Perspectives

Review of Recent Guidelines for Antiretroviral Treatment of HIV-Infected Children

James M. Oleske, MD

Reviews

Antiretroviral Adherence Interventions: A Review of Current Literature and Ongoing Studies

Jane M. Simoni, PhD, Pamela A. Frick, PharmD, MPH, David W. Pantalone, AB, Barbara J. Turner, MD, MSEd

Special Contributions

Perinatal HIV: Special Considerations

Deborah Cohan, MD, MPH

Drug Resistance Mutations in HIV-1

International AIDS Society–USA Drug Resistance Mutations Group
About This Issue

This issue of Topics in HIV Medicine features a Perspectives article drawn from a presentation by James M. Oleske, MD, MPH, given in June 2003 at the 6th annual Ryan White CARE Act Clinical Conference in Orlando, Florida. In his article, Dr Oleske presents the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children recommendations regarding when to initiate treatment, which regimens to use in initial treatment, and considerations when switching regimens in HIV-infected children. In a Review, Simoni and colleagues discuss various antiretroviral adherence interventions from current literature and ongoing studies. The authors trace the practical and sometimes innovative intervention strategies that have been used to help maintain or improve treatment adherence.

Two Special Contributions mark this final issue of the year. The first is an article reviewing special considerations in perinatal HIV, adapted from a Cases on the Web activity by Deborah Cohan, MD, MPH (available at www.iasusa.org). In this article, Dr Cohan presents insightful considerations specific to HIV-infected women considering pregnancy. Counseling, treatment modalities, and frequent misconceptions surrounding HIV and pregnancy are discussed. Finally, an update from the IAS–USA Drug Resistance Mutations Group is published in this issue. Revised recommendations for antiretroviral drug resistance testing were recently published (Hirsch et al, Clin Infect Dis, 2003) and can be found on the IAS–USA Web site at www.iasusa.org.

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Announcements
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Guidelines for Authors and Contributors
Subscription Requests
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Perspective

Review of Recent Guidelines for Antiretroviral Treatment of HIV-Infected Children

Antiretroviral treatment of HIV infection in children requires consideration of a number of factors specific to this population, including differences in drug pharmacokinetics and in virologic and immunologic markers compared with older patients, as well as age-related adherence issues. Recommendations for treatment of pediatric HIV disease have been finalized by the François-Xavier Bagnoud Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Children. Working Group recommendations included when to initiate treatment, which regimens to use in initial treatment, and considerations in switching regimens. This article, which summarizes this guideline update, is drawn from a presentation by James M. Oleske, MD, MPH, given at the June 2003 International AIDS Society–USA-sponsored 6th Annual Ryan White CARE Act Clinical Conference in Orlando, Florida.

Recent scares to society such as smallpox, severe acute respiratory syndrome (SARS), and monkeypox produced public health responses reflecting considerable investment of time, effort, and resources. This is as it should be. However, for some of us at least, there is constant incredulity over how easily it appears that some segments of society are distracted from the current suffering caused by and the ubiquitous threat posed by HIV disease—a disease that may claim the lives of one fourth of the world’s population. This abandonment is perhaps greatest in regard to HIV-infected children who depend on adults to bring them safely through childhood.

The burden of disease in places such as Chennai, India, where virtually all HIV-infected children also have cavitory tuberculosis and where many live in orphanages, is particularly alarming. This is not to say that response to HIV infection in children has been or is optimal in the United States. Our American dream continues to be plagued by disparities in treatment, quality of care, and outcomes among different demographic groups.

The recommendations for treatment of pediatric HIV disease recently finalized by the Working Group on Antiretroviral Therapy and Medical Management of HIV-Infected Infants and Children are intended for the United States, which has the resources to ensure their implementation. However, for many other locations around the world, including those with the greatest burden of disease, these US recommendations are far beyond available health care resources. Specific recommendations for the use of antiretroviral drugs in resource-poor areas of the world have recently been developed (WHO guidelines, 2003, www.who.int/3by5/publications/guidelines/en/arv_guidelines.pdf).

Special Considerations in Antiretroviral Therapy

Treating HIV-infected children involves special considerations in the areas of diagnosis, age-related differences in pharmacokinetics, age-related differences in disease natural history—including differences in virologic and immunologic markers of disease—and adherence to treatment. Diagnostic testing of HIV-exposed infants should be performed with HIV DNA polymerase chain reaction testing or HIV culture within 48 hours of birth, at 14 days (optimal), at 1 to 2 months, and at 3 to 6 months. With regard to the pharmacokinetics of antiretroviral and other drugs used in treating HIV disease and opportunistic illnesses, differences between children and adults in body composition, renal excretion, liver metabolism, and gastrointestinal function are associated with potential differences in drug distribution, metabolism, and clearance, and thus potential differences in drug dosing requirements and adverse effects.

Special considerations in the natural history of disease include recognition that growth failure and central nervous system (CNS) disease in children may require specific attention to the use of antiretroviral drugs that sufficiently penetrate the CNS. Further, young children have higher normal CD4+ cell counts than adults, with levels slowly declining to adult levels by about 6 years of age. If CD4+ cell count is to be used in treatment decisions, age-appropriate cell counts should be used. CD4+ cell percentage is likely a better marker for HIV disease progression than CD4+ cell count in children. As in adults, plasma HIV RNA level is the best indicator of risk for disease progression in children and is used to help determine when to initiate and change antiretroviral therapy in pediatric patients. Plasma HIV RNA level is characteristically very high in HIV-infected newborns and young children. For purposes of treatment decisions, changes in plasma HIV RNA level should be considered significant only if they are greater than 5-fold (0.7 log10 RNA copies/mL) in infants aged 2 years or younger and greater than 3-fold (0.5 log10 RNA copies/mL) in children older than 2 years. Special considerations in adherence will be discussed throughout this article. The importance of maintaining strict adherence (>85%) with antiretroviral schedules has become increasingly relevant.

Factors in Decisions Regarding Initiation of Treatment

As in adults, factors involved in decisions on initiation of antiretroviral treatment in children include severity of disease and risk of progression as assessed by CD4+ cell count or percentage and...
plasma HIV RNA level, and as indicated by the presence or history of severe opportunistic illness. Other factors to be considered include the availability of appropriate, palatable drugs (liquid preparations are required in many cases), the complexity of regimens, and expected adverse effects in these patients, who are still growing and developing. Decisions regarding initial treatment also need to take into account the effect of the initial choice on later treatment options, a problem heightened by the length of time that these patients conceivably will require treatment. Finally, the presence of co-morbidities and the potential drug interactions of antiretrovirals with other required medications need to be considered.

Adherence to antiretroviral regimens is crucial to successful treatment, and the ability of the child and caregiver(s) to adhere to regimens is thus a central consideration in the decision to initiate treatment. Antiretroviral treatment is most effective in treatment-naive patients, and poor adherence enhances the emergence of viral resistance. To maximize the benefit to be derived from initial treatment, it is thus essential that adherence issues are assessed, discussed, and addressed, and that all potential problems with adherence are resolved prior to initiating therapy.

**Working Group Recommendations for Initiating Antiretroviral Treatment**

**Children Younger Than 12 Months**

Risk of disease progression is inversely correlated with age in younger HIV-infected children. However, the ability to distinguish infants (i.e., children younger than 6 months) at risk for rapid progression versus slower progression is very limited at present. There are few clinical trial data on the effects of aggressive antiretroviral therapy in infants. There is potential for underdosing and overdosing of infants due to inadequate information on optimal drug levels, and there is also inadequate information on long-term toxicities in children beginning therapy at this early age.

Under the newly revised guidelines, the Working Group recommends that treatment be initiated for any infant with clinical or immunologic symptoms of HIV disease regardless of plasma HIV RNA level, and that treatment be considered for infants who are asymptomatic and have normal immune function; some experts would treat all infants aged 6 months or younger. The indications for initiating treatment according to clinical status, CD4+ cell percentage, and plasma HIV RNA level are shown in Table 1.

**Children 12 Months of Age and Older**

Risk of rapid disease progression is lower in children aged 12 months or older than in younger children, and children in this older age group with mild or moderate clinical symptoms (category A or B) or moderate immune suppression (category 2) are at reduced risk of progression compared with children having more severe findings. In children in this age group, plasma HIV RNA levels provide useful information on the risk of disease progression and should be taken into account in decisions regarding initiation of therapy.

The Working Group recommends that treatment be started in children with AIDS (category C) or severe immune suppression (category 3) and that treatment be considered in children with mild-to-moderate clinical symptoms (category A or B), moderate immune suppression (category 2), or confirmed plasma HIV RNA level of 100,000 copies/mL or higher. Factors to consider in deciding whether to initiate therapy in children in this age group include the rate of plasma HIV RNA level increases (and how close the value is to 100,000 copies/mL), the rate of CD4+ cell count or percentage declines and how close they are to that associated with severe immune suppression, and the presence of clinical symptoms. In addition, the ability of the child and caregiver(s) to adhere to the treatment regimen should have an effect on the decision whether to start treatment. Indications for antiretroviral treatment in this age group according to clinical status, CD4+ cell percentage, and plasma HIV RNA level are shown in Table 2.

**Choice of Initial Antiretroviral Therapy**

The goals of antiretroviral therapy are to achieve maximal suppression of viral replication to below assay detection limits for as long as possible and to preserve or restore immune function. The goal of viral load suppression to below detection limits is not always achievable in children, who may have very high plasma HIV RNA levels. It is recommended that treatment be initiated with triple-drug combinations, since such combinations have been shown to slow disease progression, improve survival, produce a more sustained virologic

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**Table 1. Indications for Initiation of Antiretroviral Treatment in Children Younger Than 12 Months**

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+ Cell Percentage</th>
<th>Plasma HIV RNA Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptomatic</td>
<td>OR ≤25% (category 2 or 3)</td>
<td>Any</td>
<td>Treat</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>AND &gt;25% (category 1)</td>
<td>Any</td>
<td>Consider treatment</td>
</tr>
</tbody>
</table>

Clinical categories: A indicates mild clinical symptoms with usually only nonspecific generalized lymphadenopathy; B, moderate clinical symptoms; C, AIDS; N, asymptomatic. Immunologic categories (CD4+ cell percentage): 1, >25%; 2, 15%-25%; 3, <15%.

Adapted from Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, September 2003.
response, and delay the emergence of viral resistance. Zidovudine monotherapy is recommended for prophylaxis in perinatally exposed infants with indeterminate infection status during the first 6 weeks of life (with this constituting the only recommended use of antiretroviral monotherapy). It is also recommended that viral resistance testing be considered prior to initiation of treatment in newly diagnosed infants younger than 12 months, particularly if the mother is known or suspected to have drug-resistant virus.

The Working Group recommendations on regimens for use in initial therapy have been formulated with consideration of the following: data on the durability of viral suppression and clinical and immunologic response; data on the types and incidence of toxic effects; availability and palatability of drug formulations for children; dosing frequency and food or fluid needs; and the potential for drug-drug interactions.

Drug combinations recommended for use in children consist of the following: 1) a protease inhibitor (PI) plus 2 nucleoside analogue reverse transcriptase inhibitors (nRTIs); and 2) a nonnucleoside reverse transcriptase inhibitor (NNRTI) plus 2 nRTIs. Recommendations for specific PI-based, NNRTI-based, and nRTI-based regimens are shown in Table 3. An advantage of PI-based regimens is high potency, and disadvantages include a high pill burden and difficulty with palatability. Advantages of NNRTI-based regimens include effectiveness and palatability, and disadvantages include rapid emergence of viral resistance when viral suppression is not optimal. An advantage of nRTI-based regimens is the sparing of other drug classes for future use; however, these regimens have been shown to be less potent than PI- and NNRTI-based combinations in adult clinical trials. Of note, children at a number of treatment sites have received long-term treatment with double-nRTI therapy (ie, largely treatment beginning prior to the potent antiretroviral therapy era) and have maintained good clinical status and immunologic function. Thus, dual-nRTI therapy can be used in special circumstances. Not recommended for use in initial therapy are monotherapy (except for zidovudine prophylaxis, as described above), certain dual-nRTI combinations, such as zidovudine and stavudine, and the saquinavir hard-gel capsule formulation.

Currently, there are insufficient data to recommend the following: dual-nRTIs; delavirdine; dual PIs (except for the lopinavir/ritonavir co-formulation); three-class combinations (eg, PI plus NNRTI plus nRTI); tenofovir-containing regimens; and enfuvirtide-containing regimens.

### Table 2. Indications for Initiation of Antiretroviral Treatment in Children Aged 12 Months or Older

<table>
<thead>
<tr>
<th>Clinical Category</th>
<th>CD4+ Cell Percentage</th>
<th>Plasma HIV RNA Level</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>AIDS (category C)</td>
<td>OR &lt;15% (category 3)</td>
<td>Any</td>
<td>Treat</td>
</tr>
<tr>
<td>Mild-to-moderate symptoms (category A or B)</td>
<td>OR 15%-25% (category 2)</td>
<td>OR ≥100,000 copies/mL</td>
<td>Consider treatment</td>
</tr>
<tr>
<td>Asymptomatic (category N)</td>
<td>AND &gt;25% (category 1)</td>
<td>AND &lt;100,000 copies/mL</td>
<td>Many experts would defer therapy and closely monitor clinical, immune, and viral parameters</td>
</tr>
</tbody>
</table>

Clinical categories: A indicates mild clinical symptoms with usually only nonspecific generalized lymphadenopathy; B, moderate clinical symptoms; C, AIDS; N, asymptomatic. Immunologic categories (CD4+ cell percentage): 1, >25%; 2, 15%-25%; 3, <15%.

Adapted from Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, September 2003.

### Considerations in Changing Regimens

The primary indications for changing an antiretroviral regimen are treatment failure based on clinical, virologic, or immunologic parameters, toxicity or intolerance of the current regimen, and new findings demonstrating that a new regimen is superior to the current regimen. Guiding principles in cases in which the antiretroviral regimen is to be changed because of toxicity or intolerance include the following:

1. Choose drugs with toxicity profiles different from those in the current regimen.
2. Changing a single drug is permissible.
3. If the dose of a drug is reduced, do not reduce the dose below the lower end of the therapeutic range for that particular drug.

Guiding principles in cases in which the antiretroviral regimen must be changed because of disease progression include the following:

1. Assess and review adherence.
2. Never change only 1 drug at a time—a new regimen must contain at least 2 drugs different from those in the current regimen.
3. Consider overlap of resistance patterns of drugs in the new regimen.
4. Consider potential drug interactions with other medications.
5. Discuss quality-of-life issues for patients with advanced HIV disease.

