Doctopic: Analysis and Interpretation
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[A: we have a limit of 5 references for Correspondences. I have converted ref 5 into a margin link to maintain this limit]

COVID-19 in patients with HIV: first ever clinical case series

As of March 24, 2020, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has affected almost 400 000 people in 168 countries on five continents **[A: can you supply a press release for these data?]**. Older patients **[A: can you give an age range? Eg, people Older than 70 years"?]** and those with comorbidities (eg, hypertension, diabetes, cardiovascular disease, lung disease, and chronic kidney disease) present with **[A: correct? Or "are more susceptible to"?]** more severe infection and worse prognosis.[1] Coronavirus disease 2019 (COVID-19) has been described in only one patient with HIV in Wuhan, China,[2] but case series in patients with HIV are lacking despite 37·9 million people having HIV globally **[A: edit correct?]**.[3] Here we describe the first single-centre experience of COVID-19 in patients infected with HIV-1, including clinical characteristics, antiviral and antiretroviral treatment, and outcomes.

All patients gave informed consent for publishing their clinical data. We used nasopharyngeal swab samples for all diagnoses, amplifying the betacoronavirus *E* gene and the specific SARS-CoV-2 *RdRp* gene by polymerase chain reaction.

2 weeks into the COVID-19 outbreak in Spain **[A: please provide the date here]**, 543 consecutive patients with SARS-CoV-2 infection had been admitted to hospital **[A: Ok?]** at Hospital Clínic Barcelona, Barcelona, Spain. We admitted 62 (12%) into intensive care units and we discharged 208 (38%) with supervised outpatient care. Of all patients, five (0·92%; 95% 0·39–2·14) were HIV positive, of whom three were male and two were transgender, and four identified as men who have sex with men (MSM) **[A: edit OK?]** (table). Among these patients with HIV, median age was 40 years (range 29–49), and none had comorbid conditions, except patient had asthma **[A: patient 2 has hypothyroidism in the table, does this not count as a comorbidity?]**. Two patients were sex workers (patients 3 and 5). Four were virologically suppressed: two with protease-inhibitor (darunavir-boosted cobicistat) and two with integrase-inhibitor (dolutegravir) based antiretroviral therapy. CD4+ T cells were above 400 cells per µL in all patients apart from patient 5, who was antiretroviral naive and a very advanced late presenter with a CD4+ T-cell count of 13 cells per µL **[A: edits OK?]**. Two patients had upper-respiratory tract infections, and three had viral pneumonia **[A: could you add a row in the table of "Diagnosis" to say which had upper-respiratory tract infections and which had pneumonia?]**, including two requiring admission to the intensive care unit with invasive (patient 2) and non-invasive (patient 5) mechanical ventilation. We started all five patients on anti-SARS-CoV-2 treatment on the day of diagnosis **[A; these do not appear to be listed in the table, what treatment did you give them?]**. We gave all five patients boosted-protease inhibitor antiretroviral therapy **[A: patient 1 has no changes in ART or treatment in the table, please clarify this sentence]**. We explained to experienced patients **[A: do you mean "We explained to the patients who has experience with ART"?]** that we were making a transitional change in antiretroviral treatment based on the fact that HIV protease inhibitors might have activity against the coronavirus protease and that once the treatment ended, they would return to their usual regimen. Patient 1 with darunavir-boosted cobicistat, and patients 2–4 were adapted to lopinavir-boosted ritonavir **[A: since these treatments are already listed in the table, could we delete this sentence?]**. We gave patient 5 darunavir-boosted cobicistat. We left patient 1, who had mild infection, on antiretroviral therapy alone **[A: "on their normal ART regime alone"?]**. We gave the other patients hydroxychloroquine (patients 2, 3, 4, and 5) with azithromycin (patients 3, 4, and 5 **[A: Correct? To match table. Originally it said "2 cases" here]**), and interferon beta-1b (patient 2 and 5). No patients were given remdesivir (only available through clinical trials, with very restricted access at the time these patients were evaluated) **[A: added from table]**. We administered concomitant antibacterials in all three patients who had pneumonia (patients 2, 4, and 5), and corticosteroids in two patients (patients 4 and 5) and tocilizumab in one (patients 2). **[A: "To date" or "As of MM DD"?]** We have discharged four patients (80%); one remains in hospital in the intensive care unit (patient 2).

