UNIVERSIDADE DE LISBOA
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Adherence to Antiretroviral Treatment in HIV-1 infected subjects: prevalence and associated factors

Adesão à Terapêutica Anti-Retrovírica em indivíduos seropositivos para o VIH-1: prevalência e factores associados

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Summary

Introduction: Adherence to antiretroviral regimens is recognized as an essential component of treatment success and high levels are recommended. Previous Portuguese studies regarding adherence to highly active antiretroviral therapy (HAART) reported prevalence rates ranging from 46 to 91%.

Study Aims: To characterize prevalence and determinants of patient non-adherence to HAART among HIV-1 infected adult subjects followed up at the HIV outpatient clinic from *Hospital de Santa Maria* (HSM - Lisbon, Portugal).

Methods: Retrospective cohort study with a random sample of HIV-1 infected adult subjects that had at least one antiretroviral refill between 01-01-2005 and 31-12-2008. Non-adherence was defined as medication possession ratio (MPR) <95%. HAART regimens, viral load (VL), CD4 cell count and other clinical variables related to HIV/AIDS infection were retrieved.

Results: A total of 186 subjects were included in the study. Over the period 2005-2008, the proportion of MPR <95% significantly increased from 12.3% in 2005 to 25.9% in 2008 (P=0.03), being higher among injection drug users (IDUs) and subjects with depression/anxiety and during second calendar semesters, during the study period. The proportion of detectable VL has significantly decreased from 43.5% in the first semester of 2005 to 29.2% in the second semester of 2008 (P=0.01). For the analysis of non-adherence determinants in 2008, a total of 157 subjects were included. Having periods >12 months without medical appointments previous to baseline and ≤3 years of HAART experience were significantly associated to non-adherence. The majority (81.6%) of the non-adherent subjects had more than one medication gap with length <30 days. A significant decrease in the

proportion of subjects with CD4 count <350/µl and VL >40copies/ml was observed when increasing the average adherence to HAART.

Discussion: Adherence seems to be lower among IDU and subjects with depression / anxiety, and during second calendar semesters. Subjects with less HAART experience and those that had already abandoned medical appointments are more likely to be non-adherent and should have more frequent monitoring of adherence. Future studies should provide national information on adherence to HAART.

Keywords: HIV/AIDS infection; patient adherence; antiretroviral therapy

Resumo

Introdução: A adesão à terapêutica anti-retrovírica é reconhecida como essencial para o sucesso do tratamento, sendo recomendados níveis elevados. Em Portugal, estudos anteriores sobre adesão à terapêutica anti-retrovírica combinada (HAART) reportaram prevalências de 46 a 91%.

Objectivos: Caracterizar a prevalência e determinantes da não-adesão à HAART entre indivíduos adultos infectados com VIH-1 e sob tratamento, acompanhados no Hospital de Dia de Infecciologia do Hospital de Santa Maria (Lisboa, Portugal).

Métodos: Estudo de coorte retrospectivo com amostra aleatória de adultos seropositivos para VIH-1 com pelo menos uma dispensa de medicação antiretrovírica entre 01-01-2005 e 31-12-

2008. A não-adesão foi definida como razão de posse de medicação (MPR) <95%. Foi recolhida informação sobre a HAART, carga viral (CV), contagem de células CD4 e outras variáveis relacionadas com a infecção VIH/SIDA.

Resultados: Foram incluídos 186 indivíduos. Durante o período 2005-2008, verificou-se um aumento significativo da proporção de indivíduos com MPR <95% de 12,3% em 2005 para 25,9% em 2008 (*P*=0,03), maior entre utilizadores de drogas injectáveis (UDI), indivíduos com depressão/ansiedade e durante os segundos semestres de cada ano do período em análise. A proporção de indivíduos com CV detectável diminuiu de 43,5% no 1º semestre de 2005 para 29,2% no 2º semestre 2008 (*P*=0,01). Para a análise dos determinantes da não-adesão em 2008, foram incluídos 157 indivíduos. Os principais determinantes foram a existência de períodos >12 meses de falta à consulta e ter ≤3 anos de experiência em HAART. A maioria (81,6%) dos não-aderentes tiveram mais de um intervalo sem medicação com duração <30 dias. Verificou-se uma diminuição na proporção de indivíduos com CD4 <350/μl e CV >40 cópias/ml, com o aumento da adesão média.

Discussão: A adesão parece ser menor entre UDI e indivíduos com depressão/ansiedade, e durante os segundos semestres de cada ano. Indivíduos com menos tempo em HAART e aqueles que abandonaram previamente a consulta têm maior probabilidade de serem não aderentes e devem ter uma monitorização mais frequente. No futuro, propomos um estudo de coorte multicêntrico para recolha de informação nacional sobre adesão à HAART.

Palavras-chave: infecção VIH/SIDA, adesão à terapêutica, terapêutica antiretrovírica.

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Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
CDC	Center for Disease Control (United States of America)
CNSida	National Coordination for HIV/AIDS Infection
CVEDT	Centro de Vigilância Epidemiológica das Doenças Transmissíveis
ECDC	European Centre for Disease Prevention and Control
EI	Entry (fusion) inhibitors
EMA	European Medicines Agency
FDA	U.S. Food and Drug Administration
HAART	Highly Active AntiRetroviral Therapy
HIV	Human Immunodeficiency Virus
HSM	Hospital de Santa Maria
IDU	Injecting Drug Use/User
II	Integrase inhibitors
INE	National Institute of Statistics
INFARMED	National Authority of Medicines and Health Products
INSA	Instituto Nacional de Saúde Dr. Ricardo Jorge
MSM	Men who have Sex with Men
N(t)RTI	Nucleoside (nucleotide) reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
PI	Protease inhibitors

UNAIDS	United Nations AIDS program
VL	Viral load
WHO	World Health Organization

Context of the Dissertation

This dissertation is part of the pilot study for a national, multicentre cohort study – the ATAR-VIH project – that aims to evaluate the prevalence and determinants of patient non-adherence to antiretroviral treatment, among HIV1-infected adult subjects, in Portugal.

The pilot study of the ATAR-VIH project is still ongoing and comprehends both a retrospective and a prospective phase, aiming 1) to provide a characterization of the pattern of Highly Active Antiretroviral Therapy (HAART) prescription and non-adherence, over the period from 2005 to 2008 calendar year; 2) to verify which factors may be associated to non-adherence to HAART; 3) to evaluate the completeness of the clinical and pharmacy records, and to define which variables are able to be collected from these sources, according to the study aims; 4) to gather preliminary data necessary to confirm the sample size estimation of the national study; and 5) to evaluate precision and effectiveness of different measures for assessment of adherence to HAART, and HAART change.

This dissertation integrates the retrospective phase of the pilot study and aims to address the following research questions:

- *What is the prevalence of non-adherence to antiretroviral treatment among HIV1 infected adult subjects followed up at a Portuguese HIV outpatient clinic?* (aim 1 of the pilot study)
- *Which variables are associated with this medication-taking behaviour?* (aim 2 of the pilot study)

We also aimed to evaluate completeness of the clinical and pharmacy records, according to the study variables presented in Annex IV and for the retrospective data collection (aim 3 of the pilot study). In this retrospective phase, we retrieved data from a single hospital (HIV outpatient clinic of Hospital de Santa Maria, Lisbon) to assess if a retrospective study would provide information to characterize adherence to HAART and its determinants. The sample size was calculated based in the initial assumptions for the ATAR-VIH project, which summary is presented in Annex VI.

Besides this dissertation, other analyses were conducted for the retrospective phase.

- We aimed to estimate the incidence and describe the reasons for first, second and third changes of HAART in HIV1-infected subjects. This study was proposed as a student's project in 2009/2010 scholar year and resulted in an integrated Master in Medicine' Dissertation (student: Andreia Heitor Leite). A total of 194 subjects were included, from which 136 (70.1%) had changed therapy at least once, with an incidence rate (I) of 23.4 per 100 person-year of follow-up. Furthermore, 102 (75.0%) subjects changed treatment twice (I=33.0) and 79 (77.5%) changed three times (I=34.3). First change was mainly due to adverse drug reactions, the second to immunological/virological failure and the third to resistance. Also, discontinuation was observed in 19.9% of the total number of observed HAART changes, mostly due to subjects' non-persistence to treatment. Overall treatment changes were frequent, and different reasons were observed for the three first HAART changes. A longitudinal analysis of determinants of HAART change will also be conducted as a Master in Biostatistics' Dissertation.

- Preliminary results of 60 subjects, corresponding to 1791 intervals between dispenses, were analysed. Each participant had an average of 11.4 ± 8.9 intervals with medication gaps. A 38.3% of non-adherence was determined (subjects with at least one interval with gap >30 days). However, 5% of the participants presented gaps in every interval and 92% of the patients had at least one interval with at least one day without medication. This preliminary analysis was also proposed as a student's project in scholar year 2009/2010 (student: José Alexandre Freitas). The student is now developing is Master in Medicine' Dissertation, with a focus on physician evaluation of patient adherence to HAART.

