Risk, Presentation, Treatment, and Outcomes of COVID-19 in People with HIV

Steven Johnson, MD & Roy Gulick, MD, MPH

January 27, 2021
Housekeeping

- You will need to call in to speak on the line; however, it is recommended that you call in even if you’re just listening on the line for a better user experience:
  - Conference number: 1-866-814-9555
  - Participant passcode: 723 288 1431

- All phone lines have been muted.

- During the Q&A portion, you may unmute your phone line by pressing #6. You can also use the participant chat to ask questions.

- Today’s session recording and slides will be available on the aidsetc.org website as a resource.
Speakers

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Disclosures

- No conflict of interests to disclose
Learning Objectives:

- Compare the clinical impact of HIV infection and COVID-19
- Analyze the latest data on clinical presentation and clinical outcomes of people with HIV who develop COVID-19
- Review current treatment strategies for COVID-19 (including antiretroviral drugs) for people with HIV
- Apply current guidelines for COVID-19 Vaccination in People with HIV
Compare the Clinical Impact of HIV Infection and COVID-19
Comparing the Cumulative Impact of Two Viral Pandemics (as of 1/26/21)

<table>
<thead>
<tr>
<th></th>
<th>HIV Infection</th>
<th>COVID-19</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of U.S. cases</td>
<td>1.9 million</td>
<td>25 million</td>
</tr>
<tr>
<td>Number of U.S. deaths</td>
<td>700,000</td>
<td>423,000</td>
</tr>
<tr>
<td>Number of Global Cases</td>
<td>75 million</td>
<td>100 million</td>
</tr>
<tr>
<td>Number of Global Deaths</td>
<td>32 million</td>
<td>2.1 million</td>
</tr>
<tr>
<td>Duration of Pandemic</td>
<td>40 years</td>
<td>1 year</td>
</tr>
</tbody>
</table>

For both pandemics, the number of undiagnosed infections is great. For both pandemics, the number of life-years lost is great.
Disproportionate Burden Among Racial/Ethnic Minorities

77% of people with HIV and COVID-19 were non-Hispanic Black or Latinx

40% of people with HIV in MGH Clinic are Black or Latinx

Cohort with COVID-19

- Non-Hispanic Black: 22%
- Hispanic/Latinx: 45%
- Other: 33%

General Clinic Population

- Non-Hispanic Black: 30%
- Hispanic/Latinx: 10%
- Other: 60%

Is the Clinical Presentation of COVID-19 Different in People with HIV?
Clinical Presentation of COVID-19 in People with HIV

• People with HIV often present with the same clinical signs and symptoms of COVID-19 as people without HIV
• It is unknown if viral or bacterial coinfections are more common in people with HIV who present with COVID-19
• There are several reports of opportunistic infections, including Pneumocystis pneumonia, in people with advanced HIV presenting with COVID-19

**Recommendation:** In persons with HIV who have advanced disease with a low CD4 cell count or uncontrolled viremia, consider a broader differential diagnosis for fever, pneumonia, and other clinical presentations
Immunologic Characteristics of Acute COVID-19 in 93 People with HIV

CD4 Count

CD4 Percent

Lymphocyte Count

Are Clinical Outcomes with COVID-19 Different in People with HIV?
Factors Associated with the Risk of Severe Disease in COVID-19 are Common in People with HIV

- Older age: ~50% of people with HIV are over 50
- Obesity: common in HIV, weight gain with ART
- Cardiovascular disease: HIV is a risk factor
- Lung disease: increased tobacco use in HIV
- Hypertension
- Diabetes mellitus
- Cancer: increased non-AIDS cancers in HIV
- Gender: HIV more common in men in the U.S.
- Immunocompromising diseases and medications
Outcomes of COVID-19 in Persons with HIV

• Retrospective study of 88 PWH hospitalized in the Mount Sinai Health System in NYC compared to HIV-negative controls with COVID-19. Similar outcomes to HIV-negative persons observed\(^1\).

