The ethical implications of "treatment as prevention" in the United States[1]

Since the first cases of what became known as HIV/AIDS were reported in 1981, various public health strategies have been proposed and developed to combat the HIV/AIDS epidemic. A relatively new development within this field is that of "Treatment as Prevention," or TasP, a policy that aims to reduce HIV transmission by greatly increasing HIV testing and then immediately initiating antiretroviral therapy (ART) for all patients who test positive.

It is important that we distinguish TasP, where ART is started regardless of the state of infection, from the commencement of ART when it is clinically indicated. High-quality evidence supports the individual — and public health — benefits of starting ART when an HIV infection reaches an advanced state[2] In this paper, we exclusively address the application of TasP that advocates the initiation of ART for patients with HIV *when it is not indicated by the current federal* [3] *and international*[4] *guidelines on ART*.

In 2009, Dr. Reuben Granich of the World Health Organization (WHO) and colleagues developed a compartmentalized stochastic mathematical epidemiological model, based on the South African HIV epidemic, to estimate the potential effectiveness of TasP. The results of this model were dramatic, predicting that with the universal implementation of TasP, annual new HIV infections would be reduced to less than one case per 1,000 persons within 10 years.[5]

In April 2010, the San Francisco Department of Public Health (DPH) endorsed a new policy that strongly recommended immediate commencement of ART for every person who tested HIV positive, regardless of the state of his or her infection. It is worth noting that the potential individual health benefits of starting ART immediately — not the potential public health benefits of ART as prevention — was cited as the main factor motivating this new policy.[6]

In December 2011, New York City's Department of Health and Mental Hygiene (DOHMH) adopted a similar policy, recommending the immediate start of ART for all persons who tested positive for HIV. DOHMH commissioner Dr. Thomas Farley noted in a letter to city health care professionals that the reasons for this new policy were two-fold: the individual health benefits and the public health rewards (i.e., a reduction in the HIV transmission rate).[7]

We support increasing access to both testing and clinical care, and initiating ART when it is clinically indicated. The scientific data on the relative benefits and risks of initiating ART before an HIV infection reaches an advanced state, however, are far from conclusive. Despite this lack of certainty, the enthusiastic adoption of early ART by two of the largest health departments in the United States of America represents a cause for concern. Indeed, advisory panels on HIV ART of both the WHO and the U.S. Department of Health and Human Services have consistently refused to recommend the initiation of ART before the infection reaches an advanced state, citing a lack of evidence of acceptable quality supporting the benefits of such a treatment.[8]

The implementation of this policy, based on public health guidelines promoted without high-quality supporting data demonstrating a benefit to the patient, represents a significant departure from the established procedures of evidence-based medicine. Establishing a potentially dangerous and unproven therapy as a standard of care, for a hypothesized public health benefit, represents a serious violation of three fundamental principles[9] of medical ethics: beneficence, non-malfeasance and patient autonomy.

Treatment as prevention's effect on public health

The correlation between a patient's viral load and their infectiousness is well documented within the literature. ART, when successfully implemented, reduces viral load, often to undetectable levels. Granich and his colleagues' work suggested that ART had the potential to slow down and effec-

tively halt an epidemic. However, the implicit limitations of their model must be remembered when seeking to apply it to a real-world situation. Important elements of the model that do not correspond to any known reality of the HIV epidemic include the assumption that all transmission of HIV is heterosexual;[10] that patients on ART are always fully adherent; that 100 percent of patients who tested positive would voluntarily consent to ART, regardless of the state of their infection; and that testing the whole population would not be encumbered by significant challenges.

Although this model stipulated that early intervention would be "voluntary," it is questionable how it is possible to get anything close to 100 percent of a large community to consent to testing and treatment without some form of coercion. Furthermore, the Granich model assumes that every person with HIV will take their medication exactly as prescribed with no limiting side effects, despite being prescribed medications when the person is not necessarily symptomatic.

Advocates of TasP often point to the 2011 randomized trial of HPTN 052 as empirical evidence of the epidemiological efficacy of TasP.[11] Although this trial showed that commencement of ART was effective in reducing the transmission rate within heterosexual serodiscordant couples, it did not analyze the effects of early ART outside of this small subset of the population. Importantly, patients with a CD4+ count of above 550 cells per μL were not enrolled in the study, unlike TasP as implemented in both San Francisco and New York City (where all HIV positive patients, regardless of the state infection, are urged to start ART). The HIV epidemic is an inherently complex system; empirical evidence that shows a reduction in one transmission category (i.e., heterosexual sero-discordant couples) does not necessarily imply that this would have a statistically significant effect on the transmission dynamics of the entire epidemic.[12]

Clearly, both the theoretical and empirical data on whether TasP, for patients for whom it is not clinically indicated is effective as a public health intervention are still evolving and not yet conclusive. Despite this, New York and San Francisco have implemented TasP as a public health policy.

