CHOICE OF FIRST-LINE THERAPY AND FACTORS AFFECTING REGIMEN SELECTION FOR PERSONS INFECTED WITH HIV: A SURVEY OF TORONTO AREA PHYSICIANS AND A CHART REVIEW OF ANTIRETROVIRAL NAÏVE PATIENTS

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ABSTRACT

Background: The optimal first-line regimen for HIV positive patients should incorporate a balance between proven efficacy, toxicity, and patient acceptance. The choice of an initial regimen is crucial since it is usually associated with the best response. Until recently, the standard of therapy incorporated one or two protease inhibitors (PI) in combination with two nucleoside reverse transcriptase inhibitors (NRTIs). However, emerging data suggest that protease-sparing strategies (i.e., non-nucleoside reverse transcriptase inhibitor (NNRTI) + 2 NRTI or triple NRTI regimen) may also be considered for naïve patients.

Objective: The purpose of this study is to evaluate the current prescribing trends among regional Toronto physicians and compare the prescribing practices of primary care physicians (PC) and infectious disease specialists (ID) when initiating therapy for naïve HIV positive patients. Another purpose is to better understand patient attitudes towards different aspects of drug therapy, to evaluate the issues that physicians consider when selecting a regimen and to determine patient characteristics associated with specific regimens. The accuracy of survey methodology in predicting prescribing behavior is also assessed.

Methods: We first developed a physician questionnaire and self-complete patient questionnaire. The physician survey was distributed to Toronto-area physicians at the start and conclusion of the study period (June 1, 1999 and March 31, 2000). This survey assessed physician predictions about their own prescribing habits and their attitudes about the various regimen strategies. Enrolled patients completed a questionnaire to assess factors that might have been associated with a regimen choice. Additional demographic, laboratory and medical data were gathered from chart reviews.

Results: During the 10 month study period, twenty-five physicians completed the pre-study survey; 19 physicians completed the post-study survey. A total of 47 patients comprised the patient cohort. Forty-nine percent of antiretroviral naïve patients began a PI+2NRTI (PI-regimen) and 51% began an NNRTI+2NRTI (NNRTI-regimen). The differences between the practice groups approached significance,

with 64% of PC patients and 32% of ID patients initiating a PI-regimen, while 36% and 68% started an NNRTI-regimen (p=0.056), respectively. Significantly more patients starting a PI-regimen had a concomitant illness than those initiating an NNRTI-regimen (p = 0.047). Though not reaching statistical significance, patients prescribed a PI-regimen had higher baseline viral loads, lower baseline CD4, had waited a longer time from diagnosis to start of therapy, and were more likely to have had an AIDS-defining illness. Frequency of dosing, number of pills and concern with lipodystrophy were the areas of greatest concern for patients. Physicians, regardless of practice, did not accurately predict their prescribing practices. The survey results underestimated the frequency that NNRTI-regimens were prescribed and overestimated the initiation of PI-regimens.

Conclusion: From June 1999 to March 2000, more antiretroviral-naïve patients enrolled in this study started NNRTI-based vs. PI-based regimens, even though most physicians surveyed predicted that PI-regimens would be more commonly prescribed. Physicians sited clinical efficacy, virologic and immunologic parameters as factors influencing their decision to start a PI-regimen, while patients considered frequency of dosing, number of pills and concern with lipodystrophy as areas of greatest concern overall. Therefore, despite the data supporting the various regimens, a combination of antiretrovirals that incorporates ease of administration with fewer adverse events is likely to be preferred among HIV positive patients initiating their first regimen.

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1. BACKGROUND

1.1 Introduction

The appropriate selection of first-line therapy for the treatment of HIV infection is critical. The first drug regimen affects the subsequent course of the disease. Ideally, a regimen should be chosen for its efficacy, measured by its ability to reduce morbidity and mortality, suppress viral load, and improve immune function. An initial regimen that fails to maximally suppress viral load leads to the early development of resistance, limits the effectiveness of future drug combinations due to cross-resistance, and results in clinical therapeutic failure.[1] Often times, it is not the potency or efficacy of the regimen alone that determines success of therapy. Other issues such as adherence and regimen pharmacokinetics may complicate treatment strategy. In formulating the best regimen for an individual patient, the initial drug combination must have the appropriate balance between proven efficacy, adverse effects, and patient acceptance.

Triple combination therapy consisting of a protease inhibitor (PI) and two nucleoside reverse transcriptase inhibitors (NRTI) has been the standard of care for the initial treatment of patients with HIV. The recent release of efavirenz (Sustiva®), a nonnucleoside reverse transcriptase inhibitor (NNRTI) and abacavir (Ziagen®), an NRTI, gave many physicians the option of delaying protease inhibitor therapy in naïve patients. In addition to problems with adherence, controversies surrounding the potential long-term metabolic complications of protease inhibitors prompted the development of alternative therapies. This strategy of deferring the use of protease inhibitors is termed protease-sparing. Two recently published guidelines, the International Aids Society - USA panel and the United States Public Health Service guidelines reflect the potential role of these newer agents in current practice.[2,3] These guidelines recommend the combination of efavirenz or one or two protease inhibitors plus two nucleoside reverse transcriptase inhibitors as initial therapy and triple nucleoside therapy with abacavir as an acceptable alternative to PI based regimens.

The development of the protease inhibitor was a pivotal advance in the treatment of HIV infection. Convincing data from the Merck 035 study substantiates the use of protease-containing regimens as first-line therapy. Indinavir in combination with zidovudine and lamivudine suppressed viral replication in the majority of patients. Sixty-seven percent of patients maintained a viral load of < 50 copies / ml for a minimum of 3 years after simultaneous initiation.[4,5] In addition, data has emerged with other protease inhibitors that also appear to confirm the efficacy of protease inhibitors as first-line agents.[6,7,8] In a recently published study analyzing the morbidity and mortality in 1255 clinic patients with AIDS from 1994 to 1997, the risk of mortality among patients receiving combination therapy without a PI was 1.5 times the risk among patients receiving regimens including the PI.[9] By 1997, 82% of these patients received triple combination therapy containing a protease inhibitor. [9]

Although the protease inhibitors have had a remarkable impact on patient survival, several disadvantages exist. Factors weighing against PI use include the side effect profile, the potential development of long-term metabolic complications, complexity of administration, drug interactions, likelihood of poor adherence, cross-resistance, and high cost. Protease inhibitors have been associated with a syndrome coined lipodystrophy, which is characterized by fat redistribution syndrome, elevated total cholesterol, elevated LDL, decreased HDL, and insulin-resistant diabetes. [10,11] Chronic medical illness arising from these metabolic abnormalities diminish quality of life and raise the cost of HIV management. In addition, the psychologic impact of fat redistribution has resulted in many patients refusing to initiate or discontinuing life saving treatments

Adherence to protease inhibitors can also be difficult. In general, protease-containing regimens have a high pill burden, strict dosage intervals, food requirements or restrictions, and increased dosing frequency. [12,13] Taking antiretrovirals, especially protease inhibitors, require time management skills and life-style modifications. For these reasons, protease inhibitors may not be the best option for all patients.

With the development of efavirenz and abacavir, initiating non -PI containing regimens became a feasible and attractive option. Efficacy and tolerability data provide favorable evidence in support of these drug

combinations. DMP-006, a study involving antiretroviral naïve patients, directly compares efavirenz with indinavir when used in combination with zidovudine and lamivudine. [14,15,16] At 48 and 72 weeks, efavirenz continued to demonstrate equivalent efficacy to indinavir irrespective of baseline viral load. [15,16,17] CNA3005 compares abacavir to indinavir in combination with zidovudine and lamivudine.[18] The preliminary analysis suggested that the abacavir arm might have similar efficacy as indinavir at 24 weeks. [18] However, the 48 week data indicated that when baseline viral load is greater than 100,000, the triple nucleoside arm might be less effective at reducing viral loads to less than 50 copies/ml, although both arms were found comparable at reducing viral loads to less than 400 copies/ml.[19] The benefit of both of these newer strategies is a favorable side effect profile and a more flexible administration schedule.

Preliminary results from the ATLANTIC trial provide some confidence that protease-sparing regimens may be as effective as protease-containing treatments. [20] Week 48 data from the ATLANTIC study, which directly compares three treatment strategies, 3 NRTI, NNRTI + 2 NRTI, and PI + 2NRTI, suggested that the PI sparing regimen based on the NNRTI was equally effective as the PI based regimen. However, the triple nucleoside arm appeared less effective with higher baseline viral loads.

One of the concerns with substituting a protease inhibitor with abacavir or efavirenz is the lack of long-term efficacy, durability, and safety data. These regimens lack substantial clinical data confirming their comparability to PI based regimens. Unfortunately, there has not been a long term comparative study of the various treatment tactics to draw the conclusion that one course of action is superior to another. Furthermore, other issues that remain unclear with the PI sparing regimens are sequencing of antiretrovirals and whether or not metabolic changes and fat redistribution will occur. Until long term data from the efavirenz, abacavir, and ATLANTIC trials become available, choice of first-line therapy should be based on consideration of strength of the available clinical trial data, preservation of future therapeutic options, ease of adherence, and a variety of drug-specific and patient-specific factors.

There are many factors that physicians may consider when selecting first-line antiretroviral therapy. These include side effect profile, food and scheduling requirements, dosing frequency, number of pills,

pharmacokinetic properties, and clinical trial data. In addition, patient specific characteristics such as race, insurance coverage, income, other demographic information and attendance at specific health care facilities have been shown to effect treatment choices.[21,22] The decision may also be influenced by the physician's own knowledge of the medications as well as their relationship with the various pharmaceutical companies. Finally, the way in which physicians interpret the available data, their participation in early in clinical trials or expanded access programs, and their experiences can all affect the selection of therapy. An early Canadian observational study of physicians, which analyzed the prescribing of zidovudine before and after the release of the Concorde study results, found that zidovudine initiation substantially decreased as a result of physician interpretation of the Concorde data.[23] These are some of the many factors that may play a role in the decision making process.

The advantages and disadvantages of sparing or utilizing protease inhibitors continue to be argued. Though the advocates of either side may be plentiful, the current prescribing practices are not known. The intent of this study is to identify the current trend in prescribing practices among HIV primary care and infectious disease physicians in Toronto and to analyze the many factors that play a role in selecting the initial regimen.

1.2 Rationale

The optimal approach to therapy remains uncertain, despite the widespread knowledge that combination antiretrovirals improve quality of life and prolong survival. In Toronto, the debate over the best first-line regimen continues, but the actual prescribing practices have not yet been assessed. The patient specific characteristics such as patients' preferences and demographics that play a role in the selection process are unclear and physicians' opinions and attitudes are similarly unknown. These issues may never been assessed because a useful tool to analyze this problem has not yet been developed.

