

**Epidemiology and Impact of Adherence to Antiretroviral  
Therapy on Clinical Outcomes in HIV-infected Individuals:  
Results from the Swiss HIV Cohort Study**

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presented by  
Tracy Reneè Jans-Glass

born 25 October 1972

citizen of  
Miami, Florida, USA

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Accepted by the Philosophisch-Naturwissenschaftliche Fakultät on the recommendation of

Prof. Dr. Heiner C. Bucher, examiner

Dr. Margaret May, co-examiner

Prof. Dr. Marcel Tanner, co-examiner

Prof. Sabina De Geest, co-examiner

Basel, March 2<sup>nd</sup>, 2010

Prof. Dr. Eberhard Parlow

Dean

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## Summary

The introduction of combination antiretroviral therapy (cART) in 1996 dramatically reduced the morbidity and mortality of HIV-infected patients. Despite these advances in drug development, there is no cure for HIV infection and HIV is now considered a chronic illness requiring life-long treatment. Standard treatment with cART consists of at least three drugs from two classes and the goal of treatment is the continuous suppression of viral replication to undetectable levels. For most patients, viral suppression will be achieved within several months of treatment initiation. Although adherence is not the only determinant of treatment success, it remains one of the only modifiable factors. Chapter 1 of this dissertation gives an introduction into HIV, cART, and non-adherence. Chapter 2 describes the goals and objectives of the research.

Adherence research intensified in early 2000 when results of a study indicated that patients need to take more than 95% of their drugs in order to remain virally suppressed. In 2003, the collection of adherence information by interview was included in the standard follow-up of patients registered in the Swiss HIV Cohort Study (SHCS), a nationwide study including over half of HIV-infected patients in Switzerland. Chapter 3 describes the SHCS adherence questionnaire (SHCS-AQ) and methodological issues concerning its validity.

Factors affecting adherence have been described as stemming from five intersecting dimensions. In Chapter 4, the first exploration of the SHCS-AQ is carried out and correlates of non-adherence from all five dimensions are identified. Of individuals on therapy for at least 6 months, missing one or more doses of cART was reported by 31.1% and 5.8% missed more than one dose of cART in a row. Irrespective of how non-adherence was defined, factors associated with increased odds of non-adherence were younger age, living alone, treatment with a higher number of prior regimens, and being on a boosted protease inhibitor (PI) regimen compared to being on a non-nucleoside reverse transcriptase inhibitor (NNRTI) regimen. We found significant variation in non-adherence by centers where the patients receive care, a possible proxy for differences in the system of care across centers.

Adherence is a dynamic process affected by a variety of factors that can also change over time. One of the strengths of the SHCS is the continuous collection of a comprehensive set of information about participating HIV-infected patients. In Chapter 5, we use novel approaches to assess patterns of adherence and model changes in adherence behavior. Starting injecting drug use (IDU), increasing alcohol intake, becoming depressed, loss of social support (losing a roommate or changing clinician or center of care) and onset of lipodystrophy were predictive of worsening adherence.

Regimen simplification and changing class of cART predicted improvements in adherence. This study highlights how short-term changes in a patient's circumstances can lead to changes in adherence, stressing the importance of continuously monitoring these risk factors.

Chapter 6 explores the predictive value of self-reported non-adherence on viral rebound using a time-dependent Cox proportional hazards models. Time to treatment failure was assessed in suppressed patients on cART. We detected a dose-response relationship between the number of missed doses and the risk of viral rebound. Additionally, an interaction between dosing frequency and non-adherence was found with those on a once-daily regimen being at higher risk of viral rebound than those on twice-daily regimens with the same level of non-adherence. Patients with missing adherence information were more likely to experience viral rebound emphasizing the role of regular follow-up.

The last two chapters introduce the concept of causal modeling, which attempts to replicate the results of clinical trials using observational data. Chapter 7 introduces the theory behind this modeling. In Chapter 8, marginal structural models are constructed to estimate the causal effect of non-adherence on viral rebound and mortality in naïve patients initiating cART. Patient's missing 2 or more doses of cART were 3.6 times more likely to fail treatment and 3.9 times more likely to die compared to those with perfect adherence. We could further confirm our exploratory findings from the previous study indicating that the impact of non-adherence varies by dosing frequency with patients on once daily regimens being at higher risk of poor clinical outcomes than patients on twice-daily regimens.

Taken together, these studies provide a validation of a simple self-report adherence questionnaire for use in predicting important clinical outcomes in HIV-infected patients. The results highlight the importance of continuous and consistent monitoring of drug adherence as well as risk factors for non-adherence.

## Zusammenfassung

Die Verfügbarkeit wirksamer antiretroviraler Kombinationstherapien (im Englischen combination antiretroviral therapy, cART) seit dem Jahr 1996 hat die Morbidität und Mortalität HIV-infizierter Patienten dramatisch gesenkt. Trotz dieser Fortschritte in der Arzneimittelentwicklung gibt es bis heute keine Heilung bei einer HIV-Infektion. Diese entspricht jetzt mehr einer chronischen, lebenslang behandlungsbedürftigen Erkrankung. Die cART besteht in der Regel aus mindestens 3 antiretroviralen Substanzen zweier unterschiedlicher Klassen. Ziel der HIV-Therapie ist es, die Virusreplikation weitestgehend zu hemmen und die HI-Viruslast wenn möglich unter die Nachweisgrenze zu bringen. Die meisten Patienten erreichen dieses Ziel innerhalb weniger Monate nach Behandlungsbeginn. Eine gute Therapie-Treue, auch Compliance oder Adhärenz genannt, ist gewiss nicht der einzige Einflussfaktor für den Behandlungserfolg, sie bleibt jedoch einer der wenigen modifizierbaren Faktoren. In Kapitel 1 dieser Dissertation wird eine Einführung in HIV, cART und die Problematik der mangelnden Adhärenz gegeben. Kapitel 2 beschreibt die Zielsetzungen der vorliegenden Arbeit.

Der Bereich Adhärenz findet als wichtiges Element in der Betreuung HIV-infizierter Patienten seit einigen Jahren zunehmend Beachtung. Anfang 2000 zeigten die Ergebnisse einer Studie, dass Patienten mehr als 95 % ihrer Medikamente korrekt einnehmen müssten, um einen erneuten Anstieg der HI-Viruslast nachhaltig zu vermeiden. Im Jahr 2003 wurde die Erhebung von Merkmalen, die Aufschluss über die Adhärenz eines Patienten geben, in die Schweizerische HIV-Kohortenstudie (Swiss HIV Cohort Study, SHCS), eine landesweite Studie, die über die Hälfte der HIV-infizierten Patienten in der Schweiz einschliesst, eingeführt. Dazu wird im Rahmen der regelmässigen Verlaufskontrollen der in die Studie eingeschlossenen Patienten eine mündliche Befragung durchgeführt. In Kapitel 3 wird der Fragebogen der SHCS zur Adhärenz (im Englischen SHCS adherence questionnaire, SHCS-AQ) vorgestellt und es werden methodologische Probleme in Bezug auf dessen Validität diskutiert.

Die in der Literatur für die korrekte Einnahme der Therapie beschriebenen Einflussgrössen können grob in fünf sich überschneidende Bereiche unterteilt werden. In Kapitel 4 der vorliegenden Arbeit wird der SHCS-AQ zunächst explorativ untersucht und weiter eine Zusammenhangsanalyse der mangelnden Adhärenz mit Merkmalen aus allen fünf Bereichen durchgeführt. Für Patienten, die während mindestens sechs Monaten eine medikamentöse Therapie erhalten haben, ergab sich eine Nicht-Adhärenzrate im Sinne einer unregelmässigen Medikamenteneinnahme, d.h. eine oder mehrere versäumte Einnahmen, von 31.1%. Die selbst deklarierte Nicht-Adhärenzrate im Sinne von

mehr als einer in Folge versäumten Dosis lag bei 5.8%. Unabhängig von der gewählten präzisen Definition mangelnder Adhärenz ergab sich, dass jugendlicheres Alter, alleine leben, die Anzahl vorausgegangener Umstellungen in der medikamentösen HIV-Therapie und das Therapieregimen mit einem „geboosterten“ Protease-Inhibitor (PI) im Vergleich zu einem nichtnukleosidischen Reverse-Transkriptase-Inhibitor (NNRTI) Faktoren sind, die die Chancen für Nicht-Adhärenz erhöhen. Die Analysen zeigen ausserdem eine deutliche Variabilität der Nicht-Adhärenz über die verschiedenen Zentren, in denen die Patienten betreut werden. Dies kann eventuell als Indiz für Unterschiede im Betreuungsangebot der verschiedenen Zentren gesehen werden.

Die Adhärenz entwickelt sich dynamisch und wird von einer Vielzahl Faktoren, die sich über die Zeit ändern können, beeinflusst. Die regelmässige Erhebung verschiedenartiger Merkmale für die in die Studie eingeschlossenen HIV-infizierten Patienten ist eine der Stärken der SHCS. In Kapitel 5 werden neuartige Verfahren zur Erkennung bestimmter Muster im Adhärenz-Verhalten angewendet und Änderungen modelliert. Als Risikofaktoren für eine Verschlechterung der Adhärenz ergaben sich beginnender intravenöser Drogenkonsum, zunehmender Alkoholkonsum, das Auftreten von Depressionen, der Verlust sozialen Rückhalts (d.h. Verlust eines Partners / Mitbewohners oder Wechsel des betreuenden Arztes bzw. Studienzentrums) und die Diagnose von Lipodystrophie. Die Vereinfachung des Therapieregimens und Umstellung auf eine andere cART-Klasse prognostizierten eine Verbesserung im Adhärenz-Verhalten. Aus der vorliegenden Untersuchung ergibt sich, dass kurzfristige Veränderungen der persönlichen Lebenssituation und des individuellen Therapieschemas die korrekte Einnahme der HIV-Therapie beeinflussen können. Demzufolge kommt der stetigen Beobachtung der oben genannten Risiko- und prognostischen Faktoren eine besondere Bedeutung zu.

Kapitel 6 ist der Untersuchung des prognostischen Wertes selbst deklarerter mangelnder Adhärenz für einen erneuten Anstieg der HI-Viruslast gewidmet. Dazu wurde ein Cox-Modell mit zeitabhängigen Kovariablen angepasst, um die Zeit bis zum Therapie-Versagen bei Patienten, die eine cART erhalten und bei denen die Virusreplikation anfangs erfolgreich unterdrückt werden konnte, zu untersuchen. Die Resultate zeigen eine Dosis-Wirkungs-Beziehung zwischen der Anzahl versäumter Einnahmen und dem Risiko für einen erneuten Anstieg der Viruslast auf. Ausserdem ergab sich eine signifikante Wechselwirkung zwischen der Einnahmehäufigkeit und mangelnder Adhärenz, wobei Patienten mit antiretroviralen Therapieregimen mit einer Medikamenteneinnahme alle 24h ein höheres Risiko für einen erneuten Anstieg der Viruslast hatten als Patienten mit ähnlicher Nicht-Adhärenz und einem Therapieregimen mit einer Einnahme alle 12h. Überdies zeigten Patienten, für die keine Angaben zur individuellen Therapie-Treue verfügbar waren, ein erhöhtes

Risiko für Therapieversagen. Dies unterstreicht nochmals die Wichtigkeit, auf persönliche Lebensumstände zu Beginn der Behandlung einzugehen und den Therapieverlauf nachhaltig zu beobachten.

In den letzten beiden Kapiteln dieser Arbeit werden statistische Verfahren der kausalen Modellierung vorgestellt. Die zugrunde liegende Idee ist, basierend auf Daten aus Beobachtungsstudien die Ergebnisse und Ausgangslage kontrollierter klinischer Studien nachzuempfinden. Kapitel 7 gibt eine Einführung in die zugrunde liegende Theorie. In Kapitel 8 werden so genannte „Marginal Structural Models“ angepasst, um den kausalen Effekt mangelnder Adhärenz bei HIV-Infizierten, die eine antiretrovirale Initialtherapie beginnen, auf einen erneuten Anstieg der Viruslast und das Risiko zu sterben zu untersuchen. Im Vergleich zu Patienten mit sehr guter Therapie-Treue war die Chance für Therapieversagen für Patienten, die mindestens 2 Einnahmen ihres cART-Regimens versäumt hatten, um den Faktor 3.6, die Chance zu sterben um den Faktor 3.9 erhöht. Des Weiteren konnten die Resultate der vorigen Zusammenhangsanalyse bestätigt werden, dass der Effekt mangelnder Adhärenz von der vorgeschriebenen Einnahmehäufigkeit des individuellen Therapieregimens abhängt. Die einmal täglich vorgeschriebene Medikamenteneinnahme birgt bei vergleichbarer Adhärenz ein höheres Risiko für ein ungünstigeres klinisches Ergebnis als die zweimal täglich vorgeschriebene Einnahme.

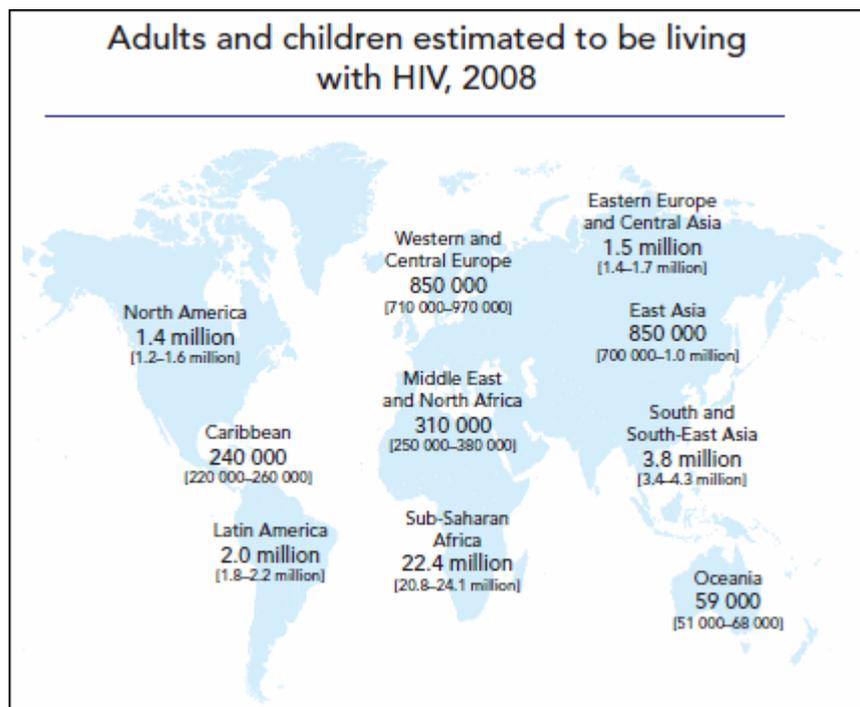
Die Untersuchungen der vorliegenden Arbeit validieren den Fragenbogen zur selbst deklarierten Adhärenz HIV-infizierter Patienten unter cART und seine Verwendung für die Vorhersage wichtiger klinischer Zielgrößen. Die Resultate zeigen die zentrale Bedeutung auf, die der fortdauernden und beständigen Überwachung der Adhärenz und relevanter Risikofaktoren für eine Verschlechterung der Adhärenz zukommt.

## Chapter 1: Introduction

### 1. The HIV epidemic

Human immunodeficiency virus (HIV) is the cause of acquired immunodeficiency syndrome (AIDS) and has killed more than 25 million people since its discovery in 1981 in the US. The global spread of HIV appears to have peaked in 1996, when 3.5 million new infections occurred [1]. In 2008, an estimated 33.4 million people were living with HIV, 2.7 million adults and children were newly infected, and there were 2.0 million AIDS-related deaths (Figure 1.1).

Figure 1.1 Estimate of global HIV-1 epidemic. Adapted from [1].

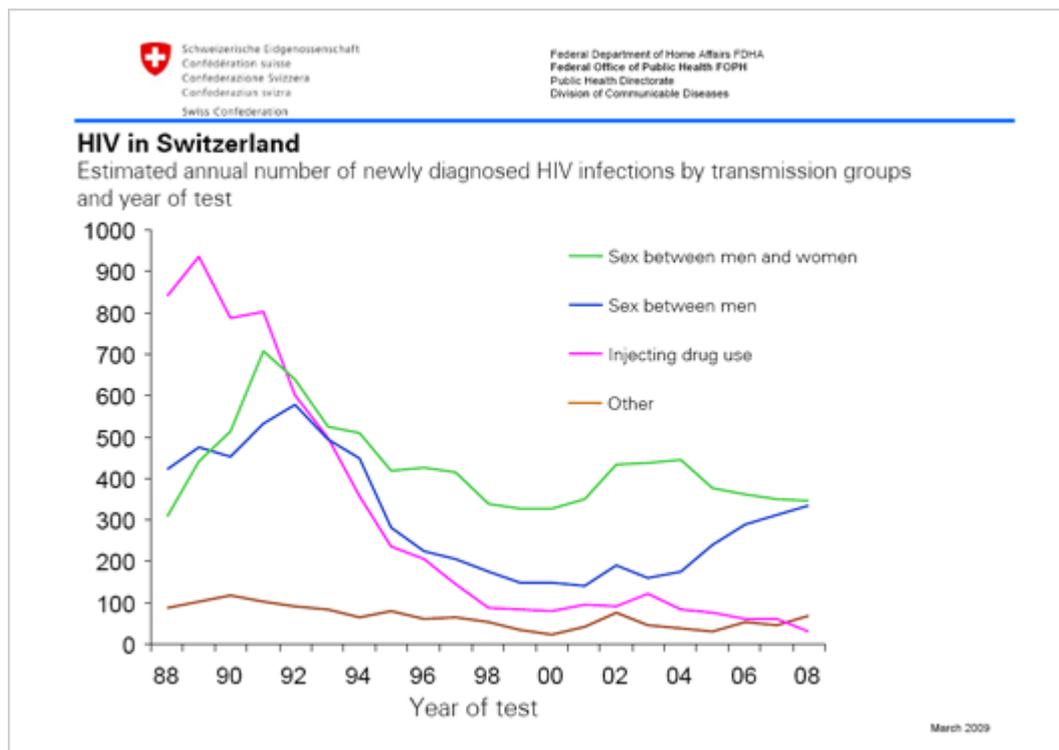


In high income countries, the number of new infections has either stabilized or increased slightly in recent years. However, the epidemic is evolving over time and in the past decade there has been a rising number of new infections in men having sex with men (MSM) paired with a decrease in new infections among injecting drug users (IDU).

In Switzerland there are an estimated 25,000 people living with HIV [1] and approximately 750-800 individuals are newly infected every year [2]. Following the decrease in HIV infections between 1992 and 2000, there was a 25% increase in new infections reported in 2002, mainly in Swiss MSM and

heterosexuals originating from countries with a high HIV prevalence [3]. Since 2002 the trend has stabilized, however the percentage of new infections have continued to increase in MSM with a corresponding decrease in the other transmission groups, particularly among heterosexuals. IDU went from being the primary mode of transmission for new HIV diagnoses in the late 1980's to accounting for only 4% of new infections in 2008 (Figure 1.2).

**Figure 1.2** Time trends in mode of HIV infection in Switzerland. Adapted from [3].



## 2. Classification of HIV

There are two species of HIV known to exist, HIV-1 and HIV-2. Both types of the virus are believed to have originated in West-Central Africa by transfection from non-human primates to humans. The HIV-1 subtype genome closely resembles lentiviruses that are derived from chimpanzees in southern Cameroon. HIV-1 is the cause of most infections globally and is both more virulent and more infective [4] than HIV-2, which is largely confined to West Africa due to its relatively poor capacity for transmission [5].

HIV-1 is further classified into 10 main subtypes and specific subtypes dominate the epidemic in different regions of the world [6]. The most frequently observed subtype is C, which accounts for

over 50% of all HIV infections worldwide and is found predominantly in Africa and India. The second largest subtype is A, which is common in Eastern Europe, and certain parts of East and West Africa. Subtype B is the most prevalent subtype in North America, Western Europe, and Australia and constitutes around 10% of all HIV-1 infections. Drug development for HIV often focuses on this subtype despite its relatively low frequency. The additional subtypes, from D to K, make up less than 5% of HIV-1 infections. In Switzerland the vast majority of HIV infections are subtype B, however the presence of other subgroups, such as A, C, and CRF\_01, are growing [7] largely due to the migration of infected patients or infections acquired abroad [8].

### 3. The natural course of HIV-1 infection

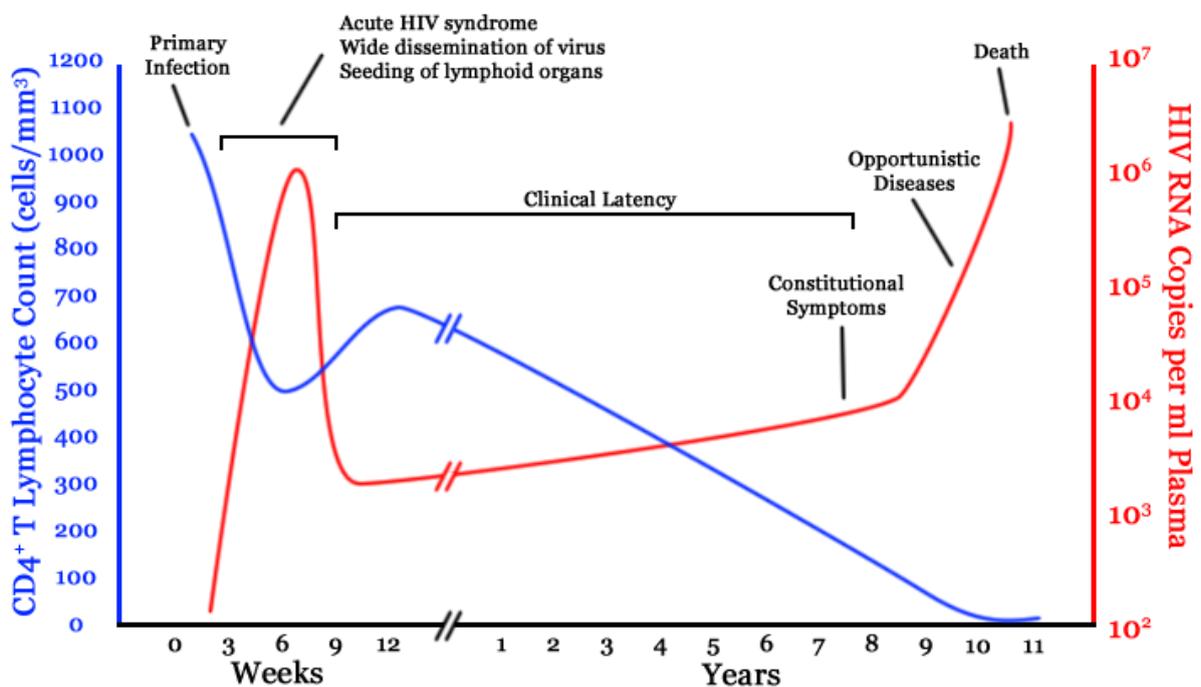
HIV-1 is a lentivirus (a member of the retrovirus family) that infects particular vital cells of the immune system, such as helper T cells (specifically CD4<sup>+</sup> T cells), macrophages, dendritic cells and microglia cells. HIV-1 entry into macrophages and CD4<sup>+</sup> T cells is mediated through the interaction of the virion envelope glycoproteins (gp120) with the CD4 molecule on the target cells and also with chemokine co-receptors. Macrophage (M-tropic) strains of HIV-1, or non-syncytia-inducing strains use the  $\beta$ -chemokine receptor CCR5 for entry and are thus able to replicate in macrophages and CD4<sup>+</sup> T cells. This CCR5 co-receptor is used by almost all primary HIV-1 isolates regardless of viral genetic subtype. Macrophages play a key role in several critical aspects of HIV infection and are the first cells infected by HIV. Macrophages and microglial cells are the cells infected by HIV in the central nervous system. In tonsils and adenoids of HIV-infected patients, macrophages fuse into multinucleated giant cells that produce large amounts of virus. T-tropic isolates, or syncytia-inducing strains replicate in primary CD4<sup>+</sup> T cells as well as in macrophages and use the  $\alpha$ -chemokine receptor, CXCR4, for entry. Dual-tropic HIV-1 strains are thought to be transitional strains of the HIV-1 virus and thus are able to use both CCR5 and CXCR4 as co-receptors for viral entry.

Infection with HIV occurs through transfer of blood, semen, vaginal fluid, and breast milk. The most common routes of transmission are sexual intercourse or needle sharing among IDU. Mother-to-child transmission has been virtually eliminated in high income countries due to pre-delivery HIV testing, antiretroviral transmission prophylaxis, and elective cesarean section [9,10], but it is still common in resource-limited countries.

When CD4 cells decline below a critical level, cell-mediated immunity is lost and the body becomes progressively more susceptible to opportunistic infections or HIV related non-Hodgkin lymphoma. The most advanced stage of HIV infection is AIDS. The rate of progression from HIV to AIDS varies according to host, viral, and environmental factors. Although HIV-specific treatment delays progression, most individuals develop AIDS within 10 years of infection [11,12].

HIV-1 infection has four stages: incubation, acute infection, chronic infection, and AIDS (Figure 1.3). The incubation period usually lasts only 2-4 weeks and is asymptomatic. The acute phase starts with infection and lasts an average of 28 days with around 50-70% of individuals experiencing a wide range of unspecific symptoms such as fever, swollen lymph nodes, sore throat, muscle pain and rash [13]. Antibodies against HIV typically develop within 3 to 6 months after infection. During this phase, there is massive viral replication leading to a sharp increase in HIV-1 RNA levels often approaching several million copies per ml. At the same time, there is a plunge in CD4 cell counts. As HIV-1 specific immune responses develop, HIV-1 RNA levels decrease and CD4 cells recover, but not to pre-infection levels. In particular, HIV-1 RNA declines to a viral set point, defined as the relatively stable level observed during the chronic infection phase. The viral set point is highly variable between patients and is determined by both host and viral factors [14]. The chronic phase is characterized by a relatively symptom-free period and can last anywhere from 2 weeks to 20 years. Viral load remains at the viral set point but there is a gradual decline in CD4 cell counts over time. When CD4 cell counts decline below a critical level of 200 cells per  $\mu\text{L}$ , an individual is considered to have entered the last stage of infection, AIDS. During this stage, cell immunity is lost and the individual becomes susceptible to opportunistic infections or other AIDS-defining illnesses, which are eventually fatal.

**Figure 1.3** Stages of HIV infection. Adapted from [15].



## 4. Treatment for HIV

There is currently no cure or vaccine for HIV or AIDS and treatment consists of antiretroviral therapy (ART) [16]. The basic principle of antiretroviral therapy is immune restoration by achieving a maximal recovery of CD4 cells with permanent and sustained virologic suppression. There are different classes of antiretroviral drugs each targeting specific stages of the HIV life-cycle [17,18] (Figure 1.4).