Impact of treatment as prevention on individual health

It is one thing for individual clinicians to promote early ART to their patients based on a combination of scientific data and clinical experience. It is entirely different, however, for a public health agency to advocate a standard of care for public health purposes and claim that it is also for the benefit of the individual patient, despite the lack of high-quality data supporting that assertion. ART is far from a benign therapeutic intervention; patients taking antiretrovirals (ARVs) often experience serious long-term side effects and toxicities. In addition, as ART transitions from an acute therapy to a chronic one, more research is needed to determine the effects of chronic use of ARVs.

For patients who have advanced HIV disease — that is, a CD4+ count of ≤ 350 cells per μL and\or certain severe clinical symptoms of infection — high-quality evidence supports the relative benefits of treatment. That is to say, the net benefit of treatment outweighs the known side effects.[13] The WHO maintains that a CD4+ count of ≤ 350 cells per μL or severe symptoms of HIV infection indicate the need for ART.[14]

It is not clear, however, if starting ART before the patient reaches an advanced stage of infection (i.e., when the patient has >500 CD4+) is, on net, beneficial or deleterious. Indeed, data from a randomized, controlled clinical trial, the START (Strategic Timing of Antiretroviral Treatment) trial, will not be available until at least 2015.[15] There have been several observational cohort trials performed. While some have demonstrated a benefit from starting ART immediately,[16] one of the largest such studies failed to demonstrate any positive benefit from starting ART early.[17]

Scientific data on the benefits of initiating ART before an HIV infection reaches an advanced state are far from conclusive.

The lack of high-quality data available, coupled with the lack of consensus within the lower-quality data, demonstrates that significant questions remain as to whether starting ART early provides any positive benefit to the patients. This, along with the serious nature of ART and its side effects, makes it inappropriate for health agencies to establish or promote a standard of care that advocates for immediate

ART when it is not justified by sufficient high-quality evidence.

Ethical implications

Public health interventions have contributed to dramatic reductions in mortality and morbidity around the world. Vaccinations are perhaps the most obvious example. Their widespread use and, in many cases, the requirement to be immunized have led to a drastic decrease in the incidence and, in some cases, eradication of serious infectious diseases.

The current implementation of TasP, however, is an inherently different situation. Before clinicians routinely administer vaccines, high-quality evidence must demonstrate that the individual benefits of that vaccine — providing immunity against a disease — are greater than the possible adverse effects. Unfortunately, high-quality evidence has not yet been provided that demonstrates that immediately initiating ART, regardless of the state of a patient's infection, is beneficial to the individual patient.

The ethical concerns of implementing a policy of vastly increased HIV testing and immediate initiation of ART, regardless of infection state, have not been ignored by the literature.[18] Other papers, including those of Ron Bayer,[19] analyze the ethics of implementing TasP within the context of a policy that, as of now, shifts the benefit from the individual to the public good. We are aware of no scholarly articles that discuss the ethical concerns of these policies being implemented by major health departments in the U.S.

TasP, as implemented by both San Francisco and New York, advocates for physicians to encourage their individual patients to start ART, regardless of the state of their infections. TasP thus may be viewed as inherently infringing on the established standards and codes of clinical medical ethics.

Three fundamental *prima facie* principles of medical ethics are those of beneficence, *primum non nocere* ("first, do no harm") and patient autonomy.[20] A physician must ensure that his or her actions are first and foremost in the best interest of the patient being treated. A physician's responsibility to the individual patient is paramount, except in certain extreme circumstances.[21] The physician must also, to the best of his or her ability, ensure that treatment will not cause harm to the patient and that, if a treatment is prescribed, the possible benefits outweigh the possible risks. Every patient has a fundamental right to autonomy and to make informed decisions about their treatment free from coercion.

Inherent to the concept of patient autonomy is the right of a patient, or his or her authorized proxy, to be accurately and honestly informed of the risks and benefits of a treatment, and to be able to accept or refuse this treatment at his or her discretion without coercion or penalty.

The New York City DOHMH and the San Francisco DPH are advising physicians to commence ART immediately, regardless of the stage of infection, and claim that ART will provide a net benefit to those patients. Yet, the scientific data are far from conclusive to support such an assertion. Clinicians heeding the advice of the public health authorities are promoting a treatment that is not known to provide a net benefit to their patients whose HIV has not reached an advanced state of infection. Therefore, a patient is not given the right to make an informed decision about his or her care. This deception represents an *ipso facto* violation of the principles of patient autonomy.

Every patient has a fundamental right to autonomy and to make informed decisions about their treatment free from coercion.

The formulation of formal standards of care for public health purposes must meet a higher standard of evidence than what is required of a clinician, who, correctly, uses the best externally-provided evidence, combined with his own clinical experience and judgment.