The retrospective data is still being analysed, aiming to address the longitudinal evaluation of adherence determinants and the comparison of adherence measures. As for the prospective phase of the pilot study, data from clinical records was complemented through patient's and physician's questionnaires. It is now being conducted at the HIV Outpatient Clinic of the *Hospital de Santa Maria.*

- Synopsis

In **Chapter I – General Introduction**, we contextualize the dissertation research questions and its relevance, by providing a brief review of HIV/AIDS infection main characteristics and treatment options (section I.1) and the impact of non-adherence on HIV infection outcomes (section I.2). We also review the heterogeneity and consequent difficulty in defining and measuring patient adherence to antiretroviral treatment, followed by a summary of variables that have been described in previous studies as associated to non-adherence (section I.2). Then, we introduce the Portuguese context with an attempt to update disperse data related to

the epidemiology of HIV/AIDS infection and to the antiretroviral expenditure (section I.3). In this final introductory section, we summarize similar Portuguese studies on patient adherence.

In **Chapter II – Study Objectives** and **Chapter III – Study Design & Methods**, we present the dissertation aims and methods, as part of the retrospective phase of the pilot study of the ATAR-VIH project.

In **Chapter IV – Results**, we present and discuss the results of the analyses addressing the dissertation research questions. First, we aimed to describe trends of patient non-adherence and HAART prescription, over the period 2005-2008. Next we assessed determinants and patterns of non-adherence, for those subjects that were prescribed to HAART during 2008. We also explore the impact of non-adherence, in terms of virological and immunological outcomes. Hence, we assessed the following specific aims:

Section IV.1. Antiretroviral Prescription and Adherence in a Portuguese Cohort of HIV-1 infected subjects: an overall analysis of changes over the years 2005 - 2008

We aimed to evaluate the trends in patient non-adherence to HAART over the period 2005-2008, for overall population receiving HAART and among the groups that had a clinical record of past or current injection drug use, a clinical record of past or current depression or anxiety or that had started antiretroviral treatment with a pre-HAART regimen. We also aimed to analyze trends in the proportion of subjects presenting detectable viral load, as well as to assess the HAART prescription pattern for overall population, regarding antiretroviral drugs and regimens, and the use of dose-fixed associations.

Section IV.2. Determinants, pattern, virological and immunological outcomes of non-adherence to HAART in a Portuguese cohort of HIV-1 infected subjects

A second analysis aimed to identify the determinants of patient non-adherence to HAART during 2008, among subject characteristics, aspects of health care utilization, and other variables related to treatment and HIV infection. We also aimed to identify possible patterns of non-adherence to HAART, namely, to assess how frequent it is for a subject to be without antiretroviral medication. Another specific aim was to analyse the association of average non-adherence and duration of medication gaps, with immunological and virological outcomes, defined as CD4 cell count <350/µl and viral load >40 copies/ml, during 2008.

Finally, **Chapter V – General Discussion & Future Research** aims to present an overall perspective and main conclusions of the study presented in this dissertation. We also present and discuss the results related to the evaluation of clinical and pharmacy records' completeness.

Chapter I

General Introduction

I.1.

A brief review of HIV/AIDS infection immunopathogenesis and antiretroviral treatment

Infection with Human Immunodeficiency Virus (HIV) leads to a chronic infection characterized by a long clinical latency period and progressive immunodeficiency. The destruction of the immune function may result in opportunistic infections, autoimmune diseases and malignancies, as well as clinical manifestations related to the virus itself [1].

- HIV-1 replication cycle and immunopathogenesis

Figure I.1.1 describes the replication cycle of HIV and targets for antiretroviral drugs [2]. After binding and fusing to the cellular membrane of Lymphocytes T, via CD4 molecules and chemokine receptors (CCR5 and CXCR4), the HIV-1 core enters the host cell and viral RNA and enzymes are released. Then, viral replication occurs through a reverse transcriptase, which synthesizes proviral DNA. The reverse transcriptase is highly prone to errors and the HIV mutations lead to viral resistance to the host's immune system and to antiretroviral drugs. Proviral DNA is transported to the nucleus and integrated into the host DNA, through the HIV integrase. At each cell division, a duplication of the integrated proviral DNA occurs along with the host DNA, followed by the transcription to viral RNA and translation to HIV proteins. The HIV proteins are assembled into HIV virions at the inner cell membrane and released from the cell surface. At the end, a protease cleaves viral proteins, converting the immature virion into a mature viral form [2, 3].

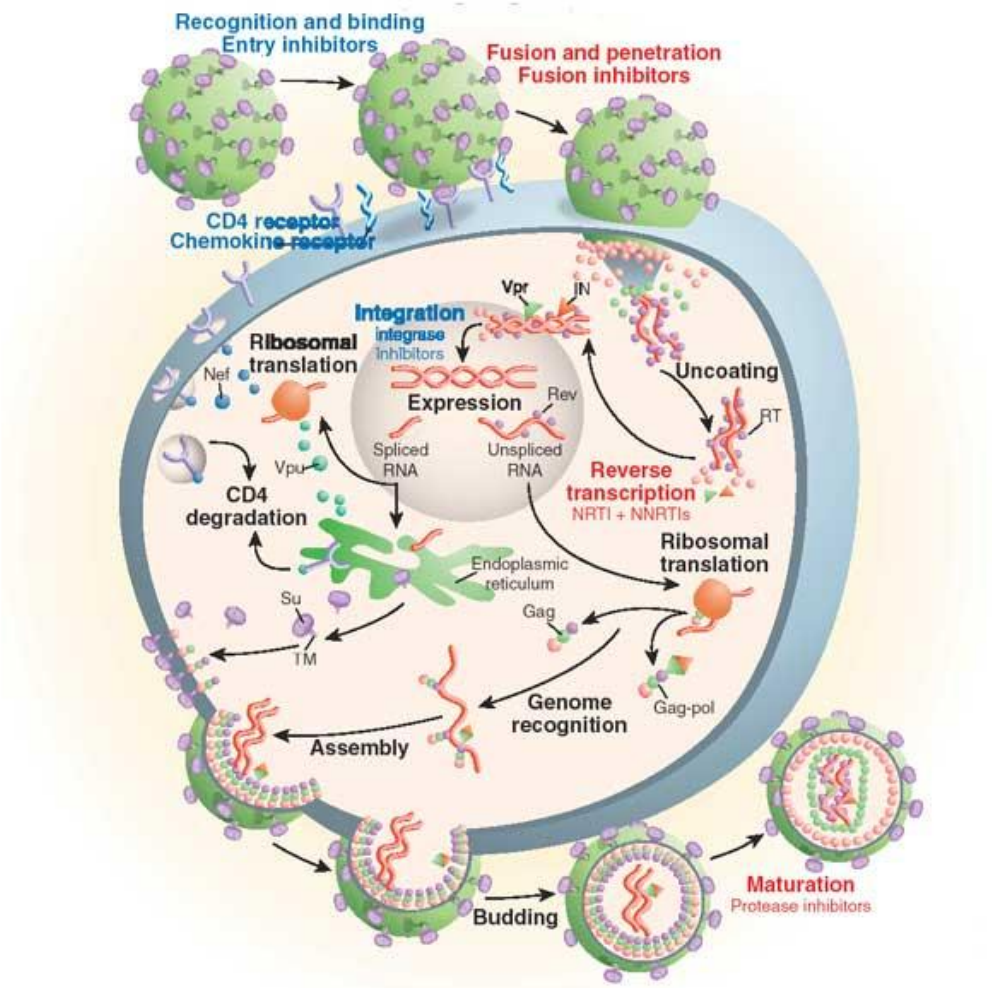

Figure I.1.1. HIV replication cycle, and targets inhibited by antiretroviral drugs [**2**].

The HIV infection is associated with several changes at the immune system level, mainly related to the CD4 cell depletion, which may result from the direct cytotoxic effects of HIV replication, cell-mediated immune cytotoxicity or thymic damage that impairs lymphocyte production [4]. When the CD4 cell count decreases to <350/µl, immunity is compromised, and when <200/µl the patient is at increased risk of various opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, and neoplasms such as lymphoma and Kaposi's sarcoma. HIV infection can affect the humoral immune system, with hyperplasia of B-lymphocyte in

lymph nodes and lymphadenopathy, and it may also disrupt nonlymphoid monocytic cells, such as blood monocyte, tissue macrophage, and nervous microglia. As a result, there is an increased susceptibility to infections by encapsulated bacteria, and HIV meningitis and peripheral neuropathy may develop [5].