• Case control study in hospitalized patients at New York Presbyterian-Weill Cornell Medical Center matching 30 persons with HIV and COVID-19 with 90 controls. No difference in outcomes including mortality. HIV-negative required a higher level of oxygenation on presentation\(^2\).

Outcomes of COVID-19 in Persons with HIV (cont.)

- This study at NYU Langone Health provided evidence that HIV coinfection did not significantly impact presentation, hospital course, or outcomes of 21 patients infected with SARS-CoV-2, when compared to 42 matched non-HIV patients\(^3\).

- Comparison of 100 HIV+ versus 4513 HIV negative in the Bronx. 94% of HIV+ on ART and 81% suppressed. Most outcomes did not differ. Higher rate of MV 21% versus 14%. Mortality similar\(^4\).

Veterans Affairs Study of Outcomes of COVID-19 in People with HIV

- Veterans Aging Cohort Study
- Evaluation of COVID-19 outcomes in HIV+ patients matched to HIV- controls

<table>
<thead>
<tr>
<th>COVID-19</th>
<th>People with HIV</th>
<th>People without HIV</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>253</td>
<td>504</td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>34%</td>
<td>35%</td>
<td>1.09 (0.85, 1.41)</td>
</tr>
<tr>
<td>ICU stay</td>
<td>14%</td>
<td>15%</td>
<td>1.08 (0.72, 1.62)</td>
</tr>
<tr>
<td>Death</td>
<td>9.5%</td>
<td>11.1%</td>
<td>1.08 (0.66, 1.75)</td>
</tr>
</tbody>
</table>

Park et al., AIDS 2020, Virtual Covid 2020
Study of HIV and COVID-19 in South Africa

- 3.45 million active public sector adult patients; 520,000 with HIV
- 532 COVID-19 deaths
- Adjusted hazard ratio for COVID-19 mortality for HIV: 2.14 (1.7, 2.7)
- Irrespective of viral suppression/immunosuppression
- Cannot rule out confounding (e.g. socioeconomic status, obesity, unrecognized comorbidities)

U.K. Studies on HIV outcome

- Huge UK database of 17.3 million adults, 27,480 with HIV. Hazard ratio for death 2.3 for HIV+ after adjustment for deprivation, ethnicity, and comorbidities\(^1\).

- Mortality among a cohort of 47,539 patients, 115 with confirmed HIV and 103 with a record of ART. After adjustment for age and disease severity on presentation, Hazard ratio for mortality in HIV+ was 1.63\(^2\).

- Similar to the South African study, there is a concern that these large studies from electronic databases may not identify all variables that could affect outcome, including all comorbidities.

Outcomes of 286 Patients with HIV and COVID-19 in a Multicenter Registry

Odds ratio (95% CI) of severe outcome (ICU, mechanical ventilation, or death)

- CD4 < 200: 3.32 (1.11-9.93)
- CD4 200-500: 1.75 (0.76-4.02)
- CD4 > 500: 1 (reference)

Immune Deficiency as a Risk Factor for Severe COVID-19

- Multicenter cohort study of 175 persons with HIV who developed COVID-19
- Almost all on ART and 94% virally suppressed
- 49 (28%) developed severe COVID-19 and 7 (4%) died
- Factors associated with severe/critical COVID-19
  - Age greater than or equal to 50 years
  - CD4 nadir < 200 cells/mm³
  - Current CD4 < 350 cells/mm³
  - Presence of at least one other significant comorbidity

Summary of Clinical Outcomes of COVID-19 in People with HIV

- The vast majority of people with HIV recover from COVID-19.
- In people with HIV who are on ART and have a normal CD4 count, the clinical outcome is likely more dependent on factors known to affect risk in COVID-19 including age and co-morbidities.
- In people with HIV who are not on ART or have a low CD4 count, there may be an increased risk of a poor outcome.
Resources: HIV and COVID-19 Guidelines

