COVID-19 update:

Reports from:
HIV & COVID-19 – no. 3 and 4
http://i-base.info/hiv-and-covid-19/

UK-CAB: 5 June 2020

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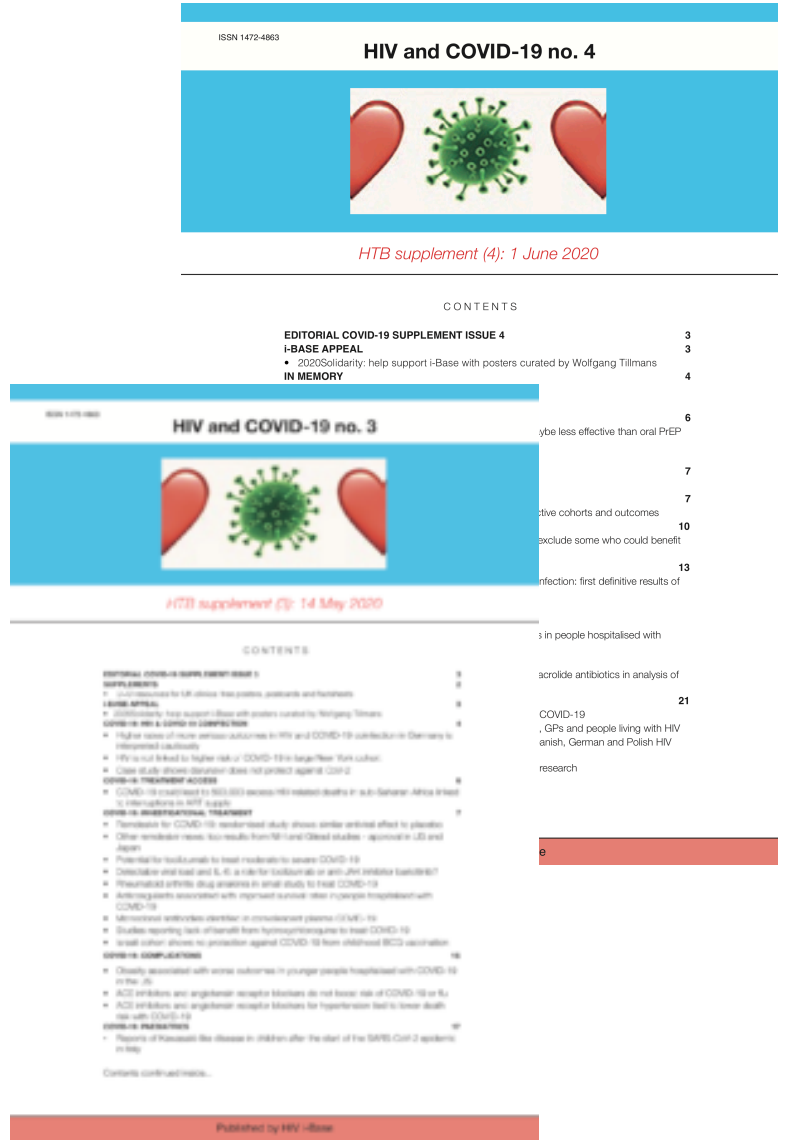
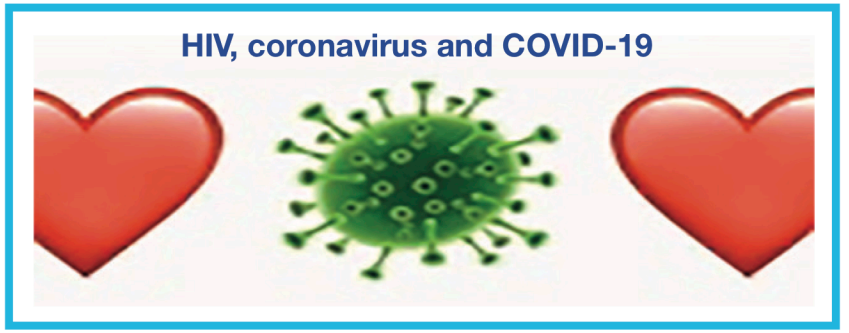
www.i-Base.info



Background



- Research in time of crisis - global and national.
- Covid-19 is short acute infection ~ 3 weeks.
- 80% with mild or asymptomatic, recovery without treatment. Viral load clears without treatment.
- 15% severe and 5% critical – hospitalised – but often late.
- Viral infection, but can progress to severe inflammatory disease. No markers to predict mild or severe infection.

