

**Pharmacologic and Adherence Factors Complicating Antiretroviral Therapy
in HIV**

Lori D. Esch, Pharm.D., Mark J. Shelton, Pharm.D., Ross G. Hewitt, MD, Gene
D. Morse, Pharm.D.

*Departments of Pharmacy Practice and Medicine, State University of New York at
Buffalo, and Immunodeficiency Services, Erie County Medical Center, Buffalo, NY.*

ABSTRACT

The complexity and duration of potent antiretroviral therapy has stimulated a search for new models of care to optimally manage patients with human immunodeficiency virus (HIV) infection. While the goal of HIV therapy is quite straightforward, successful pharmacologic management has become increasingly complex. Drug-drug interactions, adverse drug reactions and an appreciation of the development of resistance and more importantly, an increased understanding of how cross-resistance may reduce subsequent therapeutic options makes the selection of initial agents imperative. Pharmacologic characteristics of the newer antiretroviral agents contributing to the complexity of antiretroviral regimens include high pill burden, drug formulation characteristics, drug-food interactions, and multiple-daily dosing requirements. Since adherence is affected by a combination of factors, all must be assessed and addressed to optimize disease outcomes and avoid the ultimate consequence of non-adherence, drug failure. A newly developed model of care was developed through the University at Buffalo, Departments of Pharmacy Practice and Medicine and Erie County Medical Center, Immunodeficiency Services, to improve the pharmacotherapy of patients with HIV. Background to the development of this program as well as a description of the program is described.

BACKGROUND AND INTRODUCTION

The complexity and duration of potent antiretroviral therapy has stimulated a search for new models of care to optimally manage patients with human immunodeficiency virus (HIV) infection (1). Individuals infected with HIV have many drug-related needs due to the chronic, dynamic nature of their disease and the complex pharmacologic nature of new therapeutic options. The goal of antiretroviral therapy is to achieve maximal viral suppression for as long as possible in order to allow the recovery of immune function (2). Regimens containing multiple medications, the number of which increases as the viral burden increases, are now the standard of care in attempts to achieve this goal (3, 4). Ensuring the durability of these regimens and avoiding development of drug-resistant variants with time requires strict adherence to medications (5, 6). It has been suggested that greater than 90% medication adherence is required for successful antiretroviral therapy (7). Unfortunately, citations throughout the literature estimate that only 33-60% of patients with HIV are completely adherent with their antiretroviral regimens making non-adherence a major barrier to long-term viral suppression (8).

COMPLEXITY AND COMPLICATIONS OF ANTIRETROVIRAL REGIMENS

Highly active antiretroviral therapy (HAART) has become standard of care for the treatment of HIV infection (3, 4). While the goal of HIV therapy is quite straightforward, successful pharmacologic management has become increasingly complex. Initially, agents must be selected carefully to ensure adequate potency of a combination regimen, taking into account genotypic resistance profiles, as not to jeopardize future antiretroviral combinations in the face of regimen failure. All potential regimens must also take into account tolerability, potential side effects and convenience. A patient's predicted or documented adherence also must be assessed and considered. Treatment regimens are complicated by drug-related factors, patient-specific factors as well as changing treatment approaches resulting from increased understanding of viral dynamics. In addition to approved antiretroviral therapies, regimens are complicated further by the availability of unmarketed, investigational drugs, complementary therapies and nutritional products. Aside from antiretroviral agents and those for prophylaxis against opportunistic infections, drugs to treat other non-infectious conditions are also required in patients with HIV.

Pharmacologic Factors.

Pharmacologic characteristics of the newer antiretroviral agents contributing to the complexity of antiretroviral regimens include high pill burden, drug formulation characteristics, drug-food interactions, and multiple-daily dosing requirements.

Pill Burden. Table 1 outlines the number of pills (tablets or capsules) or liquid required per drug using standard dosing of the currently available antiretroviral agents.

Table 1. The HIV Armamentarium: Currently Marketed and Expanded Access Agents.

Trade name	Generic name	Dose	# per day
Nucleoside reverse transcriptase inhibitors (NRTIs)			
Retrovir®	zidovudine, AZT	300 mg bid	2
Epivir®	lamivudine, 3TC	150 mg bid	2
Combivir®	AZT + 3TC	1 bid	2
Videx®	didanosine, ddI	200 mg bid or 300- 400 mg qd	4 or 2
Hivid®	zalcitabine, ddC	0.75 mg tid	3
Ziagen®	Abacavir	300 mg bid	2
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)			
Viramune®	nevirapine	200 mg bid	2
Rescriptor®	Delavirdine	400 mg tid	12
Sustiva®	Efavirenz	600 mg qd	3
Protease inhibitors (PIs)			
Invirase®	saquinavir (hard cap)	600 mg tid	9
Fortovase®	saquinavir (soft gel)	1200 mg tid	18
Crixivan®	Indinavir	800 mg tid	6
Norvir	ritonavir (capsules or liquid)	600 mg bid	12 (15 ml)
Viracept®	Nelfinavir	750 mg tid or 1250 mg bid	9 or 10
Agenerase®	Amprenavir	1200 mg bid	16
Expanded Access Drugs			
Preveon®	adefovir Nucleotide	60 mg/d	1

