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A publication of the International AIDS Society–USA

Perspectives

Review

The International AIDS Society–USA

About This Issue

This issue features 2 Perspectives articles based on presentations given at the International AIDS Society–USA continuing medical education courses held in Sacramento and New York in fall 2003. Richard H. Haubrich, MD, reviewed the use and interpretation of phenotypic and genotypic assays in assessing HIV resistance and determining appropriate therapies. Jeanne Marrazzo, MD, MPH, discussed atypical presentations of sexually transmitted diseases, namely syphilis and genital herpes, in the HIV care setting.

In a Review article, Alice C. Thornton, MD, Frank Romanelli, PharmD, and Jana D. Collins, BS outline assisted reproductive techniques for couples affected by HIV, both serodiscordant and seroconcordant, and information for counseling such couples in reproductive decision making.

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Perspectives

Review

Announcements

Perspective

Resistance and Replication Capacity Assays: Clinical Utility and Interpretation

Resistance testing has emerged as an important tool for antiretroviral management. Research continues to refine phenotypic susceptibility cut-offs and genotypic interpretation schemes that relate resistance mutations with antiretroviral drug effectiveness. Highly sensitive phenotypic assays have allowed for the recognition of drug hypersusceptibility in HIV, and other studies have related hypersusceptibility to resistance mutations; efforts are ongoing to use what is known about hypersusceptibility to optimize the benefits of antiretroviral therapy. Resistance-associated mutations in several viral genes result in viruses that exhibit reduced replication capacity; assays to measure replication capacity are being developed that may, in the future, be useful in guiding therapy to improve treatment outcomes. This article summarizes a presentation given by Richard H. Haubrich, MD, at the International AIDS Society–USA Sacramento course in November 2003.

Resistance testing is an important component of management of antiretroviral-experienced patients, assisting in selection of appropriate regimens in patients in whom treatment is failing due to resistant virus. Such testing is also becoming an increasingly important part of determining initial antiretroviral therapy given the high (and rising) rates of resistant virus transmission in a number of areas around the world. Current options for assessing HIV resistance are phenotypic and genotypic assays.

Phenotypic Assays

Phenotypic assays assess susceptibility of clinical HIV isolates to antiretroviral drugs by comparing the concentration of drug needed to inhibit the clinical isolates with that of wild-type reference strains. Figure 1 illustrates examples of a clinical isolate that is susceptible to the drug tested, showing 50% inhibitory concentrations (IC_{50}) identical to those of the reference strain, and an isolate that has a 100-fold reduced susceptibility to the drug tested. To be optimally useful, these tests should provide results that are predictive of virologic response to therapy. Biologic cut-offs for susceptibility have been obtained for different phenotypic assays by determining mean fold change in susceptibility compared with a reference strain among a large number of isolates from treatment-naive, HIV-infected patients. The standard interpretation is that the isolate is susceptible if it is within the mean plus 2 standard deviations. This biologic cut-off varies from drug to drug and from assay to assay according to performance characteristics of the particular phenotypic assay. Although the measure provides an indication of whether a clinical isolate can be considered susceptible to a particular drug, clinical cut-point values are still needed to correlate degree of susceptibility with virologic response of the patient. Clinical cut-points are derived from data relating resistance assays to clinical response, usually by determining a phenotypic cut-point at which a drug starts to show a decreased virologic response (eg, smaller reduction in plasma HIV RNA levels). Ideally, 2 phenotypic cut-points should be derived for each drug. The first cut-point would be defined as the fold change at which there is any reduction in antiviral activity, and the second cut-point would be that for which there is no drug activity.

Cut-points may differ for different assays (eg, Virco and ViroLogic assays). Examples of cut-points for reduced susceptibility that have been determined for the ViroLogic assay (expressed as susceptibility fold change) are 1.7 for didanosine, 1.7 for stavudine, 4.5 for abacavir (6.5 for loss of antiretroviral activity), 10.0 for lopinavir, and 1.4 for tenofovir.

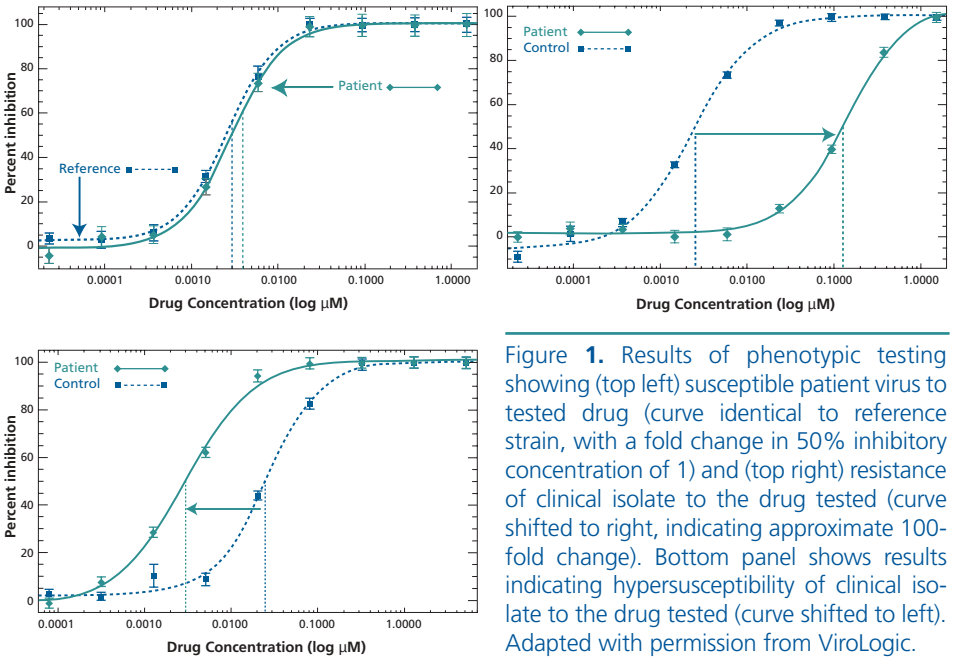

Figure **1.** Results of phenotypic testing showing (top left) susceptible patient virus to tested drug (curve identical to reference strain, with a fold change in 50% inhibitory concentration of 1) and (top right) resistance of clinical isolate to the drug tested (curve shifted to right, indicating approximate 100-fold change). Bottom panel shows results indicating hypersusceptibility of clinical isolate to the drug tested (curve shifted to left). Adapted with permission from ViroLogic.

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Drug		Matches in database	Proportion of matched samples: within normal susceptible range [2]; above normal susceptible range [2]; above normal susceptible range but below clinical cut-off [2, 3, 4]	Fold change in IC_{50} (Cut-off for normal susceptible range)	Ref.
Trade name	**Generic name**		25 50 75 (%)		
NRTI					
Retrovir®	Zidovudine	2,600		4.0 (4.0)	
Epivir®	Lamivudine	3,396		48.1 (4.5)	
Videx®	Didanosine	2,092		1.4 (2.0)	
Hivid®	Zalcitabine	1,524		1.7 (2.0)	
Zerit®	Stavudine	3,220		1.0 (1.75)	
Ziagen®	Abacavir	1,083		2.6 (3.0)	
NtRTI					
Viread™	Tenofovir DF	1,094		1.3 (3.0)	4
NNRTI					
Viramune®	Nevirapine	12,574		1.4 (8.0)	
Rescriptor®	Delavirdine	11,723		1.6 (10.0)	
Sustiva®, Stocrin®	Efavirenz	11,517		1.1 (6.0)	
PI					
Crixivan®	Indinavir	1,671		9.3 (3.0)	
Norvir®	Ritonavir	1,783		10.8 (3.5)	
Viracept®	Nelfinavir	2,050		24.1 (4.0)	
Invirase®, Fortovase®	Saquinavir	1,975		4.9 (2.5)	
Agenerase®	Amprenavir	1,689		2.3 (2.0)	
A component of Kaletra®	Lopinavir	1,026		2.5 (2.5)	3

Figure **2.** Example of virtual phenotypic output, showing predicted fold change in 50% inhibitory concentrations (IC_{50}) for drugs based on relating genotype to phenotype matches in the database. Reprinted with permission from Virco.

Genotypic Assays

Genotypic assays identify mutations in HIV genes (currently, those for reverse transcriptase and protease) that are associated with viral resistance. Interpretation of genotypes is difficult for a number of reasons, including the complexity of determining the effects of interactions among numerous resistance mutations that may be present in clinical HIV strains. There are a number of clinical tools that assist clinicians in interpreting genotype assays. Many compilations of resistance mutations, such as that maintained by the International AIDS Society–USA (Johnson et al, *Top HIV Med*, 2003) are continuously updated to provide profiles and interpretation of resistance mutations for specific antiretroviral agents (www.iasusa.org/resistance_mutations/mutations_figures.pdf).

One method of improving the interpretation of a genotypic test uses the correlation of the genetic sequences in particular clinical strains with phenotypes in a large database. With this method of genotypic interpretation, the genetic sequence from a clinical isolate is entered into a database consisting of a large number of clinical isolate genotypes and corresponding phenotypic profiles. An average phenotype for the strain of interest is then defined by "matching" the genotype of the particular strain with similar genetic sequences in the database. An example of a virtual phenotype report is shown in Figure 2. The average phenotype for the genotypic matches is displayed as the fold change for the patient's genotype. The virtual phenotypic results are dependent on the number of matches of the patient's genotype found in the database; when few matching genotypes are found, a rules-based result is given.

