

Cognitive behavioral therapy for cocaine addiction to improve antiretroviral medication adherence in HIV-positive patients

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A. Study Purpose and Rational

Many research studies have revealed that highly active antiretroviral therapy (HAART) improves HIV-related clinical outcomes, such as decreased opportunistic infections and prolonged survival as well as improves surrogate markers such as HIV viral load and CD4 cell counts [1,2]. Furthermore, optimal adherence to HAART regimens is necessary to obtain adequate viral suppression [3-5] and to avoid the emergence of viral resistance [6]. Patients who are actively abusing illicit drugs, including cocaine, have been shown to demonstrate decreased adherence to HAART as well as inferior virologic and immunologic responses to therapy as compared to both former and non-drug users [7]. Therefore, it is likely that helping these patients eliminate their illicit drug use may improve their adherence to HAART and their HIV clinical outcomes. The purpose of this study is to show that providing active cocaine abusers with cognitive behavioral therapy aimed at relapse prevention and coping skills training will increase their HAART regimen medication adherence as assessed by a self-adherence questionnaire over a 4 month period.

B. Study Design and Statistical Analysis

This is a randomized-controlled prospective study designed to assess whether or not a behavioral treatment for cocaine abuse will improve adherence to HAART therapy. The primary outcome of this study is a comparison of adherence to the prescribed HAART regimen in the intervention arm versus the standard of care arm as measured by a standardized three day recall self-assessment questionnaire administered every two weeks throughout the study. The secondary outcomes include viral suppression to undetectable levels using the RT-PCR assay (Roche) of HIV-1 viral load after 4 months and magnitude of change in the log₁₀ viral load from baseline to the 8-week visit. The endpoint of 4 months was chosen, as most individuals who achieve undetectable viral loads will have done so by this time point [1].

Once subjects are identified as cocaine users and express interest in treatment for cocaine abuse, they will be recruited, assessed to see if they fulfill all of the inclusion/exclusion criteria, consented and randomized to either the treatment/intervention arm or the standard of care arm. Randomization will be achieved by selecting an unlabeled sealed envelope from a box containing as many envelopes as potential subjects. Half of the envelopes will say "treatment arm" and half will say "standard of care". In this way, subjects will be randomized.

Subjects in the standard of care arm of the study will be provided with a list of referrals for substance-abuse treatment including Narcotics Anonymous, individual psychotherapy and rehabilitation programs at the first visit. They will be asked to return once each week for the first 6 weeks of the protocol and then every 2 weeks for the remainder of the study period, which is a total of 4 months. At each of these visits, they will be asked to provide a urine sample that will be tested for cocaine. They will also complete the 3-day adherence questionnaire with one of the investigators every two weeks. These subjects will be provided with additional drug treatment information by the regular clinic social workers and medical practitioners only if they request it according to the current standard of care. At the end of the study, they will be asked which if any of the cocaine treatment resources they utilized. Also, on the last visit, they will complete the Marlowe-Crowne social desirability questionnaire to assess the truthfulness of their self-reported data as compared to the treatment group.

Subjects in the treatment group will have the same number of visits with the same frequency as the standard of care arm, but in addition to providing urine samples every week and completing the adherence questionnaires every two weeks, they will be asked to attend to a 45 minute session at every visit with a trained addiction professional for a session of cognitive behavioral therapy specifically designed to address relapse prevention and coping skills training. Like the standard of care arm, they will be assessed with the Marlowe-Crowne at the last visit and asked about any other addiction treatments they utilized during the study period.

182 subjects will be enrolled in this study, with half participating in each of the two arms. This number will provide enough power to analyze the primary and secondary study outcomes as described below.

The primary outcome variable is percentage of total prescribed medication doses taken as assessed by a 3 day self-report adherence questionnaire. The percentage of total prescribed doses taken will be compared in the two arms with a X^2 test. Prior studies of non-drug abusers have shown that most patients report approximately a 70-80% adherence rate over the week prior to questioning with a standard deviation of around 20[8]. This self-reported adherence rate correlates with an actual adherence rate of around 55% as measured by microelectronic monitoring systems [8]. In other words, patients usually over report adherence by approximately 15-20% in a reproducible manner that still predicts changes in viral load. There is little data looking at self-reported adherence in a drug abusing population. One study has shown however that 32% of drug users obtain a viral load <400 copies/ml compared to 45% of non-users. The approximately 45% virologic response in non-users in this study is similar to the electronically monitored compliance of 55% in the previous study [7]. The lessened virologic response may be a result of pharmacokinetics and pharmacodynamics as well as viral resistance. Therefore, based on prior studies, non-users of drugs are likely to self-report around 70% adherence. Given, the lack of significant data on active drug abusers, 50% self-reported adherence is a reasonable estimate. To detect this difference, 17 subjects in each group are required.

