January 2014

Medication Persistence In The Treatment Of Hiv Infection: A New Construct For Hiv Research And Clinical Care

Jason Bae
Yale School of Medicine, jason.bae@yale.edu

Medication Persistence in the Treatment of HIV Infection: A New Construct for HIV Research and Clinical Care

A Thesis Submitted to the
Yale University School of Medicine
in Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by
Jason Woonghwan Bae
2014

MEDICATION PERSISTENCE IN THE TREATMENT OF HIV INFECTION: A NEW CONSTRUCT FOR HIV RESEARCH AND CLINICAL CARE. Jason W. Bae, Eileen C. Ing, Duncan S. Maru, William Guyer, Kristy Grimm, and Frederick L. Altice. Section of Infectious Diseases, Department of Internal Medicine, Yale University, School of Medicine, New Haven, CT

Adherence to therapy has dominated clinical and investigational conversation on how HIV patients take medications. Adherence, although a critical concept in medication-taking behavior, is becoming increasingly limited in its relevance to patient outcomes as treatment regimens and our understanding of antiretroviral resistance development evolve over time. In this thesis, a new construct of HIV medication-taking behavior called 'persistence' is introduced and defined, in order to provide researchers and practitioners with a more comprehensive understanding of patient behavior and achieve better health outcomes. Literature review of adherence, persistence, viral suppression, development of antiretroviral resistance is performed here to reveal patient, medication, and healthcare setting characteristics associated with suboptimal persistence. Impact of persistence on resistance development and clinical outcomes is also summarized. Finally, patterns of non-persistence among HIV-infected drug users undergoing directly-administered antiretroviral therapy in a prospective, randomized-controlled trial are presented along with factors associated with non-persistence. This study suggests that decreased persistence for HIV treatment, or shorter duration on therapy, is associated with increased rates of virological failure, development of antiretroviral resistance, and increased morbidity and mortality. Additionally, frequency and duration of non-persistent episodes rather than adherence may be a better predictor of clinical outcomes in HIV-infected patients on certain regimens. More emphasis on persistence when considering HIV medication-taking behavior in both clinical and research setting is warranted.

Acknowledgements

I would like to thank Professor Frederick Altice for years of persistent mentorship in research, support for career, and friendship in life. I would also like to thank Eileen Ing for her companionship in life and academia, and my parents for their never-ending trust and faith in my character and ability. I would like to thank other co-authors, Duncan Maru, Kristy Grimm, and William Guyer for their important contributions, without which this thesis would not be possible. I would like to also acknowledge Infectious Disease Society of America for Medical Scholarship Award and Korean American Medical Association for financial support and Sandra Springer for her valuable input in the revision process. I also would like to acknowledge the National Institutes on Drug Abuse (R01 DA13805 and R01 DA17059–02) for funding the Project Trust study and career development awards (K24 DA017072) awards for Professor Altice. Most importantly, I would like to thank all the patients in Project Trust who dedicated time and energy to make this study possible.

Table of Contents

1. Introduction 1

2. Aims 5

3. Methods 6

4. Results 10

5. Discussion 25

6. Figures 33

7. Tables 37

8. References 47

1. Introduction

Multiple terms, oftentimes expressing different constructs yet with some overlap, have been used to explain how well a patient takes their medications. These terms, such as adherence, compliance, persistence, and durability, are often used interchangeably, sometimes lead to inaccurate or imprecise interpretation of patient behavior, and may result in incorrect conclusions about which intervention should be appropriately deployed. Much of the early research and attention to medical management of HIV/AIDS has been focused on the construct of adherence. Especially early in the HIV/AIDS epidemic when regimens were often complicated, had large pill burdens, complex dosing schedules, and low genetic barriers to resistance, adherence played an important role in HIV treatment. Indeed, a large body of literature has repeatedly demonstrated the importance of adherence, where a high level of adherence to antiretroviral therapy was associated with successful viral suppression and decreased morbidity. Treatment strategies, however, have changed. In recognition of the changing HIV epidemic and the various subpopulations globally who will eventually access contemporary combination antiretroviral therapy (cART), we provide insight into additional considerations and define the construct of persistence, and its operationalization for clinical care and research in the context of HIV treatment. Additionally, we summarize methods for determination of persistence and current literature on persistence in HIV treatment.

The Dynamics of HIV Replication and Impact on Treatment

Decreased adherence to or discontinuation of a prescribed therapy is likely to result in unfavorable health outcomes in chronic diseases, such as hypertension, hyperlipidemia, congestive heart failure, or chronic obstructive pulmonary disease. Management of HIV differs from other chronic diseases in that successful control of the disease is more complex and also the consequences of failure may be greater. First, suppression of viral replication requires lifelong retention on cART, often consisting of 3 or more medications. Second, unlike in hypertension or diabetes, inconsistent use of medications leads to development of resistance to one or more medications in the regimen, thereby limiting future treatment options and complicating therapy. Last, failure to suppress viral replication not only affects the health of the patient, but also increases the risk of HIV transmission to others who engage in high risk behaviors, posing greater public health concerns than with non-communicable diseases.

Management of HIV has changed dramatically in recent years. Lessons learned from the SMART trial where subjects randomized to discontinue cART until pre-specified CD4 thresholds were met had increased non-HIV and HIV-related morbidity and mortality compared to those who continuously remained on therapy (1). This finding emphasizes more than ever that "remaining" on therapy is crucial, and so is the need for interventions that allow treatment to "persist over time."

Antiretroviral treatment itself has also changed. Development of highly potent, once-daily, low pill burden, and more tolerable cART has greatly improved and altered the landscape of contemporary HIV management (2). Contemporary regimens are affected less by perturbations in adherence, in part

due to the high genetic barrier to resistance by some medications (e.g., ritonavir-boosted protease inhibitors) and long half lives of others (e.g., non-nucleoside reverse transcriptase inhibitor, NNRTI). For example, nevirapine, a NNRTI, has a serum half-life of 48 hours (3) and its serum level remains detectable 1 week after discontinuation (4). On the other hand, abacavir and lamivudine, nucleoside reverse transcriptase inhibitors (NRTI), have much shorter serum half-lives of 1.5 and 6 hours, respectively (5, 6) and the intracellular concentration of the active abacavir metabolite becomes undetectable within 72 hours after the last dose (7). Therefore, discontinuation of a multi-drug regimen such as the one above for 3 days or more may result in extended nevirapine monotherapy, during which selective pressure on viral replication may result in development of resistance due to the low genetic barrier to resistance by NNRTIs (8). In the case of nevirapine administered even as a single-dose monotherapy regimen to prevent mother-to-child-transmission of HIV, high rates of NNRTI resistance have been observed among mothers and infants (9, 10). Efavirenz, a preferred NNRTI component of contemporary regimens, also has a prolonged serum half-life of 40-55 hours, and like nevirapine, can remain at a therapeutic dose for longer than 21 days after discontinuation (11). Pharmacokinetic profiles of NNRTIs like efavirenz and nevirapine have the benefit of continuing to suppress HIV replication when medications are stopped briefly, but may be detrimental when treatment regimens are discontinued for longer periods due to their low genetic barrier to resistance when HIV replication is not completely suppressed.

Ritonavir-boosted protease inhibitor regimens, also part of preferred cART regimens, do not have prolonged serum half-lives like NNRTIs. These antiretroviral agents, however, have other pharmacological advantages due to

their high genetic barrier to resistance such that even prolonged periods of monotherapy potently suppress HIV replication, yet seldom result in the development of resistance mutations (12, 13). As such, they pose few problems when there is poor adherence or decreased persistence.

In a proof-of-concept pilot study, subjects who were on a suppressive once-daily antiretroviral regimen were changed to five days on treatment and then provided with a two-day holiday (72 hours since last dose); all subjects on an efavirenz-containing regimen and 90% of those on a nevirapine-containing regimen had suppressed HIV-1 RNA levels at 48 weeks suggesting that intervals < 72 hours do not negatively impact clinical outcomes (14). On the other hand, two out of nine subjects on a PI-based regimen had experienced virological rebound by 48 weeks. In another trial, where antiretroviral therapy was interrupted every other week in a "1 week on, 1 week off" strategy, 1 of 8 patients on an efavirenz-based regimen experienced virological failure with a resultant new resistance mutation to efavirenz. In contrast, 11 of 17 patients on a regimen containing ritonavir-boosted-saquinavir experienced virological failure, however, none developed a new resistance mutation to a PI (15). These studies suggest that the duration for which therapy may be discontinued without expecting an adverse outcome differs depending on antiretroviral composition of a regimen. This "permissible gap" (see below for definition) is most likely to be between 2 to 7 days for a regimen containing efavirenz, but further investigations are needed to better characterize the permissible gap that results in adverse consequences.

Adherence, rather than persistence, has been the center of focus in research of medication-taking behaviors among HIV-infected patients (see below

for definition). Contrary to the pervasive view that low adherence leads to development of resistance, data suggest that the relationship between adherence and resistance may be more complex (16), particularly when contemporary preferred regimens are prescribed (Figure 1). For example, NRTI and PI resistances were observed predominantly in highly adherent individuals in a cohort study (17). In other studies, development of resistance to PIs was limited to individuals with adherence greater than 90% (18) and imperfect adherence of many ritonavir-boosted PI-containing regimens does not result in significant levels of resistance (19). Emerging data from recent studies question the long-taught principle that "non-adherence leads to development of resistance and virological failure" and also the construct of adherence itself and its applicability in the current setting of HIV treatment.

In sum, adherence alone when using contemporary treatment regimens may be insufficiently predictive of clinical outcomes in HIV-infected patients and is dependent on the type of regimen prescribed. Clinical care and research in the management of HIV would therefore benefit from an additional "time-dependent" measure of medication-taking behaviors.

2. Aims

The purpose of this thesis is to introduce the construct of medication persistence for HIV and present patterns of and characteristics associated with medication persistence.

Specific Aims

1) Define the construct of medication persistence in the setting of HIV treatment and propose methods for determining persistence.

2) Using a review of available literature;

   2A) Describe patterns of medication non-persistence and their impact on development of antiretroviral resistance and clinical outcomes.

   2B) Describe patient, medication, and healthcare settings characteristics associated with persistence.

3) In a retrospective analysis of a randomized controlled trial of directly-administered anti-retroviral therapy (DAART) vs. self-administered therapy (SAT);

   3A) Describe patterns of medication among HIV-infected drug users undergoing DAART.

   3B) Present medication and patient characteristics associated with non-persistence.

   3C) Explore the relationship between non-persistence and virological success.

3. Methods

Literature Review and Definition of Persistence (AIMS 1 & 2)

PubMed and Medline database were searched jointly by Jason Bae and Frederick Altice for literature review of adherence, persistence, durability and their relationship with antiretroviral resistance, viral suppression, and mortality. The original idea of the manuscript was suggested by Frederick Altice. Jason Bae

developed and refined the construct of persistence in the setting of HIV treatment. The manuscript was jointly written by Jason Bae and Frederick Altice.

Patterns of Non-Persistence and Associated Characteristics from Project Trust (AIM 3)

Persistence data from Project Trust (National Institutes on Drug Abuse R01 DA13805) were obtained as following. A 6-month, randomized controlled study of directly-administered antiretroviral therapy (DAART) was conducted among 141 drug users led by Frederick Altice. Primary outcomes of this project are published elsewhere (20). Participants were recruited from all of the HIV clinics in New Haven, Connecticut. Entry criteria included: (1) being HIV seropositive; (2) being eligible for and/or being prescribed antiretroviral medications; (3) residing within the city of New Haven; (4) active use of heroin and/or cocaine in the previous 6 months; and (5) receiving no more than a twice-daily regimen. Following informed consent, eligible participants were randomized 2:1 to DAART or self-administered therapy.