Interpretations of resistance mutations can also be obtained from such online databases as the Stanford HIV Drug Resistance Database (http://hivdb.stanford.edu), which provides an interpretation of likely drug resistance based on entry of single or numerous resistance mutations. The interpretations reflect what is currently known about the effect of interaction of resistance mutations on drug susceptibility. Currently, most companies or institutions that provide genotypic analysis supply an interpretation of the results designed to be useful in guiding clinical decision making. However, methods for arriving at interpretations are not well standardized and may differ according to the method used and the database employed. Caution is nec-

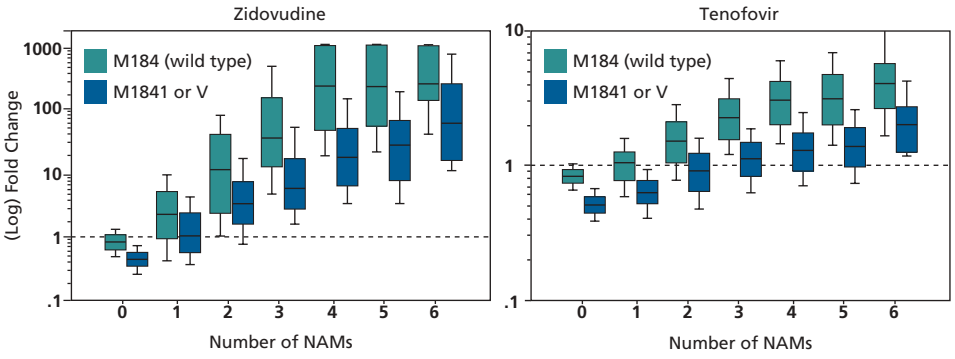


Figure **3.** Effect of the M184V mutation (blue) on susceptibility to zidovudine and tenofovir according to number of other nRTI-associated mutations (NAMs) present. NAMs include M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N. Adapted from Whitcomb et al, *J Infect Dis,* 2003.

essary in basing clinical decisions on interpretations, unless it is known that the interpretation comes from a reliable source utilizing continuously updated data. Use of several sources (ie, the International AIDS Society–USA Mutations tables as well as the Stanford Web site), may increase the clinician's confidence in the interpretation.

Hypersusceptibility

Phenotypic hypersusceptibility has recently been recognized and the clinical implications are being clarified. In phenotypic analysis, hypersusceptibility is shown by a shift in the inhibition-concentration curve to the left of the reference strain curve (Figure 1, bottom), and is expressed as a fold change of less than 1.0. For these isolates, the IC_{50} of the patient's virus is less than the IC_{50} of the control so that it might take lower concentrations of the antiretroviral to inhibit the viral strain than it would for a wild-type virus. The mechanism of hypersusceptibility is unknown, but it likely results from an interaction of mutations, in which mutations that lead to resistance to one drug lead to increased susceptibility to another drug. This has best been demonstrated for the nucleoside reverse transcriptase inhibitors (nRTIs). The nRTIs can be divided into 2 groups based on the effect of the nRTI resistance mutation M184V on the particular nRTI agent. That is, the presence of the mutation: (1) *increases* virus susceptibility to zidovudine, stavudine, and tenofovir; and (2) *decreases* susceptibility to lamivudine, zalcitabine, didanosine, and abacavir. Figure 3 shows that although susceptibility to zidovudine and tenofovir decreases with increasing number of nRTI resistance mutations (M41L, D67N, K70R, L210W, T215Y/F, and K219Q/E/N), the presence of the M184V mutation results in increased susceptibility compared with virus lacking the mutation. A practical implication of this phenomenon is that patients may benefit from maintaining the M184V mutation through drug pressure, since the phenotypic switch may be associated with improved response to treatment.

Hypersusceptibility to nonnucleoside reverse transcriptase inhibitors (NNRTIs) is observed in viral samples from patients who have never received nRTIs or NNRTIs. However, the prevalence of hypersusceptibility is greatly increased in samples from patients with prior nRTI treatment, indicating that nRTI resistance mutations in the reverse transcriptase enzyme can result in increased susceptibility to NNRTIs. Whitcomb and colleagues (*AIDS,* 2002) recently reported that among 331 nRTI/NNRTI-naive patients, hypersusceptibility to delavirdine was present in 5% of samples, and hypersusceptibility was present in 9% and 11% of samples in efavirenz and nevirapine, respectively. Among 447 nRTI-experienced, NNRTI-naive patients, hypersusceptibility to delavirdine was present in 29% of samples, to efavirenz in 26%, and to nevirapine in 21%. There is accumulating evidence that such hypersusceptibility results in improved treatment response, with 5 separate trials demonstrating improved outcomes in the presence of NNRTI hypersusceptibility (Haubrich, *AIDS*, 2002; Shulman, *AIDS,* 2001; Albrecht, 9th CROI, 2002; Mellors, 9th CROI, 2002; Haubrich, 11th CROI, 2004). For example, Haubrich and colleagues (*AIDS,* 2002) found that reduction in HIV-1 RNA in patients initiating NNRTI treatment was approximately 0.5 $\log_{10}$ RNA copies/mL greater in patients with hypersusceptible virus than in those without such virus (Figure 4).

Hypersusceptibility has also been observed for protease inhibitors (PIs). With these drugs, hypersusceptibility has been associated with improved virologic outcome. In a study by Schooley and colleagues (10th CROI, 2003), for example, the effects of amprenavir treatment were assessed in PI-experienced patients who were amprenavir-sensitive (maximum fold change in IC_{50} of 4.0 on phenotypic assay at baseline). Independent predictors of response to fewer than 200 plasma HIV RNA copies/mL at week 24 consisted of baseline viral load, number of prior PIs received, fold change in amprenavir at baseline, and baseline hypersusceptibility to amprenavir (defined as fold change in IC_{50} < 0.66).

Impact of Drug Concentrations on Resistance

Pharmacokinetic boosting of PIs with ritonavir to raise drug concentrations in the blood has been found to improve therapeutic response, and it may also curtail emergence of resistance from patients in whom their first antiretroviral regimen failed. Such reduction in resistance was perhaps first demonstrated in a clinical trial comparing lopinavir/ritonavir-based therapy with nelfinavir-based therapy for the treatment of antiretroviral-naive patients. In this trial, nelfinavir resistance was observed in 30% of patients with virologic failure of the nelfinavir regimen, but lopinavir resistance was not found in any patients with failure of the lopinavir/ritonavir regimen. Confirming data have now been reported in a study of the amprenavir prodrug fosamprenavir (Macmanus, 10th CROI, 2003). In this cross-study comparison, resistance to unboosted fosamprenavir was pres-

ent at first virologic failure in 8 (28%) of 29 patients receiving unboosted drug (mutations I54M, M46I, and V32I + I47V), whereas no resistance was found at first failure in 32 patients receiving fosamprenavir/ritonavir. By comparison, nelfinavir resistance was found at first failure in 35 (44%) of 80 patients receiving nelfinavir. It thus appears that maintaining elevated levels of PIs in a treatment regimen can reduce PI resistance for patients in whom the initial regimen is failing. The consequences of this apparent reduction in resistance in predicting augmented responses to the next PI-based regimen as compared with failure of an unboosted PI have not been demonstrated.

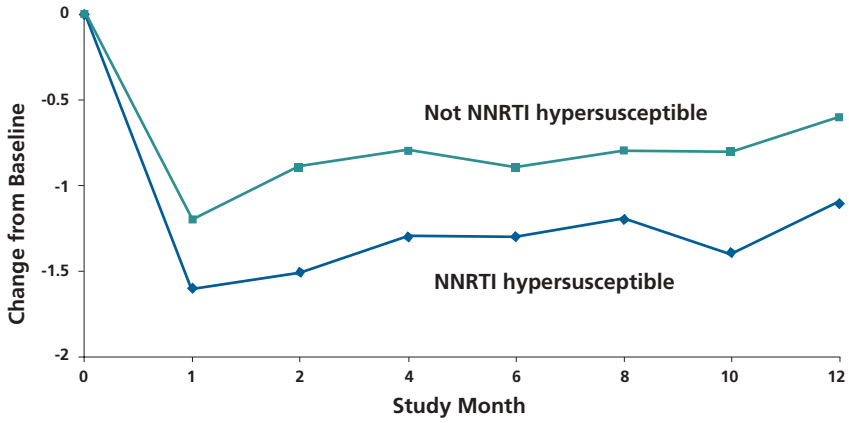
Replication Capacity

Viral replication capacity is defined as the ability of virus to multiply, in a given environment, usually compared with a reference or control (wild-type) virus. Differences in replication capacity may be intrinsic to the virus strain or may result from mutations selected by drug pressure. Determination of viral replication capacity is of clinical interest since it is hoped that virus with low replication capacity will be less pathogenic.

Available assays of replication capacity compare HIV reverse transcriptase and protease sequences in clinical and reference strains using modified phenotypic assays. Changes in other viral components, particularly the viral envelope, are also likely to be important determinants of viral replicative fitness, but are not measured in the commercially available assays. Replication capacity of a particular viral sample is expressed as a percentage of quantified replication of the reference strain. A number of reverse transcriptase and protease mutations affect the replication capacity of a virus. The nRTI resistance mutation M184V and the PI mutation D30N, for example, are single mutations that are associated with reduced viral replication compared with wild-type virus, suggesting that the "cost" to the virus of acquiring such resistance is reduced ability to replicate in the presence of the drug that selected for the resistance mutation. Such a phenomenon may help explain the ongoing benefits of antiretroviral therapy despite the presence of resistance. In a recent study, Haubrich and colleagues (XI Drug Resistance Workshop, 2002) examined CD4+ cell count changes from nadir counts in patients with detectable viral load and phenotypic resistance. Gains in CD4+ cell count from the nadir were significantly higher in those patients in whom virus had lower replication capacity, indicating that reduced capacity is indeed associated with better clinical course.

In another study, Daar and colleagues (*Antivir Ther,* 2003) evaluated stored clinical samples from HIV-infected patients with hemophilia who had received nRTI monotherapy or dual therapy prior to the potent antiretroviral therapy era to determine whether viral replication capacity was predictive of clinical progression. It was found that: (1) replication capacity was correlated with CD4+ cell count ($P = 0.025$) and plasma HIV RNA level ($P = 0.062$); (2) replication capacity ($P < 0.0001$) and viral load ($P = 0.008$) were independently predictive of CD4+ cell count decline; and (3) decreases in replication capacity were associated with delayed progression to clinical HIV disease even after controlling for viral load and CD4+ cell count. These findings indicate that replication capacity is a marker of viral fitness that independently influences HIV disease progression.

