Treatment of HIV disease as prevention.

February 2, 2010 By Joseph Sonnabend, MD

Could universal periodic testing for HIV and immediate treatment of all who test positive curb the spread of the epidemic?

The suggestion that it might do so is based on the well-established relationship between viral load and infectivity. The idea is that by reducing viral load, treatment will make an infected person less able to transmit the virus and therefore could curtail the spread of the epidemic.

Also, people who know that they are positive are more likely to take steps to prevent sexual transmission of HIV than those who are unaware of their status. But this is a benefit of testing rather than of treatment.

"Treatment as prevention" is a term that describes this proposal to treat all infected individuals who test positive. But it also can refer to the preventative effect of providing treatment only to those known to benefit from it.

Early in 2009 treatment of all infected individuals as prevention received support from an article that appeared in the Lancet, an important weekly medical journal.

(**Universal voluntary HIV testing with immediate antiretroviral therapy as a strategy for elimination of HIV transmission: a mathematical model.** *Granich, Reuben M.* and others. Lancet 2009 373: 7)

This was an exercise in mathematical modelling. Having made several assumptions, the authors calculated what might happen if a policy of universal voluntary testing with immediate anti-viral treatment were to be implemented. They concluded that it could result in a dramatic reduction in the transmission of HIV within 10 years. Their calculations indicated that this strategy could achieve an extremely low overall prevalence of infection by 2050.

This is an interesting idea deserving of every consideration.

However, there are several obstacles that stand in the way of its implementation.

Apart from feasibility, the one that seems to me to be the most important arises from the necessity that treatment should only be initiated when the infected person voluntarily decides to do so. This has been commented on and discussed by some individuals and organizations; there are links to these discussions at the end of this post.

At first sight the need for a voluntary decision may not seem to be a problem at all, because given its availability, any infected person who needs treatment would surely decide to receive it.

But what about people with very high CD4 numbers or those who have the good fortune to be non-progressors or in whom HIV disease progresses extremely slowly? In the case of such people, treatment would be used as a tool to prevent infection of others. It is far from clear that these individuals will themselves benefit.

A "treatment as prevention" proposal that aims to treat everyone who is positive is about a public health intervention on individuals, independent of whether or not it will be of benefit to the individual. Some will be included who may not themselves derive any benefit from the intervention, but will only be exposed to its risks.

Some of these individuals may choose to receive treatment for altruistic reasons, because of the assumed societal benefit. All agree that the decision to do so must be voluntary.

But what meaning can a voluntary decision have when it is not informed? Or worse, should misleading information be provided.

Before undertaking any intervention, its benefits and risks must be described as best as is possible and then weighed. We want to come out ahead. For many HIV positive individuals, and virtually all with serious immune system deterioration, the benefits of treatment clearly far outweigh the risks associated with the medications.

But let's continue to consider those individuals with high CD4 numbers or whose disease does not progress, or does so very slowly. Can we give these individuals reliable information that treatment will benefit them? There are those who believe that it will, but the evidence for this is far from solid. On the other hand, it is clear that anti-viral drugs are often associated with significant adverse effects.

Newer treatments may indeed be associated with fewer and less severe adverse reactions than older ones, but we really cannot yet know the full range of their effects. Very recently the FDA required labelling changes for Prezista (darunavir) to include some less frequent adverse effects seen in the 96 week study data, even though Prezista was approved in 2006.

This is not unusual; it can take many years of observation to recognize and understand the longer term effects of new medications, or even earlier side effects which occur in just a few individuals. Look at how long we were prescribing Stavudine (Zerit, D4T) before we understood what effect it had on fat distribution.

Recognizing adverse drug effects is particularly difficult in conditions such as HIV disease which itself can manifest in so many different ways. Sorting out what is a drug effect and what is caused by the infection may take a very long time. Added to this is the difficulty of knowing which drug is responsible for a particular reaction when several different medications are taken at the same time.

It seems likely that when fully informed about what is known and not known about these treatments, HIV positive individuals with high CD4 counts or who are slow or non- progressors may decline or delay treatment. As far as the benefit to society is concerned, I'm sure that many will feel that this can be attained by practising safer sex, including the use of condoms, rather than by relying on drugs.

The safer behavior of people who test positive has been already observed, and is one important reason to encourage widespread testing.

There is yet something else to think about.

If we are to ask people to take a risk for a benefit to others we should be able to tell them that it is probable that the endeavour will be successful; that they will not be taking a risk for nothing.

We cannot assure them that there is even a good chance that treatment as prevention, where all infected individuals are treated, will make an impact on the epidemic. Among the many uncertainties is a lack of assurance that enough people will participate, and the problem of developing resistance to the antiviral drugs (that was recently highlighted in several news reports).