Research should rapidly find signals for randomised studies.

Update: May/June

- At least 10 new studies on HIV/COVID coinfection.
- PHE report: 'Disparities in the risk and outcomes'
- Remdesivir approval in US and Japan, expanded access in EU, first publications showing significant results.
- Small studies reporting results with anakinra, tocilizumab, anticoagulants, convalescent plasma, interferon, BCG, ACE inhibitors etc.
- Hydroxychloroquine (HCQ) controversy.
- Questions: inc. practical responses: lockdowns, travel etc

HIV and COVID-19 coinfection

- Is HIV linked to higher risk of COVID-19 – and getting worse symptoms?
- Is HIV linked to lower risk of COVID-19 – and getting milder symptoms?
- Are ***some*** HIV positive people at higher/lower risk?
- What is impact of ART? Or not being undetectable?
- Is impact of comorbidities the same? etc

All these Q's need real data/evidence to inform the answers. Need to adjust for baseline factors, stage of COVID-19 etc. Earlier isolation???

1. Childs et al , 2. Vizcarra et al., 3. Suwanwongse et al. 4. Gervasoni et al. 5. Härter et al. 6. ISARCI reports

HIV and COVID-19 coinfection

>20 studies of coinfection - from China, Germany, Italy, Spain, the UK and the US **including ~10 in last month:** http://i-base.info/htb/38000

- South London: n=18 (12M, 6W). Most (17/18) were black, on long-term ART and <50 c/mL. Comorbidities were common. Five have died and one is still in hospital. [1]
- Madrid: n= 51 (43M, 8W) - 1.8% of 2873 cohort. Six critically ill and 2 have died. [2]
- South Bronx: n=9 (7M, 2W). All had comorbidities and 7/9 died (78%). [3]
- Milan: n=47 (36M, 11W). 45/47 (96%) fully recovered and 2/47 died (4%). [4]
- Germany: n=33 (30M, 3W). Mean age 48 years (range 26–82). Med CD4 670 (range 69 to 1715). 3/33 died. [5]
- UK – ISARIC etc ~ 120 cases, 45 deaths. >20,000 records (30% of total). Approx 83/17,000 (55M, 28W) with HIV data. No full report yet.

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UK data on COVID-19: general population

PHE report: 'Disparities in the risk and outcomes', 2 June 2020

Significant racial disparities, with the highest age standardised diagnosis rates of COVID-19 per 100,000 population as follows:

- 486 in females and 649 in males - in people of Black ethnic groups
  vs 220 in females and 224 in males - in people of White ethnic groups

Data on survival of COVID-19 found (adj. for sex, age, deprivation and region):

- Bangladeshi ethnicity had twice the risk of death vs white British ethnicity
- Chinese, Indian, Pakistani, Other Asian, Caribbean and Other Black ethnicity had 10% to 50% higher risk of death vs white British

Most analysis did not adjusted for comorbidities (and no explanation why). Some not for employment.

https://www.gov.uk/government/publications/covid-19-review-of-disparities-in-risks-and-outcomes

UK data on COVID-19

PHE report: 'Disparities in the risk and outcomes', 2 June 2020

89-page report
Age: >80 years old = 70x higher mortality risk vs 40 year old.
Higher in males vs females; more deprived areas > 2x vs least deprived; higher in those in Black, Asian and Minority Ethnic (BAME) groups vs White ethnic groups

Also if born outside the UK and Ireland; working in caring occupations (including social care and nursing auxiliaries and assistants); transport drivers including taxi and minicab drivers and chauffeurs; security guards and related occupations; chefs; sales and retail assistants, and those in care homes.

Adj. for age, sex, deprivation, region and ethnicity, but not comorbidities, which are strongly associated with the risk of death from COVID-19 and are likely to explain some of the differences.

https://www.gov.uk/government/publications/covid-19-review-of-disparities-in-risks-and-outcomes

Remdesivir – ACTT study.1

- US FDA approval (1 May 2020)
- Japan approval (8 May 2020)

- NIAIDS – randomised placebo-controlled phase 3 ACTT study

http://i-base.info/htb/37976

> 60 sites in Denmark, Germany, Greece, Japan, Korea, Mexico, Singapore, Spain, the UK and the US. N=1049.

