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.

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1 Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2020; **395:** 1569–78.
2 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; **382:** 1787–99.
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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.

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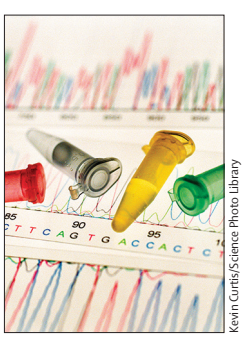
For **guidelines on use of antiretroviral agents in adults and adolescents with HIV** see http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf

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

See **Online** for appendix



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