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Letter to the Editor

A Comment on "Remdesivir and EIDD-1931 Interact with Human Equilibrative Nucleoside Transporters 1 and 2: Implications for Reaching SARS-CoV-2 Viral Sanctuary Sites"

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Miller et al.'s (2021) observation of clinically relevant interaction between remdesivir and the equilibrative nucleoside transporter (ENT) 1 and ENT2 may help to explain the relatively lackluster *in vivo* efficacy of this agent in COVID-19 despite robust *in vitro* anti-SARS-CoV-2 activity in multiple diverse human cell lines. ENT1 and ENT2 have been previously noted to undergo marked downregulation in lung epithelial and endothelial cells in both hypoxia (Eltzschig et al., 2005) and acute lung injury (Morote-Garcia et al., 2013), and HIF-1α mRNA expression is increased in severe COVID-19 (Taniguchi-Ponciano et al., 2021). Moreover, the increased extracellular adenosine levels observed in acute lung injury (Eckle et al., 2009) would be expected to compete with remdesivir for uptake via these same transporters, theoretically reducing intracellular drug levels even further. Additional studies to examine this possibility are urgently warranted.

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ABBREVIATION: ENT, equilibrative nucleoside transporter.