ABSTRACT

The treatment of patients who have the human immunodeficiency virus (HIV) and opportunistic infections (OIs) presents a number of challenges; optimal treatment strategies for these patients are not well defined. At present, there is little agreement as to whether these patients should begin antiretroviral therapy (ART) immediately, or whether ART should be deferred until the OI has resolved. Combination treatment regimens required to treat HIV and OIs simultaneously are associated with several complications, including increased risk of gastrointestinal toxicity, drug-related anemia, lack of adherence to treatment, and drug interactions. HIV-associated OIs are increasingly common among disadvantaged patient populations, who are at high risk of hepatitis C infection, substance abuse, and lifestyle factors that further complicate treatment. In addition, many patients exhibit an inflammatory immune response following treatment for certain OIs or the initiation of ART. However, it has also been shown that high-potency ART regimens that rapidly reduce the HIV viral load and improve CD4 cell counts significantly reduce the risk of subsequent OIs. A randomized, controlled clinical trial has been designed to compare treatment outcomes associated with immediate versus delayed initiation of ART in patients with OIs. (Adv Stud Med. 2005;5(2A):S111-S116)

SHOULD PATIENTS WITH AN ACUTE OPPORTUNISTIC INFECTION RECEIVE ANTIRETROVIRAL THERAPY IMMEDIATELY?*

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In patients with symptomatic acquired immunodeficiency syndrome (AIDS) who were hospitalized for the treatment of an opportunistic infection (OI), an important but unresolved issue is whether the patient should immediately begin antiretroviral therapy (ART). At present, there is no clear consensus among clinicians as to whether patients with OIs should begin ART when treatment of the OI is initiated or whether ART should be deferred until after treatment of the OI is concluded and the patient is discharged from the hospital. Before the introduction of highly active antiretroviral therapy (HAART), there were 3 general principles regarding the management of OIs in patients with human immunodeficiency virus (HIV) infection: management of the OI supersedes the management of HIV infection, OIs require lifelong therapy, and decisions regarding OI prophylaxis should be based on the lowest CD4 cell count. However, as a result of the effectiveness of HAART regimens, OI prophylaxis can now be discontinued in many patients for whom ART has produced significant immune reconstitution, and long-term antimicrobial therapy is no longer a necessity for many patients. It also is no longer clear that the acute management of the OI should supersede the management of HIV, and some clinicians have suggested that the 2 be addressed simultaneously. Several studies have demonstrated significant improvement in the number and function of CD4 cells with ART, which is often accompanied by a rapid improvement in immune function. Thus, because OIs are the result of severely compromised immune function, early initiation of ART may improve clinical outcomes in HIV-infected patients with OIs. However, some evidence suggests that starting ART early in the course of treating an OI may actually worsen outcomes, at least in the short term, as a result of either drug-to-drug interactions or drug-related toxicities.
DEFERRING ANTIRETROVIRAL THERAPY IN PATIENTS WITH OPPORTUNISTIC INFECTIONS

Clinicians may decide to delay ART until after an acute OI has resolved for many reasons, including the potential for increased risk of adverse drug reactions; increased risk of immune-mediated complications to the course of the OI after reconstitution of the immune system; and a greater chance of ART failure and/or treatment interruption, which increases the likelihood that the patient will develop drug-resistant HIV. Because of these factors, initiating ART in a patient with an active OI could result in an increased risk of morbidity and mortality over the long term, despite a short-term benefit in immunologic function.

Several treatment challenges are created when patients are treated with the complex medication regimens required to treat an OI and HIV infection simultaneously. Even the most simple polypharmacy treatment regimens are associated with an increased probability of gastrointestinal intolerance. Anemia can be a significant problem in patients in the advanced stages of AIDS, especially in patients who also have certain OIs (eg, Pneumocystis carinii pneumonia [PCP], toxoplasmosis); drugs can exacerbate this condition. For example, anemia related to zidovudine treatment is common among patients with preexisting bone marrow dysfunction. Increased hepatotoxicity is also a significant problem for patients who are undergoing treatment for HIV and hepatitis C. Although the available regimens have become more potent in recent years and are now able to produce long-term improvements in HIV viral load and immune function, treatment adherence to complicated multidrug regimens is a common problem. Clinicians face a significant challenge with patients who have HIV and are hospitalized with an acute OI: Can a patient be discharged from the hospital with prescriptions for medications to treat their HIV infection and OI and be expected to successfully manage both conditions?