With current multiple-drug regimens, the standard of care being at least triple therapy, it is not unprecedented, or even unusual, for patients to be ingesting 20-30 pills per day. In addition, drugs for opportunistic treatment of prophylaxis and non-HIV conditions further contribute to pill burden. The size of the tablets or capsules can also be restrictive and very few of the agents are available as a tolerable liquid.

Food and Gastric Acid Requirements. Simply ingesting the prescribed number of medication doses each day often is not adequate for antiretroviral efficacy. Many of

the drugs require specific gastric acid requirements for optimal absorption or need to be taken with regard to meals. For example, both didanosine and indinavir must be administered on an empty stomach; however, they have opposing acid requirements for absorption (9, 10). The buffering agent in the didanosine formulation inhibits the absorption of the indinavir which requires an acidic environment. Thus, these two drugs which both require consumption on an empty stomach, cannot be taken within 1-2 hours of each other (11). Drugs such as saquinavir, ritonavir and nelfinavir should be administered with food (12-14). Delavirdine requires an acidic gastric environment for optimal absorption (15).

Multiple administration requirements. Most of the available antiretroviral agents need to be administered multiple times during the day based on their plasma half-life. In patients who have busy schedules, each additional dosing event, has the potential to negatively affect adherence (16). Although drugs that only need to be administered once daily are preferred, the pharmacokinetics of currently available agents require multiple administrations times each day. At this time, only efavirenz (17) is approved for once daily dosing, although other agents may be soon available with this labelling. Preliminary data with didanosine suggest that, due to the long intracellular half-life of its metabolite, this drug may soon receive once-daily labelling. (18-20).

Virologic and Therapeutic Factors.

Advances in the understanding of viral dynamics and resistance patterns have had great impact on approaches to antiretroviral prescribing. Complete viral suppression to below the lowest virologic threshold is desired, demanding not only the use of highly potent regimens but precise adherence from the outset. Consequences of incompletely suppressed viral replication include outgrowth of mutant HIV and viral rebound (21-23). Appreciation of the development of resistance and more importantly, an increased understanding of how cross-resistance may reduce subsequent therapeutic options makes the selection of initial agents even more imperative. Drugs acting at different sites of viral replication and with variable penetration into different biologic fluids encourages the use of several pharmacologic classes of antiretroviral agents in naïve patients; however, use of several classes of agents, many demonstrating cross-class resistance, decreases the options for future antiretroviral regimens (24) Managing patients who have experienced treatment failures and have been exposed to many antiretroviral agents

and combinations pose a particularly significant challenge. Lack of efficacy data in many clinical scenarios further complicates therapeutic decision-making.

Adverse Effects.

Short-term and long-term adverse reactions have been identified with virtually all of the available antiretroviral agents (1). Identification of a growing number of side effects and the realization that disease management is chronic (ie. life-long), necessitates evaluation of how aggressive pharmacologic therapy should be for each individual patient, taking into account risks for long term complications, quality of life, and patient desires or priorities. Adverse drug reactions can be early and transient or evident with more prolonged use, from months to years. Both can range from mild to potentially life-threatening. Many are manageable or even avoidable with careful dose adjustment, patient counseling and adjunctive therapies.

Protease inhibitors, although the most potent class of agents, may be associated with long term metabolic sequelae, including abnormal fat distribution, glucose intolerance, and hyperlipidemias (25-28). Although widely described, the long-term impact of these metabolic effects are unclear. Acutely, the major toxicities associated with protease inhibitors are primarily related to the gastrointestinal system, although hepatitis, hyperbilirubinemia, nephrolithiasis, dermatologic manifestations and paresthesias have been reported (10, 12-14, 29-30).

Non-nucleoside reverse transcriptase inhibitors (delavirdine, nevirapine, efavirenz) have been associated with dermatologic manifestations (15, 17, 31). Although the rashes are usually mild to moderate and often can be treated, without discontinuation of the medication, life-threatening and fatal rashes have been reported. Efavirenz, the newest drug in the class, has been associated with temporarily debilitating central nervous system effects. Patients describe feelings of euphoria/dysphoria, nightmares/vivid dreams, somnolence and dizziness. Most reports are transient, resolving in 1 to 3 weeks (17).

