



COVID-19 Update

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Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial

IMPORTANCE

- Ivermectin is widely prescribed as a potential treatment for COVID-19 despite uncertainty about its clinical benefit.

OBJECTIVE

- To determine whether ivermectin is an efficacious treatment for mild COVID-19.

DESIGN, SETTING, AND PARTICIPANTS

- Double-blind, randomized trial conducted at a single site in Cali, Colombia.
- Potential study participants were identified by simple random sampling from the state's health department electronic database of patients with symptomatic, laboratory-confirmed COVID-19 during the study period.
- A total of 476 adult patients with mild disease and symptoms for 7 days or fewer (at home or hospitalized)

INTERVENTION

- Patients randomized to receive ivermectin, 300 µg/kg of body weight per day for 5 days (n = 200) or placebo (n = 200).

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial

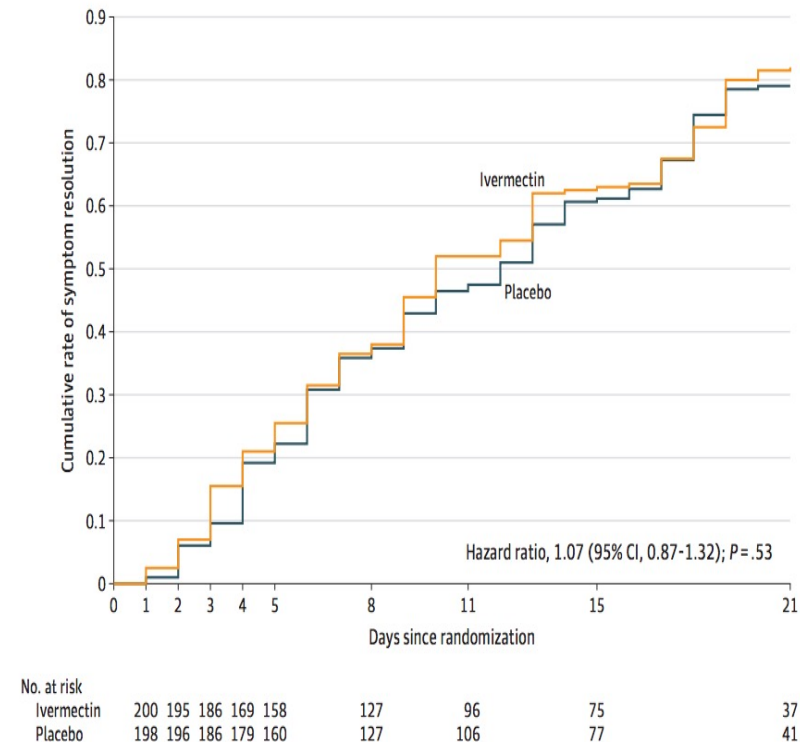
MAIN OUTCOMES AND MEASURES

- Primary outcome was time to resolution of symptoms within a 21-day follow-up period.

RESULTS: Outcomes

- Among 400 patients who were randomized in the primary analysis population (median age, 37 years; 231 women [58%]), 398 (99.5%) completed the trial.
- The median time to resolution of symptoms was:
 - **10 days** (IQR, 9-13) in the ivermectin group
 - **12 days** (IQR, 9-13) in the placebo group
- **HR, 1.07 [95% CI, 0.87 to 1.32]; P = .53**
- By day 21, 82% in the ivermectin group and 79% in the placebo group had resolved symptoms.

Figure 2. Time to Resolution of Symptoms in the Primary Analysis Population



The cumulative rate of symptom resolution is the percentage of patients who experienced their first day free of symptoms. All patients were followed up for 21 days.

Which School Would You Send Your Children?



Credit: <https://www.romper.com/p/what-will-schools-look-like-after-coronavirus-15-photos-offer-a-peek/>

Effect of Ivermectin on Time to Resolution of Symptoms Among Adults With Mild COVID-19: A Randomized Clinical Trial

RESULTS: Adverse Events

- The most common adverse event was headache, reported by 104 patients (52%) given ivermectin and 111 (56%) who received placebo.
- The most common serious adverse event was multiorgan failure, occurring in 4 patients (2 in each group).

CONCLUSION AND RELEVANCE

- A 5-day course of ivermectin, compared with placebo, did not significantly improve the time to resolution of symptoms

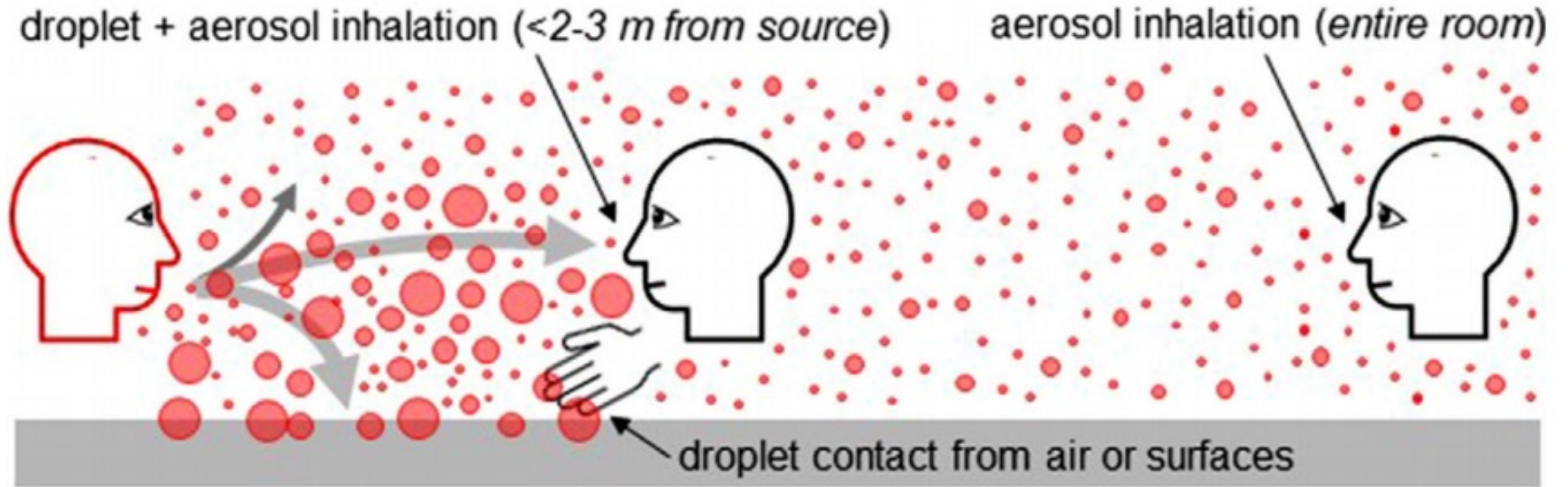
A guideline to limit indoor airborne transmission of COVID-19

