

Topics in **HIV Medicine**[™]

Formerly – *Improving the Management of HIV Disease*

A publication of the International AIDS Society–USA

Perspectives

Strategies for Management of Antiretroviral Failure 4

Scott M. Hammer, MD

Treatment Changes in Early (First) Virologic Failure • Factors Contributing to Drug Failure • Delayed Immunologic Deterioration in Protease Inhibitor Failure • Options in Multiple Failure

New Developments in HIV Care for Women 9

Meg D. Newman, MD

Epidemiology • Prognosis and Antiretroviral Therapy • Pregnancy and Mother-to-Child Transmission • Gynecologic Care

Postexposure Prophylaxis: Needles, Sex, and Drugs 14

Julie L. Gerberding, MD, MPH

Postexposure Prophylaxis for Occupational Exposure • Postexposure Prophylaxis for Sexual or Injection Drug Use Exposure

About This Issue

This issue of *Topics in HIV Medicine* (formerly *Improving the Management of HIV Disease*) is the second to feature our new design and name. It presents the first summary articles of presentations given at the current International AIDS Society—USA 2000 Winter/Spring course series, *Improving the Management of HIV Disease: HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management*.

The agendas for this course series reflect the need for information on newer complications of HIV disease and therapy, such as lipid abnormalities and mitochondrial toxicity, and newer therapeutic strategies, such as resistance testing and treatment interruption, as well as for regular updates on ongoing challenges: drug failure, the timing of treatment initiation, and how to best use new drugs.

This issue summarizes a presentation on antiretroviral failure management by Dr Scott M. Hammer in Atlanta, a review of HIV and women by Dr Meg D. Newman in Los Angeles, and Dr Julie L. Gerberding's discussion of postexposure prophylaxis, also given in Atlanta. The next issue, to be published in June, will contain a reprint of updated recommendations on antiretroviral drug resistance testing made by an International AIDS Society—USA panel, published in the May 10, 2000, issue of the *Journal of the American Medical Association*.

Unrestricted educational grants supported this issue of *Topics in HIV Medicine* and the 2000 *HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management* program. We gratefully acknowledge:

Major Grant Support

These three companies have continuously supported this program since its inception eight years ago.

Bristol-Myers Squibb Company

Glaxo Wellcome Inc.

Roche Laboratories

And joining as a major supporter this year,

DuPont Pharmaceuticals Company

Substantial Grant Support

Abbott Laboratories

Agouron Pharmaceuticals, Inc.

Merck US Human Health

Generous Grant Support

Roxane Laboratories Inc. / Boehringer Ingelheim

Virco

ViroLogic Inc.

Topics in HIV Medicine™

Topics in HIV Medicine (formerly *Improving the Management of HIV Disease*) is published by the International AIDS Society—USA. This publication is intended to be a resource for physicians and other health care practitioners who are actively involved in HIV and AIDS care.

Editorial Policy

The views and opinions expressed in this publication are those of the contributors and do not necessarily reflect the views or recommendations of the International AIDS Society—USA. *Topics in HIV Medicine* is supported through unrestricted educational grants from several commercial companies that are committed to supporting CME in the field of HIV and AIDS. In the interest of an objective, balanced, and scientifically rigorous publication, the International AIDS Society—USA seeks funding from companies with competing products; these companies have no input or control over the publication content or the selection of contributors. All course faculty and publication contributors provide disclosures of financial interests, and this information is available from the International AIDS Society—USA by request. This publication may contain information about the investigational uses of drugs or products that are not approved by the US Food and Drug Administration. Please consult full prescribing information before using any medication or product mentioned in *Topics in HIV Medicine*.

Copyrights

The contents of *Topics in HIV Medicine* are protected by copyright. We welcome reference to and use of portions of this publication; how-

ever, we request that permission to reproduce or use any part of this publication be obtained from the International AIDS Society—USA. In the case where the International AIDS Society—USA does not own the copyright to materials published in *Topics in HIV Medicine*, permission has been obtained directly from the contributor. All copyrights belong to the contributor and permission to reproduce these materials must be obtained directly from the contributor.

Subscription Information

Topics in HIV Medicine is published 4 to 6 times a year. To obtain a complimentary subscription or notify the International AIDS Society—USA of a change in address, please contact the International AIDS Society—USA at the address listed below.

Correspondence

Topics in HIV Medicine welcomes editorial correspondence. Address letters to:
Editor, *Topics in HIV Medicine*
International AIDS Society—USA
Presidio of San Francisco
1001 B O'Reilly Avenue, Box 29916
San Francisco, CA 94129-0916
Phone: (415) 561-6720
Fax: (415) 561-6740
Web site: <http://www.iasusa.org>
E-mail: topics@iasusa.org

On The Web

Current and previous issues of *Topics in HIV Medicine* are available online at www.iasusa.org.

Topics in HIV Medicine™

A publication of the International AIDS Society—USA

Perspectives

Strategies for Management of Antiretroviral Failure 4

Scott M. Hammer, MD

New Developments in HIV Care for Women 9

Meg D. Newman, MD

Postexposure Prophylaxis: Needles, Sex, and Drugs 14

Julie L. Gerberding, MD, MPH

Announcements

Resistance Testing Guidelines Update 8

Correction 8

Upcoming Events 19

Editorial Board and Board of Directors

Douglas D. Richman, MD
Editor in Chief

Professor of Pathology and Medicine
University of California San Diego and
San Diego Veterans Affairs Medical Center

Constance A. Benson, MD

Professor of Medicine
University of Colorado Health Sciences Center

Peter C. Cassat, JD

Associate
Dow, Lohnes & Albertson

Margaret A. Fischl, MD

Professor of Medicine
University of Miami School of Medicine

Donna M. Jacobsen

Executive Director
International AIDS Society—USA

Harold A. Kessler, MD

Professor of Medicine and
Immunology/Microbiology
Rush Medical College

Michael S. Saag, MD

Professor of Medicine
The University of Alabama at Birmingham

Robert T. Schooley, MD

Professor of Medicine
University of Colorado Health Sciences Center

Paul A. Volberding, MD

Professor of Medicine
University of California San Francisco

Staff and Contributors

Donna M. Jacobsen - Executive Director

Amanda Beacom - Managing Editor

Matthew Stenger - Presentation Editor

Craig High, Diana Voigts - Layout/Graphics

Steven Akers - Transcription

Michelle Tayag - Word Processor

P. S. Print Smart - Printing

Perspectives

Strategies for Management of Antiretroviral Failure

Scott M. Hammer, MD

At the Atlanta course in February, Scott M. Hammer, MD, discussed antiretroviral failure, one of the most pressing current issues for clinicians. Dr Hammer reviewed current approaches to initial failure and salvage therapy, examining the data on specific treatment regimens and on treatment interruptions.

Antiretroviral failure can be associated with a variety of factors, including drug-resistant variants, subinhibitory drug levels, and host immune failure (Figure 1). Drug failure can be defined clinically as disease progression, immunologically as CD4+ cell count decline, or virologically as plasma HIV-1 RNA increase. With the drive to identify drug failure early, increases in viral load most commonly serve as the definition for drug failure and the trigger for decisions to modify therapy. Among the issues to be considered in managing antiretroviral failure is that of what threshold of increase in viral load should serve as a trigger for modifying treatment. This decision will depend on the philosophy of the physician and patient and is also affected by whether it is the first regimen failure or a case of multiple regimen failure. If a change in regimen is considered necessary, the primary question becomes that of how the regimen may be modified to preserve virologic, immunologic, and clinical benefit.

Treatment Changes in Early (First) Virologic Failure

A central question in initial virologic failure is whether all drugs or just selected drugs in the regimen should be changed. Data from the AIDS Clinical Trials Group (ACTG) 343 study indicate that the first resistance mutations to arise in a protease inhibitor/dual nucleoside reverse transcriptase inhibitor (nRTI) regimen that

Dr Hammer is Professor of Medicine at Columbia University College of Physicians and Surgeons and Chief of the Division of Infectious Diseases at Columbia Presbyterian Medical Center in New York City.

In selective drug substitution, the goal of substituting new drugs must be to substantially bolster regimen potency

includes lamivudine are those associated with lamivudine resistance. These results have been borne out with indinavir in the Trilege study, as well as in ACTG 347 with amprenavir and in other data with ritonavir in a lamivudine-containing combination. In 17 patients exhibiting viral rebound during induction-maintenance therapy with indinavir/zidovudine/lamivudine in ACTG 343 (mean weeks on therapy, 45; mean weeks of rebound, 25), none exhibited phenotypic resistance to indinavir (1 exhibited the protease inhibitor-associated M46L resistance mutation), whereas 14 (82%) had phenotypic resistance to lamivudine and the lamivudine-associated

M184V resistance mutation. Such findings indicate that it may not be necessary to change all drugs in a failing regimen and suggest approaches that can potentially preserve drugs for current use or future recycling. However, failure in such cases should still be interpreted as regimen failure and narrow substitutions should be viewed with caution; if part of the regimen is to be maintained, the goal of substituting new drugs must be to substantially bolster the regimen potency.

