Université de Montréal

Risk factors for suboptimal adherence and facilitators of adherence to HAART in HIV-infection

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Thèse présentée à la Faculté des Études Supérieures
en vue de l'obtention du grade de Philosophae Doctor (Ph.D.)
en psychologie recherche/intervention
option clinique

Janvier, 2005

Université de Montréal

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Université de Montréal

Faculté des Arts et Sciences

Cette thèse intitulée :

Risk factors for suboptimal adherence and facilitators of adherence to HAART in
HIV-infection

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Résumé

Les thérapies antirétrovirales actives (TAA) ont significativement amélioré l'espérance de vie des personnes séropositives. Ces combinaisons de médicaments requièrent une adhésion minimale de 95% de doses prises telles que prescrites pour avoir un impact virologique optimal et éviter le développement de résistance aux médicaments. En raison de leur complexité et des nombreux effets secondaires encourus par les TAA., l'adhésion à ces combinaisons de médicaments est souvent sous optimale. Il est donc essentiel de mieux comprendre les facteurs associés à l'adhésion aux TAA, compte tenu des implications sérieuses d'une adhésion sous optimale quant au traitement des individus séropositifs et quant à la santé publique.

Cette thèse se compose de deux articles qui étudient les facteurs associés à l'adhésion aux TAA chez des individus séropositifs (N = 82). Le premier article étudie l'association entre l'adhésion sous optimale mesurée sur une période de 180 jours et les caractéristiques suivantes : (1) certaines caractéristiques démographiques, (2) certaines caractéristiques médicales, (3) certaines caractéristiques psychosociales, (4) croyances associées à l'efficacité des médicaments. Cet article explore aussi l'association entre les croyances associées à l'efficacité des médicaments et les caractéristiques des participants. Le deuxième article décrit d'une part, les raisons sous-jacentes à l'omission de doses de médicaments (barrières à l'adhésion) au moment d'adhésion le plus difficile; et d'autre part les stratégies et les motivations qui facilitent généralement l'adhésion aux médicaments (facilitateurs de l'adhésion) rapportées à un seul temps sur une période d'un an. Finalement, cet article explore aussi l'association entre l'adhésion aux TAA mesurée sur une période d'un an et le nombre ou le type de facilitateurs de l'adhésion rapportés par les participants.

Dans le premier article, les résultats de la régression logistique indiquent que les participants qui ont un problème d'alcool, un problème de drogue ou qui sont plus

sceptiques par rapport à l'efficacité des TAA présentent un risque plus élevé d'adhésion sous optimale. Les résultats indiquent aussi que les croyances quant à l'efficacité des TAA sont associées au nombre de symptômes médicaux rapportés et au stade de la maladie.

Les résultats du deuxième article indiquent que les raisons les plus fréquemment mentionnées au moment d'adhésion le plus difficile sont souvent reliées à des changements de routine quotidienne. Les catégories principales de facilitateurs de l'adhésion rapportées sont : (1) habiletés de planification; (2) perception positive des médicaments; (3) soutien social; (4) motivation interne/engagement; (5) « self-care ». L'adhésion mesurée sur une période d'un an ne semble pas être reliée au nombre ou au type de facilitateurs mentionnés.

Les résultats de ces deux articles démontrent la complexité de l'adhésion aux TAA puisque de multiples facteurs semblent l'influencer. Ces résultats mettent aussi l'emphase sur l'importance: (1) de dépister les problèmes d'alcool et de drogue, (2) d'explorer les croyances des patients envers leurs médicaments. Finalement, cette étude démontre qu'il peut être intéressant de questionner les patients au sujet des facteurs qui facilitent leur adhésion aux TAA plutôt que de se renseigner uniquement sur les barrières et les obstacles à leur adhésion aux traitements.

Mots-clés : VIH, SIDA, adhésion, facteurs psychologiques, dépression, symptômes médicaux, croyances, médicaments, drogue, alcool.

Abstract

The advent of Highly Active Antiretroviral Therapy (HAART) has significantly improved the life expectancy of HIV-infected individuals. However, a strict threshold of up to 95% of doses taken as prescribed is required for optimal virologic outcomes and to avoid the development of resistance to medication. However, adherence to these regimens is often suboptimal because they are frequently accompanied by side effects and are among the most complex medication regimens to follow. Because suboptimal adherence has serious implications for the treatment of HIV-infected individuals, as well as for public health, it is critical to get a better understanding of factors associated with adherence to HAART regimens.

This dissertation consists of two articles designed to improve the understanding of factors associated with HAART adherence in a sample of HIV-infected individuals (N = 82). The first article examined the relation between suboptimal adherence, measured over a period of 180 days, and the following risk factors measured within 60 days of baseline: (1) demographic characteristics, (2) medical characteristics, (3) psychosocial characteristics, and (4) beliefs about medication efficacy. It also explored participants' factors associated with beliefs about medication efficacy. The second article explored both the reasons for suboptimal adherence (barriers of adherence) reported at the worst adherence episode, and the strategies and motivators that facilitated adherence (facilitators of adherence) reported at one time point over the course of one year. It also examined the relation between participants adherence status measured over a one year period and the number or the type of facilitators reported by participants.

In the first article, results of a logistic regression indicated that participants who had an alcohol use problem, a drug use problem, or who were more sceptical about HAART efficacy were at increased risk for suboptimal adherence. Results also suggested that beliefs

about medication efficacy were associated with HIV-related medical characteristics, such as number of medical symptoms and CDC disease stage.

Results of the second article indicated that the reasons most commonly mentioned for missed medication doses at the worst adherence episode were interferences with daily routine. Main categories of facilitators of adherence reported by participants were: (1) planning skills; (2) positive perception of medication; (3) social support; (4) commitment / internal motivation; and (5) self-care. The number and types of facilitators mentioned were not associated with participants' adherence status measured over a 1-year period.

Results of these two articles highlighted the complexity of adherence by demonstrating that adherence is influenced by multiple factors that tend to vary between individuals. It also emphasized the importance of screening for problems with alcohol use or drug use, and of inquiring about patients' perceptions of their medication. These findings also highlighted the importance of asking patients about facilitators of adherence rather than focusing uniquely on barriers or obstacles to adherence.

Keywords : HIV, AIDS, medication adherence, psychological factors, depression, medical symptoms, beliefs, expectations, drug, alcohol.

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List of abbreviations

HIV : Human Immunodeficiency Virus

AIDS: Acquired Immune Deficiency Syndrome

NNRTI : Nonnucleoside Reverse Transcriptase Inhibitors

NRTI : Nucleoside Analogue Reverse Transcriptase Inhibitors

PI : Protease Inhibitors

CDC : Center for Disease Control

HAART : Highly Active Antiretroviral Therapy

Je dédie cette thèse à la mémoire de mon père qui m'a appris, entre autres choses, le courage, la persévérance et la patience. Je tiens aussi à dédier cette thèse à P. qui m'a permis de l'accompagner dans sa bataille courageuse contre le VIH avant d'être emporté par la maladie à l'an 2000. P., tu resteras toujours pour moi un modèle de persévérance devant l'adversité.

Remerciements

Je tiens à remercier premièrement ma mère pour ses encouragements durant les moments difficiles, pour son écoute, ainsi que pour son soutien moral et financier. Je désire remercier ma sœur Caroline et son conjoint Claude pour leur support technique. Je tiens aussi à remercier spécialement ma tante Solange et mon oncle Mark. You have both been of great support through my Ph.D. by being my "substitute" parents while I was in San Diego. Thank you for your kind words and for reviewing drafts of my papers. I also want to thank June and Kirk who are the equivalent of grand-parents for me.

Je désire remercier mon directeur de recherche, le Dr. Paul Veilleux, pour son écoute et son soutien. Je vous suis reconnaissante pour la liberté que vous m'avez laissée tout au long de mon doctorat, et plus particulièrement pour votre soutien à travers mes projets d'études à l'extérieur du Québec. I also want to thank my codirector, Dr. Sean Rourke, for allowing me to join his team in Toronto and to benefit from his research expertise. I also want to thank Dr. Rourke research team at St. Michaels' Hospital (Sarah: you've been of tremendous help!, Sherri, Lisa, Jeff and all the others…) and his collaborators Dr. Lancee and Dr. Saunders who have accepted me into their research project. Je désire remercier Monique Séguin qui a rendu mon séjour à Toronto des plus agréables. Je tiens aussi à remercier certains professeurs du département de psychologie de l'Université de Montréal : le Dr. Kiely qui a eu beaucoup d'influence sur mon parcours académique par l'intermédiaire de son enseignement exceptionnel, et le Dr. Cossette-Ricard qui, lorsque nécessaire, m'a donné de précieux conseils. Je tiens à remercier spécialement Miguel Chagnon du département de mathématiques de l'Université de Montréal pour sa capacité à rendre accessibles même les analyses statistiques qui semblent les plus incompréhensibles : merci beaucoup pour tes conseils judicieux et tes bons mots d'encouragement.

Un merci spécial à mes amies Natalie, Sophie, Lina et Martine qui ont révisé des ébauches de cette thèse. Merci aussi aux ami(e)s qui par leur sourire, leur soutien et leurs encouragements ont rendu cette longue traversée plus agréable: Louisa, Christine, Stéphanie,

Introduction

In North America, an estimated 790 000 to 1.2 million of people are living with the Human Immunodeficiency Virus (HIV) or the Acquired Immunodeficiency Syndrome (AIDS). Approximately 52 000 (5 %) of these individuals live in Canada, and the number of infected individuals has been rising at a rate of 12 percent since 1999 (SantéCanada, 2004). A large proportion of these individuals will eventually take or are already taking a combination of medication to delay HIV progression. The advent of Highly Active Antiretroviral Therapy (HAART: usually defined as a Protease Inhibitor or a Non-Nucleoside Reverse Transcriptase Inhibitor combined with at least two other antiretroviral drugs) has greatly improved the life expectancy and the quality of life of HIV-infected individuals. However, HAART combinations generally require strict adherence behaviour: not only an adherence threshold of 95% or more of medication doses taken as prescribed, but also consistency in this high rate of adherence over time. This is crucial to achieve optimal virologic outcomes and to avoid the development of drug resistance (Mannheimer, Friedland, Matts, Child, & Chesney, 2002; Paterson et al., 2000). Because suboptimal adherence has serious implications for the treatment of HIV-infected individuals and for public health, it is critical to gain a better understanding of the factors that may be associated with adherence behaviours.

The main objective of the present dissertation is to improve our understanding of factors that influence adherence behaviours. This dissertation consists of two articles: the first article uses a quantitative approach to study specific risk factors for suboptimal

HAART adherence, while the second article adopts a qualitative approach to explore both the barriers to and the facilitators of HAART adherence.

In order to introduce this dissertation, the term "adherence" will first be defined in the context of HIV-infection by briefly describing the impact of HAART on HIV-infected individuals' health. The difficulties inherent to these treatment regimens including the challenges associated with suboptimal adherence rates will also be exposed. Secondly, methodological difficulties in adherence measurements will be reviewed, and the measure of adherence used in the present dissertation will be explained. Thirdly, a general review of the literature on factors associated with adherence will be briefly presented. Fourthly, the general aim of this dissertation, as well as the specific goals, variables studied and hypotheses of each article will be presented. Lastly, the methodology used will be briefly explained.

1. Adherence in the context of HIV-infection

Since their advent, HAART regimens have been associated with reduced viral replication, improved immunity, and decreased risk of contracting opportunistic infections. These drug treatments have also delayed HIV progression, and decreased the frequency of hospitalizations and deaths due to HIV (Altice & Friedland, 1998; Carpenter et al., 2000; Chun & Fauci, 1999; Deeks, Smith, Holodniy, & Kahn, 1997; Karon, Fleming, Steketee, & De Cock, 2001; Paul, Gilbert, Ziecheck, Jacobs, & Sepkowitz, 1999). Despite the important advantages in taking HAART medication, reported rates of adherence are often suboptimal

and at least a quarter of patients report that they skipped medication doses over the last few days or the last week (Ammassari et al., 2001; Catz, Kelly, Bogart, Benotsch, & McAuliffe, 2000; Chesney, Ickovics et al., 2000; Gifford et al., 2000; Nieuwkerk et al., 2001; Schönnesson, Ross, & Williams, 2004; Sethi, Celentano, Gange, Moore, & Gallant, 2003). Indeed, adherence to HAART is complicated by the fact that these regimens are often very complex: individuals need to regularly take a large quantity of medication on a tight and regimented schedule, with special requirements associated with each type of medication taken (e.g., dietary restrictions). These regimens also have numerous side effects and require strict adherence behaviour over a long-term basis to be effective.

Mild adverse effects, including gastrointestinal problems such as nausea, diarrhea and bloating, occur frequently at initiation of treatment, and in some cases persist throughout treatment. Other common side effects such as fatigue and headaches can occur on a regular basis while on treatment (Montessori, Press, Harris, Akagi, & Montaner, 2004). Furthermore, there are growing concerns about the long-term impact of these regimens on HIV-infected individuals' health and body image. Specifically, long-term utilization of these drugs has been associated with metabolic disorders such as lipodystrophy (abnormal fat redistribution) and hyperlipidemia (elevation of lipids in the bloodstream) (Armstrong, Calabrese, & Taege, 2002; Boyle, 2003; Montessori et al., 2004; Steinhart & Emons, 2004).

In order to be effective and to avoid development of resistance to medication, HAART combinations generally require an elevated adherence threshold as well as

consistency in adherence over time. Suboptimal levels of medication exposures may permit viral replication in the presence of medication leading to the emergence of drug-resistant viruses (Clavel & Hance, 2004; Condra, Miller, Hazuda, & Emini, 2002). Patients with suboptimal adherence may then be confronted with therapeutic failure and/or the risk of transmitting a resistant strain of the virus to someone else. Levels of adherence have been associated with virologic outcomes and CD4 lymphocyte counts in several studies (Bangsberg et al., 2000; Bangsberg, Perry et al., 2001; Duong et al., 2001; Mannheimer et al., 2002; Perno et al., 2002), but the number of missed doses of medication that could lead to virological failure is unclear at this point (Deeks, 2003). However, the current recognized threshold of adherence for optimal virologic outcome is 95% of doses taken as prescribed. This is based on the results of a prospective observational study using Medication Event Monitoring System (MEMS caps) to measure the adherence level of 99 HIV-infected individuals taking a medication regimen containing a protease inhibitor. This study found that patients with 95% or greater adherence to their regimen had better virologic outcome, greater increase in CD4 lymphocyte counts, and lower hospitalization rates than those with less than 95% adherence (Paterson et al., 2000). Therefore, even small differences in levels of adherence were associated with significant differences in virologic outcome.

Consistency of adherence over time is also another critical component because patients who are generally highly adherent but who miss their medication on a few occasions have been found to develop more resistance to medication than patients who are consistently adherent to their regimen (Bangsberg et al., 2000; Perno et al., 2002; Walsh,

Pozniak, Nelson, Mandalia, & Gazzard, 2002). A study on long-term antiretroviral adherence patterns based on 2 randomized control trials followed patients on a variety of medication combinations over a 1-year period, collecting data every 4 months (Mannheimer et al., 2002). Their outcome measure was whether or not 100% adherence was reported at all of the four visits. Participants who were consistently 100% adherent to their regimen at all visits were significantly more likely to achieve suppression of the virus to an undetectable level, in comparison with others who were less consistent in their adherence. In fact, 72% of the participants who reported being 100% adherent at all four visits had an undetectable viral load, compared to 66% of the participants who reported being 100% adherent at only three visits. The percentage of individuals with an undetectable viral load gradually decreased to 41%, 35% and 13% for participants who reported respectively 100% adherence to two, one or zero of the follow-up visits. Therefore, because incomplete adherence is associated with disease progression, full medication adherence is currently considered a critical determinant of patient survival (Garcia de Olalla et al., 2002; Wood et al., 2003). A prospective study that followed 1282 HIV-infected individuals who had been on their first antiretroviral combination therapy for a mean period of 26.8 months confirmed this assumption. Participants who used antiretroviral drugs intermittently, taking less than 75% of their medication in the first 12 months of the study, were 2.97 times more likely to die than participants who used antiretroviral therapy more than 75% of the time after controlling for other factors affecting medical prognostic (Hogg et al., 2002).

Lastly, interruptions of treatment are often accompanied by resurgence of viral replication and immunological decline within a few weeks, even after periods of prolonged viral suppression (Blankson, Persaud, & Siliciano, 2002). Because antiretroviral drugs are targeting viral replication, they are only effective against actively replicating viruses when taken regularly, and these regimens might therefore necessitate lifelong adherence to control viral replication.

In this context, the current challenge in this field of practice is to help HIV-infected individuals better adhere to their prescribed treatment regimens.

2. Methodological difficulties in adherence measurement

There is currently no "gold standard" to measure adherence. Adherence assessment is not standardized, and relies mainly on estimates of adherence rates because it is not easily feasible to obtain directly observable measures (Wu, Ammassari, & Antinori, 2002). Different measures of adherence have been used in the literature including electronic devices, biologic and laboratory markers, pill counts, pharmacy records, providers assessment, patient self-reports, or a combination of these sources (Turner, 2002). There are advantages and limitations associated with each of these measures. Electronic devices such as Medication Events Monitoring Systems (MEMS; Aprex Corporation), that memorize every time pill bottles were opened, are considered to be the most accurate tools to measure adherence. However, these devices are often expensive and inconvenient to use for participants because of their large size. Further, not only is it impossible to be certain that

the medication was taken when the bottle was opened, these devices may underestimate adherence if participants remove more than one pill at a time from the pillbox. Biologic and laboratory markers are also considered to be relatively accurate measures of adherence because they provide plasma drug levels. However, they can only provide an adherence measure for the previous 24 hours, and are difficult to implement in clinical research. Pill counts and pharmacy records are sometimes used but they are often perceived as intrusive by patients, and it is not possible to know with certainty if patients actually took their medication. Furthermore, providers' assessments of patients' adherence has been shown to be very inaccurate (Bangsberg, Hecht et al., 2001). Self-reported adherence is the most commonly used method to measure adherence. Even if self-reports could be influenced by social desirability and usually tend to overestimate rates of adherence when compared to more objective measures such as electronic devices (Liu et al., 2001), they have generally been found to have a good correlation with other measures of adherence (Deeks, 2000; Duong et al., 2001; Hugen et al., 2002) and have also been shown to predict therapeutic outcome, as measured by HIV RNA level and CD4+ cell count (Mannheimer et al., 2002; Walsh, Mandalia, & Gazzard, 2002). The optimal time frame to obtain an accurate self-report of adherence is unclear, but a recent study (Godin, Gagne, & Naccache, 2003) obtained a more adequate measure while using a 7-day period compared to a 2-day or a 30-day period, when using increased viral load assays over 6 months as the validity criterion for determining accuracy of measurement.

2.1 Adherence measurement for this dissertation

For this dissertation, it was originally planned to use self-reported questionnaires with all participants, and to implement MEMS with a subgroup of participants to validate the self-reported measures. However, it was not possible to implement the use of MEMS because most participants refused to use them, therefore only a self-reported adherence measure using a time frame of 7 days was collected.

A missed dose was defined as omitting an entire scheduled dose of one medication. The number of missed doses for each day was calculated by subtracting the number of doses actually taken from the number of doses each participant was expected to take. These missed doses were then added for the 7 day-period covered by the questionnaire and divided by the number of doses the participant was expected to take during that same period of time. This result was finally multiplied by 100 to provide a percentage of suboptimal adherence to the prescribed regimen. Individuals were categorized by adherence status (adherence vs. suboptimal adherence) using the generally accepted 95% threshold of adherence discussed above.

3. Factors associated with HIV medication adherence

More than 200 different factors have been associated, more or less consistently, with adherence to treatments in various diseases (Meichenbaum & Turk, 1987). Factors generally associated with adherence to HIV medication have recently been grouped into

four different categories (Boucher & Veilleux, 2002; Chesney, 2003; Lafeuillade, 2001): (1) patient-related factors including variables such as demographic characteristics, medical characteristics, psychosocial characteristics and patients' belief system; (2) medication-related factors such as complexity of treatment, frequency of dosing, etc.; (3) quality of the doctor-patient relationship and general social support; and (4) general system of care.

However, despite a considerable amount of research to date, it is still difficult to accurately identify which group of individuals is most at risk of suboptimal adherence given the variability in results. These divergent results might be caused by the variability in the population or the HIV-medication regimens studied, in the adherence measurements, and in the operationalization of the term "adherence". While most studies have focused on the proportion of missed medication doses, a few studies have also looked at accurate timing of doses and capacity to follow dietary instructions. Furthermore, studies have often used various thresholds to define adherence varying from 80% to 100% of medication doses taken as prescribed.

Because suboptimal adherence has critical implications for the treatment of HIV-infected individuals, as well as for public health, it is important to continue to identify the essential factors associated with suboptimal adherence. This knowledge will help to develop and test interventions that target risk factors and behaviours.

Given the large body of research available on adherence to HIV medication, the present dissertation will limit its focus to factors that were examined in both articles contained herein for their potential association with suboptimal adherence.

4. Goals of the dissertation

The aim of the present dissertation is to enhance the understanding of factors related to adherence behaviours in a sample of 82 HIV-infected individuals by: (1) exploring risk factors for suboptimal adherence in article 1, and (2) exploring both the barriers to adherence (namely reasons for missed medication doses) and facilitators of adherence (namely strategies and motivators that enhance adherence) in article 2.

4.1 Goals of the first article

The first article aimed to identify risk factors that might predict suboptimal adherence measured subsequently over a 6-month period, and to explore the relationship between beliefs about medication and different participants' demographic, medical, and psychosocial characteristics. The following risk factors for suboptimal adherence were examined: (1) demographic characteristics: age, education; (2) HIV-related medical characteristics: disease stage and number of medical symptoms reported; (3) psychosocial characteristics: alcohol use problem, drug use problem, depressive symptoms, and (4) beliefs about medication efficacy.

4.11 Risk factors for suboptimal adherence to HAART studied

The risk factors for suboptimal adherence tested in the first article were selected to reflect a general cognitive-behavioural approach to study adherence. Factors selected included personal factors, emotional factors, and cognitions with the goal of predicting a given behaviour: adherence to medication.

A. Demographic variables

Demographic characteristics have generally been found to be poor predictors of suboptimal adherence to medication (Rabkin & Chesney, 1999), but a few studies have reported associations between adherence and age, as well as adherence and education or socio-economic status. Some studies found that younger age was associated with a higher likelihood of suboptimal adherence (Aloisi et al., 2002; Becker, Dezii, Burtcel, Kawabata, & Hodder, 2002; Gordillo, del Amo, Soriano, & Gonzalez-Lahoz, 1999; Moatti et al., 2000), while other studies found that younger age was associated with a lower likelihood of suboptimal adherence (Molassiotis et al., 2002; Stone et al., 2001). Furthermore, some studies did not detect any association between age and suboptimal adherence (Holzemer et al., 1999; Mohammed et al., 2004). A lower education level or a lower socio-economic status has been associated with suboptimal adherence in a few studies (Catz, Heckman, Kochman, & DiMarco, 2001; Kleeberger et al., 2001).