A better understanding of the thought processes involved in choosing a regimen can be gained by identifying the factors associated with a particular regimen choice. The decision making process is complex. A variety of factors can directly or indirectly influence treatment decision. Patient demographics

and laboratory parameters can have an influence. Similarly, physician experience and practice characteristics can affect therapy recommendations. Patients and physicians often consider different issues before accepting a particular therapy. For instance, a physician's choice may depend on the regimen's efficacy, durability, and toxicity data. On the other hand, patients may be more concerned with the number of pills, the dosing frequency and the adverse effects. A better understanding of the issues that concern patients in the Toronto region can enable practitioners to address misconceptions and target the therapeutic options to the local patient population.

By identifying currently initiated first-line strategies, local Toronto area physicians can analyze community prescribing behavior and compare their current practices to international standards. Differences between the prescribing practices at clinics and primary care offices can be addressed. Regional educational forums targeting questions, concerns, and controversies of a particular regimen can be conducted. Future research initiatives can be developed to explore optimal second line therapeutic options based on what physicians are initiating presently. Medical professionals will also be prepared to counsel newly diagnosed patients about available therapies and current approaches. Overall, care of HIV infected patients could improve as physicians and other health care professional become aware of the current prescribing patterns.

Prescribing practices are constantly changing due to the continually evolving body of knowledge presented at symposia and continuing education events, and international and national publications in the medical literature. The ability to capture and understand these changes when they occur will allow for an adequate assessment of prescribing practices.

The intent of this study is to evaluate the current prescribing trend among regional Toronto physicians and compare the prescribing practices of primary care physicians and infectious disease specialists. The purpose is also to better understand patient attitude toward different aspects of drug therapy, to evaluate the issues that physicians consider when selecting a regimen and to determine patient characteristics associated with specific regimens. The accuracy of survey methodology in predicting prescribing behavior will be also assessed.

2. HYPOTHESIS

Toronto area primary care and infectious disease physicians continue to initiate protease-containing regimens for antiretroviral naïve patients, despite the recent availability and clinical data supporting the use of triple nucleoside and NNRTI-containing regimens.

3. OBJECTIVES

3.1 Primary Objective

- To evaluate the current trend in prescribing practices among Toronto area HIV physicians when initiating therapy in antiretroviral naïve patients.

3.2 Secondary Objectives

- To assess whether HIV primary care physicians and clinic infectious disease/HIV specialists differ in the treatment strategies (protease-sparing vs protease-containing) in antiretroviral naïve patients
- To determine whether any specific patient characteristics are associated with selection of a particular drug regimen
- To identify factors which physicians consider important in choosing a particular regimen
- To identify patient concerns regarding drug-related properties
- To assess whether the physician questionnaire adequately reflects actual prescribing practices
- To evaluate if physician prescribing practices change over a 10 month period

4. ENDPOINTS

4.1 Primary Endpoint

- Percentage of patients initiating each of the different regimens
    a. 2 NRTI + PI (1 or 2)
    b. 2 NRTI + NNRTI
    c. 3 NRTI
    d. 2NRTI + NNRTI + PI (1 or 2)
    e. Other

4.2 Secondary Endpoints

- The difference in the percentage of patients in the specialty clinic and the primary care offices initiated on each of the following regimens
    a. 2 NRTI + PI (1 or 2)
    b. 2 NRTI + NNRTI
    c. 3 NRTI
    d. 2NRTI + NNRTI + PI (1 or 2)
    e. Other

- Determine which patient or laboratory parameters are associated with the use of PI containing or sparing regimens by identifying the incidences of each patient factor or laboratory value for each selected drug regimen
- Determine the major factors affecting patient preferences by assessing the mean scores for each item on the patient questionnaire
- Mean percentage of patients anticipated to be initiated on each of the different regimens

- Assess the changes in prescribing practices over the 10 month study period by identifying the percentage of patients initiated on each of the different regimens for the first 2 months of the study period versus the last 2 months of the study period

5. METHODOLOGY

5.1 Physician Questionnaire

A questionnaire was developed to determine what physicians would normally initiate as first line therapy for the HIV positive antiretroviral naïve patients in their practice (Appendix A). The questionnaire also asked physicians to determine the issues that would support the initiation of each of four regimens: one or two protease inhibitors (PI) + dual nucleoside (2NRTI), nonnucleoside reverse transcriptase inhibitor (NNRTI) + 2NRTI, three nucleoside reverse transcriptase inhibitors (3 NRTI), and PI + NNRTI + 2NRTI. The questionnaire also contained six questions to identify physician demographic information and practice characteristics. These questionnaires were mailed or personally delivered to Toronto area HIV primary care physicians and clinic infectious disease specialists at the beginning and end of the study period. Physicians returning the initial pre-study questionnaire were then reminded by telephone, fax, and mail to enroll patients initiating their first antiretrovirals for participation in the remaining components of the study.

A list of Toronto area HIV primary care physicians identified physicians whose main training was family medicine or internal medicine. Employment at Toronto hospitals with HIV clinics (St. Michael's Hospital ,Toronto General Hospital, and SunnyBrook Hospital) identified infectious disease specialists.

5.2 Patient questionnaire

A self-complete patient questionnaire (Appendix B) was developed to identify demographic information, employment, housing, and travel information not attainable from the chart. A patient preference section was also developed which contained 8 attitudinal statements about the various aspects of drug therapy.

Any patient who was antiretroviral naïve and who was initiating their first antiretrovirals between the period of June 1, 1999 to March 31, 2000 were eligible for this study and were asked to complete the patient questionnaire.

5.3 Chart Review

A chart review of participating individuals was performed between June 1, 1999 and May 1, 2000 to identify the initiated antiretroviral regimen, pertinent medical history, and laboratory data.

5.4 Sample Size Determination

A sample size determination was performed to assess the number of patients needed to detect a statistically significant difference in the initiation of a protease inhibitor based regimen between primary care physicians versus clinic infectious disease/ HIV specialists. In order to detect a 30% difference, with clinic physicians prescribing protease inhibitors in 70% and primary care doctors prescribing protease inhibitors in 40%, a sample size of 84 is needed. This will give the study 80% power and a significance level of 0.05.

5.5 Statistical Analysis

A Chi Square analysis was performed on the categorical data when the number of observations exceeded 40. Fischer's exact test was performed on the categorical data when the total number of observations was less than 20 or when the number of observation was between 20 and 40 and the expected frequency in each cell was less than 5. For the analysis of data in which there were 3 or more categories of observations, chi square was used if no more than 20% had values less than 5 and no value was less than 1. In these situations, categories were combined if appropriate or the analysis was not performed. Student's t test was performed for noncategorical data. Significance was defined as $p < 0.05$.

5.6 Informed consent procedure

To ensure that the rights and welfare of all subjects are protected, the investigators provided the subjects with written information about the nature and purpose of the study. Subjects who wished to participate in the study signed a written informed consent form. This protocol was approved by the Ethics Review Boards of the University of Toronto, University Health Network, and St. Michael's Hospital.

5.7 Funding

This research study was carried out as part of the requirements to fulfill the criteria for successfully completing the HIV Specialty Pharmacy Residency Program, Toronto General Hospital and St. Michael's Hospital. The protocol was independently prepared by the investigators, without influence or funding from industry sources.

6. RESULTS

Patients were eligible for the study if they were HIV-positive and initiated their first antiretroviral regimen between the period of June 1, 1999 to March 31, 2000. Based on these criteria, a total of 47 patients were enrolled. Twenty-five patients attended HIV specialty clinics with infectious disease physicians and 22 patients attended primary care offices with family practice or internal medicine physicians. The sites of enrollment were the Immunodeficiency Clinic –Toronto General Hospital, Positive Care Clinic – St. Michael's Hospital, 410 Sherbourne family practice clinic – St. Michael's Hospital and 7 primary care physicians' offices.

6.1 Prescribing Practice

Of the 47 patients enrolled, 49% initiated a PI +2 NRTI regimen (referred to as "PI-regimen"). Fifty-one percent initiated a regimen containing an NNRTI + 2 NRTI (referred to as "NNRTI-regimen"). None started the triple nucleoside, PI + NNRTI + 2 NRTI, or any other combinations of antiretrovirals (Table 1).

Participation in PI and NNRTI clinical trials occurred in a high proportion of the patients. Forty-three percent of the patients included in this study were enrolled in a clinical trial (Figure 1). Of these, 36.2% percent were referred to PI trials and 6.4% were referred to NNRTI trials. Participation in a clinical trial was not a specific exclusion criterion for this study, since both PI and NNRTI trials were available for enrollment during the study period. Patients and physicians were free to enroll in either a PI or NNRTI drug trial based on their pre-existing preferences regarding first-line antiretroviral therapy. If clinical trial patients were excluded from the analysis, the overall results were unchanged; more patients were still started on an NNRTI-regimen than a PI- regimen (78% versus 22%), respectively

The majority of patients seen in specialty clinics started an NNRTI-regimen whereas the majority in primary care began a PI-regimen. Sixty-eight percent of clinic patients began an NNRTI-regimen whereas only 36% of primary care patients initiated an NNRTI-regimen. Conversely, 64% of primary care patients compared to only 32% of clinic patients were started on a PI-regimen (Table 2). This difference was not found to be statistically significant ($p = .056$). When reanalyzed excluding patients in clinical trials, the

difference remained nonsignificant (p = .438). However, for both practice groups, the NNRTI-regimen predominated. The percentage of patients who initiated an NNRTI-regimen among primary care and specialty clinics was 67% and 87%, respectively.

6.2 Patient characteristics

Patient demographic information, medical history, and laboratory parameters were gathered from the patient questionnaire and chart review (Table 3). This data was analyzed to assess for differences between patients initiated on a PI-regimen versus an NNRTI-regimen.

Of all the factors evaluated, the presence of concomitant illness was the only patient category that differed between the groups. Concomitant illness was defined as any of the following: psychiatric illness, abnormal liver function tests (LFT > 2xULN), renal impairment (CrCl < 60 ml /min) elevated triglycerides (fasting TG > 2; nonfasting TG > 4), diagnosis of diabetes, obesity (> 140% of IBW), or history or current substance abuse. Significantly more patients with any concurrent illness were started on a PI-regimen than an NNRTI-regimen (p = .047). Thirty percent of patients initiating a PI-regimen had a history of psychiatric illness compared to 21% on an NNRTI-regimen. In addition, fifty-seven percent of those started on a PI-regimen had a history of illicit drug use or alcohol abuse compared to 29% who started on an NNRTI-regimen. These differences were not statistically significant (p=.109).

Though a statistically significant difference was not found between the groups for any other patient characteristic, patients initiated on a PI-regimen had a higher mean baseline viral load, lower mean CD4 count, and had waited a longer time before initiating therapy (Table 4). More patients with an AIDS defining illness were initiated on a PI-regimen than an NNRTI-regimen (Table 3).

