ADHERENCE TO HIV TREATMENT REGIMENS: RECOMMENDATIONS FOR BEST PRACTICES

Introductory comments:

There have been a growing number of abstracts, articles, monographs and presentations on the subject of treatment adherence specifically related to the use of antiretroviral therapy in the management of HIV disease (medication adherence). The term ‘treatment adherence’ refers to the ability of the patient to develop and follow a plan of behavioral and attitudinal change that ultimately serves to empower him/her to improve health and self-manage a given illness. The term ‘medication adherence’ in HIV/AIDS care specifically refers to the ability of the person living with HIV/AIDS to be involved in choosing, starting, managing and maintaining a given therapeutic combination medication regimen to control viral (HIV) replication and improve immune function. The preferential term ‘adherence’ rather than ‘compliance’ has long-standing support given the historical roots of the semantic issues. In a recent significant commentary by Noring et al., it has indeed been proposed that the time for a ‘new’ paradigm for HIV care has come that includes consideration for changing the relevant terminology to “treatment maintenance.” According to the authors, this is more characteristic of the collaborative relationship between a patient as proactive participant and a provider as professional guide. The contributing panelists for the present document do recognize there are currently several excellent resources that aim to provide current and comprehensive information on treatment adherence and patient education.

It is not only complex to attempt to define medication adherence, identify the most reliable related measurement tools and promote only the most rigorously tested interventions but may not even be possible due to lack of essential data. Accordingly it was considered appropriate to support the most practical approaches that could constitute standard of care or ‘best practices’ based on relevant available conference abstracts, clinical experience and consensus opinion of experts. The rationale for this approach has to do with the limitations of the studies on adherence to medication regimens rather than validating sub-optimal strategies, circumspect opinion or incomplete data. The purpose of this document should also be differentiated from that of standard guidelines in clinical practice such as those published by Agency for Healthcare Research and Quality (AHRQ). It is hoped that several initiatives to date provide further context to not only define further research needs in the broad area of treatment adherence but outline ethically sound principles of care that are relevant to practices for HIV treatment access, support services and public health focus.

This document serves to reinforce and expand the importance of the systems’ approaches originally advocated by the seminal Midwest AIDS Training and Education Partners’ (MATEP) initiative in 1998, which in part served as the background for the present APHA / HRSA initiative. The MATEP 100 expert-member group exhaustively reviewed the adherence literature to date, outlined principles of adherence, emphasized the need for targeted patient education material, and addressed the concepts of...
treatment readiness. Perhaps even a more significant contribution was their advocacy for systemic ‘changes’ in the ways that clinicians, behavioral scientists, counselors, policy makers and others approach the subject and practice of treatment adherence. They provided useful tools that many individuals involved with HIV/AIDS care have used to improve service delivery and medication adherence. The present document extends the kind of approach MATEP took by summarizing much of the pertinent literature since 1998-9 and offering a web-based resource to enhance the practical implementation of the recommendations.

Equally important for the panel was to introduce key concepts derived from other chronic disease models and bring attention to theories and noteworthy paradigm shifts related to adherence to treatment care plans & medication regimens. Perhaps the most important aspect of adherence to treatment plans including medication regimens concerns the chronic nature of HIV illness itself. It is in such a context that the extant models of care germane to acute infectious disease processes need critical examination for relevance to HIV patient care and disease management. Assuredly it appears that exemplary models of chronic illness have far more significance for the treatment non-adherence, its prevention and management and accompanying systems’ responses to the challenges posed by complex lifelong therapies and non-adherence related drug resistance.

There are several planned features that will be added to not only this document but to the APHA website hosting the document and its updated versions. The critical relationships between HIV epidemiology, viral resistance patterns national and international trends in the pandemic pharmacogenetics, immunogenetics and other newer therapeutic and preventive developments need further elucidation. Though at present, the emphasis of the commentary and information concerns adults and adolescents, it is planned that treatment adherence information specific to children will be an upcoming feature. This living document will attempt to identify these aspects as they are presented in the literature (published peer-reviewed and abstracted formats) and offer ongoing explication of the role of treatment adherence in the light of these complex biological and psycho-social phenomena. This type of an integrated approach will assume greater and greater importance as issues related to ethical research practices, access to drug regimens in resource-limited regions of the world and inadequate public health infrastructures need to be addressed in the global HIV/AIDS pandemic.

Asim A. Jani, MD MPH FACP
Primary Contributing Editor / Panelist
Best Practices document
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I. Overview of Adherence to HIV Treatment Regimens

The year 2001 marked the 20th year from the original MMWR report dated June 5, 1981 on the first 5 documented cases of a mysterious fatal illness involving an opportunistic infection – pneumocystis carinii pneumonia - infecting healthy gay men. Several authors have summarized many of the salient time-points and seminal events in the history of this pandemic in recent articles. The nature of infection with HIV/AIDS has been changed since the widespread availability of potent triple combination therapy. It is well established that along with improved diagnostic measures such as HIV viral load testing, the advent of Highly Active Antiretroviral Therapy (HAART) – combination regimens of different antiretroviral medications has been critical to the ongoing success of controlling the viral replication in a given individual patient. (HAART and its specific relationship to virologic suppression, adherence and drug resistance are discussed in the next section.) HAART is related to significant reductions in morbidity and mortality; however, these complicated therapies require high levels of adherence by the patient.

Adherence is often treated as the goal of medical intervention when in fact, it is a means to an end. For health care providers, the “end” is suppression of the virus, the prevention of viral resistance and the maintenance of the health of the patient. These goals may or may not coincide with those of the patient. The issue that must be addressed with patients is why adherence to HAART is crucial for achieving their goals. Unless the patient can find a reason for adherence that is meaningful to him or herself, the incentive to adhere to the rigorous dosing schedule may be lacking.

Adherence is a concept with social and emotional components. If adherence is to be attained in the setting of HIV treatment, close attention must be given to the daunting regimen to which the patient is subjected. For the patient, the “how to” of adherence is the means to achieving relevant personal goals. Unless the health care provider works with the patient to identify these goals and to understand adherence as the means to achieving them, adherence to the therapeutic regimen may be inadequate. “Therapeutic alliance” is the term used to describe a health care provider-patient relationship in which the therapeutic goals and the means to reach these goals are mutually affirmed and thus, most likely to be achieved.

There is currently no agreed-upon standard clinical definition of adherence or adherence. Stedman's Medical Dictionary defines “adherence” as “the extent to which the patient continues the agreed-upon mode of treatment under limited supervision.” Adherence to health care advice and instruction usually relates to following medical advice, either medication regimens or behavioral change regimens. Ickovics (1997) defined medication adherence as the percentage of prescribed doses taken. Adherence may be measured in the clinical setting by a variety of strategies such as self-reports of pills missed, counts of pills remaining, or recordings from devices of dates and times of bottle openings.
Adherence to medication for various diseases has been the focus of many researchers and scientists since the 1970’s. Prior to studies on adherence to HAART, authors have written that if the level of pill taking reached 80%, one could label the patient as “adherent.” However, recent evidence suggests that an 80% level with HAART adherence may be inadequate to prevent the development of antiretroviral drug resistance. This is significant in light of preliminary studies that suggest most individuals on HAART therapy are not 100% compliant. In fact, data from pilot studies suggest that in the previous two to three days, as many as 30% of patients report missing at least one dose. Studies among hypertensive patients report that these patients may be compliant with their medications at the 50% level and that adherence or adherence to medications for other diseases, as well as HIV, generally ranges from 20-80%.

Studies examining the rate of adherence to HIV medications clearly document less than 100% adherence. Muma, Ross, Parcel, and Pollard (1995) reported adherence rates of 42%, with Chow, Chin, Fong, and Bendayan (1993) documenting rates of 50%. Samet, Libman, Steger, et al. (1992) reported that 67% of their patients were compliant at the 80% level and Eldred, Wu, Chaisson, and Moore (1995) found that 46% of their sample (n=125) missed one or more doses of zidovudine (200 mg/3 times/day).

It is important to also note that patients may take the total number of prescribed doses, but may not take these at the appropriate times. Melbourne et al., (1999) noted that within a subgroup of patients who took more than 90% of doses, there was significant dosing fluctuation in 50% of patients during the first two months of treatment. The dosing fluctuation ranged from taking the medication within two hours of the prescribed dose time to greater than two hours of that defined time.

Recent industry supported surveys of knowledge, attitude and behavior regarding treatment adherence have given greater insight into patient and provider perceptions of many variables influencing the practice of medicine taking. Such population data regarding health beliefs, self-efficacy, and barrier identification are not only useful for to better understand the epidemiology HAART usage and adherence but also to provide a context for further discussion about individual patient and provider interaction. The importance of assessing HIV educational needs has been recognized since the early 90’s and tools have been developed accordingly by researchers involved in clinical care of HIV infected patients.

The consequences of missed doses or non-adherence to HAART appear to be severe, with evidence of an increasing viral load after missing only two days and the development of mutant viral strains. As drug levels fall below a critical point, the regimen’s inhibitory effect on viral replication may lessen, allowing for increases in viral load. In current clinical practice therapeutic drug monitoring though useful has a limited role. Fortunately, HIV genotyping and phenotyping are becoming more readily available and can be used to guide the selection of antiretroviral regimens. Clinicians currently recommend that adherence be as close to 100% as possible while recognizing that this recommendation poses a significant challenge to patients.

It is also pivotal to the clinical research setting that medication adherence is an integral part of clinical trials that involve the study of medications relevant to HIV disease. Ensuring scientific integrity in trials while accelerated drug development and release are supported implies that medication adherence is
strongly addressed in several aspects of clinical research – including study design, methods and analyses.62

It has been recognized that in the context of chronic HIV illness, the most important ‘time’ to address adherence to treatment and medication regimens is before starting therapy. This ‘preventive’ mode serves to identify stage of treatment readiness and provide targeted culturally relevant and lifestyle tailored options for therapeutic interventions. In so doing, potential and/or actual barriers to adherence are identified and more likely to be proactively addressed; even subsequent non-adherent patterns may well be identified earlier and therapeutic alliance issues between patient and provider more effectively approached. The International AIDS Society (IAS) conference, the 1st IAS Conference on HIV Pathogenesis and Treatment occurring in Buenos Aires in July 2001 had many relevant abstracts related to treatment readiness, factors influencing adherence and specific interventions. Hewitt 176 through psychometric testing, demonstrated that self-esteem, negative emotions and health beliefs all had impact on adherence. The Spanish GEEMA study 177 emphasized the significance of depression as an important co-morbidity that negatively influences adherence. Lal from the U. of Texas Health Ctr 178 had a questionnaire concerning potential factors influencing adherence such as lifestyle, medications and co-morbid conditions. This was seen to facilitate tailoring of regimens. The relationship between adherence and specific populations such as adolescent populations was studied by Trocme 179 who identified certain barriers such as ‘medication-dependency self-perception’, bad taste and untenable hours. Structured assessments were observed to have a beneficial role in prevention and management of non-adherence. 180, 181 Goujard 182 and Guaragna 183 both had educational interventions showing some efficacy in improving knowledge, self-management and viral control.