B. Psychosocial variables:

a) Alcohol use problems

An alcohol use problem is defined as hazardous and harmful alcohol use that could lead to alcohol dependence. Following the World Health Organization terminology (Saunders, Aasland, Babor, de la Fuente, & Grant, 1993), hazardous consumption can be defined as alcohol consumption that implies the risk of physical and / or psychological harm; while harmful alcohol use can be defined as the presence of physical or psychological complications. Alcohol use problem has been quite consistently associated with an increased risk of suboptimal adherence in several studies (Aloisi et al., 2002; Chesney, Ickovics et al., 2000; Lucas, Gebo, Chaisson, & Moore, 2002; Moatti et al., 2000; Mohammed et al., 2004; Samet, Horton, Meli, Freedberg, & Palepu, 2004).

b) Drug use problems

A drug use problem is defined as the use of "recreational drugs" such as: (1) drugs prescribed or "over the counter" drugs in excess of direction and (2) any non-medical use of drugs within the past year, excluding alcohol and tobacco (Skinner, 1982). It also reflects a drug consumption that interferes with different life domains of the individual. Current use of injection or non injection drugs has been quite consistently associated with suboptimal adherence (Aloisi et al., 2002; Bouhnik et al., 2002; Gordillo et al., 1999; Lucas, Cheever, Chaisson, & Moore, 2001; Moatti et al., 2000). However, former drug use is usually not

associated with suboptimal adherence (Holzemer et al., 1999; Lucas et al., 2001), unless it is associated with current social instability (Bouhnik et al., 2002).

c) Depressive symptoms

Depressive symptoms correspond to symptoms described in the diagnosis criteria of depressive disorders in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders – Fourth Ediction (DSM-IV; 1994). Depression or depressive symptoms have been associated with suboptimal adherence in several studies (Ammassari et al., 2004; DiMatteo, Lepper, & Croghan, 2000; Gordillo et al., 1999; Holzemer et al., 1999; Starace et al., 2002), but a few studies have also found the absence of such an association (Stone et al., 2001).

C. HIV-related medical characteristics

a) Medical symptoms

Medical symptoms studied represent a combination of symptoms of HIV or medication side effects commonly experienced by HIV-infected individuals. A greater number of symptoms of HIV (Ammassari et al., 2001; Holzemer et al., 1999; Wagner, 2002) or side effects of medication (Ammassari et al., 2001; Trotta et al., 2002) have been associated with suboptimal adherence in several studies. In a recent study (Heath, Singer, O'Shaughnessy, Montaner, & Hogg, 2002) subjects reporting at least one severe symptom were found to be more than twice as likely to have suboptimal adherence. Furthermore, gastrointestinal side effects such as nausea, vomiting and diarrhea, were usually the reasons

most often cited for discontinuation of medication (O'Brien, Clark, Besch, Myers, & Kissinger, 2003).

b) Disease stage

Disease stage is defined based on the 1993 Classification system for HIV infection from the Center for Disease Control (Castro et al., 1992). It reflects current standards of medical care for HIV-infected individuals, and categorizes these individuals into 9 mutually exclusive categories on the basis of clinical conditions associated with HIV infection and CD4+ T-lymphocyte counts (see Table I, p. 23). Individuals are classified based on CD4+ T-lymphocyte counts per microliter of blood into the following categories: (1) $\geq$ 500 cells/μ L; (2) 200-499 cells/ μ L; (3) < 200 cells/ μ L; and are concurrently classified into three clinical categories: (1) to be classified into category A an individual needs to have one or more of the following conditions: asymptomatic HIV infection, persistent generalized lymphadenopathy, acute HIV infection with accompanying illness or history of acute HIV infection; (2) to be classified into category B an individual needs to have symptomatic conditions that are not included in category C (AIDS) and to meet at least one of the following criteria: a) conditions are attributed to HIV or b) conditions are considered to have a clinical course or to require management that is complicated by HIV infection (e.g.: candidiasis, constitutional symptoms such as fever or diarrhea lasting more than 1 month); (3) to be classified into category C an individual needs to have or have had at one point the clinical conditions that are listed in the AIDS surveillance case definition (e.g.: Kaposi's sarcoma, Pneumocystis carinii pneumonia). These nine categories can be subdivided again

into three categories: asymptomatic HIV-infection, symptomatic HIV-infection, and AIDS diagnosis. Individuals are considered asymptomatic if they are at the clinical stage A, and have CD4+ counts of at least 200 cells/ μ L. Individuals are considered symptomatic if they are at the clinical stage B, and have CD4+ counts of at least 200 cells/ μ L. AIDS is diagnosed when individuals reach the clinical stage C or if they have CD4+ counts of less than 200 cells/μL.

In one study (Gao, Nau, Rosenbluth, Scott, & Woodward, 2000) participants in clinical stages B or C were more adherent to their medication than participants in stage A. Another study noted a tendency of participants in the clinical stage C to be more adherent to medication (Molassiotis et al., 2002). To our knowledge, no other study has supported the association between suboptimal adherence and less severe disease stages.

D. Beliefs about medication efficacy

Beliefs about medication efficacy are defined as the perceived health benefits that participants are expecting to gain from their HAART medication. It is also defined as the perceived positive or negative impact on functioning that participants are expecting to get from their HAART medication. A few studies in HIV have shown an association between suboptimal adherence and less positive beliefs about medication, more negative expectancies about the outcome of medication or more concerns about the adverse effect of medication (Aversa & Kimberlin, 1996; Horne et al., 2004; Johnson, Catz et al., 2003; Murphy, Roberts, Hoffman, Molina, & Lu, 2003; Remien et al., 2003; Roberts, 2000;

Roberts & Mann, 2000; Siegel, Schrimshaw, & Dean, 1999). Little is known about factors that influence beliefs about medication efficacy. To our knowledge, only one study (Reynolds et al., 2004) has explored factors associated with beliefs about medication and found that: less positive beliefs about medication efficacy were associated with personal and situational factors such as depression, stress, lower education level.

4.12 Factors tested in association with beliefs about medication efficacy

The following participants' characteristics were explored in association with beliefs about medication: (1) demographic characteristics: age, gender, education; (2) medical characteristics: disease stage, number of medical symptoms due to illness or side effects of medication, viral load (indicator of health status), hospitalization in the past 6 months; (3) depressive symptoms.

4.13 Hypotheses of the first article

Based on results of prior studies exposed above, it was hypothesized that a greater number of medical symptoms, a greater number of depressive symptoms, less positive beliefs about medication efficacy, alcohol use problem, and drug use problem would predict suboptimal adherence to medication; while demographic characteristics and disease stage would not predict suboptimal adherence. Because of the lack of knowledge about factors associated with more positive beliefs about medication efficacy, no specific hypothesis was made about their association with participants' characteristics.

4.2 Goals of the second article

The second article had for objective to increase our understanding of adherence behaviours by exploring and describing both the barriers to (namely reasons for suboptimal adherence) and the facilitators of (namely strategies and motivators of adherence) HAART adherence reported by HIV-infected individuals. The second goal was to explore the association between number or type categories of facilitators used by participants and their adherence status. Because this study was exploratory in nature, no specific hypothesis was made.

4.21 Barriers and facilitators of adherence to HAART

Most studies on adherence behaviours have had their primary focus on obstacles or barriers to adherence. In order to gain a more complete understanding of adherence behaviours, the second article explores two complementary sides of the decision making process as they were reported by HIV-infected individuals: reasons for suboptimal adherence (barriers) and strategies or motivators (facilitators) of adherence behaviours.

A. Barriers to adherence

Barriers to adherence are defined here as reasons reported by participants for missing their medication doses. Several quantitative studies have explored reasons for suboptimal adherence in HIV-infected individuals (Catz et al., 2001; Chesney, Ickovics et al., 2000; Chesney, Morin, & Sherr, 2000; DeMasi et al., 2001; Eldred, Wu, Chaisson, & Moore, 1998; Ferguson et al., 2002; Gifford et al., 2000; Kleeberger et al., 2001;

Mannheimer et al., 2002; Molassiotis et al., 2002; Reynolds et al., 2004). The reason most often cited across studies was "forgetfulness" Other common reasons were: changes in daily routine, interferences from social context such as: being too busy, being away from home, eating a meal at a wrong time, sleeping through a dose; and practical barriers such as complexity of drug regimens, and number of medication to take. In this second article, reasons for suboptimal adherence will be explored at participants' worst time of adherence within a one year period.

B. Facilitators of adherence

Facilitators of adherence represent strategies or motivators that participants believed generally helped them adhere to their medication regimens. To our knowledge, only two studies have explored facilitators of adherence and results of these studies will be described in greater details in the introduction of the second article.

5. Method

5.1 General design

Both studies included in this dissertation used a longitudinal design. However, different time frames were used to measure adherence: the first article measured adherence status over 180 days (6 months), while the second article measured adherence status over 360 days (about 1 year).

To answer our research question, it was necessary to render individuals comparable through time by organizing the adherence data into 12 fixed intervals of 30 days starting at study entry for a total period of 360 days. However, this resulted in some participants not having at least one entry every 30 days. In order to insure that we had a reliable measure of adherence behaviour, without detrimentally minimizing sample size, we required that at least 3 measures of adherence out of 6 (article 1), or 6 measures out of 12 (article 2), be available for a subject to be included in the analyses. For each 30-day interval, both the average and the "worst" self-reported adherence percentage were calculated. Individuals were categorized by adherence status (adherence vs. suboptimal adherence) using a 95% threshold of adherence, usually accepted in the literature. Therefore, participants who reported that they had taken less than 95% of their prescribed doses at least one time over a period of 6-month (article 1) or one year (article 2) were considered to have suboptimal adherence to their regimen.

5.12 Design used for article 1

The first article is a prospective longitudinal study that explores the association between potential risk factors measured within 60 days of baseline, and adherence status measured subsequently over a period of 180 days (6 months). It also explores cross-sectionnally the association between beliefs about medication efficacy and participants' characteristics both measured within a 60-day period of baseline. Most risk factors were measured within a 60-day period of baseline. Both the average and the "worst" scores were

retained for each factor. To measure alcohol and drug use problems all scores available for a period of one year were retained because these questionnaires probed retrospectively about alcohol and drug use problems within the past year. If more than one measure of alcohol problem or drug problem was available, only the "worst" score was retained for the analyses.

5.13 Design used for article 2

The second article is a descriptive, exploratory study. It uses a qualitative methodology to describe the reasons most frequently mentioned by participants at the time of their worst adherence level within a one-year period. It also describes categories of adherence facilitators reported by HIV-infected individuals at one specific time point. Finally, it explores the potential association between the number or the types of categories of facilitators mentioned, and participants' adherence status measured subsequently over a period of 360 days (one year).

It was not possible to control time of administration for the facilitators of adherence questionnaire because it was administered only once, at different time intervals within a period of 360 days of baseline. However, these facilitators should be relatively stable over a period of several months since participants in this study had been taking medication for a few years and were asked what generally helped them adhere to their regimens. It can be reasonably postulated that these individuals had already developed a set of habits and/or strategies to facilitate adherence.

5.2 Participants

One hundred and nine HIV-infected individuals undergoing HAART treatments were approached for this study. A total of 27 participants were excluded from the analyses based on specific criteria discussed further in the two articles included in this dissertation. The final sample was composed of 82 individuals of which 71 were men (86.6%) and 11 women (13.4%) with a mean age of 41 years (SD = 7.2; range 21-64) and education level of 13.3 years (SD = 2.3; range 8-19). Differences between these 82 participants and excluded subjects are discussed in more details in the articles.

5.3 Measures

All the measures used for this dissertation are presented in the two articles and are also available in Appendix A. Table II (p. 24) summarizes the variables under study for each article, and the instrument used to measure them.

5.4 Procedure

Participants were recruited in the Toronto Metro Area through community organizations and Hospital Centers for a larger multidisciplinary research project on the psychosocial, behavioural and treatment factors associated with adherence to HAART in HIV-infection. The project included two distinct but linked studies: INFORMM-HAART Study used a natural history design in order to identify the main predictors of HAART adherence over a period of time exceeding 12 months. The MAX-HAART Study

compared the tolerability and feasibility of two distinct adherence-enhancing interventions (solution-focused intervention and cognitive intervention) with a subgroup of HIV-infected individuals who had been categorized as having adherence difficulties in the INFORMM-HAART study. All participants provided written informed consent to participate in this research as approved by the St. Michael's Hospital Research Ethics Board. Individuals who gave informed consent and decided to participate in this research were scheduled for 14 regular 30 to 45 minutes visits over a period of one year to complete a variety of behavioural, neuropsychological and psychosocial questionnaires and inventories. Participants received remuneration for their participation in this study at the rate of 10$ to 20$ per hour depending on the type and scope of instruments administered.

Table I. 1993 CDC Revised Classification System for HIV infection and AIDS surveillance (adapted from Castro et al., 1992)

	Clinical categories		
	Category (A) Asymptomatic, acute (primary) HIV or PGL*	Category (B) Symptomatic, not A or C conditions	Category (C) AIDS-indicator conditions
(1) ≥500/μL	A1	B1	C1
(2) 200-499/μL	A2	B2	C2
(3) <200μL	A3	B3	C3

* PGL = persistent generalized lymphadenopathy

** Asymptomatic stage: A1 – A2

   Symptomatic stage: B1 – B2

   AIDS diagnosis: A3 – B3 – C1 – C2 – C3

Table II. Variables of interest and measures used in the two articles of this dissertation.

Variable	Measure	Article(s) where this variable appeared
Demographic information	DEMO	1 and 2
Adherence	Individualized Medical Monitor (IMM)	1 and 2
Depressive symptoms	Beck Depression Inventory (BDI-II) – total score and cognitive subscale	1
Medical symptoms	Symptoms questionnaire 2: SYM2 (21-item scale)	1
Beliefs about medication	HEXP1 (medication effect on health) HEXP2 (positive or negative impact of medication on functioning)	1
Reasons for missing medication	Reasons questionnaire (REASONS)	2
Facilitators of adherence	Adherence Facilitators Questionnaire (ADHQ)	2
HIV-disease medical information	NCOND HCOND	1 and 2
Alcohol use problems	Alcohol Use Disorders Identification (AUDIT- called ALCO)	1 and 2
Drug use problems	Drug Abuse Screening Test (DAST-20 called DRUGS)	1 and 2

Chapter 1: Article 1

The impact of substance use and medication beliefs on adherence to HAART

The impact of substance use and medication beliefs on

adherence to HAART

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Abstract

This is a prospective longitudinal exploratory study examining risk factors associated with subsequent suboptimal adherence to HAART over a 6-month period in a group of 82 HIV-infected individuals. Risk factors examined included: demographic characteristics, HIV-related medical characteristics, psychosocial functioning, and beliefs about medication efficacy. This study also examined the correlates of beliefs about HAART medication. Logistic regression analyses revealed that the presence of an alcohol use problem, a drug use problem, and less positive beliefs about medication efficacy increased the risk of suboptimal adherence. An exploration of beliefs about medication revealed an association with HIV disease staging and with number of medical symptoms due to illness or side effects. Theoretical and clinical implications of these findings are discussed.

Key Words: Medication adherence – Antiretroviral therapy – HIV-infection – Beliefs – Substance use problems

Introduction

The advent of Highly Active Antiretroviral Therapy (HAART: usually defined as a Protease Inhibitor (PI) or a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) combined with at least two other antiretroviral drugs) has greatly improved the life expectancy of HIV-infected individuals. These medication regimens have been associated with reduced viral load, improved immunity, decreased risk of getting opportunistic infection, delayed HIV progression, decreased hospitalizations frequency, and lower death rates due to HIV (Altice & Friedland, 1998; Carpenter et al., 2000; Chun & Fauci, 1999; Deeks et al., 1997; Karon et al., 2001; Paul et al., 1999). However, HAART combinations generally require an adherence threshold of up to 95% of medication doses taken as prescribed for optimal virologic outcomes and to avoid the development of drug resistance (Paterson et al., 2000). Consistency of adherence is also another critical component of therapeutic success because patients who miss taking their medication on only a few occasions, even those who are generally adherent, are more likely to develop resistance to medication than patients who are always consistent in their adherence (Bangsberg et al., 2000; Mannheimer et al., 2002; Perno et al., 2002; Walsh, Pozniak et al., 2002). The challenge is that reported rates of adherence in HIV-infected individuals are often suboptimal. In fact, at least a quarter of patients report that they skipped medication doses over the last few days (Ammassari et al., 2001; Catz et al., 2000; Chesney, Ickovics et al., 2000; Gifford et al., 2000; Nieuwkerk et al., 2001; Schönnesson et al., 2004; Sethi et al., 2003).

Over the past decade, several factors that are associated with suboptimal adherence to medication in HIV and AIDS have been identified. These factors, which are more or less consistently linked to suboptimal adherence, have been grouped into four different categories (Boucher & Veilleux, 2002; Chesney, 2003; Stone, 2001): (1) patient-related factors; (2) medication-related factors; (3) doctor-patient relationship and other social support; and (4) general system of care. However, despite a considerable amount of research to date, it is still difficult to accurately identify which group of individuals is at the most risk of suboptimal adherence given the variability in results. Because suboptimal adherence has critical implications for the treatment of HIV-infected individuals, as well as for public health, it is important to continue to identify the essential factors associated with suboptimal adherence in order to then develop and test interventions that target risk factors and behaviours. The main objectives of the present study are: (1) to investigate individual risk factors that are associated with subsequent suboptimal adherence over a 6-month period in a sample of HIV-infected individuals; and (2) to explore the relationship between beliefs about medication efficacy and demographic, medical, and psychosocial characteristics. We predict the risk of suboptimal adherence to be associated with: a higher number of medical symptoms due to illness or side effects of medication; a higher number of depressive symptoms; less positive beliefs about medication efficacy; and both alcohol and drug use problems. Like most previous studies, we anticipate that demographic variables and HIV disease stage markers will not increase the risk of suboptimal adherence. Due to the limited information available about the impact of both positive and negative beliefs about medication efficacy on adherence behaviours, we do not have specific

hypotheses about their association with other characteristics. As such, our objective is to gain a better understanding of these beliefs by exploring their associations with demographic characteristics, HIV-related medical characteristics, and psychosocial functioning.

For the present study, we focused on the following risk factors for suboptimal adherence: (1) demographic characteristics such as age and education; (2) HIV-related medical characteristics such as disease stage (CDC-93 stage of illness: asymptomatic, symptomatic, or AIDS), and number of medical symptoms due to illness or side effects of medication ; (3) psychosocial characteristics such as alcohol and drug use problems, and depressive symptoms; and (4) patients' beliefs about medication efficacy.

In terms of previous studies, demographic characteristics have usually been reported as poor predictors of suboptimal adherence to medication (Rabkin & Chesney, 1999), although there are a few studies that have linked suboptimal adherence to different age groups (Becker et al., 2002; Gordillo et al., 1999; Molassiotis et al., 2002; Stone et al., 2001), and to lower levels of educational achievement or lower socio-economic status (Catz et al., 2001; Kleeberger et al., 2001).

Among HIV-related medical characteristics, HIV disease staging (asymptomatic, symptomatic, AIDS) has been associated to adherence in only a few studies, with more severely ill patients being more adherent, and perceiving a stronger relationship between suboptimal adherence to medication and AIDS-related complications (Gao et al., 2000; Molassiotis et al., 2002). In addition, likely due to the fact that HIV-infected individuals are

often asymptomatic when starting their medication, there are consistent findings linking

a high frequency and/or intensity of medical symptoms or side effects while on medication

with suboptimal adherence to medication (Ammassari et al., 2001; Heath et al., 2002;

Holzemer et al., 1999; Wagner, 2002).

Among psychosocial variables, the presence of depressive symptoms (Ammassari et

al., 2004; Catz et al., 2000; Gordillo et al., 1999; Starace et al., 2002), active illicit drug use

(Bouhnik et al., 2002; Lucas et al., 2001; Lucas et al., 2002; Moatti et al., 2000), and

alcohol use problems (Aloisi et al., 2002; Chesney, Ickovics et al., 2000; Lucas et al., 2002;

Moatti et al., 2000; Mohammed et al., 2004), have often been associated with an increased

risk of suboptimal adherence.

Although beliefs about medication were previously studied with psychiatric patients

and patients presenting chronic illnesses (Horne & Weinman, 1999; Ruscher, de Wit, &

Mazmanian, 1997), interest in patients' beliefs about medication efficacy has only recently

been starting to emerge in the HIV literature. Studies (Aversa & Kimberlin, 1996; Johnson,

Catz et al., 2003) have also shown that patients who have less positive expectancies about

the outcome of the medication treatment were more likely to have a suboptimal level of

adherence to medication. This was also confirmed by a recent study (Horne et al., 2004)

which found that adherence was lowest among people who had more concerns about the

adverse effects of medication, especially when these concerns out weighted the perceived

necessity of taking the medication. Furthermore, several qualitative studies have found

similar results. Belief that the treatment is beneficial to health and survival was often

mentioned as a facilitating factor for taking medication, and conversely, doubts about the efficacy of the medication was often associated with more difficulty adhering to medication regimen (Murphy et al., 2003; Remien et al., 2003; Roberts, 2000; Roberts & Mann, 2000; Siegel et al., 1999).

Little is known about factors that influence beliefs about medication efficacy. To our knowledge, only one study (Reynolds et al., 2004) has explored factors associated with beliefs about medication. This study found that less positive beliefs about medication efficacy was associated with personal and situational factors such as depression, stress and lower education level.

Method

Participants

One hundred and nine adults with HIV-infection on HAART treatment were approached for this study. Twenty-seven participants of this sample (24.8%) could not be included in the final analyses: 14 (12.8%) dropped out and 13 (11.9%) were excluded for either their inability to read and write English, inability to complete the questionnaires in a reliable fashion, or because of alcohol or drug intoxication at the time of the baseline interview. Comparisons between the excluded participants (N=27) and the final sample (N=82), using chi-squares and t-tests analyses, showed that groups were comparable on all demographic characteristics, HIV disease markers, and indicators of health status, except in the case of monthly income and type of risk factor for HIV. Specifically, participants

excluded from the study generally had a lower income (t (99.9) = 3.42, p = .001) and tended to report intravenous drug use as a risk factor for HIV more often than individuals in the study sample (χ^2(1, N=95) = 5.92, p = .025).

The final sample was composed of 82 individuals of whom 71 were men (86.6%) and 11 women (13.4%) with a mean age of 41 years (SD = 7.2; range 21-64) and education level of 13.3 years (SD = 2.3; range 8-19). See Table III (p. 67) for a description of demographic and medical characteristics of participants.

Procedures

Participants were recruited, starting in the Spring of 2000, in the Toronto Metro Area through community organizations and Hospital Centers for a larger multidisciplinary research project on the psychosocial, behavioural and treatment factors associated with adherence to HAART in HIV-infection. The project included two distinct but linked studies: INFORMM-HAART Study (Identification of Necessary Factors for Medication Management of HAART) and MAX-HAART Study (Maximizing HAART Adherence Through Behavioural Interventions). The INFORMM-HAART Study used a natural history design in order to identify the main predictors of HAART adherence over a 12-month period of time. The MAX-HAART Study compared the tolerability and feasibility of two distinct adherence-enhancing interventions (solution-focused intervention and cognitive intervention) with a subgroup of HIV-infected individuals who had been categorized as having adherence difficulties during their participation in the INFORMM-HAART study. All participants provided written informed consent to participate in this research as

approved by the St. Michael's Hospital Research Ethics Board. Individuals who gave informed consent and decided to participate in this research were scheduled for 14 regular 30 to 45 minutes visits over a period of one year to complete a variety of behavioural, neuropsychological and psychosocial questionnaires and inventories. Participants received remuneration for their participation in this study at the rate of $ 10-20 per hour depending on the type and scope of instruments administered.