DAART participants received their antiretroviral medications at a mobile health unit that traveled to four New Haven inner city neighborhoods on weekdays (21). All medication doses were placed in small plastic bags in a medication bottle with a Medication Electronic Monitoring System (MEMS) Version 6 Smart Cap (Aardex). A trained outreach worker observed one daily dose; all other doses were provided for the patient to take later, with a reminder from a beeper. Weekend doses were dispensed on Fridays and each patient had up to 3 days of an emergency supply of antiretroviral medications that were stored in the MEMS bottle. In this study, only those participants who were randomized to and initiated DAART were included in the analysis.

Virological success at 6 months for this predominantly antiretroviral-experienced population was defined a priori as having achieved an HIV-1 RNA level reduction of at least 1.0 log10 copies/ml or an HIV-1 RNA level < 400 copies/ml at 6 months. Missing values were imputed as virological failure.

Persistence was calculated using a combination of daily DAART observations and MEMS event data during the 6-month period of DAART. Subjects were considered to be on treatment for a given day if either there was: (1) an observed DAART dose or (2) a MEMS event. Missed DAART appointments due to hospitalization or imprisonment were corrected from verifiable clinical records of medication administration in these institutions.

Non-persistence was defined for three thresholds at any point during the 6-month intervention period: (1) ≥ 3 days (missing more than 2 consecutive days of antiretroviral medications); (2) ≥ 5 days; and (3) ≥ 7 days. Once a participant met the defined threshold gap, he or she was considered to be non-persistent. To determine the recurrence and true extent of non-persistence, all interruptions in treatment exceeding the proposed permissible gaps were considered to be non-persistent episodes. Recurrent non-persistence was defined as having more than one non-persistent episode, defined as gaps ≥ 3 days, within the 180-day observation period of the study. Time to patient non-persistence was defined as the number of days to the 1st day of a pre-defined first episode of non-persistence. Patients who were lost to follow-up were considered non-persistent from day of DAART discontinuation to day 180 of observation.

Regimen non-persistence was defined as any change in any component of the initial antiretroviral medication regimen. Time to regimen non-persistence

was measured as the number of days between DAART initiation and regimen modification.

Baseline interviews assessed an array of psychosocial, demographic, and drug use characteristics. Addiction severity was assessed using binary outcomes (high severity if score ≥ 6) using the 10-item Drug Abuse Screening Test (DAST-10), a self-report measure of problematic substance use, widely used for clinical screening and research (22). The Center for Epidemiological Studies Depression Scale (CES-D) (23), a 20-item self-report scale to measure depressive symptomatology, is highly correlated with having major depression when scores are ≥ 16. Participants' attitudes towards DAART were also surveyed. Self-efficacy, which measures one's sense of control over his life circumstances, was assessed using the Self-Efficacy Form (24). Interviews were administered by non-clinical research assistants in research settings, but also included hospitals, prisons and drug-treatment settings if necessary. Heavy drinking was defined as more than two drinks per day for men and more than 1 per day for women on average. Heavy cocaine use was defined as use for more than 5 days per month. The following baseline demographic and psychosocial characteristics were included in analysis: age, gender, race, homelessness, education, heavy drinking, any cocaine use, heavy cocaine use, injection drug use, drug abuse severity, CES-D score, social support, self-efficacy, confidence that one can take medications as prescribed, preference for assistance with medication-taking, and willingness to travel for DAART. In addition, frequency of dosing, pill burden, and baseline viral load were included in analysis.

All statistical analyses, including creation of persistence variables using the original dataset, were performed by Jason Bae and Eileen Ing using Stata SE

(version 10.1, Stata Corp, TX, USA). Crude odds ratios were calculated using bivariate logistic regression. Univariate variables with a P –value < 0.10 were included in the multivariate logistic regression modeling, which were used to calculate adjusted odds ratios. Firth's penalized- likelihood logistic regression was used for bivariate analyses when complete separation occurred (25). Time to regimen non-persistence, stratified by the antiretroviral therapy based on the 1st day of DAART, was plotted as Kaplan–Meier curves, and a hazard ratio was calculated using Cox proportional-hazards regression.

4. Results

Definitions of Persistence in the setting of HIV Treatment

Adherence, the most frequent medication construct for HIV treatment, is defined as "the extent to which a patient's behavior corresponds with the recommendations of a healthcare provider", and is often synonymous with compliance (26). In this thesis, we will use adherence to represent this construct. When adherence refers to taking medication, it generally quantifies the extent to which a patient acts in accordance with a prescribed interval and doses of a prescribed regimen within a given time period (27). By definition, it is expressed as a percentage of correctly timed doses (doses taken/doses prescribed x 100) (27). Researchers and clinicians alike have tried to quantify the optimal level of adherence (e.g., greater than 95%) needed to simultaneously suppress viral replication and avoid development or resistance, yet these binary definitions have not been borne to be equally predictive for differing cART regimens (16).

Moreover, adherence thresholds have been plagued by measurement problems (e.g., self-report, electronic monitoring, pharmacy refills) and with quantifying exactly how much adherence is enough (16, 28).

Medication persistence, on the other hand, is also a medication-taking construct defined as "the duration of time from initiation to discontinuation of therapy (27)." By definition, it is expressed solely as a function of time, or the number of days (or months) on treatment. Alternatively, persistence can be expressed as a binary variable (persistent or non-persistent), measured at the end of a pre-specified time period. Similar to adherence, defining persistence as a binary variable is challenging due to the "permissible gap" in time that is allowed to pass after discontinuation of a prescribed regimen that is associated with a poor treatment outcome. Permissible gaps, however, are likely to differ based on the type of cART regimen prescribed.

As with adherence, the concept of persistence may be applied to a variety of situations including taking medications, following dietary advice, and changing health habits. Because persistence emphasizes the concept of continuous therapy, a permissible gap, the maximum number of consecutive doses that a patient can miss without expecting a reduced or suboptimal outcome, should be pre-specified in any assessment of persistence. Such permissible gaps are ones that should have no negative clinical consequences for patients.

Medication persistence and adherence are similar in that they both measure the extent to which a patient's behavior agrees with recommendations of a healthcare provider. They differ, however, in the dimensions of this agreement. With regard to taking medications, adherence measures the

proportion of times that a patient takes medication as prescribed within a given interval, whereas persistence measures the duration of time that a patient continuously adheres to a prescribed regimen. In other words, adherence measures "how often", whereas persistence measures "for how long." As such, these constructs are complimentary but distinct.

With regard to cART for the treatment of HIV, medication persistence merits further categorization, including: *patient persistence* and *regimen persistence*. Distinction between these constructs is described further.

Patient Persistence

According to the stringent definition of persistence as a continuous therapy, a patient is persistent in adhering to the prescribed regimen as long as the permissible gap is not exceeded. A permissible gap can be defined as the maximum duration for which a patient may discontinue medication without experiencing a suboptimal outcome or adverse consequence. Due to the high replication capacity of HIV, the permissible gap for HIV treatment is likely to be on the magnitude of days rather than weeks (see below); however, since cART consists of multiple medications, often with different pharmacokinetic profiles, the permissible gap may vary depending on individual medications within a prescribed regimen. In addition, the duration of medication discontinuation necessary for development of a suboptimal outcome may also vary depending on the adverse consequence of interest (e.g. incomplete viral suppression, development of resistance, development of an adverse clinical event). In the case of viral suppression, a permissible gap may be on the order of days while the

time to a clinical event (e.g., myocardial infarction or opportunistic infection) is likely to be on the order of months to years.

If a patient discontinues medication for a period that exceeds the permissible gap, the patient is no longer persistent with the HIV treatment. The duration of non-persistence is equivalent to the time lapsed between the first missed dose and re-initiation of therapy. A patient's persistence with medication is expressed as a continuous variable in days (or weeks) with the goal being a lifetime.

Regimen Persistence

The concept of persistence may be extended beyond that of the individual patient and be applied to an entire antiretroviral regimen. This concept is most pertinent in resource-poor regions where available cART regimens are limited and unlike contemporary regimens in resource-rich settings, are less tolerable, have higher pill burdens and are pharmacologically inferior to newer regimens. We define regimen persistence as "the duration between the initiation and discontinuation of a specified antiretroviral regimen as agreed upon by the patient and the healthcare provider." Using this definition, any change in any part of a regimen, for any reason, would result in the regimen being non-persistent at the time of regimen discontinuation or modification.

In contrast to patient persistence—a measure of a patient's continued taking of cART, irrespective of the individual medications contained within the regimen—regimen persistence measures duration of a *particular* cART regimen as a means to suppress viral replication. Regimen persistence depends on factors both intrinsic and extrinsic to the regimen. Intrinsic factors include adverse side

effects, pill burden, underlying levels of resistance to one or more components of the regimen, and cost. Extrinsic factors, those that contribute to a change in the components of the regimen, include new findings from clinical trials, new treatment guidelines, and availability of antiretroviral medications in a particular region. In contrast to patient persistence, the concept of a permissible gap is not applicable in the definition of regimen persistence; a regimen is persistent as long as it has not been explicitly modified or discontinued by either the patient or the healthcare provider.

Patient Persistence, Regimen Persistence, and Adherence

While both are important, persistence and adherence are different but inter-related, as illustrated in Figure 2. Adherence levels are indicated as a solid line, and HIV-1 RNA levels are shown as a dashed line. Optimal HIV viral suppression is observed when HIV-1 RNA levels fall below the dotted line. In this example, a patient initiates an NNRTI-based regimen and initially achieves virological suppression. Later, however, medications are discontinued completely (patient non-persistence or 0% adherence), resulting in virological rebound or replication to a detectable level. Alternatively, if the provider discontinued medications for any reason (low supply, too costly, etc), the patient would be persistent, the regimen would be non-persistent and the patient would be 100% adherent since the patient did what the clinician recommended. Since the patient has discontinued medications for a period exceeding the permissible gap, he is no longer persistent with his original regimen; the patient is non-persistent with medication for the duration between the first missed dose and the next dose of medication he takes (patient non-persistence in Figure 1). The

duration of patient persistence, in this case, is defined as the time period between the first dose and the last dose of the regimen [Patient (1) in Figure 1].

On the other hand, the regimen is persistent as long as it has not been explicitly modified or discontinued through agreement between the patient and the provider. Therefore, in this case, regimen persistence continues until the provider changes the NNRTI-based regimen to a boosted protease inhibitor (PI)-based one [Regimen (1) in Figure 1]. Patient persistence is not affected by the regimen modification as long as the patient continuously adheres to medication without exceeding the permissible gap; the second phase of patient persistence [Patient (2) in Figure 1], which began with re-initiation of medication, continues despite the modification in regimen.

As demonstrated in this example, a regimen may be persistent while the patient is non-persistent. Likewise, a patient may be persistent with medication-taking even when his regimen is changed as long as he continues to take his prescribed medications. Finally, a patient may be persistent while achieving a low level of adherence (sometimes defined as non-adherence). For example, if a patient is prescribed medication twice daily, but takes the regimen once daily everyday, he would be persistent but would maintain at a 50% adherence level.

Methods for Determining Persistence

Measurement of persistence and methods to collect persistence data have been summarized previously (29, 30), and several methods may be used to determine persistence in HIV treatment (See Table 1). Patient persistence can be determined through measurements of a patient's pill-taking history. These may include direct observation, Medication Event Monitoring System (MEMS),

patient self-report recall, review of pharmacy refill and medical records. Regimen persistence may also be determined using many of the same methods as in patient persistence plus a regimen change form on a study instrument in a prospective study. Reasons for patient or regimen non-persistence can be measured via a study instrument that assesses these constructs or by review of medical records.