Our preliminary experience highlights several issues. First, patients with HIV accounted for almost 1% of patients with COVID-19 who required admission to hospital in Barcelona. We only observed the infection in people younger than 50 years, who identified as MSM, and who have clinical pictures resembling the general population **[A: please calcify your meaning here. Do you mean "no severe comorbidities"?]**. **[A: "To date"?]** None of these five patients has died, although we admitted two to intensive care, where one remains **[A: still true?]**. More studies **[A: "of COVID-19 symptoms, treatments, and outcomes"?]** are needed in the older MSM population, drug users, and heterosexual men and women in middle-income and

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	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Demographics and baseline HIV status					
Age, years	40	49	29	40	31
Gender	Transgender	Male	Male	Male	Transgender
HIV-risk factor and exposure	MSM, gym worker	Bisexual man, health-care worker	MSM, sexual worker participant in ChemSex session 6 days before	MSM, dinner 5 days before with another person who was COVID-19 positive	MSM, sexual worker
Comorbidities*	None	None, **[A: delete?]** hypothyroidism	None	Asthma	None
HIV status					
Year of HIV diagnosis;	2007	2003	2013	2003	2020
Last CD4 T-cell count, cells per µL	616	445	604	1140	13
Last CD4:CD8 ratio	0·8	0·46	1·1	1·2	0·1
HIV viral load at or before admission, copies per mL	<50	<50	<50	<50	Pending
ART-regimen before admission	Tenofovir alafenamide, emtricitabine, and darunavir-boosted cobicistat	Abacavir, lamivudine, and dolutegravir	Tenofovir alafenamide, emtricitabine, and darunavir-boosted cobicistat	Abacavir, lamivudine; and dolutegravir	No ART: current diagnosis is late presenter **[A: OK?]**
Clinical findings on admission [A: OK?]					
Length of symptoms, days	2	5	2	3	7
Diagnosis **[A: OK?]**	XX	XX	XX	XX	XX
Symptoms and vital signs	XX	XX	XX	XX	XX
Temperature	Fever (38·7°C)	Fever (39°C)	Fever (39·5°C)	Fever (39·5°C)	Fever (38·5°C)
Symptoms	Cough, malaise, headache	Cough	Cough, malaise, headache, dyspnoea	Cough, malaise, headache, dyspnoea	Cough, dyspnoea
Blood pressure, mm Hg	140/90	110/70	129/69	115/76	127/56
Respiratory rate, breaths per min	14	28	16	24	20
Heart rate, beats per min	90	94	78	103	121
Chest x-ray findings	Normal	Bilateral ground-glass opacities	Normal	Right basal interstitial infiltrate	Right basal pneumonia with pleural effusion
O_2 saturation in ambient air	SpO_2 100%	SpO_2 <90%	SpO_2 97%	SpO2 94%	SpO2 <90%
PaO_2/FiO_2 ratio	ND	182	ND	ND	230
Laboratory results					
White blood cell count	7840	29 160	6730	6140	14 670
Lymphocyte **[A: units?]**	2700	1170 (4%) **[A: what is 4% here?]**	1500	1600	900
Platelets	345 000	135 000	124 000	186 000	309 000
LDH, U/L	ND	316	256	465	1149
C-reactive protein, mg/dL	ND	30	0·72	0·43	40
D-dimer, ng/mL	ND	>10 000	400	300	ND

(Table continues on next page)

lower-income settings **[A: "who have HIV"? Or generally in these populations?]**. Second, two patients who were MSM were sex workers, one reporting participating in a ChemSex party session 6 days before admission to hospital **[A: Correct?]**. During this pandemic, implementing health education programmes is very important to explain that such activities as these could cause clusters of SARS-CoV-2 transmission. Third, we adapted antiretroviral therapy in all patients to a regimen based on protease inhibitors: three patients were given lopinavir-boosted ritonavir and two were given darunavir-boosted cobicistat. In the past month, a clinical trial[4] has shown that lopinavir-boosted ritonavir is ineffective in monotherapy **[A: "as a monotherapy"?]** against severe pneumonia **[A: should this be "COVID-19 associated pneumonia"?]** in China. Therefore, the efficacy of this treatment in patients with COVID-19 in combined therapy in earlier stages **[A: do you mean "at earlier**

For report from **Janssen on darunavir-based treatments** for SARS-CoV-2 see https://www.janssen.com/uk/sars-cov-2-treatment

