

Topics in HIV Medicine®

A publication of the International AIDS Society—USA

Perspectives

- Unwelcome Guests With Master Keys: 100
How HIV Enters Cells and How It Can Be Stopped

Robert W. Doms, MD, PhD

- HIV and Sexually Transmitted Diseases: 104
Lethal Synergy

Myron S. Cohen, MD

Infectiousness and Susceptibility • Effect of Other STDs on HIV Acquisition and Transmission • Reversing STD Amplification of HIV Transmission and Acquisition Risk • Antiviral Therapy to Prevent HIV Infection

Review

- Secrets and Safety in the Age of AIDS: 109
Does HIV Disclosure Lead to Safer Sex?

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Review of the Literature • Limitations of Research to Date • Recommendations for Future Research

Special Contribution

- Update of the Drug Resistance Mutations 119
in HIV-1: 2004

International AIDS Society—USA Drug Resistance Mutations Group

Reprint

- Antiretroviral Treatment for Adult HIV Infection 119
in 2004: Updated Recommendations of the
International AIDS Society—USA Panel

JAMA. 2004;292:251-265



The International AIDS Society–USA

About This Issue

This issue features 2 *Perspectives* articles based on presentations from the International AIDS Society–USA continuing medical education courses held in Chicago in May 2004. Robert W. Doms, MD, PhD, outlined the processes by which HIV enters host cells and how these steps are being targeted by antiretroviral drugs in development. Myron S. Cohen, MD, discussed the effect of sexually transmitted diseases on the transmission and acquisition of HIV. In a Review article, Jane M. Simoni, PhD, and David W. Pantalone, MS, reviewed existing literature on the correlation between HIV disclosure and safer sexual practices.

This issue also features the 2004 update of the HIV drug resistance mutations figures by the International AIDS Society–USA Drug Resistance Mutations Group. Finally, this issue includes a reprint of “Antiretroviral Treatment for Adult HIV Infection in 2004: Updated Recommendations of the International AIDS Society–USA Panel,” which was published in *The Journal of the American Medical Association* in July 2004.

Topics in HIV Medicine®

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Perspective**Unwelcome Guests With Master Keys: How HIV Enters Cells and How It Can Be Stopped**

HIV entry to host cells begins with binding of the viral envelope protein to CD4 molecules on the host cell surface. This binding initiates conformational changes in the envelope protein that result in binding to a coreceptor (CCR5 or CXCR4), exposure of a previously hidden domain in the viral protein, insertion of a viral fusion peptide into the host cell membrane and fusing the viral and cell membranes. Each of these steps provides an opportunity for intervention to prevent viral entry, and a number of agents targeting these steps are in development. Studies of coreceptor inhibitors and fusion inhibitors have indicated the presence of host and viral factors that can result in variability of antiretroviral effect. Improved understanding of these factors will help to guide clinical use of these new agents. This article summarizes a presentation by Robert W. Doms, MD, PhD, at the International AIDS Society–USA course in Chicago in May 2004.

The processes of HIV binding, fusion, and entry to host cells provide targets for the development of antiretroviral drugs. Inhibition of this stage of the viral life cycle would complement approaches targeting other aspects of the life cycle, such as blocking viral replication through inhibition of the viral reverse transcriptase, protease, and integrase enzymes.

There are several steps to HIV entry into target cells. The envelope protein of HIV is a trimer, with each of the components consisting of 2 subunits, gp41 and gp120. The gp120 subunit of the viral envelope binds to the cellular CD4 molecule; this receptor binding induces conformational changes in the viral envelope protein that include exposure of a previously hidden, highly conserved domain that binds to a second receptor (coreceptor). The viral coreceptors, CCR5 and CXCR4, are members of the chemokine subfamily of 7 transmembrane domain receptors. Binding with the CCR5 coreceptor typically predominates in initial infection.

As infection progresses, mutations in the viral envelope enable the virus to utilize the CXCR4 coreceptors instead of or in addition to CCR5. The CXCR4 coreceptors are present on approximately 90% of CD4+ cells, but CCR5 corecep-

tors are present only on approximately 10%; thus the switch from CCR5 to CXCR4 as a coreceptor permits infection of a much greater number of CD4+ cells and is associated with accelerated HIV disease progression. Coreceptor binding induces conformational changes in the gp41 subunit that result in the insertion of a fusion peptide into the cell membrane and the binding of gp41 helical region 1 and helical region 2, which mechanically draws the viral and cell membranes together and permits membrane fusion.

These steps in viral entry present opportunities for intervention. Figure 1 shows some of the therapeutic agents currently in development for blocking

steps in the entry process. These include neutralizing monoclonal antibodies directed against the native trimeric structure of the viral envelope; CD4 binding inhibitors, including BMS-806 (which binds in a cleft of gp120 and thus prevents CD4 binding); CCR5 binding inhibitors and CXCR4 binding inhibitors (eg, AMD3100); and fusion inhibitors (eg, the enfuvirtide derivative, T1249).

Enfuvirtide, a fusion inhibitor, is the only entry inhibitor currently approved by the US Food and Drug Administration for use as an antiretroviral agent. Basically, enfuvirtide mimics the structure of helical region 2 of gp41, which binds with helical region 1. By binding with helical region 1, the drug molecule prevents binding to helical region 2 and thus prevents fusion of the viral and cellular membranes. As discussed further below, much has been learned about entry inhibitor drug development from the development and study of enfuvirtide.

There are a number of challenges inherent to the development and use of viral entry inhibitors. Practical implications to HIV receptor antagonist use include the potential for inhibitors to adversely affect normal cell function. This has been found to be the case for CD4 receptor inhibitors that have been

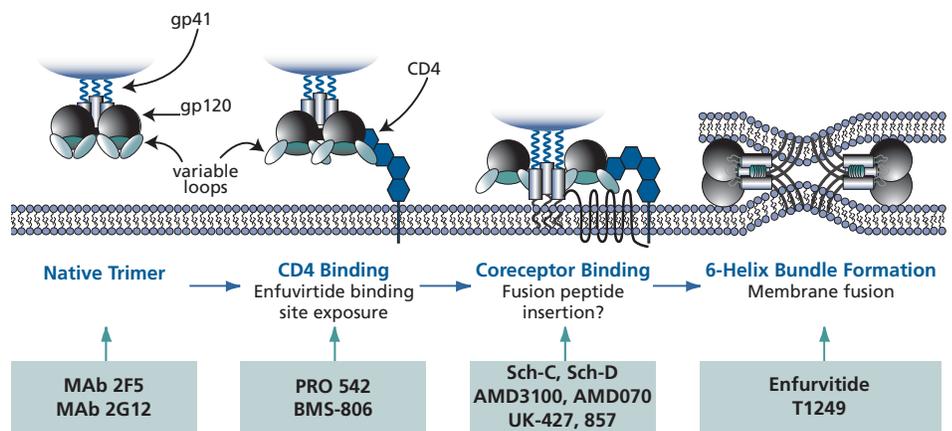


Figure 1. Steps in HIV entry into target cells and therapeutic agents to inhibit these steps. MAb indicates monoclonal antibody. All of the agents listed are investigational except enfuvirtide. Adapted from Moore and Doms, *Proc Natl Acad Sci U S A*, 2003

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tested, but it appears unlikely to occur with CCR5 inhibitors. That CCR5 is a good drug target is suggested by the fact that individuals who lack CCR5 due to a naturally occurring polymorphism are highly resistant to HIV infection and do not suffer any apparent effects from the loss of CCR5 function. However, one question with regard to coreceptor inhibitors is whether the use of CCR5 inhibitors will select for virus that uses the CXCR4 coreceptor, changing the viral population from the CCR5 phenotype to the CXCR4 phenotype that is associated with more rapid disease progression. Whether this will ever occur cannot be predicted, but it is evident that the use of coreceptor inhibitors will require monitoring of viral load as well as assessment and monitoring of viral phenotype, since, for example, the use of a CCR5 inhibitor in a patient harboring predominantly CXCR4 virus would not be expected to be very effective in reducing viral replication.

There are a number of host and viral factors that may have significant impact on how well entry inhibitors work. Experiments using primary viral isolates from different patients who have never received entry inhibitors have shown that there is a 2- to 3-log (100- to 1000-fold) variation in the amount of entry inhibitor required to block infection in different cell lines. This degree of variability is much greater than the 2- to 4-fold variation in inhibitory concentrations of HIV reverse transcriptase, pro-

tease, or integrase inhibitors in similar studies. Although these findings suggest differences in viral factors that affect the activity of entry inhibitors, others indicate a similarly important effect of host factors. In experiments in which a single viral strain is used to infect peripheral blood mononuclear cells or T cells from a number of HIV-uninfected human donors, there is also a 2- to 3-log difference in the inhibitory concentration of entry inhibitors, again compared with the smaller several-fold difference in inhibitory concentrations of reverse transcriptase, protease, or integrase inhibitors. It will thus be important to determine what host and viral factors influence the activity of entry inhibitors and to ascertain how such information might be useful in guiding therapy. It will also be important to determine how HIV might acquire resistance to entry inhibitors and the potential consequences of such resistance for viral replicative fitness (the ability of mutant virus to replicate in the presence of a drug, for example) and susceptibility or resistance to other entry inhibitors. Answers to these questions will help determine how to use these new drugs most effectively.

A number of specific factors that might influence the activity of entry inhibitors have been examined. For example, because enfuvirtide operates within a "kinetic window" that opens with CD4 binding and closes with coreceptor engagement (in the span of

approximately 10 minutes under normal conditions), it is likely that faster or more efficient viral fusion would reduce the opportunity for enfuvirtide to bind to its viral target. Also, the level of expression of the CCR5 coreceptor on target cells, which varies fairly widely among individuals, may affect the concentration of enfuvirtide required to inhibit cell infection. An increased number of receptors on the cell surface would allow the virus to locate and engage a receptor more rapidly and thus decrease the activity of enfuvirtide. In studies using peripheral blood mononuclear cells from HIV-uninfected human donors, HIV inhibitory concentrations of enfuvirtide varied by 300-fold (0.004-1.2 µg/mL) and inhibitory concentrations of the CCR5 inhibitor TAK-779 varied by nearly 3000-fold (1.3-3800 nM). That this variability is due at least in part to differences in CCR5 receptor expression was suggested by the finding of a greater than 12.6-fold difference in CCR5 expression on the donor cells as determined by monoclonal antibody binding studies (< 500-6300 binding sites).

Similarly, differences in coreceptor binding affinity among virus strains can affect entry inhibitor activity. Studies in which single amino acid changes were made in the viral protein domain that binds to the CCR5 coreceptor found a number of mutations that affected the strength of binding of the virus to coreceptor to varying degrees but did not affect CD4 binding affinity (Figure 2).

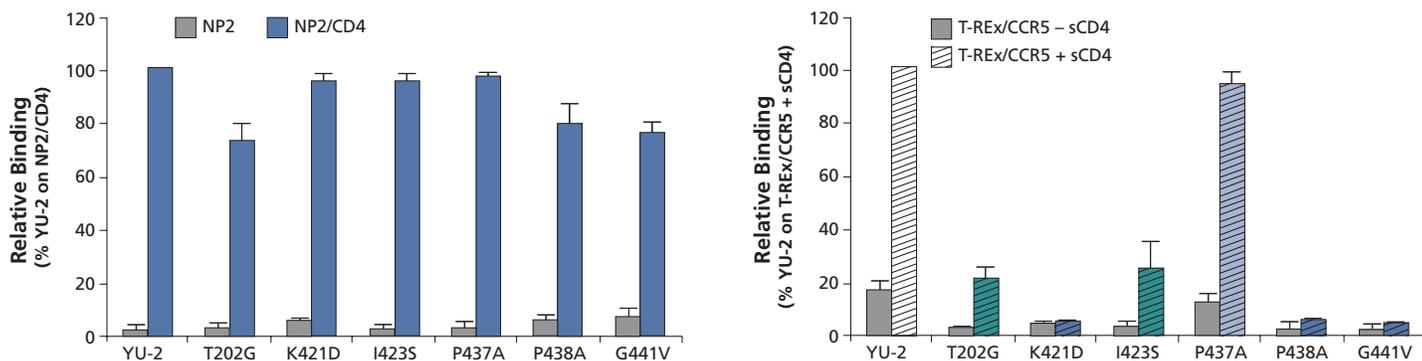


Figure 2. Effect of single amino acid changes in viral protein domain that binds to CCR5 on CD4 binding (left) and on CCR5 binding (right). In this experiment, single amino acid changes were introduced into the conserved coreceptor binding site of the envelope protein of the R5 HIV-1 strain YU-2. The designation T202G means that the threonine at position 202 has been changed to glycine. The other mutations are similarly designated. The envelope proteins were then tested for their ability to bind to NP2 cells expressing CD4. None of the mutations had significant effect on CD4 binding. The same proteins were then tested for the ability to bind to CCR5. To do this, the proteins were incubated with soluble CD4 (+sCD4) to induce the conformational changes needed for CCR5 binding and then added to cells expressing CCR5 (cell line T-REx/CCR5). Some of the mutations greatly decreased binding to CCR5 (blue bars), some had moderate effects (green bars), and one (light grey bar) had little effect on CCR5 binding. Adapted from Reeves et al, *J Virol*, 2004.