Design

The current study is a prospective longitudinal exploratory study looking at potential risk factors, measured within a 60-day period from baseline, that may predict suboptimal adherence measured over a subsequent 180-day period (6 months). We used a cross-sectional design approach to explore the association between beliefs about medication efficacy and participants' characteristics.

To answer our research question, it was necessary to render individuals comparable through time by organizing the adherence data into 6 fixed intervals of 30 days starting at study entry for a total period of 180 days. In order to insure that we had a reliable measure of adherence behaviour, without detrimentally minimizing sample size, we required that at least 3 measures of adherence out of 6 be available for a subject to be included in the analyses. For each 30-day interval, both the average and the "worst" self-reported adherence percentage were calculated. Individuals were categorized by adherence status (adherence vs. suboptimal adherence) using a 95% threshold of adherence (this threshold was used because it is well accepted in the literature as the level to achieve the best

virologic response). Therefore, participants who reported that they had missed more than 5% of their prescribed doses at least one time over a period of 6-month were considered to have a suboptimal adherence to HAART. Most predictors were measured within a 60-day period of baseline. Both the average and the "worst" scores were retained for each predictor. To measure alcohol and drug use problems, all scores available for a period of one year were retained because these questionnaires probed retrospectively about alcohol and drug use problems within the past year. If more than one measure of alcohol use problem or drug use problem was available, only the "worst" score was retained for the analyses.

Measures

The following questionnaires were administered to each participant:

A general demographic questionnaire including questions such as gender, age, education level, income, etc. was administered at baseline.

A questionnaire about general and HIV-specific medical status, including questions on prior opportunistic infections, was administered at baseline. Participants' most recent viral load and CD4 counts were obtained from their medical chart with participant consent. CDC disease stage (1993 classification system (Castro et al., 1992); asymptomatic, symptomatic, AIDS) was derived based on the medical information provided (HIV-related medical conditions and CD4 Lymphocyte counts).

Alcohol use problems were measured with the Alcohol Use Disorders Identification Test (Saunders et al., 1993). The AUDIT is one of the most widely used scales to screen for hazardous or harmful alcohol consumption. This 10-item self-reported questionnaire probed about domains of alcohol consumption, drinking behaviour, and alcohol related problems within the last year. The items are weighted on a 4-point scale and the total score ranges from 0 to 40, with a cut-off point of 8 and higher representing a strong likelihood of hazardous or harmful alcohol consumption. Earlier studies (Maltby, Lewis, & Hill, 2000) have found good internal consistency, with coefficient alphas ranging from .75 to .94. The sensitivity of the scale to predict alcohol abuse and / or dependence based on the DSM-IV criteria has been found to range from 38% to 100%; lower prediction levels usually applying to very heterogeneous primary care samples.

Drug use problems were measured with the Drug Abuse Screening Test-20 (Skinner, 1982). The DAST-20, a 20-item self-reported questionnaire, has for purpose to identify individuals who are abusing psychoactive drugs and quantify the degree of problems related to drug use. It focuses on aspects of drug dependence such as difficulty to stop using drugs, withdrawal symptoms and consequences of drug use on different life domains. Participants are asked to indicate if they agree or disagree with each statement by checking the *"yes"* or *"no"* answer. The summary score, ranging from 0 to 20, is calculated by summing all items endorsed that are in the direction of increased drug problems. A score of 6 or above is indicative of problems related to drug use. More specifically, scores from 1 to 5 indicate low level of problems, scores from 6 to 10 indicate moderate level of problems, scores greater than 11 indicate substantial to severe level of

problems due to drug abuse. In previous studies with groups of drug abusers (Conoley, Impara, Murphy, & Buros, 1996), internal consistency ranged from .74 to .86. The DAST-20 is derived from an original 28-item version (DAST) and most of the other validation data available was produced by this earlier version. However, the two versions were found to be almost perfectly correlated (r=.99). In earlier studies (Gavin, Ross, & Skinner, 1989), the DAST had been found to have good convergent and discriminant validity. Furthermore, correlations of .74 and .75 were found between DAST scores and DSM-II diagnosis of lifetime and current drug abuse / dependence.

Symptoms of depression were measured with the Beck Depression Inventory-II (Beck, Steer, & Brown). This 21-item self-reported scale measures the presence and the severity of depression in adults. It was developed based on diagnosis criteria of depressive disorders of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders Fourth Edition (DSM-IV; 1994). Individuals are asked to indicate which statement best describes the way they have been feeling over the past two weeks. Each item is rated on a 4-point scale with total scores ranging from 0 to 63. Scores from 0 to 13 indicate minimal depression, 14 to 19 mild depression, 20 to 28 moderate depression, and 29 to 63 severe depression. This scale has been found to have good psychometric properties (Beck et al., 1996), with a coefficient alpha for an outpatient population of 0.92, and a test-retest reliability of 0.93 over a one-week interval. It was also found to have good convergent and discriminant validity. The structure of the BDI-II is based on two main factors: a Somatic-Affective dimension and a Cognitive dimension. Somatic items in the BDI have been reported to confound the assessment of depression in symptomatic HIV-

infected individual or individuals living with AIDS because these items may represent symptoms of HIV. In a previous study (Savard, Laberge, Gauthier, & Bergeron, 1999), symptomatic patients and AIDS patients had higher score than asymptomatic patients on somatic items of the subscale, but not on cognitive or affective items. Because of these results, both the total score and the cognitive sub-score (regrouping pessimism, past failure, guilty feelings, punishment feelings, self-dislike, self-criticalness, suicidal thoughts or wishes, and worthlessness) were tested in the analyses. Scores on the cognitive dimension range from 0 to 24.

Medical symptoms due to illness or side effects of medication were assessed with a Symptom Questionnaire, which covers a list of 21 symptoms of HIV or side effects of medication commonly experienced by HIV-infected individuals. This symptom questionnaire was developed and modified by clinical experience and questionnaires used in different studies (Ammassari et al., 2001; Vogl et al., 1999; Whalen, Antani, Carey, & Landefeld, 1994). This questionnaire has adequate face validity and represents common symptoms reported by HIV-infected individuals. In this symptom questionnaire, participants are asked to put a check mark to indicate if they experienced each of the 21 symptoms in the past two weeks.

Beliefs about HIV medication efficacy were measured with two questionnaires:

The HIV Medication Expectation questionnaire-1 (HEXP-1) consisted of items covering beliefs about medication that were similar to those included in a recent study (Paterson et al., 2000). Participants were asked to rate on a 3-point Likert scale (*0= not at*

all confident, 1= somewhat confident and, 2= very confident) how confident they were that their anti-HIV agents would: (1) prolong life, (2) prevent symptoms, (3) boost immunity, (4) complement other agents, (5) improve functioning and (6) increase well-being. A total score on this scale was calculated with scores ranging from 0 to 12. Higher scores indicated more positive beliefs about the medication efficacy. The Cronbach's alpha with the current patient sample was .89, which indicates good internal consistency.

The HIV Medication Expectation questionnaire-2 (HEXP-2) was adapted from the Medication Attribution Scale (MAS) (Aversa, Kimberlin, & Segal, 1998) to include both the negative and positive impact of HAART (the MAS focuses only on the negative aspects). The positive impact of medication was assessed with the following question: "Specifically regarding HAART medications, how much benefit are you receiving or expect to receive from these medications". Participants were asked to rate on a 4-point Likert scale (*0=none, 1=a little, 2=some, 3=a lot*) how much this applied to the following areas of functioning: (1) energy level and/or appetite; (2) general well-being; (3) restored libido/sex drive; (4) capacity to perform daily activities; (5) likelihood of returning to part-time or full-time work. The total score on the positive impact of medication ranged from 0 to 15, with a higher score representing more perceived positive impact of medication. Negative impact of medication was assessed by asking participants how much (*0=no effect, 1=mildly, 2=moderately, 3=strongly*) the medication has negatively affected them in different areas of functioning. Spheres of functioning assessed were: (1) time spent on work or other activities; (2) ability to accomplish daily activities; (3) work or activities you would like to do; (4) ability to work at a job or go to school; (5) ability to work around your

home; (6) ability to care for yourself; (7) social activities. The total score at this negative impact scale ranged from 0 to 21, with a higher score representing more perceived negative impact of medication. When measured with the current sample, both of these subscales had adequate internal consistency with Cronbach's alphas of .76 for the positive impact scale, and .90 for the negative impact scale.

Adherence to medication was measured with an Individualized Medical Monitor (IMM), which has been adapted from the AACTG Adherence Follow up Questionnaire (Chesney, Ickovics et al., 2000). The IMM is an individualized questionnaire that first gives a brief description of the participant's prescribed medication and asks him if it represents accurately his current regimen (e.g.: "The following should be an accurate description of the medicines currently prescribed by your doctor: 150 mg 3TC:1 white diamond pill twice per day; 40 mg d4T: 1 brown pill twice per day; 400 mg Crixivan: 2 white and green pills twice per day; 100 mg Ritonavir: 2 beige pills twice per day"). If it represents accurately the participant's regimen, he is asked to circle how many times (*none, once, twice, 3X, 4X, ?*) he took each type of medication in the past 7 days, starting from yesterday. A missed dose was defined as omitting an entire scheduled dose of one medication. The number of missed doses for each day is calculated by subtracting the number of doses actually taken from the number of doses each participant was expected to take. These missed doses are then added for the 7 day-period covered by the questionnaire and divided by the number of doses the participant was expected to take during that same period of time. This result is finally multiplied by 100 to provide a percentage of suboptimal adherence to the prescribed regimen.

Overview of analyses

Descriptive analyses were used to study the distribution of the variables and to evaluate the prevalence of missing responses.

Before running the analyses, alcohol use problems were stratified into: no alcohol problem vs. alcohol problem. Because of low prevalence of severe drug use problems, results of the DAST-20 were stratified into the following categories: no drug problem, low level of drug problem, moderate to severe level of drug problem (scores from 6 to 20). Before using the adherence data in the analyses, effect of inclusion into a treatment program to improve adherence for a subgroup of subject was tested with a non parametric t-test comparing average adherence in the month preceding the intervention and average adherence in the following month.

Univariate analyses were performed with chi-squares and t-tests to study the relationship between adherence status (adherence vs. suboptimal adherence) and each of the potential risk factor. A logistic regression was performed afterward to identify potential risk factors of suboptimal adherence among the following participants' variables: (1) demographic characteristics: age, and education; (2) HIV-related medical characteristics: CDC-93 disease stage (asymptomatic, symptomatic, AIDS), and number of medical symptoms due to illness or side effects of medication; (3) psychosocial characteristics: alcohol problem/no alcohol problem, no drug problem/low level of drug problem/moderate to severe level of drug problem, total score at the depression scale, cognitive score at the depression scale; and (4) patients' beliefs about medication efficacy measured by two

different scales: (a) positive beliefs about medication efficacy (HEXP-1), (b) positive impact of medication, and negative impact of medication (HEXP-2). For most of the risk factors, both the average and the "worst" score per interval were retained in the analyses. The only exceptions were alcohol use problem, and drug use problem which were stratified based on the "worst" score at the questionnaires. All potential risk factors were entered into two logistic regression models that used different outcome measures: the average self-reported adherence, and the "worst" self-reported adherence. However, because these two models generated similar results, only the logistic regression model using the "worst" self-reported adherence measure as the outcome variable will be reported here. Furthermore, the "worst" adherence measure represents the closest measure to clinical reality since self-reports generally tend to overestimate adherence rates when compared to more objective measures such as electronic devices (Liu et al., 2001).

A forward stepwise logistic regression was used to insure validity of the results. Therefore, variable entry was based on the likelihood ratio test and the probability to enter value was set at 0.05 with a removal value of 0.10. After this sequential selection was completed, the logistic regression model was re-adjusted on the significant variables only in order to have the maximum number of subjects with no missing observation. Categories of reference were fixed to represent an "ideal" adherent patient with the following characteristics: no alcohol problem, no drug problem, no depressive symptoms, no medical symptoms, and strong beliefs about medication efficacy.

Finally, we explored the relationship between beliefs about medication efficacy and the following characteristics: (1) demographic characteristics such as age, gender, and education; (2) HIV-related medical characteristics such as CDC-93 disease stage (asymptomatic, symptomatic, AIDS), number of medical symptoms due to illness or side effects of medication, viral load, and hospitalization in the past 6 months; (3) depressive symptoms. These relationships were explored with Pearson's correlations, t-tests, and one way ANOVA with a Tukey HSD contrast test. Note that the N varies from 68 to 82 in the analyses because of the presence of missing values.

Results

Descriptive results

Eighteen participants (23% of 78) had an alcohol use problem, while 46 (58% of 79) had low level of drug use problems, and 16 (20% of 79) had moderate to severe level of drug use problems. Descriptive information for other predictors is shown in Table IV (p. 69).

Impact of adherence intervention

Among 82 study participants, 10 were included in an intervention program (MAX-HAART) during the one-year duration of the larger study because they had reported adherence difficulties. No significant impact of treatment was noted when comparing adherence results before and after the intervention program for each of these individuals (p= .06).

Results of univariate analyses

Of all the different variables tested with univariate analyses, the only variables significantly associated to suboptimal adherence were: alcohol use problems ($\chi^2(1$, N= 68) = 7.372, p= .009), drug use problems ($\chi^2(2$, N= 69) = 6.959, p= .031), the worst score with respect to beliefs about medication measured with the HEXP1 questionnaire (t (70) = -2.42, p= .02) and the average score with respect to beliefs about medication measured with the HEXP1 questionaire (t (70) = -2.35, p= .02). However, suboptimal adherence was not significantly associated with beliefs about medication measured with the HEXP2 positive impact scale (t (70) = -.27, p= .79), and the HEXP2 negative impact scale (t (70) = 1.66, p= .10). Of the 70 individuals included in the univariate analyses, 29 had suboptimal adherence to HAART.

Results of logistic regression

Because of missing data, 68 HIV-infected individuals were available to be included in the logistic regression. Among this group of individuals, 27 (39.7%) had suboptimal adherence to HAART. All potential risk factors were tested in a logistic regression model predicting suboptimal adherence to HAART. The same variables that were associated with suboptimal adherence in the univariate analyses were also risk factors for suboptimal adherence in the logistic regression model. Variables retained in the final regression model (χ^2 = 21.33, df = 4, p = 0.000) were: alcohol use problems (χ^2= 7.3, df= 1, p=0.007), drug use problems (χ^2= 6.4, df= 2, p=0.04), and beliefs about medication efficacy measured with the HEXP1 questionnaire (χ^2= 7.6, df= 1, p=0.006). Only the "worst" score of beliefs about

medication efficacy was retained in this model, but the "worst" score and the average score of beliefs about medication efficacy at the HEXP1 were highly correlated ($r=.999$, $N=82$, $p=.000$). With these risk factors, the efficiency (overall proportion of individuals adequately classified across classes (adherence vs. suboptimal adherence)) in our sample was 78%.

Results of the logistic regression (see Table V and Table VI, pp. 70-71) indicate that participants who have an alcohol use problem are 5 times more likely to have suboptimal adherence to HAART than participants without an alcohol problem. Also, for every one point increase in the degree of confidence about medication efficacy at HEXP1 scale, the risk of having suboptimal adherence to HAART decreases by 0.7 times. Finally, having a drug use problem is globally significant in the model, which means that it increases the risk of suboptimal adherence. However, it is not possible to know how much it increases the risk of suboptimal adherence because no differential effects were detected between the two levels of drug problems (low level of problem, and moderate to severe level of problem) with the Wald statistical test.

Because we expected that number of medical symptoms due to illness or side effects of medication, as well as the cognitive score at the depression inventory, would be associated with suboptimal adherence, we subsequently forced each of them in a logistic regression model to test their level of significance. The model was not significantly improved when forcing in the number of medical symptoms ($\chi^2=0.848$, $df=1$, $p=0.357$), and cognitive symptoms of depression ($\chi^2=0.909$, $df=1$, $p=0.340$).

Factors associated with beliefs about medication efficacy

Beliefs about medication efficacy measured with the HEXP1 were positively correlated with the positive impact scale of the HEXP2 (r = .511, N= 82, p=.000), and negatively correlated with the negative impact scale of the HEXP2 (r = -.294, N= 82, p=.007).

Beliefs about medication efficacy were not associated with demographic variables such as age (r = .028, N= 82, p=.80), gender (t (80) = .17, p=.87), and education level (r = .007, N= 82, p=.95). However, beliefs about medication efficacy measured with the HEXP1 were negatively correlated with the number of medical symptoms due to illness or side effects of medication reported in the past two weeks (r = -.26, N= 79, p= .02), and also negatively correlated the total score at the depression inventory scale (r = -.27, N= 71, p=.02). However, there was no correlation between HEXP1 score and the cognitive subscale at the depression inventory (r = -.13, N= 71, p=.27). Beliefs about medication efficacy were not significantly correlated with the following medical indicators of health status: viral load (r = -.17, N= 80, p= .13), and having been hospitalized in past 6 months (t=1.25(80), p= .22). However, a one-way ANOVA revealed a globally significant difference in means on beliefs about medication efficacy at the HEXP1 questionnaire as a function of disease stage (F(2, 77) = 3.31, p= .04). When using a Tukey contrast test, it showed that individuals with AIDS (M = 9.13, SD = 2.97) had significantly higher scores on the beliefs about medication questionnaire than individuals who were symptomatic (M = 7.35, SD = 2.82; HSD = 1.77, p = .04). No significant difference in beliefs about

medication efficacy was detected between individuals who were at the asymptomatic stage (M = 8.93, SD = 2.31) and the two other disease stages.

Discussion

Results of this study are generally consistent with previous research published on risk factors for suboptimal adherence to HAART. It replicated known results about the negative impact of alcohol and drug use problems, and confirmed the impact of beliefs about medication efficacy on adherence to medication.

Rates of suboptimal adherence reported in this study were comparable to rates reported in other studies (Carrieri et al., 2001; Nieuwkerk et al., 2001) but only a few studies have measured adherence over time. The logistic regression model highlighted important risk factors for suboptimal adherence. Having less positive beliefs about medication efficacy, as measured with the HEXP1 questionnaire, was identified as a risk factor for suboptimal adherence to HAART. Therefore, people who have more negative expectations about HIV medication effect on their health might need to be more closely monitored. Alcohol and drug use problems were also identified as risk factors for suboptimal adherence to HAART. In addition to measuring hazardous or harmful alcohol consumption and drug problem, the questionnaires used for this study assessed the impact of alcohol use and drug use on different life domains within the past year. More specifically, these questionnaires asked about serious consequences of alcohol or drug use on daily living and interpersonal relationships, which reflects the social instability that is an integral part of a substance abuse diagnosis based on the DSM-IV criteria. Results of our

study indicated that alcohol consumption and drug use that negatively affected different life domains within the past year, did increase the risk of suboptimal adherence. However, in our study, alcohol use problem was more clearly related to suboptimal adherence to HAART than drug use problem. Drug problem was globally significant in the model, but its impact on suboptimal adherence was not as clear because it entered in the model at the limit of significance. Furthermore, probably because of the small sample size we were not able to distinguish between differential effects of drug use problems on suboptimal adherence. This could also be explained by the fact that we grouped moderate to severe problems in the same category, therefore combining different levels of risk. However, it was not possible to test moderate, substantial, and severe levels of drug problem separately because of their low prevalence. Furthermore, this result might also be explained by the fact that we did not distinguish between types of recreational drugs used by participants, since different drugs might have different impact on adherence.

Alcohol use problems and beliefs about HIV medication efficacy were clear risk factors for suboptimal adherence to HAART that would need to be monitored carefully in clinical practice. Drug use problem would also need to be taken into consideration as a potential risk factor for suboptimal adherence, but more studies would be needed because its association with suboptimal adherence was not as significant. Because of the large confidence intervals in the odds ratio for the three risk factors of suboptimal adherence reported here, it is not possible to know accurately how much each of these factors increased the risk of suboptimal adherence to HAART. Therefore, because of the current

sample size, it was not possible to have an exact estimation of elevation in risk of suboptimal adherence and this would need to be studied further.

As expected, demographic variables, and disease stage were not associated with suboptimal adherence. However, contrary to our initial hypotheses, a higher number of medical symptoms due to illness or side effects of medication was not significantly associated with suboptimal adherence. This might partly be explained by the fact that the population studied here reported a relatively low number of medical symptoms. Furthermore, we did not take into consideration the types of medical symptoms reported by participants. We would in fact expect that gastrointestinal symptoms such nausea/vomiting, which are usually more bothersome and are among the principal causes of medication discontinuation (O'Brien et al., 2003), would have a stronger impact on adherence. Also, the symptoms covered by the questionnaire might not have been representative of the most bothersome symptoms (for example, diarrhoea was not included in the list). Also in contradiction with our initial hypotheses, a higher number of depressive symptoms was not significantly associated with suboptimal adherence. This lack of association might have been caused by the low prevalence of depression in the sample, and also partly by the type of measure used. Because our measure of depression included medical symptoms, we also tested the cognitive sub-score that might not have been sensitive enough to detect depressive affect in our medical sample.

It is interesting to note that only beliefs about medication efficacy measured with the HEXP1 questionnaire were associated with suboptimal adherence, while we did not

detect any significant association between results at the two subscales of the HEXP2 questionnaire (positive impact of medication / negative impact of medication) and suboptimal adherence, both in the univariate analyses and in the regression model. This seemed to indicate that these questionnaires measured two different theoretical concepts: the HEXP1 was centered on global beliefs about medication effect on health, while the HEXP2 referred to quality of life issues and expectations about the positive or the negative impact of medication use on daily functioning. The strong association between the HEXP1 and the positive impact scale of the HEXP2 was expected because of the strong link between global beliefs about medication effect on health and perceived benefits of medication on level of functioning. In fact, global functioning might be one aspect that influences the type of beliefs a person holds about his or her medication. However, it was surprising to find a smaller association between the HEXP1 and the negative impact scale of the HEXP2. This might indicate that people's global beliefs about medication efficacy are more strongly affected by the positive impact rather than the negative impact of medication on daily functioning.

An exploration of factors associated with beliefs about medication efficacy measured by the HEXP1 questionnaire showed that a higher number of medical symptoms and a higher total score at the depression inventory were associated with less positive beliefs about medication efficacy. However, because the cognitive symptoms of depression were not associated with beliefs about medication efficacy, it might be that the relationship between the depression inventory total score and beliefs about medication efficacy (HEXP1) was artificially created by the scale's somatic items reflecting medical symptoms

of HIV or side effects of medication. These somatic items are: loss of energy, changes in appetite, changes in sleeping pattern, tiredness or fatigue. This finding that beliefs about medication seemed to be less positive as the number of medical symptoms increased, raises an interesting question: could beliefs about medication efficacy be partly based on the number of medical symptoms people are experiencing?

