Guest Editorial

Negative Evidence: Repurposed Drugs for COVID-19: the Partisan Bone of Contention. Part II

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"Facts do not cease to exist because they are ignored."
Aldous Huxley, *"Proper Studies," 1927*

Introduction

This article is a sequel and complement to the guest editorial in the last issue,[1] and both parts belong to the series of editorials examining various aspects of the response to the COVID-19 pandemic using the ***negative evidence*** concept.[1-10] This investigative paradigm is based upon paying attention to cases in which certain data, conclusions, or facts should be present but are counterintuitively absent.[11] Negative evidence implies not just a lack of information, but the suggestion that crucial details have been deliberately hidden, usually to conceal wrongdoing. Thus, any serious investigation should always include a meticulous hunt for such negative evidence.

Part I delved into the political aspects of the heated debate about repurposing old drugs for treatment of COVID-19. It detailed the history and changing paradigms as well as promises and disappointments of repurposing drugs for new uses. It highlighted a peculiar negative shift in authorities' stance towards the robustly developing new industry of drug repurposing that took place during the COVID-19 pandemic. It has been pointed out that two medications that were repurposed for treatment of COVID-19, i.e., hydroxychloroquine (HCQ) and ivermectin (IVM), have achieved a level of public notoriety rarely seen with any other drugs—for very good reasons. Part I included extended remarks on the heated dispute regarding the role of HCQ in treating COVID-19. The controversy over IVM is similar but contains distinctive differences, as discussed here.

The politicization of medicine and the related polarization of society and the scientific community significantly hinders many potential benefits of drug repurposing, substitutions, and conversion.[1,12,13] The IVM controversy is a point of departure for the discussion of the detrimental impact of political agendas in the context of limiting access to many safe and cost-effective repurposed drugs.

Finally, we need to consider the need for future initiatives needed to bring back normalcy in place of today's chaos.

Political Context of the Repurposed Drugs Controversy

The political background of this debate is crucial for its understanding (Figures 1 and 2). Unfortunately, this aspect is frequently overlooked, possibly because it is assumed to be self-explanatory, but often is not in today's politically charged media landscapes and ideological echo chambers.

The objective of this editorial is not to duplicate the numerous already available reviews that are influenced by significant partisan bias, but is to offer readers insights that are commonly overlooked when presented from a strictly political perspective. This editorial strives to remain neutral and as unbiased as possible, not zealously supporting either of the two parties' viewpoints. Instead, it prioritizes safety and wellbeing of the individual patient in alignment with the principle "Omnia pro Aegroto" ("all for the patient"). Nevertheless, this editorial isn't entirely impartial. It favors patients' welfare and liberty over oppression and tyranny. It is unsympathetic to chaos and sides with order and normalcy.

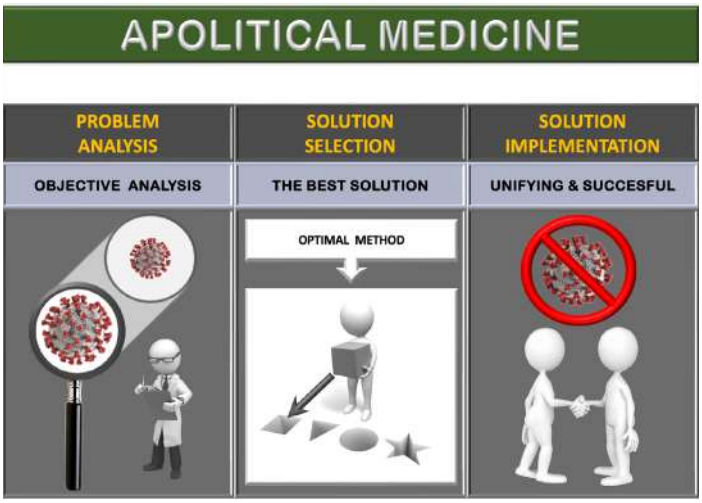

Figure 1. Apolitical medicine. Credit: Info Healer. Reproduced with permission.

