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Universal Voluntary Testing and Treatment for Prevention of HIV Transmission

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ANTIRETROVIRAL THERAPY (ART) CAN SUPPRESS THE level of human immunodeficiency virus (HIV) viremia (or “viral load”) to undetectable levels in the plasma of a substantial proportion of individuals infected with HIV and has greatly reduced HIV-related morbidity and mortality.¹ In addition, the efficiency of HIV transmission is directly proportional to the viral load in the transmitting individual.² Given the dramatic effect of ART on viral load, it is reasonable to consider using treatment of individuals infected with HIV as a means of preventing HIV transmission. The notion of treating individuals who are infected in the general population as a means of controlling the HIV/AIDS pandemic by decreasing the rate of HIV transmission—and thus lessening the societal spread of HIV—is not new.³

A recent modeling study by Granich et al⁴ reaches provocative conclusions and provides the theoretical basis for a new and potentially important public health policy strategy. This approach, referred to as “test and treat,” predicts that the implementation of an annual voluntary universal HIV testing program for persons older than 15 years and with immediate initiation of ART for those individuals who test positive regardless of their CD4 T-cell count or viral load, the HIV pandemic could be reduced within 10 years to just 1 incident case of HIV infection per 1000 people,⁴ thus theoretically bringing the pandemic to an end. This, of course, would be an extremely ambitious undertaking that would not only require substantial discussion and study, but also could not and should not be entered into lightly.

As with all mathematical models, the voluntary test and treat model is based on a number of assumptions that re-

quire validation with research. Retrospective analyses of existing data from cohort studies and clinical trials and the design and execution of new prospective cohort studies and randomized clinical trials will be required to address these issues and questions. Pivotal areas of research include the following.

Universal Testing

Even with the commendable attempt to make HIV testing a part of routine medical care as has been recommended in the United States since 2006,⁵ many individuals are not being reached by the health care system or are being reached but not being tested for HIV. The reasons a person accepts or rejects HIV testing are complex, and numerous behavioral and sociological questions, including the issue of stigma, must be addressed by a research agenda. Major structural barriers to large-scale testing also exist; these currently are being addressed by the Centers for Disease Control and Prevention as part of a focused research agenda to determine how best to implement voluntary testing in public health settings.⁵

An underlying assumption of the model by Granich et al⁴ is that all individuals who are HIV positive will be identified by voluntary universal testing and all will receive ART. However, individuals frequently are diagnosed to have HIV in settings apart from those where they ultimately will receive treatment, and significant barriers impede the efficient movement of a patient infected with HIV from diagnosis to care. These include the lack of health insurance, homelessness, substance abuse, mental illness, and denial

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by the individuals of their newly diagnosed HIV status. As with voluntary testing, a public health–systems research agenda will be needed to define efficient and effective means of entering and retaining patients in care.

Relationship of the Stage of Infection to Efficiency of Transmission

Untreated HIV disease is a multistage process measured over years, with varying durations and levels of viremia within each stage. The initial stage, acute HIV infection, has a short duration (measured in weeks to months), is difficult to diagnose, and is associated with high levels of viremia. The large amount of virus in most newly infected individuals renders them highly infectious to others.⁶ Acute HIV infection resolves relatively quickly and usually evolves in the absence of treatment into a state of chronic HIV infection characterized by a relatively stable, lower level of viremia (the viral “set point”) that can remain relatively constant for years. This period is associated with a much lower risk of transmission compared with that of acute HIV infection over similar time frames; however, because the median duration of the untreated chronic HIV infection stage is 8 years, the cumulative fraction of transmissions that occur throughout the entire stage of chronic HIV infection is substantial.^{4,7} The third phase of untreated HIV infection and disease is the advanced stage of AIDS, associated with a dramatic increase in viremia and a commensurate increased risk of transmission.

The contribution of untreated acute HIV infection to the overall HIV transmission dynamics is complex. Ultimately, the frequency with which a person with acute HIV infection transmits HIV depends on behavior. The model proposed by Granich et al assumes that 10% of transmissions are acute HIV infection–related⁴; however, this percentage is an estimate and may differ among different populations. Research defining the contribution of each stage of infection, with specific emphasis on acute HIV infection, to the maintenance and growth of the HIV epidemic will provide critical information. Additionally, research leading to rapid, accurate, and inexpensive diagnostics for each stage of infection, with particular attention to acute HIV infection, needs to be accelerated.