Baseline characteristics were well balanced: 88% severe

- Mean age 58.9 (±15.0); 64% male and 53% white, 23% Hispanic/Latino, 21% black.
- Median time to randomisation: 9 days (IQR: 6 to 12).
- Just over 50% in each arm had two or more comorbidities, mainly hypertension (49%), obesity (37%) and type-2 diabetes (29%).

Remdesivir – ACTT study.2 results

- Med. recovery: 11 days (95% CI: 9 to 12) vs 15 days (95% CI: 13 to 19)

- Significant difference RR 1.32; 95% CI, 1.12 to 1.55; p<0.001).
- Numerically fewer deaths by day 14 (n=32 vs 54; 7.1% vs 11.9%).
- Kaplan-Meier estimates of mortality (HR: 0.70; 95% CI: 0.47 to 1.04) (NS).
- All but two of the deaths (one in each arm) had severe stage disease at study entry.

- Fewer SAEs with remdesivir arm 114/541 (21.1%) vs 141/522 patients (27.0%).

Fewer serious respiratory failure: 28 (5.2%) vs 42 (8.0%).
Fewer Grade 3 or 4 events: 156 (28.8%) vs 172 (33.0%), respectively.
No deaths were judged related to remdesivir/placebo.

Conclusion: high mortality suggests combination therapy needed. No PCR data.

Potential treatments

- Small studies reporting potential positive results

- **Anakinra** (anti-rheumatic)
http://i-base.info/htb/37863
- **Convalescent plasma** (conflicting results, confirm Abs)
http://i-base.info/htb/38022
- **Famotidine** (antacid)
http://i-base.info/htb/38019
- **Interferon** (shorter recovery, but early infection)
http://i-base.info/htb/38030
- **Tocilizumab** (anti IL-6)
http://i-base.info/htb/37877

anakinra (anti-inflammatory)

Rheumatoid arthritis drug anakinra in small study to treat COVID-19: http://i-base.info/htb/37863

- N= 29 hospitalised in Milan vs n=16 control (historical).
- Daily high-dose IV infusions at 10 mg/kg bodyweight for 21 day.
- Med age 62 years, many comorbidities.
- Anakinra: Respiratory improvement, cytokine activity inc. CRP in 72% (21/29). 90% survival (26/29). 17% (5/29) needed mechanical ventilation.
- Control: continued/increased CRP in most. Respiratory function improved in 50% (8/16). 56% survived (9/16) survived. 6% (1/16) needed mechanical ventilation.

Comment: non-randomised, blinded, small numbers, safe, needs confirming – part of ongoing larger study with n=1000.

anti-coagulants (AC)

Anticoagulants associated with improved survival rates in people hospitalised with COVID-19. http://i-base.info/htb/37794

- **Mount Sinai, NYC: 786/**2773 participants (28%) received oral, subcutaneous, or intravenous AC.
- Results adj for all expected factors inc. previous AC use.
- In patients on mechanical ventilation (n=395), in-hospital mortality was 29.1% vs 62.7% and median survival 21 days vs 9 days, with vs without AC respectively.
- Longer duration of AC was associated with a reduced risk of mortality (adjusted HR of 0.86 per day, 95% confidence interval 0.82-0.89, $p<0.001$).

UK research: 42 ‘key’ studies

• No UK guidelines: 42 key studies:
http://i-base.info/htb/38094

NIHR listing: https://www.nihr.ac.uk/covid-studies

• Treatment include remdesivir (3), tocilizumab (1), canakinumab (1), otilimab (1), Gemtuzumab ozogamicin (1), baricitinib and ravulizumab (1), IFN (1), HCQ +/– azithromycin (2), Ruxolitimib (1), Brensocatib (1).

• Three studies use ‘adaptive design’ to study multiple treatment. including some of the same compounds above: (i) ACCORD: zilucoplan, bemcentinib, Medi3506, acalabrutinib; (ii) TACTIC-R: LPV/r, steroid, HCQ, azithromycin, tocilizumab; and (iii) REMAO-CAP: LPV/r, steroid, HCQ, tocilizumab, interferon-beta, anakinra, convalescent plasma, therapeutic anticoagulation.

UK research: RECOVERY study

https://www.recoverytrial.net

Randomised over 10,600 so far (2:1:1:1:1 etc control:active)

- Lopinavir/ritonavir
- Low-dose dexamethasone
- Hydroxychloroquine
- Azithromycin
- Tocilizumab
- Convalescent plasma

"regularly reviewed so effective treatment can be made available to all patients. …will constantly review new drugs and include promising ones in the trial."
– all arms still ongoing in June 2020.