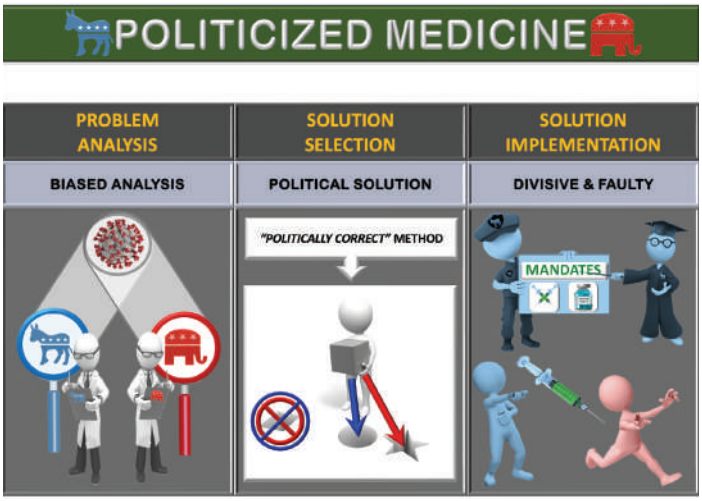

Figure 2. Politicized medicine. Credit: InfoHealer. Reproduced with permission.

Ivermectin Controversy

The IVM controversy parallels to some extent the history of HCQ repurposing. However, it contains important differences that can serve as valuable lessons, and these will be emphasized here.

Initial Hopes

IVM is a safe and effective antiparasitic medication with a remarkable history of discovery and utilization that earned the designation of *"the enigmatic multifaceted wonder drug that continued to exceed expectations"* long before COVID-19 pandemic.[14,15] It garnered significant attention as a potential treatment for COVID-19 because of in vitro studies suggesting that it could exert antiviral activity against SARS-CoV-2 virus through a variety of mechanisms (Figure 3). The drug's established safety profile, its widespread availability, and affordable price led to high hopes for its repurposing.

In Vitro Studies

The initial in vitro studies suggested that IVM might block the activity of a protein complex known as Importin (IMP) α/β1.[16] This complex is essential for transporting viral proteins into the nucleus of the host cell, which is a critical step in the viral replication cycle. By interfering with this process, IVM could, at least in theory, reduce the ability of the virus to multiply within the body.[16,17] This antiviral action is not specific to SARS-CoV-2 and has been observed with other viruses, indicating that IVM may act as a broad-spectrum antiviral agent. Additional mechanisms, as depicted in Figure 3, have been suggested; however, they were not well substantiated and some papers describing them were retracted.[18-20] In addition, the concentrations of IVM required to achieve these antiviral effects in vitro were significantly higher than those achievable in human plasma following dosing at approved levels for parasitic infections.[21] This discrepancy raised concerns about the clinical relevance of the in vitro antiviral findings. However, it did not dissuade most clinical researchers from pursuing clinical trials involving IVM since the interpretation of the in vitro studies in the context of pharmacokinetic data in humans is difficult and prone to errors. Similarly, many clinicians around the world decided not to wait for the results of elaborate clinical studies and decided to start using IVM empirically. They felt that this decision was justifiable in view of the excellent safety profile of this drug. Many practitioners considered such approach as more beneficial for their patients than the "no treatment" policy promoted by officialdom that appeared to be reflective of sole reliance on the vaccine as the one and only solution for the COVID-19 pandemic.