6.3 Patients' Preferences

Forty-four of the 47 patients enrolled completed the patient preference section of the patient questionnaire (Appendix B). Three patients did not complete this section; one was rushed for time and two for unknown reasons. This section contained 8 attitudinal statements about various aspects of drug therapy. Patients were asked to rate their agreement or disagreement with each statement using a modified 7-point Likert scale (1 = strongly disagree and 7 = strongly agree).

For the entire group of respondents, there was agreement (mean score > 4) with seven of the eight attitudinal statements and disagreement with one (mean score < 4) (Table 5). The mean scores were > 5.0 (5 = slightly agree, 6 = moderately agree, 7 = strongly agree), for number of pills, frequency of dosing, and concern with lipodystrophy. Frequency of dosing appeared to be the area of greatest concern with the highest mean score of 5.41. Other issues of importance were food and drink requirements, the preservation of certain drug classes for later use, and the size of pills. Whether or not the drugs had a storage requirement or had adverse effects were not areas of major concern.

Qualitative differences between the groups were seen once the mean scores were calculated based on the regimen initiated (Table 6). Patients started on an NNRTI-regimen were more concerned with preservation of classes, number of pills, frequency of dosing, food/ drink requirements and storage issues whereas patients beginning a PI-regimen were more concerned with lipodystrophy and side effects. Issues with a mean score of at least 5 for both groups were frequency of dosing, number of pills, and either preservation of classes (NNRTI group) or concern with lipodystrophy (PI group). For both, however, the area of greatest concern was frequency of dosing followed by number of pills.

6.4 Physician Questionnaire

The Pre-Study and Post-Study surveys (Appendix A) are identical questionnaires which were designed to identify physician demographics, medical practice, and their perceived prescribing patterns. Physicians were asked to list three factors that would support the prescribing of each regimen (PI + 2 NRTI, NNRTI +

2 NRTI, 3 NRTI, PI + NNRTI + 2NRTI) and to predict the estimated percentage of patients they anticipated starting on the various regimens in their own practices.

The first group of physicians was surveyed between the period of August 1, 1999 to January 1, 2000. Seventy-six percent of physicians had returned the survey prior to September 1, 1999. Of the 47 questionnaires distributed to area HIV primary care and infectious disease specialists, 25 were returned, for an overall response rate of 53%. The post-study questionnaire was distributed beginning March 20, 2000 and all questionnaires were submitted by April 1, 2000. Six months elapsed between the two sampling times. Twenty-nine physician questionnaires were delivered to doctors who either completed the pre-study questionnaire or who had agreed to participate in the study. Nineteen questionnaires were returned, for a response rate of 66%. Ten of the returned surveys came from physicians who completed the pre-study questionnaire; the remaining 9 were doctors not previously surveyed. There were no significant differences found for physician demographics or practice characteristics between the physicians sampled for the pre-study and post-study questionnaires (Table 7).

6.4.1 Pre-study Physician Questionnaire

Most physicians (56%) questioned predicted that a PI-regimen would be started in the majority of their naïve HIV population (Figure 2). Only 20% of physicians believed that the NNRTI-regimen would be initiated as first-line therapy in at least 50% of their patients. Similarly, when grouping the results of the questionnaire according to medical practice, 53% of primary care doctors and 67% of infectious disease specialists predicted that a majority of their patients would be started on the PI-regimen (Figure 3). The NNRTI-regimen was favored as first line therapy in only 21% of primary care and 17% of infectious disease physicians (Figure 4).

The anticipated percentage of patients beginning each regimen was calculated by averaging the responses to the question, “what percentage of patients do you anticipate beginning on each of the following regimens (PI+2NRTI, NNRTI+2NRTI, 3NRTI, PI+NNRTI+2NRTI) in the following 6 months? ”. Physicians, regardless of medical practice, had similar predictions about choice of initial regimen (Figure 5). Overall, a

mean of 58% were believed to begin the PI-regimen, 33% for the NNRTI-regimen, 4% for triple nucleoside and 3% for PI+NNRTI+2NRTI.

Low CD4 count (<200), high viral load (> 500,000), clinical efficacy/long term durability data, and side effects were the most commonly listed factors that physicians believed would support initiating a PI-regimen. Factors most in favor of the PI sparing regimens (i.e., NNRTI-regimen and triple nucleoside) were side effect profile, dosing frequency, and pill burden. For PI + NNRTI + 2 NRTI, VL > 500,000, CD4 < 200, and side effect profile were the three most common choices (Table 8).

6.4.2 Post-Study Physician Questionnaire

Fifty-three percent of physicians questioned in the post-study period predicted that a majority of their patients would begin a PI-regimen (Figure 6). This finding is similar to the pre-study questionnaire. However, there was an increase in the number of physicians who anticipated beginning an NNRTI-regimen. Twenty-percent of physicians surveyed during the pre-study period compared to 32% in the post-study period believed that this regimen would predominate.

When assessed according to medical practice, the number of both primary care and infectious disease physicians who favored an NNRTI-regimen for the majority of their patients increased between the two surveyed time periods (Figure 4). In addition, there was an increase in the percentage of primary care physicians (Post-study: 38% vs. Pre-study: 26%) who believed that less than half of their patients would start a PI-regimen (Figure 3). For the infectious disease physicians, the pre- and post- surveys reflected no changes, with 67% of infectious disease physicians still predicting that the PI-regimen would be prescribed for the majority of their naive patients (Figure 3).

The expected mean percentage of patients initiating the various regimens also reflected a change over the six-month study period (Figure 7). The average percentage of patients expected to begin a PI-regimen was reduced from 58% in the pre-study questionnaire to 48% in the post-study questionnaire. Predictions for beginning either an NNRTI-regimen or triple nucleoside regimen were almost identical (Post-study: 32%

vs. Pre-study: 33% and Post-study: 2.9% and Pre-study: 4.4%, respectively). Slightly more patients were anticipated to begin PI + NNRTI + 2 NRTI (Post-study: 7.8% vs. Pre-study: 4.4%) than at the beginning of the study period.

The factors that support the use of the various regimens did not differ dramatically between the pre-study and post-study questionnaires (Table 8). For the PI+2NRTI regimen, viral load greater than 500,000 replaced side effect profile as one of the top three most common reasons. For the combination of antiretrovirals including all three classes, the only difference in the top responses was the replacement of side effect profile with clinical efficacy / long term durability and viral load between 100,000 and 500,000. For the protease sparing regimens, the most popular responses remained the same.

6.5 Predicted and Actual Prescribing Practices

The initial responses to the questionnaire predicted that a mean of 58% would be started on a PI-regimen, 33% on an NNRTI-regimen, 4.4% on triple nucleoside, and 2.9% on PI+NNRTI+2NRTI. Collectively, actual prescribing differed from expected. No patients were initiated on the latter two regimens. Forty-nine percent of patients were started on a PI-regimen and 51% were started on an NNRTI-regimen. For the entire group of respondents, the questionnaire thus overestimated the frequency that the PI-regimen, triple nucleoside regimen, and PI+NNRTI+2NRTI combination would be prescribed, and underestimated the frequency that NNRTI-regimen would be prescribed (Figure 8). However, this was not true when assessed by practice. Primary care physicians' responses to the pre-study questionnaire better reflected their actual prescribing patterns. All predictions for the primary care group were within 10% of actual prescribing (Figure 9). The greatest difference was for the NNRTI-regimen in which it was predicted as being initiated in 58% but was subsequently prescribed in 64%. This was not the case with the infectious disease physicians who predicted that the NNRTI-regimen would be prescribed in 35% but was actually prescribed in 68% (Figure 10). In addition, the PI-regimen was anticipated to be started in 58% of their patients but was only prescribed in 32% of cases.

6.6 Change in Prescribing Practices

To assess the changes in antiretroviral prescribing practices over the study period of 10 months, the regimens initiated in the first 2 months (June 1999– July 1999) were compared to those initiated during the last two months (February 2000 – March 2000) of the study period (Table 9). It appears that prescribing practices did not change over the course of the study period. However, because of the small number of patients initiating therapy during these time periods, a comparison truly reflecting any change in prescribing practices is not possible.

7. DISCUSSION

7.1 Key Findings

The data in this study show that between the period of June 1, 1999 to March 31, 2000, 49% of antiretroviral-naïve patients in Toronto were initiated on a PI-regimen and 51% were initiated on a NNRTI-regimen (n = 47). In contrast, Palella et al [24], using data obtained from 1022 patients enrolled in the HIV outpatient study (HOPS), assessed prescribing patterns for patients initiating their first HAART from January 1994 to March 1999. Among patients with CD4 counts less than 500 cells /mm, 69% of their patient cohort were on a regimen which included a single PI with 2 NRTI, 13% had dual PI's, 16% had greater than 3 drugs, 25% included a non-nucleoside reverse transcriptase inhibitor (NNRTI), and 10% included at least one drug from each of 3 classes.

One explanation for the difference between the HOPS database and our sample is the timing of the data collection. The high percentage of NNRTI-regimens initiated in our analysis may be reflective of the recent attention to the long-term efficacy (> 48 week data) studies for the NNRTI class, specifically efavirenz, in antiretroviral naïve patients. The preliminary changes in the DHHS guidelines released in May 1999, with its final version released in January 2000, and the IDSA-USA panel guidelines published in January 2000 may have also influenced prescribing behavior.

Despite the large percentage of patients enrolled in PI clinical trials and the relatively small percentage enrolled in NNRTI trials, the NNRTI-regimen was still the predominant regimen initiated. These findings illustrate the increasing popularity of NNRTI-regimens as first-line therapy. Several advantages of such regimens include once or twice daily dosing, lower daily pill burden, and potential for less frequent adverse drug effects. These advantages coupled with the emergence of information on lipodystrophy and its association with protease inhibitors may have deterred the initiation of PI regimens in our cohort.

The differences in prescribing behavior between primary care and infectious disease physicians approached significance. A higher proportion of patients attending regular physicians offices with primary care or internal medicine physicians were prescribed PI-regimens compared to those attending HIV specialty

clinics with infectious disease specialists. The converse was true for the initiation of NNRTI-regimens. More infectious disease patients initiated an NNRTI-regimen versus primary care patients. The physician questionnaire could not explain this difference since the majority of both groups favored the PI-regimen, and only a minority of physicians favored using an NNRTI-regimen. These findings are not surprising given the abundance of published studies which demonstrate the increased use of protease inhibitors after 1996.[1,25,26,27] Various studies have also shown the dramatic impact of protease inhibitors on morbidity, mortality, and overall health care costs.[9, 21,28,29,30,31] This has not been the case with the NNRTI-regimens.