### Development of antiretroviral therapy

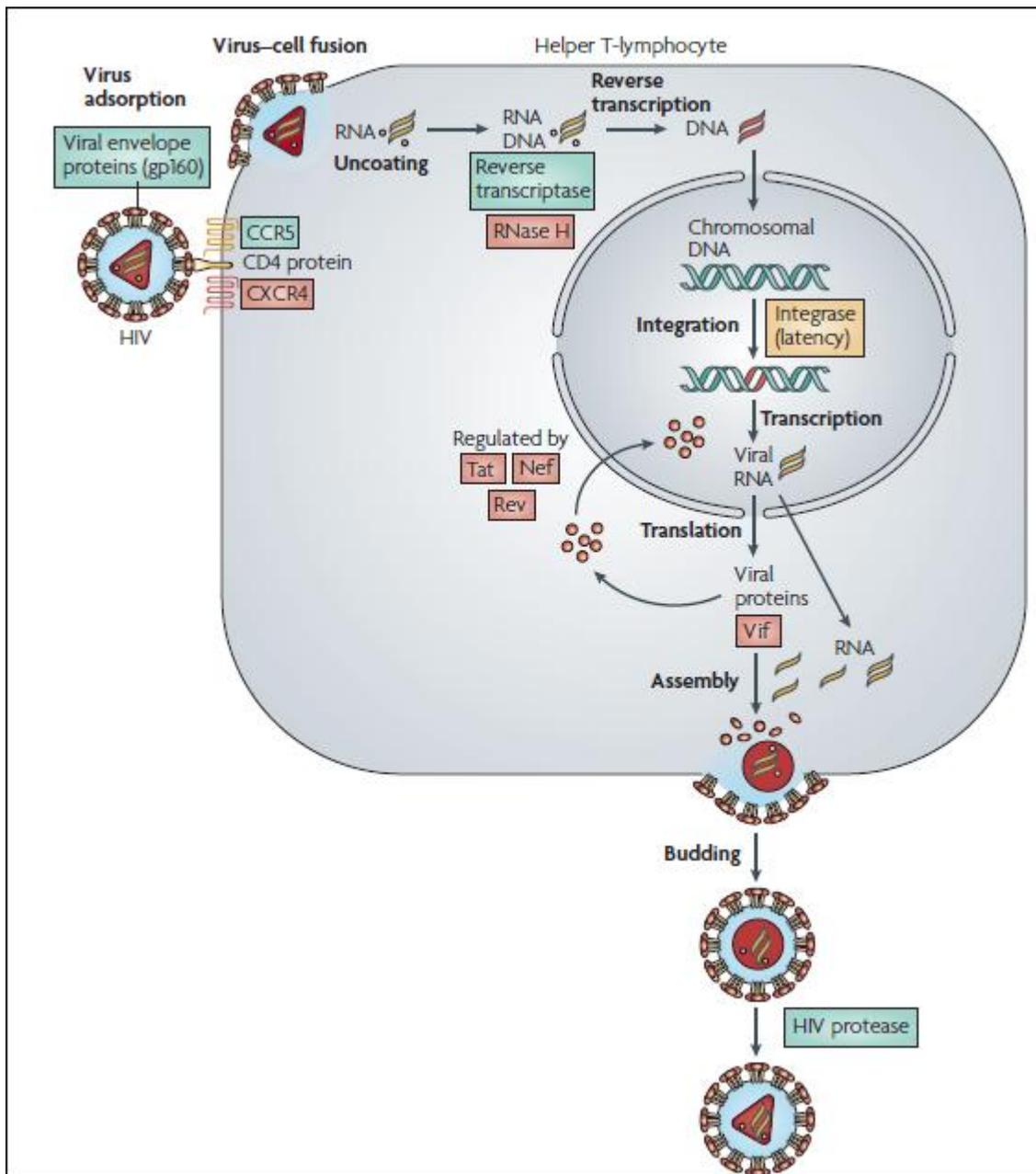
Nucleoside reverse transcriptase inhibitors (NRTI), the first and most established class of antiretroviral drugs, target the life cycle at the reverse transcription stage where single-stranded RNA is converted into a double-stranded DNA. NRTIs prevent completion of DNA synthesis, and thus prevent HIV from multiplying. In 1987, the NRTI zidovudine (AZT) became the first FDA-approved drug for the treatment of HIV infection [19] followed a few years later by didanosine, zalcitabine, lamivudine and stavudine. The process of reverse transcription is extremely error-prone and it is during this step that mutations may occur. Therefore the clinical benefits of monotherapy with AZT were limited [20] due to the rapid emergence of drug resistance strains [21].

In 1996, protease inhibitors (PI) became the second drug class available to treat HIV infection. PIs target the last stage of the life cycle, maturation. After viral particles are released from the host cell they must undergo maturation in order for the viral particle to become infectious. Shortly after the introduction of PIs such as saquinavir, ritonavir, indinavir, and nelfinavir, clinical studies showed that combination treatment with more than one drug class resulted in a significantly prolonged benefit compared to NRTI-based mono- and dual therapy [22,23]. As a result, guidelines for the treatment of HIV were updated in 1997 [24] to prescribe ART as a combination of three drugs from two different classes (2 NRTI with 1 PI).

In 1998, non-nucleoside reverse transcriptase inhibitors (NNRTI), specifically nevirapine and efavirenz, were developed to target the reverse transcription stage, similar to NRTIs. They were soon found to be a very potent class of drugs with a long half life allowing for once daily administration [25,26]. In particular, nevirapine was found to have similar potency compared to either a PI or NRTI regimen [24]. Efavirenz exhibited better or equal potency when compared to ritonavir boosted PIs [27].

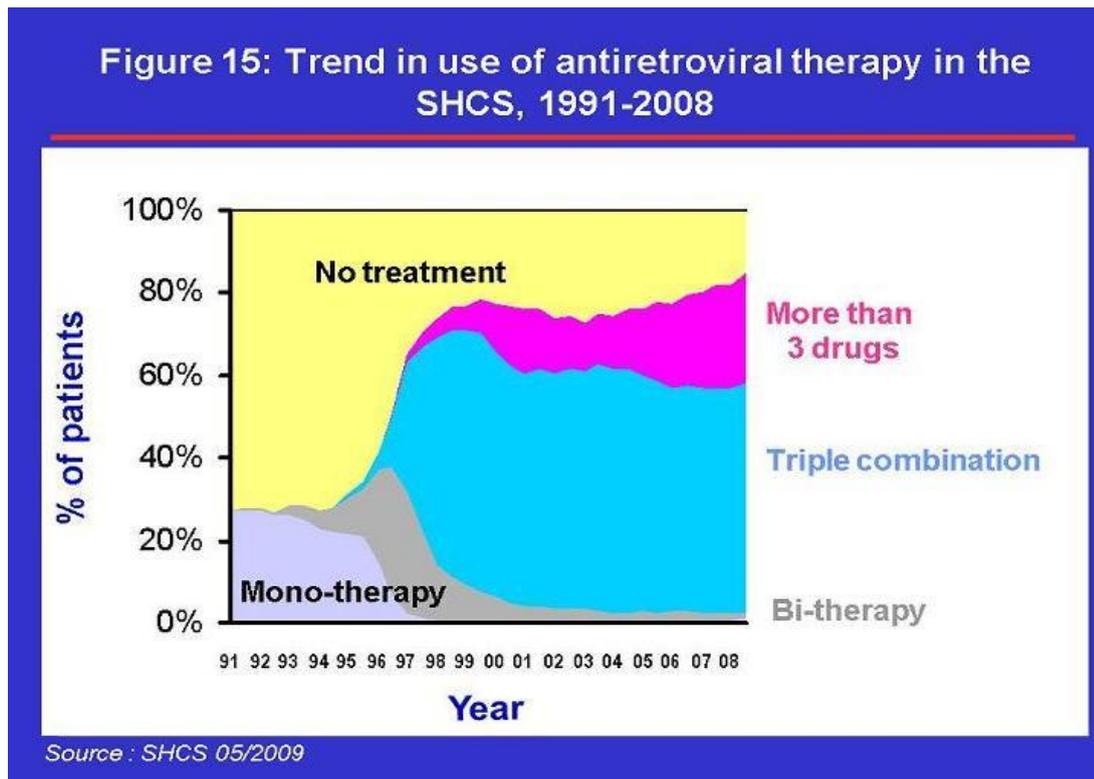
A further milestone in ART development was the concept of ritonavir-boosting, which dramatically increases the bioavailability of most PIs except nelfinavir [28]. Compared to unboosted PIs, newer combinations of boosted PIs or NNRTIs have a lower viral failure rate [26,29] as well as being more tolerable and having a lower pill burden.

**Figure 1.4** HIV replication cycle. Reproduced from [16].



In antiretroviral naïve patients, current guidelines suggest drug combinations consisting of at least three drugs belonging to at least two classes, typically two NRTIs plus either a PI or a NNRTI [30,31]. At present four ritonavir boosted PIs and two NNRTIs are licensed and recommended for the treatment of drug naïve patients. Figure 1.5 gives an overview on trends in antiretroviral therapy use in the Swiss HIV Cohort Study (SHCS), a national cohort of HIV-infected individuals in Switzerland.

**Figure 1.5** Trends in antiretroviral therapy use in the Swiss HIV Cohort Study



New classes of drugs have been introduced in recent years that at present are primarily reserved for patients with advanced HIV infection with multiple drug resistance to first line antiretroviral drugs. In 2003, fusion inhibitors, designed to intervene at the very first step of the life cycle with the entry of the virus into the host cell, became the first class of these salvage drugs and were found to be effective in treatment experienced patients [32]. In the last five years, remarkable improvements for the treatment of patients with advanced multi-resistant HIV infection were seen with the introduction of the PIs darunavir and tipranavir and the NNRTI etravirine [33-35]. In 2008, two new drugs were approved for treatment experienced patients. Raltegravir was the first approved integrase inhibitor, designed to block the action of integrase, which is a viral enzyme that inserts the viral genome into the DNA of the host cell. Integration is a vital step in retroviral replication so blocking it can halt further spread of the virus. Maraviroc was the first approved CCR5 inhibitor, blocking the entry of the virus into the host cell, similar to fusion inhibitors. Both drugs have shown promising results in multi-drug resistant HIV infection and improved surrogate marker outcomes when compared to optimized ART [36-38]. However, these drugs are not yet widely available especially in resource-limited countries.

### **Impact of combined antiretroviral therapy**

The introduction of combination antiretroviral therapy (cART) in 1996 has led to a dramatic reduction in hospitalization rates, opportunistic infections, and deaths associated with HIV infection [39-41]. In particular in Switzerland, the number of AIDS-related deaths has decreased dramatically from more than 600 in 1995 to less than 50 in 2008 [3]. In high-income countries, the life expectancy of a 20-year old individual starting cART has risen from 36.1 to 49.4 years between 1996 and 2005 [42]. Without cART, median survival after developing AIDS is only 9.2 months [43] compared to more than 5 years with cART [44]. Even when taking cART, treatment failure can occur due to a variety of reasons such as medication intolerance or infection with a drug-resistant strain of HIV. With modern antiretroviral therapy 90% of patients from an unselected population may be expected to achieve sustained virologic suppression and a satisfactory immune restoration [45]. It may well be expected that prognosis of HIV-infected patients receiving antiretroviral therapy will further improve in the future.

### **Factors associated with poor outcome in patients receiving cART**

In observational studies and clinical trials several factors have been associated with surrogate markers of HIV infection (CD4 cell count and HIV-1 viral load) and clinical endpoints (AIDS or death). Initiating cART at a late stage, with CD4 cells below 200 cells per  $\mu\text{L}$ , is associated with worse clinical outcomes [46]. The question as to whether one should initiate cART at CD4 cell counts  $> 350$  cells per  $\mu\text{L}$  or higher rather than deferring the start of cART is currently the subject of debate and under investigation in a large clinical trial. Preliminary evidence from observational studies indicates a lower risk of AIDS and deaths in patients initiating cART at higher CD4 cells compared to individuals with deferred initiation of cART [47,48]. In prospective cohort studies IDU was found to be related to worse immune restoration, higher risk of virologic failure and increased risk of death from AIDS and non AIDS-related conditions [49], although a recent study did not find increased mortality in this patient group [50]. Age was shown to be related to worse CD4 cell recovery [51,52]. Several studies have shown improved outcomes of HIV surrogate markers in females compared to males [53]. Co-infection with hepatitis B and C has been shown to be associated with compromised immune recovery and increased risk of death from liver disease when compared to non co-infected individuals [54,55]. In several observational studies non-adherence to cART was found to be associated with increased risk of virologic failure, acquisition of HIV drug resistance, and progression to AIDS [56-59].

## 5. Adherence to antiretroviral therapy

According to the World Health Organization (WHO), adherence is defined as “the extent to which a person’s behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider” [60]. The importance of adherence to cART has increased as treatment of HIV currently requires life-long therapy once initiated in order to maintain maximal viral suppression and to avoid drug failure and the emergence of resistance to HIV drugs. Compared to continuous treatment with cART, treatment interruptions, including medically guided ones, increase the risk of opportunistic disease or death from any cause largely as a consequence of increasing viral load and lowering CD4 cell count, resulting in suboptimal CD4 cell recovery once cART is reinitiated [46]. Long-term viral suppression requires very high if not perfect adherence [61]. Virologic failure not only reduces future treatment options and therefore long-term clinical success but also increases the possibility of developing drug resistant mutations [62,63]. Drug-resistant strains of HIV can then be transmitted to uninfected or drug-naïve individuals limiting their future treatment options [64], making adherence an important public-health topic.

Despite the serious consequences of non-adherence, the reported percentage of prescribed doses taken in the United States and Europe ranges from 60-70% [65]. Although adherence is not the only determinant of treatment success, it remains one of the only modifiable factors. However, health care providers have proven to be poor at assessing and improving adherence in patients [66,67]. Adherence continues to be a challenging and complicated topic that requires a commitment from both the patient and the health care team.

### Measuring adherence

Adherence is a dynamic process and has been shown to vary over time [68-72]. Therefore adherence should be monitored and measured regularly as a part of routine clinical care. However, there is no gold standard for the assessment of adherence nor is there a single optimal tool that enhances adherence to HIV/AIDS treatment regimens [73]. Each method described below has its own strengths and weaknesses and therefore the choice of measurement method often depends on the purpose and intended use of the measurement.

When focusing on the behavioral dimension of adherence to cART, four dimensions of adherence merit consideration: taking adherence (the extent to which a patient is taking the prescribed medication), timing adherence (the extent to which a patient is adhering to the prescribed schedule for drug intake), drug holidays (missing several doses of medication in a row), and food restrictions (the extent a patient is adhering to drug intake in relation to food restrictions) [60].

### *Microelectronic Monitoring System*

Microelectronic Monitoring Systems (MEMS) utilizes a computer chip embedded in a specially designed pill-bottle cap to record the time and duration of each opening of the bottle. MEMS can measure all the dimensions of adherence except food restrictions. However, the number of pills taken from the bottle at each opening is unknown and therefore additional doses withdrawn to be taken at another time (so called 'pocket doses') will not be recorded. In a study by Bova et al, 41% of patients reported pocket doses and 26% reported opening the pill bottle without removing any doses suggesting MEMS can lead to an underestimate of adherence [74]. This also prohibits the use of MEMS caps in conjunction with other adherence support devices, such as pill boxes, where large quantities of pills are withdrawn at one time. In addition, MEMS is normally used to monitor only one medication in the regimen, therefore adherence to the other drugs is not measured. However one study indicated that the adherence for one drug may be a good indicator of the adherence for the entire regimen [75].

Although MEMS cap has been shown to be the most sensitive measure of adherence [76,77] and is associated with treatment failure [78-81], its use has been primarily limited to research settings. In addition to the limitations listed above, MEMS caps are expensive making widespread use, especially in resource-limited settings, prohibitive.

### *Prescription refill*

Prescription refill data is constructed from the dates when medications were dispensed to an individual by the pharmacy. If the prescription is not refilled within the supply period of the prescription, it is assumed that the individual has missed doses during this time. This assumption does not allow for the possibility that the individual received additional medication from other sources or had a stockpile of medication at home due to missed doses during other periods of time. In addition, prescription refill measures only the taking adherence dimension as the timing of the missed doses and drug holidays, as well as violation of food restriction, during the supply period is unknown.

There are also feasibility issues with regards to data collection. Information might be missed if individuals are not required to fill their prescriptions at one particular pharmacy. Or the data may not be accessible due to privacy laws. Despite these challenges, pharmacy refill data has been shown to be associated with viral suppression, resistance, and progression to AIDS and death [57,82-84].

### *Pill counts*

Pill counts only measure taking adherence and can be conducted during clinical visits or at home during either announced or unannounced visits. If the pill count is scheduled, patients may discard missed doses (so called 'pill dumping') prior to the visit. Unannounced pill counts, however, have been found to be associated with virologic failure [85], development of resistance [62,86], and progression to AIDS [59]. Despite this, unannounced pill counts are too intrusive and labor intensive for widespread use in clinical practice.

### *Biologic markers*

The most commonly used biological marker for adherence is plasma drug concentrations with pre-dose drug concentrations lower than the limit of detection considered an indicator of non-adherence. Use of drug concentrations to measure adherence has the limitation that only recent taking adherence behavior is measured. In addition, there can be other reasons why drug concentration levels are lower than expected, such as individual genetic or metabolic differences, malabsorption, or drug interactions.

Several studies have shown biologic markers to be associated with adherence measured by self-report [87], unannounced pill counts [88], and MEMS caps [89]. Another study also reported an association between biologic markers and viral load [90].

### *Self-report*

Self-report is by far the simplest and most convenient method of measuring adherence. It is also extremely flexible and can measure all four dimensions of adherence behavior. However, it is subject to recall bias, social desirability bias (patient's desire to be seen as a 'good patient') and discomfort in disclosing non-adherent behavior [91]. While patients' reporting of non-adherence has been found to be credible [76], their estimate of adherence is often inaccurate [92,93] overestimating adherence by 10-20% compared to MEMS [94,95]. However, the reason for over reporting adherence is most often thought to be due to misremembering rather than intentional deception although both phenomenon exist in practice [96]. Nonetheless, two systematic reviews including a large number of observational studies found a robust association between self-reported adherence and viral load over varying measures and recall periods [65] and indicated that self-reported adherence measures can distinguish between clinically meaningful patterns of medication-taking behaviour [97].

There exist many different validated self-report instruments for measuring adherence complicating the comparability and interpretability of study findings. These instruments differ in length and type

of questions, as well as recall periods. Recent evidence suggests that a recall period of 30 days may be optimal with less over reporting than 3-7 day recall [65,98,99].

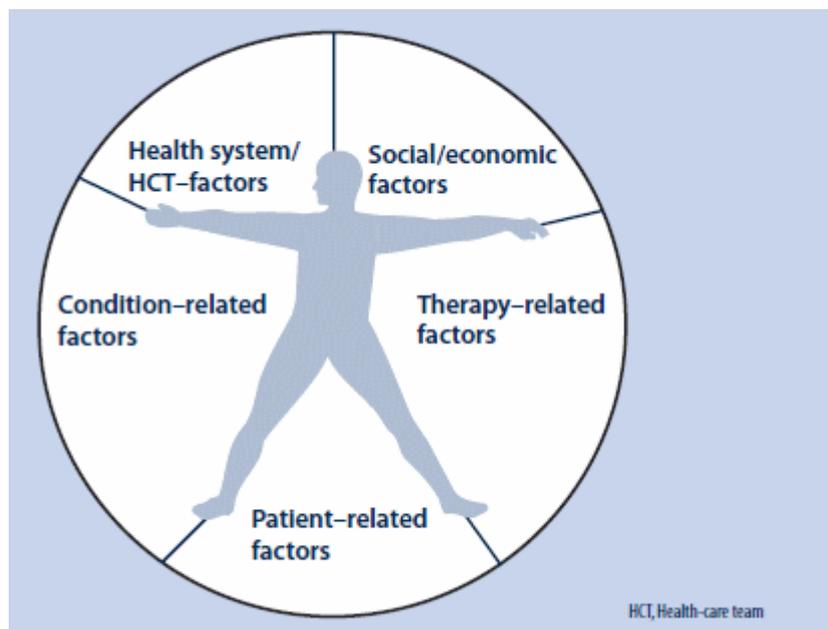
### Factors affecting adherence

The WHO developed a framework for assessing factors effecting adherence as a means of designing interventions to improve adherence [60]. Understanding these factors can increase a clinician's attention to adherence when treating particularly susceptible patients. Factors affecting adherence were divided into five intersecting dimensions (Figure 1.6).

#### *Social/economic-related factors*

In general, sociodemographic factors, such as age, gender, and education, have not been consistently associated with adherence. Social support is the exception and patients with supportive friends and family tend to adhere better compared to those without such support [100-102]. Studies have reported conflicting evidence about the association between many sociodemographic factors and adherence [103]. However, when an association was found, the nature of the relationship was consistent: older age [72,100,104], white ethnicity [71,72,105], higher education [105,106], higher income [71,106] and stable housing [100-102,107] were associated with better adherence.

**Figure 1.6** Five dimensions of factors known to affect adherence to medication. Reproduced from [108].



### *Patient-related factors*

The most important variables affecting adherence are patient-related. Even the most effective regimen will fail if a patient does not take medication as prescribed. For the most part, patient-related factors fall under the category of psychosocial variables including substance abuse, mental health, and knowledge and attitudes about HIV and its treatment. Life stress or negative life events were found to interfere with the ability to take medications [105,109] and women have cited stress of childcare as a reason for missed doses [100,107]. Both active IDU and alcohol consumption are highly correlated with non-adherence [100,103,109-112], although it has been shown that a good provider-patient relationship can mediate this effect [113]. Psychological distress in the form of depression or psychiatric comorbidity has been consistently associated with higher levels of non-adherence [71,100,103,110,111]. Belief about the effectiveness of cART, understanding the side effects of cART, as well as the relationship between adherence and important clinical outcomes, have all been found to associated with better adherence [101,103,104,112,114,115].

### *Therapy-related factors*

Therapy or treatment-related factors include regimen complexity (number of pills per day, number of doses per day, and dietary restrictions), class of cART, and side effects. Although there has been progress in the recent years towards simplification of cART regimens, adherence to HIV medication can be extremely complicated and, together with toxicity problems or side effects, can greatly influence an individual's willingness to adhere to therapy. Originally, health professionals believed that the number of daily pills in a regimen (or 'pill burden') had a strong influence on adherence [116]. The number of daily doses in a regimen (or 'dosing frequency') has been found to impact adherence with those on once or twice-daily regimens exhibiting better adherence than those on three-times daily regimens [81,100,106,117]. Other studies have shown that it is more important that a regimen fit into the daily routine or lifestyle of the patient [105,112].

Most cART regimens are potent and usually have both transient side effects such as diarrhea and vomiting as well as long-term side effects like lipodystrophy, which can manifest itself as fat accumulation or wasting. There is clear evidence that medications producing side effects are significant associated with reduced adherence [100,104,112,118,119]. In addition, side effects account for more regimen changes than treatment failure [120,121]. D'Arminio and colleagues reported that over 25% of treatment naïve patients discontinued therapy in the first year due to toxicity [122]. In particular, Kasper et al found that 37% of respondents either stopped or changed regimens due to lipodystrophy, which can be a serious long-term side effect. The actual number of

side effects was also found to be important with each additional reported side effect being associated with significant increases in non-adherence [111,123].

### *Condition-related factors*

Very few studies have examined the effect on adherence of condition or disease-related factors, such as stage and duration of HIV infection, opportunistic infections, and HIV-related symptoms. Studies assessing clinical stage produced inconsistent results [77,105,119] with only one study reporting better adherence in symptomatic patients (CDC-stage B and C disease)[114].

### *Health care/system-related factors*

Health care or system-related factors encompass the patient-provider relationship and aspects of the clinical setting. The patient-provider relationship includes patient's overall satisfaction and trust in the provider and staff, their perception of provider's competence, the provider's willingness to include the patient in treatment decisions, and the tone of the relationship. When a patient has a meaningful and supportive relationship with their provider they are better able to overcome barriers and achieve good adherence [87,101,102,112,114]. However a recent study did not find an association between patient confidence in their clinician and adherence [100].

Important aspects of the clinical setting in high-income countries include confidentiality, previous experience with the health care system, and convenience in scheduling appointments. Despite the relevance of these factors, they are not well-studied. Chesney and colleagues found that poor previous experience with the health care system was associated with non-adherence [112].

Several important system factors affecting adherence in resource-limited settings, such as cost, transportation and access, are beyond the scope of this report and not discussed further [124].

## **Impact of non-adherence**

### *Treatment failure*

The initial goal of cART - as outlined above - is to attain full and durable viral suppression. Early reports in individuals on non-boosted PIs estimated that they must take 95% of their medication to remain virally suppressed [81]. This estimate became an informal rule and persisted for many years unchallenged and resulted in more attention being focused on adherence monitoring and management. In recent years, several studies were done to explore whether the 95% rule applied to other drug classes and found NNRTI and boosted PI regimens to be more 'forgiving' – able to achieve and maintain viral suppression despite imperfect medication adherence [125-128]. The majority of

patients on potent regimens are able to maintain viral suppression at adherence rates lower than 95% [129-131]. In addition, a recent study found that the level of adherence necessary to achieve initial viral suppression is higher than what is necessary to maintain long-term viral suppression, with the risk of virologic failure for adherence levels above 50% declining with longer duration of continuous viral suppression [85].

Adherence has been shown to be associated with viral rebound using a variety of measurement tools [78-80,82,83,118,132-135]. In particular, a review found that self-reported adherence was significantly correlated with viral load in 84% of comparisons [65]. Nieuwkerk and Oort compiled 65 studies of self-reported adherence to estimate a pooled odds ratio of having a detectable viral load of 2.31 (95% confidence interval (CI): 1.99 – 2.68) in non-adherent patients compared to adherent patients [97].

### *Resistance*

The initial belief that ‘Non-adherence leads to drug-resistant HIV’ came from experience in multi-drug resistant tuberculosis, where resistance was seen almost exclusively in individuals at risk for non-adherence [136]. This view also shaped public health debates regarding the potential benefits and dangers of providing cART to populations at risk for non-adherence [64,137].

Implications for non-adherence were not just on the individual level as suboptimal adherence could lead to resistance which could then be transmitted to others [138]. However, studies of the relationship between adherence and resistance in HIV were only conducted a few years ago and indicate that the relationship is more complicated than originally thought, with each drug class having a unique adherence-resistance relationship [139-142].

The adherence-resistance relationship in regimens containing a single PI or NRTI is thought to be similar. Studies showed that most drug resistant mutations were occurring in individuals with adherence above 90% [62,143,144,144,145]. A subsequent mathematical model determined that the maximal resistance occurs at 87% adherence and declines only modestly with perfect adherence [146]. This degree of adherence is low enough to allow for viral failure while high enough to exert selective pressure for resistant virus.

Boosted PI regimens (PIs taken with another PI drug, usually ritonavir) allow for more potent viral suppression than ritonavir unboosted PIs and this reduces the emergence of resistant mutations. Boosting also increases the half-life of the PI and so PI concentrations remain in a suboptimal therapeutic range for only a brief time during periods of non-adherence [143]. Resistance to PIs

usually requires multiple mutations; therefore high level resistance requires both ongoing viral replication and sufficient drug exposure to create a selective advantage for drug-resistant virus [86].

For NNRTIs, resistance is associated with interruptions in therapy [147] and develops at a lower level of adherence than PI resistance [148]. Unlike most PI drugs, resistance to the NNRTIs nevirapine and efavirenz requires only a single mutation at the K103N codon and even a single dose of NNRTI monotherapy can result in resistance [149]. In addition, NNRTIs have long half-lives allowing the virus to replicate in the presence of consecutive missed doses. Resistance mutations are common in patients with any level of adherence that is insufficient for full viral suppression but uncommon in highly adherent patients. The clinical implications of NNRTI resistance are considerable since NNRTI resistance almost universally confers to cross-resistance to first generation NNRTIs and persists in most cases even after drug discontinuation [150].

This complicated relationship between adherence and resistance and viral suppression makes the choice of regimen challenging. The widespread use of NNRTIs could have greater public health consequences compared to boosted PIs. However, NNRTIs are less expensive, more potent, easier to administer, and more tolerable making them the natural choice for initial regimen especially in resource-limited settings.

#### *AIDS-defining illness and mortality*

A limited number of studies have examined the relationship between non-adherence and mortality [56-58] or progression to AIDS [59]. A meta-analysis of the association between adherence and mortality found a pooled odds ratio of death in the subset of HIV studies of 0.53 (95% CI: 0.41 -0.69) in adherent patients compared to non-adherent patients [151]. However, the findings of these studies are difficult to interpret due to confounders such as more advanced stages of HIV infection (lower CD4 cell counts at the start of cART), baseline HIV-1 RNA, type of cART (mono, dual, or triple therapy), year of initiation of therapy, and depression. In addition, all these studies have methodological limitations; either no adjustment for confounding or used only standard statistical models to adjust for confounding which can result in biased effect estimates.

#### *Public health implications of non-adherence to antiretroviral drugs*

The importance of adherence in the life of an HIV-infected person on cART is undisputed. However, the adherence patterns of individuals can also have public health implications. As discussed above, non-adherent individuals can develop drug resistance and then transmit this drug-resistant virus to others. However, after a period of increasing prevalence [152-154], there have been several recent

reports of stabilized or decreasing trends in transmitted drug resistant virus in newly infected patients [155] as well as treatment experienced patients [156-158].

In addition, it is thought that individuals with detectable viraemia are more infectious therefore non-adherence can lead to an increase in overall transmissibility and incidence of HIV. Vernazza and colleagues found a strong association between HIV-1 RNA viral load in the plasma with that in the seminal and vaginal fluids [159]. Suppressing the serum viral load has been shown to reduce mother-to-child transmission [160] and is believed to also reduce the risk of sexual transmission [161-164]. There has been some evidence that the introduction of cART led to an increase in risk behavior [165-167], therefore the beneficial use of cART in terms of decrease in the risk of transmission was thought to be partially negated by the increase in risk behavior [168]. Other studies however found stable or decreasing trends in risk behavior [169,170] and a meta-analysis of the association between use of cART and sexual risk behavior did not find a significant effect [171]. However, a recent randomized controlled trial of continuous versus intermittent cART found an increase in the risk of transmission in those with intermittent cART [63]. It remains an open question as to whether individuals with undetectable peripheral viral loads are still capable of transmitting drug-resistant HIV [172-174].

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## Chapter 2: Goal and objectives

### Goal

The goal of this dissertation was to enhance the current understanding of the relationship between self-reported non-adherence to antiretroviral therapy and both factors related to non-adherence and clinical outcomes in HIV-infected individuals using state of the art methodology.

### Objectives

1. To develop an understanding of the factors affecting self-reported non-adherence to cART incorporating correlates from the following 5 dimensions identified by the World Health Organization (WHO): a) social/economic, b) patient, c) condition, d) treatment, and e) system.
2. To explore patterns and changes in self-reported adherence over time and to examine predictors of changes in adherence from five dimensions of the WHO.
3. To assess the relationship between self-reported non-adherence and treatment failure as a form of validation of the Swiss HIV Cohort Study adherence questionnaire (SHCS-AQ).
4. To assess the causal relationship between self-reported non-adherence and clinical outcomes using marginal structural models to adjust for confounding due to selection bias and lost to follow-up.