General options for alternative treatment in initial treatment failure are shown in Table 1. In the case of protease inhibitor-containing initial regimens, susceptibility to protease inhibitors may be retained in subsequent regimens. However, data from ACTG 343 and the Trilege study indicate that suboptimal indinavir blood levels contributed to initial virologic failure; protease inhibitor pharmacokinetics and thus potency can be improved by addition of low-dose ritonavir. With regard to other drugs in initial regimens, resistance to lamivudine or to nonnucleoside reverse transcriptase inhibitors (NNRTIs) is likely if they were components of an initial regimen that failed. In triple nRTI initial treatment, it has been found that although lamivudine resistance is associated with some degree of abacavir cross-resistance, the relatively small

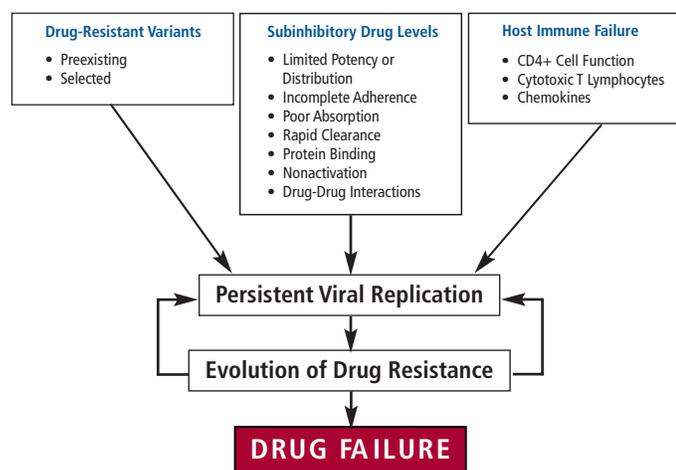


Figure 1. Factors contributing to antiretroviral failure. Adapted from Hirsch et al. *JAMA*. 1998.

Table 1. Options for Treatment Failure

Initial Regimen	Alternative Regimen	Comments on Initial Regimen
PI/2 nRTIs	2 PIs/2 nRTIs/NNRTI	PI susceptibility may be retained; lamivudine resistance likely if in regimen
NNRTI/2 nRTIs	1-2 PIs/2 nRTIs	NNRTI resistance likely; lamivudine resistance likely if in regimen
3 nRTIs	2 PIs/NNRTI/2 nRTIs	Abacavir may still be useful if in first regimen
2 PIs/2 nRTIs	2 PIs/NNRTI/2 nRTIs	PI susceptibility may be retained; lamivudine resistance likely if in regimen
PI/NNRTI/nRTI(s)	2 PIs/2 nRTIs	NNRTI resistance likely; lamivudine resistance likely if in regimen

PI indicates protease inhibitor.

decrease in abacavir susceptibility (2- to 3-fold) may permit the drug to retain some usefulness in a salvage regimen in the absence of concomitant zidovudine resistance.

Delayed Immunologic Deterioration in Protease Inhibitor Failure

Virologic failure on an initial protease inhibitor-based regimen may prompt more aggressive response in terms of altering treatment. However, a delayed CD4+ cell count decline in patients in whom protease inhibitor-based treatment is failing is frequently observed. This observation has raised the issue of how rapidly changes in regimen need to be made in treatment-experienced patients in whom therapeutic options may be limited. In a recent study by Deeks and colleagues of initiating protease inhibitor-containing therapy after a median of 24 months of nRTI exposure, 55% of the 482 patients exhibited virologic failure during the median follow up time of approximately 37 months. Median time to virologic failure was 14.7 months after beginning the protease inhibitor treatment. The rate of immunologic failure (return to CD4+ cell count at the time of starting protease inhibitor treatment) lagged behind the

rate of virologic failure. Among those patients with virologic failure, median time to return to baseline CD4+ cell count was 36.4 months. These data suggest that there may be a prolonged period during which CD4+ cell counts are relatively preserved following virologic failure on a protease inhibitor-based regimen. However, they also indicate that CD4+ cell decline is likely to occur, warranting caution in strategies that involve delay in making changes in a failing regimen. Moreover, protease inhibitor resistance and cross-resistance will become progressively more pronounced with continuing protease inhibitor use in the presence of viral replication.

Options in Multiple Failure

Options in multiple virologic failure include employing as many new drugs as possible in combination with continued or recycled drugs; use of multidrug rescue therapy involving 5 to 10 different drugs; strategic treatment interruptions (STIs); addition of hydroxyurea (with didanosine or didanosine/stavudine) to a multidrug regimen; and the use of investigational drugs.

In the CNA2007 study, abacavir, amprenavir, and efavirenz were employed in highly antiretroviral-experienced patients

in whom a protease inhibitor-based regimen failed. NNRTI-naive patients with plasma HIV RNA levels less than 40,000 copies/mL exhibited an initial decrease in viral load of 1.3 log with a 1-log decrease being maintained for 16 weeks. Viral load returned toward baseline levels within 16 weeks in all NNRTI-experienced patients and in NNRTI-naive patients with higher viral load levels. Approximately half of patients who were NNRTI-naive with a viral load of less than 40,000 copies/mL had suppression of HIV RNA levels to less than 400 copies/mL at 16 weeks, compared with 5% of those who were NNRTI-experienced and had an initial viral load of more than 40,000 copies/mL. These findings, which need confirmation in additional studies, suggest that success with such a regimen is more likely to occur in NNRTI-naive subjects, and if the switch to the regimen is made at relatively lower viral load levels. It should be noted, however, that efavirenz has been shown to lower amprenavir levels substantially; this effect may have influenced the results of the CNA2007 study. Preliminary data suggest that the addition of low-dose ritonavir may block this effect.

Data from ACTG 398 suggest that in patients in whom a protease inhibitor therapy is failing, dual protease inhibitor therapy and no prior exposure to NNRTIs are associated with improved response

The ACTG 398 study assessed whether a change to all new drugs or the addition of a second protease inhibitor to a new 4-drug class regimen improves virologic outcome in patients with virologic failure on a protease inhibitor-containing regimen. Patients with more than 16 weeks of protease inhibitor experience and plasma HIV RNA levels above 1000 copies/mL were given amprenavir, abacavir, efavirenz, and adefovir dipivoxil and randomized to one of 4 treatment arms consisting of placebo,

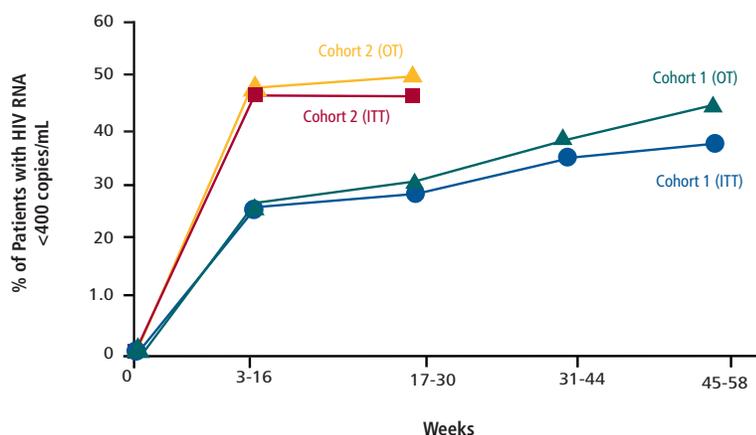


Figure 2. Proportion of patients with viral load less than 400 copies/mL in 2 cohorts receiving multidrug rescue therapy. ITT indicates intent-to-treat analysis; OT indicates on-treatment analysis. Courtesy of Julio S. G. Montaner, MD.

saquinavir (soft-gel capsule), indinavir, or nelfinavir. Patients with prior exposure to 1 protease inhibitor and those with prior exposure to 2 were randomized among 3 and 2 arms, respectively, to protease inhibitors with which they had no prior experience. Those having prior experience with 3 protease inhibitors were randomized among all 4 arms and thus may have received a protease inhibitor to which they had already been exposed. Patients were stratified according to prior NNRTI experience.

Comparison of the combined dual protease inhibitor arms and the single protease with respect to proportions of patients achieving viral load of less than 200 copies/mL at 24 weeks was significantly different in the dual versus single protease inhibitor arms (35% v 23% respectively; $P=0.002$). This level of suppression was achieved in 47% of dual protease inhibitor recipients and 33% of single protease inhibitor recipients who were NNRTI-naïve and in 19% and 8%, respectively, of those who were NNRTI-experienced. Overall, a viral load of less than 200 copies/mL was achieved in 43% of NNRTI-naïve patients and 16% of NNRTI-experienced patients (the difference was statistically significant with stratification for protease inhibitor experience and treatment arm). Among patients who stayed on treatment for 24 weeks, 65% of NNRTI-naïve patients achieved viral load of less than 200 copies/mL. Despite the fact that the proportions of patients achieving viral load levels of less than 200 copies/mL were somewhat disappointing in the ran-

domized treatment arms by intent-to-treat analysis, decreases in viral load averaged 1 log below baseline at 24 weeks; such decreases are likely to be associated with clinical benefit if sustained.

