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AIDS Rev. 2020;22:123-127

Hot News

The Resurgence of Medical Ethics During the Coronavirus Disease (COVID)-19 Outbreak

The unprecedented COVID-19 pandemic has risen a number of clinical situations where the principles of the medical act, the singularity of the patient-physician relationship and the need for revitalizing the medical vocation have all become at front line. Original articles, viewpoints, and perspectives addressing these aspects have appeared in major medical journals. Never before but perhaps with AIDS in the eighties, a disease awakened such feelings of commitment in medicine. Herein, we discuss some of these very sensitive issues for physicians that emerged during the past months of global COVID-19 crisis.

The Stress of COVID-19 Triage

In The New England Journal of Medicine, two articles highlighted the stress for clinicians confronted to make decisions about who should benefit from ventilators or who should be transferred to intensive care units. One report (*Truog et al. N Engl J Med 2020; 382: 1973-5*) proposed that "triage committees should be composed of people who have no clinical responsibilities for the care of the patient" and that "should be created as a strategy for avoiding disabling distress for clinicians." Another author added that "the first and most important is to separate clinicians providing care from those making triage decisions" (*Rosenbaum L. N Engl J Med 2020; 382: 1873-5*).

However, maximizing benefits saving the most life years or rewarding social usefulness is against equity when treating patients. Physicians should not accept that others replace them when deciding for their patients, particularly when bad news should be given.

Another article reminded that allocation of scarce medical resources should attend at least four values: "maximizing the benefits, treating people equally, promoting and rewarding instrumental value, and giving priority to the worst off" (*Emanuel et al. N Engl J Med 2020; 382: 2049-55*).

Experiences that deeply violate held moral values and beliefs can put health providers at risk for post-traumatic syndrome and depression (*Williamson et al. Br J Psychiatry 2018; 212: 339-46*). Emotional harm in care providers does not result from taking difficult decisions but from procuring orders considered unethical.

Older Patients' Care at Nursing Homes

One-third of deaths due to COVID-19 at most EU countries and the USA have occurred at nursing homes for the elderly (*McMichael et al. N Engl J Med. 2020; 382: 2005-11; Soriano et al. Ther Adv Infect Dis, in press*). This disproportionate death rate among older patients due to the coronavirus infection occurred either at clinics where they were referred on developing symptoms or at their long-term institutions. Sadly, poor health care assistance at the latest sites was frequent during the peak of the pandemic, as many doctors and nurses were sick and/or on quarantine.

High mortality among COVID-19 elderly patients, together with reactions to forced isolation, loneliness, and fear of contracting the disease – which represent big challenges for all – were particularly enhanced in frail elderly people. Therefore, this vulnerable population merits especial attention, including provision of palliative care, accompaniment at the end of life, and spiritual assistance at demand.

Refreshing Patient-physician Relationship

JAMA has recorded several pieces that addressed the uniqueness of the physician duties during the COVID-19 times. In one of these inspiring articles, entitled "What does it mean to be a physician?," signed by Thomas Schwenk, it is stated that "the role of the physician is… bringing science and humanism together to benefit patients." The author acknowledged that this task is now being challenged by a "dysfunctional profit-driven health care system that requires physicians to fulfill non-clinical functions." Indeed, many physicians spend more time looking at computer screens than confidently communicating with their patients. Furthermore, there is a growing demand to "…focus on social determinants of health… making physicians responsible for their mitigation" (*Silverstein M et al. JAMA 2019; 322: 2379-80*).

In an attempt to ensure that the fundamental value of the patient-physician relationship prevails in medicine, a focus into two actions has been proposed (*Noseworthy J. N Engl J Med 2019; 381: 2265-9*): first, providing physicians adequate time to spend with patients who need extra time and second, creating the figure of a coordinating physician that would integrate assessment from multiple specialists in a single and trusted message to patient and relatives.

While these proposals sound right and address logistical challenges, they seem too simple and naïve. It is the content of the patient-physician dialogue the critical core aspect to be worked out. However, the scarce education on ethics given at most medical schools has largely transformed clinical studies and training in just transference of technological knowledge (*Pellegrino E. N Engl J Med. 1974; 290: 1083-5*). Clearly, the experience drawn from COVID-19 should encourage to review medical programs in deep and consider the inclusion of medical ethics transversally across topics and not just as a separate matter.

As rightly pointed out by Thomas Schwenk in JAMA, "the solutions to these assaults on physician identity" should come from a refreshment of the patient-physician relationship. Particularly, when patient's healing is not envisioned as the major goal, a sense of misunderstanding and distance often rises up between patient and doctor. In the words of Edmund Pellegrino (*J Med Philos 2001; 26: 559-79*), education of physicians in humanities and the intrinsic value of the medical act, is nowadays more valuable than ever for our profession.