Nucleoside analogues are often associated with more systemic and constitutional side effects such as nausea, vomiting, headache and anemias although they also can be associated with painful and potentially irreversible peripheral neuropathies, particularly didanosine and stavudine (32, 33). Abacavir, the most recently marketed nucleoside analog, has also been associated with a potentially fatal skin rash which tends to manifest along with systemic effects such as nausea, fatigue and fever. Re-challenge of patients experiencing these effects with abacavir is contra-indicated (34).

Although the majority of adverse effects are transient and manageable, many patients discontinue them without communication with their provider, leading to potential complications of disease management with consequences to future treatment options.

Drug Interactions.

The introduction of potent new agents, particularly the protease and non-nucleoside reverse transcriptase inhibitors, exposes patients to a myriad of new potential drug-drug interactions (35). Many antiretrovirals require extensive hepatic metabolism by cytochrome p450 oxidase system but also may be capable of inducing or inhibiting these complex metabolic pathways. The probability of one or more drug interactions occurring increases as a patient's immune function weakens, likely due to the requirement for more agents for prophylaxis against opportunistic infections. The potential for drug interactions is high, up to 93%, when starting protease inhibitor therapy, especially in patients with low CD4 cell counts (35, 36).

Non-antiretroviral agents that patients are taking concurrently for other comorbidities or to treat adverse reactions from the antiretrovirals can also precipitate interactions (37). While highly active antiretroviral therapy (HAART) is capable of suppressing HIV replication on a long-term basis, interruptions, or decreased drug exposure may be related to the development of resistance. Since many of these agents have very a narrow therapeutic range, unappreciated interactions may lead to poor response and/or subsequent toxicity by virtue of changes in exposure. Due to multiple concurrent agents, two-, three- and even four-way drug interactions are possible, many of which have not been formally examined in pharmacokinetic studies. Since many of these interactions cannot be easily avoided by using substitute agents, careful management (monitoring outcomes, adjusting doses as needed) is essential. Discontinuation of a single agent within a complex regimen, either for reasons of tolerance or patient preference, can greatly alter the pharmacokinetics of the remaining agents, predisposing the patient to toxicity and/or sub-therapeutic drug levels that may lead to failure.

CHALLENGES OF ADHERENCE

Since adherence is affected by a combination of factors, all must be assessed and addressed to optimize disease outcomes and avoid the ultimate consequence of non-adherence, drug failure. Adherence decreases as the number of medications, doses and side effects increase and as competing priorities prevail in a patient's life (8). Further complicating the chronic management of HIV populations are the

vast array of social, psychological, and cultural issues which are present in an increasing number of patients. To optimize the pharmacotherapy of HIV, close attention to patient adherence and general family/caregiver education is required. These factors are often undisclosed to the physician and therefore are not addressed in the context of HIV care. Failure to recognize and address these issues may result in discordance between priorities of patients versus caregivers and subsequent inability to help improve adherence with appropriate measures (38, 39). When this complex drug therapy is placed into the context of patients who have little financial support and have cultural, social and behavioral barriers to accessing health care, the situation is prime for fragmented, ineffective health care. This may result in sub-optimal therapeutic response and increased costs.

ALTERNATIVE APPROACH TO ADHERENCE ENHANCEMENT

Contemporary care for patients with HIV must include assisting patients to identify daily living strategies that can best support long-term medication adherence. Early literature suggested that very short periods of non-adherence to antiretroviral therapy could lead to virologic failure and subsequent development of drug resistant mutant strains of HIV (5). Self-reported adherence has also been shown to correlate with viral load (40), with those patients reporting no missed doses on several consecutive interviews having a greater chance of demonstrating a viral load below quantifiable limits.

Program Goal

A newly developed model of care was developed through the University at Buffalo, Departments of Pharmacy Practice and Medicine and Erie County Medical Center, Immunodeficiency Services, to improve the pharmacotherapy of patients with HIV. In recognizing complex pharmacologic and adherence challenges, the goal of this program was to establish a practice that integrates an HIV Pharmaceutical Care Specialist (HIV-PCS) into the long-term management of patients with HIV infection being prescribed complex drug regimens.

Background to Program Development

Erie County Medical Center (ECMC), Western New York's leading trauma, burn, rehabilitation, and clinical research facility is a major teaching hospital for the State University of New York at Buffalo. Within the hospital, clinical services for persons with HIV infection and Acquired Immunodeficiency Syndrome (AIDS) are provided by Immunodeficiency Services, a department

which includes over forty professionals who deliver care to more than 800 clients. Three Infectious Diseases physicians, one Obstetrician/Gynecologist and three midlevel practitioners provide the primary medical care in the Clinic. There is also a specific Women's HIV Clinic offering primary care to HIV-infected women.