## Chapter 3: Adherence measurement in the Swiss HIV Cohort Study

### 1. The Swiss HIV Cohort Study

The Swiss HIV Cohort Study (SHCS) is an ongoing multi-center, prospective observational research study initially funded by the Swiss Federal Office for Public Health and now financed by the Swiss National Science Foundation [1]. Seven centers began enrolling patients in 1988 and a total of 15,694 individuals have been registered as of May 2009 ([www.shcs.ch](http://www.shcs.ch)). The SHCS is estimated to include approximately 45% of the total number of HIV infections declared to Swiss health authorities and 69% of people with AIDS living in Switzerland [1]. The number of newly registered patients in the SHCS has changed in parallel to the character or trends in the epidemic of the disease in the Swiss population. As of 2008, 30.5% of actively followed patients were women and the main transmission groups were heterosexual (38.8%) and MSM (40.1%).

Sociodemographic and behavioral data are collected at registration into the study. Official cohort visits occur every 6 months where laboratory and clinical data are collected. Over time, increasing amounts of information have been added to the standard data collection including cardiovascular risk factors and sexual risk behavior (2000), alcohol consumption (2005), and in-depth information on IDU (2007). Data on adherence to ART was collected in a pilot phase beginning in January 2003 with full data collection beginning in July 2003.

### 2. Adherence questions

Due to feasibility constraints the SHCS adherence questionnaire (SHCS-AQ) includes only 2 of the 4 relevant dimensions of adherence behavior, taking adherence and drug holidays. The following questions are recorded at each semi-annual cohort visit:

1. How often was a dose of ART missed in the previous 4 weeks?
  - a) Never
  - b) Once a month
  - c) Once every 2 weeks
  - d) Once a week
  - e) More than once a week
  - f) Every day
2. Did you miss more than one dose in a row in the last 4 weeks?
  - a) Yes
  - b) No

### 3. Definition of non-adherence

Given these two questions, one must still define what qualifies as non-adherence. As discussed in Chapter 1, previous research suggests that the implications of non-adherence vary by regimen class, with NNRTIs being more forgiving of missed doses with respect to viral failure but less forgiving with respect to drug resistance [2, 3]. However the exact level of adherence necessary by regimen class to achieve good clinical outcomes is not clear. Therefore, non-adherence was defined independent of regimen class with interactions between adherence and regimen class considered in models of clinical outcomes.

Three definitions of non-adherence are used throughout the manuscripts depending on the study design and analysis method. The first and most conservative definition is to consider any missed dose of ART to be non-adherence. The second definition of non-adherence is missing more than 1 dose of ART. The third definition translates the answers of the first question into number of missed doses in the last 4 weeks: 0, 1, 2, and >2. These definitions allow us to examine the effects of different levels of non-adherence.

### 4. Data collection and social desirability bias

The SHCS-AQ is administered via interview with the attending physician or nurse. This method of data collection may lead to overreporting of adherence which could be minimized with a self-administered questionnaire [4]. First, social desirability bias may lead an individual to intentionally over report their adherence to avoid discomfort. Second, misremembering of adherence is thought to be the main reason why self-report overestimates adherence as the repetitive routine of pill-taking leads to poor memory for the event [5]. Misremembering might be minimized, however, if patients were given more time to consider their answers when completing the questionnaire themselves.

Nested within the SHCS, a multi-center study exploring symptom experience and manageability, adherence, health-related quality of life, and disease progression in HIV-infected patients (SOLEXA) was conducted in 2006 [6, 7]. As part of this study, participants completed the SHCS-AQ via self-administration. As an exploratory analysis into the extent of social desirability bias, questionnaires completed by the same patient via interview and self-administration were compared. We included only those participants who completed both questionnaires within 30 days of each other for a sample of 182 (66.9%) out of the original 272 participating in SOLEXA.

The responses were the same on both questionnaires 67.6% of the time; adherence estimates were higher during the interview than self-administration during 22.5% of the time and lower 9.9% of the time (Table 3.1). We used Bowker's test of symmetry to see if the paired responses between an

individual were statistically different. The null hypothesis is that the probabilities in the square table satisfy symmetry (or that  $p_{ij} = p_{ji}$ ) for all pairs of table cells. The null hypothesis was rejected with a p-value of 0.03 indicating that the responses from the interview-administered questionnaire were significantly different from those given in the self-administered questionnaire. This provides some evidence of potential social desirability bias or over reporting of adherence during interviews with physicians.

**Table 3.1** Self-reported missed doses of antiretroviral therapy in the previous 4 weeks by mode of administration in participants of SHCS and SOLEXA (N=182) \*

	<b>SHCS Interview- administered</b>	<b>SOLEXA Self-completion</b>	<b>p-value<sup>√</sup></b>
	n (%)	n (%)	
<b>Missed doses #</b>			
0	138 (75.8)	116 (63.7)	0.03
1	33 (18.1)	42 (23.1)	
2	5 (2.8)	10 (5.5)	
>2	6 (3.3)	14 (7.7)	

\* SHCS = Swiss HIV Cohort Study; SOLEXA was a nested study within the SHCS  
# Self-reported missed doses of antiretroviral therapy in the previous 4 weeks  
<sup>√</sup> Bowker's test of symmetry.

Despite these arguments against this form of data collection, the reason for using interview to collect the data is two-fold. Adherence is an important aspect of the clinical care of a patient and should be discussed openly and regularly with their treating physician. Second, practical considerations of busy clinics make it difficult to implement other data collection methods.

## 5. Validation of adherence questionnaire

Deschamps and colleagues conducted a diagnostic study in 133 patients comparing three measures of self-reported adherence, the SHCS-AQ, European HIV treatment questionnaire, and a visual analogue scale (VAS), using both MEMS and virologic failure as reference standards [8]. Self-reported adherence was measured at baseline and again 3 months later. Adherence was monitored by MEMS for 3 months starting at baseline. Viral load was measured every 3 months for 15 months starting at baseline. Virologic failure was defined as at least one viral load > 400 copies/ml or two consecutive viral loads >50 copies/ml.

When using MEMS as the reference standard, the combination of VAS and the SHCS-AQ performed better than the SHCS-AQ alone, however the diagnostic value was still low (sensitivity 66.7%, specificity 58.2%, area under the curve (AUC) 0.63). Using virologic failure at 1 year as the reference standard, the SHCS-AQ performed better than the other two self-report measures, SHCS-AQ combined with VAS, and MEMS with a sensitivity of 88%, specificity of 79%, and an AUC of 0.83. These results demonstrated that the SHCS-AQ is not only a simple and practical way to measure adherence in daily clinical practice but a valid one as well.

This study also highlighted some of the problems discussed previously that can occur with the use of MEMS. Of the 133 eligible patients who agreed to participate in the study, 17 (12.8%) were not included due to inconsistent or incorrect use of the MEMS cap and 36% of participants admitted to using the MEMS cap inconsistently. Another 41% reported using pill boxes to organize their medications which could have led to incorrect measurements with MEMS.

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## Chapter 4: Correlates of non-adherence to antiretroviral therapy

### Correlates of self reported non-adherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study

Tracy R Glass<sup>1</sup>, Sabina De Geest<sup>2</sup>, Rainer Weber<sup>3</sup>, Pietro L Vernazza<sup>4</sup>, Martin Rickenbach<sup>5</sup>, Hansjakob Furrer<sup>6</sup>, Enos Bernasconi<sup>7</sup>, Matthias Cavassini<sup>8</sup>, Bernard Hirschel<sup>9</sup>, Manuel Battegay<sup>10</sup>, Heiner C Bucher<sup>1,10</sup>, and the Swiss HIV Cohort Study

<sup>1</sup>Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel,

<sup>2</sup>Institute of Nursing Science, University of Basel,

<sup>3</sup>Division of Infectious Diseases and Hospital Hygiene, University Hospital Zurich,

<sup>4</sup>Division of Infectious Diseases, Kantonsspital St. Gallen,

<sup>5</sup>Swiss HIV Cohort Data Center, University Hospital Lausanne,

<sup>6</sup>Division of Infectious Diseases, University Hospital Berne,

<sup>7</sup>Division of Infectious Diseases, Ospedale Civico, Lugano,

<sup>8</sup>Division of Infectious Diseases, University Hospital Lausanne,

<sup>9</sup>Division of Infectious Diseases, University Hospital Geneva,

<sup>10</sup>Division of Infectious Diseases and Hospital Hygiene, University Hospital Basel

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## **Abstract**

### **Background**

Adherence is one of the most crucial issues in the clinical management of HIV-infected patients receiving antiretroviral therapy (ART).

### **Methods**

A two-item adherence questionnaire was introduced into the Swiss HIV Cohort Study in July 2003. All 3607 eligible patients were on ART for  $\geq 6$  months and their current regimen for  $\geq 1$  month. Three definitions of non-adherence were considered: missing  $\geq 1$  dose, missing  $\geq 2$  doses and taking  $< 95\%$  of doses in the last 4 weeks.

### **Results**

Over 30% of patients reported missing  $\geq 1$  dose, 14.9% missed  $\geq 2$  doses, and 7.1% took  $< 95\%$  of doses in the previous 4 weeks. The rate of drug holidays was 5.8%. Whether using more or less conservative definitions of non-adherence younger age, living alone, number of previous regimens and boosted PI regimens were independent factors associated with non-adherence. There was a significant association between optimal viral suppression and non-adherence as well as a significant linear trend in optimal viral suppression by missed doses.

### **Conclusions**

Younger age, lack of social support, and complexity of therapy are important factors that are related to non-adherence with ART. Investment in behavioral dimensions of HIV is crucial to improve adherence in ART recipients.

## **Introduction**

Antiretroviral therapy (ART) has led to a substantial reduction in HIV associated morbidity and mortality and HIV infection has entered the stage of chronic disease management [1-4]. Lasting suppression of viral replication is the goal of ART and one of the most important factors influencing long-term prognosis of HIV-infected individuals [5,6]. Factors associated with the failure of viral suppression and progression to AIDS or death are low CD4 cell counts and viremia at the start of ART, non-naiveté to ART, adverse drug reactions and non-adherence to ART [7-11].

Non-adherence increases the risk of viral mutations, which can result in cross-resistance to other medications [12-14] or transmission of multi-resistant virus strains, and thus the risk for initial therapy failure in subsequently infected individuals [15,16]. Although preliminary evidence indicates that even high and sometimes complete adherence does not prevent accumulation of HIV drug resistance mutations, sub-optimal adherence remains a critical issue in the development of resistance [13,17]. Adherence is imperative to guarantee the effectiveness of ART [18-20].

The medication event monitoring system (MEMS) is the most reliable and sensitive method to assess adherence [18], but not feasible in a large HIV-infected population such as the Swiss HIV Cohort Study (SHCS) largely due to cost. Patient self report has the advantage of low cost, simplicity and feasibility, correlates reasonably well with viral load and suppression [21] but can overestimate adherence rates due to recall bias and social desirability [22].

The goals of this study were to determine the prevalence of self-reported adherence to ART in the SHCS and to explore relationships between socioeconomic-, patient-, condition-, therapy-, and system-related factors and self-reported adherence to ART.

## **Methods**

### *Patients*

The SHCS is a prospective cohort study with continuing enrollment of HIV-infected individuals aged 16 years or older. Beginning in July 2003, an adherence questionnaire was introduced into the cohort follow-up. Visits take place every 6 months at 7 outpatient clinics from participating HIV centers, associated hospitals, or specialized private practices. Eligible individuals were actively enrolled in the SHCS and on potent ART for at least 6 months and their current regimen for at least 1 month at the time of their first cohort visit after July 2003. Potent ART was defined as any 2-class regimen from a protease inhibitor (PI), nucleoside reverse transcriptase inhibitor (NRTI), non-

nucleoside reverse transcriptase inhibitor (NNRTI) or fusion inhibitor (FI) class, or a triple NRTI regimen. A treatment interruption of less than 4 weeks was allowed except in the 4 weeks immediately prior to the date the questionnaire was completed.

### *Outcome definition*

There are four dimensions of adherence that merit consideration when focusing on the behavioral dimension of adherence to ART: taking adherence (the extent to which a patient is taking a prescribed drug regimen), timing adherence (the extent a patient is adhering to the prescribed schedule for the drug intake), drug holidays (the extent a patient is missing several doses in a row), and food restrictions (the extent a patient is adhering to drug intake in relation to food restrictions). Due to feasibility constraints, the SHCS adherence questionnaire contains only two questions: taking adherence (How often did you miss a dose in the last 4 weeks: daily, more than once a week, once a week, once every second week, once a month, never); and drug holidays (Did you have a period of no drug intake for > 24 hours in the last 4 weeks: yes, no). As there is no standard definition of non-adherence, we considered three definitions, each increasingly less conservative: 1) missing one or more doses of medication, 2) missing two or more doses of medication, and 3) taking less than 95% of prescribed doses of ART in the last 4 weeks.

### *Covariate definitions*

At each cohort visit, laboratory measurements are taken and information on cardiovascular risk factors and social support is collected. In addition, any changes in treatment, such as dose, drugs, toxicity and reasons for switching drugs, are recorded. Using the new taxonomy of the WHO [23], correlates of non-adherence can be categorized as 1) socioeconomic-related factors, 2) patient-related factors, 3) condition-related factors, 4) treatment-related factors, and 5) system-related factors. We considered the following socioeconomic-related factors: gender, age, ethnicity, education level (completed 9 years of mandatory schooling or less vs. higher), having a stable partner in the previous 6 months, and currently living alone. Patient-related factors were current IV drug use or being in IV drug maintenance program and seeking psychiatric treatment in the last 6 months. Condition-related factors included progression to AIDS, time on current ART, and time on ART. Treatment-related factors were number of previous ART regimens, daily pill burden, dose frequency (once daily, twice daily, three or more times a day), drug class of current regimen (NNRTI, boosted PI, non-boosted PI, triple nucleoside), ART toxicity since the year 2000, fat loss or fat gain in the last 12 months, and current use of co-medications (opportunistic infections, hepatitis C, risk factors of cardiovascular disease). The system-related factor was the center where the patient had their last visit.

### *Definitions of surrogate markers for HIV infection*

Optimal viral suppression was defined as having plasma HIV RNA (viral load) < 50 copies/ml allowing for non-consecutive blips ( $50 \leq \text{HIV RNA} \leq 400$  copies/ml) over the previous 6 months. Two consecutive blips or a viral load > 400 copies/ml was considered non-optimal viral suppression. Any increases in CD4 cell count of > 50 or >100 x 10<sup>9</sup>/L in the previous 12 months was considered.

### *Statistical methods*

For each of the three outcomes, univariate and multivariable logistic regression models were used to assess the association between the outcome and covariates. Initially, univariate models were fit and factors associated with non-adherence ( $P < 0.10$ ) were entered into multivariable models. Some factors were excluded from the multivariable model due to multicollinearity. To adjust for potential correlation in adherence behavior within patients at the same center, a multilevel mixed model was fit to the data with center as a random effect. Likelihood ratio tests were used to determine significant associations between covariates and non-adherence. Odds ratios (OR) and 95% confidence intervals were estimated. The association between surrogate markers of HIV infection and the outcomes was assessed in sensitivity analyses. Linear trends in the data were assessed using the Cochran-Armitage trend test. All analyses were done with Stata 8.0 and SAS version 8.2.

## **Results**

### *Sample population and non-responders*

A total of 5861 individuals was registered in the SHCS and had not dropped out prior to July 1, 2003. Of these, 1458 were not on treatment and 128 did not complete an adherence questionnaire. In addition, 668 did not meet the treatment criteria: 619 were not on potent ART for at least 6 months and 49 were not on their current regimen for at least 4 weeks. A total of 3607 individuals were included in the analysis.

The 668 patients who did not meet eligibility criteria were more likely to be female (33.7% vs. 28.6%), have a basic education (30.9% vs. 25.7%), not be in a stable partnership (48.8% vs. 40.8%), use IV drugs (15.0% vs. 10.3%), and been HIV+ for a shorter period of time (8 vs. 10 years) compared to the analysis population.

### *Self reported non-adherence*

Self-reported non-adherence over the previous 4 weeks was as follows: 31.1% of patients reported missing one or more doses (range across centers: 26.1%-41.5%); 14.9% reported missing 2 or more

doses (range across centers: 11.0%-22.3%); and 7.1% of patients took <95% of prescribed ART doses (range across centers: 4.3%-12.3%). Almost 6% reported taking a drug holiday (no drug intake in > 24 hours) in the last 4 weeks (Table 4.1).

**Table 4.1** Self-reported non-adherence to potent ART in the SHCS

<b>Total no. of patients</b>	3607
<b>How often a dose was missed in last 4 weeks - %</b>	
Never	68.9
Once a month	17.3
Once every 2 weeks	6.7
Once a week	3.1
More than once a week	3.1
Every day	1.0
<b>Drug holidays - %</b>	
No drug intake > 24 hours	5.8
<b>Percent adherence in the last 4 weeks</b>	
≥ 95%	92.9
90-95%	6.0
< 90%	1.1
<b>Non-adherence in the last 4 weeks</b>	
Missed ≥ 1 dose	31.1
Missed ≥ 2 doses	14.9

Adherence rates by potential correlates (Table 4.2a) and surrogate markers of HIV infection (Table 4.2b) are provided. The more non-adherent individuals become the worse the HIV infection profile. Over 78% of all patients were optimally virally suppressed during the previous 6 months, this percentage dropped to 72.1% in those who missed ≥1 dose of medication, 64.0% in those who missed ≥ 2 doses and to 58.4% in those with <95% adherence. The percentage of individuals with increases in CD4 count of >50 cell per 10<sup>9</sup>/l in the previous year decreased from 57.1% to 49.8% with diminishing adherence. Of those who reported taking a drug holiday, only 52.8% were optimally virally suppressed compared to 80.4% of those who did not report taking a drug holiday. A strong linear relationship was found between the number of missed doses and optimal viral suppression (Figure 4.1) and the test for linear trend was highly significant (p<0.0001).

**Table 4.2a** Adherence rates by potential correlates and surrogate markers of HIV infection

	All patients	Missed $\geq 1$ dose	Missed $\geq 2$ doses	<95% doses
Total – n (%)	3607 (100)	1123 (31.1)	537 (14.9)	258 (7.2)
Age in years – Mean (SD)	43.5 (9.7)	42.5 (9.1)	42.2 (9.0)	41.4 (8.3)
Male Gender – %	71.4	68.6	67.2	65.5
Race – %				
Caucasian	82.7	81.0	79.0	75.2
Black	9.6	10.3	11.0	13.2
Hispano-American	1.8	2.1	2.4	2.7
Asian	3.2	2.9	3.9	4.7
Other/Unknown	2.6	3.6	3.7	4.3
Basic Education – %	25.7	29.2	31.3	37.7
Stable Partnership – %	59.2	59.3	56.8	56.0
Living Alone – %	41.5	44.6	45.4	48.0
Current IDU or drug program § – %	10.3	13.1	13.8	18.3
Psychiatric treatment § - %	7.1	8.6	8.6	8.9
AIDS - %	30.1	28.9	29.8	31.4
Years on current ART - Mean (SD)	2.2 (1.7)	2.3 (1.7)	2.2 (1.8)	2.1 (1.6)
Years on all previous ART – Mean (SD)	4.6 (2.8)	4.6 (2.8)	4.5 (2.9)	4.1 (2.8)
Years since 1 <sup>st</sup> pos HIV test – Mean (SD)	10.1 (5.5)	11.1 (5.3)	11.2 (5.2)	11.0 (5.2)
No. of previous regimens – Mean (SD)	4.3 (3.3)	4.6 (3.4)	4.9 (3.6)	4.9 (3.6)
Daily pill burden - %				
Mean (SD)	7.6 (5.1)	8.0 (5.3)	8.3 (5.2)	8.1 (5.5)
< 7	50.1	46.7	42.6	44.4
7 – 11	22.7	24.3	27.1	25.7
$\geq 12$	27.3	29.0	30.3	30.0
ART Toxicity ‡ - %				
Major toxicity	26.1	26.1	27.2	28.7
Other toxicity	19.2	19.8	23.3	24.8
None	54.8	54.1	49.5	46.5
Lipodystrophy - %				
Any fat loss	30.6	29.8	28.0	25.2
Any fat gain	28.9	28.5	28.6	28.0
Dose frequency - %				
Once daily	5.2	3.8	3.4	5.8
Twice daily	91.8	92.7	92.7	93.0
Three time or more daily	3.1	3.5	3.9	1.2
Current drug regimen - %				
NNRTI	32.2	27.8	24.8	21.7
PI – boosted	25.9	26.7	27.8	24.0
PI – non-boosted	25.0	27.3	29.8	31.8
Triple nucleoside	16.9	18.3	17.7	22.5
Current co-medication - %				
Cardiovascular risk factors	2.6	2.9	2.8	2.3
Hepatitis C	0.9	0.6	0.6	0.8
Opportunistic Infections	4.1	2.9	3.5	5.0

\* Non-adherence in the previous 4 weeks

§ In the 6 month period prior to the adherence questionnaire.

‡ Any ART toxicity since the year 2000. Major toxicities were abnormal fat distribution, hypersensitivity reaction, abdominal/GI tract, nervous system, and hematologic toxicity.

**Table 4.2B** Adherence rates by potential correlates and surrogate markers of HIV infection

	All patients	Missed $\geq 1$ dose	Missed $\geq 2$ doses	<95% doses taken
Total – n (%)	3607 (100)	1123 (31.1)	537 (14.9)	258 (7.2)
Optimal Viral Suppression †	78.9	72.1	64.0	59.2
HIV RNA viral load (copies/ml) - % ‡				
Mean (SD) of log copies/ml	1.8 (3.0)	2.4 (3.4)	3.1 (3.8)	3.7 (4.1)
< 50	79.5	72.5	64.2	58.4
50-399	9.0	9.7	10.7	11.0
$\geq 400$	11.5	17.8	25.1	30.6
CD4 increase (cells per $10^9/l$ ) - % §				
> 50	57.1	54.7	50.9	49.8
> 100	34.4	33.5	31.9	33.0
CD4 count (cells per $10^9/l$ ) - % ‡				
Mean (SD)	492.6 (279)	488.5 (268)	463.4 (268)	452.6 (263)
< 200	11.0	10.8	12.9	14.6
200 – 349	22.8	21.7	23.9	23.7
350 – 499	24.7	26.9	26.5	26.1
$\geq 500$	41.6	40.7	36.7	35.6

\* Non-adherence in the previous 4 weeks

† In the 6 month period prior to the adherence questionnaire. For definition see Methods section.

‡ Closest to the date of the adherence questionnaire

§ In the 12 month period prior to the adherence questionnaire.

### Univariable results

Across all three definitions of adherence, univariate models showed that individuals of younger age, female gender, basic education, living alone, currently using IV drugs, with higher number of previous ART regimens, higher daily pill burden, and not on an NNRTI-based regimen were more likely to non-adhere to therapy (Table 4.3). Pill burden was not included in the multivariable models due to high correlation with drug regimen.

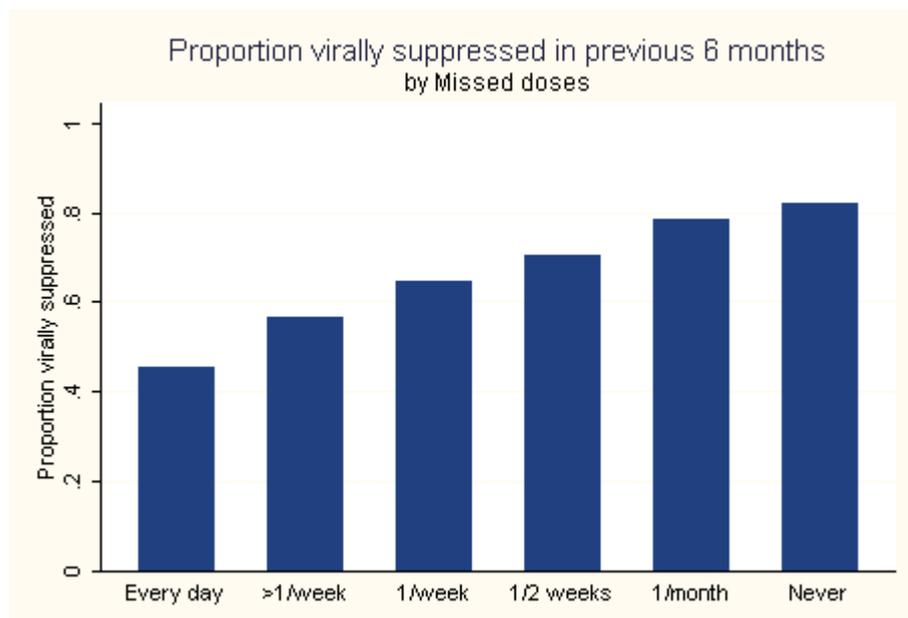
### Multivariable results

Table 4.3 provides the results of the multivariable models. For all three definitions of adherence, individuals of younger age, living alone, higher number of previous ART regimens, and those on a boosted PI regimen were significantly more likely to non-adhere to therapy in the previous 4 weeks. Odds ratios and confidence intervals were similar for all models although the effect strengthened as the definition of adherence became less conservative. In all models, there was a significant amount of variation in non-adherence explained by the center where the patient had their follow-up visit even after adjusting for all other variables in the model.

In each of the three final models, additional variables were significantly associated with non-adherence in the multivariable model. For non-adherence defined as missing  $\geq 1$  dose, individuals on

their current regimen for a longer time (OR 1.08, 95%CI: 1.02 – 1.13) were more likely to non-adhere to therapy, whereas individuals taking co-medication for opportunistic infections (OR 0.65, 95% CI: 0.43-0.98) were less likely to non-adhere to therapy. For non-adherence defined as missing  $\geq 2$  doses, individuals on a non-boosted PI regimen (OR 1.53, 95% CI: 1.15-2.04) were more likely to non-adhere to therapy, whereas individuals with reported fat loss (OR 0.76, 95% CI: 0.60-0.95) were less likely to non-adhere to therapy. For non-adherence defined as taking <95% of doses, individuals with a basic education (OR 1.42, 95% CI: 1.04-1.94), current IV drug users (OR 1.67, 95% CI: 1.12-2.51), and on a non-boosted PI regimen (OR 1.70, 95% CI: 1.12-2.57) or a triple nucleoside regimen (OR 2.03, 95% CI: 1.33-3.11) were more likely to non-adhere to therapy, whereas individuals of Caucasian race (OR 0.66, 95% CI: 0.46-0.95), and with reported fat loss (OR 0.63, 95% CI: 0.45-0.88) were less likely to non-adhere to therapy.

