Patient Adherence To HAART Regimens: Challenges For Physician Assistants And Health Care Providers

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Abstract

Patients often adhere incompletely and inadequately to highly active antiretroviral therapy (HAART) regimens used in the treatment of HIV infection. This permits the emergence of HIV variants that are resistant to current treatment. The physician assistant often assumes the responsibility for explaining to the patient the importance of adhering strictly to the regimen and for collaborating with the patient to overcome any problems. This report summarizes the major reasons for poor patient adherence regimen complexity, poor tolerability, and metabolic side effects and provides patient-friendly approaches that can be adopted in the context of the office visit to increase patients level of adherence to these challenging regimens.

INTRODUCTION

Until 1995, treatment for HIV-1 infection consisted mainly of single-drug and dual-drug therapy regimens that provided limited success. With the introduction of protease inhibitors (PIs), dramatic declines in HIV viral loads and AIDS-associated events could be achieved. This prompted revisions in national guidelines for the treatment of HIV disease, recommending the use of antiretroviral agents for HIV-infected adults and adolescents and the use of PIs in particular. At present, combination therapy involving agents from three classes of antiretroviral agents—nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), and PIs—forms the basis of potent anti-HIV regimens known as HAART (highly active antiretroviral therapy).[1] HAART regimens have dramatically changed the way that individuals with HIV-1 infection and AIDS are treated.[2] When taken diligently, these regimens have improved patients' prognosis by delaying the emergence of resistant strains of virus, thereby slowing the progression of HIV infection to AIDS.[3] However, the effectiveness of HAART depends on patients' achieving near-perfect adherence. Adherence is weakened by the complexity of current HAART regimens and associated side effects that some patients find intolerable. In addition, as patients' lifespans have been lengthened with HAART therapy, there is evidence to suggest that some complications of these therapies may persist over the long term.[4]

The danger of poor adherence in patients with HIV infection is that it correlates with clinical and virologic failure.[5] Studies have shown that, on average, 50% to 70% of patients on HAART regimens are nonadherent.[6] Conversely, good adherence to antiretroviral therapy, defined as >90% consumption of the prescribed medication, is accomplished by less than 60% of patients.[7] There is little doubt that increasingly complex regimens, tolerability issues, and metabolic side effects are presenting important challenges for both patients and health care providers alike.6 The challenges are magnified by the fact that the treatment-resistant HIV variants that develop under conditions of reduced drug exposure not only are resistant to the drugs in the regimen but also may display cross-resistance to other antiretroviral drugs, thus further limiting the treatment options available to the patient for salvage therapy.[8]

Adherence is greatly enhanced by a trusting patient-physician relationship through which the patient becomes an active participant in negotiating and thoroughly understanding the treatment plan. Often the responsibility for explaining to the patient the problems that may be encountered with the HAART regimen falls to the physician's office personnel, especially the physician assistant.[9,10] Physician assistants have been reported to have a high degree of empathy toward persons with HIV infection and to be especially adept at providing essential information.[11]

This review summarizes some of the challenges patients face

in successfully adhering to HAART regimens and discusses new treatments on the horizon and the actions that the physician assistant may take to improve both adherence and treatment outcome.

