The Multidimensional Challenge of Treating COVID-19:

Remdesivir is a Foot in the Door

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There are multiple dimensions to consider when treating COVID-19: the severity of infection, the goals of treatment, and the intervention being deployed. Most people with symptomatic SARS CoV-2 infection have mild or moderate disease but early estimates from China were that 15% develop severe disease and 5% have critical illness [1, 2]. The goals of treatment depend in part on severity of disease. In people who have mild disease, who are typically managed as outpatients, the goal is to prevent progression and hospitalization. In people who are hospitalized, the goal is to hasten recovery and prevent complications and death. A third dimension of treating COVID-19 is the specific intervention, which are sometimes grouped into categories: antiviral medications; treatments that enhance antiviral immunity; and anti-inflammatories or immune modulators. The multidimensional challenge of treating COVID-19 can be simply formulated as: What are the best interventions to meet the goals of treating COVID-19 in differing severities of disease?

To address this question, we need to understand the pathogenesis of COVID-19. Soon after infection, viral replication is thought to drive many of the initial clinical manifestations, including upper respiratory symptoms and pneumonia. However, COVID-19, particularly when severe, is a multi-system disease that encompasses a variety of neurologic, cardiac, renal, gastrointestinal and cutaneous complications. Some of these complications appear to be related to thrombo-inflammation. In people hospitalized with COVID-19, elevated coagulation and inflammatory marker levels have been associated with mortality[3]. In a pathologic study of people who died of COVID-19, the lungs showed evidence of endothelial injury, thrombosis and angiopathy[4].

Therefore, the dimensions of COVID-19 treatment – stage/severity, goals of treatment, and the intervention – are intimately related: Depending on the stage and severity of disease, the optimal

intervention may differ. Early in infection, antiviral therapies may be particularly important. These treatments may be small molecules that target the viral lifecycle (direct-acting antivirals) or antibodies against SARS-CoV-2, such as those found in convalescent plasma or monoclonal antibodies. Later in infection, anti-inflammatory medications may be more impactful, particularly if disease is being driven by an over-exuberant immune response and excess inflammation. Consistent with this conceptual model (Figure) are the ground-breaking findings from the RECOVERY trial[5]: dexamethasone reduced mortality in hospitalized patients with COVID-19 and the benefit was greatest in those who were most severely ill (on mechanical ventilation). The trial also showed that dexamethasone does not improve outcomes – and may even lead to harm – in people who were not ill enough to require supplemental oxygen, highlighting the importance, as the authors say, of using the right drug "at the right time, in the right patient".

In terms of antiviral therapy, the first drug to show clinical benefit in COVID-19 is remdesivir. Remdesivir, a nucleotide analog, binds the viral RNA-dependent RNA polymerase and acts as a non-obligate chain terminator, inhibiting RNA synthesis and viral replication. The drug is active against several RNA viruses, such as Ebola virus (for which remdesivir was evaluated in human trials[6]), and coronaviruses, including SARS-CoV-2[7-9]. In a rhesus macaque model of COVID-19, remdesivir given soon after infection reduced SARS-CoV-2 levels in the lung (but, intriguingly, not in the upper respiratory tract) and ameliorated the extent of lung damage and disease[10].

Based on in vitro and animal studies – and information from people with Ebola virus disease – remdesivir was one of the first antiviral therapies to be evaluated for COVID-19. The first published randomized trial, conducted in China, did not show a clinical benefit of remdesivir, but it was

underpowered because COVID-19 was brought under control before the study could be completed. This was the stage upon which the results of the landmark National Institutes of Health (NIH)-sponsored Adaptive COVID-19 Treatment Trial (ACTT) were announced at a time when many unproven therapies for COVID-19, including hydroxychloroquine, were in widespread use.

In ACTT, 1063 hospitalized people with COVID-19 and lower respiratory tract involvement were randomized to receive 10 days of intravenous remdesivir or placebo. In a preliminary analysis[11], remdesivir was associated with a significant decrease in recovery time (median 11 days in the remdesivir group vs. 15 days in the placebo group). In the overall study population, there was a trend towards decreased mortality in the remdesivir group as compared to the placebo group (7.1% vs. 11.9%; hazard ratio, 0.70, 95% confidence intervals, 0.47 to 1.04). Of note, the sub-group that had the clearest benefit were participants who required supplemental oxygen but did not need high-flow oxygen, non-invasive ventilation, mechanical ventilation or extra-corporeal membrane oxygenation (ECMO). There was no evidence for clinical benefit with remdesivir in participants who were on high flow oxygen/non-invasive ventilation or mechanical ventilation/ECMO (although it should be noted that the study was not powered to examine effects in different sub-groups). The finding that the most-striking clinical benefit of remdesivir was in people who were not yet critically ill is consistent with the hypothesis that antiviral therapy will have its greatest impact when given earlier in the disease course.

Now, we have another look at the clinical benefit of remdesivir in a study sponsored by the manufacturer of remdesivir. The previously-published randomized open-label GS-US-540-5773 trial, conducted in hospitalized people with severe COVID-19 (pulmonary infiltrates and oxygen saturation <=94% or requiring supplemental oxygen), showed that 5 days of remdesivir conferred similar clinical

benefit as 10 days of remdesivir[12]. In the study now published by Olender et al in *Clinical Infectious Diseases*[13], clinical outcomes in 312 participants who received remdesivir in the 5773 trial (the remdesivir cohort; data combined from the 5- and 10-day groups) were compared to outcomes in 818 people who were treated according to local standard of care and did not receive remdesivir (non-remdesivir cohort). Because the two cohorts had substantial differences in their baseline characteristics, however, the investigators used a statistical procedure, called the stabilized inverse probability of treatment weighting method, to make the groups as similar as possible to ascertain the effect of remdesivir.

