Adherence to Highly Active Antiretroviral Therapy


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Adherence to HIV Therapy: Building a Bridge to Success

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INTRODUCTION

The issue of adherence to highly active antiretroviral therapies (HAART) is multidimensional. HAART’s potential for long-term effectiveness is dependent upon maximum and durable suppression of viral replication. To meet such success requires near-perfect adherence to a complex regimen often including three or more drugs, consisting of 20 or more pills each day, taken two or three times daily at strict intervals, and with their own ingestion protocol such as fasting and high-fat or high-protein meals. Adherence is a central issue of concern in antiretroviral (AR) therapy, but a gold standard by which patients should be measured is lacking. This paper highlights relevant findings from an extensive, but not exhaustive review of peer-review journals and conference abstracts on adherence and compliance to HAART since November 1997.

In December 1995, the FDA licensed the first protease inhibitor for AIDS therapy. In July 1996, encouraging results from clinical trials of drug cocktails containing this new class of antiretroviral agent were reported at the 11th International Conference on AIDS. The three classes that make up HAART regimens are nucleoside analog reverse transcriptase (RT) inhibitors, non-nucleoside analog RT inhibitors, and protease inhibitors (PI). Since 1996, an overwhelming amount of scientific evidence has been published lending to the validity of combination therapies for HIV and AIDS patients. Substantial rates of decline in opportunistic infections and AIDS related mortality have been observed. A number of studies have consistently witnessed reductions in plasma HIV-1 RNA and increases in CD4 cell count, even among patients with initially very low counts. Adherence to complex HAART regimens are complex and inconsistent adherence to a treatment regimen may lead to the development of drug resistant mutations resulting in treatment failure. This increases the probability of at-risk
populations becoming infected with multiresistant HIV, thereby producing a potential public health consequence. Plasma HIV RNA levels have shown to quickly rebound in those with undetectable viral loads after stopping therapy, in some cases even exceeding pre-therapy levels within 21 days.\textsuperscript{17} Recent evidence has shown that patients on long-term HAART with undetectable levels of plasma viremia can harbor replication-competent HIV-1 DNA in resting memory CD4+ T cells.\textsuperscript{15-17} This new evidence sheds light on the realities of an indefinite reprieve from complex regimens even when undetectable levels of plasma viremia have been met; at best, with current medications HAART may be a life-long process. Because of this recent scientific revelation, there must be a convalescence of patients, clinician/health care workers, public health personal, the pharmaceutical industry, and other ancillary services to create meaningful answers to the myriad of questions surrounding HAART adherence.

**BENEFITS OF ADHERENCE**

Strict detailed adherence to physician-prescribed HAART regimens has been shown to be clinically beneficial. In a study of PI adherence in 84 subjects, who used an electronic pill monitoring device, 81% of subjects with > 95% adherence had complete viral suppression compared to only 64% with 90-95% adherence, 50% with 80-90% adherence, 25% with 70-80% adherence and 6% with < 70% adherence.\textsuperscript{21} In a prospective observational study of adherence, a linear trend of increasing adherence was seen for those with reduced HIV RNA and increased CD4 cells. After six months of treatment those reporting 100% adherence had a 1.1 log10 copies/ml decrease in HIV RNA and an increase of 72 x 10\(^6\) CD4 cells/l compared to a 0.2 log10 copies/ml increase in HIV RNA and a loss of 19 x 10\(^6\) CD4 cells/l for those with less than 80% adherence.\textsuperscript{31} Other studies have also shown a relationship between adherence and
undetectable plasma viremia. Adherent individuals have been shown to have reduced viral loads and increased CD4 counts, live longer, and have better quality-adjusted life years; these effects are even more pronounced for patients who were naive to treatment prior to starting a HAART regimen.