The average time from acquisition of HIV to an AIDS-defining event is 8 to10 years, without treatment (Figure I.1.2). After the primary HIV infection via the mucosal or parenteral route, an increase in viral load and a decrease of T-cells expressing CD4 antigen are observed, sometimes with fever, diarrhoea and lymphadenopathy. An immunological response occurs in weeks, resulting in partial control of viral replication [6, 7].

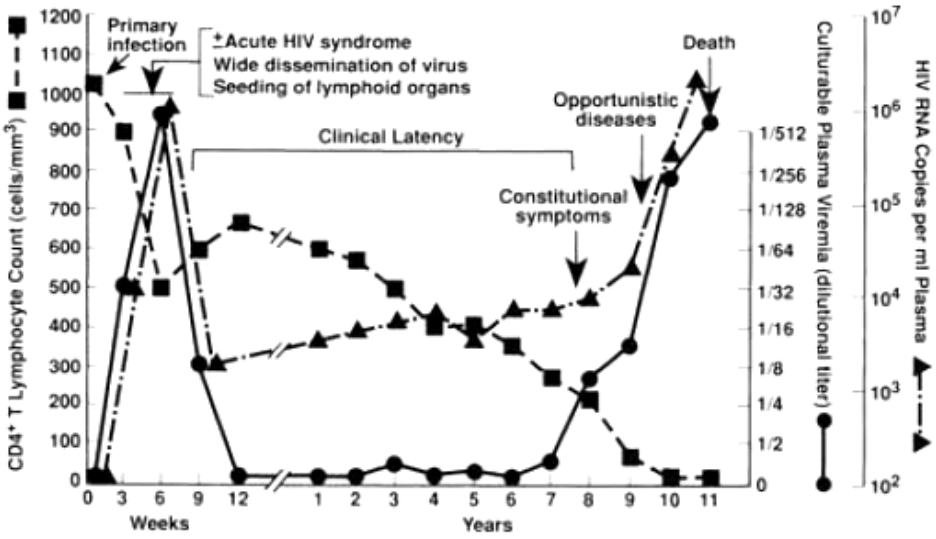

Figure I.1.2. Natural history of HIV-1 infection: evolution of CD4 cell count and plasma viremia [**6**].

The prognosis of HIV-infected persons is defined by combined measurement of plasma HIV-1 RNA and CD4 cells [8], even though the observed changes in plasma levels are poorly indicative of the much higher activity in lymphoid tissue [7]. Viral load, expressed as HIV RNA copies/ml, stabilize after about 6 months at set points that average 30000 to 100000

copies/ml. After this point, a seroconversion occurs but the immune response cannot fully control the infection due to the development of mutant forms of HIV. Thus, the 6-month viral load is a relevant prognostic indicator of the disease progression: the higher this set point, the more quickly the CD4 count decreases to levels <200 cells/μl that compromise immunity and results in the opportunistic infections and other AIDS-defining events [7, 8]. In fact, the clinically asymptomatic period of 8 to 10 years is not a "latent" period since viral replication and immunological decline also develops during this period.

Different clinical models were proposed to the dynamics of virus replication and of CD4 cell turnover. The use of antiretroviral drugs and the introduction of HAART may enable a better comprehension of HIV immunopathogenesis, including the processes that contribute to the CD4 cell recovery during treatment [7, 9].

- Antiretroviral treatment

It is recognized that antiretroviral therapy and prophylaxis against opportunistic infections have markedly improved the overall prognosis of HIV disease at individual level [10]. As a result, the availability of potent combination antiretroviral regimens is associated to a significant reduction in HIV–associated morbidity and mortality in the developed world [11,12]. This was early observed in 1998, for the US data (Figure I.1.3), when the reductions in mortality and in the hospitalization of HIV-infected patients were clearly related to specific antiretroviral regimens, namely those with protease inhibitors [11].

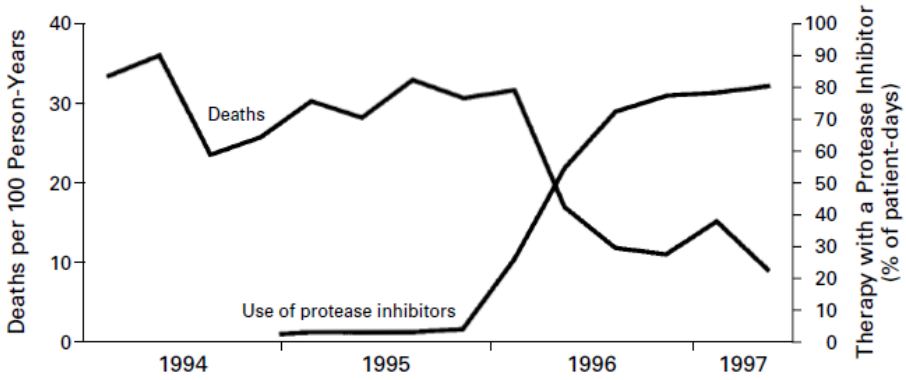

Figure I.1.3. Mortality and frequency of use of combination antiretroviral therapy including a PI, among HIV-infected patients with <100 CD4 cells/mm^3 [11].

Antiretroviral treatment aims to reduce the viral load and to restore the CD4 count and the immune function. It has undergone considerable changes (Table **I.1.1**), from early monotherapy with zidovudine, until the number of antiretroviral options that are available nowadays [2, 13].

Table I.1.1. Timeline of advances and approvals in HIV treatment in Europe (adapted from 2, 13, 14)

Year	Advances	ARV generic name (year of EMA approval)	ARV class
1981	• Recognition of a new disease to be known as AIDS	-	
1982	• Disease recognition hampered by lack of diagnostic tests • Clinical diagnosis was the only tool available	-	
1983	• Isolation of the HIV-1	-	
1985	• Isolation of the HIV-2	-	
1987	• First FDA-approved therapy directed against HIV-1	1990, Zidovudine*	NRTI
1991	• Additional NRTIs ready for FDA approval	1992, Didanosine*	NRTI
1994	• Shortcomings and limitations of monotherapy noted • Clinical trial revealed that use of zidovudine in pregnancy markedly reduces HIV-1 transmission to neonates	1994, Zalcitabine*	NRTI
1995 - 1997	• Initial understanding of HIV-1 viral dynamics • Release of the first protease inhibitors in triple combination therapy (HAART) - 1996 • Dissemination of plasma viral load testing • First NNRTI is approved by the FDA	1996, Stavudine 1996, Lamivudine 1996, Saquinavir-HCG 1996, Ritonavir 1996, Indinavir	NRTI NRTI PI PI PI

Year	Advances	ARV generic name (year of EMA approval)	ARV class
	• Ongoing declines in AIDS incidence and death in developed countries, primarily due to availability of HAART • Recognition of limitations of HAART: development of resistance and adverse effects of therapy		
1998	• Recognition of HIV latency and reservoirs • Restoration of immune function with HAART • Finding that initial treatment with efavirenz-based regimens was at least as effective as with protease inhibitors	1998, Nevirapine 1998, Nelfinavir 1997, Delavirdine** 1998, Lamivudine+ Zidovudine 1998, Saquinavir	NNRTI PI NNRTI 2NRTI PI
1999	• In treatment-experienced patients with virological failure, adding two active drugs is more likely to result in suppression than adding one • Use of new combinations of agents added to HAART, in an attempt to eradicate HIV-1 from infected subjects	1999, Efavirenz 1999, Abacavir	NNRTI NRTI
2000	• Greater understanding of reservoirs making eradication of HIV unachievable with current agents • Ritonavir boosted PIs are more effective than unboosted PIs in both treatment-experienced and naive patients; they also are less likely to select drug resistance mutations • Genotypic resistance testing can guide selection of optimal salvage and initial regimens	2000, Amprenavir 2000, Didanosine (EC)** 2000, Abacavir+ Lamivudine+Zidovudine	PI NRTI 3NRTI
2001	• Thymidine analogue reverse transcriptase inhibitors (especially stavudine) cause many of the long term adverse effects of HAART (neuropathy, lipoatrophy, lactic acidosis), with these side effects absent in tenofovir- and abacavir-based therapies	2001, Lopinavir+ Ritonavir	PI
2002	• Prevention of HIV-1 neonatal transmission in the developed world • New guidelines for initiating HAART (CD4 <350 cells/µl)	2002, Tenofovir	N(t)RTI
2003 - 2006	• Introduction of fusion inhibitors • Need to translate progress to the developing world – Millennium Declaration • Availability of potent regimens with reduced pill burden and dosing frequency; several treatments as fixed-dose combinations • Early vaccine attempts	2003, Enfuvirtide 2003, Emtricitabine 2003, Fosamprenavir 2004, Atazanavir 2004, Abacavir+ Lamivudine 2005, Tenofovir+ Emtricitabine 2005, Tripanavir	EI NRTI PI PI 2NRTI N(t)RTI+ NRTI PI
2006 - 2008	• Several antiretroviral agents in existing and novel classes with activity against highly drug-resistant viruses are approved; use of at least 2 and sometimes 3 active agents in clinical practice, yielding high rates of viral suppression even in treatment-experienced patients • Approval of fixed-dose combination, one pill, once daily	2007, Darunavir 2007, Efavirenz+ Emtricitabine+Tenofovir 2007, Maraviroc 2007, Raltegravir	PI NNRTI+ NRTI +N(t)RTI EI II
2008 - 2010	• Increased understanding of both benefits of earlier therapy and risk of interruption treatment at high CD4 cell counts • Guidelines recommend lifelong ART for asymptomatic patients and earlier initiating HAART (CD4 <500 cells/µl) • Growing interest in 'therapeutic' vaccines, to improve the immune response to act synergistically with the antiretroviral therapy		
2011	• United Nations *Political Declaration on HIV/AIDS: Intensifying Our Efforts to Eliminate HIV/AIDS*		

* INFARMED approval. ** Unavailable in Europe (FDA approval only). ARV, antiretroviral. N(t)RTI, nucleoside (nucleotide) reverse transcriptase inhibitors. NNRTI, non-nucleoside reverse transcriptase inhibitors. PI, protease inhibitors. EI, entry (fusion) inhibitors. II, integrase inhibitors.