• HHS Panel on Antiretroviral Use in Adult and Adolescents with HIV
  - Section on Interim Guidance for COVID-19 and Persons with HIV

• NIH Panel on the Management of COVID-19
  - Comprehensive Guidelines initiated in March of 2020
  - Section on COVID-19 and HIV added in October of 2020
  - Available at: https://www.covid19treatmentguidelines.nih.gov/
Current Guidelines for COVID-19 Vaccination in People with HIV
The Pfizer-BioNTech Phase III Trial

<table>
<thead>
<tr>
<th></th>
<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine Schedule</td>
<td>Day 0 and 21</td>
<td>Day 0 and 21</td>
</tr>
<tr>
<td>Total Number Enrolled</td>
<td>21,720</td>
<td>21,728</td>
</tr>
<tr>
<td>Number with HIV Enrolled</td>
<td>59</td>
<td>62</td>
</tr>
<tr>
<td>Number with Symptomatic COVID-19</td>
<td>8</td>
<td>162</td>
</tr>
<tr>
<td>Efficacy</td>
<td>95%</td>
<td>-</td>
</tr>
<tr>
<td>Severe Cases of COVID-19</td>
<td>1</td>
<td>9</td>
</tr>
</tbody>
</table>

Safety, efficacy, and immunogenicity in people with HIV has not yet been reported.

### The Moderna-NIH Phase III Trial

<table>
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<th>Vaccine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vaccine Schedule</strong></td>
<td>Day 0 and 28</td>
<td>Day 0 and 28</td>
</tr>
<tr>
<td><strong>Total Number Enrolled</strong></td>
<td>15,210</td>
<td>15,210</td>
</tr>
<tr>
<td><strong>Number with HIV Enrolled</strong></td>
<td>92</td>
<td>87</td>
</tr>
<tr>
<td><strong>Number with Symptomatic COVID-19</strong></td>
<td>11</td>
<td>185</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td>94.1%</td>
<td>-</td>
</tr>
<tr>
<td><strong>Severe Cases of COVID-19</strong></td>
<td>0</td>
<td>30</td>
</tr>
</tbody>
</table>

Safety, efficacy, and immunogenicity in people with HIV has not yet been reported

Current ACIP Guidance

• Persons with HIV infection, other immunocompromising conditions, or who take immunosuppressive medications or therapies might be at increased risk for severe COVID-19
• Data are not currently available to establish the safety and efficacy of vaccine in these groups
• These individuals may still receive COVID-19 vaccines unless otherwise contraindicated
• Individuals should be counseled about:
  - The unknown vaccine safety and efficacy profiles in immunocompromised persons
  - The potential for a reduced immune response
  - The need to continue to follow all current guidance to protect themselves against COVID-19
COVID-19 Vaccination in People with HIV: Talking Points

- People with HIV who were well-controlled on ART were included in the Phase 3 trials of both Moderna and Pfizer mRNA vaccines
- Data on immunogenicity, efficacy, and safety from these trials is not yet available
- None of the COVID-19 vaccines currently in Phase 3 trials are live vaccines
- People with HIV who are on ART with a normal CD4 count typically respond well to licensed vaccines so we might expect the same to occur with COVID-19 vaccines
- The risk of deferring COVID-19 vaccination in the current COVID-19 pandemic should outweigh concerns about the limited data on vaccination
Guidelines: Managing COVID-19 in People with HIV (PWH)
COVID-19 Treatment Guidelines Panel Members

Co-Chairs

Roy M. Gulick, MD  
Weill Cornell Medicine, New York, NY

H. Clifford Lane, MD  
National Institutes of Health, Bethesda, MD

Henry Masur, MD  
National Institutes of Health, Bethesda, MD
NIH COVID-19 Rx Guidelines: Prevention and Diagnosis of COVID-19

Use the same approach for the prevention and diagnosis of SARS-CoV-2 infection in people with human immunodeficiency virus (PWH) as in people without HIV (AIII).