Methods that yield high granularity of data, such as direct observation or MEMS, often require prospective studies and are likely to be expensive. Therefore, it is often impractical to gather this level of granularity in large retrospective studies. On the other hand, pharmacy refill records can be obtained with less cost and effort compared to other methods. Pharmacy refill data, however, lack sufficient detail to adequately measure patient persistence, cannot accurately measure small permissible gaps in treatment, or answer why a regimen is no longer persistent, but are often satisfactory to measure regimen persistence *per se*.

Impact of Persistence on Clinical Outcomes

Patient Persistence

Patient non-persistence in HIV treatment has been insufficiently assessed in current research and is associated with adverse clinical outcomes. In a Spanish cohort study where the median duration of follow-up was 8.3 years, 43% of patients had a treatment interruption longer than 3 days, and these patients had a higher risk of treatment failure (31). In a Ugandan study with the median time on therapy was 38 weeks, 23% of patients had a history of treatment interruption greater than 4 days, which was significantly associated with virological failure

(32). Among injection drug users in Baltimore, 78% of subjects had one or more treatment discontinuations, and 20% of the study population never resumed cART (33).

In a study in which pill-taking history was measured using MEMS, 65% of patients had a treatment interruption longer than 48 hours in the 24 weeks observation period and were more likely to develop drug resistance than those without an interruption (34). Similarly, patients with a history of more than one drug holiday (patient non-persistence) lasting ≥ 48 hours were more likely to fail therapy and develop a resistance to NNRTI-containing regimens compared to those with one or less drug holiday (35). In another study, intermittent use of cART in the first year of therapy was significantly associated with increased mortality (36).

Results from prospective randomized controlled trials on structured treatment interruptions confirm that patient non-persistence adversely affects clinical outcomes in HIV-infected patients eligible for cART. In one trial, scheduled treatment interruptions exceeding 4 weeks were associated with development of resistance (37). In another study, a structured "1-week-on-1-week-off" treatment strategy using cART was associated with increased likelihood of virological failure, and development of resistance among the patients taking an NNRTI-based regimen (15); these findings suggest that even missing one week of therapy has significant adverse consequences. In the randomized controlled SMART trial, planned cART discontinuation using *a priori* CD4 guidance thresholds was associated with increased rates of HIV- and

non-HIV-associated morbidity, decreased levels of HIV suppression, and lower CD4 counts, when compared to those who persisted with therapy (1).

On the other hand, in a randomized controlled treatment strategy of "five-day-on, two-day-off" schedule of therapy in patients with durable virological suppression, 11 - 22% experienced virological failure among patients on a nevirapine- or PI-based regimen, however, no failure was observed among those on efavirenz-based regimens over 48 weeks of observation (14). Parienti and *et al*., using an observational analytical approach, demonstrated that frequent and longer duration of treatment interruption (non-persistence) were better predictors of virological rebound (i.e. failure) among patients on an NNRTI-based regimen (38, 39). According to their logistic model, a treatment interruption of 15 days was associated with a 50% probability of virological rebound among those on an NNRTI-based regimen. On the other hand, higher average adherence rates overall appeared to be a better correlate of virological suppression among those on a boosted-PI-based regimen. These last two studies suggest that there may be unique properties of one or more of the components of the cART regimen that contributes to different permissible gaps in treatment interruptions that affect adverse clinical consequences

In sum, these data highlight that permissible gaps in HIV treatment may be as short as a few days and also vary depending on the unique pharmacokinetic and genetic barrier to resistance profiles of the various components of a cART regimen.

Regimen Persistence

Though reported measurements have been imperfect, persistence of an initial antiretroviral ranges from 11.8 months (40) to 34.3 months (41) with the trend toward longer persistence in more recent years. Though newer salvage regimens have resulted in markedly improved levels of viral suppression, it remains true that maintaining a patient on the initial regimen is likely to result in the greatest likelihood of virological suppression. Compared to the initial regimen, the second and the third regimens have significantly lower probability of achieving virological suppression (adjusted odds ratio 0.49 and 0.22, respectively, and $p<0.02$ for both) (41). Furthermore, each modification is associated with a more complex dosing schedule, a less favorable toxicity profile, and also decreased persistence of the subsequent regimen (41). In another study, patients who started on a persistent, NNRTI-based regimen were less likely to experience subsequent regimen modifications and a three-class regimen, compared to a less-persistent, PI-based regimen (42).

Regimen persistence is a particularly important issue in resource-poor settings, where available antiretroviral choices are limited and the medication alternatives are costly (39). Virological failure due to resistance to therapy may leave patients with few or no remaining treatment options.

Factors that Affect Persistence

Adherence, patient persistence, and regimen persistence are intimately inter-related; they may be influenced by not only a similar set of patient, medication, and socioeconomic characteristics, but also by one another. For example, low adherence and frequent patient non-persistence due to toxicity of a regimen may lead to development resistance. Subsequent virological failure will

eventually result in modification of the patient's regimen, leading to decreased regimen persistence. Existing literature on patient and medication characteristics that impact patient and regimen persistence is summarized below.

Patient Characteristics

In the treatment of HIV infection, many patient characteristics contribute to decreased persistence. Clinical characteristics of patient-associated factors that have been associated with decreased patient persistence include female gender, high HIV RNA level, current substance use disorder (33), depression, and shorter time on cART (43). Younger age and black race have also correlated with decreased patient persistence (43).

Patient characteristics associated with regimen persistence are summarized in Table 2. These include: high or increasing HIV RNA levels (43-47), low CD4 count prior to cART initation (46, 48), current high CD4 count (49, 50), short duration on therapy (51), previous cART experience (40, 51) history of opportunistic infection (52), and hepatitis C virus co-infection (53) .

Also, affective mental disorders (41), depression (43, 47), use of alternative medicine, hospitalization (51), female gender (44, 50), men who have sex with men (50), black or minority race/ethnicity (38, 43, 54), younger age (43), low weight (48), lack of medical coverage (54, 55), and incarceration (56-58) have been associated with decreased regimen persistence.

Co-morbidities such as mental illness and substance use disorders are common among HIV-infected patients, and these patients frequently transition through correctional facilities (59, 60). Non-persistence is a great challenge in this population both within community and upon transition between a correctional

and a community setting. (57, 61, 62). In a study among HIV-infected prisoners, 95% of released inmates failed to fill their cART prescription within 10 days of release (the time period for which medications were provided upon release), and patients therefore presumably did not take HIV medications beyond this period (61). Others have confirmed that HIV-1 RNA levels increase during this post-release period; the finding that the HIV-1 RNA levels return to their pre-treatment levels, and not just a partial increase, suggest that non-persistence rather than non-adherence is the mechanism of poor treatment outcomes (57). In another study of jail detainees, only 15% of those who were re-incarcerated repeatedly persisted with their medications. Those who did not persist or who were never prescribed medications had increased likelihood of having higher HIV-1 RNA levels and decreasing CD4 counts (62). This suggests that patient non-persistence after release from prison or jail is common and is an important public health concern.

Medication Characteristics

Existing data assessing the characteristics of a specific medication component or entire cART regimen on persistence primarily focus on regimen persistence. Medication characteristics associated with regimen persistence are summarized in Table 2. In Western countries, adverse events associated with cART and treatment failure were the two most common reasons for medication discontinuation or modification (44, 63). In addition, a greater number of medications within a regimen (45) and a more frequent dosing (41) were associated with early regimen discontinuation. In developing countries, in addition to adverse events and treatment failure, high cost and inadequate

supply of medications were cited as common reasons for regimen discontinuation among patients (51, 64).

Characteristics of individual antiretroviral medications within a cART regimen also influence regimen persistence. Overall, NNRTI-based regimens have been associated with increased persistence, compared to boosted or unboosted PI-based, triple-NRTI-based, or triple-class regimens (41, 65-67). Newer generations of NRTIs such as tenofovir, lamivudine, emtricitabine, and abacavir improve persistence compared to zidovudine, stavudine, and didanosine (41, 49, 50). Also, efavirenz has been associated with increased regimen persistence compared to nevirapine, and also the protease inhibitors lopinavir, saquinavir, and indinavir (33, 49, 64, 67). Among PIs, darunavir and atazanavir were less likely to result in regimen switch due to toxicity (50, 68), whereas lopinavir, saquinavir, and ritonavir were associated with discontinuation or modification of therapy (43, 44, 50).

In a recent trial in which patients were randomized to receive co-formulated tenofovir/emtricitabine or abacavir/lamivudine plus efavirenz or atazanavir boosted with ritonavir, lower rates of virological failure and increased persistence were observed among the group assigned to tenofovir/emtricitabine compared to abacavir/lamivudine (69). Adverse consequence of abacavir resulted in medication discontinuation at a higher rate than for tenofovir.

Healthcare Setting Characteristics

The organization of healthcare and even pharmacy services for patients impacts persistence. For example, the frequency with which either clinicians choose to follow their patients or even how it is dictated by insurance or

managed healthcare providers can negatively influence persistence. Prior authorization for medication changes has been associated with patient non-persistence (70), as has co-pays and requirements for patients to spend down their personal resources before prescription benefits are renewed (71). Most patients who become non-persistent do so without their provider actually knowing it until the patient's next scheduled appointment (if the patient manages to return at all). In the case of HIV-infected drug users, the onsite integration of buprenorphine treatment into HIV treatment settings resulted in improved retention in care and continuation of medications compared to those who were referred for treatment for their opioid dependence off-site (72). Thus, organizational factors may contribute either to fragmented healthcare or less frequent monitoring, especially early in cART initiation, may disrupt continuity of cART and worsen HIV treatment outcomes.

Persistence in Directly-Administered Antiretroviral Therapy among HIV-infected drug users

Patient and regimen non-persistence defined and whose relevance to clinical and investigational considerations of HIV medication has been demonstrated above, were studied among HIV-infected injection drug users undergoing DAART in a randomized controlled setting. Results from this study are presented here.

Patterns of Non-Persistence

Of the 74 participants who initiated DAART in Project Trust, 15 (20%) were completely persistent, not missing 3 or more days, during the 6-month

intervention period. The patterns of non-persistence are described in Table 3. Among the 59 (80%) participants who were non-persistent for ≥ 3 days, the mean and median numbers of non-persistence episodes were 2.66 [standard error (SE): ± 0.42] and 1.0 [interquartile range (IQR) 1–3], respectively. The mean and median lengths of non-persistence gaps were 15.0 (SE: ± 2.08) and 4.0 (IQR 3–6) days, respectively. Kaplan– Meier estimates for the time to first non-persistence gap, stratified by length of treatment lapses in therapy, are presented in Fig. 3.

Factors Associated with Patient Non-Persistence

Demographic, psychosocial, and medication characteristics along with other factors thought to be associated with patient non-persistence are presented in Table 4. Depression (CES-D≥16) was significantly associated with non-persistence ≥ 3 days (AOR= 17.4; 95% CI: 1.5 – 204.1, p= 0.02). Similarly, univariate analyses for non-persistence ≥ 7 days were significantly associated with having depression (OR=7.2; 95% CI: 1.5 – 35.7, p= 0.02) and having high addiction severity (OR=3.9; 95% CI: 1.5 – 10.2, p < 0.01). The statistical significance for these outcomes was preserved in multivariable analysis for both depression (AOR=5.4; 95% CI: 1.1 – 27.5, p= 0.04) and high addiction severity (AOR=3.2; 95% CI: (1.1 – 9.2, p= 0.03). No other factors were significantly associated with non-persistence ≥ 3 or ≥ 7 days. Non-persistence ≥ 5 days was not significantly associated with any identified covariates.