In fact, treatment of adult HIV infection is now based in the selection of different drugs, three or four taken in combination, an approach that is known as Highly Active Antiretroviral Therapy (HAART). There are several classes of antiretroviral drugs:

- **Nucleoside and nucleotide reverse transcriptase inhibitors [N(t)RTIs]** inhibit reverse transcription by being incorporated into the newly synthesized viral DNA strand as a faulty nucleotide, leading to the chain termination of HIV-1 proviral DNA.
- **Non-nucleoside reverse transcriptase inhibitors (NNRTIs)** bind directly to the reverse transcriptase enzyme, at a position distant from the active site, resulting in conformational changes at the active site with a resultant inhibition of the enzyme.
- **Protease inhibitors (PIs)** inhibit the viral protease enzyme responsible for the maturation of immature HIV virions after being released from CD4 host cells.
- **Entry inhibitors (EIs)**, or fusion inhibitors, interfere with the binding of HIV to CD4+ receptors and chemokine co-receptors which are required for HIV to enter cells.
- **Integrase inhibitors** prevent proviral DNA from being integrated into human DNA.

The choice of specific antiretroviral drugs is based on factors such as concomitant conditions, the patient's risk to develop drug interactions and regimen potential to maximize patient's adherence to treatment. With the expansion of treatment options and evolving knowledge, guidelines from expert panels were developed for the initiation and long-term management of antiretroviral treatment in adults with HIV infection [15].

Starting HAART should be decided based on the assessment of benefits of treatment on morbidity and mortality and also of its risks, such as toxicity, resistance, drug interactions, and the convenience of life-long treatment. It is important to note that the advances in

antiretroviral drug development have changed the therapeutic risk-benefit balance. The usual recommendations are to initiate treatment when CD4 count is less than 350/µl. When CD4 count >350/µl, treatment may also be considered in conditions such as HCV treated co-infection. In addition, treatment may be considered if CD4 count >500/µl for conditions such as symptomatic HIV disease (CDC classification B). [15, 16]. The lower the pre-treatment CD4 count and the higher the HIV RNA level, the less likely treatment is to succeed, but improvement is likely even in patients with advanced immune suppression or that had already developed HIV-related cancers and opportunistic infections [15].

After starting or changing HAART, it is expected that the CD4 cell count increase by more than 50 cells/µl at 4 to 8 weeks, followed by an additional increase of 50 to 100 cells/µl per year thereafter [17, 18]. Regardless previous treatment experience, effective therapy should result in viral suppression to non-detectable values (<40 copies/ml) up to 24 weeks [15]. Viral load should be monitored frequently when treatment is initiated, in order to assess virological failure. Resistance testing should be performed while the patient is receiving the failing regimen. In fact, if a patient was not on HAART recently, the full extent of resistance may not be apparent through resistance testing, but strains with resistance mutations often re-emerge when resuming treatment [19].

Once the viral load is suppressed for a year and CD4 cell counts are stable at ≥350/µl these markers can be monitored at intervals of up to 6 months. During treatment, other factors should be also monitored, such as adherence, interactions, and adverse reactions. If virological rebound occurs, poor adherence and drug interactions, as well as concurrent infections and recent vaccination, should be reviewed before the decision of changing HAART [15].

Interactions with antiretroviral drugs should always be checked before any new drug is started, to prevent toxicities and loss of efficacy. Interactions may also occur between different antiretroviral drugs, resulting in either synergistic increase efficacy (e.g., ritonavir boosted-PIs) or decreasing it (e.g., NRTI combinations).

On the other hand, antiretroviral drugs may be associated with several adverse effects, such as anemia, pancreatitis, hepatitis, and glucose intolerance, as well as hyperlipidemia and other metabolic changes among other reactions. Patients should be monitored regularly, both clinically and with appropriate laboratory testing, especially when new drugs are started or unexplained symptoms develop. In fact, if persistent adverse effects occur, delaying HAART switch may affect adherence and promote the emergence of resistance [15].

In the last decade, several advances regarding knowledge about HIV/AIDS infection pathogenesis and antiretroviral treatment were achieved. There are more drugs and fixed-dose associations available, and drug development continues to evolve. There was also a continued effort to assess complications or disease states associated with HIV or its treatment, alongside with the identification of non-AIDS events as a major cause of morbidity and mortality in people living with HIV. In fact, it has been showed that AIDS can be prevented with HAART, and recent evidence also indicates that early ART initiation may reduce the insidious damage during asymptomatic HIV infection, thus preventing AIDS and non-AIDS events [16].

On the other hand, maintaining patient's adherence to treatment, assessing and preventing drug resistance, toxicity and clinical manifestations related to both the drugs, to the HIV infection or to the increased survival of the subjects had increased the complexity of the medical follow-up. Hence, despite the above mentioned advances - and of other recent

achievements in the development of a HIV vaccine -, clinical management of the HIV/AIDS infection remains a challenge.

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I.2.

Adherence to Antiretroviral Treatment in HIV infection

The introduction of HAART in the mid-1990s has led to significant reductions in HIV-related morbidity and mortality, transforming HIV infection into a chronic medical condition [1,2]. However, effective suppression of viral replication cannot be achieved if patients do not take their prescribed regimens, thus patient adherence to therapy is considered a major determinant of HAART effectiveness [3, 4]. In fact, it has been demonstrated that adherence is fundamental to achieve viral suppression and avoid rebound [5, 6], to increase levels of CD4 cell counts [7] and to minimize the risk of drug resistance [8], progression to AIDS [17] and of death [9, 10]. The costs of antiretroviral medication are high but cost-effective, since high levels of adherence were associated with decreased healthcare utilization and related costs, namely direct costs due to hospitalizations, in different settings [11, 12]. Hence, adherence to HAART is recognized as an essential component of individual treatment success and maintaining adherence is necessary to maximize the benefits of treatment [13, 14]. Although the minimum cut-off for HAART adherence is not clearly established [15], it usually ranges between ≥90% and ≥95% [16, 17].

Nevertheless, assessing adherence remains a challenge. Besides being a complex and dynamic behaviour, there are several definitions and measures to evaluate patients' adherence to HAART, which may lead to misclassification and unclear public health messages, in both clinical and research settings [18, 19]. The 2011 European AIDS Clinical Society recommendations for the HIV management and treatment state that adherence barriers should

be assessed alongside with the patient's readiness to start HAART and that adherence' problems should be screened in each medical appointment [16]. Thus, physicians should be provided with efficient, practical, and inexpensive measures to identify subjects in need of adherence interventions [19]. On the other hand, HIV researchers and public health professionals require accurate estimates of rates and predictors of poor adherence, to identify high-risk populations that would benefit from adherence interventions as well as to verify its efficacy and effectiveness [19]. The use of different adherence measures can lead to discrepancies in conclusions about adherence rates and predictors of adherence, a problem that may even be more relevant in poor-resource settings, where second line antiretroviral options are limited if resistance occurs [17, 20].