What were the results? At day 14, 74.4% of participants in the remdesivir cohort and 59% of participants in the non-remdesivir cohort had recovery, defined as improvement of clinical status on an ordinal scale. By day 14, weighted mortality was 7.6% in the remdesivir and 12.5% in the non-remdesivir group; adjusted odds ratio for death was 0.38, indicating 62% lower mortality.

What do we learn from this study? There are several limitations that make this analysis less definitive than the findings from ACTT. Because the manufacturer-sponsored study is not randomized, it is not possible to exclude residual confounding. In addition, there were large imbalances in hydroxychloroquine use: 17% in the remdesivir group and 75% in the non-remdesivir group. The investigators excluded hydroxychloroquine from the propensity score in the primary analysis because, when it was included, there were additional imbalances in other prognostic factors. Although the study's findings were not changed when, in a sensitivity analysis, hydroxychloroquine use was included in the propensity score, there may have been other important imbalances or differences between the cohorts that could not be accounted for by statistical methods and which may have affected the results.

Nevertheless, this study yields important insights. First, the results are largely concordant with those in ACTT, which bolsters confidence in the findings. Approximately 60% of participants in the manufacturer-sponsored study were on low-flow supplemental oxygen (people who were mechanically ventilated were excluded from the 5773 trial). This is the sub-group in ACTT that derived the greatest benefit from remdesivir: in the preliminary analysis, mortality by 14 days was 2.4% in the remdesivir group and 10.9% in the placebo group (hazard ratio for death, 0.22, 95% confidence interval, 0.08-0.58). Thus, in people with COVID-19 who require supplemental oxygen but are not ill enough to require high flow oxygen, non-invasive ventilation, mechanical ventilation or ECMO, there is good evidence that remdesivir reduces mortality. In addition, the manufacturer-sponsored study demonstrates – as expected – that people who require less oxygen support and are younger have better clinical outcomes than those who require more respiratory support or are older.

Where do we go from here? Based on the conceptual model and data summarized above, there are reasons to think that antiviral therapies, such as remdesivir, may be even more effective when started earlier in the disease course. Indeed, a recent press release suggests a benefit to remdesivir in moderate COVID-19 [14]but the details of that trial are not yet published and the results cannot, therefore, be assessed. If early antiviral treatment is beneficial, then outpatient therapy may have a substantial impact on clinical progression and potentially on transmission. (Antiviral therapy prevents transmission of HIV but "treatment as prevention" has yet to be proven for SARS-CoV-2.) To test whether early treatment confers clinical benefit, many trials are underway or launching soon, including studies of inhaled remdesivir, other promising antiviral medications (such as EIDD-2801, an orally bioavailable nucleoside analog[15]), convalescent plasma and monoclonal antibodies.

In addition, even as we insist upon guaranteeing equitable access [16] to remdesivir at a reasonable cost to all those who need it, we clearly need to go beyond just remdesivir for treatment of COVID-19. In hospitalized patients who require supplemental oxygen, remdesivir and dexamethasone have each shown benefit in separate trials – remdesivir in ACTT and the current study; dexamethasone in the RECOVERY trial [5]. The logical next step is to evaluate whether adding an immunomodulator to remdesivir leads to an additional improvement over and above remdesivir alone. That concept is being tested in the ACTT-2 trial [17], now fully enrolled, in which remdesivir is being combined with baricitinib, an oral JAK1/JAK2 inhibitor. This is but one example of what is sure to be an exciting era of trials for COVID-19, that will include combinations of direct-acting antivirals, direct-acting antivirals plus monoclonal antibodies, and direct-acting antivirals plus immunomodulators (such as tocilizumab)[18].

In closing, for a perspective on where we are with COVID-19, the latest global pandemic, it is helpful to reflect on what we learned from confronting another world-wide pandemic – HIV. Although there are many differences between COVID-19 and HIV – the first is an acute infection that is usually mild; the latter is a chronic infection that, if untreated, is almost always fatal – there are some important lessons from HIV that can be applied to COVID-19. The first lesson is highlighted by the initial rush to try unproven therapies for COVID-19, which is eerily reminiscent of the pressure to give – and even approve – treatments of uncertain benefit in the early days of HIV. Now, as then, the pressure to deploy treatments – a natural impulse when people are desperately ill – must be tempered by the importance of finding out whether a medication does or does not work[19]. The comparative trials that established the role of remdesivir and dexamethasone in treatment of COVID-19 are excellent examples of the progress that can – and will -- be made if we are guided by the science. The second lesson from HIV is

that incremental progress is necessary to eventually making transformative advances in the care of a disease. With HIV, it was the development of antiretroviral medications that, when combined, led to long-term control of a previously fatal infection. With COVID-19, remdesivir is not the be-all and end-all of therapy; rather it is a foot in the door, a first step towards what will hopefully be a tipping point. We all remember that tipping point when combination antiretroviral therapy transformed the lives of people with HIV. We are not there yet with COVID-19 but progress is rapid and I have no doubt that we will arrive there in the not too-distant future.

Conflict of Interests: RTG has served on scientific advisory boards for Merck and Gilead, and reports grants from National Institutes of Health.

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Figure Legend:

Multidimensional Challenge of Treating COVID-19