Immunodeficiency Services also offers comprehensive services including Chemical Dependency Services, Neuropsychiatric Services, AIDS Clinical Trials Group (ACTG) Clinical Drug Trials and Clinical Pharmacokinetics (Antiviral Clinical Pharmacology Unit). The State University of New York at Buffalo School of Pharmacy, in association with Immunodeficiency Services and the ACTG conducts research on factors affecting the absorption, metabolism and outcomes with antiviral drugs.

Assessment of Program Need

Prior to designing the program, a needs assessment was performed by a pharmacist who spent a nine month period time in clinic, reviewing patient medical records and current practice procedures to identify where pharmaceutical care services could best be utilized. During the nine month period, the pharmacist would prospectively review the charts of patients who were to be seen during each clinic session and target those who had particularly complex regimens, reported side effects, had potential drug-related problems or demonstrated a history of poor adherence. As standard of care, prior to the development of this program, patients were seen by at least a nurse and a medical provider at each visit. In addition, dietary and social worker services were provided to appropriate patients. Patients were seen by the pharmacist at one of various points during their visit, either prior to the physician exam, to take a drug history, or after the physician, if new medications were being prescribed and counseling was necessary. Table 2 describes the types of interfaces the pharmacist made with patients over a 7 month period. The pharmacist was also available to the physicians during the clinic sessions for assessment of current drug regimens or recommendations for alternative pharmacotherapy. Tables 3 and 4 summarize the most common reasons patients were referred to the HIV-PCS and the types of activities performed for patients.

During this pre-developmental phase, it was felt that due to complexities of individual patients and their regimens, more time was needed by the pharmacist than was allotted for a clinic visit, but that not every patient needed to see the pharmacist. This was the basis for the move to a referral system. Prospective

review of the charts were time consuming due to inconsistency and ambiguity of some of the chart documentation with respect to specific medication history; therefore a more uniform documentation system was required. Refer to table 5 for summary of findings during pre-developmental assessment phase.

Table 5. Summary of Findings During Pre-Developmental Assessment Phase

Observations During Pre-developmental Stages	Recommended Action
<ul style="list-style-type: none"> • Counseling was time consuming and not conducive to the regular clinic flow. • Records of drug history & antiretroviral exposures were not consistently kept. • Poor chart documentation exists. • Not everybody required attention by the Pharmacist. • Need for increased patient dialogue & education prior to beginning new therapy. • Assessment of adherence was lacking in patients failing antiretroviral therapies; therefore subsequent therapies were also failing. • Enormous need for drug information resource specialist among health care professionals. • More timely attention of increasing HIV-RNA results required. • Physician often lacked patient-specific information needed to individualize 	<ul style="list-style-type: none"> • See patient at separate appointment or arrange designated meeting area. Develop an Adherence Clinic or designated counseling area. • Maintain a computerized database with up-to-date, easily accessible medication records. • Design standardized chart progress note. • Schedule only patients requiring Pharmacist attention. Refer or flag patients who may require additional follow-up. • Standardize pre-therapy counseling sessions for all patients prior to beginning. Address adherence barriers before changing therapy. • Standardize adherence assessment question at each clinic visit. • Allocate a Pharmacist to address complex drug information requests and prospectively address challenging issues (ie. interactions, adverse reactions). • Designate a Pharmacist to review incoming HIV-RNA results. • Institute a weekly multidisciplinary conference to address potentially

antiretroviral therapy to improve success.	challenging issues or patients.
--	---------------------------------

Model of Care

As previously described, the goal of this program was to establish a practice that integrates an HIV Pharmaceutical Care Specialist (HIV-PCS) into the complex therapeutic management of patients with HIV infection. The HIV-PCS would be integrated into the multidisciplinary team providing medical, nursing, social, neuropsychologic and nutritional services to patients. The capacities in which the HIV-PCS is intended to function is outlined in Table 6.