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
(Continued from previous page)					
Ferritin ng/mL	ND [A: OK?]	1020	ND [A: OK?]	1044	866
Procalcitonin	ND [A: OK?]	ND [A: OK?]	<0·03 ng/mL	ND [A: OK?]	ND [A: OK?]
Severity of the infection at admission	Mild	Severe	Mild	Moderate	Severe
Treatment and outcomes					
New ART†	No ART change	Tenofovir disoproxil fumarate, and emtricitabine plus lopinavir-boosted ritonavir (ongoing)	Tenofovir disoproxil fumarate, and emtricitabine plus lopinavir-boosted ritonavir (for 3 days [A: OK?])	Tenofovir disoproxil fumarate, and emtricitabine plus lopinavir-boosted ritonavir (for 14 days [A: OK?])	Tenofovir alafenamide, emtricitabine, and darunavir-boosted cobicistat (ongoing)
Other antiviral treatments	No	Interferon beta-1b (for 7 days), hydroxychloroquine (for 7 days [A: correct?])	Hydroxychloroquine (for 5 days [A: OK?])	Hydroxychloroquine (for 5 days [A: OK?])	Interferon beta-1b (for 4 days [A: OK?]), hydroxychloroquine (for 5 days [A: OK?])
Other antibiotics	No	Meropenem (for 16 days), linezolid (for 14 days)	Azithromycin (for 5 days)	Azithromycin (for 5 days), cefixime (for 5 days)	Azithromycin (for 5 days), ceftaroline fosamil [A: OK?] (for 7 days), co-trimoxazole (for 21 days, followed by 2ry prophylaxis [A: what does this mean?])
Admitted to an intensive care unit	No	Yes	No	No	Yes
Invasive or non-invasive mechanical ventilation	No	Invasive	No	No	Non-invasive
Corticosteroids or tocilizumab	No	Tocilizumab, 400 mg one single dose (on day 10)	No	Inhaled corticosteroids	Corticosteroids
Length of hospital stay, days [A1]	Jan-13	19	3	04-Oct	12 / -
Length of home hospitalisation, days‡ [A1]	[A1]	..	..	[A1]	..
Outcomes	Cured	Still at hospital	Cured	Cured	Cured
Additional comments	..	Extracorporeal membrane oxygenation since day 13 (ongoing)	..	..	Concomitant *Pneumocystis jiroveci* and bacterial pneumonia treatment

[A: the rows and columns of your table have been transposed to aid presentation. Please check all data and information has been transposed correctly] [A1: These cells are unclear. Please provide data indicated by the row title, or amend the row title as needed] [A: are all "ongoing" treatments still ongoing? Or could we put in the legend "All ongoing treatments were ongoing as of MM DD, 2020"?] Lopinavir-boosted ritonavir was given as 400/100 mg [A: 400mg of ritonavir boosted with 100 mg of lopinavir?] twice a day for 14 days; azithromycin was given as 500 mg once a day, with a loading dose on the first day, and then 250 mg once a day every four days [A: correct?]; hydroxychloroquine was given as 400 mg twice a day with a loading dose on the first day and then 200 mg twice a day for 4 days [A: correct?], and interferon beta-1b was given as 250 µg (8MU [A: what does this mean?]) every 48 h. COVID-19=coronavirus disease 2019. MSM=men who have sex with men. ND=Not done. *Hepatitis C virus, hepatitis B virus, chronic obstructive pulmonary disease, asthma, CKF [A: please spell out], hypertension, cardiovascular disease, diabetes, solid organ transplantation, use of biologics, other types of immunosuppression. †[A: how does this footnote apply to this row?] Tenofovir alafenamide, emtricitabine, and darunavir-boosted cobicistat was indicated before the information provided by Janssen on March 18, 2020. ‡Discharged with a supervised home-care programme.

Table: Demographics, clinical characteristics at admission, treatment, and outcomes of five patients with HIV and COVID-19

stages of the disease"?] is needed. Additionally, Janssen has reported that darunavir was ineffective against SARS-CoV-2 due to low affinity to coronavirus protease. Fourth, we did not give our patients remdesivir, the most active in-vitro and in-vivo antiviral drug against coronavirus to date,[5] and is currently only available through clinical trials or for compassionate use. This drug has no pharmacokinetic interactions with any medication including antiretroviral drugs. Finally, in advanced patients (ie, late presenters), we must ensure differential diagnosis and initial antimicrobial treatment to address pulmonary opportunistic infections—eg, *Pneumocystis jirovecii*, such as we saw in patient 5—presenting with similar clinical and radiological symptoms. This pandemic is a challenge affecting everyone. By generating information such as we present here, the management and

For more on **COVID-19 drug interactions** see www.covid19-druginteractions.org

prognosis of patients co-infected with HIV and SARS-CoV-2 with be improved.

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3 UNAIDS. UNAIDS Data 2019. Geneva: Joint United Nations Programme on HIV/AIDS, 2020. https://www.unaids.org/sites/default/files/media_asset/2019-UNAIDS-data_en.pdfn (accessed April 8, 2020).

4 Cao B, Wang Y, Wen D, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. *N Engl J Med* 2020; published online March 18. DOI:10.1056/NEJMoa2001282.

5 Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 2020; **11:** 222.