IRB Protocol:
Evaluation of HIV Educational Interventions and Their Impact on Clinical Outcomes

A. Study Purpose and Rationale

HIV/AIDS infections are a major health problem in the United States, with regard to both associated healthcare costs and patient morbidity and mortality. Recent estimates put the lifetime cost of HIV treatment for one patient at $618,900, and the US spends approximately $12 billion per year on HIV care-related costs[A]. A patient's risk of disease progression and death, which would be expected to increase these costs in addition to patient suffering, is directly tied to his or her CD4 count and viral load[1]. CD4 count and viral load in turn depend upon medication adherence, and so interventions to increase medication adherence have been an important focus of HIV research. Many factors have been shown to contribute to poor adherence, including a lack of education, a lack of health literacy, low income and unemployment, and alcohol/drug abuse[2-8]. Health literacy has the strongest association with poor adherence in many of these studies, and when it is utilized in analyses it has been shown to eliminate the effect of other factors, such as race, that were previously thought to be important[8].

Given the association of a lower educational level and low health literacy with poor adherence, interventions to increase patient knowledge about HIV are one potential target for improving clinical outcomes. Patient's baseline knowledge about HIV appears to have disturbing gaps, as seen in recent studies where only 56% of patients could name their medications, 55% of patients did not know what their medications did, 36% of patients did not know they needed lifelong medication, almost 86% of patients did not know what to do if they missed a medication dose, and 96% of patients failed to give a sufficient definition of resistance[9-11]. The possibility that this lack of knowledge is correlated with poor clinical outcomes was supported by Osborn et al's finding that patients' scores on an eight-question HIV knowledge test were associated with their medication adherence. Patients who scored 0-3 out of 8 had 51% adherence, while patients with a score of 4-5 had 82% adherence and those with a score of 6-8 had 91% adherence[5].

Prior studies have looked at the effectiveness of educational interventions both at improving patient knowledge and improving patient adherence. Several interventions have been shown to improve patient knowledge scores by an average of 10-15 percentage points including watching an educational video, playing an educational board game and attending a nurse practitioner-led lecture [12-14]. A variety of educational interventions, including provider-taught classes, meeting with peer educators, and computerized tutorials, have also been shown to improve adherence to medications or clinical appointments, although it has been harder to tie them to improvements in CD4 count and viral load [15-17].

The critical outcome measure of a patient educational program, however, should be whether improving patient knowledge leads to behavioral change and therefore to

improved clinical status, and so that will be the focus of this study. As noted above, prior studies have established that educational interventions tend to improve patient knowledge relative to a standard of care, which has typically been either no specific intervention, or occasionally a healthcare provider-led intervention. However, studies that compare the efficacy of multiple interventions to each other have been limited. This study will first attempt to ascertain whether specific interventions increase patient knowledge more than others with a comparison of pre and post-test scores of patients randomized to physician education, peer education, and self-directed education via a computer tutorial.

Also as noted above, the impact of interventions on adherence has been documented, but there is very limited data on whether there is a relationship between increased patient knowledge following an educational intervention and improvements in CD4 count and viral load. Patient knowledge will therefore be assessed before and after the educational interventions in this study, and patients will then be followed over the next year to evaluate for an impact of a knowledge increase, as measured by post-test score improvement, on treatment adherence as assessed by CD4 count and viral load, with hospital admission as a secondary outcome.

B. Study Design and Statistical Analysis

The first part of this study will be a randomized comparison of the efficacy of provider-led educational sessions, peer-led educational sessions, and self-directed computerized educational sessions. Subjects will be eligible if they are over 18, have a CD4 count <200 with a detectable viral load, and are currently on or initiating antiretroviral treatment. Stratified randomization of subjects will be performed according to each subject's Rapid Estimate of Adult Literacy in Medicine (REALM) score for health literacy, as this measure of health literacy has been shown to be correlated with HIV knowledge[5]. Subjects will also complete a demographic questionnaire with respect to age, sex, race, highest level of education, yearly income, substance abuse history, method of HIV transmission, number of years since diagnosis, number of HIV pills taken per day, and number of hospitalizations in the last year, and the randomized groups will be compared with respect to these categories to ensure no significant differences exist between them. (If statistically-significant differences are identified, competing risk analysis will need to be performed during analysis of the outcomes.)

Subjects will also complete a pre-test with 20 questions evaluating their knowledge about HIV in general and their personal HIV treatment history will be administered. This pre-test will be available in English and in Spanish. Subjects will also be offered the option to listen to a tape of the questions read aloud and to record their answers in either language to ensure that knowledge is tested rather than literacy, without introducing the bias of a provider reading the questions and possibly giving additional explanation or facial expression cues. Scores of 18/20 questions correct or better will exclude subjects from participation, as it would not be possible to evaluate for significant improvement following educational intervention in this

group – a prior study found an improvement of an average of 1.53 additional questions correct from pre to post-test in a control group of subjects who underwent no intervention, which suggests that some fluctuation of scores occurs and so small score differences are likely not significant[12].