An effect of a resistance mutation to the HIV fusion inhibitor enfuvirtide on replication capacity also has been observed recently. Enfuvirtide has been used in patients in whom there are few treatment options remaining; in many, an initial robust reduction in viral load is followed by rebound, and it remains unclear whether to discontinue enfuvirtide treatment in such patients. Lu and colleagues (XI Drug Resistance Workshop, 2002) found that wild-type virus outcompeted virus with the enfuvirtide-resistance mutation in the absence of enfuvirtide and that the mutant virus became the predominant species in the presence of enfuvirtide. Such findings suggest that continued benefit of enfuvirtide may occur despite resistance in those who harbor virus with enfuvirtide-associated mutations.



No. subjects								
Not HS	83	35	60	66	57	54	55	48
HS	23	11	16	20	18	19	14	14
P value		*0.1*	*0.02*	*0.04*	*0.1*	*0.1*	*0.03*	*0.2*

Figure **4.** Effect of NNRTI hypersusceptibility on virologic response ($\log_{10}$ HIV RNA copies/mL) to initiation of NNRTI therapy. Adapted with permission from Haubrich, *AIDS,* 2002. NNRTI indicates nonnucleoside reverse transcriptase inhibitor; HS, hypersusceptible.

Presented in November 2003. First draft prepared from transcripts by Matthew Stenger. Reviewed and updated by Dr Haubrich in March 2004.

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Suggested Reading

Albrecht MA, Bosch RJ, Liou SH, Katzenstein D. ACTG 364: Efficacy of nelfinavir (NFV) and/or efavirenz (EFV) in combination with new nRTIs in nucleoside experienced subjects: week 144 results. [Abstract 425-W.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

Daar E, Kesler K, Donfield S, Wrin T, Petropoulos C, Hellmann N. HIV replication capacity (IRC) predicts HIV clinical progression. *Antivir Ther.* 2003;8(Suppl 1):S251.

Haubrich RH, Kemper CA, Hellmann NS, et al. The clinical relevance of non-nucleoside reverse transcriptase inhibitor hypersusceptibility: a prospective cohort analysis. *AIDS*. 2002;16:F33-F40.

Haubrich R, Jiang H, Swanstrom R, et al. Delavirdine hypersusceptibility: virologic response and phenotypic cut-points—results from ACTG 359. [Abstract 671.] 11th Conference on Retroviruses and Opportunistic Infections. February 8-11, 2004; San Francisco, Calif.

Haubrich R, Wrin T, Hellman N, et al. Replication capacity as a predictor of immunological and virological benefit despite virological failure of an antiretroviral regimen. [Abstract 121.] XI International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications. July 2-5, 2002; Seville, Spain.

Johnson VA, Brun-Vézinet F, Clotet B, et al. Drug Resistance Mutations in HIV-1. *Top HIV Med.* 2003;11:215-221.

Lu J, Sista P, Cammack N, Kuritzkes D. Fitness of HIV-1 clinical isolates resistant to T-20 (enfuvirtide). [Abstract 67.] XI International HIV Drug Resistance Workshop: Basic Principles and Clinical Implications. July 2-5, 2002; Seville, Spain.

Macmanus S, et al. GW433908 in ART-naive subjects: absence of resistance at 48 weeks with boosted regimen and APV-like resistance profile with unboosted regimen. [Abstract 598.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

Mellors J, Vaida F, Bennet K, Hellmann NS, DeGruttola V, Hammer S. Efavirenz hypersusceptibility improves virologic response to multidrug salvage regimens in ACTG 398. [Abstract 45.] 9th Conference on Retroviruses and Opportunistic Infections. February 24-28, 2002; Seattle, Wash.

Schooley R, Haubrich R, Thompson M, et al. Effect of amprenavir hyper-susceptibility on the response to APV/ritonavir-based therapy in ART-experienced adults selected by baseline susceptibility (ESS40006): 24-week data. [Abstract 143.] 10th Conference on Retroviruses and Opportunistic Infections. February 10-14, 2003; Boston, Mass.

Shulman N, Zolopa AR, Passaro D, et al. Phenotypic hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in treatment-experienced HIV-infected patients: impact on virological response to efavirenz-based therapy. *AIDS*. 2001; 15:1125-1132.

Stanford HIV Drug Resistance Database. Available at: http://hivdb.stanford.edu. Accessed. April 12, 2004.

Whitcomb JM, Huang W, Limoli K, et al. Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates. *AIDS*. 2002;16:41-47.

Whitcomb JM, Parkin NI, Chappey C, et al. Broad nucleoside reverse-transcriptase inhibitor cross-resistance in human immunodeficiency virus type 1 clinical isolates. *J Infect Dis.* 2003;188(7):992-1000.

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Perspective

Sexually Transmitted Diseases in the HIV Care Setting: What's Really Going on Down There?

Syphilis epidemics are occurring in a number of cities in the United States and worldwide. In New York City, the number of cases of primary or secondary syphilis has increased from 130 in 1999 to 434 in 2002. The majority of new cases occur in men, with most of these occurring in men who have sex with men. The presentations of primary and secondary syphilis are varied and can be overlooked or confused with other diseases. Health care providers should be aware of atypical presentations of sexually transmitted diseases (STDs), screen for nonapparent STDs, and know how to treat such diseases once they are identified. Client-centered counseling may be successful in reducing risky behaviors and the transmission of STDs. This article summarizes a presentation given by Jeanne Marrazzo, MD, MPH, at the October 2003 International AIDS Society–USA course in New York.

Case History

A 35-year-old man with a persistent genital lesion (3 weeks) and associated rash (1 week) was initially treated for *Candida* (yeast) balanitis with topical antifungal cream at the clinic where his girlfriend receives routine care. He later presented to the STD clinic; while the original lesion was nearly resolved, a new rash appeared on his scrotum. Examination showed small erythematous, palpable, papular lesions scattered on the surface of the scrotum, a slightly pink area on the glans, and a rash consistent with tinea cruris (Figure 1, top). In a detailed interview, the man reported that he had had receptive/insertive anal intercourse with 2 men within the past 3 months, a fact that had not been related to his prior health care provider. He also stated that he "almost always" used condoms with men but never used condoms with his girlfriend. Results of immediate work-up of the scrotal lesions found that darkfield microscopy to detect *Treponema pallidum* was negative. During the patient's prior examination, his perianal area had not been checked. Both the perianal area and the oral cavity should be examined whenever a patient presents with a genital lesion. Examination of the perianal area showed numerous fleshy papules resembling flat-topped warts (Figure 1, bottom). The rapid plasmin reagin (RPR) test was positive, indicating the presence of syphilis. The serum Venereal Disease Research Laboratory (VDRL) test was positive with a titer of 1:128. HIV enzyme-linked immunosorbent assay (ELISA) was reactive and was confirmed with Western blot testing. Routine tests for chlamydia and gonorrhea at the urethra, rectum, and pharynx were negative.

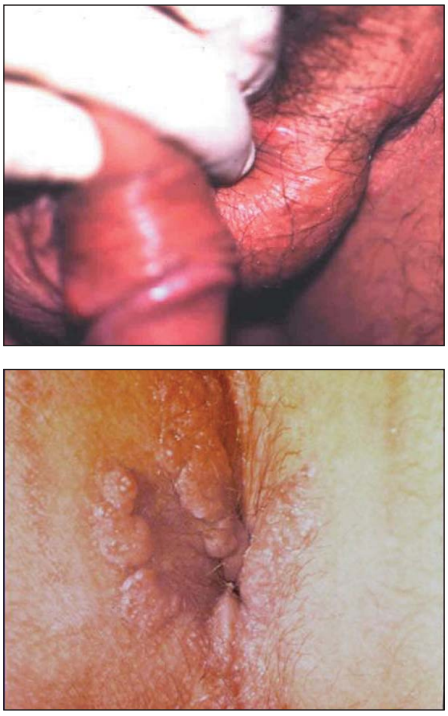

Figure **1.** Case presentation. Top: Small erythematous papules on scrotum. Pinkish area at glans is not clearly discernible. Bottom: Fleshy papules in perianal area. Photographs are courtesy of the Seattle STD/HIV Prevention Training Center.

The lesions in the perianal and scrotal areas of this patient are condyloma lata, characteristic of secondary syphilis; these lesions are foci of exuberant treponemal multiplication and are extremely contagious. It is not uncommon for these lesions to be mistaken for perianal warts and to find that treatment with liquid nitrogen has been administered due to mistaken diagnosis. The patient's groin rash is tinea cruris. Thus, he actually exhibits signs of both primary and secondary syphilis, with the healing lesion on the tip glans of the penis being the initial chancre. Approximately 15% of patients with early syphilis exhibit overlapping signs of primary and secondary disease.

Syphilis in New York City

Epidemics of syphilis are occurring in a number of cities in the United States. Data from the New York City Department of Health indicate that the number of new cases of primary or secondary syphilis—based on presentation with characteristic lesions, not serologic findings—increased from 130 in 1999 to 282 in 2001, and to 434 in 2002. Similar trends are being observed in Los Angeles, San Francisco, and Seattle, among other cities; overall, approximately 6500 new cases of early syphilis were reported in the United States in 2002. In the mid-1990s, syphilis essentially had been eradicated from several large cities on the West Coast. It is now estimated that there will have been 750 new cases of early syphilis in San Francisco in 2003, and 90 new cases are expected in Seattle (which had only 1 new case in 1995).

The majority of new cases in New York City are seen in men. Among

Dr Marrazzo is Medical Director of the Seattle STD/HIV Prevention Training Center and Assistant Professor of Infectious Diseases at the University of Washington in Seattle.

