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Towards COVID-19 Prophylaxis: An AIDS Preclinical Research Perspective

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Abstract

The success of an antiviral drug depends on its potency to neutralize the virus in vitro and its ability after administration in vivo to reach the anatomic compartments that fuel viral dissemination in the body. For instance, remdesivir, a potent SARS-CoV-2 antiviral drug based on studies in vitro, if administered orally would be poorly effective because low drug levels would reach the lungs due to its high first pass destruction in the liver. This is the reason remdesivir can only be administered intravenously, a requirement that clearly limits its use as a prophylactic agent for COVID-19, although novel formulations for its easier administration are under development. Whether an antiviral prophylaxis could further control or even stop the COVID-19 epidemic in synergy with other non-pharmacological based mitigation strategies is today unknown. Since the mid-1960s, pharmacologists have investigated the use of lipid-based nanoparticles for efficient delivery of antivirals to tissues, for example by transforming the route of administration from intravenous to oral, subcutaneous or aerosol administrations. These novel encapsulation strategies have also the potential to maintain high levels of the antiviral drugs in tissues, with reduced dose frequency compared to the non-encapsulated drug. Several lipid-based nanoparticles are today approved by the US Food and Drug Administration or being tested in clinical studies with favorable toxicity profiles.

Nonhuman primate models of coronavirus infection offer unique platforms to accelerate the search for SARS-CoV-2 antiviral prophylaxis. Paradigms, to corroborate this claim, are borrowed from nonhuman primate research studies, some of which had a profound impact on global public health in the specific setting of the AIDS pandemic. Sharing information from nonhuman primate research programs, invoking principles of scientific transparency and bioethics similar to those universally agreed for human studies, would also likely significantly help our collective fight (as the human species) against this public health emergency.

What Makes an Antiviral Potent Against SARS-CoV-2?

Remdesivir, a nucleoside analogue specific for the RNA-dependent RNA polymerase of several coronaviruses, is a potent SARS-CoV-2 antiviral drug based on studies in vitro. Its half maximal effective concentration (EC50) leans consistently towards the lowest estimates when screened, using the same assay, with other antivirals tested against several coronaviruses [1-4] hence, a relatively lower concentration of the drug is needed to cut similar levels of viral replication in vitro, compared to other antiviral drugs less successfully repurposed, so far, as medical countermeasures against COVID-19. These include the HIV-1 protease inhibitor lopinavir/ritonavir (Kaletra) and the immunosuppressive and anti-parasitic drug hydroxychloroquine [5,6].

The success of an antiviral drug in fighting a virus depends, however, not only on how potent the drug is in inhibiting the virus *in vitro* but also on how well the drug penetrates the anatomic compartments in which the virus mostly replicates *in vivo*; the lungs for COVID-19. If administered orally, for instance, remdesivir would be ineffective because low drug levels would reach the lungs due to its high first pass destruction in the liver, resulting in poor oral bioavailability. This is the reason remdesivir can only be administered intravenously to exert its viral inhibitory function, a requirement that clearly limits its use as a prophylactic agent or as a test-and-treat pharmacologic-based mitigation strategy for COVID-19.

Delivering Potent Antivirals Straight to the Lungs, without Calling a Nurse

What can be done to transform the route of administration of an antiviral or to enhance its concentration into the lungs? Since the mid-1960s, pharmacologists have investigated the use of lipid-based nanoparticles for efficient delivery of antivirals and other drugs, for example by transforming the route of administration from intravenous to oral, subcutaneous or aerosol administrations [7,8], with potentially useful ramifications in the pharmacoeconomics of developing countries [9]. These novel encapsulation strategies are capable of