It was surprising that beliefs about medication efficacy were not associated with viral load or hospitalization in the past 6 months, both of which constitute important markers of HIV disease progression. This might indicate that people's beliefs about the effect of medication on their health are less related to the clinical reality, and more a function of their own perception. However, the lack of association could also be explained by the fact that our measure of viral load was not necessarily taken at the same time as people filled the beliefs questionnaire since it was taken from their most recent medical exam. Therefore, their clinical status might have been somewhat different when they filled the belief questionnaire. We detected an association between beliefs about medication and disease stage: people with an AIDS diagnosis held more positive beliefs about their medication than people at the mildly symptomatic stage. This result seems to be partly in line with other published studies stating that more severely ill patients perceived a stronger relationship between suboptimal adherence to medication and AIDS-related complications (Gao et al., 2000; Molassiotis et al., 2002). However, this association seems to be contradicted by the fact that disease stage was not associated with adherence to HAART in our study. Since number of medical symptoms seemed to influence beliefs about medication, this distinction between AIDS and symptomatic stage is interesting because

this might mean that people interpret differently the symptoms that they have as they are diagnosed with AIDS. For those individuals with an AIDS diagnosis, symptoms might be perceived accurately as a progression of the disease, because they are more serious and can directly be associated with AIDS. In contrast, those at the mildly symptomatic stage, might misread less serious symptoms as side effects of medication. However, because the association was at the limit of significance, it would need to be tested again before making any firmer conclusions.

This study has several limitations that reduce the generalizability of the findings. First, because of a self-selection bias, participants included in our sample were not fully representative of the general population of HIV-infected individuals (i.e., this sample was primarily a sample of Causasian gay men). Participants excluded from the study sample were different from the final sample on two aspects: they tended to have a lower income and to report intravenous drug use as a risk factor for HIV more often than individuals in the study sample. It is also possible that adherence rate might have been biased by the use of a self-reported scale, which usually tends to overestimate adherence. It was originally planned to also measure adherence with Medication Event Monitoring Systems (MEMS) for a sub-group of participants to validate self-reports, but participants refused to use them because of convenience issues. However, self-reported adherence questionnaires have been found to be adequate adherence measures because of their correlation with other measures of adherence (Deeks, 2000; Duong et al., 2001; Hugen et al., 2002), and their ability to predict therapeutic outcome, as measured by HIV RNA level and CD4+ cell count (Mannheimer et al., 2002; Walsh, Mandalia et al., 2002). Because of the design of this

study, we could not control for several variables such as: changes in medication regimen over the 6-month period, time since tested HIV-positive, and type of HAART medication taken. Finally, the current sample size might have affected our ability to detect smaller associations.

Despite these limitations, this study has several clinical implications. First, it confirms the detrimental impact of alcohol use problems on adherence to medication. This highlights again the importance of screening for these problems in clinical practice to provide adequate help to patients with difficulty adhering to their medication regimens. It also reinforces the importance of beliefs about medication efficacy in HIV-infected individuals' decision to adhere to treatment or not. Therefore, it is essential to get a better understanding of how HIV-infected individuals perceive their medication to be able to intervene more effectively in clinical practice. Learning about factors associated with beliefs about medication will eventually guide us in our understanding of how these beliefs develop. It might provide the key to understand how to help HIV-infected individuals in modifying beliefs that might not be based on factual information.

In future studies, it would be interesting to explore more thoroughly beliefs about medication in association with other psychological variables. Finally, because adherence might be difficult to predict while using only participants' characteristics, it is essential to study more complex models based on sound theories. The impact of beliefs about medication on adherence, and the association between beliefs about medication and somatic symptoms need to be studied further. It would be interesting to test whether these

associations can be understood within a "self-regulatory model" (Leventhal, Diefenbach, & Leventhal, 1992). This model views adherence as a self-regulatory processs (equivalent of a coping mechanism) in which individuals adapt their medication taking behaviour as a function of the context in which they are. In this model, it is believed that people make adherence decision based on several factors, especially their own interpretation or beliefs about somatic symptoms.

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Table III. Demographic Characteristics of Participants (N=82)

Characteristic	N	%	Mean (SD)
Age (years)			41.0 (7.2)
Education (years)			13.3 (2.3)
Monthly income ($)			1382.90 (972.31)
Time since tested HIV-positive (months)			99.4 (50.6)
Gender			
Male	71	86.6	
Female	11	13.4	
Race			
Caucasian	66	80.5	
Black	8	9.8	
Other	6	7.3	
Relationship status			
Single	56	68.3	
Living with partner	26	31.7	
Work status			
Working	66	80.5	
Not working	16	19.5	
On long-term disability*			
Yes	65	79.3	
No	5	6.1	

Characteristic	N	%	Mean (SD)
Number of risk factors for HIV			
Only one	66	80.5	
More than one	14	17.1	
Type of risk factor(s) for HIV			
Same sex sexual contact	62	75.6	
Heterosexual sexual contact	16	19.5	
Intravenous drug use	11	13.4	
Blood Transfusion	2	2.4	
1993 CDC Classification (N=80)			
Asymptomatic	15	18.3	
Symptomatic	26	31.7	
AIDS	39	47.6	
Type of medication regimen			
NRTI + PI	40	48.8	
NRTI + NNRTI	24	29.3	
NRTI + NNRTI + PI	15	18.3	
3 NRTIs	1	1.2	
Viral load			
Undetectable	39	47.6	
Detectable: ≤ 35 000	33	40.2	
Detectable: > 35 000	8	9.8	

*Missing data n=12

Table IV. Descriptive information of predictors

Variables	Mean (SD)
Depression scores (N=71)	
Highest total score at BDI	15.76 (12.62)
Average total score at BDI	11.50 (9.50)
Highest cognitive score at BDI	4.93 (5.56)
Average cognitive score at BDI	3.14 (3.89)
Beliefs about medication (N=82)	
HEXP1:	
Lowest total score	8.50 (2.93)
Average total score	8.52 (2.93)
HEXP2:	
Positive scale:	
Lowest total score	8.11 (3.57)
Average total score	8.12 (3.57)
Negative scale:	
Highest total score	7.28 (5.91)
Average total score	7.27 (5.89)
Medical symptoms (SYM2) in the past 2 weeks (N=79)	
Highest number of symptoms	4.20 (4.37)
Average number of symptoms	4.18 (4.35)

Table V. Summary of Logistic Regression Analysis Predicting Suboptimal HAART Adherence (N=68)

Variable	B	SE	Odds ratio	Wald statistic	95% Confidence interval	
					Lower	Upper
Alcohol problem	1.615	0.737	5.028	4.801*	1.186	21.315
Drug problem:						
Minimal problem	-0.151	0.759	0.860	0.040	0.194	3.808
Moderate to severe problem	1.756	0.974	5.791	3.248	0.858	39.107
Positive beliefs about medication	-0.347	0.124	0.707	7.782**	0.554	0.902

*$p < .05$. **$p < .01$

Table VI. Classification Table for Predictors of Suboptimal HAART Adherence (N=68)

Observed Adherence Level	Predicted Adherence Level		
	Non adherent	Adherent	Correct percentage
Non adherent	17	10	63.0
Adherent	5	36	87.8
Overall Percentage			77.9

Model Coefficient: χ^2= 21.328, df= 4, p = 0.000

Chapter 2: Article 2

Barriers and facilitators of adherence to HAART reported by people living with HIV.

Barriers and facilitators of adherence to HAART reported by people living with HIV

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Abstract

This exploratory study examines barriers to adherence more specifically defined as the reasons reported by participants for suboptimal adherence to HAART at their "worst" adherence episode within a one-year period. It also explores facilitators of adherence defined in this study as strategies and motivators that help facilitate adherence to HAART reported by HIV-infected individuals. Types of facilitators reported are explored in relation to participants' demographic characteristics. Number and types of facilitators reported are tested in relation to adherence status measured over one year. Eighty-two participants were recruited for this study. Reasons most often reported for missing medication are interferences with daily routine. Main categories of facilitators reported are: 1) planning skills; 2) positive perception of medication; 3) social support; 4) commitment / internal motivation; 5) self-care. Some of these facilitators are associated with participants' characteristics, but not with adherence status. Clinical implications of these results are discussed.

Key Words: Medication adherence – antiretroviral therapy – HIV-infection – barriers – facilitators

Introduction

The advent of Highly Active Antiretroviral Therapy (HAART : usually defined as a Protease Inhibitor (PI) or a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) combined with at least two other antiretroviral drugs) has greatly improved the life expectancy, as well as the quality of life of HIV-infected individuals. HAART regimens have been associated with delayed HIV progression, decreased risk of getting opportunistic infections, decreased hospitalization frequency and lower death rates due to HIV (Altice & Friedland, 1998; Carpenter et al., 2000; Chun & Fauci, 1999; Deeks et al., 1997; Karon et al., 2001; Paul et al., 1999). However, HAART regimens are usually only effective against the HIV virus when taken as prescribed, and might therefore necessitate life long adherence to control viral replication.

Adherence to treatment is known to be problematic regardless of the type of disease or treatment, especially when medications need to be taken over a long-term basis (Blackwell, 1973; Myers & Midence, 1998). Adherence to HIV medication is further complicated by the fact that HAART regimens are often very complex and can have numerous negative side effects. Individuals on HAART regularly need to take a large quantity of medication on a tight and regimented schedule, with special requirements associated with each type of medication taken (e.g., dietary restrictions); while having to tolerate various side effects. These drug regimens also require a higher threshold of adherence in order to be effective and to avoid the development of resistance to medication. The current recognized threshold of adherence for optimal virologic outcome is 95% of

doses taken as prescribed, especially when protease inhibitors are part of the medication regimen (Paterson et al., 2000). Consistency of adherence over time is also critical because patients who are generally highly adherent but who missed their medication on a few occasions have been found to develop resistance to medication (Bangsberg et al., 2000; Perno et al., 2002; Walsh, Pozniak et al., 2002). Suboptimal level of medication exposures may permit viral replication in the presence of drug leading to the emergence of drug-resistant viruses (Clavel & Hance, 2004; Condra et al., 2002). Patients with suboptimal adherence may then be confronted with reduced treatment options, increased risk of therapeutic failure and/or increased risk of transmitting a resistant strain of the virus to someone else.

Reported rates of adherence in HIV-infected individuals vary widely in the literature but are often suboptimal (Gifford et al., 2000; Kleeberger et al., 2001; Nieuwkerk et al., 2001), especially when measured over time (Mannheimer et al., 2002; Roca, Gomez, & Arnedo, 2000). Taking into consideration that adherence to HAART has serious implications for the treatment of HIV-infected individuals, as well as for public health, there is a critical need for a better understanding of factors that may be associated to adherence behaviours.

In the last decade, several factors associated with adherence to medication were studied. These factors, which have more or less consistently been linked to adherence, have been grouped into four different categories (Boucher & Veilleux, 2002; Chesney, 2000, 2003; Lafeuillade, 2001): (1) patient-related factors, such as demographic and personality

characteristics, depression, and beliefs about treatment; (2) medication-related factors, such as complexity of treatment and frequency of dosing; (3) doctor-patient relationship and other social support; (4) general system of care. However, despite a considerable amount of research, it is still impossible to predict accurately which individuals are at most risk of suboptimal adherence and may necessitate intervention programs. The main objectives of this study are: (1) to describe and compare in a group of HIV-infected participants both the barriers of adherence, defined more specifically as the self-reported reasons for missed medication doses, and the facilitators of adherence, defined as the self-reported strategies and motivators that help facilitate adherence to HAART; (2) to explore the potential association between the types of category of facilitators reported and participants' demographic characteristics (age and education); (3) to explore the potential association between the number or types of identified categories of facilitators used by participants and their adherence status over a one-year period.

In terms of previous findings, several recent quantitative and qualitative studies have explored the types of reasons for missed medication doses reported by patients to gain a better understanding of adherence behaviours. There is consistency in the type of reasons most frequently mentioned in several recent quantitative studies that have used similar self-reported questionnaires to assess reasons for suboptimal adherence (Catz et al., 2001; Chesney, 2000; Chesney, Morin et al., 2000; DeMasi et al., 2001; Eldred et al., 1998; Ferguson et al., 2002; Gifford et al., 2000; Kleeberger et al., 2001; Mannheimer et al., 2002; Molassiotis et al., 2002; Reynolds et al., 2004). In all these studies, the most commonly cited reason for missing medication was forgetfulness. Other common reasons

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mentioned include: changes in daily routine, interference of social context (such as being too busy, being away from home, eating a meal at a wrong time, sleeping through a dose), and practical barriers such as complexity of drug regimen and number of medications to take. A greater number and/or intensity of reasons for missed medication doses has generally been associated with lower adherence levels (Ferguson et al., 2002; Walsh, Horne, Dalton, Burgess, & Gazzard, 2001).

Of the qualitative studies that have focused on the reasons for missed doses, there are generally similar reasons cited (Laws, Wilson, Bowser, & Kerr, 2000; Proctor, Tesfa, & Tompkins, 1999; Ryan & Wagner, 2003): forgetting or deciding not to take the medication because of interferences with daily routine, complexity of the regimen to follow, presence of medication side effects, and factors associated with the social/physical environment such as being in a public or unfamiliar environment which makes it more difficult to follow dietary requirements or to avoid that others see them taking their pills.

Most of the adherence studies, have focused primarily on obstacles or barriers to adherence, while, to our knowledge, only two published studies have explored facilitators of adherence. Roberts (2000) used in-depth interview to collect data from 28 HIV-infected patients, including both men and women who had been taking a PI-based antiretroviral cocktail regimen for at least three months prior to the interview. Participants in this study reported six main facilitators of adherence: (1) use of mechanical devices such as alarm clock and/or pillbox; (2) "making a commitment" to take the medication and having the necessary self-discipline to take it; (3) "routinizing", which consisted of integrating

medication taking into their daily routine; (4) confidence about medication effects on their health and the belief in its necessity; (5) social support, such as friends and family members reminding patients to take their pills or giving them more concrete support; and (6) general support from health care provider, especially information and advices provided by their doctor.

A second qualitative study (Remien et al., 2003) used in-depth interviews to collect information about facilitators of adherence in a sample of 152 HIV-infected men, women and injection drug users and found similar results. One of the strongest facilitators reported was the belief that the treatment was beneficial and necessary for health and survival, and that not taking it might lead to illness. Respondents mentioned using several sources of information, such as blood test results, subjective experience of energy levels and physical symptoms, to make their personal judgment about the efficacy of the medication. Among other facilitators were: (1) faith in health care professionals; (2) motivation to take care of themselves as a reason for taking the medication; (3) use of alternative or complementary therapies to treat HIV, improve overall health and well-being, or to reduce side effects of medication; (4) use of practical devices to remember to take the medication (e.g.: beepers, medication organizers, etc.), and for contingency planning; (5) staying healthy being a priority; (6) social support; and (7) desire to live long enough to take part in future. To our knowledge, the relationship between these different categories of facilitators and adherence rate has not been studied.

It would appear that a more thorough exploration of facilitators of adherence might bring a new perspective to this field by identifying and building on motivators and strategies already adopted by HIV-infected individuals in their day-to-day life to facilitate adherence behaviours. Furthermore, comparing these strategies and motivators of adherence behaviours (facilitators) with the reasons most frequently reported for suboptimal adherence (barriers) might also provide more information to guide clinical interventions.

Methods and materials

Participants

One hundred and nine adults (N=109) with HIV-infection on HAART treatment were approached for this study. Twenty-seven participants of this sample (24.8%) could not be included in the final analyses: 14 (12.8%) dropped out and 13 (11.9%) were excluded for either their inability to read and write English, inability to complete the questionnaires in a reliable fashion, or because of alcohol or drug intoxication at the time of the baseline interview. Comparisons between the excluded participants (N=27) and the final sample (N=82), using chi-squares and t-tests analyses, showed that groups were comparable on all demographic characteristics, HIV disease markers, and indicators of health status, except in the case of monthly income and type of risk factor for HIV. Specifically, participants excluded from the study generally had a lower income (t (99.9) = 3.42, p = .001) and tended to report intravenous drug use as a risk factor for HIV more often than individuals in the study sample (χ^2(1, N=95) = 5.92, p = .025).

The final sample was composed of 82 individuals of whom 71 were men (86.6%) and 11 women (13.4%) with a mean age of 41 years (SD = 7.2; range 21-64) and education level of 13.3 years (SD = 2.3; range 8-19). See Table VII (p. 110) for a description of demographic and medical characteristics of participants.

Procedures

Participants were recruited, starting in the Spring of 2000, in the Toronto Metro Area through community organizations and Hospital Centers for a larger multidisciplinary research project on the psychosocial, behavioural and treatment factors associated with adherence to HAART in HIV-infection. The project included two distinct but linked studies: INFORMM-HAART Study (Identification of Necessary Factors for Medication Management of HAART) and MAX-HAART Study (Maximizing HAART Adherence Through Behavioural Interventions). The INFORMM-HAART Study used a natural history design in order to identify the main predictors of HAART adherence over a 12-month period of time. The MAX-HAART Study compared the tolerability and feasibility of two distinct adherence-enhancing interventions (solution-focused intervention and cognitive intervention) with a subgroup of HIV-infected individuals assessed as having adherence difficulties during their participation in the INFORMM-HAART study. All participants provided written informed consent to participate in this research as approved by the St. Michael's Hospital Research Ethics Board. Individuals who gave informed consent and decided to participate in this research were scheduled for 14 regular 30 to 45 minutes visits over a period of one year to complete a variety of behavioural,

neuropsychological and psychosocial questionnaires and inventories. Participants received remuneration for their participation in this study at the rate of $ 10-20 per hour depending on the type and scope of instruments administered.

Measures

The following questionnaires were administered to each participant:

A general demographic questionnaire including questions such as gender, age, education level, etc. was administered at baseline.

A questionnaire about general and HIV-specific medical status, including questions on prior opportunistic infections, was administered at baseline. Participants' most recent viral load and CD4 counts were obtained from their medical chart with participant consent. CDC disease stage (1993 classification system (Castro et al., 1992); asymptomatic, symptomatic, AIDS) was derived based on the medical information provided (HIV-related medical conditions and CD4 Lymphocyte counts).

Reasons for suboptimal adherence (barriers to adherence) were assessed by the Reasons Questionnaire, which included a list of 19 probable reasons why people may have missed taking their HAART medication. The Reasons Questionnaire contained the 14-item scale found in the AACTG Adherence Instruments (Chesney, Ickovics et al., 2000), (the most widely used scale to study reasons for suboptimal adherence with HIV-infected individuals), and five additional items: (1) slept in late or went to bed early, (2) lost track of time, (3) didn't want to take them, (4) felt too tired, and (5) felt stressed out. This

questionnaire asked participants to rate on a 4-point Likert scale (*0: Never, 1: Rarely, 2: Sometimes, 3: Often*) how often they missed taking their medication in the previous week because of each of these 19 reasons.

Strategies and motivators of adherence behaviours (facilitators of adherence) were measured with the Adherence Facilitators questionnaire, which consisted of an open-ended question created by the research team: "What do you find particularly helpful in your life that helps you adhere to the HAART medication? That is, things you do for yourself, things you tell yourself, objects that you value, techniques that you find useful, people in your life, etc. Please describe."

Adherence to medication was measured with an Individualized Medical Monitor (IMM), adapted from the AACTG Adherence Follow up Questionnaire(Chesney, Ickovics et al., 2000). The IMM is an individualized questionnaire that first gives a brief description of the participant's prescribed medication and asks him if it represents accurately his current regimen (e.g.: "The following should be an accurate description of the medicines currently prescribed by your doctor: 150 mg 3TC:1 white diamond pill twice per day; 40 mg d4T: 1 brown pill twice per day; 400 mg Crixivan: 2 white and green pills twice per day; 100 mg Ritonavir: 2 beige pills twice per day"). If it represents accurately the participant's regimen, he is asked to circle how many times (*none, once, twice, 3X, 4X, ?*) he took each type of medication in the past 7 days, starting from yesterday. A missed dose was defined as omitting an entire scheduled dose of one medication. The number of missed doses for each day is calculated by subtracting the number of doses actually taken from the

number of doses each participant was expected to take. These missed doses are then added for the 7 day-period covered by the questionnaire and divided by the number of doses the participant was expected to take during that same period of time. This result is finally multiplied by 100 to provide a percentage of suboptimal adherence to the prescribed regimen.

Design

This is a descriptive, exploratory study using a qualitative methodology to describe the types of reasons most frequently mentioned by participants at the time of their "worst" adherence level within a one-year period. It also uses a qualitative methodology to establish categories of adherence facilitators based on the strategies or motivators that HIV-infected individuals reported using to facilitate their adherence to their HAART regimens. Finally, this study uses a quantitative longitudinal design to evaluate the association between the number or the type of categories of adherence facilitators mentioned at one time point and participants' adherence status measured over a period of one year.

To answer our research questions, it was necessary to render individual reports comparable through time by organizing the adherence data into 12 fixed intervals of 30 days starting at study entry for a total period of 360 days. However, this resulted in some participants not having at least one entry every 30 days. In order to insure that the adherence measure was reliable, without detrimentally minimizing sample size, we required that at least 6 measures of adherence out of 12 be available for a subject to be included in

the analyses. For each 30-day interval, both the average and the "worst" self-reported adherence percentage were calculated.

It was not possible to control time of administration for the Facilitators of Adherence questionnaire because it was administered only once, at different time intervals within a period of 360 days of baseline. However, the results should be relatively stable over a period of several months because participants in the study had been taking medication for a few years and were being asked what generally helped them adhere to their regimens. It can be reasonably postulated that these individuals had developed a set of habits and/or strategies to facilitate adherence.

Overview of the analyses

To explore reasons for missing medication, only participants who reported at least one episode of suboptimal adherence over a period of 360 days were included in the analyses. We used descriptive statistics to explore the frequency, as well as the intensity of each reason reported by participants at the week of their lowest adherence within this one-year period.

To explore facilitators of adherence, qualitative analyses were conducted based on multiple readings of participants' answers to strategies or motivators that usually helped them adhere to their HAART regimens. The analyses were based on Miles and Huberman mixed approach method to qualitative data analysis (Miles & Huberman, 1994), using checklist matrices to note patterns and themes emerging from the data. Categories emerged

from the data without being assumed a priori, but decisions to regroup categories were later informed by available theories on adherence to medication, as well as prior literature on the subject. Participants' answers were categorized and eventually regrouped into similar categories. Initial categorizations were discussed with a health psychology expert who has over 30 years of experience in this field of practice. The categories were also reviewed regularly with the second author, who has 13 years of clinical experience with HIV-infected individuals. A random sub-sample of participants' answers representing 15% of the total number of individuals participating in this study were reviewed and categorized independently by another rater specializing in health psychology. This independent judge reviewed the categorizations based on definitions provided for each subcategory (see Table VIII for definitions, p. 112). Minor changes to the categories' definitions were made following inter-rater agreement to improve clarity. The inter-rater agreement rate was satisfactory, with a Cohen's Kappa score of .84. Every item for which there was discordance was discussed until an agreement was reached. Following inter-rater agreement, categories with overlaps, (i.e. covering similar concepts), were discussed with the second author and a decision was made to regroup these into larger categories for clarity, as well as data analysis purpose. In order to count the number of categories reported, participants' answers were reduced to presence or absence of a given category. T-tests analyses were also used to explore the relationship between presence or absence of a given category of facilitator and participants' demographic characteristics (age and education).

Before using the adherence data information, the effect of inclusion in an adherence enhancement treatment program for a subgroup of subjects was tested using a non parametric t-test. This test compared average adherence in the month preceding and following the intervention.

The "worst" self-reported adherence score was retained as the outcome measure because it represents the closest measure to clinical reality given that self-reports generally tend to overestimate adherence (Liu et al., 2001). Participants were classified based on their adherence status (adherence or suboptimal adherence) using the critical cut-off point of 95% adherence; an accepted criterion in the literature for achieving the best virologic response. Participants who had missed more than 5% of their medication at least once over a period of one year were categorized as having a suboptimal adherence status. Relationships between adherence status and both the number and the type of categories of facilitators were investigated separately with Chi-square analyses. Note that the N varies from 63 to 82 in the analyses because of the presence of missing values.