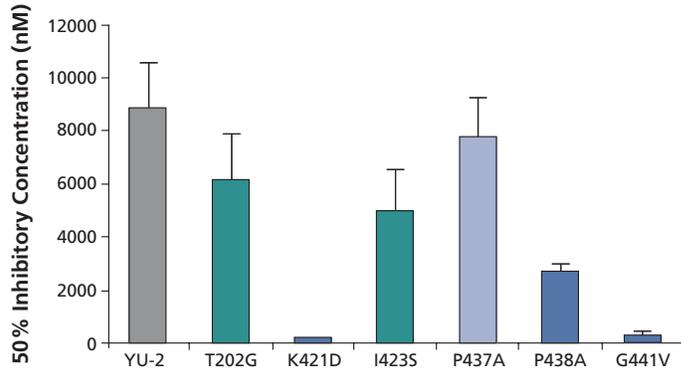


Figure 3. Relationship between CCR5 binding affinity and CCR5-inhibitor susceptibility. In this experiment, the amount of TAK-779, a CCR5 inhibitor, needed to inhibit virus infection by 50% was determined. The 50% inhibitory concentrations are shown for each virus. Viruses that bound poorly to CCR5 (blue bars) were more easily inhibited by TAK-779 than virus that bound well (light grey bar) and viruses with intermediate binding affinity (green bars). Adapted from Reeves et al, *J Virol*, 2004.

The inhibitory concentrations of CCR5 inhibitors did indeed decrease with reduced viral binding affinity and increase with increased affinity (Figure 3). Similarly, virus with higher CCR5 binding affinity, which thus fused faster,

was less susceptible to efavirtide, and virus with lower affinity was more susceptible (Figure 4).

In summary, HIV entry occurs via initial binding to CD4 receptors and conformational changes that allow corecep-

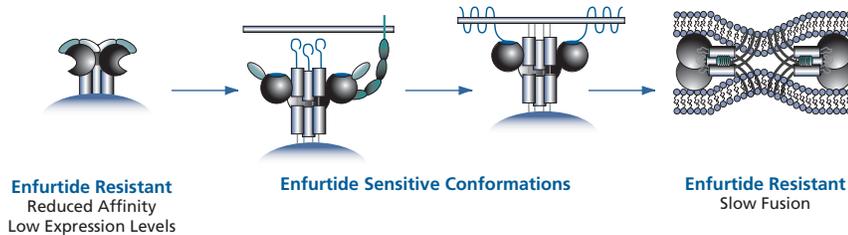
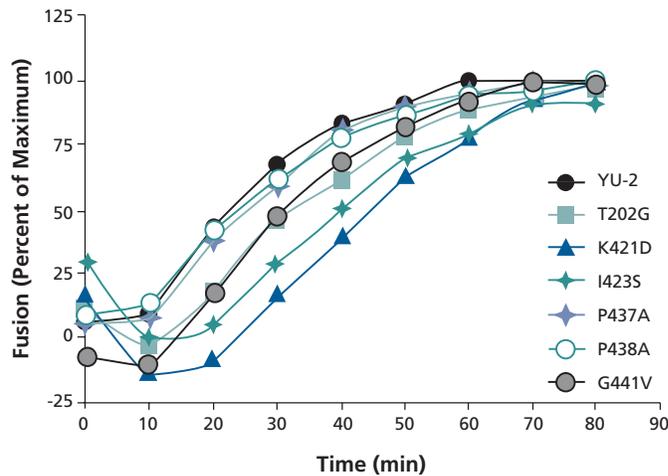


Figure 4. Correlation between CCR5 binding affinity and fusion kinetics. The rate at which each envelope protein mediated membrane fusion was measured. In general, reduced coreceptor affinity slows fusion kinetics, while high coreceptor affinity results in faster fusion kinetics. Adapted from Reeves et al, *J Virol*, 2004.

tor binding and membrane fusion. There are viral and host factors that have an impact on the rate at which the steps in entry occur. Factors that increase the rate of binding and fusion, such as high viral affinity for coreceptors or high levels of expression of coreceptors, will increase viral resistance to drugs targeting coreceptor binding or fusion. Factors that decrease binding and fusion rates, such as decreased receptor expression or viral binding affinity, will increase viral susceptibility to such drugs.

These considerations also raise issues regarding the potential combination use of entry inhibitors. For example, since coreceptor inhibitors act to reduce the number of coreceptors available to the virus and thus act to prolong availability of the enfurviride binding site by slowing fusion kinetics, the combined use of coreceptor antagonists and enfurviride might be expected to have a synergistic effect in inhibiting viral entry. Such an effect has been observed in in vitro studies of CCR5 inhibitors, and clinical development of these latter agents should include studies in combination with enfurviride or other candidate fusion inhibitors.

Presented in May 2004. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Doms in September 2004.

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Suggested Reading

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Perspective

HIV and Sexually Transmitted Diseases: Lethal Synergy

Sexually transmitted diseases (STDs) can increase risk for acquisition and transmission of HIV via a number of mechanisms, including breaching of mechanical barriers to infection, increased inflammation and higher levels of HIV cellular targets, and increased genital tract HIV levels. Studies in Malawi clinic populations indicate that treatment of STDs can reduce genital tract HIV levels. Work in Africa and India has indicated that genital herpes infection is associated with increased risk of acquisition of HIV and that presence of genital ulcer disease is associated with increased risk of transmission of HIV disease. Acute HIV infection has been found to be more frequent in individuals with active STDs, and cotransmission may be a common phenomenon. Acute HIV infection, which is not currently routinely diagnosed, is associated with increased risk of transmission. Greater efforts are needed in identifying acute HIV infection in STD clinics. This article summarizes a presentation by Myron S. Cohen, MD, at the International AIDS Society–USA course in Chicago in May.

Worldwide, approximately 85% of cases of HIV transmission occur through sex. HIV transmission depends on infectiousness and susceptibility.

Infectiousness and Susceptibility

HIV infectiousness is modulated by size of the inoculum of the infectious agent (ie, the concentration of virus) and phenotypic factors. With regard to phenotypic factors, there are many reasons to believe that the HIV clade B virus involved in infections in the United States, for example, is not as infectious as the clade C virus (Cohen, *New Eng J Med*, 2000) found in Africa or the recombinant BC virus found in China.

Susceptibility to infection is modulated by such factors as hereditary resistance, innate resistance, and acquired (immune) resistance (Buchacz et al, *AIDS*, 1998). An example of hereditary resistance is the CCR5 coreceptor deletion observed in a small percentage of the white population, which makes it more difficult for such individuals to acquire infection. A type of innate resistance is observed in the case of differences in vaginal flora: the typical vaginal flora in women in the United

States, for example, is characterized as generally free of the factors associated with bacterial vaginosis and appears to confer some protection against HIV acquisition; the typical vaginal flora in Africa (occurring in some 70% of women) consists of few lactobacilli and a predominance of anaerobes and appears to be more conducive to HIV infection. An example of acquired resistance is observed among sex workers who have never acquired HIV infection despite what is likely to be repeated exposure to virus. The factor(s) responsible for this type of resistance remain elusive.

Ejaculate from an infected man contains cell-free and cellular HIV. Semen dwells in the vagina for 2 to 3 days, providing a long period of time for virus

to penetrate barriers and find appropriate receptors in the submucosa. Epidemiologic studies have estimated the risk of HIV transmission to range from 5 in 10,000 to 26 in 10,000 penile/vaginal acts (Chakraborty et al, *AIDS*, 2001). The sense of rarity of transmission conveyed by such statistics is misleading, particularly when it is considered that many populations have very high prevalence rates of HIV infection occurring as a result of what must certainly be much lower numbers of sexual encounters. In fact, there are a number of factors that amplify risk of transmission and that need to be taken into account in efforts to prevent transmission. Factors that amplify the risk of HIV transmission include those that increase infectiousness, such as stage of HIV disease and presence of certain coinfections (eg, malaria, helminthic infections, tuberculosis), and those that can increase both infectiousness and susceptibility, such as other sexually transmitted diseases (STDs).

The risk of transmission correlates with the concentration of HIV in the ejaculate (Figure 1; Chakraborty, *AIDS*, 2001). Compared with a probability of transmission of roughly 1 in 1,000 at a viral concentration of 50,000 HIV RNA copies/mL, the estimated probability of transmission increases markedly with

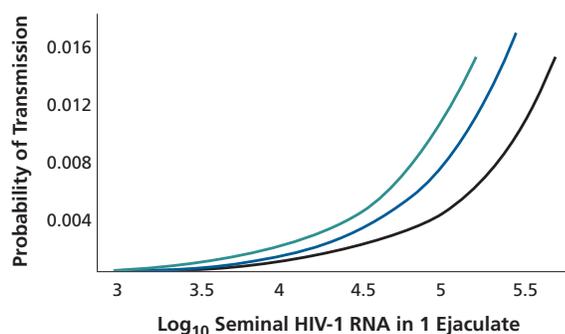


Figure 1. Estimated probability of male-to-female HIV-1 transmission per sexual contact according to seminal HIV RNA level and cervical CCR5 receptor cell count. Three lines represent receptor cells/ μ L counts: 75th percentile (green), 50th percentile (blue), 25th percentile (black). Adapted from Chakraborty et al, *AIDS*, 2001.

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increasing concentrations (eg, substantially greater than 1 in 100 at 1 million copies/mL). Figure 2 shows the relationship between viral load in semen and risk of transmission by disease stage. The high viral load present in semen during acute infection is associated with markedly increased risk of transmission. Although practices for diagnosing acute infection will change in the United States in the coming years, routine diagnosis depends on enzyme-linked immunosorbent assay (ELISA) with Western blot confirmation; this approach misses acute infection at this stage, since antibody testing is not positive for a few weeks after infection. The mononucleosis-like symptoms of acute HIV infection (present in approximately half of cases) are often missed or overlooked. Data indicate that about half of all cases of HIV transmission may occur during the early phase of HIV (Wawer, 10th CROI, 2003). This important window of transmission requires increased attention in efforts to reduce spread of HIV disease.

Effect of Other STDs on HIV Acquisition and Transmission

Other STDs can facilitate acquisition and transmission of HIV in a number of ways. On the susceptibility side, STDs can reduce physical and mechanical barriers of the virus (eg, by causing lesions in the mucosa), increase the numbers of receptor cells or density of their receptors (eg, by causing persistent inflammation), and produce a vaginal environment that is more conducive to transmission (eg, via presence of bacterial vaginosis and increased levels of anaerobes or amines). On the infectiousness side, STDs might evoke a more infectious HIV variant (Ping, *J Virol*, 2000) and can increase HIV concentrations in genital lesions, semen, or both (Cohen, *Lancet*, 1997). Cotransmission of HIV and another STD appears to be a common occurrence.