maintaining high levels of the antiviral drugs in tissues, with reduced dose frequency. For instance, Kaletra in its oral formulation requires daily administration due to its rapid clearance, but data produced from nonhuman primates have demonstrated that the equivalent mass of one pill of Kaletra formulated as a lipid-nanoparticle for subcutaneous administration achieves approximately 10-fold higher concentrations in lymph nodes for about one week [10]. Similarly, the lipid-nanoparticle encapsulation of tenofovir, a nucleotide analogue used to treat HIV and hepatitis B infection that has some structural and functional similarities with remdesivir, has also been shown to enhance tissue concentrations and prolong retention of its active phosphorylated moieties in nonhuman primate studies [11]. The opportunity offered by nanoparticle technologies, not only to simplify the administration of a candidate antiviral drug, but also to enhance its concentrations in tissues, is relevant in the search for SARS-CoV-2 antiviral prophylaxes, especially given the limited data we have today for the penetration in the lungs or in the upper airways of most anti-SARS-CoV-2 repurposed antivirals [12], including lopinavir/ritonavir [13] and nelfinavir (another HIV-1 protease-inhibitor with a favorable EC50 against coronaviruses [14]). It is well known that lipophilic drugs preferentially penetrate the lungs and, in fact, this formed the rationale for encapsulating certain hydrophilic drugs in liposomes to promote delivery to the pulmonary compartment [15,16]. One example is amphotericin, an antifungal drug encapsulated in nanocochleates (soy-bean organic-based lipid particles) which can be formulated as an oral drink. Pharmacodynamic animal studies have advanced to phase-II clinical trials, in which patients are being administered the oral nanocochleate antifungal formulation, which appears to offer an overall effective oral formulation associated with low toxicity after prolonged (more than one year) continuous treatment [17]. Several lipid-based nanoparticles are today approved by the US Food and Drug Administration or being tested in clinical studies with favorable toxicity profiles [18]. Indeed these nanocarriers, by affecting the biodistribution in the body of the encapsulated antiviral compound, can substantially modify toxicological properties of the formulated drug. Of note, subcutaneous and aerosol formulations of remdesivir are now under development [19].

Consistent with the ranking by in vitro potency (the EC50), clinical trials in which these drugs have been administered to COVID-19 patients have thus far shown clear evidence of therapeutic potential only for remdesivir (intravenous formulation) [5,6]. Pharmacodynamic correlates of poor clinical responses could guide efforts in the search for an optimal prophylaxis. For instance, the antiviral drug Kaletra (available in pills) has been administered to COVID-19 patients with the same dose used to treat HIV-1 infected patients; however, its potency in vitro against SARS-CoV-2 is known to be significantly weaker than against HIV-1 [20].

Lessons Learned from the History of HIV-Prophylaxis Research

A successful antiviral prevention strategy is Truvada-PrEP for HIV, a combination of two nucleo(t)side analogues, that is lighter than the combination therapies (Highly Active Anti-Retroviral Therapy, HAART) used to treat HIV-1 infected patients, with important toxicological implications. Of note, dosing and administration strategies to conceive Truvada-PrEP (tenofovir+emtricitabine) were generated primarily from two monkey studies that produced, through invasive experimental designs not implementable in humans, precious data on the minimal drug levels needed in tissues to achieve protection from viral challenges [21,22]. These molecules attack the polymerase of HIV (or of lentiviruses that possess replication capacity in monkeys similar to HIV in humans, e.g. the simian-human immunodeficiency virus, SIV/SHIV) with a mechanism similar to the one adopted by remdesivir to attack the polymerase of several coronaviruses (including SARS-CoV-2), i.e. as chain terminators by mimicking the structure of a natural nucleoside [23].

Those studies demonstrated that the administration of two pills of Truvada (two hours prior to viral exposure) followed by two consecutive pills at 24 and 48 hours post-exposure provided sufficient drug levels in the rectal mucosa tissue to cut most viral transmissions. That prophylactic regimen (later called "On-Demand") achieved in monkeys a protection similar to that achieved through daily drug administrations. This data prompted randomized clinical trials of "On-Demand-PrEP" prophylaxis, which confirmed an efficacy similar to the one estimated with the heavier "Daily-PrEP" regimen [24] and which later received endorsement in revised HIV treatment and prevention recommendations issued by the International Antiviral Society–USA [25]. Hence the former are two examples of nonhuman primate studies that have had a profound impact on public health worldwide.