Results

Reasons for suboptimal adherence

Forty-two participants (51% of the study sample, N=82) reported at least one reason for suboptimal adherence during their worst week of adherence. We used two approaches to determine the most frequently mentioned reasons for suboptimal adherence (see Table X, p. 114). Using the highest percentage reported on the scale item "often", the reasons most

frequently reported were: "busy with other things" (14%), "didn't want to take them" (7%), "was traveling or away from home" (7%), and "wasn't feeling well" (7%). By collapsing scale items into a dichotomous category: present ("often", "sometimes" and "rarely") versus absent ("never") the reasons most frequently mentioned were "busy with other things" (55%) and "forgot" (55%). Other common reasons were: "slept in late or went to bed early" (45%), "was traveling or away from home" (43%), "fell asleep/ slept through dose time" (41%), "had a change in daily routine" (38%), and "wasn't feeling well" (38%).

Facilitators of adherence

There were 75 participants who completed the open-ended questions about those factors that facilitated adherence to HAART medication. Seven categories of adherence facilitators emerged from the data: (1) "planning skills", (2) "positive perception of medication", (3) "social support", (4) "commitment/internal motivation", (5) "self-care", (6) "research participation" and (7) other answers (see Table IX for frequencies, p. 113). The following is a more thorough description of specific categories of facilitators mentioned by participants.

1) Planning skills:

Most participants (69%) described using several organizational and general planning skills to integrate medication into their daily life. This category included two types of planning strategies: one relying on participants' "internal resources" to remember to take medication and another relying on "external sources" as reminders.

Among "internal resources", several participants reported associating their medication schedule with their daily activities or daily routine. A typical example of these answers is:

> *I take my pills at convenient times for me: 1ˢᵗ thing in the morning 7:00 AM. I know I can eat after 8:00 and I usually get up then. I take my next pills at 3:00 again knowing that between 1:00 and 4:00 is a good time not to eat because I work, etc. the last set at 11:00 is when I go to bed. I find these times don't interfere with my life and actually work with it (ID 201).*

Other strategies cited in this category were: using localization of pills as a reminder to take them, as well as planning ahead of time, such as having the right type of food available to take with doses of medication and carrying pills when away from home. A typical example is:

> *I make sure I have a ready supply of convenient fatty foods on hand to take with the Saquinavir. I leave my meds in the kitchen for convenience, i.e. eating with meds. I always carry at least 2 doses of my meds with me in case I am not conveniently close to home (ID 202)*

Among "external sources" of planning, participants also reported using accessories such as beepers, pillboxes or drug charts to remind them to take their medication.

2) Positive perception of medication

The second most cited category (36%) was "positive perception of medication", subdivided in three subcategories: "health benefits", "positive attitude toward medication", and "few disadvantages of medication use".

"Health benefits" regrouped feedback provided from medical test about current health status or improvements in health. Examples of these health benefits noticed by participants are:

> *The great improvement in my health over the past two and a half years has motivated me to take my medication as prescribed (ID 203)*

> *Drugs are working – higher T count / Ø viral load – gives motivation when dealing with drug side effects (ID 204)*

> *The fact that after being on meds for 3 months my viral load went from 77 000 to undectectable and my CD4 went from 508 to 672 is the main reason I take the meds (ID 205)*

Having a "positive attitude toward medication" was also mentioned by participants:

> *Think positive that pills are working for you (ID 206)*

> *I do feel that when I get my results back from the doctor, and he says that my counts are good and steady it makes me feel that the meds are working the way they should (ID 207)*

A few participants also mentioned that having only a "few disadvantages of medication use" such as absence of side effects, easy regimen to follow, helped them adhere to their regimens.

3) Social support

Twenty-five participants (33%) mentioned that emotional and practical support provided by a significant person in their life helped them adhere to their regimens. Twenty four participants (32%) said that reminders or positive feedback from partner, close family,

general social network or friends who are themselves HIV-infected helped them adhere

to their medication regimens. Here are a few excerpts from patients' answers:

> *As for people, having a few friends call and ask if I have taken my meds helps sometime, especially if I am feeling like I do not wish to take my meds (ID 208)*

> *Social support network tells me how great I'm looking – acts as an incentive to continue HAART medication (ID 209).*

A few participants (8 %) also mentioned support provided by medical staff as a

motivator to take their medication regularly.

4) Commitment / Internal motivation

Some participants (21%) mentioned that being committed to take their medication

and using their "internal motivation" to do so help them adhere to their medication

regimens. However, the reason why a person was committed to take the medication was

reported as either positive or negative, with positive reasons being most often cited.

Positive reasons were centered on the desire to live; conversely negative reasons were

centered on the fear of dying or suffering.

5) Self-care

A few participants (15%) reported that general self-care strategies such as rewarding

oneself, using complementary therapies, having healthy living habits (e.g.: regular sleeping

schedule), or general improvement in their quality of life, helped them adhere to their

medication regimens.

6) Research participation

Some participants (8%) indicated that participating in the current research helped them adhere to their medication by providing tools, support or reminders to take the medication.

7) Other answers

A few participants' (11%) answers could not be included in any of the categories above and could not form a new category because of absence of a common theme between them and/or low prevalence (e.g.: using certain type of food to help with swallowing pills).

Number of categories of facilitators mentioned

Most participants mentioned using more than one category of strategy to facilitate their adherence to medication. Among the 45% of participants who mentioned only one category, the most common answers were: using "planning skills" (62%), using "social support" (15%) and having a "positive perception of medication" (12%). Fifty-five percent of participants reported more than one category, with 28% reporting use of two different categories of facilitators and 24% use of three to five different categories of facilitators. Among participants who reported more than one category, the most common answers were: using "planning skills" (76%), having a "positive perception of medication" (56%), and using "social support" (49%) to facilitate adherence to medication.

Facilitators and participants' demographic characteristics

Education level was significantly associated with "planning skills" ($t(73) = -3.12$, $p = .003$) and "positive perception of medication" ($t(73) = -2.23$, $p = .03$): participants who reported these two categories generally tended to have a higher education level than people who did not report them. No significant association was detected between education level and the following categories of facilitators: "social support" ($t(73) = .071$, $p = .94$), "self-care" ($t(73) = -1.38$, $p = .17$) and "commitment / internal motivation" ($t(73) = -1.37$, $p = .18$)

Age of participants was significantly associated with "commitment / internal motivation" ($t(73) = -2.29$, $p = .03$): participants who mentioned this category tended to be older than participants who did not mention it. No significant association was detected between age and the following categories of facilitators: "planning skills" ($t(73) = -.78$, $p = .044$, "social support" ($t(73) = -.44$, $p = .66$), "self-care" ($t(73) = -1.32$, $p = .19$), "positive perception of medication" ($t(73) = -1.74$, $p = .09$).

Impact of adherence intervention

Among 82 study participants, 10 were included in an intervention program (MAX-HAART) during the one-year duration of the larger study because they had reported adherence difficulties. No significant impact of treatment was noted when comparing adherence results before and after the intervention program for each of these individuals ($p= .06$).

Facilitators and adherence status

Of the 63 individuals included in the analyses, 30 (48%) were considered to have suboptimal adherence to medication. No significant differences were detected in adherence status (adherence vs. suboptimal adherence) between participants who mentioned one, two and three to five categories of facilitators (χ^2 (2, N=63) = 0.95, p = .62). There was also no significant differences in adherence status detected between participants who mentioned or did not mention each of the following categories: "planning skills" (χ^2 (1, N=63) = 1.15, p = .42), "positive perception of medication" (χ^2 (1, N=63) = 0.08, p = .80), "social support" (χ^2(1, N=63) = 1.15, p = .42), "commitment/internal motivation" (χ^2 (1, N=63) = 0.66, p = .55), "self-care" (χ^2 (1, N=63) = 3.64, p = .09). See Figure 1 (p. 119).

Discussion

Results from this study are consistent with previous research on reasons for suboptimal adherence and facilitators of adherence. Interferences with daily routine were the reasons most frequently mentioned by HIV-infected participants at their "worst" time of adherence. However, one needs to be careful when reporting reasons most frequently mentioned by separating reasons that most frequently appeared as present and reasons that happened most often. For example, "forgetting", which has been reported as the most prevalent reason for suboptimal adherence in the literature, was also found to be highly prevalent when using a yes/no format of answer in this study, but was not as prevalent when looking at how frequently this reason interfered with medication taking. It is interesting to note that most studies have either reported the presence or the absence of any

given reason or have combined reasons that happened "often" with reasons that happened "sometimes", instead of focusing on those that happened "often" only.

Although the use of this 'reasons' questionnaire is interesting in that it helps to describe the most common reasons for suboptimal adherence, it does not inform us about the context surrounding each reason. Some of these reasons might be determined by more than one factor. This limits the type of conclusions we can generate from this data. For example, forgetting could be caused by several factors such as neurological factors or distractions from daily routine.

Results from previous studies on some of the most common types of facilitators of adherence were also replicated. In descending order, facilitators of adherence mentioned by at least 15 % of the participants were: (1) planning skills; (2) positive perception of medication; (3) social support; (4) commitment/internal motivation; and (5) self-care. Grouping participants' answers into these categories of facilitators has helped to inform us about strategies and motivators of adherence behaviours that are commonly used by participants in their day-to-day life.

A more thorough clinical understanding of adherence behaviours is obtained by comparing facilitators of adherence with reasons reported for suboptimal adherence. The adherence facilitator most often reported was "planning skills", which is centered around routine and integration of medication into activities of daily living. Because most of the reasons for suboptimal adherence were centered on interferences with daily routine, the category "planning skills" might be less efficient under a changing context if it is the sole

strategy used to facilitate adherence. A recent study (Ryan & Wagner, 2003) found that a routine for pill taking is a critical component to successful adherence, and that people whose lives were more chaotic and less centered around routine were at a higher risk for suboptimal adherence. These authors also pointed out the difficulty of using this strategy under emotional stress or a changing context. As HIV-infected individuals regain better health with medication, new challenges emerge as they return to a more active life, and may thus need to adapt to disruptions in daily routine more often. This emphasizes the need to rely on other types of strategies than just routine to remember to take medication.

Rates of suboptimal adherence reported in this study were comparable to rates reported in other studies, but only a few studies have measured adherence over time (Mannheimer et al., 2002; Sethi et al., 2003). The lack of association between adherence status and the number of categories, as well as the type of category of facilitators could be explained by several reasons. First, a higher number of categories of facilitators might not necessary imply that these strategies or motivators are all equally useful and working efficiently. The number of categories of facilitators used might also reflect individual differences: one type of category of facilitator might work by itself for someone, while someone else might need to rely on several strategies to adhere successfully to his treatments. The fact that no specific type of category was related to adherence could also be explained by individual differences in preferences toward various kinds of strategies. In fact, in our sample, the categories "planning skills" and "positive perception of medication" tended to be mentioned more often by participants with a higher education level. Furthermore, the category "commitment/internal motivation" tended to be reported more

often by older participants. However, we might have not been able to detect associations between some of the category of facilitators and demographic characteristics because of the smaller prevalence of participants who mentioned these categories (e.g., self-care was mentioned by only 11 individuals). The associations detected between type of facilitators and participants' demographic characteristics should be considered preliminary and will need to be replicated with additional samples before generating any conclusion.

This study has also several limitations that limit the generalizability of the findings. First, because of a self-selection bias, our sample was not completely representative of the general population of HIV-infected individuals (i.e. sample was comprised of mainly Caucasian gay men). Participants excluded from the study sample were also different from the final sample on two aspects: they tended to have a lower income and to report intravenous drug use as a risk factor for HIV more often than individuals in the study sample. Secondly, it is possible that adherence rate might have been biased by the use of a self-reported scale, which usually tends to overestimate adherence. It was originally planned to also measure adherence with Medication Event Monitoring Systems (MEMS) for a sub-group of participants to validate self-reports, but participants refused to use them because of convenience issues. However, self-reported adherence questionnaires have been found to be adequate adherence measures. They correlate with other measures of adherence (Deeks, 2000; Duong et al., 2001; Hugen et al., 2002), and they also predict therapeutic

outcome, as measured by HIV RNA level and CD4+ cell count (Mannheimer et al., 2002; Walsh, Mandalia et al., 2002)

Thirdly, the measure of facilitators was also limited in some ways. The question might have been too broad to get at the core of the most important adherence facilitators. It also did not distinguish between motivators and strategies. Furthermore, there is the possibility that its written format limited the information provided by not allowing us to probe participants' answers to clarify them. Finally, because time of administration of the questionnaire on facilitators could not be controlled for, the type of facilitators used might have changed through time. It would have been interesting to administer this question several times to note if there were any changes in adherence facilitators mentioned through time.

Despite these limitations, this study has several clinical implications. It informs us about some of the most common types of facilitators used by a group of HIV-infected individuals in their day-to-day lives. It replicates with a different group of subjects some of the results obtained in two previous qualitative studies on facilitators of adherence. These results also suggest the need to adapt adherence interventions to individual differences in motivation and to reinforce efficient strategies already used by HIV-infected individuals. The more we learn about motivations underlying adherence to medication, the more likely it is that we can intervene successfully with people who have adherence difficulties. It also reminds health care providers of the importance of assessing each person's adherence facilitators to understand all the underlying factors that might contribute to adherent

behaviours. This study suggests that it might be useful for health care providers to also ask patients what facilitates medication-taking to understand their day-to-day strategies instead of focusing only on obstacles. Although exploratory, results of this study might also indicate that the number or the types of adherence facilitators used by patients is not directly related to their efficacy in adhering to HAART. Finally, this description of reasons for missed medication doses and facilitators of medication taking could also guide our understanding of adherence behaviours, and inform future research efforts. It would be interesting to study adherence facilitators in a more structured way by asking participants about the most common types of strategies and motivations that they used to improve their adherence behaviours in their day-to-day experience. It would also be interesting to explore how these different adherence facilitators might interact together to improve adherence to HAART.

Conclusion

Common reasons for suboptimal adherence and facilitators of adherence were identified among a group of HIV-infected individuals. Results from this study have clinical implications. Knowledge about what impedes and facilitates adherence behaviours in patients' day-to-day lives can provide guidance for clinical practice. Furthermore, knowledge about individual differences in preferences toward various kinds of strategies might help health care providers adapt their interventions to patients and to reinforce efficient strategies already used by HIV-infected individuals in their day-to-day lives.

Acknowledgments

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Figure 1. Categories of facilitators by adherence status (N=75)
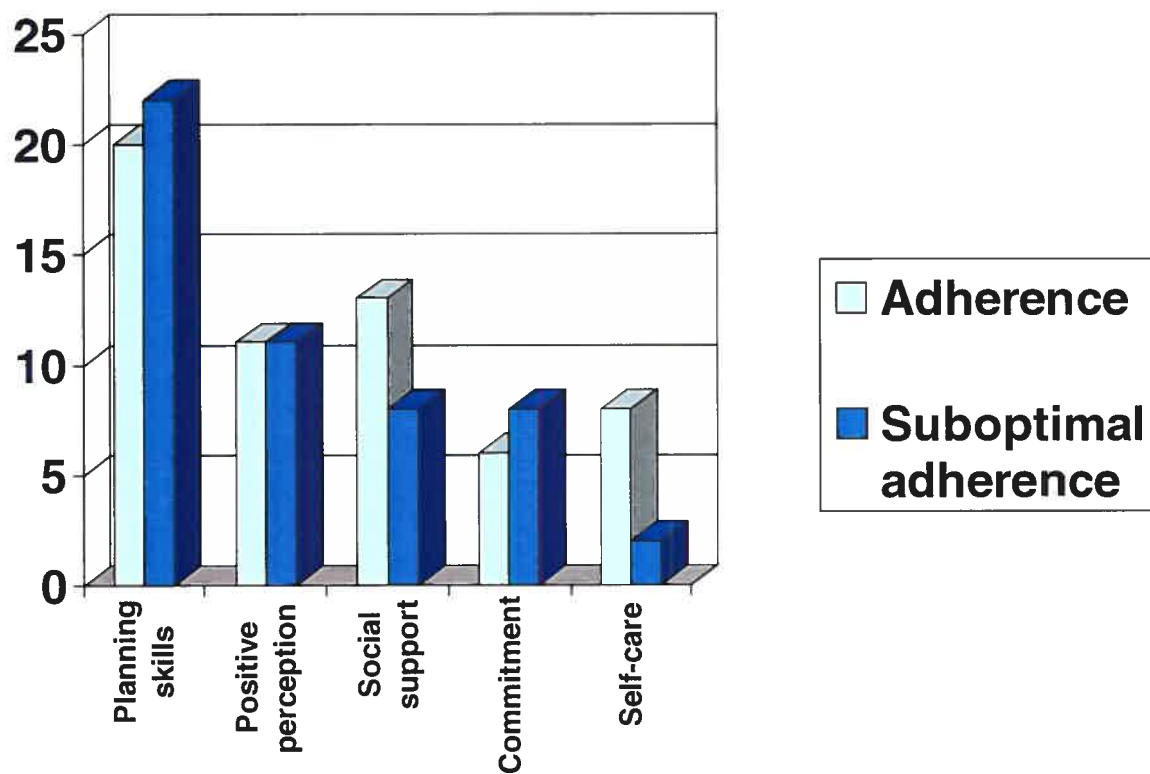
Table VII. Demographic Characteristics of Participants (N=82)

Characteristic	N	%	Mean (SD)	
Age (years)			41.0	(7.2)
Education (years)			13.3	(2.3)
Monthly income ($)			1382.90	(972.31)
Time since tested HIV-positive (months)			99.4	(50.6)
Gender				
Male	71	86.6		
Female	11	13.4		
Race				
Caucasian	66	80.5		
Black	8	9.8		
Other	6	7.3		
Relationship status				
Single	56	68.3		
Living with partner	26	31.7		
Work status				
Working	66	80.5		
Not working	16	19.5		
On long-term disability*				
Yes	65	79.3		
No	5	6.1		

Characteristic	N	%	Mean (SD)
Number of risk factors for HIV			
Only one	66	80.5	
More than one	14	17.1	
Type of risk factor(s) for HIV			
Same sex sexual contact	62	75.6	
Heterosexual sexual contact	16	19.5	
Intravenous drug use	11	13.4	
Blood Transfusion	2	2.4	
1993 CDC Classification (N=80)			
Asymptomatic	15	18.3	
Symptomatic	26	31.7	
AIDS	39	47.6	
Type of medication regimen			
NRTI + PI	40	48.8	
NRTI + NNRTI	24	29.3	
NRTI + NNRTI + PI	15	18.3	
3 NRTIs	1	1.2	
Viral load			
Undetectable	39	47.6	
Detectable: $\leq 35\ 000$	33	40.2	
Detectable: $> 35\ 000$	8	9.8	

*Missing data n=12

Table VIII. Definitions of categories of adherence facilitators (listed in descending order of importance)

Categories	Definition	Subcategories
Planning skills	Patient uses his organization skills, general planning skills, daily routine (activities of daily living), and accessories such as pillboxes to facilitate his adherence to medication.	Internal resources: location of pills, routine/ medication integrated with daily activities, planning ahead ; External sources: accessories
Positive perception of medication	Perceived benefits of taking the medication and medication characteristics that makes it easier for the patient to adhere to his regimen. This includes patient's acceptance and positive attitude toward medication, his beliefs about medication effect on his health and requirements associated with medication-taking (medication characteristics).	Health benefits Positive attitude toward medication Few disadvantages of medication use
Social support	Emotional and practical support provided by a significant person in the patient's life (e.g.: partner, friend, family, medical staff, HIV community, etc.) that facilitate adherence to medication.	Family, partner, and friends Medical staff
Commitment / internal motivation	Patient is committed to take his medication and uses his internal motivation or will power to do so. The reasons why a person is committed can be either positive (e.g.: desire to live) or negative (e.g.: fear of dying or suffering).	Desire to live Fear
Self-care	Patient's adherence to medication is facilitated when he takes care of himself. This includes rewarding oneself, having healthy living habits, using complementary therapies, health alternatives or psychotherapy, as well as anything he does to improve his physical and mental health, as well as his quality of life.	Healthy living habits (e.g.: exercise) Complementary therapies / health alternatives Rewarding oneself Improvement in quality of life
Other	Any other answer that could not be regrouped and classified in another category.	

Table IX. Categories of adherence facilitators reported by participants (N=75)

Categories	N	%
Planning skills	52	69.3
Positive perception of medication	27	36.0
Social support	25	33.3
Internal motivation	16	21.3
Self-care	11	14.7
Research participation	6	8.0
Other answers	8	10.7

Table X. Types of reasons reported for suboptimal adherence (N=42)

Reasons	F	%	Reasons	F	%
Busy with other things			Could not find a place where no one would see you taking medicines		
Often	6	14.3			
Sometimes	7	16.7	Often	1	2.4
Rarely	10	23.8	Sometimes	1	2.4
Never	19	45.2	Rarely	1	2.4
			Never	39	92.9
Didn't want to take them					
Often	3	7.1	Felt depressed		
Sometimes	7	16.7	Often	1	2.4
Rarely	4	9.5	Sometimes	2	4.8
Never	28	66.7	Rarely	5	11.9
			Never	34	81.0
Was traveling/away from home					
Often	3	7.1	Could not follow eating pattern required by medication		
Sometimes	6	14.3			
Rarely	9	21.4	Often	1	2.4
Never	24	57.1	Sometimes	3	7.1
			Rarely	2	4.8
Wasn't feeling well			Never	36	85.7
Often	3	7.1			
Sometimes	9	21.4	Felt drug was toxic/harmful to health		
Rarely	4	9.5	Often	1	2.4
Never	26	61.9	Sometimes	3	7.1
			Rarely	0	0
Slept in late/went to bed early			Never	38	90.5
Often	2	4.8			
Sometimes	9	21.4	Ran out of pills		
Rarely	8	19.0	Often	1	2.4
Never	23	54.8	Sometimes	0	0
			Rarely	1	2.4
Fell asleep/slept through dose time			Never	40	95.2
Often	2	4.8			
Sometimes	6	14.3	Was having problems with side effects		
Rarely	9	21.4	Often	0	0
Never	25	59.5	Sometimes	4	9.5
			Rarely	2	4.8
Lost track of time			Never	36	85.7
Often	2	4.8			
Sometimes	8	19.0	Felt too tired		
Rarely	5	11.9	Often	0	0
Never	27	64.3	Sometimes	11	26.2
			Rarely	3	7.1
Had a change in daily routine			Never	28	66.7
Often	2	4.8			
Sometimes	9	21.4	Felt stressed out		
Rarely	5	11.9	Often	0	0
Never	26	61.9	Sometimes	4	9.5
			Rarely	4	9.5
Felt good			Never	34	81.0
Often	2	4.8			
Sometimes	2	4.8	Had too many pills to take		
Rarely	1	2.4	Often	0	0
Never	37	88.1	Sometimes	1	2.4
			Rarely	2	4.8
Forgot			Never	39	92.9
Often	1	2.4			
Sometimes	8	19.0			
Rarely	14	33.3			
Never	19	45.2			

Conclusion

The two articles included in this dissertation used complementary approaches with the goal of improving the understanding of adherence behaviours. The first article focused on behavioural prediction by studying risk factors for suboptimal adherence to HAART; while the second article examined the day-to-day adherence process by exploring both the reasons that might disrupt adherence behaviour at the most difficult time of adherence, and the facilitators of adherence reported by participants. In the conclusion of this dissertation, the main findings of both articles will be summarized and their clinical implications will be presented. The theoretical implications of these findings will also be highlighted. Finally, limitations and strengths of this dissertation will be addressed, and future research directions will be suggested.

