Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

The Panel on Antiretroviral Guidelines for Adults and Adolescents with HIV and the American Association for the Study of Liver Diseases guidelines for hepatitis C virus treatment suggest that combination therapy for severe acute respiratory syndrome coronavirus 2 infection will outperform single drugs. Yeming Wang and colleagues[1] reported that the hazard of 28-day clinical improvement for 158 patients with severe COVID-19 randomly assigned to remdesivir was 1·2 times (95% CI 0·9 to 1·8) the hazard of patients randomly assigned to placebo, but the 28-day mortality in both these groups was similar. Relatedly, Cao and colleagues[2] reported that the hazard of 28-day clinical improvement for 99 patients with severe COVID-19 randomly assigned to lopinavir-ritonavir was 1·3 times (95% CI 1·0 to 1·8) the hazard among 100 patients randomly assigned to standard care, and the 28-day mortality was reduced by 6% (95% CI –17 to 6). Nearly 20% of patients in the Wang and colleagues[1] trial were also receiving lopinavir-ritonavir, but their results are not stratified by lopinavir-ritonavir status. Reporting estimates stratified by concomitant lopinavir-ritonavir use would help guide the design of future (factorial) trials that investigate the joint effects of these two therapies, even if imprecise. Also, reporting the proportion of patients clinically improved at 28 days is more interpretable than the hazard ratio.

Additionally, Wang and colleagues[1] report that the effect of remdesivir on clinical improvement appeared stronger among patients who started treatment within 10 days of symptom onset than among those who started later. Cao and colleagues[2] reported similar strengthening of the lopinavir-ritonavir treatment effect among patients who started treatment within 14 days of symptom onset. As in HIV,[3] timing of treatment initiation for COVID-19 appears to be of crucial importance in the design of future research.

AAA reports consulting fees from Gilead, Merck, and ViiV, unrelated to this Correspondence. All other authors declare no competing interests.

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In a Chinese clinical trial by Yeming Wang and colleagues,[1] remdesivird did not show significant benefits for patients with severe COVID-19. Shortly after their study was published, remdesivir was authorised in the USA by the US Food & Drug Administration[2] and approved in Japan[3] for patients with severe COVID-19 on the basis of preliminary phase 3 trial results.[4] We find it puzzling that the discrepancy of results between China and the USA is merely justified by different study designs.

Genetic factors can influence drugs' efficacy and toxicity. Therefore, it is reasonable to seek answers from the genetic backgrounds of patients with COVID-19 and of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China and the USA. From the GnomAD database, we collected: 9977 genomes from east Asia that represented Chinese people; and 64 603 genomes from Europeans, 17 720 from Latinx, and 12 487 from African Americans, which represented the three majority ethnicities in the USA.[5] Genetic diversity was found in seven pharmacogenes that mainly related to pharmacokinetics and pharmacodynamics of remdesivir.[6] Notably, the mutation frequency of *CYP2D6* (rs1065852) in east Asia (57·7%) was much greater than that of the American ethnicities (12·3–21·7%), whereas the mutation frequency of *SLCO1B3* (rs60140950) showed the opposite result (appendix). Meanwhile, we also collected 432 SARS-CoV-2 samples from China and 2754 SARS-CoV-2 samples from the USA using an online database.[7] The frequency of potential functional variations such as p.P4715L (c.14144C>T) in polyprotein 1ab, which is the target of remdesivir, were largely different in the genomes from the USA (63·0%) and China (11·2%). These variations could generate the efficacy discrepancy of remdesivir among these clinical trials.

Similar to remdesivir, ethnic diversity was also found in pharmacogenes related to other drugs, such as chloroquine, in COVID-19 treatment. In summary, pharmacogenomic studies for COVID-19 therapy seem to be needed urgently.

J-YY and C-XG report grants from the National Natural Science Foundation of China (81773823, 81974511), and the National Science and Technology Major Project of China (2017ZX09304014, 2019ZX09201-002–006, 2020ZX09201010). All other authors declare no competing interests.

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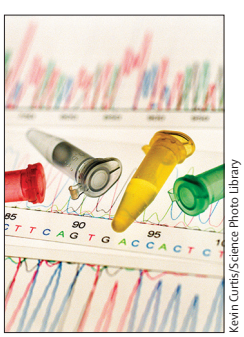
For **guidelines on use of antiretroviral agents in adults and adolescents with HIV** see http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

For **guidelines on initial treatment of adults with HCV infection** see https://www.hcvguidelines.org/treatment-naive

See **Online** for appendix



Kevin Curtis/Science Photo Library

For the **GnomAD database** see https://gnomad.broadinstitute.org/

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Authors' reply

We thank the clinicians and researchers around the world for their comprehensive interpretation of the results of our randomised controlled trial of remdesivir for COVID-19.[1] They shared valuable thoughts from different perspectives according to related evidence from in vitro and animal models, and pharmacogenomic studies. A suggestion was made for subgroup analyses by concomitant lopinavir-ritonavir use. Concerns for not reaching the predetermined sample size in our study were also expressed. These comments are appreciated and helpful for future conduct and interpretation of COVID-19 therapy studies.

Matthew Glaus and Serena Von Ruden point out that the therapeutic effect of remdesivir might be lost when treatment initiation was delayed, based on results from animal studies.[2,3] We certainly agree that initiating remdesivir at an earlier stage might contribute to better clinical benefits. However, it is challenging to initiate early antiviral therapy due to possible delays in screening and diagnosis of COVID-19. In our trial, we set 12 days from symptom onset as one of the inclusion criteria.[4]

Alicia Dennis questioned the fact that our trial was terminated by March 12, 2020, due to reasons we have stated and further commented that ongoing study recruitment would probably have been possible. Although the number of confirmed COVID-19 patients at the time was still large in Wuhan, China, there were only a limited number of new-onset severe patients. A detailed recruitment process has been reported elsewhere.[5]

The suggestion made by Jessie K Edwards and colleagues to report the effect of remdesivir stratified by lopinavir-ritonavir is important, although the potential effect of lopinavir-ritonavir was not confirmed in COVID-19 patients. Evaluating whether an interaction exists between lopinavir-ritonavir and remdesivir is still important and can also provide evidence for the feasibility of factorial trial of these two drugs. The result from our trial showed that there was no statistically significant interaction between lopinavir-ritonavir and remdesivir on time to clinical improvement (p=0·35).

We appreciate the possible explanation raised by Lei-Yun Wang and colleagues that the genetic backgrounds of patients might be one of the reasons for discrepant results between the Chinese and American remdesivir clinical trials.[1,6]. The relationship between seven pharmacogenes and the plasma concentration of remdesivir in two populations should be confirmed. Whether the different strains of severe acute respiratory syndrome coronavirus 2 between China and the USA contribute to the discrepant effect of remdesivir also needs to be confirmed. McCreary and Angus[7] speculate that differences in study design could be the reason to explain the variation in results from the trials of remdesivir. They also provide several valuable questions about the variable effects of remdesivir in different trials. Although the conclusions between the three trials have discrepancies,[1,6,8] we still want to emphasise that the main findings from remdesivir trials showed similar but limited beneficial effect of remdesivir in patients with COVID-19.

We declare no competing interests.

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Gains and losses in translation of SDGs at sub-national levels

Samira Asma and colleagues[1] show the complexity of the global monitoring of health-related Sustainable Development Goals (SDGs) and argue for convergence, harmonisation, and strong data science. However, many offspring of SDG monitoring systems have emerged beyond the monitoring of UN SDG indicators, either at supra-national level