### Adherence and Other Special Considerations in Children and Adolescents

There are a number of issues in adherence to antiretroviral treatment specific to pediatric patients that must be addressed to ensure maximum benefit of treatment. Drugs must be available in a palatable liquid or mixable formulation for infants and younger children. Requirements for administering drugs with or without food can be difficult to meet in younger children because of eating schedules. Further, the reluctance
Table 3. Recommended Initial Antiretroviral Therapy for Children

<table>
<thead>
<tr>
<th>Protease Inhibitor-Based Regimens</th>
<th>Strongly recommended</th>
<th>2 nRTIs plus lopinavir/ritonavir or nelfinavir or ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alternative recommendation</td>
<td>2 nRTIs plus indinavir or amprenavir (children ≥4 years old)</td>
<td></td>
</tr>
<tr>
<td>Use in special circumstances</td>
<td>2 nRTIs plus saquinavir soft gel capsule</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nonnucleoside Reverse Transcriptase Inhibitor-Based Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strongly recommended</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Alternative recommendation</td>
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<table>
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<tr>
<th>Nucleoside Reverse Transcriptase Inhibitor-Based Regimens</th>
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<tr>
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</tr>
<tr>
<td>Alternative recommendation</td>
</tr>
<tr>
<td>Use in special circumstances</td>
</tr>
</tbody>
</table>

nRTI indicates nucleoside reverse transcriptase inhibitor. Adapted from Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection, September 2003.

of families to disclose the child’s HIV diagnosis may interfere with medication administration during day care or school hours. A child’s developmental level influences his or her ability and willingness to take medications; this should be taken into account when enlisting the child’s cooperation. Finally, the child is dependent on the caregiver(s) for medication administration, and commitment and vigilance on the part of the caregiver(s) is necessary.

For adolescents in particular, there may be psychosocial needs that have to be addressed to maximize the chances of adherence to treatment. Developmental issues that have to be confronted in patients in this group include those surrounding their characteristic concrete thought processes and their desire to be like their peers (ie, those who do not have to take medications). Homelessness and lack of family support are formidable barriers to adherence in many infected adolescents. Treatment adherence is a responsibility for everyone involved with the patient, including the patient him- or herself, the family, the social worker, the nurse, and the physician.

Other issues arise for patients with advanced disease who have extensive prior antiretroviral experience. How does one approach the very sick long-term survivor who must still continue to take numerous medications? What is the best course when there are limited remaining treatment options? What happens when all treatment options are exhausted?

No matter what the status of our patients, caring about them matters. We cannot always provide an intervention that dramatically improves their condition. What we can always do is pay attention to the little things, such as making the medication more palatable and easier to take, relieving pain, and making and keeping regular appointments with patients. As AESOP said, “No act of kindness, no matter how small, is ever wasted.”


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Suggested Reading


Review

Antiretroviral Adherence Interventions: A Review of Current Literature and Ongoing Studies

Jane M. Simoni, PhD, Pamela A. Frick, PharmD, MPH, David W. Pantalone, AB, Barbara J. Turner, MD, MSEd

Adherence has proven to be the Achilles’ heel of antiretroviral therapy. To achieve the nearly perfect adherence apparently necessary for optimal effects, individuals often require assistance. In this review, we examine antiretroviral therapy adherence intervention studies and reviews published through January 2003 as well as abstracts of ongoing National Institutes of Health-funded research projects aimed at enhancing antiretroviral therapy adherence. The 21 published studies we located utilized 4 intervention strategies: cognitive-behavioral, behavioral, directly observed therapy, and affective. Most of these were pilot or feasibility studies. However, the 4 randomized controlled trials conducted with adequate methodologic rigor suggest some promising yet preliminary effects of a pharmacist-led individualized intervention, a cognitive-behavioral educational intervention based on self-efficacy theory, and cue-dose training when combined with monetary reinforcement. The 39 ongoing federally funded studies offer superior methodologic sophistication and include some innovative strategies, such as the use of handheld devices, two-way pagers, and alarmed medication vials, along with enhancement of social and emotional support.

Numerous reports have documented that combinations of antiretroviral medications can inhibit HIV replication and result in precipitous declines in HIV-associated morbidity and mortality. However, the high degree of success with antiretroviral therapy in achieving HIV-1 RNA levels below assay detection limits reported in clinical trials (ie, 60%–90%) has seldom been achieved in everyday practice. Indeed, studies in primary care settings suggest that, on average, only 50% of patients achieve HIV-1 RNA levels below detection limits. A primary reason for the lack of success in clinical practice appears to be either intentional or non-intentional poor adherence to medication regimens. The level of antiretroviral therapy adherence needed to obtain optimal long-term benefits appears to be over 90%. Compared with therapy for most other clinical conditions, antiretroviral therapy requires an unprecedentedly high level of adherence for an indefinite time period to achieve optimal viral suppression. Consequently, adherence has proven to be the Achilles’ heel of antiretroviral therapy.

Adherence to demanding antiretroviral regimens requires substantial support and monitoring. Effective approaches to promote and improve patient adherence to antiretroviral therapy are the focus of intensive, time-consuming research. Most intervention studies are still incomplete. Nonetheless, results from available studies can offer instructive examples for clinicians and patients to consider while awaiting more definitive results.

In this review of the emerging research on interventions to improve antiretroviral adherence, we consider various conceptualizations of adherence and its correlates as well as interventions designed to enhance adherence. We review published reports as well as summaries of ongoing federally funded studies and conclude with recommendations for practice and directions for future research.

Conceptualizations of Adherence and Its Correlates

There is no universally accepted definition of medication adherence. With respect to HIV/AIDS care specifically, “medication adherence” has been defined as “the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing, and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function.”

In addition, few studies concur in their operationalization of adherence. Two common approaches to defining a categoric outcome are to consider whether the patient missed any pills over a specific interval or whether the patient has exceeded a set percentage of doses taken. The latter threshold approach may also consider the timing of taking the medications. Less commonly, adherence is analyzed as a continuous variable, such as the proportion of prescribed doses taken as measured by an electronic monitoring device, self-report, or pill counts; the percentage of pills available for consumption by pharmacy refill records; or the number of missed doses over a specified time period, such as the last 3 days.

Many correlates of nonadherence have been identified from cross-sectional studies. Ickovics categorized these factors into 4 groups: patient characteristics; aspects of the provider and the patient-provider relationship; variables related to the treatment regimen or illness; and contextual or environmental factors. With respect to correlates of nonadherence to antiretroviral...
therapy, 1 review found that several factors were often associated with nonadherence, including symptomatic disease and presence of adverse drug effects, psychologic distress, lack of social or family support, increased complexity of the antiretroviral therapy regimen, low patient self-efficacy, and inconvenience of treatment.16

Previous Reviews of Antiretroviral Adherence Interventions

The seriousness and urgency of problems related to nonadherence to antiretroviral medications have sparked increasing attention to this issue; however, scant empiric research on adherence interventions for HIV-infected persons has been published. Notwithstanding the embryonic stage of this research, there are 3 reviews summarizing current knowledge.

Haddad and colleagues reviewed controlled research studies published from January 1996 to April 1999 on interventions offering patient support and education to promote antiretroviral therapy.17 They identified only one intervention (by Knobel and colleagues in a Spanish-language publication) that met the strict selection criteria.18 Another review of the field through April 1999 identified 16 interventions designed to enhance HIV medication adherence, of which 12 were reported in conference abstracts and 4 in published articles.19 The interventions incorporated strategies that were cognitive (ie, designed to teach, clarify, or instruct); behavioral (ie, designed to shape, reinforce, or influence behavior); or affective (ie, designed to optimize social and emotional support). Of the 16 reports, only 11 included data on intervention efficacy, and the effects of these interventions were generally weak. Among these, only 5 were RCTs, with a mean sample size of 58. Four of these reported no treatment effect between the intervention and control groups, and the fifth, a DOT study, reported temporary effects that disappeared after the intervention ended.14,15

A third review focused on reports of RCTs of interventions to enhance adherence to antiretroviral therapy that were published or presented at the International AIDS Conference in Barcelona in July, 2002.20 The authors cited published reports of 2 promising interventions by Tuldra and colleagues and Rigsby and colleagues, as well as the Knobel and colleagues study cited above.18,21,22 From the AIDS Conference presentations, the authors cited 2 successful RCTs, one involving an internet-based paging system and the other using continuous and personalized counseling. However, 2 other RCTs that were presented, 1 assessing a problem-solving and enhanced support intervention and the other based on motivational interviewing, showed no intervention effects.

Data Sources for the Current Review of Adherence Interventions

For the present review, we updated and expanded the existing literature reviews and included a description of ongoing federally funded research.

We searched PsychINFO and MEDLINE for articles published through January 2003 that contained various combinations of the terms HIV/AIDS, adherence (or compliance), and intervention (also keywords for specific types of interventions, such as education, telephone, pager, peer, and alarm). We selected from this list all research articles describing primary reports of interventions to enhance antiretroviral adherence. We also scanned bibliographies of relevant articles for additional studies. Given the early stage of research in this field, we included descriptions of all relevant studies in our review regardless of methodologic rigor. However, common methodologic weaknesses of the work (eg, no randomization, no control group, sole reliance on self-report, no follow up, insufficient power, no statistical significance testing, and no intent-to-treat analyses) are noted below.

Additionally, we searched CRISP (Computer Retrieval of Information on Scientific Projects), a searchable online database of ongoing federally funded biomedical research projects, using the terms HIV, medication, adherence, nonadherence, compliance, noncompliance, antiretroviral, and HAART.

Findings from Current Review of Adherence Interventions

Our review of the published literature identified 21 interventions focused on enhancing adherence to antiretroviral therapy (Table 1); we excluded the few that focused on antiretroviral monotherapy.

The interventions in Table 1 are divided into 4 categories of strategies, based loosely on the review by Fogarty and colleagues:14 cognitive and behavioral, behavioral only, (modified) DOT, and affective. Although Ickovics and colleagues identified 4 distinct groups of factors that affect adherence,23 most of the intervention strategies that we identified in these 4 categories targeted only patient characteristics.

Nine studies combined cognitive and behavioral strategies. The interventions were delivered in group settings, one-on-one, or via both modalities. A trained facilitator or adherence counselor was usually the intervener, but when a provider was involved, it was typically a nurse or pharmacist. Four intervention studies evaluated strictly behavioral strategies. The types of interventions spanned a drop-in storefront center, a pager system, frequent HIV-1 RNA monitoring, and monetary reinforcement.

The third category involved 6 interventions that provided some form of DOT where a provider, outreach worker, or peer delivered every dose (or, in the case of modified DOT, almost every dose) of prescribed medication and watched the patient ingest each dose. The expense and complicated logistics of having a professional deliver every dose makes this strategy unfeasible, but researchers have designed creative alternatives. Some interventions take advantage of having a captive population (eg, in prisons, hospitals, or methadone clinics) or deliver only the morning dose of a twice-daily scheduled medication or only the weekday doses, leaving other doses to be self-administered. The average duration of the interventions varied from 12 to 40 weeks, with some involving a gradual tapering of observed doses; however, there seems to be no consensus as to the optimal timeframe. In terms of affective strategies, 2 studies were identified. They utilized peer support and optimistic writing.
Table 1. Published Studies of Interventions to Enhance Antiretroviral Therapy Adherence, by Type of Intervention

<table>
<thead>
<tr>
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<tr>
<td><strong>Cognitive and Behavioral Strategies</strong></td>
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</tr>
<tr>
<td>Nursing case management (32)</td>
<td>Uncontrolled pilot study with 10-day F/U</td>
<td>Home care patients in San Francisco, CA (N=10)</td>
<td>Nurse case manager assessment of client needs during initial home visit and implementation of tailored ARV therapy intervention strategies (eg, education, alarm, pill box, etc); F/U telephone calls on days 2, 4, and 10</td>
<td>Self-report of any missed doses the day before was 1 on day 2 and 0 on days 4 and 10</td>
</tr>
<tr>
<td>Individualized pharmacist advice (18)</td>
<td>RCT with 24 wks F/U</td>
<td>Patients in Barcelona, Spain (N=170)</td>
<td>Arm 1) 1 one-on-one pharmacist session providing individualized assessment and adherence advice with F/U telephone support available as needed (N=60) Arm 2) SOC (N=110)</td>
<td>At F/U, adherence levels over 90% (by self-report or pill counts) were identified for 77% of Arm 1 and 53% of Arm 2</td>
</tr>
<tr>
<td>Pharmacist counseling (33)</td>
<td>Uncontrolled pilot study with unspecified F/U period</td>
<td>Male veterans who did not refill their ARV Rx in Miami, FL (N=21)</td>
<td>Doctoral-level pharmacist provided 1 individual counseling session that included participants role-playing their medication dosing schedule and learning to fill their weekly pill container</td>
<td>At F/U, adherence as measured by monthly refill records increased from 48% to 75% 50% of participants had ≥0.5 log reduction in HIV-1 RNA levels</td>
</tr>
<tr>
<td>Group education and individual counseling (34)</td>
<td>2-arm randomized trial with undefined F/U</td>
<td>Mainly male IDUs on ARVs for &gt;6 months and received care in an HIV unit for &gt;1 year in Madrid, Spain (N=115)</td>
<td>Arm 1) Group education sessions conducted by family physicians to determine reasons for nonadherence and reinforce positive attitudes at baseline, 1 mo, and 3 mo, plus individualized counseling Arm 2) Individualized counseling alone conducted by nurses</td>
<td>Inclusion phase stopped because of 74% refusal rates, making it impossible to form groups with more than 4 patients (59% refused for “personal reasons”)</td>
</tr>
<tr>
<td>Behavioral and educational strategies and social support (24)</td>
<td>RCT with 3 mo F/U</td>
<td>HIV clinic patients referred by PCP because of nonadherence who self-reported missing ≥1 dose per wk (N=79)</td>
<td>Arm 1) 5 alternating individual and group sessions consisting of behavioral strategies, patient information, social support, CBT, and psychiatric nursing over 7 wks Arm 2) SOC</td>
<td>At end of intervention and at 3-mo F/U (N=33), no significant treatment effect by self-report of dose adherence or of schedule adherence</td>
</tr>
<tr>
<td>Pharmacist education (35)</td>
<td>Non-randomized cohort study with concurrent matched controls</td>
<td>Men, primarily African American veterans in Miami, FL, with past or active drug use who did not refill their ARV Rx or who are on ≥4 ARVs and matched controls (N=42)</td>
<td>Arm 1) 5 monthly 20- to 25-min one-on-one meetings with doctoral-level pharmacist who provided education and positive reinforcement for self-management of regimen Arm 2) SOC</td>
<td>At 5 mo, significant adherence increase from baseline as measured by refill records for the intervention condition</td>
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### Cognitive and Behavioral Strategies, Continued

