The Clinical Relationship Between HIV and COVID-19

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Financial Relationships With Ineligible Companies (Formerly Described as Commercial Interests by the ACCME) Within the Last 2 Years:

Dr Gandhi has no relevant financial affiliations with ineligible companies to disclose. (Updated 10/05/22)

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Learning Objectives

After attending this presentation, learners will be able to:

- Describe the impact of HIV on COVID-19 outcomes
- Summarize the importance of COVID-19 vaccination in persons with HIV (PWH)
- Assess COVID-19 treatment options for PWH

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Outline

- Are PWH at higher risk for severe COVID-19?
- Preventing COVID-19 in PWH
- Treating COVID-19 in PWH
- Lessons from HIV and COVID-19

Slide 4

Are People with HIV at Higher Risk for Severe COVID-19?

Are PWH at higher risk for severe COVID-19?

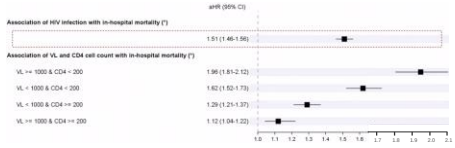
- Early studies did not find a difference in COVID outcomes in people with HIV (PWH) as compared with people without HIV
- Initial studies that showed a link between HIV and severe COVID may have been confounded by high rates of comorbidities and social determinants of disease in PWH
- Recent studies which attempt to adjust for confounding suggest PWH have worse COVID outcomes, particularly if they have low current or nadir CD4 cell counts or high HIV viral loads

Slide 6

Triant V and Gandhi R, CID 2021

Higher mortality rates in PWH hospitalized with COVID

- 362,941 people hospitalized with COVID-19; 29,530 (8.1%) PWH
- PWH: 50% higher in-hospital mortality
- HIV RNA >1000 and CD4<200 doubled COVID-19 death risk



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Low CD4 count associated with worse outcomes

- 649 PWH with COVID-19 (March to Dec, 2020)
  - 95% on ART; 86% undetectable VL
- Current CD4 <350, nadir CD4 <200, cardiovascular/liver comorbidities all highly predictive of COVID hospitalization
- CKD/liver dysfunction, COPD, diabetes, hypertension, and obesity all associated with increased risk of severe COVID
- Minoritized racial/ethnic groups disproportionately affected

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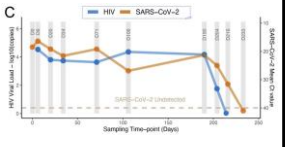
Shapiro & Bender Ignacio et al, *JAIDS*, 2022

Prolonged SARS CoV-2 Replication in Person with Advanced HIV

- Woman with HIV, CD4: 6. HIV RNA 34,000
- SARS CoV-2 PCR+ for 216 days (Ct 16 to 32)
- Anti-S protein IgM, IgG negative
- Emergence of multiple spike gene mutations: E484K, K417T, F490S, L455F, F456L, D427Y, N501Y



- SARS CoV-2 cleared after HIV was suppressed on ART

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Karim F et al, https://www.medrxiv.org/content/10.1101/2021.06.03.21258228v1.full.pdf

Why PWH May Have Worse COVID-19 Outcomes

- **Immunodeficiency**
  - Patients with advanced HIV may have prolonged SARS CoV-2 replication
- **Immune dysregulation**
  - Residual inflammation
  - Most pronounced in PWH with low CD4 count nadirs, incomplete CD4 reconstitution, low CD4/CD8 ratio
  - Immune dysregulation "legacy effect": impact not certain
- **Comorbidities**
  - High rates of comorbidities that are also risk factors for severe COVID
- **Social determinants of health**
  - PWH more likely to be racial/ethnic minorities, poor – risk factors for worse COVID outcomes

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Triant V and Gandhi R, CID 2021

Long COVID in PWH

- 39 PWH and COVID compared with 43 people without HIV who had COVID (before vaccine available)
- PWH had lower SARS-CoV-2-specific CD8 T cells, higher PD-1 expression on SARS-CoV-2-specific CD4 cells, higher IL-6 levels
- PWH 4-fold higher odds of post-acute sequelae of COVID-19 (PASC) (95% CI: 1.45–11.1)

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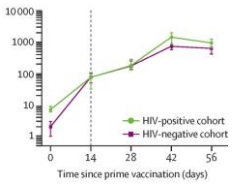
Peluso M, AIDS, 2022

Prevention of COVID-19 in PWH

Immune Responses to COVID Vaccines in PWH

- PWH on ART with high CD4 counts have good immune responses (antibodies, T cells) to vaccines
- PWH may have lower antibody responses to mRNA vaccines than people without HIV, particularly if they have low CD4 counts, unsuppressed HIV RNA