The rationale for
multidrug rescue
therapy is that
viral quasi species
exhibit differential
resistance patterns
that may be attacked
by various components
of the regimen

Multidrug rescue therapy regimens usually consist of 5 to 10 drugs, including recycled drugs that are not specifically selected on the basis of *in vitro* resistance patterns. These regimens may include 2 or 3 protease inhibitors, 1 or 2 NNRTIs, 2 to 4 nRTIs, a nucleotide reverse transcriptase inhibitor (nRTI) if available, and hydroxyurea (plus didanosine with or without

stavudine). The rationale for use of such a regimen in salvage therapy is that viral quasi species exhibit differential resistance patterns that may be attacked by various components of the multidrug regimen. Montaner and colleagues have reported on the use of treatment regimens consisting of the nRTIs stavudine, didanosine, lamivudine, and abacavir, the NNRTI nevirapine with or without delavirdine, 2 protease inhibitors, and hydroxyurea. Substantial proportions of patients in 2 cohorts have achieved virologic response to viral load levels below 400 copies/mL on such regimens (Figure 2). Tolerance, adherence, cost, and toxicity are obvious problems with such demanding and complicated regimens.

Strategic treatment interruption as an approach to regaining virologic control has received considerable attention recently. The rationale for this approach is that removal of selective pressure will permit more sensitive, wild-type virus to gain predominance, and result in renewed activity of recycled drugs. In studies of this approach performed by Miller and colleagues in the Frankfurt HIV Cohort, patients with extensive treatment experience, including at least 1 year of protease inhibitor treatment, who were receiving regimens containing at least 2 protease inhibitors, underwent treatment interruptions for at least 2 months. Pre- and post-interruption data are available for 39 patients in the cohort. Interruption was associated with significant increases in the proportions of patients with HIV that exhibited increased susceptibility to each of the drugs used. Overall, a shift to a wild-type virus occurred in 26 of 39 patients previously exhibiting resistance to a median of 8 drugs. The remainder of the patients, in whom no shift occurred, also exhibited resistance to a median of 8 drugs. During interruption, median viral load increased by 0.71 log (from 5.07 to 5.87 log) and median CD4+ cell count decreased by 89/ μ L (from 155/ μ L to 49/ μ L). At 8 weeks after reinitiation of antiretroviral therapy, viral load had decreased by 2.8 log in those with a shift to wild-type virus and by 1.02 log in those with no shift. Viral load of less than 500 copies/mL was achieved within 24 weeks in 18 of 25 patients with a shift to wild-type virus and in 2 of 12 with no shift. Patients with a shift to wild-type virus had a significantly higher CD4+ cell count prior to treatment interruption than did those without a shift. These patients also had a significantly greater decrease in CD4+ count during

treatment interruption (122 v 29 cells/ μ L). Overall, only 22 of 42 patients had returns to their pre-interruption CD4+ cell count; median times to return to the baseline CD4+ cell count were 336 days among those with a shift to wild-type virus and 209 days among those with no shift to wild-type.

Deeks and colleagues reported an assessment of virologic and immunologic outcome of STI in patients with failure (viral load >500 copies/mL) of a protease inhibitor-based regimen for at least 1 year and current viral load greater than 2500 copies/mL. Patients had been on a stable treatment regimen for more than 16 weeks. In the 18 patients reported on thus far, average baseline CD4+ cell count was 245/ μ L and viral load was 4.6 log; patients had been on protease inhibitor therapy for an average of 36 months and with virologic failure for 31 months, exhibiting an average 56-fold decrease in protease inhibitor susceptibility. After 12 weeks off treatment, average CD4+ cell count had declined by 94 cells/ μ L and viral load had increased by 0.82 log, changes similar to those observed by Miller and colleagues, and isolates in 16 of 17 patients had reverted to protease inhibitor susceptibility. The mean time to phenotypic switch to wild-type virus in these patients was 8.5 weeks. The switch to wild-type virus appeared to be associated with an increased rate of viral load increase and CD4+ cell count decline, suggesting increased replicative fitness and pathogenicity of the wild-type virus.

Findings with STI to date suggest that reversion to drug-susceptible virus frequently does occur and that subsequent treatment is associated with decreases in viral load and increases in CD4+ cell count. However, the acute declines in CD4+ cell count during interruption may result in risk for opportunistic disease and return to baseline CD4+ cell counts may require prolonged periods of time or may fail to occur in some patients. An additional potential problem with such interruption is that archived viral subpopulations are not eliminated, and viral drug resistance is likely to reemerge in the absence of a maximally suppressive regimen. Finally, the longer-term effectiveness of this approach remains to be ascertained.

Conclusions

A number of general conclusions regarding management of antiretroviral failure

can be offered:

- All potential reasons for failure should be evaluated, including adherence, pharmacokinetics, and resistance.
- Increasingly difficult challenges are posed by progression from first failure to second failure to multiple failures.
- As the therapeutic options become more limited, so do the goals of therapy.
- The role of resistance testing in guiding therapy is increasing and such testing will become a routine part of clinical management.
- The current suboptimal success rates in salvage therapy are a function of drug class cross-resistance, overlapping toxicities, and limited therapeutic alternatives.
- The principles of successful salvage therapy are established. The key to success is the availability of new drugs active against viruses resistant to the current generation of drugs.

Suggested Reading

Ait-Khaled M, Rakik A, Thomas D, et al. HIV-1 baseline genotype/phenotype and virological response following salvage therapy with Ziagen (abacavir, ABC), Amprenavir (APV), and Sustiva (efavirenz, EFV). [Abstract 133.] 6th Conference on Retroviruses and Opportunistic Infections. January 31-February 4, 1999; Chicago, Ill.

Albrecht M, Katzenstein D, Bosch R, et al. ACTC 364-nelfinavir (NFV) and/or efavirenz (EFV) in combination with new NRTIs in nucleoside experienced subjects (subj): week 48 ultrasensitive (US) HIV RNA results. [Abstract 531.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Carpenter CCJ, Cooper DA, Fischl MA, et al. Antiretroviral therapy for HIV infection in adults: updated recommendations of the International AIDS Society-USA panel. *JAMA*. 2000;283(3):381-390.

Deeks S, Brun S, Xu Y, et al. ABT-378/ritonavir (ABT-378/r) suppresses HIV RNA to <400 copies/ml in 84% of PI-experienced patients at 48 weeks. [Abstract 532.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Deeks SG, Grant RM, Beatty G, et al. Activity of a ritonavir plus saquinavir-containing regimen in patients with virologic evidence of indinavir or ritonavir failure. *AIDS*. 1998;12:F97-F102.

Deeks SG, Hecht FM, Swanson M, et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. *AIDS*. 1999;(13):F35-F43.

Deeks SG, Wrin T, Hoh R, et al. Virologic and immunologic evaluation of structured treatment interruptions (STI) in patients experiencing long-term virologic failure. [Abstract LB10.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Devereux HL, Youle M, Johnson MA, et al. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS*. 1999;13(18):F123-F127.

Fatkenheuer G, Hoetelmans RM, Hunn N, et al. Salvage therapy with regimens containing ritonavir and saquinavir in extensively pretreated HIV-infected patients. *AIDS*. 1999;13(12):1485-1489.

Hammer S, Mellors J, Vaida F, et al. A randomized, placebo-controlled trial of saquinavir (SQV)sgc, indinavir (IDV) or nelfinavir (NFV) in combination with amprenavir (APV), abacavir (ABC), efavirenz (EFZ) and adefovir (ADV) in patients with protease inhibitor (PI) failure. [Abstract LB7.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Hammer S, Squires K, DeGruttola V, et al. Randomized trial of abacavir (ABC) and nelfinavir (NFV) in combination with efavirenz (EFV) and adefovir dipivoxil (ADV) as salvage therapy in patients with virologic failure receiving indinavir (IDV). [Abstract 490.] 6th Conference on Retroviruses and Opportunistic Infections. January 31-February 4, 1999; Chicago, Ill.

Harrigan PR, Hertogs K, Verbiest W, et al. Baseline HIV drug resistance profile predicts response to ritonavir-saquinavir protease inhibitor therapy in a community setting. *AIDS*. 1999;13(14):1863-1871.

Havliir D, Gilbert P, Bennett K, et al. Randomized trial of continued indinavir (IDV)/ZDV/3TC vs. switch to IDV/ddI/d4T or IDV/ddI/d4T + hydroxyurea in patients with viral suppression. [Abstract 456.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Lori F. Hydroxyurea and HIV: 5 years later-from antiviral to immune-modulating effects [editorial]. *AIDS*. 1999;13(12):1433-1442.