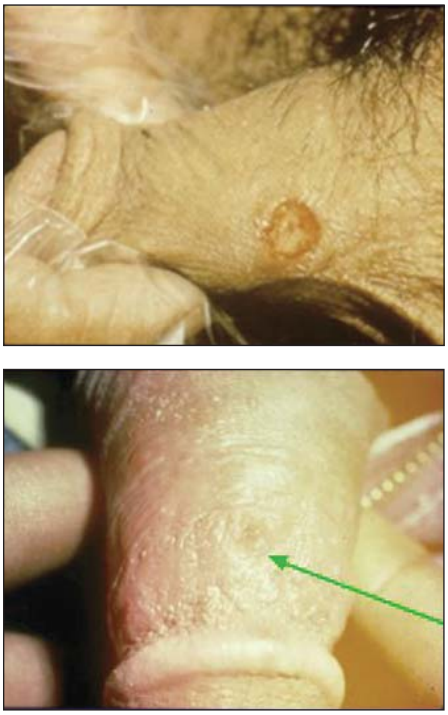

Figure **2.** Primary syphilis in men may have a number of presentations, including the classic chancre (top) or a small noninflammatory lesion (bottom). Photographs are courtesy of the Seattle STD/HIV Prevention Training Center.

patients who were interviewed, the number of syphilis cases occurring in men who have sex with men increased dramatically from 2000 to 2002. Among men with known HIV status, the proportion of new syphilis cases occurring in HIV-infected men increased from 20% in 1999 to 61% in 2002.

There are likely a number of factors contributing to the resurgence of syphilis. In the HIV-infected community, increased survival and well-being resulting from effective antiretroviral therapy have been associated with a return to normal activities, including sexual activities. Many at-risk individuals erroneously believe that HIV disease is now "curable" and that HIV cannot be transmitted when plasma HIV RNA levels are controlled on potent antiretroviral therapy. There is also reduced visibility of end-stage AIDS, which, in the past, may have served as a deterrent to unsafe sexual practices. In addition, there appears to be a general "fatigue" or "burnout" with regard to practicing safer sex. Other factors contributing to the rise in cases of syphilis may include increased use of recreational drugs (eg, methamphetamine [eg, crystal meth], nitrates [eg, poppers], and sildenafil citrate [Viagra]); the reemergence of old ways to meet anonymous partners (eg, baths, parks); and the emergence of new ways to meet partners (eg, Internet dating; in fact, in Seattle, a surprisingly high proportion of new patients with syphilis reported meeting their anonymous partners via the Internet).

Presentation of Syphilis

In men, primary syphilis may present as the classic chancre on the penile shaft (Figure 2). Typically, the chancre is painless and nontender to palpation, is indurated with a heaped-up border, and has a clean (nonpurulent) base. The lesion is RPR- or VDRL-positive in approximately 70% of cases. However, primary disease does not always take the classic form; for example, the chancre may appear as a small, noninflammatory lesion (Figure 2). Only serologic evaluation or darkfield microscopy can provide a definitive diagnosis. Chancres can appear anywhere that inoculation has occurred via direct contact—eg, fingers, mouth, and perianal area. Chancres in the perianal area are sometimes mistaken for genital herpes.

Secondary syphilis can be protean in its manifestations, including presentation as a nephrotic syndrome, hepatitis, or febrile lymphadenitis. The classic presentation is a macular rash on the palm of the hand or sole of the foot (Figure 3, top); differential diagnosis of the rash includes Rocky Mountain spotted fever and drug reactions. The rash is highly contagious. As noted, condyloma lata (Figure 1) are also characteristic of the secondary stage, and are often confused with condyloma acuminata resulting from infection with human papilloma virus (HPV) types 6/11. Condyloma lata can occur at any moist body site. Their fleshy, flat-topped appearance may help to distinguish them from HPV-associated warts, which are less fleshy and more verrucous. Anal sex is not a prerequisite for perianal condyloma lata or HPV-associated warts. Secondary syphilis may also appear as mucous patches on the background of a "coated" tongue (Figure 3, bottom). These lesions contain large numbers of treponemes and are also highly contagious. The patches can be confused with oral hairy leukoplakia. RPR testing and VDRL testing are positive in almost 100% of cases of secondary syphilis.

Genital Herpes

Approximately 45 to 60 million individuals in the United States have genital herpes. The classic presentation of initial infection in men is that of vesicles on the penile shaft. However, the presentation can also occur in forms that are difficult to distinguish from the chancres of syphilis; thus, presentation may occur as eroded ulcers suggestive of syphilis or as a single ulcer with a clean base suggestive of syphilis. In women, presentation on the external genitalia often occurs as ulcers rather than as the classic vesicles. The specific diagnosis of genital herpes can be made by culture or direct antigen test, involving swabbing of a lesion. In some circumstances, herpes serology can also be a highly useful tool. Until about 3 or

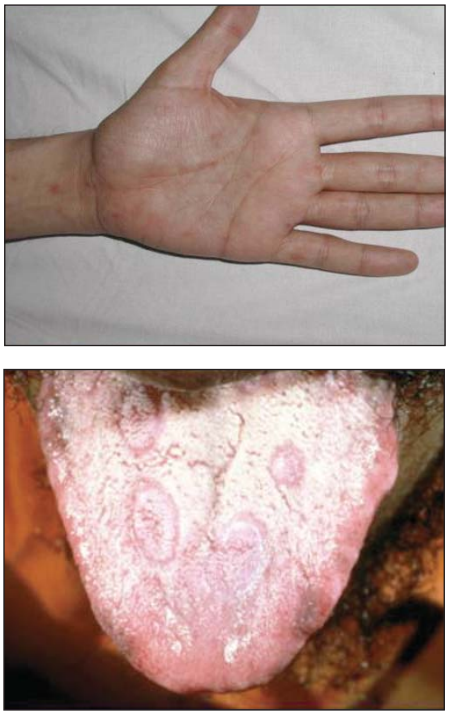

Figure **3.** Secondary syphilis. Top: Classic macular rash. Bottom: Mucous patches on "coated" tongue. Photographs are courtesy of the Seattle STD/HIV Prevention Training Center.

4 years ago, serum antibody tests that claimed to be specific for herpes simplex virus (HSV)-1 and -2 were not actually type specific, since they were not based on glycoprotein G. Glycoprotein G-based serology kits are shown in Table 1. Herpes serology can be used to confirm clinical diagnosis, especially when direct detection of virus is unlikely—that is, when lesions are negative for virus, when they cannot be sampled, or when they are healed or otherwise not present. Most genital herpes cases are subclinical, with about 90% of people infected with HSV-2 claiming never to have had an outbreak. Serology is thus useful for detecting cases of subclinical infection in individuals at high-risk—for example, those with a partner who has genital herpes or those with other symptoms suggestive of atypical or undiagnosed genital herpes.

Table **1.** Commercial Type-Specific Glycoprotein G-Based Serology Kits*

	Manufacturer	HSV Type
FDA Approved		
HerpeSelect® ELISA	Focus	HSV-1, HSV-2
HerpeSelect® Immunoblot	Focus	HSV-1, HSV-2
POCkit® HSV-2	Diagnology	HSV-2
Off the market		
Premier™ ELISA	Meridian	
Off the market		
Not FDA Approved		
Cobas®-HSV-2	Roche	HSV-2
QuickVue® HSV-2	Quidel	HSV-1, HSV-2

*The Western blot assay, which is considered the gold standard, is not commercially available. HSV indicates herpes simplex virus; FDA, Food and Drug Administration; ELISA, enzyme-linked immunoabsorbent assay.

How to Prevent Sexually Transmitted Diseases

Crucial components in preventing transmission of STDs include prompt identification, effective treatment of infections, and appropriate risk counseling. Health care providers must be aware of epidemiologic trends so that nonapparent STDs or cases with atypical presentations can be identified. Assessment must include a thorough sexual history (STD-related risk assessment) in all patients. Every patient should also be screened for nonapparent STDs. Once risk behavior is identified, the adverse consequences of the behavior and the need to prevent it should be addressed. Providers must also know how to treat an infection (or whom to call for expert guidance) once an infection is identified.

A recent *Morbidity and Mortality Weekly Report* (February 2003) provides an excellent source for STD screening procedures in men. It is recommended that all male patients be asked, as part of a thorough and appropriate sexual history, whether they have sex with men; it is crucial to remember that reported sexual orientation does not always predict specific sexual behaviors. If sex with men is reported, it should be determined whether such activity has occurred within the past year. If so, and screening for STD has not been performed previously, providers should screen for STD as detailed below. The recommendations for screening apply to both self-reported HIV-seropositive and HIV-seronegative men, since patients may be unaware of HIV status. The recommendations also apply irrespective of reported condom use for anal sex, since reported condom use is not predictive of occurrence of a new STD. Appropriate STD screening should be performed at least annually and at 3-month intervals in individuals who remain at risk for STDs. A recent *Morbidity and Mortality Weekly Report, Recommendations and Reports* from July 2003 is an excellent compendium of recommendations for the management, prevention, and diagnosis of STDs in HIV-infected patients. These include laboratory screening strategies for asymptomatic STDs and available diagnostic tests for STDs to be used at the first visit and subsequent routine visits. Every patient should be tested for syphilis, gonorrhea, and chlamydia at the initial visit. Women should also have a Pap smear and undergo evaluation for vaginitis. Patients reporting receptive anal sex should be tested for rectal gonorrhea and chlamydia; patients reporting receptive oral sex should be tested for pharyngeal gonorrhea.

There is evidence that behavioral intervention can be successful in reducing the risk of STDs. Project Respect, performed among heterosexual individuals attending an STD clinic, showed that client-centered counseling could reduce the incidence of STDs by 40%; however, there was a follow-up rate of only 66%, and the preventive effect appeared to wane after 12 months. Nevertheless, such findings suggest the potential efficacy of client-centered counseling.

Key features of such counseling include:

- Establishing client rapport and trust
- Maintaining a nonjudgmental attitude
- Using open-ended questions
- Maintaining client confidentiality
- Facilitating risk reduction on the client's terms (eg, basing efforts on realistic goals)
- Limiting information to essential facts that reduce misinformation
- Encouraging active participation of the client

Interactive tools and exercises in client-centered counseling can be found at www.stdhivpreventiontraining.org.