SARS-CoV-2 is known to be transported by respiratory droplets exhaled by an infected persons.

There are thought to be three possible routes of human-to-human transmission of COVID-19:

- **Large Drop Contact**
 - Large drop transmission from the mouth of an infected person to the mouth, nose or eyes of the recipient;
 - Physical contact with droplets deposited on surfaces (fomites) and subsequent transfer to the recipient's respiratory mucosae;
- **Airborne Transmission**
 - Inhalation of the microdroplets ejected by an infected person and held aloft by ambient air currents
 - Short range or Long range

”The distinction between large-drop and airborne transmission is somewhat nebulous given the continuum of sizes of emitted droplets”



Review of indoor aerosol generation transport and control in the context of COVID

There are 3 ways of transmission

1. Large droplets inhaled auto inoculated
2. Short range aerosols
3. Large range aerosols

A guideline to limit indoor airborne transmission of COVID-19

PNAS April 27, 2021 118 (17) e2018995118

The Six-Foot Rule is a social distancing recommendation by the CDC is based on the assumption that the primary vector of pathogen transmission is the large drops ejected from the most vigorous exhalation events, coughing and sneezing

- Indeed, high-speed visualization of such events reveals that 6 ft corresponds roughly to the maximum range of the largest, millimeter-scale drops

Compliance to the Six-Foot Rule will thus substantially reduce the risk of such large-drop transmission.

Liquid drops expelled by respiratory events are known to span a considerable range of scales, with radii varying from fractions of a micron to millimeters

A guideline to limit indoor airborne transmission of COVID-19

There is now overwhelming evidence that indoor airborne transmission plays a dominant role in the spread of COVID19 , especially for so-called “superspreading events” which invariably occur indoors

- **At the choir practice that took place in Washington State**, some 53 of 61 attendees were infected, presumably not all of them within 6 ft of the initially infected individual
- **When 23 of 68 passengers were infected on a 2-h bus journey in Ningbo, China**, their seated locations were uncorrelated with distance to the index case
- **The outbreak between residents of a Korean high-rise building** whose apartments were linked via air ducts
- **An analysis of 7,324 early cases outside the Hubei Province**, in 320 cities across mainland China found that:
 - All clusters of three or more cases occurred indoors, 80% arising inside apartment homes and 34% potentially involving public transportation;
 - Only a single transmission was recorded outdoors.

The fact that face mask directives have been more effective than either lockdowns or social distancing in controlling the spread of COVID-19 is consistent with indoor airborne transmission as the primary driver of the global pandemic.

A guideline to limit indoor airborne transmission of COVID-19

PNAS April 27, 2021, 118 (17) e2018995118

By assuming that the respiratory droplets are mixed uniformly through an indoor space a theoretical model was developed that generated a safety guideline for mitigating airborne transmission

The model imposes an upper bound on:

- The product of the number of occupants
- The time spent in a room.

The model also quantifies the extent to which transmission risk is reduced in large rooms with

- High air exchange rates that can:
 - Be increased for more vigorous respiratory activities
 - Dramatically reduced by the use of face masks.

In closed, well-mixed spaces, the pathogen is distributed uniformly throughout.