- Defining Adherence to Treatment

The World Health Organization (WHO) defines adherence to long-term therapy as "the extent to which a person's behaviour – taking a medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [18]. Nevertheless, adherence is usually considered as related to medication, at both clinical practice and research settings, and several definitions have been proposed to describe the medication-taking behaviour [21]. Adherence was first described as patient compliance, regarding "the extent to which a person's behaviour coincides with medical healthcare or health advice", a definition proposed in 1979 by Haynes *et al.* [22]. In the following years, patient compliance was associated with a negative and judgmental connotation of the patient, which led to the introduction of the term adherence [23]. The definition adopted by WHO aimed to recognize patients as active collaborators in the treatment process, but both terms are

frequently used as synonyms, revealed to be uninformative, and its application to patients who do not consume all medication at the desired time can stigmatize them and impact their future relationships with health care providers [23,24]. Concordance is a recent and wider term that focuses in the process in which physician and patient agree on therapeutic goals and decisions, referring to the extent to which patients are successfully involved in shared decision processes about medication and medication intake [23,25]. However, concordance is difficult to be quantified as it may be considered as an ongoing process, and compliance or adherence are the recommended terms when assessing the intensity of medication intake [23,25]. For instance, a recent study has found that physician-patient concordance in HIV treatment decision-making was associated with greater adherence, although stating that more research is needed to clarify the relationship between concordance and adherence [26].

It is recognized that non-adherence to HAART can take many different forms. The patient may unintentionally fail to fill the prescription, forget a dose or may take it incorrectly because misunderstanding or forgetfulness of health professional's instructions. On the other hand, non-adherence may also be defined as intentional, when patients consciously self-adjust their regimen or prematurely terminate the medication, because of side-effects and toxicity, personal beliefs or convenience [18,27]. As a consequence, intentional versus unintentional non-adherent HIV-positive patients may struggle with different adherence determinants, requiring different interventions [27].

Finally, another feature of medication-taking behaviour is related to its dynamic and variability through different moments of patients' dosing histories [28]. As shown in Figure

I.2.1, it has been proposed a new definition of adherence that comprehends three main attributes associated with medication-taking behaviour [28]:

- acceptance, representing if whether or not the patient ever starts the treatment;
- compliance, also described as "quality of execution" [29] and defined as the extent to which the patient's drug dosing history conforms to the prescribed regimen;
- persistence, defined as the time between the first and the last dose or time between the first dose until the compliance fall below a defined minimal level.

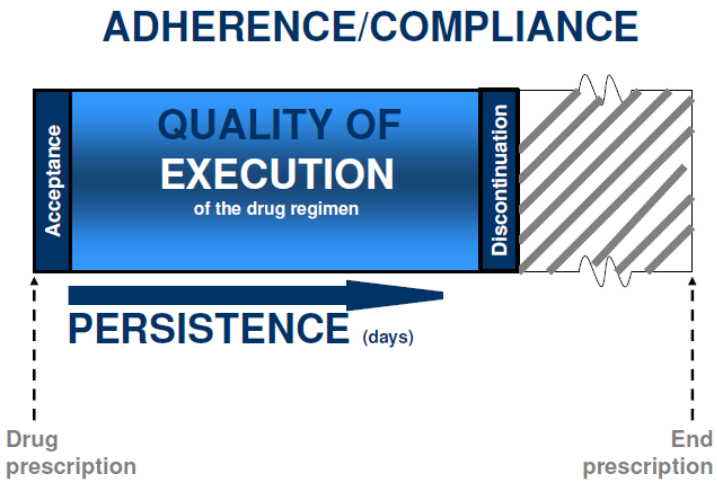

Figure I.2.1. Attributes of patient adherence to treatment [30].

Regarding antiretroviral use for the HIV/AIDS infection, an adherent subject should accept and maintain the prescribed regimen, with a high compliance level [28]. We have found few studies on HAART acceptance, mostly related to evaluation of access to HAART in poor-resource settings [31,32]. On the other hand, evaluating compliance seems to be a more common approach. A recent meta-analysis has reviewed eighty-four observational studies on adherence assessed mainly as compliance [17]. With the inclusion of studies conducted across twenty countries, the average rate of subjects who reported ≥90% adherence to HAART was

62%. Persistence on HAART seems to have been less assessed [33]. A 2000 study quantified persistence rate at 12 months of 87% among a cohort of 100 HIV-infected subjects, followed at a regional HIV treatment centre in Canada [34]. Other studies have assessed treatment interruptions and its association with virological failure. In a cohort with 8.3 years of median duration of follow-up, 43% of the subjects had an interruption longer than 3 days, therefore with a higher risk of treatment failure [35]. In a poor-resource setting, another study showed that 23% of the subjects had a history of treatment interruption higher than 4 days which was associated with virological failure [36]. Treatment interruptions also seemed to be frequent among injection drug users, in the setting of active drug use and disruption of health care, as a study showed that 78% of individuals had one or more treatment discontinuations, and that 20% never resumed HAART [37].

- Measuring Patient's Adherence to Antiretroviral Treatment

The measurement of patient's adherence to HAART is a difficult endeavour both in clinical care and research settings [19]. There is no gold standard to measure adherence, although several strategies are available, with specific strengths and weaknesses (Table I.2.1).

Some authors also classify the available measures as objective or more reliable *vs.* subjective or which information is more susceptible to being modified by patients [29,38]. Table I.2.2 presents this classification and its relation to continuous assessment over time.

Table I.2.1. Characteristics of the available methods to assess adherence [19, 24, 39].

Method	Advantages	Disadvantages	Challenges and Comments
Measurement of the level of medicine or metabolite in blood **-** ***Therapeutic Drug Monitoring***	• Objective, direct adherence measure • Plasma concentration directly determines virological response • May allow for detection or prevention of drug toxicity • May be advantageous for populations at risk for altered pharmacokinetics	• Susceptible to variations in metabolism and "white-coat adherence" • Only provides information of recent adherence • Expensive • Invasive • Non-standard procedures for collection, testing and interpretation • Cannot routinely measure NRTI levels because active metabolites are intracellular • Levels may be low for other reasons than non-adherence • Higher plasma levels may be necessary to suppress replication of resistant virus	• Standardize of procedures for collection, testing, and interpretation • Develop protocols for quality assurance • Determine optimal monitoring frequency • Determine optimal parameters (e.g., minimum concentration, ratio of an individual's level to a population or expected level, or area under the concentration-time curve)
Patient questionnaires, patient diaries, patient self-reports	• Simple • Inexpensive • Useful and easily implemented in clinical settings • Moderate correlation with virological outcomes • Allows discussion of reasons for non-adherence • Low participant burden • Patient diaries help to correct for poor recall	• Susceptible to error with increases in time between visits • No standardized questions • Overestimates adherence • Relies on recall of forgotten events • Vulnerable to social desirability bias • Poor sensitivity	• Mitigate ceiling effect • Include measurement of all aspects of adherence (e.g., dose-interval) • Continue to rigorously develop and test new measures (e.g. cognitive interviewing or item response theory)
Pill count	• Objective, quantifiable, and easy to perform • Moderate correlation with virological outcomes	• Time consuming • Inappropriate for most clinical settings • May overestimate adherence • Vulnerable to "pill dumping" • Difficult to determine refill start date • Assumes no medication stockpile or alternative supply	• Manage logistic challenges of unannounced pill counts
Prescription / Pharmacy refill	• Objective • Data are easily obtained in "closed pharmacy systems" • Moderate correlation with virological outcomes • Allows for population level analyses • Immune to social desirability, recall bias, and tampering	• Feasible only in "closed pharmacy systems" • May poorly adherence • Cannot measure dose-interval adherence • Cannot differentiate non-adherence from other forms of treatment interruptions (e.g. discontinuation by provider)	• Evaluate use in "open systems" • Determine optimal method for evaluate adherence

Method	Advantages	Disadvantages	Challenges and Comments
		• Assumes that patients have one source of medication • Assumes that medication acquisition reflects adherence - a prescription refill is not equivalent to ingestion of medication • No standard method for operationalize adherence • Not useful if refills are mailed automatically or if several months' supply is dispensed at one time	
Electronic medication monitors	• Precise • High sensitivity • results are easily quantified; • Best correlation with virological outcomes • Allows analysis of dose-interval adherence and patterns of adherence over time	• Expensive • Not feasible for most clinical settings • May underestimate adherence • Vulnerable to technological malfunction • Potential for selection bias • High participant burden • Potential Hawthorne effect	• Understand interventional effect • Accurately censor of data (e.g. standard questions about periods of non-use, "pocket doses," or "curiosity openings") • Develop evidence based guidelines for use, quality control, and data management
Clinical response - *viral load and CD4 cell count*	• Objective • High sensitivity • Applicable in poor-resource settings	• Factors other than medication adherence can affect clinical response	
Directly observed therapy	• Most accurate	• Patients can hide pills in the mouth and then discard them; • Impractical for routine use	• Interventional rather than a observational measure of adherence

Table I.2.2. Classification of the different methods to assess adherence [29,38]

	Provide information about aggregate medication omissions but unable to show when omissions occurred	Continuous assessment of adherence over time
Susceptible to censorship of the data by the patient	• Pill counts • Self-report questionnaire	• Patient diary
Reliable / Objective	• Therapeutic drug monitoring • Pharmacy refill data	• Electronic monitoring

Self-reports

Patient self-reports of adherence is one the most commonly used measure in both clinical and research settings, due to its low burden, being inexpensive and, in clinical setting, allowing the physician to review patient's reasons for missed doses [19]. Simoni *et al.* (2006), found that self-reported adherence was significantly correlated with viral load in 84% of comparisons, while Nieuwerk *et al.* (2005) found that the pooled odds ratio of having detectable HIV viral load was 2.31 in non-adherent patients compared to adherent patients [40,41]. However, self-report measures tend to overestimate adherence, due to a recall provider and social-desirability bias [42]. Also, some patients often improve medication-taking behaviour around a scheduled medical appointment, drug monitoring or viral load assessment. This is defined as white-compliance and can only be identified when considering adherence as a continuous variable [18]. Other factors that may contribute for this "ceiling effect" are questions' misinterpretation and poor or differential recall between adherents and non-adherents [19]. Self-report shows lack of sensitivity for identifying non-adherence, and even specificity may also be affected by inaccurate reports among patients who report missing doses [19]. Finally, there is a high variety of self-report questions and the lack of standardization on aspects such as time frames, questions and response tasks indicates a need to optimize and validate this measure [42].