Treatment for COVID-19?

What is the best treatment for COVID-19?

http://i-base.info/qa/15773

- Lack of UK guidelines.
- Joining a study (if you are at a centre)
- Caution: many randomised studies still include no treatment as one of the options.

- New standard of care:

open label compassionate remdesivir (need to be in hospital):
http://i-base.info/htb/37976

Other promising treatments include anakinra, anticoagulants, or possibly convalescent plasma or interferon.

Hydroxychloroquine

Controversial history for COVID-19: Use in China, plus small French study with azithromycin – (Gautret et al). Lead to 100s of studies for treatment and PrEP.

Two issues (can be separated) – ie to support research at a safe dose.

(1) Efficacy – does it work? Questions of dosing for activity, timing after infection/symptoms, stage of infection.

(2) Safety – is it safe? Questions of dose for toxicity, risk (age, CVD etc)

Important because so many large studies include HCQ arms including WHO SOLIDARITY (DISCOVER in EU), RECOVERY (UK >10,600 pts)

Hydroxychloroquine: new studies

Studies reporting lack of benefit from hydroxychloroquine to treat COVID-19

http://i-base.info/htb/37803

1. No association between HCQ and intubation or death in 1446 consecutive patients at a single centre in New York. [1]

2. Retrospective analysis of 368 patients hospitalised with COVID-19 in the US Veterans Affairs hospitals (n=97 HCQ; n=113 HCQ+AZ, n=113; n=158 no HCQ). Rates of death were 27.8%, 22.1%, 11.4% and ventilation were 13.3%, 6.9%, 14.1% in the HCQ, HCQ+AZ, and no HC groups, respectively. Compared to the no HCQ group, the risk of death from any cause was higher in participants using HCQ (adj. hazard ratio, 2.61; 95% CI: 1.10 to 6.17; p=0.03). [2]

3. *Nature Research paper reported lack of effect from HCQ in vitro and also in macaques. No benefit as PEP. [3]*

1. Geleris J et al. 2. MagagnoliJ et al. 3. Maisonnasse P et al. Also Prescrire.

Hydroxychloroquine: new studies

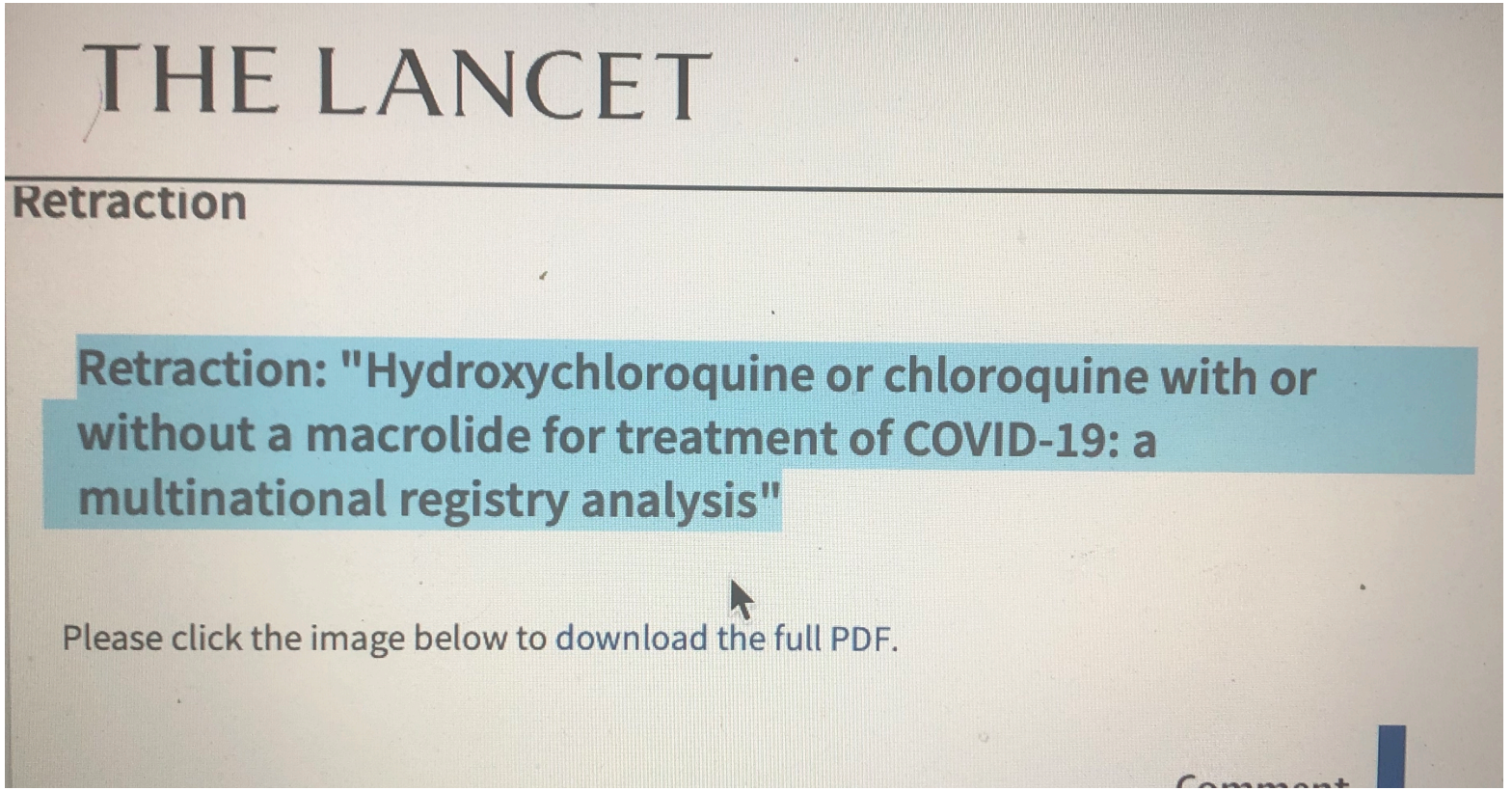
Watson JA et al. Concentration-dependent mortality of chloroquine in overdose. Before peer review. DOI: 10.1101/2020.04.24.20078303. (29 April 2020). https://www.medrxiv.org/content/10.1101/2020.04.24.20078303v1