**Figure 4.1** Proportion virally suppressed in previous 6 months



### *Sensitivity analyses*

As a sensitivity analysis, surrogates of HIV infection (optimal viral suppression and increases in CD4 count of >50 cells) were added to the final multivariable models. Individuals who were optimally virally suppressed over the previous 6 months were significantly less likely to non-adhere ( $p < 0.001$ ) in all three multivariable models ( $\geq 1$  dose: OR 0.62, 95% CI 0.51-0.75;  $\geq 2$  doses: OR 0.49, 95% CI 0.39-0.62; <95% adherence: OR 0.44, 95% CI 0.32-0.60). Individuals with increases in CD4 cell count of >50 cells x 10<sup>6</sup>/l were significantly less likely to non-adhere only as the definition of non-adherence

**Table 4.3** Correlates of self-reported non-adherence to potent antiretroviral therapy (ART) in the last 4 weeks

Factor dimensions	Missed ≥ 1 dose			Missed ≥ 2 doses			<95% of drugs taken		
	Univariate OR (95% CI)	Multivariable OR (95% CI)	p-value	Univariate OR (95% CI)	Multivariable OR (95% CI)	p-value	Univariate OR (95% CI)	Multivariable OR (95% CI)	p-value
<b>Socioeconomic-related</b>									
Age (in years)	0.98 (0.98-0.99)	0.98 (0.97-0.99)	<0.001	0.98 (0.97-0.99)	0.98 (0.97-0.99)	0.002	0.97 (0.96-0.99)	0.98 (0.96-1.00)	0.02
Male Gender	0.83 (0.71-0.97)	0.88 (0.74-1.05)	0.16	0.81 (0.67-0.99)	0.90 (0.72-1.13)	0.36	0.78 (0.59-1.02)	0.98 (0.72-1.35)	0.92
Caucasian race	0.88 (0.73-1.07)			0.79 (0.63-0.99)	0.88 (0.67-1.16)	0.37	0.67 (0.49-0.90)	0.66 (0.46-0.95)	0.03
Basic Education	1.25 (1.06-1.49)	1.11 (0.93-1.33)	0.23	1.37 (1.11-1.69)	1.15 (0.91-1.45)	0.23	1.76 (1.33-2.32)	1.42 (1.04-1.94)	0.03
Stable Partnership	1.01 (0.87-1.17)			0.89 (0.74-1.08)			0.87 (0.67-1.13)		
Living Alone	1.19(1.03-1.37)	1.26 (1.08-1.47)	0.003	1.18 (0.98-1.42)	1.27 (1.04-1.56)	0.02	1.30 (1.00-1.68)	1.55 (1.17-2.05)	0.002
<b>Patient &amp; Condition-related</b>									
Current IDU or drug program	1.47 (1.18-1.84)	1.18 (0.92-1.52)	0.19	1.50 (1.14-1.98)	1.22 (0.89-1.68)	0.22	2.05 (1.46-2.88)	1.67 (1.12-2.51)	0.01
Psychiatric treatment	1.42 (1.09-1.85)	1.26 (0.92-1.52)	0.12	1.32 (0.95-1.85)	1.14 (0.78-1.65)	0.50	1.37 (0.87-2.15)		
AIDS	0.92 (0.78-1.07)			1.00 (0.81-1.22)			1.09 (0.83-1.43)		
Time on current ART (years)	1.06 (1.02-1.11)	1.08 (1.02-1.13)	0.004	1.03 (0.97-1.08)			1.00 (1.00-1.00)		
Time on ART (years)	1.00 (0.98-1.03)			0.99 (0.95-1.02)			0.94 (0.89-0.98)	0.96 (0.91-1.01)	0.12
<b>Treatment-related</b>									
No. of previous regimens	1.04 (1.01-1.06)	1.05 (1.02-1.07)	<0.001	1.05 (1.02-1.08)	1.06 (1.03-1.10)	<0.001	1.04 (1.00-1.07)	1.08 (1.03-1.12)	0.001
Daily pill burden									
< 7	1.0			1.0			1.0		
7 – 11	1.31 (1.09-1.57)			1.76 (1.39-2.22)			1.52 (1.10-2.10)		
≥ 12	1.34 (1.13-1.59)			1.72 (1.37-2.16)			1.64 (1.20-2.24)		
ART Toxicity †									
Other toxicity	0.99 (0.83-1.17)			0.88 (0.71-1.10)			0.79 (0.58-1.08)		
None	1.02 (0.82-1.26)			1.19 (0.92-1.56)			1.18 (0.83-1.68)		
Lipodystrophy in previous year									
Any fat loss	0.91 (0.78-1.06)			0.82 (0.67-1.01)	0.76 (0.60-0.95)	0.02	0.70 (0.52-0.94)	0.63 (0.45-0.88)	0.008
Any fat gain	0.92 (0.78-1.07)			0.93 (0.75-1.15)			0.89 (0.66-1.18)		
Dose frequency									
Once daily	0.62 (0.43-0.88)	0.69 (0.46-1.03)	0.07	0.58 (0.35-0.95)	0.56 (0.31-1.01)	0.06	1.06 (0.61-1.83)		
Twice daily	1.0	1.0	-	1.0	1.0	-	1.0		
Three times or more daily	1.26 (0.85-1.89)	1.16 (0.75 -1.78)	0.51	1.52 (0.93–2.49)	1.31 (0.77 –2.22)	0.31	0.41 (0.13-1.31)		
Current drug regimen									
NNRTI	1.0	1.0	-	1.0	1.0	-	1.0	1.0	
PI – non-boosted	1.48 (1.21-1.81)	1.19 (0.95-1.48)	0.13	1.80 (1.39-2.34)	1.53 (1.15-2.04)	0.004	1.76 (1.20-2.59)	1.70 (1.12-2.57)	0.01
PI – boosted	1.52 (1.25-1.86)	1.37 (1.10-1.69)	0.004	1.89 (1.46-2.44)	1.53 (1.15-2.03)	0.003	2.23 (1.56-3.19)	1.98 (1.32-2.92)	0.001
Triple nucleoside	1.31 (1.05-1.62)	1.19 (0.95-1.50)	0.13	1.31 (0.98-1.75)	1.24 (0.91-1.69)	0.18	1.95 (1.32-2.87)	2.03 (1.33-3.11)	0.001
Co-medication									
Cardiovascular	1.16 (0.74-1.80)			1.11 (0.63-1.96)			0.92 (0.40-2.14)		
Hepatitis C	0.65 (0.28-1.53)			0.68 (0.20-2.26)			1.05 (0.25-4.47)		
Opportunistic Infections	0.61 (0.41-0.91)	0.65 (0.43-0.98)	0.04	0.89 (0.54-1.46)			1.37 (0.76-2.47)		

† Any ART toxicity since the year 2000. Reference group was major toxicities defined as abnormal fat distribution, hypersensitivity reaction, abdominal/GI tract, nervous system, and hematologic.

became less conservative ( $\geq 2$  missed doses: OR 0.73, 95% CI 0.59-0.91,  $p=0.004$ ;  $<95\%$  adherence: OR 0.69, 95% CI 0.51-0.93,  $p=0.02$ ).

With all three adherence outcomes, most odds ratios for original covariates remained very similar with slightly wider confidence intervals but with no resulting change in significance. Exceptions were that once daily became significant (OR 0.48, 95% CI 0.25-0.92) for missing  $\geq 2$  doses, and age, basic education, and non-boosted PI regimen became non-significant ( $p>0.05$ ) for  $<95\%$  adherence.

## Discussion

To our knowledge, this is the largest study so far to look at correlates of self-reported non-adherence in HIV-infected individuals. The analysis population includes individuals receiving ART for at least 6 months and has large proportions of women and patients from different ages and HIV transmission groups.

A clinically meaningful definition of the level of adherence below which patients with HIV are at risk for poor virologic outcome has yet to be determined. For this reason, we chose relatively conservative definitions of non-adherence because even minimal deviations in dosing are known to affect outcome [18] and self-report is associated with underreporting of non-adherence [23,24]. With the most conservative definition of non-adherence we found 31.1% of patients missing  $\geq 1$  doses of ART, which is lower than non-adherence rates between 40% and 80% that have been found by others both in clinical trials and clinical practice settings. These differences may in part depend on operational definitions, case finding or measurement methods for non-adherence [23].

We were unable to detect a significant association between non-adherence and gender and the significance of ethnicity and education depended on the definition of non-adherence, which could explain the conflicting results found in previous studies [18,19,25,26]. We included an indicator of those seeking psychiatric treatment in the previous 6 months, as this may capture those who suffer from anxiety or depression, known correlates of non-adherence [18,27,28]. However, we did not have sufficient power to detect an association. We did not detect an association between non-adherence and reported ART toxicity, which was defined as the reason an individual stopped a particular drug since the year 2000. This definition might not accurately measure symptom distress due to side effects, which was found to significantly correlate with non-adherence [29,30].

Utilizing more liberal definitions of non-adherence strengthened several trends found with the most conservative definition with respect to race, education, IV drug use, triple nucleoside therapy, and

fat loss. Individuals on a non-boosted PI regimen were just as likely to miss  $\geq 1$  dose, but were more likely to miss  $\geq 2$  doses or to take  $< 95\%$  of ART doses when compared to those on an NNRTI-based regimen. This could be due to the higher pill burden and dosing frequency for PI-based regimens.

It is increasingly recognized that system factors are an understudied but important set of determinants of compliance [31]. This study found that for definitions of non-adherence, compliance rates differed between centers even after controlling for a range of other factors. This is an important finding as these center differences might be a proxy of differences in clinical and behavioral management of patients among centers, such as continuous compliance assessment, support provided in patient's self management, and quality of relationship between patient and health care provider.

In a sensitivity analysis, we found a statistically significant association between non-adherence and optimal viral suppression that strengthened, as the definition of non-adherence became less conservative. Our results add to evidence from previous studies that have demonstrated acceptable correlation between self-reported drug adherence and HIV-1 plasma viral load [12,17,21,32-34], thus providing clinical validation of self-reported drug intake in HIV-infected individuals taking ART. Previously, conflicting results were found between CD4 cell counts and non-adherence [19,30]. In this analysis, we found a significant association between non-adherence and increases in CD4 cell count only with the two least conservative definitions of non-adherence.

This study has several strengths. We defined adherence in three different ways using two simple questions that are easy to understand and clinically relevant. We have detailed data on treatment from a large cohort of HIV-infected individuals and our analysis had the power to verify suspected trends in adherence. In addition, detailed treatment information is collected on individuals in the SHCS allowing us to explore a large range of treatment-related variables. We controlled for variations in non-adherence across centers providing a more accurate picture of real trends in the data.

This study also has several limitations. The analysis is based on cross-sectional, not prospective, data and therefore no causal conclusions can be drawn. In addition, we did not have information on food restrictions or alcohol abuse, variables known to be correlated with non-adherence [18,27,28].

Adherence has become one of the most crucial issues in the clinical management of HIV-infected patients receiving ART to achieve sustained long-term suppression of HIV replication and to avoid resistance to antiretroviral drugs. These results confirm the importance of understanding the necessary level of non-adherence as it relates to patient outcomes. Health care providers need to

provide the foundation and support for the behavioral dimension of long-term disease management and recognize that younger patients and those without social support are at increased risk for non-adherence. Preliminary evidence from our study suggests that patients on NNRTI regimens, especially when compared to those on PI regimens, may be at lower risk for non-adherence.

**Contributors:** TR Glass, S De Geest, and HC Bucher designed the study and interpreted the results. TR Glass did the statistical analysis. R Weber, PL Vernazza, H Furrer, E Bernasconi, M Cavassini, B Hirschel, M Battegay were responsible for patients recruitment and clinical assessment, M Rickenbach was involved in data management. The paper was written by TR Glass and reviewed by all other contributors.

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**Conflict of Interest**

There are no conflicts of interest. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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## Chapter 5: Patterns and predictors of changes in adherence over time

### Longitudinal analysis of patterns and predictors of changes in self-reported adherence to antiretroviral therapy: Swiss HIV Cohort Study

Tracy R Glass<sup>1</sup>, Manuel Battegay<sup>2</sup>, Matthias Cavassini<sup>3</sup>, Sabina De Geest<sup>4</sup>, Hansjakob Furrer<sup>5</sup>, Pietro L Vernazza<sup>6</sup>, Bernard Hirschel<sup>7</sup>, Enos Bernasconi<sup>8</sup>, Martin Rickenbach<sup>9</sup>, Huldrych F Günthard<sup>10</sup>, Heiner C Bucher<sup>1,2</sup>, and the Swiss HIV Cohort Study

<sup>1</sup>Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel

<sup>2</sup>Division of Infectious Diseases and Hospital Epidemiology, University Hospital Basel

<sup>3</sup>Division of Infectious Diseases, University Hospital Lausanne

<sup>4</sup>Institute of Nursing Science, University of Basel

<sup>5</sup>Division of Infectious Diseases, University Hospital Berne

<sup>6</sup>Division of Infectious Diseases, Kantonsspital St. Gallen

<sup>7</sup>Division of Infectious Diseases, University Hospital Geneva

<sup>8</sup>Division of Infectious Diseases, Ospedale Civico, Lugano

<sup>9</sup>Swiss HIV Cohort Data Center, University Hospital Lausanne

<sup>10</sup>Division of Infectious Diseases and Hospital Hygiene, University Hospital Zurich

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## **Abstract**

### **Background**

Adherence to antiretroviral therapy (cART) is a dynamic process however changes in adherence behavior over time are insufficiently understood.

### **Methods**

Data on self-reported missed doses of cART was collected every 6 months in Swiss HIV Cohort Study participants. We identified behavioural groups associated with specific cART adherence patterns using trajectory analyses. Repeated measures logistic regression identified predictors of changes in adherence between consecutive visits.

### **Results**

6709 individuals completed 49,071 adherence questionnaires (median 8 (interquartile range (IQR): 5 – 10) during a median follow-up time of 4.5 years (IQR: 2.4 – 5.1). Individuals were clustered into 4 adherence groups: good (51.8%), worsening (17.4%), improving (17.6%), and poor adherence (13.2%). Independent predictors of worsening adherence were younger age, basic education, loss of a roommate, starting intravenous drug use, increasing alcohol intake, depression, longer time with HIV, onset of lipodystrophy, and changing care provider. Independent predictors of improvements in adherence were regimen simplification, changing class of cART, less time on cART, and starting co-medications.

### **Conclusion**

Treatment, behavioural changes and life events influence patterns of drug intake in HIV patients. Clinical care providers should routinely monitor factors related to worsening adherence and intervene early to reduce the risk of treatment failure and drug resistance.

## **Introduction**

Combination antiretroviral therapy (cART) has led to dramatic reduction in hospitalization rates, opportunistic infections, and deaths associated with HIV infection [1-4]. Continuous and lasting suppression of viral replication is essential to allow for maximal CD4 cell recovery, the most important factors influencing long-term prognosis of HIV-infected individuals [5,6]. Adherence to cART is paramount to achieving these goals and non-adherence to therapy has been shown to be one of the strongest predictors of virological failure [7,8]. In addition, non-adherence has been linked to the emergence of drug resistance, often associated with cross-resistance to other members of the same class, limiting future treatment options and possible transmission of multidrug resistant virus [9-11].

Factors associated with adherence have been well documented [12-15]. Findings from our previous research have shown that younger age, lack of social support, increasing number of previous regimens, taking a protease inhibitor (PI), regimen complexity, and taking medication for opportunistic infections were significantly associated with non-adherence [12]. However, adherence is a dynamic process and only a few studies have addressed patterns and changes in adherence over time [16-20]. Most of these studies only considered special populations, such as men having sex with men (MSM) [16,18] or women [16]. In addition, all studies had methodological limitations, such as dichotomizing or summarizing adherence data leading to inefficient use of data [16,18,19] and short follow-up [17-20].

In order to optimally design adherence intervention studies, there is a need for a detailed and sophisticated analysis of adherence patterns. The Swiss HIV Cohort Study (SHCS) provides a unique opportunity to achieve this with 6 years of follow-up in a large prospective cohort where women, heterosexuals and intravenous drug users (IDU) are well-represented. The goals of this study were to identify clusters of individuals with unique patterns of adherence behaviour and to assess factors, especially changes in factors, associated with changes in adherence over time.

## **Methods**

### *Design*

This longitudinal study was based on prospectively collected data from individuals enrolled in the SHCS and followed at one of the 7 outpatient clinics (Basel, Berne, Geneva, Lausanne, Lugano, St. Gallen, Zurich) or associated clinics and private urban practices ([www.shcs.ch](http://www.shcs.ch)). At these routinely

scheduled visits, patients' self-reported drug adherence and additional psychosocial, clinical and lab data are collected. Eligible individuals were either treatment experienced or starting cART and responded to at least two adherence questionnaires between its introduction on January 1, 2003 and the end of study on January 1, 2009. Baseline was the date of the first completed adherence questionnaire.

### *Measure of adherence*

The simplified SHCS adherence questionnaire contains two questions addressing *taking adherence* and *drug holidays*, 2 of the 4 dimensions of adherence to cART [21]. *Taking adherence* is defined as the number of missed doses in the last 4 weeks (daily, more than once a week, once a week, once every second week, once a month, never). *Drug holidays* are defined as missing two or more consecutive doses in the last 4 weeks (dummy variable).

### *Definition of changes in adherence behaviour*

For the definition of change in adherence behaviour we formed consecutive visit pairs which constitute the unit of analysis. For each consecutive visit pair, changes in adherence from one visit ( $V_i$ ) to the next ( $V_{i+1}$ ) is the outcome. We defined three possible groups: 1) individuals with no reported change in missed doses between two visits, 2) individuals who reported a change for the worse with more missed doses since the last visit and 3) individuals who reported improvements in adherence with less missed doses than the previous visit.

### *Predictors of changes in adherence behaviour*

To model behaviour change in drug adherence we included predictors from five dimensions identified by the World Health Organization as affecting adherence to cART [21]: sociodemographic-, patient-, health condition-, treatment-, and health system-related factors. For time-updated predictors, changes in a predictor from one visit ( $V_i$ ) to the next ( $V_{i+1}$ ) is modelled unless otherwise specified. The sociodemographic factors were age at baseline, gender, ethnicity (Caucasian vs. others), education (basic education vs. higher education), changes in stable partnership (loss of partner, gain of partner, no change) and living conditions (loss of roommate, gain of roommate, no change). Patient-related factors were collected via self-report at every follow-up visit and defined as follows. Changes in cigarette smoking (started smoking, quit smoking, no change), intravenous drug use (IDU) (started IDU, stopped IDU, no change), participation in drug substitution program (started drug program, stopped drug program, no change), and legal problems (developed legal problems, resolved legal problems, no change). Risky sex behaviour was defined as unprotected sex (without condoms) with either an HIV-negative stable partners or occasional partners. Changes in sexual risk

behaviour were included (riskier behaviour, less risky behaviour, no change). Daily alcohol intake was translated into health risk categories developed by the WHO [22]: light (<20 g for women and <40 g for men), moderate (20-40 g for women and 40-60 g for men) and severe health risk (>40 g for women and >60 g for men) as done in a recent study [23]. Changes in categorization of alcohol risk were categorized as increased risk, decreased risk, or no change. Psychiatric treatment was defined as seeing a psychiatrist, diagnosis of depression or taking antidepressants. Although most patients seeking psychiatric treatment were likely suffering from depression, specific information on depression was only collected as of July 2008. Changes in psychiatric treatment were classified as started treatment, stopped treatment, or no change. Health condition-related factors, collected via patient interview and hospital records, were hospitalization since the previous visit, co-medication for opportunistic infections (OI), cardiovascular disease (CVD) prevention/treatment, hepatitis C or cancer (started co-medication, stopped co-medication, no change), and time since first HIV-1 positive test at baseline (in years). Treatment-related factors were number of previous cART regimens at baseline, time on cART at baseline, changes in dosing frequency (increase in frequency, decrease in frequency, no change), and changes in class of cART since the previous visit (Yes, No). Class of cART is defined as non-nucleoside reverse transcriptase inhibitor (NNRTI), boosted PI, non-boosted PI, or triple nucleoside/other. Boosted PI regimens were defined as ritonavir with at least one other PI. Body fat changes, defined as peripheral lipoatrophy or central or nuchal body fat gain as diagnosed by the clinician and confirmed by the patient, were included (new report of body fat changes, resolution of body fat changes, no change). Health system-related factors were changes in the physician or center where the individual was being followed since the previous visit.

### *Statistical analysis*

#### *Identification of patterns in adherence behaviour*

Due to the infinite number of possible individual-specific adherence patterns, we used group-based trajectory modeling for the identification of clusters of individuals with similar observed temporal patterns of adherence to cART [24]. Similar to latent class analysis [25], this method assumes that the population is composed of a mixture of distinct groups defined by their behavioral trajectories. This procedure allows joint modeling of the probability of group membership and group-specific trajectories. The latter are modeled semi parametrically via flexible polynomial functions fitted to individual adherence responses over time. Given a specified number of groups, the model estimates membership probabilities in each group for every participant, based on the participant's observed patterns of adherence over time. Estimated variability in parameter estimates accounts for uncertainty in group membership and between-individual and within-individual variation in

observed longitudinal responses. The modeling was performed for 2 up until 6 groups with final selection of the optimal number of groups based on comparison of model fits using the Bayesian information criterion. Group assignments were based on posterior model-based probability calculations, with actual assignment based on the maximal group membership probability for each participant. Model results were summarized graphically with each groups predicted trajectories and their 95% confidence intervals. Baseline characteristics by group membership were summarized.

### *Changes in adherence behavior*

To model changes in adherence behaviour, we constructed two datasets, one for improvements in and one for worsening of adherence. All visit pairs with no reported changes in adherence (where the adherence on the initial visit pair was not perfect) and those with reported improvements in adherence at visit  $V_{i+1}$  were included in the model exploring the likelihood of an improvement in adherence since the previous visit. All visit pairs with no reported changes in adherence (where the adherence on the initial visit pair was not in the lowest possible category) and those with reported decreases in adherence at visit  $V_{i+1}$  were included in the model exploring the likelihood of a decrease in adherence since the previous visit. Both models included all pre-selected predictors from the 5 WHO dimensions. For time-independent factors (age, gender, ethnicity, education, time since HIV-1 positive test, number of previous cART regimens), the value of the predictor at visit  $V_i$  was included in the model. For time-dependent factors, their change from one visit ( $V_i$ ) to the next ( $V_{i+1}$ ) was modelled. We used generalized estimating equations to evaluate the repeated measures logistic regression models. This model adjusted for the correlation between visit pairs in the same individual. Results are presented with odds ratios and 95% confidence intervals.

### *Sensitivity analyses*

To check the consistency of our results we performed several sensitivity analyses. For the description of adherence behaviour clusters, we repeated the trajectory analysis, stratifying the population by cART treatment – naïve or pre-treated. For the identification of adherence patterns, we performed three sensitivity analyses. First, we stratified the analysis by gender to check if different factors affect changes in adherence for men and women. Second, we repeated the primary analysis stratifying by number of missed doses on the initial visit pair ( $V_i$ ) to see if different factors influenced the likelihood of adherence changes depending on the initial adherence. Third, we removed changes in alcohol risk category from the multivariable model as this variable was only collected in the SHCS as of August 2005. Therefore, multivariable models including alcohol lose a lot of information which might impact the results even though these values were missing by design (completely at random).

All analyses were done with SAS version v9.1 (SAS Institute Inc., Cary, NC, USA) and Stata version v9 (StataCorp. College Station, TX, USA).

## Results

A total of 7466 individuals completed 69,144 adherence questionnaires between January 1, 2003 and January 1, 2009. Of these, 19,238 were not completed during an official follow-up visit and 105 were completed when an individual was not on cART; 654 individuals completed only one adherence questionnaire. The final analyses included 6709 individuals who completed 49,071 questionnaires and had 42,362 visit pairs during the 6 year study period. The median number of adherence questionnaires per individual was 8 (interquartile range (IQR): 5 – 10) and the median follow-up time was 4.5 years (IQR: 2.4 – 5.1). The population consisted largely of males (69.6%), Caucasians (82.1%), those with suppressed HIV-1 RNA at baseline (64.8% with <50 copies/ml), 38.4% were heterosexuals, median age was 41 years and individuals were diagnosed with HIV a median of 7.9 years ago (IQR: 3.0 – 13.5)(Table 5.1).

Missing 0 doses of cART was reported by patients on 78.1% of visits, missing 1 dose 13.1%, missing 2 doses 4.7%, and missing >2 doses 4.2% of visits. Missing more than one dose in a row was reported on 3.5% of visits. Overall, self-reported adherence was found to be improving over time, with 70% reporting missing 0 doses of cART at the beginning of the 6-year study period compared to 83% at the end (Figure 5.1). In the subset of naïve patients, this trend remained but reports of missing 0 doses increased from 81% to 87% over time (data not shown).

Trajectory analysis was used to identify group patterns of adherence to cART. We considered groups of size 2 to 6 and selected a model of 4 groups as optimal based on fit (comparing the Bayesian Information Criterion between models), parsimony (comparing clusters in both naïve and pre-treated individuals) and interpretability. Group 1 (labelled “good adherence”) was estimated at 51.8% and characterized by consistently high adherence (Figure 5.2). Group 2 (labelled “worsening adherence”) was estimated at 17.4% and included individuals with good adherence at baseline followed by steadily worsening adherence. Group 3 (labelled “improving adherence”) was the opposite of Group 2 characterized by reports of poor adherence at baseline followed by steadily improving adherence and had an estimated group membership of 17.6%. Group 4 (labelled “poor adherence”) was estimated at 13.2% and characterized by consistent reports of poor adherence over time. There was very little overlap in the confidence intervals of the groups indicating the trajectories are relatively distinct. The same four adherence patterns were identified in separate

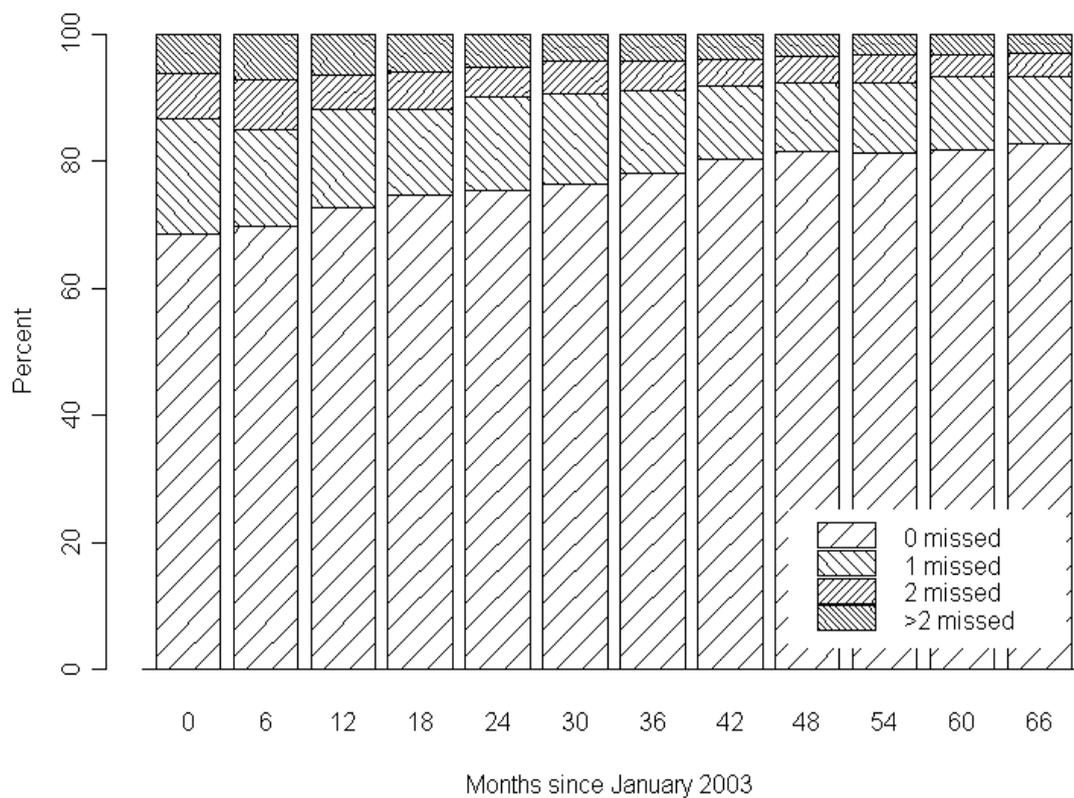
**Table 5.1** Baseline characteristics of population by membership in adherence pattern group identified by trajectory analysis

Variable	Overall	Group 1: Good adherence	Group 2: Worsening adherence	Group 3: Improving adherence	Group 4: Poor adherence
N (%)	6709	3837 (57.2)	927 (13.8)	1118 (16.7)	827 (12.3)
Age – median (IQR)	41 (36-47)	42 (36-49)	41 (35-46)	41 (36-46)	40 (36-45)
Male gender - %	69.6	71.3	66.7	68.4	65.7
Caucasian - %	82.1	82.5	81.9	81.3	81.4
Basic education # - %	26.7	23.3	29.4	30.9	34.1
Risk group for HIV infection	37.5	41.8	32.9	33.7	27.6
MSM	38.4	38.9	39.7	38.6	34.6
Heterosexual	19.9	14.6	23.7	24.7	33.9
IDU	4.2	4.7	3.7	3.0	4.0
Other					
Past or current IDU	22.3	16.6	27.1	27.3	36.6
Past or current psychiatric treatment	22.8	19.4	24.4	27.4	30.2
Past or current legal problems	9.9	6.9	13.2	11.6	17.7
Living alone	41.1	40.3	39.3	42.6	45.0
Stable partnership	57.3	58.9	55.5	54.9	54.9
Baseline viral load (copies/ml) - %	64.8	66.1	64.7	63.1	61.3
< 50	15.4	15.9	14.9	15.5	13.7
50 – 399	19.8	18.0	20.4	21.5	25.0
≥ 400					
Baseline CD4 cell count (µ/L) - %	16.4	16.0	16.7	16.1	18.7
< 200	26.8	26.9	29.2	25.7	24.7
200 – 349	24.2	24.1	24.0	24.5	24.4
350 – 499	32.6	33.0	30.1	33.8	32.2
≥ 500					
cART regimen at baseline					
NNRTI	35.5	38.7	33.8	33.8	25.2
PI boosted	14.6	12.5	16.6	16.1	20.0
PI non-boosted	37.0	36.7	40.1	34.9	37.8
Triple nucleoside/Other	13.0	12.1	9.5	15.2	17.1
No. of cART regimens v					
Median (IQR)	2 (1-5)	2 (1-4)	2 (1-4)	3 (1-5)	3 (2-6)
Years on cART *					
Median (IQR)	3.9 (0.6 - 6.7)	3.1 (0.5 - 6.5)	4.0 (0.9 – 6.4)	4.7 (1.2 – 7.0)	5.4 (2.9 – 7.1)
Years since HIV diagnosis					
Median (IQR)	7.9 (3.0- 13.6)	6.9 (2.2- 12.8)	7.9 (3.6-13.1)	9.5 (4.0-14.5)	10.6 (6.0-15.4)

# 9 years of mandatory schooling or less  
v Number of cART regimens at baseline, including the current one, taken while registered in the cohort  
\* For those cART taken while registered in the cohort  
IQR=interquartile range, MSM=men who have sex with men, IDU=intravenous drug use, cART=combined antiretroviral therapy, NNRTI= non-nucleoside reverse transcriptase inhibitors, PI = protease inhibitors

analyses of naive and pre-treated patients, only the CIs widened and the predicted group membership changed. Compared to the model with all patients, naive patients were more likely to belong to the group with worsening adherence (27.0%), and less likely to belong to the poor adherence (6.9%). Table 5.1 provides baseline characteristics by group membership from the analysis including all individuals. Individuals with consistently poor adherence more often had only a basic education, were IDU (less often MSM), were under psychiatric treatment, had legal problems, on an NNRTI, on cART for longer, and living with HIV for a longer time.

