Universal voluntary HIV testing and immediate antiretroviral therapy

In Reuben Granich and colleagues’ mathematical model on the benefits of antiretroviral therapy for HIV prevention (Jan 3, p 48),1 everyone is tested and everyone with HIV is treated immediately (irrespective of CD4+ cell count). However, the relation of this theoretical model to reality rests entirely on the veracity of the assumptions employed.

First, the hypothesis that suppressive antiretroviral therapy can reduce HIV transmission within a sexual partnership is plausible, but unproven. Several studies have shown that antiretroviral therapy suppresses HIV in genital secretions, and two observational studies2,3 have reported greatly reduced HIV transmission in couples when the infected person received antiretroviral therapy. However, neither the magnitude nor the durability of this benefit is known. Accordingly, the US National Institutes of Health has launched a randomised trial (clinicaltrials.gov identifier NCT00074581) designed to answer these questions.

Second, although detection of all HIV-infected people through widespread testing is a desirable goal, no evidence exists that this can be accomplished even in wealthy countries highly committed to HIV prevention.

Third, the decision to treat everyone irrespective of CD4+ cell count should not be taken lightly. Little doubt exists that suppressing HIV benefits the HIV-infected person. However, much of the immune damage to the host occurs during acute HIV infection—a phase of the disease not detected by most current strategies. These “invisible” patients with acute HIV infection might contribute disproportionately to the spread of HIV.4 They have not been factored into most mass treatment models because they cannot be readily detected.

Additionally, we do not know the long-term toxic effects of many of the best antiretroviral therapy regimens; cardiovascular complications are of no small importance.

The WHO model1 challenges us to marry treatment and prevention. The time has arrived for the drug discovery and treatment communities to fully embrace the public health benefits of antiretroviral therapy. Using drug combinations that will render patients durably less contagious can only be viewed as a salutary benefit of required therapy. Perhaps, in the coming years, it will turn out that we can provide enough antiretroviral therapy to enough people to curb the epidemic. The job now is to be realistic in our expectations and to generate the essential data to lay the tracks so the treatment-for-prevention train can leave the station.

We declare that we have no conflict of interest.

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Contrary to Reuben Granich and colleagues’ interpretation, the results of their model-based analysis2 actually suggest that, even under optimum conditions, early and sustained universal treatment cannot eradicate HIV.

Their assumptions about the effect of this strategy are highly optimistic: they assume that HIV-infected people would reduce risk behaviour by an average of 40%; that second-line therapy is immediately available on failure of first-line; and that antiretroviral therapy reduces infectiousness by 99%. This level of reduction is unlikely.2

Granich and colleagues calculate that an eradication phase would only be possible if HIV-infected individuals start antiretroviral therapy at a CD4+ T-cell threshold of about 1150 cells per μL. But this would be impossible since the average CD4+ count immediately after seroconversion is about 884 cells per μL in Africa.2 Even if the average testing frequency is once per year it would be difficult to catch early seroconversions since diagnoses will occur an average of 6 months after seroconversion.

Various theoretical studies have indicated that increasing treatment coverage can substantially reduce incidence if supplemented with behaviour change,4 but the epidemiological impact is likely to be moderate unless testing rates increase substantially. Even in resource-rich settings there is a large proportion of people at high risk who are never tested for HIV.5

Therefore, although universal treatment should be strived towards, the notion that universal testing and treatment at high CD4+ concentrations can be attained in the foreseeable future seems unrealistic. The important message from the study is that large increases in testing and early treatment can have a substantial preventive effect at the population level. The paper should be a call to promote serious international discussion between public-health officials, clinicians, and other researchers about the viability of this intervention strategy, the ethics of individualism versus utilitarianism, and the possibility of using prevention funds to further increase treatment access.
We commend the creativity of Reuben Granich and colleagues1 in proposing universal voluntary HIV testing and immediate treatment to reduce HIV incidence to less than 0.1% in a generalised epidemic such as South Africa’s. However, in addition to programmatic, clinical, social, behavioural, financial, and ethical obstacles, we are concerned that their model underestimates the role of acute transmission. The proposed yearly testing would miss most acute infections (which cannot be detected by standard antibody tests), and thus would fail to stop potential rapid chains of early transmissions during peak (acute) infectivity.

Granich and colleagues assume acute infection to be ten times as infectious as chronic infection, partly on the basis of the Rakai, Uganda, cohort, which provides the best direct evidence (although it was not designed to assess acute infectivity). However, modelling based on Rakai data has indicated relative acute infectivity of 26-fold2 to 43-fold.3

Additionally, Granich and colleagues’ assumption of eight partners per year is strikingly at variance with survey data (even if such data probably significantly under-report multiple partnerships), such as a 2005 South African survey that found only 16-3% of men and 2-6% of women reported two or more partners in the past year.4 Nor does an epidemic doubling time of 1.2 years approximate the current epidemic in South Africa.

Finally, the model’s estimated effect is based on optimistic assumptions, including a “full package” of standard interventions reducing transmission by 40% (something rarely, if ever, achieved).5 According to the model, the other 60% reduction in transmission would be achieved by universal testing and treatment (in a near-perfect scenario), but it would be very sensitive to rates of drop-out, infectivity while on antiretroviral therapy, and especially coverage of testing, making practical concerns about implementation all the more daunting.

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Reuben Granich and colleagues explore a policy of universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission.6 I wonder how relevant their findings are, given that the models used do not account for concurrency—ie, overlapping, long-term partnerships—which are likely to account for a substantial amount of HIV transmission in South Africa.7 Granich and colleagues do state that their model “allows for a high level of concurrency and for a much higher infectiousness during the acute phase than during the chronic phase.” However, the reference they use to support this statement6 does not model concurrency, but uses a basic risk-category, deterministic model combined with a factor for changes in viral load. This is not the same thing as modelling concurrency, which is a network effect enhanced by, but independent of, viral load fluctuations.

For deterministic models to approximate the observed prevalence of HIV, they must make unreasonable assumptions about African sexual behaviour. The authors of the cited paper,2 and presumably Granich and colleagues, assume that 1% of people have on average 77 partners per year. Behavioural surveys from Africa have never found such high levels of “promiscuity.”4 The authors’ assumption is derived not from behavioural data, but from the demands of the model itself. The model would not predict actual prevalence otherwise.

Network models5 do not require unrealistic assumptions, and are much better able to derive prevalence estimates on the basis of actual behavioural data. Thus, it would seem worth modelling the effect of testing and antiretroviral therapy with a network model that includes concurrent partnerships.

At the very least, factoring in concurrency would increase the relative amount of transmission attributable to the “acute” phase—ie, when infection is not even detectable on an HIV test—beyond that calculated by Abu-Raddad and Longini5 (and presumably Granich and colleagues). That would reduce the effect of testing and early treatment significantly, I suspect.

I declare that I have no conflict of interest.

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