COVID-19 update:

Summary of studies

EATG/i-Base zoom meeting:

19 May 2020

Simon Collins

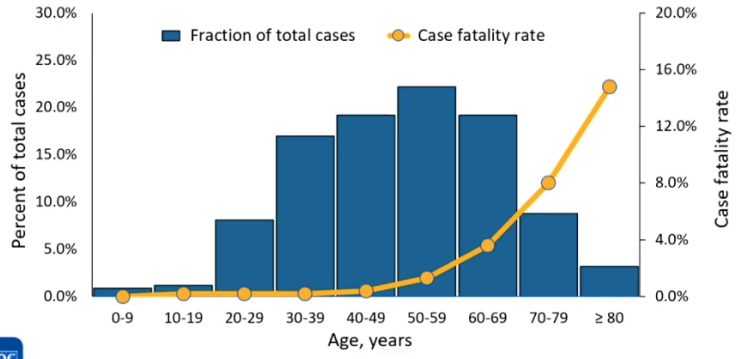
www.i-Base.info

Introduction

- As with HIV, part of response to pandemic is to understand about SARS CoV-2: the virus that causes COVID-19.
- This will help people living with HIV to understand this aspect of our health.
- Same skills as treatment activists.
- This talk highlights research studies, guidelines and resources from the last three issues of the i-Base HIV and COVID-19 bulletin.

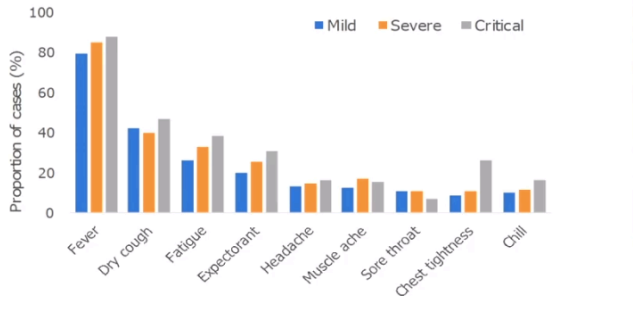
COVID-19: first information from China

Age Distribution and Case Fatality Rate COVID-19
China through 11-Feb-2020 (N = 44,672 confirmed cases)



adapted from Zhang 2020, China CDC Weekly Rep; 2(8):113-122.

Common Symptoms of COVID-19 in China



19230 Confirmed cases with detailed epidemiological investigation information

China CDC/NHC 2020

Key epi/technical insights from China (2 of 3)

2-Natural history:

- At **diagnosis**: approx. 80% are mild/moderate; 15% severe; 5% critical
- **Progression**: approx. 10-15% of mild/moderate cases become severe, and approximately 15-20% of severe become critical
- **Average times:**
  - from exposure to symptom onset is 5-6 days;
  - from symptom onset to recovery for mild cases is 2 weeks and for severe cases is 3-6 weeks;
  - from symptom onset to death is 2-8 weeks
- Truly **asymptomatic** infection is unknown without serology, but appears to be rare using molecular testing (<1%)
  - an estimated **75%** of 'asymptomatic' cases at time of diagnosis soon progress to disease
- **Children** tend to have milder disease than adults

Aylward B et al, WHO-China Mission, 2020

Epidemiology links

Total tests, diagnoses, deaths, by-country, total and adjusted by population etc.
~4,600,00 cases, 312,000 deaths.

- UK data

https://covid.joinzoe.com/data#interactive-map

- WHO daily situation reports

https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports or https://covid19.who.int

- Johns Hopkins:

https://coronavirus.jhu.edu

- Worldometers

https://www.worldometers.info/coronavirus/#repro

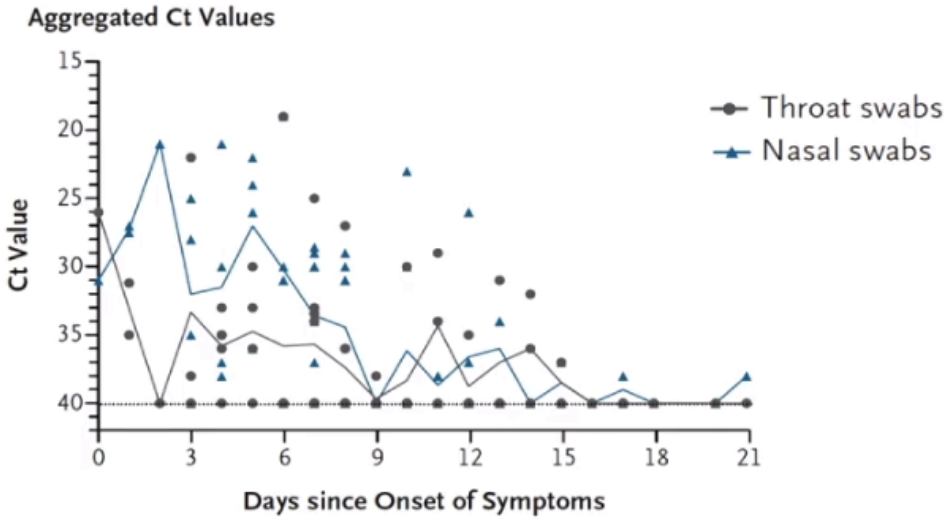
Transmission

- Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1
  http://i-base.info/htb/37421
- Median est. incubation period of COVID-19 is five days – but can be two weeks
  http://i-base.info/htb/37423
- Four papers on CoV-2 transmission: sometimes easy, sometimes rare
  http://i-base.info/htb/37652
- Studies stoke concern about coronavirus contagion through air via speech
  http://i-base.info/htb/37659
- Sexual transmission: saliva, heavier breathing, confined space, two metres…
  http://i-base.info/htb/37451

COVID-19

Viral Shedding Greatest At Time Symptoms Start

- SARS-CoV-2 viral loads in 17 symptomatic patients
- No data regarding duration of replication-competent virus shedding (e.g., culture)



Zou 2020, N Engl J Med; DOI: 10.1056/NEJMc2001737

Symptoms (NHS info)

https://www.nhs.uk

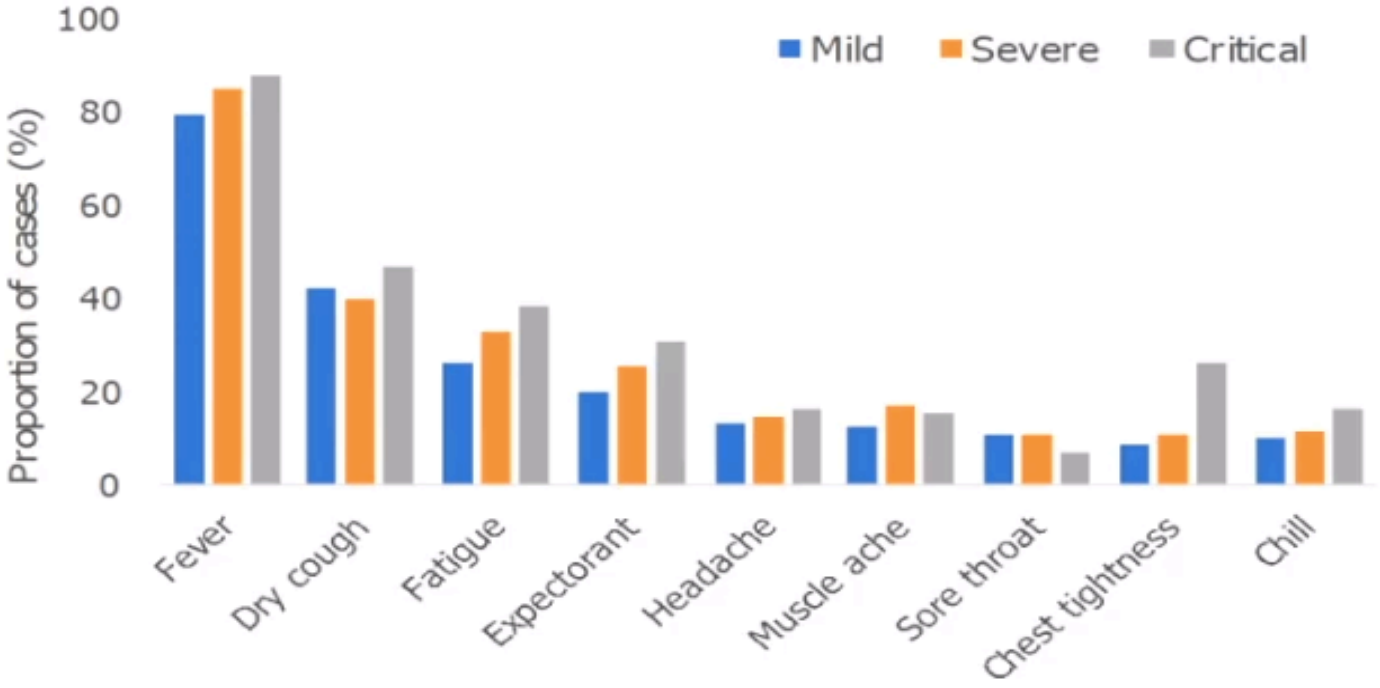
1. High temperature – this means you feel hot to touch on your chest or back (you do not need to measure your temperature)