To detect a 0.9 \log_{10} difference in change in HIV-1 RNA viral load at 8 weeks (the time interval it takes to detect a 1 \log_{10} change in viral load according to national guidelines) between groups assuming a standard deviation of 1.5 by unpaired t-test, a sample size of 45 subjects in each arm is required. Change in viral load is defined as the difference in \log_{10} copies/ml between the value measured at the time of the initial visit and the value at the 8-week visit. In a study comparing drug users and non-users, a 0.9 \log_{10} difference was detected (0.8 \log_{10} change in the drug users and a 1.7 \log_{10} change in the non-users) [7].

To compare the proportion of subjects who obtain undetectable HIV-1 RNA viral loads at 16 weeks in the two arms a X^2 test will be performed. In order to have power to detect a 20% difference between groups, assuming 40% will achieve undetectable levels in treatment arm and 20% will achieve undetectable levels in the standard of care arm, 91 subjects are required in each group.

Multiple linear regression analysis of the data will be performed to correlate adherence with other variables including age, gender, ethnicity, percentage of urine samples positive for cocaine during the study, utilization of alternate treatment modalities, and other variables shown to affect adherence in other research such as drug side effects or not being able to meet food and water requirements of the regimen [8b].

Data will be analyzed by an intention to treat analysis.

C. Study Procedure

All subjects participating in the study are to be followed by medical care providers in the outpatient HIV clinic and all medical management will be left to the discretion of those providers. The time intervals chosen in this study for checking viral loads after the initiation of HAART therapy correspond with national treatment guidelines [9]; however additional blood tests are at the discretion of the medical provider. Although it is not possible to blind this study, no data will be shared with either the subjects or their providers. The study period will last 4 months. Study visits will occur once a week for the first 6 weeks and then every 2 weeks thereafter. Subjects in both arms will have a urine dip test to

check for cocaine at every visit which will only take 5 minutes to collect and process. Also, every two weeks the subjects will be asked the questions on the 3-day adherence questionnaire to assess their medication adherence. The questionnaire will take about 15 minutes at these visits. The urine samples and questionnaires will be completed with an investigator in the HIV outpatient clinic prior to any medical visit that subject might have that day. The subjects in the treatment arm will have therapy sessions in the addiction medicine research clinic on the same days as their other study activities. All subjects will receive compensation for coming to the scheduled visits and providing urine samples in the form of vouchers. They will receive a \$15 voucher at each visit in the form of subway fare (Metrocard) or a voucher to a local fast food chain. If they complete the study and come to all of the scheduled visits, they will receive a \$50 gift certificate to Old Navy.

At the first visit, informed consent will be obtained and the study will be explained to the patient by one of the investigators. Also, the primary medical provider will initiate HAART therapy. Because adherence to the prescribed regimen is the primary outcome, patients may be placed on any of the "strongly recommended" regimens according to current national guidelines [9] at the discretion of the primary medical provider as long as the regimen is a class sparing regimen. (e.g. NNRTI-sparing, PI-sparing or a PI- and NNRTI-sparing regimen) The medical care provider will choose a regimen at the first study visit while still blinded to which arm of the study the patient is in to avoid biasing the choice.

The treatment intervention is cognitive behavioral therapy aimed at relapse prevention and coping skills training. It is an entity well described in psychiatric literature as an effective means of treating cocaine addiction. Cocaine addiction is being targeted in this study because it has a high prevalence amongst HIV positive patients and because it is not associated with a physical withdrawal syndrome upon cessation that would require detoxification. The treatment is essentially a problem-solving process and a reorientation of life attitudes consisting of psychotherapy, self-observation and monitoring, homework assignments, the use of guided imagery and role-play and bibliotherapy [10]. The therapy will have a "boost" period of visits every week followed by visits every two weeks thereafter. Psychotherapists trained in addiction treatment and this type of therapy will give the treatment. One review of 25 randomized trials looking at this relapse prevention therapy across all substances found that it was more effective than no treatment at enhancing the durability of cessation attempts and decreasing the severity of relapses [11].