Providers' Assessment

In the clinical setting, physicians often estimate patients' adherence to HAART, but evidence suggests that estimates made by health care providers are frequently inaccurate and may return an overestimated adherence [43,44]. In fact, many providers believe that factors

associated with socioeconomic status, such as lack of education and poverty, are good predictors of non-adherence. However, predictors of adherence vary greatly across populations and settings and no factor has been consistently associated with non-adherence across all studies [18].

Patient self-reports

Pill counts can be conducted at clinical appointments or scheduled visits, to which the subject brings his medication [19,39]. The assessment of adherence based in pill counting is calculated by counting the remaining doses of medication since the start date of the prescription and assuming that remaining pills in excess of what is expected represent missed doses [45]. This measure has shown moderate correlations with viral load but its sensitivity is compromised by patient's "pill dumping" that leads to an overestimation of adherence. Other factors that limit the use of pill count in clinical practice are the inability to define a start date for the prescription or to correctly count medication when the patient uses multiple pill containers, as well as the lack of time during the clinical appointment to perform this assessment [19]. Subjects may also perceive pill counting as intrusive and suggestive of lack of trust in their self-reported adherence [19]. In the research setting, unannounced pill counts remain costly and often impractical, and the above mentioned problems are prone to happen, even though the bias due to pill dumping may be reduced [19,46]. Nevertheless, recent studies have evaluated unannounced phone-based pill count, which seems to offer an economically and feasible method for monitoring medication adherence, providing estimates that are associated to patient viral load [46,47].

Biological assays and Therapeutic Drug Monitoring

Biological assays are direct ways of measuring adherence to antiretroviral therapy that may be feasible in clinical and research setting [19]. When performed by a quality-assured laboratory, monitoring of PI and NNRTI levels may be useful to minimize toxicity and adverse effects, to identify drug-drug interactions, or to evaluate virological failure in the absence of resistance in patients such as those with renal or liver impairment [15]. Nevertheless, the relevance of therapeutic drug monitoring (TDM) in patients' management remains controversial, and the existing evidence is not enough to recommend that the drug levels should be checked in all patients who use antiretrovirals [15, 48]. Thus, although low drug levels have been associated with virological failure, a recent review shown that the included studies were underpowered to show outcomes of TDM compared with standard of care [19,48]. When used to assess adherence, TDM provide limited information: due to short half-lives of antiretroviral medication, it can only assess adherence for the most recent doses taken and white-compliance may occur [19, 49]. The evaluation of TDM value is also constrained by heterogeneity of procedures for sample collection, cross-validation of analytic procedures, and interpretation of assay results, as well as the poor uptake of expert recommendations by the physicians [19,48,50]. Also, other factors besides adherence may affect drug levels, such as drug interactions and patient variability of pharmacokinetics parameters [48,50].

There are other surrogate markers being evaluated, although with limited use in clinical practice [51]. An increased mean corpuscular volume has been associated with zidovudine and stavudine treatment [51, 52]. One study identified an association between serum lactate levels with viral suppression in children receiving NRTI or PI, suggesting that elevated lactate levels may be useful in evaluating adherence [53]. Recently, antiretroviral concentrations in hair samples were associated to virological outcomes and presented as a patient-friendly

method to be used in the identification of subjects in need of adherence' interventions or resistance testing, in poor-resource settings [54,55].

Electronic Drug Monitoring

Prescription refills and electronic monitoring systems relay on patients' having medication and actually taking it. Electronic monitoring has been considered by some authors as the gold standard method, associated with virological outcomes and presenting a high sensitivity in the estimate of non-adherence [28,29,56]. Another advantage is its ability to examine patterns of adherence over time and dose-interval adherence [45,57,58]. In fact, a recent study showed that a mean dose-timing error $\leq$ 3hours over a one-month period was independently associated with viral suppression, and this time precision is only possible with a continuous measurement of medication intake [5]. It also seems more feasible when compared to unannounced pill counts, and with a moderate correlation with self-report estimates [59, 60].

The 'electronic medication event monitoring' is obtained by incorporating micro-circuitry into pharmaceutical packages (for instance, a bottle), such that the manoeuvres needed to remove a dose of drug are detected, time-recorded, analysed, stored and communicated to the appropriate caregiver. In this way, it is assumed that each opening corresponds to a dose intake and average adherence is determined by dividing the number of time-appropriate openings by the number of expected doses over the study period [29].

However, this method presents potential limitations at methodological and feasibility levels, besides its high costs [19]. Underestimates of medication adherence may result from inappropriate use of the device or "pocket dosing", e.g., the act of removing more than one dose for each bottle opening and pocketing the extra doses to ingest at a later time [61].

Overestimates of adherence may result from "curiosity opening", e.g., opening the monitored pill bottle without removing any pills. Other sources of measurement error are being unable to assess adherence to more than one prescribed antiretroviral, as well as the number of pills withdrawn at each opening [61]. Studies on electronic monitoring have also shown that pill box users are more reluctant to travel with this device, and that some subjects felt uncomfortable using it in front of others, perceptions that may lead to a biased estimate of adherence [19,62].

Another important feature of electronic monitoring is that it seems to promote an improvement in patient adherence in the first months of assessment, suggesting that a short-term electronic monitoring period is insufficient to obtain valid data [63, 64].

Other factors that can affect validity of electronic monitoring data are related to the optimal interval between adherence data downloads, to the HAART discontinuation by the physician and to the inclusion of periods of time when a subject is not responsible for his or her medication taking (e.g., hospitalizations, incarceration, drug treatment programs). Based in a predefined and clear algorithm, it is possible to adjust electronic monitoring data based on additional patient information [65].

Pharmacy Refills

Pharmacy data have been used to assess adherence for several chronic treatments [66]. The use of pharmacy refill counts to assess medication adherence has been increasing, due to the availability of accurate data in a less expensive way than previous measures [67,68]. Considering that data is easily obtainable from electronic records without additional efforts from the subjects, it is possible to perform retrospective assessments of patient adherence,

namely in those settings where an evaluation method was not early defined [69]. It also provides objective estimates on account of being less susceptible to patient recall or social desirability bias, which are disadvantages of self-reports [66].

Pharmacy refill provides assessment of medication possession, based on refill dates and on the number of doses that were provided to the patient [68]. The evaluation of patient adherence assumes that patient will use a given drug starting the day of prescription refill, as prescribed and until medication runs-over [68]. On the other hand, if a subject does not receive timely refills, it is assumed that he is missing doses or not taking the medication during this period of time. This premise may be invalid if patients are obtaining medication in free samples, family and friends or from other pharmacies [19,70].

Nevertheless, the relationship between antiretroviral adherence and HIV-related clinical outcomes was mainly established with the results of large pharmacy refill studies [19, 66]. In 1999, Maher *et al.* showed that patients who consistently refill antiretroviral prescription for longer than 4 months, were significantly more likely to achieve viral suppression and better immunological outcomes than were less-adherent patients [71]. Pharmacy refill measures were also associated with viral load and CD4 cell count [7, 72], as well as with the risk of drug resistance and progression to AIDS and death in several studies [8, 9]. In fact, Low-Beer *et al.* (2000) found a significant dose-response relationship between adherence to PIs and virological failure, in which 84% of the subjects showing pharmacy adherence ≥95% had undetectable viral load whereas only 64% of those with adherence between 90% and <95% achieved this clinical outcome [72]. In the same year, Paterson *et al.* (2000) presented a similar study based on electronic monitoring, with similar results [14].