Treatment with antiviral medications can thus have two objectives. One is to benefit the infected individual; the other is to limit the spread of the epidemic by preventing infection of others. Both objectives will be met when treatments are offered for the benefit of the infected person.

In another mathematical model where treatment would be provided only to those with about 350 CD4 cells, Julio Montaner calculated that two thirds of new infections in British Columbia could be avoided. In this instance the purpose of treatment is to benefit the infected person, but as a result most new infections may be averted.

Most people in care in developed nations, with 350 or fewer CD4 cells will receive treatment, and this may well have an impact on preventing new infections.

The type of treatment as prevention, where *all* HIV positive individuals are offered treatment is much like a clinical trial, which is an exercise of uncertain outcome based on an hypothesis, in this case supported somewhat by mathematical modelling. It should require informed consent from

the participants, as is required for participation in a clinical trial.

I wonder what a consent form would look like.

It is important that we are careful not to exert even subtle coercion on healthier HIV positive people. This means that we must be clear that for individuals with higher CD4 numbers, unlike people with more advanced disease, the benefits of treatment have not yet been clearly shown to outweigh the risks.

Central to this consideration is the still unanswered question of when, in the course of HIV disease, it is best for healthier HIV positive people to start anti-viral treatment.

Of course people with higher CD4 numbers may also benefit from treatment, but we don't know this with the same degree of confidence we have regarding people with more advanced disease. We need to be upfront with this information.

It is possible that morbidity not traditionally associated with HIV, perhaps resulting from inflammatory reactions, may prove to be a significant problem in HIV positive individuals, and which could be prevented or treated by antiviral medications. But again, this has not been firmly established.

The fact remains that we still do not know when it is best for people with higher CD4 numbers to start treatment. After almost fifteen years this remains one of the most important issues in HIV medicine waiting to be resolved. This uncertainty creates, among other difficulties, an ethical problem in implementing treatment as prevention where all positive people would be treated. As already noted, we have to explain the risks and benefits of treatment to healthier individuals, where the benefits remain conjectural, but the risks of adverse drug effects are known more clearly.

The surest way to obtain the kind of evidence needed to make a decision about when it's best to start is to complete a randomized prospective clinical trial that directly addresses the question.

Such trials could have started in the late 1990s and by now we could have had evidence of the highest quality to help us make a decision about when it's best to start treatment.

Such trials may be expensive, and last a long time, but in the end, probably much more time and money is lost by turning to evidence of inferior quality such as that provided by retrospective analyses like the NA-ACCORD trial that is so frequently relied on to justify an earlier initiation of treatment.

In retrospective observational studies of this type, past records are examined, and outcomes

among people who start treatment early and those who defer it are compared.

Because people are not randomly assigned to receive treatment early, or to defer it, the causative interpretation of such retrospective observations are difficult because of what are called confounding factors and some are impossible to overcome.

We don't know why some people choose to start treatment early while others start later. The different decisions may reflect the possibilities that those choosing an earlier start to treatment may have better access to medical care, may receive better care in general, or may be more likely to be people concerned with overall health. Without randomization, the reasons why a particular course of action was chosen, whatever these may have been, might explain differences in outcome between the groups rather than the effect of the time treatment was initiated. It is impossible to adjust for all the possibilities for confounding that arise when randomization is absent.

The START study is a prospective randomized "when is it best to start" trial in people with higher CD4 numbers.

I wonder how enrolment is proceeding in the face of what seems to be an increasing belief among providers that the answer to the question of when it is best to start treatment is already known. Some of my colleagues have stated that all HIV infected persons are better off receiving treatment irrespective of their immune status. They may or may not be right.

Individuals with higher CD4 numbers and who are slow or non-progressors may want more reliable evidence than such opinions, or that provided by retrospective studies such as NA-ACCORD, in coming to a decision to start or to defer treatment. A prospective randomized trial can supply such evidence.

If anti-viral drugs were completely benign we would have no problem, apart from cost in treating every infected individual. But it is quite possible that a person starting treatment at say, 700 or 500 CD4 cells who may be a slow progressor, will remain healthier for longer with a better quality of life if treatment is deferred.

In the early 1990s I was involved in an unsuccessful attempt to pilot a "when to start" randomized prospective trial using AZT in individuals with higher CD4 numbers. I do not remember precisely how many providers in New York and California agreed to enrol patients. The endeavour was stopped because of poor enrolment.

Quite remarkably, almost all the patients who had agreed to be randomized to start treatment immediately, or to defer it came from the practice of one physician in San Jose. When asked how he was able to enrol so many patients his answer was that he told them that he did not know which course of action was better. There was no difficulty in agreeing to let the toss of a coin determine what to do, particularly since doing this would help provide an answer to the question.

Maybe the other participating providers were either not so uncertain or perhaps found it difficult to admit to being so.