Of the 59 DAART participants who had any type of predefined non-persistence, 31 (52.5%) had 2 or more episodes of non-persistence (Table 4). Univariate analyses showed statistically significant associations with injection drug use (OR=7.1; 95% CI: 1.4 – 36.9, p= 0.02), low self-efficacy (OR=0.3; 95%CI:

0.1 - 0.9, p= 0.03), and high-confidence in taking medications as prescribed (OR=0.3; 95% CI: 0.01 – 0.80, p=0.02). In multivariate analysis, and injection drug use (AOR=15.2; 95% CI:1.8 – 129.1, p= 0.02) was significantly associated with recurrent non-persistence. Twice daily dosing had a trend towards an increased risk of recurrent non-persistence compared to once daily dosing (AOR= 6.3, 95% CI:1.0 – 40.0, p= 0.05).

Correlates of Virological Success

In a univariate linear analysis, there was no statistically significant association between virological success and non-persistence (data not shown).

Regimen Non-Persistence

Among the 74 DAART participants, 20 (26%) modified their antiretroviral regimen during the 6-month intervention period and were thereby defined as having regimen non-persistence. Of the demographic and psychosocial characteristics, only low social support (AOR=2.9; 95% CI: 1.0 – 8.4, $p < 0.05$) was statistically associated with regimen non-persistence. Time to regimen non-persistence was significantly shorter for NNRTI-based regimen compared to a PI-based regimen (HR=3.0; 95% CI: 1.1 – 7.9; p= 0.03). No significant relationship between regimen non-persistence and patient non-persistence was observed.

5. Discussion

Definition of medication persistence and review of literature

Much of research on HIV medication-taking behavior continues focus on adherence and mistakenly incorporates elements of persistence into its construct. Adherence and persistence are similar in that both constructs measure accordance of patient behavior with a prescribed therapy. In contrast to adherence, persistence is a longitudinal measure of antiretroviral therapy, with the emphasis on continuity rather than frequency.

In this thesis, we define medication persistence in the setting of HIV treatment and present patterns of non-persistence among HIV patients undergoing directly administered antiretroviral therapy. We deconstruct persistence into two types: patient persistence and regimen persistence. The former measures continuous adherence to cART without exceeding a permissible gap, and the latter measures duration of a pre-specified cART regimen.

As cART regimens become more tolerable, less complex and are created with higher barriers to development of resistance, interventions designed to improve medication-taking behaviors need to increasingly focus on non-persistence in addition to non-adherence. Such interventions will likely need to incorporate measurement of persistence in real-time so that lapses in medication-taking are averted promptly.

As summarized here, patient non-persistence is associated with adverse clinical outcomes, including higher rates of treatment failure, development of drug resistance, and increased mortality. Importantly, a longer duration and a higher frequency of patient non-persistence appear to increase the risk of adverse outcomes.

Patient non-persistence is of a major public health concern because viral resistance may develop during non-persistent periods and subsequently require

a more costly and toxic regimen for viral suppression. Furthermore, a higher viral load observed during non-persistent periods increases the risk of transmission of a potentially drug-resistant virus, if the patient engages in a risky behavior.

In addition to interventions that address patient characteristics associated with decreased persistence and clinical outcomes, such as substance abuse, incarceration, mental illness, and depression, new approaches may benefit both patients and the public. For example, a system in which failure of a patient to refill his or her medication in a scheduled time period leads to notification of his or her healthcare provider by the pharmacy would enable the physician to address the persistence issue with the patient and may prevent the patient from being non-persistent. Additionally, an improved coordination between a correctional and a community healthcare system would help many recently incarcerated HIV patients to remain persistent with therapy. Education of clinicians and patients of importance of continuous adherence, and impact of non-persistence and "drug holidays", especially for NNRT-based regimens, may lead to a better decision-making with regards to selection and continuation of therapy. Adherence tools, such as schedules, dosettes, and electronic reminder systems, may also increase both adherence and persistence (73). Finally, in patients with a high risk of non-adherence and non-persistence may benefit from a directly observed therapy (20, 74, 75).

Each regimen change is associated with a diminished chance of viral suppression as well as higher toxicity and cost, and thus regimen persistence is an important issue from both clinical and public health perspectives. As summarized in this thesis, fewer drugs in a regimen, fixed-dose combinations,

newer generations of NRTIs, boosted-PIs, and efavirenz correlate with greater regimen persistence. Consideration of effects of each antiretroviral on regimen persistence is needed to maximize chances of prolonged viral suppression.

Limited availability of antiretroviral medications makes regimen persistence an especially important issue in resource-limited settings. Additionally, inconsistent supply of drugs may be a hindrance to patient as well as regimen persistence. Unfortunately, newer generations of antiretrovirals associated with increased persistence tend to be more costly and unavailable in developing countries.

Last, the improved adherence with contemporary treatment regimens and data from the SMART trial remind clinicians and researchers that persistence, has become the "Achilles Heel" of HIV treatment and interventions that retain patients on effective treatment are urgently needed.

Patterns of non-persistence in HIV-infected drug users receiving DAART in a randomized-controlled trial

We found a high rate of patient non-persistence among HIV-infection drug users receiving DAART. Among 74 subjects, 59 (80%) were non-persistent with therapy for 3 or more consecutive days, and 33 subjects (45%) for ≥7 consecutive days. Thirty-one patients (42%) had more than one episode of non-persistence lasting ≥3 days. These rates of medication non-persistence are higher than previously reported among diverse population within cohorts (31, 32, 34, 35, 76).

Several factors may be contributing to the high rate of non-persistence reported in this paper. First, our sample includes only active drug users and

drug users have been demonstrated to have problematic adherence to therapy (77, 78). This study also confirms that drug use, even in the setting of an evidence-based adherence intervention, is associated with problematic non-persistence. Second, patient persistence data obtained through self-report in other studies may unrealistically underestimate the true frequency and length of non-persistent events, despite some studies suggesting adherence patterns can be accurately reported (79).

In analysis of factors associated with non-persistence, high levels of addiction severity and depression were associated with an increased risk of non-persistence. Additionally patients actively using injection drugs were more like to have multiple episodes of non-persistence. These results are consistent with other studies that have correlated active drug use and underlying psychiatric disorder with treatment interruptions, non-adherence, and poor HIV treatment outcomes (33, 77, 78, 80, 81)

In this thesis, we did not find a significant association between patterns of patient non-persistence and virologic success, which is contrary to findings reported in previous studies reviewed here (31, 34, 35). Failure to find an association between non-persistence and virologic success in this study may be attributed to several factors.

First, the small sample size likely resulted in an inadequate power avoid a Type II error. Second, both persistence and virologic outcome data were limited to 6 months of intervention, and it is possible that this period may have been insufficiently long enough to detect a statistically significant association, in contrast to other studies in which patients were followed for years. Third, the impact of non-persistence on virologic outcomes is likely different depending on

a patient's antiretroviral regimen. Because of a low genetic barrier to resistance development as well as long half-lives of NNRTI's, it is hypothesized that longer term non-persistence may have a greater negative impact on patients on an NNRTI-based regimen than those on a PI-based one; however, short treatment gaps may favor NNRTI-based regimens due to their longer half lives (38). A high proportion (60%) of patients on a PI-based regimen in this cohort may have required a greater power to detect a statistically significant association between non-persistence and virologic outcomes.

In analysis of factors associated with non-persistence, high levels of addiction severity were associated with an increased risk of non-persistence of 7 days or more. Additionally, patients actively injecting drugs were more like to have multiple episodes of non-persistence. This study is the first to confirm the association of active drug use and severity on non-persistence in patients receiving DAART.

Previous studies have reported that active drug users are at an increased risk of treatment interruptions (33), non-adherence (80) , and poor HIV treatment outcomes (77, 78). Our findings that patients with high levels of addiction severity and active use are at an increased risk of non-persistence and recurrent episodes of treatment gaps are consistent with existing literature, and therefore not surprising. Because of the grave impact active drug use has on adherence, persistence, and HIV outcomes, a substance dependence treatment program must be considered as an integral part of HIV treatment for active drug users. Buprenorphine/naloxone integrated into HIV treatment settings has shown promising results, and was associated with improved HIV treatment outcomes

among opioid-dependent patients infected with HIV, especially those treated for longer durations (82).

HIV-infected patients with substance use disorders frequently have an underlying psychiatric disorder (60, 83). Since depression has been linked to decreased adherence and shorter survival as well as increased treatment interruptions (81), it is not surprising that patients with higher levels of depressive symptoms were less persistent with therapy. Incorporation of effective pharmacotherapy and counseling, as has been shown among homeless persons with HIV (84), in addition to treatment of active drug use, would benefit patients triply diagnosed with HIV, substance use, and depression.

Finally, PI-based regimens were associated with increased regimen persistence compared to NNRTI-based regimens. This finding is also inconsistent with existing literature that NNRTI-based regimens tend to be more persistent than PI-based, triple-NRTI-based, or triple-class regimens (41, 65-67). One explanation for these results is that among drug users with high rates of non-adherence and non-persistence, PI-based regimens may yield favorable treatment outcomes due to the shorter half-lives and higher genetic barrier to resistance development of PIs compared to NNRTIs; however, due to unavailability of data on reasons explaining regimen non-persistence (i.e. regimen modification), we cannot determine if this is in fact the case in this study.

There are several important limitations to this study. The study population was small, restricted to a single inner-city community, and studied among those who received antiretroviral therapy via direct observation. This limits the generalizability of these findings. Furthermore, the analyses presented

here were not part of preplanned analyses comparing randomized groups. As such, the inferences made here must be considered as tentative and hypothesis-generating rather than definitive. Patients who dropped out were considered non-persistent for the remaining duration of the study, although it is possible that they resumed or continued therapy in a non-research setting. Finally, pill-pocketing or non-adherence to MEMS caps instructions, and associated bias in persistence data cannot be excluded.

Further prospective studies are therefore needed to better understand both patient and regimen persistence, factors associated with them, and their impact on HIV treatment outcomes.

6. Figures

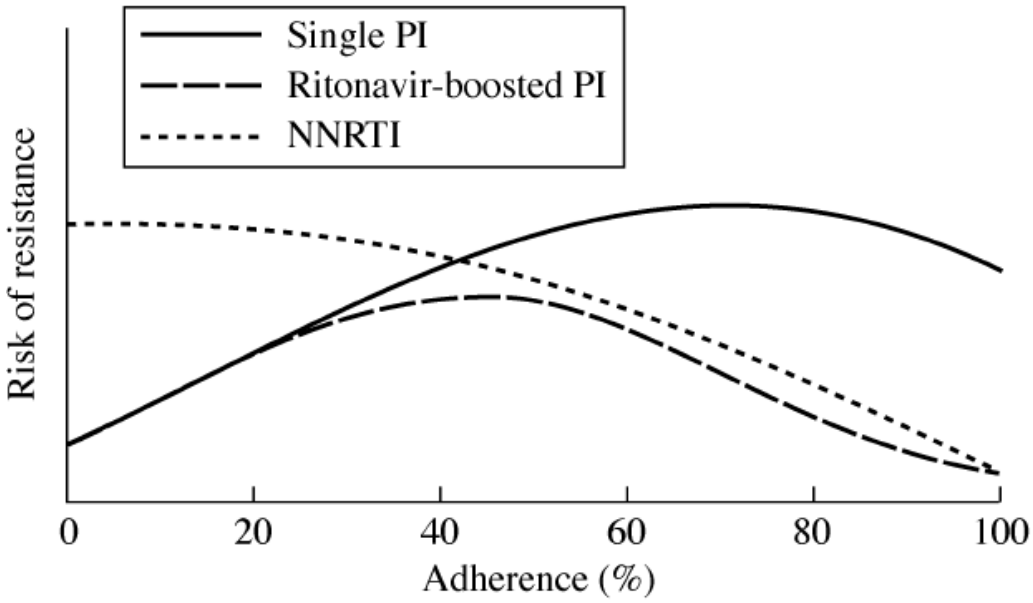

Figure 1. Schematic figure outlining the relationship between medication adherence and the risk of developing PI or NNRTI drug resistance. NNRTI-treated individuals rarely develop resistance at high levels of adherence due to the virological effectiveness of these regimens. NNRTI resistance develops rapidly at moderate to low levels of resistance due to the low 'fitness' costs associated with single mutations. Single PI-treated individuals may develop resistance at high levels of adherence because residual viral replication is often seen in such patients. PI resistance is uncommon at low levels of adherence because of the significant fitness costs associated with these mutations. Resistance to a ritonavir- boosted PI is only possible in a narrow range of adherence where there is sufficient drug around to select for mutations that reduce 'fitness' while still allowing residual viral replication. Data in this figure are conceptual and based on trends observed in a number of recent studies (see text). PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

Reprinted from "Paradoxes of adherence and drug resistance to HIV antiretroviral therapy" by Bangsberg DR, Moss AR, Deeks SG. 2004 J Antimicrob Chemother 53: 696-699.