Although many techniques for measuring adherence have been tried, all of them have been correlated with patient self-assessment questionnaires with good reproducibility. Self-assessment questionnaires have been compared to measuring serum antiretroviral drug levels [4], electronic monitoring (MEMS) caps [8], and provider-reported adherence [12] with similar correlations between HAART medication adherence and virologic and immunologic markers. Self-assessment questionnaires have many advantages over these other methods in that they are inexpensive, simple to administer, and do not require patients to follow complicated instructions.

D. Study Drugs

There are no study drugs included in this protocol. All antiretroviral therapy to be used is FDA approved and will be prescribed according to accepted national treatment guidelines.

E. Medical Devices

The HIV-1 RNA-PCR assay by Roche is the recommended assay for guiding patient treatment according to current national guidelines and is FDA approved for this purpose [9]. The urine dip-stick test is likewise a widely used and FDA approved means of tracking cocaine use via a urine test. There are no experimental or investigational medical devices included in this protocol.

F. Study Questionnaires

Following is a list of all questionnaires to be used in this study. Please see the appendix for examples of all study instruments.

1. The Drug Abuse Screening Test (DAST) – An instrument shown to be effective and valid for drug abuse screening [13-15]. With a cut-off level of 6 positive responses on the test, it demonstrates 85% overall accuracy in classifying patients with drug abuse problems as compared to a diagnostic interview for DSM criteria [16].
2. The Marlowe-Crowne Social Desirability Scale (SDS)- An instrument used to assess a subject's reluctance to express unpopular beliefs or behavior in order to avoid making a negative impression. Validated as a means of estimating the likelihood that a given subject is over reporting adherence to treatment. [17] To be administered at the end of the study period to all subjects to verify that the social desirability characteristics of the two arms are similar.
3. Three Day Adherence Questionnaire (Part A and B) – A questionnaire to be filled out by the patient with the assistance of the investigator who will be blinded in regards to the medication regimen that the patient is actually on. The investigator can provide assistance in the form of visual cues (such as photos of pills). This form requires subjects to actually recall their medication regimen to further verify that their statements regarding adherence are accurate. The form also includes some questions for the subject to answer in the event that any doses were missed to assess the reasons for missing doses. [18]

G. Study Subjects

In order to be included in this study, the patient must meet the following inclusion criteria:

- 1) Have documentation of HIV-1 positive status
- 2) Have a positive score on the Drug Abuse Screening Test (DAST)
- 3) Use cocaine regularly and more often than any other drug or alcohol
- 4) Express an interest in stopping their cocaine use
- 5) Must not be currently taking antiretroviral therapy
- 6) Have a viral load >55,000 copies/ml and a CD4 count < 200; thereby placing the subject in a category that should definitely receive therapy according to national guidelines [8b]. Treatment at higher CD4 loads and lower viral loads has still not been shown to affect clinical outcomes of time to disease progression and given the likelihood of non-adherence in drug-abusing populations is higher than in the general population, it may be unethical to start people on HAART when there are uncertain recommendations at present.

If a subject meets any of the following exclusion criteria, they will not be allowed to participate in the study:

- 1) On any form of antiretroviral therapy within the 4 months prior to the study
- 2) Exhibiting signs of physical dependence on any drug other than cocaine
- 3) Living in a facility where medicines are dispensed for them
- 4) Unable to give informed consent

Subject participation will not be limited on the basis of gender or race. Based on population of the community in which the study is to take place, Caucasian, Latino and African-American subjects will be primarily recruited. It is likely that slightly more men will be included in men as there are a larger proportion of male drug abusers in the general population.

H. Recruitment of Subjects

Subjects will be recruited at New York Presbyterian Hospital's Columbia Presbyterian Medical Center over a two-year period in both the outpatient HIV clinic as well as in the inpatient setting. All patients who present to the HIV clinic or the inpatient service for treatment of HIV or HIV-related

diseases will be screened with the Drug Abuse Screening Test (DAST). If it is positive, the patient would like help with their drug abuse and the patient's primary drug of abuse is cocaine, they will be recruited to participate in the study.