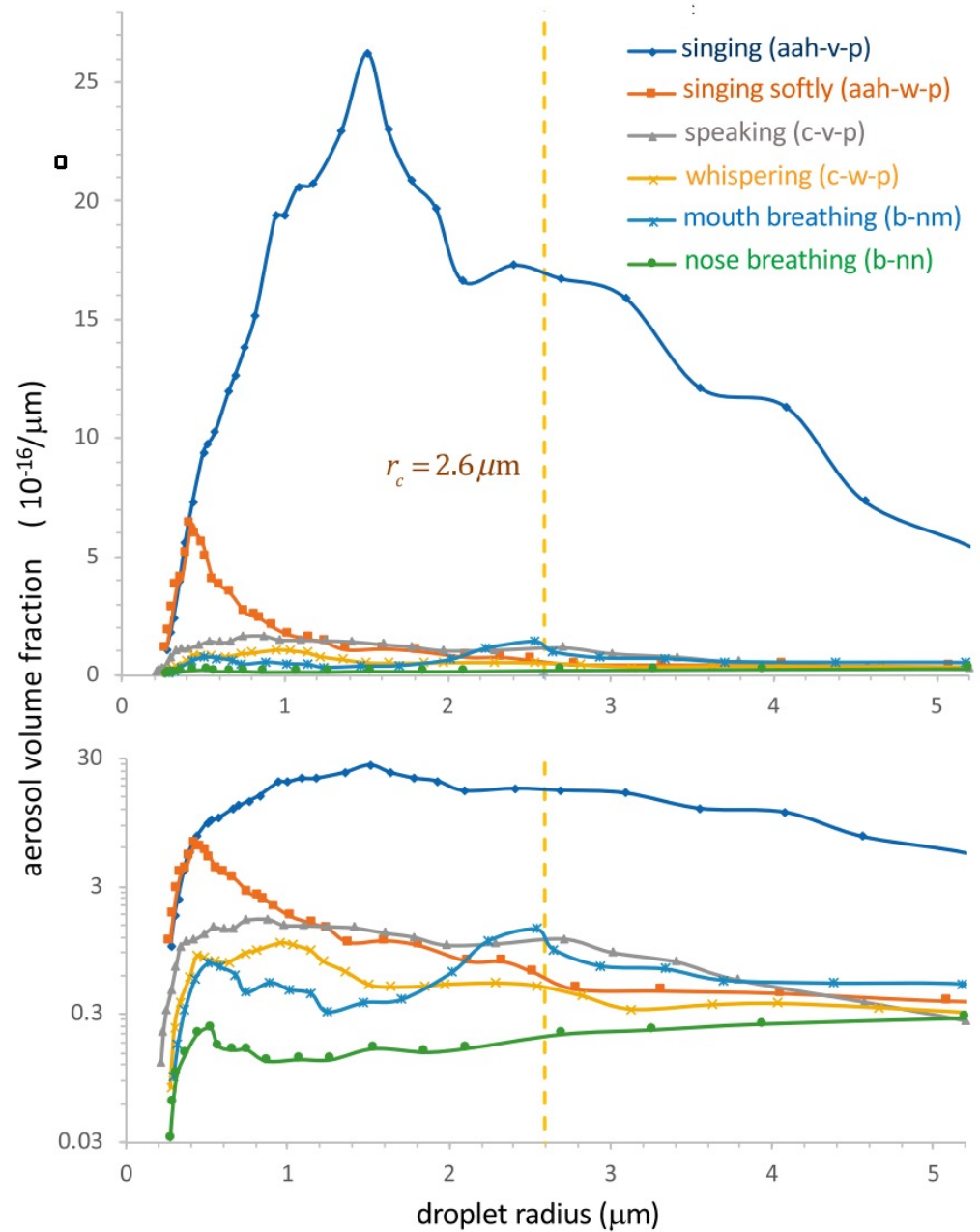
One is no safer from airborne pathogens at 60 ft than 6 ft.

We thus arrive at a simple guideline, appropriate for steady-state situations, that bounds the cumulative exposure time (CET),

$$(N - 1) \tau < \epsilon \frac{\bar{\lambda}_c V + \bar{v}_s A}{Q_b^2 p_m^2 C_q s_r}.$$

A guideline to limit indoor airborne transmission of
COVID-19

A guideline to limit indoor airborne transmission of COVID-19



A guideline to limit indoor airborne transmission of COVID-19

About Room Specifications - Details Human Behavior - Details Frequently Asked Questions

Room Specifications - Details

Total floor area (sq. ft.):

Average ceiling height (ft.):

Ventilation: **3.0 hr⁻¹ (outdoor ACH)**

Filtration System: **MERV 6**

Recirculation Rate: **1.0 hr⁻¹**

Relative Humidity: **60%**

1%: Very Dry 30%: Dry 60%: Average 99%: Very Humid

Need more control over your inputs? Switch to Advanced Mode using the dropdown at the top of the page.

Room Specifications: **Human Behavior:** **Age Group:**

Viral Strain:

To limit COVID-19 transmission* after an infected person enters this space, there should be no more than:

- 2 people for 30 hours
- 5 people for 8 hours
- 10 people for 4 hours
- 25 people for 89 minutes
- 100 people for 28 minutes

In contrast, the six-foot (or two-meter) rule would limit occupancy to 25 people which would violate the guideline* after 89 minutes.

*The guideline restricts the probability of airborne transmissions per infected person to be less than the risk tolerance (10%) over the cumulative exposure time listed. Other risk scenarios are considered in Advanced Mode. Specifically, one may consider the prevalence of infection in the population, immunity acquired through vaccination or previous exposure, and the risk to a specific individual.

A guideline to limit indoor airborne transmission of COVID-19

Navigation: About | **Room Specifications - Details** | Human Behavior - Details | Frequently Asked Questions

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Room Specifications:

Human Behavior:

Age Group:

Viral Strain:

To limit COVID-19 transmission* after an infected person enters this space, there should be no more than:

- 2 people for 44 minutes
- 5 people for 16 minutes
- 10 people for 9 minutes
- 25 people for 5 minutes
- 100 people for 2 minutes



In contrast, the six-foot (or two-meter) rule would limit occupancy to **25 people** which would violate the guideline* after **5 minutes**.

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A guideline to limit indoor airborne transmission of COVID-19

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Room Specifications:

Human Behavior:

Age Group:

Viral Strain:

To limit COVID-19 transmission* after an infected person enters this space, there should be no more than:

- 2 people for >14 days
- 5 people for >14 days
- 10 people for 160 hours (7 days)
- 25 people for 60 hours (3 days) ←
- 100 people for 15 hours

In contrast, the six-foot (or two-meter) rule would limit occupancy to 25 people which would violate the guideline* after 60 hours (3 days).

*The guideline restricts the probability of [airborne transmissions](#) per infected person to be less than the risk tolerance (10%) over the cumulative exposure time listed. Other risk scenarios are considered in Advanced Mode. Specifically, one may consider the prevalence of infection in the population, immunity acquired through vaccination or previous exposure, and the risk to a specific individual.