www.covid19treatmentguidelines.nih.gov 10/9/20

- Triage, management, and rx of COVID-19 in people with HIV are the same as those for the general population (AIII).
- With advanced HIV and suspected/documentated COVID-19, HIV-associated OIs should also be considered in the differential diagnosis of febrile illness (AIII).
- When starting COVID-19 rx in PWH, pay attention to potential drug-drug interactions and overlapping toxicities among COVID-19 treatments, ART, antimicrobial therapies, and other medications (AIII).
- PWH should be offered the opportunity to participate in clinical trials.
COVID-19: Clinical Course and Interventions

Modified from: Biocentury
COVID-19 Treatment:
Antivirals
Life Cycle of SARS-CoV-2

1. Attachment
2. Fusion + endocytosis
3. Uncoating
4. Replication complex
5. Assembly
6. Release

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

Coronavirus Proteases and Inhibitors

- SARS-CoV-2 replication depends on the cleavage of polyproteins → RNA-dependent RNA polymerase + helicase
- 2 protease enzymes are responsible for this cleavage:
  - 3-chymotrypsin-like protease (3CLpro)
  - papain-like protease (PLpro)
- HIV-1 protease inhibitors lopinavir/ritonavir were evaluated in SARS and MERS
- Clinical experience with SARS  
  Chu Thorax, 2004;59:252-256
  - Non-randomized trial of 41 patients treated with LPV/r + ribavirin (vs. historical controls)
  - Results: ARDS/death at day 21: 2.4% (LPV/r + RBV) vs 29% (historical controls), p<0.001
- Effective for SARS-CoV-2?
  - Protease inhibitors suggested to be tested  
    Morse Chemiochem 2020;21:730-738
  - Lopinavir/ritonavir is an inhibitor of SARS-CoV 3CLpro *in vitro*, and this protease appears highly conserved in SARS-CoV-2.  
    Liu J Genet Genomics 2020;47:119-121
Lopinavir/Ritonavir for COVID-19 (1)

- FDA-approved HIV protease inhibitor combination
- In vitro activity against SARS-CoV-2
  - Pharmacokinetics do not support
    - 60-120X ↑ concentrations required to achieve EC$_{50}$ Schoergenhofer Ann Intern Med 2020;173:670-672

- Randomized, controlled open-label study
  - Hospitaized pts with severe COVID-19 (N=199)
  - No difference in:
    - time to clinical improvement
    - 28-day mortality
    - detectable viral RNA Cao NEJM 2020;382:1787-1799
Lopinavir/Ritonavir for COVID-19 (2)

RECOVERY: 11,500 patients at 175 National Health Service Hospitals in UK

Study pts: Hospitalized pts with COVID-19 (N=6425)
- 4% mechanical vented, 70% on O2, 26% no O2

Study rx:
randomized to LPV/RTV (n=1596) vs. usual care (n=3376)

Study stopped early by Trial Steering Committee

Primary endpoint: 28-day mortality:
- 22% (LPV/RTV) vs. 21% (usual care) p=0.58

Also, no effect on progression to intubation or hospital stay

RECOVERY Collaborative Group, Lancet 2020;173:670-672
Darunavir for COVID-19: *in vitro*

CPE = cytopathogenic effect

MTT = Method of assessing CPE

Conclusion: DRV has no effect on SARS-CoV-2

De Meyer, Int J Infect Dis 2020;97:7-10
The COVID-19 Treatment Guidelines Panel recommends against using lopinavir/ritonavir (AI) or other HIV protease inhibitors (AIII) for the treatment of COVID-19, except in a clinical trial.