Numerous studies have shown a higher risk of acquiring HIV infection in the presence of STDs. Odds ratios for HIV seroconversion increase in the presence versus absence of chlamydia, gonorrhoea, and trichomoniasis and in the presence versus absence of genital ulcers. The evidence for facilitated HIV acquisition in the presence of herpes simplex virus 2 (HSV-2) infection is very

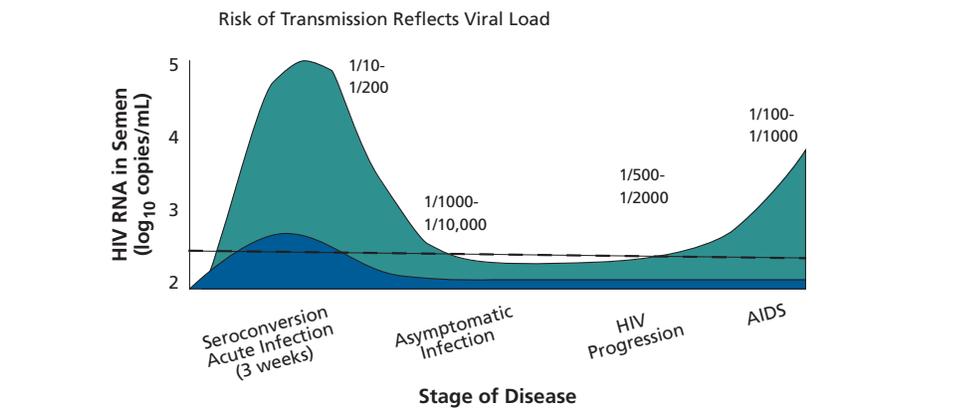


Figure 2. Risk of HIV transmission by seminal HIV RNA concentration and disease stage. Adapted from Cohen et al, *Lancet*, 2001.

compelling (Wald and Link, *J Infect Dis*, 2002). HSV-2 is ubiquitous in the United States, with approximately 1 in 5 persons having the disease. Among African Americans, nearly 70% acquire HSV-2 by age 50 years. Of the approximately 50 million affected individuals, only 1 million have lesions, but all infected individuals intermittently shed the virus. As shown in Figure 3, a recent study in India showed an increased risk of HIV acquisition in individuals with HSV-2-seropositive status compared with seronegative status and a dramatically increased risk of HIV acquisition in those with recently acquired HSV-2 infection (Reynolds, *J Infect Dis*, 2003). A study of HIV acquisition in 174 HIV-serodiscordant monogamous couples in Rakai, Uganda (Gray, *Lancet*, 2001; Grosskurth et al, *Lancet*, 2000), showed that risk of HIV acquisition was higher in HSV-2-seropositive partners of HIV-infected individuals with the lowest HIV viral load than in HSV-2-seronegative partners of HIV-infected individuals with the highest HIV viral load. From the transmission perspective, study of this population in Rakai showed that the risk of HIV transmission was markedly elevated for individuals with genital ulcers versus those without genital ulcers at every level of plasma HIV viral load (Gray, *Lancet*, 2001). In general, data on the effects of STDs on HIV transmission are inadequate, partly because STD studies have focused on acquisition rather than transmission. Indeed, such focus is prevalent in HIV clinics throughout the world, and more attention needs to be given to viewing the individual with HIV infection not only as an individual who needs care

for the disease, but as one who requires management to reduce the risk of transmitting the virus to others (*MMWR*, March 2003).

Reversing STD Amplification of HIV Transmission and Acquisition Risk

Goals of research to determine how best to reduce the increased risk of HIV transmission and acquisition associated with other STDs include demonstrating reduced genital tract HIV levels with STD treatment and demonstrating

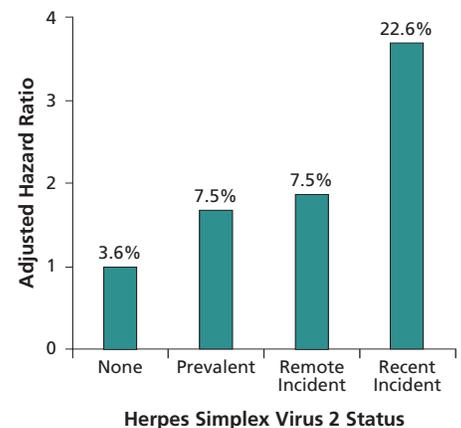


Figure 3. Risk of acquiring HIV-1, by herpes simplex virus type 2 (HSV-2) infection status, in a cohort of patients at 3 sexually transmitted infection clinics and 1 reproductive tract infection clinic in Pune, India, May 1993 through April 2000. HIV-1 incidence per 100 person-years is given above each column. Adapted from Reynolds et al, *J Infect Dis*, 2003.

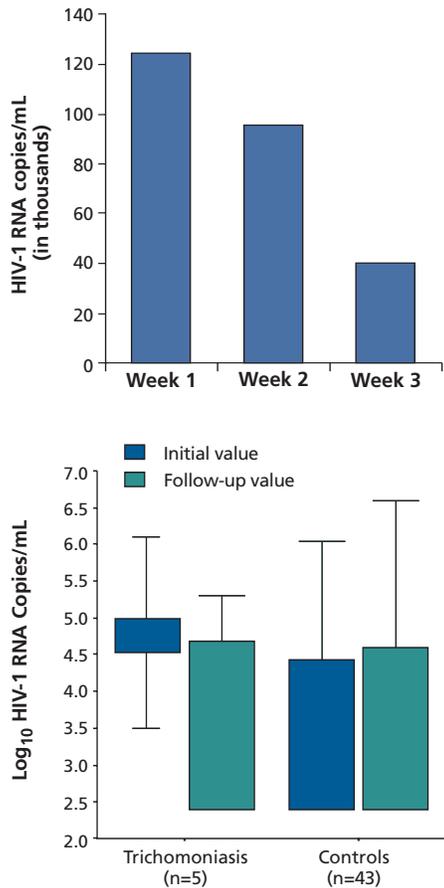


Figure 4. Top: Effect of a single ceftriaxone injection in reducing seminal HIV level in 86 men with urethritis (median values). Adapted from Cohen, *Lancet*, 1997. Bottom: Effect of treatment for trichomoniasis on genital tract viral load in 5 patients compared with controls. Adapted from Price et al, *Sex Transm Dis*, 2003.

reduced acquisition of HIV with STD therapy for the HIV-infected index case or the HIV-uninfected susceptible host. The University of North Carolina project in Malawi has provided data indicating the benefits of STD treatment in reducing HIV risk. Malawi has a population of 10 million, 90% of which is rural, and a per capita income of US \$190. Among the population, 900,000 are living with HIV disease; the disease prevalence is 15% in the adult population and 47% in the STD clinic population. In a study conducted in an STD clinic, a single injection of ceftriaxone for presumptive gonorrhea in 86 men with urethritis produced a reduction in median seminal HIV RNA concentration from approximately 120,000 copies/mL to 40,000 copies/mL over 3 weeks, with no change

occurring in plasma viral load (Figure 4, top). Such findings indicate that the amplified transmission risk associated with high seminal HIV level can indeed be markedly reduced. Similarly, treatment for trichomoniasis in the STD clinic produced a reduction in genital tract viral load (Figure 4, bottom).

Findings in clinics in Lilongwe, Malawi, emphasize both the potential association of other STDs with HIV acquisition risk and the need to focus attention on acute HIV infection. Of 1361 men screened for HIV infection in STD and dermatology clinics (Pilcher et al, *AIDS*, 2004), 40.6% were HIV antibody-positive. An additional 24 (1.8%) were found to have acute infection by positive plasma HIV RNA assay and negative antibody results. Individuals with acute HIV infection accounted for 11.4% of individuals with affected inguinal lymph nodes, 7.8% of those with genital ulcer, and 9.1% of those who admitted to sex with a commercial sex worker. Cases of acute HIV infection were found only in men with another STD. Median plasma HIV RNA levels were approximately 100,000 copies/mL in men with chronic infection and 1 million copies/mL in those with acute infection (Figure 5); since viral loads in semen are likely similar to the plasma viral loads, the men with acute infection carry a substantially higher risk of transmitting virus in sexual encounters.

Diagnosis of acute (incident) HIV provides an opportunity for emergent pre-

vention by identifying transmission chains. In North Carolina during 9 months in 2003 and 2004, routine assessment for HIV RNA in more than 100,000 samples collected in testing centers resulted in diagnosis of a substantial number of cases of acute infection and, through follow-up, permitted detection of an outbreak of HIV transmission in a college population. Routine identification of acute infection may also eventually provide greater opportunity for therapeutic intervention aimed at preventing the establishment of chronic infection, should such strategies ever prove to be feasible and effective. Finally, detection of acute HIV in STD clinics provides an opportunity for merging HIV and STD prevention efforts.

Antiviral Therapy to Prevent HIV Infection

A number of studies are under way to determine the logistics and effects of antiretroviral therapy or antiviral therapy for herpes simplex virus (HSV) infection in preventing HIV transmission. Five trials of preexposure prophylaxis are planned in which HIV-uninfected commercial sex workers will take tenofovir once daily to assess whether any effect on HIV acquisition can be ascertained. Studies of the logistics of postexposure antiretroviral prophylaxis are also being performed, in the absence of being able to sufficiently power a study to determine preventive effect. Two large-scale trials of antiviral

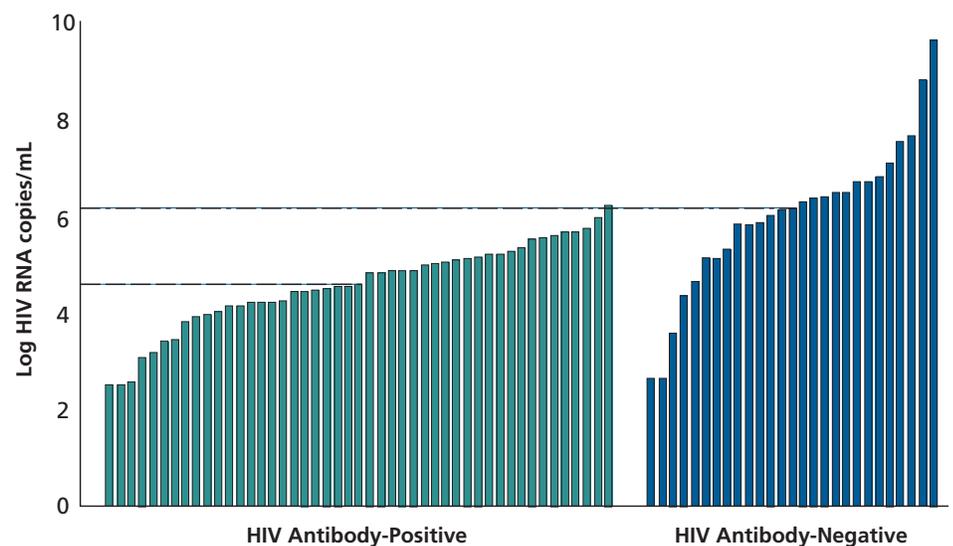


Figure 5. Plasma HIV RNA levels in men in a clinic population in Malawi with chronic (HIV antibody-positive) or acute (HIV antibody-negative) HIV infection. Adapted from Pilcher et al, *AIDS*, 2004.

therapy for HSV infection have been designed. In the HIV Prevention Trials Network (PTN) 039 study, HIV-seronegative high-risk individuals who are HSV-2-seropositive will take acyclovir daily for 1 year to determine whether such suppressive therapy reduces acquisition of HIV infection. In a trial funded by the Gates Foundation, individuals with HSV-2 and HIV infection who have HIV-seronegative sex partners will take acyclovir to determine if rate of transmission to their partners is thereby reduced. The PTN 052 study is a randomized trial of antiretroviral therapy to prevent HIV transmission in HIV-serodiscordant couples. It has previously been shown that triple-drug potent antiretroviral therapy markedly reduces HIV RNA concentration in seminal plasma. In the PTN 052 study, 1750 HIV-serodiscordant couples with the HIV-infected partner having CD4+ cell count greater than 300/ μ L and less than 500/ μ L will be enrolled at 7 sites (2 in Malawi, 2 in India, and 1 each in Thailand, Zimbabwe, and Brazil) and randomized to triple-drug antiretroviral therapy or primary care. The study is scheduled to go on for 7 years, and has a 90% power to detect a 35% reduction in sexual transmission of HIV.

Summary

After 20 years, HIV detection still depends on voluntary counseling and testing or detection of AIDS, and there are clear limitations to such an approach. HIV and STDs are probably frequently cotransmitted, and acute HIV infection can and should be detected in STD clinics and in patients with STDs. Detection of acute HIV infection is of benefit to prevention efforts. Identification and treatment of other STDs can be effective in reducing risk of HIV acquisition and transmission. Reduction of HIV concentrations in genital secretions, by whatever means, is likely to be effective in reducing HIV transmission.