Similarly, two decades earlier, the simian-human immunodeficiency virus (SIV/SHIV)-monkey model had been used to generate the HIV Post-Exposure Prophylaxis (PEP) guidelines we are using today for both occupational and non-occupational exposure to HIV, by demonstrating the effectiveness of a cocktail of HIV drugs (a combination of antiretrovirals similar to the one administered to HIV-1 infected patients, for four consecutive weeks), in preventing viral transmission if administered within 72 hours (but the sooner the better) from viral exposure [26,27]. The length of this window of opportunity for HIV PEP was identified, again, through nonhuman primate studies, in which lentiviruses replicate with dissemination capacity and antiviral drugs distribute in tissues with kinetics, much more similar to humans than any other animal model in our hands. In general, although animal models (including nonhuman primates) are known to be poor predictors (for obvious reasons) of the efficacy of specific HIV vaccines in humans [28], the monkey models proved to be valuable resources, during the past decades, in predicting the efficacy of antiviral HIV strategies not only as prophylaxis but also in the therapeutic arena.

The lessons learned from HIV and Truvada-PrEP studies include the following: 1) an antiviral may show a weak therapeutic effect, especially if administered late in the course of the viral induced disease, yet can effectively cut most viral transmissions if administered prophylactically. This observation holds true also for COVID-19. For instance, a recent study in a coronavirus rodent model showed that another nucleoside analogue with in vitro inhibitory activity similar to remdesivir can efficiently reduce viral replication in the lungs yet may

fail to prevent disease progression if administered too late [29]; and 2) the higher the drug concentration in the anatomic compartments that fuel viral dissemination in the body, the higher the efficacy of the pharmacologic prevention strategy aimed at promptly eradicating the virus from the body [30]. The latter observation built the rationale for encapsulating HIV drugs in lipid-nanoparticles in research programs developed in the past decades [31], with the dual objective of simplifying (by reducing dosing frequency) and optimizing (by enhancing drug tissue levels) the delivery of antiretroviral drugs for both HIV-1 prevention and treatment, through proof-of-concept studies in nonhuman primate models of AIDS; an important experimental step for its effective translation into human studies.

The same experimental designs can be efficiently conceived to develop medical countermeasures to COVID-19 through the SARS-CoV-2 rhesus macaque model [32], which induces a respiratory disease milder than in COVID-19 patients, but that replicates at similar levels in the lungs [33,34]. In general, although non-invasive in vivo imaging technologies have also been used to study the biodistribution of antiviral drugs (including in the upper and lower respiratory tracts of humans [35,36]), our understanding of how an antiviral prophylaxis strategy succeeds or fails in protecting people from SARS-CoV-2 infection would inherently advance (as it did for HIV prophylaxis), by designing viral challenge experiments and producing measurements directly in tissues using these animal models. Sharing information from nonhuman primate research programs on what antiviral strategies are being tested on these animal models for COVID-19 throughout the world, invoking principles of scientific transparency and bioethics similar to those universally agreed for human studies (e.g. by registering studies in public databases) [37], would also likely significantly help our collective fight (as the human species) against this public health emergency [38].

These studies could also, in principle, be efficiently designed using other nonhuman-primate coronavirus animal models [39], especially if the antiviral target is the polymerase gene, given its high level of sequence conservation through evolution [29]. To date, remdesivir is the only antiviral drug tested in nonhuman primate models of SARS-CoV-2 with published observations [39,40]. Macaques infected with either the MERS-CoV [39] or the SARS-CoV-2 [40] rapidly cleared the virus following intravenous administration of remdesivir compared to untreated controls, consistent with the successful therapeutic effect of remdesivir observed in COVID-19 patients [6]. Data from both monkey studies also predict that remdesivir could prevent SARS-CoV-2 infection in humans, if used prophylactically. Prophylactic remdesivir (intravenous) treatment had been also successfully tested in nonhuman primates models of Ebola virus [41] and Nipah virus infection [42], two RNA viruses with an RNA-dependent RNA polymerase also highly sensitive to its inhibitory activity [43]. Indeed, both the cynomolgus [44] and the rhesus macaque models [45] of SARS-CoV-2 infection are being interrogated in these weeks to test the prophylactic efficacy of hydroxychloroquine.