.**2. New, continuous cough** – this means coughing a lot for more than an hour, or three or more coughing episodes in 24 hours (or having a worse cough than usual)

.

- Loss of smell or taste
- Chest pain or tightness in the chest
- New diarrhoea
- New muscle aches
- Feeling unusually tired
- An unusually hoarse voice
- Unusual stomach pain
- New headaches
- Skipped more meals than normal
- Feeling confused, disorientated or drowsy

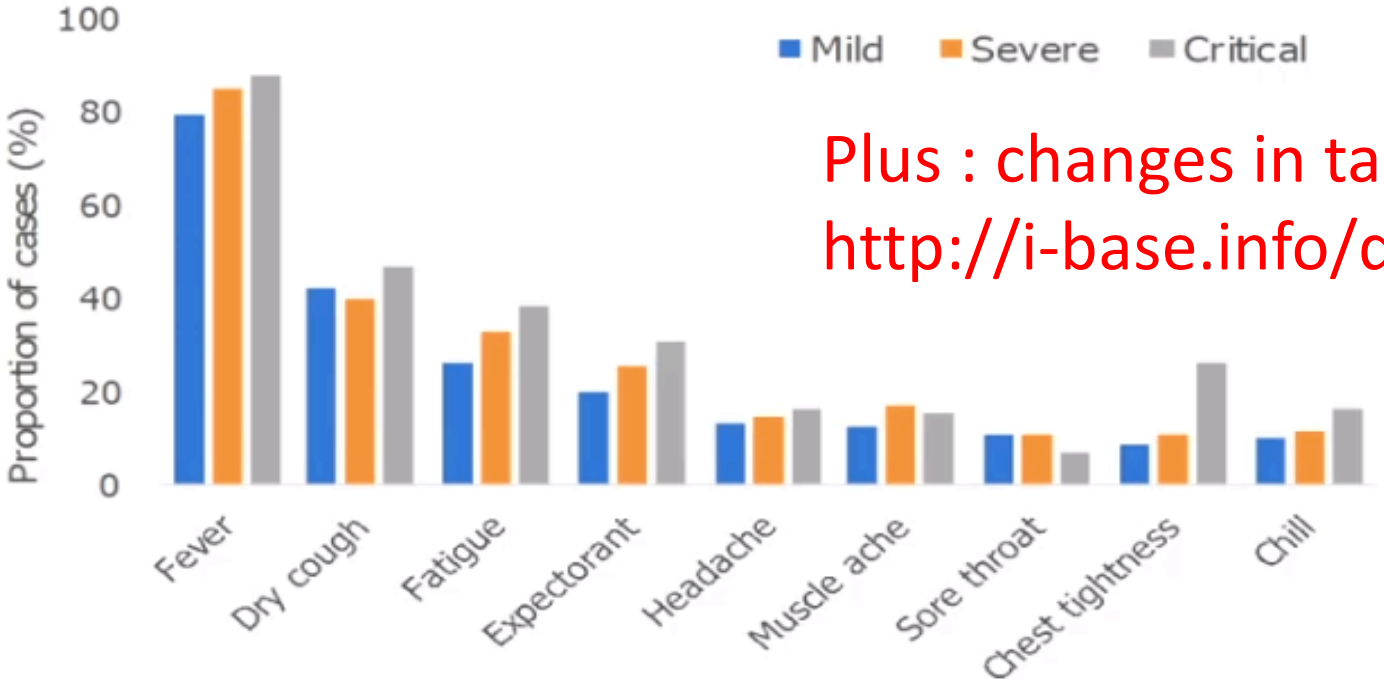
Common Symptoms of COVID-19 in China



19230 Confirmed cases with detailed epidemiological investigation information

China CDC/NHC 2020

Common Symptoms of COVID-19 in China



Plus : changes in taste and smell:
http://i-base.info/qa/15688

19230 Confirmed cases with detailed epidemiological investigation information

China CDC/NHC 2020

ACTION

https://www.nhs.uk

1. 999 if medical emergency

2. symptom checker : NHS 111 - you and/or people you live with
   https://111.nhs.uk/covid-19