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<tr>
<td><strong>Multimedia education (36)</strong></td>
<td>Uncontrolled pilot study</td>
<td>Treatment-naive youth at clinical sites (N=65)</td>
<td>8-wk program of one-on-one sessions with study coordinators at every clinical encounter, including audio, video, and reading materials based on stages of change model</td>
<td>At 8 wks (N=11) 50% maintained adherence “most of the time” during the year</td>
</tr>
<tr>
<td><strong>Single-session counseling and medication monitoring (37,38)</strong></td>
<td>Uncontrolled pilot study of 2 interventions with 12 wks F/U</td>
<td>Fenway Community Health Center clients in Boston, MA considered at risk for nonadherence, or self-reported &lt;100% adherence in last 2 wks (N=56)</td>
<td>Arm 1) Single-session intervention presented by clinician or videotape utilizing CBT, problem-solving, and motivational interviewing techniques + F/U telephone call at 1 wk. Arm 2) Self-monitoring: 2-wk minimal contact intervention utilizing pill diary</td>
<td>Self-reported % of pills taken in past 2 wks increased significantly from baseline to wk 2 for Arm 1 (from 74% to 95%). Adherence in Arm 2 increased, but not significantly (from 84% to 90%). At 12-wk F/U, levels were maintained</td>
</tr>
<tr>
<td><strong>Psycho-educational Intervention (22)</strong></td>
<td>RCT with 48 wks F/U</td>
<td>Consecutive patients starting 1st or 2nd ARV regimen in a university-affiliated HIV clinic (N=116)</td>
<td>Arm 1) Psychologist provided 1 one-on-one education session about the importance of adherence, how to manage adherence problems based on self-efficacy theory; at F/U visits (4, 24, and 48 wks), adherence was reinforced and any problems addressed. Arm 2) SOC</td>
<td>At F/U in as-treated analysis (N=70), 94% of Arm 1 vs 69% of Arm 2 achieved ≥95% self-reported adherence in past mo. 89% of Arm 1 vs 66% of Arm 2 had HIV-1 RNA levels ≤400 copies/mL</td>
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### Behavioral Strategies Only

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<tr>
<td><strong>Store-front, drop-in program (39)</strong></td>
<td>Uncontrolled pilot study</td>
<td>Self-referred indigent patients in San Francisco, CA (N=68)</td>
<td>Store-front, drop-in program of up to 5 mo duration provided place to pick-up medications 6 days/wk, weekly $10 incentives, and pager that provided dose reminders</td>
<td>At 2 mo (N=25), 64% had HIV-1 RNA level &lt;500 copies/mL. 12% had at least a 2-log reduction in HIV-1 RNA levels</td>
</tr>
<tr>
<td><strong>2-way pager (40)</strong></td>
<td>Uncontrolled pilot study</td>
<td>Patients at HIV university-affiliated clinic for underserved population in Seattle, WA (N=25)</td>
<td>For a median duration of 7 mo, a 2-way pager sent messages to remind participants to take doses; the pager also educate, support, and encourage their adherence</td>
<td>Among 19 participants with ≥3 mo with pager, 58% of paged responses indicated perfect adherence over the past few days. 79% felt pager improved adherence</td>
</tr>
<tr>
<td><strong>Frequent HIV-1 RNA monitoring (41)</strong></td>
<td>2-arm RCT</td>
<td>Predominantly low-income patients from 5 university-affiliated HIV clinics in CA (N=173)</td>
<td>12 mos of: Arm 1) Bimonthly feedback of HIV-1 RNA results. Arm 2) Semi-annual feedback of HIV-1 RNA results</td>
<td>Compared with Arm 2, at 6 months (N=119), Arm 1 did not have improved self-reported adherence. Arm 1 had a greater average reduction in HIV-1 RNA (0.85 vs 0.43 log&lt;sub&gt;10&lt;/sub&gt; copies/mL)</td>
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| Cue-dose training with monetary reinforcement (21)                                                                                   | 3-arm randomized trial with mean F/U of 8 wks                                       | Mainly male, African American, formerly drug-using clinic patients in West Haven and Hartford, CT (N=55) | 4 weekly sessions of:  
  Arm 1) CD: Counselor-led personalized CD training (subjects identify daily cues for remembering dose times) + weekly feedback from MEMS®  
  Arm 2) CD + CR: CD and weekly cash reinforcement for correctly timed MEMS® bottle openings  
  Arm 3) Control group: Counselor-led inquiries and encouragement about adherence | During sessions (wks 0-4), CD + CR group (but not CD group) relative to controls had enhanced MEMS® adherence  
During F/U (wks 5-12), CD + CR group (but not CD group) had a significant loss of previous MEMS® adherence gains relative to controls |
| (Modified) DOT Strategies                                                                                                         |                                                                                             |                                                                                                          |                                                                                                                                                                                                                                                                                                                                                                                                     |
| DOT (42)                                                                         | Pilot study with comparison group          | Predominantly male IDU prisoners in Italy (N=84)                                    | For a mean duration of 8.6 mo, 37 prisoners at 9 prisons were given DOT by nurses; at 9 other prisons, 47 prisoners were given medications once daily for self-administration                                                                 | At end of trial (range 3-19 mo), more in DOT group had plasma HIV-1 RNA levels below detection (62% vs 34%)  
Fewer in DOT group had CD4+ lymphocyte count <200/µL (5% vs 32%) |
| DOT (43)                                                                         | Uncontrolled pilot study                   | Antiretroviral-naive inmates from 5 prison sites with HIV-1 RNA >400 copies/mL and no AIDS diagnosis (N=108) | 24 wks of DOT with witnessed swallowing or patient visited dispensing site at specified times to receive doses twice daily | At 24 weeks, overall 68% with HIV-1 RNA ≤400 copies/mL  
Overall self-reported adherence to prescribed doses was 94% |
| DOT (44)                                                                         | Pilot study with comparison group          | Arm 1) 19 prisoners  
Arm 2) 30 outpatients in Northeastern Italy                                           | 24 wks of:  
Arm 1) DOT under strict nursing control  
Arm 2) Self-administered medication                                                                 | At 12 weeks; mean HIV-1 RNA level lower for Arm 1 (65 vs 5541 copies/mL in Arm 2)  
Percentage achieved HIV-1 RNA below detection greater in Arm 1 |
| Modified DOT (45)                                                                | Uncontrolled pilot study                   | Patients on complex ARV regimens adjusted to account for genotypic resistance referred by PCP or self in Jacksonville, FL (N=44) | For 12-16 wks, outreach worker observed weekday AM doses in home; PM and weekend doses were self-administered | At 12-16 wks (N=23), 26% achieved HIV-1 RNA <50 copies/mL |
### Table 1. Published Studies of Interventions to Enhance Antiretroviral Therapy Adherence, by Type of Intervention, Continued

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<tr>
<td><strong>Modified DOT (46)</strong></td>
<td>Uncontrolled pilot study</td>
<td>Modified DOT (46)</td>
<td>For 24 wks, received AM ARV therapy doses 6 days per wk at time of methadone dosing and telephone call as reminder to take Sunday doses; PM doses were self-administered</td>
<td>At 8 wks, 80% had HIV-1 RNA level &lt;400 copies/mL Mean self-reported adherence was 97%-100%</td>
</tr>
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</table>
| **Modified DOT (47)** | Uncontrolled pilot study | Patients with a history of or anticipated poor adherence referred by PCP in Providence, RI | For a mean duration of 10 mo, outreach worker observed weekday AM doses, usually in home; PM and weekend doses were self-administered
Observation was tapered to weekly visits after several mo | 82% of participants with complete 12-mo data (N=17) self-reported missing ≥1 dose in past 4 days at baseline, but only 35% reported the same at both 3 and 12 mo
Participants enrolled 12 or more mo (N=18), the mean decrease in plasma HIV-1 RNA level from baseline was 1.53 log₁₀ copies/mL (No P values reported) |
| **Affective Strategies** | | | | |
| **Peer support (48)** | Uncontrolled pilot study | PCP-referred “poorly adherent” active IDUs in New Haven, CT | Peer-driven intervention with mean duration of 9 wks in which each subject acts as (1) an advocate to provide weekly support and counseling to peers and (2) as a peer, advocates earned weekly nominal monetary rewards for eliciting positive responses from peers | At 9 wks, mean overall adherence as measured by advocate-conducted weekly pill counts was 90% |
| **Optimistic future writing (49)** | RCT | Women of low socioeconomic status | For 4 wks: Arm 1) Wrote for at least 10 min 2 times per wk about a somewhat positive future in which they only had to take 1 pill each day for HIV
Arm 2) Did not write | All participants reminded of the importance of adherence |

All participants were HIV-infected adults on combination antiretroviral therapy unless otherwise noted. All comparative results (not descriptives) included were statistically significant at P≤0.05. F/U indicates follow up; ARV, antiretroviral; SOC, standard of care; Rx, prescription; RCT, randomized controlled trial; mo, month(s); wk, week; CBT, cognitive-behavioral therapy; MEMS®, Medication Event Monitoring System; IDU, injection drug user; CD, cue-dose training; CR, cash reinforcement; PCP, primary care provider; DOT, directly observed therapy; min, minute.
Methodology

Most of these intervention studies lacked methodologic rigor. Specifically, half were feasibility or pilot studies without follow up after the intervention to evaluate sustainability of the effects. Only 36% reported descriptive information about adherence indicators at the end of the program. Few studies provided data for a within-subject pre or post comparison. Only the study by Tuldra and colleagues explicitly referred to a theoretic framework.22 Most studies were small and likely underpowered: the average sample size was 66, with only 5 samples larger than 100. Less than one third of the studies incorporated a follow-up assessment period; among those that did, time of follow up ranged from 1.4 to 48 weeks, with 2 studies’ time unspecified.

Two studies reporting improvements in adherence used only a self-reported adherence measure. Ten studies noted improvement in virologic or immunologic outcomes, but many offered descriptive information without testing for statistical significance. Most studies lacked controls or random assignment to conditions.

Randomized Controlled Trials (RCT)

Ten studies included control or comparison groups, but only 7 of these included the randomization to conditions and control groups that define RCTs. Of these, only 4 incorporated a follow-up period of assessment. The most comprehensive intervention employed behavioral and educational strategies as well as social support.24 Unfortunately, it did not find any significant effects. The other 3 studies had encouraging findings but had numerous methodologic issues.18,21,22

The intervention described by Knobel and colleagues involved a pharmacist who offered a single one-on-one individualized educational session designed to provide detailed information about therapy and to help the participant fit the medication regimen into his or her lifestyle, followed by telephone support. At 24 weeks, participants in the intervention condition self-reported significantly improved adherence but the rate of achieving an HIV-1 RNA level below detection in this group was not statistically significantly better than the control group.18

The study by Tuldra and colleagues, based on Bandura’s self-efficacy theory,25 involved a psychologist who provided one-on-one individualized educational session designed to provide detailed information about therapy and to help the participant fit the medication regimen into his or her lifestyle, followed by telephone support. At 24 weeks, participants in the intervention condition self-reported significantly improved adherence but the rate of achieving an HIV-1 RNA level below detection in this group was not statistically significantly better than the control group.18

The study by Tuldra and colleagues, based on Bandura’s self-efficacy theory,25 involved a psychologist who provided one-on-one education about the importance of adherence and managing adherence problems with the goal of increasing the patient’s self-efficacy. In addition, a daily dosage schedule was developed. During follow-up visits at 4, 24, and 48 weeks, adherence was reinforced and any problems addressed. At 48 weeks, 32 patients (94%) in the intervention group, and 25 patients (69%) in the control group achieved a level of adherence of 95% or greater as measured by self-report (P = 0.008). In addition, 89% of the intervention group and 66% of the control group had a plasma HIV-1 RNA level of 400 copies/mL or below (P = 0.026). However, the significant intervention effects were not statistically significant at week 48 were from an “as-treated” and not an “intent-to-treat” analysis of only 70 of the original 116 participants.22

The intervention conducted by Rigsby and colleagues involved cue-dose training and monetary reinforcement. In 4 weekly sessions, counselors trained patients to time their doses based on personalized cues such as meal times or other regular daily activities. They also used feedback from the Medication Event Monitoring System (MEMS®), which uses electronic monitors that record the date and time of every opening of the medication vial. For example, if a particular dose was not taken within 2 hours of the specified dosing time, the reinforcement was reset to $2. During the intervention (weeks 0 to 4), participants who received both strategies (but not those receiving only cue-dose training) demonstrated enhanced adherence according to electronic monitoring relative to controls. However, the change was not sustained at follow up (weeks 5-12).21

Ongoing Research Funded by the National Institutes of Health (NIH)

Our Computer Retrieval of Information on Scientific Projects (CRISP) search identified 39 abstracts for ongoing federally funded research involving interventions to enhance antiretroviral adherence (Appendix). The studies in progress involve a variety of methods that further expand research within the 4 categories previously described for the published studies. Novel strategies utilize technology such as a handheld device to provide educational, affective, and behavioral components; a two-way pager; telephone-delivered habit training; and a medication storage device that incorporates a reminder alarm. Other innovative strategies include the optimization of social and emotional support through peer support groups, stress management, risk reduction, and the treatment of depression.

As expected given the highly competitive nature of NIH awards, these projects exhibit substantial methodologic sophistication. Most programs were theoretically based and were to be tested in RCTs with sufficient power, adequate follow up, and a variety of outcome measures. Consequently, these studies, compared with the current literature, will provide better evidence of intervention effects.

Guidelines for Best Practice

The empiric data necessary to make strong recommendations regarding the most efficacious way to improve antiretroviral therapy adherence are currently lacking. Indeed, the only encouraging evidence from methodologic RCTs with follow-up assessments suggested there might be some promise in pharmacist-led individualized interventions, cognitive-behavioral educational interventions based on self-efficacy theory, and a combination of cue-dose training and monetary reinforcement.

In response to this dearth of empirically sound data, a common response from experts has been to recommend strategies based on methodologically limited data, research from adherence in other fields, empirically demonstrated correlates of adherence, and clinical experience. For example, the Best
most of the intervention strategies have focused on patient characteristics; interventions are also needed that focus on the provider and the patient-provider relationship, variables related to the treatment regimen or illness, and contextual factors. Better communication and collaboration among investigators may enhance the development of knowledge and reduce duplication of efforts. Most important, researchers need to submit and editors need to publish reports of interventions with nonsignificant treatment effects if the field is to avoid past mistakes and the needless re-evaluation of unpromising strategies.