These studies have been run in laboratories with the highest levels of biological safety (biosafety level-3 [39,40,44,45] and biosafety level-4 [41,42]) due to the high risk these pathogens pose to research personnel, which are very expensive to build and maintain, hence not readily available in most countries [46]. The modification of an antiviral, e.g. through lipid nanoparticle technology, as anticipated above, requires preliminary testing in vitro as well as in animal models. Specifically, there is need to demonstrate that the lipid structure does not impair the inhibitory activity of the encapsulated antiviral (e.g. does not increase its EC50 against the challenge virus). In healthy uninfected animals, biodistribution studies are subsequently needed to demonstrate that the encapsulated antiviral is capable of reaching the tissues in which the virus is expected to mostly replicate in vivo, and, in the case of a nucleoside analogue (like remdesivir), that its active phosphorylated moieties are produced at sufficient concentrations in those tissues. These preliminary pharmacokinetic studies will inform on the optimal dose of the encapsulated antiviral under scrutiny and on how frequently it will need to be administered in the pharmacodynamic studies. The latter studies can demonstrate the feasibility of the modified antiviral drug to exert its inhibitory activity in an infected host, hence an important step for the translation of the nanoparticle approach to human studies.

While alternative animal models could possibly serve the pharmacodynamic study objectives, the nonhuman primate model is likely the best model to accelerate this area of research. To my knowledge, coronaviruses less pathogenic to humans [47] but still sensitive to the inhibitory activity of remdesivir [48] (and possibly to other antiviral drugs [29]) have not been tested in nonhuman primates, although serologic studies suggest that these viruses may be able to replicate well in these hosts [49]. Indeed, a 229E coronavirus experimental infection study in normal volunteers failed to demonstrate efficacy of a nucleoside analogue for prophylaxis, as previously shown in rodent models, possibly due to the differential tissue pharmacokinetics of the specific drug under scrutiny in the two evolutionarily distant hosts [50].

In other words, "non-perfect" nonhuman primate models (i.e. those in which the SARS-CoV-2 or an older cousin does not cause disease yet replicates in tissues at levels similar to humans) can still generate useful data to screen prophylactic antiviral strategies, including, for instance, lipid nanoparticle formulations of "non-perfect" antiviral drugs (i.e. a putative antiviral drug failing to demonstrate a robust therapeutic effect in patients with advanced COVID-19 or if suboptimal drug levels in the lungs are confirmed from preclinical or post-mortem studies). Had we not discovered the rhesus-macaque model of HIV infection (in which the simian immunodeficiency virus [SIV] causes a disease similar to AIDS), we likely still would have generated pharmacodynamic data using the natural hosts of SIV infection (in which SIV does not cause disease, but still replicates in the body at levels similar to HIV in humans or SIV in the non-natural nonhuman-primate hosts [51]) equally useful for their inference to HIV-(post- and pre-exposure) prophylaxis (PEP and PrEP, respectively) in humans.

Had We the Equivalent of Truvada-Prep for SARS-CoV-2, How Would We Use it to Mitigate COVID-19?

Pharmacologic-based mitigation strategies to curb epidemics have been postulated [52], but their efficacy in synergy with social distancing and face mask wearing mitigation strategies (with or

without digital contact-tracing technology [53]) for an epidemic with a doubling-time and dynamic features similar to COVID-19 [54,55] is today unknown. Consensus is growing among modelers, however, that mitigation strategies interventions (which primarily act on reducing the same variable of the viral transmission dynamic models adopted in their studies, i.e. the infectivity rate) work best in keeping the number of new cases at bay (or could even stop the epidemic [53]), if administered when the pool of infected people is small, i.e. during the early steps of a viral outbreak or when the R-naught (average number of people that one infected person will pass the virus to) has been sufficiently reduced, for instance following a period of effective lock-down [53,55]. The larger the initial pool of infected people, the more aggressive the interventions aimed to promptly control an epidemic may need to be (including voluntary centralized quarantine) [56].

Efforts in this area of mathematical modeling research are critically needed to serve this and any future viral outbreak. For bioethical reasons, similarly to what happened for PEP studies in the 1990s, once the effectiveness of the first available COVID-19 prophylaxes is demonstrated, it will be difficult to estimate the relative contribution of each mitigation strategy to the curve of new cases in a given region. Epidemiological models of COVID-19 for instance predict that a 50% reduction in within-population contact rates can already have a dramatic effect in slowing the course of the epidemic [54]. Massive data sharing among countries, which will likely adopt different combinations of those strategies at different times, will be of utmost importance to produce that knowledge.