**DEVICES USED TO MEASURE ADHERENCE**

Adherence to AR therapy has been measured by a variety of mechanisms. The most common modes seen in the literature are pill count, pharmacy records, and self-report. Others include drug plasma concentration, plasma HIV-1 RNA and CD4 cell count; medical appointment keeping, electronic medication monitoring/medication event monitoring system (MEMS), patient reporting track-screen PC, and clinician/provider estimate of adherence. Some modes of measurement appear to be more accurate than others and no one measure has been established as a gold standard. For example, in a six-month study, evaluating 195 adherence estimates, objective evaluations of clinicians’ estimates of patients’ adherence with PIs, using MEMS, found clinicians to be overestimating patients’ adherence. In fact, 25% of patients whose providers estimated to have greater than 90% adherence actually had adherence of less than 80%. The appropriate number of days used, prior to interview, to measure adherence varies greatly in the literature. Measurement of adherence the day before interview is predictive of one's previous month adherence behavior. Weidle and colleagues found that adherence the day before interview is consistent with adherence one month before interview. Those who reported non-adherence on the day prior to the adherence interview were 9.9 times more likely to report non-adherence the prior month than those who reported adherence.
RATES OF ADHERENCE

Estimates for adherence rates differ considerably from study to study. The range for adherence to ARs in recent analyses was from 25% to 85%. By analyzing plasma samples for concentrations of assigned drug(s), researchers can estimate the levels of adherence among patients, in addition to their reliability of self-report. For example, seven hundred twenty-two plasma samples were analyzed from the AIDS Clinical Trials Group protocol 175, a large, double-blind, randomized study of monotherapy versus combination dideoxynucleoside therapy. Samples were analyzed for assigned drugs particular to each patient. Approximately 75% of the 722 analyzed samples had detectable concentrations of their assigned drugs.

FACTORS THAT INFLUENCE ADHERENCE

A multitude of variables has been investigated and shown to affect adherence to AR medications, some more than others. For example, The HIV Cost and Utilization Study, a national representative probability sample of 1910 persons taking ARs, found 57% of the subjects to be 100% adherent over the seven days prior to interview. Heavy alcohol and drug users were significantly less likely to adhere to ARs (45% vs. 59%, p=0.003). Being older (p<0.0001), male sex (p=.008), non-minority (p=0.001), and insured (p=0.003) were significantly related to better adherence to ARs. In addition, drug regimens that worked well with patients schedules (p<0.0001) and the perception that ARs are effective and that non-adherence leads to viral resistance (p<0.0001) were also predictive of good adherence.

FACTORS ASSOCIATED WITH POOR ADHERENCE

A number of variables have been shown to be related to poor adherence. Untoward effects/toxicities, including nausea, forgetting to take dose, and drug (including
IDU) and alcohol use were the most commonly seen predictors. In a study of 505 patients receiving PIs for 4 months, 35% (n=177) discontinued treatment. Thirty-two percent of those who discontinued treatment did so because of nausea to ritonavir, 26% and 24% because of failure of therapy for indinavir and saquaniivir, respectively. In a diverse sample of AR recipients, twenty-nine poorly adherent patients listed a total of 50 reasons for not adhering to their therapy. Over half were related to side effects/toxicity and forgetfulness, 28% and 24%, respectively. In a diverse sample of 235 individuals from London, Oslo and San Francisco, reported that they forgot to take their HIV medication. In multi-center study with 151 patients receiving PIs a history of alcohol dependence or drug use predicted poorer adherence (p<0.05).

Variables associated with access to care, including problems with getting medicines resupplied or lack of medicines, lack of insurance or money for treatment, government subsidized health insurance and health care from public/University clinics, long distances to travel and lengthy waiting times for physicians and at pharmacies, and lack of housing were predictive of decreased adherence. The facility from which one receives his or her health care may have an effect on adherence. Among an ethnically diverse sample of 463 men who have sex with men (MSM) from New York City and San Francisco, 48.9% of those currently taking ARs reported at least one day in which a dose of medication was missed. Those receiving health care at a public facility were more likely to miss doses than those receiving health care from a private physician ($X^2=11.74$, p=.039).