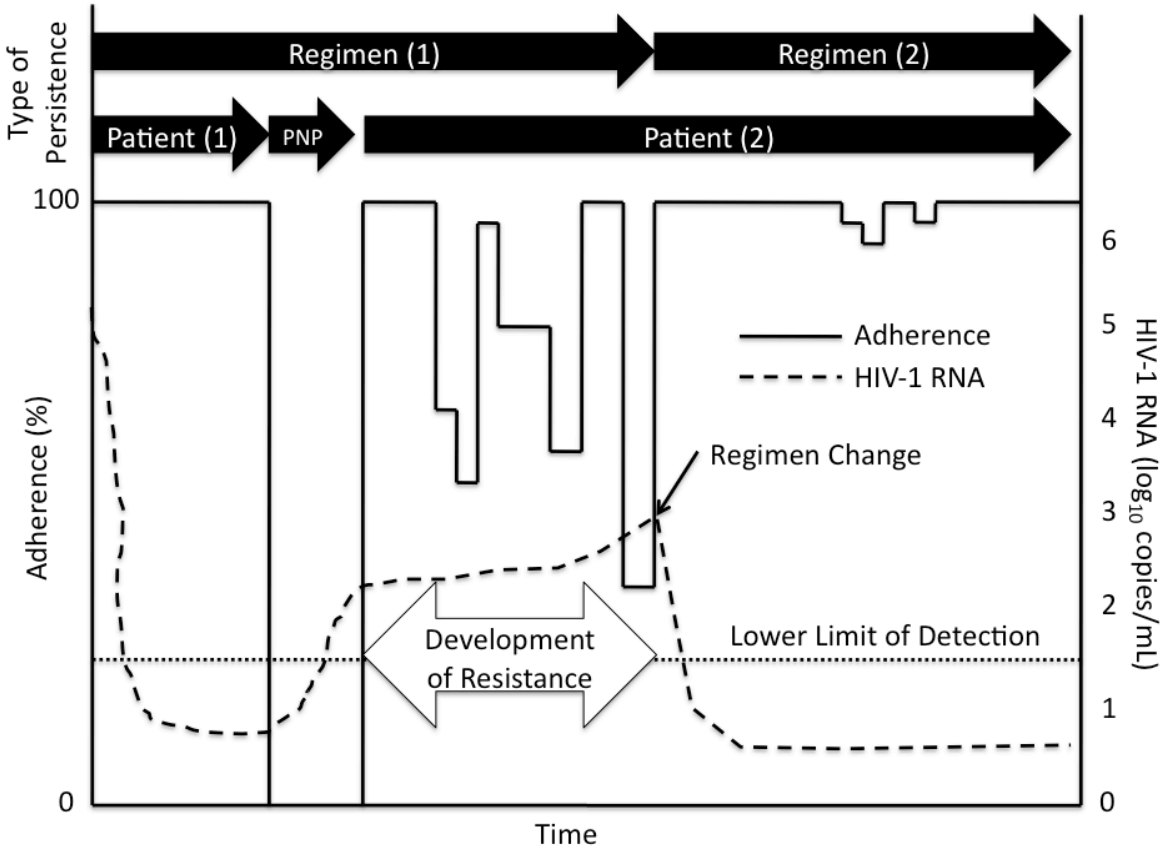

Figure 2. The relationship between patient persistence, regimen persistence, and adherence. Adherence levels are shown as a solid line and HIV-1 RNA levels as a dashed line. The dotted line represents optimal HIV viral suppression.
PNP*= patient non-persistence

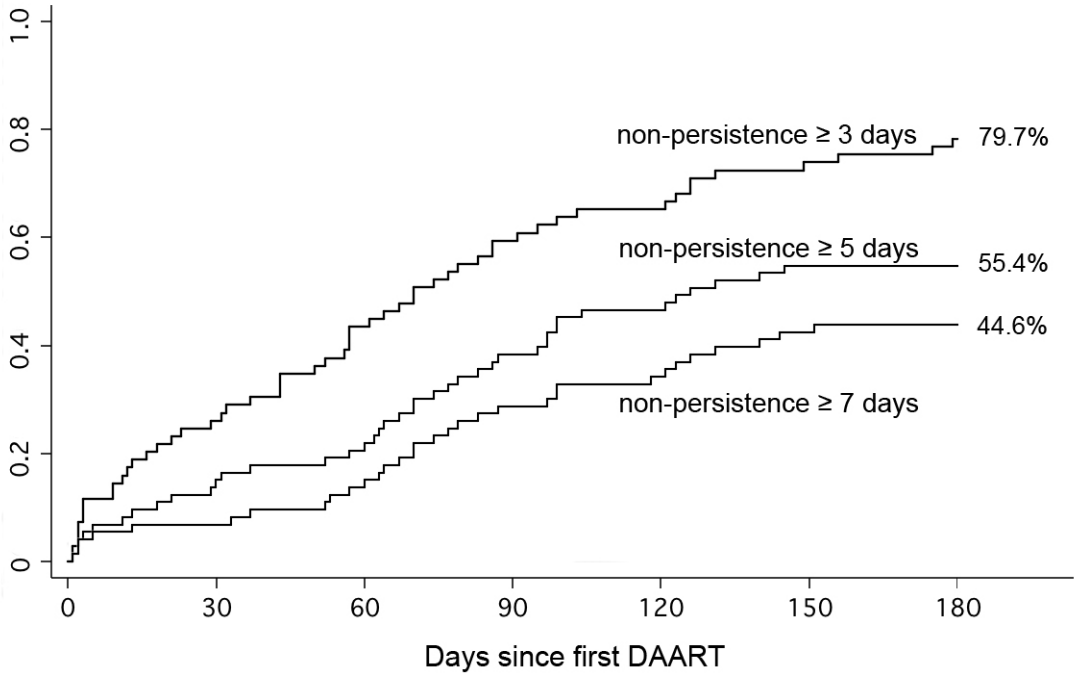

Figure 3. Time to patient non-persistence among DAART subjects, stratified by the length of non-persistence. A subject was categorized as "non-persistence ≥ 3 days" if he missed 3 or more consecutive days of antiretroviral medications at any point during the DAART intervention period. Non-persistence ≥ 5 days and non-persistence ≥ 7 days were defined similarly. Each Kaplan-Meier failure curve represents the same population of subjects (N=74).

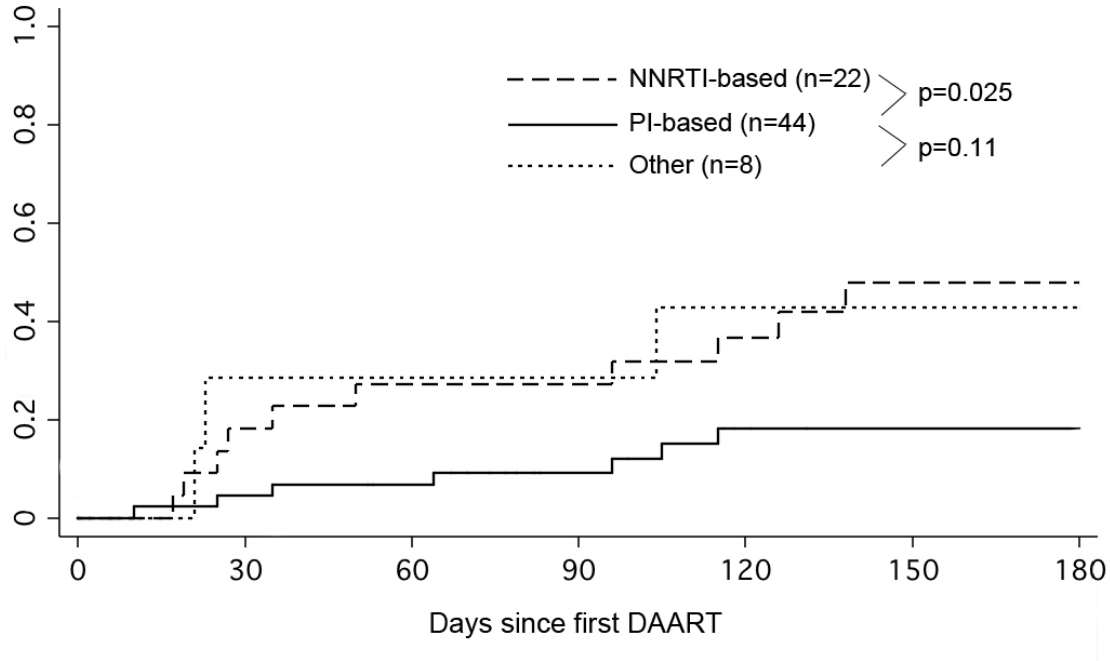

Figure 4. Time to regmien non-persistence among DAART subjects, stratified by the antiretroviral therapy backbone on the first day of DAART (N=74). Regimen non-persistence was defined as any change in antiretroviral medication during the intervention period of the study. The p-value was calculated with Cox proportional-hazards regression. (Legend: NNRTI = non-nucleoside reverse transcriptate inhibitors; PI = protease inhibitor)

7. Tables

Table 1: Methods and Study Types to Measure Persistence

	Prospective	Retrospective
Patient Persistence		
Directly Observed Therapy	X	
MEMS cap	X	
Patient recall	X	
Pharmacy refill records	X	X
Medical record review (e.g., notation of change or discontinuation)		X
Reason for patient non-persistence (e.g., time gap)		
Questions on a study instrument	X	
Review of medical records (e.g. adverse effects)		X
Regimen Persistence		
Regimen change form on a study instrument	X	
Patient recall	X	
Pharmacy refill records	X	X
Medical record review (e.g., notation of change or discontinuation)		X
Reason for regimen non-persistence (e.g., regimen change)		
Questions on a study instrument	X	
Review of medical records (e.g., viral load, adverse effects)		X

