WILL NEW MEDICATIONS PRODUCING LOW VIRAL LOADS REDUCE THE INFECTIOUSNESS OF HIV? RESEARCH NEEDS AND PUBLIC HEALTH IMPLICATIONS FOR NEW PREVENTION STRATEGIES

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New Strategic Considerations in HIV Prevention Strategy

The availability of new anti-retroviral drugs, and their ability in combinations to achieve undetectable plasma viral levels (e.g., two reverse transcription inhibitors and a protease inhibitor) and sensitive tests for viral load have revolutionized HIV treatment since 1994. Through research utilizing such tests, we now know that untreated seropositive patients typically experience high-level and rapid viral replication throughout the course of their infections (Mellors). Although the late stages of AIDS are associated with increasing viral loads, primary infection is associated with some of the highest titers of all. These findings have focused new attention on the advantages of reducing viral load in persons with early HIV infection.

The public health implications of the new discoveries and medications have not yet been adequately explored, however, in either research studies or in strategic planning for prevention. Although treatment of infected persons is a fundamental element in controlling many communicable diseases, the potential for medications to reduce HIV infectiousness has been inadequately studied. In the few published reports on this subject, monotherapy with zidovudine (ZDV) reduced perinatal and sexual transmission of susceptible strains.

Figure 1 shows a new model to classify the various potential strategies for interrupting the cycle of exposure and infection for any communicable disease. Treatment of infected persons to reduce the shedding of the infectious organism is clearly a key method used with other diseases of public health importance, e.g., tuberculosis (TB) and syphilis. The possibility of using drugs to decrease viral load, not only to improve clinical course but also to decrease the chances of an HIV positive person transmitting the virus to a sexual or needle-sharing partner, has been the subject of speculation since 1989 Anderson RM), and now needs to be tested, with incorporation into HIV prevention research and contingency planning.

Regimens capable of reducing viral plasma loads to undetectable levels, if they prove to have similar effects on viral titers in semen and vaginal secretions, should logically decrease infectiousness. The reasoning that reduced viral shedding will correlate with reduced transmission has already been accepted by CDC with respect to promotion of STD treatment, because diseases such as gonorrhea can raise the concentration of HIV shed in genital secretions severalfold (St. Louis); however this line of attack has not been extended in published articles or recommendations to the use of medications against HIV itself, apparently due to the paucity of data on the subject. Indeed, CDC still states that as of March 1997, "there is no evidence to date that new therapies provide any protection against HIV transmission" (CDC: *HIV/AIDS Prevention,* p. 4).

It is rather alarming that gay males have already made the logical connection ahead of the public health community, and are considering whether to discontinue condom use, while the extent of reduction of communicability that can be expected is unknown (CDC: *HIV/AIDS Prevention* p. 4; Gallagher J, *The Advocate*, February 18, 1997, p. 39). In March 1996, the California Medical Association adopted my resolution (attached), calling for research on the potential of antiretroviral treatment to reduce HIV transmission, but this has not yet become incorporated into the study protocols for US drug trials or other research studies.

Treatments prolonging survival without decreasing infectiousness (e.g., prophylactic medications for opportunistic diseases) may paradoxically increase HIV transmission, as infected - and infectious - persons live longer and have more opportunities to transmit (Anderson RM). This prospect is real, as the prevalence of persons living with AIDS in the US is rising even as the incidence, prevalence, and mortality of full-blown AIDS is declining (CDC: *HIV/AIDS Prevention,* p. 5). In contrast, treatments effective at reducing infectiousness (i.e., combination antiretroviral regimens), if initiated early, maintained, and monitored with the help of both viral load testing and case management to assist compliance, might provide an additional public health prevention strategy for HIV. It is thus essential to determine the degree to which medication can reduce transmission, and to explore the resulting public health potential.

Until now, promotion of early onset of treatment, attention to treatment compliance, and monitoring effectiveness in suppression of the organism have not been considered public health priorities with HIV, even though they have been with TB. These should be reevaluated as potential strategic objectives for control of the HIV epidemic. Treatment of infected persons and supporting services to assure that the treatment is administered, if it can be reasonably expected to protect the public from exposure as well as to benefit the recipients, would be in the public interest, making public funding for such programs no less appropriate for HIV than for TB. Early identification of infected persons through HIV antibody testing will be more important than ever, while partner notification, referrals to treatment, and assistance in developing personal adherence plans will be critical additional elements (currently underfunded or unutilized in many areas) in effective prevention planning (see **Figure 2** for a model demonstrating the central role of early testing and follow-up in prevention).