The burden of medication on lifestyle (finished drug-course before scheduled medical visit (not motivated to get refill), too many different medications and pills, avoiding side-effects in key situations/embarrassment (job interview, dating), work-place related intake problems, lack of interest in getting information on HIV, and too busy to work medication schedule into
daily routine, also affected adherence. Gregory and colleagues analyzed the charts of 273 PI-naive patients at the Johns Hopkins University HIV Clinic. In logistic regression analysis, only adherence to clinical visits remained independently associated with HIV-1 RNA suppression. Analysis of phone records from 179 counseling/psychological HIV therapy patients in Buenos Aires, Argentina, found a medication adherence rate of 43%. Quoted reasons for poor adherence included problems in getting medication re-supplied (24%), avoiding side-effects in key situations (20%), and work-place related intake problems (17%).

Patient health beliefs, attitudes, and psychosocial health also had an affect on adherence. For example, failure of therapy, no improvement in health status, belief about the effectiveness of ARs (medication causing harm), taking unconventional treatments with ARs, non-detectable plasma virus/asymptomatic state, and extreme levels of anxiety and psychosocial problems were all associated with poorer adherence. In addition, a small number of studies found demographic variables such as younger age, low education/literacy, female gender, minority status, and increased age to be additional factors associated with poor adherence.

**FACTORS ASSOCIATED WITH BETTER ADHERENCE**

Variables most predictive of better adherence in the literature were a strong relationship (support, trust, and a feeling of being well cared for) between the patient and the clinician/health care provider and/or system, improved CD4 cell counts and a lowered viral load, and emotional support and continued interaction with peers. In a diverse sample of 727 HIV positive individuals, 22.8% female and 56.8% non-white, those who reported the ability to maintain social interactions and rated their social support highly were more likely to be adherent to medication, follow advice and instruction, and keep appointments for visits.
The belief that PIs will extend life, and that poorer adherence leads to viral resistance were related to increased adherence. Demographic variables associated with good adherence included higher income, education, older age, and Caucasian race. Other factors included stable mental health and long-term plans/goals, having health insurance and addiction care, improved sex drive and, surprisingly, an increase in the amount of pills taken per day. Adherence data for 1910 individuals, analyzed from The HIV Cost and Services Utilization Study found AR adherence strengthened with an increase in the number of drugs and pills prescribed per day (1-10 pills 53%, 11-20 pills 61%, > 20 pills 59%). For well over half (62%) of those receiving PIs in a multicenter study of 248 patients, the belief that PIs will extend one’s life was the leading motivating factor for adherence. In a study of adherence to PIs, for 74 subjects over a six-month period, Kaplin and colleagues found that those who initially responded to therapy with a decreased viral load adhered better to PIs over the length of the study period compared to those subjects whose viral load did not decrease.

Adherence Among the Homeless

ARs are sometimes withheld from HIV-positive homeless and marginally housed persons (H/M) in fear of poor adherence to therapy. Bangsberg and colleagues investigated adherence among a representative sample of 154 HIV-positive H/M persons in San Francisco. Access to PIs in this sample was poor; at baseline only 7% were currently taking ARs. Cohort retention was high (82%). Adherence was good among H/Ms taking PIs; 80% of these subjects reported missing less than 2 doses per week (n=23). Of adherent subjects, 88% had detectable AR medication in their plasma (n=18). In a representative cohort of 132 HIV-infected H/M subjects, 22% had received PI and reverse transcriptase inhibitor (RTI) therapy. Cohort retention after nine months was 95%. Eighty percent of the H/M subjects reported taking greater than 90% of their prescribed
doses, and plasma drug levels were consistent with self-reported adherence (88% detectable, n=17).  

Adherence Among IV Drug Users

It has also been hypothesized that HIV-positive individuals who are currently using, or have a history of using drugs, may be less adherent to AR therapy than those without this behavior or history. In a large sample of 727 individuals, 56.8% reporting never using injection drugs and 39.3% reporting being a former or current user, injecting drug use was not related to keeping appointments or following healthcare advice and instruction. Active IDUs were more likely to report lower medication adherence scores, although the amount of variance explained (1.3%) in step-wise regression was modest. Information from a sub-sample of 66 individuals from a sample of 314 HIV-infected IDUs enrolled in a cohort study in France was analyzed. All 66 individuals had received double or triple combination therapy. Active drug users were no more less compliant than ex-IDUs, but one-third of these patients did have problems with AR adherence. Among patients taking triple combination therapy, those who were enrolled in drug maintenance treatment programs tended to be more compliant than those who were not (85.7% vs. 56.4%). A qualitative study of factors related to adherence of AR among IDUs who were stabilized on methadone was carried out with twenty-three individuals. Having a positive attitude toward the future, a good relationship with one’s medical team, a belief that ARs improve survival and help compliance with a heroin free state, and being in prison were factors positively affecting continuance of therapy.

