USING MEDICATIONS TO REDUCE THE INFECTIOUSNESS OF HIV: AN UNDERUTILIZED PREVENTION STRATEGY

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Abstract

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. The few published reports suggest that zidovudine reduces perinatal and sexual transmission of susceptible strains. New, more potent anti-retroviral combinations should better prevent viral shedding, might inhibit resistance, and could be monitored by sensitive new viral load assay techniques.

Treatments prolonging survival without decreasing infectiousness may paradoxically increase AIDS mortality. In contrast, treatments reducing infectiousness, if initiated early, maintained, and monitored, might provide an additional public health prevention strategy for HIV.

Introduction

A decade after the development of methods to detect the presence of infection with human immunodeficiency virus type 1 (hereafter referred to as HIV), there are concerns that current methods of prevention have not proven adequate and that new approaches are needed to control the spread of the HIV/AIDS pandemic.**1-5** While the incidence of AIDS is stabilizing and even decreasing in many areas, this may be due in considerable part to depletion of susceptible persons among highly infected cohorts **6** and to reduction of the viral reservoir resulting from die-off among cohorts infected a decade and longer ago. Meanwhile, incidence rates of new HIV infections in the United States have increased among younger cohorts, minorities, and women, and in new geographical areas.**7**

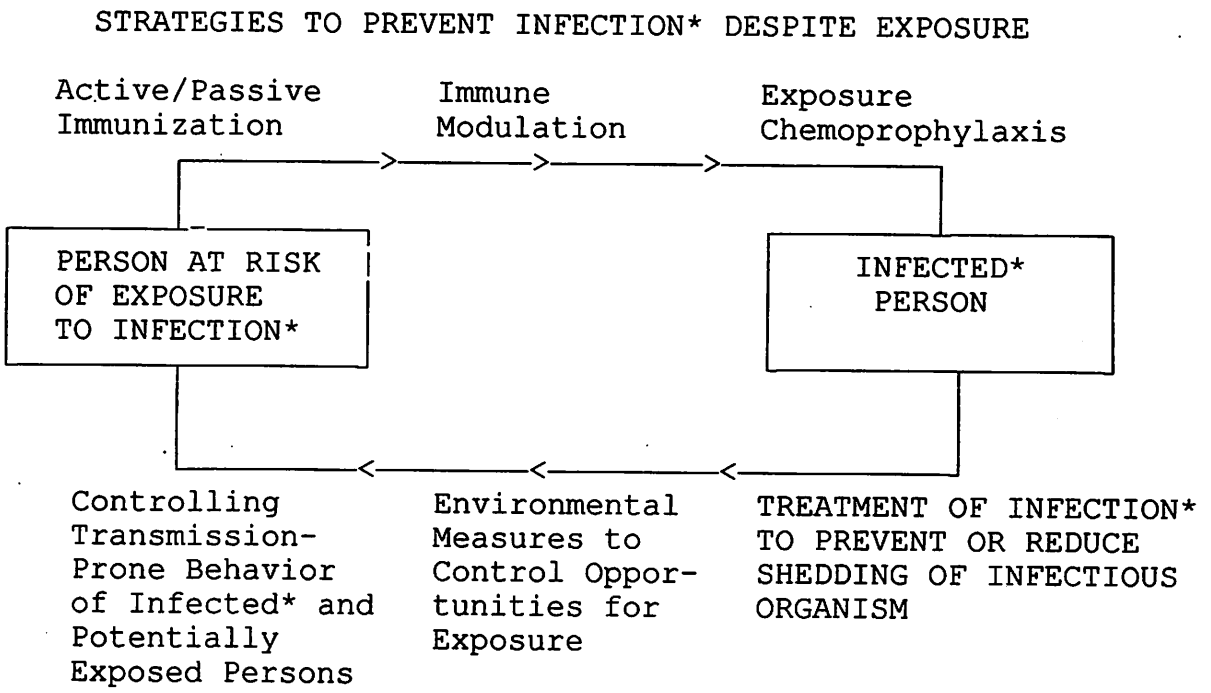
We suggest that not all potential strategies for prevention have been adequately explored. Specifically, not enough attention has been devoted to the reduction of HIV communicability at its source, i.e., the infected person. The time is opportune to explore the potential for newer drug combinations, monitored by new laboratory techniques, to accomplish this.

Interrupting the Chain of Transmission

Strategies for the prevention and control of communicable diseases employ various methods to prevent transmission by breaking the vicious cycle of exposure and infection. We present a model in Figure 1, classifying these into two groups: methods to prevent exposure (bottom half of figure), and methods to prevent infection despite exposure (top half of figure). (Our references to infection may all be expanded to colonization if it is capable of transmission; however colonization is not known with HIV.) By exposure, we mean contact with a pathogenic organism that could potentially cause infection (or colonization). In infection (and sometimes in colonization), the organism grows within the body such that it may potentially result in further exposure.