Because of its explicit text, we feel adequate to record here a few sentences of the code of ethics of the American Medical Association: "the practice of medicine, and its embodiment in the clinical encounter between a patient and a physician, is fundamentally a moral activity that arises from the imperative to care for patients and to alleviate suffering. The relationship between a patient and a physician is based on trust, which gives rise to physicians' ethical responsibility to place patients' welfare above the physician's own self-interest or obligations to others, to use sound medical judgment on patients' behalf, and to advocate for their patients' welfare."

How to Rebuild Physician Identity after COVID-19

With the COVID-19 pandemic, medicine has reached a crisis point. Health-care professionals have responded with an astounding display of selflessness, caring for patients despite the risk of profound personal harm. Our efforts have been recognized and applauded. This altruism has unexpectedly catalyzed the restoration of some elements of autonomy, competency, and relatedness, the three pillars that support the professionals' motivation (*Gagne M and Deci E. J Organiz Behav 2005; 26: 331-62*).

In a courageous article written by Harvard University colleagues, the authors begun saying that "before the onset of the COVID-19 pandemic, each day seemed to bring another headline about the crisis of physician burnout" (*Hartzband and Groopman. N Engl J Med 2020; in press*). Ultimately, there was a "profound lack of alignment between caregivers' values and the reconfigured health care system, nowadays centered *in the prominently* the widespread implementation of the electronic health record (EHR) and performance metrics." The authors end saying that "the EHR, initially lauded for its potential as a repository of patient information, has become a tyrannical, time-consuming billing tool; it must be reconfigured to work for physicians rather than forcing physicians to work for it."

In summary, the unexpected and abrupt confrontation with COVID-19 at global scale has hit the pillars of the medical profession. Caring for critically ill patients has awakened many deep feelings of our medical practice. Virtues such as compassion, benevolence, prudence, justice, fortitude, and temperance have resurged as a call aloud. It would be worth to retain all these experiences for the benefit of our patients and our own lives.

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Received: 03-06-2020
Accepted: 04-06-2020
DOI: 10.24875/AIDSRev.M20000034

Very Long-acting Antivirals as Chemovaccines for Preventing Viral Infections

Following the advent of penicillin as first widely used antibiotic during World War II, viruses have steadily replaced bacteria as major agents of infections, particularly for microorganisms that can spread globally. Good examples are pandemics caused by HIV, hepatitis B, hepatitis C, and nowadays severe acute respira-

