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Statement on risk of COVID-19 for people living with HIV (PLWH)

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COVID-19 & HIV

Case series of HIV-patients with COVID-19 have been published from China, Spain, Germany, Italy and the United States (1-6). So far there is no clear evidence for a higher COVID-19 infection rate or different disease course in people with HIV than in HIV-negative people. Of note, most HIV case series report a younger age in their study population than in HIV-negative hospitalised COVID-19 patients but comparable rates of comorbidities. In a UK cohort study reporting outcomes on 16,749 hospitalised patients with COVID-19 only 1% involved PLWH, but HIV did not adversely impact survival [7].

Current evidence indicates that the risk of severe illness increases with age, male gender and with certain chronic medical problems such as cardiovascular disease, chronic lung disease, obesity and diabetes. Although people with HIV who are on treatment with a normal CD4 T-cell count and suppressed viral load may not be at an increased risk of serious illness, many people with HIV have other conditions that increase their risk. Indeed, almost half of people living with HIV in Europe are older than 50 years and chronic medical problems, including cardiovascular and chronic lung disease, are more common in people living with HIV. 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.

It has to be assumed that immune suppression, indicated by a low CD4 T-cell count (<200/µl), or not receiving antiretroviral treatment, will also be associated with an increased risk for a more severe

disease presentation. Data in such patients however, is sparse as most HIV-coinfected COVID-19 patients so far have been under antiretroviral therapy and successfully treated with mostly suppressed HIV-RNA levels. 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. This is not aiming at preventing a more severe course of COVID-19 but rather complications through additional opportunistic infections. More information regarding recommendations for prophylaxis and treatment of specific opportunistic infections can be found in the BHIVA/EACS guidelines for HIV/AIDS.

The ongoing discussion about potential COVID-19 vertical transmission remains controversial. Although few case reports have claimed perinatal transmission several other large case series could not find any case of vertical transmission [8-11]. Pregnant women with critical COVID-19 who deliver during their disease course mostly deliver preterm via caesarean section [11]. So far clinical outcome of the newborn however, has been uneventful.

Existing national guidelines should be followed in terms of reducing risk for acquiring a COVID-19 infection and managing symptoms [12-15].

COVID-19 treatment: antiretrovirals

Expedited research and publication are welcomed with the caveat that results may be disseminated pre-publication and/or published without usual peer review. There is ongoing discussion and research around some HIV antiretrovirals which may have some activity against COVID-19. The first randomised clinical trial with lopinavir/ritonavir started a median of 13 days after symptom onset and demonstrated no benefit over standard care in 199 hospitalised adults with severe COVID-19 [16]. There is no evidence to support the use of other antiretrovirals, including protease inhibitors; indeed, structural analysis demonstrates no darunavir binding to COVID-19 protease. Moreover, an Italian case series suggest darunavir does not prevent SARS-CoV-2 infection in people living with HIV or protect against worsening respiratory function, at least not at a dose of 800 mg daily [17].

In silico data suggest that TDF/FTC may bind to SARS CoV-2 Nsp1 protein [18], while two unreviewed studies show that TDF and TAF may be inhibitors of the SARS-CoV-2 polymerase [19,20], however there is no in-vitro data to support antiviral activity of TDF/FTC against CoV-2 [21]. Currently a large randomised phase 3 placebo-controlled study in Spain using the HIV pre-exposure prophylaxis (PrEP) combination TDF/FTC and low-dose hydroxychloroquine (HCQ) as prophylaxis for COVID-19 in health

workers is planned [22], but the clinical trial results have to be awaited to shed light on the usefulness of this PrEP strategy.

Currently no evidence is available to justify switching a patient from their usual antiretroviral therapy. Additionally, there is no evidence to support HIV-negative people taking antiretrovirals outside the context of PrEP to prevent HIV acquisition – PrEP should be taken as directed and there is no current evidence that PrEP is effective against COVID-19.

