COVID-19 epidemic in Europe: What have we learned? And does underlying HIV-infection make a difference?

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Conflict of Interest: JKR

- Honoraria for lectures and/or consultancies from Gilead, Janssen, Merck, Theratechnologies and ViiV.
- Research grants from Dt. Leberstiftung, DZIF, Hectorstiftung, NEAT ID.

COVID-19

- Epidemiology
- Testing
- Clinical course
- Experimental treatments
- Patients with HIV-coinfection
- Learnings

COVID-19

- » **Epidemiology**
- » **Testing**
- » **Clinical course**
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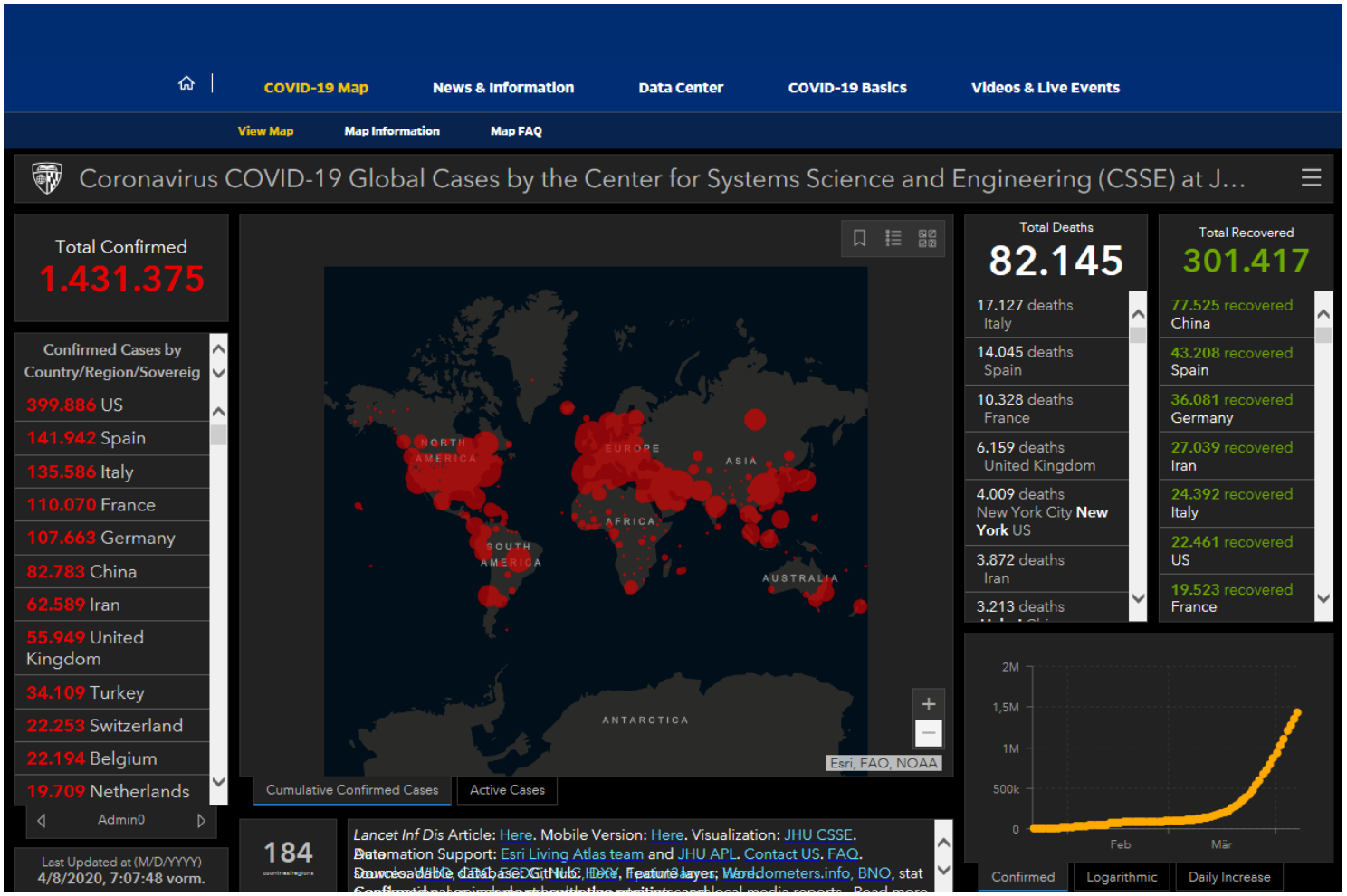
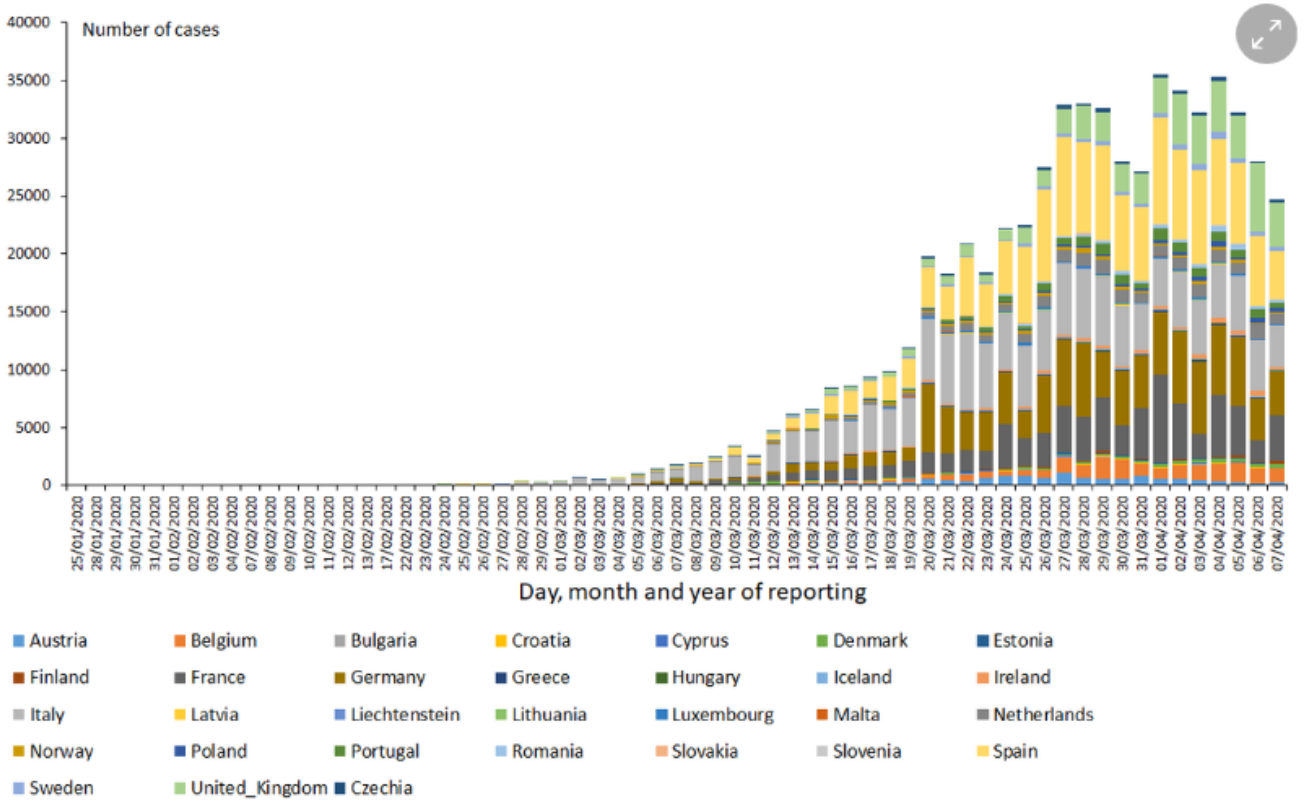
John Hopkins Coronavirrus Resource Center 8 April 2020