Figure 1.

STRATEGIES FOR PREVENTION AND CONTROL OF COMMUNICABLE DISEASES



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

Options are limited for potential strategies to prevent HIV infection despite exposure. Immunization is still an unrealized dream **1,2**, and there is as yet no known reliable means of increasing host resistance through the strengthening of general immunity.

Chemoprophylaxis throughout a period of exposure, as used for malaria, has not so far been reported or recommended as an HIV prevention strategy. We suggest that it be studied as a potential back-up to barrier methods for spouses and other regular sexual partners of HIV infected persons. The theoretical limitations of this strategy for other uses include lack of awareness by many exposed persons that their partners are infected, and the unplanned timing of many sexual and needle exposure events. Post-exposure chemoprophylaxis with zidovudine (hereafter called ZDV; also known as AZT) has been utilized for health care workers after parenteral or mucous membrane exposures, and may be of value, **8** but failures have been reported.**9,10,11**

The ACTG Protocol 076 study reported that ZDV could reduce the infection rate of infants born to HIV-infected mothers by 67.5%

(from 25.5% with placebo to 8.3% on ZDV).**12,13** Currently recommended regimens for perinatal prophylaxis based on this study include a combination of prenatal oral and intrapartum parenteral ZDV treatment of infected women, followed by postnatal treatment of their infants.**(13)**. It is unknown how much protection would be provided by treatment of the newborns alone, or how much is due to fetal uptake as opposed to suppression of maternal viremia.

Strategies for the prevention of exposure have been the mainstay of HIV/AIDS prevention programs, but those employed to date require behavior changes, which are difficult to achieve. For HIV, even environmental controls, such as barrier techniques for sex and medical care and the use of clean needles, are heavily dependent on human behavior. Although some effective programs have been reported, efforts to permanently change high-risk behaviors on a large scale have not been consistently effective.**14-17** It may not be realistic to depend exclusively on lifelong, consistent avoidance of certain pleasurable acts by vast numbers of people, for control of a disease with such a capacity to decimate human populations.

Controlling Transmission by Treating the Infected Person

The remaining strategy for exposure prevention, chemotherapeutic treatment of infected (or colonized) persons to reduce their communicability, has in our opinion been underutilized. It has not yet been employed as a recognized HIV control measure except in the maternal treatment component of the perinatal CDC protocol based on ACTG 076.**17** For other indications and contexts, it has not even been widely studied.

Strategic Advantages

Treating infected rather than exposed persons has the advantages of prevention at the source, placement of responsibility on persons aware that they might transmit disease, potential protection of many persons by treating a few, and compliance motivation derived from clinical benefit. For many infectious bacterial diseases, such as syphilis, gonorrhea, and chlamydia, this strategy is a critical one in disease control, and usually involves delivering curative doses of antimicrobial medication to the infected person. However, eradication of an organism may not

be essential if a treatment can reduce shedding or virulence.

The Tuberculosis Analogy

For example, tuberculosis infectiousness is proportional to the number of organisms excreted into the air and seen on sputum smears.**18** Active cases responding to treatment probably become non-communicable even before bacilli totally disappear from smears.**19** Yet even completed treatment, though considered curative, does not eradicate tubercle bacilli from the body. Preventive therapy for infected persons with isoniazid is likewise aimed, from a public health standpoint, at avoiding progression to the stage where infectious organisms are shed **18,20**, rather than at eradicating tuberculosis infection.

The Herpes Analogy

Treatment to decrease transmission risk need not be limited to bacterial diseases. Maintenance treatment of genital herpes with acyclovir, although incapable of eradicating the organism, does reduce viral shedding, and deserves study as a potential means of

reducing infectiousness.**21**

Drugs and Viral Load

Fewer viral particles in semen, vaginal secretions, and blood should theoretically translate into reduced HIV transmission. Since 1989, Anderson and May have speculated about 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.**22-24** This prospect is supported by recent studies showing strong correlations between viral load in the plasma of pregnant women and vertical transmission.**25,26**

Zidovudine and HIV Transmission

ZDV has been known since 1989 to reduce mean viral titers in blood.**27** Reports on the effects of ZDV on HIV levels in semen have been conflicting.**28,29**

Two observational, non-randomized studies of pregnant, HIV-

infected women 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.**30,31** The mechanism of protection is most likely reduction of prenatal viremia.**26**