A guideline to limit indoor airborne transmission of COVID-19

About Room Specifications - Details Human Behavior - Details Frequently Asked Questions

Human Behavior - Details

Breathing Rate: 0.29 ft³/min
Resting

Respiratory Activity: 2.04 q/ft³
Talking (normal)

Mask Type/Efficiency: 50%
Cotton, Flannel

Mask Fit/Compliance: 95%
0%: None 50%: Poor 95%: Good

Need more control over your inputs? Switch to Advanced Mode using the dropdown at the top of the page.

Room Specifications: Classroom

Human Behavior: Custom

Age Group: Children (<15 years)

Viral Strain: SARS-CoV-2 (Wuhan Strain)

To limit COVID-19 transmission* after an infected person enters this space, there should be no more than:

- 2 people for 110 hours (5 days)
- 5 people for 28 hours
- 10 people for 12 hours
- 25 people for 5 hours ←
- 100 people for 79 minutes

In contrast, the six-foot (or two-meter) rule would limit occupancy to 25 people which would violate the guideline* after 5 hours.

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A guideline to limit indoor airborne transmission of COVID-19

This study makes clear the inadequacy of the Six-Foot Rule in mitigating indoor airborne disease transmission

It offers a rational, physically informed alternative for managing life in the time of COVID-19.

If implemented, our safety guideline would impose a limit on the CET in indoor settings, violation of which constitutes an exposure for all the room's occupants.

HIV and COVID: Questions

- Are HIV positive individuals more susceptible to SARS-CoV-2?
- Is HIV a risk factor for COVID-19 Progression?
- What is the effect of ART in Susceptibility and Outcomes of COVID-19?
- What is the impact of COVID on the HIV Epidemic
- What were the lessons from the HIV Pandemic for the COVID-19 Pandemic

VACS: COVID-19 Testing and Outcomes in PWH vs Persons Without HIV

- Compared PWH and COVID-19 (n = 253), PWH and no COVID-19 (n = 2346), HIV-uninfected persons with COVID-19 (n = 504), and HIV-uninfected persons without COVID-19 (n = 4473)
- Persons with HIV were more likely to be tested for COVID-19; HIV did not increase susceptibility to COVID-19, nor incidence of severe disease

COVID-19 Testing	PWH	HIV-	OR (95% CI)*
Alive in 2020, n	30,981	76,745	--
Total tested, n (%) [†]	2599 (8.4)	4977 (6.5)	1.36 (1.29-1.43)
Total COVID-19+, n	253	504	
▪ % of total alive	0.8	0.7	1.38 (1.18-1.61)
▪ % of those tested	9.7	10.1	1.05 (0.89-1.24)

COVID-19 Outcomes, n (%)	PWH (n = 253)	HIV- (n = 504)	HR (95% CI) [‡]
Hospitalization	86 (34.0)	178 (35.3)	1.09 (0.85-1.41)
ICU admission	35 (13.8)	75 (14.9)	1.08 (0.72-1.62)
Intubation	16 (6.3)	40 (7.9)	0.89 (0.49-1.59)
Death	24 (9.5)	56 (11.1)	1.08 (0.66-1.75)

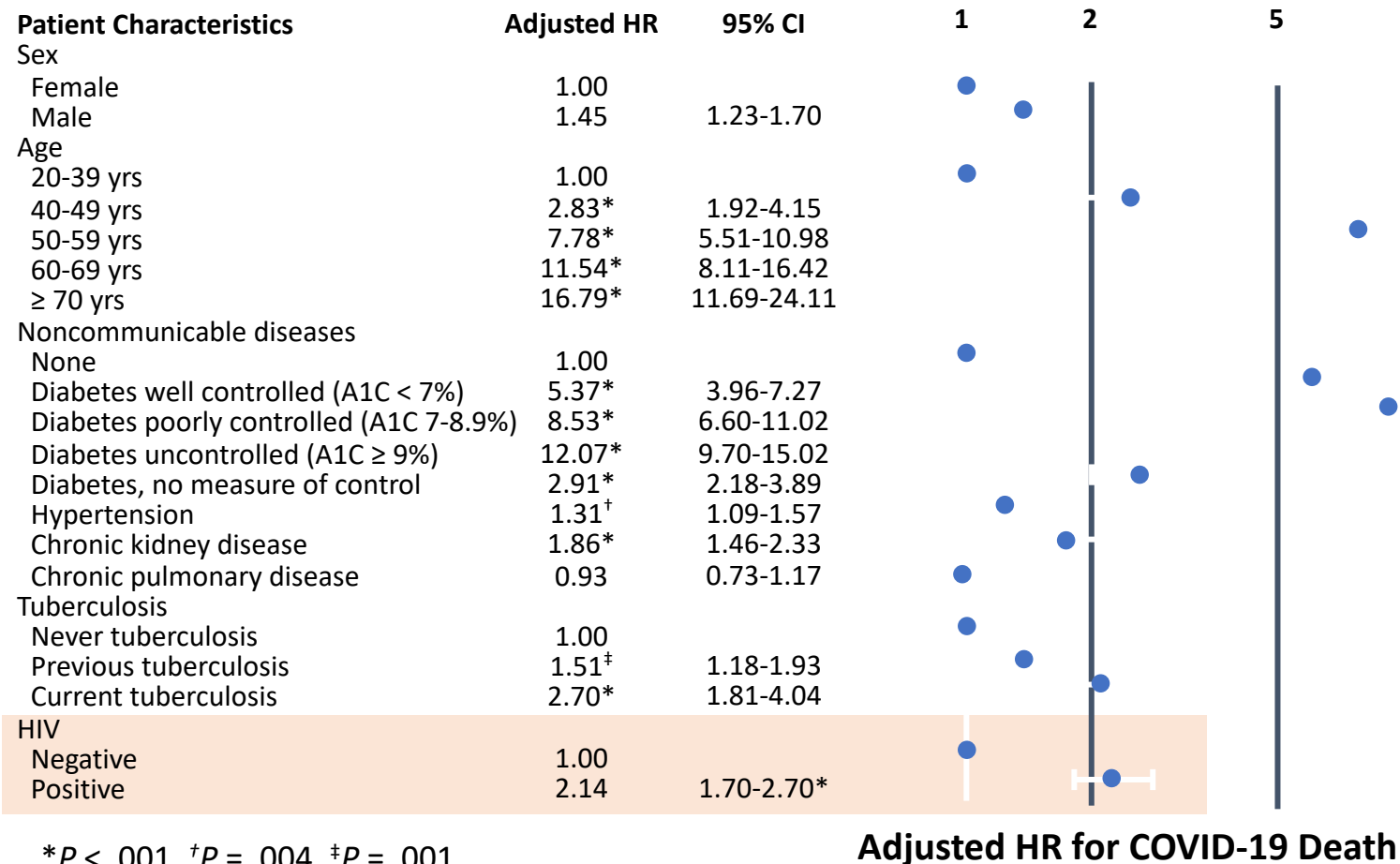
*Adjusted for age, race/ethnicity, sex, BMI, alcohol consumption, smoking. [†] % of total alive in 2020. [‡]Adjusted for age, race/ethnicity, sex.