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Review

Secrets and Safety in the Age of AIDS: Does HIV Disclosure Lead to Safer Sex?

Jane M. Simoni, PhD, and David W. Pantalone, MS

To fuel the HIV/AIDS epidemic, HIV-seropositive individuals must interact unsafely with HIV-seronegative individuals. Research indicates that up to one third of individuals diagnosed with HIV infection continue to have unprotected sex, at times without informing their sexual partners, who may be of negative or unknown serostatus.¹⁻³ Some research and public health interventions have focused on encouraging HIV-seropositive individuals to reveal their serostatus to their partners, predicated upon the assumption that disclosure will increase the safety of subsequent sexual activity with informed partners. This review examines the empirical literature on disclosure of HIV serostatus and subsequent sexual risk behaviors of HIV-infected individuals. Only 15 of the 23 studies reviewed provided data that allowed us to examine the association between disclosure and safer sex. Fewer still provided a methodologically sound analysis, and those that did provided conflicting results, often with significant effects limited to only 1 subgroup of participants. However, this failure to demonstrate a consistent association does not necessarily mean that disclosure is irrelevant to the practice of safer sex. The limitations of the research to date and implications for policy and practice are discussed.

“It is difficult to identify a more charged issue in AIDS prevention than that of nondisclosure of positive HIV status to sexual partners.” ^{4(p 949)}

Introduction

The annual number of new HIV infections in the United States has remained consistent, at approximately 40,000 per year, for more than 10 years, and the incidence of new infections among men who have sex with men (MSM) has begun to rise for the first time in as many years. The US Centers for Disease Control and Prevention (CDC) estimates that 77% of men and women with HIV/AIDS through 2002 were infected through sexual contact; thus, interventions aimed at reducing risky sexual behaviors have played and will continue to play an integral role in HIV prevention efforts.⁵

To fuel the epidemic, HIV-seropositive individuals must interact unsafely with HIV-seronegative individuals. In fact,

research indicates that up to one third of individuals diagnosed with HIV infection continue to have unprotected sex, at times without informing partners, who may be of negative or unknown serostatus.¹⁻³ Nondisclosure in such instances may involve active deception, not merely passive omission.⁶

In response to reports of increasing numbers of new infections, many public health officials are shifting their HIV prevention efforts from populations at risk for HIV infection to those individuals who are already infected. Notably, the CDC in 2000 initiated an innovative Serostatus Approach to Fighting the Epidemic (Project SAFE)⁷ and expanded these efforts in 2003 with the initiative “Advancing HIV Prevention: New Strategies for a Changing Epidemic.”⁸ The CDC and the public health establishment hope to slow the spread of the epidemic by, among other approaches, making HIV prevention a part of routine medical care, targeting individuals who are already infected, developing interventions to increase rapid testing, facilitating and expediting access to treatment, and decreasing transmission risk behaviors of HIV-seropositive individuals. A major component of preventive efforts directed at HIV-infected individuals involves encouraging them to disclose their HIV serostatus to their sexual partners.

Indeed, since 1988, the US Public Health Service has been recommending that all persons with HIV notify their sexual partners of their serostatus, and since 1987, the CDC has been mandating discussions of disclosure to partners in posttest counseling.⁹ Furthermore, a coalition of public and professional organizations representing a variety of health care providers has recently come forward to advocate for brief HIV prevention interventions in the context of routine medical care, including discussing safer sex practices with HIV-infected patients and encouraging them to disclose their HIV serostatus to all sexual partners.¹⁰

Underlying the attempt to encourage HIV-seropositive individuals to reveal their serostatus to their sexual partners is the assumption that disclosure will increase the safety of subsequent sexual activity with informed partners. As Norman et al remarked, “... it is reasonable to assume that a couple’s diligence in using condoms consistently and correctly would be enhanced by one partner’s disclosure of positive serostatus.”^{11(p541)} Miller and colleagues concurred that open communication is likely to facilitate safer sexual practices.¹² Indeed, dis-

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closure may facilitate the discussion of safe sexual activities or the negotiation of protection to prevent HIV. Moreover, it may increase the motivation of the informed partners to use protection, especially if they are uninfected.

Barriers to HIV Status Disclosure

However, significant disincentives and barriers to revealing one's HIV diagnosis persist.⁴ These include fears of rejection and abandonment, discriminating treatment such as eviction or termination of employment, retribution, violence, and other forms of abuse. Most of these possible outcomes are based on the social stigma that is widely acknowledged to be associated with an HIV diagnosis.¹³ Additionally, divulging that one is HIV-infected may expose other stigmatized behaviors or identities (eg, that one is gay or an injection drug user).¹⁴ Disempowered individuals may be particularly reluctant to risk these adverse reactions.

There is another impetus to remain silent about one's HIV serostatus. State legislatures and prosecutors emphasized from early in the epidemic that HIV-infected individuals who are sexually active may be liable to prosecution under assault, reckless endangerment, and attempted murder statutes. Particular cases and statutes now address exposure (whether or not condoms were involved) and not just infection.¹⁵ As of 1999, 31 states had statutes making sexual contact without disclosure a criminal offense.¹⁶ Also, in many states, health professionals are now mandated to report to the appropriate authorities HIV-seropositive individuals who have unprotected sex without informing their partners of their HIV infection.¹⁷ Civil liberty lawyers contend that these statutes may actually hamper disclosure by opening up the possibility of later arrest.

These psychosocial, practical, and legal barriers may contribute to the refusal of many individuals with HIV to divulge their serostatus to sexual partners. According to early studies before the advent of antiretroviral therapy, primarily of MSM on the West Coast, nondisclosure to sexual partners ranged from 2% to 52%, with disclosure generally more frequent to steady partners than to casual partners.¹⁸ In later studies in populations with more diverse samples, nondisclosure to sexual partners ranged from 13% to 41%.¹⁸

HIV Status Disclosure and Sexual Safety

Even when individuals surmount the barriers to disclosure and reveal their serostatus to sexual partners, there is no guarantee of their subsequent sexual safety. As Serovich and Mosach¹⁹ cautioned, disclosure does not mean individuals will use the information to protect themselves or others; in fact, some will knowingly place themselves at risk for infection. "Thus, it is erroneous to assume that disclosure would lead to safer behaviors or a lowering of risk," they concluded.^{19(p78)} Marks and Crepaz expressed a similar viewpoint, explaining that some HIV-infected individuals may disclose their serostatus but then eschew protection (what they termed "informed exposure"), possibly to attest to their commitment to the relationship or because of the effects of substance use prior to sexual activity.²⁰ Others engage in informed exposure because their partners made the final decision to forgo protection. In the extreme, a subset of the MSM community seeks out opportunities for

"barebacking," or the intentional participation in unprotected anal intercourse.²¹

Similarly, nondisclosure does not necessarily lead to unsafe sex. Some HIV-infected individuals may refrain from divulging their HIV serostatus to protect their privacy and avoid the negative consequences of disclosure, such as stigma or rejection. However, they may engage in protected sexual activity, perhaps out of a sense of personal responsibility toward their partners. Marks and Crepaz labeled this strategy "uninformed protection."²⁰

Clearly, disclosure is neither necessary nor sufficient to ensure safer sex; yet is the association between disclosure and subsequent sexual safety strong enough to warrant HIV-prevention policies that place considerable emphasis on disclosure? To address this important question, we reviewed the available empirical literature on the association between HIV disclosure and safer sex. We end with a discussion of the implications of the findings for future research, practice, and policy.

Review of the Literature

Methods

We searched PsychInfo and Medline for articles published through February 2004 that contained various combinations of the terms *HIV/AIDS*, *infected*, *infection*, *positive*, *seropositive*, *serostatus*, *disclosure*, *self-disclosure*, *nondisclosure*, *notification*, *protected*, *unprotected*, *sex*, *sexual*, *risk behavior*, *safer*, *partner*, and *prevention*. We consulted with experts in the field and inspected the references in the articles we obtained.

Findings

Only recently has there been an increase in studies examining disclosure or sexual practices among HIV-seropositive individuals. Still, very few studies examine both of these constructs among an HIV-infected population, and fewer still collect or report the data in ways that address the relationship between disclosure and safer sex. Table 1 presents the 15 studies we found that considered both disclosure and sexual safety, regardless of whether they were explicitly designed to assess the relationship between these 2 variables.

For each study, when available, we provided information about the sample (ie, number of subjects, basic demographic description, geographic location, and setting and date of recruitment) as well as any descriptive findings related to disclosure of HIV and to sexual safety. If any conclusions could be made about the association between disclosure and sexual safety, whether they were explicitly reported in the article or not, these were included as well. Studies in the table are grouped by the sex composition of their samples: only men, only women, or both men and women.

We located 10 studies of disclosure and sexual safety with only men in their samples. Two of these studies reported no data on the association between disclosure and sexual safety, and these were not included in the table.^{11,22} Findings among the remaining 8 studies were mixed, with 4 reporting no significant association.^{20,23-25} In both a multiethnic sample of men recruited in Los Angeles²⁶ and a sample of mostly gay or bisexual

Table 1. Published Studies Examining HIV Disclosure and Sexual Safety

Citation and Sample	Disclosure to Sexual Partners	Sexual Safety	Association Between Disclosure and Sexual Safety
Men Only (8)			
Crepaz and Marks (2003) ²³ 105 HIV+ male outpatients (64% African American) at HIV clinic in Los Angeles, 1996-1997	53% disclosed to most recent HIV- or HIV? partner	28% engaged in unprotected anal or vaginal intercourse with at-risk partner	Disclosure was NOT related to safer sex; however, disclosers who discussed safer sex (vs. those who disclosed only) had a higher prevalence of protected anal or vaginal intercourse
Marks and Crepaz (2001) ²⁰ 206 multiethnic HIV+ men whose most recent partner was HIV- or HIV?, recruited at an outpatient clinic in Los Angeles, 1995-1997	52% disclosed to HIV- or HIV? partner	25% engaged in unprotected anal or vaginal intercourse; unsafe sex was associated with substance use before sex, having an HIV? partner, less emotional involvement with partner, and more recent HIV diagnosis	Unsafe sex not more prevalent among disclosers than nondisclosers; strategies employed were 40% informed protection, 12% informed exposure, 35% uninformed protection, and 13% uninformed exposure
De Rosa and Marks (1998) ²⁶ 255 HIV+ multiethnic men who were sexually active in the last 2 months, recruited at 2 HIV outpatient clinics in Los Angeles, 1992-1993	93% told all their HIV+ partners, 57% told all their HIV- partners, and 23% told all their HIV? partners	Percentage of informed partners with whom all oral, anal, and vaginal sex was protected: 26%; for uninformed partners: 16%	Among HIV- but not HIV+ or HIV? partners: exclusively protected sexual activity occurred with a significantly greater percentage of informed than uninformed partners
Wolitski, Rietmeijer, Goldbaum, and Wilson (1998) ² 701 mainly white MSM from 4 US cities who recently received their HIV test result, 1987-1991	89% of HIV+ MSM informed primary sex partner; 34% informed nonprimary partner	16% of HIV+ MSM reported inconsistent condom use during anal intercourse with an uninformed nonprimary partner within the last 90 days	With primary partners, HIV+ disclosers and nondisclosers did not differ in sexual practices or condom use; with nonprimary partners, disclosers more likely than nondisclosers to report consistent condom use for insertive anal intercourse
Geary, King, Forsberg, Delaronde, and Parsons (1996) ²⁴ 167 suburban, 77% white HIV+ males (12-25 years old) with hemophilia in US	42% disclosed to their most recent partner	Among disclosers, 64% reported consistent condom use and 81% used a condom during last sexual intercourse; for nondisclosers, 66% and 85%	No significant association between disclosure and condom use
King, Delaronde, Dinoi, and Forsberg (1996) ²⁵ 306 HIV+ mostly white adolescent males with hemophilia, recruited at 11 hemophilia treatment centers, 1992	30% of individuals who used alcohol or other drugs (AOD) as a coping strategy for their diagnosis disclosed to all partners, 55% non-AOD copers	68% reported using condoms every time for sex	No difference in disclosure was found between those who used condoms every time for sex and those who were less consistent
Marks, Ruiz, Richardson, et al (1994) ¹ 609 HIV+ multiethnic men recruited at 2 HIV outpatient clinics in Los Angeles, 1991-1992	86% disclosed to HIV+ anal sex partners, 46% HIV-, 18% HIV?	9% engaged in unprotected insertive anal intercourse in the past 2 months (3.27 times more likely with HIV+ than HIV- or HIV? partners)	HIV+ respondents had unprotected insertive anal sex with 18% of HIV- partners who were informed and with 23% of HIV- partners who were not informed (26% and 28%, receptive)
Marks, Richardson, and Maldonado (1991) ²⁷ 138 HIV+ mainly Hispanic sexually active men, mostly gay or bisexual, recruited at a public HIV outpatient clinic in Los Angeles	48% of sexually active men disclosed to all partners; disclosure more common to HIV+ than HIV- partners	17% engaged in unprotected insertive anal intercourse with HIV- partners without disclosure (29%, receptive)	Disclosure to HIV+ partners generally occurred in combination with unprotected contact, whereas disclosure to HIV- partners generally occurred in combination with protected contact