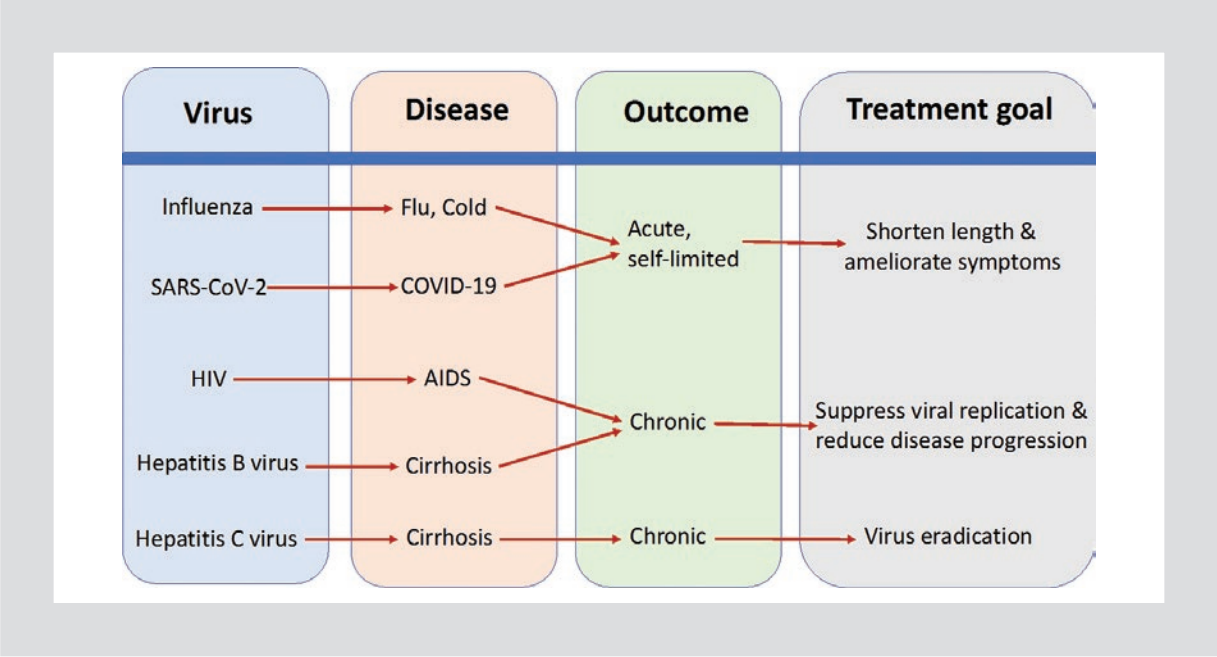

Figure 1. *Goals of antiviral therapy for distinct viral infections with epidemic potential. The aim of antiviral therapy for acute, self-limited infections is to shorten the length and ameliorate the symptoms, as it is the case for influenza using oseltamivir. In contrast, the aim of antiviral therapy for HIV and viral hepatitis B, that establish lifelong chronic infections, is sustained suppression of viral replication, since this goal is associated with lower risk of disease progression (AIDS and cirrhosis, respectively). Finally, the aim of antiviral therapy for conditions such as chronic hepatitis C is to eradicate viral infection and cure the patient.*

tory syndrome coronavirus 2 (SARS-CoV-2), the coronavirus of coronavirus disease (COVID)-19.

The battle against viruses with epidemic potential mostly relies on antivirals and vaccines. Depending on the ability of a given virus to produce persistent or self-limited infection, antivirals may pursue to: (i) shorten and ameliorate symptoms, (ii) eradicate infection, or (iii) suppress viral replication and prevent disease (Fig. 1). In the last scenario, well exemplified by HIV or hepatitis B, antiviral therapy has to be given lifelong to each patient. Otherwise, viral rebound and resumption of disease progression occur.

Vaccines have been developed with success for many viral infections, including measles, polio, rubella, papillomavirus, yellow fever, flu, etc. However, only smallpox was eradicated from humans half a century ago following massive vaccine campaigns. Unfortunately, vaccines have remained elusive for certain human pathogenic viruses, such as HIV, being antiretroviral therapy (ART) the only available weapon to confront it.

Since it first appeared in 1981, AIDS has expanded globally with cumulative estimates of roughly 80 million people infected with HIV up to date, of whom 38 million are alive. Since the advent of combination ART in the mid-nineties, the prognosis of the HIV illness changed dramatically. Indeed, under good adherence to medications, immunological damage no longer occurs, and the life expectancy of treated HIV-positive individuals approaches that seen in the general population. As result, AIDS is nowadays rarely seen, being mostly restricted to persons unaware of their infection that present late to clinics.

Improvements in ART during the past 25 years have resulted in tremendous achievements. Current HIV medications depict unique appealing profiles, often in the form of one single multidrug pill given once daily. Furthermore, they are highly efficacious virologically, well tolerated and safe, with few and manageable drug interactions, and high barrier to resistance. ART is nowadays recommended for all HIV positives, including those asymptomatic and with preserved immune status. Indeed, "rapid initiation of ART" is desirable and should be considered right after being diagnosed with HIV (*García del Toro, M. AIDS Rev. 2019; 21: 55-64*).

A major observation that followed the widespread use of antiretrovirals was the recognition of its power to halt HIV transmission. Individuals with HIV infection being treated and having long-term undetectable viremia do not transmit the virus to others, including sexual partners. This effect is known as "treatment-as-

prevention" (*Rodger, A. et al. JAMA 2016; 316: 171-81*) and globally has fostered the use of ART.

Another further step for expanding the use of ART came from the recognition that HIV-negative persons at risk for HIV acquisition could prevent infection taking antiretrovirals in advance. HIV "pre-exposure prophylaxis" (PrEP) is nowadays recommended for seronegative individuals engaged in risky behaviors, such as men having sex with men with multiple partners, prostitutes, or injection drug users sharing needles (*Fernández-Montero, J. et al. AIDS Rev. 2012; 14: 54-61*). Nowadays, PrEP is prescribed as single pills taken either daily, 2-3 times/week, or at demand. It is very efficacious, preventing HIV acquisition in more than 95% of users with good drug adherence.

Efforts to make easier daily oral ART have resulted in the recent development of long-acting antiretrovirals, such as cabotegravir and rilpivirine, that are administered monthly intramuscularly (*Swindells, S. et al. N Engl J Med. 2020; 382: 1112-23; Orkin, C. et al. N Engl J Med. 2020; 382: 1124-35*). In the clinic, these formulations are being considered for both maintenance therapy in patients already suppressed under conventional daily ART as well as for PrEP in HIV-negative persons at risk (*Benitez-Gutierrez L, et al. Expert Rev Clin Pharmacol. 2018; 11: 507-17*). However, these medications may produce local injection site reactions, may be associated with drug interactions, and require monthly visits to clinics (*Currier, J. N Engl J Med 2020; 382: 1164-5*).

