

COMPLIANCE/ADHERENCE ISSUES

128. Which is more harmful, for a patient to miss a few doses a week, or to miss dosages for a few weeks or months altogether?

Dr Carpenter: In theory it is more harmful for a patient to miss a few doses of a protease inhibitor each week than to stop therapy entirely for periods of weeks or months. HIV resistance develops when the antiretroviral drug is present, but at levels that are too low to completely inhibit viral replication. The presence of low plasma levels of the drug would therefore be more conducive to development of resistance than prolonged periods in which the patient took no antiretroviral drug.

Dr Volberding: The effect of noncompliance of varying types may not be the same for different treatments. Although strict compliance is not thought to be essential for nucleosides alone, rigid adherence may be crucial when using more potent drugs such as protease inhibitors or NNRTIs. With the latter classes, it is probably better to stop the drug completely for a period than to chronically underdose the virus through decreasing doses or skipping treatments. The plasma HIV RNA titer may, however, provide some guidance. If a patient admits to routine nonadherence but nevertheless continues to document complete viral suppression, it may be acceptable to allow this more relaxed approach for that patient with that specific combination.

129. Compliance may be a more formidable hurdle than drug development. Comment on compliance and resistance and ways to improve compliance.

Dr Carpenter: Compliance does represent a hurdle that may be of the same order of magnitude as drug development at the present time. Inadequate compliance, especially taking a protease inhibitor in inadequate dosages, will enhance the development of viral resistance. Widespread lack of compliance would lead to increase of drug resistant viral strains in the population. There are many approaches to improving compliance. An effective approach appears to be education of patients, *by peers whenever possible*, with regard to the great benefit that is derived from the appropriate use of new combination antiretroviral regimens. Dissemination through the community of the knowledge that colleagues have benefited dramatically from three-drug combinations has enhanced the demand for, and compliance with, such regimens, despite the large number of pills and frequent dosing involved. Compliance is further improved by discussing plasma viral load results with patients, having them fully understand the goal of reducing plasma viral load to lowest possible levels.

Dr Volberding: We are only beginning to consider the issue of antiretroviral adherence and have much to learn from our behavioral medicine colleagues who have studied these issues in other chronic diseases. Certainly, adherence is easier with drugs with less frequent dosing schedules, with drugs with fewer toxic effects, and with drugs that the patient perceives to be important. We might start with these considerations in selecting otherwise equi-potent antiretroviral drugs. We must recognize that nonadherence is very common and should be addressed before and during drug therapy.

130. What percentage of asymptomatic patients will be adherent to triple therapy? For antihypertensive monotherapy it's about 50% at best.

Dr Carpenter: It is impossible to know what percentage of asymptomatic patients will be adherent to triple therapy. It is, clear, however, that patients' full understanding of the goal of reducing the plasma viral load to the lowest possible level, and discussion of plasma viral load results with the patient at periodic intervals can be enormously helpful in enhancing adherence to triple-drug therapy. Emerging information suggest that adherence to triple drug therapy may be greater than that to monotherapy, which suggests that patients are willing and able to follow complicated regimens if they are fully aware of the benefits that can be achieved.

Dr Volberding: Again, we are only beginning to study adherence to antiretroviral therapy. The high frequency of complete viral suppression in clinical trials of protease-containing regimens does, however, suggest that compliance can be quite good. Clearly, it may be less complete in the "real world" of clinical medicine.

131. Should a known noncompliant patient be given antiretroviral therapy with the attendant risk of developing resistant viral strains and spreading these strains into the community?

Dr Volberding: It is appropriate to consider clinical settings where aggressive antiretroviral therapy might not be recommended for nonmedical reasons. As resistance to protease inhibitors or NNRTIs is almost certain to develop quickly, these drugs might not be prescribed for patients with established records of medication noncompliance. However, the benefits of such therapy should be discussed with such patients in the hope that compliance may be

supported by a stronger belief in the chance of clinical improvement. The reason to withhold aggressive antiretroviral therapy should be delineated in the medical record and can include the expectation of minimal personal benefit by that specific patient, as well as the concern that incomplete therapy might increase the community prevalence of HIV isolates resistant to effective therapies.

Dr Hammer: It should be a last resort to refuse to prescribe antiretroviral therapy to a noncompliant patient. Through a process of education, close follow-up, and the selection of an easy to take and tolerable regimen, many previously noncompliant patients can be gradually introduced to the concept of taking medications on a regular basis.

132. What do you mean by need for adherence to drug regimen? Of people I know on zidovudine, virtually everyone "takes a break" from zidovudine (maybe a weekend-free of zidovudine once every few months). But they won't tell their provider. Is this the kind of behavior that could jeopardize utility of protease inhibitors?

Dr Carpenter: Certainly lack of adherence to a multidrug regimen is a reality for almost all patients. Taking "drug holidays" is, however, not as likely to enhance the development of antiretroviral resistance as continued inadequate dosage of the antiretroviral medication. It is important to encourage optimal doses of medications at all times, acknowledging that "drug holidays" will occur.

Dr Volberding: Adherence to therapy is quite often a relative term, since few patients absolutely remember to take each and every dose as intended in the prescription. The consequences of various types of noncompliance probably vary depending on the therapy and the goals of treatment. With nucleosides alone, where the goal is partial long-term suppression, underdosing may be less a problem than intermittent therapy. With the protease inhibitors and NNRTIs, occasional periods of discontinuation may be less harmful than chronic inadequate dosing as they may predispose the patient to the appearance of high-level resistance. The provider's responsibility increasingly includes fully informing patients of the need for adherence to prescriptions.

133. More drug options and combination therapy means more widespread intolerance and noncompliance and more resistance circulating in the community. Are we soon going to be treating largely "naive" patients who have resistant viruses de novo?

Dr Carpenter: The risk of more resistant viral strains circulating in a community as a result of noncompliance presents a real problem. Lessening the impact of this problem requires both adherence to therapeutic regimens by patients, and prompt changes of drug regimen by physicians when increasing plasma viral load indicates failure of a given therapeutic regimen.

Dr Volberding: There is a definite possibility that therapy may result in the increased community prevalence of HIV with pre-existing resistance mutations. As with any antibiotic, this problem can be minimized by appropriate selection of drugs, and, with HIV, by better selection and education of patients beginning such treatments. To date, there is little evidence that this is a common clinical problem, but it almost certainly will become one in the future as more patients receive antiretroviral therapy and yet continue to engage in high-risk transmission behavior.

134. Different clinics are addressing compliance in different ways—peer-support groups, counseling upon each prescription fulfillment, withholding treatment from active drug users. Should we develop compliance guidelines, perhaps through a consensus conference?

Dr Carpenter: Different clinics are clearly addressing compliance in different ways. To a certain extent this is healthy, as problems in compliance vary with geographic region, gender, risk-taking activity and a number of other factors. Nonetheless, it may be reasonable to attempt to develop compliance guidelines, perhaps through a consensus conference, since the issue of compliance has been greatly heightened by the development of two new classes of antiretroviral agents, to both of which resistance can develop rapidly in the absence of close adherence to prescribed therapeutic regimens.

Dr Volberding: The most important issue with compliance is to understand its importance in HIV therapy, to open a dialogue with each patient, and to support calls for a linkage between physicians treating HIV and behavioral medicine experts.