The role of an antiviral prophylaxis goes beyond its ability to substantially impact the curve of cases. The high likelihood of SARS-CoV-2 transmission among individuals living in households with infected people [57] offers an important context in which a safe antiviral drug is highly desired to protect, first of all, those at high risk of severe disease, such as the elderly with chronic health conditions, as well as those at high risk of contracting the virus through occupational exposure. This would enhance the quality of life not only for uninfected adults living in the same household but also for the COVID-19 patients who could go through the quarantine period with less fear of infecting those who gravitate around their lives; a peace of mind that carries priceless benefits to patient welfare, somewhat similar (within the limitations of the proposed parallelism) to those experienced by HIV serodiscordant couples with the advent of Truvada-PrEP.

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References

1. Wang M, Cao R, Zhang L, Yang X, Liu J, et al. (2020) Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 30: 269-271. [crossref]

2. Martinez MA (2020) Compounds with Therapeutic Potential against Novel Respiratory 2019 Coronavirus. *Antimicrob Agents Chemother* 64.

3. Liu J, Cao R, Xu M, Wang X, Zhang H, et al. (2020) Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 6: 16. [crossref]

4. Sheahan TP, Sims AC, Leist SR, Schäfer A, Won J, et al. (2020) Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* 11: 222. [crossref]

5. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB (2020) Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. *JAMA* [crossref]

6. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, et al. (2020) Remdesivir for the Treatment of Covid-19 - Preliminary Report. *N Engl J Med*. [crossref]

7. Milovanovic M, Arsenijevic A, Milovanovic J, Kanjevac T, Arsenijevic N (2017) In: Antimicrobial Nanoarchitectonics, A. M. Grumezescu (Eds.). (Elsevier, 2017) Pg No: 383-410.

8. Pandey R, Khuller GK (2004) Subcutaneous nanoparticle-based antitubercular chemotherapy in an experimental model. *J Antimicrob Chemother* 54: 266-268. [crossref]

9. Salamanca-Buentello F, Persad DL, Court EB, Martin DK, Daar AS, et al. (2005) Nanotechnology and the developing world. *PLoS Med* 2: e97. [crossref]

10. McConnachie LA, Kinman LM, Koehn J, Kraft JC, Lane S, et al. (2018) Long-Acting Profile of 4 Drugs in 1 Anti-HIV Nanosuspension in Nonhuman Primates for 5 Weeks After a Single Subcutaneous Injection. *J Pharm Sci* 107: 1787-1790. [crossref]

11. Koehn J, Iwamoto JF, Kraft JC, McConnachie LA, Collier AC, et al. (2018) Extended cell and plasma drug levels after one dose of a three-in-one nanosuspension containing lopinavir, efavirenz, and tenofovir in nonhuman primates. *Aids* 32: N2463-2467. [crossref]

12. Arshad U, Pertinez H, Box H, Tatham L, Rajoli RKR, et al. (2020) Prioritization of Anti-SARS-Cov-2 Drug Repurposing Opportunities Based on Plasma and Target Site Concentrations Derived from their Established Human Pharmacokinetics. *Clin Pharmacol Ther*. [crossref]

13. Twigg HL, Schnizlein-Bick CT, Weiden M, Valentine F, Wheat J, et al. (2010) Measurement of antiretroviral drugs in the lungs of HIV-infected patients. *HIV Ther* 4: 247-251. [crossref]

14. Yamamoto N, Yang R, Yoshinaka Y, Amari S, Nakano T, et al. (2004) HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. *Biochem Biophys Res Commun* 318: 719-725. [crossref]

15. Nanoformulations for the Therapy of Pulmonary Infections (2017) In: Nanostructures for Antimicrobial Therapy, Sagar Dhoble, Vinod Ghodake, Manasi Chogale, Vandana Patravale (eds.). Elsevier, 457-480.

16. Pea F, Viale P (2006) The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? *Clin Infect Dis* 42: 1764-1771. [crossref]

17. Aigner M, Lass-Florl C (2020) Encochleated Amphotericin B: Is the Oral Availability of Amphotericin B Finally Reached? *J Fungi (Basel)* 6: 66. [crossref]

18. Bulbake U, Doppalapudi S, Kommineni N, Khan W (2017) Liposomal Formulations in Clinical Use: An Updated Review. *Pharmaceutics* 9: 12. [crossref]

19. https://www.reuters.com/article/us-health-coronavirus-gilead-sciences/gileads-next-step-on-coronavirus-inhaled-remdesivir-other-easier-to-use-versions-idUSKBN2391FP