Evidence that Transmission Can Be Reduced by Medication, Via Reduced Viral Shedding:

The prospect of using treatment to reduce transmission is supported by recent studies showing strong correlations between viral load in the plasma of pregnant women and vertical transmission (Dickover). Two observational, non-randomized studies of pregnant, HIV-infected women (Frenkel, Matheson) suggest that antenatal oral ZDV, with no parenteral administration and no treatment of the infants after birth, can reduce neonatal infections. Maternal treatment thus probably accounts for most of the protection found in the ACTG 076 trial, and the mechanism of protection is most likely reduction of prenatal viremia.

Small studies by two Italian groups (Chirianni, Musicco) have suggested that ZDV treatment of infected persons can reduce heterosexual transmission.

Areas Requiring Further Research:

We have found no studies reporting on infectiousness related to medications other than ZDV, or on the effect of any medication on homosexual or parenteral transmission. No U.S. prospective or case control studies are known to have been designed to determine the effect of medications on HIV transmission to uninfected sexual or needle-sharing partners.

In the future, it is likely that the standard of care will be to switch drugs whenever necessary to maintain minimal viral loads, rather than to continue with a particular drug regimen for long periods of time. Given this trend, combined with the logical hypothesis that viral load will be the bottom line for preventing transmission, future studies should perhaps focus more on correlating transmission with viral load rather than with specific drugs. Yet, we have found no studies anywhere in the world that have yet applied the new viral measurement techniques (i.e , reverse transcriptase polymerase chain reaction, branched DNA, and nucleic acid sequence-based analysis), to correlate with rates of sexual or needle transmission. The high correlation between maternal viral load and perinatal transmission has been confirmed, however, suggest that this line of inquiry will likely be fruitful.

However, when it comes to sexual transmission, more than plasma levels is involved. It will in addition be critical to have extensive data on correlations between reduced viral loads in plasma and viral titers in semen and vaginal secretions, and between the latter and transmission. Initial results with semen have been conflicting (Anderson DJ, Krieger). If studies should show inconsistency in reduction of these titers, various drug combinations will need to be compared, as genital

tissue penetrations might vary.

We also need more information on the relative clinical benefits of starting anyone with detectable viral load on antiretroviral treatment vs. waiting for a threshold value of viral load (e.g., 5,000 or 30,000 copies). Even if treatment were proven effective in reducing transmission, in order to have a significant impact on incidence, medication would obviously need to be started before the average patient had already transmitted the disease. From a public health perspective, the earlier infection were detected and treatment were begun, the better, and any detectable viral load posing a risk of communicability would be an indication for treatment. In general, the earlier an infection of any type is treated with antimicrobial drugs, the better the results (Corey), however HIV is not necessarily like all other infections. If it should turn out that maximal clinical benefit-to-risk ratio for the patient were associated with somewhat later onset or treating only viral loads above a certain level, there could be conflicts between public health and individual clinical strategies, with resulting ethical and political dilemmas. No such conflicts have arisen with TB treatment, but the issues are less clear with HIV, in part because of uncertainty about the duration that medications will be effective. Additional areas of uncertainty include whether it is necessary to stop viremia entirely to avoid a continual increase in the number of infected cells, whether this burden can be reversed if treatment is started later, and whether actual cures are possible after 2-3 years of maintaining undetectable viral loads,as suggested by Perelman and Ho (Gorman C, *Time*, December 30-January 6, 1997, pp. 56-64), as infected cells continue to die out faster than new ones are infected.

The evidence for benefits of early treatment onset is encouraging so far. Drug regimens that make viral loads in plasma undetectable have been shown to halt the progression of HIV disease (Mellors), and have reduced the incidence of some opportunistic diseases among compliant patients. However, rises in CD4 counts are generally modest and remain at reduced levels, and there is no evidence that immune competence can be restored to pre-infection levels. Moreover, not all patients can achieve undetectable viral loads (CDC: *HIV/AIDS Prevention*, p. 4). A consensus has developed that if viral loads are moderate or high, these drugs should be started without waiting for the CD4 count to drop below 500 (as had earlier been recommended for zidovudine monotherapy) for maximal clinical benefit, but there is no consensus on whether counts below approximately 30,000, and particularly under 5,000, deserve immediate onset of treatment.