Table 6. Functioning Capacities of the HIV-PCS within an Ambulatory Care HIV Clinic

- | |
|---|
| <ul style="list-style-type: none"> • Assessing, monitoring and optimizing patient adherence • Providing consultation regarding the optimal selection and dosing of antiretroviral agents • Monitoring the overall drug therapy (short-term and long-term) • Minimizing drug interactions • Providing patient and family education regarding medications • Being a liason with other caregivers (homecare, casemanagers, outreach, etc) regarding patient pharmacotherapy issues |
|---|

Program Development

Tools for Implementation

Integrated Database (Buffalo Antiretroviral Cohort, BARC)

It was observed during the pre-developmental stage that it was time consuming to extract precise medication histories from the medical record at each review. Because various providers were involved in care, there was significant heterogeneity in chart documentation. To facilitate pharmaceutical care interventions, an interactive, computerized database, developed at the University at Buffalo in the Department of Pharmacy Practice, was utilized to enhance efficiency and accuracy. It was first necessary to review the charts of all clinic patients to collect basic demographic information and drug history to input into the new

database. This took approximately 120 hours and has been maintained on an on-going basis, with quality assurance and continual update occurring with each subsequent chart review. The database contains a record of all patients in the outpatient clinic with detailed histories of current medications and start dates, previous medications and any intolerances experienced, calculated duration of antiretroviral exposures, patient self-reported adherence, surrogate marker responses in response to therapies and/or other interventions and survival data. A computerized printout displays all of these data in tabular and graphical form.

Duplicate Progress Notes

To facilitate the development and up-keep of this dynamic database, a duplicate progress note with a structured format was designed and its use was implemented in the clinic (See Appendix 1). At each patient visit, the progress note is completed by the providers seeing the patient with one copy remaining in the chart while the other is forwarded to the HIV-PCS. The HIV-PCS reviews the copy to identify new therapies being initiated, potential drug interactions or other potential drug-related problems. This review also enables identification of any patients who may benefit from additional counseling if they have not already been referred to the HIV-PCS. Pertinent patients are flagged for follow-up at this time.

After review by the HIV-PCS, the progress note is forwarded to the data entry manager to enter pertinent data into the database. At this step, changes in drug therapy are entered into the database along with any inter-current illnesses, drug intolerances, patient weight, self-reported adherence and updated surrogate markers (HIV-RNA and CD4 count). Approximately 8 hours a week of technical time are required to maintain the database.

Services for Implementation

Viral load monitoring

With improved technology enabling viral quantification, HIV RNA (viral load) monitoring has become an invaluable clinical tool used to prognose as well as monitor disease progression and therapeutic efficacy. During the pre-developmental assessment, it was noted that there appeared to be significant delay in the time of viral load result reporting from the laboratory and the next clinic visit at which time the results were addressed (approximately 1-2 months). If adherence was poor, the several months may have been crucial to antiretroviral efficacy and not addressing potential problems could lead to resistance. Since viral escape is often a sign of

non-adherence or sub-optimal drug exposure preceding development of resistance, the goal was to be able to act on changes in viral load in a more timely manner. In the new model, the HIV-PCS became the center point for receiving all HIV-RNA results. This allowed for prompt data entry into the computer and timely review of results in context of drug exposure. Once received, the data manager enters the new viral load results into the database and records directly on the printed report the date and result of the previous viral load for comparison. The HIV-PCS then reviews these and determines, based on response, who requires additional attention.

It was often necessary to differentiate between short-term non-adherence resulting in viral load fluctuations versus true virologic failure. Those who have failed to achieve a desired response or have demonstrated at least a 1 log₁₀ increase in viral load are either contacted by a nurse to enquire about missed doses, interactions, drug discontinuation and asked to schedule an Adherence Clinic appointment for a full review of antiretroviral therapy, other medications and adherence. Patients with newly undetectable viral loads are contacted by either the HIV-PCS or a nurse for positive feedback and continued encouragement on their medications. Complex patients are referred to the weekly Virology Conference for multidisciplinary consideration.

Virology Conference

The link between drug efficacy (how well it performs in clinical studies) and drug effectiveness (how well it works in the general population) can be related to adherence. Since adherence is made up of a combination of factors it was felt that the best approach to assessing and optimizing patient outcomes was through an interdisciplinary approach. Since no one person is able to successfully address all of the components of adherence with expertise (patient-specific factors, patient-provider relationship and the treatment regimen itself), a weekly multidisciplinary setting was created to share information about the patient between health care workers and discuss a suitable plan/approach to the patient. Since this is a time consuming process, certain patients are flagged by the HIV-PCS as appropriate candidates for this evaluation and are presented by the HIV-PCS at a weekly Virology Conference. Example of patients who may be considered candidates for discussion include those who present unique potential barriers to adherence and may benefit from specially designed outreach services, patients with previously suppressed HIV-RNA values with rebounds that cannot be easily accounted for, or patients failing current therapy and require consideration for complex “salvage”

regimens. Decisions and plans of action are made at this meeting and implemented by the appropriate individuals.