The presence or absence of concomitant illnesses was the only patient variable that was found to be statistically different between the treatment groups. Significantly more patients with concomitant illnesses initiated a PI-regimen compared to an NNRTI-regimen. A greater percentage of these patients also had a history of illicit drug or alcohol abuse or a diagnosis of a psychiatric illness. One factor that may have contributed to this observation may have been the concern of development or exacerbation of psychiatric symptoms by an NNRTI, specifically efavirenz.

Patient variables such as gender, age, HIV risk factor, employment, medication coverage, and education level did not differ between the groups. This is in contrast to the results of several studies which have identified various demographic and economic factors as associated with a lower likelihood of optimal therapy.[32,33,34,35]One reason that our study was unable to mimic these findings may have been because of the small sample size and fairly homogenous population.

Patients starting a PI-regimen also had higher viral loads, lower CD4 counts, had waited a longer time from diagnosis before initiation of therapy and were more likely to have an AIDS defining illness compared to those starting an NNRTI-regimen. Though these differences were not statistically significant, they reflect the general perception that regimens containing protease inhibitors may be more powerful.

Dosing frequency and number of pills ranked highest as drug attributes that concern patients. Similar to these results, Woodward demonstrated that when patients were given the option of choosing a regimen,

66% picked the twice daily regimen and only 33% picked a three times a day regimen.[36] Patients' perceptions of HAART have also been shown to affect therapy decisions. Battegay reported that the most common reason behind not starting antiretrovirals was patient perception that it was too complicated.[37] The ability of a patient to continue taking medications appropriately has also been associated with dosing frequency and how well the medications fit into a patient's life. [13,38,39] In addition, fear of adverse effects has been associated with a reluctance to initiate and adhere to therapy. [36,39] In this analysis, adverse effects was the area in which patients expressed neutrality. When reevaluated according to the regimen initiated, both groups disagreed with the statement that adverse effects would be a concern. Sixty-four percent of our patient cohort were either symptomatic or had experienced an AIDS defining illness. Thus, medication related adverse effects might have been a minor concern when faced with a life threatening opportunistic infection. Or alternatively, the remaining patients who were asymptomatic might have never experienced the impact of adverse effects and hence were not concerned. Lipodystrophy, which was assessed separately, ranked as the second most important issue of concern. Long-term changes that may be difficult to correct and which are obvious to outsiders, are serious concerns to patients who may require life-long therapy.

The question of whether patient preference truly affected regimen selection could not be assessed in this study. However, it appeared that patients starting the NNRTI-regimen were more concerned with preservation of classes for use as backup, number of pills, frequency of dosing, food/drink requirements, and storage issues than those on a PI-regimen. Patients starting the PI-regimen expressed greater concerns about the development of lipodystrophy and side effect profile. We could not conclude definitively that these differences in opinions led to the initiation of either regimen. What is clear is that dosing frequency and number of pills, regardless of the regimen initiated, are major issues to patients initiating therapy. Since adherence has been positively correlated with virological success, a regimen which is perceived as easy to take and which promotes adherence would be an optimal choice as first-line therapy.[40,41]

Physician perception about the patient's ability to adhere to medications and their patients' fear of adverse effects have been associated with physicians' withholding of therapy.[37] In this analysis, results from the

physician questionnaire did not reflect such a relationship. Physicians had the option of choosing patient-related factors that they perceived would interfere with adherence, such as educational level, employment, household income, drug coverage, and IVDU. However, rather than selecting any patient-related factors, the surveyed physicians focused on drug characteristics, clinical efficacy or long-term durability data, and laboratory results. The factors that physicians found in favor of the various regimens differed depending on whether the regimen was PI-based (PI+2NRTI or PI+NNRTI+2NRTI) or PI-sparing (NNRTI+2NRTI or 3NRTI). Based on the physician survey, the presence of a more progressive illness marked by higher baseline viral load and lower CD4 might increase the likelihood of prescribing a PI-regimen. Clinical efficacy and long term durability data were other factors supporting the use of a protease inhibitor in the initial regimen. On the other hand, for physicians concerned with quality of life and adherence issues such as pill burden, schedule of medications, and side effect profile, a triple nucleoside or NNRTI-regimen might alternatively be prescribed.

7.2 Study Limitations

There are several limitations associated with this study. A sample size of 84 was needed to detect a significant difference between the prescribing patterns of primary care and infectious disease physicians. Only 47 patients were enrolled. Post hoc power analysis revealed that with our sample size, we would have been able to detect a difference in PI prescribing with 70% of primary care physicians and 40% of infectious disease specialists prescribing the PI-regimen with a power of 60%. Furthermore, our findings may not reflect the true prescribing practices of Toronto area physicians since a small number of physicians accounted for a large proportion of antiretrovirals initiated.

Other weaknesses involve the design of the study. One of the objectives was to determine whether the questionnaire reflected true prescribing habits. All survey responses were included in the analysis regardless of whether or not the physician recruited patients. A true interpretation of whether the survey reflected actual prescribing for each physician could not be assessed since less than 50% of physicians completing the survey actually enrolled patients. A better way to approach this objective would have been to select physicians who recruited patients over a period of 1 year and compare the questionnaire responses

to actual prescribing patterns for each surveyed physician. In our study, the prescribing practice was recorded for each individual site, not each physician, and thus we were unable to make such comparisons. A longer study period might have enabled a greater patient database to truly validate the study.

Another objective was to assess the changes in prescribing practices over 10 months by comparing the regimens initiated in the first and last two months of the study period. The number of patients initiating therapy during these time periods was small. Again, making comparisons over a longer duration of time might have enabled a greater sample size and strengthened the comparison.

8. CONCLUSIONS

New treatment strategies for the management of HIV infection are constantly being developed. Although, the optimal type of regimen for treating antiretroviral naïve patients is unknown, recent data supporting the various treatment tactics is continually emerging. Our findings suggest that Toronto area physicians were influenced by new information presented at various conferences and symposia. A greater percentage of patients were initiated on an NNRTI- regimen than anticipated. Tracking such changes is relevant to assess whether information is equally disseminated and interpreted. It is also imperative to understand the pattern of prescribing regionally to better anticipate optimal second line therapies.

The choice of first-line antiretrovirals should be based on a combination of physician and patient preferences. Physicians surveyed in this study indicated that CD4 count, side effect profile and dosing frequency were issues of utmost importance when selecting a regimen, while number of pills, fear of lipodystrophy, and frequency of dosing were the most important criteria identified by patients.

Another important finding of this study was that patients initiating therapy in the Toronto region had a median CD4 of 200 and a median viral load of 4.94 logs. Sixty four percent of the patients were either symptomatic or had an AIDS defining illness. Regional studies should focus on including patients with more advanced disease. This might be more clinically relevant for local physicians.

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TABLES

Table 1: Antiretroviral regimens initiated in antiretroviral naïve patients from June 1999-March 2000*

Regimen	Initiated Patients, No. (%)
PI (1 or 2) + 2NRTI	23 (49)
1 NNRTI + 2 NRTI	24 (51)
3 NRTI	0 (0)
PI (1 or 2) + 1 NNRTI + 2 NRTI	0 (0)
Other	0 (0)

*N =47

Table 2: Antiretroviral regimens initiated in antiretroviral naïve patients, grouped by medical practice*

	Primary Care, No. (%)	HIV Specialty Clinic No. (%)	P-value[#]
PI regimen	16 (64)	7 (32)	
NNRTI regimen	9 (36)	15 (68)	0.056

*N =47

[#]The chi square statistical test was used to determine the difference between the practice groups.

Table 3: Patient characteristics and initiated regimen*

CHARACTERISTICS[#]	PI-Regimen (n = 23)		NNRTI-Regimen (n = 24)		Total (n = 47)		
	No.	%	No.	%	No.	%	P-value[+]
Sex							
Male	22	96%	18	75%	40	85%	
Female	1	4%	6	25%	7	15%	.115
Age							
<=34 years old	5	22%	6	25%	11	23%	
>34 years old	18	78%	18	75%	36	77%	.936
Race							
Caucasian	16	70%	16	67%	32	68%	
Non-caucasian	6	26%	8	33%	14	30%	.900
Education							
<College/university	7	30%	7	29%	14	30%	
>=College/University	14	61%	15	63%	29	62%	.826
Employment							
Employed	11	48%	7	29%	18	38%	
Unemployed	7	30%	10	42%	17	36%	
Other**	4	17%	6	25%	10	21%	.407
Housing							
Stable Housing	20	87%	19	79%	39	83%	
Unstable Housing	1	4%	3	13%	4	9%	.634
HIV Risk Factor							
Injection drug use	0	0%	0	0%	0	0%	
Homosexual contact	19	83%	13	54%	32	68%	
Heterosexual contact	1	4%	5	21%	6	13%	
Blood/blood product	1	4%	1	4%	2	4%	
Unknown	0	0%	5	21%	5	11%	
Drug Coverage							
Government Assistance	8	35%	14	58%	22	47%	
Private drug plan	8	35%	10	42%	18	38%	
No drug plan	4	17%	0	0%	4	9%	
Time from diagnosis to start of therapy							
Less than 6 months	5	22%	14	58%	19	40%	
6 months – 1 year	2	9%	0	0%	2	4%	
1-5 years	7	30%	5	21%	12	26%	
Greater than 5 years	9	39%	5	21%	14	30%	.103
Baseline Viral Load (copies/ml)							
VL<10,000	1	4%	3	12.5%	4	9%	
VL 10000-50000	6	26%	4	17%	10	21%	
VL 50000-100000	5	22%	9	37.5%	14	30%	
VL >100000	11	48%	8	33%	19	40%	.823
Baseline CD_4 (cells / mm^3)							
<200	13	57%	11	46%	24	51%	

CHARACTERISTICS[#]	PI-Regimen (n = 23)		NNRTI-Regimen (n = 24)		Total (n = 47)		
	No.	%	No.	%	No.	%	P-value[+]
200-500	10	43%	11	46%	21	45%	
>500	0	0%	2	8%	2	4%	.659
Presentation prior to drug initiation							
Asymptomatic	9	39%	8	33%	17	36%	
Symptomatic	6	26%	12	50%	18	38%	
AIDS indicator condition	8	35%	4	17%	12	26%	.185
Concurrent Illness							
Concurrent illness	18	78%	11	46%	29	62%	
No concurrent illness	5	22%	13	54%	18	38%	.047
Psychiatric illness	7	30%	5	21%	12	26%	
Diagnosis of diabetes	0	0%	0	0%	0	0%	
Hypertriglyceridemia (Fasting TG>2; random TG>4)	2	9%	1	4%	3	6%	
Hepatic impairment (LFT>2XULN)	3	13%	4	17%	7	15%	
Renal impairment (CrCl< 60 ml/min)	0	0%	0	0%	0	0%	
Obesity (≥140% of IBW)	1	4%	0	0%	1	2%	
Heavy etoh consumption or history of abuse	5	22%	6	25%	11	23%	
Illicit drug use (past or present)	8	35%	5	21%	13	28%	

*N =47 for the total number of patients enrolled in the study.