Table 2: Summary of Recent Studies on Regimen Persistence

Study, Sample Size, Study Design, Time Period & Location	Factors associated with decreased regimen persistence	Factors associated with increased regimen persistence	Reasons for regimen change or discontinuation
Vo et al., 2008 (49) N=1866 Sub-analysis study in a prospective cohort study 2000-2005 Switzerland	ddI/another NRTI (ref: ZDV/3TC; aRRR: 2.06; 95% CI: 1.29-3.31) IDV/r (ref: EFV; aRRR: 2.28; 95% CI: 1.24-4.17) HIV RNA >5 $\log_{10}$ copies/mL (aRRR: 1.35; 95% CI: 1.07-1.71) CD4 count >350 cells/μl (ref: 200-350 cells/μl; aRRR: 1.50; 95% CI: 1.04-2.17)	TDF/FTC or TDF/3TC (ref: ZDV/3TC; aRRR: 0.65; 95% CI: 0.43-0.97)	Reasons for regimen change included intolerance (51%), patient wish (15%), doctor decision (15%), and virological failure (7%).
Lodwick et al., 2008 (50) N=508 Retrospective study of existing medical records 2000-2005 UK	d4T (ref: ZDV; IRR: 1.67; 95%CI: 1.28–2.17) LVP (ref: EFV; IRR: 1.53; 95% CI: 1.21-1.94) SQV (ref: EFV; IRR: 1.75, 95% CI: 1.04–2.95) Higher CD4 count (for 100 cells/μl increase; IRR: 1.06; 95% CI: 1.02-1.11)	ABC (ref: ZDV; IRR: 0.29; 95% CI: 0.12-0.67) TDF (ref: ZDV; IRR: 0.61; 95% CI: 0.48-0.79) Heterosexual men (ref: homosexual men or heterosexual women; p<0.05) Longer viral suppression (per	

		two-fold longer time; IRR: 0.90; 95% CI: 0.85-0.86)
Willig et al., 2008 (41) N=542 Retrospective study of existing medical records 2000-2007 USA	Affective mental disorder (aHR: 1.43; 95% CI: 1.06-1.93) Twice-daily dosing (ref: once daily; aHR: 1.92; 95% CI: 1.29-2.88) ddI or d4T (ref: ABC or TDF; aHR: 2.16; 95% CI: 1.09-4.26) Triple NRTI (ref: NNRTI; aHR: 1.76; 95% CI: 1.14-2.73) Unboosted PI (ref: NNRTI; aHR: 1.58; 95% CI: 1.02-2.46) Boosted PI (ref: NNRTI; aHR: 1.57; 95% CI: 1.02-2.41)	
Braithwaite et al., 2007 (67) N=6394 Retrospective study of existing medical records 1996-2004 USA	Single PI (ref: EFV, aHR: 1.16; p=0.003) Triple NRTI (ref: EFV, aHR: 1.22; p=0.011) d4T/3TC (ref: ZDV/3TC, aHR: 1.08 p=0.032)	
Li et al., 2005 (43) N=687 Nested cohort study of a multicenter prospective cohort	Younger age (per 5 year decrease; aOR: 1.20; 95% CI: 1.03-1.40) High HIV RNA level (per 1 $\log_{10}$ increase; aOR: 1.42; 95% CI: 1.17-1.72)	

study 1997-2001 USA	Depression (aOR: 2.03; 95% CI: 1.24-3.32) ABC (aOR: 1.82; 95% CI: 1.03-3.20) LPV (aOR: 4.68; 95% CI: 1.56-13.99)	
Pence et al., 2008 (85) N=435 Sub-analysis of a prospective cohort study 2001-2002 USA	Minority race/ethnicity (aHR: 2.44; 95% CI: 1.33-4.49; p<0.05)	
Kiguba et al., 2007 (51) N=686 Cross-sectional study 2005-2006 Uganda	Previous cART experience (aOR: 3.70; 95% CI: 2.13-6.25) Use of alternative medicines (aOR: 2.18; 95% CI: 1.06-4.47) Hospitalization (aOR: 2.36; 95% CI: 1.32-4.20) One year or less on cART (aOR: 11.11; 95% CI: 5.00-25.00). Being unmarried (aOR: 1.64; 95% CI: 1.02-2.70) 3 months or less on cART (aOR: 3.13; 95% CI: 1.16-8.33).	Reasons for discontinuation of cART included high cost (43.0%), adverse events (21.1%), drugs being out of stock (10.5%). Reasons for modification of cART were adverse events (71.8%) and high cost (23.3%).

Kumarasamy et al., 2006 (64) N=1443 Retrospective study of existing medical records 1996-2004 India	NVP (ref: RTV or EFV), median 66 vs. 131 days; p=0.150).		Reasons for regimen modification included adverse events (64%) and cost (19%). Reasons for regimen discontinuation included cost (64%) and adverse events (21%).
Willig et al., 2009 (48) N=546 Retrospective study of existing medical records 2004-2007 Peru	Weight < 60kg (aHR: 1.77; 95% CI: 1.25-2.51) Baseline CD4 <200 (aHR: 1.73; 95% CI: 1.03-2.91) ZDV use at in the first 120 days of therapy (aHR: 2.09; 95% CI: 1.22-3.57)	ZDV use >120 days after initiation of therapy (aHR: 0.52; 95% CI: 0.28-0.95)	
Sax et al., 2009 (69) N=1858 Partially blinded randomized controlled trial 2006-2009 USA	ABC-3TC (ref: TDF-FTC; HR: 1.87; 95% CI (1.38-2.54); p<0.001)		
Domingo et al.,	LPV/r (ref: EFV, HR: 2.10, 95%		

2008 (86) N=1550 Sub-analysis of a prospective cohort study 1999-2007 Spain	CI (1.40-3.15), p=0.0003)	
Springer et al., 2007 (65) N=1099 Retrospective cohort study 1999-2002 USA	Three class regimen (ref: Triple NRTI, NRTI-based, or PI-base regimen; p<0.05)	
MacArthur el al., 2006 (66) N=1397 Randomized controlled trial 1999-2002 USA	Three class regimen (ref: NRTI-based or PI-base regimen; HR: 1.58; p<0.0001)	Most common adverse effects cited as a reason for discontinuation were nausea or vomiting, diarrhea, and rash.

Abbreviations: 3TC, lamivudine; ABC, abacavir; aHR, adjusted hazard ratio; aOR, adjusted odds ratio; ATV, atazanavir; CI, confidence interval; d4T, stavudine; ddI, didanosine; EFV, efavirenz; FTC, emtricitabine; cART, combination antiretroviral therapy; HIV, human immunodeficiency virus; HR, hazard ratio; IDV/r, indinavir/ritonavir; IRR, incidence rate ratio; LPV, lopinavir; LPV/r, lopinavir/ritonavir; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; NVP, nevirapine; OR, odds ratio; PI, protease inhibitor;

RNA, ribonucleic acid; aRRR, adjusted relative risk ratio; RTV, ritonavir; SQV, saquinavir; TDF, tenofovir; ZDV, zidovudine

Table 3. Patterns of patient non-persistence among subjects receiving directly administered antiretroviral therapy.

	Non-persistence ≥ 3 days	Non-persistence ≥ 5 days	Non-persistence ≥ 7 days
All (n=74)	59 (80%)	41 (55%)	33 (45%)
PI *(n=44)*	35 (80%)	23 (52%)	20 (45%)
NNRTI *(n=22)*	17 (77%)	12 (55%)	7 (32%)
Other *(n=8)*	7 (87.5%)	6 (75%)	6 (75%)
Frequency of Dosing			
QD *(n=21)*	15 (71%)	10 (48%)	9 (43%)
BID or more *(n=53)*	44 (83%)	31 (58%)	24 (45%)
Pill Burden			
<10 pills daily *(n=40)*	50 (83%)	35 (58%)	29 (48%)
≥10 pills daily *(n=34)*	9 (64%)	6 (43%)	4 (29%)

A subject was categorized as "non-persistence ≥ 3 days" if he missed 3 or more consecutive days of antiretroviral medications at any point during the DAART intervention period. Non-persistence ≥ 5 days and non-persistence ≥ 7 days were defined similarly.

Table 4. Adjusted odds ratios of factors associated with patient non-persistence among subjects receiving directly administered antiretroviral therapy.

	Non-persistence ≥ 3 days	**Non-persistence ≥ 7 days**	**Recurrent episodes of gaps (≥ 3 days)**
Homeless			
No *(n=45)*	Referent		
Yes *(n=29)*	0.10 (0.01 – 1.01)		
Drug Abuse Severity (DAST-10)			
Low or moderate *(n=38)*		Referent	
High *(n=36)*		3.17 (1.1 – 9.14)*	
Injection drug use in past 30 days			
No			Referent
Yes			15.20 (1.79 – 129.11)*
Depression (CES-D≥16)			
No *(n=14)*	Referent	Referent	Referent
Yes *(n=55)*	17.38 (1.48 – 204.13)*	5.41 (1.06 – 27.53)*	2.89 (.60 – 13.95)
Preference for medication taking			
Prefers assistance *(n=18)*	Referent		
Prefers no assistance *(n=53)*	0.30 (0.04 – 2.59)		
Baseline viral load			
VL<400 copies/mL *(n=21)*	Referent		
VL≥400 copies/mL *(n=53)*	2.73 (0.67 – 11.23)		
Social Support			
High			Referent

Low			3.29 (.84 – 12.87)
Self-Efficacy			
High			Referent
Low			0.37 (.11 – 1.28)
Frequency of dosing			
Once daily			Referent
Twice daily			6.32 (1.00 – 39.98)
Confidence can take medications as prescribed			
9 or 10 (Extremely confident)			Referent
8 or lower			.40 (.10 – 1.60)

Univariate analysis between the following variables in non-persistence ≥ 3, ≥ 5, and ≥ 7 days, and recurrent episodes of gaps ≥ 3 were performed. Age, gender, race, homelessness, education, drug abuse screening test, CES-D score, social support, self-efficacy, confidence that one can take medications as prescribed, preference for assistance with medication-taking, willingness to travel for DAART, frequency of dosing, pill burden, and baseline viral load. Those variables with a p-value <0.10 on univariate analysis were included in the multivariate logistic regression and their adjusted odds ratios are presented here. Analyses for non-persistence ≥ 5 are not shown because no univariate association had a p –value <0.10.

*p<0.05

8. References

1. Strategies for Management of Antiretroviral Therapy (SMART) Group. 2006. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 355:2283-2296.
2. Department of Health and Human Services. December 1, 2009; 1-161. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. . Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents.
3. Mirochnick, M., Fenton, T., Gagnier, P., Pav, J., Gwynne, M., Siminski, S., Sperling, R.S., Beckerman, K., Jimenez, E., Yogev, R., et al. 1998. Pharmacokinetics of nevirapine in human immunodeficiency virus type 1-infected pregnant women and their neonates. Pediatric AIDS Clinical Trials Group Protocol 250 Team. *Journal of Infectious Diseases* 178:368-374.
4. Mackie, N.E., Fidler, S., Tamm, N., Clarke, J.R., Back, D., Weber, J.N., and Taylor, G.P. 2004. Clinical implications of stopping nevirapine-based antiretroviral therapy: relative pharmacokinetics and avoidance of drug resistance. *HIV Med* 5:180-184.
5. Kumar, P.N., Sweet, D.E., McDowell, J.A., Symonds, W., Lou, Y., Hetherington, S., and LaFon, S. 1999. Safety and pharmacokinetics of abacavir (1592U89) following oral administration of escalating single doses in human immunodeficiency virus type 1-infected adults. *Antimicrob Agents Chemother* 43:603-608.
6. Johnson, M.A., Moore, K.H., Yuen, G.J., Bye, A., and Pakes, G.E. 1999. Clinical pharmacokinetics of lamivudine. *Clin Pharmacokinet* 36:41-66.
7. Hawkins, T., Veikley, W., St Claire, R.L., Guyer, B., Clark, N., and Kearney, B.P. 2005. Intracellular pharmacokinetics of tenofovir diphosphate, carbovir triphosphate, and lamivudine triphosphate in patients receiving triple-nucleoside regimens. *JAIDS Journal of Acquired Immune Deficiency Syndromes* 39:406-411.
8. Richman, D.D., Havlir, D., Corbeil, J., Looney, D., Ignacio, C., Spector, S.A., Sullivan, J., Cheeseman, S., Barringer, K., and Pauletti, D. 1994. Nevirapine resistance mutations of human immunodeficiency virus type 1 selected during therapy. *J Virol* 68:1660-1666.
9. Kassaye, S., Lee, E., Kantor, R., Johnston, E., Winters, M., Zijenah, L., Mateta, P., and Katzenstein, D. 2007. Drug resistance in plasma and breast milk after single-dose nevirapine in subtype C HIV type 1: population and clonal sequence analysis. *AIDS Res Hum Retroviruses* 23:1055-1061.
10. Eshleman, S.H., Hoover, D.R., Chen, S., Hudelson, S.E., Guay, L.A., Mwatha, A., Fiscus, S.A., Mmiro, F., Musoke, P., Jackson, J.B., et al. 2005. Resistance after single-dose nevirapine prophylaxis emerges in a high proportion of Malawian newborns. *Aids* 19:2167-2169.
11. Ribaudo, H.J., Haas, D.W., Tierney, C., Kim, R.B., Wilkinson, G.R., Gulick, R.M., Clifford, D.B., Marzolini, C., Fletcher, C.V., Tashima, K.T., et al. 2006. Pharmacogenetics of plasma efavirenz exposure after treatment