HIV+ indicates HIV-seropositive; HIV-, HIV-seronegative; HIV?, HIV serostatus unknown.

continued, next page

Table 1. Published Studies Examining HIV Disclosure and Sexual Safety, continued

Citation and Sample	Disclosure to Sexual Partners	Sexual Safety	Association Between Disclosure and Sexual Safety
Women Only (1)			
Sturdevant, Belzer, Weissman, et al (2001) ³¹ 153 HIV+ and 90 HIV- sexually active adolescent girls (73% African American) from 13 US cities	Among HIV+ girls, disclosure related to perception partner was HIV+	59% of HIV+ and 80% of HIV- girls reported oral, anal, or vaginal sex without condom in past 3 months; among HIV+ girls, non-use of condoms was associated with older partner age, greater partner age difference, partner being HIV+, and longer duration of partnership	Among HIV+ girls, without disclosure (vs. with disclosure) less condom use was reported, after controlling for perception that partner was HIV+
Both Men and Women (6)			
Kalichman, Rompa, Luke, and Austin (2002) ³⁴ 269 HIV+ men and 114 HIV+ women (71% African American) from HIV agencies and clinics in Milwaukee, WI	78% of those with a regular partner had disclosed; 54% for nonregular partner	71% of the 257 who engaged in vaginal or anal intercourse in the last 3 months did so with serodiscordant partners	Percentage of protected intercourse with regular and nonregular serodiscordant partners (68-77%) was similar regardless of whether disclosure had occurred
D'Angelo, Abdalian, Sarr, Hoffman, and Belzer (2001) ³⁶ 203 HIV+ male and female adolescents who were part of an ongoing national multisite study	48% of 242 partners were informed; disclosure was more likely to HIV+ (vs. HIV?) and main (vs. casual) partners		Disclosers reported a mean of 14 unprotected sexual encounters (time frame not reported), 41% had HIV- partner(s); non-disclosers reported a mean of 10 unprotected sexual encounters, 67% had HIV- partner(s)
Kalichman and Nachimson (1999) ¹⁴ 165 HIV+ men and 101 HIV+ women sexually active in last 6 months (67% African American) from HIV agencies and clinics around Atlanta	59% had disclosed to at least 1 sex partner in the last 6 months; 78% of men and 79% of women had disclosed to last partner	77% of male and 89% of female nondisclosers had HIV- or HIV? partners in last 6 months	Among men but not women, disclosers reported higher rates of condom use (especially during anal intercourse) than nondisclosers
Nicolai, Dorst, Myers, and Kissinger (1999) ³⁵ 147 male and female HIV+ outpatients (88% African-American) participating in a risk reduction/partner notification intervention trial in New Orleans, LA, 1994-1998	76% informed (actively or passively) their last partner	76% reported consistent condom use; 85% reported using condoms the last time they had sex; 81% reported having only 1 partner in the previous 2 months	Those who used condoms consistently were 2.7 times more likely to have disclosed their status than those who reported inconsistent condom use; disclosure also related to condom use at last sex act, and having only 1 sex partner
Stein, Freedberg, Sullivan, et al (1998) ⁶ 203 multiethnic HIV+ men and women presenting for outpatient care in Boston, MA and Providence, RI, 1994-1996	60% had disclosed to all partners in the past 6 months; among individuals with 1 partner, 21% had not disclosed; 2+ partners, 58% did not disclose to all (ie, were inconsistent)	Overall, 43% reported using condoms all the time	Consistent disclosers, inconsistent disclosers, and nondisclosers reported similar rates of condom use; disclosure was related to fewer sexual partners
Sobel, Shine, DiPietro, and Rabinowitz (1996) ³³ 200 HIV+ male and female outpatients (ethnicity not reported) at a municipal hospital in the South Bronx, NY, 1994	77% disclosed	50% of 119 sexually active in last 4 months reported consistent condom use and 41% reported inconsistent or no condom use; the only difference between these 2 groups was in proportion of partners who were HIV- or HIV?, which were 65% and 49%, respectively	No difference in proportion of consistent condom users vs. inconsistent/non-users who disclosed

Articles not summarized because they reported no association between disclosure and safer sex include: Norman et al (1998)¹¹ and Prestage et al (2001)²² for the men-only group; Simoni et al (1995),²⁸ Clark et al (1997),²⁹ and Simoni et al (2000)³⁰ for the women-only group; and Kalichman (1999),³² Ciccarone et al (2003),⁴ and O'Brien et al (2003)¹⁸ for the group of studies examining both men and women.

ual Hispanic men in Los Angeles,²⁷ safer sex was more likely to occur in the context of disclosure with respect to HIV-seronegative partners but not for partners with a positive or unknown HIV serostatus. Disclosers reported a smaller proportion of partners with whom they had unprotected anal insertive sex than nondisclosers in a multiethnic sample of male outpatients from Los Angeles.¹ Finally, among a US sample of mostly white MSM, no association between disclosure and sexual safety was reported with primary partners, but among nonprimary partners, disclosers were more likely than nondisclosers to report consistent condom use for insertive anal sex.²

Four of the studies we located had samples exclusively of women, but 3 did not provide data on the association between disclosure and sexual safety²⁸⁻³⁰ and thus were omitted from the table. In all 4 studies, at least one third (and up to two thirds) of the sexually active HIV-seropositive women and girls reported unprotected sex. Data on disclosure, where reported, indicated that most informed their partners. Only Sturdevant and colleagues³¹ provided data addressing the association between HIV disclosure to sexual partners and safer sex. They concluded that disclosure influenced safer sex among adolescents, based on analyses controlling for the perception that a partner was also HIV-infected, which indicated that without disclosure (vs. with disclosure), participants reported less condom use. However, there was no partner-level analysis (condom use was computed for up to 3 partners for each participant), and the timing of disclosure in relation to safer sex was not considered. Additionally, these results were obtained from a combined sample of HIV-seronegative and HIV-seropositive individuals.

In 9 studies, both men and women participated. Three reports did not provide data that would allow us to determine the relationship between disclosure and safer sex.^{4,18,32} As shown in Table 1, 3 studies that did provide such data found no significant association. All 3 studies involved men and women who were recruited while seeking outpatient medical care: one recruited a sample in the Bronx, NY³³; another sampled a predominantly African-American population in Milwaukee, WI³⁴; and the third used comparable survey methods in both Providence, RI, and Boston, MA.⁶ Three studies did show an association between disclosure and safer sex. One outpatient sample in New Orleans demonstrated that consistent condom users were more likely to disclose their serostatus than inconsistent condom users.³⁵ A study of adolescents indicated an association between unprotected sexual encounters and disclosure.³⁶ The remaining study reported a significant association for men but not women, with higher rates of condom use (especially during anal intercourse) among disclosers than among nondisclosers.¹⁴

In summary, only 15 of the 23 studies reviewed provided data that allowed us to examine the association between disclosure and safer sex. Fewer still provided a methodologically sound analysis, especially with respect to women. Those that did provided conflicting results, often with a significant effect limited to a subgroup of participants, such as HIV-seronegative or nonprimary partners. These findings provide little justification for concluding, as did Chen and colleagues, that there is an "urgent need" for prevention messages promoting disclosure of HIV serostatus to sexual partners.^{37(p169)} (Note that their recommendation was based on a study that did not assess disclosure.)

Limitations of Research to Date

Lack of Partner-Level Analyses and Nonassessment of Timing

Our review of the studies in Table 1 revealed several methodological limitations of the published literature on disclosure and unsafe sex that future researchers should avoid. The greatest concerns are related: the dearth of partner-level analyses and the failure to assess the timing of HIV disclosure in relation to sexual activity. Researchers need to inquire about specific partners and perhaps even particular sexual incidents. It does not suffice to know whether an individual has informed partners and then whether protection was used over some specific time-frame. Many studies failed to accurately assess timing, if they considered the issue at all. For example, Ciccarone and colleagues⁴ acknowledged they did not assess the timing of unprotected sex in relation to disclosure (they assessed only timing of any sex) and that it was possible that some participants had unprotected sex only after disclosing their positive serostatus. They proceeded to label this scenario "unlikely," although that possibility is exactly what studies like theirs are attempting to investigate. Furthermore, it is not sufficient to simply assess the number of partners and whether disclosure and safer sex ever occurred with each because, again, we cannot be sure that disclosure preceded safer sex. Of course, even if we know that disclosure preceded safer sex, the causal association is not assured.

Confounding Variables

Another major methodological limitation we noted was the failure of most studies to account for confounding variables. Numerous factors have been shown to be associated with disclosure, sexual safety, or both, and any of these might account for a demonstrated association or lack of association between disclosure and safer sex. Specifically, type of partnership should always be considered because research has shown it is often related to both disclosure and safer sex. Also, including partnership variables can help researchers avoid the problem of a third variable. As Sturdevant and colleagues noted in their study of adolescent girls, "There may be some quality to the relationship, unmeasured in the study, which may not only facilitate disclosure but permits more effective condom negotiation."^{31(p68)} Research on partnership variables has demonstrated that "main/steady/close" partnerships are more likely to involve disclosure and more likely to involve unprotected sexual activity than "other/casual/unfamiliar" partnerships.³⁸ Also, as demonstrated among samples of both gay and bisexual men and heterosexual women, sex without disclosure is more likely to occur in nonexclusive than exclusive partnerships.^{4,29} Finally, among HIV-infected women in steady partnerships, Simoni and colleagues found that being married, having a longer relationship, and receiving greater partner support were related to safer sex.³⁰

Factors beyond the partnership might also confound the relationship between disclosure and safer sex. Specifically, illness severity and length of time since HIV diagnosis have been shown to positively relate to disclosure.³⁹ Younger age has been

related to less occurrence of disclosure to a main partner¹⁸ and greater frequency of overall disclosure,²⁸ as well as riskier sexual practice after notification⁴⁰ and greater risk for transmitting HIV.³² Perception that a partner's viral load is low or below detection has been associated with unprotected sex among HIV-infected MSM.¹³ Race and ethnicity as well as level of acculturation among Latinos have been associated with both disclosure^{28,41} and risky behavior.⁴² Researchers also need to consider the context of the sexual activity, which might affect disclosure. As Serovich and Mosack explained, there is a difference between making love in one's private residence, where some verbal exchange might be expected, and an anonymous sexual encounter in a public restroom or other public sex venue, where norms of silence may prevail.¹⁹ Finally, Marks and Crepaz found that different patterns of disclosure and sexual risk behavior were related to annual income and the use of alcohol or drugs before sex, among other factors.²⁰

HIV Serostatus of Partner

Another partner variable that is crucial to include in any analysis of disclosure or safer sex is the HIV serostatus of the sexual partner, which has consistently been shown to correlate with both of these variables. For example, in 1994 Marks and colleagues reported that HIV-infected MSM disclosed to 90% of partners who were HIV-seropositive, 45% of partners who were HIV-seronegative, and 17% of partners with unknown serostatus.¹ Additionally, Marks and colleagues reported that disclosure to HIV-seropositive partners generally occurred in combination with unprotected contact, whereas disclosure to HIV-seronegative partners generally occurred in combination with protected contact.²⁷ HIV-infected individuals may be more likely to disclose to a partner who they know is HIV-seropositive for many reasons, such as their assessment of lowered risk of rejection. They then might have unsafe sex with this partner because they feel less threatening to the partner's health. Indeed, in a recent qualitative study, Sheon and Crosby found that disclosure of HIV serostatus appeared to facilitate unprotected anal intercourse among MSM in San Francisco.⁴³

Sex and Sexual Orientation

Sex is another important variable with likely effects on disclosure and safer sexual behavior that many studies have ignored, often collapsing data across subgroups of men and women and making it impossible to determine direct effects of male or female sex. Dividing men into self-identified gay or bisexual versus heterosexual subgroups, as did Ciccarone and colleagues,⁴ also may be illuminating because behavioral norms may differ in these respective communities. As these researchers pointed out, messages in the gay community encouraging the assumption that every partner is HIV-seropositive may have contributed to norms that consider disclosure optional.⁴ Perhaps, alternatively, dividing samples into MSM and others (eg, men on the "down low," that is, men who have sex with men but who identify as heterosexual, and often wives or girlfriends with whom they have unprotected sex⁴⁴) or separating self-identified gay from bisexual men may be necessary

to avoid masking the effects of group differences in the potentially culturally bound behaviors of disclosure and safer sex.