[#]Data on race, education, employment, housing, risk factor, and medication coverage are missing for some patients

[+]For comparison of the number of patients initiated on a PI-regimen or an NNRTI-regimen for that category of the characteristic, by the chi square test. For differences between more than 2 categories of the characteristic, data was combined in order for Chi Square test to be applicable

**Includes retired or self-employed persons.

Table 4: Mean Baseline VL, CD4 and time from diagnosis to start of therapy*

	PI-Regimen (n = 23)	NNRTI-Regimen (n = 24)	P-value[#]
Baseline VL (mean ± SD) copies /ml	205043 ± 257913.65	149907 ± 175121.49	
Baseline VL (mean ± SD) $\log_{10}$ copies/ml	4.99 ± 0.57	4.82 ± 0.64	.361
Baseline CD4 (mean ± SD) cells / mm^3	190.00 ± 135.82	256.46 ± 160.99	.134
Time (months) from diagnosis to start of therapy (mean ± SD)	52.13 ± 48.02	34.75 ± 57.14	.266

* N = 47

[#] Student's t-test was performed to determine the difference between two means

Table 5: Mean patient score for each attitudinal statement about drug therapy in descending order of importance*#+

Drug Attribute	Mean ± SD
Frequency of dosing	5.41 ± 2.02
Concern with Lipodystrophy	5.30 ± 2.29
Number of pills	5.25 ± 2.04
Food / drink requirements	4.98 ± 2.16
Preservation of certain drugs for later use	4.84 ± 1.98
Size of pills	4.28 ± 2.14
Side Effects	4.07 ± 2.15
Storage requirements	3.82 ± 2.23

* N = 44 for the number of patients who completed the patient preference section of the patient questionnaire

[#] N = 47 for the total number of patients enrolled in the study

[+] Modified 7-point Likert Scale where 1 = Strongly Disagree, 2 = Moderately Disagree, 3 = Slightly Disagree, 4 = Neutral, 5 = Slightly Agree, 6 = Moderately Agree, 7 = Strongly Agree

Table 6: Mean patient score for each attitudinal statement about drug therapy grouped by initiated regimen[*#]

Drug Attribute	PI-regimen (n = 21)		NNRTI-regimen (n = 23)	
	Mean ±SD	Order of Importance	Mean ±SD	Order of Importance
Number of pills	5.16 ± 1.99	2	5.27 ± 2.14	2
Size of pills	4.35 ± 2.08	5	4.34 ± 2.21	6
Frequency of dosing	5.32 ± 1.96	1	5.39 ± 2.14	1
Food / drink requirements	4.68 ± 2.18	3	4.73 ± 2.24	5
Side Effects	3.84 ± 2.06	6	3.76 ± 2.25	7
Concern with Lipodystrophy	5.16 ± 2.41	2	4.88 ± 2.48	4
Storage requirements	3.61 ± 2.16	7	3.70 ± 2.31	8
Preservation of certain drugs for later use	4.65 ± 1.99	4	5 ± 1.90	3

*N = 44 for the number of patients who completed the patient preference section of the patient questionnaire
[#] N = 47 for the total number of patients enrolled in the study

Table 7: Pre-study and post-study physician demographic and practice characteristics

	Pre-Study (n = 25)	Post-Study (n = 19)
Demographics		
Sex	No. (%)	No. (%)
Male	21 (84)	14 (74)
Female	4 (16)	5 (26)
Year of Graduation		
1990 or later	6 (24)	5 (26)
1980-1989	8 (32)	5 (26)
1970-1979	10 (40)	9 (47)
1969 or earlier	1 (4)	0 (0)
Practice Characteristics		
Medical Practice		
HIV Specialty clinic	6 (24)	3 (16)
Primary Care	19 (76)	16 (84)
Practice Configuration		
Solo	6 (24)	5 (26)
Group	19 (76)	14 (74)
Percentage of patients who are HIV +		
<20%	9 (36)	9 (47)
20-50%	10 (40)	8 (42)
>50%	5 (20)	2 (11)
Number of HIV + patients		
<25	2 (8)	2 (11)
25-100	13 (52)	11 (58)
>100	10 (40)	6 (32)

Table 8: Factors influencing choice of initial regimen: results from the pre-study and post-study physician questionnaire

Choices	PI + 2NRTI		1 NNRTI + 2NRTI		3NRTI		PI + NNRTI + 2 NNRTI	
	Pre-study	Post-study	Pre-study	Post-study	Pre-study	Post-study	Pre-study	Post-study
CD4<200	13	10	0	2	1	3	7	12
CD4 200-500	1	2	5	4	4	1	1	1
CD4 > 500	0	0	1	4	3	3	0	0
VL < 100000	2	1	7	0	5	0	0	0
VL 100000-500000	5	5	1	2	2	1	3	5
VL > 500000	9	8	2	1	2	1	8	11
Side effect profile	10	5	14	10	11	10	9	3
Dosing frequency	8	4	14	7	8	5	2	1
Pill burden	3	2	10	9	9	7	5	3
Food requirements	2	0	3	0	0	0	0	0
Drug coverage	2	1	1	3	2	1	3	2
Household income	0	0	0	0	1	0	0	0
Educational level	0	0	0	0	0	1	0	1
English as a 2nd language	0	0	0	0	0	0	0	0
IVDU/illicit drug use	0	0	1	1	0	0	0	0
Type of employement	0	1	0	0	0	0	0	0
Housing situation	0	0	0	0	0	1	0	0
Gender	0	0	0	0	0	0	0	0
Age < 35	0	0	0	0	0	0	0	0
Age > 35	0	0	0	0	0	0	0	0
Other concurrent infections	0	1	0	0	0	0	3	1
Clinical efficacy / long term durability	10	10	4	5	2	4	4	5
MD experience with regimen	5	7	2	2	2	2	0	1
Relationship with drug company	0	0	0	0	0	0	0	0

Table 9: Regimens initiated in the first and last two months of the study period

	June 1999 – July 1999 (n = 18) No. (%)	February 2000 – March 2000 (n =7) No. (%)
PI+2NRTI	11 (61)	3 (43)
NNRTI + 2NRTI	7 (39)	4 (57)
3 NRTI	0	0
PI + NNRTI + 2 NRTI	0	0

FIGURES

Figure 1: Percentage of patients initiating a PI- or NNRTI- regimen and the proportion enrolled in clinical trials

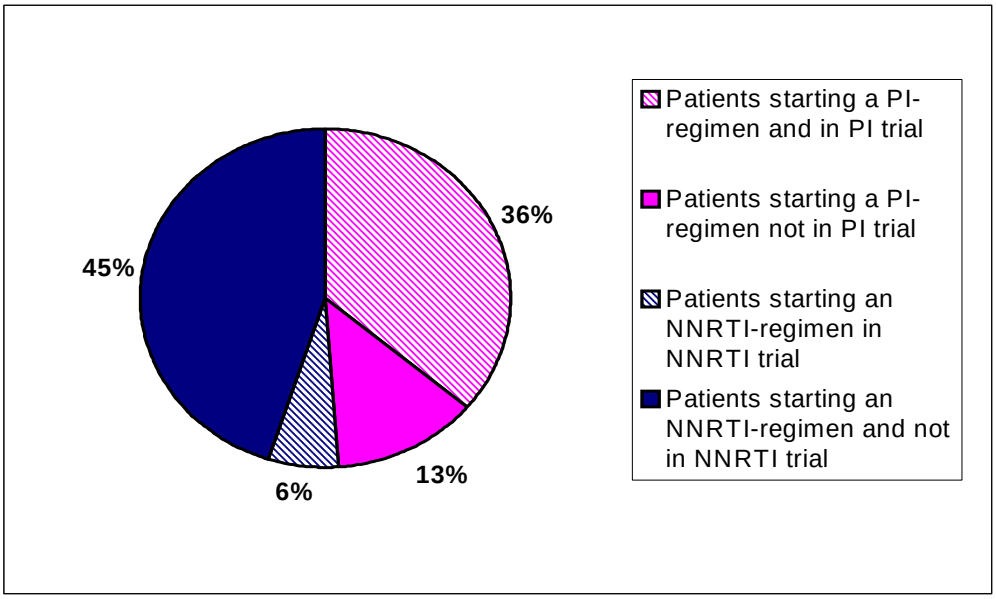
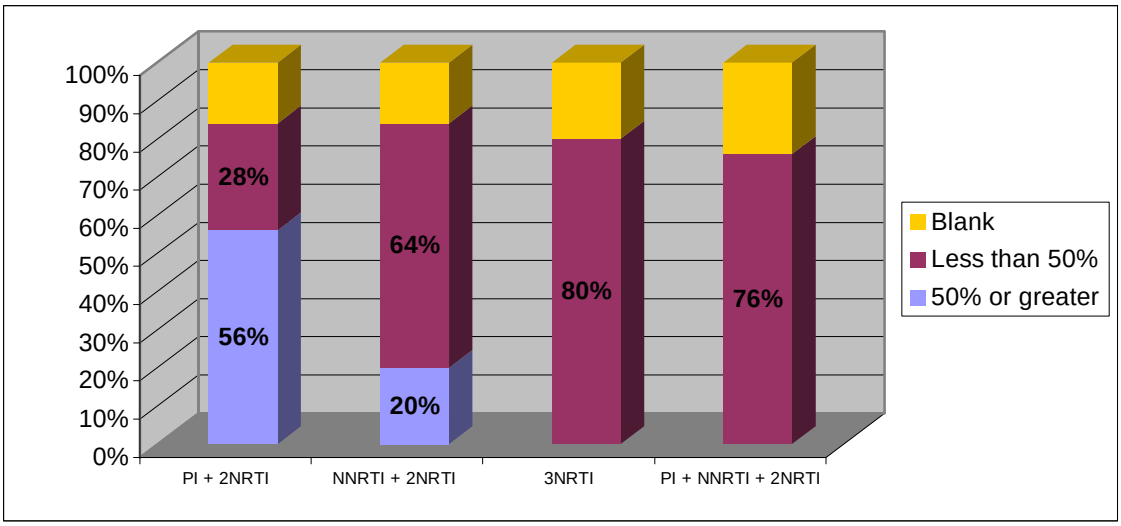
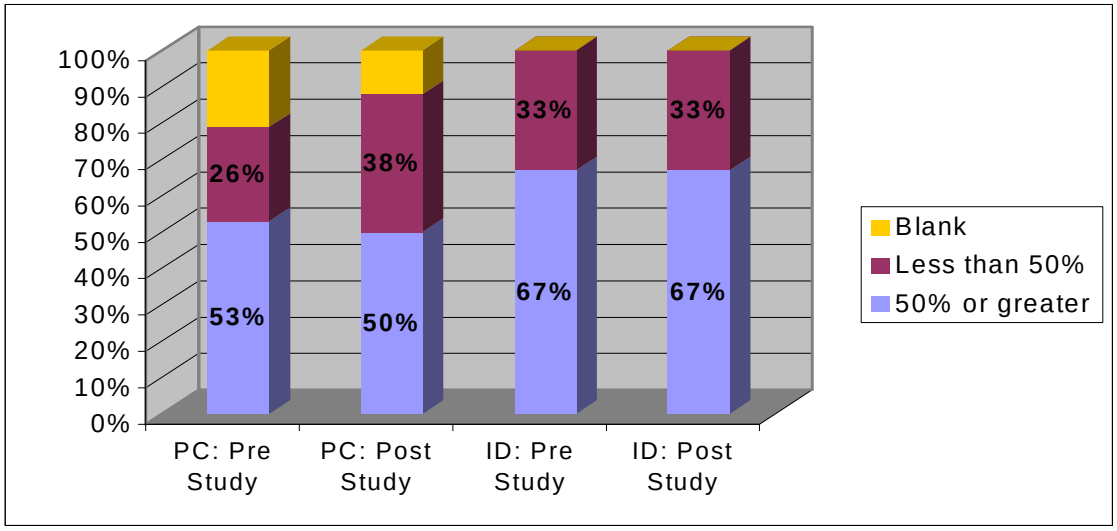