Remdesivir (RDV)

- Antiviral agent
- RNA polymerase inhibitor – adenine derivative
- Antiviral activity in vitro and animal models
  - SARS, MERS, and SARS-CoV-2
- Tested in a clinical trial for Ebola (N>500) Li Nat Rev Drug Discov 2020;19:149
- Clinical trials in COVID-19
  - Compassionate Use (N=61) Grein NEJM 2020;382:2327-2336
    - Moderate and Severe COVID-19
  - NIH ACTT-1 Randomized Study (N=1062) Beigel NEJM 2020;383:1813-1826
    - Severe COVID-19
  - SINGLE study in severe COVID-19 Goldman NEJM 2020;383:1827-1837
  - SINGLE study in moderate COVID-19 Spinner JAMA 2020;324:1048-1057
- FDA-approved for hospitalized patients with COVID-19 10/22/20
Remdesivir (RDV) – Clinical Trials (1)

- **ACTT-1**: Phase 3 multicenter, randomized, double-blind placebo controlled study
  - Study population: adults hospitalized with COVID-19 with evidence of lower respiratory tract involvement (N=1062)
  - Study treatment: RDV vs. placebo X 10 days
  - Study endpoint: time to clinical recovery (to discharge or equivalent)

- Mortality (28d): 11% (RDV) vs. 15% (PBO) p=NS
- Conclusion: RDV superior to placebo

Beigel NEJM 2020;383:1813-1826
Remdesivir (RDV) – Clinical Trials (2)

- **SOLIDARITY**: Phase 3 multinational, randomized, open-label controlled study
- Study population: adults hospitalized with COVID-19 in 405 hospitals in 30 countries (N=11,330)
- Study treatment: RDV (n=2750) or control (n=2725)
- Study endpoint: In-house mortality
- Mortality: 11% in both groups (death rate ratio 0.95; p=0.50)
- Conclusion: No mortality benefit
COVID-19 Treatment: Immunomodulators

COVID-19 Cytokine Storm
Dexamethasone

- University of Oxford  Horby, NEJM 2020 (epub 7/17/20)
- 11,500 patients at 175 National Health Service Hospitals in UK
- Study pts: Hospitalized pts with COVID-19 (N=6425)
- Study rx: randomized to dexamethasone 6mg daily X 10 days (or discharge) (n=2104) vs. usual care (n=4321)
- Primary endpoint: 28-day mortality: 482 (23%) on dexamethasone vs. 1110 (26%) usual care
- Study stopped early by Trial Steering Committee

Conclusion: Dexamethasone associated with mortality benefit in COVID-19 patients requiring oxygen
COVID-19 Prevention
# Selected COVID-19 Vaccine Candidates

<table>
<thead>
<tr>
<th>Platform</th>
<th>Developer</th>
<th>Phase 1/2</th>
<th>Phase 2/3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleic acid</strong></td>
<td>moderna</td>
<td>Enrolled</td>
<td>Enrolled</td>
</tr>
<tr>
<td></td>
<td>BIONTECH</td>
<td></td>
<td>Baden NEJM (epub 12/30/20)</td>
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<tr>
<td></td>
<td>pfizer</td>
<td>Enrolled</td>
<td>Polack NEJM;383:2603-15</td>
</tr>
<tr>
<td><strong>Viral vector</strong></td>
<td>AstraZeneca</td>
<td>Enrolled</td>
<td>Enrolled</td>
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<tr>
<td></td>
<td>Janssen</td>
<td></td>
<td>Voysey Lancet (epub 12/8/20)</td>
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<tr>
<td></td>
<td>MERCK</td>
<td>Enrolled</td>
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</tr>
<tr>
<td><strong>Protein subunit</strong></td>
<td>NOVAVAX</td>
<td>Ongoing</td>
<td>Ongoing</td>
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<td>gsk SANOFI</td>
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RNA polymerase inhibitors

Remdesivir (GS-5734)

tenofovir disopropil fumarate (TDF)
Incidence and Severity of COVID-19 in HIV-Positive Persons Receiving Antiretroviral Therapy
A Cohort Study