Distribution of laboratory confirmed cases of COVID-19 in the EU/EEA and the UK, as of 7th April 2020 (ECDC)



Distribution of laboratory confirmed cases of COVID-19 in the EU/EEA and the UK

Situation update for the EU/EEA and the UK, as of 7th April 2020 (ECDC)

EU/EEA and the UK	Cases	Deaths
Spain	135032	13055
Italy	132547	16525
Germany	99225	1607
France	74390	8911
United_Kingdom	51608	5373
Belgium	20814	1632
Netherlands	18803	1867
Austria	12297	220
Portugal	11730	311
Sweden	7206	477
Norway	5755	59
Ireland	5364	174
Czechia	4822	78
Denmark	4681	187
Poland	4413	107
Romania	4057	157
Luxembourg	2843	41
Finland	2176	27
Greece	1755	79
Iceland	1562	6
Croatia	1222	16
Estonia	1108	19
Slovenia	1021	30
Lithuania	843	14
Hungary	817	47
Bulgaria	549	22
Latvia	542	1
Slovakia	534	2
Cyprus	465	14
Malta	241	0
Liechtenstein	78	1
Total	**608500**	**51059**

COVID-19 in Germany
7.4.2020

Germany:

- 103.375 confirmed cases
- 1810 deaths
- 36.081 resolved infections

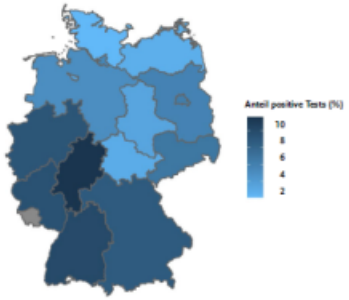
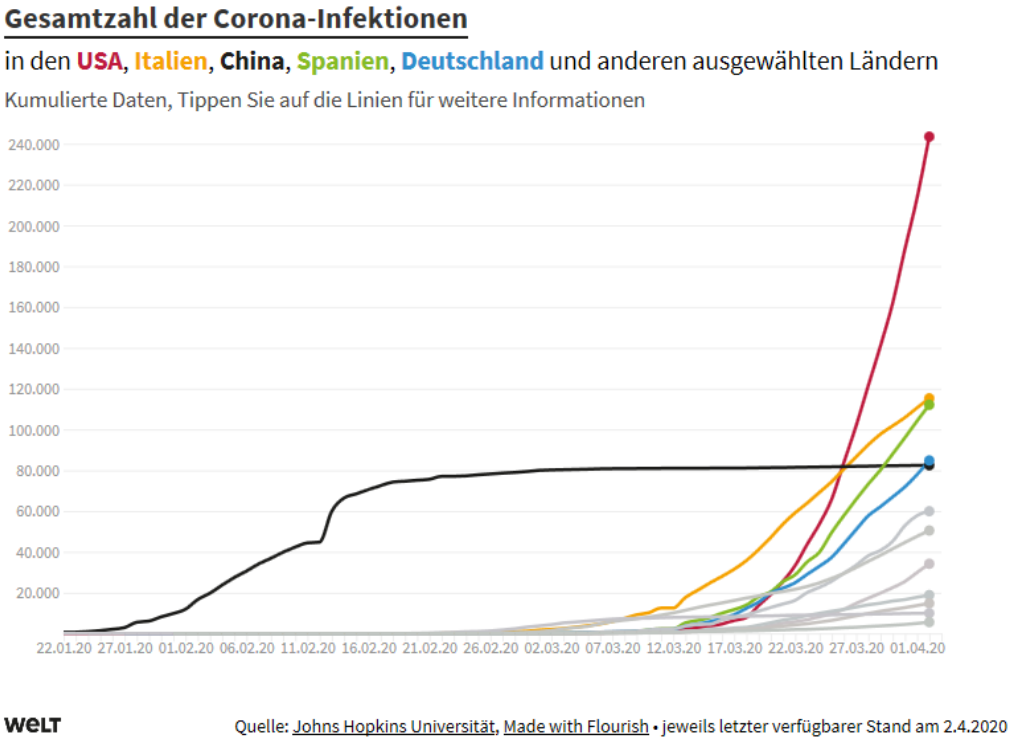


Abb. 3 | Anteil der positiven Tests nach Bundesland; bei weniger als 100 übermittelten Tests werden für das Bundesland keine Ergebnisse angezeigt.



Why are there so big differences in the mortality rates by country?

- Different testing strategies (only testing in symptomatic disease patients versus early screening and self-isolation)
- Difference in median age (15 years difference between Italian COVID-19 patients and German COVID-19 patients)
- In Italy more “3 generation households”
- Differences in intensive care bed equipped with ventilators (In Germany 28,000 intensive care beds equipped with ventilators, or 34 per 100,000 people. By comparison, that rate is 12 in Italy and 7 in the Netherlands.)

COVID-19 in Norway

- **The government in Norway introduced strict measures early in the Corona epidemic including lockdown, closing of borders for foreigners, 14 days quarantine for Norwegians coming back to Norway and closure of schools, churches, universities and more.**
- **Each Corona infected subject now infects on average 0.7 other persons, originally this number was 2-3.**
- **Monday 6th April 2020 5755 infected with Sars-CoV-2 and 59 deaths associated with Covid-19-disease in Norway.**
- **Initiation of general population testing including all asymptomatic individuals**

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Testing

- Using real-time reverse transcription polymerase chain reaction (rRT-PCR) the test can be done on respiratory samples obtained by various methods, including nasopharyngeal swab or sputum sample.
- Results are generally available within a few hours to 2 days.
- Part of the immune response to infection is the production of antibodies including IgM and IgG. These can be used to detect infection in individuals starting 7 days or so after the onset of symptoms, to determine immunity, and in population surveillance.
- Assays can be performed in central laboratories (CLT) or by point-of-care testing (PoCT).
- Medical staff, at particular risk of contracting and spreading the virus, are regularly tested. To streamline the procedure, some hospitals have started doing block tests, using the swabs of 10 employees, and following up with individual tests only if there is a positive result.

Ad hoc laboratory-based surveillance of SARS-CoV-2 by 1 real-time RT-PCR using 2 minipools of RNA prepared from routine respiratory samples

Table 2: Number of minipools tested for SARS-CoV-2 RNA at five different sites, Germany, February – March 2020 (n=60).