Incidence and Severity of COVID-19 in Persons With HIV Receiving ART in Spain

- Of 77,590 PWH receiving ART, 236 were diagnosed with COVID-19 in February - April 2020
- Calculated 75-day risk for COVID-19 diagnosis; hospital, ICU admission; and death
 - 151 hospitalizations, 15 admitted to the ICU, 20 deaths
- **PWH did not have increased risk of COVID-19 diagnosis**
- Higher age- and sex-standardized mortality from COVID-19 in PWH (3.7 per 10,000) than in the general population (2.1 per 10,000)
 - In-line with greater all-cause mortality of PWH vs HIV-negative population in Spain
- Study unable to exclude residual confounding, but separately published sensitivity analyses did not change results

COVID-19 and HIV: Routine Public Sector Data in Western Cape, South Africa

- Evaluated factors among all adult public sector patients (N = 3,460,932)



*P < .001. [†]P = .004. [‡]P = .001.

22,308 total persons including 3978 PWH diagnosed with COVID-19

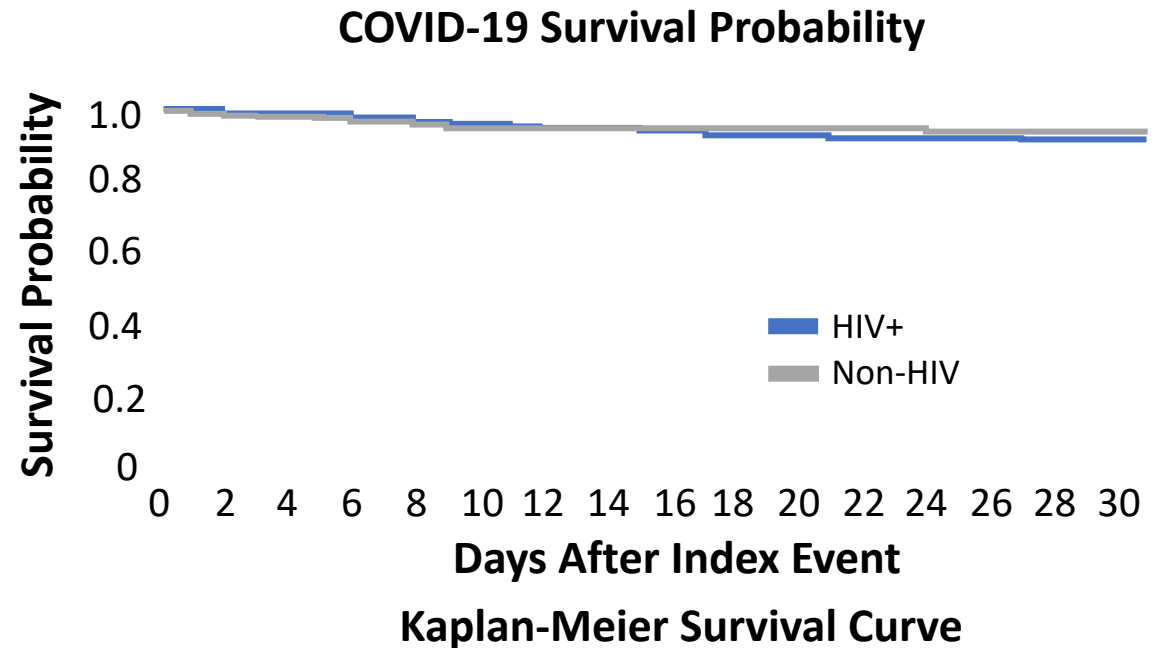
**Standard mortality ratio for COVID-19 death *with vs without* HIV:
2.39 (95% CI: 1.96-2.86)**