With increasing patient & provider advocacy, political & economic responsiveness and cultural & humanitarian consciousness, the integration of active antiretroviral therapy into resource-limited countries presents many challenges, not the least of which is medication adherence in such settings. The Buenos Aires conference also had several abstracts related to the concerns of the developing world in relation to medication adherence. Orrell 184 had fairly high levels of adherence (94% and 88% at 12 & 48 weeks, respectively) among the cohort of Capetown patients who spoke English, Xhosa, and Afrikaans; language barriers were likely not the only factor contributing to differential proportions of adherence. Sanne 185 showed the care benefits and adherence proportions through the use of multidisciplinary clinical research teams. Many challenges such as discrimination concerns, HIV diagnosis disclosure issues and medication storage problems were outlined in the 60 patient cohort by Ensama. 186 Drug access and necessary laboratory support were the focus of the Kenya-based survey by Kimani. 187
II. Highly Active Antiretroviral Therapy

In 1996, for the first time since the HIV epidemic surfaced in the United States, the death rate from AIDS began to decline, coinciding with the introduction of highly active antiretroviral therapy (HAART). While the number of newly diagnosed cases of HIV infection remains stable, the prevalence of HIV continues to rise. Females and communities of color, such as African Americans, Hispanics and Latin Americans, are disproportionately represented in newly reported cases of HIV and AIDS.13

Since 1996, new classes of antiretroviral drugs have become available, and today, combination therapy with multiple-class drugs is the standard of care. Management of HIV disease with combination therapy requires that patients be monitored on three different levels to assess the response: 1) virologic response is characterized by significant reductions (> 1 log unit) in HIV RNA (copies/ml) in plasma. Clinical research has shown that survival is significantly enhanced among patients who achieve an optimal virologic response to treatment as defined by an undetectable viral mRNA level (<50 copies/ml of plasma by ultrasensitive HIV RNA test); 2) immunologic response is usually measured by improvement in CD4 T-cell counts. Such increases in CD4 T-cell counts typically accompany a virologic response to therapy but may also be seen independent of optimal virologic suppression; 3) clinical responses that have been noted include increased stamina, weight gain, decreased incidence of opportunistic infections and malignancies, reversal of opportunistic infection processes, and improvements in quality of life. HIV replication involves high virus turnover rates with large numbers of CD4 T-cells being destroyed and replenished daily. The administration of HAART significantly decreases viral replication and allows immune reconstitution to begin. The degree to which immune reconstitution occurs remains uncertain; however, the reduced risk of experiencing an opportunistic infection has been clearly documented among patients taking HAART.

In addition to the high level of HIV replication, there is a significant mutational drift innate in the replication process. It is becoming clear that patients are not infected with a single HIV genotype, but rather with mutant varieties of the virus. Antiretroviral pressures may eliminate pools of susceptible virions, but if drug resistant mutants are present, they may rapidly replace the eliminated viruses. Because of this virologic resistance phenomenon, most experts believe that therapy must be maximal at the outset to prevent selection of drug resistant variants. A correlate of this principle is that therapy-naive patients are believed to have the best chances for optimal antiretroviral response. On balance, the data regarding timing of HAART initiation converge and indicate that more durable and efficacious control of viral replication is achieved earlier when baseline CD4 values are relatively higher. 188, 189, 190 Over the last few years, both clinical guidelines and scientific data appear to ‘favor’ a later initiation of drug therapy given more and more data factoring in the burdens of pill related complexity, side effects, toxicity, adherence issues, chances for drug resistance and greater availability for newer agents in development. In fact the relative advantages and disadvantages of early vs. later initiation of HAART have been enumerated in a recent conference. 191 Moreover, a Spanish study 192 explored the implications of continuing the same regimen of HAART in a cohort of patients (90 drug naïve individuals on two nucleoside agents + a protease inhibitor - nelfinavir) with identified ‘poor’ adherence (self-report and sub-optimal viral load decreases). Only a third of individuals initially found to be ‘non-adherent’ improved and got an ‘acceptable’ VL < 500 copies/cc. Though this lends support to the concept of early adherence to HIV Treatment Regimens: Recommendations for Best Practices
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intervention to improve treatment adherence, it does not necessarily indicate limited efficacy of potentially useful interventional strategies to improve adherence if a patient is initially non-adherent.

While a single optimal regimen of HAART drugs has yet to be defined, certain principles have emerged. Current Public Health Service (PHS) guidelines recommend that patients be treated with combinations of three to four antiretroviral drugs with at least two of the three available classes of drugs represented in the regimen, i.e., nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), and protease inhibitors (PIs). Most combinations include a backbone of nucleoside agents used in conjunction with NNRTIs and/or protease inhibitors. The goal of therapy is to achieve an undetectable viral load after the administration of combination HAART therapy. Some investigators, however, consider the suppression of HIV viral load by at least one log as a partial success since it correlates, at times, with clinical success.

It is important to note that resting memory T-lymphocytes continue to be present even in patients who achieve an undetectable plasma viral load. These resting T-lymphocytes contain replication-competent HIV and while these cells do not have an indefinite survival, they may persist for many decades. These observations suggest that complete eradication of HIV is unlikely given the available antiretroviral therapy. Hence, a major goal of therapy is sustained suppression of viral replication as measured by undetectable HIV viral load using currently available assays, i.e., less than 50 copies/cc. If the viral load is not reduced to these very low levels, there remains the possibility of residual virus replication leading to drug resistant viral subtypes. This may cause eventual viral breakthrough and clinical failure.

Patients who fail to achieve undetectable viral loads while taking antiretrovirals may have mutations within the reverse transcriptase (RT) and/or protease gene of their predominant HIV strain. A significant body of research correlates viral genotype mutations with treatment efficacy of antiretroviral drugs. It has not, however, been established whether particular RT or protease genotypes associated with in vitro viral resistance to a specific drug are predictive of treatment failure with that drug. Since the susceptible genotype may not exclude the presence of resistant subtypes in a given patient, the issue may be complicated by the phenomenon of swarms of HIV clones which may be present simultaneously during the course of an infection.

Some resistant mutations in HIV are associated with cross-class resistance so that resistance to a particular NRTI, NNRTI, or PI may confer resistance to other members of that type of drug. Cross-class resistance implies that failure with a particular drug may result in failure with the entire class in that patient. Since HIV resistance primarily develops in the setting of ongoing viral replication, antiretroviral combination therapy that suppresses HIV replication decreases the risk of developing resistant mutants. The first potent antiretroviral regimen often has the best chance of completely suppressing HIV replication and hence maximally reducing the risk of HIV resistance to antiretroviral medications.

While HAART therapy, along with the improved management of opportunistic infections, has dramatically reduced mortality from HIV infection, there is growing evidence that it may not be successful for a significant number of individuals, particularly for those who have been heavily pretreated. Deeks, Beatty, Cohen, Grant, and Volberding (1998) reported that as many as 50% of the patients in a
retrospective chart audit who were heavily pretreated, were unable to completely suppress HIV viral replication despite treatment with combination antiretroviral therapy and hence had detectable viral loads.20

Treatment failure is typically defined as a detectable viral load usually accompanied by a falling CD4 T-cell count. Initially, these changes may not be related to clinical deterioration. Treatment failure is thought to be due to several factors including level of drug potency, extent of drug absorption, development of resistant viral mutants, and patient adherence. Reduced absorption may be due to the poor bioavailability or altered metabolism of the medication(s) with enhanced excretion of the medication.

Because of the need for sustained viral suppression, adherence to HIV therapy is of paramount importance. Given the high rate of viral replication and the long-term survival of HIV reservoirs within treated patients, it has been estimated that at least 95% adherence with therapy is required to maintain HIV viral suppression and to prevent the emergence of drug resistance.21,22,23 Drug resistance and class resistance are theoretical concerns for relatively drug inexperienced patients but very challenging and real issues for patients who have been heavily pre-treated; salvage regimens provide hope for many such patients. Thus, during a person's course of treatment, the possibility of limited future drug options as a result of resistance can be an influential factor in promoting improved medication adherence. A recent abstract from Chen 193 suggested only some 2/3 of antiretroviral-naïve patients stay on the original regimen 1 year after starting HAART. Observational data involving this cohort of 358 ART-naïve patients revealed that the patients were still relatively advanced (baseline median CD4 = 175 cells); in fact having a prior opportunistic infection (OI) was the most important factor associated with a shorter durability of the initial regimen. Cycling through several regimens limits future drug options; Chen’s data also support a more realistic appraisal of anticipated HAART usage and duration of reliable HAART in the first year.

While viral suppression with HAART is believed to reduce the infectiousness of an individual, it does not, however, completely eliminate the risk of transmission. Replication competent virions have been recovered from the secretions of patients on HAART who have undetectable viral loads. Transmission of HIV from HAART responders to uninfected patients has been documented. Transmission of drug resistant HIV from patients with treatment failure also appears to be a growing problem. The emergence of drug resistance during therapy and transmission of drug resistant HIV underscores the role that adherence plays in controlling HIV in the individual, as well as in preventing a larger public health problem.

Recent studies have focused on the role of structured treatment interruptions (STI) of triple drug therapy in both post-primary infection and in later stages of chronic infections. The observation that ‘drug holidays’ in the time period following initial infection can serve to ‘prime’ the immune system and possibly result in the preservation of cytotoxic T-cell lymphocyte responses has given support to the concept of relative benefit of short term interruptions in otherwise continuous HAART. Importantly the data support the use of such strategies in the early phase of disease rather than systematically interrupting therapy for specific periods of time in individuals who have been chronically well-suppressed for years.
Pill fatigue, recurrent non-adherent periods, changes in health beliefs, persistent side effects and treatment toxicity are but a few reasons why patients and providers have considered treatment interruptions a valid strategy in later stage chronic infection. However, there are a number of STI related risks warranting careful analysis of the need, timing and types of drug holidays and preferential use of such strategies mainly in the clinical research setting for post-primary infection. These include: decrease in CD4 counts after STI, emergence of drug resistance, poorer adherence after STI, loss of immune response repertoire and reseeding of cellular reservoirs with HIV. These issues must be considered when ‘non-adherence’ to regimens and/or drug side effect-toxicity result in the patient and provider considering STI as an interim option for better disease management; the current state of STI is at best controversial.
NOTE: Some recent abstracts from the Retrovirus 2002 (www.retroconference.org) conference are presented below in tabular format:
The links to the abstract and related posters were obtained through the website www.thebody.com (specifically http://www.thebody.com/confs/retro2002/retro2002.html - last accessed March 30, 2002). (The information is originally from the www.retroconference.org website.)