20. Cao B, Wang Y, Wen D, Liu W, Wang J, et al. (2020) A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. *N Engl J Med* 382: 1787-1799. [crossref]

21. Garcia-Lerma JG, Otten RA, Qari SH, Jackson E, Mian-er Cong, et al. (2008) Prevention of rectal SHIV transmission in macaques by daily or intermittent prophylaxis with emtricitabine and tenofovir. *PLoS Med* 5: e28. [crossref]

22. Garcia-Lerma JG, Mian-er Cong, Mitchell J, Youngpairoj AS, Zheng Q, et al. (2010) Intermittent prophylaxis with oral truvada protects macaques from rectal SHIV infection. *Sci Transl Med* 2: 14ra4. [crossref]

23. Deval J (2009) Antimicrobial strategies: inhibition of viral polymerases by 3'-hydroxyl nucleosides. *Drugs* 69: 151-166. [crossref]

24. Molina JM, Capitant C, Spire B, Pialoux G, Cotte L, et al. (2015) On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection. *N Engl J Med* 373: 2237-2246. [crossref]

25. Saag MS, Benson CA, Gandhi RT, Hoy JF, Landovitz RJ, et al. (2018) Antiretroviral Drugs for Treatment and Prevention of HIV Infection in Adults: 2018 Recommendations of the International Antiviral Society-USA Panel. *JAMA* 320: 379-396. [crossref]

26. Tsai CC, Emau P, Follis KE, Beck TW, Benveniste RE, et al. (1998) Effectiveness of postinoculation (R)-9-(2-phosphonylmethoxypropyl) adenine treatment for prevention of persistent simian immunodeficiency virus SIVmne infection depends critically on timing of initiation and duration of treatment. *J Virol* 72: 4265-4273. [crossref]

27. Black RJ (1997) Animal studies of prophylaxis. *Am J Med* 102: 39-44. [crossref]

28. Herati RS, Wherry EJ (2018) What Is the Predictive Value of Animal Models for Vaccine Efficacy in Humans? Consideration of Strategies to Improve the Value of Animal Models. *Cold Spring Harb Perspect Biol* 10: a031583. [crossref]

29. Sheahan TP, Sims AC, Zhou S, Graham RL, Pruijssers AJ, et al. (2020) An orally bioavailable broad-spectrum antiviral inhibits SARS-CoV-2 in human airway epithelial cell cultures and multiple coronaviruses in mice. *Sci Transl Med* 12: eabb5883. [crossref]

30. Patterson KB, Prince HA, Kraft E, Jenkins AJ, Shaheen NJ, et al. (2011) Penetration of tenofovir and emtricitabine in mucosal tissues: implications for prevention of HIV-1 transmission. *Science translational medicine* 3: 112re114-112re114. [crossref]

31. Kraft JC, Freeling JP, Wang Z, Ho RJ (2014) Emerging research and clinical development trends of liposome and lipid nanoparticle drug delivery systems. *J Pharm Sci* 103: 29-52. [crossref]

32. Munster VJ, Feldmann F, Williamson BN, Doremalen NV, Pérez-Pérez L, et al. (2020) Respiratory disease in rhesus macaques inoculated with SARS-CoV-2. *Nature*. [crossref]

33. Pan Y, Zhang D, Yang P, Poon LLM, Wang Q (2020) Viral load of SARS-CoV-2 in clinical samples. *Lancet Infect Dis* 20: 411-412. [crossref]

34. Wichmann D, Sperhake JP, Lütgehetmann M, Steurer S, Edler C, et al. (2020) Autopsy Findings and Venous Thromboembolism in Patients With COVID-19. *Ann Intern Med*. [crossref]

35. Bergstrom M, Cass LM, Valind S, Westerberg G, Lundberg EL, et al. (1999) Deposition and disposition of [11C]zanamivir following administration as an intranasal spray. Evaluation with positron emission tomography. *Clin Pharmacokinet* 1: 33-39. [crossref]

36. Dabisch PA, Xu Z, Boydston JA, Solomon J, Bohannon JK, et al. (2017) Quantification of regional aerosol deposition patterns as a function of aerodynamic particle size in rhesus macaques using PET/CT imaging. *Inhal Toxicol* 29: 506-515. [crossref]