Definitions of Unprotected Sex and Disclosure

Another limitation of the current research that needs to be addressed in future work is the imprecise and nonstandard operationalization of unprotected sex. Ciccarone and colleagues conducted one of the few studies to explicitly define unsafe sex as "unprotected anal insertive sex to ejaculation"^{4(p951)}; in other studies, precise terminology is lacking. Some studies included unprotected oral contact under the category of unsafe sex (eg, Simoni et al^{28,30}), others limited their definition to unprotected anal or vaginal intercourse (eg, Crepaz and Marks²³), and some studies did not define the term "sex" at all for their participants (eg, Stein et al⁶). In one of the few studies that acknowledged this potential problem, Marks and Crepaz²⁰ conducted a secondary analysis of their data, widening their definition of unsafe sex to include unprotected insertive oral sex. The prevalence of unsafe sex in their sample increased from 25% to 40%; however, the association between disclosure and safer sex remained statistically nonsignificant.

Disclosure itself, though seemingly an uncomplicated behavior, also needs to be more explicitly operationalized and assessed. Some individuals may think they have disclosed their diagnosis when, in fact, their partners remain unaware of their serostatus. For example, some HIV-seropositive men who encounter HIV-seronegative men willing to engage in unprotected anal intercourse will assume their partners must also be HIV-infected, because no one would choose to put himself at risk of infection. The HIV-seronegative partners, in turn, may assume that their partners are also HIV-seronegative, otherwise, why would these men be putting others at risk? As Marks and Crepaz pointed out, disclosure may be a direct statement of the diagnosis or a more subtle communication such as leaving antiretroviral medications within view.²⁰ Among MSM in San Francisco, inferred preferences for sexual position, such as "top" or "bottom," are often construed as tacit disclosures of serostatus.⁴³

Social Desirability

Finally, the effect of socially desirable reporting, which most authors failed to mention, may be a potential limitation in current studies and one that needs to be addressed in future research. Participants in the studies we reviewed were asked to acknowledge behaviors that are at least unethical if not also illegal. Few individuals could be expected to admit easily that they had knowingly exposed loved ones to a life-threatening illness without informing them of their risk. The stigmatizing nature of these assessed behaviors most likely has resulted in underreporting of their prevalence. Most problematic for the interpretation would be participants who might acknowledge one behavior but not the other, perhaps reasoning that it is not so incriminating to acknowledge having unprotected sex if they have at least divulged their HIV serostatus, or vice-versa. These observations might partially account for reports of the lack of a demonstrated association between disclosure and safer sex.

The social desirability a participant encounters in a study may be affected by the study's design and procedures. For example, studies that do not assure anonymity or that are conducted by persons affiliated with participants' clinic care may be particularly susceptible to the underreporting of nondisclosure and unsafe sex. Studies conducted in conjunction with behavioral counseling may promote response biases by establishing socially desirable behaviors.⁴⁵ Longitudinal studies, which exclude patients unwilling to adhere to follow-up visits, are prone to selection bias, which may affect reported rates of disclosure or safer sex. In fact, O'Brien and colleagues found that nondisclosure to sexual partners was less than 30% in 4 studies that were set in the context of longitudinal studies with behavioral counseling and greater than 30% in 6 of 8 studies that did not require follow-up or include counseling.¹⁸

Recommendations for Future Research

It is, of course, easier to critique past studies than to design and conduct improved ones. The host of methodological issues raised here underlies the difficulty of empirically determining whether disclosure of one's HIV-positive serostatus leads in a causal manner to safer sex. Indeed, it is difficult to imagine what the ideal study would involve. For obvious practical and ethical reasons, a researcher could not simply randomly assign HIV-infected people to "disclosure" or "nondisclosure" conditions and then assess the safety of their sexual activity with subsequent partners. Furthermore, decisions regarding sexual safety often cannot be made unilaterally and, even if they are, they may vary according to sexual partner. Most problematic is that disclosure, of course, does not actually "cause" safer sex any more than nondisclosure "causes" riskier sex. As suggested by the apt title of Marks and Crepaz, sexual activity takes place "within the context of" disclosure.²⁰ Finally, no design can possibly control for every possible third variable. For example, ethical responsibility might lead an individual to decide always to disclose and always to use condoms. In this case, the disclosure per se is not the cause or main reason for the safer sexual practices.

Theory specific to the disclosure of HIV is rare, and few studies have investigated any theoretical hypotheses empirically. Early theoretical work on self-disclosure (eg, Jourard, 1971⁴⁶), is not highly relevant to the issue of HIV as it does not consider context (eg, the emotionally charged moment when disclosure often takes place), content (the highly stigmatizing nature of an HIV diagnosis), or consequences (which are often deleterious and include the potential loss of social support). Further, the work to date generally neglects cultural values (eg, the Latino value of "familismo"^{28,41}) and the notion that disclosures can be dependent on contextual and situational factors (eg, the discloser's relationship to the target individual).⁴⁷ Mason and colleagues⁴¹ assert that the theory of reasoned action⁴⁸ can explain most of the research on disclosure, although this hypothesis has not been fully tested. Building on work from earlier in the epidemic (eg, Marks, 1992⁴⁹), in one of the few conceptual pieces on the topic, Serovich found good support for the consequence theory, which presumes that the relationship between disease progression and disclosure is

moderated by anticipated consequences of disclosure.⁵⁰ However, this theory was still not predictive of disclosure to sexual partners. Additional empirical studies on theoretical aspects of HIV serostatus disclosure to sexual partners are clearly warranted.

A final recommendation for future research in this area is the need for more qualitative studies that focus specifically on HIV serostatus disclosure to sexual partners (eg,^{43,51-54}). Many studies have used qualitative methodologies to focus on the consequences of disclosure to friends, employers, and even children. These studies are instructive but do not directly address the idea of safer-sex negotiation with a partner after disclosure has occurred. The complex and multiple emotions and motivations underlying decisions about disclosure and sexual protection might best be illuminated with qualitative methods of inquiry. For example, as Wolitski and colleagues² uncovered, disincentives to protected sex include the belief that condoms diminish sexual pleasure and intimacy, the desire to avoid acknowledging the risk of HIV infection, the heat of the moment, a shared sense of fatalism, and the desire to conceive among heterosexual couples. One theme that emerged in a recent study is that many MSM used substance use during sex as justification for not asking about or revealing HIV serostatus.⁴³ Ominously, these authors further concluded that the "men's fundamental unwillingness to ask or disclose suggests that [public health] messages focusing on the importance of knowing a partner's serostatus are misguided."^{43(p2111)} Clearly, qualitative work on disclosure can be extremely enlightening regarding the cultural mores of subsets of the population, as well as the relative utility of prevention messages that focus on disclosure.

Summary and Conclusions

In a review of the published literature, we located 23 empirical studies on disclosure of HIV serostatus and sexual safety, among which 15 provided some data on the association between these 2 variables. However, methodological limitations in most of these precluded our making interpretations about the association of the 2 variables, let alone determining whether they were causally connected. In most of the studies that did adequately examine the association, the variables were not related. The implicit assumption that HIV serostatus disclosure leads to sexual safety may not be supported empirically because of informed exposure and uninformed protection, as detailed by Marks and Crepaz.²⁰ With respect to prevention efforts, the good news is that uninformed exposure is relatively rare; the bad news is that even a small number of such cases can fuel the epidemic.

The failure to demonstrate a consistent association between disclosure and safer sex does not necessarily mean that disclosure is irrelevant to the practice of safer sex; rather, as Marks and Crepaz suggested, it may be related in part to the frequency of uninformed protection and informed exposure.²⁰ Alternatively, Crepaz and Marks offered that disclosure does not always correlate with safer sex because disclosure is a relatively general communication.²³ It is insufficient to ensure the use of protection because it fails to focus specifically on the target

behavior of safer sex. The key to safer sex, as they suggested and their data supported, is whether the partners have explicitly discussed using protection and reached agreement about it.

Future researchers face the daunting task of designing and implementing methodologically rigorous studies that specifically measure disclosure and unprotected sexual behavior,

employ a partner-level analysis, and control for potential confounding variables, including the partner's HIV serostatus and the type of relationship. Research suggests that practitioners from different disciplines and in numerous venues should not stop at encouraging disclosure of serostatus but, in addition, make the effort to help HIV-infected individuals develop the

Table 2. Practice and Policy Implications for Health Care Practitioners From Existing Empiric Literature on HIV Disclosure and Sexual Safety

Providers' Roles	<p>Health care practitioners of all types can encourage HIV-positive patients to discuss their serostatus with their sexual partners.^{10,15}</p> <p>Mental health providers can assist HIV-infected individuals in divulging their diagnosis to sexual partners⁵⁶ using the following strategies:</p> <ol style="list-style-type: none"> 1) Encourage clients to create a list of all persons they would consider telling 2) Have clients focus on those to be told first, as disclosure to these individuals should be planned strategically 3) Clients should pick the time and place (a relaxed atmosphere with minimal distractions, at a time when the target person is not tired, stressed, or emotionally unavailable) 4) Clients should consider how much they want to share regarding the activities that led to their HIV infection, including the option of not discussing the topic at all 	<ol style="list-style-type: none"> 5) Role-playing the likely scenarios can facilitate a successful exchange 6) Forewarn clients that disclosure is not a one-time event, but an unfolding process involving follow-up conversations
Populations to Target	<ul style="list-style-type: none"> • Certain subgroups of HIV-seropositive individuals are more likely to withhold disclosure and engage in risky sex. These include those who: <ul style="list-style-type: none"> – Recently tested seropositive for HIV²³ – Are of lower socioeconomic status²³ – Have experience with at-risk partners²³ – Are younger than 25 years of age^{18,40} – Are involved in HIV-serodiscordant relationships⁵⁷ 	<ul style="list-style-type: none"> • Interventions may be particularly effective among gay men and their primary partners¹
Intervention Strategies Should:	<ul style="list-style-type: none"> • Be more intensive^{26,58} • Consider that disclosure is a process and not a one-time event²⁶ • Guard against furthering the stigmatization or marginalization of HIV-infected individuals² • Focus interventions on communication-skills training generally: encourage disclosure and also target negotiating condom use^{11,23} • With regard to HIV-seropositive women, who can control disclosure but not necessarily condom use^{31,59,60}: <ul style="list-style-type: none"> – Consider gender roles – Acknowledge power differentials – Incorporate male partners 	<ul style="list-style-type: none"> • Attempt to understand the reasons each individual chooses to disclose or not and address those issues specifically: <ul style="list-style-type: none"> – Focus altruistically on the needs and rights of partners¹⁹ – Focus on personal benefits to disclosers, such as avoiding additional STDs or HIV superinfection that could limit the effectiveness of current or future antiretroviral treatment^{61,62} • Incorporate, where appropriate, voluntary health department contact-tracing programs¹⁵ • Tailor messages to circumstantial variables; for example, encourage sexually uninvolved men to disclose by addressing commonly perceived negative consequences of disclosing to prospective partners¹¹
Policy Makers Should:	<ul style="list-style-type: none"> • Focus on increasing condom use and other safer sexual techniques rather than on disclosure specifically or exclusively^{23,24} • Consider that only a small minority of HIV-infected adults do not disclose AND do not practice safer sex and that many of these individuals have HIV-seropositive partners²⁰ 	<ul style="list-style-type: none"> • Consider that advocating for disclosure may lead to a false sense of security: HIV-seronegative individuals might adjust their sexual safety based on a potential partner's disclosure, but a partner claiming to be HIV-seronegative may be unaware of an actual HIV infection

communication skills necessary to explicitly negotiate safer sex (see Table 2). Policymakers should rely on empirical evidence to guide their decisions in this arena. Based on the findings of this review, although information about a partner's HIV serostatus may play a role in one's choices about safer sex, disclosure alone does not automatically lead to safer sex in the way one might presume.