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Suggested Reading

Centers for Disease Control and Prevention. Incorporating HIV prevention into the medical care of persons living with HIV. Recommendations of CDC, the Health Resources and Services Administration, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. *MMWR Recomm Rep.* 2003; 52(RR-12):1-24.

Centers for Disease Control and Prevention STD Treatment Guidelines (2002). Available at: http://www.cdc.gov/std/treatment. Accessed April 12, 2004.

Ciesielski CA. Sexually transmitted diseases in men who have sex with men: an epidemiologic review. *Curr Infect Dis Rep.* 2003;5:145-152.

HIV/STD risks in young men who have sex with men who do not disclose their sexual orientation—six US cities, 1994-2000. *MMWR Morb Mortal Wkly Rep.* 2003;52:81-86.

Katz MH, Schwarcz SK, Kellogg TA, et al. Impact of highly active antiretroviral treatment on HIV seroincidence among men who have sex with men: San Francisco. *Am J Public Health.* 2002;92: 388-394.

National Network of STD/HIV Prevention Training Center. Available at: http://www.stdhivpreventiontraining.org. Accessed April 12, 2004.

Top HIV Med. 2004;12(2):57-60

Review

Reproduction Decision Making for Couples Affected by HIV: A Review of the Literature

Alice C. Thornton, MD, Frank Romanelli, PharmD, Jana D. Collins, BS

Medical issues faced by HIV-affected couples include transmission risks between partners and between mother and child, as well as the technologies and procedures available to reduce those risks. Assisted reproductive techniques discussed are artificial insemination, in vitro fertilization, intracytoplasmic sperm injection, self-insemination, and timed intercourse. It is important that physicians be aware of reproductive options available to couples affected by HIV and be prepared to engage in nonjudgmental dialogue with patients. This review is the result of a literature search performed to identify useful information to counsel HIV-serodiscordant and HIV-seroconcordant couples facing decisions on reproduction.

Introduction

As HIV is transmitted increasingly through heterosexual contact, physicians need to be comfortable counseling HIV-affected patients on their reproductive choices.[1] Currently, heterosexuals make up the second largest exposure group of HIV in the United States, and 30% of all new cases diagnosed are women, approximately 85% of whom are of reproductive age (ie, 13-44 years old).[2-4] Worldwide, 37 million adults are living with HIV/AIDS, and 50% are women.[5]

Historically, the medical community has considered HIV a serious barrier to reproduction. In 1985, the Centers for Disease Control and Prevention (CDC) encouraged HIV-infected women to defer pregnancy because of poor prognoses associated with HIV infection and the risk of perinatal transmission.[6,7] In 1987, the American College of Obstetrics and Gynecology (ACOG) advised physicians to encourage women infected with HIV not to become pregnant, and to inform pregnant HIV-infected women of termination options.[8] The Ethics Committee of the American Society for Reproductive Medicine suggested in 1994 that physicians "counsel couples about the consequences of using potentially infected sperm and discuss the options of donor sperm, adoption, or not having children."[9] Over the past 10 years the introduction of potent antiretroviral therapy has resulted in HIV-seropositive patients living longer, healthier lives.[7] Many health care providers now view HIV infection as a manageable chronic illness and encourage patients to maintain normal lives.[10]

The desire for HIV-infected patients to conceive has been a topic of recent research.[10-13] Similar to the general population, HIV-affected couples desire to have children.[11,13] Chen and colleagues found that 28% to 29% of 1421 HIV-infected adults surveyed desired to have children sometime in their lives.[11] In a retrospective study, HIV-infected subjects cited raising children as a way to give purpose to life.[14] In addition, many HIV-infected women reported pregnancy and childbirth as a way to regain their sense of womanhood and sexuality, often making childbearing a high personal priority.[15] In view of these data, health care professionals must balance concerns about the risks of HIV transmission with the patients' desire to have children.[16] Physicians must respect patient rights and autonomy by providing them with information that will allow them to make informed reproduction decisions.

Prior to potent antiretroviral therapy, HIV-infected women had a 25% chance of delivering an HIV-infected child, compelling physicians to recommend bilateral tubal ligation to prevent perinatal HIV transmission.[3,17] Between 1991 and 1993, early trials conducted by the Pediatric AIDS Clinical Trial Group (PACTG) found that zidovudine reduced mother-to-child transmission from 25% to 8%.[18] With antiretroviral therapy and elective cesarean section, the risk of perinatal transmission has dramatically decreased to 1% to 2%. Recent studies have also demonstrated mother-to-child transmission rates as low as 1% to 2% in women with HIV RNA levels below 1000 copies/mL regardless of mode of delivery, suggesting that perinatal transmission can be prevented in 99% of all cases.[17,19,20]

In 2001, the CDC amended its previous recommendations, stating that HIV-infected pregnant women should receive information about all reproductive options and that reproductive counseling should be nondirective and supportive of the patient's decision.[21] Currently ACOG now states that "assisted reproductive technologies should not be denied to HIV-infected couples solely on the basis of their positive HIV serostatus."[7] Unfortunately, HIV infection is the seventh-leading cause of death among children aged 1 to 4 years, and perinatal trans-

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mission is still responsible for 90% of pediatric HIV infections.[2,22] This attests to the infectivity of the disease and the importance of bringing reproductive issues to the forefront.

In 1999 Duggan and colleagues interviewed a group of 69 HIV-infected women about reproductive concerns (ie, counseling, contraception, and pregnancy choices). Less than 50% thought that their physician had adequately counseled them regarding contraception. The group cited social workers and nurses as its main source of reproduction counseling.[23-25] Through education and a willingness to discuss reproductive options with affected couples, health professionals can alleviate patients' fears and anxieties concerning HIV infection and reproduction.

The medical and social conditions of these couples vary widely. A serodiscordant couple is defined as 1 HIV-infected partner and 1 HIV-uninfected partner. A seroconcordant couple is defined as 2 HIV-infected partners. The following case studies demonstrate the various struggles faced by couples affected by HIV as they consider reproduction. Table 1 may be useful to physicians assisting HIV-affected couples seeking reproduction.

Serodiscordant Couples

Alex and Darlene

Alex is a 30-year-old Hispanic man who was diagnosed with HIV in 2001. His HIV risk group is multiple heterosexual partners. Alex and his wife Darlene (HIV-uninfected) have a 4-year-old daughter. Alex is adherent to his therapy of zidovudine/lamivudine (combined formulation) and nevirapine, and he uses condoms regularly. His initial CD4+ cell count was 170/µL and plasma HIV RNA level was 3,013 copies/mL. On antiretroviral therapy his CD4+ cell count is 377/µL and his HIV RNA level is below 75 copies/mL.

Alex and Darlene have discussed having a second child but have not tried to conceive because of HIV transmission concerns. In 2002, Alex and Darlene began asking his physician questions about reproductive options. They were given several pamphlets on the topic but still had many questions. Alex and Darlene are interested in pursuing safe reproductive alternatives that will assure mother and child safety, but they have significant financial concerns.

Serodiscordant couples face many obstacles to considering reproduction, specifically the risk of HIV transmission between partners and transmission to the child. Men and women are each at risk of transmission from their HIV-i nfected partners. Studies indicate that although the risk of heterosexual transmission is relatively low, rate of male-to-female transmission per contact is significantly greater (0.001) than the risk of female-to-male transmission (< 0.001).[21,22,26] These probabilities increase with higher plasma HIV-1 RNA levels in the HIV-infected partner and the presence of other sexually transmitted diseases in either partner.[27]

A meta-analysis conducted by Davis and Weller in 1999 reported 0.9 seroconversions per 100 person-years of observation among participants who reported always using condoms, compared with a seroconversion rate of 6.7 per 100 person-years of observation among those who reported never using

Table **1**. Suggested Preconception Steps[7,10,12,36,67]

Disclosure of serostatus
Practicing safe sex
Preconception counseling:
Discussion of risk to partner and baby
Current and future health of infected partner(s)
HIV testing pre- and post-pregnancy
Absence of an active AIDS-defining illness
CD4+ cell count >350/µL and HIV RNA level <50,000 copies/mL
Patients receiving antiretroviral therapy:
HIV RNA level <400 copies/mL
Regimen without teratogenic drugs
Adequate therapy for at least 1 year with appropriate follow-up (stable viral load and CD4+ cell count)
Normal Physical Examination:
Women
Vaginal Papanicolaou smear
Cervical mucous culture
Screen for bacterial vaginosis
Vaginal ultrasound of uterus and ovaries
Sonohysterogram
Basal (cycle day 3) follicle stimulating hormone <15 MIU/mL and estradiol <65 pg/mL
Men
Sperm specimen analyzed for count, motility, progression, and morphology
Men and Women
Laboratory workup
Complete blood cell (CBC) differential
Liver panel
Hepatitis virus screening
Pelvic exam
Absence of active or acute sexually transmitted disease
Full sexual health screen for both partners:
HIV
Syphilis
Gonorrhea
Chlamydia
Trichomniasis
If not previously checked:
Tuberculin skin test
Chest radiograph
Immunization screening

condoms. This analysis suggests that consistent use of condoms provides an 85% reduction in HIV transmission risk, compared with no use of condoms.[28] Despite transmission risks with unprotected sexual intercourse, HIV-discordant couples are often willing to practice unsafe sexual intercourse in order to conceive. Klein and colleagues reported that 80% of HIV-affected couples surveyed who had previously conceived had engaged in unprotected intercourse to achieve pregnancy.[12] Cusick and Rhodes found that HIV-affected couples associated condom use with the "early stages" of a relationship, and that encouraging continued safer sex seemed to threaten love and intimacy as the relationship matured.[29] Because serodiscordant couples are willing to take these risks, physicians should be willing to participate in honest discussions regarding reproduction.