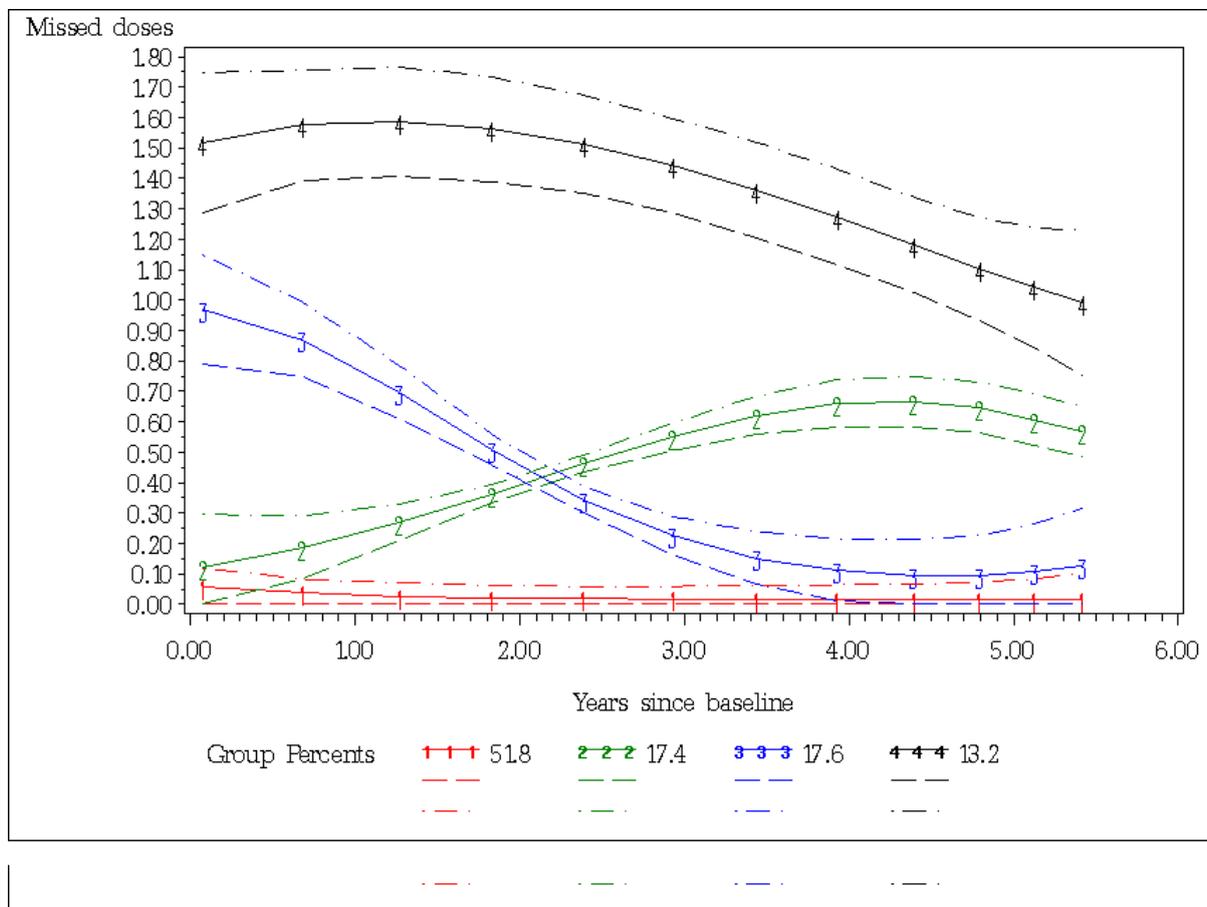
**Figure 5.1** Self-reported missed doses of cART over time since introduction of the adherence questionnaire in January 2003.



Of the 42,362 visit pairs, no change in adherence was reported 76.2% of the time with 12.4% reported improvements and 11.4% reporting decrements in adherence. Different factors were found to be associated with worsening and improving adherence (Table 5.2). In multivariable models adjusted for adherence on the first visit of the pair, factors significantly associated with worsening

adherence were younger age, basic education, loss of a roommate, starting IDU, increasing daily alcohol intake (resulting in categorization in a higher alcohol risk category), starting psychiatric treatment, longer time living with HIV, onset of lipodystrophy, and changes of the physician or center where the individual was followed. In multivariable models, factors significantly associated with improvements in adherence were starting co-medications, changes in the class of cART, and regimen simplification (decreases in dosing frequency). Individuals with basic education and those on cART for a longer time at baseline were significantly less likely to improve their adherence.

**Figure 5.2** Trajectories with 95% CIs of adherence groups identified by clustering the number of missed doses over time: group 1 = consistently good adherence group, group 2 = steadily worsening adherence group, group 3 = steadily improving adherence group, and group 4 = consistently poor adherence group. The predicted probabilities of group membership are given.



Several sensitivity analyses were performed: 1) stratification by gender, 2) stratification by reported missed doses at the initial visit of the pair, and 3) removing alcohol from the model due to a large number of missing values (data collection began only in 2005). All models returned similar results demonstrating the robustness of our results (data not shown).

**Table 5.2** Independent predictors of worsening or improving adherence using repeated measures logistic regression\*

Predictor	Worsening adherence OR (95% CI)	Improving adherence OR (95% CI)
<i>Sociodemographic-related factors</i>		
Age (per 5 years) §	0.92 (0.89-0.95)	1.05 (0.99-1.10)
Male gender	0.91 (0.81-1.02)	0.86 (0.72-1.03)
Caucasian	0.98 (0.84-1.14)	0.82 (0.65-1.05)
Basic education #	1.16 (1.03-1.31)	0.82 (0.68-0.99)
Began living alone v	1.30 (1.06-1.60)	0.84 (0.61-1.15)
Ended a stable partnership v	1.06 (0.86-1.32)	0.98 (0.72-1.33)
<i>Patient-related factors</i>		
Started IDU v	1.89 (1.30-2.77)	1.11 (0.59-2.11)
Started drug maintenance program v	0.78 (0.47-1.29)	0.96 (0.49-1.86)
Increase in alcohol intake v‡	1.25 (1.10-1.43)	0.82 (0.67-1.01)
Started smoking v	1.11 (0.84-1.46)	1.07 (0.70-1.65)
Began riskier sex behavior v	1.09 (0.94-1.26)	1.13 (0.91-1.40)
Began psychiatric treatment v	1.26 (1.04-1.52)	1.08 (0.79-1.48)
Release from prison release or resolution of legal issues v	1.24 (0.76-2.03)	0.74 (0.37-1.50)
<i>Health condition-related factors</i>		
Hospitalization v	1.12 (0.95-1.31)	0.85 (0.66-1.09)
Started co-medication v	0.95 (0.73-1.23)	1.95 (1.29-2.94)
Time living with HIV (per 5 years) §	1.11 (1.05-1.17)	0.94 (0.87-1.02)
<i>Treatment-related factors</i>		
Change in class of cART v	0.90 (0.72-1.13)	1.48 (1.08-2.04)
Decrease in dosing frequency v	0.86 (0.70-1.05)	1.45 (1.08-1.94)
Time on cART (per year) §	0.99 (0.97-1.01)	0.95 (0.91-0.99)
Number of previous cART regimens §	1.02 (0.99-1.04)	1.02 (0.97-1.06)
Onset of lipodystrophy v	1.21 (1.00-1.47)	1.09 (0.81-1.46)
<i>Health system-related factors</i>		
Change of physician or center v	1.22 (1.10-1.36)	1.08 (0.91-1.27)

\* Results are from 2 models, one for worsening of and one for improvements in adherence. Both models are adjusted for correlation between visit pairs from the same individuals. Adjusted for reported adherence on first visit ( $V_i$ ) of the consecutive pair

§ At baseline

# Nine years of mandatory schooling or less

v Changes in the covariate between consecutive visit pairs or since the previous visit

‡ Increase in daily alcohol consumption so that patient falls into a higher alcohol risk category (as defined by WHO [21])

OR = odds ratio, CI = confidence interval, IDU = intravenous drug use, cART=combined antiretroviral therapy

## Discussion

We did an in-depth and novel exploration of self-reported adherence to cART over time in individuals participating in the SHCS. Self-reported adherence was quite high with individuals reporting missing 0 doses of cART on almost 80% of visits. We identified four distinct adherence patterns based on almost 50,000 adherence questionnaires. We did a comprehensive and unique assessment of the effect of both time fixed and time updated predictors on changes in adherence over the 6 year study period.

These same four adherence patterns (good, improving, worsening, and poor) observed in all patients were also detected in a population of only naive patients as well as pre-treated patients. The pattern of consistently good adherence had the highest estimated group membership for all sub-populations while naive patients were more likely to fall into the worsening adherence pattern than pre-treated individuals. There were observed differences in group membership by several baseline factors most notably that individuals with a history of psychiatric treatment or legal problems, were more often in the poor adherence group. In future work we plan a validation of these adherence groups on clinical outcomes.

Our analysis of changes in adherence included factors from all five dimensions identified by the WHO as determinants of adherence [21]. Some of these variables, in particular the social support variables, co-medication, and health system factors, have not been studied previously. In addition, no other study to our knowledge has included changes in factors as predictors of changes in adherence to explore potential triggers for periods of worsening adherence. We could confirm several factors found in other studies to be associated with worsening or improving adherence such as age [18,20], education [18], IDU [16,18], alcohol intake [16,18], depression [18], taking a PI-based regimens [16], and symptoms [16,20]. In addition to these variables, we found loss of a roommate, longer time since HIV diagnosis, and health system changes such as disruption of the continuity of care by the same physician or hospital were significantly more likely to be associated with reported worsening adherence. Newly identified factors significantly associated with improvements in adherence were changes in cART class, regimen simplification and starting to take medication for OI, CVD, hepatitis C or cancer.

Our results demonstrate that not only demographic factors such as age, gender, and education influence adherence, but short-term *changes* in factors can impact changes in adherence as well. These changes can serve as signals to the clinicians to provide additional adherence support. Changes in a patient's living situation (such as loss of a roommate) or changes to their physician or

center of care can signal a loss of social support and lead to lapses in medication taking. It may be the challenge of moving house or the difficulty in building a trusting relationship with a new physician that impacts adherence behaviour. Changes to regimens with higher daily administration frequency or one with known side effects such as lipodystrophy – can all result in worsening adherence. These results suggest clinicians need to anticipate the possibility of added stress during periods of change for patients and provide additional support during these times.

The SHCS is a long-standing and well-described prospective cohort that collects a variety of information longitudinally in a diverse population of heterosexuals and women, making the results generalizable. This study includes a large sample of HIV-infected individuals followed for up to 6 years. We have identified a number of new factors that affect adherence and thus impact drug failure. We conducted extensive sensitivity analyses to ensure the robustness of the results.

A limitation of this study is that our results are based on self-reported adherence provided in an interview with a clinician. These reports can be subject to recall bias or social desirability bias, leading to underreporting of non-adherence behavior [26,27]. However, two systematic reviews including a large number of observational studies found a robust association between self-reported adherence and viral load over varying measures and recall periods [28] and indicated that self-reported adherence measures can distinguish between clinically meaningful patterns of medication-taking behaviour [29]. Other information in the SHCS is also collected via self-report, such as sexual risk behavior, drug use, psychological and legal problems, which could also result in reporting bias due to the sensitivity of these topics. Another limitation is the observational nature of the study which can lead to biased results due to unmeasured confounding. In addition, there is likely confounding by indication with respect to the choice of cART, especially in groups at risk for adherence problems.

Adherence was found to be improving over time (Figure 5.1), contrary to results from other studies [19,20] performed prior to 2001. A more recent study also detected a decreasing trend in adherence until 2003 and then adherence started to improve [16]. We can hypothesize that regimen simplification in recent years has facilitated improved adherence. It is also likely that introducing systematic adherence assessments resulted in increased attention in both patients and clinicians to the issue of adherence and therefore led to improvements in adherence. Also, the SHCS is an open cohort and the population is changing over time– for example the number of individuals from IDU risk group has decreased dramatically over time with a corresponding increase in MSM and heterosexuals, groups known to have better adherence. Therefore our results provide unbiased measures of associations (but not causation) between covariates and outcome.

In conclusion, our results indicate that clinicians should routinely enquire about factors that may disrupt regular drug intake such as changes in substance and alcohol use, psychiatric treatment and important lifestyle changes including loss of social support. In particular, clinicians should be sensitive to the risk of worsening drug adherence when changes in the patient care provider relationship are planned. Additional adherence counselling should be provided to patients experiencing potentially stressful situations so that they can learn the skills to cope with these changes without disruption in their drug intake. Future studies should investigate whether simple patient focussed interventions suitable to busy clinical practice, such as routine checking of risk factors for changes in regular drug intake identified by this study, may enhance drug adherence and reduce risk of treatment failure and drug resistance.

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## Chapter 6: Non-adherence as a predictor of treatment failure

### Self-reported non-adherence to antiretroviral therapy repeatedly assessed

### by two questions predicts treatment failure in virologically suppressed patients

Tracy R Glass<sup>1</sup>, Sabina De Geest<sup>2</sup>, Bernard Hirschel<sup>3</sup>, Manuel Battegay<sup>4</sup>, Hansjakob Furrer<sup>5</sup>, Matthias Cavassini<sup>6</sup>, Pietro L Vernazza<sup>7</sup>, Enos Bernasconi<sup>8</sup>, Martin Rickenbach<sup>9</sup>, Rainer Weber<sup>10</sup>, Heiner C Bucher<sup>1,4</sup>, and the Swiss HIV Cohort Study

<sup>1</sup>Basel Institute for Clinical Epidemiology and Biostatistics, University Hospital Basel,

<sup>2</sup>Institute of Nursing Science, University of Basel,

<sup>3</sup>Division of Infectious Diseases, University Hospital Geneva,

<sup>4</sup>Division of Infectious Diseases and Hospital Hygiene, University Hospital Basel,

<sup>5</sup>Division of Infectious Diseases, University Hospital Berne,

<sup>6</sup>Division of Infectious Diseases, University Hospital Lausanne,

<sup>7</sup>Division of Infectious Diseases, Kantonsspital St. Gallen,

<sup>8</sup>Division of Infectious Diseases, Ospedale Civico, Lugano,

<sup>9</sup>Swiss HIV Cohort Data Center, University Hospital Lausanne,

<sup>10</sup>Division of Infectious Diseases and Hospital Hygiene, University Hospital Zurich

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## **Abstract**

### **Background**

The aim of this study was to explore the predictive value of longitudinal self-reported adherence data on viral rebound.

### **Methods**

Individuals in the Swiss HIV Cohort Study on combined antiretroviral therapy (cART) with RNA < 50 copies/ml over the previous 3 months and who were interviewed about adherence at least once prior to March 1, 2007 were eligible. Adherence was defined in terms of missed doses of cART (0, 1, 2 or >2) in the previous 28 days. Viral rebound was defined as RNA >500 copies/ml. Cox regression models with time-independent and -dependent covariates were used to evaluate time to viral rebound.

### **Results**

A total of 2,664 individuals and 15,530 visits were included. Across all visits, missing doses was reported as follows: 1 dose 14.7%, 2 doses 5.1%, >2 doses 3.8%, taking <95% of doses 4.5%, and missing  $\geq 2$  consecutive doses 3.2%. In total, 308 (11.6%) patients experienced viral rebound. After controlling for confounding variables, self-reported non-adherence remained significantly associated with the rate of occurrence of viral rebound (compared to 0 missed doses: 1 dose, HR 1.03, 95% confidence interval (CI): 0.72-1.48; 2 doses, HR 2.17, 95% CI: 1.46-3.25; >2 doses, HR 3.66, 95% CI: 2.50-5.34). Variables significantly associated with an increased risk of viral rebound irrespective of adherence were identified: being on a protease inhibitor or triple nucleoside regimen (compared to non-nucleoside reverse transcriptase inhibitor), >5 previous cART regimens, seeing a less experienced physician, taking co-medication, and shorter time virally suppressed.

### **Conclusions**

A simple self-report adherence questionnaire repeatedly administered provides a sensitive measure of non-adherence that predicts viral rebound.

## Introduction

Adherence to combined antiretroviral therapy (cART) is fundamental for achieving and maintaining viral suppression, preventing drug resistance, and improving survival in HIV-infected individuals [1-3]. However, there remains no definitive approach to adherence assessment [4,5] and no standard definition of non-adherence. Many studies have indicated that high levels of adherence to cART are necessary to achieve optimal suppression of HIV-1 RNA [6,7], but the exact level of adherence necessary is unknown and likely to vary by cART regimen [8,9].

The ongoing debate on the best way to measure and utilize adherence data is fueled by the need for simple and accurate methods to measure adherence to cART in routine clinical practice.

Standardized measurement tools are needed as physicians experience difficulties in assessing patient adherence to cART accurately [10,11]. Self report of drug adherence offers the primary advantages of ease of administration, flexibility and low cost. However, self-report is subject to recall bias. Patients' reporting of non-adherence has been found to be credible [12,13] but their estimate of the degree of adherence is often inaccurate [14], overestimating adherence by 10-20% compared to electronic monitoring (EM) [15,16]. Despite these disadvantages, two recent systematic reviews both including a large number of observational studies found a robust association between self-reported adherence and viral load over varying measures and recall periods [5], and indicated that self-reported adherence measures can distinguish between clinically meaningful patterns of medication-taking behaviour [17].

Although other methods such as pill count and prescription refill have been used successfully to measure adherence, these methods are not practical over the long-term, suffer from implementation problems and do not provide detailed information such as drug holidays. Although EM provides an accurate, detailed measure of adherence, it is not practical for routine use and would be better used to educate naïve individuals starting therapy or as an aid for individuals with known adherence problems.

Most observational studies - independent from the measurement method for adherence – suffer from additional shortcomings. The majority of studies are of cross-sectional design, precluding the ability to make causal inferences. Longitudinal studies with multiple adherence measurements in the same patient often summarize adherence behaviour over the whole study period leading to a loss of efficiency and information; this approach also ignores the important dynamic of adherence changes over time [18,19].

In a previous cross-sectional analysis of the Swiss HIV Cohort Study (SHCS) we showed a strong linear relationship between self-reported non-adherence by interview over the previous 28 days and optimal viral suppression [20]. The goal of this study of HIV-infected individuals with complete viral suppression on cART was to use all the information from repeatedly applied questionnaires in a time-updated analysis to test whether the two-item questionnaire of the SHCS predicts viral rebound.

## **Methods**

### *Patients*

The SHCS is a prospective cohort study with continuing enrollment of HIV-infected individuals aged 16 years or older. Visits take place every 6 months at 7 outpatient clinics from participating HIV centers, associated hospitals or specialized private practices. Eligible individuals were: actively enrolled in the SHCS, on cART, virally suppressed (HIV-1 RNA $\leq$ 50 copies/ml) for at least 3 months prior to baseline and had at least one follow-up HIV-1 viral load measurement. Baseline is taken as the official cohort visit prior to completion of their first adherence questionnaire.

### *Outcome definition*

The primary endpoint of the study was time to virologic rebound defined as time to HIV-1 RNA $>$ 500 copies/ml. Confirmed viral rebound (two consecutive RNA $>$ 500 copies/ml) was also considered as an outcome. The majority of recent treatment guidelines suggest that intermittent viraemia (isolated HIV-1 RNA levels between 50 and 500 copies/ml) are often of no clinical consequence, but consecutive rebounds of HIV-1 RNA $>$ 500 copies/ml can be associated with virologic failure [21].

### *Adherence definitions*

An adherence questionnaire was introduced into the follow-up of the SHCS in July 2003 and has been previously described [20]. Individuals were asked two questions by their clinician: (i) How often did you miss a dose of your medication in the last 4 weeks? Daily, more than once a week, once a week, once every two weeks, once a month, never; and (ii) Did you miss more than one dose in a row? Yes, no. The questionnaire has been validated in a study comparing the European HIV treatment questionnaire, a visual analogue scale, and EM [22]. Using virologic failure as the gold standard, the SHCS adherence questionnaire in the validation study performed slightly better than either EM or a combination of the adherence questionnaire and a VAS with a sensitivity of 88% and a specificity of 79%. In this study, non-adherence was categorized into the number of missed doses: 0,

1, 2, and >2. Several methods for handling missing adherence data were considered: missing data was excluded from the analysis, the last non-missing observation was carried forward (LOCF), 'missing' was added as a category of missed doses, and missing data was replaced by an indicator of non-adherence (missing 2 doses).

### *Covariate definitions*

Covariates that were potential confounders of the relationship between adherence and viral rebound were considered for inclusion in the analysis. The following time-independent covariates were measured at baseline: gender, age, prior intravenous drug use, CD4+ T-cell count (cells per  $10^9$  /l), duration of viral suppression, prior AIDS diagnosis, number of previous cART regimens ( $\leq 5$  or  $>5$ ), physician experience (defined as the number of HIV-infected patients in the SHCS previously treated by a physician at the time of the patient's baseline visit), and time on cART. The following time-dependent (i.e., time-updated) covariates were measured at each follow-up visit: having a stable partner, taking co-medications (for risk factors for cardiovascular disease [dyslipidaemia, diabetes, or hypertension], opportunistic infections [OI], hepatitis C, or cancer), hospitalization, and current cART (non-nucleoside reverse transcriptase inhibitor [NNRTI], non-boosted protease inhibitor [PI], boosted PI, triple nucleoside). An interaction between adherence and cART regimen and dosing frequency was tested for inclusion in the model.

### *Statistical methods*

A time-to-event analysis was performed using a Cox proportional hazards model to study the effects of both time-independent and time-dependent explanatory variables on the event incidence. Events were defined as the first date where HIV-1 RNA was  $>500$  copies/ml. For individuals who did not experience an event, follow-up was censored on March 1, 2007, on the date when cART was stopped for  $\geq 45$  days, the date of loss to follow-up or death. The association between explanatory variables and viral rebound were assessed by using hazard ratios (HR) and 95% confidence intervals (CI); HRs  $>1$  indicate a covariate is positively associated with the event probability. Variables known to be confounders were automatically considered for inclusion in the final adjusted model while all other previously untested variables were included only if there was some evidence of an association ( $p < 0.25$ ) in unadjusted models. Following the fit of the multivariable model, the importance of the variable as a confounder (as measured by its impact on the hazard ratio of the other variables) was verified or the variable was eliminated from the final model. All analyses were carried out with SAS v9.1 (SAS Institute Inc., Cary, NC, USA). The manuscript was written to comply with STROBE guidelines for observational studies [23].

### *Sensitivity analyses*

As an additional validation of the adherence measurement, several additional measures of non-adherence were calculated. To explore the impact of previous reports of non-adherence, we constructed an indicator of the highest number of reported missed doses (0, 1, 2, or >2) at each time point for all follow-up visits including the current visit. To make our results comparable with other studies, non-adherence was calculated as taking <95% of doses. However, as we do not collect adherence information as a percentage of doses taken, this definition had to be approximated based on the number of missed doses in the previous 28 days and the dosing frequency of the current cART regimen. For example, an individual on a once-daily regimen who missed two doses in the previous 28 days was calculated to have taken <95% of doses ( $26/28=92.8\%$ ). In addition, we tested whether missing at least two consecutive doses of cART was an independent predictor of virologic failure.

### **Results**

In total, 7,539 patients were actively registered in the SHCS between 1 July 2003 and 1 March 2007. Of these, 5368 had at least one follow-up visit within 1 year of the baseline visit where they completed an adherence questionnaire and had corresponding laboratory data recorded. Of these, 2,704 were excluded for several reasons: not virally suppressed (HIV-1 RNA $\geq$ 50 copies/ml) for a minimum of 3 months (n=2,689), off treatment at baseline visit (n=10), cART-naïve (n=2), no follow-up HIV-1 RNA values (n=2), and stopped treatment 1 day after baseline (n=1). A total of 2,664 patients with 15,530 visits were included in the analysis. The total prospective follow-up until the event date or until the censoring date for those without an event was 7,693 person-years, with a median individual follow-up time of 3.3 years (interquartile range [IQR] 2.5-3.6). The median number of follow-up visits after baseline was 6 (range 1-8). A total of 308 (11.6%) patients experienced viral rebound during the study period, with a median time to viral rebound of 16 months (IQR 9.5-29).

Baseline characteristics of the analysis population are displayed in Table 5.1. Over all visits in the study period, missing doses were reported as follows: 1 dose 14.7%, 2 doses 5.1%, >2 doses 3.8%, taking <95% of doses 4.5%, and missing  $\geq$ 2 consecutive doses 3.2%. A total of 49% of patients reported a change in the number of missed doses over the study period. Individuals were mostly on twice daily regimens (87.1%) with only marginal numbers on either once daily (10.7%) or three times daily regimens (2.2%); however the number of individuals on once daily regimens was increasing over the study period with a corresponding decrease in both those on twice daily and three times daily regimens.

**Table 5.1** Baseline characteristics of individuals included in the analysis

<b>Characteristic</b>	
Total – n (%)	2664 (100)
Median age, years [IQR]	42 [37-48]
Male gender – %	70.8
Past or present intravenous drug use – %	22.9
Smoker* - %	46.4
Stable partnership* - %	60.8
Living alone* - %	39.9
Previous AIDS diagnosis - %	28.6
Hospitalization* - %	7.7
Experience of physician ± - median [IQR]	170 [102-294]
CD4 count (cells per 10 <sup>9</sup> /l )	
Median [IQR]	478 [331-677]
< 200 (%)	8.6
200 – 349 (%)	19.0
350 – 499 (%)	25.1
≥ 500 (%)	47.3
Current cART regimen - %	
NNRTI	34.8
PI non-boosted	21.9
PI boosted	24.5
Triple nucleoside and other	18.8
Number of previous cART regimens	
Median [IQR]	3 [2 - 5]
Time on cART (years)	
Median [IQR]	5.7 [3.4 – 7.3]
Mean [SD]	5.6 [2.7]
Time optimally virally suppressed (years)	
Median [IQR]	2.4 [1.1 – 4.3]
Mean [SD]	2.7 [1.8]

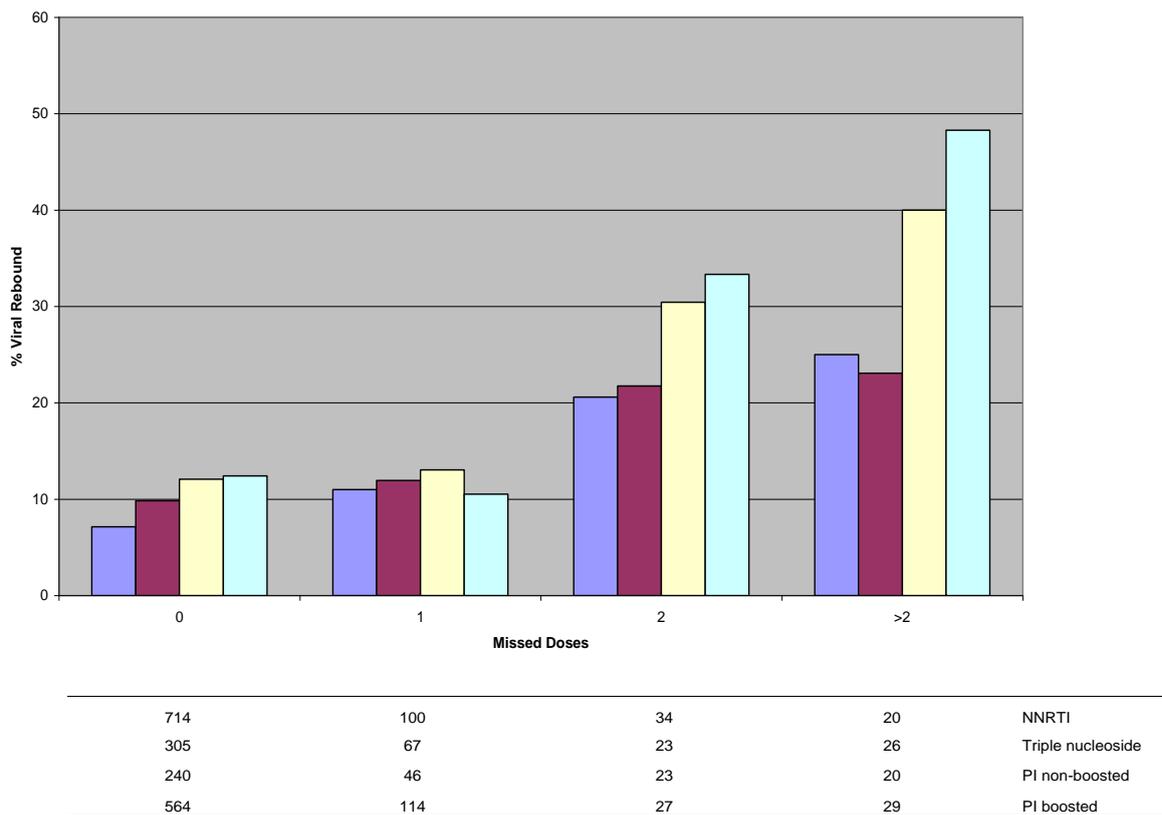
\* In the previous 6 months  
¶ In the previous 28 days  
± Number of HIV-infected patients treated by a physician at the time of the patient's baseline visit  
SD=standard deviation, IQR=interquartile range, cART=combined antiretroviral therapy, PI=protease inhibitors, NNRTI=non-nucleoside reverse transcriptase inhibitor

Adherence data was missing for 452 (3.3%) visits and the rate of missing data steadily increased over time (1.3% to 5.3%). All four methods of replacing missing data were explored in unadjusted Cox models. All methods yielded similar results and only the HR for missing >2 doses was slightly lower but still highly significant with LOCF, known to be a conservative method for handling missing data. In addition, when missing adherence information was included as a category of non-adherence, individuals with missing adherence data were significantly more likely to experience viral rebound than individuals with no reported missed doses with an estimate similar to that of missing two doses (HR 2.39, 95% CI 1.62-3.51). Although there is some indication that missing information is

informative, individuals with missing adherence data was excluded from the final analysis as the overall percentage of missing was very small.