The Compliance Problem as a Special Strategic Public Health Issue:

Unfortunately, onset of treatment is only the beginning of the obstacles with utilizing antiretroviral therapy as a public health measure. Longterm (possibly lifelong) dependable compliance with multiple drugs taken several times a day is already known to be necessary to discourage the proliferation of drug resistant strains, another public health problem). It would be essential as well to make transmission reduction effective. Anyone who has taken even one medication several times a day for as little as 10 days knows the difficulty of such compliance, and with antiretroviral combinations, the problem is made more severe by the sheer number of pills required, the inability to take all the pills at one time (e.g., indinavir must be taken separate from meals but with large amounts of fluids, while other drugs must be taken with meals), the great expense and difficulty in obtaining and affording a continuous supply of all agents, the many side effects that can occur, and the human tendency to resist continuing a difficult and unpleasant regimen indefinitely. These issues were addressed by several presentations at the Ninth National AIDS Update conference in San Francisco, March 18-22, 1997. Both patients and physicians will need education on the importance of consistently using drugs in combination and developing practical schedules and plans to facilitate each patient's successful treatment. Physicians' prescribing practices nationwide with antibiotics, and the emergence of multi-drug resistant bacteria, do not provide much reassurance. Resistant strains can develop rapidly during monotherapy, or even with some two-drug combinations. Failure to develop appropriate combination treatment strategies could neutralize the effectiveness of the remarkable new drugs in just a few years, with the specter of drug-resistant strainsspreadiing widely (CDC: *HIV/AIDS Prevention*, p. 4). The wonder drugs of 1997 could become the shortest-lived medical miracle of the age.

Because several doses of various medications are needed each day with current regimens, directly observed therapy (as used with TB) is not practical, however frequent contacts with a case manager might prove effective in influencing patient behavior, e.g., by providing reinforcement and by providing or suggesting solutions to everyday obstacles. Little has been

done to provide effective publicly funded case management services directed toward assisting patients with adherence to such difficult regimens.

Such programs could also encourage continued maintenance of safer sexual practices and avoidance of needle sharing, the need for which should have been obvious since the beginning of the epidemic, but services for which are lacking in most locations. The temptation of patients to discontinue such safer practiceswhen told that there is no detectable virus in their blood makes the need for such follow-up more acute than ever.

In about 22 states, including some like California and New York with the largest populations of infected persons, HIV infection is still not reportable until the increasingly irrelevant criteria of AIDS are reached, so the infected persons in need of services that might help prevent secondary cases during the early years of their disease are not even known to public health authorities. Even in most states where HIV is reportable, there are insufficient funds for public health follow-up, let alone case management, directed toward these issues for infected persons (let alone high risk HIV-negative persons), and as noted, medication compliance has not yet even been formally addressed as an area for public health funded services.

Fortunately, there is a potential remedy that would utilize an existing infrastructure and would not add as greatly to current expense as the establishment of totally new public health programs. The psychosocial support services provided by the Ryan White Act and by other government-funded programs, which do include case management by social workers or other professionals in many cases, could be directed in part toward assisting patients with adherence to both behavior changes and taking medications as prescribed, and also to assistance with the awkward and socially difficult task of partner notification and referral for testing and counseling. If the agencies providing these services would take on these responsibilities, effective interventions could be introduced even in states where the public health departments do not officially know of the existence of most of the patients. This may require new federal legislation (e.g., amendments to the Coburn bill) or regulations. The same legislation could be designed to assure that Ryan White funding to states would be proportional to the total number of HIV patients known to reside in the jurisdiction, rather than the number of AIDS cases by jurisdiction of diagnosis, which should provide more adequate and fairly distributed funding and might encourage the remaining states that do not yet have HIV reporting to institute this important surveillance measure. At the same time, funds should be sought for voluntary follow-up and social services to assist behavior change, for very high-risk persons who test HIV negative at publicly funded test sites (See Figure 2).