Adherence Among Women

As is the case with other demographic variables, studies have found both poor and
good levels of AR adherence among women. In a study of 102 female prisoners, predictors of good medication adherence included trust in medications and the health care system, and interpersonal relationships with physicians and peers. Factors relating to decreased adherence among woman in a number of studies included forgetting to refill medications and not understanding how to take them, older age, and side effects. Other studies have also addressed adherence among HIV-positive pregnant women and have found mixed results.

**Adherence and Race**

The majority of studies have not found race to be related to adherence rates. Though race overall may not be an indicator, there may be characteristics or confounding factors within different racial groups that affect levels of adherence. For example, in a cross-sectional study of 158 outpatient HIV clinic patients, African Americans were no less likely to adhere to ARs than Caucasians (race OR=1.06). Caucasians reported inconvenience of medications (p=0.02) and taking more medication as directed as barriers to adherence; whereas, African-Americans reported that no storage place for medications (p=0.024), ceasing medication use because of feeling better (p=0.033), not taking medication away from home (p=0.014), and being to embarrassed to get refills (p=0.019) were barriers. In a study of 74 HIV-infected patients that investigated the association of literacy with AR adherence regimens among African-Americans and Caucasians. African-Americans were found to be significantly less adherent to ARs (31% vs. 11%, p<.05), understood less the meaning of CD4 lymphocyte counts (56.3% vs. 77.1%, p<0.0001), and were less likely to understand the meaning of HIV-viral load measurement (87.5% vs. 28.6%, p<0.0001). Over three-quarters (83.3%) of Caucasian patients were always adherent to ARs compared to 66.7% of African-Americans with high literacy; only 34.1% of African-Americans with less than a 6th grade reading level adhered to ARs (p<0.0001). It should be noted,
however, that this study did not compare groups with equal literacy levels.\textsuperscript{74}

**Adherence to Prophylactics**

Adherence to prophylactic medications for preventing opportunistic infections is also a concern for many clinicians. High rates of non-adherence to opportunistic infection prophylaxis among HIV-positive patients have been seen.\textsuperscript{91-93} Data was analyzed for 419 subjects in order to predict adherence to mycobacterium avium complex (MAC) prophylaxis. Intentions to keep all medical appointments (OR 3.20, p=0.008) and having a higher level of education (OR 1.90, p=0.026) were associated with increased adherence. Not being interested in getting more information about HIV (OR 0.34, p=0.026), being too busy (OR 0.40, p=0.026), and being concerned about long clinic waiting times (OR 0.47, p=0.034) were also associated with decreased adherence.\textsuperscript{66} In a Centers for Disease Control (CDC) study of 839 interviewed patients, prescribed prophylaxis for pneumocystis carinii pneumonia (PCP), 79\% said they always took their medications as prescribed. Side effects (34\%), forgetting to take medication (28\%), and difficulty working medications into daily schedule (15\%) were the most frequent reasons for not being 100\% adherent. Non-adherence to PCP prophylaxis was greatest among younger persons (18-25) (p=0.02), IDUs (p=0.02), individuals with knowledge of their HIV status > 2 years (p=0.02), taking PCP prophylaxis > 6 months (p=0.02), a history of crack cocaine use (p=0.05), and asymptomatic HIV infection status (p=0.06).\textsuperscript{46}