Adherence Clinic and Enhancement Interventions

To provide an innovative model for integrating patient adherence assessment with pharmacokinetic and pharmacodynamic outcome analysis the Medication Adherence Clinic (MAC) at Erie County Medical Center was established. Several programs have initiated pharmaceutical care services with the attempts to optimize therapy and ensure continuity of care. Most reported programs, however, are limited in scope and fail to address the important issues of documented outcomes and mechanisms for integrating the pharmacist into the overall health care team efforts to contribute to continuity of care. The HIV-PCS in this model is committed to documenting outcomes on several levels. During initial visits to the MAC, a baseline adherence survey is obtained to document patient attitudes, beliefs and fears around beginning new antiretroviral therapy. At this time and throughout therapy, HIV surrogate markers (viral load and CD4 count) are measured and attempts are made to correlate with progression of adherence. Other surrogate markers and clinical outcomes such as development of AIDS-related illnesses, progressive weight loss, hospitalization and incident of adverse drug reactions are also documented. Drug concentrations of antiretrovirals, including protease inhibitors, are also quantified with attempts to correlate with changes in adherence, development of resistance, and for comparisons with population pharmacokinetic observations.

Referrals to the HIV-PCS Medication Adherence Clinic (MAC) for Virologic Failure

Patients from Ambulatory Care clinics and Tertiary Care facilities in the Buffalo area are referred to the Pharmacist-operated Medication Adherence Clinic (MAC) for adherence assessment and enhancement on current medications for recommendations of new treatment strategies and for counseling prior to initiating new antiretroviral regimens. Patients are referred to the MAC for evaluation of the potential pharmacologic factors leading to treatment failure as judged by loss of HIV RNA suppression.

The patient's history is reviewed prior to their scheduled appointment using a BARC database print-out and the medical record clinic chart. During the appointment, a detailed medication history is performed, focusing on the patient's current prescribed and over-the-counter medications, complimentary therapies, adverse drug reactions, adherence and symptomatology. In selected patients,

pharmacokinetic sampling is performed in the MAC to assess protease inhibitor concentrations. The HIV-PCS evaluates the patient and assesses them for appropriate interventions such as remedial education, therapeutic drug monitoring, adherence enhancement (altered administration schedule, pill box, programmable beeper). If necessary, the HIV-PCS will discuss options for a new regimen that will be acceptable to the patient, and preparation to set them up to be successful with the new medications. Following a comprehensive assessment of the patient, written recommendations are made in the chart and discussed with the referring provider. All changes that are implemented are followed up by the HIV-PCS.

Pre-therapy Counseling/Naïve Patient Protocol

Prior to initiating therapy, patients are also referred to the MAC for pre-therapy counseling to discuss the rationale for medications and the importance of commitment to therapy. The goal of our one-on-one interactions is to assist patients to identify daily living strategies that can best support long-term medication adherence. By acknowledging up front that adherence will be a challenge, provisions can be made in a collaborative effort to set patients up for success by anticipating their unique barriers. Services provided to the patients include the following:

- Discussion of treatment goals with the patient and family (or other supportive caregiver).
- Provision of clear counseling and detailed instruction on the regimen, providing explicit detail on food/fluid restrictions.
- Anticipation of adherence barriers and provision of tips for remembering to take medication by tailoring the regimen to the patient's individual lifestyle.
- Anticipation and disclosure to the patient of all potential adverse drug reactions, providing instruction on management/avoidance of side effects.

These services are provided to patients through a series of sequential baseline visits structured to address the following topics.

HIV Education. At the first appointment in the Adherence Clinic, usually 20 to 40 minutes in duration, basic HIV disease education is provided, addressing disease progression, surrogate markers, the goals of antiretroviral therapy, and the consequences on non-adherence. At this appointment an assessment of patient understanding and level of commitment is made.

Medication. At this appointment, the role of medications in HIV is discussed and the need for commitment to therapy and strict adherence is re-enforced. Specific antiretroviral options are discussed and, based on individual considerations, an appropriate regimen is selected. At this time, or, if necessary, after further deliberations with the physician, the patient is given prescriptions for the medications in the new regimen and are instructed to have them filled and return to the Adherence Clinic, with their medications, for a final appointment before actually starting the medications. This appointment takes approximately 30 minutes.

Regimen Individualization. This is the final visit with the patient (with family or supportive friends/significant others) before they begin their medications. The primary goal is to design an individualized administration schedule for the patient, incorporating medication dosing events with activities of daily living. Patients bring their medication into the appointment to visualize during counseling and a written, personalized schedule is constructed. Patients are also given any appropriate devices such as pill organizers, carrying cases, oral syringes, pre-programmed reminder beepers, calendars, etc. to enhance adherence. The duration of this appointment is approximately 20-30 minutes, depending on the patient's specific needs.

Patient progress is followed up by telephone within the first week. Patients beginning therapy for the first time are requested to return to the MAC for a follow-up visit at 2 weeks to assess concerns, medication tolerance, scheduling and adherence. Adherence is assessed by a combination of interview, self-report, pill count, and plasma concentration monitoring.