Efficacy of ART in Preventing Transmission of HIV

Currently, data support the notion that by lowering viremia in treated, adherent patients, ART is effective in preventing transmission. This information is derived from studies of couples whose HIV status is discordant, analyses of the effect of ART on mother-to-child transmission of HIV, and modeling studies.^{1,2,8-10} For example, an analysis by the Swiss National AIDS Commission concluded that the risk of sexual transmission of HIV was negligible if an individual infected with HIV had an undetectable viral load after 6 months of ART and had no other sexually transmitted

infections.¹¹ The outcomes of the model by Granich et al⁴ are based on ART being 99% effective in blocking transmission at a population level. Additional data on the efficacy of ART in preventing infection in multiple risk groups and populations will help determine the feasibility of a test and treat strategy.

Drug Resistance

A critical issue in the test and treat model is the effect of the emergence of antiretroviral drug resistance. This issue can be further divided into 2 parts. The first part is the effect of drug resistance on the clinical management of the disease. Here, it will be important to determine the baseline level and rate of emergence of drug resistance in populations in which a test and treat approach would be implemented. The second part is the effect of resistance, with its potential for contributing to the rebound of viremia, on the efficacy of ART in preventing transmission. Other critical questions are how transmissible are the drug-resistant strains and what mutations are of particular concern? Additionally, it will be important to develop a behavioral and biomedical research agenda that can determine improved methods to foster adherence to ART in a culturally specific context, to improve monitoring of patient responses to ART, and to determine the optimal frequency of follow-up.

Behavioral Disinhibition

Significant behavioral research questions are embedded in the issues defining a test and treat agenda. These include behaviors that lead individuals to decline testing. For treated HIV-infected populations, important questions on how to promote adherence and risk reduction counseling in the context of testing and treatment need attention. Additionally, it is essential to define the effect of repeated HIV-negative tests on levels of risk-taking behavior and to develop strategies to promote safer sexual practices. In 1 study,³ modeling of the effect of significantly increased behavioral disinhibition during the implementation of a treatment program showed increased transmission, leading to a loss of the prevention benefits of expanded treatment.

Benefit to the Individual

In the majority of cases when ART is accessible and used properly, HIV is a manageable chronic condition. Clearly, there is significant benefit to the individual when ART is provided within the current treatment guidelines, which recommend initiating therapy of adults and adolescents who have 350 or less CD4 T cells/ μ L of plasma.¹ According to the model of Granich et al,⁴ treating everyone at the 350 CD4 T-cell threshold and below modestly attenuates the HIV epidemic. To have a profound impact, everyone who is infected must be treated if the significant benefit to society is to be realized. For a test and treat strategy to be ethically sound, there must be a benefit of early treatment to the individual, as well as to society as a whole. The question of

whether life-long treatment, initiated as early as possible (even before the time recommended by existing guidelines), provides long-term benefit to the individual that is not overcome by drug toxicities and long-term complications of the therapies is central to the test and treat research agenda and ultimately to the decision to implement such a policy.

Early treatment has been shown to have a significant benefit for children infected with HIV, albeit only as measured in the first few years of life.¹² Highly effective ART regimens have been available since early 1996 and, during this almost 14-year period, studies in adults have shown that starting treatment earlier than recommended by treatment guidelines provides clinical benefit to the individual^{13,14} for at least several years. Although ART will probably continue to show benefit,¹³ a definitive answer will depend on further retrospective and prospective studies to evaluate the effects of early initiation of therapy.

Cost-effectiveness for Society

For public health officials and societies in general to make a determination about the validity and feasibility of a test and treat strategy, biomedical evaluation must be inextricably linked to cost-effectiveness evaluation. With cost-effectiveness research, the key components of each step in the process can be dissected and assessed for impact on cost and effectiveness. Cost-effectiveness analyses can provide a dynamic assessment of the financial costs for a test and treat program over time and make predictions about where specific, focused changes could have a significant impact. As research studies with relevance to the test and treat agenda are developed and implemented, prospective cost data must be captured to facilitate these kinds of evaluations.

In conclusion, the mathematical model of Granich et al⁴ for voluntary testing and treatment sets forth a testable strategy that potentially could curtail the global HIV pandemic. A number of important issues arise when a program of this potential magnitude and impact is considered. As a model, the influence of specific variables, such as increased behavioral disinhibition, drug resistance, and the higher frequency of transmission during acute HIV infection, should

be mathematically evaluated. These kinds of further evaluations will be helpful in prioritizing the series of questions that must be debated and answered by the research community to provide the necessary data to validate or refute this approach.

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