2. self isolation: you and people you live with

3. need for hospital care

Pathogenesis/Staging

A clinical-therapeutic staging proposal for COVID-19

http://i-base.info/htb/37627

STAGE I (MILD) – EARLY INFECTION

The initial stage occurs at the time of inoculation and early establishment of disease. For most people, this involves an incubation period associated with mild and often non-specific symptoms such as malaise, fever and a dry cough.

STAGE II (MODERATE) – PULMONARY INVOLVEMENT (IIA) WITHOUT AND (IIB) WITH HYPOXIA (LOW BLOOD OXYGEN):

In the second stage of established pulmonary disease, viral multiplication and localised inflammation in the lung is the norm. During this stage, patients develop pneumonia, with cough, fever and possibly hypoxia (defined as a PaO2/FiO2 of <300 mmHg).

STAGE III (SEVERE) – SYSTEMIC HYPERINFLAMMATION:

A minority of COVID-19 patients will transition into the third and most severe stage of illness, which manifests as an extra-pulmonary systemic hyperinflammation syndrome. In this stage, markers of systemic inflammation appear to be elevated. COVID-19 infection results in a decrease in helper, suppressor and regulatory T cell counts.

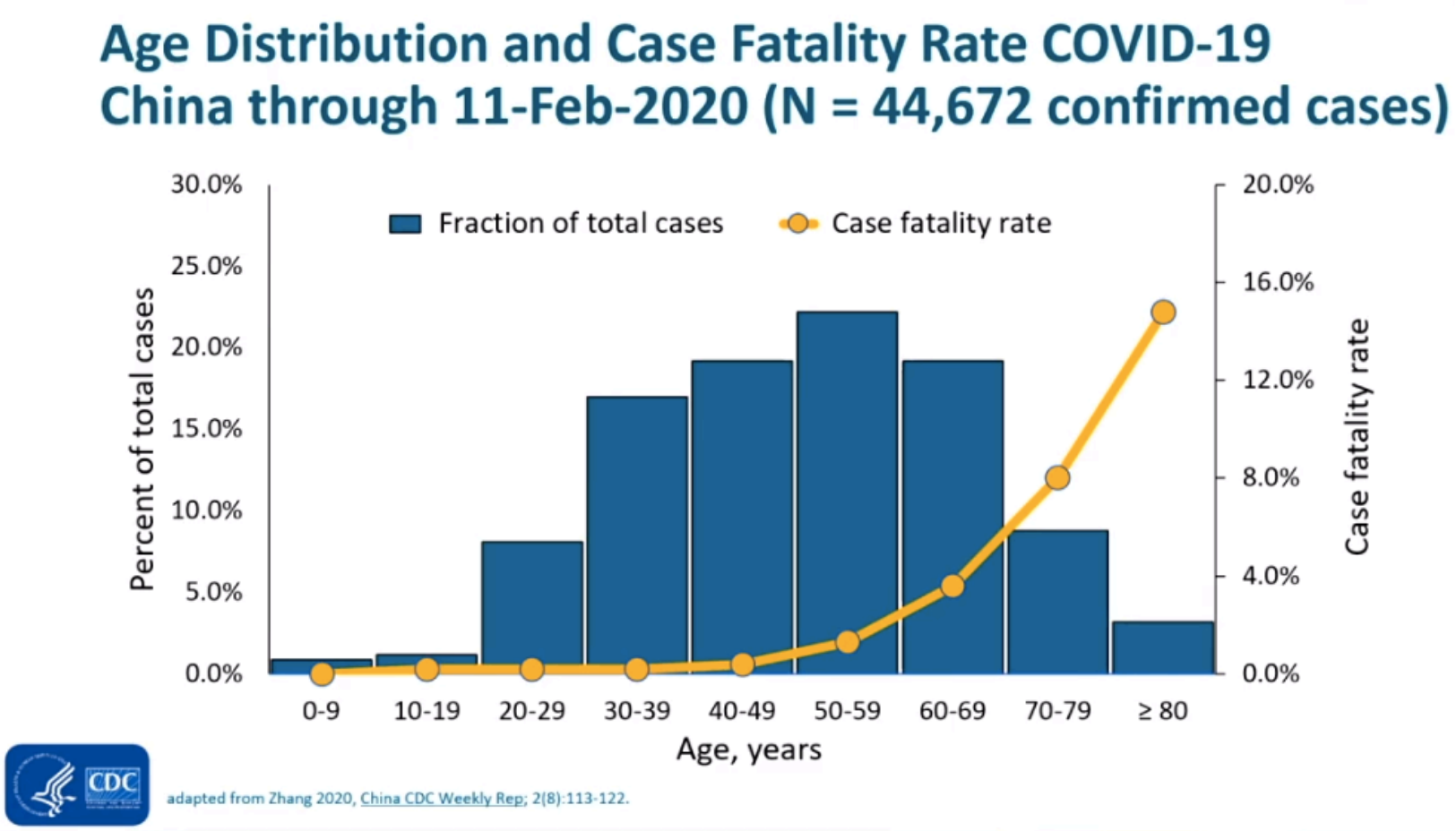
Risk factors

- Clinical characteristics of COVID-19 in China (NEJM)

http://i-base.info/htb/37429

– older age
– male sex
– other health problems (comorbidities):
  - lung and breathing problems (asthma, COPD etc)
  - diabetes
  - heart disease (current)
  - liver and kidney disease
  - cancer (and being on chemotherapy)
  - immunedeficiency (CD4 <50) – in some guidelines, organ transplant recipients
  - high BMI/obesity

Risk factors: age



HIV and COVID-19 coinfection

- Why it is important to include HIV status and HIV testing in managing COVID-19
http://i-base.info/htb/37588
- COVID-19 symptoms in HIV positive people similar to general population in Wuhan
http://i-base.info/htb/37542
- Higher rates of serious outcomes in HIV and COVID-19 coinfection in Germany: cautious review