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<td>465-M.</td>
<td>Adherence to medication regimens is a critical necessity for individuals who with all patients especially those advanced HIV disease and CD4 values of &lt; 200 cells; the data reflect the relative poorer response to initiation of therapy at lower baseline CD4 values (i.e., &lt;200) compared to those starting therapy at CD4 &gt; 200 cells. <em>Given higher mortality among ‘patients with a baseline lower’ CD4 (&lt;200), even when adjusted for adherence rates, it is reasonable to start therapy with higher baseline CD4 counts and still emphasize adherence to treatment regimens.</em></td>
<td>Significance of treatment adherence</td>
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<td><strong>465-M.</strong> The Impact of Baseline CD4 T-Cell Count and Adherence on Rates of Disease Progression among HIV-Infected Patients Initiating Triple Drug Therapy</td>
<td>E. Wood*, R. Hogg, B. Yip, K. Craib, M. O'Shaughnessy, and J. Montaner</td>
<td>BC Ctr. for Excellence in HIV/AIDS and Univ. of British Columbia, Vancouver, Canada</td>
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<tr>
<td>546-T.</td>
<td>Increased levels of medication adherence result in prolonged exposure to drug. This study presents data indicating a higher risk of developing drug resistance mutations in those individuals who in fact achieve high levels of adherence. Ironically, those individuals with lower proportions of adherence (based on unannounced pill counts) had higher percentages of treatment discontinuation. A provocative implication is that individuals with high levels of adherence may still acquire drug resistance mutations but stopping medication altogether may be relatively ‘better’ than continuing to take ‘some’ medication in a ‘sub-optimal’ manner over the long run.</td>
<td>Significance of treatment adherence</td>
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<td><strong>546-T.</strong> Low Levels of Adherence Do Not Increase Risk of HIV Drug Resistance Mutations</td>
<td>D. R. Bangsberg*, E. D. Charlebois¹, R. M. Grant², M. Holodniy³, S. Perry⁴, K. Nugent Conroy⁴, D. Guzman⁴, A. Zolopa⁵, and A. R. Moss⁵</td>
<td>¹San Francisco Gen. Hosp., CA; ²Gladstone Inst. of Virology, San Francisco, CA; ³Palo Alto VA Med. Ctr., CA; and ⁴Stanford Univ., Palo Alto, CA</td>
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<td>S20. The Role of Therapeutic Drug Monitoring (TDM) in Clinical Practice</td>
<td>- TDM in its current applicability is limited for many reasons including cost, technical difficulties, interpretation challenges, practicality and uncertainty when correlating with resistance data. The role of obtaining inhibitory quotients (IQ) of specific HAART medication classes (non-nucleosides and protease inhibitors) - referring to trough levels above the amount of drug needed to inhibit replication - needs further investigation. <strong>Though this can be useful to determine some aspects of medication usage and adherence, it will likely not ‘replace’ the preferred multi-pronged assessment of adherence involving self-reporting, provider and indirect assessments.</strong></td>
<td>Measurement of medication adherence</td>
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<td>D. Back*, S. Khoo, and S. Gibbons *Univ. of Liverpool, UK</td>
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<td>547-T. Longitudinal Assessment of the Effects of Drug and Alcohol Abuse on HIV Treatment</td>
<td>- Substance abuse (heroin, cocaine or heavy alcohol use) in an inner city population of HIV positive patients has a negative impact on adherence and medication efficacy; there is a “temporal association” between substance abuse and regimen efficacy that is a potential factor influencing medication adherence.</td>
<td>Factors influencing treatment adherence</td>
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<td>750-W. The Impact of Socioeconomic Status and Physician Experience on Survival from HIV-Disease Since 1996</td>
<td>- A retrospective study involving a total cohort of 1408 patients showed that when adjusted for adherence, independent predictors of mortality included physician experience and baseline CD4 cell counts. Lower socioeconomic status (lower income) was associated with shorter survival and non-triple drug therapeutic regimens; with the increasing importance of triple drug therapy and adherence, this has implications for ensuring appropriate guidelines for equitable access to drugs and experienced practitioners.</td>
<td>Factors influencing treatment adherence</td>
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<td>E. Wood*, J. Montaner, K. Chan, M. M. Schechter, M. V. O'Shaughnessy, and R. Hogg British Columbia Ctr. for Excellence in HIV/AIDS, Vancouver, Canada</td>
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<td>540-T.</td>
<td>• In a sub-study of a larger multicenter study (ACTG 388), 282 patients were studied with approximately 50% receiving ‘usual’ approach to medication adherence counseling and 50% receiving additional ‘intensive’ telephone counseling (16 calls over 96 wks). No increased level of adherence or virologic improvement was noted in those individuals receiving more intensive telephone counseling. <em>It should be noted that other trials have demonstrated some increased efficacy with ‘telephone’ counseling as yet another component of overall care.</em></td>
<td>Adherence intervention</td>
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<td><strong>Randomized Study of Telephone Calls to Improve Adherence to Antiretroviral Therapy</strong></td>
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<td>C. Pradier*1, 2, L. Bentz2, B. Spire1, C. Tourette-Turgis1, M. Morin1, J. G. Fuzibet1, A. Pesce2, P. Dellamonica1, 2, J. P. Moatti1, and 4 INSERM U379, Marseilles; CISH, L’Archet Hosp., Nice; Univ. of Rouen; and Univ. of the Mediterranean, Marseilles, France</td>
<td>Counseling Interventions Can Improve Adherence to Highly Active Antiretroviral Therapy: Results of a French Prospective Controlled Study</td>
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<td><strong>542-T.</strong>&lt;br&gt;Mock Antiretroviral Therapy Trials as an Assessment Tool for Adherence: Correlates with Subsequent HIV Suppression&lt;br&gt;R. Lubelchek*, C. Gabler, G. Berry, N. Wiederhold, J. Cacciabando, G. Highstein, and L. Mundy&lt;br&gt;Washington Univ. Sch. of Med., St. Louis, MO</td>
<td>• Using the benefit of medication electronic monitoring (MEMS caps) as part of a ‘mock trial’ of medications prior to using actual antiretroviral therapy, it was noted in this small study of 54 female participants with 86 mock trials that the proportion of individuals achieving &gt;95% adherence at the 2 month and 6 month follow up visits was higher in those whose baseline mock trial adherence was a ‘success’ (&gt;95%) vs those who did not have mock trial success. ‘Practice dose improve medication adherence.’</td>
<td>Adherence intervention</td>
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<p>| <strong>543-T.</strong>&lt;br&gt;Predictors of Adherence and Efficacy in HIV-1-Infected Patients Treated with Abacavir/Combivir (ABC/COM) or Indinavir/Combivir (IDV/COM): Final 48-Week Data from CNA3014&lt;br&gt;J. Jordan*, P. Cahn, and A. Vibhagool for the CNA3014 Study Team&lt;br&gt;1GlaxoSmithKline, Res. Triangle Park, NC; 2Fndn. HUESPED, Buenos Aires, Argentina; and 3Ramathibodi Hosp., Mahidol Univ., Bangkok, Thailand | • In an open label study comparing efficacy between a relatively simpler triple nucleoside regimen (Abacavir / Combivir ( ZDV + 3TC) - [ABC/COM] - and a two nucleosides (Combivir) plus a protease inhibitor (Indinavir) - [COM/IDV] , it appeared that at a 48 week follow up period, greater adherence to the ABC/COM regimen was noted; male gender and adherence to any antiretroviral therapy were two other co-variables significantly associated with adherence. In general, simpler regimens involving a lighter pill burden and fewer doses/day facilitate medication adherence. | Adherence intervention |</p>
<table>
<thead>
<tr>
<th>Abstract # / title</th>
<th>Brief synopsis / implications</th>
<th>SUBJECT CATEGORY</th>
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<td>545-T. Nevirapine (NVP) and Protease Inhibitor (PI)-Based Regimens in a Directly Observed Therapy (DOT) Program for Intravenous Drug Users (IDUs)</td>
<td>• Directly observed therapy for antiretroviral therapy (using once or twice daily regimens) in a specific context such as outpatient methadone clinics for drug rehabilitation for intravenous drug users (IDUs) is an useful intervention. Provocatively, nevirapine-based regimens were used and long-term observation did not demonstrate increased hepatotoxicity even in this cohort that involved co-infection with Hepatitis C. DOT should be viewed as an alternative option with potential for enhancing medication adherence in specific situations, including drug rehabilitation facilities.</td>
<td>Adherence intervention</td>
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The measurement of medication adherence is a difficult endeavor both in clinical care and research settings. Quantifying the levels and types of medication adherence involved patient care has been the focus of many studies resulting in the identification of multiple direct and indirect measures. Given the significance of viewing medication initiation and continuation as a process involving stages of change, measurement tools have been developed to attempt ‘matching’ communication strategies to readiness for treatment. Some of the most recent work in the area of antiretroviral medication adherence measurement has supported the independent association of patient and provider reported adherence with multiple variables that influence adherence; accordingly areas to be explored more fully include incorporating a combination of patient and provider reporting and pharmacy refill data.

Flexner (1997) wrote, “There is no way to measure adherence in the outpatient setting with absolute precision and accuracy.” While there may be no gold standard with which to measure adherence, there are several strategies available, each with its respective strengths and weaknesses. These include:

- **Self-reports**: Three main types of self-report adherence measures have been used including surveys, interviews and diaries. Each is relatively easy to use and inexpensive, although data from several studies suggest that self-reports tend to overestimate actual adherence. One study that explored adherence rates in hypertensive patients found that 67% overestimated their adherence when self-reports from diaries were compared with data from the Medication Event Monitoring System (MEMS) caps. Researchers also found that 30% of the diary entries differed from the MEMS recordings. Among investigators studying HAART adherence, there is agreement that self-report surveys that ask about missed doses within a very short time frame, i.e. within one to four days, are more valid and reliable than surveys that ask the respondent to remember a week or more ago.

- **Clinician Assessments**: There appear to be few HIV-related studies that have assessed the accuracy of clinician assessments of actual or potential adherence of their patients. Preliminary data presented in abstract form suggest that physicians overestimate patient adherence to HIV medication.

- **Pill Counts**: One strategy to evaluate adherence is to view the actual pill container and calculate how many pills should be left, given the date of the inspection, dosing and last refill. Because pill counts often occur in provider offices, clients are able to manipulate the number of pills remaining prior to the visit. Unscheduled home visits to conduct pill counts have the potential to be more accurate. Regardless of where the count actually takes place, Rudd, et al., (1989) reported that weekly pill counts demonstrated marked intersubject and intrasubject variability, obscured by
long-term averages. Studies within the AIDS Clinical Trials Group (ACTG) have not found pill counts to be helpful in assessing patient adherence, particularly in studies of combination antiretroviral medication.

- **Prescription Refills**: Prescription refills may be a mechanism for assessing adherence to antiretroviral medications. Theoretically, pharmacists could work closely with health care providers and patients, informing both parties when medications are not being filled as directed. Unfortunately, such a close working relationship rarely exists in practice and patients may fill their prescriptions at different pharmacies. Although prescription refills could be monitored by the payer, insurance status often changes and thus, the payer source. Gaining access to pharmacy records remains difficult and the relationship between refills and actual ingestion of medications is not always clear.

- **Biological Assays**: Blood or urine biological assays can be used to measure adherence to treatment. Two main types of assays are available, but their use in monitoring adherence is controversial. Marker assays are based on materials that can be added to a drug and are easily detected, typically in the urine. Direct assays refer to testing for the presence of the medication itself in the blood or urine. Given the half-life of most medications, direct and indirect assays have the capacity to only measure adherence for the most recent doses taken, and not over longer periods. Biological assays to measure levels of antiretroviral medications and their metabolites are not commercially available at this time, thus further limiting this as a viable strategy to monitor adherence. Studies assessing composite ‘scores’ derived from self-administered questionnaires and plasma levels of protease inhibitors (PI) have supported the value of plasma PI levels as an objective marker of antiretroviral therapy.

- **Medication Event Monitoring System**: Medication Event Monitoring System (MEMS) bottle caps are thought by some to provide a valid and reliable measure of medication adherence. These devices are special bottle caps that contain computer chips that fit on standard medication containers. The microchip stores the date and time each time the medication container is opened and closed. A long-life battery that cannot be switched on or off is also included. Data are retrieved by downloading the information from the cap device to a computer, which provides a spreadsheet display of an overview of individual adherence. Cramer, et al. (1988) compared pill counts and drug serum concentrations with MEMS data and concluded that neither drug serum concentrations nor pill counts would have identified the frequency of missed doses for newly diagnosed and long-term epilepsy patients that were revealed with MEMS continuous dose observations.

This strategy may not work well when a large number of pills and complex treatment regimens are prescribed. In a sample of hypertensive patients, Lee et al. (1996) compared pill counts and MEMS data and found that each method identified different patients as being non-compliant. Investigators at the University of California at San Francisco note that MEMS data can be scored
only as “opened/closed” as many patients take out their entire supply of pills for the day and place them in their pockets instead of carrying around the medication bottle.\textsuperscript{1} Geletko, Segarra, Ravin, and Babich (1996) examined zidovudine adherence in an HIV ambulatory clinic and found that adherence rates varied significantly by data source. MEMS data provided ranges for adherence rates of 9-100%, pill counts from 50-100%, self-report rates of 80-100% and physician assessments of 30-100%. The researchers concluded that “...a combination of adherence assessment tools produces a more accurate representation of zidovudine dosing and facilitates identification of patient errors...”\textsuperscript{46}

\begin{itemize}
  \item \textbf{Directly Observed Therapy:} Directly Observed Therapy (DOT) has been used extensively in the management of tuberculosis and in residential psychiatric facilities.\textsuperscript{52} The key component in DOT is that someone directly observes the patient ingesting the medication. Due to the frequency with which HIV-infected patients must take their medications, DOT may not be feasible. As more medications are developed which can be taken once or twice a day, this approach may become more useful. Studies are currently being developed to assess the use of DOT within the AIDS Clinical Trial Group Protocols (ACTG). \textit{This topic is explored further in the Adherence Models section.}
\end{itemize}
IV. Factors Impacting Treatment Adherence

Factors that impact adherence to treatment regimens may well influence the adherence to other health behaviors. Though the focus of this document is adherence to medication regimens, the process of care is a continuum and indeed adherence to specific health behaviors may conversely be related to abilities and skills needed to adhere to complex drug regimens. This monograph will be expanded in future updates to include material specific to adherence to healthy behaviors, including prevention and management of certain co-morbid conditions that indirectly affect overall health for HIV/AIDS patients – obesity, substance abuse, cardiovascular disease, diabetes, liver disease. Adherence to safe sexual practices (e.g. condom use) is associated with medication adherence with potential counseling implications.

Avoidance of other high-risk behaviors including sharing needles may be seen as necessary for achieving specific health goals that patients may have even in the context of harm reduction models.