I. Confidentiality of Study Data

None of the data being collected during the study will be shared with the medical providers, the subjects or anyone else other than the primary investigators. Each subject will be assigned a unique identifier code number to identify his or her data (lab tests, drug tests, questionnaire data). This number will have no relationship to the arm of the study the subject is participating in. Hence, the support staff performing urine drug tests, serologic tests (viral loads and CD4 counts) and administering the adherence questionnaires will be blinded to which arm of the study the patient is participating in. All data will be stored in a secure database accessible only to the investigative team.

J. Potential Conflict of Interest

The investigators have no financial, material or proprietary interest in this study.

K. Location of the Study

This study will be conducted primarily out of the Division of Infectious Diseases outpatient HIV clinic with cooperation of the division. The Division of Addiction Medicine will also be involved in this study and the subjects in the treatment arm will receive their treatment intervention in the division's outpatient research clinic with the cooperation of the division.

L. References:

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14. Crowne, D.P. & Marlowe, D. (1960). A new scale of social desirability independent of psychopathology. *Journal of Consulting Psychology*, 24, 349-354.
15. Robinson, J.P., Shaver, P.R. & Wrightsman, L.S. (1991). *Measures of personality and social psychological attitudes*. New York: Academic Press.
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17. Welte JW, Russell M. Influence of socially desirable responding in a study of stress and substance abuse. *Alcoholism: Clinical & Experimental Research* 1993, 17(4):758-61.
18. Manheimer S. Diamond B. informally borrowed study instrument that is currently being used in a number of ongoing HAART adherence trials at Harlem Hospital.

The Drug Abuse Screening Test (DAST)

*For each question below, please circle either a **Yes** or **No***

- | | |
|---|------------------|
| 1. Have you used drugs other than those required for medical reasons? | Yes or No |
| 2. Have you abused prescription drugs? | Yes or No |
| 3. Do you abuse more than one drug at a time? | Yes or No |
| 4. Can you get through the week without using drugs (other than those required for medical reasons)? | Yes or No |
| 5. Are you always able to stop using drugs when you want to? | Yes or No |
| 6. Do you abuse drugs on a continuous basis? | Yes or No |
| 7. Do you try to limit your drug use to certain situations? | Yes or No |
| 8. Have you had "blackouts" or "flashbacks" as a result of drug use? | Yes or No |
| 9. Do you ever feel bad about your drug abuse? | Yes or No |
| 10. Does your spouse (or parents) ever complain about your involvement with drugs? | Yes or No |
| 11. Do your friends or relatives know or suspect you abuse drugs? | Yes or No |
| 12. Has drug abuse ever created problems between you and your spouse? | Yes or No |
| 13. Has any family member ever sought help for problems related to drug use? | Yes or No |
| 14. Have you ever lost friends because of your use of drugs? | Yes or No |
| 15. Have you ever neglected your family or missed work because of your use of drugs? | Yes or No |
| 16. Have you ever been in trouble at work because of drug abuse? | Yes or No |
| 17. Have you ever lost a job because of drug abuse? | Yes or No |
| 18. Have you gotten into fights when under the influence of drugs? | Yes or No |
| 19. Have you ever been arrested because of unusual behavior while under the influence of drugs? | Yes or No |
| 20. Have you ever been arrested for driving while under the influence of drugs? | Yes or No |
| 21. Have you engaged in illegal activities in order to obtain drugs? | Yes or No |
| 22. Have you been arrested for possession of dangerous drugs? | Yes or No |
| 23. Have you ever experienced withdrawal symptoms as a result of heavy drug intake? | Yes or No |
| 24. Have you had medical problems as a result of your drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)? | Yes or No |
| 25. Have you ever gone to anyone for help for a drug problem? | Yes or No |
| 26. Have you ever been in a hospital for medical problems related to drug use? | Yes or No |
| 27. Have you ever been involved in a treatment program specifically related to drug care? | Yes or No |
| 28. Have you been treated as an out-patient for problems related to drug use? | Yes or No |

The score is equal to the number of questions you answered **Yes**
 A score of 5 or less points indicates a Normal Score.
 A score of 6 or more points indicates a Drug Problem.

Marlowe-Crowne Social Desirability Scale

Listed below are a number of statements concerning personal attitudes and traits. Read each item and decide whether the statement is true or false as it pertains to you.