The proportion of individuals experiencing viral rebound increased with increasing number of missed doses. In addition, with two or more reported missed doses, there were differences in the rate of viral rebound by class of ART (Figure 5.1).

**Figure 5.1** Percentage of patients with viral rebound (RNA>500 copies/ml) by self-reported missed doses and current class of cART regimen



The results of the Cox proportional hazards models of the association between time-updated non-adherence and virologic rebound are provided in Table 5.2. In unadjusted models, two or more missed doses were significantly associated with the risk of viral rebound when compared to perfect adherence (1 dose, HR 1.11, 95% CI 0.78-1.57; 2 doses, HR 2.34, 95% CI 1.57-3.50; >2 doses, HR 4.04, 95% CI 2.78-5.87). After controlling for potential confounding variables, self-reported non-adherence remained significantly associated with the rate of occurrence of viral rebound (compared to 0 missed doses: 1 dose, HR 1.03, 95% CI 0.72-1.48; 2 doses, HR 2.17, 95% CI 1.46-3.25; >2 doses, HR 3.66, 95%

CI 2.50-5.34). Five variables significantly associated with an increased risk of viral rebound irrespective of adherence were identified: (i) being on a PI or triple nucleoside regimen (compared with a NNRTI regimen), (ii) having experienced >5 previous cART regimens, (iii) seeing a physician with less experience, (iv) taking co-medication, and (v) less time with viral suppression at baseline. Age, gender, stable partnership, AIDS diagnosis and hospitalization were not significantly associated with viral rebound in adjusted models and exhibited no evidence of confounding and therefore were excluded from the final analysis.

**Table 5.2** Association of baseline and time-updated covariates with the rate of occurrence of viral rebound, RNA>500 copies/ml (both confirmed and unconfirmed), using a Cox proportional hazards model.

Variables	Adjusted model VR = RNA >500 copies/ml (n=308 events)		Adjusted model VR = two consecutive RNA >500 copies/ml (n=102 events)	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Intravenous drug use (current or past)	1.20 (0.92 – 1.57)	0.19	1.15 (0.71 – 1.86)	0.573
Increases in baseline CD4 cell count of 100 (cells per 10 <sup>9</sup> /l)	1.02 (0.98 – 1.07)	0.39	1.02 (0.95 – 1.04)	0.60
cART regimen				
NNRTI	Reference		Reference	
Non-boosted PI	1.50 (1.04 – 2.17)	0.03	1.23 (0.61 – 2.49)	0.56
Boosted PI	1.53 (1.13 – 2.09)	0.007	1.67 (0.96 – 2.91)	0.07
Triple nucleoside/other	1.63 (1.13 – 2.35)	0.01	1.62 (0.82 – 3.23)	0.17
> 5 previous cART regimens at baseline	1.44 (1.09 – 1.89)	0.009	1.96 (1.23 – 3.11)	0.005
Physician experience ± (per 100 patients)	0.83 (0.76 – 0.92)	<0.001	0.84 (0.71 – 0.99)	0.04
Co-medication √	1.44 (1.06 – 1.96)	0.02	2.42 (1.50 – 3.90)	<0.001
Time virally suppressed at baseline (per year)	0.77 (0.71 – 0.83)	<0.001	0.82 (0.72 – 0.94)	0.005
Non-adherence (missed doses):				
0	Reference		Reference	
1	1.03 (0.72 – 1.48)	0.86	1.25 (0.68 – 2.30)	0.48
2	2.17 (1.46 – 3.25)	<0.001	1.24 (0.50 – 3.12)	0.64
>2	3.66 (2.50 – 5.34)	<0.001	4.51 (2.47 – 8.24)	<0.001

± Number of HIV-infected patients treated by a physician at the time of the patient's baseline visit

√ For cardiovascular problems, opportunistic infections, hepatitis C, or cancer

\* In the previous 28 days

cART, combined antiretroviral therapy; CI, confidence interval; HR, hazard ratio; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; VR, viral rebound

To further explore the effect of co-medication, the indicator of taking any co-medication was replaced in turn in the final adjusted model by an indicator of taking co-medication for each indication separately. Only medication taken for risk factors for cardiovascular disease showed no evidence of effect on treatment failure. Receiving treatment for OI, hepatitis C and cancer were all independently associated with an increased hazard for treatment failure, although hepatitis C was

only marginally significant. When all four indicators of taking specific co-medication were entered simultaneously into the adjusted model, the results remained the same (Table 5.3).

There is evidence to suggest that missing doses of medication has different implications for treatment failure depending on both the class of ART regimen and the dosing frequency of the regimen [24-27]. The interaction between missed doses and class of ART regimen was non-significant and therefore not included in the final model. With regards to dosing frequency, interaction variables for both consecutive missed doses and missed doses were constructed. However, due to low numbers of individuals on once daily and three times daily regimens, the HRs were not estimable for most categories. The only additional comparisons produced from this analysis were between those reporting perfect adherence (over all dosing frequencies) and those who reported missing one dose on a once daily regimen (HR 2.82, 95% CI 1.32-6.01) and missing one dose on a twice daily regimen (HR 0.91, 95% CI 0.60-1.36).

**Table 5.3** Exploring the association of use of any co-medication as well as co-medication use by individual indication with the rate of occurrence of viral rebound (unconfirmed RNA>500 copies/ml) using Cox proportional hazards model

Variables	Unadjusted model		Adjusted model *	
	HR (95% CI)	p-value	HR (95% CI)	p-value
All co-medication √	1.52 (1.14 – 2.03)	0.004	1.44 (1.06 – 1.96)	0.02
Co-medication by indication ±				
Risk factors for CV disease #	1.07 (0.70 – 1.63)	0.75	1.01 (0.64 – 1.59)	0.97
Opportunistic infections	2.17 (1.50 – 3.14)	<0.001	1.80 (1.20 – 2.69)	0.004
Hepatitis C	1.69 (0.90 – 3.17)	0.10	1.73 (0.91 – 3.29)	0.09
Cancer	4.13 (1.32 – 12.88)	0.01	3.20 (1.01 – 10.17)	0.05

\* adjusted for IV drug use, baseline CD4 cell count, ART regimen, number of previous ART regimens, physician experience, time virally suppressed at baseline, and non-adherence (see Table 5.2).

√ For risk factors for cardiovascular disease, opportunistic infections, hepatitis C, or cancer

± The indicator for taking any co-medication was replaced in the adjusted model by the four separate indicators of taking co-medication for the individual indication.

# For dyslipidemia, hypertension, or diabetes

CV, cardiovascular; HR, hazard ratio; CI, confidence interval

When the outcome was time to confirmed viral rebound (two consecutive RNA>500 copies/ml), the adjusted Cox model yielded very similar results to the model with unconfirmed viral rebound (Table 5.2). CIs were generally wider and some variables were no longer significant likely due to having only one-third of the number of events (102 versus 308).

In sensitivity analyses, we explored whether these results could be validated when different levels of non-adherence were considered. The time-updated indicator of the highest number of missed doses up to the point of the current follow-up visit provided similar results to the primary analysis although the hazard ratios were lower (1 dose, HR 0.73, 95% CI 0.53-1.02; 2 doses, HR 1.51, 95% CI 1.08-2.11; >2 doses, HR 2.44, 95% CI 1.78-3.34). Taking <95% of doses of cART in the previous 4 weeks was significantly associated with viral rebound as a time-updated predictor in an adjusted model (HR 3.18, 95% CI 2.20-4.60). The estimates for covariates were almost identical to the primary analysis (data not shown). Missing two or more consecutive doses of cART in the previous 4 weeks was found to be an independent predictor of time to viral rebound in an adjusted model (HR 3.53, 95% CI 2.42-5.15). Effect estimates and CIs for covariates were also almost identical to those in the primary analyses (data not shown).

## **Discussion**

This study demonstrates that in HIV-infected individuals on cART with prior viral suppression, self-reported missed doses are associated with a higher risk of virologic failure. Increasing number of missed doses in the previous 4 weeks was associated with an increasing hazard of virologic failure. Missing two or more consecutive doses of cART was reported on fewer than 4% of visits but was associated with 3.5 times increased risk of viral failure.

Although several other studies have collected longitudinal self-reported adherence information [1,28-30], we know of no other study that has used time-updated measurements of self-reported adherence to predict viral rebound. With this approach, we avoid the loss of information inherent in analyses that summarize adherence information over time. In addition, an individual's adherence pattern is allowed to vary in a dynamic way which is a better reflection of reality and is supported by the finding that almost 50% of individuals reported a change in the number of missed doses over the study period. This approach gave a precise and sensitive estimate of the risk of viral rebound by missed doses after adjusting for a comprehensive list of potential confounders. Also important to note was that we considered several additional definitions of non-adherence in sensitivity analyses and our results were highly consistent, with similar effect estimates for all confounders.

The simplification of regimens will certainly have a positive impact on adherence and treatment outcomes [26,31], but the introduction of an increasing number of once daily regimens will not eliminate concerns about adherence to ART. We found evidence that individuals missing only one dose of ART on a QD regimen are at 2.8 times increased risk of treatment failure, whereas those

missing one dose on a twice daily regimen showed no increased risk. Although there were not sufficient numbers on either once daily or three times daily regimens to fully explore the effect of an interaction between missed doses and dosing frequency, these findings should be explored further and incorporated into future adherence definitions.

This study considered a large number of important confounders: clinical factors (including the previously unstudied effect of co-medication) as well as psychosocial factors such as stable partnership and health system factors such as physician experience. Independent of reported adherence to cART, several factors were significantly associated with an increased hazard of viral rebound. Individuals on NNRTI regimens were at a decreased risk of virologic failure compared with individuals on all other regimens, although previous studies have shown varied results [1,9,32]. Similar to other studies where suboptimal HIV management was associated with physicians who care for only a few HIV-infected patients [33-35], we found a significant association between lower physician experience and higher incidence of virologic failure, although a recent study did not confirm these findings [32]. Individuals taking any co-medication for the treatment of risk factors for cardiovascular disease, OI, hepatitis C, or cancer had a 1.4 times higher risk of viral rebound (see Table 5.3). Additional analyses suggested that this effect is largely driven by the taking of medication for OI, hepatitis C, and cancer. Treatment for some OI, hepatitis C, and cancer may result in side effects, drug interactions and potential treatment interruption and thus risk of virological failure. The lack of an effect from co-medication taken for cardiovascular risk factors is encouraging news as an increasing number of treated individuals will likely be at risk for ART-induced metabolic disorders [36]. Our findings suggest that the condition of the co-morbidity and its treatment and not necessarily the additional pill burden of co-medication, are related to treatment failure. The effect of co-medication has not been studied previously and our finding has important implications for the management of an ageing HIV-infected population in need of both drug treatment for HIV and other chronic conditions.

Our data confirm recent evidence suggesting that different classes of cART regimens can require varying levels of adherence to maintain viral suppression [4,9]. However, previous studies did not include individuals on either boosted PI regimens or triple nucleoside regimens. Individuals on NNRTIs and triple nucleosides had lower rates of viral rebound than those on PI regimens with similar levels of self-reported adherence (Figure 1). It has been suggested that boosted PI regimens may provide forgiveness as well [37,38], however we did not find evidence to support this. This could be related to a selection bias with individuals with more treatment experience and greater

adherence problems being placed on boosted PIs due to higher resistance barrier or because of concerns related to drug interactions, for example, with methadone.

The rate of missing adherence information increased in proportion to the length of time patients were under follow up. As the adherence questionnaire is administered by interview with the clinician, this is suggestive of several potential problems. It is possible the clinician has assumed to know the adherence of an individual from past information, although we know from our data and others that adherence is a dynamic process. Another issue could be that with the focus of health care on acute illnesses and with only short consultation times, physicians might only have time to discuss clinical aspects of a patient's care and therefore behavioral aspects, such as adherence, might be given a lower priority. Regardless of the reasons behind this finding, it is extremely important that clinicians find a way to address the adherence of their patients as part of their regular follow-up.

Our data has several limitations. As discussed above, patients are asked about their adherence by their clinician, and therefore may be reluctant to admit non-adherence. However, previous studies have failed to find a relationship between self-report and social desirability bias [15-16] and one study even found that anonymous surveys increased individuals' reluctance to disclose non-adherence [17]. We cannot, however, rule out the possibility that changing the mode of administration of the questionnaire would minimize potential social desirability bias and provide more accurate responses. Second, missing adherence information was excluded from the analysis leading to a loss of information. However, several other methods of handling missing data provided consistent results. An in-depth study into adherence patterns may reveal a more meaningful way to impute adherence information for these patients, but it is beyond the scope of this study. Third, our results are limited to virally suppressed individuals on cART and therefore the effect of adherence on viral load for those who are not suppressed is unknown.

In conclusion, our simple two-item questionnaire, which is easy to implement in routine clinical practice, is an independent predictor for future viral failure in individuals with well-suppressed viral load. Even though self-report is known to overestimate adherence and suffers from a ceiling effect [14,16,39], the questionnaire was sensitive enough to detect both the increased risk of missing one dose of ART on a once daily regimen and some level of forgiveness in twice daily regimens. Adherence should be monitored continuously and systematically in all HIV-infected individuals on cART. Self-report provides the most practical approach and, our instrument, with only two questions, provides a sensitive indicator of future virologic failure. These results warrant further investigation in other populations and cultural settings.

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Conflict of interests: None

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## Chapter 7: Causal modeling of observational data

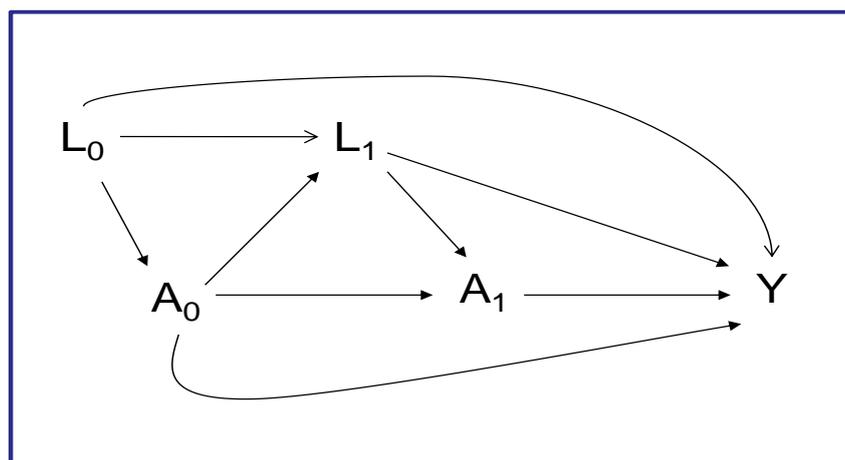
### Introduction

In a randomized controlled trial (RCT), individuals are assigned to the exposure or treatment group at random and this ensures that members of each exposure group are representative of the study population, a concept called exchangeability. In a well-designed RCT, the causal effect of exposure on outcome can be estimated. Observational studies, on the other hand, can estimate only the associational effect of exposure on outcome due to confounding. Confounding is a bias that occurs when the exposure and the outcome share a common cause. This bias is the primary disadvantage of observational studies and can be thought of as a lack of exchangeability among exposed and unexposed. For example, we would like to assess the impact of non-adherence on mortality in HIV-infected individuals in Swiss HIV Cohort Study (SHCS). Because adherence behavior is not randomly assigned, the effect of non-adherence on outcome is likely confounded by other factors. For example, one can imagine that injecting drug use (IDU) can increase both the risk of adherence problems and the risk of death. Standard methods to adjust for confounding include stratification, for example using Mantel-Haenszel methods, or using regression methods that include both the exposure and the confounder as covariates in the model. Assuming exposure does not vary with time, it is possible to use these standard approaches to estimate the causal effect of exposure on outcome in an observational study if all confounders are correctly measured and adjusted for in the analysis. However, this assumption of no unmeasured confounding can not be tested and is unlikely to be true.

When the exposure can change over time, the usual approach to estimate the effect of non-adherence on survival would be to model the hazard of failure at a given time as a function of past exposure history using a time-dependent Cox proportional hazards model. However since the exposure varies with time, the confounders can also vary with time. Even if one further adjusts for past covariate history, these standard approaches will produce biased effect estimates [1] when 1) there is a time-dependent covariate that is a predictor of outcome and also predicts subsequent exposure and 2) past exposure history predicts the risk factor [2-4]. Covariates satisfying condition 1 are considered time-dependent confounders. As discussed above, IDU is a confounder of the relationship between non-adherence and mortality. Since IDU can change over time, it is called a time-dependent confounder. Variables that meet conditions 1 and 2 are time-dependent covariates that are simultaneously confounders and intermediate variables (on the causal pathway between exposure and outcome). For example, class of combined antiretroviral therapy (cART) is both a risk factor for mortality and a predictor of adherence. In addition, prior adherence can influence what

future type of cART is selected for the patient due to either resistance or concerns about future adherence problems. Standard regression methods would suggest adjusting for class of cART by including it in the model. However since class of cART is on the causal pathway from non-adherence to mortality, it should not be included in the regression model if it is of interest to estimate the total or overall causal effect of exposure. To better illustrate the problem, we have constructed a directed acyclic graph (DAG), useful for depicting causal structure in epidemiologic settings (Figure 7.1). Arrows can be interpreted as direct causal effects.

**Figure 7.1** Causal graph for time-dependent exposure and confounders.  $A_t$  represents the exposure at time  $t$ ,  $L_t$  is the measured confounders at time  $t$ , and  $Y$  is the outcome.



## Causal model estimators

There are several common types of estimators of causal models: the inverse-probability-of-treatment-weights (IPTW) [1, 5], g-estimators [6, 7], targeted maximum likelihood estimation (TMLE) [8, 9], and double-robust (DR) methods [10]. Only IPTW and g-estimation will be discussed in further detail here.

### *Inverse-probability-of-treatment-weights estimators*

The bias in observational studies comes from two sources: confounding as discussed above, and selection bias due to loss to follow-up. IPTW estimation views the problem of confounding as one of biased sampling. In observational data, certain types of people are likely over- or under-represented in the different exposure groups. The IPTW estimator creates a new weighted data set, which has the same properties as if the exposure had been randomized. In an unweighted regression model, all participants are essentially given a weight of 1, whereas in a marginal structural model using IPTW

each individual is assigned a weight at each time point that depends on the likelihood of their exposure status given their covariates. In our study, an individual will be assigned a weight that is larger than 1 if their observed adherence is rare given their covariates and smaller than 1 if their observed adherence is common given their covariates. The average of the weights should be equal to one; otherwise this is an indication of a violation of the model assumptions.

The formula for the stabilized weights is given by

$$sw_i(t) = \prod_{k=0}^{int(t)} \frac{pr(A(k) = a_i(k) | \bar{A}(k-1) = \bar{a}_i(k-1), V = v_i)}{pr(A(k) = a_i(k) | \bar{A}(k-1) = \bar{a}_i(k-1), \bar{L}(k) = \bar{l}_i(k))}$$

where  $A(k)$  is a subject's exposure at time  $k$ ,  $V$  is a vector of time-independent baseline covariates, and  $\bar{L}(k)$  is a vector of time-dependent covariates satisfying condition 1 and 2 discussed above. Overbars are used to represent the history of a covariate, so  $\bar{A}(t) = (A(0), A(1), \dots, A(k))$  is a subject's exposure history up to time  $t$ . The numerator of the weights is informally the probability that a subject received his own observed treatment at time  $k$  conditional on his past treatment history and baseline covariates. The denominator further adjusts for past time-dependent prognostic factor history ( $V$  is included in  $L(0)$ ).

These weights are called 'stabilized' weights. The goal of stabilization is to minimize the difference between the numerator and denominator of the weights such that what remains is a reflection of the confounding due to the time-updated covariates in  $\bar{L}(k)$ . However, the result of this stabilization means that the weighting creates a pseudopopulation in which exposure is randomized only within levels of the covariates in  $V$ . For this reason, the baseline covariates must be included in the marginal structural model as there may still be confounding due to  $V$ . The causal effect estimate then assumes the effect is constant across levels of  $V$ . One can test whether this is true by adding product (or interaction) terms to the marginal structural model.

'Nonstabilized' weights replace the numerator by 1 and can also be used. Although in most cases the use of nonstabilized weights should not affect the consistency of the estimate, the variation in nonstabilized weights, especially when the exposure is time-updated, can be very large and result in a highly variable estimate and a non-normal sampling distribution. In addition, stabilized weights generally yield a 95% confidence interval (CI) that is more efficient and has actual coverage rates closer to 95% [2, 11].

So far we have assumed there was no drop out or censoring by the end of follow-up. Censoring can occur in both RCT and observational studies and can induce a bias in the estimate of the effect of

exposure on outcome. Similar to the adjustment for confounding bias described above, censoring bias can also be corrected using weights. In the end, the outcome in the uncensored subjects must represent the unobserved outcomes in the censored subjects with the same covariate values, i.e. there must be exchangeability between censored and uncensored individuals.

The weights to adjust for censoring can be estimated by

$$sw_i^\dagger(t) = \prod_{k=0}^t \frac{pr[C(k) = 0 | \bar{C}(k-1) = 0, A(k-1) = \bar{a}_i(k-1), V = v_i]}{pr[(C(k) = 0 | \bar{C}(k-1) = 0, \bar{A}(k-1) = \bar{a}_i(k-1), \bar{L}(k-1) = \bar{l}_i(k-1))]}$$

where  $C(k)$  is a censoring indicator that is 1 if a subject is right-censored by time  $k$  and 0 otherwise. These weights are informally the ratio of a subject's probability of remaining uncensored up to time  $t$ , calculated as if there had been no time-dependent determinants of censoring except past treatment history, divided by the subject's conditional probability of remaining uncensored up to time  $t$ .

The product of the stabilized weights for confounding and censoring,  $sw_i(t) \times sw_i^\dagger(t)$ , form the weights used in the final marginal structural model. The denominator is informally the probability that an individual has his observed treatment and censoring history through time  $t$ . Weighting the model by the stabilized weights will produce a consistent estimate of the causal effect of exposure on outcome assuming the measured covariates are sufficient to adjust for both confounding and selection bias due to loss to follow-up.

### *G-estimators*

Analyses using g-estimation generalizes and improves upon analyses based on the G-computation and G-null test [7, 12]. Causal models using g-estimation will estimate the causal effect of adherence, for example, by calculating the difference in mortality that would have been observed if the entire study population would have been adherent versus if the entire study population would have been non-adherent. These theoretical outcomes are referred to as 'counterfactuals' because it is only possible to observe one of the two outcomes for each person. Therefore the counterfactual framework has turned the problem of estimating causal effects into a problem of missing data. G-estimation is an iterative procedure that involves searching for the causal parameter,  $\psi$ , which ensures that the unobserved or counterfactual outcome is independent of a subject's exposure given their exposure history and covariates. It is assumed that exposure accelerates failure time by a factor of  $\exp(-\psi)$ . In order to find  $\psi$ , we need to model the probability of exposure including time-independent and time-dependent covariates as well as the subject's observed outcome. For

example, with a failure-time exposure variable the following model can be fit with a logistic regression relating measured exposure  $e_{it}$  at each measurement occasion  $t$  to  $U_{i,\psi}$  controlling for all confounders  $x_{ijt}$

$$\text{logit}(e_{it}) = \alpha U_{i,\psi} + \sum_j \beta_j x_{ijt}$$

A series of logistic regression models are fit for a range of different  $\psi$ . The G-estimate  $\psi_0$  is the value of  $\psi$  for which the test of  $\alpha=0$ , known as a g-test, cannot be rejected with a p-value of 1. Confidence intervals can be constructed by the Wald statistic using the estimated variance or with a test-based method. The test-based 95% CI for  $\psi$  is constructed using those values of  $\psi$  in which the g-test fails to reject at the 5 percent level. By separately examining exposure status at each time interval, g-estimation succeeds in controlling for confounding by intermediate variables.

## Assumptions of marginal structural models

For the marginal structural model to estimate the causal effect of non-adherence on clinical outcomes, the following assumptions must be true: 1) consistency, 2) exchangeability, 3) positivity, and 4) no model misspecification [11].

Consistency is informally that a subject's counterfactual (or unobserved) outcome under his observed exposure history is equal to his observed outcome. When estimating the effect of medical treatments, it is reasonable to assume that consistency holds.

The second assumption requires that, within the strata defined by all measured covariates, the exposure group is randomized. In other words, the individuals in each exposure group are comparable (i.e., exchangeable) given the measured covariates and therefore representative of the study population. This assumption is called exchangeability, the sequential randomization assumption or the assumption of no unmeasured confounders. This is not a testable assumption and relies on the knowledge of the investigator.

Marginal structural models also rely on the assumption that one is not able to perfectly predict the assignment of the intervention given the predictors. In other words, each subject must have some positive probability of non-adhering to their cART regimen, regardless of his or her covariate values. This condition is called positivity or the experimental treatment assumption (ETA). If there is a probability of zero in a level of a confounder that is random rather than structural (when it is impossible to be exposed at a certain covariate level), parametric models can smooth over these random zeros by borrowing information from individuals with similar covariate histories [11, 13]. Violation of this assumption will lead to weights with a mean far from one or extreme values. The

magnitude of the nonpositivity bias increases with the number of confounders and time points but decreases with the use of stabilized weights which are discussed in Chapter 8.

Marginal structural model requires fitting several models: 1) the final structural model, 2) the model to adjust for confounding bias, and 3) the model to adjust for selection or censoring bias. Each of these models must be correctly specified. A necessary condition for correct model specification is that the stabilized weights have a mean of one at each time point [14].

## Comparison of causal models

IPTW estimators are the most commonly used estimator in practice. However, these models rely heavily on the assumptions listed above. Specifically, if the ETA assumption is violated, the IPTW estimator can be biased. G-estimators, however, can still be used to consistently estimate the model parameters if the ETA assumption is violated but they depend heavily on extrapolation, which relies on parametric modeling assumptions instead of real information in the data [2, 10].

IPTW allows for effect modification by baseline covariates but not time-updated covariates. Structured nested models (SNM) using g-estimation were specifically designed to overcome this difficulty and are especially useful when evaluating dynamic treatment regimens where treatment on a given month is decided partly based on a subject's covariate history. However with complex models, g-estimation may not converge resulting in no single point estimate. In addition, if the algorithm converges, a local maximum is found but there is no guarantee that this is a unique solution. In addition, SNMs for binary outcomes cannot be fit with g-estimation unless the outcome is rare [15].

In the next chapter, marginal structural models using IPTW are applied to address the question of the causal effect of non-adherence on clinical outcomes. Causal modeling has yet to be utilized in the context of adherence and represents a novel approach in the field of adherence research.

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## Chapter 8: Causal effect of non-adherence on clinical outcomes

**Marginal structural models to estimate the causal effect of non-adherence on clinical outcomes in HIV-infected individuals in the Swiss HIV Cohort Study (SHCS)**

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A manuscript based on a shortened version of this chapter is being prepared for submission

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## **Introduction**

A limited number of studies have examined the relationship between non-adherence to combined antiretroviral therapy (cART) and progression to AIDS or death [1-5]. The findings of these studies are difficult to interpret due to confounders such as more advanced stages of HIV infection (lower CD4 cell counts at the start of cART), baseline HIV-1 RNA, type of cART (mono, dual, or triple therapy), year of initiation of therapy, and depression. The association between non-adherence and viral rebound has been studied extensively and confounders of this relationship include injecting drug use (IDU), class of cART, length of viral suppression, and physician experience [6-15]. Studies addressing both mortality and viral rebound, however, all have methodological limitations; either no adjustment for confounding or used only standard statistical models to adjust for confounding which can result in biased effect estimates. No studies to date on adherence and clinical outcomes have adjusted for confounding by indication – the presence of time-dependent covariates that are simultaneously confounders and intermediate variables. Marginal structural models can be used to estimate the causal effect of non-adherence on clinical outcomes when there exists confounding by indication.