A variety of factors impact a patient’s ability to comply with a prescribed treatment regimen and are apparent at the patient, provider and treatment level. Together with the characteristics of HIV disease and therapies, these factors make adherence to treatment difficult. To assess or improve treatment adherence, the potential impacts of these factors must be considered. Based on prior theory, Icovics and Meisler (1997) outlined a multi-variable framework for clinical HIV/AIDS research and care to organize the factors that impact medication adherence. As even outlined in the sections below, this framework has had widespread influence and is a very useful practical system within which to approach treatment adherence.

Patient-based Factors

Demographics, such as age, gender, ethnicity, and socio-economic status have been included in almost every analysis of adherence, although they do not seem to be consistent correlates of whether or not a patient keeps appointments or follows a medication regimen. Data from HIV studies suggest that such demographic information is not necessarily predictive of antiretroviral adherence but rather identifies particular populations that may benefit more extensively from targeted interventions that address specific barriers.

Cultural aspects of the patient’s health beliefs and life goals must be considered as important influential factors in the context of treatment adherence. Many useful studies and reviews on certain ethnocentric and androcentric biases in not only research but clinical care provide information upon which assessment of treatment readiness, treatment adherence and components of the therapeutic alliance are better understood. Flaskerud has conducted insightful surveys on various female populations about their beliefs related to AIDS, health and illness. Such studies outline misconceptions about HIV transmission and reframing traditional conceptualization of illness among the ethnically diverse samples. Useful feminist critiques of the term and concept of ‘non-adherence’ have been delineated. Sexuality and gender issues have an impact on the communication process; social identity concerns...
stemming from personal sexual preferences must be considered in the patient/provider dialogue. Other factors that seem to have a stronger relationship to treatment adherence than demographics include: 1) patient’s knowledge of the treatment plan and regimen; 2) presence and management of side effects/symptoms; 3) cultural and health beliefs towards disease and treatment; 4) presence or absence of a social support system; and 4) specific co-morbidities such as substance abuse and mental health problems. Each of these factors contributes to a patient’s readiness to accept a treatment plan.

Patient readiness refers to the understanding of, motivation and commitment to their treatment plan. Before a prescription is written, it is important to establish the patient’s readiness to accept the treatment plan offered. This involves educating the patient and engaging the patient in problem-solving in an effort to remove obstacles to treatment adherence. Assessing patient readiness and commitment to the treatment plan on a regular basis during the course of treatment allows the provider to evaluate adherence and prevent or deal with issues such as missing doses or treatment fatigue.

A very useful approach to assessing treatment readiness and meeting therapeutic goals is derived from the Transtheoretical Model of Learning. This model provides a framework in which treatment readiness is viewed as a continuum along which patients move according to their own volition but which is staged and assisted throughout by the provider. The decision-making process encompasses the stages of ‘pre-contemplation’, ‘contemplation’, ‘preparation’, ‘readiness’, ‘action’, ‘maintenance’ and ‘relapse’. The approach not only recognizes that changing health behavior, such as starting or changing an antiretroviral regimen, is considered an important ‘action’ step for ultimate clinical success, but also recognizes that there are several phases before and after this action step that need to be addressed with proactive dialogue and patience. This dialogue facilitates appropriate matching of adherence intervention to any specific problem associated with non-adherence (potential and/or actual) in the context of a specific stage or readiness. The provider considers it more important to assist a patient from one given stage to the subsequent one rather than viewing treatment initiation or adherence modification as simply a ‘on-off’ phenomenon in which patients are either demonstrating full adherence to a regimen, treatment or behavior change or not. Very practical schematics and examples of communication based on the stages-of-change model are available.

The stage of the patient’s HIV disease also appears to influence treatment adherence. Depending on the patient, the presence or absence of symptoms can be either an incentive or a deterrent to adherence to treatment. Some patients might feel more motivated to adhere to treatment even in the presence of side effects, if their viral load goes down or becomes undetectable. Other patients might feel that an undetectable viral load and the absence of symptoms means that they do not need to continue taking their medications. Many patients present with mental illness and/or a history of substance use. In such cases, thinking and memory problems can be yet additional factors related to non-adherence.

Substance abuse and mental health problems are not insurmountable barriers to adhering to a treatment regimen. Lessons learned from adherence to tuberculosis treatment among substance abusers indicate making suitable modifications to treatment regimens, increasing the number of clinic visits, building stronger doctor/patient relationships and incorporating TB treatment into drug abuse treatment or...
Persons who are actively using or abusing substances are capable of adhering to complex medication regimens. As with all patients, it is important to perform a pre-treatment assessment prior to the initiation of medications. Crucial to this assessment is the analysis of the person’s drug of choice, frequency of use, and living situation. Because the interaction of street drugs and antiretrovirals is for the most part unknown, it is very important that the patient realize there is a potential for harmful, if not fatal, drug-drug interactions.

The important of adherence to the regimen and an appropriate discussion about the potential for resistance and cross-resistance to future medications must be included in the pre-treatment analysis of readiness. It may be necessary to schedule more frequent follow-ups for the patient, with bi-weekly if not weekly laboratory and adherence monitoring. Education and discussions need to take place in a safe environment with culturally appropriate medication teaching guides being utilized. Even complex information such as resistance and virology can be tailored to be understandable for most patients. Patients who understand the need for adherence are more likely to adhere to regimens and to follow the instructions from their providers.

It is important that an open, non-judgmental environment be fostered between the patient and provider. An open arena for discussion about substance use with a patient is not the same as giving approval, advocating for or encouraging use of legal and/or illegal substances. The issue of detoxification, recovery assistance and harm reduction in the setting of overall health maintenance can often be effective when working with substance users.

Symptom management is a vital part of successful adherence to HAART. Not offering symptom control medications to those with a substance abuse history may lead to self-medication. Nausea related to initiating antiretroviral therapy may be confused with feelings of drug sickness and withdrawal which may lead to relapse or more frequent substance abuse. Pre-medication with effective anti-emetics for drugs known to cause nausea and/or vomiting can be very useful during the first few weeks of therapy. Coaching patients through side effects is very important. Because trust can be an issue with persons who have a history of substance use, it is necessary to discuss all potential side effects with the patients before they begin the medications to prevent feelings of premeditated non-disclosure. Although there may be instances when HAART is not appropriate for active substance abusers, each patient must be assessed individually for readiness to adhere to a complex medication regimen. Individual-based factors cannot, however, be considered in isolation or as something that the patient needs to solve alone after HIV prescriptions have been written. The impact of the above factors on the patient’s treatment regimen and adherence needs to be assessed and discussed with the patient by the medical provider and the health care team.

Of all patient-based factors affecting adherence, perhaps the single most under-addressed is the effect of co-morbid mental illness. Substance abuse may be seen as a single behavior with multiple aspects. Mental illness, however, presents a variety of challenges that cannot be addressed by ‘mental health counselors’ alone. While such counseling is valuable, patients with treatable mental illness should
receive psychiatric care with medication as appropriate to optimize the effects of HAART as well as the quality of their lives. It has been established that specific mental illnesses are associated with high risk behaviors:207, 208, 209 the perceived invulnerability of those with bipolar disorder during the manic phase, the response to hallucinations and delusions associated with schizophrenia and similar conditions, the time distortion common in depression, and the suspiciousness common to many individuals who are affected by psychiatric illness. These symptoms can manifest in ways that affect adherence as usually measured (medication reliability) as well as in other ways that may have serious consequences.

For many patients, psychiatric illness predates infection with HIV. Treatment with appropriate medication can provide control of symptoms, while mental health counselors can work with patients to help them deal with life conditions. Failure to refer and follow-up on treatment can seriously compromise adherence. In addition, close follow-up is necessary in order to coordinate medication in consideration of side effects and clearance stress on compromised organs210. Incomplete medical control of bipolar disorder may lead to behaviors such as unplanned travel, sleeplessness, uncontrolled spending, and a disregard for safety. Measures of viral load may not relate well to medication adherence for an individual who is re-infected with a resistant strain while engaging in unprotected sex or needle sharing. Not only treatment but also valid evaluation of medication effectiveness may be compromised. Patients responding to internal stimuli may be afraid to take medication, while those with delusions may perceive medication to be dangerous. Paranoid ideation may fixate on providers or treatments, and the patient may respond by selectively refusing treatment and/or reporting information inaccurately. In both of these situations, the problem may be intermittent, and may not be evident during office visits. Depression in the patient with HIV is not necessarily situational, and may represent a longstanding condition characterized by self-destructive behavior. For this population, it is not only medication adherence but also the challenges of maintaining prescribed diet and activity patterns that is perceived as overwhelming. Principles of tertiary prevention mandate that active treatment of psychiatric illness occur during HAART.

Provider-based Factors

Provider characteristics and the medical system also affect patients’ adherence. Overall patient satisfaction with medical care has been found to correlate with increased adherence.59 The perception of providers as being warm and caring has been related to greater adherence, a finding also replicated in HIV treatment.60, 61 Long waiting time and other procedural barriers have been found to decrease adherence to both keeping appointments and taking medications.62 Consistent access to health care and medicines also appear to influence treatment adherence. The level of services, communication, and rapport between the pharmacist and patient often impact adherence and deserve further attention.

Medical care providers need to possess the necessary knowledge and clinical skills to take care of HIV patients and keep abreast of new treatment developments. In a patient-centered approach, care providers also need to acknowledge that the uncertainties of HIV disease demand a flexible response in their medical practice. This response must involve the patient in decision-making about the treatment plan and must support the patient’s goals in monitoring and treating their HIV disease.63 Interactional styles of communication between patients and different types of providers, e.g., physicians cf. to nurse practitioners have been studied; shared decision making as it expresses through the actual dialogue...
Because treatment adherence is a challenge not only for the patient but also for the provider, the locus of responsibility and commitment to treatment adherence shifts from being solely a function of the individual to also becoming a function of the provider and the health care team. The relationship between the patient and the provider becomes a therapeutic alliance where both parties work toward a common goal: improving the health of the patient. Defining this goal and the patient’s commitment to it largely depends on the therapeutic alliance and the ability of the provider to assess the patient’s readiness for treatment. A potentially effective strategy to enhance patient-provider interaction would be to discuss and initiate antiretroviral therapy in the context of an informed consent process, possibly including patient-provider therapy contracts. This approach can exemplify the spirit of a therapeutic alliance in which patient and provider define not only therapy goals, side effects, medication management and levels of adherence, but mutually agreed upon ‘rights & responsibilities’ that form the basis of an ongoing relationship. The significance of a collaborative client-centered model of consultation is inherent in establishing a proactive therapeutic alliance between patient and provider. Evidence-based decision-making has been promoted through the use of patient decision aids as outlined in a recent editorial.

Bakken, Holzemer, Brown, et al. (2000) examined the relationships between the patient’s perception of engagement with their health care provider and demographic characteristics and adherence to therapeutic regimen in persons with HIV/AIDS. Bakken, Holzemer, Brown, et al. (2000) examined the relationships between HIV/AIDS patients’ demographic characteristics, perception of engagement with their provider, and adherence to therapeutic regimens. A convenience sample of 707 non-hospitalized persons receiving health care for HIV/AIDS were recruited from seven U.S. sites. All measures were self-report. The patient-provider relationship was measured by a newly developed scale titled-Engagement with Health Care Provider. Adherence to the therapeutic regimen included adherence to medications, provider advice, and appointments. There were no significant relationships between engagement with health care provider and participants’ age, gender, ethnicity, and type of health care provider. Patients who were more engaged with their health care provider reported greater adherence to medication regimen and provider advice. Patients who missed at least one appointment in the last month or who reported current or past substance use were significantly less engaged.

The patient-provider relationship is considered of general importance in health care and has the potential for greater influence in chronic diseases, such as HIV/AIDS, that are associated with wide variations in health status, complex treatment regimens, and relatively high levels of non-adherence with therapeutic regimen. Both patients’ rights and provider responsibilities are important in establishing a therapeutic alliance; predicting adherence to treatment is fraught not only with methodological challenges but ethical concerns when processing management decisions about for whom and when should therapy be initiated.