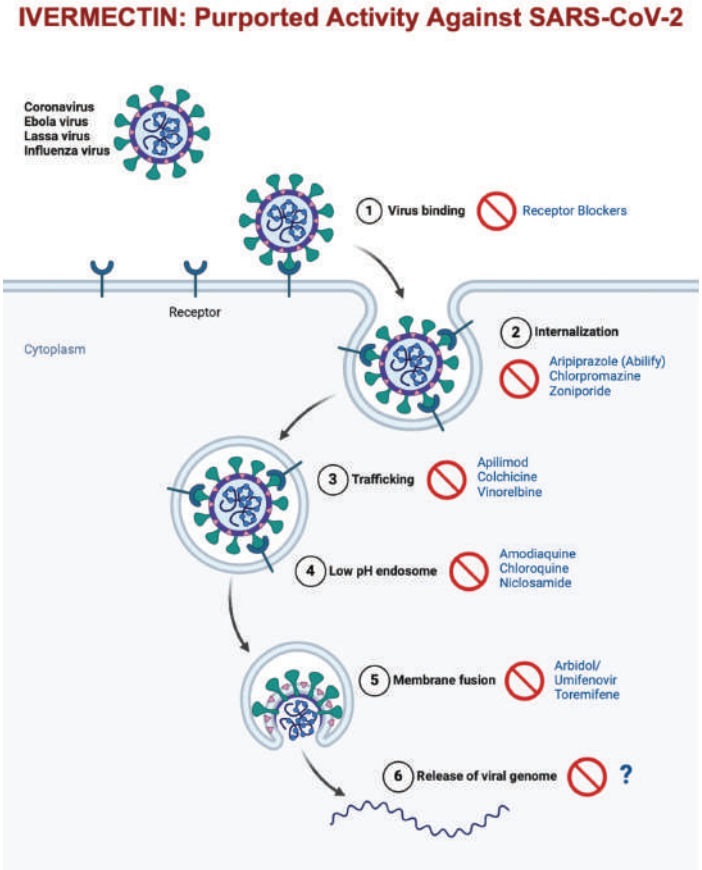

Figure 3. Purported IVM activity against SARS-CoV-2 virus. Six major points of putative interference of IVM with the natural cycles of various viruses including coronaviruses are indicated by the numbers in circles. Known compounds that act via similar interference points are listed in blue text next to circles with numbers.

Clinical Trials and Their Interpretations

Fueled by the hopes described above, numerous clinical trials were conducted to test the efficacy and safety of IVM in various dosages and patient populations. However, instead of providing the eagerly awaited definitive answers, those multiple projects resulted in creation of chaos and confusion of enormous proportions.[22,23] The significance, quality, validity, and implications of those studies have been assessed differently along partisan lines. Neither side of the conflict was convinced by the data contradicting its favored answer.

The mainstream experts who oppose the use of IVM aver that high-quality clinical research disproves any usefulness of this medication in treatment of COVID-19.[24] For instance, in 2023 the National Institutes of Health (NIH) Panel reviewed more than 30 clinical trials involving IVM, including ACTIV-6, TOGETHER, COVID-OUT, IVERCOR-COVID19, I-TECH, and COVER trials, and concluded that IVM is useless as antiviral medication.[24] The August 2024 Systematic Review and Meta-Analysis by the group of experts from the major academic centers has confirmed those conclusions.

At the same time, the advocates of IVM use keep claiming that the results of reliable clinical studies, including thousands of studies listed at the "c19early" website, favor the efficacy of IVM in the treatment of COVID.[25-27]

This disappointing outcome should perhaps not be surprising. The initial studies were performed under the enormous pressure of an active global health emergency of COVID-19 that resulted in the lowering of publication standards. Most importantly however, they were done in the setting of the severe politicization of medicine. Strong political agendas may influence both the process of conducting research and the *interpretation* of its findings. In an environment fraught with political tension, the outcomes of research can be altered, withheld, or even fabricated. The evaluation of a study's validity and importance can be affected by the political leanings of the experts reviewing it.

An additional very disturbing result of the politicization of the medical profession combined with the power asymmetry favoring one side of the dispute is the fact that the empowered side does not hesitate to use its administrative authority to punish those who disagree with them. Many well-trained and accomplished physicians have lost their specialty board certification for the "thoughtcrimes" that included questioning the "consensus" over repurposed drugs such as IVM.