Miller V, Rottmann C, Hertogs K, et al. Mega-HAART, resistance and drug holidays. [Abstract 30.] *Antiviral Therapy*. 1999;4(4):249-250.

Miller V, Gute P, Rottmann C, et al. Mega-HAART, resistance and scheduled treatment interruptions (STI). [Abstract 587.] 7th European Conference on Clinical Aspects and Treatment of HIV-Infection. October 23-27, 1999; Lisbon, Portugal.

Montaner JSG, Harrigan R, Raboud J, et al. Multidrug rescue therapy (MDRT) in two cohorts

of HIV+ individuals. [Abstract 536.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Piketty C, Race E, Castiel P, et al. Efficacy of a five-drug combination including ritonavir, saquinavir and efavirenz in patients who failed on a conventional triple-drug regimen: phenotypic resistance to protease inhibitors predicts outcome of therapy. *AIDS*. 1999;13:F71-F77.

Shulman N, Zolopa A, Havlir D, et al. Ritonavir intensification in indinavir recipients with

detectable HIV RNA levels. [Abstract 534.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Tebas P, Patick AK, Kane E, et al. 60-week virologic responses to a ritonavir/saquinavir containing regimen in patients who had previously failed nelfinavir. [Abstract 392.] 6th Conference on Retroviruses and Opportunistic Infections. January 31-February 4, 1999; Chicago, Ill.

Verhofstede C, Wanzele FV, Van Der Gucht B, et al. Interruption of reverse transcriptase

inhibitors or a switch from reverse transcriptase to protease inhibitors in a fast reappearance of virus strains with a reverse transcriptase inhibitor-sensitive genotype. *AIDS*. 1999;13(18):2541-2546.

Zolopa AR, Hertogs K, Schafer R, et al. HIV-1 genotype resistance patterns predict response to saquinavir/ritonavir therapy in patients in whom previous protease inhibitor therapy has failed. *Ann Intern Med*. 1999;131:813-821.

Announcement

Resistance Testing Guidelines Updated *

The International AIDS Society—USA panel on the use of antiretroviral drug resistance testing in adult HIV-1 has issued updated recommendations. The report of the international panel of experts was published in the May 10, 2000 issue of the *Journal of the American Medical Association*. Available data correlating viral resistance and poor response to therapy, the genotype and phenotype assay methods to assess potential resistance, the current limitations of resistance testing, and the further research that is warranted, are reviewed. In this con-

text, specific clinical situations in which resistance testing is recommended or may be considered to aid in optimizing individual patient care are presented.

The report can be accessed from the *JAMA* Web site: <http://jama.ama-assn.org/>. Reprints will be included in the next issue of this publication.

*Hirsch MS, Conway B, D'Aquila RT, et al. *Antiretroviral drug resistance testing in adult HIV-1 infection: recommendations of an International AIDS Society—USA Panel*. *JAMA*. 2000;283:2417-2426.

Correction

The March 2000 issue of *Topics in HIV Medicine* contained an error on page 35, Table 4 (Trials in Antiretroviral-Experienced Patients). In the ACTG 364 study (Abstract 531), the correct proportion of patients with plasma viral loads below 50 copies/mL in the 1-2 new nRTIs/efavirenz group was 44% and in the 1-2 new nRTIs/nelfinavir group it was 22%.

Perspectives

New Developments in HIV Care for Women

Meg D. Newman, MD

Dr Newman provided a broad review of HIV disease characteristics and treatment considerations in women. Her presentations at the Los Angeles and San Francisco courses examined factors underlying the increased incidence of HIV infection among women.

Epidemiology

Studies initially reported in 1993 provided an indication of the socioeconomic forces driving the HIV epidemic among women. In a study in 600 women in Madras, India, 90% reported feeling powerless to negotiate condom use with their husbands and 95% were financially dependent on their husbands. In a US study in 697 women, 67% of Latino women and 60% of Caucasian women never used condoms, with partner anger at the request often being cited as the reason.

A sampling of more recent reports (culled from a 2-week period in November 1999) indicates that such forces continue to operate: a group of 14 HIV-seropositive women incarcerated for crack cocaine use had a history of childhood and adult sexual and physical abuse that led to unsafe sex; 90% of 57 newly incarcerated women experienced domestic violence from their partners, with most having had high-risk HIV exposures but not perceiving themselves to be at risk; rates of HIV infection in incarcerated women are twice those in men in 9 of 10 US jurisdictions; a gynecologist in Ethiopia has reported that some 30,000 teenage prostitutes working in the capital city are contributing to the spread of HIV; high poverty and unemployment rates are forcing young women in Zambia to trade sex for food, housing, and money.

The changing epidemiology of HIV infection in the United States is illustrated by recent data on AIDS case distribution.

Dr Newman is Assistant Professor of Medicine and Director of AIDS Education in the Positive Health Program at the University of California San Francisco.

Whereas women accounted for 16% of the total 711,244 cases of AIDS reported by June 1999, 23% of cases reported between July 1998 and June 1999 were in women (Figure 1). AIDS is now the third leading cause of death in all women and the leading cause of death in African American women. The incidence of AIDS in African American women was estimated at 49.8 per 100,000 in 1998; in Eastern seaboard cities (New York, Newark, Miami, and Tampa), AIDS rates ranged from 49 to 150 per 100,000.

Women accounted for
23% of AIDS cases
reported in the
United States
between July 1998
and June 1999

Heterosexual transmission is the leading cause of HIV infection in women. Between July 1998 and June 1999, proportions of female adult and adolescent reported AIDS cases caused by heterosexual transmission of HIV ranged from 23% to 47% by ethnic group (Figure 2). Overall, among the 13- to 19-year-old patients with AIDS reported during this period, 37% of 54 women and 4% of 5 men acquired infection by heterosexual transmission. Among adults aged 20 to 24 years, heterosexual transmission occurred in 51% of women (n=311) and 9% of men (n=77).

HIV exposure categories for women between July 1998 and June 1999 indicate that 40% acquired infection through heterosexual contact, with 66% of these women being unaware of risk in their heterosexual partners (Table 1). In 31% of all cases of infection, risk was not reported or identified. When such cases are reviewed, most of those in women are reclassified as

attributable to heterosexual contact. However, current statistics may even underestimate the risk of heterosexual transmission, because risk factors are prioritized so that injection drug use (IDU) is identified as the means of infection before heterosexual transmission. Of a total of 115,364 cases initially classified as "risk not reported or identified" through June 1999, 55,363 cases were reclassified; of the 14,056 reclassified for women, 68% were reclassified as risk through heterosexual contact, 27% through IDU, and 4% through exposure to blood products. In 41,307 cases in men, 54% were reclassified as attributable to homosexual contact, 23% to IDU, and 16% to heterosexual contact.

Prognosis and Antiretroviral Therapy

Although studies in the mid- and late 1980s suggested that prognosis in HIV disease was worse for women than men, subsequent analysis indicated that the poorer outcome was explained by inferior access to medical care. In a study performed prior to the era of potent antiretroviral therapy, Carpenter and colleagues found that CD4+ cell counts in women declined to below 500/ μ L in 4 to 5.1 years and to below 200/ μ L in 9.6 years, values consistent with the respective durations of 4.1 years and 8 years in men. Similarly, a recent Center for Disease Control and Prevention (CDC) study showed that 24-month probabilities of survival in AIDS cases, diagnosed by a CD4+ cell count of less than 200/ μ L between 1993 and 1997, were 0.79 for women (n=37,687) and 0.77 for men (n=150,634). Sixty-month probabilities of survival in AIDS cases diagnosed on the basis of opportunistic disease were 0.63 in women (n=19,409) and 0.60 for men (n=83,922). These and other studies in the 1990s have confirmed that the most important predictors of disease progression and survival are AIDS-specific diagnosis, CD4+ cell count, viral load, and age, with gender not appearing to be associated with a significant predictive value.