Treatment-related Factors

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Adherence to HIV Treatment Regimens: Recommendations for Best Practices
June 2002
Characteristics of the medical regimen constitute another important correlate of adherence. For example, the longer the regimen the poorer the adherence, and more complex regimens have been similarly associated with poorer adherence.\textsuperscript{65} This is even more pronounced in the treatment of co-morbidities when complicated polypharmacy regimens are prescribed. For some patients, sustained behavior change might also constitute a particular challenge to adherence.\textsuperscript{66} Most of the current strategies for regimen simplification, drug cocktail sequencing and the drug development process for newer agents are important in the treatment related factors. However, emphasis on the success of simpler, better tolerated regimens cannot preclude the significance of understanding and incorporating psychosocial, cultural and behavioral aspects in clinical care of the HIV/AIDS patient. This perspective assumes even greater importance when systems’ approaches are advocated for treatment adherence.\textsuperscript{23} Simplification of regimens is occurring by several means: making doses compressed into smaller and/or fewer pills, reducing pill burden by going to once and twice daily regimens, combining classes and agents within classes by taking advantage of pharmacokinetic characteristics that enhance therapeutic blood levels and manufacturing formulations with extended half-lives. Other modes of reducing pill burden over time involves ‘de-intensification’ by ‘front-loading’ potent regimens to reduce viral load precipitously and to undetectable levels and subsequently reducing medication classes or agents while continuing control on viral replication. Finally, newer ‘investigational’ methods are being explored that involve structured treatment interruption – or drug holidays – primarily to prime the immune system into controlling viral replication and preserving function. This may have a role in chronic infection by reducing overall exposure over time to potentially toxic regimens and may reduce non-adherence and pill burden while preserving drug options for the patient’s future. These themes are exemplified and expanded in the newest guidelines for antiretroviral therapy\textsuperscript{15} - \textit{Guidelines for the Use of Antiretroviral Agents in HIV-Infected Adults and Adolescents}.

Regimens with significant adverse side effects, such as antiretroviral medications, have also been associated with poor adherence. These reactions range from nausea and diarrhea that may be controlled, to severe hypersensitivity reactions, bone marrow suppression, pancreatitis, and long-term lipodystrophy syndromes and glucose intolerance. In addition, the long-term consequences of HAART therapy with these agents remain difficult to predict. The number and array of side effects associated with the treatment regimen may be overwhelming for patients. Furthermore, the typical HAART regimens carry a significant pill burden, frequently in excess of 20 pills per day. Adverse medication side effects, complexity of daily routines, pill burdens, lowered genetic barriers leading to drug and drug class resistance, and long-term uncertainties are all major factors that challenge a patient's ability to successfully adhere to a regimen. The patient’s perception of barriers to implementation of the medical regimen has also been associated with decreased adherence.\textsuperscript{67}
V. Adherence Models and Other Disease Entities

Medication adherence as a major challenge to the implementation of various regimens is certainly not unique to HIV/AIDS. Tuberculosis and diabetes but also chronic heart disease and hypertension are just some examples of diseases with their respective care models and solutions that can be in part applied to HIV/AIDS.214, 215, 216, 150, 151, 152, 153

Tuberculosis, Directly Observed Therapy (DOT) and Applicability to HIV/AIDS

The use of directly observed therapy (DOT) for the prevention and treatment of tuberculosis provides a useful case study on the issue of adherence. Tuberculosis is both treatable and preventable; however, both interventions require prolonged courses of therapy usually for at least six months. Many studies have shown that the only effective means of achieving high completion rates for the treatment of active tuberculosis is the use of DOT. There are many variations of DOT, although the unifying theme is a health professional witnessing the ingestion of the medication by the patient at each dosing.68 The effectiveness of DOT for reducing tuberculosis incidence rates has been demonstrated in many regions. Baltimore is a well-known success story where rates of tuberculosis dropped 60% over a 15-year interval following the introduction of DOT.69 Larger regions such as Tarrant County, Texas also illustrate the utility of DOT.71 Key ingredients in the success of DOT are a steady source of public health funding and a stable infrastructure system.

In spite of the success of DOT for the treatment of tuberculosis, there are significant differences between DOT for tuberculosis and the application of such a tool for HIV therapy. First, tuberculosis treatment is finite, and patients are believed to be cured upon completion of treatment. Second, clinical trials have shown that the medications for tuberculosis may be administered twice weekly without compromising their effectiveness. Indeed, IDSA/USPHS guidelines recommend the use of twice weekly intermittent DOT for most of the 6-month course of treatment for active tuberculosis.72,73 The necessity of patient-provider interactions twice weekly provides significant manpower cost savings for DOT programs.74 Third, since tuberculosis is communicable via airborne spread, public funding for tuberculosis DOT programs is justified on the basis of this general public health risk to all members of society. A recent monograph, available on-line, outlines the comparative features of DOT for TB vs HIV.217 Two important observations that support the view that the DOT methodology is not currently considered feasible or appropriate for widespread routine application to the clinical management of antiretroviral medications are simply that current HAART regimens generally include multiple daily doses and HIV treatment is life-long. From an infection control/public health perspective the significant risks of airborne spread of tuberculosis do not apply to current transmission of HIV. Finally, though more ‘user-friendly once daily regimens are being developed, these options are still limited; accordingly the complex food-drug interactions with the polypharmacy issues of antiretrovirals may preclude supervised therapy on a daily or even weekly basis.

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However there are very appropriate apropos situations in special settings. With the advent of newer once daily HAART regimens \(^{218}\) and clinical trials of a modified DOT (e.g., one of two twice daily doses is monitored), DOT will likely be increasingly used in specific situations such as methadone clinics \(^{219, 220, 221}\) and of course as standard-of-care in prison settings. \(^{222, 154}\) There are other community-based approaches with DOT reporting some success in the US and also in developing nations \(^{223, 224}\) One large initiative in the US will likely yield useful information in the future. \(^{225, 155}\)

The Diabetes Experience as Applicable to HIV Management

Because of the multiple dimensions of its causation, treatment, course, complications, and impacts, diabetes serves as an excellent model for understanding chronic disease, including HIV and AIDS. Moreover, as new treatments for HIV / AIDS enhance survival and makes being HIV positive a chronic condition, which can have increased abdominal fat, insulin resistance, and the metabolic syndrome associated with a greater risk for developing type 2 diabetes and cardiovascular disease as a side effect of the HAART. \(^{226, 227}\) The incidence of lipodystrophy may be > 60\% after one year of continuous protease inhibitor treatment. \(^{228}\) Therapeutic advances have largely shifted the focus of care from addressing medical crises and fatality from an acute infection to self-management issues associated with a chronic condition involving a complex medical regimen. A growing number of patients will be on HAART for their HIV status and receiving addition medications to address the effects insulin resistance as concomitant conditions. Diabetes can illustrate a key management issue that is highly applicable:

> Paradoxically, involving patients in making serious decisions regarding choice of treatment enhances treatment effectiveness.

It is understandable to react to serious disease by prescribing treatments solely with regard to maximizing efficacy. But the role of patients’ adherence and participation in their own care governs the benefits of a regimen. Accordingly, collaboration of patients and professionals in determining treatment plans will, over time, yield the most effective treatments. \(^{76}\)

Adherence Issues in Diabetes – Comparison and Contrast with HIV

- **Features shared by HIV infection and Diabetes Mellitus, and which influence adherence to or utilization of treatment:**

  1. Patients with early HIV infection and those with minimally (inadequately) treated diabetes are mostly asymptomatic. Promoting adherence with an asymptomatic patient is very different than with a symptomatic patient, as unpleasant symptoms are a great motivator to take corrective action of some kind.
2. Treatment itself causes symptoms, and sometimes introduces or increases risk of other serious problems.

3. Treatment must be continued for the patient's life the primary objective of which is to prevent deterioration of the patient's health.

4. The treatment regimen is complex:
   - multiple drugs used concurrently
   - multiple daily doses
   - timing of doses is important
   - therapy must be coordinated with food intake

5. There is a continuous, dose-response relationship between adherence to treatment and the amount of benefit the patient will receive. This is not always obvious to the patient. It is unclear the extent to which this is true for HIV.

After the diagnosis is made, both diabetes and HIV "treatment" are long term, secondary prevention programs. HIV survival has dramatically improved resulting in increasingly longer-term HAART, which has increased risk of metabolic disorders and diabetes. The optimal outcome for years of hard work on everyone's part is for “nothing to happen” i.e., no discernable consequence. But since humans respond most to clear, immediate consequences of their behavior, this makes promoting adherence difficult. Early in the course of diabetes, nonadherence is likely to result in a worsening ‘glycohemoglobin’ level (the major biomarker of glucose control ~ ideally <7%), but not clinical symptoms. Likewise, nonadherence early in the course of HIV infection may result in a rise viral load but the absence of the clinical symptoms of disease. Indeed, for patients have who have experienced medication side effects, nonadherence could result in perception of improved well being.

6. The patient must actively participate in treatment.

Adherence takes place in the daily lives of adults: not in the clinic nor in circumstances under the control of health systems or providers (a partial exception being Directly Observed Therapy in TB care). Adults are responsible for implementing their disease management routines. If adherence is dependent on influences that are strong within the clinical setting but are weak in adults’ daily living situations, adherence will be poor. For example, strong intentions to adhere that are sincerely voiced on the examining table in response to a physician’s admonition may fade quickly at home and work. Thus, it is critical that efforts to encourage adherence focus on factors that will be active in adults’ daily lives. Good programs vary in tactics and ways of conceptualizing them, from self-efficacy to family involvement, but all share an attention to those circumstances that will be present when people either adhere or do not. In particular, the individual’s active
involvement in setting goals and making plans to achieve them is critical to ensuring that regimens and adherence tactics will fit with the realities of their lives outside the clinic.

7. Both conditions occur disproportionately in groups that are underserved by the health care system, that face substantial and diverse social and economic stressors in their lives, and that maintain patterns of behavior that place their health at substantial risk.

8. Both conditions are associated with negative social stigma. Treatment may be difficult to conceal from others. Both these factors may pose barriers to routine adherence at work or other social settings.

9. Treatment is life-long. Variability in motivation and adherence over time may be expected to increase as the duration of treatment grows.

10. Other factors besides adherence to treatment influence the success of therapy. In spite of excellent adherence, patients may still realize devastating outcomes. This undermines motivation for adherence and leads to appreciable demoralization in the event of such outcomes.

11. Treatment is financially costly.

• **Features that Distinguish Diabetes and HIV and that May Complicate Adherence**

1. The general public considers HIV to be a more serious disease than diabetes. (Historically being HIV positive has been considered a “death sentence”. In contrast, having diabetes may be considered having “a slightly high blood sugar” or “just a touch of sugar”.

2. Being HIV-positive was originally characterized associated with body wasting whereas Type 2 diabetes (most common form) is typically associated with obesity. However, with advances in treatment they often share in common visceral obesity, and the metabolic syndrome associated with insulin resistance. Visceral obesity can occur as the result of HIV treatment regimens even with coexisting peripheral wasting.

3. The treatment goals in diabetes appear to be more flexible than in treating HIV, and the biomarkers of control differ with respect to indication of risk. As a measure of diabetes control, glycated hemoglobin is a continuous variable with benefit occurring with any decrease in levels above the normal range. In HIV, the detection of the virus is considered abnormal and the treatment goal is to have an undetectable level.

4. The “window of opportunity” for beneficial treatment of diabetes may extends over a few years. Gradual development of symptoms may provoke increased adherence that, in turn, may have appreciable benefits in delaying progression of complications. In contrast, the “window of opportunity” for achieving health benefits from adherence in HIV treatment appears to be considerably shorter. This encourages health care providers to promote adherence vigorously,
seeking high levels of adherence to best treatments within the relatively brief time that those treatments may be maximally effective. But overzealous pressure to adhere may undermine the relationship with the patient and, consequently, the patient’s adherence. The trade-offs among these factors are not well understood.

5. Side effects of medications are major barriers to adherence in HIV. These are less a problem in diabetes. However, side effects such as hypoglycemia and weight gain can affect adherence to insulin and medications that enhance insulin secretion. Other diabetes medication can cause gastrointestinal side effects that are milder than those associated the HAART.