Study did not control for social determinants of care



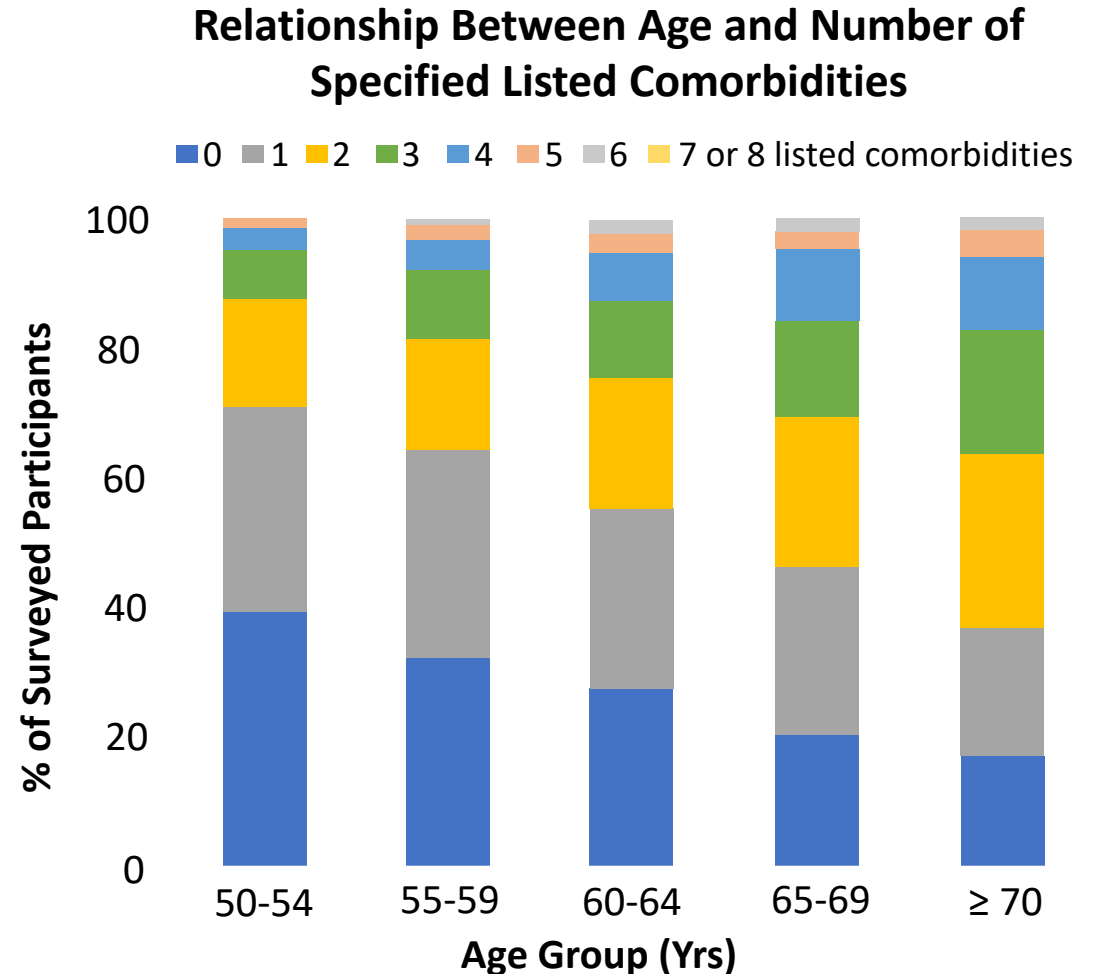
Characteristics and Outcomes of COVID-19 in PWH: Multicenter Research Network

- Outcomes in COVID-19–positive patients with HIV (n = 404) compared with a propensity-matched cohort of patients without HIV (n = 49,763)
- In unmatched analysis, crude mortality higher for HIV
- **After 1:1 matching** (BMI, diabetes, hypertension, chronic lung diseases, chronic kidney disease, race, history of nicotine dependence and sex), mortality no longer significantly different with vs without HIV (risk ratio: 1.33; 95% CI: 0.69-2.57)



Comorbidities Increasingly Common as PWH Age

- National survey of PWH ≥ 50 yrs in UK (n = 4959)
- 97% on ART with viral load measured in last 9 mos
- Comorbidities: hypertension, 31%; hyperlipidemia, 31%; depression, 24%; renal impairment, 15%; CVD, 12%; obesity, 11%; type 2 diabetes, 11%; osteoporosis, 5%
- Multiple comorbidities common in older age groups



Susceptibility



Decreased incidence

Barcelona (n = 53)¹⁴: Standardized incidence rate ratio 38%

Madrid (n = 236)¹⁵: Lower rate of COVID-19 than general population (30 per 100K vs 41.7 per 100K)

Almost all patients on ART, COVID-19 testing limited



Similar incidence

France (n = 12)¹⁶: case series estimated similar crude attack rates (0.31% vs 0.24%); HIV not associated with COVID-19 in multivariable analysis

Wuhan (n = 35)¹⁷: standardized incidence rate 0.38% vs 0.45%

Similar test positivity in VACS (n = 253)¹⁸

Almost all patients on ART, studies conducted during extreme lockdown



Increased test positivity

Higher test positivity among PLWH in San Francisco (n=193)¹⁹

Outcomes



Similar clinical course

Multiple case reports and case series from around the world describe similar disease trajectories among PLWH and HIV-uninfected^{14,17,28-32,33-35}

No increase in severe outcomes in VACS (n = 253) or San Francisco PLWH (n = 193) diagnosed with COVID-19^{18,19}

Small sample sizes, limited duration of follow-up, data collected during exponential growth phase of local epidemic



Worse clinical outcomes

Wuhan (n = 14)²⁰: Higher proportion of severe cases (46% vs 26%) and mortality (18% vs 8%)

South Africa (n = 3,978)²⁰: Higher hazard of death (SMR 2.39 [95% CI 1.96 - 2.86])

Small sample sizes, inadequate comparison populations

Outcomes of COVID-19 in Persons With HIV Receiving ART in Spain—Effect of ART?