Among the issues to be considered in whether the effects of antiretroviral thera-

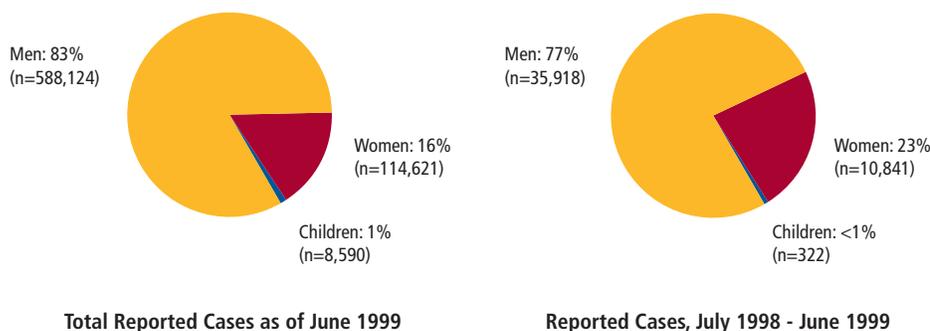


Figure 1. Gender and age distribution in 711,344 total reported AIDS cases as of June 1999 (left), and in 47,083 cases reported between July 1998 and June 1999. Adapted from the Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report*. 1999.

py are different in women and men is that women tend to weigh less and thus to receive a higher dose per kilogram with standard drug doses. Further, women may exhibit changes in drug metabolism and clearance during phases of the menstrual cycle, and hormonal changes may play a role in viral replication. In one study assessing the safety and efficacy of nelfinavir in 78 women and 616 men, women experienced more abdominal pain, itching, and rash, had similar decreases in viral load, and had greater increases in CD4+ cell count (116/ μ L v 84/ μ L). In an Italian study examining the effects of a number of factors in predicting zidovudine intolerance in 56 male and 37 female patients, female sex was associated with a greater risk for gastrointestinal or neurologic intolerance (66% v 34%), a finding that may reflect higher peak drug concentrations in women. In a Federal Drug Administration evaluation of 60 cases of lactic acidosis associated with nucleoside reverse transcriptase inhibitor (NRTI) use, 20 cases were fatal, with 17 of the 20 fatalities occurring in women and 11 of these occurring in obese women. These data are limited, and further information on these potential gender differences is needed.

A number of studies have suggested that viral load levels are different in women and men with similar CD4+ cell counts. In one study in injection drug users, initial plasma HIV RNA and CD4+ cell counts were 3000 copies/mL and 518/ μ L, respectively, in women, and 9000 copies/mL and 518/ μ L, respectively, in men. Three-year follow-up values were 45,000 copies/mL and 417/ μ L, respectively, in women, and 93,000 copies/mL and

390/ μ L, respectively, in men. Another study found that viral load levels in women were 24% lower than those in men when CD4+ cell counts were between 200/ μ L and 500/ μ L, but that viral load levels were similar at CD4+ cell counts of less than

Although there are data suggesting that women have lower viral load levels than men at comparable CD4+ cell counts, gender does not appear to be predictive of disease progression

200/ μ L. The CDC reviewed data from 3776 participants (2467 men and 1309 women) in 4 CDC-supported studies to further investigate potential differences in this regard. Viral load in women was 57% lower for patients with CD4+ cell counts above 500/ μ L, 48% lower for those with counts between 200/ μ L and 499/ μ L, and 40% lower in those with counts below 200/ μ L, although none of these differences were statistically significant. Gender was not significantly associated with either time to

an AIDS-defining opportunistic illness or time to death. On the basis of these data and the other studies indicating absence of a significant effect of gender on disease progression, the CDC, the Department of Health and Human Services, and the International AIDS Society—USA do not currently recommend changing antiretroviral prescribing guidelines in women.

The CDC has also collected data on causes and rates of mortality of 871 known HIV-infected women and 14 who seroconverted to HIV-positive during the period of April 1993 to December 1998. Of 196 deaths, 176 had verifiable causes; of these, 16% of patients died with AIDS-defining illnesses and 40% died of HIV-related disease. A total of 44% of deaths were not attributable to HIV disease or AIDS, with one third of these deaths being associated with drug use (eg, endocarditis, sepsis, or hepatitis). Potent antiretroviral therapy use was reported by only 24% of patients with CD4+ cell counts below 200/ μ L. Overall, no use of potent antiretroviral therapy, viral load above 10,000 HIV RNA copies/mL, and CD4+ cell count below 200/ μ L were strong predictors of mortality ($P < 0.001$). That there is a large group of women at high risk of poorer outcome indicates that more attention needs to be focused on services for such women, including appropriate provision of drug treatment and counseling.

Pregnancy and Mother-to-Child Transmission

Transmission of HIV from mother to infant primarily occurs in the intrapartum period via the conjunctival or oral mucosa. Duration of rupture of the membrane is correlated with increased transmission for both vaginal and cesarean deliveries, with transmission rates of 8% at 2 hours and 31% at 24 hours having been documented. This increased risk of HIV transmission with increased duration of membrane rupture was not observed in women without AIDS; however, this finding should not reduce attention to the standard of care of bringing HIV-infected women to delivery as soon as possible.

The benefits of cesarean delivery in reducing mother-to-child transmission have been called into question by recent findings. In the French Perinatal Cohort Study, the benefits of cesarean delivery were lost if zidovudine therapy was not used. The group undergoing cesarean delivery, which was found to be highly selected in the cohort, exhibited

decreased transmission rates compared with vaginal delivery only if cesarean delivery occurred prior to labor and membrane rupture. In the randomized European Mode of Delivery Collaboration involving 370 infants, 70% of whom received zidovudine, elective cesarean delivery was associated with a transmission rate of 1.8%, compared with 10.5% for vaginal delivery. By intent-to-treat analysis, transmission rates were 4.3% for vaginal delivery with zidovudine and 0.8% for cesarean delivery with zidovudine. The difference between groups became smaller when outcome was assessed by the actual mode of delivery used among those receiving zidovudine.

A number of recent studies have underlined the lack of attention given to the adverse effects of cesarean delivery in HIV-infected women. Two series suggest that cesarean delivery may be associated with a 2-fold increase in perioperative complications in HIV-infected women and another study has indicated an increase in major complications (odds ratio, 6.0) and minor complications (odds ratio, 3.0) with cesarean delivery in these women. Viral load data were not reported in most of the studies that have indicated that cesarean delivery is more effective than vaginal delivery in preventing transmission, a factor that can confound the reported outcome rates. Further, no combination therapy was used in any of the studies; this is particularly important given that case series including approximately 200 women treated with combination therapy and no cesarean delivery have shown no cases of

Table 1. Exposure Categories for Women, July 1998 to June 1999

	Number	Percent
Injection Drug Use	3043	28
Hemophilia	21	<1
Heterosexual Contact	4296	40
Injection Drug User	1208	29
Bisexual Man	200	4.6
Person with Hemophilia	27	<1
Transfusion Recipient	18	<1
HIV-Infected Person, Risk Not Identified	2843	66
Blood Products	120	1
Risk Not Reported or Identified	3361	31

Adapted from the Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report*. 1999.

vertical transmission of HIV to date.

Intrauterine transmission may occur early or late in pregnancy. Infections acquired early in utero may be more frequently associated with fetal death, and babies surviving in utero infection may have more rapidly progressive disease than those acquiring infection in delivery or through breast-feeding.

It is now the standard of care to offer potent antiretroviral therapy to all pregnant women with HIV. Optimal regimens are determined by the mother's CD4+ cell

count, viral load level, and comorbidities. Risks and benefits of beginning therapy before the 14th week should be discussed and the paucity of data regarding safety of treatment in the first trimester should be acknowledged. Currently, initiation is recommended after the 14th week unless the mother prefers earlier initiation. Viral load should be followed monthly and therapy changed if viral breakthrough occurs.

With regard to specific regimens, standard of care for pregnant women should be the same as that for nonpregnant adults, with one caveat. Efavirenz is contraindicated for pregnant women due to data showing alarming rates of anencephaly in primates receiving the drug. It is not known if a similar teratogenic effect could also occur in humans. Zidovudine is generally thought to be safe. If prior zidovudine use has been associated with detectable viral load or if genotypic analysis indicates presence of resistance mutations, an alternative regimen should probably be used.

A single dose of nevirapine can reduce plasma viral load by 1.3 log. The drug crosses the placental barrier and has a half-life of 61 to 66 hours in the mother during labor and 45 to 54 hours in the newborn. A single dose maintains blood concentrations of 10 times the 50% inhibitory concentration for HIV for a week in the newborn. In the HIVNET 012 Study, 626 women were allocated at onset of labor to receive nevirapine 200 mg or zidovudine 600 mg followed by 300 mg

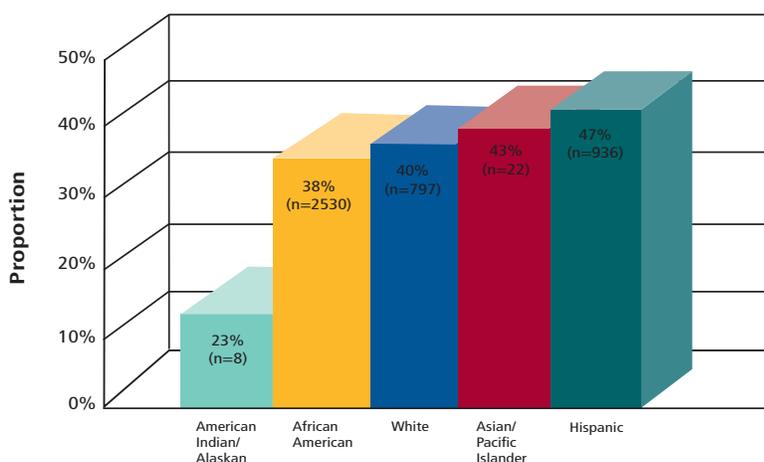


Figure 2. Proportion of female adult and adolescent AIDS cases reported between July 1998 and June 1999 attributed to heterosexual transmission by ethnic group. Adapted from the Centers for Disease Control and Prevention. *HIV/AIDS Surveillance Report*. 1999.

each hour until delivery. The babies received nevirapine 2 mg/kg within 72 hours of birth or zidovudine 4 mg/kg orally twice a day for 1 week. A total of 98.8% of infants were initially breast-fed, with 95.6% being breast-fed at 16 to 18 weeks. Estimated risks of transmission at birth were 8.2% in the nevirapine group and 10.4% in the zidovudine group. Risks at 6 to 8 weeks were 11.9% in the nevirapine group and 21.3% in the zidovudine group; and risks at 14 to 16 weeks were 13.1% and 25.1%, respectively. These findings are encouraging with regard to the use of single-dose nevirapine to prevent mother-to-child transmission.

