Remdesivir: An antiviral still seeking a *raison d'être*

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Manuscript Text

Given all that has happened during the ongoing COVID-19 pandemic, it can be forgiven if we have collectively forgotten that remdesivir, a broad-spectrum viral RNA polymerase inhibitor (1), was not initially developed for its current and only FDA-approved indication for the treatment of COVID-19 requiring hospitalization (2). Dr. Higgs' and colleagues' report on the PREVAIL IV trial in this issue of *Clinical Infectious Diseases* is a suitable reminder that there have been and will continue to be infectious diseases other than COVID-19, and that we are all still trying to figure out the best ways to use this novel antiviral agent.

The PREVAIL (Partnership for Research on Ebola Vaccines in Liberia) group has previously published remarkable trials investigating novel Ebola virus vaccines (3, 4) and therapeutics (5) in relation to the 2014-2016 Ebola outbreak in West Africa. The PREVAIL IV trial was designed to address a potentially important complication of Ebola virus disease (EVD) – persistent viral shedding in semen in EVD survivors that may contribute to epidemic or endemic spread through sexual transmission. Thirty-eight male EVD survivors from the West Africa Ebola epidemic, who had Ebola virus RNA detectable in the semen a median of 2 years after onset of clinical disease, were enrolled and randomized to receive 5 days of intravenous remdesivir or placebo control. Repeated semen samples were collected during two phases, a 28-day "treatment phase" and a 5-month "follow up phase" and assessed for presence of Ebola virus RNA by RT-PCR. The pre-specified primary outcome was the difference in mean "assay negativity rate" (ANR), or the average frequency of negative samples out of all the samples tested during the two phases.

Enrollment of the trial was terminated early due to decreasing probability of enrollment with increasing time from the end of the epidemic and therefore limited the power

of the study. This limitation is well discussed by the investigators, and an anticipated possibility when conducting clinical trials in an epidemic setting, including for COVID-19. Despite this notable limitation, remdesivir treatment was associated with an increased ANR compared to placebo during the follow-up phase of sampling (p=0.041), but not during the treatment phase. The authors rightfully conclude that a larger follow up study is necessary to confirm whether remdesivir treatment reduces Ebola virus persistence in semen. One could argue that a more important outcome, though, would be prevention of sexual transmission of EVD, but such a study would be formidable to design and conduct in optimal settings, and probably impossible to conduct during an ongoing EVD epidemic.

On the other hand, there are several aspects about this study that are worth reviewing in detail, as they may be informative in a broader sense about the clinical utility of remdesivir, and antiviral therapy strategies in general. First, the participants were enrolled a median of 2 years after onset of the initial EVD, which is typically considered an acute viral infection, albeit with potential long-term sequelae. Second, the participants were considered to have Ebola virus "persistence" in the semen because of this time lapse from overt clinical disease. However, viral RNA was measured by nucleic acid testing, the presence of which does not *de facto* prove infectious virus persistence, in the truest meaning of that term, but could instead represent shedding of non-viable virus or virus particles. Furthermore, a semi-quantitative RT-PCR was used to detect Ebola virus RNA, and samples were dichotomized to positive or negative status, based on a cycle threshold count (Ct) of 39 or lower. The mean pre-treatment screening Ct values though were around 40, and most of the participants had only one of two pre-treatment screening samples positive for Ebola virus RNA. What we might infer from these details is that the study participants had very little, if any, ongoing active viral replication at the time of the study intervention, a distinct possibility the authors also discuss well.