We used data from the Swiss HIV Cohort Study (SHCS) to estimate the causal impact of non-adherence to cART on viral rebound and all-cause mortality in naïve patients starting cART and compared these results to those from standard statistical models.

## **Study Description**

### *Study population*

This longitudinal study was based on prospectively collected data from HIV-infected individuals registered in the SHCS. Eligible individuals were antiretroviral naïve and initiated cART between January 1, 2003 and June 1, 2009, and completed at least one SHCS adherence questionnaire (SHCS-AQ) prior to December 1, 2009. Baseline was the date of cART initiation. Follow-up continued until the outcome was observed, the individual was lost to follow-up (>12 months since their last visit), or December 1, 2009, whichever came first. Additionally, in the model for viral rebound, individuals were censored if they discontinued cART for >7 days. Individuals were not censored for treatment discontinuation in the model for mortality. If most patients stopped therapy due to toxicity, then it is the intention-to-treat effect that is the causal estimate of public health interest. Follow-up of participants missing any time-dependent covariate at baseline is started at the first subsequent visit at which the values were observed.

### *Outcome*

The study had two primary outcomes: all-cause mortality and viral rebound. Viral rebound which was defined as the first HIV-1 RNA viral load >400 copies/ml after either achieving viral suppression or being on therapy for at least 6 months.

### *Exposure*

The main predictor was self-reported adherence to cART as measured by the SHCS-AQ, which has been described elsewhere [6, 16]. In brief, individuals are asked how often they missed a dose of cART in the previous four weeks (none, once a month, once every 2 weeks, once a week, more than once a week, and every day). We collapsed the last 3 categories of the question on missed doses to define non-adherence as missing 0, 1, 2, or >2 doses of cART in the last 4 weeks. In previous work using standard Cox models, this definition of non-adherence has been shown to be associated with viral rebound [6]. In order to avoid trying to model countless variations of possible exposure histories, we modelled the impact of recent adherence on outcome after adjusting for past adherence, defined as missed doses on the previous visit. We assumed that once we adjusted for prior adherence, an individual's current adherence was no longer dependent on their history of adherence.

### *Covariates*

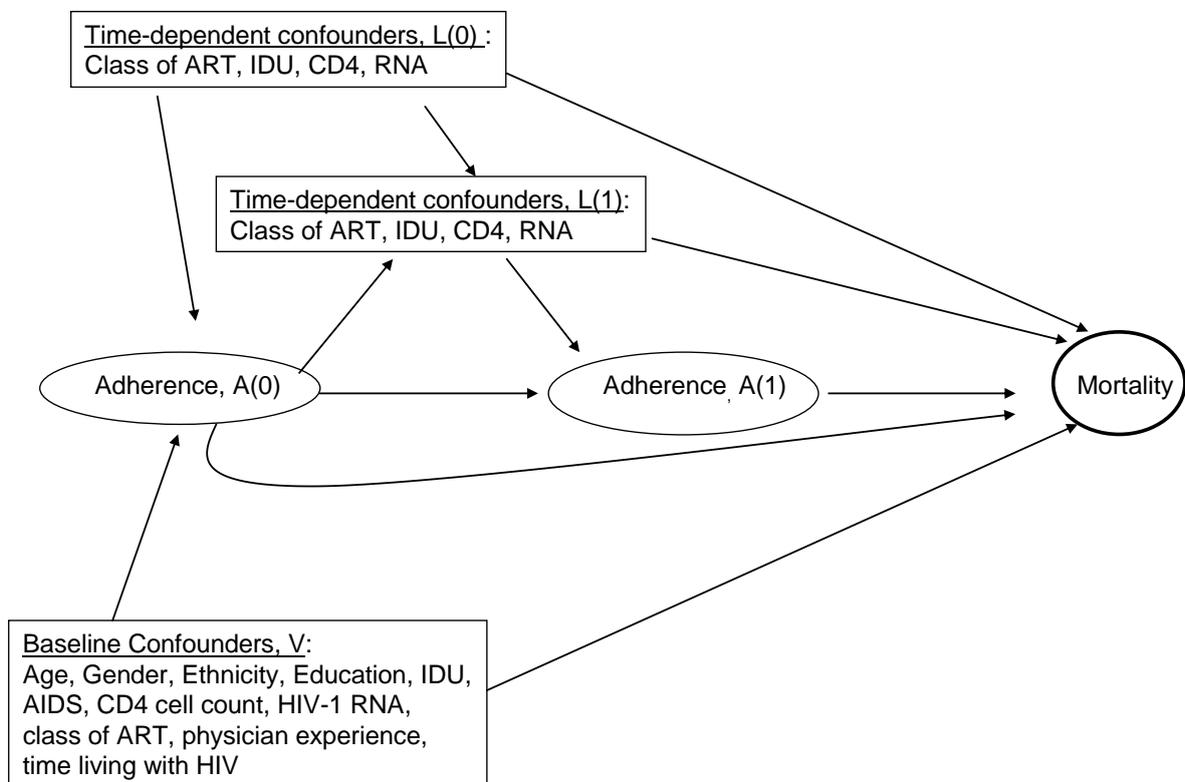
The following baseline confounders of the relationship between non-adherence and clinical outcomes were included in the model: age, gender, basic education, ethnicity, prior or current IDU, AIDS-defining illness, CD4 cell count (<200, 200-349, 350-499  $\geq$ 500 per  $\mu$ L), HIV-1 viral load (<50, 50-399,  $\geq$ 400 copies/ml), class of cART (non-nucleoside reverse transcriptase inhibitors (NNRTI), ritonavir boosted and unboosted protease inhibitors (PI), triple nucleoside/other), time since HIV diagnosis, and experience of the treating physician (estimated by number of SHCS patients seen by the physician at time of individual's baseline visit).

The time-dependent covariates for the model of mortality include most recently available information prior to the exposure: injecting drug use (IDU), CD4 cell count, HIV-1 viral load, class of cART, living alone, having a stable partner, and psychological problems (seeing a psychiatrist, diagnosis of depression or taking anti-depressants). For the outcome of treatment failure, viral load after baseline was not included as it defines the outcome. Additionally, the time-dependent variable of length of time virally suppressed at each visit was included.

### Data set and model parameterization

Data points were constructed by dividing up time into person-months of observation with most individuals contributing more than one data point. Each data point has an indicator for the exposure, the outcome, and a set of covariates. We used the same parameterization described by Hernan, Brumback and Robins [17, 18]. We defined  $T$  to be the subject's time until death measured in months starting with their initiation of cART. We denoted  $A(t)$  to be a subject's adherence to cART at time  $t$ . Overbars were used to represent the history of a covariate. So  $\bar{A}(t) = (A(0), A(1), \dots, A(k))$  is a subject's adherence history up to time  $t$ .  $V$  denotes the vector of time-independent baseline covariates measured prior to the start of follow-up.  $L(t)$  denotes the vector of time-dependent covariates measured at time  $t$ . Figure 8.1 gives the directed acyclic graph (DAG) depicting the causal structure of the model. Arrows can be interpreted as direct causal effects.

**Figure 8.1** Directed acyclic graph of the causal structure for the impact of adherence on mortality



## Statistical analysis

The traditional approach to modeling the effect of non-adherence on either mortality or treatment failure would be to fit a time-dependent Cox proportional hazards model. The conditional hazard of death or treatment failure given non-adherence history and baseline covariates is modeled as

$$\lambda_T(t|\bar{A}(t), V) = \lambda_0(t) \exp(\gamma_1 A(t) + \gamma_2 V)$$

If there is unmeasured confounding, this model will provide a biased estimate of the association parameter of non-adherence  $\gamma_1$ . However, even if there is no unmeasured confounding, the model will provide a biased estimate of the causal effect if there exists time-dependent covariates that are simultaneously confounders (associated with both the exposure and the outcome) and intermediate variables (on the causal pathway between exposure and outcome). For example, viral load is associated with both non-adherence and mortality and is also affected by prior non-adherence. Standard regression methods would adjust for the confounder viral load by including it as a covariate in the regression model. Intermediate variables, on the other hand, should not be included in regression models trying to estimate the total (direct and indirect) causal effect of non-adherence and puts the analysis at risk for induced selection bias [19, 20].

Marginal structural models allow the estimation of the causal effect of a time-dependent exposure in the presence of time-dependent confounders that are also intermediate variables. This is accomplished by weighting the analysis so that time-dependent covariates  $L(t)$  no longer predicts non-adherence at time  $t$ . Therefore the parameter  $\gamma_1$  of the weighted Cox model will estimate the causal association between recent non-adherence and mortality as in the original study population [17].

Most standard statistical programs do not allow for Cox models with subject-specific weights that vary over time. To overcome this, we fit a weighted pooled logistic regression model treating each person-month as an observation.

$$\text{logit } pr[D(t) = 1 | D(t-1) = 0, \bar{A}(t-1), V] = \beta_0(t) + \beta_1 A(t-1) + \beta_2 V$$

This model is equivalent to a Cox model [21] when the hazard in any single month is small.

## *Estimation of Inverse probability-of-treatment-and-censoring weights*

### *Confounding weights*

The conundrum described above - when time-dependent covariates are simultaneously confounders (resulting in them being included in the model) and intermediate variables (resulting in them being excluded from the model) - can be solved by using time-dependent covariates to calculate the weights rather than adding them to the model as regressors. This will allow us to eliminate or reduce the bias encountered using standard statistical models.

To construct the weights to adjust for confounding, we fit two polytomous logistic regression models for the probability of non-adherence to obtain their predicted values. The outcome for both models returns the relative risk ratio for the non-adherence category compared to the base category. The model returns the relative risk of mortality of missing 1 dose, for example, compared to the base category of 0 missed doses. The results of the first model will become the numerator of the weights and includes only the time-independent predictors of remaining adherent to cART. This model will return the probability of an individual remaining adherent to cART conditional on their adherence history and baseline covariates. The second model includes both the time-independent and time-dependent predictors of remaining adherent to cART. This model will form the denominator of the weights and returns the probability of an individual remaining adherent to cART given their previous adherence and prognostic factor history.

The denominator of the weights is providing the bias adjustment and the numerator, which does not depend on time-updated covariates, is added for stabilization. By including the model for the numerator of the weights in place of 1, we aimed to minimize the difference between the numerator and denominator such that the remaining difference reflected only the confounding due to time-dependent covariates. Stabilized weights generally produce narrower (more efficient) 95% CI that have coverage rates closer to 95% [17, 18].

### *Censoring weights*

Similar to the procedure for calculating the confounding weights, two pooled logistic regression models were constructed to obtain the predicted values for the probability of remaining uncensored. A subject is censored if he or she was lost to follow-up (>12 months since the last visit) or reached the administrative end of the study without experiencing the outcome. Additionally, in the model for viral rebound, subjects were censored if they discontinued cART for >7 days.

The outcome is a censoring indicator  $C(t)$  set to 1 if an individual was right-censored at time  $t$  and  $C(t)=0$  otherwise. The first model forms the numerator of the weights and includes baseline covariates, and adherence. The second model forms the denominator and includes baseline covariates, time-dependent covariates, and adherence.

### *Stabilized weights*

The product of the stabilized weights for confounding and censoring form the inverse probability-of-treatment-and-censoring (IPTC) weights used in the final pooled logistic regression model. The denominator is informally the probability that an individual has his observed adherence and censoring history through month  $t$ . Weighting the logistic regression model by the product of these two stabilized weights will produce a consistent estimate of the causal effect of non-adherence on clinical outcomes assuming the measured covariates are sufficient to adjust for both confounding and selection bias due to loss to follow-up.

### *Time-dependent intercept*

For our causal estimates of the effect of non-adherence on clinical outcomes to be consistent, it is necessary that the denominator of the weights is consistently estimated. To do this, we would need to estimate a separate intercept for each month  $k$ . However this is not possible so we need to borrow strength from other subjects with the same adherence in months other than  $k$  to estimate the intercept for month  $k$ . This can be done by assuming the intercept is a smooth function of the time since the beginning of follow-up and can be estimated using smoothing techniques. We use natural cubic splines with 5 knots corresponding to the percentiles 5, 25, 50, 75, and 95 for month and add these splines to the models for the weights and the marginal structural model.

### *Standard error estimates*

Another difficulty is that the use of weights induces a within-subject correlation that invalidates the standard errors produced by standard logistic regression models. Therefore, the weighted logistic model should be fit using generalized estimating equations [22, 23] that allow for correlated observations and provide robust variance estimators. The corresponding 95% robust Wald confidence intervals (CI) will provide a conservative CI for the effect estimate which will cover the true estimate 95% of the time in large samples.

### *Sensitivity analyses*

In a previous study of individuals starting a new cART regimen, we found that individuals missing one dose of cART on a once-daily regimen were more likely to experience treatment failure than those

with perfect adherence. However, we did not detect an effect of missing 1 dose in individuals on twice daily regimens, suggesting an interaction between dosing frequency and non-adherence [6]. To explore if we can replicate these findings in naïve patients using marginal structural models, we will stratify by dosing frequency at the time of starting cART.

For the marginal structural model to estimate the causal effect of non-adherence on clinical outcomes, the following assumptions must be true: 1) consistency, 2) exchangeability, 3) positivity, and 4) no misspecification of the model [24]. It is reasonable to assume consistency holds in studies of medical treatments [25]. The remaining assumptions are either not empirically verifiable [26] or computationally intensive [27], however we informally explored how sensitive our estimates were to these assumptions. First, we explored the sensitivity of our causal estimate to the parameterization of prior non-adherence. We considered several definitions of past adherence, such as missed doses at baseline, missing any doses since baseline, and missed doses on the previous visit. Second, we also explored different parameterizations of CD4 cell count and HIV-1 RNA – as categories with varying number of categories and as linear terms. With a linear parameterization we added restricted cubic splines with either 3 or 5 knots. This flexible parameterization of time-dependent confounders is preferred and can reduce residual confounding or finite-sample bias inherent to categorical variables. It can also reduce the potential bias due to model misspecification from strong linearity assumptions. Third, we tested for inclusion and exclusion of parameters, such as adding lagged variables for CD4 and RNA, including baseline variables for social support and psychological problems despite this information being missing for many individuals. Lastly, we explored the effect of progressive weight truncation. Specifically, the weights are truncated by resetting the weights greater (lower) than the percentile  $p$  ( $1-p$ ) to the value of the percentiles  $p$  ( $1-p$ ). All of these sensitivity analyses serve to explore violations of assumptions as well as the tradeoff between bias and variance that one must make when attempting to make inferences under these assumptions.

It was preferred to use stabilized instead of nonstabilized weights in the marginal structural models. However, the result of this stabilization means that the weighting creates a pseudopopulation in which exposure is randomized only within levels of the baseline covariates. For this reason, the baseline covariates must be included in the marginal structural model as there may still be confounding due to these variables. The causal effect estimate then assumes the effect is constant across levels of the baseline variables. We tested whether this assumption was true by adding product (or interaction) terms to the marginal structural model. For mortality, we tested for effect modification of non-adherence within levels of IDU, CD4 category, and class of cART. For viral rebound, we considered including product terms for non-adherence and class of cART.

**Table 8.1** Baseline characteristics of study population for mortality

<b>Variable</b>	<b>Overall</b>
N (%)	2422
Age – median (IQR)	39 (32 – 46)
Male gender - %	70.6
Caucasian - %	74.9
Basic education # - %	26.1
Risk group for HIV infection %	
MSM	41.3
Heterosexual	44.1
IDU	10.5
Other	4.2
Past or current IDU	11.9
Past or current smoker	61.9
Past or current psychiatric treatment	15.6
Living alone	41.7
Stable partnership	60.9
HIV-1 RNA viral load (copies/mL) - %	
< 50	2.8
50 – 399	5.5
≥ 400	91.7
CD4 cell count (μ/L) - %	
< 200	41.8
200 – 349	39.9
350 – 499	11.2
≥ 500	7.1
cART regimen	
NNRTI	44.6
PI boosted	3.0
PI non-boosted	48.6
Triple nucleoside/Other	3.8
Dosing frequency	
Once daily	54.7
Twice daily	45.1
Three times daily	0.2
Taking concomitant medication √	14.1
Number of other HIV patients seen by physician	
Median (IQR)	19 (8 – 50)
Time since HIV diagnosis (years)	
Median (IQR)	0.9 (0.1 – 3.9)

# 9 years of mandatory schooling or less  
√ For opportunistic infections, hepatitis C, cardiovascular risk, or cancer  
IQR=interquartile range, MSM=men who have sex with men, IDU=intravenous drug use,  
cART=combined antiretroviral therapy, NNRTI= non-nucleoside reverse transcriptase inhibitors,  
PI = protease inhibitors

## Results

During the almost 7 year study period, 2836 naïve individuals initiated cART. Of these, 156 (5.5%) never completed the SHCS-AQ, 240 (8.5%) did not complete the SHCS-AQ within 1 year of starting cART, and 30 (1.1%) did not have any follow-up information on covariates. The final sample included 2410 individuals with 79,893 person-months of observation. Individuals were followed for a median of 2.7 years (interquartile range (IQR): 1.4 – 4.4). By the end of follow-up, 682 (28.3%) of individuals had reported missing one dose, 244 (10.1%) missed 2 doses, and 191 (7.9%) missed >2 doses of cART on at least one occasion. There were 242 (10.0%) individuals lost to follow-up and 65 died for a crude mortality rate ratio of 2.7 (95% CI: 2.6-2.8).

Baseline characteristics of included individuals are provided in Table 8.1. For the outcome of viral rebound, an additional 260 individuals could not be evaluated for the endpoint. Of the 2150 included individuals, 256 (11.9%) individuals were lost to follow-up and 191 (8.9%) experienced viral rebound. Baseline characteristics were almost identical to those in the mortality study population (data not shown).

### *Standard Cox model*

As a first step, standard unweighted time-dependent Cox models were constructed including, at each month  $t$ , non-adherence  $A(t)$ , previous non-adherence  $A(t-1)$ , baseline covariates  $V$ , as well as the most recent value of the time-dependent covariates,  $L(t)$ . In models for all-cause mortality including past adherence and a time-dependent intercept, only non-adherent individuals who missed >2 doses were at significantly higher risk of death compared to individuals missing 0 doses (hazard ratio (HR) 4.01, 95% confidence interval (CI): 1.56 – 10.31) (Table 8.2). While the other effect estimates did not change considerably, the association between missing >2 doses of cART and mortality increased when adjusting for confounding by baseline variables (HR 5.06, 95% CI: 2.06 – 12.46) and attenuated when additionally including time-dependent covariates (HR 2.39, 95% CI: 0.79 – 7.20), as would be expected due to adjusting for time-dependent variables on the causal pathway.

Similarly, for models of viral rebound, only missing >2 doses of cART was significantly associated with a higher risk of treatment failure compared to missing 0 doses (HR 3.80, 95% CI: 1.42 – 10.18). This effect was also increased after adjusting for baseline covariates but there was no attenuation after adjusting for time-dependent covariates (HR 4.08, 95% CI: 1.47 – 11.38) (Table 8.2).

### *Marginal structural model*

To adjust for confounding by indication, we estimated the parameters of marginal structural Cox models using stabilized IPTC for each person-month as described above. The marginal structural

model included a time-dependent intercept, most recent non-adherence, non-adherence on the previous visit, and baseline variables. The estimated causal mortality hazard ratio for missing doses of cART compared to missing 0 doses was 0.39 (95% CI: 0.10 – 1.49) for missing 1 dose, 0.30 (95% CI: 0.04 – 2.44) for missing 2 doses, and 3.88 (95% CI: 1.56 – 9.68) for missing  $\geq 2$  doses of cART (Table 8.2). The causal effect estimates are slightly attenuated compared to the unadjusted associational estimate.

**Table 8.2:** Marginal structural models with inverse probability-of-treatment-and-censoring weights for the causal effect of non-adherence to antiretroviral therapy on clinical outcomes

	Death		Viral rebound	
	HR	95% CI	HR	95% CI
<b>Unweighted estimates †</b>				
Adjusted for past adherence ‡				
Missing 1 dose	0.61	0.19 – 1.97	1.12	0.62 – 2.01
Missing 2 doses	0.67	0.09 – 4.93	1.46	0.58 – 3.66
Missing >2 doses	4.01	1.56 – 10.31	3.80	1.42 – 10.18
Adjusted for baseline covariates ¶				
Missing 1 dose	0.64	0.19 – 2.17	1.16	0.64 – 2.12
Missing 2 doses	0.74	0.11 – 4.93	1.20	0.43 – 3.35
Missing >2 doses	5.06	2.06 – 12.46	4.09	1.47 – 11.38
Adjusted for baseline & time-varying covariates §				
Missing 1 dose	0.52	0.17 – 1.61	1.20	0.64 – 2.23
Missing 2 doses	0.42	0.11 – 1.55	1.14	0.42 – 3.13
Missing >2 doses	2.39	0.79 – 7.20	4.08	1.47 – 11.38
<b>Weighted estimates √</b>				
Stabilized				
Missing 1 dose	0.39	0.10 – 1.49	1.08	0.53 – 2.19
Missing 2 doses	0.30	0.04 – 2.44	0.62	0.19 – 2.05
Missing >2 doses	3.88	1.56 – 9.68	3.63	1.07 – 12.33

† Unweighted noncausal estimates are shown for comparison purposes only. The unadjusted model includes non-adherence, month, and the time-varying intercept.

‡ Same as model in † with past adherence added – last missed doses and first report of non-adherence (0, 1, 2, >2 doses).

¶ Models include non-adherence, past non-adherence, and a time-varying intercept as well as the following baseline covariates: age, gender, basic education, ethnicity, IDU, AIDS, CD4 (<200, 200-349, 350-499  $\geq 500$  per  $\mu\text{L}$ ), HIV-1 viral load (<50, 50-399,  $\geq 400$  copies/ml), class of ART, time since HIV diagnosis, and experience of the treating physician.

§ Models include variables as described in ¶ plus the most recent value of the following time-varying covariates: IDU, CD4, RNA, class of ART, living alone, stable partnership, and psychological problems. NOTE: For the outcome viral load, RNA is not included since this defines the outcome. Length of time an individual has maintained viral suppression is added.

√ Weighted causal estimates from the marginal structural model are calculated as described in text using data on baseline and time-varying covariates.

ART=antiretroviral therapy, HR = hazard ratios for the event, CI = confidence intervals, IDU=injecting drug use

**Table 8.3** Inverse probability-of-treatment-and-censoring estimates of the parameters of a marginal structural model for the causal effect of non-adherence on clinical outcomes

Covariates †	Death		Viral rebound	
	HR	95% CI	HR	95% CI
Current non-adherence to ART				
Missing 0 doses	1.0			
Missing 1 dose	0.39	0.10 – 1.49	1.08	0.53 – 2.19
Missing 2 doses	0.30	0.04 – 2.44	0.62	0.19 – 2.05
Missing>2 doses	3.88	1.56 – 9.68	3.63	1.07 – 12.33
Non-adherence at previous visit				
Missed 0 doses	1.0		1.0	
Once a month	2.26	0.79 – 6.47	1.36	0.73 – 2.53
Every 2 weeks	2.40	0.27 – 21.22	0.39	0.05 – 3.05
Every week	2.69	0.47 – 15.25	1.41	0.24 – 8.22
More than once a week	13.56	4.35 – 42.26	1.45	0.27 – 7.80
Every day	NE #		9.42	1.30 – 68.36
Age at baseline, years	1.10	1.07 – 1.14	0.99	0.97 – 1.01
Male gender	1.42	0.63 – 3.16	1.06	0.66 – 1.68
Basic Education ¶	1.08	0.51 – 2.29	1.18	0.73 – 1.91
Caucasian	0.57	0.17 – 1.95	0.69	0.40 – 1.17
Past or current IDU	8.86	3.38 – 23.19	1.27	0.68 – 2.40
AIDS-defining illness	2.08	1.09 – 3.94	0.91	0.56 – 1.47
Baseline CD4 cell count, per µl				
<200	1.0		1.0	
200 – 349	1.18	0.60 – 2.31	0.94	0.62 – 1.41
349 – 499	1.50	0.27 – 8.40	1.04	0.54 – 2.02
≥ 500	2.44	0.69 – 8.60	2.30	1.14 – 4.64
Baseline RNA, copies per mL				
<50	1.0		1.0	
50 – 399	0.16	0.01 – 4.74	0.38	0.08 – 1.87
≥ 400	0.49	0.05 – 4.43	0.38	0.14 – 1.02
Class of ART at baseline				
NNRTI	1.0		1.0	
PI nonboosted	4.07	0.82 – 20.32	1.77	0.62 – 5.05
PI boosted	2.24	1.09 – 4.59	1.31	0.88 – 1.94
Triple nucleoside/Other	4.42	1.38 – 14.15	1.41	0.56 – 3.55
Time since HIV diagnosis, years	0.97	0.91 – 1.03	1.03	0.98 – 1.07
Experience of treating physician §	0.99	0.93 – 1.06	1.00	0.97 – 1.04

† Weighted logistic model including a time-dependent intercept (not shown), current non-adherence, prior non-adherence, and the baseline variables listed in the table. Weights were estimated by  $sw_i(t) \times sw_i^\dagger(t)$  as defined in the text.

¶ 9 years of mandatory schooling or less.

§ Number of HIV patients seen by the physician at the individual's baseline visit.

# NE = not estimable. Missing doses everyday perfectly predicted failure.

ART=antiretroviral therapy, HR = hazard ratios for the event, CI = confidence intervals, IDU=injecting drug use, NNRTI=non-nucleoside reverse transcriptase inhibitor, PI= protease inhibitor

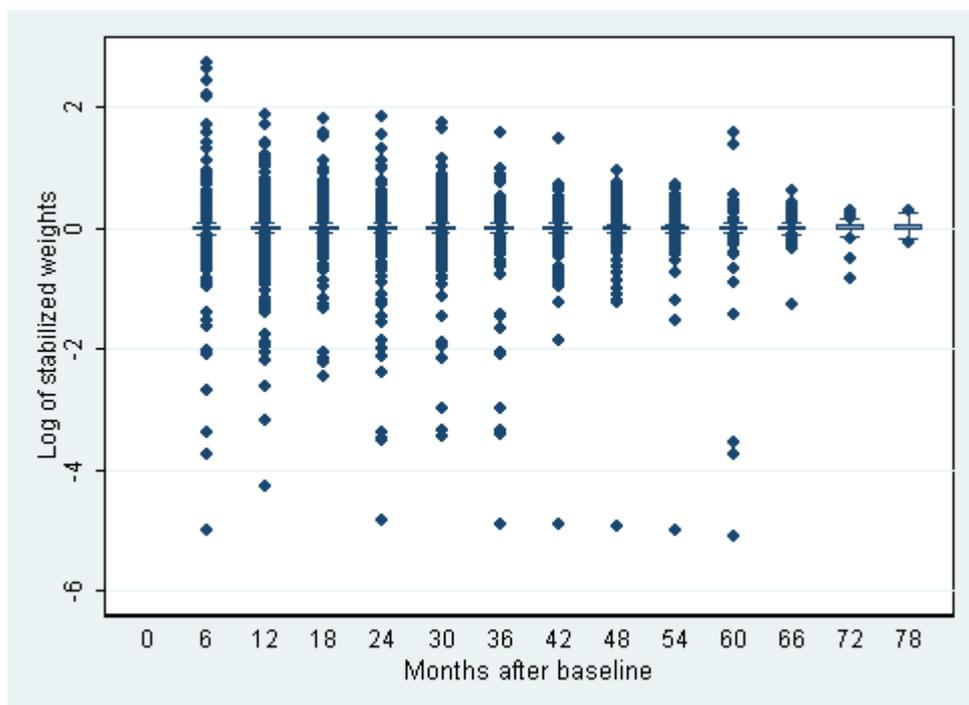
The causal estimate of the hazard of viral rebound for those missing doses of cART compared to missing 0 doses was 1.08 (95% CI: 0.53 – 2.19) for missing 1 dose, 0.62 (95% CI: 0.19 – 2.05) for missing 2 doses, and 3.63 (95% CI: 1.07 – 12.33) for missing  $\geq 2$  doses. Again the causal effect is even closer to 1 than the unadjusted associational effect.

The parameter estimates of the marginal structural model are provided in Table 8.3. After adjusting for current non-adherence, past non-adherence reported on the previous visit only had a significantly negative impact on outcome when the number of missed doses was very high (at least once a week).

#### *Stabilized and nonstabilized IPTC*

The stabilized weights of the marginal structural model for mortality had a mean of 1.02 (standard deviation (SD) 0.39) and ranged from 0.005 to 24.36. Estimated weights with a mean far from one or extreme values are indications of model violations. As the weights should have a mean of one at each time point, we selected the weights at each 6 month interval after baseline and graphed the distribution of the log of the stabilized weights (Figure 8.2). The distribution of the non-transformed weights is centered at one at each time point and the variation gets smaller with time.