CHALLENGES TO SUCCESSFUL ADHERENCE TO HAART REGIMENS

COMPLEXITY OF THE REGIMENS

One of the biggest challenges to successful adherence to HAART regimens is their complexity—it is clear that they do not easily fit into patients' lifestyles. Commonly reported complexity-related reasons for not following HAART regimens include being too busy with daily activities and simply forgetting to take a dose, or being away from home and experiencing a break in the daily routine. Because of regimen complexity, patients often cannot adhere adequately enough to their current therapy to effectively reduce HIV RNA to "undetectable" levels and to control HIV replication over the long term. The critical nature of adherence in HIV therapy has led to a reexamination of the considerable body of research on medication compliance issues, with particular attention to the issues relevant to anti-HIV therapy. It is well known that the degree to which adherence to a regimen interferes with daily life is an important contributor to nonadherence and that adherence decreases as the number of doses per day increases.3,6,[12] Once-daily and twice-daily regimens are associated with significantly better compliance rates (73% and 70%, respectively) than are three-times-daily (52%) and four-times-daily regimens (42%).12 HAART regimens, in addition to requiring many daily doses with multiple pills, often impose very specific food requirements that must be observed in order to ensure adequate blood levels of the drugs. Doses must be taken in precise relationship to meals, and the composition of the meals and the amount of fluid intake are often quite exacting. Maintaining drug levels consistently high enough to suppress HIV replication to levels that are undetectable by current technologies is crucial for therapeutic efficacy. Although newer regimens have reduced the frequency of daily dosing, lowered the pill burden, and minimized the special instructions regarding timing the dosing with meals, many PI-containing regimens still require patients to take more than 20 pills per day over multiple dosing times.3 Table 1 summarizes the complexity of dosing just one of the drug classes (PIs) associated with HAART.[13,14,15]

Figure 1

Table 1. Dosing Frequency and Pill Burden for the PI Class of Antiretroviral Drugs

PI	Number of Doses per Day	Number of Pills per Day
Current PIs		
Saquinavir (hard gel)[1]	3	9
Saquinavir (soft gel)[1]	3	18
Nelfinavir[2]	3	9
Indinavir[3]	3	6
Amprenavir[4]	2	16
Ritonavir	2	12
Lopinavir/ritonavir	2	6
PIs in Development		
Atazanavir	1	2
Tipranavir[5] (PNU-140690)	2	–

[1]400 mg bid with ritonavir [2]Dosed also as 1250 mg bid [3]800 mg bid with ritonavir [4]600 mg bid or 1200 mg qd with ritonavir [5]With ritonavir boosting.15 Formulation(s) under development.

The presence of other conditions in addition to HIV infection, such as depression and substance and alcohol abuse, can exacerbate the effects of regimen complexity on adherence.7,[16] Similarly, patients with social problems, arising from an accumulation of stressful life events such as family separation, divorce, and lack of a social support network, may have difficulty adhering to complex HAART regimens.7,[17] Age, education, and employment status have also been suggested to be influencing factors.7

POOR TOLERABILITY

Although most HIV-infected patients understand that their current therapy will inevitably result in side effects, dealing with side effects is nonetheless highly stressful.[18] All too often, medication side effects will limit the effectiveness of HIV therapy because patients cannot continue with the regimen. Despite the development of new antiretroviral agents, side effects are still very common.18 In a study by Duran et al assessing the impact of side effects on adherence to HAART, among 336 patients taking a triple-combination regimen (two NRTIs and one PI), 33% of the patients were unable to maintain complete adherence.[19] This type of regimen—a PI in combination with two NRTIs—is recommended first-line therapy in the Department of Health and Human Services guidelines.[20] Combination regimens can lead to a whole constellation of side effects, each contributed by the individual drugs within the regimen. For example,

NRTIs can produce a wide range of side effects, while gastrointestinal problems are common to all of the PIs (Table 2). Most PIs cause nausea and vomiting to some degree, ultimately undermining adherence to current PI-containing regimens.20