37. Zarin DA, Keselman A (2007) Registering a clinical trial in ClinicalTrials.gov. *Chest* 131: 909-912. [crossref]

38. Brouillette M (2017) To Treat Primates More Humanely: Transparency Scientists look to open-data initiatives to lessen the burden of research on our closest animal relatives. *Sci Am* 316: 14. [crossref]

39. Wit ED, Feldmann F, Cronin J, Jordan R, Okumura A, et al. (2020) Prophylactic and therapeutic remdesivir (GS-5734) treatment in the rhesus macaque model of MERS-CoV infection. *Proc Natl Acad Sci U S A* 117: 6771-6776. [crossref]

40. Williamson BN, Feldmann F, Schwarz B, Meade-White K, Porter DP, et al. (2020) Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*. [crossref]

41. Warren TK, Jordan R, Lo MK, Ray AS, Mackman RL, et al. (2016) Therapeutic efficacy of the small molecule GS-5734 against Ebola virus in rhesus monkeys. *Nature* 531: 381-385. [crossref]

42. Lo MK, Feldmann F, Gary JM, Jordan R, Bannister R, et al. (2019) Remdesivir (GS-5734) protects African green monkeys from Nipah virus challenge. *Sci Transl Med* 11: eaau9242. [crossref]

43. Pardo J, Shukla AM, Chamarthi G, Gupte A (2020) The journey of remdesivir: from Ebola to COVID-19. *Drugs Context* 9: 4-14. [crossref]

44. https://www.researchsquare.com/article/rs-27223/v1

45. https://www.biorxiv.org/content/10.1101/2020.06.10.145144v1

46. Peters A (2018) The global proliferation of high-containment biological laboratories: understanding the phenomenon and its implications. *Rev Sci Tech* 37: 857-883. [crossref]

47. Bende M, Barrow I, Heptonstall J, Higgins PG, Al-Nakib W, et al. (1989) Changes in human nasal mucosa during experimental coronavirus common colds. *Acta Otolaryngol* 107: 262-269. [crossref]

48. Parang K, El-Sayed NS, Kazeminy AJ, Tiwari RK (2020) Comparative Antiviral Activity of Remdesivir and Anti-HIV Nucleoside Analogs Against Human Coronavirus 229E (HCoV-229E). *Molecules* 107: 262-269. [crossref]

49. Dijkman R, Mulder HL, Rumping L, Kraaijvanger I, Deijs M, et al. (2009) Seroconversion to HCoV-NL63 in Rhesus Macaques. *Viruses* 1: 647-656. [crossref]

50. Higgins PG, Barrow GI, Tyrrell DAJ, Snell NJC, Jones K, et al. (1991) A study of the efficacy of the immunomodulatory compound 7-thia-8-oxoguanosine in coronavirus 229E infections in human volunteers. *Antiviral Chemistry & Chemotherapy* 2: 61-63.

51. Gordon SN, Dunham RM, Engram JC, Estes J, Wang Z, et al. (2008) Short-lived infected cells support virus replication in sooty mangabeys naturally infected with simian immunodeficiency virus: implications for AIDS pathogenesis. *J Virol* 82: 3725-3735. [crossref]

52. Ferguson NM, Cummings DAT, Fraser C, Cajka JC, Cooley PC, et al. (2006) Strategies for mitigating an influenza pandemic. *Nature* 442: 448-452. [crossref]

53. Ferretti L, Wymant C, Kendall M, Zhao L, Nurtay A, et al. (2020) Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science* 368: eabb6936. [crossref]

54. Wu JT, Leung K, Leung GM (2020) Nowcasting and forecasting the potential domestic and international spread of the 2019-nCoV outbreak originating in Wuhan, China: a modelling study. *Lancet* 395: 689-697. [crossref]

55. Hellewell J, Abbott S, Gimma A, Bosse NI, Jarvis CI, et al. (2020) Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Health* 8: e488-e496. [crossref]

56. Pan A, Liu L, Wang C, Guo H, Hao X, et al. (2020) Association of Public Health Interventions With the Epidemiology of the COVID-19 Outbreak in Wuhan, China. *JAMA* 323: 1-9. [crossref]

57. Li W, Zhang B, Lu J, Liu S, Chang Z, et al. (2020) The characteristics of household transmission of COVID-19. *Clin Infect Dis*. [crossref]

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