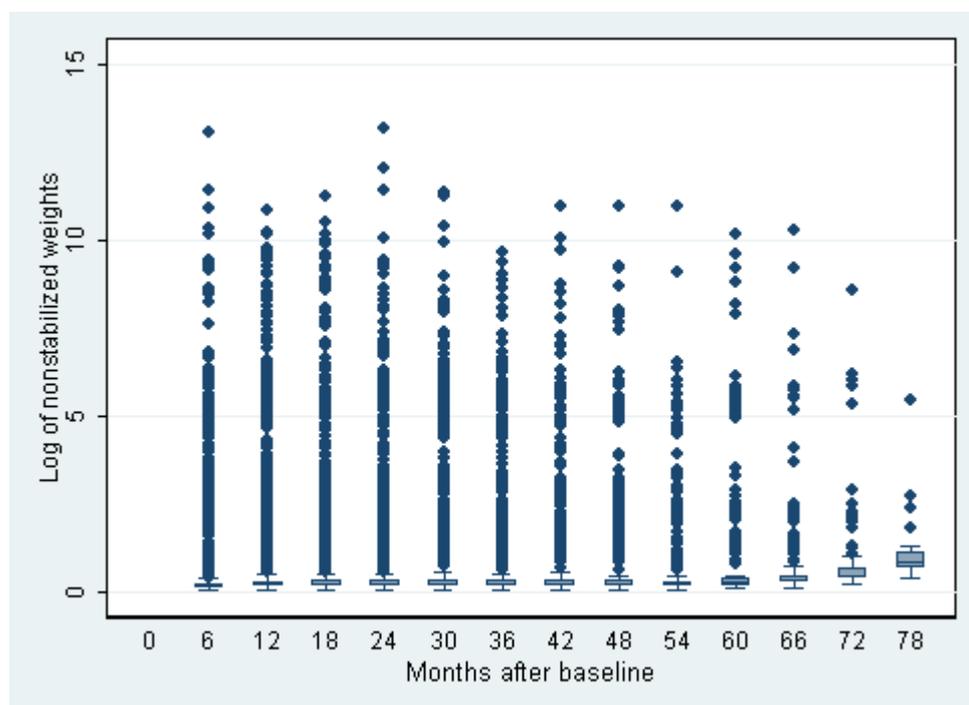
**Figure 8.2** Distribution of the stabilized inverse probability-of-treatment-and-censoring weights, SW, for the model of mortality.



The nonstabilized weights for mortality were extremely large with a mean of 232.14 (SD 3371.56) and ranged from 1.04 to 228,557.40 (Figure 8.3). In the pseudopopulation created by the weighting, most individuals would be represented by the median weight of 1.29 copies or less of themselves but a select few individuals would be represented by over 200,000 copies. The use of stabilized weights is critical in this study to increase the efficiency of the analysis so that some individuals are not contributing most of the observations in the pseudopopulation.

The stabilized weights for the marginal structural model for viral load had a mean of 1.00 (standard deviation (SD) 0.18) and ranged from 0.03 to 7.50. The distribution of the weights was very similar to that for mortality but the range and the variance was smaller. However, the nonstabilized weights were even more extreme than the nonstabilized weights for mortality with a mean of 239.45 (SD 3854.11) and a range from 1.04 to 325,012.80.

**Figure 8.3** Distribution of the nonstabilized inverse probability-of-treatment-and-censoring weights, SW, for the model of mortality.



### *Sensitivity analyses*

#### *Stratified analysis*

At baseline, 54.8% of naive individuals started cART on a once-daily regimen, 45.0% on twice daily and only 0.2% were on a three times daily regimen. During the study period, 680 (28.2%) underwent

changes to their cART regimen that resulted in a change to their dosing frequency. Of these changes, 554 (81.5%) were regimen simplifications.

In stratified marginal structural models, the causal impact of non-adherence to cART on clinical outcomes differed depending on baseline dosing frequency (Table 8.4). Individuals starting cART on a once-daily regimen had a significantly higher risk of death if they missed >2 doses compared to those with missing 0 doses (HR 2.90, 95% CI: 1.09 – 7.72). The effect of missing 2 doses was not estimable as there were very few patients and no deaths in this group. In individuals starting on a twice or three times daily regimen, there was no significant causal effect found for missing doses compared to perfect adherence. In the models for viral rebound, the causal estimate of the hazard of viral rebound for those starting on a once daily regimen and missing doses of cART compared to missing 0 doses was 5.49 (95% CI: 1.69 – 17.67) for missing 1 dose, 6.87 (95% CI: 1.07 – 44.01) for missing 2 doses, and 9.26 (95% CI: 2.26 – 37.99) for missing  $\geq 2$  doses. For those on twice daily or three times daily, although the causal effect estimate for missing >2 doses was 2.72, the confidence interval was very wide; therefore there was no significant causal effect detected for non-adherence and viral rebound.

#### *Model assumptions*

We performed several sensitivity analyses to explore the effect of the model assumptions on our results. We considered several possible definitions for prior non-adherence including highest past reported missed doses, first reported missed doses, and any past missed doses, but it did not appreciably alter the results.

We explored several different scenarios for the models to estimate the IPTC weights (Table 8.5). The first model in this table gives the results from the primary analysis presented in Table 8.3. The second and third models explore variations in the adjustment for past adherence. We change the parameterization of missed doses on the previous visit from 6 categories to 4 due to sparse data. This increased the variance and range of the weights and increased the effect estimate. The third model adjusted for first reported non-adherence in addition to missed doses on the previous visit (6 categories). This did not affect the weights substantially but moved the effect estimate closer to one indicating first reported adherence is potentially an effect modifier for recent non-adherence and mortality. The fourth and fifth model includes CD4 and RNA as linear terms adding restricted cubic splines with 3 or 5 knots, respectively, so as not to introduce model misspecification from strong linearity assumptions. For both models the mean of the weights remained the same but the

standard deviation and the range of the weights increased dramatically. Model 6 adds time-lagged variables for both CD4 and RNA which does not change the weights substantially or the effect estimates for missing 1 or 2 doses. The estimate for missing 2 doses increases in absolute value suggesting better control of confounding, but the standard deviation, and therefore the precision, of the estimate decreases. Model 7 adds variables for baseline social support and psychological problems. Prior to initiation of cART, 26% of patients did not have any information on these variables. Including them in the model for the weights decreased the standard deviation of the weights significantly. The effect estimates increase for missing 1 dose and missing >2 doses suggesting better control of confounding. However, due to a loss of 32% of the observation time, there is a substantial loss of precision. The eighth model reduces the number of categories of CD4 and RNA in an effort to decrease potential bias due to nonpositivity. The result is weights with a mean closer to one and a smaller standard deviation. However the effect estimates and variance increase substantially.

**Table 8.4** Marginal structural models with inverse probability-of-treatment-and-censoring weights for the causal effect of non-adherence to antiretroviral therapy on clinical outcomes stratified by dosing frequency\*

	Death		Viral rebound	
	HR	95% CI	HR	95% CI
<b><i>Stabilized weighted estimates stratified by dosing frequency at baseline v</i></b>				
Once daily				
Missing 1 dose	0.29	0.02 – 3.37	5.46	1.69 – 17.67
Missing 2 doses	NE #	-	6.87	1.07 – 44.01
Missing>2 doses	2.90	1.09 – 7.72	9.26	2.26 – 37.99
Twice daily or more				
Missing 1 dose	0.63	0.13 – 3.06	0.85	0.38 – 1.91
Missing 2 doses	0.44	0.04 – 5.15	0.25	0.06 – 1.12
Missing>2 doses	0.99	0.25 – 4.00	2.72	0.56 – 13.25

\* Non-adherence is defined as missing 0, 1, 2, or >2 doses of antiretroviral therapy. Missing 0 doses is the comparison or reference group. Weighted causal estimates from the marginal structural model are calculated as described in text using data on baseline and time-varying covariates. Models include non-adherence, past non-adherence, and a time-varying intercept as well as the following baseline covariates: age, gender, basic education, ethnicity, IDU, AIDS, CD4 (<200, 200-349, 350-499 ≥500 per µL), HIV-1 viral load (<50, 50-399, ≥400 copies/ml), class of ART, time since HIV diagnosis, and experience of the treating physician. The following time-varying covariates were also included: IDU, CD4, RNA, class of ART, living alone, stable partnership, and psychological problems. NOTE: For the outcome viral load, time-varying RNA is not included since this defines the outcome. A time-dependent variable of the length of time an individual has maintained viral suppression was also included.

v At baseline, 55% of patients were on once daily regimens, 45% on twice daily, and only 0.2% on three or more times daily regimens.

# NE= not estimable. Due to sparse data, it was not possible to estimate the effect of missing 2 doses in this sub sample.

HR = hazard ratios for the event, CI = confidence intervals, ART=antiretroviral therapy, IDU=injecting drug use

**Table 8.5** Effect of non-adherence to antiretroviral therapy on mortality under a series of models for the construction of the inverse probability-of-treatment-and-censoring weights \*

	Description	Estimated weights		Estimate		
		Mean (SD)	Minimum/Maximum	HR	SE †	
1	Marginal structural model †	1.02 (0.39)	0.005 / 24.36	1 dose	0.39	0.27
				2 doses	0.30	0.32
				>2 doses	3.88	1.81
2	Changed definition of past non-adherence to 0, 1, 2, and >2 missed doses	1.02 (0.50)	0.005 / 41.54	1 dose	0.46	0.30
				2 doses	0.35	0.37
				>2 doses	4.37	1.96
3	Add baseline self-reported adherence to model	1.02 (0.41)	0.004 / 31.10	1 dose	0.37	0.25
				2 doses	0.61	0.52
				>2 doses	2.68	1.28
4	Change baseline and time-varying CD4 and RNA to linear terms with 3 knot splines	1.02 (0.56)	0.002 / 99.35	1 dose	0.33	0.26
				2 doses	0.63	0.63
				>2 doses	3.66	3.66
5	Change baseline and time-varying CD4 and RNA to linear terms with 5 knot splines	1.02 (0.55)	0.003 / 97.71	1 dose	0.32	0.24
				2 doses	0.51	0.48
				>2 doses	2.96	1.41
6	Add time-lagged variables for time-varying CD4 and RNA	1.02 (0.39)	0.005 / 23.91	1 dose	0.40	0.28
				2 doses	0.28	0.31
				>2 doses	4.21	2.16
7	Adding baseline variables for stable partnership, living alone, and psychological problems	1.02 (0.16)	0.11 / 23.98	1 dose	0.52	0.37
				2 doses	0.17	0.18
				>2 doses	7.87	5.05
8	Reduce the number of categories for CD4 and RNA were reduced ‡	1.01 (0.34)	0.005 / 22.45	1 dose	0.57	0.42
				2 doses	0.36	0.39
				>2 doses	7.88	5.80

\*Non-adherence is defined as missing 0, 1, 2, or >2 doses of antiretroviral therapy. Missing 0 doses is the comparison or reference group. Past non-adherence is defined as missing doses: never, once a month, once every 2 weeks, once a week, more than once a week, and every day. Each model starts with Model 1 and then implements changes described.  
† This is the weighted marginal structural model as defined in the text and Table 8.3  
‡ CD4 was categorized as: <200, 200-499 ≥500 per µL. HIV-1 viral load was categorized as: <399, ≥400 copies/mL

We explored the bias-variance tradeoff in another simple way by progressively truncating the weights [28] as described in the methods section. The first row of Table 8.6 corresponds to the marginal structural model presented in Table 8.3 while the last row of the table is equivalent to the unweighted baseline adjusted model. Assuming the marginal structural model estimate is correct; one can see how the bias is increasing (estimates moving toward the estimate from the unweighted model) with progressive truncation. In addition, the precision is also decreasing. Therefore, the causal effect estimate from the marginal structural model is potentially an improvement in both bias and precision from the unweighted model.

We were unable to detect any effect modification by baseline covariates in our marginal structural model. However, due to sparse events, some product terms were not able to be estimated and therefore we lacked the power to address this issue satisfactorily.

**Table 8.6** Effect of non-adherence to antiretroviral therapy on mortality under progressive truncation of inverse probability-of-treatment-and-censoring weights \*

Truncation percentiles	Estimated weights		Estimate		
	Mean (SD)	Minimum/ Maximum	HR		SE †
0, 100 ‡	1.02 (0.39)	0.005 / 24.36	1 dose	0.39	0.27
			2 doses	0.30	0.32
			>2 doses	3.88	1.81
1, 99	1.00 (0.15)	0.46 / 1.90	1 dose	0.45	0.29
			2 doses	0.35	0.37
			>2 doses	4.43	2.05
5, 95	1.00 (0.07)	0.85 / 1.18	1 dose	0.58	0.37
			2 doses	0.66	0.68
			>2 doses	5.35	2.55
10, 90	1.00 (0.04)	0.93 / 1.08	1 dose	0.63	0.40
			2 doses	0.73	0.75
			>2 doses	5.39	2.55
25, 75	0.99 (0.02)	0.97 / 1.01	1 dose	0.67	0.43
			2 doses	0.78	0.79
			>2 doses	5.49	2.59
50, 50 ‡	0.99 (0.00)	0.99 / 0.99	1 dose	0.64	0.40
			2 doses	0.74	0.71
			>2 doses	5.06	2.33

\* Non-adherence is defined as missing 0, 1, 2, or >2 doses of antiretroviral therapy. Missing 0 doses is the comparison or reference group.

† Robust Wald standard errors

‡ No truncation corresponds to the estimates of the standard marginal structural model described in the text and setting all weights to the 50<sup>th</sup> percentile corresponds to the standard model adjusted for baseline covariates (see Table 8.2)

HR = hazard ratios for the event, SD = standard deviation, SE = standard errors

## Discussion

The associational effect of non-adherence to cART on clinical outcomes has been studied in many observational settings with varying degrees of methodological rigor. The major limitation of all these prior studies has been the lack of proper adjustment for bias. To our knowledge this is the first study to use causal modeling methodology to assess the causal impact of non-adherence on treatment

failure and mortality. Our results indicate that missing >2 doses of cART results in a more than 3-fold increase in the hazard of viral rebound and death. It is difficult to compare our results with previous studies due to different measurement methods and definitions of non-adherence. Our effect estimate is slightly higher than that reported in earlier studies [1, 2, 5], likely due to adjustment for time-dependent confounding, and less precise due to the limited number of events. Standardization of adherence measurement and definition is needed to facilitate comparisons across studies.

The availability of once-daily regimens was met with great enthusiasm and its use has skyrocketed over the last years. At the start of our study in 2003, 93.5% of naïve individuals initiated cART on a twice-daily regimen. Over the last 7 years this rate has declined steadily and in 2009 only 15.4% of patients initiated cART on a twice-daily regimen. We detected an interaction between dosing frequency and non-adherence indicating missing doses on a once-daily regimen comes with higher consequences than missing doses on a twice-daily regimen. We were not able to detect any effect of missing doses on either mortality or viral rebound in those on twice-daily regimens. On the other hand, individuals missing >2 doses of cART on a once-daily regimen had a significantly higher risk of mortality. There was a clear dose-response relationship between missed doses and viral rebound in those on once-daily regimens with each missed dose causing a significant increased risk of treatment failure.

The present results should be interpreted within the context of the following limitations. Like all observational studies, the effect estimates have a causal interpretation only if there is no unmeasured confounding. Due to the rich data collection of the SHCS, we were able to include many important confounders of the relationship between adherence and clinical outcomes. We did many sensitivity analyses to explore variation in our causal estimate due to model misspecification. We found some indication that our causal effect estimate was sensitive to model specification and the tradeoff between confounding control and efficiency could be substantial. This analysis should be repeated in a larger population to further explore the stability of the effect estimates. The results of the different sensitivity analyses did not, however, change the substantive conclusions from our analysis. Marginal structural models are sensitive to model misspecification, especially in the construction of the weights. It would be of interest to compare these results to analyses using g-estimation of structural nested models (SNM). These models have the advantage that they are not as sensitive to model misspecification and can estimate effect modification by time-dependent confounders. Development of SNM and comparison of results with marginal structural models is the subject of future work.

The adherence questions were collected via interview with the patient during their semi-annual clinic visit. This form of data collection could lead to an overestimate of their adherence due to poor recall or unwillingness to admit undesirable behavior to their clinician. Despite this potential bias of the estimate towards the null, with two simple self-report questions we were able to detect a significant effect of missed doses on clinical outcomes.

Our results present a novel approach to adherence research and our findings draw a spotlight on the issue of regimen complexity, in particular the harmful consequences of missing doses after starting on a once-daily regimen. Due to the increasing use of once-daily regimens, clinicians should consider carefully which dosing frequency suits their patients best. An additional validation of these findings in a larger dataset and other patient populations is warranted.

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## Future work

### Additional causal modeling

There are several different estimators for causal models [1], as discussed briefly in Chapter 7. The analysis in Chapter 8 focused only on marginal structural models using IPTC estimators. I would like to explore the sensitivity of our results to the choice of estimator used to calculate the weights and the type of model. For this reason, it would be of interest to use targeted maximum likelihood estimation (TMLE), which targets the maximum likelihood estimate of a parameter in a way that reduces bias [2]. This reduction in bias, however, can be accompanied by an increase in the variance of the estimate.

Structural nested models (SNM) are another method of causal modelling and can be estimated using g-estimation [3, 4], discussed in Chapter 7. An advantage of using SNM is that one can model the interaction of treatment with a time-dependent or time updated covariate, which is not possible using a marginal structural model. In our study, we considered the effect modification of dosing frequency at baseline, but it was not possible to evaluate the effect of this variable after baseline. SNM would allow us to explore this very important time-updated confounder and its effect on time-updated adherence.

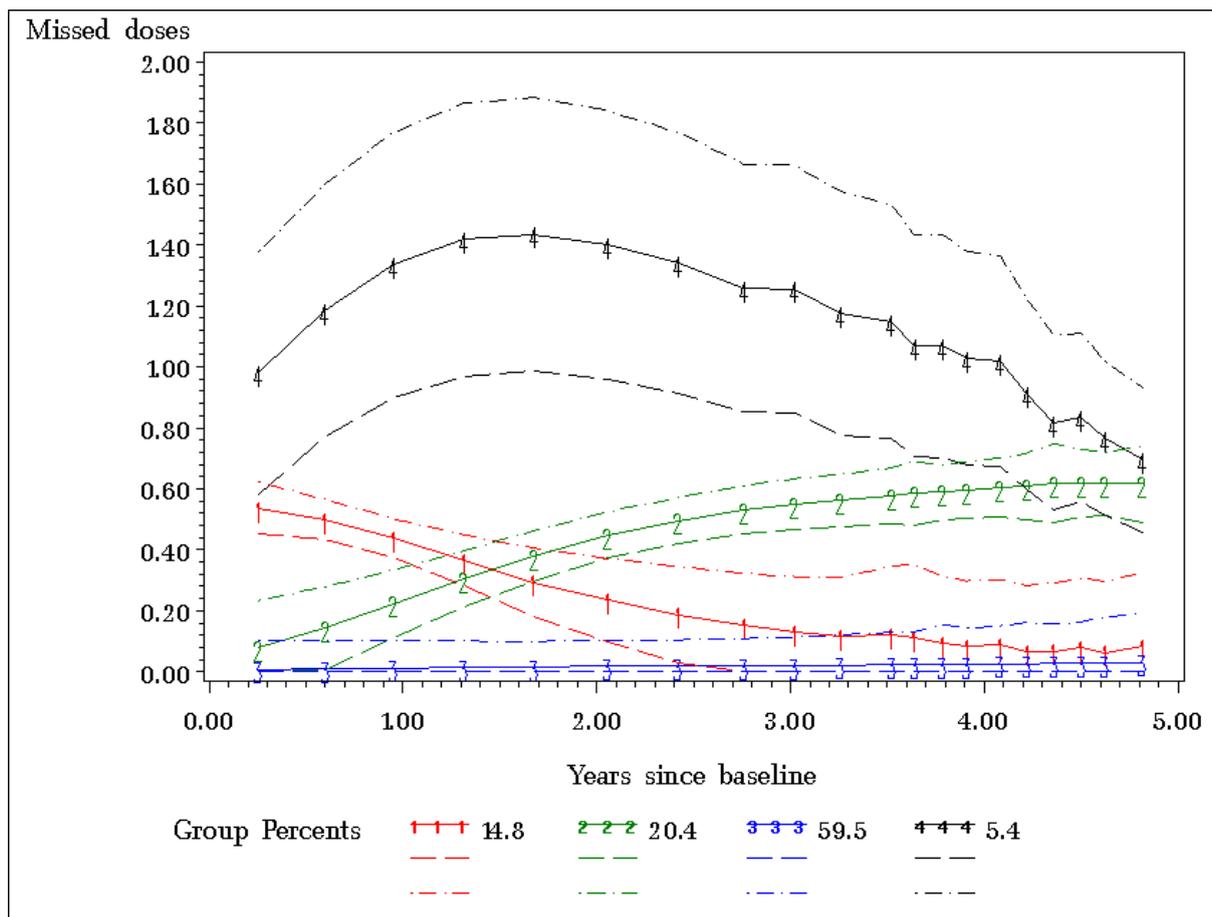
History-adjusted marginal structural models (HA-MSM) are a generalization of marginal structural models and an alternative to SNM. They can be estimated using IPTW or TMLE [5]. A standard marginal structural model is assumed at each time point and covariates and treatment history up to that time point are treated as baseline data. The output of the HA-MSM is then the causal effect of exposure at that time point. These models have been criticized suggesting that they can produce logically incompatible parameter estimates therefore resulting in contradictory substantive conclusions [6].

### Prediction models

One of the remaining gaps in adherence research is the availability of effective prediction models for at-risk patients with respect to non-adherence and therefore worse clinical outcomes. The trajectory analysis presented in Chapter 5 provided a novel way to explore patterns in adherence behavior. The resulting groups were both distinct and intuitive. I explored these models further with respect to clinical outcomes to see if they could provide some sort of framework for constructing prediction models. I repeated the trajectory analysis in the naïve population described in Chapter 8. As we had

already performed this analysis in a naïve (although slightly different) population, it was not surprising that the patterns identified by the trajectory analysis were similar (Figure 1).

Figure 1: Trajectories with 95% confidence intervals of adherence groups identified by clustering the number of missed doses over time in naïve patients initiating ART after January 1, 2003: group 1 = steadily improving adherence group, group 2 = steadily worsening adherence group, group 3 = consistently good adherence group, and group 4 = consistently poor adherence group. The predicted probabilities of group membership are given.



I then took these group assignments to see how well they could predict mortality. The death rate was double in the groups who started with missing doses (groups 1 and 4) compared to those starting with near perfect adherence (groups 2 and 3) (group 1 = 5.19%, group 4 = 5.43%, group 2 = 1.74%, and group 3 = 2.32%). This provided the motivation to explore the role of initial adherence on outcome comparing mortality rates by first self-reported non-adherence (0, 1, 2, >2 doses). Again there was an increase in the percentage of deaths with more missed doses (0 missed doses = 2.48%, 1 missed dose = 3.31%, 2 missed doses = 0%, and missing >2 doses = 12.77%), although the category

of missing 2 doses did not fit this pattern likely due to sparse data. This exploration led to adding a variable for first reported measure of adherence to the marginal structural models presented in Chapter 8. The result was that first reports of adherence are predictive of both future adherence behavior and clinical outcomes.

Similarly, with the outcome viral rebound, there was a difference in rates of viral rebound by group membership. The group with consistently good adherence has a rebound rate of only 6.4% compared to 11.43% in those with steadily worsening adherence, 13.11% in those with steadily improving adherence and 14.74% in those with consistently poor adherence. The trend in viral failure by first reported non-adherence showed a clear dose-response relationship (0 missed doses = 8.17%, 1 missed dose = 8.82%, 2 missed doses = 17.86%, and missing >2 doses = 37.50%), although the difference between 0 and 1 missed dose was minimal.

The next step of interest would be to develop a prediction model for future adherence behavior. A model could be built to predict membership in one of the groups identified by the trajectory analysis above including important baseline variables and first adherence report. This model could then be cross-validated on other populations or within the data from the SHCS by splitting the data into a training and validation set. A validated model would be helpful in daily clinical practice as an indicator of what type of adherence support an individual is likely to need in the future.

## Resistance

Resistance is a key issue in the understanding of the relationship between adherence and clinical outcomes. Other researchers have shown that the adherence-resistance relationship is different for classes of ART. However, this has yet to be explored in the SHCS or using causal modelling and would give a fuller picture of the relationship between adherence and outcomes.

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## Conclusions

Despite advances in therapy for HIV-infected individuals, non-adherence to combined antiretroviral therapy (cART) remains one of the biggest obstacles to successful treatment. The Swiss HIV Cohort Study (SHCS) provided a rich framework with which to study the mechanisms impacting adherence and the consequences of non-adherence to cART.

Although more focus has been placed on adherence research in the last decade, universal measures and definitions of adherence are still lacking. Adherence support has also not been fully integrated into the clinical management of HIV patients and very little data exists about successful and sustainable adherence interventions. Future adherence research would benefit from a standardization of adherence definitions and measurements.

The continuous collection of adherence data as well as other psychosocial and clinical data allowed for a comprehensive analysis of longitudinal patterns of adherence behavior. We were able to show how life events - such as moving house or city, or bouts of depression or increased alcohol intake - can quickly result in adherence problems. The future development of a prediction model for adherence patterns and clinical outcomes would provide a simple tool for clinicians working with HIV patients initiating cART. This together with the knowledge of risk factors for changes in adherence could help clinicians to enhance the care they provided to patients.

The finding that the effect of adherence is mediated by dosing frequency is new and has important clinical implications. Together with the observed increasing trend for individuals to start cART with once daily regimens, this result should be carefully considered by clinicians and patients when preparing to choose a first regimen.

These results provide a validation of the effectiveness of a simple self-report questionnaire as a causal predictor of clinical outcomes. I hope that these findings will have an impact beyond Switzerland by providing a feasible approach to future adherence research. In particular, in resource-limited settings where it is not possible to measure viral load, a practical measurement tool that is easy to implement and at the same time provides a sensitive measure of clinical outcomes would be extremely valuable.



## Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
AUC	Area Under the Curve
cART	Combined Antiretroviral Therapy
CI	Confidence Interval
DAG	Directed Acyclic Graph
DR	Doubly Robust
ETA	Experimental Treatment Assumption
HA-MSM	History-adjusted Marginal Structural Model
HIV	Human Immunodeficiency Virus
HR	Hazards Ratio
IDU	Injecting Drug Use(r)
IPTC	Inverse Probability-of-Treatment-and-Censoring
IPTW	Inverse Probability-of-Treatment-Weights
IQR	Interquartile Range
MEMS	Microelectronic Monitoring System
MSM	Men having Sex with Men
NRTI	Nucleoside Reverse Transcriptase Inhibitors
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitors
OR	Odds Ratio
PI	Protease Inhibitors
RCT	Randomized Controlled Trial
SD	Standard Deviation
SE	Standard Error
SHCS	Swiss HIV Cohort Study
SHCS-AQ	Swiss HIV Cohort Study Adherence Questionnaire
SNM	Structural Nested Models
TMLE	Targeted Maximum Likelihood Estimation
VAS	Visual Analogue Scale
WHO	World Health Organization



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## Curriculum vitae

Full Name	<b>Tracy Jans-Glass</b>
Date of Birth	October 25, 1972
Nationality	American
Marital Status	Married
Citizenship	Miami, Florida

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### EDUCATION

1990	High school diploma, Palmetto Senior High School, Miami, Florida, USA
1990 – 1994	Bachelor of Arts degree in Mathematics and Psychology, Vanderbilt University, Nashville, TN, USA
1997 – 1999	Master's of Science degree in Statistics, University of Washington, Seattle, Washington, USA
July 2006 – March 2010	PhD studies in Clinical Epidemiology, University of Basel, Basel Switzerland Title of thesis: Epidemiology and Impact of Adherence to Antiretroviral Therapy on Clinical Outcomes in HIV-infected individuals: Results from the Swiss HIV Cohort Study  Supervised by: Heiner C. Bucher (CEB), Margaret May (University of Bristol), Sabina De Geest (Institute of Nursing Science, University of Basel), and Marcel Tanner (Swiss Tropical and Public Health Institute)

### PROFESSIONAL EXPERIENCE

1997 – 1998	Teaching Assistant, University of Washington, Seattle, Washington, USA
1998 – 1999	Research Assistant, University of Washington, Seattle, Washington, USA
July 1999 – August 2001	Statistical Research Assistant, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA
November 2001 – May 2002	Statistical Consultant for GlaxoSmithKline, Iberoamerican Cochrane Center, and Institut Municipal d'Investigació Mèdica, Barcelona, Spain
June 2002 – March 2003	Statistical Contractor, Novartis Pharma, Basel, Switzerland
April 2003 – Present	<b>Biostatistician</b> , Basel Institute for Clinical Epidemiology and Biostatistics (CEB), Basel, Switzerland



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