1. Main findings

Article 1

Twenty-seven individuals out of 68 (40%) reported at least one episode of suboptimal HAART adherence over a period of 6 months. The impact of 8 potential risk factors was tested with a logistic regression predicting suboptimal adherence to medication. Results indicated that out of these 8 potential risk factors studied, the following 3 factors were significantly associated with suboptimal adherence to HAART: alcohol use problems, lower levels of confidence about the positive impact of HAART on health, and drug use

problems. Results confirmed three of the initial hypotheses. With these three risk factors, the overall proportion of individuals adequately classified across classes (adherence vs. suboptimal adherence) in the current sample was 78%. Results of the logistic regression indicated that the risk of suboptimal adherence was 5 times ((CI): 1.2 – 21.3) higher in participants who had a hazardous or harmful alcohol consumption and alcohol related problems (e.g., guilt or remorse after drinking, injuring oneself or someone else because of drinking, etc.) compared to participants without such alcohol use problems. It also indicated that for every one point increase in the degree of confidence about medication efficacy (measured with the HEXP1 questionnaire), the risk of having suboptimal adherence decreased by 0.7 times in the sample (CI: 0.6 – 0.9). Therefore, participants who were more confident about the positive impact of HAART on their health were less likely to have suboptimal HAART adherence, and conversely participants who were more sceptical about the positive impact of HAART on their health tended to be at increased risk for suboptimal adherence. Also, participants who had drug use problems such as dependence on drugs (e.g., difficulty to stop using drugs, withdrawal symptoms) or serious consequences of drug use in different life domains (e.g., interpersonal relationships, work difficulties, legal problems) were found to be generally more likely to have suboptimal HAART adherence than participants without such drug use problems. However, the impact of a drug use problem on suboptimal adherence was not as straightforward in the current sample: drug use problem was significant in the overall model but the different levels of drug use problems (e.g., low level, moderate level and substantial to severe level of problems) did not attain significance individually. As a result, it was not possible to estimate the potential

increase in the level of risk due to a drug problem, nor discriminate the impact of different levels of drug use problems on adherence. Finally, because of the large confidence intervals in the odds ratio, estimates of the potential increase in the risk of suboptimal adherence for these 3 risk factors should be seen as preliminary and will need to be replicated in future studies.

Five factors among the 8 potential risk factors studied were not significantly associated with suboptimal adherence. Two of the initial hypotheses were confirmed: suboptimal adherence was not associated with demographic characteristics (age and education), or severity of the disease (measured by disease staging). However, three of the initial hypotheses were not confirmed. Suboptimal adherence was unrelated to: (1) a greater number of medical symptoms due to illness or side effects of medication; (2) a greater number of depressive symptoms; and (3) both the positive and the negative impact of medication use on daily functioning (measured with the HEXP2 questionnaire).

Secondly, the association between participants' beliefs about the positive impact of HAART on their health (HEXP1 questionnaire) and their demographic, medical and psychosocial characteristics was explored. Beliefs about medication efficacy were unrelated to: demographic characteristics (age, gender, and education level), markers of disease progression (such as viral load and hospitalization in the past 6 months), and the cognitive sub-score at the depression inventory. Beliefs about HAART effect on health were found to be related to: the number of medical symptoms and the severity of the disease (disease staging). Participants with a greater number of medical symptoms due to illness or side

effects of medication tended to be more sceptical about the positive impact of HAART on their health. Also, participants in the two following disease stages were found to have significantly different beliefs about medication efficacy: participants with an AIDS diagnosis held more positive beliefs about the impact of HAART on their health than people at the HIV symptomatic stage of the disease. However, the significance of this relation was marginal (p=0.04) and the current sample size did not allow for detection of differences between these two stages and the asymptomatic stage of HIV. These results should therefore be replicated in future studies before making firm conclusions.

Article 2

This exploratory study had for goal to describe both the barriers to and the facilitators of adherence reported by HIV-infected individuals. The reasons most often reported by participants (N=42) at their "worst" point of adherence over a one-year period centered around interferences with daily routine. On the other hand, facilitators of adherence reported by at least 15% of the participants (N=75) were classified into 5 main categories (listed in descending order of frequency): (1) "planning skills"; (2) "positive perception of medication"; (3) "social support"; (4) "commitment/internal motivation"; (5) "self-care". These categories were similar to results found in other studies on facilitators of adherence (Remien et al., 2003; Roberts, 2000). Demographic characteristics of participants who mentioned these different categories of adherence facilitators were explored. In the present sample, participants who mentioned some of these facilitators shared a few demographic characteristics in common. Participants who reported using "planning skills"

and a "positive perception of medication" to facilitate their adherence to HAART tended to have higher levels of educational achievement than participants who did not mentioned these facilitators. Also, participants who reported using "commitment/internal motivation" to facilitate their adherence to HAART generally tended to be older than individuals who did not mention this facilitator. Based on these associations it seems that participants' age and education level might influence the choice of adherence facilitator reported in the current sample.

The relation between adherence status (adherence vs. suboptimal adherence) and the number or the type of facilitators reported was also investigated. Among the 63 individuals included in the analyses, 39 (48%) had suboptimal adherence when measured over a period of one year (360 days). No significant association was found between adherence status and the number or the types of category of facilitators mentioned by participants. However, because of the exploratory nature of this study these relations will need to be replicated before one can make definite conclusions about them.

2. Clinical implications

Rates of suboptimal adherence found in both articles were comparable to results obtained in the few studies that have measured adherence over time (Mannheimer et al., 2002; Sethi et al., 2003). Because most HIV studies have assessed adherence over the past week or the past few days, this dissertation provides additional clinical information on adherence to HAART over longer periods of time.

This dissertation was also able to identify important risk factors for suboptimal adherence to HAART that need to be explored in clinical practice. It highlighted the need to monitor for hazardous or harmful alcohol consumption and alcohol related problems (e.g., guilt or remorse after drinking, injuring oneself or someone else because of drinking, etc.) as they represent clear risk factors for suboptimal adherence to HAART. It also suggested that drug dependence or serious consequences of drug use on different life domains can potentially increase the risk for suboptimal adherence to HAART. Therefore, these results indicated that substance use that negatively affected different life domains within the past year increased the risk of suboptimal HAART adherence. Social instability, which is part of a substance abuse diagnosis based on the DSM-IV criteria, may be important to consider in clinical practice. In fact, an earlier study (Bouhnik et al., 2002) found that even former drug users who met the criteria for social instability were at increased risk for suboptimal adherence. Considering these findings, it would be important to screen for substances use problems and serious consequences of substance use while discussing adherence to HAART. It might be necessary to concurrently treat substance use problems and to provide concrete help with consequences associated with substance use in order to improve adherence to HAART when these treatments are initiated.

Results of both articles included in this dissertation highlighted the need to ask patients about their beliefs concerning the impact of HAART on their health status. In fact, having a "positive perception of medication" was frequently mentioned as a facilitating factor for HAART adherence in the second article of this dissertation. It was also found in the first article of this dissertation that participants who were more confident about the

positive impact of HAART on their health were less likely to have suboptimal adherence to HAART. However, beliefs about the positive or the negative impact of HAART on daily functioning did not appear to have such a direct impact on adherence.

The lack of association between suboptimal adherence and demographic characteristics or severity of the disease (measured by disease staging) highlighted again the dynamic nature of adherence to treatment. In fact, adherence is not a "static" phenomenon and is seldom associated with stable patients' characteristics, but usually changes through time for a given individual. The fact that a greater number of depressive symptoms was not significantly associated with suboptimal adherence was surprising as depressive symptoms are often reported as risk factors for suboptimal adherence (Ammassari et al., 2004; DiMatteo et al., 2000; Gordillo et al., 1999; Holzemer et al., 1999; Starace et al., 2002). This lack of association should be interpreted carefully as it might be explained by the low prevalence of depression in the current sample, and by the type of measure used. Because the total score at the depression inventory included medical symptoms, the cognitive sub-score was used for the analyses. This score might not have been sensitive enough to detect depressive affect in the current medical sample. It was also surprising to note the lack of association between suboptimal adherence and number of medical symptoms due to illness or side effects of medication because they have often been reported as risk factors for suboptimal HAART adherence (Ammassari et al., 2001; Holzemer et al., 1999; Trotta et al., 2002; Wagner, 2002). However, this lack of association should also be interpreted carefully as it might partly be explained by the fact that the population studied here reported a relatively low number of medical symptoms.

Furthermore, the questionnaire did not distinguish between symptoms of HIV and side effects of medication and the different types of medical symptoms reported by participants were not taken into consideration. It would be expected that gastrointestinal symptoms such nausea/vomiting, which are usually more bothersome and are among the principal causes of medication discontinuation (O'Brien et al., 2003), would have a stronger impact on adherence. Also, the symptoms covered by the questionnaire might not have been representative of the most bothersome symptoms (for example, diarrhea was not included in the list of symptoms).

This dissertation also provided some insight into factors that might be associated with more scepticism about the positive impact of HAART on health status (beliefs about medication efficacy). This exploration of factors associated with scepticism about medication efficacy has important clinical implications since these beliefs about medication efficacy were significantly associated with suboptimal adherence to HAART. The fact that positive beliefs about medication tended to decrease as the number of medical symptoms due to illness or side effects of medication increased is clinically important. Another clinically important association was noted between beliefs about medication and severity of the disease (disease staging): people with an AIDS diagnosis held more positive beliefs about their medication than people at the mildly symptomatic stage. Theses results are interesting because both the number of medical symptoms due to illness or side effects of medication and the severity of the disease were not directly related to HAART adherence, but seem to be indirectly associated to adherence by their impact on participants' beliefs about HAART effect on their health. This finding that participants seemed to be more

sceptical about HAART effect on their health as their number of medical symptoms increased raised an interesting question: could beliefs about medication efficacy be partly based on the number of medical symptoms people are experiencing? Since number of medical symptoms seemed to influence beliefs about medication, this distinction between AIDS and symptomatic stage was also interesting because this might mean that people interpret differently the symptoms that they have as they are diagnosed with AIDS. For those individuals with an AIDS diagnosis, symptoms might be perceived accurately as a progression of the disease, because they are more serious and can directly be associated with AIDS. In contrast, those at the mildly symptomatic stage might misread less serious symptoms as side effects of medication. These hypotheses would need to be tested further before making firm conclusions. However, if these associations were founded, this might emphasize the need for health care providers to be aware of a possibility to misattribute symptoms due to illness progression as side effects of medication in the mildly symptomatic stage.

The lack of association between participants' beliefs about the impact of HAART on their health and important markers of disease progression, such as viral load and having been hospitalized in the past 6 months found in the first article was surprising. This might indicate that people's beliefs about the effect of medication on their health are less related to the clinical reality, and more a function of their own perception. This result was surprising because this seemed to contradict results of the second article in which several participants mentioned that receiving feedback from medical test helped them to better adhere to HAART by improving their "positive perception of medication". However, the

lack of association found in the first article could also be explained by the fact that our measure of viral load was not necessarily taken at the same time as people filled the beliefs questionnaire since it was taken from their most recent medical exam. Therefore, their clinical status might have been somewhat different when they filled the belief questionnaire. Nonetheless, health care provider should be aware that beliefs about medication efficacy may not always reflect the clinical reality of patients and represent instead patients' prior beliefs about medication. It might then be useful to confront theses perceptions with clinical reality (improvements in viral load, CD4 counts, etc.) and to emphasize regularly to patients any progress in health status that could be attributed to medication use.

Exploring other facilitators of adherence mentioned by participants also gave us a clearer idea of the type of day-to-day strategies and motivators that they use to facilitate their adherence to HAART. Knowing what type of strategies HIV-infected individuals use or what motivates them to take their medication in their day-to-day lives may help health care providers tailor their strategies of communication to each individual so as to emphasize the need for strict adherence. It might also be useful to explore the clinical utility of capitalizing on strategies or motivators already adopted by participants in this study such as: internal or external sources of planning, having a globally positive perception of medication use, the use of close social support, making a commitment or using internal motivation, and using self-care strategies.

In addition, comparing reasons for suboptimal adherence to facilitators of adherence raised questions about the use of "planning skills", centered on routine and integration of medication into activities of daily living, as the sole strategy to facilitate adherence. Because reasons for suboptimal adherence at the "worst" adherence time point concerned interferences with daily routine, the use of "planning skills" might not be optimal under a changing context. For example, as HIV-infected individuals regain better health with medication, new challenges emerge as they return to a more active life and have to adapt to disruptions in daily routine on a frequent and unpredictable basis.

The lack of association between adherence status and number or types of facilitators mentioned confirms clinical observations about the complexity of the adherence phenomenon and the individual differences in how to deal with challenges raised by adherence. This could reflect individual preferences toward various kinds of strategies: one type of facilitator might be sufficient on its own for someone, while someone else might need to rely on several facilitators to adhere successfully to his treatments. Exploratory analyses showed that the choice of facilitators tended to be associated with certain participants' characteristics. Based on these preliminary results, health care providers might want to keep in mind patients' characteristics and lifestyle when providing guidance about useful strategies that could improve adherence. This highlights again the importance of listening to patients' stories, and to try to understand their perceptions about medication to have a better grasp at their decision making process. It is even more important to carefully listen to patients given the inherent difficulty of adhering to HAART regimens because of their stringent demands and their impact on quality of life (e.g., side effects).

3. Theoretical implications

Results of both of these articles can provide a better theoretical understanding of adherence behaviours in the context of HAART regimens. Similar to the present studies, much of research in the field of HIV uses an atheoretical approach to study factors associated with suboptimal adherence to medication. Because the two studies included in this dissertation were mainly exploratory, an atheoretical approach offered the advantage of identifying, based on prior studies, a subset of participants' factors that might impact adherence in the current sample. Contrary to other atheoretical approaches that focused on stable patients' characteristics, most of the participants' characteristics studied in article 1 (especially depressive symptoms, beliefs about medication efficacy, substance use problems) were amenable to change. These factors were chosen based on the fact that adherence is not a "static" or "trait" phenomenon and usually varies over time for the same person. Using an atheoretical approach also provided the opportunity to explore new concepts such as beliefs about medication efficacy in order to generate theories or increase our understanding of adherence behaviours.

3.1 Conceptualization of beliefs about medication

Implications for the conceptualization of the types of beliefs that might impact adherence are provided by the results of the first article included in this dissertation: participants' beliefs about the positive impact of HAART on their health (HEXP1 questionnaire) were associated with suboptimal adherence, while beliefs about the positive or negative impact of HAART on daily functioning (HEXP2 questionnaire) were not

associated with adherence. These questionnaires appeared to measure two different theoretical concepts: the first questionnaire was centered on global beliefs about medication effect on health, while the second referred to quality of life issues and expectations about the positive or the negative impact of medication use on daily functioning. Therefore, it seems that global beliefs about medication effect on health directly impact adherence to treatment, while medication impact on functioning or quality of life may have a less direct influence on adherence. However, the strong correlation between these two questionnaires showed the complementary aspect of both concepts. In fact, global functioning is one aspect that influences the type of beliefs a person holds about medication effect on her health. However, the smaller correlation between beliefs about the positive impact of HAART on health (HEXP1) and beliefs about the negative impact of HAART on daily functioning (HEXP2 negative scale), compared to the positive impact of HAART on functioning, may indicate that people's global beliefs about medication effect on health are more strongly affected by the positive impact rather than the negative impact of medication on daily functioning. The second article included in this dissertation also provided a better understanding of factors that influenced "positive perception medication". These conceptual distinctions in types of beliefs about medication efficacy associated with HAART adherence behaviours are important and might need to be distinguished further. It would, in fact, be interesting to distinguish between other types of beliefs that have previously been associated with medication use in other illnesses such as: long-term dangers, danger of medication because of its chemical nature, addiction and dependence, and medicine perceived as a poison (Horne, 1997).

3.2 Theoretical models

Some of the results that emerged in the two articles included in this dissertation point to additional research avenues and may be understood within the context of existing theories. Given that being more skeptical about the positive impact of HAART on health represents a risk factor for suboptimal adherence, and that more skepticism about HAART efficacy is associated with a greater number of medical symptoms due to illness or side effects of medication, one might suggest that the number of medical symptoms may indirectly affect adherence by influencing patients' beliefs. Furthermore, beliefs about HAART efficacy also seemed to be associated with disease stage: patients with an AIDS diagnosis tended to have more positive beliefs about HAART impact on their health than patients at the symptomatic stage of the disease. As exposed earlier, because the number of medical symptoms seemed to influence beliefs about medication, this distinction between AIDS and symptomatic stage might mean that people interpret differently the symptoms that they have as they are diagnosed with AIDS. For those individuals with an AIDS diagnosis, symptoms may be perceived accurately as a progression of the disease, because they are more serious and can directly be associated with AIDS. In contrast, those at the mildly symptomatic stage might misread less serious symptoms as side effects of medication. It would be interesting to test these preliminary hypotheses regarding symptoms representation within a Self Regulatory Model of Illness (Leventhal et al., 1992).

The Self Regulatory Model of Illness (SRMI, see Figure 2, p. 137) implies that health-behaviours are the equivalent of coping responses that are influenced by patients'

beliefs about their illness. It emphasizes the impact of concrete symptom experience in producing representations of illness and guiding the coping response (coping = adherence in the current context). This assumes that individuals' attempts to comprehend and cope with illness are guided by implicit and personal cognitive, as well as emotional representation of illness structured around 5 themes: identity, cause, timeline, consequences and cure/control. Treatment beliefs were recently added to this model by a different author (Horne, 1997). It is believed that representation of treatment or medication will follow the same process as illness representation with symptoms representations influencing beliefs about medication efficacy. The association between beliefs about medication efficacy and adherence, as well as beliefs about medication efficacy and number of medical symptoms due to illness or side effects of medication found in the first article of this dissertation seem to support the importance of the subjective symptom experience in guiding representation of medication and finally adherence (seen here as a coping strategy). This was also outlined in the second article of this dissertation with some participants stating that by perceiving changes in their health status, they believed that the medication was working as it should.

In the same line, Cioffi's Somatic-Perceptual Model (SPM, see Figure 3, p. 138) states that a perceived or inferred somatic change can initiate an interpretative process that creates an internal representations of the symptom which can then be mediated by factors such as: affect, motivation, general disposition, as well as prior hypotheses about this symptom, to eventually produce a given behaviour (Cioffi, 1991).

The problem with both of these models (SRMI and SPM) is that their complexity renders them difficult to test in clinical settings. Very few studies have used this approach in the HIV literature. Results of one recent study (Johnson, Stallworth, & Neilands, 2003) suggested that most HIV-infected individuals made causality attributions regarding physical symptoms experienced and that these attributions varied widely across individuals and physical complaints. This study also found that patients made their own distinctions between symptoms of the disease and side effects of medication.

The second article of this dissertation highlighted important strategies or motivators of adherence behaviours in patients' day-to-day reality, regrouped in categories of adherence facilitators. It is interesting to note that some of the categories of facilitators identified in this second article, namely: "planning skills", "positive perception of medication", "social support", "commitment/internal motivation", reflected some of the 8 key elements of behavioural performance that were identified across the following 5 theoretical models: Health Belief Model, Social Cognitive Theory, Theory of Reasoned Action, Theory of self-regulation, Theory of subjective Culture and Interpersonal relations (Fishbein et al., 2001). The 8 following key elements of behavioural performance were identified by the committee composed of the experts who created each of these 5 theoretical models: (1) a positive intention to perform the behaviour, (2) the lack of environmental constraints that interfere with the behaviour, (3) necessary skills to perform the behaviour, (4) positive anticipated outcomes of performing the behaviour (or positive attitude), (5) normative pressure to perform the behaviour, (6) self-standards: the behaviour is consistent with self-image, (7) emotional reaction to performing the behaviour is more positive than

negative, and (8) belief in the capacity of performing the behaviour (self-efficacy).

Therefore, a more in depth study of adherence facilitators might help provide additional

information on key aspects of adherence behaviours by providing guidelines for further

theoretical development.

3.3 Conceptualization of "adherence"

The questionnaire used to describe the most common reasons for suboptimal

adherence (included in the second article of this dissertation) highlighted the need for a

better operationalization of the term "suboptimal adherence" by taking into consideration

the different motivations that might underlie such adherence difficulties. Because these

reasons were not conceptually regrouped and could have been determined by more than one

factor, the types of conclusions that could be generated from this data were limited. For

example, forgetting could be caused by several factors such as neurological factors or

distractions from daily routine. Therefore, in addition to the inherent difficulties associated

with adherence measurement that were discussed in the introduction of this dissertation, an

added complexity to this field of research is to adequately conceptualize the term

"adherence". "Adherence" is often not operationalized clearly in the current literature and

frequently regroups different types of adherence behaviours. For example, a distinction can

be made between unintentional and intention non-adherence. Horne (Horne, 1997) defines

unintentional non-adherence as: non-adherence that happens when the patient's intentions

are hindered by barriers such as forgetting, inability to follow treatment because of poor

understanding, or physical problems such as poor eyesight. Intentional non-adherence is

defined as: non-adherence that is deliberate or intentional and happens when the patient's actively decides to not follow his treatment as instructed. It might also be beneficial to distinguish between consistent self-tailoring of regimen that does not follow medical advice, and intentional non-adherence that results in skipping doses once in a while, as they might be generated by different types of motivations and might not be comparable. By regrouping different kinds of adherence behaviour we are in fact studying different concepts which could explain the divergent results found in the literature on the influence of several aspects such as demographic characteristics, as well as other psychological characteristics on adherence to medication.

4. Limitations

Both studies included in this dissertation have limitations that affect the generalizability of the findings. Firstly, like most studies that explored adherence to medication over the long term, the current sample of participants might not have been representative of the general HIV-infected population because they "adhered" to a year-long study. Secondly, people who dropped out or were excluded from our sample were significantly different from the final sample on two aspects: they tended to have a lower income and to report intravenous drug use as a risk factor for HIV-infection more often than individuals in the study sample. Third, the sample was mainly composed of Caucasian gay men. It was also possible that the adherence rate might have been biased by the use of self-reported scale, which usually tends to overestimate adherence rates. It was originally planned to use MEMS caps with a subgroup of participants but they refused to use them

because of convenience issues. However, self-reported adherence questionnaires have been found to provide adequate adherence measures because of their correlation with other adherence measures (Deeks, 2000; Duong et al., 2001; Hugen et al., 2002) and their ability to predict therapeutic outcome, as measured by HIV RNA level and CD4+ cell counts (Mannheimer et al., 2002; Walsh, Mandalia et al., 2002).

Because of the study design, it was not possible to control for several variables such as: changes in medication regimens over time, time since tested HIV-positive, and type of medication taken (various HAART regimens). The fact that HAART medication regimens were not identical might also have influenced the results of this dissertation, as different types of medication come with more or less bothersome side effects and have different impacts on functioning. However, because this study was not based on a clinical trial and used a convenience sample it was not possible to control the type of HAART medication taken given the variability of medication combinations available for patients. The measure of adherence facilitators was also limited by the design of this research which did not allow to control for time of administration (the measure was taken at different time intervals from baseline). However, the results at the Adherence Facilitators Questionnaire should be relatively stable over a period of several months because participants in the study had been taking medication for a few years and were being asked what generally helped them adhere to HAART. It can be reasonably postulated that these individuals had developed a set of habits and/or strategies to facilitate adherence. In addition, the question that probed about participants' adherence facilitators might have been too broad and did not distinguish adequately between strategies and motivators of adherence. Also, its written format did not

allow to clarify participants' answers. Finally, the current sample size may have affected the ability to detect smaller associations, and did not allow a clear estimate of the impact of each risk factor for suboptimal adherence in the first article of this dissertation.