Figure 2

Table 2. Common Adverse Effects of PIs20,43

PI	Adverse Effects
Saquinavir	Diarrhea, nausea, abdominal pain, dyspepsia, flatulence, headache, fatigue, elevated AST and ALT, fat redistribution and lipid abnormalities, hyperglycemia
Indinavir	Nephrolithiasis, diarrhea, vomiting, hyperbilirubinemia, abdominal pain, nausea, headache, fat redistribution and lipid abnormalities, hyperglycemia
Ritonavir	Nausea, diarrhea, taste perversion, elevated AST and ALT, asthenia, headache, vomiting, anorexia, perioral dysthesia, hypertriglyceridemia, hepatitis, pancreatitis, hypercholesterolemia, fat redistribution and lipid abnormalities, hyperglycemia
Nelfinavir	Diarrhea, nausea, fat redistribution and lipid abnormalities, hyperglycemia
Amprenavir	Rash, nausea, headache, vomiting, fat redistribution and lipid abnormalities, hyperglycemia
Lopinavir/ritonavir	Nausea, vomiting, diarrhea, asthenia, elevated AST and ALT, possible increased bleeding episodes in hemophilia patients, fat redistribution and lipid abnormalities, hyperglycemia

Note. ALT, alanine aminotransferase; AST, aspartate aminotransferase

Dyslipidemia is a troubling side effect that occurs with all current PIs and may require treatment with lipid-lowering drugs. PI-related dyslipidemia is characterized by elevated low-density lipoprotein (LDL) cholesterol, total cholesterol, and triglyceride levels and reduced levels of high-density lipoprotein (HDL) cholesterol. Lipodystrophy is a disfiguring condition that often accompanies PI-induced dyslipidemia. The lipodystrophy syndrome causes a change in body fat distribution characterized by fat loss in the face, buttocks, and limbs and by central adiposity; insulin resistance is also present.[21] A HAART regimen that erodes self-image, despite its effectiveness in treating HIV infection, presents an inherent obstacle to adherence.21

METABOLIC SIDE EFFECTS AND TOXICITIES AND THEIR MANAGEMENT

As a correlation to the alterations in lipid metabolism seen with the use of all current PIs, it is not surprising that patients may be at an increased risk for the development of coronary artery disease.[22,23,24] Treatment with current PIs in treatment-naïve patients results in dyslipidemia that is prompt, marked, and sustained in a significant proportion of patients. A study by Melroe et al found that a statistically significant increase in total cholesterol occurred in 80% of ritonavir/saquinavir patients, in 51% of indinavir patients, and in 47% of nelfinavir patients.1 Overall, 56% of the patients assessed had elevated lipid levels. Danner et al reported that the most common laboratory abnormality observed with the use of ritonavir was elevated triglycerides.[25]

These types of lipid elevations—elevated triglycerides and LDL cholesterol and reduced HDL cholesterol—correspond to those that, along with hypertension, were identified by the Framingham Heart Study as major risk factors for the advancement of atherosclerotic cardiovascular disease.[26] A few studies have specifically linked the lipid abnormalities associated with the PI-induced lipodystrophy syndrome to an increased risk of cardiovascular disease.[27,28]

In PI-treated patients, lipids can be elevated to the point at which the National Cholesterol Education Program (NCEP) recommends considering treatment with lipid-lowering agents. Current recommendations by the Adult Treatment Panel III (ATP III) for lipid-lowering therapy are based on fasting LDL cholesterol levels alone. (Previous recommendations of ATP II had been based on fasting LDL cholesterol concentrations in addition to total cholesterol and fasting triglycerides.22,[29] The 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, or "statins," widely used for lowering cholesterol, may be considered for use in the HIV-infected population. One drawback to their use in the treatment of PI-associated hyperlipidemias, however, is that PIs inhibit the hepatic cytochrome P-450 (CYP450) 3A4 system, through which the majority of the statins are metabolized. This interaction can result in very high blood levels of the lipid-lowering drug, introducing a host of possible complications. Many of the statins also interact with medications used to treat AIDS-related complications. Of the statins approved by the Food and Drug Administration for the treatment of hyperlipidemia, pravastatin is the most favorable for treatment of PI-associated dyslipidemia, from the standpoint of drug interactions and safety, as it is not significantly metabolized by the CYP450 3A4 system.22 Cerivastatin has been withdrawn from the market due to the occurrence of rhabdomyolysis.