CDC's Role:

As the nation's lead public health, disease control, and prevention agency, CDC has a special responsibility for helping to focus prevention strategies to keep up with new scientific knowledge and the potential new methodologies that result from it. Methods available to CDC for influencing national policy and clinical and public health practice include funding for research and for prevention services, developing educational programs for health care providers and patients, and developing revisions to its influential guidelines. In collaboration with allied organizations and agencies, CDC can encourage and help fund research along the lines suggested above, and assuming federal Administration willingness to support a more effective strategy against HIV, can encourage legislation to provide the case management and compliance assistance services that are already clearly needed.

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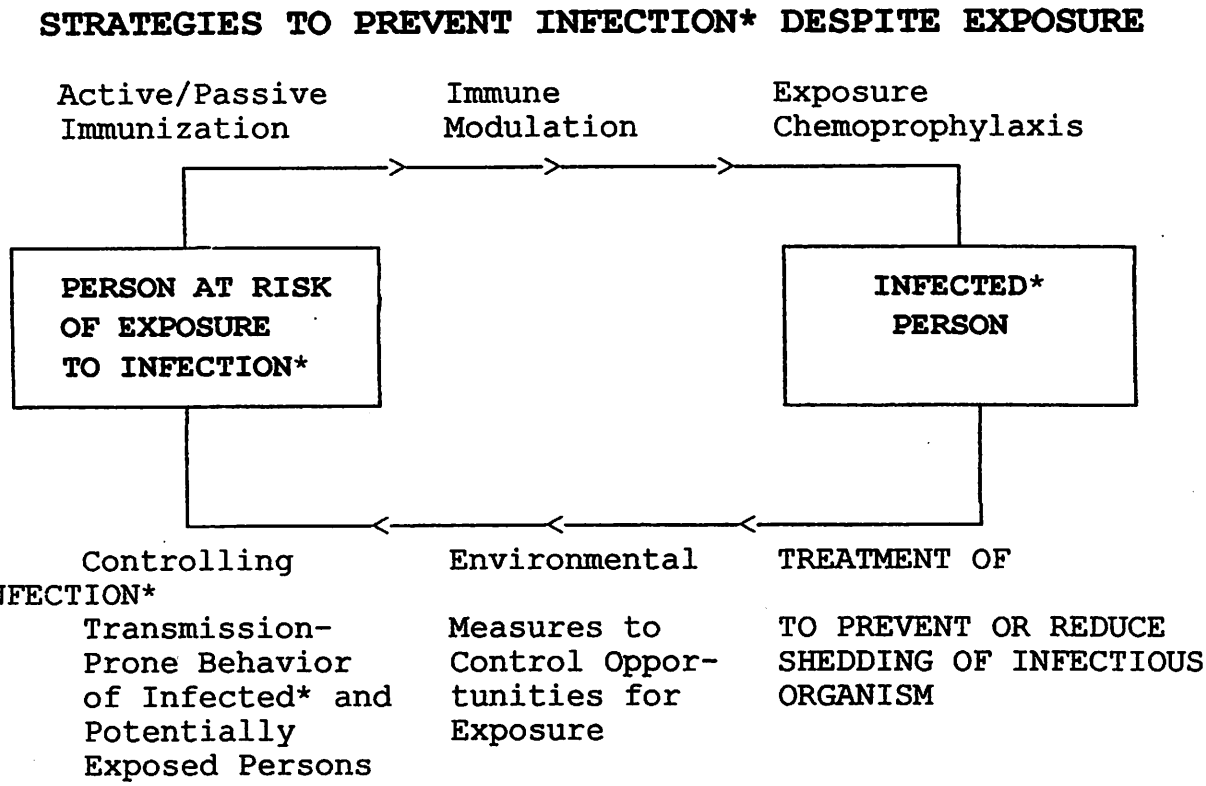
Figure 1

STRATEGIES FOR PREVENTION AND CONTROL OF COMMUNICABLE DISEASES

A Model for Conceptualizing the Opportunities for Interruption of the Cycle of Exposure and Infection, with Emphasis on the Use of Medications to Reduce Shedding of the Causative Organism



* May also apply to colonization (which is not a feature of HIV) if the colonized person can transmit the infectious organism