Laboratory site	Minipools tested (n=)	Individual samples (n=)	SARS-CoV-2 RT-PCR positive patients (n=)
A (Freiburg)	42	420	1
B (Bonn)	6	100	0
C (Leipzig)	9	90	0
D (Regensburg)	8	80	0
E (Frankfurt)	5	70	0
Total	70	700	0

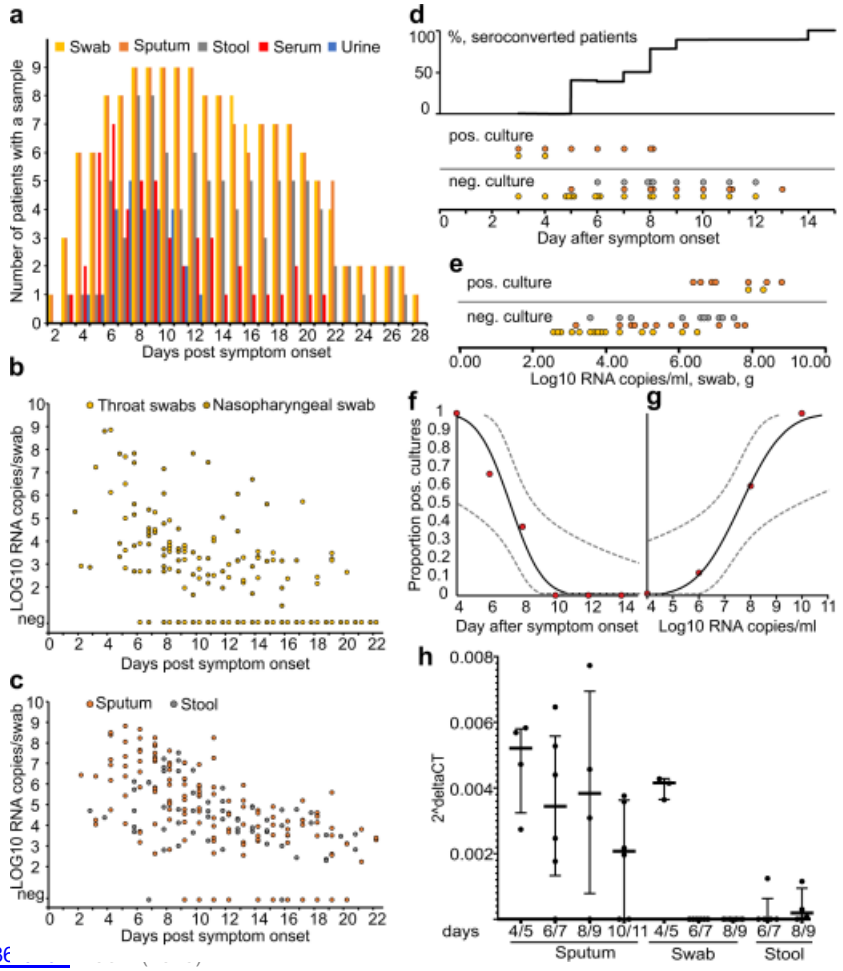
Eis-Hübinger AM et al. MedRxiv 2020; doi: https://doi.org/10.1101/2020.03.30.20043513

Virological assessment of hospitalized patients with COVID-2019

- **Pharyngeal virus shedding was very high during the first week of symptoms (peak at 7.11 × 108 RNA copies per throat swab, day 4).**
- **Infectious virus was readily isolated from throat- and lung-derived samples, but not from stool samples, in spite of high virus RNA concentration. Blood and urine never yielded virus.**
- **Active replication in the throat was confirmed by viral replicative RNA intermediates in throat samples.**
- **Shedding of viral RNA from sputum outlasted the end of symptoms. Seroconversion occurred after 7 days in 50% of patients (14 days in all), but was not followed by a rapid decline in viral load.**

Wölfel, R. et al. Virological assessment of hospitalized patients with COVID-2019. Nature https://doi.org/10.1038/s41586-020- 2196-x (2020).

Hallmarks of viral shedding in aggregated samples.



Testing: remaining challenges

- **With declining viral load pharyngeal PCR can become negative in later stages of disease whereas sputum is still positive.**
- **ELISA tests may have low specificity and sensitivity; more test evaluations need to happen**
- **Increasing testing capacities**
- **Different testing strategies: range from one center centrally to public health organized testing sites, drive-through testing and more…..**

UMC Utrecht: COVID Response

Testing: Covid-19 drive through testing site for employees

Testing of patients and HCW by real time PCR (n= currently 400/day)

Drive through and walk through in the parking garage of the hospital to test health care workers with clinical symptoms

Capacity: 228 HCW/day

Also open to employees of ambulance and other health care organisations

Reports by email to occupational physician and to authorities

Drive through: one **central place** for Covid-19 testing for HCW

Drive through UMC Utrecht

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Natural course of disease

» **There seem to be different stages of illness that patients may move through.**

- (#1) Replicative stage – Viral replication occurs over a period of several days. An innate immune response occurs, but this response fails to contain the virus. Relatively mild symptoms may occur due to direct viral cytopathic effect and innate immune responses.
- (#2) Adaptive immunity stage – An adaptive immune response eventually kicks into gear. This leads to falling titers of virus. However, it may also increase levels of inflammatory cytokines and lead to tissue damage – causing clinical deterioration. There is a suggestion that this could lead to virusiniduced hemophagocytic lymphohistiocytosis (HLH)

- Incubation is a median of ~4-5 days (interquartile range of 2-7 days), with a range up to 14 days
- Typical evolution of severe disease
  - Dyspnea ~ 6 days post exposure.
  - Admission after ~8 days post exposure.
  - ICU admission/intubation after ~10 days post exposure. However, this timing may be variable (some patients are stable for several days after admission, but subsequently deteriorate rapidly).

Symptoms of COVID-19

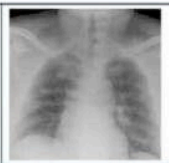
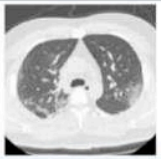
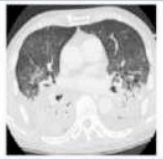
Symptoms near the time of presentation in various cohorts

	Guan et al. NEJM (largest cohort)	Shi et al Lancet	Yang et al. Lancet (critically ill pts)	Chen et al.	Huang et al.	Xu et al. BMJ
Constitutional						
Fever	473/1081 (43%)	18/21 (86%)	46/52 (88%)	82/99 (83%)	40/41 (98%)	48/62 (77%)
Myalgia	164/1081 (15%)		6/52 (12%)	11/99 (11%)		
Headache	150/1081 (14%)	2/21 (10%)	3/52 (6%)	8/99 (8%)	2/38 (8%)	21/62 (34%)
Upper respiratory						
Rhinorrhea	53/1081 (5%)	5/21 (24%)	3/52 (6%)	4/99 (4%)		
Sore throat	153/1081 (14%)			5/99 (5%)		
Lower respiratory						
Dyspnea	205/1081 (19%)	9/21 (43%)	33/52 (64%)	31/99 (31%)	22/40 (55%)	2/62 (3%)
Chest tightness		5/21 (24%)				
Cough	745/1081 (68%)	15/21 (71%)	40/52 (77%)	81/99 (82%)	31/41 (76%)	50/62 (81%)
Sputum	370/1081 (34%)	3/21 (14%)			11/39 (28%)	35/62 (56%)
Hemoptysis	10/1081 (1%)				2/39 (5%)	2/62 (3%)
Gastrointestinal						
Nausea/Vomiting	55/1081 (5%)	2/21 (10%)	2/52 (6%)	1/99 (1%)		
Diarrhea	42/1081 (4%)	1/21 (5%)		2/99 (2%)	1/38 (3%)	3/62 (8%)

-The Internet Book of Critical Care, by @PulmCrit

Global picture of severe cases

Typical features according to current publications
Age Mean (SD) 55,5 (13-1), Male (68%)
Exposure to Huanan seafood market in Wuhan, China (49%)
Chronic medical underlying illness (51%)
Admission to Intensive Care Unit (23%)