In the absence of high-quality evidence demonstrating the individual health benefits, it is unethical for public health authorities to, in pursuit of their public health goals, recommend TasP to clinicians as an appropriate standard of care. Recommendations from public health authorities, who often control or influence funding and other resources, can have an inhibiting effect on a clinician's ability to determine whether a treatment is consistent with the principles of beneficence and non-malfeasance.

The goal of reducing HIV transmission is an admirable one. We cannot support, however, a policy, which as of now violates fundamen-

tal principles of medical ethics. If conclusive, high quality data demonstrate that starting ART immediately, regardless of the state of the patient's infection, is in the net interest of the individual patient, we see no reason why this approach should not be supported. This has not yet been demonstrated, and may never be.

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[1] The authors gratefully acknowledge critical and insightful comments of L. Sprague, J.A. Sonnabend, M.D. and D.J. Krellenstein, M.D. Ph.D., during the preparation of this article.

[2] World Health Organization, *Antiretroviral therapy for HIV infection in adults and adolescents: Recommendations for a public health approach: 2010 revision*, 2010.

[3] Department of Health and Human Services, "Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents," 10 January 2011.

[4] World Health Organization, *supra*, note 2.

[5] R. M. Granich et al., "Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model," *The Lancet* 373, 9657 (2009): pp. 48–57.

[6] S. Russell, "City Endorses New Policy for Treatment of H.I.V.," *The New York Times*, 3 April 2010.

[7] T. Farley, "Health Department Releases New HIV Treatment Recommendations," New York City Department of Health and Mental Hygiene, 1 December 2011.

[8] World Health Organization and Department of Health and Human Services, *supra*, notes 2 and 3.

[9] R. Gillon, "Medical ethics: four principles plus attention to scope," *BMJ* 309, 6948 (1994): p. 184.

[10] In the United States, over 50 percent of transmission is through homosexual contact. See H. I. Hall et al., "Estimation of HIV Incidence in the United States," *Journal of the American Medical Association* 300, no. 5 (2008): pp. 520–529.

[11] M. S. Cohen et al., "Prevention of HIV-1 Infection with Early Antiretroviral Therapy," *New England Journal of Medicine* 365, no. 6 (2011): pp. 493-505.

[12] Importantly, HIV-positive patients with a CD4+ count of above 550 cells per µL were not enrolled in the HPTN 052 study. This is in direct contrast to the TasP policy, as implemented by San Francisco and New York, in which all patients, regardless of CD4+ count or other clinical indicators are urged to start ART.

[13] See P.G. Yeni et al., "Antiretroviral Treatment for Adult HIV Infection in 2002," *Journal of the American Medical Association* 288, no. 2 (2002): pp. 222–235; P.G. Yeni et al., "Treatment for Adult HIV Infection," *Journal of the American Medical Association* 292, no. 2 (2004): pp. 251–265; and S.M. Hammer et al., "Antiretroviral Treatment of Adult HIV Infection," *Journal of the American Medical Association* 300, no. 5 (2008): pp. 555–570.

[14] World Health Organization, *supra*, note 2.

[15] "Strategic Timing of Antiretroviral Treatment," ClinicalTrials.gov. On-line: http://clinicaltrials.gov/ct2/show/NCT00867048.

[16] M. M. Kitahata et al., "Effect of Early versus Deferred Antiretroviral Therapy for HIV on Survival," *New England Journal of Medicine* 360, no. 18 (2009): pp. 1815–1826; C. M. Hogan et al., "The Setpoint Study (ACTG A5217): Effect of Immediate Versus Deferred Antiretroviral Therapy on Virologic Set Point in Recently HIV-1–Infected Individuals," *Journal of Infectious Diseases* 205(1) (2012): pp. 87-96.

[17] Writing Committee for the CASCADE Collaboration, "Timing of HAART Initiation and Clinical Outcomes in Human Immunodeficiency Virus Type 1 Seroconverters," *Archives of Internal Medicine* 171(17) (2011): pp. 1560–1569.

[18] Indeed, the 3 January 2009 issue of *The Lancet* contained two letters discussing the possible ethical implications of implementing a policy similar to the one modeled in Granich et al. See K. M. De Cock et al., "Can antiretroviral therapy eliminate HIV transmission?" and G. P. Garnett and R. F. Baggaley, "Treating our way out of the HIV pandemic: could we, would we, should we?" *The Lancet* 373, no. 9657: pp. 7–11.

[19] R. Bayer, "Mass Testing and Mass Treatment for Epidemic HIV: The Ethics of Medical Research is No Guide," *Public Health Ethics*, vol. 3, no. 3 (2010): pp. 301–302.

[20] R. Gillon, *supra*, note 9.

[21] The American Medical Association, *Principles of Medical Ethics*. June 1957.