Negative Evidence of Lack of Safety

Considering that there are literally hundreds of studies examining the efficacy of IVM, it is quite noteworthy that there is a significant absence of comprehensive studies challenging its safety. The official experts who are citing concerns regarding the purportedly "significant side effects" of IVM often reference merely two rather unsatisfactory studies to substantiate their assertions.[28,29] And those papers deal mostly with the situations described below that involve the use of veterinary preparations that were neither formulated nor approved for human use.[28]

The Harm Resulting from Over-zealous Regulations

The regulatory agencies began to arbitrarily restrict the off-label use of IVM under the false pretense of concerns about the possible severe side effects that were not backed up by persuasive evidence as described above.[30] Consequently, desperate patients started to resort to the veterinary versions of the drug, which did not require a prescription.[30] Human use of any veterinary medication is associated with known risks related to purity, dosage, form, pharmacokinetics, and use of excipients that may not be safe for humans.[31] Thus, as expected by any rational observer, there was a sharp increase in poison control centers regarding cases of poisoning due to use of veterinary formulation of Ivermectin.[30] In turn, the Food and Drug Administration (FDA) initiated the public relations campaign aimed at curbing those cases, using the deceptive slogan *"You are not a horse. You are not a cow. Seriously, y'all. Stop it."* This implied that IVM was not approved for human use.[32] In other words, the governmental agencies rushed eagerly to remedy the problem that they created themselves by irrational, overzealous regulations. To add insult to the injury, the regulators decided to fight the alleged "misinformation" by perpetuating the clearly misleading catch phrase.

The Unexpected Legal Success of Ivermectin Advocates

The misleading FDA campaigns have been ultimately met with a legal challenge from the IVM-prescribing doctors. Those clinicians could no longer stand the arbitrary, capricious, and abusive interference of administrators with their legitimate practice of off-label prescribing. In an unusual display of common sense and fairness, the court ruled that the FDA had indeed overstepped its jurisdiction, affirming that physicians have the autonomy to prescribe "off label" as they see fit.[32]

Unfortunately, the comments from the court cases were inaccurately portrayed by some overly enthusiastic social media influencers. They claimed that the FDA had changed its stance on use of IVM in treatment of COVID-19, while the FDA opinion on this matter has clearly remained the same.[33] Ultimately, in March 2024, the FDA resolved pending legal issues and deleted any social media content that might be interpreted as providing medical advice beyond its legal power. At the same time, however, FDA has strongly reaffirmed its contrarian stance on IVM by explicitly stating that existing clinical trials do not show IVM to be effective against COVID-19.[34]

Current Official Recommendations

At the time of writing, the position of medical officialdom on the role of IVM in treatment of COVID-19, which is said to reflect the "prevailing scientific consensus," can be accurately summarized as follows:[35]

- High-quality data indicate that **IVM does not effectively treat COVID-19** and its use for such treatments **is not recommended.** This statement is based upon the evidence collected at the NIH-maintained webpage "The NIH COVID-19 Treatment Guidelines."[35-37] **That website was shut down on Aug 16, 2024, and is no longer available at its original internet address.** According to NIH, the archived version of this website is available as part of the Global Health Events web archives collection of the National Library of Medicine.[36,37] Nevertheless, this internet purge of the huge amount of COVID-19 information from the official governmental websites has caused considerable confusion and problems for certain database users. The links to those materials that were incorporated into databases of various reference-managed systems have become suddenly non-functional, creating numerous glitches and malfunctions across interconnected platforms.
- Numerous meta-analyses incorporating prior studies have pointed out that the effectiveness of IVM is still ambiguous at best due to the absence of robust data, marked by imprecision and potential for bias.[35] Furthermore, in more recent trials of higher quality, the absence of efficacy of IVM is said to have been established.[38-41] For instance, in a randomized study of 1,358 adult outpatients with mild COVID-19 and risk factors for worsening, the IVM treatment (400 mcg/kg orally once daily for three days) given within seven days after symptoms began did not lower the likelihood of emergency department visits or hospital stays at 28 days as compared to a placebo.[38]
- Regarding the side effects of IVM it is emphasized that significantly more calls about IVM toxicity have been made to poison control centers than before the pandemic. Many of these cases involve IVM acquired without a legitimate prescription, such as from online or veterinary sources, leading to hospitalizations due to neurological side effects from unclear dosages.[28,29]