The risk of clinically significant drug interactions may also be dramatically increased when patients are treated for HIV infection and an OI. An example is the use of antimycobacterial therapy in patients who also are receiving protease inhibitors (PIs). Although there are alternatives to this combination, the specific protocols are not always well defined. For example, the appropriate dose of efavirenz for patients who are on rifampin-based therapies is still uncertain. There are recommendations from the Centers for Disease Control and Prevention, although the evidence to support those recommendations is relatively limited. There are also data to suggest that acute infection can reduce the activity of the hepatic cytochrome P450 enzyme system, which is important in the metabolism of many drugs. Studies conducted in experimental animal models have demonstrated the downregulation of CYP enzymes with infection and inflammation. Although the relationship between infection and CYP 450 enzyme function has not been extensively studied in clinical populations, some data suggest that acute illness modifies drug metabolism and increases the risk of medication toxicity. In a study of patients with asthma who were on stable theophylline doses, the incidence of theophylline toxicity increased during an influenza epidemic, suggesting that because the theophylline treatment was constant over time, the viral infection had altered the pharmacology of theophylline by inactivating drug-metabolizing hepatic enzymes. Although this result raises the possibility that patients with HIV infection on ART may experience increased drug toxicity during exacerbations of OIs, it is unclear whether a similar alteration of the pharmacokinetics of HIV medications occurs in patients with HIV and OIs.

Another challenge for treating patients with HIV is the increased incidence of OIs in more disadvantaged patient populations. The concurrent treatment of HIV and an OI is often more complicated in these patients because they are less likely to have access to medical care and are more likely to have social issues that interfere with their treatment. Many of these patients have difficulty remaining adherent to complex medication regimens that are typical in HIV treatment. Many of these patients only recently have been diagnosed with HIV. They also are at higher risk of developing other comorbid conditions; the most important of which, in terms of drug tolerability and interactions, is probably hepatitis C. These patients are more likely to have substance abuse disorders, which further complicates their self-management following discharge from the hospital. Clinicians reasonably may argue that the best management of these patients is to first treat the acute OI and then to begin ART in the clinic.

Several studies have shown that for some OIs, such as active PCP or cytomegalovirus (CMV), the initiation of treatment for the OI produces an inflammatory reaction that may contribute to the worsening of
the patient's condition and may increase the risk of mortality. In addition, many OIs may become worse when ART is initiated, as a result of an inflammatory reaction to microbial antigens (eg, CMV, Mycobacterium avium complex [MAC]) in patients without signs of clinical infection.9,10 A report from France involving 3 patients with HIV infection who began ART during acute treatment for PCP exhibited significant clinical deterioration, increasing hypoxia, and new pulmonary infiltrates.11 However, all 3 patients had discontinued corticosteroid treatment when ART was initiated, making it difficult to clearly implicate ART as the cause of the PCP exacerbation. A recent study suggested that as many as 40% of patients being treated for cryptococcal meningitis had complications within 3 months of starting ART, which was attributed to immune reconstitution inflammatory syndrome (IRIS).12

INITIATING ANTIRETROVIRAL THERAPY IN PATIENTS WITH OPPORTUNISTIC INFECTIONS

In contrast, several arguments have been proposed in favor of beginning ART early in patients with OIs. Early initiation of ART is associated with more rapid recovery of immune function and an increased likelihood of long-term survival and fewer AIDS-defining OIs, which could contribute to better control of the OI. However, there are few well-designed, long-term studies that have evaluated survival rates among patients with OIs as a function of ART treatment. Dworkin et al examined survival among patients with PCP infection during the 24 months after diagnosis in a total of 4412 patients (with a total of 5222 episodes of PCP), comparing 3 patient cohorts (those patients treated in 1992-1993, 1994-1995, or 1996-1998).13 As shown in the Figure, the probability of survival was greater for patients in the later cohorts, who entered the study during the period in which HAART regimens were entering clinical practice. The probability of a 12-month survival rate increased from 40% among patients enrolled during 1992 and 1993 to 44% among patients who enrolled in 1994 or 1995 to 63% among patients who enrolled from 1996 to 1998. The likelihood of survival was significantly lower among patients with a prior history of PCP, older age, and lower CD4 cell count. The likelihood of early death was significantly lower among patients who received concurrent combination ART (odds ratio, 0.2). These data suggest that deferring ART may be associated with poorer survival among patients with OIs. Similarly, an analysis of data pooled from 4 ART clinical trials has shown that patients who have an OI are at higher risk of developing a subsequent infection and that the risk of infection for several specific OIs, including PCP, CMV, and MAC, is strongly associated with a higher HIV viral load and lower CD4 cell counts at baseline.14 Currier et al extended these findings by examining the effects of early improvement in CD4 counts and HIV viral load on the subsequent risk of OIs in patients enrolled in the AIDS Clinical Trials Group (ACTG) 320 clinical trial, one of the first randomized studies to evaluate a combination treatment regimen (zidovudine/ lamivudine/indinavir) representative of the regimens used in current practice (Currier et al, Unpublished observations). Patients who had a 1-log reduction in HIV viral load and an improvement in CD4 count of at least 25 cells/µL during the first 8 weeks of therapy had the lowest chance of developing a subsequent opportunistic infection (<5% for developing any OI). Patients who had virologic responses or CD4 responses, but not both, had some protection against the development of subsequent OIs, with approximately 10% to 15% of