Interventions

Assisted Reproduction Techniques

Two assisted reproductive technologies have been studied in HIV serodiscordant couples: artificial insemination and in vitro fertilization (IVF). Some research suggests that the use of assisted reproductive techniques decreases the chance of horizontal transmission to almost negligible rates, which provides HIV-infected couples with the possibility of pregnancy while minimizing the number of "unprotected" exposures necessary to conceive.[7,30,31]

Several studies have been conducted to determine the infectivity of seminal and spermatozoal cells in order to assess the possibility of transmission from an HIV-infected man to his partner.[32-34] Quayle and colleagues reported that HIV could be found in seminal cell preparations but not in spermatozoal fractions.[34] Kim and coworkers also demonstrated that seminal plasma and nonspermatozoal cells serve as the main viral reservoir, whereas motile sperm were unlikely to be infective because of a lack of expression of CD4+ and CCR5 receptors on the spermatozoal cell surface.[29] Although there is no evidence that any of these methods will consistently provide HIV-free sperm, there are 3 established methods used to remove HIV from seminal fluid or from nonspermatozoal cells: basic sperm washing, density gradient centrifugation, and the "swim up" method. These methods can be used separately or in combination.

Basic sperm wash is based on the premise that HIV-infective material exists primarily in the seminal fluid and not within sperm cells.[35] The process begins as sperm is separated from seminal fluid by repeated cycles of centrifugation. The seminal fluid, which will then contain low-motile, dead, or abnormal spermatozoa and seminal nonspermatozoa, is discarded, and the final spermatozoal pellet can be prepared for "swim up."[33,36]

Density gradient centrifugation is used to separate seminal plasma by particle weight and size to achieve a final preparation of isolated sperm, which is then washed and layered on a dual density gradient.[7] The gradient is a colloidal silica suspension layered with the heaviest layer on the bottom and the human ejaculate on top.[37,38] The test tube is then centrifuged to separate the motile spermatozoa from human ejaculate. The nonmotile, poor-quality sperm and nonspermatozoal cells remain in the supernatant located in the top layers, and the motile sperm can swim to the bottom. The sperm pellet at the bottom of the tube can then be used for insemination.[36,37]

Following the centrifugation process, the final sperm pellet can be resuspended and overlaid in a fresh medium and allowed to incubate for 20 to 60 minutes to allow the motile sperm to "swim up" to the supernatant.[30,36] The swim-up fraction should then contain only the enriched preparation of motile spermatozoa without the other, possibly disease-laden, cellular components.[7,33]

Two groups have published data using variations of sperm washing for intrauterine insemination (IUI) in serodiscordant couples and suggest that "with appropriate processing of samples ... horizontal transmission can be avoided."[7] Semprini and colleagues assessed the feasibility of removing infective cellular components in ejaculate using gradient centrifugation, repeated washings, and swim-up techniques.[30] Indirect immunofluorescent assays using monoclonal antibodies were used to verify the absence of infected cells. Twenty-nine discordant HIV-affected couples underwent 59 insemination attempts, which resulted in 17 pregnancies—a 29% success rate. Of the 18 women inseminated, none seroconverted after 18 months of follow-up. As of 2002, Semprini and colleagues report no seroconversions in the 2000 inseminations of 800 women.[39,40]

In a study conducted by Marina and colleagues, the processed semen of 63 HIV-infected men was evaluated for HIV.[31] Researchers processed semen utilizing sperm washing, density gradient centrifugation, and swim-up techniques. They evaluated the specimens by HIV RNA and DNA polymerase chain-reaction (PCR) testing to verify lack of HIV DNA. Thirty-one pregnancies were reported, and 37 children were born with no evidence of transmission to the HIV-uninfected mother. Mothers were HIV seronegative at least 6 months after their last IUI.

A study conducted by Sauer and Chang used in vitro fertilization with intracytoplasmic sperm injection (ICSI) to reduce the risk of transmission from an HIV-infected man to an HIV-uninfected woman. To eliminate the presence of HIV-infected semen and nonspermatozoal cells, this process used a single sperm to fertilize (in vitro) the egg of an HIV-uninfected woman. Semen samples from asymptomatic HIV-infected men were processed using density gradient centrifugation to produce a pellet of purified motile sperm, which was then used to inseminate the egg. Thirty-four women underwent 55 treatment cycles, resulting in 25 pregnancies and 17 deliveries. During this study, no seroconversions were noted in 6 months for those women who did not get pregnant, and for 3 months after delivery for the 17 mothers. Also, there were no seroconversions reported among the 25 delivered infants.[10]

Limitations of Reproductive Techniques

Although assisted reproductive technologies seem to provide a possible alternative for HIV-affected couples who desire reproduction, many remain unconvinced that these are entirely risk-free procedures. In editorials, CDC experts questioned the apparent success of the European studies that serve as the

backbone of the assisted reproductive research.[41,42] The CDC authors assert that because of lack of follow-up in the European studies, their statistical relevance remains unproven, and that "it would be difficult to assess whether intrauterine insemination (IUI) with processed semen is less risky than unprotected intercourse because the rate of sexual transmission is very low (one to two transmissions per 1000 acts of protected intercourse)."[41] They argue that small sample sizes in the European studies limit the applicability of assisted reproduction to a larger population.

Twinning is also considered a potentially negative consequence of assisted reproductive technologies. For the US population, there are approximately 29.3 twin births per 1,000 total births, a twinning rate of 2.93%.[43] The twinning rates with assisted reproductive technologies are much higher. For example, Marina and colleagues reported a 20% twinning rate in 37 births to 31 women.[31] Sauer and Chang's research reported 17 pregnancies with a twinning rate of 35%.[10] Finally, in 2003, Marina and colleagues reported a twinning rate of 30% in 58 women undergoing IVF and ICSI.[44]

Assisted reproductive techniques are expensive ($10,000 to $17,000 per cycle) and thus many couples find them exclusionary. In a study of serodiscordant couples who sought in vitro fertilization, the majority of patients were employed (90%) and had college degrees (82%-84%).[12] National surveillance studies, however, suggest that the poor (ie, not employed and less educated) are disproportionately affected by HIV, placing expensive reproductive procedures out of reach for the majority of couples.[1]

Physicians can still provide useful guidance to couples with little or no access to these expensive procedures. Oyesiku and Turner describe timed ovulatory intercourse as a "relatively safe and cost-effective" reproductive option, provided that the male partner's HIV viral load is below detectable levels and the CD4+ cell count is above 400/µL.[35] Gilling-Smith also described timed intercourse using ovulation detection methods, citing a 4% transmission rate in 92 serodiscordant couples, with seroconversions restricted only to partners who reported inconsistent condom use outside the "fertile period."[36] Both partners should be screened for factors known to reduce fertility prior to timed intercourse to prevent unnecessary exposure to the seronegative partner (Table 1). Men can provide single semen specimens that can be analyzed for count, motility, progression, and morphology in both ejaculate and swim-up. Women should receive pelvic ultrasonographic scans during the early follicular phases of their cycles, as well as endocrine profiles of follicle-stimulating, luteinizing, and thyroid functioning hormones.[36] Physicians can then more accurately advise patients with regard to engaging in unprotected intercourse during the "fertility period."

The fertility period is defined as the specific days relative to ovulation during which a woman is most likely to conceive,[45] which consists of 6 days: the day of ovulation and 5 days prior.[46] There are 5 recognized methods used to identify the fertility window: basal body temperature, calendar calculation, serial ovarian ultrasound, hormones in urine, and vaginal discharge. Calendar calculation and basal body temperature are considered the most unreliable methods of ovulation detection. Calendar calculation depends on statistical averages, which are variable and may unduly expose HIV-uninfected women to HIV, and basal body temperature typically does not rise until after ovulation, creating difficulty in identifying the actual day of ovulation.[45] Serial ovarian ultrasound is highly accurate but expensive and not readily available. Urine luteinizing hormone (LH) kits detect a rise in LH, which occurs between 16 and 48 hours before ovulation, making them moderately effective in determining ovulation. Monitoring changes in cervical and vaginal discharge is considered the most effective method of determining ovulation. Type E (estrogenic) mucus occurs 5 days to 6 days prior to ovulation, during the fertility window. The clear, stretchy, slippery discharge facilitates the transport and survival of sperm in the cervix, and is known to be the best indication of ovulation.[38]

Beth and Sam

Beth is a 26-year-old white woman who was diagnosed with HIV in October 1999. She contracted HIV and hepatitis C virus (HCV) through heterosexual intercourse with a previous boyfriend, an injection drug user. Beth now lives with her current boyfriend, Sam, who has consistently tested seronegative for HIV. Beth's most recent CD4+ cell count was 690/µL, and her most recent HIV RNA level was 2,362 copies/mL. She is not currently on antiretroviral therapy.

Sam and Beth are practicing safe sex (they use condoms) but are ready to do "whatever it takes" to have a child. The couple has questioned Beth's physician about available options and has extensively researched their options. They are now confident that they are aware of every option available to date. However, Beth thinks they should defer any procedure until they can be guaranteed 100% safety for Sam and the child.