The source material quoted for this position constitutes the integral part of the Clinical Decision Support Modules of the electronic health records of many academic medical centers.[35,42] That virtually assures that the NIH-endorsed recommendations against the use of IVM as an early treatment option for COVID-19 are followed in numerous prestigious academic outpatient clinic and tertiary hospitals across the country.

Naturally, the reach of negative recommendation goes way beyond the elite institutions that use electronic health records with CDS modules. The opinion presented above has been echoed by a multitude of major American and global health organizations such as the U.S. FDA, the European Medicines Agency, and the World Health Organization.[43-45]

The Ivermectin Advocates' Approach

There are many IVM advocates who disagree with the "mainstream consensus" and maintain as they did from the beginning of the COVID-19 pandemic that IVM is a safe and effective antiviral drug to treat COVID-19 disease. To back up their claims they do not rely only on substantial clinical experience (while finding it still very persuasive) nor on the results of basic science studies. Instead, many dissenters refer their naysayers to the webpage https://c19early.org that is a depository and ongoing analysis of the numerous studies examining the early treatment of COVID-19.[27]

From those numerous studies favorable for IVM use they frequently quote the two Systematic Reviews / Meta-analyses

papers published by Rago et al.[46] and Bryant et al.[47] Systematic reviews and meta-analyses are considered to be the highest quality of evidence, and therefore they are placed on the top of the Evidence Based Medicine (EBM) pyramid (Figure 3).

Figure 4. Trust is the overlooked foundation of the EBM pyramid reflecting the quality of evidence. Credit: InfoHealer, published with permission.

The EBM paradigm is the approach favored by officialdom for assessing the effectiveness of treatments. Hence, one could assume that arguments in favor of IVM that are rooted in EBM methodology would hold considerable significance for the mainstream scientific community. However, the mainstream medical community has responded by claiming that they rely on a much larger number of better designed studies that are vastly superior to those quoted by the IVM proponents.

The dissenters to the "consensus" responded to this by pointing out that their critics are overlooking the fact that their EBM pyramid of evidence must be based upon the solid foundation of trust (Figure 3). According to the proponents of IVM, the antiviral properties studies that are quoted by the mainstream consensus are not trustworthy due to the strong ideological bias of their authors.[48] That argument has been turned around by the official experts who have accused their opponents of reliance on obviously fraudulent studies.[49,50] Furthermore, the official experts repeatedly made claims that the webpages like https://c19early.org are fraudulent hoaxes they have dubbed as "misleading meta-analysis websites," which employ numerous impressive, colorful, and legitimate-appearing but deceptive graphics to mislead the naïve public. Citing several sources, they claim that these sites breach fundamental meta-analysis standards.[51-55] Oftentimes, they incorporate studies using varying treatment doses, non-blinded designs where both experimenters and subjects know the control group, inferior control groups potentially impacting results, or lack a control group entirely.[51-55]

Neither side is willing to admit defeat, and both sides claim "the victory" over their opponents by quoting and counter-quoting a large volume of the obscure research data that the general audience finds hard to comprehend.[56]