Multifactorial interventions leave a study vulnerable to the critique that it is impossible to distinguish which aspect of the intervention is the most effective. It is important to emphasize to reviewers and to researchers that adherence studies need to provide a combination of interventions to promote a long-term behavior such as adherence to medication. Since adherence behavior is dynamic, often decreasing initially in response to side effects or disease status, further research is needed about the timing of interventions.20 Front-loaded, prophylactic strategies are probably best, but when should they begin and how long should they last? What type and quantity of booster sessions are required? Studies need to demonstrate, if possible, how much time is required for complex behaviors, such as antiretroviral therapy adherence, to become habitual and to provide information regarding how quickly such behaviors extinguish.

As successfully tested interventions emerge, we also need to address the issue of efficacy versus effectiveness: what works in RCTs might not work in clinics challenged by limited staff time, inadequate resources, and diverse patient populations.

Suggestions for Future Research

The body of research on improving adherence to antiretroviral therapy, although in its infancy, is likely to grow rapidly in the near future. The gold standard for research is the RCT, but RCTs need to have: appropriate theoretical frameworks; adequate sample sizes; psychometrically sound and clinically useful outcome measures; clear and consistent operationalization of adherence and outcome; and better adherence assessment methods.30 Moreover, RCTs will likely need to combine interventions, given the relatively small effects observed from studies of single interventions, as well as expand the breadth of adherence issues addressed by these interventions. As mentioned above, most of the intervention strategies have focused on patient characteristics; interventions are also needed that focus on the provider and the patient-provider relationship, variables related to the treatment regimen or illness, and contextual factors. Better communication and collaboration among investigators may enhance the development of knowledge and reduce duplication of efforts. Most important, researchers need to submit and editors need to publish reports of interventions with nonsignificant treatment effects if the field is to avoid past mistakes and the needless re-evaluation of unpromising strategies.

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The body of research on improving adherence to antiretroviral therapy, although in its infancy, is likely to grow rapidly in the near future. The gold standard for research is the RCT, but RCTs need to have: appropriate theoretical frameworks; adequate sample sizes; psychometrically sound and clinically useful outcome measures; clear and consistent operationalization of adherence and outcome; and better adherence assessment methods.30 Moreover, RCTs will likely need to combine interventions, given the relatively small effects observed from studies of single interventions, as well as expand the breadth of adherence issues addressed by these interventions. As mentioned above, most of the intervention strategies have focused on patient characteristics; interventions are also needed that focus on the provider and the patient-provider relationship, variables related to the treatment regimen or illness, and contextual factors. Better communication and collaboration among investigators may enhance the development of knowledge and reduce duplication of efforts. Most important, researchers need to submit and editors need to publish reports of interventions with nonsignificant treatment effects if the field is to avoid past mistakes and the needless re-evaluation of unpromising strategies.

Multifactorial interventions leave a study vulnerable to the critique that it is impossible to distinguish which aspect of the intervention is the most effective. It is important to emphasize to reviewers and to researchers that adherence studies need to provide a combination of interventions to promote a long-term behavior such as adherence to medication. Since adherence behavior is dynamic, often decreasing initially in response to side effects or disease status, further research is needed about the timing of interventions.20 Front-loaded, prophylactic strategies are probably best, but when should they begin and how long should they last? What type and quantity of booster sessions are required? Studies need to demonstrate, if possible, how much time is required for complex behaviors, such as antiretroviral therapy adherence, to become habitual and to provide information regarding how quickly such behaviors extinguish.

As successfully tested interventions emerge, we also need to address the issue of efficacy versus effectiveness: what works in RCTs might not work in clinics challenged by limited staff time, inadequate resources, and diverse patient populations.
What types of ancillary medical and mental health providers can assist the physician, physician’s assistant, or nurse practitioner in the job of promoting and reviewing adherence? Can pharmacists take on the additional work of adherence counseling, and how can they be compensated for their time in the current managed care climate? Is there a role for non-health care providers, such as peers or near-peers, in ongoing adherence work?

Given the complex array of factors associated with nonadherence, no single strategy is likely to be effective for every patient. Therefore, different sets of targeted interventions may be needed for special groups such as children, pregnant women, or active substance users. For example, all patients do not need DOT, but it may be that DOT and self-efficacy training in the context of a drug treatment program are necessary to help drug users successfully adhere to therapy. Unfortunately, because of the cost of such highly individualized interventions, it may be unfeasible to incorporate these interventions into most clinics. Cost-effectiveness data are needed in the long term to assess the practical value of various types of interventions to promote adherence.

Finally, the international AIDS pandemic requires us to consider antiretroviral therapy access and adherence in resource-poor settings such as developing countries. Initial studies are disproving fears about inadequate adherence levels in resource-poor settings, but other issues remain unresolved. For example, will DOT or other strategies such as culturally relevant information, motivational, and skills-building strategies be most cost effective? Given the possibility of transmission of resistant virus to drug-naive individuals, it is important when initiating antiretroviral therapy in resource-poor countries to emphasize the importance of adherence and the risk of sharing medications.

Conclusions

Some of the initial optimism regarding the efficacy of antiretroviral therapy has dissipated in the face of the onerous challenges of maintaining nearly perfect adherence indefinitely. Current research on correlates of adherence to HIV medications offers preliminary support for the efficacy of such strategies as assessing and addressing individual patient needs and barriers; nurturing the therapeutic alliance as well as other sources of social support; employing comprehensive and individualized cognitive, behavioral, and affective strategies; and continuously monitoring adherence with a variety of assessment methods. Empiric research focusing specifically on interventions to bolster antiretroviral therapy adherence is in a nascent stage of development. Results of 4 RCTs conducted with adequate methodologic rigor lend some support to a pharmacist-led individualized intervention, a cognitive and behavioral educational intervention based on self-efficacy theory, and cue-dose training combined with monetary reinforcement. However, even these encouraging findings were marred by methodologic limitations. Finally, a review of ongoing federally funded research revealed 39 adherence intervention projects evaluating a diversity of adherence strategies. Fortunately, intensive work is underway to address the seemingly intractable problem of antiretroviral therapy nonadherence.

Appendix. Ongoing Research on Antiretroviral Therapy Adherence Interventions Funded by the National Institutes of Health

Cognitive and Behavioral Strategies

ATKINSON, JH. (DA012800-03). Better Antiretroviral Adherence: HIV+ Amphetamine Users. Research of HIV-infected methamphetamine-dependent individuals in early recovery. This RCT (N=75 per arm) of an 8-week intervention compared (1) SOC, (2) informational-motivational-behavioral (IMB)-based adherence training alone, and (3) IMB-based adherence training with stimulant relapse prevention. At baseline, end of treatment, and 4 and 6 months after baseline, the investigators will measure adherence, HIV-1 RNA level, urine toxicology, substance use, quality of life, and neuropsychiatric status. ARV therapy will be measured by self-report, MEMS®, and serum medication concentrations.

BUNTING, SM. (NR007718-01). Modifying Facilitators and Barriers to HIV Adherence. Pilot test of RCT (N=88) of 3-month intervention comparing (1) SOC with (2) individualized assessment, education, counseling, and referrals administered by a research nurse in-person with telephone-based follow-up sessions. Adherence to all prescribed medications will be measured at times 1, 2, and 3 by self-report and pill counts. Adherence to 1 antiretroviral medication will also be monitored by MEMS®.

CATZ, SL. (MH065858-02). Adherence Intervention—Late Middle–Aged/Older Adults. For HIV-infected late middle-aged and older persons, development and pilot testing of individual-level and group-level adherence interventions based on motivational interviewing techniques and behavioral skills training.

CROSBY, GM. (AA012009-04). HIV Treatment Adherence Among Alcohol Abusers. Among HIV-infected alcohol-dependent patients (globally), RCT (N=617) of (1) SOC and (2) 6-session individualized intervention based on social action theory.
Investigators will measure plasma HIV-1 RNA levels, plasma CD4+ lymphocyte counts, and rates of self-reported adherence confirmed through MEMS® data.

DIORIO, CK. (NR004857-04). An Adherence Intervention for Antiretroviral Regimens. RCT (N= 222) of 12-week intervention comparing (1) SOC and (2) HOLZEMER, WL. (NR004846-04). Outpatient Nurse-Managed patient participation on adherence. Physician satisfaction with the medical visit, and the impact of the intervention on patient participation, patient and back and follow up over a 12-week period. Study will assess the impact of monthly peer health educator home visits. An intensive intervention consisting of 8 nurse-led 90-minute sessions over 4 months. Adherence will be measured by self-report diaries, pill counts, and MEMS®. Clinical response will be assessed using HIV-1 RNA levels and CD4+ lymphocyte count.

ERLEN, JA. (NR004749-05). Adherence to Protease Inhibitors. RCT (N= 200) of 24-week intervention comparing (1) SOC with (2) 12 weeks of telephone-delivered habit-training and problem-solving sessions, followed by 12 weeks of telephone-delivered maintenance sessions. Adherence will be measured with self-report diaries, pill counts, and MEMS®. Clinical response will be assessed using HIV-1 RNA levels.

GOLIN, CE. (MH001862-04). Adherence To Antiretroviral Therapy: a Controlled Trial. Develops an intervention for seropositive patients starting new ARV regimens, trains patients to participate in medical decision making, and provides feedback and follow up over a 12-week period. Study will assess the impact of the intervention on patient participation, patient and physician satisfaction with the medical visit, and the impact of patient participation on adherence.

HOLZEMER, WL. (NR004846-04). Outpatient Nurse-Managed HIV Adherence Trial. RCT (N= 222) testing (1) SOC and (2) Client Adherence Profiling-Intervention Tailoring (CAP-IT), implemented by nurse case managers during regularly scheduled home care visits. Investigators will measure adherence as well as CD4+ lymphocyte count, HIV-1 RNA level, and antiretroviral therapy resistance.

HOSEK, SG. (MH064348-02). A Pilot Adherence Intervention for HIV-Infected Youth. For HIV-infected adolescents and young adults, pilot RCT comparing (1) SOC and (2) cognitive-behavioral depression and coping skills intervention.

KALICHMAN, SC. (MH062287-04). HIV Treatment Adherence for Persons with Low Literacy. For HIV+ persons who demonstrate poor literacy skills, develop and field test an RCT (N= 80) comparing (1) a wait-list control group with (2) an intervention using pictograph-based IMB skills training to improve adherence. Investigators will measure self-report adherence and variables relevant to testing the IMB skills adherence intervention model.

KANOUSE, DE. (MH061695-03). A Training Intervention to Enhance Adherence to Antiretroviral Therapy. RCT (N= 270) of (1) SOC, (2) an adherence training intervention with psycho-educational components alone, or (3) the psycho-educational intervention delivered in the context of a brief training trial of an inert medication that mimics antiretroviral therapy. Adherence will be assessed using self-report and MEMS®. Investigators will measure the clinical outcomes of HIV-1 RNA levels and resistance assays.


MCDONNELL, MK. (NR008094-01A1). Motivating HIV+ Women: Risk Reduction and ART Adherence. RCT of (1) SOC of an 8-session attention equivalent control condition consisting of a health promotion program led by a nurse health educator, and (2) a group intervention based on motivational interviewing consisting of 8 nurse-led 90-minute sessions over 4 months. Adherence will be measured by self-report via Audio Computer-Assisted Self-Interviewing (ACASI), MEMS® and a Multi-Component Adherence Index. HIV-1 RNA levels and CD4+ lymphocyte counts will be obtained by chart review.

PARSONS, JT. (AA013556-02). Adherence Intervention for HIV+ Alcohol Users. RCT of 8-session intervention comparing (1) an attention control condition of standard education with (2) motivational interviewing and behavioral skills training based on the IMB skills model. Primary outcome measures will be the biological markers for HIV-1 RNA level, CD4+ lymphocyte count, and tests for alcohol use. Other outcome measures will include self-reported adherence, prescription refill data (via pharmacy records), adherence to medical appointments (via chart review), and self-reported alcohol use and alcohol-related problems.

REMIEH, RH. (6R01MH061173-04). Serodiscordant Couples, Medical Adherence, and HIV Risk. For serodiscordant couples, RCT of (1) SOC and (2) a brief, structured, theory-based intervention with the couples. Investigators will measure adherence to HIV medications, clinic appointment attendance, and prescription refills. Secondary aims of the study are to examine the relationship between attitudes and beliefs about effective medical treatments and sexual risk and participants’ behaviors.

SAFREN, SA. (MH066660-01A1). CBT for HIV Medication Adherence and Depression. For patients with major depression and a detectable HIV-1 RNA level, RCT of 4-month inter-
vention comparing (1) a single-session adherence intervention with (2) CBT for both major depression and antiretroviral therapy adherence. Control group participants will be re-assigned to CBT after the initial phase of the study if they have not improved on key outcome variables.

SMITH-DAHL, CB. (MH068202-01). Video Tool for Low-Literacy Antiretroviral Therapy Adherence. Targeting African-American and Hispanic individuals with low functional literacy, an informational intervention in video format based on the Health Belief Model. Investigators are currently completing development of the video and will next evaluate its effectiveness.

WEISS, SM. (MH055463-07) and TOBIN, JN. (SR01MH061208-02). Behavioral Interventions for Women with HIV/AIDS. Two linked interactive research project grant applications for a multi-site clinical trial focused on poor women of color living with HIV/AIDS. Phase I: RCT (N=450) of (1) individual psychoeducational comparison condition and (2) cognitive-behavioral stress management training combined with expressive-supportive therapy. Phase II: RCT comparing (1) individual health educational control with (2) a group skills training program. Outcome measures will include medication adherence, nutritional intake and physical activity, sexual risk taking, and substance use behaviors.

Behavioral Strategies Only

BRUE, V. (AI052634-01). A Novel Technology to Improve HIV Medication Compliance. The aim of this project is to design and develop a prototype device to allow convenient storage and transport of antiretroviral medications, incorporating reminder alarms at dosing times and usage reporting functions. Once developed, the device will be tested in clinical trials to determine its usability and functionality in increasing medication compliance in persons infected with HIV.

BUDMAN, SH. (AI043750-03). Compliance Enhancement in HIV/AIDS Patients. An uncontrolled feasibility study (N= 156) will follow patients for 9 months to test the effectiveness of the MedMate® system, a user-friendly handheld device that will contain educational, affective, and behavioral components designed to enhance antiretroviral therapy adherence, monitor side effects, and permit customized adherence feedback.

GREENE, PG. (AI045403-03). Promoting Adherence to Antiretroviral Regimens. RCT (N= 216) of 6-month intervention of (1) SOC Adherence Promotion Program and (2) a theory-based behavioral intervention addressing specific psychosocial issues associated with medication adherence. Adherence will be measured by self-report and pill counts. Secondary outcome measures will be HIV-1 RNA levels, CD4+ lymphocyte counts, and genotypic viral resistance.

