC depicted as medians and interquartile ranges (IQR), are shown on the y-axis for each CrAgSQ score obtained in **Panel C**: plasma (n=745) or **Panel D**: CSF (n=756) on the x-axis. **SQ scores increase with increasing fungal burden.** Kruskal-wallis (plasma: test statistic=26.99, p<0.00001 CSF: test statistic= 37, p<0.00001). SQ scores can potentially be used to estimate baseline fungal burden.

- The **risk of mortality increased with increasing plasma CrAg SQ scores**.
- This could help to stratify patients that require more intensive management of cryptococcal meningitis

Boyd FK et al. CROI 2024, Denver, CO March 2-6 2024; P#893.

# Recent ART Initiation Increased Mortality in Cryptococcal Meningitis

- We hypothesized that **patients presenting with cryptococcal meningitis following very recent ART initiation (within 14 days) were at higher risk of mortality** than ART-naïve individuals or those on ART for longer periods, and that **ART interruption reduces this excess mortality.**
- **Primary outcome of 2- and 10-week mortality** was determined from AMBITION-cm trial data.
- **Participants were grouped according to ART status** (Not taking ART, ART naïve, ART defaulters and on ART) and duration of ART.

**Table 1**: Mortality outcomes among AMBITION participants with HIV-associated cryptococcal meningitis stratified by ART status at the time of presentation

| ART status | | 2-week mortality | | 10-week mortality | |
|---|---|---|---|---|---|
| | | Mortality risk (95% CI) | N | Mortality risk (95% CI) | N |
| A. | Impact of ART status and duration on risk of mortality | | | | |
| Not on ART | | 12.4% (9.1-16.2) | 51/412 | 26.0% (21.7-30.2) | 107/412 |
| On ART | Overall | 13.3% (10.0-16.7) | 53/398 | 27.8% (23.4-32.2) | 111/398 |
| | ≤14 days | 20.8% (11.5-30.2) | 15/72 | 37.2% (26.1-48.3) | 27/72 |
| | >14 days ≤2 months | 10.4% (3.6-17.2) | 8/77 | 22.0% (12.8-31.2) | 17/77 |
| | >2 months ≤6 months | 7.1% (0.0-14.9) | 3/42 | 23.9% (11.0-37.8) | 10/42 |
| | >6 months | 13.0% (8.5-17.6) | 27/207 | 27.5% (21.5-33.6) | 57/207 |

Moyo M et al. CROI 2024, Denver, CO March 2-6 2024; P#886.

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|---|---|---|---|---|---|
| | | Mortality risk (95% CI) | N | Mortality risk (95% CI) | N |
| B. | Mortality effect of ART interruption | | | | |
| On ART ≤14 days, ART continued | | 34.8% (8/23) (0.15-0.54) | | 52.2% (12/23) (0.32-0.73) | |
| On ART ≤14 days, ART stopped | | 14.3% (7/49) (0.05-0.24) | | 30.6% (15/49) (0.18-0.44) | |

- **Recent ART initiation is associated with excess mortality** from cryptococcal meningitis **which may be offset by ART interruption at diagnosis**

Moyo M et al. CROI 2024, Denver, CO March 2-6 2024; P#886.


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March 14th 2024

# Histoplasmosis in Advanced HIV Disease in Vietnam

- We report the results of a **multi-center prospective diagnostic validation study of the IMMY Clarus Histoplasma GM enzyme immunoassay (HAg EIA) in hospitalized patients with AHD in Vietnam**.

## METHODS

**Study population:** 901 hospitalized patients with **AHD (CD4 count ≤ 100 cells/µL OR WHO stage III or IV disease).**

- Aged ≥ 18 years
- Not on ART, on ART ≤ 3 months, OR on ART > 12 months
- Not on effective antifungal therapy for systemic mycoses

Urine *Histoplasma* antigen (HAg): using the IMMY HAg EIA

Fungal blood culture: using the Myco/F Lytic bottle (incubated x 6 weeks)

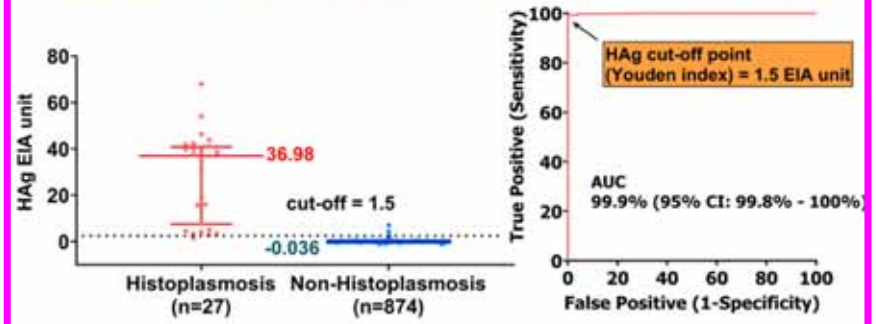
Conventional microscopy, cultures, and histopathology as clinically indicated