**A recent meta-analysis
found no association
between deaths
in children who were
HIV-exposed but
uninfected and
evidence of
mitochondrial toxicity**

Potential downsides of nevirapine use include the rapid development of the K103N resistance mutation. This mutation was present in 3 of 15 women in this study at 6 weeks after the single dose; assessment of isolates at 1 week after dosing is being performed to determine if more of the women initially developed the mutation. A related issue is the efficacy of nevirapine in second and third pregnancies, especially for mothers who breast-feed.

A recent concern regarding treatment to prevent mother-to-child transmission is the potential for mitochondrial toxicity in the infant. Blanche and colleagues reported on the neurologic deaths of 2 HIV-exposed but uninfected infants who had been exposed to zidovudine or zidovudine/lamivudine. Six cases of nonfatal mitochondrial toxicity in infants who had been exposed to NRTIs were subsequently reported. These cases prompted reassessment of data from approximately 20,000

Any known pregnancy in which antiretroviral drugs have been used may be reported to the Antiretroviral Pregnancy Registry at:

1-800-722-9292 or 919-483-9437

children from the National Institutes of Health, Women and Infants Transmission Study, Pediatric AIDS Clinical Trials Group, and CDC cohorts to determine presence of findings such as failure to thrive, cardiomyopathy, metabolic acidosis, liver failure, bone marrow failure, seizure, developmental delay, ataxia, brain stem alteration, blindness, retinitis pigmentosa, and sudden infant death syndrome. None of the deaths in children who were HIV-exposed but uninfected were associated with limited or definitive evidence of mitochondrial toxicity. These findings have allayed some of the fears regarding the potential for such toxicity with in utero exposure to antiretroviral therapy.

Gynecologic Care

Women with HIV infection should undergo a full pelvic exam with a Pap smear, and the exam should include careful inspection of the vulvar, vaginal, and perianal areas. If findings are normal, Pap smear and inspection should be repeated every 6 months; in some cases, women who have had significant and maintained immune reconstitution on antiretroviral therapy can be seen on an annual basis. Colposcopy should be performed in women with low-grade or high-grade squamous interstitial lesions, atypical squamous cells of undetermined origin, atypical glandular cells of undetermined origin, or persistent inflammation. The pelvic exam should include wet mounts and serum rapid plasma reagin and testing for chlamydia and gonococci. Patients should also receive routine counseling on sexually transmitted disease, including human papilloma virus (HPV) infection and cervical intraepithelial neoplasia, as well as on pregnancy, contraception, and safer sex.

A recent analysis of oncogenic HPV findings in 507 women with measurements at 3 visits in the Women's Interagency HIV Study cohort indicates that the overall rate of progression on Pap smear was associated with number of HPV infections detected at the 3 visits. Progression occurred in 16% of women with an infection detected at 1 visit (37% of the women had 1 infection), 24% of those with infection at 2 visits (29%), and 25% of those with infection at

all 3 visits (34%). Analysis by CD4+ cell count and Pap smear status showed that women who were receiving potent antiretroviral therapy were 1.4 times more likely to show regression on follow up Pap smear. This finding is particularly important for women with HIV infection, since it is estimated that 20% to 36% have abnormal Pap smear results.

Recent data from a study of the effect of the menstrual cycle on the presence of HIV in the genital tract showed that among 55 women with CD4+ cell counts below 350/ μ L and median plasma HIV RNA of 3.73 log₁₀, there were significant increases in levels of viral nucleic acids in the genital tract just prior to menses (assessed by endocervical wicking) and during menses (assessed by cytobrush and lavage), with no change in peripheral blood viral load being observed during menses. These findings suggest the potential for increased risk of transmission prior to and during menses. Finally, another small study has suggested that antiretroviral therapy is not associated with alteration in hormone levels. In this report, progesterone and estradiol levels in 55 women with HIV infection with self-reported normal menstrual cycles were similar to those in 9 uninfected women with normal cycles. Only 5 of the HIV-infected women were not receiving antiretroviral therapy, with 41 receiving a regimen including a protease inhibitor and 9 receiving a regimen without a protease inhibitor.

Suggested Reading

Becker-Pergola G, Guay L, Mmiro F, et al. Selection of the K103N nevirapine (NVP) resistance mutation in Ugandan women receiving NVP prophylaxis to prevent HIV-1 vertical transmission (HIVNET-006). [Abstract 658.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Blair J, Hanson D, Jones J, et al. Do gender differences in viral load predict differences in HIV disease progression? [Abstract 195.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Blanche S, Tardieu M, Rustin P, et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet*. 1999;354(9184): 1084-1089.

Brundage RC, Fletcher CV, Fenton T, et al. Efavirenz (EFV) and nelfinavir (NFV) pharmacokinetics (PK) in HIV-infected children under 2 years of age. [Abstract 719.] 7th Conference on

Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Centers for Disease Control and Prevention. HIV/AIDS Surveillance Report. Atlanta, Ga: Centers for Disease Control and Prevention; 1999; 11(1).

Cu-Uvin S, Wright D, Anderson D, et al. Hormonal levels among HIV-seropositive women during the menstrual cycle. [Abstract 681.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Frenkel LM, Mullins JI, Learn GH, et al. Detailed case history information relevant to genetic evaluation of suspected cases of transient HIV-1 infection of infants. Available at: <http://www.sciencemag.org/feature/data/974996.shl>.

Frenkel LM, Mullins JI, Learn GH, et al. Genetic evaluation of suspected cases of transient HIV-1 infection of infants. *Science*. 1998;280(5366):1073-1077.

Guay LA, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: HIVNET 012 randomised trial. *Lancet*. 1999;354(9181):795-802.

Hanson C, Frederick M, McIntosh K. Evaluation of living uninfected children for mitochondrial defects: women and infants transmission study. [Abstract 665.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

International Perinatal HIV Group. The mode of delivery and the risk of vertical transmission of human immunodeficiency virus type 1-a meta-

analysis of 15 prospective cohort studies. *N Engl J Med*. 1999;340(13):977-987.

Kuhn L, Coutsoudis A, Moodley D, et al. HIV-1-specific T-helper cell responses detected at birth: protection against intrapartum and breast feeding-associated transmission of HIV-1. [Abstract 702.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Massad S, Ahdieh L, Benning L, et al. Incidence and progression of cervical squamous lesions among women with HIV: insights from the first 13,038 pap smears of the Women's Interagency HIV Study. [Abstract 675.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

McIntosh K. Mitochondrial toxicity of perinatally administered zidovudine. [Abstract S14.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Minkoff H, Ahdieh L, Massad S, et al. Effect of highly active antiretroviral therapy (HAART) on cervical cytologic changes associated with oncogenic HPV among HIV+ women. [Abstract 674.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Mirochnik M, Siminski S, Fenton T, et al. Pharmacokinetics of nevirapine (NVP) in pregnant women and in their infants following in utero exposure. [Abstract 716.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Read J. Duration of ruptured membranes and vertical transmission of HIV-1: a meta-analysis from fifteen prospective cohort studies. [Abstract 659.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Reichelderfer PS, Coombs RW, Wright D, et al. HIV-1 viral nucleic acid levels in the female genital tract: impact of the menstrual cycle and implications for transmission. [Abstract 184.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Richman DD, Havlir D, Corbeil J, et al. Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. *J Virol*. 1994;68(3):1660-1666.

Shapiro D, Tuomala R, Samelson R, et al. Antepartum antiretroviral therapy and pregnancy outcomes in 462 HIV-infected women in 1998-1999 (PACTG 367). [Abstract 664.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Smith DK, Phelps R, Hamburger M, et al. Causes and rates of death among HIV-infected women 1993-1998: the contribution of illicit drug use and suboptimal HAART use. [Abstract 682.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Williams A, Yu C, Tashima K, et al. Weekly treatment for prophylaxis of candida vaginitis. [Abstract 677.] 7th Conference on Retroviruses and Opportunistic Infections. January 30-February 2, 2000; San Francisco, Calif.