At this point in the epidemic, given the lack of success in decreasing the number of annual new infections, public health advocates might emphasize more innovative prevention strategies that rely on multiple target areas (eg, HIV education, availability of barrier protection, communication skills to negotiate safer sex) and multiple messengers (eg, primary care physician, mental health counselor, public health outreach worker). One lesson we learned from this review of HIV disclosure and sexual behavior may be useful in these endeavors: namely, human relationships and sexual interactions are vastly complex, with myriad motivations, incentives, and risks involved. Deceptively

simple HIV prevention interventions such as encouraging disclosure will probably never succeed on their own.

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Update of the Drug Resistance Mutations in HIV-1: 2004

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The International AIDS Society-USA (IAS-USA) Drug Resistance Mutations Group is a volunteer panel of experts in HIV-1 virology, research, and clinical care that meets regularly to review and interpret new data on HIV-1 resistance to antiretroviral drugs, and to maintain a list of mutations that may contribute to a reduced virologic response to drug.

The mutations included on the figures have been identified by 1 or more of the following criteria: (1) *in vitro* passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded-access mechanisms are included. Additional information on the mutations is provided, where necessary, in the accompanying user notes. Although the group works to maintain a complete and current list of these mutations, it cannot be assumed that the list presented here is exhaustive, and readers are encouraged to consult the literature and experts in the field for clarification or more information about mutations not listed in the figure.

The IAS-USA drug resistance mutations figures are designed for use in identifying mutations associated with HIV-1 resistance and in making therapeutic decisions. Care should be taken when using this list of mutations for surveillance or epidemiolog-

ic studies of transmission of drug-resistant virus. A number of amino acid substitutions, particularly minor mutations, represent polymorphisms that in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

In the context of making clinical decisions regarding antiretroviral therapy, evaluating the results of HIV genotypic testing includes: (1) assessing whether the pattern or absence of a pattern in the mutations is consistent with the patient's antiretroviral history; (2) recognizing that in the absence of drug (selection pressure), resistant strains may be present at levels below the limit of detection of the test (analyzing stored samples, collected under selection pressure, could be useful in this setting); and (3) recognizing that virologic failure of the first regimen typically involves HIV-1 isolates with resistance to only 1 or 2 of the drugs in the regimen (in this setting, resistance most commonly develops to lamivudine or the nonnucleoside reverse transcriptase inhibitors).¹⁻⁵ This paradox may involve patient nonadherence, laboratory error, drug-drug interactions leading to subtherapeutic drug levels, and possibly compartmental issues, indicating that drugs may not reach optimal levels in specific cellular or tissue reservoirs.

A copy of the current recommendations for antiretroviral resistance testing from the IAS-USA HIV Resistance Testing Guidelines Panel⁶ can be found on the IAS-USA Web site at www.iasusa.org.

This October 2004 version of the IAS-USA drug resistance mutations figures replaces the version published in this journal in October 2003.

Revisions to the Figures in the October 2004 Update

In the nucleoside and nucleotide reverse transcriptase inhibitor (nRTI) category, the vertical pink lines that represent nucleoside- or nucleotide-associated mutations (NAMs) have been added to emtricitabine (see user note 2 on NAMs). The figures had previously identified the NAMs for lamivudine but not for emtricitabine (these 2 drugs are assumed to be similar). However, based on available data, there are insufficient data to suggest any *in vivo* difference in NAM resistance patterns between emtricitabine and lamivudine.

In the protease inhibitor (PI) category, the I84V mutation is now listed as a major mutation for atazanavir. The mutation is associated with a reduced virologic response to atazanavir and it meets the group's criteria for a "major" mutation (see user notes 18 and 23).^{7,8}

In addition, for both atazanavir and ritonavir-boosted tipranavir, the L33V mutation has been removed. The L33I/F mutations for both drugs remain, as recent studies support.⁹ The L33V appears (continued, page 124)

The IAS-USA Drug Resistance Mutations Group was originally a subgroup of the IAS-USA HIV Resistance Testing Panel. In 2000, the Drug Resistance Mutations Group became an independent entity and forged a collaborative process to identify key HIV-1 drug resistance mutations. The goal of the group is to quickly deliver accurate and unbiased information to clinical practitioners on HIV-1 resistance.

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MUTATIONS IN THE REVERSE TRANSCRIPTASE GENE ASSOCIATED WITH RESISTANCE TO REVERSE TRANSCRIPTASE INHIBITORS

Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

Multi-nRTI Resistance: 151 Complex	A	V	F	F	Q					
	62	75	77	116	151					
	V	I	L	Y	M					
Multi-nRTI Resistance: 69 Insertion Complex ¹	M	A	D	▼	K			L	T	K
	41	62	67	69	70			210	215	219
	L	V	N	Insert	R			W	Y	Q
								F	E	E
Multi-nRTI Resistance: NAMs ²	M	E	D	K	V			L	T	K
	41	44	67	70	118			210	215	219
	L	D	N	R	I			W	Y	Q
								F	E	E
Zidovudine ^{3,4}	M	E	D	K	V			L	T	K
	41	44	67	70	118			210	215	219
	L	D	N	R	I			W	Y	Q
								F	E	E
Stavudine ^{3,5}	M	E	K	D	K	V		L	T	K
	41	44	65	67	70	118		210	215	219
	L	D	R	N	R	I		W	Y	Q
								F	E	E
Didanosine ^{6,7}			K		L					
			65		74					
			R		V					
Zalcitabine			K	T	L		M			
			65	69	74		184			
			R	D	V		V			
Abacavir ⁸			K		L	Y	M			
			65		74	115	184			
			R		V	F	V			
Lamivudine ^{9,10}	E	K			V		M			
	44	65			118		184			
	D	R			I		V			
							I			
Emtricitabine ¹⁰		K					M			
		65					184			
		R					V			
							I			
Tenofovir ^{3,11}		K								
		65								
		R								

Nonnucleoside Reverse Transcriptase Inhibitors

Multi-NNRTI Resistance ^{12,13}		K	V			Y			
		103	106			188			
		N	M			L			
Multi-NNRTI Resistance: Accumulation of Mutations ¹⁴	L	V			Y	G		M	
	100	106			181	190		230	
	I	A			C	S		L	
					I	A			
Nevirapine	L	K	V	V	Y	Y	G		
	100	103	106	108	181	188	190		
	I	N	A	I	C	C	A		
			M		I	L	H		
Delavirdine ¹⁵		K	V		Y	Y		P	
		103	106		181	188		236	
		N	M		C	L		L	
Efavirenz ¹⁵⁻¹⁷	L	K	V	V	Y	Y	G		P
	100	103	106	108	181	188	190		225
	I	N	M	I	C	L	S		H
					I	A			

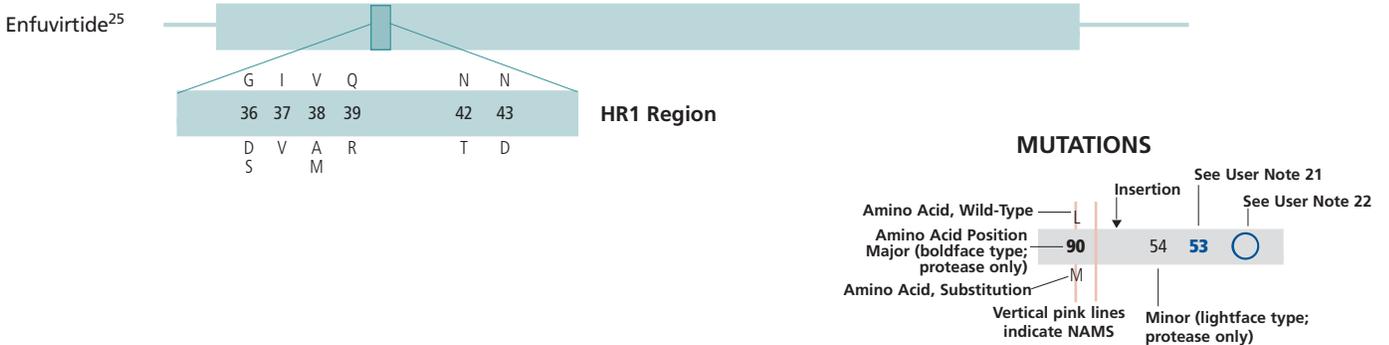
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MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS

Protease Inhibitors¹⁸

Multi-PI Resistance: Accumulation of Mutations ¹⁹	L	V					M	I	V					I	L		
	10	32					46	54	82					84	90		
	F	I					I	V	A					V	M		
	I						L	M	F					A			
	R							L	T					C			
	V							L	S								
Indinavir ²⁰	L	K	L	V	M	M	I	A		G	V	V	I	L			
	10	20	24	32	36	46	54	71	73	77	82	84	90				
	I	M	I	I	I	I	V	V	S	I	A	V	M				
	R	R				L		T	A		F						
	V										T						
Ritonavir	L	K		V	L	M	M	I	A		V	V	I	L			
	10	20		32	33	36	46	54	71	77	82	84	90				
	F	M		I	F	I	I	V		I	A	V	M				
	I	R				I		L			F						
	V										T						
Saquinavir	L						G	I	A		G	V	V	I	L		
	10						48	54	71	73	77	82	84	90			
	I						V	V	V	S	I	A	V	M			
	R							L	T								
	V																
Nelfinavir	L	D			M	M	A			V	V	I	N	L			
	10	30			36	46	71	77	82	84	88	90					
	F	N			I	I	V	I	A	V	D	M					
	I					L	T		F	V	S						
									T		S						
(Fos) amprenavir	L	V					M	I	I	G		I	L				
	10	32					46	47	50	54	73	84	90				
	F	I					I	V	V	L	S	V	M				
	I						L			V							
	R									M							
	V																
Lopinavir/Ritonavir ^{21,22}	L	K	L	V	L	M	I	I	F	I	L	A	G	V	I	L	
	10	20	24	32	33	46	47	50	53	54	63	71	73	82	84	90	
	F	M	I	I	F	I	V	V	L	V	P	V	S	A	V	M	
	I	R				L	A			L		T		F			
	V													T			
														S			
Atazanavir ²³	L	K	L	V	L	M	M	G	I	I	A		G	V	I	N	L
	10	20	24	32	33	36	46	48	50	54	71	73	82	84	88	90	
	F	R	I	I	I	I	V	L	L	V	C	A	V	S	M		
	I	M			F	L					S						
	R	I			L	V					T						
	V										A						
Tipranavir/Ritonavir (expanded access) ²⁴	L	K	L			M	I					V	I	L			
	10	20	33			46	54					82	84	90			
	I	M	I			I	V					A	V	M			
	V	L	F									F					
		T										L					
												T					

MUTATIONS IN THE GP41 ENVELOPE GENE ASSOCIATED WITH RESISTANCE TO ENTRY INHIBITORS



User Notes

The IAS–USA Drug Resistance Mutations Group reviews new data on HIV drug resistance in order to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug. These mutations have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded access protocols are included. Additional information on the mutations is provided, where necessary, in these user notes.

1. The 69 insertion complex, consisting of a mutation at codon 69 (typically T69S) and followed by an insertion of 2 or more amino acids (S-S, S-A, S-G, or others), is associated with resistance to all FDA-approved nRTIs. The 69 insertion complex is often accompanied by mutations at other sites. Some other amino acid changes from the wild-type T in codon 69 without the insertion may also be associated with broad nRTI resistance.