Serodiscordant couples in which the woman is HIV-infected have significant concerns about HIV transmission to the child and transmission to the HIV-uninfected man. Although recent data indicate that a low viral load greatly reduces perinatal transmission risk, more than 90% of HIV infections in children are acquired from mother-to-child transmission, with most cases occurring during labor, delivery, or via breast-feeding.[7]

Nearly 33% of HIV-infected individuals are coinfected with HCV, which should be a factor when considering reproduction.[7] Women on antiretroviral therapy who are coinfected with HCV are at risk of liver cirrhosis and have higher mortality than those with HCV infection alone.[47] Because of reports of increased risk of perinatal HIV transmission among women who are coinfected with HIV and HCV, women with HCV coinfection should be evaluated by a hepatologist experienced with HIV coinfection.[7,48]

Pregnancy does not exacerbate HIV disease progression in women with asymptomatic, controlled disease. However, it is advisable to avoid certain antiretroviral drugs during pregnancy.[49-53] Drug combinations that include didanosine and stavudine, for example, are associated with complications, albeit rarely, including metabolic acidosis, which may occur at a higher rate in pregnancy.[54] Hepatic toxicity with nevirapine may also be more common in pregnancy, and recent recommenda-

tions suggest frequent liver-function monitoring, particularly early in therapy.[55] HIV-infected pregnant women taking protease inhibitors (PIs) should be closely monitored because of the association of metabolic disturbances (including hyperglycemia and diabetes mellitus), which deserve particular attention given the rate of gestational diabetes among HIV-uninfected pregnant women.[56,57] The PIs indinavir and atazanavir can cause hyperbilirubinemia and thus carry a risk of kernicterus.[56,58] Efavirenz and amprenavir are associated with tetratogenicity and should be avoided during pregnancy.[7] The long-term outcomes of in utero exposure to antiretroviral drugs have yet to be determined.[7]

Artificial insemination and self-insemination can be used to decrease the risk of HIV transmission to the male partner. Ohl and colleagues identified IVF and ICSI as the artificial insemination techniques of choice for an HIV-infected woman in a serodiscordant couple.[59] IVF optimizes the probability of success and diminishes the number of attempts necessary to conceive. The ICSI method, the most expensive assisted-reproductive procedure, involves the injection of a single sperm directly into the cytoplasm of a mature egg, and reduces the delay of conception. However, neither process is available to HIV-infected women in the United States. Instead, at Columbia University's Center for Women's Reproductive Care in New York, IUI is performed on HIV-infected women with sperm from an HIV-uninfected man.[60] Self-insemination is a viable, low-cost alternative for the serodiscordant couple. Women can inseminate themselves with freshly ejaculated semen using a syringe (without the needle) or a disposable plastic Pasteur pipette.[61]

Seroconcordant Couples

Jose and Marianne

Jose is a 37-year-old man diagnosed in 1992 with HIV, which he contracted through heterosexual contact. He is coinfected with HCV. Jose is married to Marianne, who he met at an HIV support group, and together they have a 4-year-old daughter (HIV-uninfected). His most recent CD4+ cell count was 703/µL, and his plasma HIV RNA level was less than 50 copies/mL. He has been on a regimen of zidovudine/lamivudine (combined formulation) and indinavir for more than five years.

Marianne is a 33-year-old woman who contracted HIV in 1993 through intravenous drug use and has been clean for 8 years. Her most recent CD4+ cell count was 414/µL, and her most recent HIV RNA level was 4,000 copies/mL. She is on no antiretroviral medications, but she previously took zidovudine during her first pregnancy, with which she had a cesarean section.

Marianne is pregnant with their second child. Marianne was not on antiretroviral therapy while they were trying to conceive, and she is now concerned about starting antiretrovirals because of possible effects of the medications on her unborn child. Jose and Marianne usually use condoms during sexual activity.

Current treatment guidelines suggest seroconcordant couples like Jose and Marianne should practice safe sex because of possible transmission of drug-resistant HIV strains or superinfection.[62] However, Rhodes and Cusick found that unprotected sex was deemed an acceptable risk by partners in a seroconcordant relationship, citing that no HIV-infected respondents continued "safe sex" beyond the "early stages" of their relationship.[63] Adam and Sears interviewed 60 people with HIV or AIDS and 40 of their caregivers, and their results confirm that HIV-infected individuals thought seeking a seroconcordant partner was an acceptable alternative to celibacy.[64] Once relationships became more intimate, the use of condoms served as a sign of "emotional distance" and "a protection from one another."[63] However, Squires notes the necessity of safe sex between seroconcordant partners, citing the possible threat of horizontal and vertical transmission of a drug-resistant strain of HIV.[65]

HIV-infected women may worry about the effects that antiretroviral drugs will have on the pregnancy and the child. The International AIDS Society–USA (IAS–USA) suggests that before establishing a peripartum therapy, mothers should undergo drug resistance testing to ensure that the treatment chosen is effective for the mother herself and for preventing transmission of a drug-resistant strain of HIV to the child.[66] In June 2003, the Public Health Service Task Force's *Recommendations for Use of Antiretroviral Drugs in Pregnant HIV-1-Infected Women for Maternal Health and Interventions to Reduce Perinatal HIV-1 Transmission in the United States* noted that pregnancy requires "unique considerations, including the possible need to alter dosage as a result of physiologic changes associated with pregnancy and the potential for adverse short- or long-term effects on the fetus and newborn."[67] No studies have indicated that there is an increase in birth defects related to HIV infection; however, efavirenz is not recommended in the early stages of pregnancy.[68] Birth defects (anencephaly, anopthalmia, or cleft palate) occurred in 15% of monkeys born after efavirenz exposure during the first trimester of pregnancy.[69] According to the Antiretroviral Pregnancy Registry (http://www.apregistry.com/), the rate of birth defects among infants born to 400 women exposed to zidovudine or lamivudine during the first trimester has been no higher than the rates among infants who were exposed after the first trimester.[69] Additionally, there are no well-controlled studies of teratogenicity using nevirapine, therefore it should be used with caution and in accordance with its label.

There may also be enhancement of metabolic side effects, such as mitochondrial toxic effects leading to increased lactic acidosis in pregnant women on nucleoside reverse transcriptase inhibitors (nRTIs).[67,69] Some researchers question that there may be mitochondrial dysfunction in infants exposed to nRTIs; however, a review examining 16,000 children in cohorts in the United States showed no increase in the rate of death in children exposed to nRTIs, compared with children with no such exposure, and "no deaths were found to be definitely related to mitochondrial toxicity."[67,69] Although reports have been conflicting, physicians should also be aware of the potentially increased risk of preterm delivery among HIV-infected women who are receiving combination antiretroviral therapy.[67,69]

Physicians should consider screening women with HIV for vaginal disease. Bacterial vaginosis is associated with adverse pregnancy outcomes, including premature rupture of mem-

branes, preterm labor, preterm birth, and postpartum endometritis.[70] Trichomoniasis, which can be found in women with HIV, is also associated with adverse pregnancy outcomes such as premature rupture of the membranes, preterm delivery, and low birth weight.[70] Additionally, HIV-infected women should be carefully assessed for anovulation or amenorrhea secondary to HIV infection, or other causes such as hypothalamic disorders or substance abuse.

Before considering pregnancy, some studies suggest it is important to have a viral load below the limits of detection.[16] Expensive procedures such as IVF and ICSI with prepared sperm, as mentioned for serodiscordant couples, are viable alternatives for seroconcordant partners.[7] Though not without risks, timed intercourse combined with suppressed viral load and proper prenatal care can often produce a healthy, HIV-uninfected child.[16]

Conclusion

Sauer, in a recent commentary, summarizes the state of assisted reproductive care in HIV serodiscordant couples.[39] Sauer points out that although European centers have been using IUI or IVF in serodiscordant couples with no seroconversions, many US physicians are concerned about transmission occurring through IUI. Currently, there are no established laboratory measures to ensure the safety of the uninfected spouse and fetus. Additionally, knowingly inseminating a woman with sperm from an HIV-infected man has been established by several states as a criminal act. At Columbia University in New York, ICSI is performed on HIV-uninfected women with sperm washed from HIV-infected men. The group also performs IUI on HIV-infected women with sperm from HIV-uninfected men.[60]

Couples affected by HIV may be interested in engaging their medical provider in discussions about available reproductive options. It is important that physicians are aware of the reproductive options available to serodiscordant and seroconcordant couples. Recognizing the issues these couples face will enable physicians to offer honest, nonjudgmental preconception counseling. For couples affected by HIV, preconception care must focus on infection status, viral load, immune status, and education regarding risk of HIV transmission.[67] A multidisciplinary team (infectious diseases, obstetrics, etc) may be beneficial.

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References

1. Karon JM, Fleming PL, Steketee RW, DeCock KM. HIV in the United States at the turn of the century: an epidemic in transition. *Am J Public Health*. 2001;91:1060-1068.
2. Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report*. Midyear ed. 2001:13(1). Available at: www.cdc.gov/hiv/stats/hasr1301.htm.
3. Drapkin-Lyerly A, Anderson J. Human immunodeficiency virus and assisted reproduction: reconsidering evidence, reframing ethics. *Fertil Steril*. 2001;75:843-858.
4. Pomeroy EC, Green DL, Van Laningham L. Couples who care: the effectiveness of a psychoeducational group intervention for HIV serodiscordant couples. *Social Work in Practice*. 2002;12:238-252.
5. UNAIDS. AIDS epidemic update: December 2003. Available at: http://www.unaids.org/en/resources/epidemiology/epidemicupdateslides.asp. Accessed April 13, 2004.
6. Centers for Disease Control and Prevention. Current trends recommendations for assisting in the prevention of perinatal transmission of human T-lymphotropic virus type III/lymphadenopathy-associated virus and acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep*. 1985;34:721-726.
7. Al-Khan A, Colon J, Palta V, Bardeguez A. Assisted reproductive technology for men and women infected with human immunodeficiency virus type 1. *Clin Infect Dis*. 2003;36:195-200.
8. Kass NE. Policy, ethics, and reproductive choice: pregnancy and childbearing among HIV-infected women. *Acta Paediatr Suppl*. 1994;400:95-98.
9. Special considerations regarding human immunodeficiency virus and assisted reproductive technologies. *Fertil Steril*. 1994;62(Suppl 1):85S.
10. Sauer MV, Chang PL. Establishing a clinical program for human immunodeficiency virus 1-seropositive men to father seronegative children by means of in vitro fertilization with intracytoplasmic sperm injection. *Am J Obstet Gynecol*. 2002;186:627-633.
11. Chen JL, Philips KA, Kanouse DE, Collins RL, Miu A. Fertility desires and intentions of HIV-positive men and women. *Fam Plann Perspect*. 2001;33:144-52, 165.
12. Klein J, Pena JE, Thornton MH, Sauer MV. Understanding the motivations, concerns, and desires of human immunodeficiency virus 1-serodiscordant couples wishing to have children through assisted reproduction. *Obstet Gynecol*. 2003;101:987-994.
13. Van DeVanter N, Cleary PD, Moore J, Thacker AS, O'Brien TR. Reproductive behavior in HIV-discordant heterosexual couples: implications for counseling. *AIDS Patient Care STDS*. 1998;12:43-49.
14. White J, Melvin D, Moore C, Crowley S. Parental HIV discordancy and its impact on the family. *AIDS Care*. 1997;9:609-615.
15. Wesley Y, Smeltzer SC, Redeker NS, Walker S, Palumbo P, Whipple B. Reproductive decision making in mothers with HIV-1. *Health Care Women Int*. 2000;21:291-304.
16. Ethics Committee of the American Society for Reproductive Medicine. Human immunodeficiency virus and infertility treatment. *Fertil Steril*. 2002;77:218-222.
17. Minkoff H. Human immunodeficiency virus infection in pregnancy. *Obstet Gynecol*. 2003;101:797-810.
18. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of human immunodeficiency virus type 1 with zidovudine treatment. Pediatric AIDS Clinical Trials Group Protocol 076 Study Group. *N Engl J Med*. 1994;331:1173-1180.
19. Cooper ER, Charurat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1 transmission. *J Acquir Immune Defic Syndr*. 2002;29:484-494.
20. Dorenbaum A, Cunningham CK, Gelber RD, et al. Two-dose intrapartum/newborn nevirapine and standard antiretroviral therapy to reduce perinatal HIV transmission: a randomized trial. *JAMA*. 2002;288:189-198.
21. Centers for Disease Control and Prevention. Revised guidelines for HIV counseling, testing, and referral. *MMWR Recomm Rep*. 2001;50(RR-19):1-57.
22. Horvath PM. Should we screen couples for HIV status when they are seeking IVF treatment. *Contemporary OB/GYN*. 2001;46:29-34.
23. Duggan J, Walerius H, Purohit A, et al. Reproductive issues in HIV-seropositive women: a survey regarding counseling, contraception, safer