![Figure. Long-term Probability of Survival](image-url)

patients developing an OI. Patients who had no response to therapy had the highest risk (approximately 40%), suggesting that initiation of ART immediately to lower HIV viral load and to improve CD4 cell counts may help to reduce the occurrence of OIs.

To further define the management of patients with OIs, a randomized controlled trial recently has been initiated within the Adult ACTG to directly compare the initiation of standard ART immediately after presentation with an acute OI (beginning within 14 days) versus deferred treatment (at least 4 weeks after treatment of the OI). The primary endpoint is the combined incidence of survival, AIDS progression, and virologic control over 48 weeks of treatment. The success of ART will be evaluated by virologic response and changes in CD4 count after the initiation of ART; success of OI treatment will be evaluated by the duration of hospitalization, complication rates, adverse events, and serious toxicities during the course of treatment. Patients with tuberculosis (TB) are specifically excluded from this study. During the study design, investigators had some concern regarding the significant problem of drug interactions between ART treatments and rifamycines. In addition, some reports have suggested there is an increased risk of (and morbidity from) IRIS in patients with TB. Ideally, a similar study should be conducted involving patients with TB.

**CONCLUSIONS**

In HIV-infected patients with OIs, deferring ART until after the OI has resolved may be preferable to treating both conditions simultaneously. Initiating ART while attempting to treat the OI may introduce a number of complications, including gastrointestinal intolerance, anemia, other adverse effects, and drug interactions. Initiating ART in patients with OIs also may trigger an inflammatory reaction as a result of immune reconstitution. However, cohort studies suggest that patients who are treated with HAART regimens are less likely to develop OIs and that lowering HIV viral load and increasing CD4 cell counts are associated with reduced rates of new OIs. The results of an ongoing, randomized controlled trial comparing outcomes between patients who start ART immediately after presentation with an acute OI and patients who start ART at least 4 weeks after the OI has resolved should help to clarify the role of ART in HIV-infected patients with OIs.

**DISCUSSION**

**Dr Hirsch:** You mentioned that if you are going to treat TB acutely with antiretroviral agents, there are some drugs you would be more likely to use than others. In other acute OIs, are there preferred regimens you would use and others that you would not use?

**Dr Powderly:** I really am not aware of any data that have addressed that concern. There has been, I think, as you are well aware, an urban myth that patients with advanced cases of AIDS do better with certain regimens or should be treated with protease inhibitors. Again, I’m not sure that’s actually supported by any data whatsoever; I certainly do not advocate that clinicians should automatically use a protease inhibitor just because a patient has a CD4 count less than 50 cells/µL and a high viral load.

**Dr Masur:** In South Africa, our clinicians feel strongly that compliance is such an issue that they don’t want to recommend individual drugs. Therefore, having a combination tablet for anti-TB therapy is important—this is not possible with many regimens, other than abacavir sulfate/lamivudine/zidovudine.

**Dr Gulick:** Outside the United States, there are combination tablets available with stavudine, lamivudine, and nevirapine, probably the most commonly used combination tablet in the world at present.

However, I think the point is that, unfortunately, we have to decide between treating a patient’s TB most effectively or treating their HIV most effectively. I think all clinicians would prefer to do both. Currently, it’s complicated to treat TB because of adherence issues and pharmacokinetic issues. These issues are influencing a clinician’s choice of antiretrovirals, which is the reason the triple combination of abacavir sulfate/lamivudine/zidovudine is so attractive. However, the clinician loses the ultimate control of HIV infection, which is not our intention. In the ACTG study, researchers are investigating a quad regimen of abacavir sulfate/lamivudine/zidovudine plus tenofovir—a simple regimen of 3 pills with no expected drug-to-drug interactions. However, the drug’s activity cannot be gauged because it has never been compared with anything else.