COVID-19 treatment: other options

A recent case series on hydroxychloroquine, with or without azithromycin, was not able to demonstrate a clear clinical benefit, despite in vitro inhibition of SARS-CoV-2, due to methodological issues [23]; although the same group has postulated an infection control benefit of more rapid viral clearance there was a lack of control arm for comparison [24]. One small RCT demonstrated trends for reduced time to clinical recovery and short-term radiological improvement for hydroxychloroquine [25], though another showed no benefit in terms of viral clearance, clinical or radiological endpoints [26]. Despite lack of evidence, indeed no acute viral infection has ever been successfully treated with either product [27], the FDA has issued an Emergency Use Authorisation to allow hydroxychloroquine and chloroquine products to be used for certain hospitalised patients with COVID-19 [28] while awaiting results from randomised trials. Of great concern are recently published results from a retrospective analysis of data from patients hospitalised with confirmed SARSCoV-2 infection in all United States Veterans Health Administration medical centres which found no evidence that use of hydroxychloroquine, either with or without azithromycin, reduced the risk of mechanical ventilation in patients hospitalised with COVID-19 and even found an association of increased overall mortality in patients treated with hydroxychloroquine alone [29]. Subsequently, two further observational studies have been published looking at treatment with hydroxychloroquine, azithromycin, or both, compared with neither treatment showing no difference in in-hospital mortality and/or intubation rate [30,31]. Finally, a multinational registry analysis for treatment of COVID-19 in over 96,000 individuals was published online, which was unable to confirm a benefit of hydroxychloroquine or chloroquine, when used alone or with a macrolide, on in-hospital outcomes for COVID-19 [32]. Each of these drug regimens was associated with decreased in-hospital survival and an increased frequency of ventricular arrhythmias when used for treatment of COVID-19 [32]. As a consequence, the FDA now cautions against use of hydroxychloroquine or chloroquine for COVID-19 outside of the hospital setting or a clinical trial due to risk of heart rhythm problems.

A further potential drug candidate for treatment of COVID-19 is remdesivir, originally developed for Ebola therapy. Remdesivir has broad in vitro antiviral activity against SARS-CoV-2 [33]. First cases from the expanded access program using remdesivir for COVID-19 patients suggested potential clinical benefit [34]. More recently however, data published from a first randomised clinical trial from China in adults with severe COVID-19, demonstrated that remdesivir was not associated with statistically significant clinical benefits [35]. Remdesivir was stopped early in 18 (12%) patients because of adverse effects, compared with 4 (5%) in the control group [34]. Of note, the study was stopped early due to low patient enrolment which may limit its power. Preliminary data on remdesivir was presented recently in an NIAID press release from the Adaptive COVID-19 Treatment Trial (ACTT), in which 1063 hospitalised patients with advanced COVID-19 and lung involvement randomised to remdesivir recovered faster than similar patients who received placebo [35]. Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (p=0.059) [36]. Meanwhile, Gilead also reported top-line results from their late-stage SIMPLE study, showing that a five-day dosing duration of remdesivir led to "similar improvement in clinical status" as the 10-day treatment course being evaluated in the NIAID study and other ongoing trials. The initial phase of the SIMPLE trial, which is not placebo-controlled, randomised 397 hospitalised patients with severe manifestations of COVID-19 disease to receive intravenous remdesivir until either day five or 10, on top of standard care. An expansion phase of the study has recently been added and will enrol an additional 5600 patients, including patients on mechanical ventilation.

A third agent that has recently been associated with improved clinical outcome of COVID-19 is famotidine. In reviewing 6212 COVID-19 patient records in China, the doctors noticed that many survivors had been suffering from chronic heartburn and were on famotidine rather than more-expensive omeprazole. Hospitalised COVID-19 patients on famotidine appeared to be dying at a rate of about 14% compared with 27% for those not on the drug, although the result was not statistically significant. Currently, around 200 COVID-19 patients in critical status, including many on ventilators, have been enrolled in a trial in New York, which aims for a total of 1174 people [37].

The full results from these trials, as well as other ongoing clinical trials especially in early COVID-19 disease, are eagerly awaited. A list of currently ongoing or planned COVID-19 studies in PLWH can be found under: https://www.clinicaltrials.gov/ct2/results?term=hiv+covid&Search=Search

Maintaining HIV care during the COVID-19 pandemic

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 [38]. Moreover, timely linkage to HIV care as well as ART continuation, will be hindered during the COVID-19 pandemic, as physicians from HIV-clinics are sharing HIV care and COVID-19 care duties as recently demonstrated for more than 50% of clinics in central and eastern Europe [39]. In many countries with high COVID-19 case load there is a need to prepare for operating under minimal medical resources with the aim to secure retention on ART. Non-governmental organisations are needed to second medical efforts to ascertain the continuity of ART deliverance.

COVID-19 data collection & resources

A COVID-19 drug interactions website (www.covid19-druginteractions.org) has been developed for the experimental drugs being trialed to treat COVID-19 in different parts of the world. EACS and BHIVA are happy to announce that they have agreed to financially support this very useful website. A useful Spanish interaction resource can be found under: http://www.interaccionesvih.com/docs/Interacciones%20importantes%20con%20Kaletra%20e%20Hidroxicloroquina_20%20marzo%202020_COVID.pdf.

We would like to highlight three resources for reporting COVID-19 cases:

- The NEAT ID Foundation has developed a 'data dashboard' to monitor COVID-19 case numbers, hospitalisations and mortality in people with HIV and/or hepatitis 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 are 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
- EASL is supporting a registry which can be found under the following link https://www.covid-hep.net/

The coronavirus outbreak is rapidly evolving. EACS, BHIVA, DAIG and GESIDA will continue to share any updates to specific guidance for people with HIV. Wishing you all well. Stay healthy.

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