http://i-base.info/htb/date/2020/05
- Five HIV positive people diagnosed with COVID-19 in Spain
http://i-base.info/htb/37661
- HIV is not linked to higher risk of COVID-19 in large New York cohort
http://i-base.info/htb/37739

HIV risk and COVID-19?

Are HIV positive people at higher risk from COVID-19?

http://i-base.info/qa/15483

People with CD4 above 200 and undetectable on ART: follow general population advice (ie social physical distancing).

People with CD4 that is 50 to 200, who have detectable viral load or who are not on ART: follow social distancing advice very closely.

People with a CD4 count <50 or opportunistic illness in last 6 months: follow shielding advice for extremely vulnerable. This includes avoiding face-to-face contact for 12 weeks – and you will need support to do this.

Refs: BHIVA and EACS statements

Guidelines – no recommended treatment

- Evidence review for treatment: IDSA guidelines for COVID-19
  http://i-base.info/htb/37617
- US interim guidelines on COVID-19 and HIV
  http://i-base.info/htb/37387
- WHO guidance on severe acute respiratory infection when COVID-19 is suspected
  http://i-base.info/htb/37582
- BMJ guidelines resources page
  https://bestpractice.bmj.com/topics/en-gb/3000168/guidelines
- BHIVA and EACS joint guidelines and statements
  https://www.bhiva.org/Coronavirus-COVID-19

IDSA
Infectious Diseases Society of America

AIDSinfo

BHIVA
British HIV Association

COVID-19: research

NIH U.S. National Library of Medicine
ClinicalTrials.gov

- COVID-19 studies – >1600 studies, treatment and prevention (May 2020) - https://clinicaltrials.gov

Many studies duplicate, some use combination therapy:
- antiviral drugs (remdesivir, HIV drugs: Kaletra)
- antimalarial hydroxychloroquine – many different doses – with or without antibiotic azithromycin
- anti-inflammatory drugs: anti-rheumatism, NSAIDS, tocilizumab (to reduce IL-6)
- convalescent plasma
- corticosteroids (not recommended by WHO for pneumonia).