Other studies with assessment of adherence through pharmacy refills have shown different impact in viral load and drug resistances according to individual drug classes. Nachega *et al.*

(2007) have observed that, for NNRTI-based regimens, virological outcomes improved with lower adherence levels (beyond 50%) than the one defined for PI-based regimens [73]. Regarding drug resistance, Tam *et al.* (2008) described that cumulative resistance among PIs and NRTIs showed a weaker adherence-resistance relationship, compared to lamivudine and NNRTIs [74, 75].

Even though most of the studies that have used pharmacy refill data have been conducted in developed countries, there is now some evidence that this method may also be feasible and valid in developing world [66]. A recent study conducted in Côte d'Ivoire showed a pharmacy-measure of adherence to be strongly associated with virological outcomes, thus recommending its use at month 6 of follow-up, to identify patients who might benefit from interventions to reinforce adherence [76]. Other studies have also demonstrated that refill adherence estimates were associated to CD4 cell counts and were accurate for detecting virological failure, in patients receiving HAART from countries in southern Africa, thus recommending the inclusion of adherence-based monitoring approach in poor-resource settings [77, 78].

Several measures and definitions of adherence have been described in studies conducted using automated pharmacy databases (Table I.2.3), with differences that would be expected to make the comparison of results difficult [79]. Some methods assess the duration or continuation of drug refills while others assess the sufficient amount or timely refill of medication within a period of consecutive refills [80]. The "anniversary model" and "minimum-refills model" are two simple and rough estimates of patient adherence that follow the first approach. The anniversary model classifies a subject as adherent based on having or not one refill at the end

of the study period. The minimum-refills model assesses if a specified number of prescriptions is refilled during the study period [81].

Table I.2.3. Adherence measures reported in studies with pharmacy refills [68,79,80]

Measure	Formula	Value	Type
CMA ***Continuous Measure of Medication Acquisition***	• cumulative days' supply of medication obtained / total days to next fill or to end of observation period	• adherence value for cumulative time period	• medication availability
CMG ***Continuous Measure of Medication Gaps***	• total days of medication gaps / total days to next fill or end of observation period	• non-adherence value for cumulative period, censored at zero	• based upon medication gaps
CMOS ***Continuous Multiple Interval Measure of Oversupply***	• (total days of medication gaps - leftovers) / total days in observation period	• non-adherence value for cumulative period, allowing for leftovers	• based upon medication gaps
CR ***Compliance Ratio***	• (total days supplied – last days' supply) / (last claim date-first claim date) x100	• adherence value for period between fills	• medication availability
CSA ***Continuous, Single interval measure of medication Acquisition***	• days' supply obtained at beginning of interval / days in interval	• adherence value for interval of study participation	• medication availability
DBR ***Days Between fills adherence Rate***	• 1 – {[(last claim date – first claim date) – total days' supply] / (last claim date – first claim date)} x100	• overall adherence percentage	• refill adherence
MPR ***Medication Possession Ratio***	• days' supply / days in period	• ratio of medication available	• medication availability
MPRm ***Medication Possession Ratio, modified***	• [total days supplied/(last claim date-first claim date + last days' supply)] x100	• adherence percentage, adjusted to include final refill period	• medication availability
MRA ***Medication Refill Adherence***	• (total days' supply/total number of days evaluated) x100	• overall adherence percentage	• medication availability
PDC ***Proportion of Days Covered***	• (total days' supply/total number of days evaluated) x100, capped at 1.0	• percentage of days with medication available	• medication availability
RCR ***Refill Compliance Rate***	• [sum of quantity dispensed over interval / quantity to be taken per day) x100] / number of days in interval between first and last refill	• overall adherence percentage	• medication availability
GAP	• total days of the maximum medication gap / total days in observation period	• non-adherence value for cumulative period	• based upon medication gaps

When considering the amount of medication provided to the patient, it is possible to evaluate medication availability (e.g. through the use of continuity measures) or potential medication gaps (e.g. discontinuity measures), in single or multiple time periods [68, 79, 80]. The comparison of these approaches in the assessment of adherence to HAART is not clear but equivalent results were shown in other chronic medication [68,80]. Thus, the choice of a specific measure should consider its potential advantages and limitations, as well as the overall goals and definitions of the study [79]. Furthermore, there are other questions to be addressed when defining how to measure adherence to HAART using refill measures, namely, whether to include or not leftover medications, to compare pharmacy refill data with prescribed treatment time, and whether to use an index drug, the lowest adherence percentage among the individual drugs in the regimen or to calculate the regimen average adherence [67]. Additionally, it is also relevant to define how to control bias due to patients receiving medication from other sources and if it is feasible to collect adherence data when patients may use multiple pharmacies [67].

More recently, pharmacy-based measures are being reviewed to account for the assessment of the dynamics of adherence and for the earlier identification of non-adherence in shorter periods of time. Gross *et al.* (2006) proposed a time-to-refill approach, by measuring adherence in each patient, across multiple prescription intervals, and found this time-updated measure of adherence was associated with viral suppression [66, 82]. This approach was recently used to assess the impact of including or not leftovers in the adherence estimates, a study that showed that 43% of the subjects were misclassified as non-adherent when disregarding leftover medication [67]. Both studies used a prescription interval of at least three monthly refills. Shorter intervals might allow more rapid detection of non-adherence in

clinical practice but if intervals are too short, they might overestimate this problem because few missed doses may decrease adherence below the defined thresholds, leading to useless interventions [66,83]. Acri *et al.* (2010) found that pharmacy refill adherence over 60-day and 30-day periods were significantly associated with virological outcomes and with 90-day adherence if these periods started at least 90 days before the measure of viral load, a finding that suggest that upstream measures of adherence are better predictors of virological outcome than adherence measured more proximally of the viral load assessment. [83].

The comparison of pharmacy-based adherence with other measures is needed. Refill adherence was compared to a 4-day recall self-report measure, and presented a higher sensitivity to non-adherence [66, 69]. On the other hand, a recent study with retrospective pharmacy data and electronic monitoring reveal a lack of association between both measures [84]. The small sample size and limitations on data availability could affect the validity of these results. Further studies are required, to reassess the relation between pharmacy refills and electronic monitoring, as well as to evaluate its predictive value of virological failure in both treatment naïve and experienced subjects receiving different HAART regimens [85].

Composite Measures and other approaches

It is usually recommended to use more than a single strategy, since "a multi-method approach that combines feasible self-reporting and reasonable objective measures is the current state-of- the-art in measurement of adherence behaviour" [17, 18].

In fact, it has been shown that pharmacy refill and pill count measures result in lower estimates of adherence than those self-reported and higher than those obtained from electronic

monitoring, which indicates a measurement error associated to each measure, and that a best method includes multiple measures [19, 51].

Composite measures may be obtained in two approaches, through the combination of information from different adherence measures or through the inclusion of adherence determinants in the final estimate.

Liu *et al.* (2001) proposed a first composite adherence score, which is based on an algorithm among different measures (Figure I.2.2) [45].

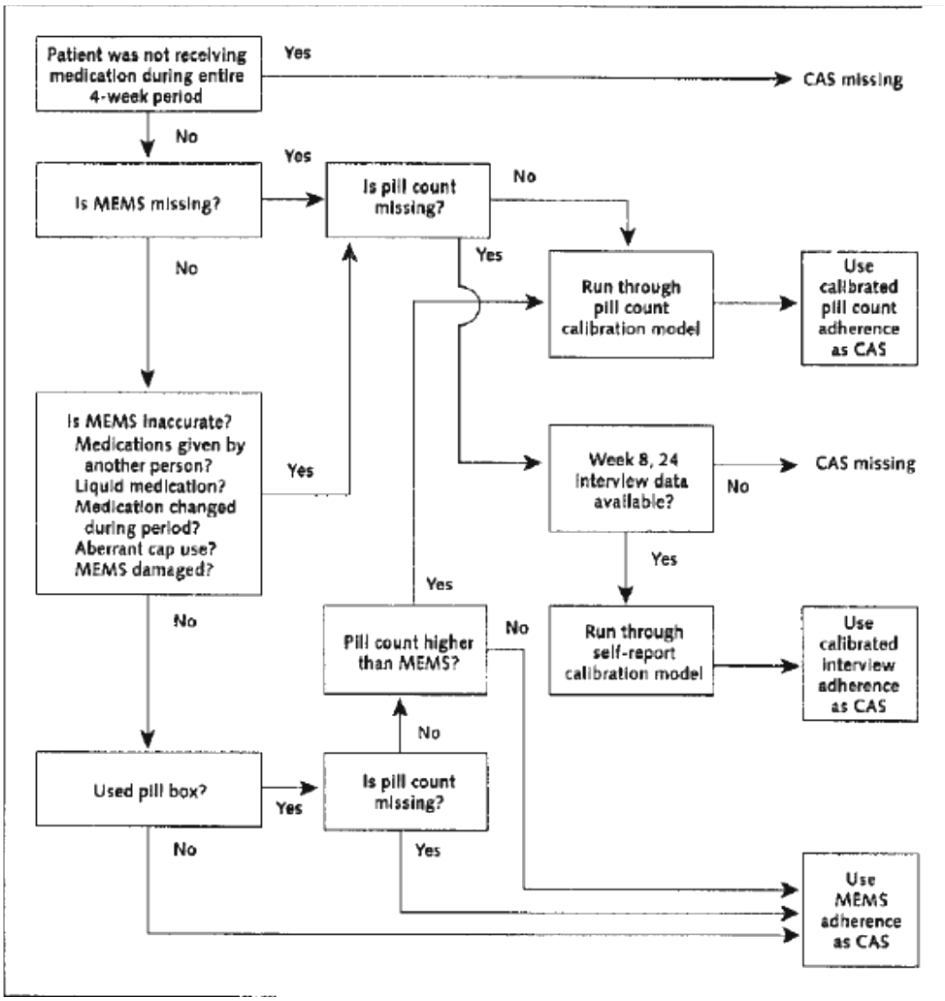

Figure I.2.2. Algorithm for calculating composite adherence score (CAS) [45].