Subjects who score 17/20 or worse will undergo the stratified randomized according to their REALM score as described above to one of three educational interventions. Each intervention will involve three 45–minute sessions conducted individually, as a review of prior studies found that individual interventions were more likely to have an adherence benefit when compared to group interventions[16]. Subjects will either work with a provider, a peer educator, or a version of the LifeWindows educational computer program, which has previously shown to improve medication adherence[15]. Modifications will be made to this computer program to ensure that the same information is covered in the provider, peer, and computer sessions so that the medium of information delivery can be compared without concern for bias introduced by different educational curricula. Subjects can schedule these interventions at their convenience over a 3 month period, as a review of prior studies also found that interventions done over 12 weeks or more were more effective than those done in a shorter time period[16].

This portion of the study is not blinded, as subjects will know which type of education they are receiving and the study investigators will know which subjects have been randomized to each group. However, the people conducting the provider and peer-led sessions will not know the pretest knowledge scores of the subjects with whom they are working to prevent any bias introduced by assuming that a subject needs more or less information about a topic.

Once subjects have completed three educational sessions, they will take a post-test with the same options for language and delivery method as the pre-test. Questions on the post-test will be the same as on the pre-test, but will be in a different numerical order with the answer choices to multiple choice questions also in a different order to attempt to avoid any rote memorization of the answers.

Previous studies have shown a 10-15 percentage point improvement in knowledge scores from pre-test to post-test after an educational intervention, with the 15% improvement seen in a study with a larger sample size[12, 14]. Therefore, the sample size needed to achieve 80% power was calculated assuming an effect size of a 15% score difference. Pre-test scores in these two prior studies ranged from 50-75% correct, so an expected pre-test score of 60% was used as the baseline with an expected improvement to 75% correct on the post-test. The sample size needed given these assumptions is 165 patients per group, or approximately 500 patients total.

Following the completion of the post-test, patients will be monitored for a year with CD4 count and viral load measured at 3, 6, 9, and 12 months after taking the test. At the conclusion of the year, changes in CD4 count and whether or not suppression of

viral load to <50 copies was achieved will be compared across the three intervention groups and with respect to HIV knowledge score improvement. Two groups will be compared to assess whether an increase in HIV knowledge results in an increase in CD4 count and suppression of viral load – subjects with an improvement in score ≥3 points and subjects with a change of ≤2 points. As discussed previously, some fluctuation in scores may occur by chance based on some minimal improvement in a control group in a prior study[12], and so patients whose score changes by 2 points or less will be assumed to have insignificant improvement. Comparison of the three original groups with respect to CD4 count and viral load will also be performed to evaluate for any benefit of an intervention not related to knowledge increase that impacts clinical outcome.

The knowledge comparison groups will not be randomized, so their demographics will be analyzed during the final statistical analysis to evaluate for any possible confounding factors contributing to any changes seen in clinical outcome. There is also no way to ensure equal numbers of subjects in these two groups, so while the ideal sample size of each group to ensure 80% statistical power can be calculated, it may not be possible to achieve this. Patients should achieve viral load suppression if they are adherent to medication, and so if all patients were adherent, it would be expected that all patients would have an undetectable viral load at the conclusion of the study. However, studies have shown 33-66% non-adherence at baseline in populations with poor health literacy[2, 3]. Adherence and viral load suppression do not have a 1:1 relationship, as patients can have perfect adherence on a sub-optimal regimen or a regimen to which they have developed resistance, so assuming that the lower end of the adherence range would be most likely to be accurate as a representation of viral load suppression and using the percentage of 33%, a significant clinical improvement would be an effect size of a 20% improvement. This would necessitate at least 105 subjects in each of the two groups in order to detect this improvement.

With respect to CD4 count, a mean increase of 100 cells in the first year of ARVs was seen in a population of patients with an average initial CD4 count of 200[18]. A reasonable assumption is that a CD4 count increase of 25 might be seen in a non-adherent group, and a clinically-significant target would be an increase of 75 given that some patients in the study will have been on ARVs for a longer time period. The expected range of CD4 counts in the study could start as low as 1 and would likely have a peak of 350, given everyone enrolled starting at a count <200 and an expected increase of up to 100 with good adherence. This therefore gives a standard deviation of 87.5, and a needed sample size of 50 subjects per group.

If the sample size of 105 subjects per group needed to detect differences in viral load suppression is not reached (either as a result of a majority of subjects having significant knowledge improvement, or a majority of subjects failing to make an improvement), there will be several options. If the number in each group is close to 105, additional subjects could be enrolled until the target number is reached. If the majority of subjects have a knowledge improvement, their improvements in CD4

count/viral load could be compared to a historical or current control set at the clinic who had similar baseline counts but underwent no intervention. If the majority of subjects do not improve, it may be an important indicator that

C. Study Procedure

Patients will be randomized to an educational intervention as detailed above. Each of the educational interventions will consist of three 45-minute sessions that the patient can schedule at their convenience over a 3 month period. Patients will be given a calendar of available dates and times so that they can coordinate with other appointments at CUMC or with other scheduling needs.