Remdesivir.1

- Remdesivir for COVID-19: compassionate access (n=53). NEJM, (10 April 2020). http://i-base.info/htb/37593
- Remdesivir for COVID-19: published paper shows no evidence of direct antiviral effect. Lancet, Chinese Study. (29 April 2020). (Also WHO early release) http://i-base.info/htb/37750
- NIAIDS placebo study (n>1000) – 11 vs 15 days recovery (29 April 2020) https://www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19
- Gilead SIMPLE study: 5-day vs 10day treatment http://i-base.info/htb/37859
- Gilead: trials, EAP, drug supply etc https://www.gilead.com/purpose/advancing-global-health/covid-19/about-remdesivir

Remdesivir.2

• Other remdesivir news: top results from NIH and Gilead studies – emergency approval in US and Japan
http://i-base.info/htb/37859

- EMA opened rolling data review (30 April)
- Expanded access in EU.
- FDA emergency approval in US for 'late-stage use (1 May)
- FDA exceptional approval in Japan (7 May)

* Gilead ramp up manufacturing and license to generic companies for global access.

Q: optimal time for use might be earlier?

Q_ why no impact on viral load?

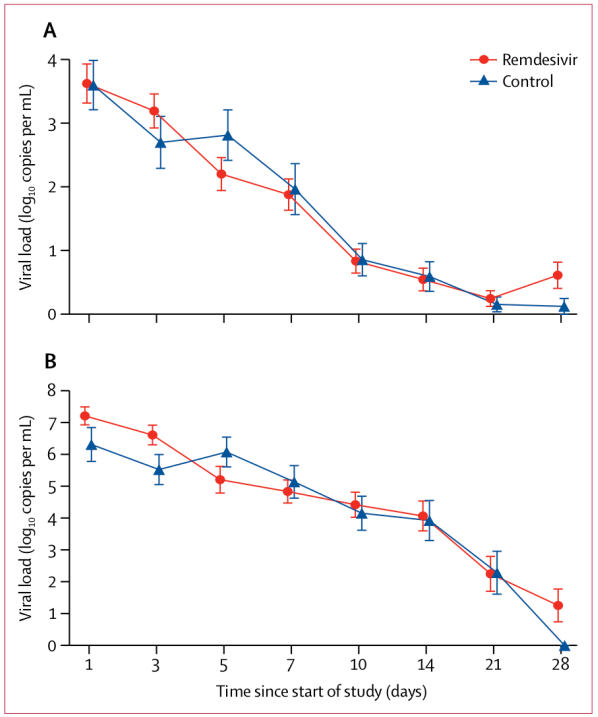


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual value; results of patients with viral-negative RNA are imputed with 0 log_{10} copies per mL.

Hydroxychloroquine

- Guatret et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7102549

- No benefit of HCQ and azithromycin in people hospitalised with COVID-19.
http://i-base.info/htb/37524

- High-dose chloroquine study for COVID-19 stopped with worse outcomes: high risk of cardiovascular events.
http://i-base.info/htb/37691

- Hydroxychloroquine study (HCQ) – HIV (2011) no impact on inflammation
http://i-base.info/hydrochloroquine-study

- Studies reporting lack of benefit from HCQ to treat COVID-19
http://i-base.info/htb/37803

Data on other options being reported

- Potential for tocilizumab to treat moderate to severe COVID-19

http://i-base.info/htb/37877

- Detectable viral load and IL-6: a role for tocilizumab or anti-JAK inhibitor baricitinib?

http://i-base.info/htb/37880

- Rheumatoid arthritis drug anakinra in small study to treat COVID-19

http://i-base.info/htb/37863

- Convalescent Plasma Therapy:

  Zeng Q-L et al. Journal of Infectious Diseases, jiaa228,
  https://doi.org/10.1093/infdis/jiaa228
  Chen C et al. JAMA. 2020;323(16):1582-1589.
  https://jamanetwork.com/journals/jama/fullarticle/2763983
  Duan et al., 2020 – PNAS (28 April 2020)
  https://www.pnas.org/content/117/17/9490

- Interferon-α2b Treatment for COVID-19. Front. Immunol., 15 May 2020. Zhou Q et al.

https://doi.org/10.3389/fimmu.2020.01061

PrEP for health workers

- COVID-19 prophylaxis studies – >100 studies, many dual treatment.

https://clinicaltrials.gov/ct2/results?cond=&term=COVID-19+prophylaxis&cntry=&state=&city=&dist=

- Hydroxychloroquine – many different doses.
- antibiotics (azithromycin etc).
- anti-parasite (nitroxinide, levamisole).
- antiviral drugs (isoprinosine, HIV: Kaletra, TDF/FTC) etc.
- vitamins C, D, zinc.
- 12 BCG vaccine studies (but Israeli study not hopeful from childhood): http://i-base.info/htb/37832

- COVID-19 prophylaxis using TDF/FTC and low-dose hydroxychloroquine in Spanish health workers (n=4000).

http://i-base.info/htb/37625

Masks ?