discontinuation: an Adult AIDS Clinical Trials Group Study. *Clin Infect Dis* 42:401-407.
12. Arribas, J.R., Pulido, F., Delgado, R., Lorenzo, A., Miralles, P., Arranz, A., Gonz√°lez-Garc√≠a, J.J., Cepeda, C., Herv√°s, R., Pa√±o, J.R., et al. 2005. Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *JAIDS Journal of Acquired Immune Deficiency Syndromes* 40:280-287.
13. Swindells, S., DiRienzo, A.G., Wilkin, T., Fletcher, C.V., Margolis, D.M., Thal, G.D., Godfrey, C., Bastow, B., Ray, M.G., Wang, H., et al. 2006. Regimen simplification to atazanavir-ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression. *Journal of American Medical Association* 296:806-814.
14. Cohen, C.J., Colson, A.E., Sheble-Hall, A.G., McLaughlin, K.A., and Morse, G.D. 2007. Pilot study of a novel short-cycle antiretroviral treatment interruption strategy: 48-week results of the five-days-on, two-days-off (FOTO) study. *HIV Clin Trials* 8:19-23.
15. Ananworanich, J., Nuesch, R., Le Braz, M., Chetchotisakd, P., Vibhagool, A., Wicharuk, S., Ruxrungtham, K., Furrer, H., Cooper, D., Hirschel, B., et al. 2003. Failures of 1 week on, 1 week off antiretroviral therapies in a randomized trial. *AIDS* 17:F33-37.
16. Bangsberg, D.R., Moss, A.R., and Deeks, S.G. 2004. Paradoxes of adherence and drug resistance to HIV antiretroviral therapy. *J Antimicrob Chemother* 53:696-699.
17. Bangsberg, D.R., Hecht, F.M., Charlebois, E.D., Zolopa, A.R., Holodniy, M., Sheiner, L., Bamberger, J.D., Chesney, M.A., and Moss, A. 2000. Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population. *Aids* 14:357-366.
18. Walsh, J.C., Pozniak, A.L., Nelson, M.R., Mandalia, S., and Gazzard, B.G. 2002. Virologic rebound on HAART in the context of low treatment adherence is associated with a low prevalence of antiretroviral drug resistance. *J Acquir Immune Defic Syndr* 30:278-287.
19. Bangsberg, D.R., Charlebois, E.D., Grant, R.M., Holodniy, M., Deeks, S.G., Perry, S., Conroy, K.N., Clark, R., Guzman, D., Zolopa, A., et al. 2003. High levels of adherence do not prevent accumulation of HIV drug resistance mutations. *AIDS* 17:1925-1932.
20. Altice, F.L., Maru, D.S., Bruce, R.D., Springer, S.A., and Friedland, G.H. 2007. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis* 45:770-778.
21. Altice, F.L., Mezger, J.A., Hodges, J., Bruce, R.D., Marinovich, A., Walton, M., Springer, S.A., and Friedland, G.H. 2004. Developing a directly administered antiretroviral therapy intervention for HIV-infected drug users: implications for program replication. *Clin Infect Dis* 38 Suppl 5:S376-S387.
22. Yudko, E., Lozhkina, O., and Fouts, A. 2007. A comprehensive review of the psychometric properties of the Drug Abuse Screening Test. *J Subst Abuse Treat* 32:189-198.

23. Radloff, L.S. 1977. The CES-D Scale. *Applied Psychological Measurement* 1:385-401.
24. Huba, G.J., Melchior, L. A., Staff of The Measurement Group, and HRSA/HAB's SPNS Cooperative Agreement Steering Committee 1996. Module 64: Self-Efficacy Form. Culver City, California: The Measurement Group.
25. Heinze, G., and Schemper, M. 2002. A solution to the problem of separation in logistic regression. *Statist Med* 21:2409-2419.
26. Haynes, R.B., Sackett, D.L., McMaster University. Medical, C., and Workshop/Symposium on Compliance with Therapeutic, R. 1976. *Compliance with therapeutic regimens / David L. Sackett and R. Brian Haynes, editors*. Baltimore :: Johns Hopkins University Press.
27. Cramer, J.A., Roy, A., Burrell, A., Fairchild, C.J., Fuldeore, M.J., Ollendorf, D.A., and Wong, P.K. 2008. Medication compliance and persistence: terminology and definitions. *Value Health* 11:44-47.
28. Bangsberg, D.R. 2008. A paradigm shift to prevent HIV drug resistance. *Plos Med* 5:e111-e111.
29. Peterson, A.M., Nau, D.P., Cramer, J.A., Benner, J., Gwadry-Sridhar, F., and Nichol, M. 2007. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health* 10:3-12.
30. Gwadry-Sridhar, F.H., Manias, E., Zhang, Y., Roy, A., Yu-Isenberg, K., Hughes, D.A., and Nichol, M.B. 2009. A framework for planning and critiquing medication compliance and persistence research using prospective study designs. *Clin Ther* 31:421-435.
31. Knobel, H., Urbina, O., Gonzalez, A., Sorli, M.L., Montero, M., Carmona, A., and Guelar, A. 2009. Impact of different patterns of nonadherence on the outcome of highly active antiretroviral therapy in patients with long-term follow-up. *HIV Med* 10:364-369.
32. Spacek, L.A., Shihab, H.M., Kamya, M.R., Mwesigire, D., Ronald, A., Mayanja, H., Moore, R.D., Bates, M., and Quinn, T.C. 2006. Response to antiretroviral therapy in HIV-infected patients attending a public, urban clinic in Kampala, Uganda. *Clin Infect Dis* 42:252-259.
33. Kavasery, R., Galai, N., Astemborski, J., Lucas, G.M., Celentano, D.D., Kirk, G.D., and Mehta, S.H. 2009. Nonstructured treatment interruptions among injection drug users in Baltimore, MD. *J Acquir Immune Defic Syndr* 50:360-366.
34. Oyugi, J.H., Byakika-Tusiime, J., Ragland, K., Laeyendecker, O., Mugerwa, R., Kityo, C., Mugyenyi, P., Quinn, T.C., and Bangsberg, D.R. 2007. Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda. *AIDS* 21:965-971.
35. Parienti, J.J., Massari, V., Descamps, D., Vabret, A., Bouvet, E., Larouze, B., and Verdon, R. 2004. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clin Infect Dis* 38:1311-1316.
36. Hogg, R.S., Yip, B., Chan, K.J., Wood, E., Craib, K.J., O'Shaughnessy, M.V., and Montaner, J.S. 2001. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 286:2568-2577.

37. Dybul, M., Nies-Kraske, E., Daucher, M., Hertogs, K., Hallahan, C.W., Csako, G., Yoder, C., Ehler, L., Sklar, P.A., Belson, M., et al. 2003. Long-cycle structured intermittent versus continuous highly active antiretroviral therapy for the treatment of chronic infection with human immunodeficiency virus: effects on drug toxicity and on immunologic and virologic parameters. *J Infect Dis* 188:388-396.
38. Parienti, J.J., Das-Douglas, M., Massari, V., Guzman, D., Deeks, S.G., Verdon, R., and Bangsberg, D.R. 2008. Not all missed doses are the same: sustained NNRTI treatment interruptions predict HIV rebound at low-to-moderate adherence levels. *PLoS ONE* 3:e2783-e2783.
39. Parienti, J.J., Ragland, K., Lucht, F., de la Blanchardi√®re, A., Darg√®re, S., Yazdanpanah, Y., Dutheil, J.J., Perr√©, P., Verdon, R., and Bangsberg, D.R. 2010. Average Adherence to Boosted Protease Inhibitor Therapy, rather than the Pattern of Missed Doses, as a Predictor of HIV RNA Replication. *Clin Infect Dis* 50:1192-1197.
40. Palella Jr, F.J., Chmiel, J.S., Moorman, A.C., Holmberg, S.D., and Investigators, H.I.V.O.S. 2002. Durability and predictors of success of highly active antiretroviral therapy for ambulatory HIV-infected patients. *Aids* 16:1617-1626.
41. Willig, J.H., Abroms, S., Westfall, A.O., Routman, J., Adusumilli, S., Varshney, M., Allison, J., Chatham, A., Raper, J.L., Kaslow, R.A., et al. 2008. Increased regimen durability in the era of once-daily fixed-dose combination antiretroviral therapy. *AIDS* 22:1951-1960.
42. Klein, M.B., Willemot, P., Murphy, T., and Lalonde, R.G. 2004. The impact of initial highly active antiretroviral therapy on future treatment sequences in HIV infection. *Aids* 18:1895-1904.
43. Li, X., Margolick, J.B., Conover, C.S., Badri, S., Riddler, S.A., Witt, M.D., and Jacobson, L.P. 2005. Interruption and discontinuation of highly active antiretroviral therapy in the multicenter AIDS cohort study. *J Acquir Immune Defic Syndr* 38:320-328.
44. d'Arminio Monforte, A., Lepri, A.C., Rezza, G., Pezzotti, P., Antinori, A., Phillips, A.N., Angarano, G., Colangeli, V., De Luca, A., Ippolito, G., et al. 2000. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naive Patients. *Aids* 14:499-507.
45. Mocroft, A., Youle, M., Moore, A., Sabin, C.A., Madge, S., Lepri, A.C., Tyrer, M., Chaloner, C., Wilson, D., Loveday, C., et al. 2001. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *Aids* 15:185-194.
46. van Roon, E.N., Verzijl, J.M., Juttmann, J.R., Lenderink, A.W., Blans, M.J., and Egberts, A.C. 1999. Incidence of discontinuation of highly active antiretroviral combination therapy (HAART) and its determinants. *J Acquir Immune Defic Syndr Hum Retrovirol* 20:290-294.
47. Ahdieh-Grant, L., Tarwater, P.M., Schneider, M.F., Anastos, K., Cohen, M., Khalsa, A., Minkoff, H., Young, M., and Greenblatt, R.M. 2005. Factors and temporal trends associated with highly active antiretroviral therapy discontinuation in the Women's Interagency HIV Study. *J Acquir Immune Defic Syndr* 38:500-503.