Consults: Pharmacologic and Pharmacokinetic Assessment/Monitoring

Patients are referred by health care providers to the HIV-PCS to review complex pharmacologic interactions, reactions, toxicities, and disease state management for both HIV- and non HIV-related issues. Therapeutic drug monitoring is also performed on applicable drugs.

Conclusion

The progression in antiretroviral therapy to complex regimens containing 3- or 4-drug regimens has made pharmacologic assessment of the patient an important aspect of chronic HIV management. The HIV-PCS is highly qualified to evaluate patients with complex drug regimens who are facing barriers to successful care, target the appropriate intervention(s), and follow-up with the

patients on a long-term basis. In our clinic, the HIV-PCS has been a rapidly accepted program that has integrated a health care provider with the database needed for managing the complex array of pharmacologic issues that face the clinician and patient during chronic antiviral therapy.

References

1. Kaul DR, Cinti SK, Carver PL and Kazanjian PH. HIV protease inhibitors: advances in therapy and adverse reactions, including metabolic complications. *Pharmacother* 1999;19(3):281-98.
2. Mellors JW, Rinaldo CR, Gupta P, White RM, Todd JA, Kingsley LA. Prognosis in HIV-1 infection predicted by the quantity of virus in plasma. *Science* 1996;272:1167-70.
3. Carpenter C, Fischl MA, Hammer SM, Hirsch MS, Jacobson DM, Katzenstein DA, Montaner JS, Richman DD, Saag MS, Schooley RT, Thompson MA, Vella S, Yeni PG, Volberding PA. Antiretroviral therapy for HIV infection in 1998: Updated recommendations of the international AIDS society – USA panel. *JAMA* 1998; (July 1)280(1): 78-86.
4. Department of Health and Human Services. Panel of Clinical Practices for Treatment of HIV Infection: Guidelines for the use of antiretroviral agents in HIV-1 infected adults and adolescents. 31 March 1998 document.
5. Vanhove GR, Schapiro JM, Winter MA et al. Patient compliance and drug failure in protease inhibitor monotherapy. *JAMA*. 1996;276:1955-6.
6. Blaschke TF. Noncompliance and resistance to protease inhibitors. Presented at 4th National Conference on Retroviruses and Opportunistic Infections. Washington, DC; Jan 25, 1997.
7. Bangsberg D, Robertson M, Charlebois E, Tulsy J, Hecht R, Bamberger J, Moss A. Protease inhibitors in the HIV+ homeless and marginally housed: good adherence but rarely prescribed [abstr]. Presented at the 12th World AIDS Conference, Geneva, Switzerland June 28-July 3, 1998.
8. Tseng AL. Compliance issues in the Treatment of HIV Infection. *Am J Health-Syst Pharm* 1998;55:1817-24.
9. Bristol-Myers Squibb. Videx (didanosine) package insert. Princeton, NJ; 1998.
10. Merck and Co. Crixivan (indinavir) drug information. West Point, PA; 1997.
11. Mummeneni V, Kaul S, Krupp CA. Single dose pharmacokinetic interaction study of didanosine and indinavir sulfate in healthy subjects [abstr]. Presented at the American Society of Clinical Pharmacology & Therapeutics 1997.
12. Abbott Laboratories. Norvir (ritonavir) drug information. North Chicago, IL; 1998.
13. Agouron Pharmaceuticals. Viracept (nelfinavir) prescribing information. LaJolla, CA; 1999.
14. Roche Pharmaceuticals. Fortovase (saquinavir soft gel caps) package insert. Nutley, NJ; 1997.
15. Pharmacia and Upjohn. Rescriptor (delavirdine mesylate) product information. Kalamazoo, MI; 1997.