A randomized prospective trial would give us reliable evidence about when, on average, in the course of HIV disease it is best to start treatment. Fine tuning will be needed to determine when it is best for each individual to start. This will include consideration of many different factors, some non-medical ones such as domestic and housing issues, and some medical ones such as co-morbidities.

One of the most important medical factors in fine tuning the best time for a particular individual to start treatment is that individual's rate of disease progression. This can vary widely from person to person and surely should be considered when making a decision to start.

Individualization of treatment to consider the rate of disease progression for each person seems to be receiving just a little attention now, after so many years of neglect. It is an important subject and I will leave a discussion of it for another post.

In conclusion I'm going to add a letter I sent to DHHS almost thirteen years ago regarding this very issue. This was in a response to a call for comments when the very first treatment guidelines were published. Evidently not enough people who shared these concerns chose to respond to this invitation to comment.

This letter also asks that an individual's rate of disease progression be taken into account when making a decision to start treatment.

July 16,1997

Regarding the Guidelines for the use of Antiretroviral Agents in HIV-infected adults and adolescents.

The panel convened by the Department of Health and Human Services to develop guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents has performed a valuable service. Their recommendations will undoubtedly be greatly relied on by the many physicians without extensive experience in the management of HIV-infected patients.

The recommendations regarding treatment in more advanced disease (where evidence derived from controlled clinical trials is available), will be of great benefit to patients in this category. However it is far from clear that this will be the case for asymptomatic patients, even some of those with fewer than 500 CD4 lymphocytes / mm3 . The potential risks detailed in Table III are far from trivial. For an individual facing more than 5, or even possibly 3 years free of disease,

instigation of combination antiretroviral therapy with agents whose long term toxicity is unknown, may in fact have the net effect of shortening that individuals life. The issue of quality of life is also of concern, as is the likelihood of a failure in compliance over a long period, with the attendant risk of the development of resistance, with the possible consequence that effective therapies may be unavailable at later stages of the disease.

For asymptomatic individuals it is quite possible that the risks of early intervention outlined in Table III will outweigh the benefits. The potential benefits listed in the table are conjectural; the potentially serious risks cannot even be approximately quantified with the little experience accumulated thus far. Faced with such difficulty in recommending when to initiate therapy in asymptomatic individuals, I believe that the panel might have devoted more consideration to the rate of disease progression in individual patients as a factor that should influence the decision as to whether or not to start antiretroviral therapy. Rates of disease progression vary widely, and it might require a 6 to 12 month period of observation to assess this rate in an individual patient.

Given the availability of potent antiretroviral agents and the potential benefit that may be associated with their use, the uncertainty as to when to start therapy with these agents in asymptomatic patients is perhaps the most important issue that needs to be addressed at this time. It was therefore most surprising that the panel did not call for controlled clinical trials to resolve this important question. There is the unfortunate implication that in the area of AIDS medicine, convening a panel to make recommendations on such areas of clinical uncertainty has now replaced clinical studies as a means of guiding treatment decisions.

The recommendations regarding treatment of patients with advanced disease are sound as they are supported by evidence derived from clinical studies. I would suggest that the recommendations regarding treatment of asymptomatic individuals, and treatment of acute HIV infection rather be called interim suggestions pending the results of controlled studies. I hope the department of Health and Human Services will acknowledge the pressing need to obtain a clear answer to the question of whether early intervention is of benefit, is harmful or is without effect, and encourage the development of appropriate studies. Admittedly enrolment in such trials would be difficult at this time - in part because of the availability of recommendations regarding treatment , with the implication that the questions have been answered. It is therefore also to be hoped that the Department of Health and Human Services will help to prepare the ground for such trials by educating patients and providers that there is indeed considerable uncertainty regarding when treatment should begin in asymptomatic individuals, and that the clearest answer to this question can only be obtained through appropriate clinical studies.

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Here are some links to several reports on treatment as prevention that highlight concerns that any

decision to participate in such a project should be voluntary. I am grateful to Sean Strub who has written and spoken on this issue, for bringing my attention to these reports.

http://www.catie.ca/eng/PreventingHIV/PreventioninFocus/Issue1/treatment-as-prevention_interviews.shtml

http://www.cdnaids.ca/web/setup.nsf/ActiveFiles/Microsoft+Word+-+Resolution+Report+2009+-final/$file/Microsoft%20Word%20-%20Resolution%20Report%202009%20-final.pdf

http://74.125.113.132/search?q=cache:FmGEdBOj3HAJ:data.unaids.org/pub/Report/2009/20091128_phdp_mr_lr_en.pdf+%22treatment+as+prevention%22+informed+consent+hiv/aids&cd=23&hl=pt-BR&ct=clnk&gl=br

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