Providers who participate in the educational intervention will receive a training session to go over the material that needs to be presented and the resources used. Peer educators will be recruited from the HP6 clinic population; providers will be asked to recommend patients who have 90% or better appointment adherence, an undetectable viral load, a CD4 count >500, and no known problems with treatment adherence, and who have good verbal communication skills in either English and/or Spanish. Peer educators will receive 10 hours of training divided into 3 sessions, and must achieve a score of 20/20 on the patient post-test at the conclusion of training in order to participate.
The computer program will be set up in an exam room or office for patients to use. Patients will check in and out with the clinic secretary when they come to use the computer program in order to document that they were present for the full time.

The patient's medical provider will be informed when the patient has completed the post-test portion of the study so that they can schedule follow-up appointments tied to the patient's schedule for monitoring of CD4 counts and viral load. Laboratory test follow-up will be ordered by the primary care physician, as this monitoring is clinically-indicated and incorporation of the monitoring into normal clinic practice will prevent the patient from incurring additional costs. Monitoring should be done at 3, 6, 9, and 12 month intervals, although deviation of 10 days before or after the target date will be accepted.

D. Study Drugs

Patients will continue on the ARV regimen prescribed by their primary physician; no other medications will be utilized as part of the study.

E. Medical Device

Not applicable

F. Study Questionnaire

Patients will have the Rapid Estimate of Adult Literacy in Medicine (REALM) test administered by a trained screener upon enrollment into the study prior to randomization to an educational intervention arm.

Patients will then complete a pre-test and post-test designed to assess their knowledge about HIV in general and their personal HIV treatment history. Questions will assess knowledge about what HIV is and the difference between HIV and AIDS, how HIV is transmitted, what a CD4 count and viral load are and whether we want these numbers to go up or down, what antiretroviral resistance is and how it develops, what HIV medications the patient is on and has been on in the past, how these medications work, the risk of opportunisitic infections, and whether HIV can be cured. Development of this questionnaire will draw on the BEHKA score developed by Osborn et al [5]and the 22 question survey used by Hicks et al in their assessment of HIV knowledge[19].

G. Study Subjects

Patients will be eligible for the study if they are 18 or older, have a CD4 count <200 with a detectable viral load, and are currently on or initiating antiretroviral medication. Demographic data will be collected about each patient as noted in Study Design but will not affect study eligibility (other than age criteria). Patients will be excluded from participation if they have a pretest score of 18/20 or higher, as it would be impossible to assess for statistically-significant knowledge improvement in these patients.

H. Recruitment of Subjects

Eligible patients will be identified by their HP6 clinic provider or by the admitting physician on an inpatient admission to CUMC. The identifying provider will inquire as to whether patients are interested in hearing more about a study to evaluate whether receiving education about HIV affects how well a patient

I. Confidentiality of Study Data

Patients enrolled in the study will be given an identifying number separate from their medical record number, and any document connecting a patient's name or MR number to this identifier will be encrypted. The unique identifying number will be used to label a patient's REALM exam, demographic questionnaire, and pre- and post-tests. The primary investigator will have access to the encrypted document that identifies patients in order to access their medical records to obtain laboratory results for CD4 count and viral load, but this document will not be shared with anyone outside the study. After lab results are accessed, CD4 and viral load information will be recorded using the unique identifying number, not the patient's medical record number or name.

Because one of the study arms involves peer education, the trained peer educators will be aware of the HIV status of the patient they are counseling and will know that the patient's CD4 count is low and viral load is high by virtue of their enrollment in the study. In the course of providing educational information to the patient, they may also become aware of what antiretroviral medications the patient is on or has been on in the past. They will have no access to any other information in the patient's medical record, and will not be informed of the patient's REALM score, demographic data information, pre/post test scores, or subsequent CD4/viral load measurement results. They will also be instructed that any information about the

patient(s) with whom they are working is confidential, including their names, as a condition of their employment. Patients enrolling in the study will be informed that they may be randomized to work with an HIV-positive peer counselor who will know that they are also HIV positive.

J. Potential Conflict of Interest

No conflicts of interest exist.

K. Location of the Study

The study will take place at Columbia University Medical Center; patients will be enrolled either when visiting the HP6 clinic for an appointment or when admitted to the hospital. Study educational sessions will all take place at CUMC.

L. Potential Risks

Educational interventions will take place separately from the patient's standard HIV care, so there should be no risk related

M. Potential Benefits

Patients will receive three 45-minute educational sessions about HIV, including information about the medications that they are taking and strategies for improving their health.

It is not clear whether patients will receive any benefit with respect to their HIV clinical status, although the intent of the study is to provide knowledge with the hope of improving medication adherence.

N. Alternative Therapies

Not applicable.

O. Compensation to Subjects

No compensation will be provided.

P. Costs to Subjects

The only potential cost incurred by subjects would be transportation for 3 visits to CUMC for the educational interventions, although subjects will be able to schedule their study visits at the time of other appointments if they wish to do so to minimize this cost. Patients will also need laboratory monitoring at 3, 6, 9, and 12 months, but checking CD4 count and viral load at these intervals should be clinically-indicated and patients should therefore not incur additional costs.

Q. Minors as Research Subjects

Not applicable

R. Radiation or Radioactive Substance

Not applicable

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