That brings us back to the study intervention – the viral RNA polymerase inhibitor remdesivir. This had previously been shown to reduce Ebola virus replication and significantly improve survival after lethal challenge in Ebola virus infected rhesus macaques (6). However, during a RCT for EVD in the Democratic Republic of Congo from 2018-2019, enrollment into the remdesivir arm was terminated early due to inferiority with respect to mortality compared to two other antibody-based treatment groups (Mab114 and REGN-EB3) (7). Despite the FDA-approval of remdesivir for treatment of COVID-19 requiring hospitalization, its impact in the published clinical trials in COVID-19 is mixed at best, with two placebo-controlled RCTs showing remdesivir treatment modestly shortened time to clinical improvement in COVID-19 (8, 9), whereas two did not show any benefit with remdesivir (10, 11). More trials, "living" meta-analyses and systematic reviews will try to tease out the hint of a possibility of small therapeutic benefits of remdesivir for COVID-19. It is safe to say that if remdesivir truly had a clinically meaningful impact, with a reasonable number needed to treat, on important outcomes in COVID-19, it would have been evident by now.

It is fair, then, to ask how can that be? Remdesivir has broad *in vitro* antiviral activity and recently published Phase I clinical trials in health humans suggest very favorable pharmacokinetics, with high intracellular concentrations of the active metabolite in PBMCs relative to the antiviral EC_{50} (12). Historically, there are effective antivirals only for select chronic viral infections, i.e. some herpes viruses, Hepatitis B and C, and HIV. There are not highly effective (clinically meaningful reductions in morbidity or mortality) antivirals for viruses that cause acute infection, such as influenza, RSV, or SARS-CoV-2. Viral RNA polymerase inhibitors, such as remdesivir, by definition inhibit viral replication. These agents can only be effective when viruses are actively replicating, as correctly pointed out by the

authors in the context of the current study, in which evidence for active Ebola virus replication was minimal to absent.

It is likely that any viral replication that would be biologically important to inhibit therapeutically, in the context of an acute viral infection, such as EVD or COVID-19, occurs prior to: 1) the recognition of the viral infection (based on symptom or diagnostic testing), 2) initiation of treatment, and 3) accumulation of sufficient active drug in the relevant cellular and tissue compartments that would be needed to inhibit said replication. The battle is over, and the enemy has moved on before the first defensive maneuver is even begun. Anything after that results only in loud noises and wasted bullets to no effect. It seems then, that attempting to treat most acute viral infections with current antivirals is probably a losing strategy using tools still searching for a useful function. Dr. Higgs et al suppose that treating EVD survivors closer to the time of the acute infection with remdesivir may improve the therapeutic effectiveness in clearing persistent Ebola virus from the semen, and propose this strategy for the next, bigger study. Based on the above, it is unclear if that will increase the apparent therapeutic benefit of remdesivir for this indication.

There is another way, and hope yet for remdesivir, and antivirals for acute viral infections in general. Although Benjamin Franklin's adage of "An ounce of prevention is worth a pound of cure" is nearly three centuries old, "Prevention is Treatment" is a recent concept popularized by the effectiveness use of antiretroviral medications for HIV pre-exposure or post-exposure prophylaxis. Similarly, post exposure influenza prophylaxis with neuraminidase inhibitors is a much more impactful interventional use of antiviral medications for influenza than therapy for acute influenza infection (13). So far, in the current pandemic, RCTs for post-exposure prophylaxis have been disappointing. However, most have used repurposed drugs not generally classified as antivirals, e.g. the immunomodulator hydroxychloroquine, and were performed as large placebo-controlled trials in the setting of

the potential for multiple community based exposures, making the issue of timing critically important. An interesting variation of post-exposure prophylaxis is exemplified by an ongoing Swiss open-label RCT of lopinavir/ ritonavir as pragmatic same-day ring COVID-19 prophylaxis for adults exposed to SARS-CoV-2 (NCT04364022). It may be hard to justify a same-day ring prophylaxis trial of intravenous remdesivir for COVID-19 post-exposure prophylaxis, due to the imbalance in drug and administration cost versus absolute risk of severe complications, except in the highest risk individuals. However, the individual risk for morbidity and mortality in EVD are so much greater than COVID-19. Perhaps the use of remdesivir as ring prophylaxis for EVD, with or without concomitant monoclonal antibody therapy, would better prevent Ebola virus persistence in semen of male survivors of EVD and ongoing sexual transmission, than its use during or shortly after acute EVD. It might also prevent EVD, which would indeed be worth a pound of cure, and provide a *raison d'être*.

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