In addition to dyslipidemia, several other metabolic disturbances can limit successful adherence to HAART. New-onset diabetes has been reported with the use of PIs.[1,30] The diabetes may be preceded by loss of glycemic

control, as evidenced by elevated glucose and insulin levels. Kidney stones and bone density loss are other metabolic complications that can limit adherence to the HAART regimen.

OTHER REASONS FOR POOR ADHERENCE

Adherence can also be interrupted when patients run out of medication. Monetary issues can also be a factor, because some patients simply cannot afford the cost of their treatment.

MONITORING ADHERENCE

Several strategies exist for monitoring adherence, including pill counts, electronic monitors, and self-report questionnaires. The methods used for monitoring adherence have both strengths and weaknesses and can yield widely varying results.[31,32] A study measuring adherence in a single population of HIV-infected patients by different methods demonstrated an 89% adherence level by patient self-report, 73% adherence level by pill count, and 67% adherence level by electronic monitoring.32 Patients tend to overestimate adherence when self-reporting, whereas electronic monitoring may be inaccurate because patients can remove multiple doses at a single time or not take a dose when it is removed.31,[33] Many of the adherence monitoring methods are also limited in that they fail to detect nonadherence when it is related to not following required dietary restrictions or dosing intervals.31

OVERCOMING THE CHALLENGES TO ADHERENCE

Physician assistants can play an important role in reinforcing patients' knowledge about the challenges involved in initiating HAART and in ensuring that they have a good understanding of the long-term benefits of adhering closely to therapy.11 Since most patients will have difficulty following self-administered treatments, the approach that the physician assistant takes toward promoting adherence can be vital to overcoming behaviors that have a negative impact on treatment outcome. Physician assistants who foster effective doctor-patient communication and facilitate a team approach toward patient care can certainly help patients adhere to their regimens. The first and foremost course of action, however, is to understand the needs of the patient, explain their treatment options, and continually motivate them to remain adherent (Table 3).

Figure 3

Table 3. Strategies to Facilitate Improved Patient Adherence to HAART: The Physician Assistant's Office Visit

Action	Outcome
Explain complexity of HAART	• Selection of HAART regimen best suited to patient's specific lifestyle needs • Simplicity
Describe likely tolerability issues	• Patient knows what to expect • Selection of HAART with best likelihood of good long-term tolerability and fewest metabolic complications
Explain consequences of poor adherence	• Patient understands choices available to facilitate adherence • Selection of HAART with best likelihood of preserving treatment options in the event of HAART failure
Communicate regimen options available	• Patient can participate in the selection of HAART regimen that is most likely to succeed
Conduct patient lifestyle evaluation	• HAART regimen selected fits best into patient's lifestyle • Simplicity • Well-tolerated regimen with fewest metabolic toxicities

Recognition of regimen complexity as one of the most important challenges to regimen adherence has lead to a number of useful strategies to address the issue. The most difficult to follow HAART regimens are those that are composed of three or more drugs that must be taken multiple times per day, with each dose comprising numerous pills. Having the patient do a practice run of the regimen using candy or vitamins can help assess the patient's ability to stay on the regimen. The practice run should simulate the same strict instructions as the true regimen with regard to the timing and the nature of the meals that must be taken along with the “medication.” It is a good idea to ask patients to monitor their own success with the practice regimen and thus to assess their readiness to begin HAART.20

Other strategies to address regimen complexity involve regimen simplification. A number of antiretroviral agents are already approved for once-daily use (didanosine, efavirenz, tenofovir), while still other established agents are under investigation for once-daily dosing (lamivudine, stavudine, nevirapine). In order to simplify PI-containing HAART regimens and increase adherence, “boosting” other PIs by combining them with ritonavir has also gained increasing acceptance. Ritonavir is a strong inhibitor of the CYP450 3A4 enzyme system, and since PIs are metabolized by this system, ritonavir may increase levels of the co-administered PI, potentially reducing the overall pill burden and frequency of dosing.[34,35] However, boosting with ritonavir has been

associated with an increased risk of metabolic complications that may ultimately compromise adherence in the long run, so lipid levels, for example, should be monitored if this strategy is undertaken.