GROSS, R. (MH001584-04). Adherence to Protease Inhibitors in HIV. Planned RCT will evaluate (1) SOC, (2) a MEMS®-based beeper as a “mnemonic aide,” (3) a case management intervention based on the social problem-solving model, or (4) both a beeper and a program of case management.

HOFMANN, RH. (AI044558-03). A Computer-Based HIV Medication Adherence Intervention. A computer-assisted, self-administered adherence medication assessment program aimed at assessing medication adherence, reducing regimen misunderstandings, delivering an adherence intervention, and producing adherence reports for providers. The goals of this project are to simplify the assessment tool, to develop the intervention component, and to test the complete program's efficacy.

INGERSOLL, KS. (MH001688-04). HIV Adherence Mentored Research Scientist Development Award. RCT (N=189) of 12-week intervention comparing (1) SOC, (2) prospective self-monitoring, and (3) prospective self-monitoring with a “trial run” of their selected antiretroviral therapy regimen using vitamins to practice. Adherence will be measured using a novel telephone reporting system to record patient-reported adherence, which has been studied in a prior research project by the same investigator.

PETRY, NM. (DA014618-01A1). Lower-Cost Contingency Management in a Group Setting. For HIV-infected individuals recovering from substance abuse, RCT (N= 172) of 6-month intervention comparing (1) standard 12-step group treatment and (2) voucher contingency management intervention. Participants can earn prizes for submitting clean urine specimens and taking steps toward treatment goals such as keeping medical appointments, maintaining a medication diary, and filling prescriptions. Investigators will measure group attendance, drug use, medical problems and services received, and risky drug use and sexual behaviors.

REYNOLDS, NR. (NR005108-03). Improving ARV Adherence: Effects of Telephone Follow Up. RCT (N= 200) of 9-month intervention comparing (1) SOC and (2) Registered Nurse (RN)-delivered telephone-based behavioral intervention rooted in the Self-Regulation Model. In addition to adherence, clinical outcomes will be measured (virologic, immunologic, and clinical events).

ROSEN, MI. (MH061169-03). Improving Compliance With Antiretroviral Medications. RCT (N= 90) of (1) SOC or (2) 24 weeks of the intervention condition, where patients’ MEMS®-generated printouts are reviewed with them by a therapist trained in Motivational Enhancement Therapy. The primary outcome measure will be MEMS®-measured adherence to correct dose time. The clinical outcome measure will be HIV-1 RNA level.
SAMET, JH. (AA011785-05). Medication Adherence in Alcohol Abusing HIV Patients. For alcohol-using HIV-infected individuals, RCT (N=240) of (1) SOC and (2) RN-delivered individualized behavioral intervention comprised of 3 clinic visits and 3 home visits. Outcome measurements will include adherence, clinical, laboratory, and health status outcomes. Adherence reports will be corroborated by MEMS®.

WILSON, IB. (DA015679-01). Understanding and Improving Adherence in HIV Disease. Multiple baseline RCT (N=150) comparing (1) SOC to (2) MEMS® data being fed back to physicians in the form of a report, prior to outpatient medical visits. Detailed patient interviews will collect adherence data in addition to the MEMS®. Primary outcome measures for the intervention study will be changes in adherence as assessed by MEMS® and changes in HIV-1 RNA levels.

( Modified) DOT Strategies

FLANIGAN, TP. (DA013767-03). Directly Observed Antiretroviral Therapy for Active Substance Abusers. For active substance users on a 1-a-day antiretroviral therapy regimen, RCT (N=120) of 18-month intervention comparing (1) SOC self-administration of medications with (2) 12 months of daily directly observed therapy (DOT) followed by a 6-month gradual tapering phase. Adherence will be assessed by patient self report in an ACASI questionnaire. HIV-1 RNA quantification, drug resistance testing by genotype, and CD4+ lymphocyte count determinations will be used to assess the effect of DOT on virologic suppression and development of resistance.

LUCAS, GM. (DA015616-01). Directly Observed Antiretroviral (ARV) Therapy in Drug Abusers. For HIV-infected patients in a methadone treatment center, prospective matched RCT comparing (1) SOC with (2) 1-year of antiretroviral therapy. Outcomes measured include virologic and immunologic responses to therapy, incidence of opportunistic diseases, and death.

TULSKY, JP. (DA013892-02). A clinical trial of DOT for antiretroviral therapy in jailed drug users. In jailed drug users, RCT testing (1) SOC DOT and (2) an intervention of structured self-administered therapy. Outcome measurements will be virologic and immunologic outcomes in jail and following release from jail, as well as physical and mental health status and lifetime and current antiretroviral therapy adherence.

Group 4—Affective Strategies

BANGSBERG, DR. (MH063011-02). Depression Treatment to Improve ARV Therapy Adherence. For HIV-infected homeless and marginally housed persons with depression, RCT testing the efficacy of (1) SOC and (2) antidepressant therapy. Investigators will examine 5 primary aims, including depression treatment, antiretroviral therapy adherence, duration of sustained antiretroviral therapy treatment, initiation of treatment, and viral suppression.

MANNHEIMER, SB. (DA012363-04). Harlem Adherence with Retroviral Therapy Study. RCT (N=160) of 12-month intervention comparing (1) SOC and (2) individual and group intervention based on the Transtheoretical Model of Change, to provide social support and assistance in overcoming barriers to adherence. Adherence will be assessed via a self-report adherence questionnaire, confidential participant survey, and by provider and peer assessments. Biologic surrogates of adherence will include plasma HIV-1 RNA levels and HIV genotypic resistance patterns.

MURPHY, DA. (MH059419-05). Medication Adherence Intervention for HIV-infected Persons. RCT (N=144) of (1) SOC and (2) a 5-session social support and patient education group intervention facilitated by a behavioral psychologist and a nurse practitioner, followed by 4 subsequent booster sessions.

NAAR-KING, S. (DA014710-02). Motivational Therapy/Reduce Risk Behaviors/HIV/Youth. For HIV-infected youth, pilot of 3-month RCT (N=60) with wait-list control comparing (1) SOC with (2) Motivational Enhancement Therapy, an empirically validated risk reduction intervention.

SIKKEMA, KJ. (MH062965-03). Intervention for Coping with HIV and Trauma. For individuals who are HIV-infected and experiencing trauma-related stress and psychiatric distress, RCT (N=240) comparing (1) SOC support group and (2) an HIV trauma coping group. Outcomes include measurements of psychiatric distress, quality of life, rates of adherence to medical treatment, levels of substance use and sexual risk behaviors, and health status as indicated by HIV symptomatology, CD4+ lymphocyte count, and HIV-1 RNA level.

SIMONI, JM. (MH058986-05). Peer versus Pager Support to Enhance Antiretroviral Adherence. RCT (N=240) of 3-month intervention comparing (1) SOC, (2) carrying an alphanumeric programmable pager, (3) having an HIV-infected buddy to give peer support, and (4) having both a pager and a buddy. Adherence will be assessed using self-reports, pharmacy refills, 3-day recall telephone interviews, and MEMS®. HIV-1 RNA level and CD4+ lymphocyte count will be assessed as clinical outcomes.

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Special Contribution
Perinatal HIV: Special Considerations

Deborah Cohan, MD, MPH

The percentage of AIDS cases among women—particularly women of color—in the United States is increasing yearly. Despite this increase, there has been a relatively steady decline in the number of AIDS cases occurring perinatally. Regardless of the reasons HIV-infected couples choose to become pregnant, studies indicate that providing support, such as contraceptive counseling and assisted reproduction techniques, can improve the health outcome in the face of HIV-related challenges. Issues specific to antiretroviral therapy, including viral resistance, pregnancy outcomes, and adverse fetal effects, complicate the treatment of perinatal HIV. Postpartum care is yet another area that requires special consideration when supporting HIV-infected families. The growing body of data on pregnancy and HIV may indicate a rising commitment to research of and support for the unique challenges HIV-infected families face. This article was adapted from an IAS–USA interactive, case-based program, Cases on the Web, in November 2003.

According to UNAIDS, a joint United Nations program on HIV/AIDS, there are approximately 19.2 million women living with HIV or AIDS, accounting for nearly half of all infections worldwide.1 Similarly, an estimated 3.2 million children under the age of 15 are living with HIV or AIDS, the overwhelming majority of whom acquired HIV through perinatal transmission and live in Sub-Saharan Africa.1 Although this article focuses on the care of the HIV-infected pregnant woman in resource-rich settings, it is crucial to appreciate that the burden of the HIV/AIDS epidemic lies within the developing world.

In the United States, the prevalence of HIV/AIDS among women varies dramatically by geographic region, with the largest share of AIDS cases in the northeast and southeast regions of the country. In 2001, the overall prevalence of AIDS was 9.1 cases per 100,000 women. New York had the highest prevalence with 30.3 AIDS cases per 100,000 women. Moreover, AIDS incidence and the percentage of AIDS cases are increasing yearly among women, particularly among women of color. Although the majority of HIV infections in the United States are among men, an estimated 29% of HIV infections are among women, in those areas with reporting to the Centers for Disease Control and Prevention (CDC).2

Epidemiology of Perinatal HIV Transmission

There has been a steady decline in the number of perinatally acquired AIDS cases among infants in the United States, with an estimated incidence of 101 pediatric AIDS cases in 2001, down from a peak of 954 cases in 1992.3,4 This change likely represents not only decreased perinatal HIV transmission but also increased use of Pneumocystis carinii pneumonia (PCP; also known as Pneumocystis jiroveci pneumonia) prophylaxis and combination therapy for children, with consequent prolonged AIDS-free survival among perinatally infected infants. It is difficult to estimate perinatal HIV prevalence. Wang-modeled perinatal AIDS surveillance data show an apparent decline in perinatal HIV acquisition in the United States, from 1650 cases in 1991 to 480 cases in 1996.4 This difference likely represents an increase in the use of zidovudine among HIV-infected pregnant women. Since publication of the landmark AIDS Clinical Trials Group (ACTG) 076 study5,6 perinatal zidovudine use has dramatically increased among pregnant women identified as HIV infected, from 28% in 1994 to 76% in 1997.4

The likelihood of perinatal transmission varies dramatically based on numerous risk factors, which will be described below. Nevertheless, most of the early placebo-controlled trials and observational studies conducted in industrialized, non-breast-feeding settings demonstrate a transmission prevalence of approximately 25% without any HIV-specific interventions.5,7

Reproductive Choices Among HIV-Infected Women

Numerous studies have demonstrated that most women and men continue to be sexually active after receiving a diagnosis of HIV infection.8-13 The reasons individuals and couples decide to conceive or contracept, or to continue or to terminate a pregnancy, are complex, particularly in the context of HIV infection.10,14,20 Often overlooked by the general HIV provider is a patient's desire to become pregnant.21 As people with HIV infection are living longer, healthier lives, and as antiretroviral therapy has dramatically decreased the likelihood of mother-to-child transmission, some HIV-infected women are choosing to become pregnant.15,16 Similarly, 1 study found that exposing HIV-infected women to an educational brochure about mother-to-child transmission that included information about zidovudine increased some women’s intentions to continue their current pregnancy and to plan for future pregnancies.22 In fact, there is a growing body of literature addressing the ethics and science of providing assisted reproduction techniques to HIV-
infected women and HIV-serodiscordant couples, both for infertility treatment and for HIV transmission prevention.23,26

Impact of Pregnancy on HIV

Pregnancy is an immensely complex physiologic and immunologic state, but it does not appear that pregnancy accelerates the course of HIV infection.37 Several investigators have sought to understand the immunology of pregnancy among HIV-infected women. There is evidence, for instance, of altered T-cell function,26 a decline in mean CD4+ cell count,26,30 and altered CD8+ cell count23,31 among HIV-infected pregnant women. However, the immunologic implications of these changes are unclear. Newell and colleagues have demonstrated that, although the absolute CD4+ cell count tends to drop during pregnancy, CD4+ and CD8+ cell percentages appear stable, likely representing the physiologic hemodilution of pregnancy.20 Moreover, a number of studies have now demonstrated that pregnancy itself does not appear to accelerate the progression to AIDS, severe immunosuppression (ie, CD4+ count <100 cells/µL), opportunistic infections, or death.32-36 Furthermore, there does not appear to be an association between pregnancy and increased plasma HIV-1 RNA level.37

Impact of HIV on Pregnancy

Overall, obstetrical outcomes of pregnant women infected with HIV appear to be similar to those of uninfected women. Yet, the Women and Infant Transmission Study (WITS) found an association between significant immunosuppression during pregnancy (<14% CD4+ cells) and delivery of a low birth weight neonate (adjusted odds ratio [OR], 3.81; 95% confidence interval [CI], 1.41-10.28).38 This study also noted a trend toward increased risk of preterm birth (OR, 2.5; 95% CI, 0.98-6.28) in women with a CD4+ cell percentage less than 14.38

Diagnosis of HIV in Pregnancy

Given the many successful interventions now available to prolong AIDS-free survival and to reduce mother-to-child transmission, attention must be turned to ensuring universal HIV testing among pregnant women and access to quality prenatal care among those women known or found to be HIV-infected. Many perinatal HIV cases in the United States represent missed opportunities, in that they lack prenatal care26 and lack HIV testing despite prenatal care.40 Among the 329 children with perinatally acquired AIDS born in 1995 and 1996, 34% were born to women who underwent HIV testing after delivery.4 Similarly, an estimated 40% of US women who delivered HIV-infected infants in 2000 had not been tested for HIV prior to delivery.41

Considerable controversy exists regarding the most effective and ethical approach to HIV testing in pregnant women. The 2 most common strategies are “opt-out” and “opt-in.” In an opt-out approach, women are informed of the inclusion of HIV testing in the standard battery of prenatal labs and may decline such testing. Opt-in strategies use more traditional voluntary HIV counseling and testing techniques, with a specific informed-consent process. The CDC recently documented widely disparate prenatal HIV testing frequencies throughout the United States and Canada.42 Prenatal HIV testing was most common in areas with an opt-out approach, including Tennessee (85%) in the United States and Alberta (98%) and Newfoundland/Labrador (94%) in Canada. Regions using an opt-in approach had testing frequencies as low as 25% (3 counties in the Portland, Oregon, area) and 39% (3 counties in the San Francisco bay area). Similarly, among the 83 pregnancies complicated by HIV infection in the Kaiser Permanente Northern California health care system, only 20% were identified through an opt-in strategy.43

Although the opt-out strategy appears to increase prenatal HIV testing on a population level, it is important to appreciate the implications of testing an individual woman for HIV during her pregnancy. For instance, the overall prevalence of domestic and sexual violence among HIV-infected women is nearly 50% in some studies.44 Some authors report increased risk of domestic violence with disclosure of HIV seropositivity,45 although other studies have not found such an association.47

Rapid HIV testing has received much attention due to the increasing availability of reliable technology and a growing body of literature demonstrating the effectiveness of abbreviated intrapartum and neonatal antiretroviral therapy.48 In November 2002, the US Food and Drug Administration (FDA) approved a rapid HIV-1 antibody test. This test is a lateral-flow immunoassay that may be used on whole blood, with results available in approximately 20 to 30 minutes. Reported sensitivity and specificity are 99.6% and 100%, respectively, compared with enzyme-linked immunosorbent assay (ELISA) technology.49 Single Use Diagnostic System for HIV-1 (SUDS), which was approved in 1992, requires centrifugation and immediate confirmatory testing and takes approximately 1 hour overall. SUDS has a sensitivity of 100% and a specificity of 98% as compared with standard ELISA, with a positive predictive value (PPV) of only 33%, reflecting the overall low prevalence of HIV in this cohort.50 Both the new rapid test and SUDS require a confirmatory Western blot or immunofluorescent antibody (IFA).