48. Willig, J.H., Echevarria, J., Westfall, A.O., Iglesias, D., Henostroza, G., Seas, C., Mugavero, M.J., Allison, J., Paz, J., Hernandez, F., et al. 2009. Durability of Initial Antiretroviral Therapy in a Resource Constrained Setting and the Potential Need for Zidovudine Weight-Based Dosing. *J Acquir Immune Defic Syndr*.
49. Vo, T.T., Ledergerber, B., Keiser, O., Hirschel, B., Furrer, H., Battegay, M., Cavassini, M., Bernasconi, E., Vernazza, P., and Weber, R. 2008. Durability and outcome of initial antiretroviral treatments received during 2000--2005 by patients in the Swiss HIV Cohort Study. *J Infect Dis* 197:1685-1694.
50. Lodwick, R.K., Smith, C.J., Youle, M., Lampe, F.C., Tyrer, M., Bhagani, S., Chaloner, C., Sabin, C.A., Johnson, M.A., and Phillips, A.N. 2008. Stability of antiretroviral regimens in patients with viral suppression. *Aids* 22:1039-1046.
51. Kiguba, R., Byakika-Tusiime, J., Karamagi, C., Ssali, F., Mugyenyi, P., and Katabira, E. 2007. Discontinuation and modification of highly active antiretroviral therapy in HIV-infected Ugandans: prevalence and associated factors. *J Acquir Immune Defic Syndr* 45:218-223.
52. Chen, R.Y., Westfall, A.O., Mugavero, M.J., Cloud, G.A., Raper, J.L., Chatham, A.G., Acosta, E.P., Taylor, K.H., Carter, J., and Saag, M.S. 2003. Duration of highly active antiretroviral therapy regimens. *Clin Infect Dis* 37:714-722.
53. Hooshyar, D., Napravnik, S., Miller, W.C., and Eron, J.J., Jr. 2006. Effect of hepatitis C coinfection on discontinuation and modification of initial HAART in primary HIV care. *Aids* 20:575-583.
54. Crystal, S., Sambamoorthi, U., Moynihan, P.J., and McSpiritt, E. 2001. Initiation and continuation of newer antiretroviral treatments among medicaid recipients with AIDS. *J Gen Intern Med* 16:850-859.
55. Robison, L.S., Westfall, A.O., Mugavero, M.J., Kempf, M.C., Cole, S.R., Allison, J.J., Willig, J.H., Raper, J.L., Wilcox, C.M., and Saag, M.S. 2008. Short-term discontinuation of HAART regimens more common in vulnerable patient populations. *AIDS Res Hum Retroviruses* 24:1347-1355.
56. Palepu, A., Tyndall, M.W., Chan, K., Wood, E., Montaner, J.S., and Hogg, R.S. 2004. Initiating highly active antiretroviral therapy and continuity of HIV care: the impact of incarceration and prison release on adherence and HIV treatment outcomes. *Antivir Ther* 9:713-719.
57. Springer, S.A., Pesanti, E., Hodges, J., Macura, T., Doros, G., and Altice, F.L. 2004. Effectiveness of antiretroviral therapy among HIV-infected prisoners: reincarceration and the lack of sustained benefit after release to the community. *Clin Infect Dis* 38:1754-1760.
58. Kerr, T., Marshall, A., Walsh, J., Palepu, A., Tyndall, M., Montaner, J., Hogg, R., and Wood, E. 2005. Determinants of HAART discontinuation among injection drug users. *AIDS Care* 17:539-549.
59. Zahari, M.M., Bae, W.H., Zainal, N.Z., Habil, H., Kamarulzaman, A., and Altice, F.L. Psychiatric and substance abuse comorbidity among HIV seropositive and HIV seronegative prisoners in Malaysia. *Am J Drug Alcohol Abuse* 36:31-38.
60. Altice, F.L., Kamarulzaman, A., Soriano, V.V., Schechter, M., and Friedland, G.H. Treatment of medical, psychiatric, and substance-use

comorbidities in people infected with HIV who use drugs. *Lancet* 376:367-387.
61. Baillargeon, J., Giordano, T.P., Rich, J.D., Wu, Z.H., Wells, K., Pollock, B.H., and Paar, D.P. 2009. Accessing antiretroviral therapy following release from prison. *Jama* 301:848-857.
62. Pant Pai, N., Estes, M., Moodie, E.E., Reingold, A.L., and Tulsky, J.P. 2009. The Impact of Antiretroviral Therapy in a Cohort of HIV Infected Patients Going in and out of the San Francisco County Jail. *PLoS ONE* 4:e7115-e7115.
63. O'Brien, M.E., Clark, R.A., Besch, C.L., Myers, L., and Kissinger, P. 2003. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. *J Acquir Immune Defic Syndr* 34:407-414.
64. Kumarasamy, N., Vallabhaneni, S., Cecelia, A.J., Yepthomi, T., Balakrishnan, P., Saghayam, S., Flanigan, T.P., Carpenter, C.C., Solomon, S., and Mayer, K.H. 2006. Reasons for modification of generic highly active antiretroviral therapeutic regimens among patients in southern India. *J Acquir Immune Defic Syndr* 41:53-58.
65. Springer, S.A., Friedland, G.H., Doros, G., Pesanti, E., and Altice, F.L. 2007. Antiretroviral treatment regimen outcomes among HIV-infected prisoners. *HIV Clin Trials* 8:205-212.
66. MacArthur, R.D., Novak, R.M., Peng, G., Chen, L., Xiang, Y., Hullsiek, K.H., Kozal, M.J., van den Berg-Wolf, M., Henely, C., Schmetter, B., et al. 2006. A comparison of three highly active antiretroviral treatment strategies consisting of non-nucleoside reverse transcriptase inhibitors, protease inhibitors, or both in the presence of nucleoside reverse transcriptase inhibitors as initial therapy (CPCRA 058 FIRST Study): a long-term randomised trial. *Lancet* 368:2125-2135.
67. Braithwaite, R.S., Kozal, M.J., Chang, C.C., Roberts, M.S., Fultz, S.L., Goetz, M.B., Gibert, C., Rodriguez-Barradas, M., Mole, L., and Justice, A.C. 2007. Adherence, virological and immunological outcomes for HIV-infected veterans starting combination antiretroviral therapies. *AIDS* 21:1579-1589.
68. Ortiz, R., Dejesus, E., Khanlou, H., Voronin, E., van Lunzen, J., Andrade-Villanueva, J., Fourie, J., De Meyer, S., De Pauw, M., Lefebvre, E., et al. 2008. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. *Aids* 22:1389-1397.
69. Sax, P.E., Tierney, C., Collier, A.C., Fischl, M.A., Mollan, K., Peeples, L., Godfrey, C., Jahed, N.C., Myers, L., Katzenstein, D., et al. 2009. Abacavir-Lamivudine versus Tenofovir-Emtricitabine for Initial HIV-1 Therapy. *N Engl J Med*.
70. Zhang, Y., Adams, A.S., Ross-Degnan, D., Zhang, F., and Soumerai, S.B. 2009. Effects of prior authorization on medication discontinuation among medicaid beneficiaries with bipolar disorder. *Psychiatr Serv* 60:520-527.
71. Wilson, J., Axelsen, K., and Tang, S. 2005. Medicaid prescription drug access restrictions: exploring the effect on patient persistence with hypertension medications. *Am J Manag Care* 11 Spec No:SP27-SP34.
72. Lucas, G.M., Chaudhry, A., Hsu, J., Woodson, T., Lau, B., Olsen, Y., Keruly, J.C., Fiellin, D.A., Finkelstein, R., Barditch-Crovo, P., et al. Clinic-

Based Treatment of Opioid-Dependent HIV-Infected Patients Versus Referral to an Opioid Treatment Program: A Randomized Trial. *Ann Intern Med* 152:704-711.
73. Ostrop, N.J., and Gill, M.J. 2000. Antiretroviral medication adherence and persistence with respect to adherence tool usage. *AIDS Patient Care STDS* 14:351-358.
74. Maru, D.S., Bruce, R.D., Walton, M., Mezger, J.A., Springer, S.A., Shield, D., and Altice, F.L. 2008. Initiation, adherence, and retention in a randomized controlled trial of directly administered antiretroviral therapy. *AIDS Behav* 12:284-293.
75. Maru, D.S., Bruce, R.D., Walton, M., Springer, S.A., and Altice, F.L. 2009. Persistence of virological benefits following directly administered antiretroviral therapy among drug users: results from a randomized controlled trial. *J Acquir Immune Defic Syndr* 50:176-181.
76. Glass, T.R., De Geest, S., Weber, R., Vernazza, P.L., Rickenbach, M., Furrer, H., Bernasconi, E., Cavassini, M., Hirschel, B., Battegay, M., et al. 2006. Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study. *J Acquir Immune Defic Syndr* 41:385-392.
77. Lucas, G.M., Cheever, L.W., Chaisson, R.E., and Moore, R.D. 2001. Detrimental effects of continued illicit drug use on the treatment of HIV-1 infection. *J Acquir Immune Defic Syndr* 27:251-259.
78. Lucas, G.M., Gebo, K.A., Chaisson, R.E., and Moore, R.D. 2002. Longitudinal assessment of the effects of drug and alcohol abuse on HIV-1 treatment outcomes in an urban clinic. *AIDS* 16:767-774.
79. Knobel, H., Alonso, J., Casado, J.L., Collazos, J., Gonzv°lez, J., Ruiz, I., Kindelan, J.M., Carmona, A., Juega, J., Ocampo, A., et al. 2002. Validation of a simplified medication adherence questionnaire in a large cohort of HIV-infected patients: the GEEMA Study. *AIDS* 16:605-613.
80. Arnsten, J.H., Demas, P.A., Grant, R.W., Gourevitch, M.N., Farzadegan, H., Howard, A.A., and Schoenbaum, E.E. 2002. Impact of active drug use on antiretroviral therapy adherence and viral suppression in HIV-infected drug users. *J Gen Intern Med* 17:377-381.
81. Lima, V.D., Geller, J., Bangsberg, D.R., Patterson, T.L., Daniel, M., Kerr, T., Montaner, J.S., and Hogg, R.S. 2007. The effect of adherence on the association between depressive symptoms and mortality among HIV-infected individuals first initiating HAART. *AIDS* 21:1175-1183.
82. Altice, F.L., Bruce, R.D., Lucas, G.M., Lum, P.J., Korthuis, P.T., Flanigan, T.P., Cunningham, C.O., Sullivan, L.E., Vergara-Rodriguez, P., Fiellin, D.A., et al. 2011. HIV Treatment Outcomes Among HIV-Infected, Opioid-Dependent Patients Receiving Buprenorphine/Naloxone Treatment within HIV Clinical Care Settings: Results From a Multisite Study. *J Acquir Immune Defic Syndr* 56:S22-S32.
83. Zahari, M.M., Bae, W.H., Zainal, N.Z., Habil, H., Kamarulzaman, A., and Altice, F.L. 2010. Psychiatric and substance abuse comorbidity among HIV seropositive and HIV seronegative prisoners in Malaysia. *Am J Drug Alcohol Abuse* 36:31-38.
84. Tsai, A.C., Weiser, S.D., Petersen, M.L., Ragland, K., Kushel, M.B., and Bangsberg, D.R. 2010. A Marginal Structural Model to Estimate the Causal

Effect of Antidepressant Medication Treatment on Viral Suppression Among Homeless and Marginally Housed Persons With HIV. *Arch Gen Psychiatry* 67:1282-1290.

85. Pence, B.W., Ostermann, J., Kumar, V., Whetten, K., Thielman, N., and Mugavero, M.J. 2008. The influence of psychosocial characteristics and race/ethnicity on the use, duration, and success of antiretroviral therapy. *J Acquir Immune Defic Syndr* 47:194-201.
86. Domingo, P., Suárez-Lozano, I., Torres, F., Teira, R., Lopez-Aldeguer, J., Vidal, F., Muñoz, A., Viciana, P., Lozano, F., Vergara, A., et al. 2008. First-line antiretroviral therapy with efavirenz or lopinavir/ritonavir plus two nucleoside analogues: the SUSKA study, a non-randomized comparison from the VACH cohort. *J Antimicrob Chemother* 61:1348-1358.