Perspectives

Postexposure Prophylaxis: Needles, Sex, and Drugs

Julie L. Gerberding, MD, MPH

Current rationale for and practice of prophylaxis after occupational, sexual, or injection drug use exposure to HIV-1 were discussed by Julie L. Gerberding, MD, MPH, at the Atlanta course.

Postexposure Prophylaxis for Occupational Exposure

Statistics for the United States through mid-1999 and for other countries through the end of 1997 indicate totals of 97 documented cases and 192 possible cases (ie, seroconversion was not documented) of occupational HIV-1 infection in health care personnel. The majority of these cases (55 documented and 136 possible) have been in the United States, a finding that may reflect the absence of accurate reporting in many other parts of the world. A retrospective study by Cardo and colleagues from the Centers for Disease Control and Prevention (CDC) showed that risk factors for transmission include deep injury, visible blood on the sharp device causing injury, exposure to blood from a source patient with preterminal AIDS, and injury caused by a device that had been inserted in an artery or vein.

A large number of prospective cohort studies have provided convincing evidence that on average, 99.7% of occupational exposures to HIV do not result in infection. Available data suggest that immunologic mechanisms during the first few days after exposure may be the key to determining the final outcome. These findings also provide the rationale for postexposure prophylaxis.

In brief, simian immunodeficiency virus infection models have shown that at 24 hours after inoculation of the vaginal mucosa, virus is largely associated with

dendritic cells in the mucosal tissue, with no evidence of active replication. At 24 to 48 hours later, virus is found in the germinal centers of the lymph nodes and is undergoing immune processing and active replication. By 5 days, both free and cell-associated virus can be detected in the circulation. Cell-mediated immune response to viral antigens can be detected even in animals that do not subsequently exhibit established infection, suggesting a role for cell-mediated immunity in preventing infection. Similar T-cell responses to specific HIV antigens have been observed in humans with high-risk exposures in whom infection fails to become established. In addition to indicating that immune response may be active in clearing infection, these findings support the biologic plausibility of antiretroviral treatment aiding in the clearance of virus during the early stage after exposure.

Current CDC guidelines for postexposure prophylaxis recommend use of 2 antiretroviral drugs, with the basic regimen consisting of zidovudine 200 mg 3 times a day (or 300 mg bid) and lamivudine 150 mg twice daily (125 mg bid if patient <60 kg). Alternative regimens are often used when the source patient is likely to harbor circulating virus resistant to zidovudine or lamivudine. Selection of these regimens is complicated, but is based on an approach similar to that used for selecting salvage therapy for infected patients. The demonstration of effectiveness of alternative regimens in postexposure prophylaxis is lacking. According to the CDC, use of 3-drug regimens including indinavir 800 mg every 8 hours or nelfinavir 750 mg 3 times a day generally is recommended when a high-risk exposure has occurred, or drug resistance is suspected.

The CDC currently is updating guidelines with the aim of better matching recommended drug regimens to presumed resistance patterns in the source patient. Treatment should be initiated as soon as possible after exposure, with treatment after 72 hours still being recommended for high risk exposures. Treatment should continue for 4 weeks, with laboratory monitoring at baseline and every 2 weeks during treatment. HIV antibody testing should be

performed at baseline, 6 weeks, 3 months, and 6 months after exposure. Testing at 12 months may also be prudent in some circumstances; cases have been observed in which simultaneous exposure to HIV and hepatitis C virus has resulted in symptomatic hepatitis C infection and delayed HIV-seroconversion. HIV viral load testing is recommended if acute symptoms suggestive of HIV infection are present, but is not recommended for routine management due to the possibility of false-positive results.

Information on actual practice of postexposure prophylaxis in occupational exposure is available from the CDC national surveillance system for occupational infections in healthcare personnel. A total of 4154 blood exposures involving 3692 known source patients were reported

Free consultation for clinicians treating occupational exposure to HIV and other bloodborne pathogens is available 24 hours a day from PEPLine (a joint program of the University of California San Francisco and San Francisco General Hospital Community Provider AIDS Training Project and Epidemiology and Prevention Interventions Center):

1-888-HIV-4911

between June 1995 and January 1999, with 9% (n=340) involving source patients known to be HIV-seropositive, 57% (n=2087) involving HIV-seronegative source patients, and 1265 involving source patients with unknown HIV serostatus. Of 300 health care workers exposed to HIV-seropositive sources for whom information was available, 173 (58%) initiated postexposure prophylaxis; of 107 whose treatment status was known, 62 (58%) completed the regimen. In comparison, 29% of workers (293/1012) with exposure from HIV-seronegative source patients initiated prophylaxis, with the regimen being completed by 20% (38/186). This information indicates reliance on prophylaxis even in cases in which the exposure does not involve HIV. It also indicates relatively poor adherence of medical personnel to recommended regimens.

Dr Gerberding is Director of the Hospital Infections Program at the Centers for Disease Control and Prevention in Atlanta, Georgia and Associate Professor of Medicine (Infectious Diseases) at the University of California San Francisco.

Postexposure Prophylaxis for Sexual or Injection Drug Use Exposure

The potential role of postexposure prophylaxis in HIV exposure through sexual contact or needle sharing by injection drug users is controversial. What should a clinician do in the case of a patient presenting within a short time after such exposure? Should treatment be offered on the basis of risk of exposure? The per-episode risk of infection following sexual exposure is difficult to define, although epidemiologic studies suggest many factors that may increase risk of transmission (Table 1). Data primarily based on modeling have indicated probabilities of infection of 0.8% to 3.2% per episode of receptive anal intercourse and of 0.05% to 0.15% per episode of receptive vaginal intercourse. By comparison, the estimated risk following a percutaneous occupational exposure is 0.32% and that following sharing of a needle is 0.67%. In other words, the per-episode transmission risk for occupational, sexual, and injection drug exposures to HIV appear similar, varying within a single order of magnitude.

A potential scheme for offering treatment, used in San Francisco and some other locales, is based on the risk assessed at the time of presentation. Treatment is

offered for anal and vaginal exposures, and for oral receptive sexual exposures involving mucosal contact with semen. However, thresholds for treatment differ among the clinicians and programs offering postexposure prophylaxis.

The rationale for postexposure prophylaxis in cases of sexual or needle exposure is similar to that in cases of occupational exposure: efficacy of prophylactic therapy is biologically plausible, the per-episode transmission risk is low but not zero, and current treatments appear to be reasonably safe. At present, however, there are no data on effectiveness of prophylaxis following sexual or injection drug use (IDU) exposure, whereas there is at least some evidence of effectiveness in cases of occupational exposure. Occupational exposure prophylaxis has been endorsed by authoritative bodies (the Occupational Safety and Health Administration, the US Public Health Service) but there has been limited endorsement of prophylaxis for sexual or IDU exposure by the International AIDS Society–USA and others.

The other issues surrounding use of prophylaxis for community exposures to HIV include its cost, its feasibility, particularly with regard to adherence, and most importantly, its public health impact. The public health impact of post-exposure prophylaxis for occupational exposures is

CDC surveillance data indicate that the prophylaxis regimen was completed by 58% of health care workers with exposure to a source patient known to have HIV infection

small, given that such exposure accounts for a very small fraction of incident HIV infection. In theory, programs for prophylaxis for sexual or IDU exposure could have a great public health impact. However, it is not clear if such programs would be beneficial or harmful. In the pessimistic view, the existence of such programs may result in disinhibition of risk behavior (Figure 1), resulting in increased exposure and incidence of infection. In addition, if prophylaxis is ineffective, the risk for emergence of drug-resistant virus increases. In the optimistic view, the incidence of infection would be decreased by the effectiveness of prevention counseling in decreasing risk behavior, the effectiveness of prophylaxis in preventing established infection, and the detection of undiagnosed infections among persons presenting for treatment. A number of projects supported by the CDC and National Institutes of Health are designed to evaluate program feasibility and assess the magnitude of these potential risks and benefits.