sex, and pregnancy choices. *J Assoc Nurses AIDS Care.* 1999;10:84-92.
24. Epstein RM, Morse DS, Frankel RM, Frarey L, Anderson K, Beckman HB. Awkward moments in patient-physician communication about HIV risk. *Ann Intern Med.* 1998;128:435-442.
25. Manning DT, Barenberg N, Gallese L, Rice JC. College students' knowledge and health beliefs about AIDS: implications for education and prevention. *J Am Coll Health.* 1989;37:254-259.
26. Royce RA, Sena A, Cates W, Cohen MS. Sexual transmission of HIV. *N Engl J Med.* 1997;336:1072-1078.
27. Lee TH, Sakahara N, Fiebig E, Busch MP, O'Brien TR, Herman SA. Correlation of HIV-1 RNA levels in plasma and heterosexual transmission of HIV-1 from infected transfusion recipients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;12:427-428.
28. Davis KR, Weller SC. The effectiveness of condoms in reducing heterosexual transmission of HIV. *Fam Plann Perspect.* 1999;31:272-279.
29. Cusick L, Rhodes T. Sustaining sexual safety in relationships: HIV positive people and their sexual partners. *Cult Health Sex.* 2000;2:473-487.
30. Semprini AE, Levi-Setti P, Bozzo M, et al. Insemination of HIV-negative women with processed semen of HIV-positive partners. *Lancet.* 1992;340:1317-1319.
31. Marina S, Marina F, Alcolea R, et al. Human immunodeficiency virus type 1—serodiscordant couples can bear healthy children after undergoing intrauterine insemination. *Fertil Steril.* 1998;70:35-39.
32. Kim LU, Johnson MR, Barton S, et al. Evaluation of sperm washing as a potential method of reducing HIV transmission in HIV-discordant couples wishing to have children. *AIDS.* 1999;13:645-651.
33. Pasquier C, Daudin M, Righi L, et al. Sperm washing and virus nucleic acid detection to reduce HIV and hepatitis C virus transmission in serodiscordant couples wishing to have children. *AIDS.* 2000;14:2093-2099.
34. Quayle AJ, Xu C, Tucker L, Anderson DJ. The case against an association between HIV-1 and sperm: molecular evidence. *J Reprod Immunol.* 1998;41:127-136.
35. Oyesiku JO, Turner CF. Reproductive choices for couples with haemophilia. *Haemophilia.* 2002;8:348-352.
36. Gilling-Smith C. Assisted reproduction in HIV-discordant couples. *AIDS Read.* 2000;10:581-587.
37. Fertility Center of California. Fertility tests and other services. Available at: http://www.fertilityctr.com/fertilit.htm. Accessed April 13, 2004.
38. The National Fertility Directory. Sperm washing. Available at: http://www.fertilitydirectory.org/sperm_washing.html. Accessed April 13, 2004.
39. Sauer MV. Providing fertility care to those with HIV: time to re-examine healthcare policy. *Am J Bioeth.* 2003;3:33-40.
40. Semprini AE, Vuccetich A, Oneta M. Amp intra conjugale: quelle strategie de prise en charge? L'experience italienne. Communication a la journee: Le desir d'enfant chez les couples VIH serodifferents. *Toulouse.* 2002;28-29.
41. Jamieson DJ, Schieve L, Duerr A. Semen processing for HIV-discordant couples. *Am J Obstet Gynecol.* 2001;185:1433-1434.
42. Duerr A, Jamieson D. Assisted reproductive technologies for HIV-discordant couples. *Am J Bioeth.* 2003;3:45-47.
43. Martin JA, Hamilton BE, Ventura SJ, Menacker F, Park MM. Births: final data for 2000. *Natl Vital Stat Rep.* 2002;50:1-101.
44. Marina S, Semprini AE, Marina F, et al. Results of 219 IVF-ICSI cycles in serodiscordant couples (seropositive men) to HIV-1. *Hum Reprod.* 2003;18:52.
45. Stanford JB, White GL, Hatasaka H. Timing intercourse to achieve pregnancy: current evidence. *Obstet Gynecol.* 2002;100:1333-1341.
46. Wilcox AJ, Weinberg CR, Baird DD. Timing of sexual intercourse in relation to ovulation. Effects on the probability of conception, survival of the pregnancy, and sex of the baby. *N Engl J Med.* 1995;333:1517-1521.
47. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with human immunodeficiency virus and the role of hepatitis C or B virus infection. *JAMA.* 2000;283:74-80.
48. Hershow RC, Riester KA, Lew J, et al. Increased vertical transmission of human immunodeficiency virus from hepatitis C virus-coinfected mothers. Women and Infants Transmission Study. *J Infect Dis.* 1997;176:414-420.
49. Berrebi A, Kobuch WE, Puel J, et al. Influence of pregnancy on human immunodeficiency virus disease. *Eur J Obstet Gynecol Reprod Biol.* 1990;37:211-217.
50. Saada M, Le Chenadec J, Berrebi A, et al. Pregnancy and progression to AIDS: results of the French prospective cohorts. SEROGEST and SEROCO Study Groups. *AIDS.* 2000;14:2355-2360.
51. Weisser M, Rudin C, Battegay M, Pfluger D, Kully C, Egger M. Does pregnancy influence the course of HIV infection? Evidence from two large Swiss cohort studies. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1998;17:404-410.
52. Hocke C, Morlat P, Chene G, Dequae L, Dabis F. Prospective cohort study of the effect of pregnancy on the progression of human immunodeficiency virus infection. The Groupe d'Epidemiologie Clinique Du SIDA en Aquitaine. *Obstet Gynecol.* 1995;86:886-891.
53. Bessinger R, Clark R, Kissinger P, Rice J, Coughlin S. Pregnancy is not associated with the progression of HIV disease in women attending an HIV outpatient program. *Am J Epidemiol.* 1998;147:434-440.
54. Mandelbrot L, Kermarrec N, Marcollet A, et al. Case report: nucleoside analogue-induced lactic acidosis in the third trimester of pregnancy. *AIDS.* 2003;17:272-273.
55. Boehringer Ingelheim. Viramune (nevirapine). Ridgefield, CT: Boehringer Ingelheim, Pharmaceuticals; 2003.
56. Jennings PR, Romanelli F, Ridings H, Pomeroy C. Managing HIV-infected pregnant patients. *Physician Assist.* 2000;28-39.
57. Vigouroux C, Gharakhanian S, Salhi Y, et al. Adverse metabolic disorders during highly active antiretroviral treatments (HAART) of HIV disease. *Diabete Metab.* 1999;25:383-392.
58. Powderly W. Limitations of current HIV therapies: opportunities for improvement. *J Acquir Immune Defic Syndr.* 2003;33(Suppl 1):S7-S12.
59. Ohl J, Partisani M, Wittemer C, et al. Assisted reproduction techniques for HIV serodiscordant couples: 18 months of experience. *Hum Reprod.* 2003;18:1244-1249.
60. Foley TN. Personal communication. Donor Coordinator, Columbia University Center for Womens' Reproductive Care. January 27, 2000.
61. Malpani A, Malpani A. *How to have a baby: overcoming infertility.* New Dehli, India: USB Publishers' Distributors; 2001.
62. Kahn F. Does safe sex matter in HIV-positive couple? *Cortlandt Forum.* 1995;8:92.
63. Rhodes T, Cusick L. Love and intimacy in relationship risk management: HIV positive people and their sexual partners. *Sociol Health Illn.* 2000;22:1-26.
64. Adam BD, Sears A. Negotiating sexual relationships after testing HIV-positive. *Med Anthropol.* 1994;16:63-77.
65. Squires KE. Women's issues: treating HIV infection and AIDS in women. *AIDS Read.* 2003;13:228-240.
66. Hirsch MS, Brun-Vézinet F, D'Aquila RT, et al. Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society-USA Panel (updated guidelines are in press). *JAMA.* 2000;283:2417-2426.
67. Public Health Service Task Force. Recommendations for use of antiretroviral drugs in pregnant HIV-1 infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. Available at: http://www.aidsinfo.nih.gov/guidelines/perinatal/archive/PER_061603.pdf. Accessed April 26, 2004.
68. Fundaro C, Genovese O, Rendeli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS.* 2002;16:299-300.
69. Watts DH. Management of human immunodeficiency virus infection in pregnancy. *N Engl J Med.* 2002;346:1879-1891.
70. Workowski KA, Levine WC. Sexually transmitted diseases treatment guidelines. *MMWR Morb Mortal Wkly Rep.* 2002;51:42-45.

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