**Follow up:** weekly over first month, then monthly over 6 months

Table 1. Characteristics of 27 participants with histoplasmosis

| Characteristics | |
|---|---|
| Median CD4 count (IQR) – cells/µL | 17 (7.5 – 28.5) |
| Specimens positive for *H. capsulatum* cultures – n (%) | |
| *Blood culture* | 12 (44.4%) |
| *Bone marrow culture* | 11 (40.7%) |
| *Skin lesion culture* | 1 (3.7%) |
| Time to culture positivity (Mean ± SD) – days | |
| *Blood cultures (n=11)* | 15.5 ± 7.5 |
| *Bone marrow cultures (n=8)* | 11.5 ± 5.8 |
| Mortality over 6 month – n (%) | 08 (29.6%) |

Figure 1. Diagnostic performance of the IMMY Histoplasma GM EIA




Nguyen HT et al. CROI 2024, Denver, CO March 2-6 2024; P#895.

# Histoplasmosis in Advanced HIV Disease in Vietnam

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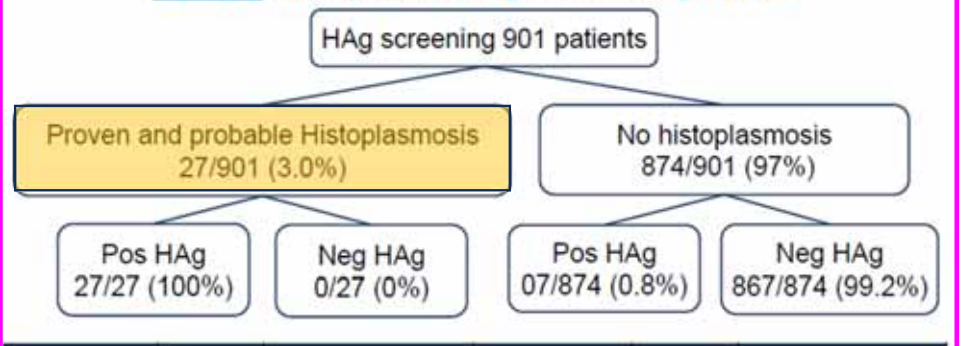
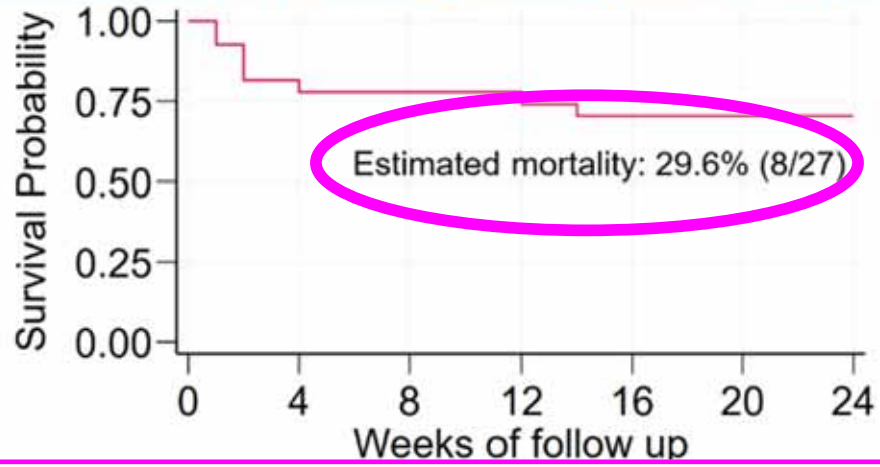
**Figure 2. Histoplasma antigen screening results**




| | Value | 95% CI | | Value | 95% CI |
|---|---|---|---|---|---|
| Sensitivity: | 100% | 87.2% – 100% | Specificity: | 99.2% | 98.4% - 99.7% |
| PPV: | 79.4% | 64.8% - 89.0% | NPV: | 100% | 99.6% - 100% |

***Abbreviations*: HAg**: Histoplasma antigen; **PPV:** Positive Predictive Value; **NPV:** Negative Predictive Value

**Figure 3: Survival estimates of patients with proven and probable histoplasmosis on antifungal therapy over 24 weeks**




- **Disseminated histoplasmosis accounts for 3.0% of hospitalized patients** with AHD in Vietnam.
- The IMMY Histoplasma EIA has an excellent diagnostic performance: **sensitivity 100%, specificity 99.2%**, accuracy 99.9%, PPV 79.4%, and **NPV 100%** in screening for histoplasmosis in patients with AHD.
- **High mortality (29.6%) despite antifungal therapy** highlights the need of **earlier screening of Histoplasma antigen** in patients with AHD

Nguyen HT et al. CROI 2024, Denver, CO March 2-6 2024; P#895.


# COVID-19 & Opportunistic Infections (OIs) at CROI 2024

# and that's all folks!

March 14th 2024