INCUBATION PERIOD and ONSET OF SYMPTOMS 3 DAYS AGO

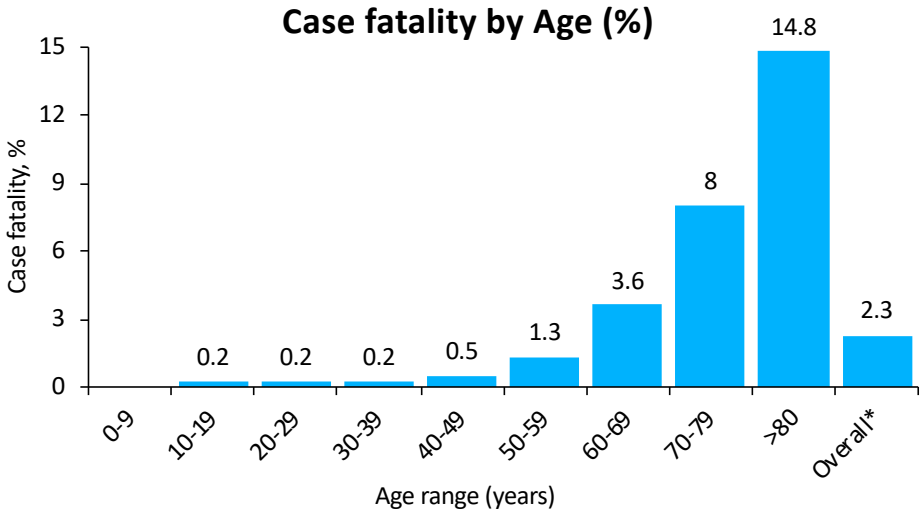
	FIRST WEEK				SECOND WEEK				LONG TERM INFO PENDING
SETTING	WARD Illness day 4	WARD Illness day 5	WARD Illness day 6	WARD Illness day 7	WARD/ICU Illness day 8	ICU Illness day 9	ICU Illness day 10	ICU Illness day 11	
REPEATED SAMPLING OF THE NASOPHARYNX AND TRACHEAL ASPIRATES (IF INTUBATED) BY rRT-PCR FOR THE COVID-19	Initial important viral shedding		Decrease of the viral shedding sometimes associated with transient respiratory deterioration		Respiratory failure, increase of the viral shedding and viremia or Decrease of the viral shedding, and superinfections			Duration of viral excretion unknown	
OXYGEN THERAPY AND MECHANICAL VENTILATION	NO		Consider oxygen support	FNC	FNC followed by MV	MV		MV	
ORGAN FAILURE	**Typical signs according to current publications** Fever, cough, and shortness of breath (15%) bilateral pneumonia (75%), lymphopenia (35%), thrombocytopenia (12%), prothrombin time decreased (30%), elevated liver enzyme levels (about 30%)		Deterioration of respiratory status with most often spontaneous recovery		ARDS If shock beware of superinfections ⚠ Possible renal failure Neurological failure unlikely Hemostasis disorders			YES	
CO-INFECTION/SUPERINFECTION	NOT LIKELY				Consider a possible HAP/VAP and other nosocomial infections (see text for diagnostic procedures)			Profound immune paralysis and late onset infections	
ANTIBIOTICS	NO				Consider antibiotic therapy			YES	
ANTIVIRAL AGENTS	NO				Consider antiviral agents if deterioration[a]				

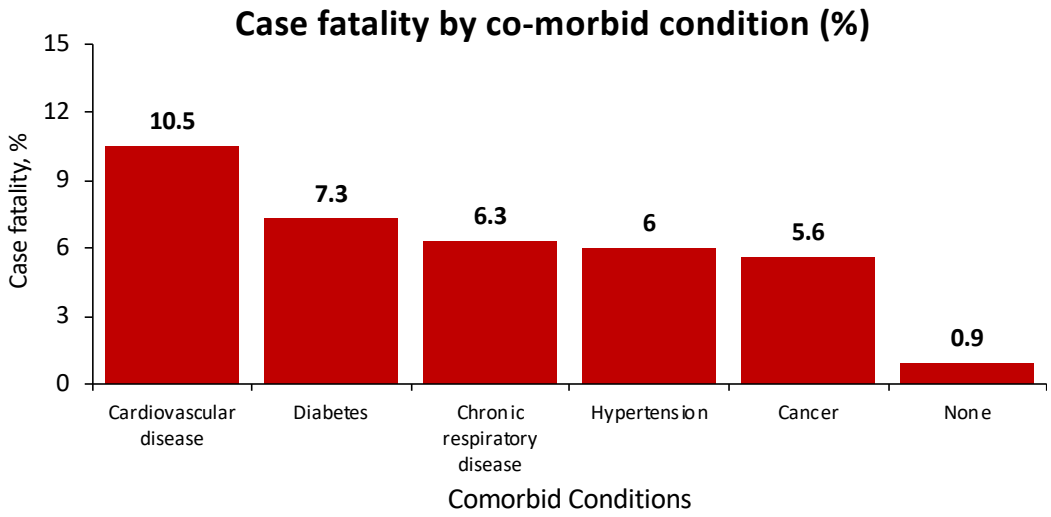
FNC = flow nasal cannula; HFNC = high flow nasal cannula; HAP = healthcare-associated pneumonia; VAP = ventilator-associated pneumonia; MV = Mechanical ventilation;
[a] The use of immunomodulation including corticosteroids is unlikely but debated

Fig. 1 Global picture of severe cases

Bouadma L et al. Intensive Care Med

Case Fatality Rate Based on Age and Comorbidities





The global case fatality rate for COVID-19 infected patients is estimated to be 2.3%* and disproportionally affects those of older age and those with comorbidities

* Case fatality rate ranges from 1-3%; Infection is ongoing and additional research is needed

1. Liu et al. 2020;41(2):145–151. DOI:10.3760/cma.j.issn.0254-6450.2020.02.003
2. China CDC Weekly Fb 17, 2020 http://weekly.chinacdc.cn/en/article/id/e53946e2-c6c4-41e9-9a9b-fea8db1a8f51

Cardiovascular involvement

JAMA Cardiology | Review

Potential Effects of Coronaviruses on the Cardiovascular System
A Review

Mohammad Madjid, MD, MS; Payam Safavi-Naeini, MD; Scott D. Solomon, MD; Orly Vardeny, PharmD

IMPORTANCE Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19) has reached a pandemic level. Coronaviruses are known to affect the cardiovascular system. We review the basics of coronaviruses, with a focus on COVID-19, along with their effects on the cardiovascular system.

OBSERVATIONS Coronavirus disease 2019 can cause a viral pneumonia with additional extrapulmonary manifestations and complications. A large proportion of patients have underlying cardiovascular disease and/or cardiac risk factors. Factors associated with mortality include male sex, advanced age, and presence of comorbidities including hypertension, diabetes mellitus, cardiovascular diseases, and cerebrovascular diseases. Acute cardiac injury determined by elevated high-sensitivity troponin levels is commonly observed in severe cases and is strongly associated with mortality. Acute respiratory distress syndrome is also strongly associated with mortality.

CONCLUSIONS AND RELEVANCE Coronavirus disease 2019 is associated with a high inflammatory burden that can induce vascular inflammation, myocarditis, and cardiac arrhythmias. Extensive efforts are underway to find specific vaccines and antivirals against SARS-CoV-2. Meanwhile, cardiovascular risk factors and conditions should be judiciously controlled per evidence-based guidelines.

JAMA Cardiol. doi:10.1001/jamacardio.2020.1286
Published online March 27, 2020.