Why face masks to prevent COVID-19 might now be recommended…

http://i-base.info/qa/15571

Refs:
Greenhaulgh T et al. Face masks for the public during the COVID-19 crisis. BMJ 2020; 369:m1435. doi: 10.1136/bmj.m1435 (09 April 2020).
https://www.bmj.com/content/369/bmj.m1442

Gandhi M and Havlir D. The time for universal masking of the public for coronavirus disease 2019 is now. Open Forum Infect Dis. (15 April 2020).
https://academic.oup.com/ofid/article/7/4/ofaa131/5820544

More information: webinars and talks

- WHO
  http://i-base.info/htb/37703
- IAS webinar
  https://www.youtube.com/watch?v=25ve6LevLpY
- Other online talks and webinars
  http://i-base.info/htb/37455
- i-Base news and resources including HIV and COVID-19:
  http://i-base.info/covid-19
- Other community HIV organisations including:
  www.NATAP.org

Thanks – and Questions

Chinese response to COVID-19

Measures in Numbers

Nationwide:

≈1.4 billion people underwent 10 days of at-home isolation

Hubei:

≈59.2 million people were subjected to cordon sanitaire

>50,000 hospital beds were opened for COVID-19 patients
(including 3 new hospitals + 16 temporary module hospitals)

>40,000 healthcare workers were deployed to Hubei

COVID-19

COVID-19 in High-Risk Groups

- **Comorbidity and advanced age increase risk for severe illness and death**
  - Cardiovascular disease, diabetes, chronic respiratory disease (CFR >5%)
- **Immunocompromised (medical, acquired) – no data at present**
  - For persons with HIV, risk likely greatest at low CD4 cell counts or if not virally suppressed
  - Nonetheless all should take precautions given this is a new virus
  - CDC estimates that ≥ 50% of people with HIV are more than 50 years old
- **Pregnancy**
  - Current observational data only exist for women infected in third trimester
  - Maternal morbidity similar to that of uninfected women without COVID-19
  - No definitive evidence infection transmitted perinatally

Zhang 2020, China CDC Weekly Report; 2(8):113-122 Rasmussen 2020; Am J Obstet Gynecol: https://doi.org/10.1016/j.ajog.2020.02.017

COVID-19

Therapeutics for SARS-CoV-2 (COVID-19)

- **Antivirals, monoclonal antibodies and other agents are being tested**
  - **Remdesivir (nucleotide analogue)**, has shown promise against coronaviruses in animal models
  - **Kaletra (lopinavir/ritonavir) (protease inhibitors)** and **interferon-beta** have been used investigationally for other coronaviruses
  - Other **broad-spectrum antivirals**
  - **Chloroquine**
  - **Drug screening and targeted drug design**
  - **Monoclonal antibodies being isolated and tested**

Clinical Testing of Remdesivir for Treatment of COVID-19

- Five randomized controlled trials in hospitalized patients with diagnosed COVID-19

COVID-19 Study Design	Location	Sponsor	Study size (randomization)	First patient enrolled	Primary endpoint
Severe Double-blind Placebo-controlled	Wuhan, China	Capital Medical University, China	N = 453 (2:1) 10d RDV:Placebo	Feb 6, 2020	Time to clinical improvement by Day 28
Mild/Moderate Double-blind Placebo-controlled	Wuhan, China	Capital Medical University, China	N = 308 (1:1) 10d RDV:Placebo	Feb 13, 2020	Time to clinical recovery by Day 28
All hospitalized* Double-blind Placebo-controlled	Global	NIAID	N = 394 (1:1) 10d RDV:Placebo	Feb 21, 2020	Clinical status at Day 15 based on 7-point ordinal scale
Severe Open-label	Global	Gilead	N = 400 (1:1) 10d RDV:5d RDV	Enrollment not yet started	Normalization of fever and O_2 saturation by Day 14
Moderate Open-label	Global	Gilead	N = 600 (1:1:1) 10d:5d RDV: Placebo	Enrollment not yet started	Hospital discharge by Day 14

** Stratified by disease severity at enrollment*