Figure 2: Percentage of physicians who anticipated prescribing each regimen in at least 50% or less than 50% of their patients: data from the pre-study physician questionnaire*



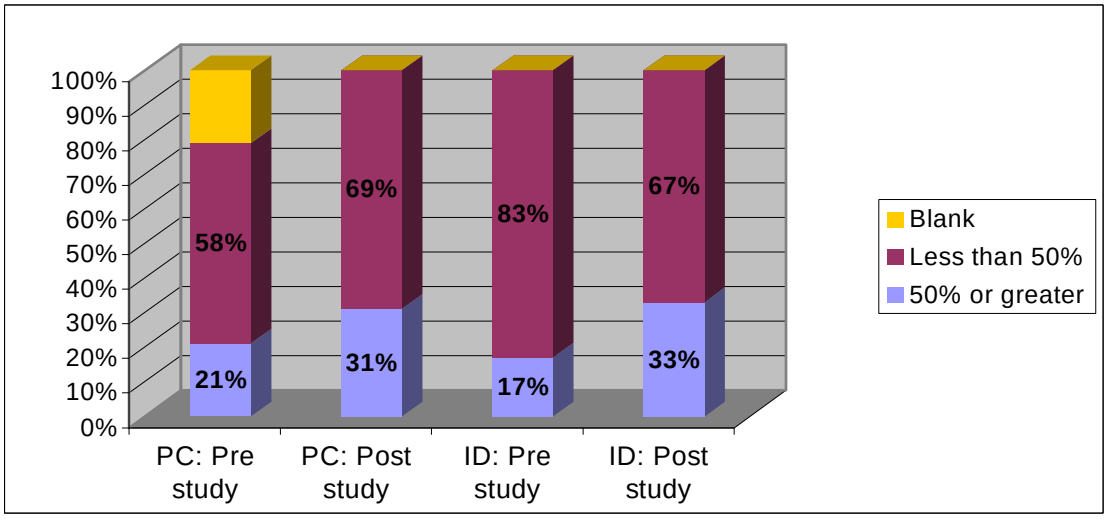
*N = 25 for the number of physicians who completed the pre-study physician questionnaire

Figure 3: Percentage of primary care and infectious disease physicians who anticipated prescribing a PI-regimen in at least 50% or less than 50% of their patients: data from the pre-study and post-study physician questionnaire*[#]



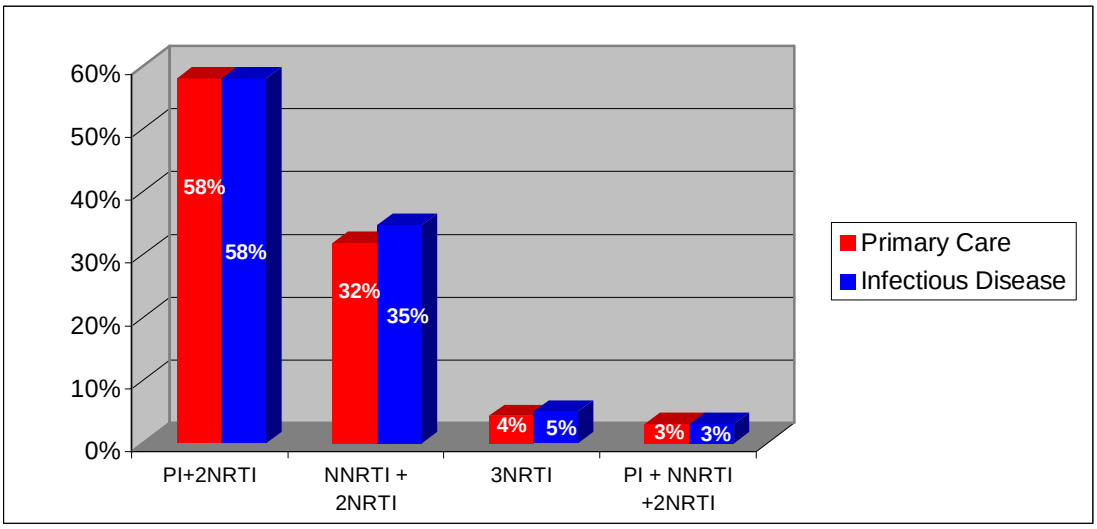
*PC = primary care, ID = infectious disease
[#] N = 25 for the number of physicians who completed the pre-study questionnaire (19 primary care physicians; 6 infectious disease physicians); n = 19 for those who completed the post-study questionnaire (16 primary care physicians; 3 infectious disease physicians)

Figure 4: Percentage of primary care and infectious disease physicians who anticipated prescribing an NNRTI-regimen in at least 50% or less than 50% of their patients: data from the pre-study and post-study physician questionnaire*[#]



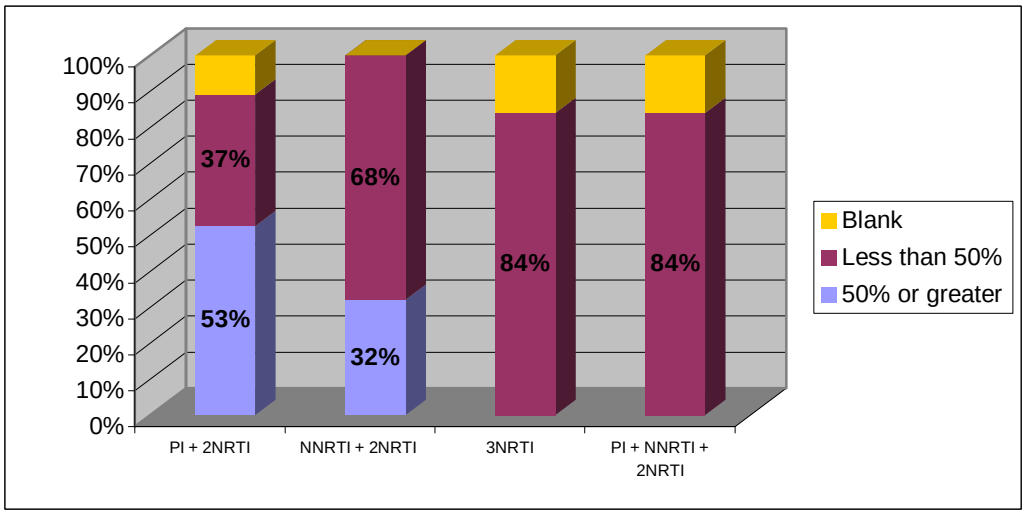
*PC = primary care, ID = infectious disease
[#] N = 25 for the number of physicians who completed the pre-study questionnaire (19 primary care physicians; 6 infectious disease physicians); n = 19 for those who completed the post-study questionnaire (16 primary care physicians; 3 infectious disease physicians)

Figure 5: Mean expected percentage of patients prescribed each regimen grouped by medical practice: data from pre-study questionnaire*



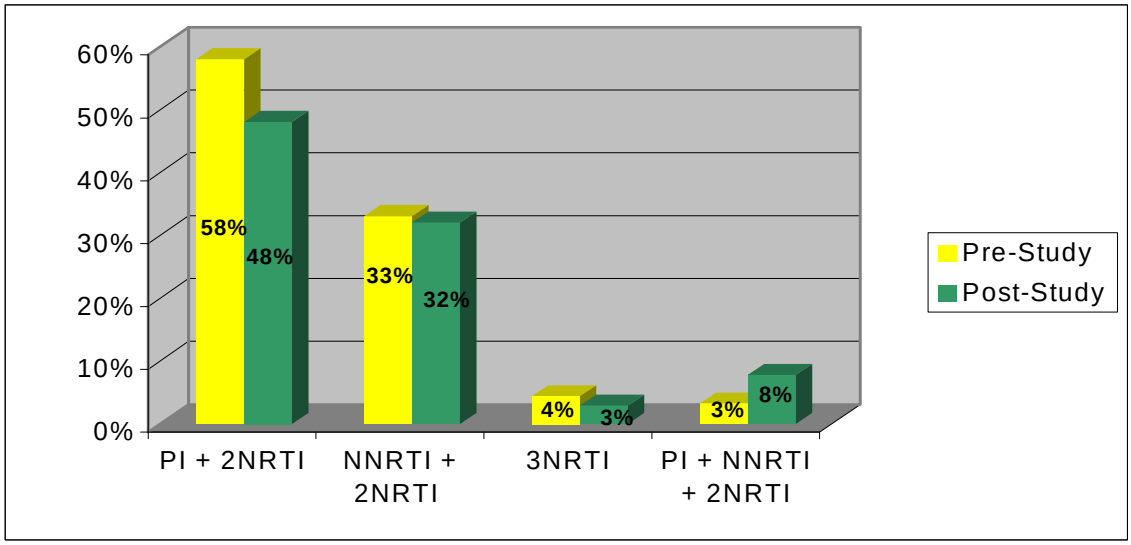
*N = 25 for the number of physicians who completed the pre-study questionnaire (19 primary care physicians; 6 infectious disease physicians)

Figure 6: Percentage of physicians who anticipated prescribing each regimen in at least 50% or less than 50% of their patients: data from the post-study physician questionnaire*