- T F 1. Before I vote, I thoroughly investigate the qualifications of all of the candidates.
- T F 2. I never hesitate to go out of my way to help someone in trouble.
- T F 3.* It is sometimes hard for me to go on with my work if I am not encouraged.
- T F 4. I have never intensely disliked anyone.
- T F 5.* On occasion, I have had doubts about my ability to succeed in life.
- T F 6.* I sometimes feel resentful when I don't get my way.
- T F 7. I am always careful about my manner of dress.
- T F 8. My table manners at home are as good as when I eat out in a restaurant.
- T F 9.* If I could get into a movie without paying and be sure I was not seen, I would probably do it.
- T F 10.* On a few occasions, I have given up doing something because I thought too little of my ability.
- T F 11.* I like to gossip at times.
- T F 12.* There have been times when I felt like rebelling against people in authority even though I knew they were right.
- T F 13. No matter who I'm talking to, I'm always a good listener.
- T F 14.* I can remember "playing sick" to get out of something.
- T F 15.* There have been occasions when I took advantage of someone.
- T F 16. I'm always willing to admit it when I make a mistake.
- T F 17. I always try to practice what I preach.
- T F 18. I don't find it particularly difficult to get along with loudmouthed, obnoxious people.
- T F 19.* I sometimes try to get even rather than forgive and forget.
- T F 20. When I don't know something, I don't mind admitting it.
- T F 21. I am always courteous, even to people who are disagreeable.
- T F 22.* At times I have really insisted on having things done my own way.
- T F 23.* There have been occasions when I felt like smashing things.
- T F 24. I would never think of letting someone else be punished for my wrongdoings.
- T F 25. I never resent being asked to return a favor.
- T F 26. I have never been irked when people express ideas very different from my own.
- T F 27. I never make a long trip without checking the safety of my car.
- T F 28.* There have been times when I was quite jealous of the good fortune of others.
- T F 29. I have almost never felt the urge to tell someone off.
- T F 30.* I am sometimes irritated by people who ask favors of me.
- T F 31. I have never felt that I was punished without cause.
- T F 32.* I sometimes think when people have a misfortune, they only got what they deserved.
- T F 33. I have never deliberately said something that hurt someone's feelings.

Note: Items marked with an asterisk are keyed negatively. To compute the social desirability score, sum the number of T responses to non-asterisked questions and the number of F responses to asterisked questions.

Three Day Adherence Questionnaire (Part A)

Note: The chart below should be customized to the client's antiretrovirals. Steps 1-3 should be generated interactively with the client, and should be an accurate representation of the client's current drug regimen. Please use prompts or visual aids if necessary to complete the table with the client. Please fill in "dk" for don't know if patient is unable to fill in an area of the chart.

Step 1 Names of antiretroviral drugs	Step 2 # pills taken at each dose	Step 3 # times dose is taken per day	Step 4 # doses missed Yesterday	Step 5 # doses missed 2 days ago	Step 6 # doses missed 3 days ago
1)					
2)					
3)					
4)					
5)					

If there were no reported missed doses in the chart above, please ask the following questions:

6. When was the last time you skipped any of your medications?
 - a. never skip medications
 - b. more than two weeks ago
 - c. 1-2 weeks ago
 - d. within the past week

Three Day Adherence Questionnaire (Part B)

Check one response for each of the following questions regarding reasons why you missed taking your medication: **N=Never, R=Rarely, S=Sometimes, O=Often.**

- | | |
|--|----------------|
| a) Taking pills didn't fit in with your daily routine? | N R S O |
| b) Simply forgot? | N R S O |
| c) Too hard to take so many pills according to a schedule? | N R S O |
| d) Wanted to avoid side effects? | N R S O |
| e) Felt like the drug was toxic/harmful? | N R S O |
| f) Did not want others to notice you taking medication? | N R S O |
| g) Feel asleep/slept through dose time? | N R S O |
| h) Felt sick or ill? | N R S O |
| i) Felt depressed/overwhelmed? | N R S O |
| j) Ran out of pills? | N R S O |
| k) Felt good? | N R S O |
| l) Didn't understand regimen? | N R S O |
| m) You knew what was best for you? | N R S O |
| n) Didn't fit with meals/didn't have water? | N R S O |
| o) Didn't feel like taking pills? | N R S O |
| p) Were drunk or high? | N R S O |