• **Successes in Adherence in Diabetes – Lessons Learned from Diabetes that May Enhance Efforts to Promote Adherence in HIV**

1. Optimal treatment requires a paradigm shift in the conceptualization of the health care provider role. The traditional biomedical model in which the health care provider tells the patient what to do is inadequate. A better model is that of the collaborative relationship, in which the health care provider’s role includes application of technical knowledge and skill, development of the patient’s self-management skills, and assistance with integration of disease management with other activities of daily living.

2. Research in diabetes as well as many other areas of health behavior makes clear an important and strong generalization: Continuing contact and support over time is critical to sustained adherence. Adherence will be fostered when each patient-provider interaction includes attention to issues of self-management.

3. All patients can improve their self-management, no matter where they are on the spectrum, though very few will reach “perfection.”

4. “Adherence” is not a personality characteristic, but varies across the different behaviors required for self-management. Non-adherence can be viewed as a symptom, not a diagnosis. Like other symptoms, the first step in diagnosis is a detailed assessment (history). The purpose of diagnosis is to define the conditions and circumstances leading to the adherence problem, prioritize these in some rational manner, and identify potential strategies to improve adherence and select objectives for trials.

5. There is no single recipe for promoting adherence or appropriate self-management. The health care provider needs a repertoire of strategies from which to choose, depending on the behavioral demands of treatment, patient characteristics, and the specific environmental obstacles concerned.

6. Promoting optimal self-management is time consuming. To the extent that optimal self-management is essential to the success of therapy, the professional time required must be considered a legitimate cost of care, just as important as the cost of drugs, for example.

7. Most health care providers have not been adequately trained and lack the skills needed for dealing
with adherence problems. Training and skills for promoting adherence often reside in health care providers other than physicians. Thus, a multidisciplinary team that is able to share work in ways that maximize the contributions of each discipline should be encouraged.
VI. Current and Practical Approaches to Medication Adherence

The preceding sections presented the various components related to medication adherence in an effort to provide a detailed format; this concluding section aims to summarize and operationalize the most relevant features of this topic. There is a significant shift in major care delivery paradigms when applied to the diagnostic, preventive and therapeutic aspects of HIV disease. This shift is characterized by a willingness to complement the process of individualized care with systems’ responses to optimize successful outcomes. This movement is accompanied by an increasing recognition of the importance of improving community standards in the context of health disparities especially among marginalized populations. The prominent themes of the International AIDS Conference in Durban, South Africa recognized the necessity for a radically different and proactive approach to eliminating inequities in medication access, substandard care practices and stigmatization in HIV infected individuals. Such themes were symbolized by the very motto of the conference, “Break the Silence.” There were many abstracts and presentations related to medication adherence among which some of the most significant were those describing the widespread efforts to create multidisciplinary and collaborative responses to improve care for people living with HIV/AIDS. In the two years since the July 2000 Durban conference, there has been much more literature supporting a comprehensive multi-disciplinary team approach to prevent, identify and manage ‘non-adherence’ to treatment and medication regimens.

Many of these projects and initiatives endeavor to optimize patient goals, improve medication adherence and support patient education. Notably, the Washington HIV/AIDS Treatment Adherence Demonstration Project (www.hapdeu.org) has been conducting a multi-center pilot study evaluating HIV treatment adherence projects in communities across Washington state. Data has been collected from multiple sources including surveys, review of participants’ files, key informant interviews, and focus groups. A number of useful recommendations regarding staffing, training needs, service components, agency coordination and community supports have been made. The San Francisco “Project Action Point” is a government sponsored program that assists multi-diagnosed individuals living with poverty to adhere to complex medication regimens so that all HIV+ individuals in the community can benefit equally from advances in anti-HIV medications. Constant intervention and reassessment using a multidisciplinary team model as well as incentives and adherence tools are key to the project's success with this population.” At the Durban AIDS conference, Brazil was notable as a developing country that presented several innovative and effective approaches in the areas of primary and secondary prevention including the improvement of medication access and adherence for its infected population. Another example of a systems’ response to the many challenges involved in providing better access to medical care and therapies is the Center for HIV Education, Empowerment, Research and Support (C.H.E.E.R.S.) to improve medication adherence in the context of indigent patients by providing an integrated care delivery system incorporating: 1) medical/pharmacy services; and 2) a public health clinic based center for education. This program emphasizes individualized patient management and health education for patients and providers. The program is currently initiating other features including: Internet access for consumer health information and a peer education component called “C.H.E.E.R.S. for Peers.” (Jani, personal communication) There are other initiatives addressing medication adherence using peer
education support, multidisciplinary team approaches and the Transtheoretic Model of behavior change. \textsuperscript{233, 234, 235} There is an innovative and long standing peer education program with a ‘pioneering’ secondary prevention approach to HIV positive individuals.\textsuperscript{236}

Given the enormous challenges and limited funding support for many ‘system’ responses, the ultimate measures of program effectiveness must include the practicality of design and interventions. Accordingly, simple and effective solutions to the problem of medication non-adherence ought to be founded on a strategic approach that is realistic and methodical. The Washington Demonstration project is unique with its well-designed evaluation component - HAART Treatment Adherence Project Evaluation Design, described in detail at http://www.hapdeu.org/adherence/prog_eval.htm. There are several projects funded through the HRSA Bureau of HIV/AIDS Special Projects of National Significance (SPNS) - http://hab.hrsa.gov/special/spns-adherence.htm with a listing of previously funded projects - ftp://ftp.hrsa.gov/hab/SpnsRpt5.pdf. These endeavors aimed to provide innovative approaches to improve treatment adherence especially to HAART among underserved populations.

A practical approach to HIV medication adherence is an organized, four-step process that incorporates principles of learning theory, the daily living challenges of the HIV-infected individual and the complexity of medical and psychosocial factors specific to HIV practice.\textsuperscript{77, 128, 127} The four-step process, which is outlined below in Table 1, is recommended because of its ease of implementation in the clinical setting.\textsuperscript{237}
TABLE 1

Practical Approaches to Medication Adherence

- **First**, a thorough assessment of those factors that may influence adherence and function as potential barriers to adherence should be reviewed and identified. This corresponds to the collaborative definition of problems.

- **Second**, efforts to develop and maintain a therapeutic alliance with the patient should be made. This will foster the identification of goals and formulation of a plan.

- **Third**, the utilization of preferably multiple measures of adherence to be incorporated in the care plan. For this step, provider and system support are needed for the optimal self-management training phase for the patient.

- **Fourth**, multiple targeted interventions focused to resolve the barriers to adherence should be implemented based on whatever barriers were defined to be potentially or actually present in the clinical situation. These implementations should be repeated as often as needed; evaluation of the efficacy of those interventions ought to be an ongoing process for the clinician. This step necessitates the active sustained follow up phase of the collaborative process.
Step One: Assess Clinical Factors That May Influence Adherence

A variety of factors can influence medication adherence, therefore, it is critical that clinical factors are assessed prior to initiation of therapy. Specifically, assessment includes the proposed medication regimen, the decision making process used to initiate therapy, medication efficacy and success in medication adherence. It is advisable to assess the potential and/or actual factors in a patient’s life that could influence medication adherence. These factors are summarized below:

- **General Health Status**: medical history, nutritional assessment, opportunistic infections; behavioral factors – such as needle exchange activities.
  - Pertinent website: [http://www.projinf.org/pdf/tracking.pdf](http://www.projinf.org/pdf/tracking.pdf) - allows the patient to keep track of specific goals, health issues and lab data; [www.numedex.com](http://www.numedex.com)

- **Life Goals**: to understand deeper life issues such as: what gives meaning to a patient’s life; the context of illness and treatment in their life; their definition of quality of life; and learning of their attitudes and motivations based on their self-perception.

- **Medication History**: past experience, current regimens; side effect profile experienced on all medications;

- **Stage of Readiness**: (see in section below on Therapeutic Alliance)

- **Co-Morbidities**: psychiatric, substance abuse, medical illnesses (e.g., TB, STD, diabetes, liver disease, renal insufficiency, etc.);
  - Pertinent website: [http://www.projinf.org/indexS.html#ois](http://www.projinf.org/indexS.html#ois) - contains many useful short monographs on pertinent co-morbid illnesses, e.g., Hepatitis C, Depression, etc.

- **Social Stability**: housing status, food resources, transportation needs; financial status & insurance status;
  - Pertinent website: [http://www.ssa.gov/other.html](http://www.ssa.gov/other.html) - many links to government and housing assistance agencies – general and national info

- **Employment Status**: type of job, constraints, on the job disclosure issues;

- **Health Beliefs and Cultural Background**: language and perceptions towards illness, HIV disease, diagnosis, prognosis, role of medications, understanding of consequences of medication non-adherence, their spiritual/religious orientation in reference to their life and health goals;
  - Culturally specific sites / information can be acquired through the following link:
    - [http://www.hivcarenet.net/cultural_community/cultural_sensitivity.html](http://www.hivcarenet.net/cultural_community/cultural_sensitivity.html)

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Adherence to HIV Treatment Regimens: Recommendations for Best Practices
June 2002
MENTAL STATUS: assessment of past and current psychological, emotional and psychiatric challenges and related coping skills; \cite{133,121}

* Pertinent website - \url{http://www.mentalhealth.org/cmhs/HIVAIDS/links.asp} - several useful links to mental health resources (both general and specific to HIV/AIDS)

FAMILY AND SOCIAL SUPPORT: identification of personalized medication facilitator (buddy system) and network of social support; \cite{117}

EDUCATIONAL BACKGROUND: educational level, literacy level, baseline knowledge regarding HIV, viral load, CD4 count, medications and significance of adherence. \cite{77,87}

BEHAVIORAL FACTORS: risky sexual or needle-sharing behaviors
**STEP TWO: CREATE AND MAINTAIN A THERAPEUTIC ALLIANCE BETWEEN THE PATIENT AND PROVIDER**

By gaining a better understanding of the factors that can potentially influence adherence, the foundation for creating a therapeutic alliance has been established. This foundation will serve as the framework in which a trusting and caring relationship can develop and patient goals for personal health can be supported. By establishing a proactive patient-provider dialogue, a treatment care plan can be developed that is compatible with the patient’s goals and concerns. The therapeutic alliance between provider and patient may serve to promote mutual understanding of not only the goals of therapy but also the specific methods that are appropriate to help the patient reach those goals. This alliance will also support discussions that explore treatment success and failure. The areas central to the dialogue process are summarized below:

- **COMMUNICATION PROCESS & INFORMED CONSENT:** Specific training and skills development for clinical interviewing is needed in order to establish a therapeutic alliance keeping in mind the specific cultural and language background of the patient. A contractual agreement based on informed consent can assist in galvanizing the patient-provider rapport and commitment for medication adherence.
  - Use the following links to begin the process of communication and dialogue to establish patient & provider relationship:
    - [http://www.projinf.org/fs/dr-patie.html](http://www.projinf.org/fs/dr-patie.html) - provide/patient relationship
    - [http://www.projinf.org/fs/decisions.html](http://www.projinf.org/fs/decisions.html) - shared decision making
    - [http://www.projinf.org/fs/resources.html](http://www.projinf.org/fs/resources.html) - a comprehensive listing of those treatment, support and education services for HIV/AIDS

- **INDIVIDUALIZED PROFILE OF PERTINENT FACTORS:** An individualized profile of pertinent factors that may influence issues regarding medication adherence should be created. These factors should be identified in the preliminary assessment; A very useful web-based tool is available to start a dialogue between patient and provider – [www.aidsmap.com](http://www.aidsmap.com). It is an interactive ‘wheel’ (free online brief questionnaire) that can be completed and printed out for the patient to take to his/her provider. **There is an important listing of those factors that need to be considered in tailoring an antiretroviral regimen on the next page – Table 2**

- **IDENTIFY BARRIERS TO REACHING HEALTH GOALS:** Potential and actual barriers to reaching health goals of the patient should be identified, including medication adherence. Conversely, it is important to identify special support systems that may be present and could be further strengthened;