Lessons from Hydroxychloroquine and Ivermectin Controversies

Stalemate

As in many similar disputes in the ongoing cultural war, the conflict over IVM's usefulness in treatment of COVID-19 appears to be suspended in a perpetual stalemate.[56] The two sides of the acrimonious debate are deadlocked in an unresolvable impasse. They keep quarrelling incessantly over complex and specialized research, the understanding of which is beyond the grasp of the lay audience and even of the less scientifically apt part of the medical community. This unresolved conflict is made worse by the power asymmetry that favors the critics of IVM use for treatment of COVID-19. To use a sports analogy, the IVM advocates seem to believe that the sports team consisting of enthusiastic amateurs led by several former professional athletes can decisively defeat the top-ranking professional team on their own homefield. While certainly miracles like that did occur, those are rare exceptions. It is remarkable that the team of motivated amateurs is not being decimated by the seasoned professional athletes, but the professionals keep the upper hand in this game. A different approach is needed to break the stalemate.

The Pragmatic Approach

As discussed in Part I, the opposing camps in this debate both rely too much on elaborate clinical trials. These have a place in assessment of treatment efficacies under certain circumstances, but they should not be fetishized. The accuracy and reliability of clinical trials are severely diminished in the setting of the severe politization of medicine. Moreover, clinical trials are focused on populations rather than on individual cases. Doctors, however, attend to single patients, not large groups. It is plausible that some patients can benefit more from certain individualized therapies (especially with a favorable risk:benefit ratio) than is predicted by the computation model that derives its results from studying of large groups. More importantly, the overzealous regulators with tyrannical tendencies should stop trying to "protect" fully competent adult patients from themselves. As discussed above, such over-protective polices are bound to cause more harm than benefit. The decisions about treatment should be between the patient and his physician, without the interference of meddlesome regulators. All those points are valid for the cases of both HCQ and IVM.

The Failure of Past Strategies and the Need for New Ones

The stalemate between two opposing camps is very disheartening, but the lack of decisive victory does not equal defeat. "The science" is not settled despite claims to the contrary. The opposition to officialdom's dictates is not expressed by a small "fringe group" that has been "confused by misinformation." And those "experts" themselves are to blame for this regrettable situation. Both official experts and those who control them can keep disregarding the obvious and continue to deny reality while being overconfident that that their current power will last forever. However, as Aldous Huxley astutely noted, "Facts do not cease to exist because they are ignored." Real facts have real consequences, and such consequences may be impossible to ignore.

This keen observation by Huxley should also serve as guidance to those who oppose the tyranny of the arrogant "experts." It should be clear to them by now that those in power are not interested in a "respectful dialogue" and that they will not be persuaded by the "best arguments." As described in Part I, many proponents of repurposing old drugs for COVID-19 have consistently applied seemingly rational approaches in

their efforts to secure regulatory approval, yet they kept failing miserably.[1] These tactics involved presenting government and public officials with peer-reviewed scientific papers (especially systemic reviews and meta-analyses) that they believe challenge the established narrative, or identifying weaknesses in research studies cited by authorities. They also sought support from powerful and supposedly unbiased institutions (like courts) to compel regulators' endorsement. Many tried to challenge notable officialdom's figures to live public debates. Some of those strategies had visible PR value but resulted in nothing more than "applause to the preacher from the choir." The opposing side remained unmoved and only redoubled its zeal in the counterattacks.

As the old true but frequently misattributed saying states: doing the same thing over and over again and expecting a different result is a definition of insanity.[57] Different effective strategies are needed to obtain the desired results. Based upon observation of the current cultural battles, legislative measures appear to be the most effective strategy with a strong potential for success, even though they are open to legal disputes.[1] Legislative measures can empower patients and physicians to access safe and effective treatments that are otherwise unreasonably denied or restricted by the regulatory agencies. They can also challenge the monopoly and influence of the pharmaceutical industry and its allies, who often have vested interests in suppressing repurposed drugs. Lawsuits can be filed against the regulators, industry, and nongovernmental [activist] organizations (NGOs). All those potential plaintiffs will be supported by the academic experts and the mainstream media. The legislative initiatives can also fail, owing to political manipulation and corruption. Therefore, legislative measures require careful planning, anticipation of legal challenges, accumulation of strong but easily understandable evidence, and broad support from the voters and members of the medical community.