Rapid HIV testing is cost effective among women presenting in labor with no prenatal care, with an estimated savings of more than $10 million to the US health care system compared with the cost of treating all unregistered women presenting in labor with zidovudine or not treating any unregistered women.51 The Mother Infant Rapid Intervention at Delivery (MIRIAD) study is a multisite study evaluating the feasibility of rapid testing and the effectiveness of intrapartum therapy to reduce mother-to-child transmission.41 As of November 2002, 1771 women in the study had undergone rapid HIV testing. Twelve women had been identified as being infected with HIV, with no false-negative or false-positive tests thus far. Although this technology will bring a new level of perinatal HIV prevention, the social and psychological implications of intrapartum testing will likely be profound. Research on abbreviated antiretroviral therapy regimens abroad raises many ethical issues given the current standard of care of the HIV-infected individual in the resource-rich setting.52-54 Although controversial, the results from these studies offer insight into mechanisms of transmission and may influence decisions about
antiretroviral therapy regimens among HIV-infected, untreated women presenting to labor and delivery.

Timing of Mother-to-Child Transmission
Among non–breast-feeding women, approximately 25% to 35% of transmissions occur during the antepartum period, with 95% of in utero infections appearing to occur in the last 2 months of pregnancy. One study demonstrated transmission of HIV among late-second-trimester (17-24 weeks) abortus fetuses, with a transmission prevalence of 11.1% among women with plasma HIV-1 RNA levels greater than 100,000 copies/mL and 3.1% among women with plasma HIV-1 RNA levels less than 100,000 copies/mL. Of the 65% of infections that occur at the time of delivery, the median duration to detectable virus in infants is approximately 10 days (95% CI, 6-14 days).

Mother-to-Child Transmission Risk Factors
There are numerous risk factors that increase the chance of mother-to-child transmission of HIV infection, including maternal, obstetrical, and neonatal variables.

Maternal Factors
In most recent studies, maternal HIV-1 RNA level at delivery remains the most consistent predictor of mother-to-child transmission. However, no threshold HIV-1 RNA level exists below which transmission does not occur or above which transmission always occurs. Among pregnant women taking zidovudine, each log copies/mL increment in HIV-1 RNA level at delivery was associated with an OR of 3.4 (95% CI, 1.7-6.8). Transmission prevalence has been seen as high as 63.3% among women with HIV-1 RNA levels greater than 100,000 copies/mL without zidovudine treatment. Further, an HIV-1 RNA level greater than 1000 copies/mL appears to be particularly predictive of transmission among women with a CD4+ count greater than 500 cells/µL (OR, 2.7; 95% CI, 1.5-5.1 per log10 HIV-1 RNA level). Low maternal CD4+ cell count is similarly associated with higher transmission of HIV. One study found a decreased CD4+ cell percentage to be associated with increased risk of transmission (OR, 1.4; 95% CI, 1.1-1.7). Maternal viral properties, such as viral homogeneity and rapid replication kinetics, have also been linked to increased risk of HIV transmission.

There is limited and conflicting evidence that viral resistance may increase the likelihood of mother-to-child transmission. Among women receiving zidovudine monotherapy in the early years of the WITS, any reverse transcriptase resistance mutation was associated with increased risk of transmission (OR, 5.16; 95% CI, 1.40-18.97). A substudy of ACTG 076 did not note an association between zidovudine resistance and mother-to-child transmission (OR, 4.8; 95% CI, 0.2-131), but, as the wide confidence interval suggests, the study was too small to find such an association. Issues of antiretroviral therapy resistance in the perinatal setting will likely only become more troublesome as the prevalence of primary resistance grows in this population. For instance, Juethner and colleagues detected genotypic nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance among 17% of antiretroviral therapy-naive pregnant women in St. Louis, Missouri, between 1999 and 2001.

Obstetrical Factors
Prolonged rupture of membranes (ROM) has been shown to be a risk factor for HIV transmission among women both treated and untreated with antiretroviral therapy during pregnancy. Prolonged ROM appears to be particularly risky among women with low CD4+ cell counts and women at preterm gestation. A meta-analysis conducted by the International Perinatal HIV Group found an increased probability of transmission from 8% at 2 hours to 32% at 24 hours after membrane rupture among women with AIDS. Among those women without AIDS, the likelihood of transmission increased with prolonged ROM but not significantly so. Preterm delivery is an additional risk factor for intrapartum HIV transmission. Similarly, chorioamnionitis, an infection of the chorion-amnion space, increases the risk of mother-to-child transmission. One study found an association between intrapartum fetal scalp electrodes/fetal scalp sampling and transmission to the neonate (OR, 3.5; 95% CI, 1.2-9.6). Older studies that do not adjust for plasma HIV-1 RNA level have demonstrated increased transmission with intrapartum maternal hemorrhage, maternal sexually transmitted infections, and amniocentesis.

Neonatal Factors
Neonatal variables such as premature birth at less than 35 weeks gestation and birthweight less than 2500 g are associated with neonatal HIV acquisition. HLA class I maternal-neonatal concordance also appears to increase the risk of transmission (OR, 3.79; 95% CI, 1.14-12.7). Of note, neonatal CCR5-32 heterozygosity does not appear to confer a protective effect on HIV acquisition.

Breast-feeding
Numerous studies have demonstrated HIV transmission through breast-feeding. A meta-analysis found a 15% additional risk of transmission due to breast-feeding. Nduati and colleagues confirmed these results in a randomized controlled trial of breast-feeding versus bottle-feeding in Kenya, with a documented 16% transmission rate via breast-feeding. In this cohort of women, 44% of mother-to-child transmissions appeared attributable to breast-feeding.

Antiretroviral Therapy in Pregnancy
ACTG 076 revolutionized the management of HIV-infected women by demonstrating a nearly 70% decrease in perinatal transmission among non–breast-feeding women from 25.5% (placebo arm) to 8.3% (prenatal/neonatal zidovudine arm). Since the publication of this landmark study, other trials have demonstrated the effectiveness of abbreviated regimens of zidovudine, zidovudine/lamivudine, and nevirapine in reducing mother-to-child transmission among both breast-feeding and
non-breast-feeding cohorts. Nonetheless, since the mid-1990s, there has been an increased appreciation of the value of highly active antiretroviral therapy (HAART) in achieving maximum viral suppression and prolonging AIDS-free survival among adults and children. No clinical trial has compared HAART with either zidovudine monotherapy or 2-drug regimens among pregnant women. However, several observational studies have demonstrated remarkably low mother-to-child transmission in the setting of HAART. The lowest transmission prevalence observed is among women with maximally suppressed virus at the time of delivery, and this is certainly most likely to occur among women on HAART. In the WITS cohort, transmission occurred in 20% of women with no pre-natal antiretroviral therapy, 10.4% of women who received zidovudine monotherapy, 3.8% of women who received dual therapy, and 1.2% of women who received HAART. Similarly, the PACTG 367 study found the lowest transmission frequency among women on multiagent regimens (1.8%), compared with those on zidovudine monotherapy (5.3%) and those taking no therapy (20%). The authors reported an overall transmission of only 0.9% among women with HIV-1 RNA levels less than 1000 copies/mL near delivery. Among these women with low delivery HIV-1 RNA levels, transmission prevalence differed, though not significantly, by complexity of regimen (1.8% for monotherapy vs. 0.8% for multiagent). However, PACTG 316 found that the addition of 2-dose intrapartum and neonatal nevirapine to standard antiretroviral therapy does not confer additional protection given the already low risk of transmission (1.6% in placebo arm vs. 1.4% in nevirapine arm).

Even among women with an HIV-1 RNA level less than 1000 copies/mL at the time of delivery, antiretroviral therapy likely protects against mother-to-child transmission. One European and US collaborative study specifically evaluated transmission among women with HIV-1 RNA levels less than 1000 copies/mL at or near delivery. The researchers demonstrated an independent protective effect of antiretroviral treatment (OR, 0.10) among these women with an already low risk of transmission. There is controversy, however, about the optimal regimen for immunocompetent HIV-infected pregnant women with low baseline HIV-1 RNA levels. Some have proposed zidovudine monotherapy as per ACTG 076 given the low risk of transmission, ease of administration, and low maternal and fetal/neonatal toxicity. Zidovudine monotherapy is not without its risks, however. Eastman and colleagues found that 1 of 39 women in a subanalysis of ACTG 076 developed an incident K70R mutation, with no one developing a T215Y/F mutation. The Swiss HIV and Pregnancy Study, on the other hand, reported a 9.6% prevalence of the T215Y/F mutation (6 of 62 women). Of those 6 women, 5 women likely had the mutation emerge after exposure to zidovudine monotherapy, 1 in whom it emerged after only 17 weeks. As we learn more about latent reservoirs and resistance and are able to detect even lower levels of HIV in plasma, the provision of HAART to pregnant women with very low baseline viral loads will likely become standard of care.

The initial "hit early, hit hard" paradigm more recently has been tempered by growing evidence of adverse sequelae of long-term HAART. When choosing an antiretroviral regimen for any HIV-infected individual, it is crucial to weigh the full range of issues, including immune status, past regimens, genotypic and phenotypic resistance, medication potency, tolerability, future medication options, comorbidities such as viral hepatitis, pill burden, and risk of medication nonadherence. Additional considerations for pregnant women include maternal, fetal, and neonatal toxic effects, as discussed below. A clinician must also explore the goal of antiretroviral therapy in pregnancy, whether it is for long-term viral suppression or simply for chemoprophylaxis to prevent mother-to-child transmission. Clinicians (or medical providers) must try not to compromise long-term options while seeking to prevent mother-to-child transmission.

Resistance

Resistance most commonly arises in the setting of incomplete viral suppression. Perinatal regimens that include zidovudine monotherapy, dual therapy, or postpartum treatment interruptions may make women vulnerable to acquiring resistance mutations. A substudy of ACTG 076 demonstrated a 6.7% prevalence of K70R at study entry and a 2.6% incidence of K70R. Among 83 pregnant women delivering at Bellevue Hospital in New York between 1995 and 1999, T215Y prevalence was 9.7%. The WITS cohort found 25% zidovudine resistance among women exposed to zidovudine monotherapy between 1989 and 1994. The rapid development of resistance has been noted among pregnant women taking zidovudine/lamivudine, with 80% (4 of 5) of pregnant women developing a M184V mutation prior to delivery and the remaining 20% acquiring an M184V mutation postpartum.

Nevirapine has also been associated with rapid development of the K103N mutation among pregnant women. HIVNET 012116 and HIVNET 006117 detected 19% and 20% prevalence of nevirapine resistance, respectively, among women after a single intrapartum dose of nevirapine. Reversion to wild-type virus was seen within 12 to 24 months among these women, who did not receive postpartum antiretroviral therapy. Nonetheless, reemergence of nevirapine resistance is highly likely if those women are ever re-challenged with nevirapine. The PACTG 316 trial evaluated the benefit of adding intrapartum nevirapine to standard perinatal antiretroviral therapy in the United States, Brazil, Bahamas, and Europe. Fifteen percent of women in the nevirapine arm developed nevirapine resistance by 6 weeks postpartum. Development of resistance was not associated with delivery CD4+ cell count, HIV-1 RNA level, or antepartum regimen, although the study was too small to determine such associations. Interestingly, 21% of the women who acquired nevirapine resistance had HIV-1 RNA levels less than 1000 copies/mL at the time of nevirapine exposure. There was no analysis by postpartum continuation versus discontinuation of antiretroviral therapy, and the high incidence of resistance may be explained by the prolonged half-life of nevirapine.

Resistance is an evolving issue among infants as well. Among HIV-1-infected infants in New York state, 6.3% of those born in 1992 to 1994 compared with 33.3% of those born in 1998 to 1999 had a 215 mutation detected. Forty-six percent of infected infants exposed to 2-dose maternal and postpartum neonatal nevirapine in HIVNET 012 demonstrated nevirapine...
resistance. The transmission of multidrug-resistant HIV-1 from mother to infant has also been documented, with serious consequences for future treatment options.

**Pregnancy Outcomes**

There are numerous case reports of severe lactic acidosis and hepatic failure among pregnant or postpartum women on nucleoside reverse transcriptase inhibitor (nRTI) therapy. Three women who died of lactic acidosis were taking stavudine and didanosine as part of triple-drug regimens. These cases prompted manufacturer Bristol-Myers Squibb Company to label those medications with specific warnings on their use in pregnancy. It is not entirely clear what role pregnancy, per se, played in those cases, although lactate levels naturally rise in the third trimester and may contribute to an increased risk of serious lactic acidosis. Confounding the diagnosis of lactic acidosis in pregnancy are the many obstetric-related etiologies of hepatic dysfunction, including acute fatty liver of pregnancy; severe preeclampsia; hemolysis, elevated liver enzymes, and low platelet count (HELLP); and cholestasis of pregnancy.