- **ASSESS PATIENT READINESS:** Assess the stage of readiness for behavior change, including medication usage and adherence. This staging will assist the provider in the potential application of motivational interviewing to move the patient to the next level of readiness, if and when the patient is empowered to do so;
* Pertinent website(s) -
http://pharmacy.auburn.edu/pcs/pypc0471/motivationalinterviewing/ - a website with materials on motivational interviewing and stages of change

➤ DETERMINE MEDICATION REGIMEN AND IMPLEMENTATION: Establish definitions of success and failure in both the virologic and clinical arenas, drug sequencing, implications of resistance testing, tailoring to daily lifestyle and potential utility of a pre-treatment simulation trial.\textsuperscript{106,139} An example of a web-based resource that facilitates the provider to develop a medication scheduler for the patient and check pertinent drug interactions easily: http://www.medscape.com/px/hivscheduler
### TABLE 2: FACTORS TO CONSIDER IN TAILORING AN ANTIRETROVIRAL REGIMEN

- **Pill characteristics** – size, taste, aftertaste concerns
- **Side effects** – list and prioritize the ones of concern
- **Symptom relieving medications** – availability and utilization
  - Link to Project Inform’s Side effect monograph: [http://www.projinf.org/fs/sideeffects.html](http://www.projinf.org/fs/sideeffects.html)
  - Link to HIVInsites Side effect monograph: [http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03&doc=kb-03-02-02](http://hivinsite.ucsf.edu/InSite.jsp?page=kb-03&doc=kb-03-02-02)
- **Toxicity concerns** – short & long term
- **Timing and frequency of doses** – once daily or twice daily associated with better adherence
- **Food restrictions** – find out about dietary preferences in conjunction with pills (whether patient prefers pills with food or fasting issues required)
- **Baseline viral load and CD4 cell count** – these will influence timing of HAART initiation to some extent; (as non-protease inhibitors containing regimens are demonstrating efficacy and durability, baseline viral load and CD4 cell counts may not be as significant factors determining specific agents)
- **Treatment history** – heavily experienced patients may have more limited options; additionally prior medications may have caused minor or major morbidity – these ought to be avoided
- **Health status of the patient** – more advanced patients have lower thresholds for toleration of side effects
- **Known or suspected viral resistance profiles** (class specific) – genotype / phenotype may be needed (see DHHS guidelines [http://hivatis.org/trtgdlns.html](http://hivatis.org/trtgdlns.html))
- **Existing comorbidities** – conditions may limit HAART options because of drug interactions and side effect profiles of concurrent medications
- **Domestic issues** – living situation / storage restrictions; concern regarding stability and storage issues for medications
- **Employment disclosure issues** – may need a regimen that can be taken outside of the work context or safely & discreetly within the work context
- **Polypharmacy concerns** – HAART meds have multiple drug interactions that may limit options; adherence to polypharmacy pill burden and pill fatigue are real issues; pill burden – desired vs. tolerable

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**STEP THREE: MONITOR THE LEVEL OF MEDICATION ADHERENCE**

If the HIV viral load goal is achieved, it is reasonable to assume that there is ongoing adherence to medications. If the goal, however, is not achieved, this may signal a number of possible causes for virologic failure, including non-adherence. There is a complex relation between what is considered an adequate, if not optimal, level of medication adherence and the degree of viral suppression necessary to reduce future viral resistance and retain clinical benefit.

Given the current limitations of medication complexity, rigors of dosing schedules, finite number of treatment options and risks of virologic and clinical failure, the question arises as to what level of medication adherence is truly necessary, practical and sustainable in the daily life of a patient for months and years. Perhaps, the best suggestion is that the strictest level of adherence be considered necessary to achieve the most durable viral suppression. There are significant data to suggest that high levels of medication adherence (90-95% of doses taken) are necessary for durable suppression of viral load measurements below the level of detection. Moreover, recent data suggest there are significant poor prognostic implications of non-adherence. Despite the documented necessity for such high and persistent levels of adherence, it is likely that actual adherence proportions may be no more than 50-60% in clinical care and community settings. This is understandable in the context of chronic illness since achieving such levels of adherence and maintaining them is simply too difficult for the heterogeneous HIV infected patient populations for several reasons as previously outlined. Both the shifting illness perspectives model and collaborative management care model of chronic illness add context and realism to what is otherwise an apparently impossible situation – i.e., maintaining complex polypharmacy regimens flawlessly over a lifetime considering quality of life issues, side effect management, pill fatigue, and potentially serious toxicities. To compound all these issues, there is a continuous threat of developing resistance and cross resistance to drugs with limited drug options for salvage situations.

One may wonder if it is truly realistic for patient and provider to expect some kind of definite threshold such as 85%, 90%, 95% let alone 100% medication adherence over the course of a lifetime. First of all, there are no other chronic disease models that have been able to show the feasibility or strict necessity of extremely high levels of medication adherence. Second, it has already been observed that some patients can achieve at least short-term virologic success and clinical success with relatively high levels of medication adherence that fall below the 100% ‘cutoffs’. Third, medication adherence should be seen in light of the patient’s overall willingness and specific health goals. Finally, despite the availability of multiple antiretroviral medications and combination regimens, there are associated significant pill burdens and side effects that do not facilitate adherence. The data still support that the optimal approach to HAART must include the highest level of medication adherence possible for a given patient in order to gain the maximal benefits of antiretroviral therapy: sustaining HIV virologic suppression, minimizing viral mutations, gaining immune reconstitution and keeping therapy options available for the longest time possible.
THE FOLLOWING LISTING OF SITES, SOME COMMERCIAL VENDORS, ARE NOT ASSOCIATED WITH ANY ENDORSEMENT, PROMOTION OR CONTRACTUAL RELATIONSHIPS BETWEEN THE AUTHOR(S), THE APHA AND ANY LISTED ORGANIZATION.

There are several direct and indirect measures of ongoing medication adherence that can be employed. The use of multiple measurements is more effective than a single method. A summary of the various strategies to measure adherence are listed below and on an extremely useful website:


- **VIRAL LOAD MEASUREMENTS** - [http://www.projinf.org/fs/HIVDiagTest.html](http://www.projinf.org/fs/HIVDiagTest.html) (informative page about viral load and other bloodwork that is used in disease management for patients)

- **PILL COUNTS**

- **PHARMACY TRACKING OF MEDICATION PICK-UPS**

- **CLINIC VISITS**: for scheduled visits, processing of disability paperwork, patient education related activities and dietitian visits;

- **MEMS BOTTLE CAP DEVICES**: if available; other commercial organizations also provide ‘reminder / monitoring’ tools: [http://www.aardex.ch/](http://www.aardex.ch/) (AARDEX Ltd); [www.epill.com](http://www.epill.com) (ePill);

- **SELF-REPORTS**: self-reporting tools and methods; both clinical care and epidemiological purposes;
  * ACTG – [see below](#) (CAPS site) **
  * Pediatric ACTG questionnaires: [http://www.fstrf.org/qol/peds/pedadhere.html](http://www.fstrf.org/qol/peds/pedadhere.html)

- **OBJECTIVE REPORTING**: objective reports of patient taking medication provided by caregiver, medication facilitator, home nursing, outreach worker, peer educators, etc.;

- **SIMULATION TRIAL RESULTS**: missed doses and confusion about treatment

- **CERTAIN LABORATORY VALUES**: i.e., MCV values which increase with the use of ZDV routinely; and

- **SURVEY TOOLS**: written forms of self-reporting, patient-centered group or one-on-one sessions that facilitate open discussion and frank reporting of medication management & adherence.

There is a recently developed tool on a notable website that is called “Adherence Attitude Inventory.” It is available at: [http://www.aac.org/hivhealth_adherence_survey.html](http://www.aac.org/hivhealth_adherence_survey.html). It is available as a link on the AIDS Action Committee website.

** The following web resource (CAPS) is a very useful listing of available survey instruments relevant to many aspects of HIV prevention and management:
http://www.caps.ucsf.edu/projects/instrumentindex.html - from the Center for AIDS Prevention at University of California San Francisco (accessed March 31, 2002)
STEP FOUR: IDENTIFY STRATEGIES TO IMPROVE MEDICATION ADHERENCE

If the patient is not adhering satisfactorily to the defined treatment regimen, the first step is to define the pattern of non-adherence. For instance, the patient could be missing doses, skipping doses, taking the wrong amount of medication or not modifying the diet to coincide with the treatment regimen. It is important to identify the specific barrier(s) that promote non-adherence and identify factors that can be modified which will enhance the patient’s ability to adhere to the regimen. Despite the sense of urgency and legitimate issues related to maintaining a failing regimen, it is nevertheless most important to thoroughly address these barriers before changing the regimen. If this is not done, it is quite likely that those unidentified and unaddressed issues will negatively influence adherence to the next regimen. It is also important to establish a culturally sensitive therapeutic alliance and cooperative dialogue to implement solutions that improve adherence that in turn help patients realize their own health goals.

These solutions can be targeted to match the specific barrier(s) that impedes adherence and/or to facilitate the specific factor(s) in their lives that promote adherence. Specific strategies to improve medication adherence are presented below:

- Review with the patient about his/her perception of health goals, HIV disease, purpose of HAART medication, role of adherence and consequence of non-adherence.  
- More effectively tailor the regimen to fit lifestyle, job situation and food habits.  
- Simplify the regimen by changing all or parts of the regimen to facilitate a better match of acceptable side effects, pill burden, dosing and timing. Regimens should be chosen with food requirements to which the patient has agreed.  
- Management of side effects should include an assessment of their impact on the patient’s life. Management of side effects should include changes in diet and alternatives such as acupuncture and herbal remedies where appropriate.  
- Identify barriers to non-adherence, focusing on prior/current causes of non-adherence so that subsequent new regimens are not likely to fail due to uncorrected problems.  
- Provide timely referrals and/or interventions for diagnosed co-morbidities that may negatively influence adherence. Problem-solve strategies to take medicines even if the patient does not want to stop using illicit drugs. Explore harm-reduction strategies that might help the patient avoid missing doses.  
- Take a ‘team’ multidisciplinary approach to non-adherent patients who may require multiple sources of expertise and support (e.g., case manager, nurse, social worker, medical provider, pharmacist, substance abuse & mental health counselors, health educators).  
- Make available a range of reminder devices, such as pagers, reminder watches, pillboxes with alarms and supportive computerized devices. Patients should also be assisted in
developing skills to incorporate treatment needs to their lifestyle, such as use of cues from the daily routine to remember to take medicines. For example, using the evening news as a reminder or standing in line to go to the night shelter as a cue to take medicines.

- Problem-solve with patients to develop strategies on how to take medications in places where they might have to hide to take their medicines, such as work, public places or in the presence of family members who are unaware of the HIV status.

- Utilize culturally sensitive peer educators who may assist the patient in a variety of areas: such as educational needs, medication adherence training, motivational interviewing and social support.

- Coordinate clinical care with case management to optimize support for critical needs and services (e.g., housing, food resources, transportation). Help the patient recruit family, significant others and friends to participate in the patient’s treatment plan and adherence efforts. If a support system does not exist, focus on creating a support system or linking with treatment support groups.

- Inform and educate the patient to be aware of major anticipated side effects of the drug therapies. Proactively provide prescriptions for symptom-relieving medications that may alleviate difficulties and enhance medication adherence.

- Enhance patient education by utilizing a variety of approaches, such as: culturally relevant, language specific patient education materials; health educator/health care provider–based intensive education or empowerment visits which are independent of clinic visits; provide self-management training for taking daily medications; provide educational reinforcement for concepts and skills learned, including successful adherence. There is an excellent resource for people living with HIV/AIDS that emphasizes self-management, personal and practical concerns.

- Closely assess and reassess the strategy for treatment initiation with the patient to optimize timing of starting therapy when the patient is sufficiently empowered. Timing of initiation of medications should allow for sufficient time to optimize prerequisite patient education, availability and encouragement for simulation trials and allow enough scope for patient autonomy in medication selection.

- Enable the patient to assume greater participation in the learning process by using motivational interviewing techniques and framing the dialogue regarding medications, adherence and side effects in a context of helping the patient be an active learner.