60 Spanish Hospitals
- 77,590 HIV+ persons on ART
  - NRTI
    - TDF/FTC 16%
    - TAF/FTC 33%
    - ABC/3TC 26%
    - Other 25%
  - 3rd drug
    - NNRTI 21%
    - PI 19%
    - Integrase 50%
    - Other 10%
- 236 dx’ed with COVID-19
  - 151 were hospitalized
  - 15 were admitted to ICU
  - 20 died

Del Amo, Ann Intern Med 2020;173:536-541
Western Cape / South Africa

Effect of different ARVs on COVID-19 death among cases with HIV on ART

N=3903 COVID-19 cases and 115 COVID-19 deaths

Until January 2020

- First-line: TDF + XTC + EFV unless renal failure
- Second-line: ZDV + XTC + LPV
- DTG introduced from January 2020

Davies IAS 2020 #OAXLB01
Guidelines: Managing HIV during COVID-19
COVID-19 Treatment Guidelines Panel Members

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National Institutes of Health, Bethesda, MD

Henry Masur, MD
National Institutes of Health, Bethesda, MD
NIH COVID-19 Rx Guidelines: Management of HIV

- PWH who develop COVID-19 should continue ART and OI prophylaxis whenever possible (AIII).
- Clinicians treating COVID-19 in PWH should consult with an HIV specialist before adjusting or switching ART (AIII).
- ART should not be switched or adjusted (i.e., by adding ARVs to the regimen) for the purpose of preventing or treating SARS-CoV-2 infection (AIII).
- For COVID-19 and a new HIV diagnosis, clinicians should consult an HIV specialist to determine the optimal time to initiate ART.

www.covid19treatmentguidelines.nih.gov 10/9/20
Guidelines for the Use of Antiretroviral Agents in Adults and Adolescents with HIV

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

https://clinicalinfo.hiv.gov/
DHHS HIV Guidelines: Guidance for All Persons with HIV

- Help persons with HIV maintain adequate supply of ART and concomitant medications.
- Keep influenza and pneumococcal vaccines up to date.
- PWH should follow all applicable recommendations of the U.S. CDC to prevent COVID-19, such as social distancing and proper hand hygiene.
- CDC also provides information about COVID-19 prevention during pregnancy and for children.

www.aidsinfo.nih.gov
DHHS Guidelines: Guidance for HIV and COVID-19

- Limited data indicate COVID-19 does not differ in persons with/without HIV.
- Before ART, advanced HIV infection (i.e., CD4 cell count <200) was a risk factor for complications of other respiratory infections. Unknown for COVID-19.
- People with HIV have comorbidities (e.g., CV disease, lung disease, smoking) that increase the risk of severe COVID-19.
- Additional caution for all persons with HIV, especially those with advanced HIV or poorly controlled HIV, is warranted.

www.aidsinfo.nih.gov
DHHS Guidelines: ART and COVID-19

*Persons with HIV Should:*

- Maintain on-hand at least a 30-day (ideally 90-day) supply of ART and other medications.
- Explore changing to mail order delivery of medications when possible.
- Delaying any ART switch until close follow-up and monitoring are possible.
- Some ARV agents (e.g., LPV/RTV, boosted DRV, TDF/FTC), are being evaluated in clinical trials or are prescribed for off label use for the treatment or prevention of COVID-19.
- Do not switch or add ARV drugs to prevent or treat SARS-CoV-2 infection.
DHHS Guidelines: Visits Related to HIV Care

- Weigh risks and benefits of attending, versus not attending in-person, HIV-related clinic appointments at this time.
- Factors to consider:
  - extent of local COVID-19 transmission
  - health needs that will be addressed during the appt
  - HIV status (e.g., CD4, viral load) and overall health
- Telephone or virtual visits may replace face-to-face encounters.
- For persons who have a suppressed HIV viral load and are in stable health, routine medical and laboratory visits should be postponed to the extent possible.
Thanks to:

-- Weill Cornell Division of ID, Department of Medicine, Joint Clinical Trials Office (JCTO)

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https://aidsetc.org/resource/hiv-sars-cov-2-webinar-series