Viewpoint and Editorial
Related articles

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Renin–Angiotensin–Aldosterone System Inhibitors in Patients with Covid-19

Key Points Related to the Interplay between Covid-19 and the Renin–Angiotensin–Aldosterone System

- ACE2, an enzyme that physiologically counters RAAS activation, is the functional receptor to SARS-CoV-2, the virus responsible for the Covid-19 pandemic
- Select preclinical studies have suggested that RAAS inhibitors may increase ACE2 expression, raising concerns regarding their safety in patients with Covid-19
- Insufficient data are available to determine whether these observations readily translate to humans, and no studies have evaluated the effects of RAAS inhibitors in Covid-19
- Clinical trials are under way to test the safety and efficacy of RAAS modulators, including recombinant human ACE2 and the ARB losartan in Covid-19
- Abrupt withdrawal of RAAS inhibitors in high-risk patients, including those who have heart failure or have had myocardial infarction, may result in clinical instability and adverse health outcomes
- Until further data are available, we think that RAAS inhibitors should be continued in patients in otherwise stable condition who are at risk for, being evaluated for, or with Covid-19

Vaduganathan M et al. N Engl J Med 2020

Coagulopathy Associated with COVID-19

- •Upon presentation of COVID-19, the measurements advised, in order of importance, are of d-dimer, prothrombin time, and platelet counts.
- •Increased d-dimers are commonly reported in patients with severe illness and may predict mortality.
- •Prolongation in prothrombin times and degree of thrombocytopenia (100–150 × 109/L) have been modest.
- •In addition to the above parameters, fibrinogen should be monitored; nonsurvivors with severe illness have developed disseminated intravascular coagulation around day 4; significant worsening in these parameters at days 10 and 14 was also reported.
- •The panel advises use of prophylactic dose low-molecular-weight heparin unless there is active bleeding or a platelet count of <25 × 109/L; it is hoped that this strategy will impact septic-like coagulopathy and protect against venous thromboembolism.
- •Bleeding has been rare, but if present, panelists advise keeping platelet counts >50 × 109/L (and >20 × 109/L goal in nonbleeding patients), fibrinogen >2.0 g/L, and the prothrombin ratio <1.5.

Thachil J et al. ISTH interim guidance on recognition and management of coagulopathy in COVID‐19. J Thromb Haemost 2020 Mar 25; [e-pub]. (https://doi.org/10.1111/JTH.14810)
Stein B. NEJM Journal watch 2020

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Treatment: lopinavir/r

- After the emergence of severe acute respiratory syndrome (SARS) in 2003, screening of approved drugs identified lopinavir, a HIV aspartate protease inhibitor, as having in vitro inhibitory activity against SARS-CoV, the virus that causes SARS in humans.
- Lopinavir showed in vitro antiviral activity against SARS at concentration of 4 ug/ml. However, when combined with ribavirin, lopinavir appears considerably more effective (with an inhibitory concentration of 1 ug/mL (Chu et al. 2004).
- Up-front treatment in SARS with lopinavir/ritonavir combined with ribavirin correlated with reduced mortality (2.3% versus 16%). However, rescue therapy with lopinavir/ritonavir (often without concomitant ribavirin) didn't seem to make any difference (Chan 2003)

Treatment: lopinavir/r

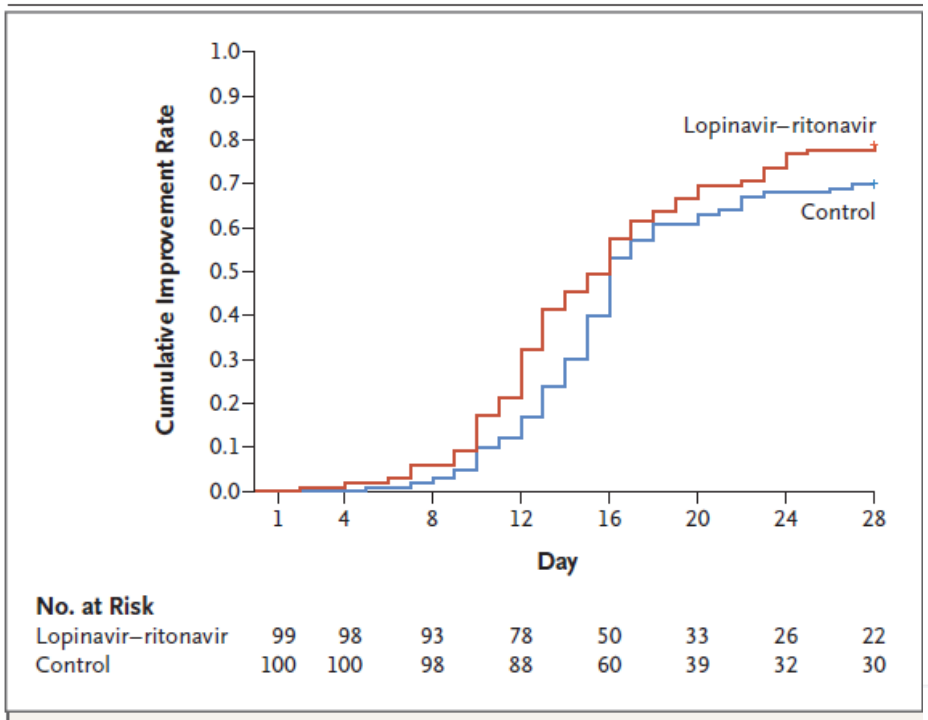

Figure 2. Time to Clinical Improvement in the Intention-to-Treat Population.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19

B. Cao, Y. Wang, D. Wen, W. Liu, Jingli Wang, G. Fan, L. Ruan, B. Song, Y. Cai, M. Wei, X. Li, J. Xia, N. Chen, J. Xiang, T. Yu, T. Bai, X. Xie, L. Zhang, C. Li, Y. Yuan, H. Chen, Huadong Li, H. Huang, S. Tu, F. Gong, Y. Liu, Y. Wei, C. Dong, F. Zhou, X. Gu, J. Xu, Z. Liu, Y. Zhang, Hui Li, L. Shang, K. Wang, K. Li, X. Zhou, X. Dong, Z. Qu, S. Lu, X. Hu, S. Ruan, S. Luo, J. Wu, L. Peng, F. Cheng, L. Pan, J. Zou, C. Jia, Juan Wang, X. Liu, S. Wang, X. Wu, Q. Ge, J. He, H. Zhan, F. Qiu, L. Guo, C. Huang, T. Jaki, F.G. Hayden, P.W. Horby, D. Zhang, and C. Wang

ABSTRACT

BACKGROUND

No therapeutics have yet been proven effective for the treatment of severe illness caused by SARS-CoV-2.

METHODS

We conducted a randomized, controlled, open-label trial involving hospitalized adult patients with confirmed SARS-CoV-2 infection, which causes the respiratory illness Covid-19, and an oxygen saturation (Sao_2) of 94% or less while they were breathing ambient air or a ratio of the partial pressure of oxygen (Pao_2) to the fraction of inspired oxygen (Fio_2) of less than 300 mm Hg. Patients were randomly assigned in a 1:1 ratio to receive either lopinavir–ritonavir (400 mg and 100 mg, respectively) twice a day for 14 days, in addition to standard care, or standard care alone. The primary end point was the time to clinical improvement, defined as the time from randomization to either an improvement of two points on a seven-category

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Cao at caobin_ben@163.com, to Dr. C. Wang at cyh-birm@263.net, or to Dr. D. Zhang at 1813886398@qq.com.

Drs. Cao, Y. Wang, Wen, W. Liu, Jingli Wang, Fan, L. Ruan, Song, Cai, and M. Wei and Drs. D. Zhang and C. Wang contributed equally to this article.

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ART and COVID-19

Systematic review of the efficacy and safety of antiretroviral drugs against SARS, MERS, or COVID-19: initial assessment

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1. Department of HIV, Hepatitis and Sexually Transmitted Infections, World Health Organization, Geneva, Switzerland.