5. Strengths

The main strength of this dissertation is the use of both a quantitative and a qualitative methodology to gain a better understanding of adherence behaviours. Medication adherence was also measured longitudinally over periods of approximately 6 months to 1 year. This is very uncommon in HIV research given the inherent difficulties of following patients over long periods of time. In fact, adherence behaviours are often only measured over the past few days in most of the HIV literature.

This dissertation replicated previous results and identified important risk factors for suboptimal adherence. This dissertation also explored a newly developing area of adherence behaviour research: beliefs about HAART efficacy. Even if the results of this dissertation should be considered exploratory, they provided some guidelines for clinical practice as well as for further theoretical conceptualization of adherence behaviours. This dissertation also added a complementary perspective to the field of HIV medication adherence by looking at both sides of adherence behaviours: what impedes and what facilitates adherence to HAART as expressed by HIV-infected individuals. In this regard, it has the strength of listening to what participants' believe is helpful and including their perspective on HAART adherence. Most of the adherence studies, while providing

additional information about patient's behaviours, limited their focus on obstacles or barriers to adherence. As such, it is interesting to study the other side of the problem by also exploring facilitators of adherence. Focussing on strategies or motivators of adherence already used effectively by patients in their day-to-day lives may bring a more positive outlook in this field. It might also empower patients by taking into consideration their daily efforts and struggles with adhering to HAART regimens. It also has the added advantage of giving a voice to patients in a field where it has often been neglected.

6. Future directions

Several avenues are left to be explored to better understand adherence behaviour as it pertains to the field of HIV research. Definition and measurement of adherence have to be studied further. It will be important to define the concept of "adherence" more precisely in order to distinguish between types of suboptimal adherence that might be conceptually different (e.g.: intentional non-adherence vs. unintentional non-adherence). A better operationalization of the term "adherence" may bring more clarity to this field of research. It will also become essential to improve adherence measurement in order to obtain more consistent results.

As it is important to use atheoretical approaches to explore new avenues in regard to factors associated with adherence, it is as important to understand the underlying reasons why a factor may interfere with adherence within existing theories. Therefore, there is a need for sound theory-based research in the field of HIV medication adherence.

It would also be interesting to study the meaning of HAART medication in patients' life and to explore more thoroughly patients' beliefs about the efficacy of HAART. In order to have a more complete conceptual understanding of beliefs about medication efficacy, these beliefs would need to be studied in a longitudinal design to see if they fluctuate and to measure their impact on HAART adherence over time. It will be essential to combine research and clinical intervention studies in order to generate clearer guidelines on how to help HIV-infected individuals handle such challenging medication regimens on a day-to-day basis over long periods of time.

Individuals taking HAART regimens have difficult living conditions which need to be taken into consideration while providing support for HAART adherence. It is also important to keep in mind that these regimens might be perceived as a constant reminder of the "sick role" identity. In this context, it will be essential to study more thoroughly the likely ambivalence patients have about taking medication that will help them live longer, but will negatively affect other spheres of their life and often produce distressing side effects. In this regard, studying both sides of the decision making process regarding adherence to HAART is essential in order to get a better understanding of patients' ambivalence toward medication use. Could exploring both side of the decision making process bring a better understanding of patients' representations of HAART and help us understand how these regimens are integrated into patients' identify?

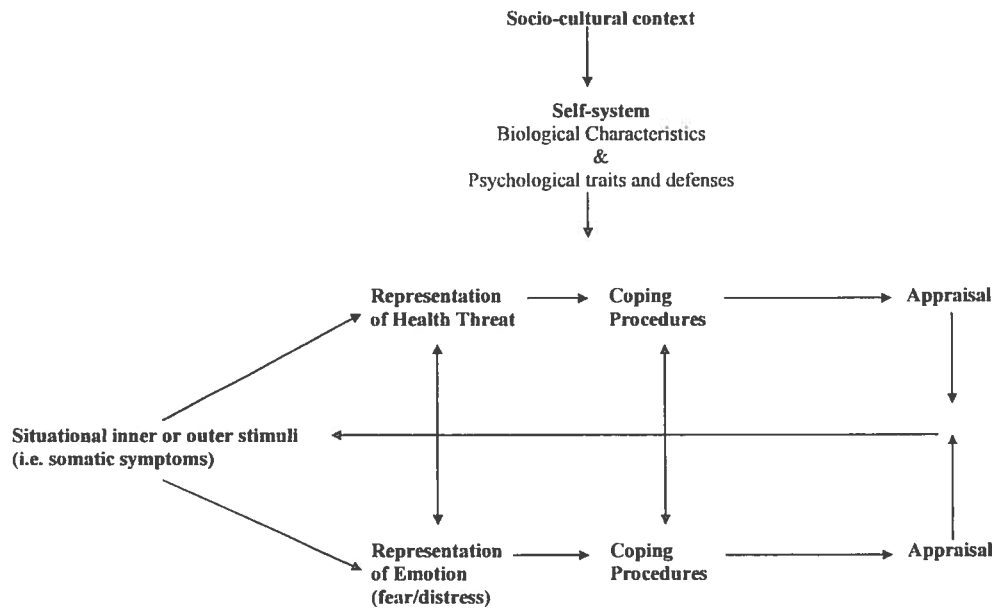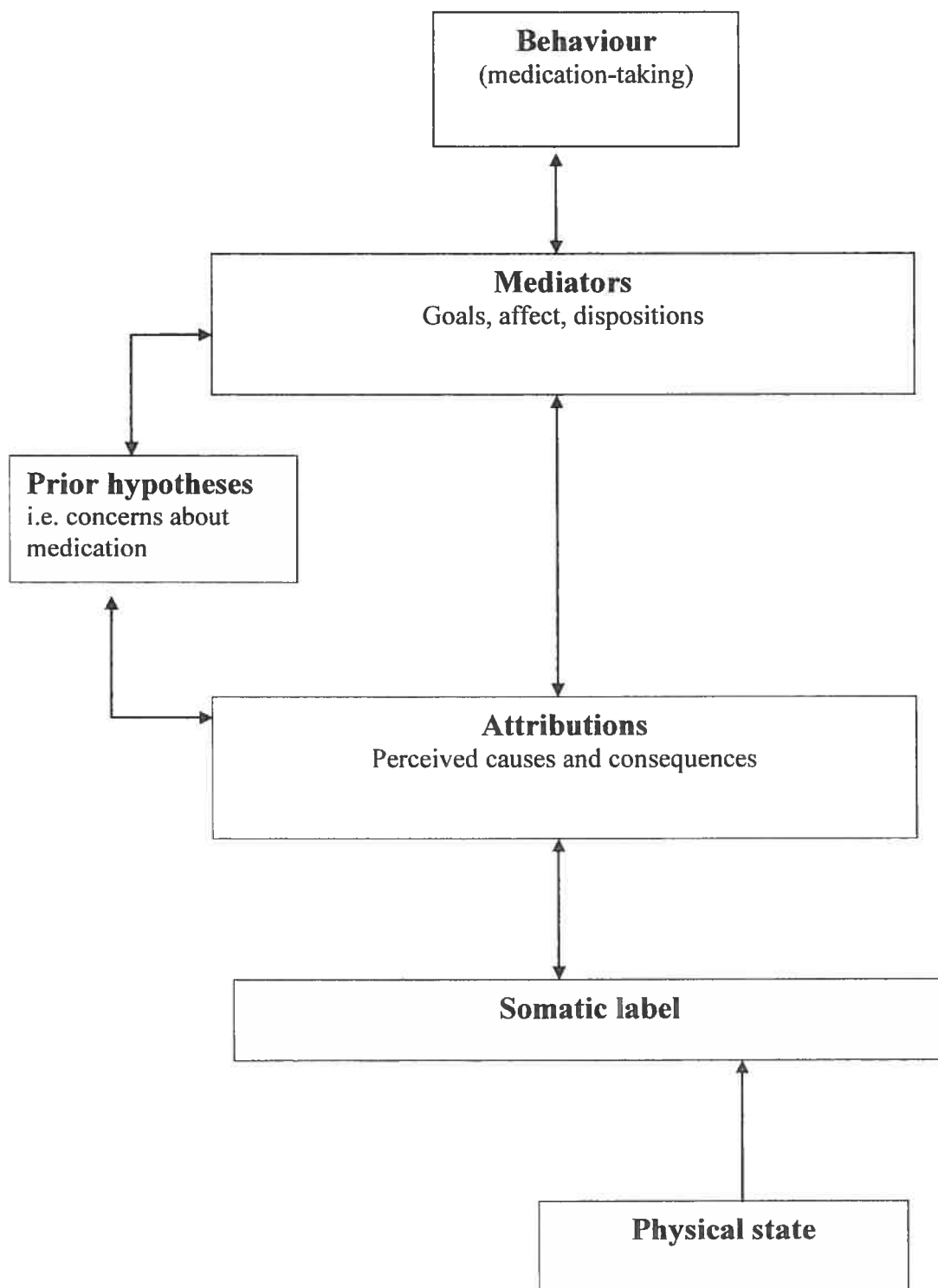Figure 2. Self Regulation Model (adapted from Leventhal, 1992)

Figure 3. Cognitive-Perceptual Model of Somatic Interpretation (adapted from Cioffi, 1991)

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Annex A :Questionnaires

How did you find out about this study?

(or who referred you?)_____

Date of Birth: (dd-mon-year)___ - _____-_____Age___

Gender   male ☐
female ☐
transgender ☐

EDUCATION

The highest grade level obtained in school: Total number of years in school_____ years

grades 0 to 8 ☐   grades 9 to 11 ☐   grades 9 to 12 ☐   Received high school diploma? Yes ☐
No ☐

Years of university or college completed: Bachelor ☐   Masters ☐   PhD ☐   MD ☐   JD ☐
1 ☐   2 ☐   3 ☐ 4 ☐   5 or more ☐   Diploma obtained: _____

RELATIONSHIP STATUS   single ☐   married ☐   separated/divorced ☐
common-law ☐   living with partner ☐   partner/spouse died ☐

CURRENT EMPLOYMENT STATUS   paid full-time ☐   paid part-time ☐ #hours/week___
self-employed full-time ☐   self-employed part-time ☐ #hours/week___
Volunteer ☐   unemployed ☐   student ☐   retired ☐   longterm disability ☐
#hours/week___

If not currently employed when did you work last   dd - mon - year   How long on disability?
____years   _____months
---- ------- -------

MEDICATION PAYMENT PLAN (check all that apply)   private/group insurance ☐ %coverage_____
Trillium plan ☐   ODSP (Family Benefits) ☐   Homecare ☐
Social Assistance (Welfare) ☐ Personal/household income ☐
Personal savings ☐   Other ☐ _____

Monthly Payments for HIV medications (typical) $_____

Monthly Income (typical) $_____

SOURCE OF INCOME (check all that apply)   long-term disability ☐   Canada pension plan disability ☐
support from friends/family ☐   ODSP(Family Benefits) ☐
employment ☐   social assistance (welfare) ☐   Other ☐ _____
personal

	DEMO1	id#
HAART Adherence in HIV Infection Project	dd - mon - year ___ _____ _____	eval#

savings☐ _____

Number of dependents: None☐ How many?_____

HAART Adherence in HIV Infection Project	DEMO2	id#
	dd - mon - year	eval#
	____ _____ _____	

What is your birthplace?	Country_____	If not Canada then how long in Canada? ___years
What is your mother's birthplace?	Country_____	If not Canada then how long in Canada? ___years
What is your father's birthplace?	Country_____	If not Canada then how long in Canada? ___years
When you were growing up as a child, what language(s) did you speak?	_____ _____ _____	Where was this? Country_____
At what age did you first learn to speak English?	_____	Do you consider yourself fluent in English? No☐ Yes☐
Do you have any religious or spiritual affiliation?	No☐ Yes☐	If yes, what is the religion? _____
What is your current sexual orientation?	gay☐ heterosexual☐ bisexual☐ lesbian☐ other☐	
Are you involved in community activities? No☐ Yes☐ (meetings, festivities, fundraising, advocacy)	If yes, how would you describe the community? _____	

This is your individualized medication monitor.
(C:.DAT revised on December 12, 2001)

The following should be an accurate description of the medicines currently prescribed by your doctor:

150mg 3TC: 1 white diamond pill twice per day.

40mg d4T: 1 brown pill twice per day.

400mg Crixivan: 2 white and green pills twice per day.

100mg ritonavir: 2 beige pills twice per day.

If this is NOT correct, ask your HAART project contact person to create a new up-to-date individualized medication monitor for you and do not complete this outdated form.

CIRCLE all appropriate answers. If you can't remember, give your best estimate. If that is not possible, circle the question mark at the end of the line so that all lines are marked with one circle.

Think about yesterday.
Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

How many times did you take the white diamond pill   none   once   twice   3x   4x   ?

How many times did you take the brown pill   none   once   twice   3x   4x   ?

How many times did you take both of the 2 white and green pills   none   once   twice   3x   4x   ?
How many times did you take only one of the 2 white and green pills   none   once   twice   3x   4x   ?

How many times did you take both of the 2 beige pills   none   once   twice   3x   4x   ?
How many times did you take only one of the 2 beige pills   none   once   twice   3x   4x   ?

Think about the day before yesterday (2days ago).
Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

How many times did you take the white diamond pill   none   once   twice   3x   4x   ?

How many times did you take the brown pill   none   once   twice   3x   4x   ?

How many times did you take both of the 2 white and green pills   none   once   twice   3x   4x   ?
How many times did you take only one of the 2 white and green pills   none   once   twice   3x   4x   ?

How many times did you take both of the 2 beige pills   none   once   twice   3x   4x   ?

How many times did you take only one of the 2 beige pills   none once twice 3x 4x ?

Think about your actvities 3 days ago.

Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

How many times did you take the white diamond pill   none once twice 3x 4x ?

How many times did you take the brown pill   none once twice 3x 4x ?

How many times did you take both of the 2 white and green pills   none once twice 3x 4x ?
How many times did you take only one of the 2 white and green pills   none once twice 3x 4x ?

How many times did you take both of the 2 beige pills   none once twice 3x 4x ?
How many times did you take only one of the 2 beige pills   none once twice 3x 4x ?

Think about your actvities 4 days ago.

Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

How many times did you take the white diamond pill   none once twice 3x 4x ?

How many times did you take the brown pill   none once twice 3x 4x ?

How many times did you take both of the 2 white and green pills   none once twice 3x 4x ?
How many times did you take only one of the 2 white and green pills   none once twice 3x 4x ?

How many times did you take both of the 2 beige pills   none once twice 3x 4x ?
How many times did you take only one of the 2 beige pills   none once twice 3x 4x ?

Think about your actvities 5 days ago.

Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

How many times did you take the white diamond pill   none once twice 3x 4x ?

How many times did you take the brown pill   none once twice 3x 4x ?

How many times did you take both of the 2 white and green pills   none once twice 3x 4x ?
How many times did you take only one of the 2 white and green pills   none once twice 3x 4x ?

How many times did you take both of the 2 beige pills   none once twice 3x 4x ?
How many times did you take only one of the 2 beige pills   none once twice 3x 4x ?

Think about your actvities 6 days ago.

Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

	none	once	twice	3x	4x	?
How many times did you take the white diamond pill	none	once	twice	3x	4x	?
How many times did you take the brown pill	none	once	twice	3x	4x	?
How many times did you take both of the 2 white and green pills	none	once	twice	3x	4x	?
How many times did you take only one of the 2 white and green pills	none	once	twice	3x	4x	?
How many times did you take both of the 2 beige pills	none	once	twice	3x	4x	?
How many times did you take only one of the 2 beige pills	none	once	twice	3x	4x	?

Think about your actvities 7 days (a week) ago.

Day of the week(circle one): [MON   TUE   WED   THU   FRI   SAT   SUN]

	none	once	twice	3x	4x	?
How many times did you take the white diamond pill	none	once	twice	3x	4x	?
How many times did you take the brown pill	none	once	twice	3x	4x	?
How many times did you take both of the 2 white and green pills	none	once	twice	3x	4x	?
How many times did you take only one of the 2 white and green pills	none	once	twice	3x	4x	?
How many times did you take both of the 2 beige pills	none	once	twice	3x	4x	?
How many times did you take only one of the 2 beige pills	none	once	twice	3x	4x	?

Instructions: This questionnaire consists of 21 groups of statements. Please read each group of statements carefully, and then pick out the **one statement** in each group that best describes the way you have been feeling during the **past two weeks, including today.** Check (√) the box beside the statement that you have picked. If several statements in the group apply equally well, check off the highest number for that group. Make sure to read all statements in each group before marking a statement.

Place one and only one check (√) in each group.

1. Sadness
0□ I do not feel sad.
1□ I feel sad much of the time.
2□ I am sad all the time.
3□ I am so sad or unhappy that I can't stand it.

2. Pessimism
0□ I am not discouraged about my future.
1□ I feel more discouraged about my future than I used to be.
2□ I do not expect things to work out for me.
3□ I feel my future is hopeless and will only get worse

3. Past Failure
0□ I do not feel like a failure.
1□ I have failed more than I should have.
2□ As I look back, I see a lot of failures.
3□ I feel I am a total failure as a person.

4. Loss of Pleasure
0□ I get as much pleasure as I ever did from the things I enjoy.
1□ I don't enjoy things as much as I used to.
2□ I get very little pleasure from the things I used to enjoy.
3□ I can't get any pleasure from the things I used to enjoy.

5. Guilty Feelings
0□ I don't feel particularly guilty.
1□ I feel guilty over many things I have done or should have done.
2□ I feel quite guilty most of the time.
3□ I feel guilty all of the time

6. Punishment Feelings
0□ I don't feel I am being punished.
1□ I feel I may be punished.
2□ I expect to be punished.
3□ I feel I am being punished.

7. Self-Dislike
0□ I feel the same about myself as ever.
1□ I have lost confidence in myself.
2□ I am disappointed in myself.
3□ I dislike myself.

8. Self-Criticalness
0□ I don't criticize or blame myself more than usual.
1□ I am more critical of myself than I used to be.
2□ I criticize myself for all of my faults.
3□ I blame myself for everything bad that happens.

9. Suicidal Thoughts or Wishes
0□ I don't have any thoughts of killing myself.
1□ I have thoughts of killing myself, but I would not carry them out.
2□ I would like to kill myself.
3□ I would kill myself if I had the chance.

10. Crying
0□ I don't cry anymore than I used to.
1□ I cry more than I used to.
2□ I cry over every little thing.
3□ I feel like crying, but I can't.

11. Agitation

0☐ I am no more restless or wound up than usual.

1☐ I feel more restless or wound up than usual.

2☐ I am so restless or agitated that it's hard to stay still.

3☐ I am so restless or agitated that I have to keep moving or doing something.

12. Loss of Interest

0☐ I have not lost interest in other people or activities.

1☐ I am less interested in other people or things than before.

2☐ I have lost most of my interest in other people or things.

3☐ It's hard to get interested in anything.

13. Indecisiveness

0☐ I make decisions about as well as ever.

1☐ I find it more difficult to make decisions than usual.

2☐ I have much greater difficulty in making decisions than I used to.

3☐ I have trouble making any decisions.

14. Worthlessness

0☐ I do not feel I am worthless.

1☐ I don't consider myself as worthwhile and useful as I used to.

2☐ I feel more worthless as compared to other people.

3☐ I feel utterly worthless.

5. Loss of Energy

0☐ I have as much energy as ever.

1☐ I have less energy than I used to have.

2☐ I don't have enough energy to do very much.

3☐ I don't have enough energy to do anything.

16. Changes in Sleeping Pattern

0☐ I have not experienced any change in my sleeping pattern.

1☐ I sleep somewhat more than usual.

1☐ I sleep somewhat less than usual

2☐ I sleep a lot more than usual.

2☐ I sleep a lot less then usual.

3☐ I sleep most of the day.

3☐ I wake up 1-2 hours early and can't get back to sleep.

17. Irritability

0☐ I am no more irritable than usual.

1☐ I am more irritable than usual.

2☐ I am much more irritable than usual.

3☐ I am irritable all the time.

18. Changes in Appetite

0☐ I have not experienced an change in my appetite.

1☐ My appetite is somewhat less than usual.

1☐ My appetite is somewhat greater than usual.

2☐ My appetite is much less than before.

2☐ My appetite is much greater than usual.

3☐ I have no appetite at all.

3☐ I crave food all the time.

19. Concentration Difficulty

0☐ I can concentrate as well as ever.

1☐ I can't concentrate as well as usual.

2☐ It's hard to keep my mind on anything for very long.

3☐ I find I can't concentrate on anything.

20. Tiredness or Fatigue

0☐ I am no more tired or fatigued than usual.

1☐ I get more tired or fatigued more easily than usual.

2☐ I am too tired or fatigued to do a lot of the things I used to do.

3☐ I am too tired or fatigued to do most of the things I used to do.

21. Loss of Interest in Sex

0☐ I have not noticed any recent change in my interest in sex.

1☐ I am less interested in sex than I used to be.

2☐ I am much less interested in sex now.

3☐ I have lost interest in sex completely.

HAART Adherence in HIV Infection Project	SYMP2	id#
	dd - mon - year	eval#
	____ _____ _____	

Have you experienced any of the following? (place check marks √ in all boxes that apply)	Never	For 2 or more weeks in past 6 months	In past 2 weeks	In past week
1. stiffness				
2. cravings				
3. nausea or vomiting				
4. muscle weakness				
5. poor appetite				
6. heartburn				
7. muscle pain				
8. numbness and/or tingling				
9. constipation				
10. severe cramps				
11. chills				
12. enlarged glands				
13. difficulty getting to sleep				
14. dizziness				
15. enlarged lymph nodes				
16. headache				
17. low libido				
18. body change				
19. poor quality of sleep				
20. difficulty with concentration				
21. forgetfulness				

If you experienced any of the above in the the past 6 months:

How much did it affect your day-to-day functioning? not at all☐   somewhat☐   a great deal☐

How much did it reduce your quality of life?   not at all☐   somewhat☐   a great deal☐

Please check the box (√) that best describes how confident you are of receiving these benefits from the medications you are taking:

1. Anti-HIV agents (e.g., AZT1, 3TC, d4T, ddl, crixivan, ritonavir, saquinavir etc.)...

	not at all confident	somewhat confident	very confident
Prolong Life			
Prevent Symptoms			
Boost Immunity			
Complement Other Agents			
Improve Functioning			
Increase Well-Being			

2. Preventative Medications (e.g. Septra,dapsone,pentamidine,etc.) for infections like CMV,PCP, etc.

	not at all confident	somewhat confident	very confident
Prolong Life			
Prevent Symptoms			
Boost Immunity			
Complement Other Agents			
Improve Functioning			
Increase Well-Being			

3. Alternative Treatments (e.g., herbal medicines, high dose vitamins, etc.)

	not at all confident	somewhat confident	very confident
Prolong Life			
Prevent Symptoms			
Boost Immunity			
Complement Other Agents			
Improve Functioning			
Increase Well-Being			

4. Nutritional Supplements (e.g., Boost, Ensure, etc.)

	not at all confident	somewhat confident	very confident
Prolong Life			
Prevent Symptoms			
Boost Immunity			
Complement Other Agents			
Improve Functioning			
Increase Well-Being			

Specifically regarding HAART medications, how MUCH <u>benefit</u> are you receiving, or expect to receive from these medications

(please check √ one answer only for each item)

	None	A Little	Some	A Lot
1. Increase in energy levels and/or appetite				
2. General well-being				
3. Restored libido/sex drive				
4. Increase your capacity to perform daily activities				
5. Increase the likelihood of returning to part-time or full-time work				
6. Increase in CD4 cell count				
7. Decrease in viral load				

How much do you feel these medications are <u>NEGATIVELY</u> affecting the following:

(please check √ one answer only for each item)

	Strongly	Moderately	Mildly	No Effect
1. The amount of time you spent on work or other activities				
2. Your ability to accomplish what you want in your regular daily activities				
3. The kind of work or activities you would like to do				
4. Your ability to work at a job or go to school				
5. Your ability to work around your home (e.g., cooking, cleaning)				
6. Your ability to care for yourself				
7. Your social activities (like visiting with friends or close relatives)				

	REASONS	id#
HAART Adherence in HIV Infection Project	dd - mon - year ---- ------- -------	eval#

People may miss taking their medications for various reasons. Here is a list of possible reasons why you may have missed taking your medications in the past week.