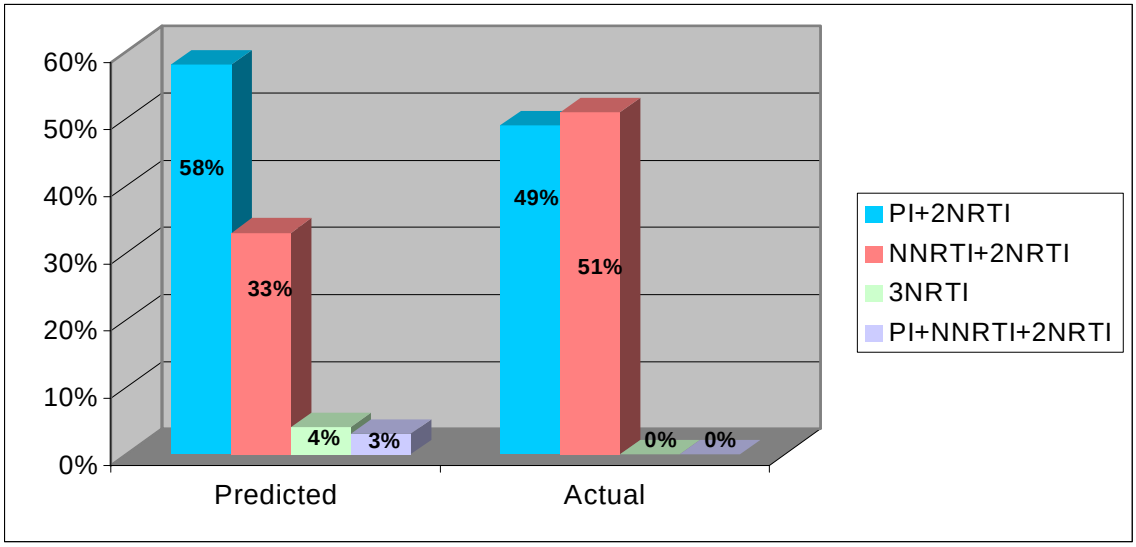
* N = 19 for the number of physicians who completed the post-study questionnaire

Figure 7: Mean expected percentage of patients prescribed each regimen: data from the pre-study and post-study questionnaire*



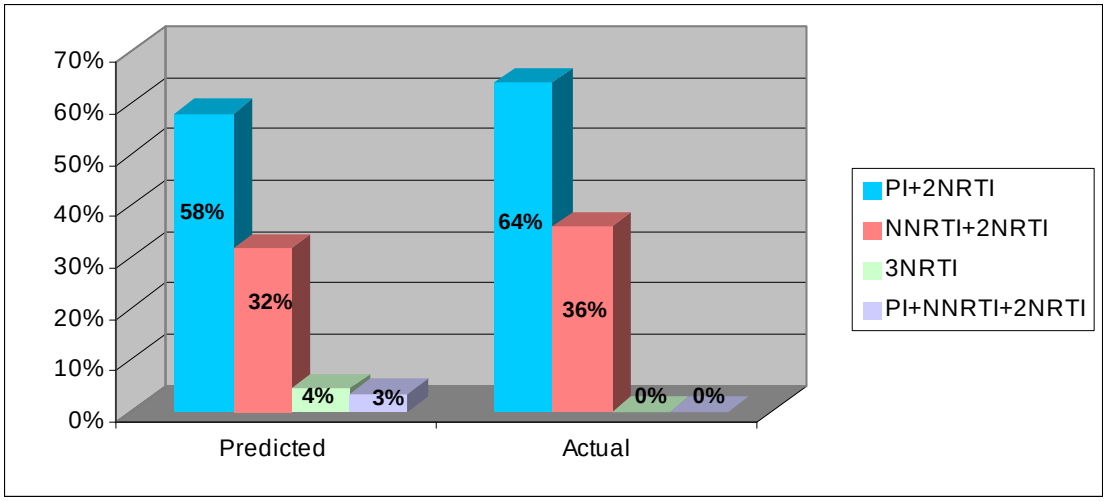
*N = 25 for the number of physicians who completed the pre-study questionnaire; n= 19 for the number of physicians who completed the post-study questionnaire

Figure 8: Mean predicted versus actual prescribing of each regimen*#



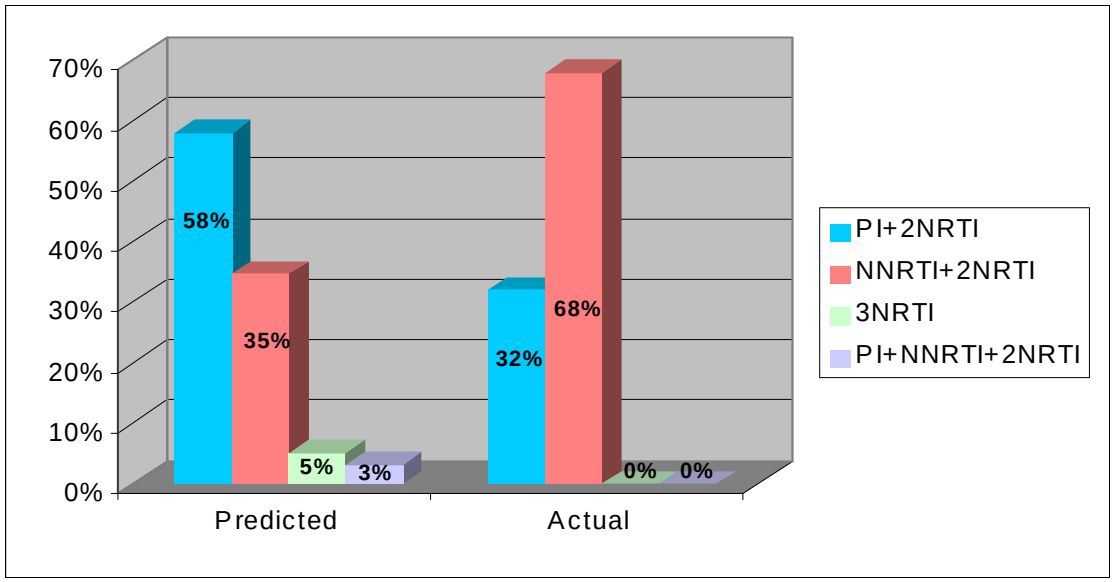
*For the predicted percentages, data was obtained from the pre-study physician questionnaire.
#N = 25 for the total number of physicians who completed the pre-study questionnaire; n=47 for the number of patients enrolled in the study for the actual analysis.

Figure 9: Mean predicted versus actual prescribing practices of primary care physicians*[#]



*For the predicted percentages, data was obtained from the pre-study physician questionnaire.
[#]N = 19 for the number of primary care physicians who completed the pre-study questionnaire; n=25 for the number of primary care patients enrolled in the study for the actual analysis.

Figure 10: Mean predicted versus actual prescribing practices of infectious disease physicians*[#]



*For the predicted percentages, data was obtained from the pre-study physician questionnaire.
[#]N = 6 for the number of infectious disease physicians who completed the pre-study questionnaire; n=22 for the number of clinic patients enrolled in the study for the actual analysis.

APPENDIX A

STUDY QUESTIONAIRE

Physician and Practice Characteristics:

1. Medical Practice: Primary Care Physician Infectious Disease/ HIV Specialist

2. Practice configuration: Solo Group

3. Year of graduation: 1990 or later 1980-1989 1970-1979 1969 or earlier

4. Gender: Male Female

5. Percentage of practice that is HIV positive: < 20% 20% - 50% > 50%

6. Number of HIV positive patients: < 25 25 - 100 > 100

7. Estimated percentage of antiretroviral naïve patients that will be started on the following regimens in the next 6 months:

   2NRTI + PI (1or2) _____ PI + 2NRTI + NNRTI _____

   2NRTI + NNRTI _____ 3 NRTI _____

Case Scenario:

In your office, you are evaluating an antiretroviral naïve HIV positive patient. The decision was made to start drug therapy.

If you were to consider *each* regimen listed below, what would be the most important factors that would make you choose that regimen for your patient? Indicate for each regimen the *three* factors having the most influence on your decision. Please choose from the box below and write the corresponding number in the spaces provided.

1. 2 NRTI + PI (1 or 2)	_____	_____	_____
2. 2 NRTI + NNRTI	_____	_____	_____
3. PI + 2 NRTI + NNRTI	_____	_____	_____
4. 3 NRTI	_____	_____	_____

Key: NRTI = nucleoside reverse transcriptase inhibitor (e.g. AZT, 3TC, ddC, d4T, ddI, abacavir)
NNRTI = nonnucleoside reverse transcriptase inhibitor (e.g. nevirapine, delavirdine, efavirenz)
PI = protease inhibitor (e.g. indinavir, nelfinavir, ritonavir, saquinavir, amprenavir)

1. CD4 < 200	9. Pill burden	17. Housing situation
2. CD4 200 –500	10.Food/hydration requirements	18. Gender
3. CD4 > 500	11. Drug Coverage	19. Age ≤ 35
4. VL < 100,000	12. Household income	20. Age > 35
5. VL 100,000 – 500,000	13. Educational level	21. Other concurrent infections
6. VL > 500,000	14. English as a 2nd language	22. Clinical efficacy/ long - term durability data
7. Side effect profile	15. IVDU/Illicit drug use	23. Physician experience with regimen.
8. Dosing frequency	16. Type of employment	24. Relationship with drug company

Please return the completed survey in the envelope provided to:

Mary E. Nguyen, Pharm D
Immunodeficiency Clinic - Toronto Hospital
College Wing, ground floor, rm 315
101 College Street
Toronto, ON M5G 2C4

APPENDIX B

Choice of First-Line Therapy and
Factors Affecting Regimen Selection: A Survey of Toronto Area HIV Physicians and a Chart Review of Antiretroviral Naïve Patients

We are currently conducting a study to identify and evaluate the various factors that influence people's decisions regarding selection of antiretroviral therapy. The ultimate goal of this study is to gain a better understanding of the things that affect people's medication choices so that we can all work together more effectively to achieve your goals and desired outcomes.

This questionnaire is divided into 3 sections: basic demographics, medication coverage, and your personal preferences. It will take approximately 10 minutes to complete this survey. Your responses are completely confidential, and will have no impact on the care you receive. Answers will only be reported in terms of group responses.

I. DEMOGRAPHIC INFORMATION

1. Sex

☐ Male
☐ Female

2. Age

☐ ≤ 17
☐ 18-34
☐ 35-49
☐ ≥ 50

3. Self identified race

☐ African/black
☐ Aboriginal
☐ Mexican/Hispanic/Latino
☐ Asian/Pacific Islander
☐ Caucasian/European descent
☐ Other_____

4. Level of completed education

☐ ≤ Grade 8
☐ High School
☐ Vocational Training
☐ College/University
☐ Post-graduate
☐ Other _____

5. Employment

☐ Unemployed
☐ Shift work
☐ Part-time work
☐ Full-time work
☐ Volunteer work
☐ Temporary
☐ Other _____

6. Housing

☐ Subsidized housing
☐ Shelter
☐ Hospice
☐ Rent
☐ Own
☐ Other _____

7. Travel

Do you travel?