**ADHERENCE INTERVENTIONS**

A variety of interventions have been tested and implemented in order to increase adherence to ARs. One approach that seems to be having particular success is the pharmacist counseling intervention. Though the intervention components may differ slightly from study to study, the basic
approach of the hospital/clinic pharmacy intervention or individually advised intervention is that of counseling patients individually. This approach consists of adapting treatment to the patient’s lifestyle (writing out a medication schedule and setting up a pill box), explaining the clinical benefits of optimal adherence and identifying any risk factors for non-compliance, and providing telephone support. In a one year study testing the pharmacy intervention approach, 186 patients, 73% male and 48% IDU, were randomized (2/1) to conventional care (attending physician prescribed treatment) or hospital pharmacy intervention. Good adherence was defined as more than 90% of the drug regimen being taken. Those in the pharmacy intervention group were significantly more adherent than those under conventional care (p=0.0005). This adherence coincided with a decrease in viral load (p=0.04). Knobel et al. studied a similar intervention on 170 patients who were assigned (2/1) to the conventional care or individually advised group. Correct adherence, defined as greater than 90% for prescribed drugs, was estimated at 52.7% for those receiving conventional care and 76.7% for those being individually advised (p=0.002). Reliability of adherence was strengthened with evidence of change in viral load at the 24-week follow-up from baseline. Undetectable viral load (<50 copies/ml) was found in 54.5% of those receiving conventional care compared with 65% of those being individually advised (p=0.18). Even more pronounced was the reduction in viral load of 1.02+/- 0.5 log10/ml for the conventional care group compared to 1.98+/- 0.7 log10/ml for those being individually advised.

Interventions such as alarm devices and directly observed therapy have also been shown to increase adherence. Mannheimer and colleagues investigated adherence among 49 patients, 88% minority and 47% former IDUs, using an ALR (tm), a small, portable medication alarm programmed to sound daily at medication dosing times. The frequency of 100% pill, time and diet
adherence was dramatically improved from baseline (N=49, 25% adherence) to month one (N=36, 67% adherence, p<.005) and month three (N=18, 89% adherence, p<.001) follow-up. Modified directly observed therapy (MDOT) is a procedure in which an outreach worker meets with a patient Monday through Friday morning, at the patient’s house or site of his or her choice, in order to observe a completed medication dose. The outreach worker asks about and records missed doses that are to be self-administered during the evenings and weekends. The number of meetings is tapered based on the participant’s readiness. After 10 months of MDOT, for a very diverse group of 32 patients in a pilot program, of which 24 completed the study, 46% successfully had their number of visits reduced from 5 to 1-3 per week. Missing one or more doses in the preceding four days was decreased from 47% at baseline to 15% at 6 months for the thirteen patients for which 6 months of data was available.

Other adherence interventions which deserve further investigation based on preliminary findings include, but are not limited to mass media adherence campaigns; Medication Management (labeled pill boxes for dosing and dosing instruction cards) and Patient Support (patient planner, newsletter, and graphs of HIV RNA and CD4 cell counts); videos/booklets, devised by people with HIV, that have laymen explanations of the science of HIV disease in addition to the importance of adherence and approaches to increase adherence; a customized compliance check list which tracts the number of screenings completed each month, changes in self-reported adherence, viral load and CD4 counts, and completed interventions in order to evaluate the degree to which the adherence program is working; automated telephone communications technology mixed with live counselor calls in order to deliver counseling support for adherence enhancement; a case-by-case triaged approach using nurse educators, social case management and mental health interventions, which includes psychosocial evaluation and treatment
to improve adherence, and a newsletter with up-to-date research findings including aspects of HIV/AIDS therapies and adherence.

Interventions made for the purpose of fully guiding the clinician/health care worker in his or her treatment implementation have also been addressed. A good example of this is the HIV Medication Guide, which includes over 350 drugs involved in the management of HIV and opportunistic infections, and can be used by clinicians/health care workers and community organizations. It assists in guiding the health care provider in designing individualized, optimal drug administration schedules, while simultaneously helping to detect drug interactions and giving the appropriate nutritional and pharmaceutical tips that will lead to reduced side effects and improved compliance.

DISCUSSION AND RECOMMENDATIONS

Original research on HAART adherence in peer-review journals is limited but growing. The majority of articles that have been published are often based on the application of adherence studies in other fields of medicine, and how such findings may be applicable to HIV. The bulk of the original research reported on here was found in books of abstracts from a variety of conferences that specifically feature HIV research.