SARS CoV-2 anti-spike protein IgG after AZ ChAdOx1 vaccine



Frater J et al, Lancet HIV, 2021; Madhi S et al, Lancet HIV 2021; Woldemeskel, CID, 2021; Ruddy JA et al., AIDS, 2021; Spinelli M, et al, abstract LB8, IDWeek 2021; Antinori A, et al, European AIDS Conference 2021, Oral Abstract OS3/4

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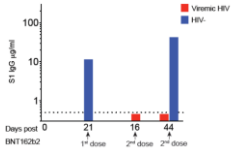
Failure to Seroconvert after COVID-19 Vaccine in Patient with Uncontrolled HIV

- Patient with uncontrolled HIV who was not on ART
- Received 2 doses of Pfizer vaccine
- Did not develop anti-spike IgG response to the vaccine

No anti-spike IgG after 2nd COVID vaccine dose in patient with uncontrolled HIV



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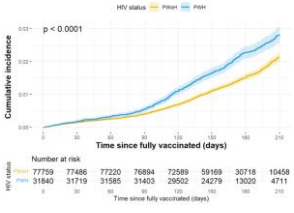
Touizer E et al, Lancet HIV, 2021.

Breakthrough COVID After Vaccination More Common in PWH

- 109,599 fully vaccinated individuals (31,840 PWH, 77,759 PWoH)
- Breakthrough infections: 44 vs. 31/1000 person years
  - 41% increased risk in PWH vs. PWoH
- Cumulative incidence at 210 days: 2.8% vs. 2.1%



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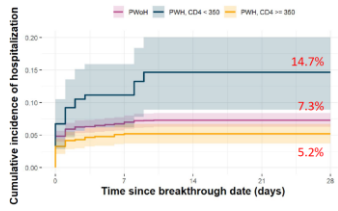
SB Coburn et al, JAMA Network Open, 2022

Hospitalization after Breakthrough COVID Higher in PWH with CD4 <350



Among those with breakthrough infection, PWH and CD4 count <350 had increased risk of hospitalization relative to people without HIV and PWH with higher CD4 cell counts

Lang R et al, medRxiv preprint doi: https://doi.org/10.1101/2022.04.15.22273913

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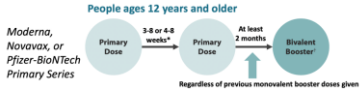
COVID-19 Vaccination Schedule for People who are NOT Moderately or Severely Immunocompromised



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

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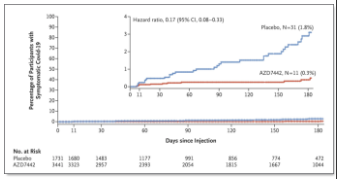
Tixagevimab/cilgavimab for Pre-exposure prophylaxis

- Tixagevimab/cilgavimab: anti-SARS CoV-2 monoclonal antibodies (half life ≈90 days)
- 5197 participants randomized 2:1 to receive single IM dose of tixagevimab + cilgavimab (150/150 mg) or placebo
- Unvaccinated
- 3.8% immunocompromised

83% reduction in symptomatic Covid in tixagevimab/cilgavimab group



Levin M et al, NEJM, April 20, 2022

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Tixagevimab/cilgavimab for COVID-19 Pre-Exposure Prophylaxis

- **FDA Emergency Use Authorization**:
  - Who have moderate to severe immune compromise due to a medical condition or receipt of immunosuppressive medications or treatments **and**
  - May not mount an adequate immune response to COVID-19 vaccination ***or***
  - For whom vaccination is not recommended due severe adverse reaction
- Includes advanced or untreated HIV: CD4 <200, history of AIDS defining illness without immune reconstitution, or clinical manifestations of symptomatic HIV
- Wait 2 weeks *after* vaccination to administer tixagevimab/cilgavimab

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

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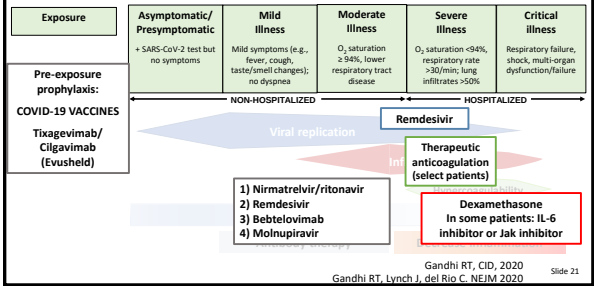
Treatment of COVID-19 in PWH

Treatment Across the COVID-19 Spectrum



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

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How do therapies for high risk outpatients stack up?