☐ Yes
☐ No

If yes, what is the reason?

☐ Work
☐ Leisure

If yes, how often do you travel?

☐ < 2 months/year
☐ 3 – 6 months/year
☐ 7-12 months/year

8. HIV Risk Factor(s) – check all that apply

☐ Injection drug use
☐ Other illicit drug use _____
☐ Homosexual contact
☐ Heterosexual contact
☐ Blood/Blood product (i.e.: occupational or transfusion)
☐ Other_____
☐ Unknown

II. MEDICATION COVERAGE

Please indicate how your prescription medications are paid (check <u>all</u> that apply):

☐ Ontario Drug Benefit (ODB)
☐ Trillium – Is your annual deductible ☐ > $500 or ☐ < $500 ?
☐ Private drug plan - Indicate your percent deductible _____
☐ No drug plan
☐ Other _____

III. YOUR PREFERENCES REGARDING TYPE OF DRUG THERAPY

Since there are now a number of different anti-HIV medications available, it is possible to come up with a variety of effective first-line combinations. The selection of an anti-HIV regimen may depend upon many things, including your personal preferences or feelings about taking medications.

To help us better understand the things that are most important to you in terms of choosing a first-line drug regimen, please indicate how strongly you agree or disagree with each of the following statements by **circling one number per line.**

	Strongly Disagree	Moderately Disagree	Slightly Disagree	Neutral	Slightly Agree	Moderately Agree	Strongly Agree
1. I am concerned about the number of pills I need to take each day	1	2	3	4	5	6	7
2. I am concerned about the size of my medications, since it may be hard for me to swallow very large pills.	1	2	3	4	5	6	7
3. It matters to me how many times a day I will have to take my medications.	1	2	3	4	5	6	7
4. I will be able to take my medications regularly even though they have a lot of food or drink requirements.	1	2	3	4	5	6	7
5. I will be able to deal with ongoing side effects such as nausea or diarrhea.	1	2	3	4	5	6	7
6. I am concerned about the risk of lipodystrophy (changes in body shape).	1	2	3	4	5	6	7
7. It will be difficult for me if my medications have special storage requirements (e.g., need to be kept in the fridge).	1	2	3	4	5	6	7
8. I prefer to save certain classes of medications for later use as back-up.	1	2	3	4	5	6	7

If there are any other factors that influence your choice of medications, please list them here.

APPENDIX C

Choice of First-Line Therapy and Factors Affecting Regimen Selection: A Survey of Toronto Area HIV physicians and a Chart Review of Antiretroviral Naïve Patients

Principal Investigators: Mary E. Nguyen, Pharm.D. , Alice Tseng, Pharm.D.,
Sharon Walmsley M.D.

Sponsors: Immunodeficiency Clinic - Toronto Hospital
St. Michael's Hospital

CONSENT FORM

Background

The choice of first-line therapy to treat infection with the HIV (Human Immunodeficiency Virus) is very important. The success or failure of the first drug regimen can determine the course of the HIV disease. It can also affect which drugs can be used after the first set. The ideal regimen would be one that lowers the amount of virus in the body to undetectable levels for long periods of time. A drug regimen that fails to do this can lead to the emergence of virus resistant to the current drugs as well as future drugs. However, in order to take the treatment consistently, the drugs also need to be safe, easily tolerated, and convenient to take. These are issues that must be considered when selecting the drugs.

The International AIDS Society recommends that the standard of care for treating HIV infection is with combination therapy of three or more anti-HIV medications. Drugs that are often used together often include the reverse transcriptase inhibitors (e.g., AZT/zidovudine/Retrovir®, 3TC/lamivudine, d4T/stavudine/Zerit®, ddI/didanosine/Videx®, and abacavir/1592/Ziagen®) and protease inhibitors (e.g., indinavir/Crixivan®, saquinavir/Invirase® or Fortovase®, nelfinavir/Viracept®, or ritonavir/Norvir®). The drugs listed above are those which are currently approved for use in Canada. More are under development. Triple combination therapy that includes a protease inhibitor has dramatically improved the outcome of patients diagnosed with HIV. However, this combination does not work for everyone. Such regimens are often associated with a lot of pills, frequent dosing times, strict food or storage requirements, and side effects. For these reasons, many patients and physicians are reluctant to initiate this type of treatment as they have concerns about their ability to be consistent with the therapy.

Instead of including a protease inhibitor in the drug regimen, some physicians and patients are choosing to substitute other classes of drugs such as the non-nucleoside reverse transcriptase inhibitor (e.g., nevirapine/Viramune®, delavirdine/Rescriptor®, and efavirenz/DMP-266/Sustiva®). Others support the use of three drugs from the nucleoside

reverse transcriptase inhibitor class (listed above). These strategies are often called "protease-sparing", since the protease inhibitors are not included, but may be used later on if necessary. Some studies have shown that these protease-sparing regimens may be just as effective as combinations with protease inhibitors. In addition, these newer regimens may be easier to take and have fewer short term side effects. However, the long-term effectiveness and side effects is still unknown. Physicians and patients must balance all these factors when choosing a regimen.

Purpose

I have been asked to participate in a study designed to identify the regimen that my physician and I chose to initiate for my HIV disease. I have been asked to participate because I am starting my initial course of anti-HIV treatment between June 1, 1999 and March 31, 2000. The study will look at different aspects of my disease and what role they played in our decision about therapy. These include things such as laboratory values (ie: CD_4, viral load), my past medical history, economic, and basic demographic information (ie: race, gender, education, income).

I understand that as part of the study, I will be asked to complete an anonymous questionnaire containing personal information about myself and my health. The questionnaire will take less than 10 minutes to complete. I will be identified only by a code number and the information I submit will not be directly linked to me. An investigator will have access to my medical records at my doctor's office to clarify any details during the study period of June 1, 1999 to May 1, 2000.

The information collected from me will be combined with that from other patients to form the basis of the report. I will not be identified by name in any presentation or publication arising from this research.

BENEFITS OF PROPOSED STUDY

I am aware that my participation in the study will not benefit me specifically but that the information I am providing will identify the commonly used regimens and help others understand the factors which guide these decisions.

My decision not to participate in this study will have no impact on my care. I may also leave the study at any time without impacting on my care. If there are any questions on the questionnaire that I do not feel comfortable answering, I may leave them blank.

CONFIDENTIALITY

I understand that all information gathered from my medical record will remain confidential and that I will not be identified in any way.

CONSENT

I understand that the study can be stopped by an internal review board at any time.

I have read this information sheet. If I have any further questions, I may call Mary E. Nguyen at 340-4800 x8307. I may also call Dr. Ron Heslegrave at (416)–340-4557 who is not involved in this trial but who will answer questions about participating in a research study.

I agree to participation in this clinical study.

Dated at my doctor's office this_____day of _____ 19___.

_____ _____

Participant Name (please print) Participant Signature

_____

Witness signature

_____ _____

Investigator Name Investigator Signature

APPENDIX D

Choice of First-Line Therapy and Factors Affecting Regimen Selection: A Survey of Toronto Area HIV physicians and a Chart Review of Antiretroviral Naïve Patients

Principal Investigators: Mary E. Nguyen, Pharm.D. , Alice Tseng, Pharm.D.,
Sharon Walmsley M.D.

Sponsors: Immunodeficiency Clinic - Toronto Hospital
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Instead of including a protease inhibitor in the drug regimen, some physicians and patients are choosing to substitute other classes of drugs such as the non-nucleoside reverse transcriptase inhibitor (e.g., nevirapine/Viramune®, delavirdine/Rescriptor®, and efavirenz/DMP-266/Sustiva®). Others support the use of three drugs from the nucleoside

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I understand that as part of the study, my medical records at the clinic will be reviewed by a study investigator in order to obtain medical information. I will also be asked to complete an anonymous questionnaire containing personal information about myself and my health. The questionnaire will take less than 10 minutes to complete. I will be identified only by a code number and the information I submit will not be directly linked to me. An investigator will have access to my medical records at my doctor's office to clarify any details during the study period of June 1, 1999 to May 1, 2000.

The information collected from me will be combined with that from other patients to form the basis of the report. I will not be identified by name in any presentation or publication arising from this research.

BENEFITS OF PROPOSED STUDY

I am aware that my participation in the study will not benefit me specifically but that the information I am providing will identify the commonly used regimens and help others understand the factors which guide these decisions.

My decision not to participate in this study will have no impact on my care. I may also leave the study at any time without impacting on my care. If there are any questions on the questionnaire that I do not feel comfortable answering, I may leave them blank.

CONFIDENTIALITY

I understand that all information gathered from my medical record will remain confidential and that I will not be identified in any way.

CONSENT

I understand that the study can be stopped by an internal review board at any time.

I have read this information sheet. If I have any further questions, I may call Mary E. Nguyen at 340-4800 x8307. I may also call Dr. Julie Spence , Chair of the Research Ethics Board, at 416-864-6060 x 2557 who is not involved in this trial but who will answer questions about participating in a research study.

I agree to participation in this clinical study.

Dated at my doctor's office this_____day of _____ 19___.

_____ _____

Participant Name (please print) Participant Signature

_____

Witness signature

_____ _____

Investigator Name Investigator Signature

APPENDIX E

Choice of First-Line Antiretroviral Therapy
and
Factors Affecting Regimen Selection

CLINIC CODE_____ PATIENT NUMBER _____

DATE OF DATA COLLECTION_____

1. Physician Practice

☐ Primary care ☐ Clinic

2. Date of HIV diagnosis _____

3. Date of antitretroviral drug initiation _____

4. Initiated Regimen

☐ (1 or 2) PI + 2 NRTI ☐ 1 NNRTI + 2 NRTI ☐ 3 NRTI

☐ 2 NRTI + 1 PI + 1 NNRTI

5. Drugs and doses initiated – please list

6. Baseline viral load at start of therapy _____copies/ml

7. Baseline CD4 at start of therapy _____ cells/mm^3

8. Presentation at time of drug initiation

☐ AIDS indicator condition ☐ Symptomatic non-AIDS ☐ Asymptomatic

9. Concurrent Illnesses – check all that apply

☐ Diabetes

☐ Renal Insufficiency (Crcl < 60 ml/min)

☐ Hepatic insufficiency (LFT > 5x normal) or evidence of cirrhosis

☐ Depression

☐ Obesity (≥ 140% IBW)

☐ Active substance abuse
- ☐ IV
- ☐ other

10. Does the patient have any social support? – check all that apply

☐ Family ☐ Friends ☐ Support group ☐ Partner ☐ Stable housing

11. Rationale behind regimen selection