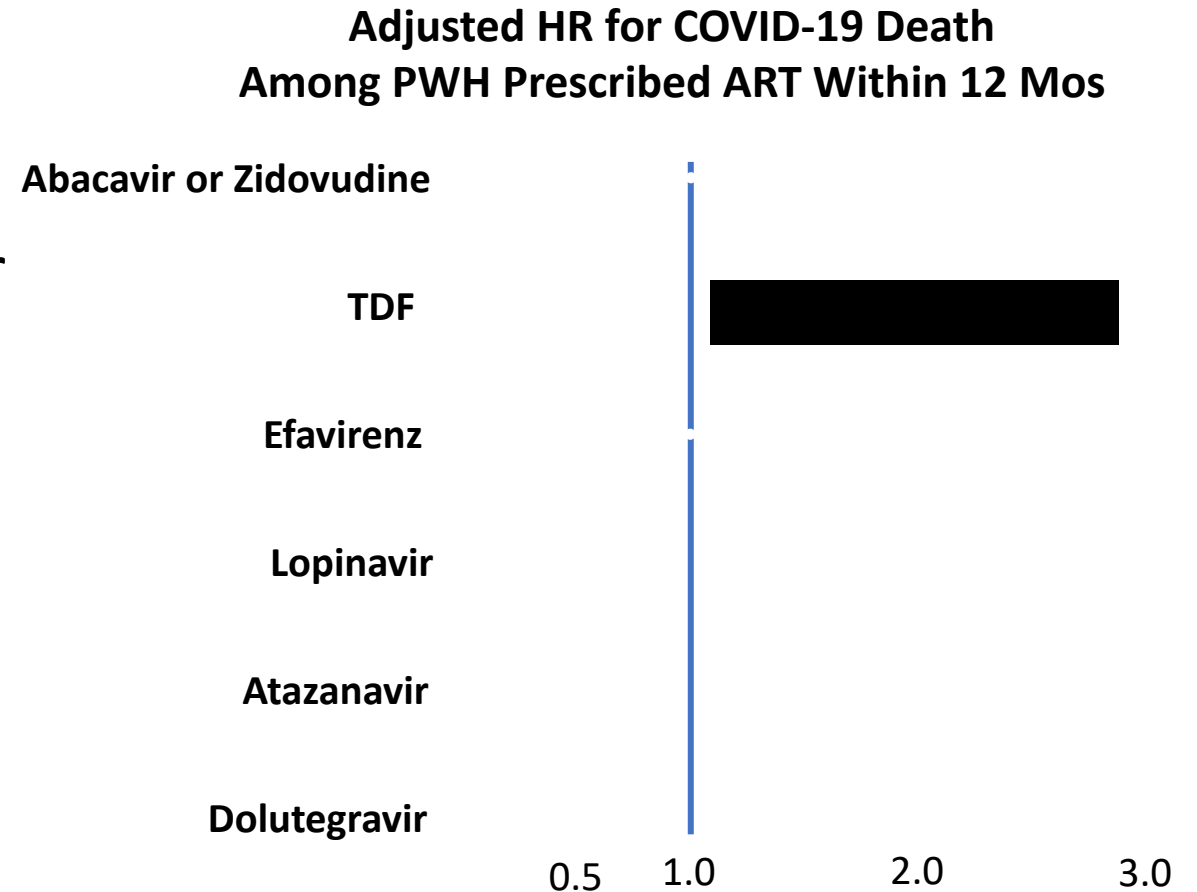
- Patients receiving TDF (but not TAF) had *BETTER* outcomes:
Is TDF protective or are those receiving TDF healthier?

Risk per 10,000 Persons Among PWH Receiving ART (95% CI)		PCR-Confirmed COVID-19 Diagnosis	COVID-19 Hospital Admission	COVID-19 ICU Admission	COVID-19 Death
Overall		30.4 (26.7-34.6)	19.5 (16.5-22.8)	1.9 (1.1-3.2)	2.6 (1.6-4.0)
Standardized*		30.0 (29.8-30.2)	17.8 (17.7-18.0)	2.5 (2.4-2.6)	3.7 (3.6-3.8)
NRTI	▪ FTC/TDF	16.9 (10.5-25.9)	10.5 (5.6-17.9)	0 (-2.9) [†]	0 (-2.9) [†]
	▪ FTC/TAF	39.1 (31.8-47.6)	20.3 (15.2-26.7)	2.7 (1.1-6.5)	3.9 (1.9-7.2)
	▪ ABC/3TC	28.3 (21.5-36.7)	23.4 (17.2-31.1)	3.0 (1.1-6.5)	4.0 (1.7-7.8)
	▪ Other regimens	29.7 (22.6-38.4)	20.0 (14.2-27.3)	1.0 (0.1-3.7)	1.0 (0.1-3.7)

*Standardized by age and sex of general Spanish population aged 20-79 yrs. [†]1-sided 97.5% CI.

COVID-19 Mortality and HIV: Effect of Specific ART in South African Public Sector Data