	1) Nirmatrelvir/r	2) Remdesivir	3) Bebtelovimab	4) Molnupiravir
Efficacy (prevention hospitalization or death)	• **Relative risk reduction: 88%** • Absolute risk: 6.3%→0.8% • NNT: 18	• **Relative risk reduction: 87%** • Absolute risk: 5.3%→0.7% • NNT: 22	• **Observational data are supportive but only phase 2 clinical trials data**	• **Relative risk reduction: 30%** • Absolute risk: 9.7%→6.8% • NNT: 35
Pros	• Highly efficacious • Oral regimen • Ritonavir studied (safe) in pregnancy	• Highly efficacious • Studied in pregnancy • Few/no drug interactions	• Monoclonals typically safe in pregnancy • Few/no drug interactions	• Oral regimen • Not anticipated to have drug interactions
Cons	• Drug drug interactions	• Requires IV infusion on 3 consecutive days	• Requires IV infusion followed by 1 hour observation • Limited clinical data	• Low efficacy • Concern: mutagenicity • Not recommended in pregnancy/children

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

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Which PWH Should be Treated?

- Outpatient therapies authorized for high-risk outpatients within 5-7 days of symptom onset
- Consider all risk factors, including age, comorbidities and disease stage, not just HIV immune and virologic status
- People with HIV should be treated the same as people without HIV
- Refer to NIH and IDSA COVID-19 Treatment Guidelines

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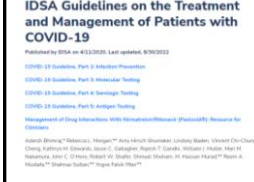
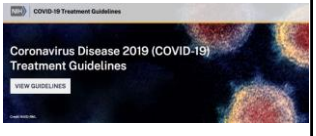
COVID-19 Treatment Guidelines





Nirmatrelvir/ritonavir: Drug Drug Interactions including with ART

- Ritonavir inhibits CYP3A: affects metabolism of many medications
- Effect on CYP3A during treatment (5 days) and for additional 2-3 days after treatment completed
- Antiretroviral considerations:
  - Continue ART, including boosted-PI regimens
  - Ok in untreated HIV – low risk for resistance with 5 days of treatment

Useful resources: NIH Guidelines & Liverpool Checker

Paxlovid Package insert

Patients on ritonavir- or cobicistat-containing HIV regimens should continue their treatment as indicated. Monitor for increased PAXLOVID or protease inhibitor adverse events with concomitant use of these protease inhibitors *[see Dosage and Administration (2.4)]*.

https://www.covid19treatmentguidelines.nih.gov
https://www.covid19-druginteractions.org/
https://www.fda.gov/media/155050/download

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

- Clinical improvement with negative antigen/PCR -> relapse of URI symptoms 4 to 10 days after completing NMV/r, sometimes with antigen positivity - no hospitalizations reported, typically resolves without further treatment
- How often?
  - PCR rebounds reported in ~2% of EPIC-HR trial of NMV/r, equal in placebo and treated groups
  - TriNetX (EHRs) - suggest ~3.5% within 7 days

Modified from slide from Dr. Arthur Kim

Charness NEJM Sept 15, 2022; Wang Preprint 2022

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

- Transmission?
  - Series of 10 patients, all fully vaccinated with booster, putative transmission in 2 instances
  - MGH series, 7 patients – rebound SARS-CoV-2 levels similar to pre-treatment values; 3 of 7 patients were culture positive during rebound
- Why?
  - Early reports: no decrements in antibody levels or adaptive immunity
  - Thus far, no resistance detected before or after NMV/r
  - Rebound may occur even without NMV/r; not known whether incidence different

Modified from slide from Dr. Arthur Kim

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

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

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

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ART in COVID-19 Treatment & Prevention

- No evidence of benefit of LPV/r, TDF, other ARVs against SARS-CoV-2
  - Observational data from Spain and from US Veterans Aging Cohort Study suggesting benefit of TDF may have been confounded
  - Focus on attaining or maintaining viral suppression with any appropriate regimen
- Hospitalized patients with COVID-19:
  - Continue ART without change
  - If not on ART, initiate ART once clinically stable (including prior to hospital discharge)

Del Amo J et al, Ann Int Med, 2020; Li G et al, AIDS, Oct 1, 2022

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Lessons from HIV and COVID-19

Lesson # 1: Randomized Clinical Trials Critical to Identify What Does and Doesn't Work

The NEW ENGLAND JOURNAL of MEDICINE

Treatment with Indinavir, Zidovudine, and Lamivudine in Adults with Human Immunodeficiency Virus Infection and Prior Antiretroviral Therapy

Roy M. Gulick, M.D., M.P.H., John W. Mellors, M.D., Diane Havlir, M.D., Joseph J. Eron, M.D., Charles Gonzalez, M.D., Deborah McMahon, M.D., Douglas D. Richman, M.D., Fred T. Valentine, M.D., Leslie Jonas, B.S., Anne Meibohm, Ph.D., Emilio A. Emini, Ph.D., Jeffrey A. Chodakewitz, M.D., et al.