New paper references in comment to show problems with HQC dosing and risk of serious side effects. Showed serious problems with high-dose Brazilian study and potential safety of other ongoing studies.

Other studies report that an any tolerable dose, unlikely to be active.

Upcoming announcements on HCQ.

Hydroxychloroquine: study retracted



4 June 2020:

Meta-analysis in 96,000 people globally.

Lancet article retracted.

Refusal to allow independent investigation of dataset.

If hospitalised with COVID-19?

What should HIV+ do is hospitalised with COVID-19?

http://i-base.info/qa/15765

via BHIVA:

- Disclose HIV and other medical conditions.
- Continue ART throughout.
- Switch formulations if you can't swallow pills.
- Don't change ART to help against COVID-19.
- Get advice on treatment options.

- New standard of care:

open label compassionate remdesivir (need to be in hospital):
http://i-base.info/htb/37976
Other promising treatments include anakinra, anticoagulants, or possibly convalescent plasma or interferon.

Questions. 1

Are there any interim results published other than Gilead's. Could we arrange a small call with Gilead to ask some confidential questions? same as above for the testing company
When the lockdown is relaxed how do we get the message across that the R value changes by location and mode of transmission? People want to feel safe. More detailed knowledge about transmission risks from indirect contact (from hard surface) or airborne (aerosolised) risk can help us to avoid transmission/infection. Travelling on the bus (increased risk of indirect contact) to the clinic with have a different R value to staying 2 metres apart in the supermarket (risk likely airborne, maybe from someone laughing without a mask).
How do you see Covid impacting on clinical and third sector HIV specific commissioning services and provision ? Any Evidenced UK regional variances that we need to consider ?
What is the impact of COVID 19 on those undetectable and take vitamin C and D on a regular basis?

Questions. 2

is anyone looking at the mental health impact on a person already living with one virus and now having to go through the process of dealing with another and a new stigma, with all the old baggage of HIV being dragged back into the present.
Do you have any information on contact tracing - maybe from the example of HIV - you could share?
Have you seen any results on SARS-Cov-2 antibody titers in a non-hospitalised cohort, and duration of titer (this second part is very wishful thinking I know)
what percentage of HIV, hepatitis and STI testing services are operating and how right now. And also if those services can be seen as the foundation for COVID-19 testing.

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

http://i-base.info/htb/37707

Thanks – and other questions