How often have you missed taking your medications because you:	Place a checkmark ✓ in the appropriate box			
	Never	Rarely	Sometimes	Often
Slept in late OR went to bed early				
Fell asleep and slept through dose time				
Busy with other things				
Lost track of time				
Forgot				
Could not find a place where no one would see you taking medicines				
Was having problems with side effects				
Didn't want to take them				
Had a change in daily routine				
Was traveling or away from home				
Wasn't feeling well				
Felt too tired				
Felt depressed				
Felt stressed out				
Could not follow eating pattern required by medication				
Had too many pills to take				
Felt like the drug was toxic or harmful to health				
Ran out of pills				
Felt good				

	ADHQ	id#
HAART Adherence in HIV Infection Project	dd - mon - year	eval#
	___ ___ ___	

What do you find particularly helpful in your life that helps you adhere to the HAART medication? That is, things you do for yourself, things you tell yourself, objects that you value, techniques that you find useful, people in your life, etc. Please describe.

_____

_____

_____

_____

_____

_____

_____

HAART Adherence in HIV Infection Project

NCOND1

id#	
dd - mon - year	eval#
____ _____ _____	

	NO	YES	month	year
1. Premature weight, i.e., more than 4 weeks				
2. Weight less than 5 pounds				
3. Mother had difficult pregnancy				
4. Birth complications				
5. Special observation due to medical problems at birth				
6. Major illness before 6 yrs				
7. Seizures 2nd to fevers before 6 years				
	NO	YES	month	year
8. Learning difficulties in school				
9. Attended speech therapy in school				
10. Required special education classes or tutoring				
11. Diagnosed with a learning disability				
12. Diagnosed with Dyslexia				
13. Diagnosed with ADHD				
14. Held back a grade in school				
	NO	YES	month	year
15. 1st head injury with unconsciousness				

Length of loss of consciousness for 1st head injury(in mins) ..._____
Days hospitalized for 1st head injury ...._____
Number of days amnesic with 1st head injury ...._____
Residual neurological symptoms with 1st head injury ....Yes☐   No☐

	NO	YES	month	year
16. 2nd head injury with unconsciousness				

Length of loss of consciousness for 1st head injury(in mins) ..._____
Days hospitalized for 1st head injury ...._____
Number of days amnesic with 1st head injury ...._____
Residual neurological symptoms with 1st head injury ....Yes☐   No☐

	NO	YES	month	year

	NO	YES	month	year
17. Additional head injuries (>2) with complications				
18. Evaluated by neurologist or neurosurgeon				
19. Estimated number of seizures				
20. History of epilepsy				
21. History of meningitis				
22. History of encephalitis				
23. History of migraines or severe headaches				
24. Given EEG				
25. Given MRI scan				
26. Given CT scan				
27. Given other brain test (see code)				
28. Previous cognitive/NP testing				
29. Alcohol blackouts				
30. Seizures secondary to ethanol or drugs				
31. Unconscious due to drug overdose				
32. Unconscious due to ethanol overdose				
33. Received general anesthesia				
34. Loss of consciousness because of lack of oxygen				
35. Loss of consciousness because of toxic fumes				
36. Received CPR				
37. High blood pressure (>140/90)				
38. History of coronary artery disease				
39. Currently elevated liver function tests				
40. History of elevated liver function tests elevated				
41. Diagnosis of hepatitis A				
42. Diagnosis of hepatitis B				

	NO	YES	month	year
43. Diagnosis of hepatitis C				
44. Diagnosis of cirrhosis				
45. History of kidney disease or complications				
46. History of thyroid complications				
47. Chronic lung disease (e.g., COPD)				
48. Diagnosis of asthma				
49. Anemia/chronic blood disease				
50. Diagnosis of Type I diabetes				
51. Diagnosis of Type II diabetes				
52. Other metabolic disease				

	NO	YES	month	year
53. Elevated cholesterol or triglycerides				
54. Diagnosis of lipodystrophy				
55. Diagnosis of arthritis				
56. Current neuropathy in hands				
57. Current neuropathy in feet				
58. History of neuropathy (not current)				
59. Diagnosis of cancer				
60. Number of overnight hospitalizations				
61. Other medical condition_____				
62. Other medical condition_____				

	No never	In past 6 months	In past year	More than a year ago
1. Received psychiatric and/or psychologic help				
2. Diagnosed as having a psychiatric condition describe_____				
2. Hospitalization for psychiatric condition describe_____				
3. Medication for psychiatric condition describe_____				

4. Other treatment for psychiatric condition: describe_____				
5. Psychotherapy or counseling				

HCOND1	id#

HAART Adherence in HIV Infection Project

dd - mon - year	eval#
____ _____ _____	

Please review the illnesses listed below and if you have ever experienced any of these, provide the date when last experienced (specify approximate month and year only)	Date when last occurred
1. Pelvic Inflammatory Disease (PID)	Month_____ Year____
2. Cryptosporia	Month_____ Year____
3. Salmonella septicemia	Month_____ Year____
4. Hairy Leukoplakia, oral	Month_____ Year____
5. Tuberculosis (TB)	Month_____ Year____
6. Cytomegalovirus (CMV)	Month_____ Year____
7. Kaposi's Sarcoma	Month_____ Year____
8. Cervical Dysplasia	Month_____ Year____
9. Histoplasmosis	Month_____ Year____
10. Toxoplasmosis	Month_____ Year____
11. Lymphoma	Month_____ Year____
12. Coccidioidomycosis	Month_____ Year____
13. Pneumonia (PCP)	Month_____ Year____
14. Folliculitis	Month_____ Year____
15. Progressive Multifocal Leukoencephalopathy (PML)	Month_____ Year____
16. Encephelolopathy	Month_____ Year____
17. Shingles (zoster) involving at least two distinct episodes	Month_____ Year____
18. Isosporiasis	Month_____ Year____
19. Mycobacterium Avium Intracellulare (MAI) or Complex (MAC)	Month_____ Year____
20. Peripheral Neuropathy	Month_____ Year____
21. Constitutional symptoms (fever 38.5°C or more; diarrhea) for more than 1 month	Month_____ Year____
22. Idiopathic Thrombocytopenic Purpura	Month_____ Year____
23. Listeriosis	Month_____ Year____
24. Bacillary Angiomatosis	Month_____ Year____
25. Candidiasis, vulvovaginal	Month_____ Year____
26.	Month_____ Year____
27.	Month_____ Year____
28.	Month_____ Year____

HAART Adherence in HIV Infection Project	HCOND2	id#
	dd - mon - year	eval#
	____ _____ _____	

Hospitalizations in past 6 months:

1. When?_____ Duration_____ Reason_____

   _____

2. When?_____ Duration_____ Reason_____

   _____

3. When?_____ Duration_____ Reason_____

   _____

4. When?_____ Duration_____ Reason_____

   _____

What hand do you use for writing?   Right☐   Left☐   Both right and left☐

Race: Black☐   Caucasian☐   Asian☐   South Asian☐   North-American Aboriginal☐   Hispanic☐   Other_____

Date first tested HIV positive (dd MMM yyyy) _____

Risk factor(s) for HIV (mark all that apply)

heterosexual sexual contact☐   same sex sexual contact/MSWM☐   blood transfusion☐   intravenous drug use☐

other_____

Please mark (√) the answer that is correct for you.

			Two to four times a month	Two to three times a week	Four or more times a week
1. How often do you have a drink containing alcohol?	Never or less ☐	Monthly ☐	☐	☐	☐

	none	1 or 2	3 or 4	5 or 6	7 or 9	10 or more
2. How many drinks containing alcohol do you have on a typical day when you are drinking?	☐	☐	☐	☐	☐	☐

	none	1-4	5-8	9-12	13-15	16 or more
3. How many drinks containing alcohol do you have on a typical week?	☐	☐	☐	☐	☐	☐

	Never	Less than monthly	Monthly	Weekly	Daily or almost daily
4. How often do you have six or more drinks on one occasion?	☐	☐	☐	☐	☐
5. How often during the last year have you found that you were not able to stop drinking once you had started?	☐	☐	☐	☐	☐
6. How often during the last year have you failed to do what was normally expected from you because of drinking?	☐	☐	☐	☐	☐
7. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?	☐	☐	☐	☐	☐
8. How often during the last year have you had a feeling of guilt or remorse after drinking?	☐	☐	☐	☐	☐
9. How often during the last year have you been unable to remember what happened the night before because you had been drinking?	☐	☐	☐	☐	☐

	No		Yes, but not in the last year		Yes, during the last year
10. Have you or someone else been injured as a result of your drinking?	☐		☐		☐
11. Has a relative or friend, or a doctor or other health worker been concerned about your drinking or suggested you cut down?	☐		☐		☐

		DRUGS1	id#
HAART Adherence in HIV Infection Project		dd - mon - year	eval#
		___ ____ _____	

Have you ever smoked tobacco?	never☐	started at age_____	still smoking☐ or quit at age_____

The following questions concern information about your potential involvement with drugs excluding <u>alcohol and tobacco</u> during the <u>past 12 months</u>. Carefully read each statement and decide if your answer is "No' or "Yes'. Then, check (√) the appropriate box beside the question.

The phrase *"recreational drugs"* means any non-medical use of drugs and the use of prescribed or over-the-counter drugs in excess of the directions. The various classes of drugs may include: cannabis (e.g., marijuana, hash), tranquilizers (e.g., Valium), barbiturates, cocaine, stimulants (e.g., speed), hallucinogens (e.g., LSD) or narcotics (e.g., codeine or heroin) or solvents. Remember that the following questions <u>do not</u> indude alcohol or tobacco.

	No	Yes
1. Have you used drugs other than those required for medical reasons?		
2. Have you used prescription drugs in excess of directions?		
3. Do you use more than one recreational drug at a time?		
4. Can you get through the week without using recreational drugs?		
5. Are you always able to stop using recreational drugs when you want to?		
6. Have you had "blackouts" or "flashbacks" as a result of recreational drug use?		
7. Do you ever feel bad or guilty about your recreational drug use?		
8. Does your partner/spouse (or parents) ever complain about your involvement with drugs?		
9. Has the use of drugs created problems with your partner/spouse or your parents?		
10. Have you lost friends because of your recreational drug use?		
11. Have you neglected your family because of your use of recreational drugs?		
12. Have you been in trouble at work because of your use of recreational drugs?		
13. Have you lost a job because of your use of recreational drugs?		
14. Have you gotten into fights when under the influence of recreational drugs?		
15. Have you engaged in illegal activities in order to obtain recreational drugs?		
16. Have you been arrested for possession of illegal drugs?		
17. Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking recreational drugs?		
18. Have you had medical problems as a result of your recreational drug use (e.g., memory loss, hepatitis, convulsions, bleeding, etc.)?		
19. Have you gone to anyone for help for a drug problem?		
20. Have you been involved in a treatment program specifically related to recreational drug use?		

Annex B : Consent forms

GENERAL INFORMATION

INFORMM-HAART Study
(Identification of Necessary Factors for Medication Management of HAART)

The **INFORMM-HAART Study** focuses on identifying key things that might affect a person's ability to strictly follow antiretroviral medication directions as prescribed. The reason why this is important is that if we can identify specific things that are associated with helping people better manage their medications effectively, then we can help to maximize the therapeutic effectiveness of the medications (i.e., in reducing plasma viral load or to maximize CD4 Lymphocyte counts).

In this study, we will be recruiting and following over 9 months 250 individuals with HIV-infection on highly active antiretroviral therapy (HAART) or triple-drug antiretroviral therapy.

Here are the essential requirements of the study:

We will ask you to come in to the study office to complete questionnaires and cognitive tests at various intervals across the 9 months of the study. You will be asked to complete (a) 3-hour assessment during the 1st and 9th month of the study and (b) 1-hour assessments during the 3rd and 6th month of the study. For the 3-hour assessments, you will receive $ 50.00, and $ 20.00 for the 1-hour assessments.

Over the course of the 9 months of the study, we will ask you to complete weekly medication checklists that take about 5-10 minutes to complete. We will ask you to keep track of these ratings and we will ask that every month we go over these ratings with you at least twice (i.e., once every 2 weeks). We would like for you to come in to the study office for at least one of these 2 monitoring sessions, but the other can be done by phone. These sessions will take 15-30 minutes and you will receive $10.00 for each one completed. If it does not interfere with your regular medication schedule, we may ask you to use an electronic pill bottle for one of your medications. This electronic pill bottle has a microchip in its cap that keeps track of when you open and close your medication bottle. If you agree to use it, we would have you bring in it every two weeks (which would coincide with your bi-weekly medication monitoring session) so that we can download the information into a computer.

All sessions will be arranged at times that are convenient for you any time Monday thru Friday from 8:00 am until 7:00 pm.

The interviews, tests, and questionnaires that you will receive during the course of study involve no specific risks or discomforts beyond that of a standard clinical interview situation.

We will ask you for permission to contact your primary care physician to get confirmation of your HIV status and also to collect regular blood results (e.g., CD4, viral load, etc). We are asking your permission to do this so that we do not have to ask you to have any additional blood draws.

There is certain information that is collected as part of this study that you may want for us to communicate to your primary care physician or specialist and we would be glad to do this with your consent. Related to this, there may be information collected as part of this study that you may not want your primary care physician or specialist to know about. Because this is a confidential study, it is important that you know that none of the information that is collected as part of this study can be released without your permission.

You may refuse or stop participation in this study at any time without affecting you current and/or future care at St. Michael's Hospital (The Wellesley Central and/or Bond Street Sites).

Finally, you may be asked to participate in the MAX-HAART Study but a separate consent form will be presented to you for this study; this will occur after at least one month of monitoring in the INFORMM-Study.

Study Title

HAART ADHERENCE IN HIV-INFECTION PROJECT:

INFORMM-HAART Study
(Identification of Necessary Factors for Medication Management of HAART)

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Study Sponsor

Ontario Ministry of Health AIDS Bureau (Positive Action Fund)

Before agreeing to participate in this research study, it is important that you read and understand this research consent form. This form provides all the information we think you will need to know in order to decide whether you wish to participate in the study. If you have any questions after you read through this form, ask your questions to a doctor or study personnel. You should not sign this form until you are sure that you understand everything on this form. You may also wish to discuss your participation in this study with your family doctor or close friend. It is important that you are completely truthful with your study doctor with respect to your health history and any medications you may be taking, in order to prevent any unnecessary harms to you should you decide to participate in this study.

Consent to Act as a Research Participant

I. Purpose of the Research Project

We are conducting a Project in HIV-infection that involves 2 distinct but linked studies, each with its own consent form:

(1) The INFORMM-HAART Study
(2) The MAX-HAART Study

The **INFORMM-HAART Study** is a natural history study that focuses on identifying factors that are associated with managing antiretroviral medication regimens for the treatment of HIV-infection. For this study, we will be recruiting and following over 9 months 250 individuals with HIV-infection on highly active antiretroviral therapy (HAART) or triple-drug antiretroviral therapy.

The **MAX-HAART Study** is an intervention study that will compare the efficacy of three different behavioural interventions to help HIV-infected individuals achieve maximal HAART adherence. If I agree to participate in the MAX-HAART Study (and sign a separate consent form), I will be randomly assigned to receive one of these three interventions. Two of the three interventions were chosen because there is preliminary evidence to suggest that they may be beneficial in helping people keep to the schedule of their HAART medication regimen. By doing this, the expectation is that stricter adherence to HAART regimen will lead to maximum viral load response and minimal development of drug resistance to HIV. The third intervention is a "placebo" or control condition where participants will receive an education-focused intervention that is designed to increase knowledge of HAART agents and the behavioural causes of adherence difficulties to help maximize HAART adherence.

Through the identification of individual risk factors for HAART adherence problems and with behavioural interventions to improve HAART adherence, we expect that the results from this Project will help to optimize clinical care and to maximize the health and vitality of HIV-infected individuals.

II. Procedure

The following consent is specifically for the INFORMM-HAART Study

If I agree to participate in this study, I will be asked to do the following:

(1) At study enrollment and completion (i.e., 9 months later), I will be asked to complete a 3-hour assessment that will include:

(a) Standardized neuropsychological tests (generally paper and pencil-type tasks) to quantify my attention, thinking skills, memory and motor functioning. These tests may take up to 2 hours to complete.
(b) I will be asked to fill out several questionnaires about my mood, coping style, support system, health, and about any medical or cognitive complaints that I may have. These questionnaires may take up to 1 hour to complete.

I will receive $ 20.00 for each 3-hour assessment visit I complete. This will help to cover transportation and other incidental costs.

(2) Minor assessment sessions (i.e., 1-hour sessions) will take place at 1, 3 and 6 months. This will include 20 minutes of standardized neuropsychological tests and up to 40 minutes of questionnaires. Both the neuropsychological and questionnaires are similar to those given at study enrollment and study completion (i.e., 9 months). I will receive $ 10.00 for each minor assessment visit I complete. This is to help cover transportation and other incidental costs.

(3) My HAART medication adherence will be monitored over a 9-month period using both self-report adherence questionnaires and an electronic drug exposure monitoring device (eDEM). The eDEM is an electronic pill bottle that I will be asked to use to hold one of my HAART medications. The eDEM will keep track of each time that I open the bottle to take one of my HAART medications at the prescribed time.

I understand that I will be required to come in to the laboratory at the following intervals so that my HAART adherence can be monitored:

- Weekly for the first month of the study
- A minimum 1-2 times per month (depending upon my schedule) for months 2 and 3 of the study
- For the last 6 months of the INFORMM-HAART Study, I will be required to come in once per month

I will receive $ 10.00 for each monitoring visit. This is to help cover transportation and other incidental costs.

(4) I understand that my HIV infection will need to be documented by consultation with my primary care/family physician, who will have records of HIV infection through either ELISA antibody testing or positive viral load testing by PCR technique. I also understand that it will be helpful to obtain my current and past blood test results, including CD4 Lymphocyte counts, viral load counts, liver function test results, and general blood chemistry results (e.g., hemoglobin, glucose, cholesterol, etc.) from my primary care/family physician. I understand that the investigators will need to contact my primary care physician in order to obtain this documentation and they have my permission to do so.

(5) I understand that Dr. Rourke, or his associates, will answer any questions that I may have at any time concerning the details of the procedures performed as part of this study. I understand that I may also contact Dr. Rourke at 926-5053, ext. 3737 at a later time, if I have any questions concerning this study.

(6) If I am interested, Dr. Rourke can give me feedback on my test results at any time. Also, if it would be helpful for my medical treatment, Dr. Rourke can arrange to communicate pertinent test results to my primary care physician or health care professional, but only with my informed consent and written permission (signed Form 14).

(7) I understand that I may refuse or stop participation in the study at any time without affecting my current and/or future care at St. Michael's Hospital (The Wellesley Central and/or Bond Street Sites).

(8) I understand that at the end of the 9 months, I may be asked to participate in a follow-up study. If so, a separate consent form will be presented to me at that time. I may choose not to participate further.

(9) I understand that I may be asked to participate in the MAX-HAART Study to help improve my ability to follow my HAART medications. A separate consent form will be presented to me at that time; this will occur after at least one month of monitoring in the INFORMM-Study. However, my refusal to participate in the MAX-HAART Study will not hinder my participation in the INFORMM-HAART Study.

III. Benefits

There are two main benefits in participating in this research study:

(1) Dr. Rourke can meet with me to give me feedback on my test results over the study period. In addition, if I am interested, Dr. Rourke can also arrange to communicate these findings to my primary care physician or other clinicians involved in my medical care with my informed consent and written permission (Form 14).

(2) My participation in the INFORMM-HAART Study is helping to ascertain the essential factors that are associated with maximizing HAART medication adherence. I understand that while this will not directly help me at the present time, it will be helping to collect information and knowledge in this area and might help others with HIV-infection in the future.

IV. Discomforts and Risks

The interviews, tests, and questionnaires that I will receive during the course of study involve no specific risks or discomforts beyond that of a standard clinical interview situation, such as feeling upset at a review of my medical or mental health status, or a feeling of boredom or fatigue. Although most research participants and patients have found the experience of neuropsychological testing to be beneficial in the management of their HIV disease, a small minority of patients find it upsetting to participate in these tasks, as they find out that their cognitive skills (e.g. their memory or concentration skills or problem-solving ability) are below what they expected.

V. Confidentiality and Privacy

Confidentiality will be respected and no information that discloses my identity will be released without my consent, unless required by law. I will be given a research number and my personal identity will not be revealed on any forms, questionnaires, or in any publications.

VI. Compensation for Injury

If I suffer a physical injury as a direct result of the administration of study procedures, medical care may be obtained in the same manner as I would ordinarily obtain any other medical treatment. In no way does signing this form waive my legal rights nor relieve the investigators, sponsors, or involved institutions from their legal and professional responsibility.

VII. Participation and Withdrawal

Participation in research is voluntary. If I choose not to participate, I will continue to have access to customary care at St. Michael's Hospital (Wellesley Central and Bond Street Sites). If I choose to participate in this study, I can withdraw from the study at any time without any affect on the care that I will receive at St. Michael's Hospital (Wellesley Central and Bond Street Sites).

Consent to Act as a Research Participant

VIII. <u>Consent</u>

I acknowledge that the research study described above has been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at St. Michael's Hospital for me and for other members of my family. As well, the potential risks, harms and discomforts have been explained to me and I also understand the benefits of participating in this research study.

I understand that I have not waived my legal rights nor released the investigators, sponsors, or involved institutions from their legal and professional duties. I know that I may ask now, or in the future, any questions I have about the study or the research procedures.

I have been assured that records relating to me and my care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law. I have been given sufficient time to read and understand the above information.

If I have any questions or concerns about this study, I may contact Dr. Julie Spence the Chair of the St. Michael's Hospital Research Ethics Board at (416) 864-6060, ext 2557.

By signing this document, I am giving my informed consent to participate in this study. I have also been given a copy of this consent form.

_____   _____   _____
Participant signature   Print Name   Date

I, the undersigned, have fully explained the relevant details of this study to the patient named above and believe that he/she understands the nature of the study.

_____   _____   _____
Person obtaining consent   Print Name   Date