The challenges of high pill burden and frequent dosing are also being addressed in the development of new antiretroviral agents. Several new agents are being tested in clinical trials. One PI in development is PNU-140690 (tipranavir), which is dosed twice daily in combination with ritonavir (Table 1). Tipranavir appears to have antiretroviral activity in vitro against known PI multidrug-resistant isolates, possibly making it useful in patients who have already failed a PI-containing regimen.[36]

Another PI in development is atazanavir, a safe, well-tolerated PI that has a low pill burden (two capsules/day) and is dosed once daily (Table 1). Atazanavir is effective in rapidly and durably suppressing HIV RNA levels and durably increasing CD4 cell count.[37] In subjects failing a prior regimen, atazanavir co-administered with saquinavir was also safe and well tolerated, rapidly and durably suppressing HIV RNA levels and durably increasing CD4 cell counts. In addition, atazanavir has a favorable resistance profile in vitro.[38] It does not elevate total cholesterol, fasting LDL cholesterol, or fasting triglyceride concentrations in either treatment-naïve or treatment-experienced subjects.[39] This advantage suggests that atazanavir does not lead to dyslipidemia and may be associated with a reduction in the risk of cardiovascular events that is linked with dyslipidemia in this population.

With respect to transient side effects and potentially long-term metabolic effects, physician assistants who are discussing HAART regimens with their patients should be sure to inform them of all potential adverse conditions that they might encounter and potential management techniques, as this has been shown to help improve adherence.[40] Although some adverse effects are common to an entire class of antiretroviral drugs, each drug is nevertheless distinct. The physician assistant should review and monitor every drug regularly with the patient.

Every attempt should be made to individualize the drug regimen, basing the choice on a careful assessment of the patient's medical history and lifestyle. A regimen that fits well into a patient's routine has been shown to improve adherence.[41] Patients may find adherence easier by associating dosing schedules with meals or other routine activities rather than specific times of day.[42] Physician assistants should help patients make contingency plans to maintain adherence in the event that the routine changes.

All of the approaches that facilitate adherence—selecting a HAART regimen that fits into a patient's lifestyle, educating the patient with respect to the importance of adherence, and recognizing and managing side effects—are most easily accomplished using a team approach.20 The physician assistant can facilitate the development of a multidisciplinary team and its interactions. Gaining the patient's trust of the team members is critical. Various team members should regularly reinforce the importance of adherence and be available in a supportive and nonjudgmental manner so that the patient will be comfortable in reporting adherence problems should they arise.20

Ultimately, better tolerability and improved safety profiles, including a reduction in metabolic toxicities, will succeed in making adherence to antiretroviral regimens easier. Patient education about HAART in the context of an office visit with the physician assistant and other health care providers has become an important component in the design of the HAART regimen. This discussion can provide the patient with much-needed information on topics that have a bearing on adherence, including potential side effects and ways of dealing with them, strategies for monitoring compliance, and features of new drugs under development that may facilitate adherence with HAART.

CONCLUSIONS

Although current HAART regimens are complex, educational programs provided to patients at the time HAART is initiated can improve adherence. The physician assistant, as a compassionate, dedicated source of information and as a pivotal member of a multidisciplinary team, is well suited to serve in this capacity. Discussion with the patient should revolve around the challenges to adherence that current HAART regimens present—complexity, poor tolerability, and less-than-optimal safety profiles derived from metabolic toxicities—and the need for disciplined adherence to minimize the risk of treatment failure and the emergence of drug-resistant variants. New antiretroviral drugs are being developed that have simpler dosing intervals, lower pill burdens, and fewer metabolic complications such as dyslipidemia. Incorporation of these drugs into HAART regimens may alleviate some of the problems with adherence and improve responses to antiretroviral therapy.

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