Two small Italian studies have suggested that ZDV treatment of infected persons can reduce heterosexual transmission. In 1992, Chirianni *et al* described a retrospective heterosexual partner study (N=46) in which there was a 5.5% annual seroconversion rate among 27 partners of male patients not treated with ZDV, and 0% annual seroconversion rate among 19 partners of male patients receiving 500-1200mg/day of ZDV.**32** These authors had reported similar preliminary results in 1989 and 1990, noting in the latter a p value of < .01. **33,34**

Musicco *et al* reported in a 1994 heterosexual partner study, including 436 monogamous seronegative female sexual partners of HIV-1 infected males, that the rate of transmission in men treated with 500-1000mg of ZDV per day was lower than in

untreated men (relative risk, 0.5; 95% confidence interval, 0.1 to 0.9), but this became apparent only after adjusting for markers of advanced disease progression.**35**

In contrast to the encouraging findings above, five out of eight reported failures of ZDV post-exposure chemoprophylaxis to prevent HIV infection after needle stick exposures involved source patients also taking ZDV.**13** ZDV-resistant viral strains might have been a factor in such cases. Heterosexual transmission of a ZDV-resistant strain of HIV by a patient taking ZDV has been reported,**36** as has perinatal transmission of ZDV-resistant HIV.**25,31** ZDV can fail to prevent perinatal transmission of even susceptible strains, if the mother's viral titer is high.**26**

Research Opportunities

Gaps in Current Knowledge

The above ZDV study reports on heterosexual transmission have been small and limited in details. 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. clinical drug trials have apparently been designed to study, or have reported on, the effect of medications on HIV transmission to uninfected sexual partners. Given the importance of this line of research, testing of various treatments using large study groups would appear beneficial.

Promising New Drug Combinations

Newer medications and combinations may provide hope for more effective regimens to reduce infectiousness. Several classes of known and potential agents are being investigated, e.g., new nucleosides, non-nucleoside reverse transcriptase inhibitors, and

protease inhibitors, each attacking the cycle of viral replication in a different way.**37** Other drugs which enhance AIDS survival, such as acyclovir, might act synergistically with anti-retroviral agents.**38** A promising triple combination to test for inhibition of HIV transmission is ZDV, 3TC, and indinavir (a new protease inhibitor), reported at the Third Conference on Retroviruses and Opportunistic Infections to eliminate measurable viremia in 24 of 26 (85%) of previously viremic subjects after 6 months of use (*L.A. Times*, January 30, 1996).

Some multi-drug combinations might be capable of inhibiting resistance, or the viability of resistant mutations, especially if they target the same protein (e.g., reverse transcriptase) by different mechanisms.**39** Although a regimen of ZDV and ddI (didanosine) did not prevent emergence of a strain resistant to both,**40** a combination of ZDV and 3TC (lamivudine) has prevented coresistance in vitro **41**.

New Quantitative Viral Assays

Branched DNA viral assay, utilized in the latter study, is an

example of new technology to measure viral burden. Studies using this method have also shown decreases in blood titers with combinations of ZDV and ddI.**42** Quantitative polymerase chain reaction and nucleic acid sequence-based amplification are additional methods for measuring low HIV viral titers.**26,43** All three techniques are less labor-intensive, easier to standardize, and more sensitive to low titers than previous methods.**43**

Drug combinations most likely to suppress both infectiousness and disease progression, and therefore most suitable to study, should be those shown by these methods to produce the greatest reductions of viral titers in blood, semen, and vaginal secretions. Titers could also be used to detect drug resistance or decreased effectiveness that would necessitate drug regimen changes.

Suggested Study Designs

Several potentially suitable types of study designs could correlate different treatment regimens with secondary infections. In prospective studies, new clinical trials comparing the effects

of different regimens could be designed to include studies of seroconversions among steady sexual partners of the participants. Longitudinal studies of high-risk HIV negative persons **44** could be expanded to compare seroconversion rates among those whose steady HIV positive sexual partners were taking various medication regimens vs. no treatment. Studies following HIV discordant couples for seroconversion, as done by De Vincenzi and her European Study Group,**45** could likewise be adapted to compare histories of medication regimens between those experiencing seroconversion and those in which no new infections occurred.

In case-control studies, odds ratios could be rapidly determined by comparing HIV-infected couples who have experienced documented seroconversion of the second partner during the relationship (cases) with similar couples remaining discordant(controls), with respect to history of anti-retroviral and other chemotherapy over a period of exposure. Case-control methodology might be especially suitable for injection drug users, to avoid any suggestion of condoning prospective needle-sharing relationships. However, such studies would lack ongoing viral assays or a time course for the acquisition of new infections among partners.