There are conflicting data regarding the association between antiretroviral therapy and other pregnancy outcomes, including preterm delivery and gestational diabetes. A combined analysis of the European Collaborative Study and Swiss Mother + Child HIV Cohort Study found that women on combination therapy (with or without a protease inhibitor [PI]) were significantly more likely to deliver an infant before 37 weeks gestation than HIV-infected women not receiving any medication (OR, 2.60; 95% CI, 1.43-4.75 for PI-containing regimens and OR, 1.82; 95% CI, 1.13-2.92 for PI-sparing regimens). Importantly, however, the multivariate analysis of data from this study did not include known risk factors for preterm delivery such as tobacco and drug use, low maternal weight, and history of preterm delivery. A more recent study found no such association between antiretroviral therapy and preterm delivery among 2123 HIV-infected pregnant women. This latter study, however, did find an association between PI-containing regimens and delivery of a very low birth weight infant (OR, 3.56; 95% CI, 1.04-12.19). Women on PI-containing regimens, however, were more likely to have advanced HIV disease, and researchers did not adjust for stage of disease in the multivariate model. Preliminary data from 1 study reported that the risk of preeclampsia was significantly lower among HIV-infected women who did not receive treatment than among women on triple antiretroviral therapy and HIV-seronegative controls.

The authors suggested that the restoration of preeclampsia risk to that of HIV-seronegative controls might be due to HAART-induced immune reconstitution.

There is evidence of an increased risk of new-onset diabetes among nonpregnant women on PIs. Moreover, pregnancy is a relatively diabetogenic state. One study demonstrated an increase in glucose tolerance among women on PI-based HAART compared with zidovudine monotherapy historical controls. Although these women on PI-based HAART had increased initial glucose tolerance screening, there was no increased risk of gestational diabetes on follow-up diagnostic testing compared with non-HIV-infected women. No study has yet definitively documented an increased risk of gestational diabetes among pregnant women on PIs.

**Adverse Fetal and Neonatal Effects**

Table 1 provides data on placental passage, carcinogenicity, teratogenicity, and FDA pregnancy categories for the various antiretroviral medications used in humans. The Antiretroviral Pregnancy Registry (www.apregistry.com) maintains a voluntary database of birth defects among infants exposed to in utero antiretrovirals. It has found no difference in birth-defect prevalence among infants with either first-trimester or anytime exposure to antiretrovirals compared with US population-based proportions as monitored by the CDC. Although most antiretrovirals appear to be safe to use during pregnancy, there are a few notable exceptions. Efavirenz has been linked to anencephaly and anophthalmia in monkeys, at doses comparable to those taken by humans. There has since been a case report of neural tube defects in infants exposed to efavirenz in utero.

Amprenavir has been associated with delayed skeletal ossification in rats. High-dose tenofovir is linked to slightly decreased bone porosity among exposed monkeys, though the clinical significance of this finding is uncertain. Considerable controversy exists regarding the role of mitochondrial dysfunction among exposed, uninfected infants. Although some reports note a possible association between perinatal exposure and clinically relevant neonatal mitochondrial dysfunction, the largest study failed to find an association. One recent study noted a decrease in mitochondrial DNA in cord and infant peripheral blood leukocytes among HIV-exposed versus HIV-unexposed infants. Those HIV-exposed infants who were exposed to zidovudine were at highest risk. The clinical significance of this finding, however, remains to be seen. Although data indicate minimal transplacental passage of PIs, one observational study noted a possible association between PI-containing HAART regimens and very low birth weight (< 1500 g). This may be due to metabolic changes in the mother as opposed to direct in utero effects and certainly warrants further investigation.

**Mode of Delivery**

Significant attention has been paid to the role of delivery mode on the risk of HIV transmission. The European Mode of Delivery Collaboration was a randomized controlled trial of elective cesarean delivery versus trial of labor among 436 HIV-infected women. Elective cesarean delivery was defined as abdominal delivery at 38 weeks gestation in the absence of labor or ruptured membranes. Transmission occurred in 10.5% of women in the trial of labor arm compared with 1.8% in the elective cesarean delivery arm (OR, 0.2; 95% CI, 0.1-0.6). This difference was only statistically significant, however, in the absence of antepartum zidovudine. The International Perinatal HIV Group performed a meta-analysis of 15 prospective cohort studies, including 8533 mother-child pairs. Those researchers, too, found a decreased risk of transmission in women undergoing cesarean delivery (OR, 0.43; 95% CI, 0.33-0.56). This association held even among women with antepartum, intrapartum, or neonatal antiretroviral therapy. However,
### Table 1. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>FDA Pregnancy Category</th>
<th>Placental Passage (model) [newborn: mother drug ratio]</th>
<th>Long-term Animal Carcinogenicity</th>
<th>Animal Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleoside and nucleotide analogue reverse transcriptase inhibitors</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Zidovudine (AZT, ZDV)</td>
<td>C</td>
<td>Yes (human) [0.85]</td>
<td>Positive (rodent, noninvasive vaginal epithelial tumors)</td>
<td>Positive (rodent, near lethal dose)</td>
</tr>
<tr>
<td>Zalcitabine (ddC)</td>
<td>C</td>
<td>Yes (rhesus monkey) [0.30-0.50]</td>
<td>Positive (rodent, thymic lymphomas)</td>
<td>Positive (rodent, hydrocephalus at high dose)</td>
</tr>
<tr>
<td>Didanosine (ddl)</td>
<td>B</td>
<td>Yes (human) [0.50]</td>
<td>Negative (no tumors, lifetime rodent study)</td>
<td>Negative</td>
</tr>
<tr>
<td>Stavudine (d4T)</td>
<td>C</td>
<td>Yes (rhesus monkey) [0.76]</td>
<td>Positive (mice and rats, at very high dose exposure, liver and bladder tumors)</td>
<td>Negative (but sternal bone calcium decreases in rodents)</td>
</tr>
<tr>
<td>Lamivudine (3TC)</td>
<td>C</td>
<td>Yes (human) [~1.0]</td>
<td>Negative (no tumors, lifetime rodent study)</td>
<td>Negative</td>
</tr>
<tr>
<td>Abacavir (ABC)</td>
<td>C</td>
<td>Yes (rat)</td>
<td>Positive (malignant and non-malignant tumors of liver, thyroid in female rats, and preputial and clitoral gland of mice and rats)</td>
<td>Positive (rodent anasarca and skeletal malformations at 1000 mg/kg [35x human exposure] during organogenesis; not seen in rabbits)</td>
</tr>
<tr>
<td>Emtricitabine (FTC)</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Tenofovir (TDF, PMPA)</td>
<td>B</td>
<td>Yes (rat and monkey)</td>
<td>Not completed</td>
<td>Negative (osteomalacia when given to juvenile animals at high doses)</td>
</tr>
<tr>
<td><strong>Nonnucleoside reverse transcriptase inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nevirapine (NVP)</td>
<td>C</td>
<td>Yes (human) [~1.0]</td>
<td>Positive (hepatocellular adenomas and carcinomas in mice and rats)</td>
<td>Negative</td>
</tr>
<tr>
<td>Delavirdine (DLV)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in male and female mice but not rats; bladder tumors in male mice)</td>
<td>Positive (rodent, ventricular septal defect)</td>
</tr>
<tr>
<td>Efavirenz (EFV)</td>
<td>C</td>
<td>Yes (cynomologus monkey, rat, rabbit) [~1.0]</td>
<td>Positive (increased hepatocellular adenomas and carcinomas, and pulmonary alveolar/bronchiolar adenomas in female but not male mice)</td>
<td>Positive (cynomologus monkey, anencephaly, anophthalmia, microphthalmia)</td>
</tr>
</tbody>
</table>
Table 1. Preclinical and Clinical Data Relevant to the Use of Antiretrovirals in Pregnancy, Continued

<table>
<thead>
<tr>
<th>Antiretroviral Drug</th>
<th>FDA Pregnancy Category</th>
<th>Placental Passage (newborn: mother drug ratio)</th>
<th>Long-term Animal Carcinogenicity</th>
<th>Animal Teratogenicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
<tr>
<td><strong>Protease inhibitors</strong></td>
<td></td>
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</tr>
<tr>
<td>Indinavir (IDV)</td>
<td>C</td>
<td>Minimal (human)</td>
<td>Positive (thyroid adenomas in male rats at highest dose)</td>
<td>Negative (but extra ribs in rodents)</td>
</tr>
<tr>
<td>Ritonavir (RTV)</td>
<td>B</td>
<td>Minimal (human)</td>
<td>Positive (rodent, liver adenomas and carcinomas in male mice)</td>
<td>Negative (but cryptorchidism in rodents)</td>
</tr>
<tr>
<td>Saquinavir (SQV)</td>
<td>C</td>
<td>Minimal (human)</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Nelfinavir (NFV)</td>
<td>B</td>
<td>Minimal (human)</td>
<td>Positive (thyroid follicular adenomas and carcinomas in rats)</td>
<td>Negative</td>
</tr>
<tr>
<td>Amprenavir (APV)</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (hepatocellular adenomas and carcinomas in male mice and rats)</td>
<td>Negative (but deficient ossification and thymic elongation in rats and rabbits)</td>
</tr>
<tr>
<td>Atazanavir (ATZ)</td>
<td>B</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative</td>
</tr>
<tr>
<td>Lopinavir/Ritonavir (LPV/r, ABT-378/r)</td>
<td>C</td>
<td>Unknown</td>
<td>Not completed</td>
<td>Negative (but delayed skeletal ossification and increase in skeletal variations in rats at maternally toxic doses)</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>C</td>
<td>Unknown</td>
<td>Positive (increased benign and malignant liver tumors in male rodents)</td>
<td>Negative (deficient ossification with amprenavir but not fosamprenavir)</td>
</tr>
<tr>
<td><strong>Fusion inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enfuvirtide (T-20)</td>
<td>B</td>
<td>Unknown</td>
<td>Not done</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>US Food and Drug Administration pregnancy categories:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>A</strong> Adequate and well-controlled studies of pregnant women fail to demonstrate a risk to the fetus during the first trimester of pregnancy (and there is no evidence of risk during later trimesters). the drug should not be used unless the potential benefit outweighs the potential risk to the fetus.</td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>B</strong> Animal reproduction studies fail to demonstrate a risk to the fetus, and adequate and well-controlled studies of pregnant women have not been conducted.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>C</strong> Safety in human pregnancy has not been determined; animal studies are either positive for fetal risk or have not been conducted;</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

there was no information on HIV-1 RNA levels, and most of the women on antiretroviral therapy in this study were receiving zidovudine monotherapy. More recently, among women with predelivery HIV-1 RNA levels less than 1000 copies/mL, PACTG 367 found no difference in transmission prevalence among women with vaginal deliveries (0.8%), elective cesarean deliveries (0.8%), or nonelective cesarean deliveries (1.1%).

Although some studies have found a potential protective role of elective cesarean delivery among women with HIV-1 RNA levels greater than 1000 copies/mL, many study results point to significant morbidity associated with cesarean delivery among HIV-infected women. It is crucial also to consider the maternal morbidity associated with subsequent deliveries, whether repeat cesarean deliveries or vaginal births after cesarean delivery.

**Postpartum Care for the Woman and Neonate**

**Immunization**

Although measles-mumps-rubella (MMR) is a live attenuated virus, there has been no evidence of severe or unusual adverse events among HIV-infected individuals without severe immunosuppression who receive MMR vaccination. There is a case report of severe measles pneumonia in a severely immunocompromised adult with AIDS. Therefore, the Advisory Committee on Immunization Practices (ACIP) recommends MMR vaccination for all susceptible, asymptomatic HIV-infected individuals in the absence of severe immunosuppression. ACIP also states that MMR vaccination should be considered for symptomatic HIV-infected individuals in the absence of severe immunosuppression. The CDC defines severe immunosuppression as a CD4+ count below 200 cells/µL or a CD4+ percentage of total lymphocytes of less than 14. Because MMR contains a live attenuated virus, immunization should be deferred until the postpartum period, although there has never been a reported case of vaccine-associated congenital rubella.

There are limited data on the safety of varicella vaccination of individuals with HIV infection. PACTG 265 is evaluating the safety and efficacy of varicella vaccination among asymptomatic or mildly symptomatic HIV-infected children (CDC stage N1 or A1). Preliminary data from this study indicate that varicella vaccination is not associated with serious adverse effects, progression of HIV disease, or an increase in HIV-1 RNA level. Furthermore, the vaccine induced immunity in the majority of children studied.

Brady and colleagues reported on the safety of varicella vaccine among HIV-infected adults with CD4+ counts greater than 400 cells/µL who previously had been infected with varicella. There are no data specifically addressing the safety and efficacy of varicella vaccination in HIV-infected, susceptible women in the preconception or postpartum period. As such, varicella-zoster immunoglobulin is recommended for susceptible HIV-infected children and adults in the context of a significant exposure to varicella-zoster virus (VZV), regardless of immune status.

**Adherence to Medication**

Medication adherence is the cornerstone of sustained viral suppression. Medication nonadherence is common among all HIV-infected individuals. Adherence may be particularly difficult for postpartum women who juggle many demands, including a 4-times-a-day zidovudine regimen for the neonate. One study found that 41% of women took none of their zidovudine or zidovudine/lamivudine in the first 3 weeks postpartum. Mean postpartum adherence fell to its nadir of 29.3% in the first week postpartum. Demas and colleagues found that 71% of postpartum women self-reported 100% adherence to the neonatal zidovudine regimen. Nearly 18% of infants had no detectable zidovudine in plasma samples drawn within 1 week before the interview. Poor adherence, as defined by low infant zidovudine levels, was associated with maternal asymptomatic HIV disease and poor prenatal maternal medication adherence. For women requiring HAART for their own health postpartum, it is essential for providers to counsel them about medication adherence, with an understanding of the complex social and psychological issues facing those women.

**Contraception**

A key component of postpartum care of the HIV-infected woman includes counseling about and provision of contraception. Ideally, a patient will have decided on a plan prior to delivery. Although hormonal contraception offers excellent protection against future pregnancy, there are several issues concerning its use that are relevant to the HIV-infected woman. First, hormonal contraception has been linked to increased genital shedding of HIV-1. In the largest observational study to date, Mostad and researchers found an association between hormonal contraceptives and cervical HIV-1 shedding. In particular, women on high-dose oral contraceptives (50 µg estradiol) had the highest adjusted OR for shedding (12.3; 95% CI, 1.5-101). Researchers also detected a significant association between cervical HIV-1 shedding and both low-dose oral contraceptives (OR, 3.8; 95% CI, 1.4-9.9) and depot medroxyprogesterone acetate (DMPA) (OR, 2.9; 95% CI, 1.5-5.7). More recently, Baeten described an association between DMPA and a higher baseline HIV-1 RNA level as well as an increased risk of viral diversity, suggesting that HIV-infected women taking DMPA may be at risk of faster progression of HIV disease. Furthermore, women taking hormonal contraception may be less likely to concurrently use condoms. Not surprisingly, one study found that HIV-infected women on oral contraceptives were significantly less likely to use condoms, putting them at risk of acquiring sexually transmitted infections and transmitting HIV. Lastly, antiretrovirals that induce CYP3A may decrease plasma levels of hormonal contraceptives. Mildvan and colleagues demonstrated a 29% median decrease in the area under the plasma concentration-time curve (AUC) of hormonal contraceptives among women taking concurrent estradiol/norethindrone and nevirapine.