16. Eisen S, Miller D, Woodward R, et al. The effect of prescribed daily dose frequency on patient medication compliance. *Ann Intern Med* 1990;150:1881-4.
17. DuPont Pharmaceuticals. Sustiva (efavirenz) general information. Wilmington, DE; 1998.
18. Petrak RM, Boyer N, Hines D et al. A study to evaluate the clinical and virologic efficacy of a Crixivan, ddI, and d4T combination. Paper presented at 35th Annual Meeting of the Infectious Diseases Society of America. San Francisco, CA; 1997 Sep 13-16.
19. Keiser P, Turner D, Ramilo O et al. An open label, pilot study of the efficacy and tolerability of once daily ddI versus twice daily ddI. Presented at 35th Annual Meeting of the Infectious Diseases Society of America. San Francisco, CA; 1997 Sep 13-16.
20. Reynes J. Once daily administration of didanosine in combination with stavudine in antiretroviral-naïve patients. Presented at European Zert Symposium. Cannes, France; Mar 22, 1997.
21. Molla A, Korneyeva M, Gao Q, et al. Ordered accumulation of mutations in HIV protease confers resistance to ritonavir. *Nature Med* 1996;2:760-6.
22. Condra JH, Schleif WA, Blahy OM, et al. In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature* 1995;374:569-71.
23. Kempf DJ, Rode RA, Xu Y, Sun E, Heath-Chiozzi ME, Valdes J, Japour AJ, Danner S, Boucher C, Molla A, Leonard JM. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS* 1998;12:F9-F14.
24. Condra JH and Emini EA. Preventing HIV-1 drug resistance. *Science and Medicine* 1997;4(1);2-11.
25. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary artery disease with protease inhibitors. *Lancet* 1998;351:1328.
26. Viraben R, Aquilino C. Indinavir-associated lipodystrophy. *AIDS* 1998;12:F37-9.
27. Kaufman MB and Simionatto C. A review of protease inhibitor-induced hyperglycemia. *Pharmacother* 1999;19(1):114-7.
28. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998;12:F51-8.
29. Adkins JC and Faulds D. Amprenavir. *Drugs* 1998;55(6):837-42.
30. Kopp JB, Miller KD, Mican AM, et al. Crystalluria and urinary tract abnormalities associated with indinavir. *Ann Intern Med* 1997;127:119-25.
31. Roxane Laboratories. Viramune (nevirapine) general information. Columbus, OH; 1998
32. Simpson DM, Citak KA, Godfrey E, Godbold J, Wolfe DE. Myopathies associated with HIV and zidovudine: can their effects be distinguished? *Neurology* 1993;43:971-6.
33. Markarian Y, Wulff EA, Simpson DM. Peripheral neuropathy in HIV disease. *AIDS Clinical Care* 1998;10:89-91;93.
34. Glaxo Wellcome. Ziagen (abacavir) general information. Research Triangle Park, NC; 1999.
35. Van Cleef GF, Fisher EJ and Polk RE. Drug interaction potential with inhibitors of HIV protease. *Pharmacother* 1997;17(4):774-8.

36. Preston SL et al. Drug interactions in HIV positive patients initiated on protease inhibitors. [abstr]. Presented at the 5th Conference on Retroviruses and Opportunistic Infections, Chicago, 1997.
37. Michaellets EL. Update: Clinically significant cytochrome P450 drug interactions. *Pharmacother* 1998;18(1):84-112.
38. Gallant JE and Block DS. Adherence to antiretroviral regimens in HIV-infected patients: results of a survey among physicians and patients. *J Internation Assoc Physicians AIDS Care*. May 1998;4(5):32-5.
39. Chesney MA. New antiretroviral therapies: adherence challenges and strategies. Paper presented at Symposium on Evolving HIV Treatments: Advances and the Challenge of Adherence. Toronto, Canada; Sep 27, 1997.
40. Shelton MJ, Esch LD, Hewitt RG et al. Correlation between self-reported adherence and virologic outcome [abstr]. Presented at the 38th Interscience Conference on Antimicrobial Agents & Chemotherapy. 1998.

Table 2. Types of interfaces made by the HIV-PCS during the pre-implementation phase (n=438)

<i>Type of interactions</i>	<i>Total (%)</i>
During patient's medical clinic appointment with physician	201 (46%)
By telephone	110 (25%)
During a specific HIV-PCS scheduled appointment	58 (13%)
Chart review	69 (16%)

Table 3. Primary reason a patient was referred to the HIV-PCS (n=438)

<i>Reason for Referral to HIV-PCS</i>	<i>Percent of all Cases</i>
Recommendations based on HIV-RNA results	24
Non-adherence (provider perceived or patient documented)	17
Prior to initiation of new antiretrovirals	16
Adverse drug reactions	12
Follow-up after medication changes	11
To assess or manage real or potential drug interactions	5
Assessment of genotype results	4

Table 4. Breakdown of types of activities performed by the HIV-PCS during all 438 patient encounters (several may apply to each encounter).

<i>Pharmacist (HIV-PCS) Activity</i>	<i>Total # of Events</i>
General medication counseling	287
Recommend follow-up HIV-PCS appointment	107
Recommend new antiretroviral regimen	90
Medication administration schedule designed	87
Alter dose of one or more medications	74
Add a new medication	50
Recommend HIV-RNA test	40
Provide medication organizer, pill box or pill carrier	40
Treat side effect(s)	30
Provided specific pre-antiretroviral counseling	26
Recommend therapeutic drug monitoring of an antiretroviral agent	23
Recommend viral genotyping	5