- Assist the patient to have a greater sense of responsibility for his/her own health care, defining goals and creating and implementing strategies to reach those goals, e.g., instituting a ‘care contract’ based on a therapeutic alliance and informed consent prior to treatment initiation.
Provide incentives to enhance therapy such as tokens, certificates, food vouchers, bus tickets, restaurant gift certificates, etc.  

Provider education to enable greater understanding of adherence issues: factors influencing adherence, cultural sensitivity, motivational interviewing, and client-centered decision making.
### TABLE 3 – USEFUL WEBLINKS for HIV/AIDS & Treatment Adherence

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<th>Practical links (regimen tailoring tools; patient education materials, advocacy)</th>
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VII. Case Scenarios

The following 2 case scenarios are provided as examples to assist the provider in identifying issues related to medication adherence that should be explored in the context of a time line of care. (The UCSF website HIVInsite has within a link to the AIDS Education and Training Center Adherence Curriculum, that takes a similar ‘case-based’ approach; it is a notably valuable resource for provider training and can be accessed at: http://hivinsite.ucsf.edu/InSite.jsp?page=kbr-03-02-09&doc=2098.4504)

Case Scenario 1, Part A: A 38 year old HIV-infected woman presents for her first health care visit for HIV. She tested positive 6 months ago and is currently doing well after recently completing an alcohol rehabilitation program. Activities to undertake and areas to explore include:

<table>
<thead>
<tr>
<th>ACTIVITY</th>
<th>AREA(S) TO EXPLORE</th>
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</table>
| Assess HIV knowledge and prior HIV testing | **HIV knowledge:**  
• Assess the level of understanding of her disease  
• Identify the patient’s major source of information about HIV and determine knowledge of newer medications  
**HIV testing:**  
• Determine when the 1st positive test result was received  
• Determine whether a negative test result was ever received  
**HIV history:**  
• Assess risk behaviors and explore mode of transmission  
• Identify symptoms of HIV disease that have been experienced  
• Determine whether CD4 cell counts or viral loads have been conducted and if so, what the results were. |
| Obtain detailed history | **Past medical history:**  
• Identify ongoing medical problems, history of pneumonia, STDs, herpes zoster or cervical disease  
• Discuss past hospitalizations  
• Determine whether she has been exposed to anyone with TB and date of last screening  
• Identify allergies and reactions to medications  
**Habits:**  
• Assess current use of tobacco, alcohol or illicit drugs  
• Quantify amounts of substances used and frequency  
**Medications:**  
• Identify medications taken on a regular basis |
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<thead>
<tr>
<th>ACTIVITY</th>
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<tr>
<td></td>
<td>• Assess pattern of adherence to past medication regimen, if any</td>
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<td>Social History:</td>
<td>• Assess the living situation and source of support</td>
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<td></td>
<td>• Determine whether patient has a place to live</td>
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<td></td>
<td>• Identify mode of transportation and determine whether assistance is needed for appointments</td>
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<td></td>
<td>• Determine employment status and need for after hour services</td>
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<td></td>
<td>• Determine source of funding for medications, e.g. insurance, ADAP</td>
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<tr>
<td></td>
<td>• Identify need for child care</td>
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<td></td>
<td>• Discuss level of sexual activity, partners and use of condoms</td>
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<tr>
<td>Review of Systems:</td>
<td>• Explore patient's health concerns</td>
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<tr>
<td></td>
<td>• Assess presence of fevers, chills, night sweats, diarrhea, fatigue, appetite suppression, headache,</td>
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<td></td>
<td>shortness of breath, visual changes, sleep problems, mood changes, numbness or tingling of hands or feet</td>
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<td></td>
<td>• Review GYN history, including past abnormal pap smears</td>
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<tr>
<td>Assess physical health</td>
<td><strong>Conduct a thorough physical examination with special attention to:</strong></td>
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<td></td>
<td>• Mouth: thrush, oral hairy leukoplakia, poor dentition</td>
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<td></td>
<td>• Lymph nodes: neck, axilla, groin</td>
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<tr>
<td></td>
<td>• Skin: rash., seborrheic dermatitis, molluscum contagiosum, KS</td>
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<tr>
<td></td>
<td>• Abdomen: enlarged liver or spleen</td>
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<td></td>
<td>• Weight: usual weight compared to current weight, abnormal fat distribution</td>
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<td></td>
<td>• Mental health: depressed mood, coping skills</td>
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<tr>
<td>Assess immunologic status</td>
<td>• Complete blood count and differential</td>
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<tr>
<td></td>
<td>• Total CD4 cell count</td>
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<td></td>
<td>• HIV viral load</td>
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<td></td>
<td>• Repeat HIV serology if prior documentation is not obtainable</td>
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Once these activities have been completed, an overall assessment and a management plan can be completed. In doing so, the provider should review with the patient what was learned about her and the preliminary assessment of her HIV status should be discussed. The patient should be informed of the potential treatment options and be provided with written materials appropriate for her literacy level. Pertinent patient education materials include information about HIV disease, treatment options, potential side effects of medications, and resources available in the community. During the initial visit, the concept and importance of adherence should be introduced.
information should be presented in a straightforward manner and potential problems that may arise if the medications are not taken as prescribed should be explored.

*It is important to note that antiretroviral medication is rarely prescribed during this initial encounter.* It is more important to begin to learn about the patient, understand her wishes for treatment, and determine her level of immunosuppression. This will enable the provider to select an antiretroviral regimen that is best suited to her personal health goals and lifestyle. During subsequent medical appointments, the patient’s level of adherence can be assessed and barriers to care can be determined and addressed. Despite the new diagnosis and HAART naïve status, it is necessary for the patient and provider to engage in a proactive dialogue to determine the actual stage of readiness before proceeding. If indicated, other non-antiretroviral medications such as vitamins or pneumocystis carinii pneumonia (PCP) prophylaxis should be prescribed during the initial visit.

**Case Scenario 1, Part B:** Three weeks later, the patient returns to the clinic for her second appointment. She has alcohol on her breath but is well groomed and punctual. The patient is interested in antiretroviral medication, but is concerned about taking medication three times a day. She indicates the number of pills is less important than the number of times per day she must take the medication. She has applied for ADAP, but has Medicaid which covers antiretroviral medications. The test results completed during the initial visit document a CD4 cell count of 375 (30%) and a viral load of 43,000 copies/ml.

The second visit may or may not be an appropriate time to explore treatment options. In this case, the patient has expressed interest in starting a regimen. While the provider notes alcohol on her breath, it is clear that the patient has thought about the medications and has taken steps to ensure financial coverage is available. Based on this and the preliminary assessment, the decision to move forward with a treatment regimen should be explored. If available in the area, clinical trials might be an option to consider.

Working in tandem, the provider and patient should agree upon a treatment regimen that is thought to have the best chance of success. In this case, Combivir and Nelfinavir may be a viable option as both can be taken BID. Once a regimen is outlined, the potential side effects should be discussed and presumptive prescriptions should be offered for such side effects as diarrhea. The patient should be provided with a written schedule and if possible, pictures of the medications that will be used. Other assistive devices such as pillboxes or timers can be provided to aid in the adherence efforts.

As the treatment regimen is being discussed, it is also important to reiterate the importance of adherence to the prescribed regimen and once again outline the potential ramifications of non-adherence, such as emergence of resistant viral mutants. If appropriate, it may be helpful to consider recruiting family and friends to support the treatment plan and encourage adherence. To provide an opportunity for ongoing
education, the patient should be provided with a phone number to call if any questions arise. It may also be helpful to obtain permission to have a member of the health care team call her in the next week or so to see how she is getting along with the new medications.

It is important to address the alcohol use and make referrals, as appropriate. Depending on the level of use and her willingness to seek treatment, harm reduction strategies and problem solving may be useful. Once a treatment regimen is prescribed, a follow-up appointment should be scheduled within two to three weeks to obtain a follow-up viral load and CD4 cell count.

From that point on, an interim history should be obtained to determine if the patient is experiencing any problems with or concerns about the antiretroviral medications. It is helpful to review the schedule of medications in light of her usual daily activities and meals. Positive feedback should be provided on her progress with adherence and the difficulty in taking the medications should be acknowledged. If the patient is having difficulty adhering to the regimen, is experiencing bothersome side effects, or the medications are not controlling her viral load, the provider may wish to consider monitoring her more closely, e.g. every two to four weeks. As indicated, CD4 cell counts, viral loads and other laboratory values should be assessed.

**Case Scenario 2:** A 44-year old man diagnosed with HIV eight years ago presents for routine follow-up. He has a long history of injection drug use and depression. Prior to his first clinic evaluation 3 years before, he had started using drugs after being released from prison where he had lived for the previous four years. At the initial visit, the patient requested help with his drug problem and successfully completed an inpatient detoxification program and enrolled in a methadone maintenance program. The patient also began seeing a counselor for his depression and was placed on antidepressants for the first time. As his mood improved, he was started on antiretroviral therapy approximately one year after the initial visit. With the exception of one relapse, the patient has been drug free for over one year and is currently living in safe and affordable housing.
The patient has done well on antiretroviral medications over the last two years but has recently developed lower back pain and kidney stones, presumably from the protease inhibitor medication. The patient stopped the protease inhibitor but continued his other two nucleoside analog medications. The most recent viral load was 12,000 having been undetectable for the previous six months. Activities to undertake and areas to explore include:

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<th>ACTIVITY</th>
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<tr>
<td>Assess adherence</td>
<td>• Review the current treatment regimen and adherence pattern</td>
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<td></td>
<td>• Determine when and if patient takes each of the medications</td>
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<td></td>
<td>• Explore strategies that were undertaken to overcome side effects</td>
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<td></td>
<td>• Identify other medications that may be affecting HAART</td>
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<td></td>
<td>• Review with the patient the known drug interactions between HAART, methadone and antidepressants</td>
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<td></td>
<td>• Explore patient’s thoughts about new antiretroviral medications</td>
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<tr>
<td>Assess physical health</td>
<td>• Perform thorough physical examination</td>
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<td>• Obtain routine blood work and other tests as indicated, e.g. urinanalysis to assess possible hematuria, amylase if concerned about pancreatitis, fasting lipid panel if abnormal fat distribution is noted</td>
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<tr>
<td>Assess immunologic status</td>
<td>• Complete blood count and differential</td>
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<tr>
<td></td>
<td>• Total CD4 cell count</td>
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<tr>
<td></td>
<td>• HIV viral load</td>
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<tr>
<td></td>
<td>• Consider genotypic and/or phenotypic analyses to rule out possible genetic mutations of the virus</td>
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Upon completion of the overall assessment, the provider should review what is learned with the patient and explore potential treatment options. It is reasonable to assume that the detectable viral load has occurred on a sub-optimal dual nucleoside regimen since the patient presumably stopped the third medication – likely a protease inhibitor. It is useful to engage the patient in a dialogue that will better define self-reported patterns of adherence and even seek supplemental information from others who have a significant role (if any) in the patient’s health. It is worthwhile to delve into specific medication habits, water intake and any changes in stage of readiness also. It is possible these were contributory factors to the detectable viral load; indeed these may have been operative in leading to gaps in the medication adherence even to the dual nucleoside regimen. If necessary, additional written materials should be provided. Information related to salvage protocols...
should be shared and together, an optimal treatment regimen should be identified. Because the patient elected to stop a medication due to a perceived side effect, it is important to stress the need to talk with the provider prior to discontinuing any medications. Successful adherence strategies that have been employed in the past should be revisited.

In each of the case scenarios, regardless of whether the patient is drug-naive or experienced, it is important to establish a patient-provider partnership where information and feedback will be provided to patients on a regular basis. Questions and concerns should be addressed in a non-judgmental fashion and the social, physical and medical needs all need to be confronted in order to successfully develop an acceptable treatment plan. Providers can also enhance the likelihood of an effective partnership by accurately assessing the readiness of the patient to make behavior changes, and by determining if the patient has ambivalence about the treatment plan. If so, options to address the specific issues should be explored.

It is also important to reinforce the need to adhere to the treatment regimen at each clinic visit. Constructive, positive feedback should be provided to promote the patient’s progress. This process includes maintaining the treatment regimen, utilizing potential enhancers, and identifying obstacles to adherence. Tips to help with adherence over time should be provided. It is critical to consider and adjust medical regimens to fit the lifestyle and desires of the patient.
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