ACTG AIDS CLINICAL TRIALS GROUP

RECOVERY Randomised Evaluation of COVID-19 Therapy

COVID-19 Prevention Network

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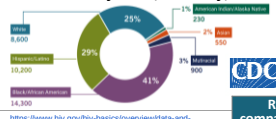
Lesson # 2: Disproportionate Impact of HIV and COVID-19 on Vulnerable Populations

HIV Incidence by Race, Ethnicity, 2019



https://www.hiv.gov/hiv-basics/overview/data-and-trends/statistics

https://www.cdc.gov/coronavirus/2019-ncov/covid-data/investigations-discovery/hospitalization-death-by-race-ethnicity.html

Risk for COVID-19 Infection, Hospitalization, and Death by Race, Ethnicity

Rate ratios compared to White, Non-Hispanic persons	Black or African American persons	Hispanic or Latino persons
Cases	1.1x	1.5x
Hospitalization	2.4x	2.3x
Death	1.7x	1.8x

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HIV and COVID-19: Mass General Hospital Series

- People with HIV with confirmed or probable COVID-19 in March/April 2020
- ~80% racial/ethnic minorities

Disproportionate burden of coronavirus disease 2019 among racial minorities and those in congregate settings among a large cohort of people with HIV

Eric A. Meyerowitz[a], Arthur Y. Kim[a,b], Kevin L. Ard[a,b], Nesli Basgoz[a,b], Jacqueline T. Chu[a,b,c], Rocio M. Hurtado[a,b,d], Catherine K. Lee[a], Wei He[e], Theresa Minukas[a], Sandra Nelson[a,b], Bisola O. Ojikutu[a,b], Greg Robbins[a,b], Sarimer Sanchez[a], Virginia A. Triant[a,b,c,e], Kimon Zachary[a,b] and Rajesh T. Gandhi[a,b]

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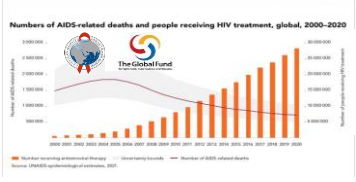
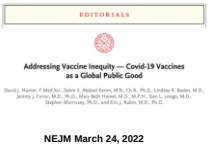
Meyerowitz E/Gandhi RT et al, AIDS 2020

Lesson # 3: Inequitable Access to Treatments, Vaccines and Diagnostics Needs to Be Addressed by Advocacy





NEJM March 24, 2022

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Lessons from HIV and COVID-19 for Future Pandemics

- Pressure to deploy interventions must be tempered by importance of finding out if treatment or vaccine works
- Randomized trials can and must be done during pandemic
- Equity must be at the center of our response

Siedner M, Gandhi RT, Kim AY, JID, 2020

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Conclusions

- COVID-19 outcomes may be more severe among PWH, particularly if they have low CD4 counts or untreated infection
- All PWH should receive COVID-19 vaccination, including boosters; for people with advanced HIV, pre-exposure prophylaxis with tixagevimab/cilgavimab also indicated
- Treatment of PWH should follow general population guidelines
- Lessons from HIV and COVID include importance of clinical trials and advocacy as well as an unwavering focus on addressing inequities

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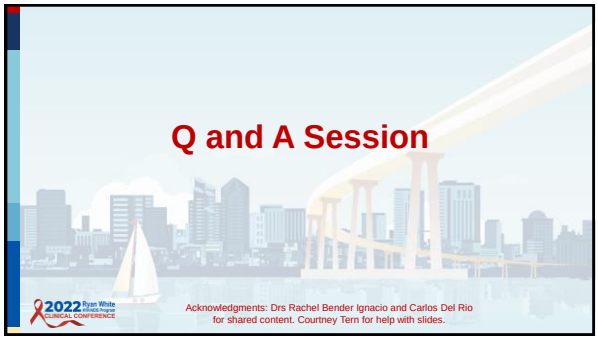
Q and A Session
2022 Ryan White HIV/AIDS Program CLINICAL CONFERENCE
Acknowledgments: Drs Rachel Bender Ignacio and Carlos Del Rio for shared content. Courtney Tern for help with slides.