A group from Nebraska recently reported the biochemical characterization and pharmacokinetics of NM2CAB, a cabotegravir prodrug in the form of nanocrystals (*Kulkarni T, et al. Nat Mater 2020; in press*). The molecule administered as single-dose intramuscular injection of 45 mg/Kg, provided plasma cabotegravir concentrations above the protein-adjusted 90% inhibitory concentration for up to 1 year in rhesus macaques. The medication exhibited unique properties in terms of prolonged drug release due to selective macrophage drug uptake and wide biodistribution across different organ tissues, including lymphoid, mucosal, gut, and brain. Given the nanocrystal formulation, volumes of less than 1 mL would be needed for yearly administration in humans, reducing the likelihood of local injection site reactions. Furthermore, the authors acknowledged that a further advantage would be in terms of easy scalability of the medication.

There are several advantages of having very long-acting antiretrovirals such as NM2CAB with respect to monthly injectable cabotegravir. At first sight, very long-acting medications would represent a version 2.0 addressing important challenges such as injection site reactions and the need to attend monthly visits to clinics. Special populations that would primarily benefit from once a year injectables are persons in jail, children and adolescents, homeless, mentally ill, refugees, etc., for whom regular attendance of visits at healthcare sites might be difficult. For similar reasons, infected people in some of the poorest countries would benefit the most from yearly instead of monthly medications. Additional advantages would be in terms of lower risk for selecting drug resistance and increased efficacy, issues that would help to surpass current tough requirements for approving new drugs (*de Mendoza C. and Soriano V. Lancet HIV 2020; 7: e150-1*).

A second look to very long-acting antiretrovirals might be even more appealing. In the absence of an HIV vaccine, these medications might act as chemoprophylaxis for uninfected people at risk. In some extent, these medications would behave as the boosters recommended for some classical vaccines for which immunity wanes over the years (*Sha B. JAMA 2019; 322: 1097-8*). In this way, very long-acting antiretrovirals might work as vaccine mimetics.

A few caveats that may preclude the widespread use of the yearly long NM2CAB medication must be highlighted. First, an oral lead-in dose with oral cabotegravir must be used before administering the yearly NM2CAB nanoformulation, to ensure good tolerance to the drug and prevent unexpected reactions to the medication. Second, the potential for drug interactions must be keep in mind to avoid administration of drugs with potentially harmful pharmacokinetic interactions (i.e., rifampin). Third, at the end of the yearly dosing, drug exposure may go down to threshold inhibitory concentrations with a long tail, increasing the risk for viral escape with selection of drug resistance. This could be troublesome if the next dosing is not given on time. Fourth, given that roughly 10% of the HIV population worldwide is coinfected with hepatitis B, attention should be given to add specific antivirals (i.e., tenofovir) when treating HIV-HBV coinfected patients, since cabotegravir is not active against it (*Soriano V, et al. Curr HIV/AIDS Rep. 2015; 12: 344-52*). Fifth, combination of drugs is critical for the success of ART (2 or 3 agents), and therefore, yearly long NM2CAB should not be given as monotherapy. Thus, a companion with a similar yearly dosing would be much appreciated to really make a changing paradigm in HIV therapeutics. Finally, the need to administer the NM2CAB nanoformulation intramuscularly, even once

a year, would challenge patients with some coagulopathies (i.e., hemophiliacs) or thrombocytopenia. Therefore, efforts for developing subcutaneous forms of the medication should be encouraged.

The new paradigm of very long-acting antivirals developed against HIV might well apply to other viral conditions, for which antivirals exist but no vaccines. For instance, envision a very long-acting antiviral that blocks or mitigate SARS-CoV-2 infection, for which prevention of contagions is challenged by the fact that the virus is transmissible from carriers during the incubation period before symptoms develop (*Gandhi M, et al. N Engl J Med 2020; 382: 2158-60*). In other words, imagine that remdesivir (*Beigel J, et al. N Engl J Med. In press*) could be modified and that a long-acting form might allow prescription once a year as a single intramuscular injection to prevent acquisition of SARS-CoV-2 in persons at risk for disease severity. Furthermore, the provision of such a medication to potential contacts of new diagnoses could help controlling the unprecedented COVID-19 global outbreak.

In summary, the development of long extended release nanoformulations for some antivirals that may be given once a year may provide an appealing alternative option to vaccines for preventing viral infections.

The advent of very long-acting antiviral formulations may provide a further aim for antiviral therapies, which is chemoprophylaxis for uninfected persons at risk, behaving as vaccine mimetics.

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Received: 03-06-2020
Accepted: 04-06-2020
DOI: 10.24875/AIDSRev.M20000035