Conclusions

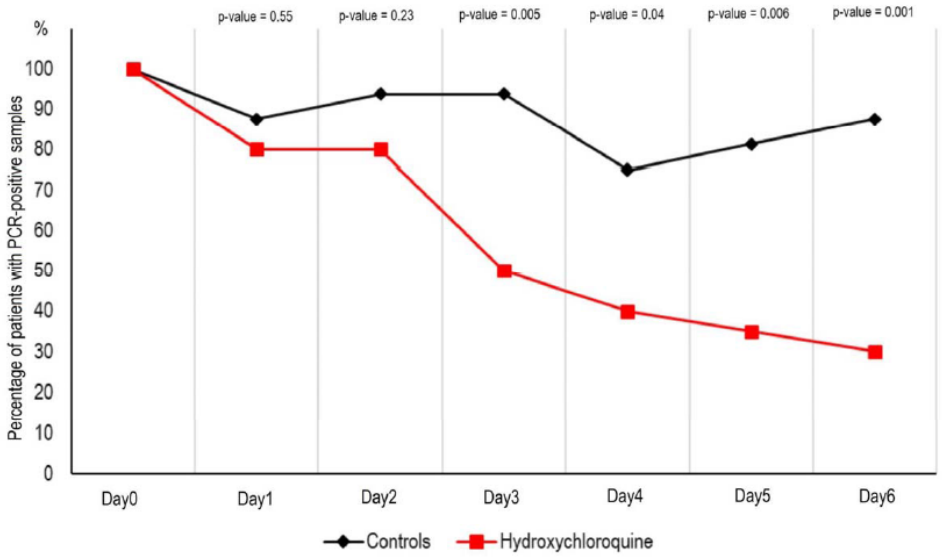
On the basis of the available evidence it is uncertain whether LPV/r and other antiretrovirals improve clinical outcomes or prevent infection among patients at high risk of acquiring COVID-19.

Treatment: hydroxychloroquin/chloroquin

- Chloroquine appears to work via multiple mechanisms, including: Interference with the cellular receptor ACE2 (potentially making it particularly effective against SARS and COVID-19).
- Impairment of acidification of endosomes, which interferes with virus trafficking within cells.
- Chloroquine also has immunosuppressive activities. It's unknown whether such immunosuppressive action could be beneficial or harmful (analogous to steroid therapy).
- In vitro data using cell lines shows that chloroquine can inhibit COVID-19 with an 50% inhibitory concentration of 1 uM, implying that therapeutic levels could be achieved in humans (Wang 2020)
- The 50% inhibitory concentration of chloroquine for SARS is closer to 9 uM, suggesting that chloroquine could be more effective against COVID-19 than SARS (Al-Bari 2017)

Treatment: hydroxychloroquin/chloroquin

Figure 1. Percentage of patients with PCR-positive nasopharyngeal samples from inclusion to day6 post-inclusion in COVID-19 patients treated with hydroxychloroquine and in COVID-19 control patients.



Please cite this work as Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI : 10.1016/j.ijantimicag.2020.105949

Treatment: hydroxychloroquin/chloroquin

	Age (years)			Male gender		Clinical status				Time between onset of symptoms and inclusion (days)		
	Mean ± SD	t	p-value	n (%)	p-value	Asymptomatic	URTI	LRTI	p-value	Mean ± SD	t	p-value
Hydroxychloroquine treated patients (N=20)	51.2 ± 18.7	-1.95	0.06	9 (45.0)	0.65	2 (10.0)	12 (60.0)	6 (30.0)	0.30	4.1 ± 2.6	-0.15	0.88
Control patients (N=16)	37.3 ± 24.0			6 (37.5)		4 (25.0)	10 (62.5)	2 (12.5)		3.9 ± 2.8		
All patients (36)	45.1 ± 22.0			15 (41.7)		6 (16.7)	22 (61.1)	8 (22.2)		4.0 ± 2.6		

URTI: upper tract respiratory infection, LRTI: lower tract respiratory infection

Gautret et al. (2020) Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. International Journal of Antimicrobial Agents – In Press 17 March 2020 – DOI : 10.1016/j.ijantimicag.2020.105949

Journal Pre-proof

No Evidence of Rapid Antiviral Clearance or Clinical Benefit with the Combination of Hydroxychloroquine and Azithromycin in Patients with Severe COVID-19 Infection

Jean Michel Molina Dr Constance Delaugerre Jerome Le Goff Breno Mela-Lima Diane Ponscarme Lauriane Goldwirt Nathalie de Castro

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Key words : Severe acute respiratory syndrome coronavirus 2 Corona virus disease-19 Novel coronavirus pneumonia Hydroxychloroquine Treatment outcome Safety

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Treatment: remdesivir

- Remdesivir might be an excellent antiviral, based on a study involving in vitro and animal data with MERS (e.g. Sheahan 2020).
- Unfortunately, remdesivir is not commercially available. Remdesivir was used on the basis of “compassionate use” for one of the first patients with COVID-19 in the United States (Holshue 2020).
- Remdesvir is currently evaluated in various clinical trials.

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-019-13940-6 OPEN

Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV

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Middle East respiratory syndrome coronavirus (MERS-CoV) is the causative agent of a severe respiratory disease associated with more than 2468 human infections and over 851 deaths in 27 countries since 2012. There are no approved treatments for MERS-CoV infection although a combination of lopinavir, ritonavir and interferon beta (LPV/RTV-IFNb) is currently being evaluated in humans in the Kingdom of Saudi Arabia. Here, we show that remdesivir (RDV) and IFNb have superior antiviral activity to LPV and RTV in vitro. In mice, both prophylactic and therapeutic RDV improve pulmonary function and reduce lung viral loads and severe lung pathology. In contrast, prophylactic LPV/RTV-IFNb slightly reduces viral loads without impacting other disease parameters. Therapeutic LPV/RTV-IFNb improves pulmonary function but does not reduce virus replication or severe lung pathology. Thus, we provide in vivo evidence of the potential for RDV to treat MERS-CoV infections.

Antiviral therapy in asymptomatic or mild disease

» **Limited data**

Treatment: Empiric antimicrobial therapy?

- COVID-19 is no indication for prophylactic antibiotic treatment
- In case of suspected bacterial superinfection
  - Blood cultures and PCT prior to empiric antimicrobial therapy
  - Discontinue < 48h if bacterial superinfection not confirmed
- Secondary infections found in 16% (11/68) of deaths COVID-19 associated (Ruan Q, Yang K, Wang W et al. Intensive Care med 2020
- Diagnostics and treatment similar to ventilator or hospital acquired pneumonia

Treatment for severe acute respiratory distress syndrome

Therapy	Implementation
High-flow nasal oxygen	Might prevent or delay the need for intubation
Tidal volume	Use 6 mL/kg per predicted bodyweight (can reduce to 4 mL/kg per predicted bodyweight)
Plateau airway pressure	Maintain at <30 cm H_2O if possible
Positive end-expiratory pressure	Consider moderate to high levels if needed
Recruitment manoeuvres	Little value
Neuromuscular blockade	For ventilator dyssynchrony, increased airway pressure, hypoxaemia
Prone positioning	For worsening hypoxaemia, PaO_2:FiO_2 <100–150 mm Hg
Inhaled NO	Use 5–20 ppm
Fluid management	Aim for negative fluid balance of 0·5–1·0 L per day
Renal replacement therapy	For oliguric renal failure, acid-base management, negative fluid balance
Antibiotics	For secondary bacterial infections
Glucocorticoids	Not recommended
Extracorporeal membrane oxygenation	Use EOLIA trial criteria[3]

Figure: **Therapeutic options for severe acute respiratory distress syndrome related to coronavirus disease 2019**
ppm=parts per million.