2. The nRTI-associated mutations (NAMs), including M41L, E44D, D67N, K70R, V118I, L210W, T215Y/F, and K219Q/E, are associated with cross-resistance to nRTIs and are represented by vertical pink lines. Zidovudine and stavudine select for these mutations, and as such, the positions and mutations are indicated on the bars along with the pink lines. For other nRTIs, the NAMs are not commonly selected by those drugs, but the presence of the NAMs confers cross-resistance to the drugs. This is represented by pink lines only at the positions.

The E44D and V118I mutations are listed as NAMs. In a recent study, the E44D and V118I mutations were more common in virus from patients who had been on zidovudine and lamivudine, and were associated with higher-level resistance to zidovudine (Stoeckli et al, *Antimicrob Agents Chemother*, 2002). When present together with other NAMs, the E44D and V118I mutations confer resistance to lamivudine. Analysis from the AIDS Clinical Trials Group (ACTG) study 136 has shown that the V118I mutation is commonly selected by a zidovudine/didanosine regimen (Shafer et al, *J Infect Dis*, 1995). Findings from ACTG study

241 have shown that the E44D mutation is commonly selected by zidovudine/didanosine (Hanna et al, *J Infect Dis*, 2002) and that the E44D mutation is associated with a significantly worse response to treatment with zidovudine and didanosine, with or without nevirapine (Precious et al, *AIDS*, 2000). The significance of E44D or V118I when each occurs in isolation is unknown (Romano et al, *J Infect Dis*, 2002; Walter et al, *Antimicrob Agents Chemother*, 2002; Girouard et al, *Antivir Ther*, 2002).

3. The M184V mutation may enhance susceptibility to zidovudine, stavudine, or tenofovir. This effect may be overcome by an accumulation of NAMs or other mutations. The clinical significance of this effect is not known.

4. Data on revertant mutations in codon 215 indicate that the T215D/C/S/E/N/A/V substitutions confer increased risk of virologic failure of zidovudine and stavudine in antiretroviral-naïve adults starting therapy with these drugs (Riva et al, *Antivir Ther*, 2002). In vitro studies and preliminary clinical studies suggest that the T215Y mutant may emerge quickly from these mutations in the presence of zidovudine or stavudine (Garcia-Lerma et al, *Proc Natl Acad Sci USA*, 2001; Lanier et al, *Antivir Ther*, 2002; Riva et al, *Antivir Ther*, 2002).

5. Mutations at codon 75 (V75T/M/S/A) have been observed in vitro and may confer a low-level change in susceptibility to stavudine (Lacey et al, *Antimicrob Agents Chemother*, 1994).

6. The K65R mutation or the L74V mutation, alone or in combination with the NAMs or T69D/N can lead to didanosine resistance.

7. Based on preliminary, yet-unpublished data, the M184V mutation does not appear to have a negative impact on in vivo responses to didanosine, even though the mutation reduces susceptibility in vitro (Winters et al, *Antivir Ther*, 2002; Eron et al, *Antivir Ther*, 2002; Pozniak et al, *Antivir Ther*, 2002).

8. When present with NAMs, the M184V mutation contributes to reduced susceptibility to abacavir and is associated with impaired response in vivo. However, when present alone, the M184V mutation does not appear to be associated with a reduced virologic response to abacavir in vivo (Harrigan et al, *J Infect Dis*, 2000).

9. The E44D and V118I mutations were

reported to confer low-level resistance to lamivudine when accompanied by several other nRTI-associated mutations (M41L, D67N, L210W, T215Y/F, K219Q/E) in the absence of a concurrent M184V mutation (Hertogs et al, *Antimicrob Agents Chemother*, 2000). Data presented but not yet published (D'Arminio-Monforte et al, 8th CROI, 2001), reported no association over the short term between E44D or V118I and virologic response to a lamivudine-containing combination regimen. (See also user note 2.)

10. Emtricitabine and lamivudine have similar reverse transcriptase M184V/I patterns (Quinn et al, *JCAAC*, 2003). In addition, the K65R mutation can confer cross-resistance to emtricitabine and lamivudine (Miller et al, *JCAAC*, 2003; Miller et al, *Antivir Ther*, 2003; Miller et al, 10th CROI, 2003; Parikh et al, *Antivir Ther*, 2003; Ruane et al, *Antivir Ther*, 2003; McArthur et al, *Antivir Ther*, 2003). Additional mutations that confer resistance or cross-resistance to emtricitabine are possible, but are yet to be described.

11. The accumulation of NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E [note: data here do not include E44D and V118I]) increases resistance to tenofovir. Mutations M41L and L210W contribute more than others. Therefore, the number and type of NAMs will determine the degree of reduced response. T69D/N/S may also contribute to a reduced response to tenofovir (Miller et al, *Antivir Ther*, 2002; Lu et al, *Antivir Ther*, 2002; Masquelier et al, *Antivir Ther*, 2002).

12. The K103N or Y188L mutation alone can substantially reduce the clinical utility of all currently approved NNRTIs.

13. The V106M mutation confers high-level resistance in vitro to nevirapine, delavirdine, and efavirenz (Brenner et al, *AIDS*, 2003). This mutation has been observed only in HIV clade C clinical isolates, although site-directed mutagenesis indicates that V106M confers cross-resistance to all NNRTIs in HIV clade B virus.

14. Accumulation of 2 or more of these mutations substantially reduces the clinical utility of all of the currently approved NNRTIs.

15. The prevalence of the Y318F mutation in clinical isolates along with mutations K103N, Y181C, or P236L was approximately 5%, 2%, and 15%, respectively (Kemp et al, *Antivir Ther*, 2001). In vitro this mutation confers resistance to nevirapine, delavirdine, and efavirenz.

16. The Y181C/I mutation is not selected by efavirenz, but its presence contributes to low-level cross-resistance to the drug. Clinical impact of this mutation may be overcome with a fully active antiretroviral combination regimen, although no clinical trial data yet address this question.

17. V108I and P225H each contribute to efavirenz resistance when present in combination with other NNRTI-associated mutations. Although V108I or P225H alone does not confer measurable resistance in laboratory strains of HIV-1, their presence in a clinical isolate may indicate prior selection for efavirenz-resistant variants.

18. Resistance mutations in the protease gene are classified as either "major" or "minor" (if known).

Major: In general, major mutations are either (1) selected first in the presence of the drug; or (2) shown at the biochemical or virologic level to lead to an alteration in drug binding or an inhibition of viral activity or viral replication. By themselves, major mutations have an effect on phenotype. In general, these mutations tend to be the major contact residues for drug binding.

Minor: In general, minor mutations appear later than major mutations, and by themselves do not have a significant effect on phenotype. In some cases, their effect may be to improve replicative fitness of virus carrying major mutations.

19. Accumulation of 4 or more of these mutations is likely to cause multi-PI resistance (Palmer et al, *AIDS*, 1999; Shafer et al, *Ann Intern Med*, 1998).

20. For indinavir, the mutations listed as major may not be the first mutations selected, but they are present in most clinical isolates in combination with other mutations.

21. Major and minor mutations have not been designated for lopinavir/ritonavir-associated resistance since currently there are no clear data defining degrees of influence with this drug combination. The accumulation of 6 or more of these mutations is associated with a diminished response to lopinavir/ritonavir. The product information states that accumulation of 7 or 8 mutations confers resistance to the drug. However, recent data suggest as few as 4 mutations can be associated with such high-level resistance (Prado et al, *AIDS*, 2002). Further clinical experience and research are needed to

better define the mutations that affect the clinical effectiveness of lopinavir/ritonavir. It is reasonable to consider phenotyping to assess this in individual cases.

22. Protease mutation L63P is common in viruses that have never been exposed to PIs (Kozal et al, *Nat Med*, 1996) and may be more prevalent in viruses from patients in whom a PI-containing regimen has failed. However, by itself, L63P does not cause any appreciable increase in the IC₅₀ for any PI.

L63P is listed for lopinavir/ritonavir (and not any other PI) because studies have shown that this mutation, when present with multiple other mutations, is associated with clinical failure.

23. When administered to patients as the initial PI, atazanavir selects for the mutations I50L and A71V (Colonno et al, *Antivir Ther*, 2002). When used as a subsequent PI in combination with saquinavir, atazanavir selects for I54L and I84V (Colonno et al, *Antivir Ther*, 2002). In vitro, atazanavir selects for V32I, M46I, I84V, and N88S (Gong et al, *Antimicrob Agents Chemother*, 2000). Although other mutations, such as V82A and L90M, have not been selected for by atazanavir either in vitro or in vivo, these mutations have been shown to confer cross-resistance to atazanavir, particularly when present in combination with each other or with other known PI resistance mutations (Colonno et al, *Antivir Ther*, 2000). Recent data show the high impact of I84V (7- to 9-fold increase in IC₅₀) when in the background of A71V (Weinheimer et al, 11th CROI, 2004).

24. Tipranavir/ritonavir is currently available through an expanded-access protocol and is not approved by the FDA.

25. To date, resistance mutations in the gp41 envelope gene have been identified primarily at positions 36 to 45 of the first heptad repeat (HR1) region. These mutations have been identified in viruses from patients having been on enfuvirtide and have been shown to confer resistance or reduced susceptibility (Wei et al, *Antimicrob Agents Chemother*, 2002; Sista et al, *Antivir Ther*, 2002; Mink et al, *Antivir Ther*, 2002). It is important to note that wild-type viruses lacking any mutations in the depicted HR1 region vary 500-fold in susceptibility and such pretreatment susceptibility differences were not associated with differences in clinical response (Labrosse et al, *J Virol*, 2003; Greenberg et al, 10th CROI, 2003, Ab 141). Furthermore, it is possible that mutations and/or polymorphisms in other regions in

the envelope (eg, the HR2 region or those yet to be identified) as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, *PNAS*, 2002). Further research is needed to define the full spectrum of clinically relevant mutations conferring enfuvirtide resistance. Testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure of regimens including enfuvirtide and must be interpreted in the context of resistance testing results for all other components of the regimen.

Figure legend. For each amino acid residue, the letter above the bar indicates the amino acid associated with wild-type virus and the letter(s) below indicate the substitution(s) that confer viral resistance. The number shows the position of the mutation in the protein. Mutations selected by protease inhibitors in Gag cleavage sites are not listed because their contribution to resistance is not yet fully defined. HR1 indicates first heptad repeat; NAMs indicates nRTI-associated mutations; nRTI indicates nucleoside reverse transcriptase inhibitor; NNRTI indicates nonnucleoside reverse transcriptase inhibitor; PI indicates protease inhibitor.

Amino acid abbreviations: A, alanine; C, cysteine; D, aspartate; E, glutamate; F, phenylalanine; G, glycine; H, histidine; I, isoleucine; K, lysine; L, leucine; M, methionine; N, asparagine; P, proline; Q, glutamine; R, arginine; S, serine; T, threonine; V, valine; W, tryptophan; Y, tyrosine.

to be a natural polymorphism; there has been no evidence of an increase in the prevalence of this mutation in isolates from drug-experienced patients in whom therapy with trial agents has failed.

Also in the PI category, the name of the bar representing “amprenavir” has been changed to “(fos) amprenavir” to indicate that the mutations listed are relevant to the prodrug of this agent.

Future Revisions of the Figures

The Drug Resistance Mutations Group is currently revising the figure, including redeveloping the user notes to focus on the most current clinical information. The new figure and user notes will include any new data from upcoming scientific conferences and publications and will be available in early 2005.

The group is discussing the HIV-1 resistance mutations that are associated with non-subtype B virus and plans to introduce current data into the figures. Other topics under consideration include mutations in gag cleavage sites, transmitted drug resistance, drug hypersusceptibility, and emerging classes of drugs (eg, RNase H inhibitors).

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The IAS–USA Drug Resistance Mutations Group thanks Jennifer Ham, MPH, for managing the efforts of the group.

Comments?

The IAS–USA Drug Resistance Mutations Group welcomes comments on the mutations figures and user notes. Please send your evidence-based comments, including relevant reference citations, to the IAS–USA at resistance2004“at”iasusa.org or by fax at (415) 544-9401. Please include your name and institution.

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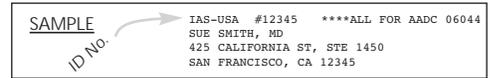


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