Although there are theoretical concerns about the use of intrauterine devices (IUDs) among HIV-infected women, no study has yet demonstrated an increase in viral shedding or an increase in infectious morbidity associated with their use. Among 98 HIV-infected women in Kenya, there were no changes in HIV-1 DNA cervical shedding before or after IUD insertion. Sinei and researchers found no significant differ-
quences in overall complications, incident pelvic inflammatory disease, or overall infection-related morbidity between 156 HIV-infected and 493 HIV-uninfected women who underwent IUD insertion. Although it is often difficult to find the ideal method of contraception for any woman, it is crucial to assist the HIV-infected woman in weighing the risks and benefits of all options.

Neonatal Management

The standard management of the HIV-exposed neonate includes a 6-week course of zidovudine, laboratory evaluation for HIV infection and medication side effects, and PCP prophylaxis with trimethoprim-sulfamethoxazole from 6 weeks to 4 months of age. The US Department of Health and Human Services maintains living document guidelines at www.aidsinfo.nih.gov. Zidovudine is dosed as 2 mg/kg every 6 hours for the term infant. Ideally, at least 2 of the doses correspond to maternal dosing for those women continuing on antiretroviral therapy postpartum. The infant is weighed weekly for dose adjustments. Laboratory evaluation of the infant includes birth HIV-1 DNA polymerase chain reaction (PCR), complete blood cell count, and liver function tests. Many providers also obtain a blood-glucose reading on those infants born to women who received antepartum PIs. Because maternal IgG antibodies readily cross the placenta, HIV-1 antibody testing is not considered diagnostic of infant HIV infection and is therefore avoided until the child is 18 months of age. DNA-PCR testing is typically performed at birth (to detect in utero infection), 4 weeks, and 4 to 6 months. An additional PCR may be obtained at 2 weeks, to detect intrapartum exposure in particularly high-risk situations, such as limited or absent maternal antiretroviral medication. Serial DNA-PCR testing increases the sensitivity of HIV detection. Before 1 week of age, the sensitivity of DNA-PCR is approximately 38% to 50%. The sensitivity increases to 96.2% by 4 to 6 weeks and to 100% after 7 weeks of age. HIV infection is diagnosed in the infant by 2 separate positive HIV virologic tests. In the setting of bottle-feeding, HIV is excluded by 2 separate negative HIV virologic tests, 1 at 1 month of age or later and 1 at 4 months of age or later. HIV is also excluded with a negative HIV antibody test at 18 months, though one study found that no additional cases of HIV were identified following 3 negative DNA-PCR tests. Despite initial concerns, zidovudine does not apparently affect the detection of HIV by DNA testing among infants. Little is known, however, about the impact of HAART or non-clade B virus on the sensitivity of PCR testing in the neonate.

Conclusions

We are remarkably close to eliminating perinatal HIV in the United States. It is one of the starkest examples of the countless political, social, and economic inequities that exist between the industrialized and resource-poor settings of the world. With our success, we must advocate for women in our own neighborhoods and around the world to have effortless access to contraception and abortion services, supportive prenatal care, and HIV testing and treatment.

Written by Dr Cohan for the July 2003 IAS-USA Cases on the Web presentation. Adapted and updated in current article form by Dr Cohan in November 2003. The Case on the Web version is currently available for CME credit at www.iasusa.org/cow.

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Drug Resistance Mutations in HIV-1

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The International AIDS Society–USA (IAS–USA) Drug Resistance Mutations Group is a volunteer panel of experts that meets regularly to review and interpret new data on HIV-1 resistance. The focus of the group is to identify mutations associated with clinical resistance to HIV-1. These mutations have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded access protocols are included.

The IAS–USA Drug Resistance Mutations Figures are designed for use in identifying mutations associated with drug resistance and in making therapeutic decisions. Care should be taken when using this list of mutations for surveillance or epidemiologic studies of transmission of drug-resistant virus; a number of amino acid substitutions, particularly minor mutations, represent polymorphisms, which in isolation may not reflect prior drug selective pressure or reduced drug susceptibility.

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

The IAS–USA Drug Resistance Mutations Figures are available on a pocket-sized folding card. Copies of the card can be ordered by phone at (415) 544-9400, at www.iasusa.org/resistance_mutations/index.html, by mail, or by e-mail at: resistance@iasusa.org.

Revisions to the Figures in this October 2003 Update

In the nucleoside and nucleotide reverse transcriptase inhibitor (nRTI) category, mutations for emtricitabine have been added. Emtricitabine and lamivudine share a similar reverse transcriptase M184V/I mutation pattern (see User Note 10). In addition, the K65R mutation has been added to stavudine, lamivudine, and emtricitabine. Data presented at recent conferences indicate that this mutation can confer resistance to stavudine and cross-resistance to lamivudine and emtricitabine. In the protease inhibitor (PI) category, the V32I and the I84V/C have been added to the list of accumulated mutations conferring multi-PI resistance (see User Note 9). In addition, mutations have been added for tipranavir/ritonavir, which is currently available through an expanded access protocol and is not approved for use by the US FDA. A number of major (L33I/F/V, V82L/T, I84V, and L90M) and minor (L10I/V, K20M/L/T, M46I, and I54V) mutations were identified for tipranavir/ritonavir from data presented at the XII International HIV Drug Resistance Workshop in Los Cabos, Mexico. Based on data published by Colombo and colleagues, 7 minor mutations associated with resistance to atazanavir (L31I/F/V, K20I/M/L, L24I, L33I/F/V, M36I/L/V, G48V, and G73C/S/T/A) have been added. For lopinavir/ritonavir, the I54V/L mutation has been expanded to I54V/L/A/M/T/S and the I47V mutation has been expanded to I47V/A. In the fusion inhibitor category, the discussion in User Note 25 has been expanded to include current findings on issues that affect susceptibility to enfuvirtide.

The group is currently summarizing the HIV-1 resistance mutations that are associated with non-subtype B virus and plans to include it in the next update. Data continues on HIV susceptibility to antiretroviral drugs. (cont’d, pg 220)
### Mutations in the Reverse Transcriptase Gene Associated with Resistance to Reverse Transcriptase Inhibitors

#### Nucleoside and Nucleotide Reverse Transcriptase Inhibitors

<table>
<thead>
<tr>
<th>Inhibitor</th>
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<td>65 74</td>
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<td>Zalcitabine</td>
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<td>Abacavir</td>
<td>65 74</td>
<td>115 154</td>
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<td>Lamivudine</td>
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<td>118 184</td>
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<tr>
<td>Emtricitabine</td>
<td>65</td>
<td>184</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>65</td>
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#### Nonnucleoside Reverse Transcriptase Inhibitors

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<tr>
<td>Nevirapine</td>
<td>100 103 106 108</td>
<td>181 188 190</td>
</tr>
<tr>
<td>Delavirdine</td>
<td>103 106</td>
<td>181 188 236</td>
</tr>
<tr>
<td>Efavirenz</td>
<td>100 103 106 108</td>
<td>181 188 225</td>
</tr>
</tbody>
</table>
**MUTATIONS IN THE PROTEASE GENE ASSOCIATED WITH RESISTANCE TO PROTEASE INHIBITORS**

### Protease Inhibitors

<table>
<thead>
<tr>
<th>Multi-PI Resistance: Accumulation of Mutations</th>
<th>L</th>
<th>V</th>
<th>M</th>
<th>I</th>
<th>V</th>
<th>I</th>
<th>L</th>
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<tr>
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<tr>
<td>Nelfinavir</td>
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<td>71</td>
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</tr>
<tr>
<td>Amprenavir</td>
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<td>32</td>
<td>46</td>
<td>47</td>
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<td>Lopinavir/Ritonavir</td>
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<td>20</td>
<td>24</td>
<td>32</td>
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</tr>
<tr>
<td>Tipranavir/Ritonavir (expanded access)</td>
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<td>82</td>
<td>84</td>
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</tbody>
</table>

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

**HR1 Region**

- **Enfuvirtide**
  - Amino Acid, Wild-Type: G, V, Q, N
  - Amino Acid Position Major (boldface type; protease only): 35
  - Amino Acid, Substitution: G, I, V, Q, N
  - Insertion: See User Note 21
  - Vertical pink lines indicate NAMs
  - Minor (lightface type; protease only): See User Note 22
The IAS–USA Drug Resistance Mutations Group reviews new data on HIV drug resistance in order to maintain a current list of mutations associated with clinical resistance to HIV. This list includes mutations that may contribute to a reduced virologic response to a drug. These mutations have been identified by 1 or more of the following criteria: (1) in vitro passage experiments or validation of contribution to resistance by using site-directed mutagenesis; (2) susceptibility testing of laboratory or clinical isolates; (3) genetic sequencing of viruses from patients in whom the drug is failing; (4) correlation studies between genotype at baseline and virologic response in patients exposed to the drug. Drugs that have been approved by the US Food and Drug Administration (FDA) or are available through expanded access protocols are included. Additional information on the mutations is provided, where necessary, in these user notes.

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

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

The E44D and V118I mutations are listed as NAMs. In a recent study, the E44D and V118I mutations were more common in virus from patients who had been on zidovudine and lamivudine, and were associated with higher-level resistance to zidovudine (Stoeckli et al., Antimicrob Agents Chemother, 2002). When present together with other NAMs, the E44D and V118I mutations confer resistance to lamivudine. Analysis from the AIDS Clinical Trials Group (ACTG) study 136 has shown that the V118I mutation is commonly selected by a zidovudine/didanosine regimen (Shafer et al., J Infect Dis, 1995). Findings from ACTG study 241 have shown that the E44D mutation is commonly selected by zidovudine/didanosine (Hanna et al., J Infect Dis, 2002) and that the E44D mutation is associated with a significantly worse response to treatment with zidovudine and didanosine, with or without nevirapine (Precious et al., AIDS, 2000). The significance of E44D or V118I when each occurs in isolation is unknown (Romano et al., J Infect Dis, 2002; Walter et al., Antimicrob Agents Chemother, 2002; Grouard et al., Antivir Ther, 2002).

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

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

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

6. The K65R mutation or the L74V mutation, alone or in combination with the NAMs or T69D/N/S may lead to didanosine resistance. Additional mutations that confer resistance or cross-resistance to emtricitabine are possible, but are yet to be described.

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

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

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

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

11. The accumulation of NAMs (M41L, D67N, K70R, L210W, T215Y/F, K219Q/E) increases resistance to tenofovir. Mutations M41L and L210W contribute more than others. Therefore, the number and type of NAMs will determine the degree of reduced response. T69D/N/S may also contribute to a reduced response to tenofovir (Miller et al., Antivir Ther, 2002; Lu et al., Antivir Ther, 2002; Masquelier et al., Antivir Ther, 2002).

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

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

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

15. The prevalence of the Y318F mutation in clinical isolates along with mutations K103N, Y181C, or P236L was approximate 5%, 2%, and 15%, respectively (Kemp et al., Antivir Ther, 2001). In vitro this mutation confers resistance to nevirapine, delavirdine, and efavirenz.
16. The Y181C/I mutation is not selected by efavirenz, but its presence contributes to low-level cross-resistance to the drug. Clinical impact of this mutation may be overcome with a fully active antiretroviral combination regimen, although no clinical trial data yet address this question.

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

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

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

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

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

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

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

22. Protease mutation L63P is common in viruses that have never been exposed to PIs (Kozal et al, Nat Med, 1996) and may be more prevalent in viruses from patients in whom a PI-containing regimen has failed. However, by itself, L63P does not cause any appreciable increase in the IC50 for any PI. L63P is listed for lopinavir/ritonavir (and not any other PI) because studies have shown that this mutation, when present with multiple other mutations, is associated with clinical failure.

23. When administered to patients as the initial PI, atazanavir selects for the mutations IS10L and A71V (Colono et al, Antivir Ther, 2002). When used as a subsequent PI in combination with saquinavir, atazanavir selects for IS4L and IS4V (Colono et al, Antivir Ther, 2002). In vitro, atazanavir selects for V32I, M46I, I84V, and N88S (Gong et al, Antimicrob Agents Chemother, 2000). Although other mutations, such as V82A and L90M, have not been selected for by atazanavir either in vitro or in vivo, these mutations have been shown to confer cross-resistance to atazanavir, particularly when present in combination with each other or with other known PI resistance mutations (Colono et al, Antivir Ther, 2000).

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

25. To date, resistance mutations in the gp41 envelope gene have been identified primarily at positions 36 to 45 of the first heptad repeat (HR1) region. These mutations have been identified in viruses from patients having been on enfuvirtide and have been shown to confer resistance or reduced susceptibility (Wei et al, Antimicrob Agents Chemother, 2002; Sista et al, Antivir Ther, 2002; Mink et al, Antivir Ther, 2002). It is important to note that wild-type viruses lacking any mutations in the depicted HR1 region vary 500-fold in susceptibility and such pretreatment susceptibility differences were not associated with differences in clinical response (Labrosse et al, J Virol, 2003; Greenberg et al, 10th CROI, 2003). Furthermore, it is possible that mutations and/or polymorphisms in other regions in the envelope, yet to be identified, as well as coreceptor usage and density may affect susceptibility to enfuvirtide (Reeves et al, PNAS, 2002). Further research is needed to define the full spectrum of clinically relevant mutations conferring enfuvirtide resistance. Testing to detect only the depicted HR1 mutations may not be adequate for clinical management of suspected failure of regimens including enfuvirtide and must be interpreted in the context of resistance testing results for all other components of the regimen.

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

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

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

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IAS-USA courses this year included the 11th annual winter/spring series, Improving the Management of HIV Disease® HIV Pathogenesis, Antiretrovirals, and Other Selected Issues in HIV Disease Management; the 9th annual fall series, Current Challenges in HIV Disease: A Case-Based, Advanced Course in Clinical HIV Management; and Clinical Pathway, the 6th annual HIV clinical conference for Ryan White CARE Act Title III and IV providers.
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The Drug Resistance Mutations Group was convened in 2000 to maintain an ongoing, up-to-date database of HIV drug resistance mutations reflecting current research in the field. Each year, the group issues several updates to its list of mutations, the most recent of which appears in this issue of Topics in HIV Medicine and at www.iasusa.org.

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Antiretroviral Therapy Panel


Resistance Testing Panel


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Metabolic Complications Panel

The Metabolic Complications Panel was convened in 2000, and its recommendations were published in 2002.

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