Comment

Treatment for severe acute respiratory distress syndrome from COVID-19

In *The Lancet Respiratory Medicine*, Kollengode Ramanathan and colleagues[1] provide excellent recommendations for the use of extracorporeal membrane oxygenation (ECMO) for patients with respiratory failure from acute respiratory distress syndrome (ARDS) secondary to coronavirus disease 2019 (COVID-19). The authors describe pragmatic approaches to the challenges of delivering ECMO to patients with COVID-19, including training health-care

a PaO_2:FiO_2 ratio of less than 100–150 mm Hg, there are several therapeutic options. The level of positive end-expiratory pressure can be increased by 2–3 cm H_2O every 15–30 min to improve oxygen saturation to 88–90%, with the goal of maintaining a plateau airway pressure of less than 30 cm H_2O. Lower driving pressures (plateau airway pressure minus positive end-expiratory pressure) with a target of 13–15 cm H_2O can also be used. If the patient

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See Online/Health-care Development
https://doi.org/10.1016/S2213-2600(20)30123-1

COVID-19

- Epidemiology
- Testing
- Clinical course
- Experimental treatments
- **Patients with HIV-coinfection**
- Learnings

EACS/BHIVA Statement on risk of COVID-19 for PLWH

- **So far there is no evidence of a higher infection rate or different disease course in people living with HIV (PLWH) than in other people.**
- **Current evidence indicates that risk of severe illness increases with age, male sex and various co-morbidities such as cardiovascular disease, hypertension and diabetes.**
- **Although people with HIV with normal CD4 T-cell count and suppressed HIV RNA have an increased risk of serious illness, many people living with HIV do not have factors that increase their risk. Indeed, almost half of PLWH in the UK are older than 50 years and chronic non-communicable diseases, such as cardiovascular and chronic lung disease, are more common in PLWH than HIV.**
- **It has to be assumed that PLWH who are characterized by a low CD4 T-cell count (<200/µl), or who are not receiving treatment, will also be associated with an increased risk of severe disease presentation.**

In Spain, we have sadly surpassed 100,000 cases of COVID-19 at the time of this writing (April 1, 2020), with a mortality rate of 8.9% among those diagnosed. Quite unexpectedly, we have seen that PLWH are not at increased risk of acquiring COVID-19 or of progressing to acute respiratory distress syndrome (ARDS) once infected, across the 3 risk classes defined above. For reasons that are as yet unknown, it appears that their risk may even be lower than that of the general population.
Josep M. Llibre CCO

CD4-counts during COVID-19

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Reduction and Functional Exhaustion of T Cells in Patients with Coronavirus Disease 2019 (COVID-19)

Posted February 20, 2020.

Bo Diao, Chenhui Wang, Yingjun Tan, Xiewan Chen, Ying Liu, Lifeng Ning, Li Chen, Min Li, Yueping Liu, Gang Wang, Zilin Yuan, Zeqing Feng, Yuzhang Wu, Yongwen Chen

doi: https://doi.org/10.1101/2020.02.18.20024364

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This article is a preprint and has not been peer-reviewed [what does this mean?]. It reports new medical research that has yet to be evaluated and so should *not* be used to guide clinical practice.

Abstract | Info/History | Metrics | Preview PDF

COVID-19 SARS-CoV-2 preprints from medRxiv and bioRxiv

Subject Area

Infectious Diseases (except HIV/AIDS)

Abstract

BACKGROUND The outbreak of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed great threat to human health, which has been declared a public health emergency of international concern (PHEIC) by the WHO. T cells play a critical role in antiviral immunity but their numbers and functional state in COVID-19 patients remain largely unclear. METHODS We retrospectively reviewed the counts of total T cells, CD4+, CD8+ T cell subsets, and serum cytokine concentration from inpatient data of 522 patients with laboratory-confirmed COVID-19, admitted into two hospitals in Wuhan from December 2019 to January 2020, and 40 healthy controls, who came to the hospitals for routine physical examination. In addition, the expression of T cell exhaustion markers PD-1 and Tim-3 were measured by flow cytometry in the peripheral blood of 14 COVID-19 cases. RESULTS The number of total T cells, CD4+ and CD8+ T cells were dramatically

Subject Areas

All Articles

Addiction Medicine
Allergy and Immunology
Anesthesia
Cardiovascular Medicine
Dentistry and Oral Medicine
Dermatology
Emergency Medicine

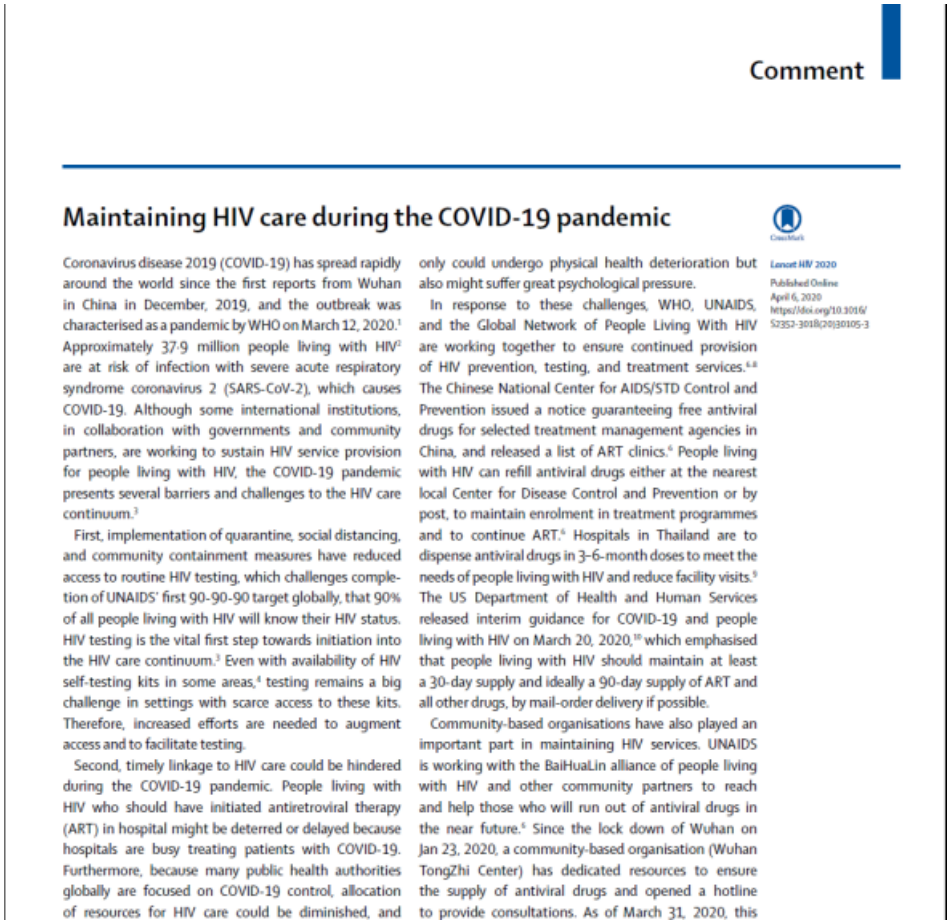
EACS/BHIVA Statement on risk of COVID-19 for PLWH: Recommendations

- For patients with low CD4-counts (<200/ml), or who experience a CD4-decline during a COVID-19 infection, remember to initiate opportunistic infection (OI) prophylaxis.
- More information regarding recommendations for prophylaxis and treatment of specific opportunistic infections can be found in the BHIVA or EACS guidelines for HIV/AIDS.
- Smoking is a risk factor for respiratory infections; smoking cessation should therefore be encouraged for all patients.
- Influenza and pneumococcal vaccinations should be kept up to date.