Legislative measures are relatively fast-paced and direct ways to address the specific issue of repurposing old drugs for COVID-19 treatment. However, they cannot solve the deeper and broader problems that plague not just our medical system but also our whole society. The politicization of medicine, deep societal polarization, and imbalances of power have been accumulating slowly. It is now clear that they threaten not only our health, but also our personal freedom and our dignity.

The pervasive politicization of medicine has eroded the trust and autonomy of physicians and patients. The ideology-based polarization of society has divided our previously united nation into opposing political camps that are getting isolated from each other by being sequestered in hermetic information bubbles. The creeping imbalances of power created a system that visibly favors people aligned with left-wing ideologies over everybody else.

Addressing all these serious threats is vital for the preservation of our society and our cultural heritage. It will be a lengthy and arduous process demanding great determination, perseverance, and continuous effort. It is necessary to focus first on reclaiming all the essential powers that have been slowly taken over by our political opponents. This is not a task that can be accomplished overnight. It will require a long-term vision. The highest priority should be given to developing our own sources of credible scientific expertise. We need in-depth discussions on creating alternatives to the current academic institutions that are controlled by officialdom. This can be done by mirroring the efforts that resulted in the establishment of alternatives to mainstream media.

Other Repurposed Drugs

Due to their notoriety, IVM and HCQ have brought public attention to the fact that other old drugs could be successfully repurposed for variety of conditions, but those plans have been thwarted by the pressure from the profit-oriented pharmaceutical industry.[58,59] The examples include attempts to repurpose colchicine for a variety of uses;[60] sarracenia purpurea for treatment of smallpox;[61] quinine and zinc for yellow fever;[62] use of antimalarial drugs as "desludging" agents in vascular disease processes;[63] applications of intravenous vitamin C for treatment of herpes zoster and cancer;[64,65] use of HCQ for treatment of influenza; applications of fenbendazole, IVM, and doxycycline in oncology; use of indomethacin as antiviral drug; and potential for human applications of alternative antibiotics such as crocodillin.[66] The detailed discussion of those specific cases is beyond the scope of this review, but readers are encouraged to review the literature cited here.

Conclusions

The time-honored approach to discovering new treatments by repurposing existing drugs has evolved from a serendipitous and random *practice* to a rigorous *method* grounded in bioinformatics. This improved paradigm can provide safe, effective, and cost-effective treatments for a variety of serious diseases. It has been previously enthusiastically endorsed by the mainstream academia and regulators but has inexplicably lost their support during COVID-19 pandemic.

The recent heated debates that surround repurposing of two drugs: HCQ and IVM for early treatment of COVID-19 illustrate well how politicization of medicine can adversely impact patients' access to safe and cost-effective therapies. Despite their established long-term safety and many well-founded doubts about purported "inefficacy" and "harm" of those two drugs, they remain designated as *"pharmaceutical pariahs"* by medical officialdom.

Many physicians are breaking from this very suspicious *"prevailing scientific consensus"* and are willing to consider using those medications as a part of the early treatment protocol for COVID-19. They are motivated not only by the desperate pleas from their patients, but most importantly by the presence of both positive and negative evidence regarding those drugs' potential as antiviral treatments.

However, in the current regulatory climate the hands of such forward-thinking practitioners are tied. Theoretically, patients can access those blacklisted medications through the "off-label" use option. Regrettably, this method presents considerable legal hazards for the prescribing doctors and dispensing pharmacists. It is unwise to rely on such a provisory method that is so prone to repression by arbitrary, capricious, and abusive regulators. A more stable solution is needed as soon as possible. Legislative actions seem to be the strategy with the highest likelihood of success. In the long term, the basic problems of the politicization of medicine, societal polarization, and power asymmetry must be solved to permit the survival of our civilization and culture.

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