**Dr Masur:** Regarding the issue of drug interactions, the treatment of TB and HIV with nevirapine raises the possibility of hepatotoxicity, which will be complicated. If a fixed combination of rifampin with efavirenz is used, isn’t that going to complicate the dosing regimen?
**Dr Bartlett:** Well, I understood that efavirenz could be used in a standard dose; the need for an increased dosage was not uniformly supported by pharmacology studies.

**Dr Powderly:** Actually usage of an increased dose of efavirenz still remains controversial. One of the better studies was a randomized trial in Thailand, in which a Thai patient weighing 50 kilograms could be prescribed 600 mg of efavirenz, but that result does not translate to other populations. In that study, 3 of 30 patients who received efavirenz at 600 mg had efavirenz levels that were below recommended targets, although all 3 patients had virologic responses. Whereas each patient who received an 800-mg dosage had efavirenz levels above the current recommended targets. The investigators did not find a dramatically different rate of toxicity in terms of dropout from the higher doses of efavirenz. Although it was a relatively small study, I think pharmacologists would still argue that 800 mg of efavirenz should be used when rifampin is prescribed. Problems usually occur with regimens in which the rifampin dose must be changed, which is not required with efavirenz, and results in issues with fixed-dose combinations because rifampin cannot be altered.

**Dr Stone:** It certainly is important for clinicians to think about the patient’s potential regimen adherence when they are deciding whether to start HAART treatment at the time of a patient’s acute OI. This actually is a good argument for starting the patient’s HAART regimen in the hospital. In many of the most challenging cases, patients usually are hospitalized for 1 week or more for treatment of an acute OI while the clinicians determines suitable follow-up care based on the patient’s other issues. During this 1 week (or sometimes 10 days), a patient could be receiving HAART treatment and learning how to manage the dosage. This is often a good learning experience for the patient. The clinician has the opportunity to review the regimen with the patient, including the number of pills to be taken, possible adverse effects, and whether medication should be taken with food. Also, the hospitalized patient has the advantage of experiencing the adverse effects and having on-site clinical assistance in managing those adverse effects rather than undergoing the experience at home with no assistance, thus being at higher risk for treatment interruption.

**Dr Powderly:** I don’t disagree with you, but I think the challenge many clinicians would experience is not having the opportunity to keep the patient in the hospital long enough to be taught how to take oral therapy. In many situations, if the patient is improved to the point that they are switched over to oral therapy, the physician’s ability to keep the patient hospitalized for another 24 hours is quite limited.

**Dr Hirsch:** Isn’t treatment likely to be individualized? For example, most physicians would agree that if a patient has thrush, ART should be initiated immediately. TB treatment is the polar opposite. And aren’t other ARTs in the middle some place? Isn’t treatment initiation going to vary by OI?

**Dr Masur:** It presumably varies by OI pathogen and severity. For a condition such as MAC in which therapy is not terribly effective, presumably there would be more urgency to start antiretrovirals even though there are drug-interaction problems. For example, with *Pneumocystis carinii* or *cryptococcosis*, therapy is likely to be successful, but the patients can be quite ill and presumably a clinician would be reluctant to use ART.

**Dr Glick:** It is also treatment-specific. Cryptococcal meningitis is treated with fluconazole, a drug that doesn’t have drug interaction and is simple to take. In treating toxoplasmosis with sulfadiazine and trimethoprim 4 times a day, the risk of cytopenias and hepatitis will also complicate antiretroviral agents.

**Dr Masur:** ART also is not very effective for the diarrheal illnesses, not just *Cryptosporidium* but *Mycrosporidia*. Therefore, clinicians would like to start antiretrovirals, but they should balance that by not getting suboptimal levels and promoting resistance. That becomes a complex part of the equation.

**Dr Lucas:** Is the ACTG trial enrolling treatment-naive and -experienced patients who come into the hospital but are not on therapy?

**Dr Powderly:** The study is designed to enroll patients who have an OI. Most patients who have enrolled to date have never undergone ART. Many patients who present with OIs have been diagnosed with HIV, may have been treated at a clinic, and may have even been given a prescription for ART but did not return to the clinic for follow-up care. Those patients would be eligible for this trial. Because the investigators are looking at the effect from this antiretroviral therapy, the key to the ACTG study is whether the clinician can devise an effective, potent regimen. For that reason, patients who would be in “salvage situations” are not being included in the study.
because the benefit of effective therapy cannot be examined if effective therapy cannot be administered.

**Dr Lucas:** In a “salvage situation” such as you mentioned, I don’t think there is a problem with giving a boosted PI in a month’s prescription to a patient for whom there are extensive socioeconomic issues and major questions about adherence. In fact, the trials indicate that those patient populations will not experience any drug resistance.

**REFERENCES**