An ongoing postexposure prophylaxis program in San Francisco is designed as a postexposure prevention program that (1) focuses on risk avoidance counseling, (2) clearly conveys the message that postexposure prophylaxis is a back-up measure at best, and (3) devotes considerable resources to the monitoring of adherence and behavioral outcomes, as well as of treatment and virologic outcomes. The criteria for administration of postexposure prevention in the program include an eligible HIV exposure or high-risk exposure within the past 72 hours, negative baseline HIV-antibody test, and patient commitment to adherence to the drug treatment

Table 1. Factors That May Increase Risk of HIV Infection During Sex

HIV-Infected Partner	High plasma viral load High viral load in semen/vagina Menses at time of exposure Inflammatory genital exposure Lack of circumcision
Uninfected Partner	Genetic susceptibility Genital ulcer disease Inflammatory genital disease Lack of circumcision Cervical ectopy
Characteristics of the Sexual Act	Trauma (eg, fisting) Douching prior to anal or vaginal sex Increased duration or intensity of intercourse
Viral Characteristics	Macrophage tropism Nonsyncytium-inducing phenotype

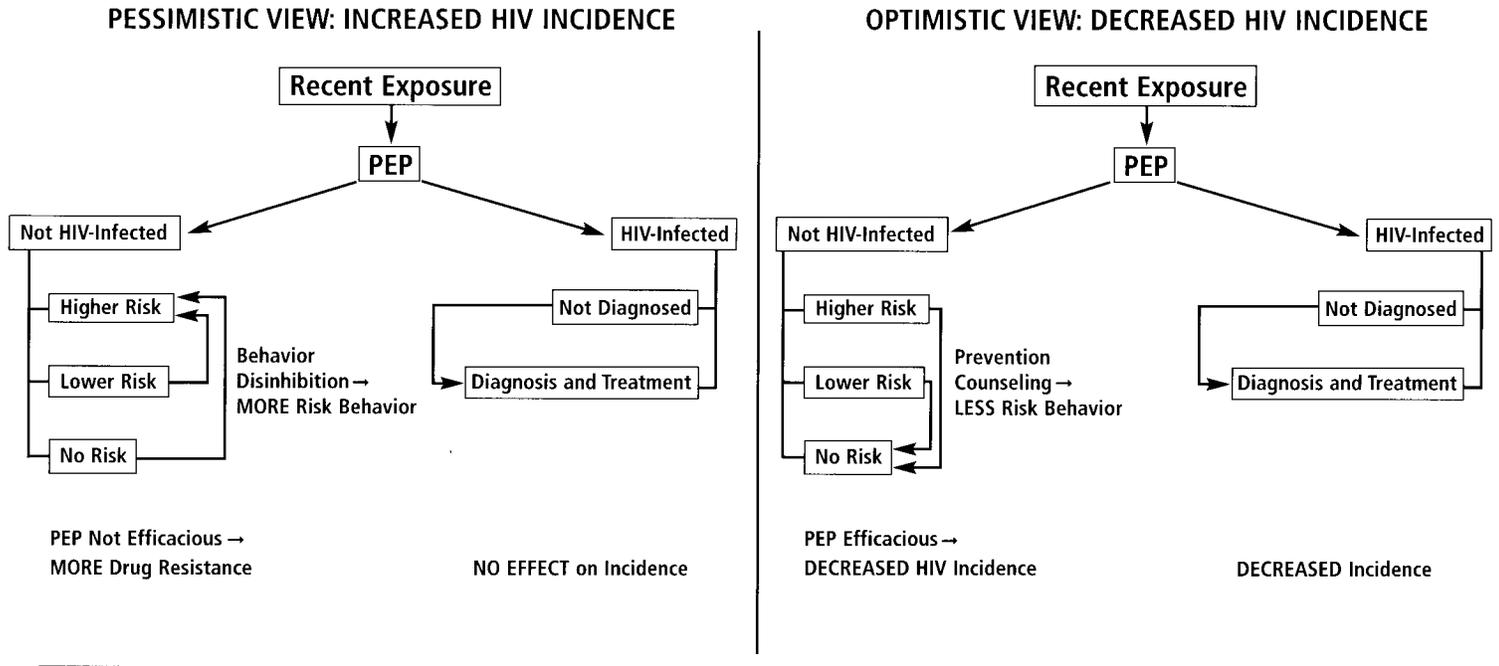


Figure 1. Pessimistic (left) and optimistic (right) views of impact of postexposure prophylaxis (PEP) and prevention programs.

and to follow-up. Convenient program access sites are employed, and personnel are experienced in risk counseling, as well as treatment, monitoring, and adherence counseling. Preliminary data from the program indicate that more than 80% of the exposures for which treatment was offered were sexual exposures. Most patients received 2-drug regimens; only 3% received a protease inhibitor. Thus far, more than 70% of patients have completed the recommended 4 weeks of therapy without changing treatment, an adherence rate equivalent to or somewhat better than that observed among health care workers.

Information from this and other ongoing projects can be expected to provide important insights into the feasibility and potential public health impact of postex-

posure prevention programs. A focus on risk prevention and behavior modification is a critical element in the success of such programs.

Suggested Reading

Bamberger JD, Waldo CR, Gerberding JL, et al. Postexposure prophylaxis for human immunodeficiency virus (HIV) infection following sexual assault. *Am J Med.* 1999;106(3):323-326.

Bell DM. Occupational risk of human immunodeficiency virus infection in healthcare workers: an overview. *Am J Med.* 1997;102(5B):9-15.

Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Diseases Control and

Prevention Needlestick Surveillance Group. *N Engl J Med.* 1997;337(21):1485-1490.

Centers for Disease Control and Prevention. Public health service guidelines for the management of health-care worker exposures to HIV and recommendations for post-exposure prophylaxis. *MMWR Morb Mortal Wkly Rep.* 1998;47:1-33.

Clerici M, Levin IM, Kessler HA. HIV-specific T-helper activity in seronegative health care workers exposed to contaminated blood. *JAMA.* 1994;271:42-46.

Gerberding JL. HIV exposure risk assessment and prophylactic treatment. In: Sande MA, Volberding P, eds. *The Medical Management of AIDS.* Philadelphia, Pa: W. B. Saunders Co; 1999.

Katz MH, Gerberding JL. Care of persons with recent sexual exposure to HIV. *Ann Intern Med.* 1998;128:306-312.

Upcoming Events of the International AIDS Society–USA

Established in 1992, the International AIDS Society–USA is a not-for-profit physician education organization. The mission of the International AIDS Society–USA is to improve the treatment, care, and quality of life of persons with HIV and AIDS through balanced, relevant, innovative, and state-of-the-art education and information for physicians who are actively involved in HIV and AIDS care. The organization's educational activities are particularly intended to bridge clinical research and patient care.

ICAAC Interactive Symposium

International AIDS Society–USA Symposium at the 40th Annual ICAAC:

Current Issues in the Management of HIV-Infected Patients: A Case-Based, Interactive Program

Tuesday, September 19, 2000

Metro Toronto Convention Centre, Toronto, Ontario, Canada

Chairs: Constance A. Benson, MD, and Paul A. Volberding, MD

IDSA Interactive Session

International AIDS Society–USA Interactive Session at the 38th Annual IDSA Meeting:

Management of HIV Infection

Saturday, September 9, 2000 (*tentative date*)

Ernest N. Morial Convention Center, New Orleans, Louisiana

Chairs: William G. Powderly, MD, and Michael S. Saag, MD

Sixth Annual Fall CME Course Series

Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management

Thursday, September 28, 2000

New York Hilton and Towers, New York, New York

Chairs: Douglas T. Dieterich, MD, and Roy M. Gulick, MD, MPH

Early Registration Fee: \$35

The fall course series will present recent advances in clinical HIV management through a mix of didactic lectures and clinically relevant cases developed by a panel of HIV/AIDS experts. Topics will include updates on HIV pathogenesis, new drugs and regimens, strategies for managing antiretroviral failure, and the changing course of HIV disease.

Additional courses will be held in Chicago, San Francisco, Los Angeles, and in a location to be determined in Florida.

Cases on the Web - <http://hivinsite.ucsf.edu/iasusa/cme>

A collaboration of the International AIDS Society–USA and HIV InSite, *Cases on the Web* is an ongoing series of case-based, advanced online CME activities sponsored by the International AIDS Society–USA.

Cases Now Available:

Metabolic Complications of Antiretroviral Therapy

Frank J. Palella, MD

Guest Editor: Steven K. Grinspoon, MD

Resistance Testing in Antiretroviral Management

Michael S. Saag, MD

Guest Editor: Daniel R. Kuritzkes, MD

Clinical Management Issues in Antiretroviral-Experienced Patients

Paul A. Volberding, MD

For information about any of these programs, please contact the International AIDS Society–USA Symposium Voice Mail: (415) 561-6725 • Fax: (415) 561-5740 • E-mail: info@iasusa.org

A publication of the International AIDS Society—USA

Upcoming Events

International AIDS Society—USA Symposium at the 40th Annual ICAAC:

Current Issues in the Management of HIV-Infected Patients:

A Case-Based, Interactive Program

Tuesday, September 19, 2000

Toronto, Ontario, Canada

International AIDS Society—USA Interactive Session at the 38th Annual IDSA Meeting:

Management of HIV Infection

Saturday, September 9, 2000 (*tentative date*)

New Orleans, LA

Current Challenges in HIV:

A Case Based, Advanced Course in Clinical HIV Management

Thursday, September 28, 2000

New York, NY

International AIDS Society—USA
Presidio of San Francisco
1001 B O'Reilly Avenue Box 29916
San Francisco, CA 94129-0916

Address Service Requested

Presorted First Class Mail U.S. Postage Paid Permit No. 3842 San Francisco, CA
--