While there is a wide array of adherence measurements, there is no gold standard and a variety of measures may be best. Of the available measurements, MEMS caps, drug plasma concentrations, HIV-1 plasma RNA copies, and CD4 cell counts, though more expensive than conventional means (pill count, pharmacy records, and self-report), must continue to be used and improved on in order to obtain more accurate rates of adherence. Though ALR(tm) shows promise as a device to increase adherence, certain limitations must be addressed in order to improve upon attrition; 50% of the subjects, in the study by Mannheimer and colleagues, experienced
malfunctioning with their devices. Since dramatic changes were seen for those without malfunctioning devices, technological advances in this area may have great potential in improving patient adherence.

AR adherence for those in hard to reach populations must be addressed. Preliminary data on adherence to ARs, though by use of small samples, among the homeless and marginally housed may be higher than hypothesized. Therefore, not only should ARs be made more available to this population, but also clinicians and outreach workers should not assume their patients’ homelessness would result in poor adherence. Adherence rates for individuals currently using drugs is not favorable, but do not necessarily seem to differ from that of other groups in some studies. Physicians should not make unwarranted assumptions about the ability of adhere to therapy because of a history of drug use. Factors influencing those who do comply with regimens seem to be similar to other populations. Those in drug maintenance treatment programs seem to have better rates of adherence. Research exploring the causes of adherence among IDUs in treatment setting warrants further research.

Most analyses of patient data in the literature and presented at conferences have not found any particular race to be more or less adherent than another. Though variables associated with adherence within race may differ from group to group.

Low literacy has been identified as a factor affecting adherence rates. Interventions that help to increase the understanding of HIV disease, including literature appropriate for the patient’s level of reading, may go far toward increasing HIV adherence among those with lower literacy.

One untapped commodity of adherence intervention that may provide researchers with adherence questions may lie in the clinical trial setting. A retrospective chart review comparing adherence among individuals enrolled in an open label drug trial and those receiving antiretroviral
drugs in the same clinical care setting found improved adherence for the former. Eighty-four percent (43/51) of patients in the clinical trial group had a plasma viral load of <400 copies/ml compared to 59% (15/36) of those in the clinical setting. Other studies comparing clinical trials and outpatient clinics have yielded similar results. Thus, the clinical trial setting may offer clues into variables associated with adherence and should be explored.

Quality adherence to AR therapy is an ongoing process in which the patient needs to be directly involved, it is not something an individual naturally possesses or lacks. Interventions to increase adherence must address cultural differences within race, gender, sexual orientation, and even religion. They must be tailored to meet culturally relevant barriers, including differences in language. Efforts must continue that help patients complete treatment, paying close attention to sociocultural circumstances as well as the psychological and economic factors that may impede upon adherence. Physicians should not automatically assume a future of poor adherence by their patients on the basis of demographic and behavioral characteristics. These assumptions, on the part of the clinician, could stigmatize the clinician-patient relationship, thereby possibly introducing an additional impediment to adherence. An emphasis on language that stresses the inability of the patient to adhere to the devised medication regimen should be dropped and supplemented with language that stresses the role of the patient in devising and implementing an individualized treatment plan. Such language should be as elementary as possible with no reference to medical jargon.

Differences in access to health care are an important factor in adherence rates. Lack of insurance, dependence on public health care, and inability to fill prescriptions all effect adherence rates. Ensuring quality and consistent health care delivery is essential in promoting good adherence to therapy.
The current literature offers little information about the effect on adherence rates of pill burden, differences between drug regimens, stage of HIV disease, time on therapy, and mental health status. In other disease areas, these are cited as important factors in treatment adherence. Further study of these factors in HAART adherence is needed. Evaluations of adherence intervention tools, including counseling programs, DOT, methods to assist patients in deciding whether to start antiretroviral therapy, and educational materials are also needed. The success or failure of HAART, both as a treatment strategy for patients and a public health strategy to prevent the spread of multi-drug resistant HIV, is dependent upon the ability of patients to adhere to therapy. Support to assist patients in their adherence efforts should be comprehensive and considered a high priority in the delivery of HIV primary care and social services.

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