Cohort/Observational studies in HIV-coinfected patients with COVID-19

- **The NEAT ID Foundation has developed a ‘data dashboard’ to monitor COVID-19 case numbers, hospitalisations and mortality in people with HIV at European and country level. The data will be available for public viewing via www.NEAT-ID.org and if your centre has not signed up, you can do so via this link.**
- **The Lean European Open Survey on SARS-CoV-2 Infected Patients (LEOSS) launched by the German Society for Infectious Diseases (DGI) and ESCMID’s Emerging Infections Task Force (EITaF) an open register based on anonymous questionnaires and they re keen to collaborate with other registries. See https://leoss.net, contact them by email at info@leoss.net and the register can be accessed here https://leoss.net/statistics**

Maintaining HIV care during the COVID-19 pandemic



Comment

Maintaining HIV care during the COVID-19 pandemic

Lancet HIV 2020
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April 6, 2020
https://doi.org/10.1016/S2352-3018(20)30105-3

Coronavirus disease 2019 (COVID-19) has spread rapidly around the world since the first reports from Wuhan in China in December, 2019, and the outbreak was characterised as a pandemic by WHO on March 12, 2020.[1] Approximately 37·9 million people living with HIV[2] are at risk of infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. Although some international institutions, in collaboration with governments and community partners, are working to sustain HIV service provision for people living with HIV, the COVID-19 pandemic presents several barriers and challenges to the HIV care continuum.[3]

First, implementation of quarantine, social distancing, and community containment measures have reduced access to routine HIV testing, which challenges completion of UNAIDS' first 90-90-90 target globally, that 90% of all people living with HIV will know their HIV status. HIV testing is the vital first step towards initiation into the HIV care continuum.[3] Even with availability of HIV self-testing kits in some areas,[4] testing remains a big challenge in settings with scarce access to these kits. Therefore, increased efforts are needed to augment access and to facilitate testing.

Second, timely linkage to HIV care could be hindered during the COVID-19 pandemic. People living with HIV who should have initiated antiretroviral therapy (ART) in hospital might be deterred or delayed because hospitals are busy treating patients with COVID-19. Furthermore, because many public health authorities globally are focused on COVID-19 control, allocation of resources for HIV care could be diminished, and only could undergo physical health deterioration but also might suffer great psychological pressure.

In response to these challenges, WHO, UNAIDS, and the Global Network of People Living With HIV are working together to ensure continued provision of HIV prevention, testing, and treatment services.[6,8] The Chinese National Center for AIDS/STD Control and Prevention issued a notice guaranteeing free antiviral drugs for selected treatment management agencies in China, and released a list of ART clinics.[6] People living with HIV can refill antiviral drugs either at the nearest local Center for Disease Control and Prevention or by post, to maintain enrolment in treatment programmes and to continue ART.[6] Hospitals in Thailand are to dispense antiviral drugs in 3–6-month doses to meet the needs of people living with HIV and reduce facility visits.[9] The US Department of Health and Human Services released interim guidance for COVID-19 and people living with HIV on March 20, 2020,[10] which emphasised that people living with HIV should maintain at least a 30-day supply and ideally a 90-day supply of ART and all other drugs, by mail-order delivery if possible.

Community-based organisations have also played an important part in maintaining HIV services. UNAIDS is working with the BaiHuaLin alliance of people living with HIV and other community partners to reach and help those who will run out of antiviral drugs in the near future.[6] Since the lock down of Wuhan on Jan 23, 2020, a community-based organisation (Wuhan TongZhi Center) has dedicated resources to ensure the supply of antiviral drugs and opened a hotline to provide consultations. As of March 31, 2020, this

Jiang H Lancet 6th April 2020

Liverpool Website on drug-drug interactions

- **http://www.covid19-druginteractions.org/**
-

COVID-19

- » Epidemiology
- » Testing
- » Clinical course
- » Experimental treatments
- » Learnings

Learnings

- **Testing availability and roll-out as well as time-point of implementing lockdown and social distancing measures, determines exponential growth in new infection numbers.**
- **Mortality rates again depend on who is tested and affected predominant populations.**
- **Implementation of infection prevention and control (IPC) strategies are essential.**
- **Experimental therapies at best should be studied in controlled clinical trials.**

COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation

- **1.Testing, followed by contact tracing and isolation of those with positive test results has been applied by all countries that have managed to keep the SARS-CoV-2 virus in check. The epidemiological reasoning is straightforward. Current estimates of the basic reproduction number R0 of COVID-19 are around 2−3. To bend the epidemic curve downwards (which will only happen once the effective reproduction number R <1), we must prevent 50−70% of possible transmissions. Isolation of cases and precautionary self-isolation of contacts are key measures to do that, and the COVID-19 experience from other countries demonstrates that forcefully. Following a positive test result, that person should be isolated to prevent onward transmission. The person's close contacts should be followed up and advised to go into precautionary self-isolation, unless a risk/benefit analysis deems this counterproductive. These measures can prevent a large fraction of possible transmission chains.**

Marcel S et al. Swiss Med Wkly. 2020;150:w20225

COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation

» **2.The Republic of South Korea has had a large epidemic of COVID-19, the cumulative number of cases exceeded 1000 on 26 February. A central part of the control strategy was widespread and easily accessible SARS-CoV-2 testing, linked to contact tracing, and self-isolation. The epidemic curve suggests that the control strategy in South Korea has curtailed the epidemic. The number of new cases peaked on 29 February and had fallen to 84 by 17 March.**

Marcel S et al. Swiss Med Wkly. 2020;150:w20225

COVID-19 epidemic in Switzerland: on the importance of testing, contact tracing and isolation

» **6. A system for antibody testing (serology) will also need to be implemented at large-scale as soon as possible. Antibody testing provides additional information to that obtained from polymerase chain-reaction (PCR) detection of active infection. Antibody testing is the only way to reliably establish the fraction of the population that was infected by the virus − albeit with a delay of a few weeks. A cohort of people with documented infection should be monitored to determine the time to seroconversion, providing crucial input for large-scale testing. People with suspected exposure, healthcare workers in particular, should be tested as high antibody titres likely mean that they are no longer at risk of contracting or spreading the disease and can be preferentially employed in high-risk areas.**

Marcel S et al. Swiss Med Wkly. 2020;150:w20225

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Start › Politik › Innenpolitik › Coronavirus: Kurz für erweiterte Maskenpflicht und „Containment"

Coronavirus: Kurz für erweiterte Maskenpflicht und „Containment"

Online seit: 5. April 2020

Bundeskanzler Sebastian Kurz © APA/Jäger

Für das nach Ostern angekündigte schrittweise Ende des „Shutdown" überlegt die Regierung die Ausdehnung der Maskenpflicht. „Was im Supermarkt Sinn macht, macht natürlich auch in anderen Bereichen des Lebens Sinn", so Kanzler Sebastian Kurz (ÖVP) am Samstag.

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MEISTGELESEN

Coronavirus: 12.026 Infizierte in Österreich

THANK YOU

» **“You cannot fight a fire blindfolded. And we cannot stop this pandemic if we don’t know who is infected.” (World Health Organization Director-General, 16 March 2020).**