Study designs would require careful matching or otherwise controlling for differences in use of barrier techniques, frequency and the type of sexual contact, and needle sharing. Because advanced disease correlates with high viral titers and infectiousness, adjustment would also be required for stage of HIV disease as determined by CD4 counts, antigenemia, and other appropriate markers.**30,35** No drug or combination can yet be expected to decrease the probability of HIV transmission to zero, therefore condom use and avoidance of needle sharing would need to be stressed equally for all experimental groups, for ethical reasons.

Public Health Implications

The Hazards of Treatment that Does Not Reduce Infectiousness

Advances in prophylaxis and treatment of opportunistic infections and anti-retroviral therapy have increased mean survival time of HIV-infected persons,**46,47** which can increase the prevalence of HIV positive individuals and the length of time that each has to transmit HIV. If treatment is clinically effective but does not

reduce HIV infectiousness via sexual activity or needles, it may ironically result in an increase in overall HIV transmission and AIDS death rates, if there is no change in infectiousness or in behaviors that foster transmission.**22**. This consideration increases the urgency of identifying, and including in treatment regimens, medications that will decrease infectiousness.

Cost-Benefit Considerations

Calculations using 1991-1992 cost estimates suggest that each HIV infection in the United States may result in an average of $119,000 - $135,000 in medical costs alone.**48,49** or $56,000-80,000 with discounting for inflation.**50** Thus, a treatment regimen costing as much as $10,000 per year per person and preventing as few as one new infection per 5-8 person-years of use could still produce savings to the national health care budget. Total savings would be far greater if lost productivity, non-medical support for infected persons, rising medical costs over time, and especially the costs of further generations of secondary cases were taken into account.

The Impact of Treatment to Date

Since the licensure of ZDV in 1987, and the subsequent availability of ddI and ddC (zalcitabine), thousands of patients in the U.S. and other developed countries have had access to nucleosides with weak, usually temporary ability to suppress HIV. Treatment with these drugs has until now generally been recommended after CD4 cell counts fell below 500/mm^3.51 This delay permits up to several years for potential pre-treatment transmission, but does cover the late stages when viral burden and infectiousness are greatest.**30,35** Except for recent perinatal applications, treatment has been directed solely at benefitting the infected patient, and a large proportion of eligible patients have declined or discontinued medication.**52**

Despite these limitations, the HIV epidemic in these countries may already have been moderated as a result of inhibition of transmission by these (and perhaps other) drugs.**53** Meanwhile, decreases in new HIV infections among partners in some studied groups have been attributed solely to behavior change.**54** If the drugs' contagion-suppressing effects should be verified by

additional research, some of these studies might deserve reanalysis to appropriately assign partial credit to treatment.

Potential Public Health Programs

Conclusive evidence that medications can reduce HIV contagiousness via sex and needles would provide a powerful argument for more effective realization of this potential through expanded public health programs. Comprehensive, prevention-oriented care (which, for insured patients, might include a combination of services from private and public health providers) should incorporate the earliest possible identification of infections through testing and contact tracing; prompt referral for early initiation of compassionate, confidential, subsidized treatment capable of both reducing transmission and providing clinical benefit; viral titers to help individualize drug treatment; and ongoing case management. The latter could include monitoring to encourage sustained treatment, with the help of clinic or home visits, and/or directly observed therapy, as appropriate to any difficulties with compliance experienced by the individual patient. These visits could simultaneously reinforce and assist patients in maintaining behavioral changes

(which could be particularly critical to avoid patient rationalization that safer practices were no longer necessary on medication), and could provide psychosocial support and referrals as needed. In the absence of legal mandates as exist for tuberculosis, such programs would need to be sufficiently attractive to draw voluntary participation.

All of the types of services described above are considered by the Centers for Disease Control and Prevention to be essential components of any tuberculosis program,**55** but a number of them are not currently recognized and funded elements in most local HIV/AIDS programs. Proof that treatment protects the public would eliminate much of the rationale for this contrast. The prospect of better control of the global pandemic would also justify international aid from developed countries to finance drug treatment in developing countries that could not otherwise afford this strategy.

Conclusions

Since no one method of HIV prevention is likely to be totally effective, we should seek and utilize a combination of partially effective methods.**56** Increased research in the area of drug combinations to decrease viral shedding and hence infectiousness is possible, timely in view of new drugs and laboratory techniques, and badly needed. Early and maintained administration of such drugs could become an effective public health strategy to achieve and maintain gradual reduction in the incidence and prevalence of HIV infection.

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