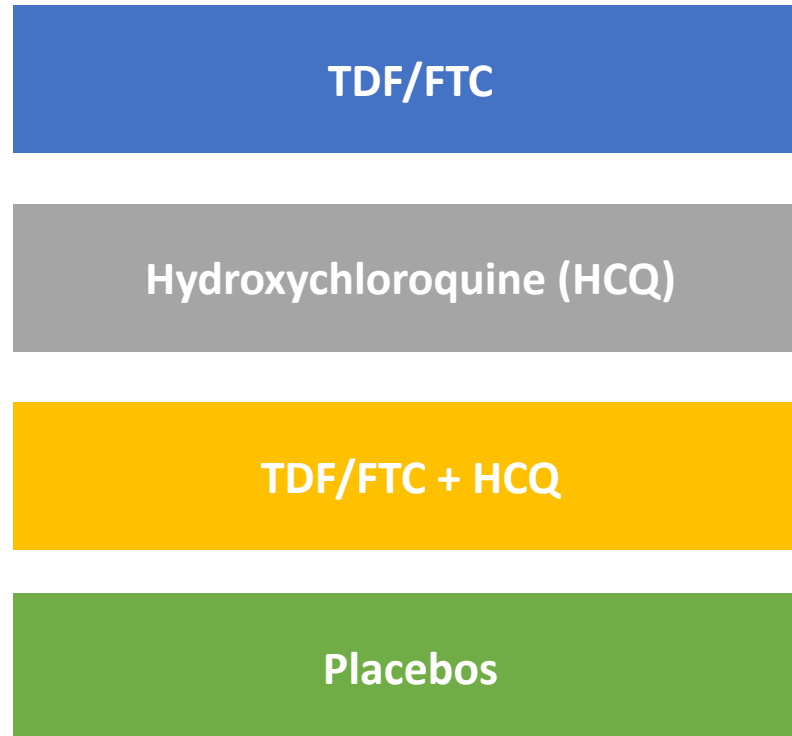
- First line: TDF + XTC + EFV
- Second line: ZDV + 3TC + LPV/r
- DTG introduced January 2020 for both first- and second-line therapy
- Reduced risk of death in TDF group—group “enriched” for first-line therapy, possible confounder



Ongoing Investigation: Drug Prevention of COVID-19

- EPICOS: Randomized trial for prevention of SARS-CoV-2 infection in healthcare personnel

Healthcare workers
(N = 4000)



Endpoint =
Confirmed
symptomatic
COVID-19

Impact of COVID-19 on HIV: HIV Susceptibility

May decrease initially due to the impact of lockdown

Likely to increase due to socioeconomic conditions

Survey of 20238 LGBTW individuals from 138 countries in April-May 2020

- 57.8% reported employment insecurity
- 44% experienced reductions in salary
- 23% reported new food insecurity
- 1% had exchanged sex for money or resources

Impact of COVID-19 on HIV: HIV Testing and Prevention

In LGBTQ study, 50 % uncertain/no access to PrEP during the pandemic

Study of 3,520 PrEP users in Boston reported

- A 72% decrease in PrEP initiation
- A 278 % increase in refill lapses
- A 18% decrease in overall PrEP users

San Francisco reported

- 40% decrease in HIV testing citywide
- 90% decrease in community based HIV testing
- 70% decrease testing for STIs

Sexual Health Clinic in Boston reported 85% decrease in HIV testing

Contact tracers have been deployed to COVID-19 tasks

Impact of COVID-19 on HIV: HIV Treatment

Factors that have affected treatment access:

- Disruption of care services
 - Hospitals, Clinics and Personnel dedicated to HIV redeployed for COVID-19
- Cessation of public transportation due to lockdowns
- Deepening of socioeconomic vulnerabilities
 - Loss of social support and increased food insecurity

Survey of over 10,000 MSM (1000 PLWH) across 20 countries

- Reported that 20 % of PLWH did not have access to their provider
- And that only 14 % had access to telemedicine
- Almost 50% had not been able to refill their HIV medicine remotely

HIV Clinic in San Francisco reported

- 31% increase in the odds of unsuppressed viral loads despite care through telemedicine
 - Homeless disproportionately impacted



Susceptibility

COVID-19 may *increase* HIV risk by socioeconomic downturn^{66,67} or increased injection drug use¹⁰⁵

COVID-19 may *decrease* HIV risk via physical distancing/reducing sexual encounters



Testing

HIV testing *down* in PrEP clinic in Boston⁷⁰

Decreased HIV testing citywide in San Francisco⁷⁸

HIV testing likely *down* in emergency departments with increased SARS-CoV-2 testing



Prevention

PrEP uptake and refills *down* in Boston PrEP clinic⁷⁰

Decreased access to PrEP globally^{67,70,71,77}



Treatment

Decreased access to ART^{76,77,80-83}

Virologic suppression odds *down* in large San Francisco clinic⁸³

Lessons from the HIV Pandemic for the COVID-19 Pandemic

Brown LB, Spinelli MA, Gandhi M. Current
Opinion in HIV AIDS16,(1) January 2021

Racial and ethnic
disparities

Regulatory and approval
process

Public Health Responses

US Guidance on COVID-19 and HIV

CDC^[1]

- Older adults and those with underlying medical conditions (eg, diabetes, heart conditions, COPD, obesity) are at highest risk of life-threatening COVID-19
- PWH not receiving effective ART or with low CD4+ cell counts may also be at increased risk for severe disease
- PWH should not switch their HIV medicine in an attempt to prevent or treat COVID-19
- In case of suppressed HIV viral load, PWH may discuss temporary postponement of routine medical and laboratory visits

NIH^[2]

- Recommendations for treatment in PWH are the same as those for the general population
- In persons with advanced HIV and suspected or documented COVID-19, HIV-associated OIs should be considered in the differential diagnosis of febrile illness
- Pay attention to potential DDIs and overlapping toxicities among COVID-19 treatments, ARV medications, and other comedications
- PWH should be offered the opportunity to participate in clinical trials of vaccines and potential treatments for COVID-19

1. CDC. What to know about HIV and COVID-19. Last updated February 1, 2021.

2. NIH COVID-19 Treatment Guidelines. Special considerations in people with HIV. Last updated October 9, 2020.



Conclusions

To date evidence does not support that people living with HIV have a higher susceptibility to SARS-CoV-2 infection

In Europe and in the US the literature does not support worst outcomes on individuals with HIV and COVID-19

- In South Africa higher deaths were reported in HIV positive individuals with COVID-19 but other confounding factors could explain this

COVID-19 is leading to decrease HIV care in testing, prevention and Treatment, hampering the End the HIV Epidemic effort