In this model, adherence assessment is first based in electronic monitoring data that may be substituted for pill counts or self-reported data in a third option. When compared to individual measures, this composite score showed the strongest predictive relationship with viral load [45]. However, this measure relies primarily on electronically measured adherence, and minimal additional data from pill counts or patient interviews will be integrated if adherence data from electronic monitors is nearly complete, besides the high costs related to electronic devices [86].

More recently, it has been proposed that periods of non-adherence can be identified retrospectively based on the relationship between changes in viral load and mutation. However, the combination of these two clinical parameters was not compared to other adherence measures and access to and costs of sequencing limit its application in clinical setting [87].

Other studies aimed to improve the sensitivity of self-reported measures to detect non-adherence, by the use of calibration models adjusted by self-reported attitudinal measures [88]. Calibration models have been used to improve the accuracy and precision of measurement. Liu *et al.* used those models predicting electronic monitoring measured adherence to test whether multiple attitudinal measures corrected the bias from self-reported adherence, and propose a model including self-reported adherence and whether the patient were able to take medication according to the healthcare provider instructions [88]. Similar results were also found in another study, in which questions about psychosocial, clinical and environmental characteristics associated with poor adherence were combined, resulting in a composite score that had a sensitivity of 71% for detecting non-adherence [19, 89].

Modelling and statistical approaches have also been useful in evaluating the impact of adherence on the estimated exposure-response relationship and in addressing the challenges of confounding and measurement error which arise in the clinical trials context [90]. Although the calibration approach was mainly explored for categorical measures of adherence retrieved from self-reported measures, modelling may be applied to pharmacy refills data, in order to assess compliance and persistence [90]. For instance, longitudinal Markov models combined with clustering techniques can be used to describe patterns of patient adherence, to assess its determinants, and to predict the future event and progression to AIDS [90, 91].

Composite measures may improve the accuracy of adherence measurement but are still difficult to implement in clinical setting, and more practical measurement methods are needed [19, 45]. Furthermore, the research setting also requires additional data on ways to combine measures, including how many measures and time points to combine [19].

- Assessing Factors associated to Non-adherence

Four types of factors associated to patient adherence are usually described (Figure I.2.3): social and psychological characteristics of the patient, regimen characteristics, patient-provider relationship and clinical setting, and HIV infection related factors [18, 92]. Table I.2.4 describes potential factors related to patient adherence to antiretroviral drugs [18].

The association between adherence and demographic characteristics remains unclear [18, 93]. Nevertheless, some variables have been frequently described as predictors of non-adherence, namely female sex, younger age, and lower educational and literacy level [18, 92].

The association between adherence and ethnicity is unclear [18]. Some studies have shown that black ethnicity was associated to non-adherence but confounding by socioeconomic status may be present [94], since this association was not reported in other studies from countries were access to health care and antiretroviral treatment is free [95].

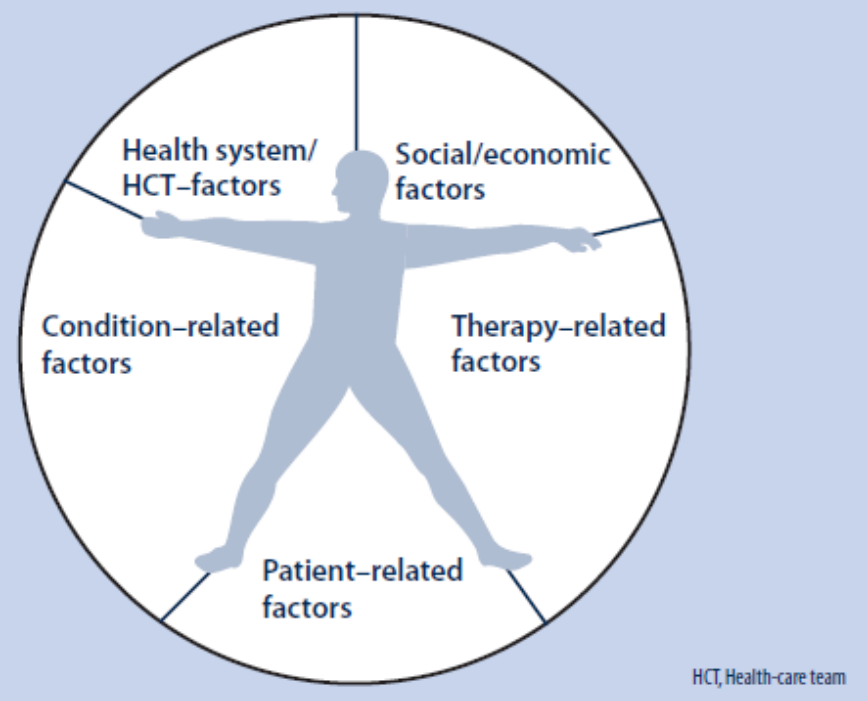

Figure I.2.3. The five dimensions of adherence, proposed by WHO (reprinted from [18]).

Among patient-related variables, factors such as being an injection drug user and active substance abuse were other variables found to be associated to non-adherence, as well as lack of social support, depression and stress [18, 96] . On the other hand, patients' knowledge and beliefs about disease and medication can also affect adherence. For instance, lower perceived effectiveness of medication and concerns that taking it might lead to disclosure of the subject's HIV condition were associated with poor adherence to treatment [92,97].

Table I.2.4. Potential factors affecting adherence to HAART, and interventions (adapted from [18, 98]).

	Factors affecting adherence	Interventions to improve adherence
Socioeconomic-related factors	(–) • women: stress of childcare • low income • lack of social support (+) • support of family and friends	• family preparedness • support of community-based organizations • intensive education on use of medicines for patients with low levels of literacy • assessment of social needs
Patient-related factors	(–) • forgetfulness • life stress • alcohol use • drug use • depression • hopelessness and negative feelings • negative beliefs about disease and medication (+) • positive beliefs regarding the efficacy of antiretroviral medication • patients' belief in their ability to take medication as prescribed (self-efficacy)	• monitoring drug and/or alcohol use • psychiatric consultation • behavioural and motivational intervention • counselling/psychotherapy • telephone counselling • memory aids and reminders • self-management of disease and treatment
Condition-related factors	(–) • asymptomatic patients • (+) • symptomatic patients • understanding the relationship between adherence and viral load	• education on use of medicines • supportive medical consultation • screening for comorbidities • attention to mental illness, as well as abuse of alcohol and other drugs
Therapy-related factors	(–) • complex regimens, pill burden • close monitoring • severe lifestyle alterations due to medication • adverse effects of treatment (+) • less frequent dose, fewer pills per day • fewer dietary restrictions • fitting medication to individual's lifestyle	• simplification of regimens • education on use of medicines / adherence • patient-tailored prescriptions • medications for symptoms • assessment and management of side-effects • continuous monitoring and reassessment of treatment
Health care team / Health system-related factors	(–) • lack of clear instructions from health professionals • poor implementation of educational interventions • dissatisfaction with past experience of healthcare system, leading to avoidance (+) • good patient-physician relationship • support of nurses and pharmacists	• promote a good patient–physician relationship • multidisciplinary care • training of health professionals on adherence education and monitoring • training caregivers • identification of the treatment goals and strategies to meet them • shared-management of HIV/AIDS infection • ready availability of information • regular consultations with nurses/physicians • non-judgmental attitude and assistance • rational selection of medications
(+) factors having a positive effect on adherence; (–) factors having a negative effect on adherence.		

The relationship with healthcare providers is also pointed out as a determinant of patient's non-adherence to antiretroviral treatment [18, 98, 99]. This relationship may be strengthened when patient perceives the healthcare provider as competent, with clear and open communication, showing compassion and willingness to include patients in treatment decisions, among other characteristics [98]. On the other hand, some identified barriers to physicians' communication with HIV-positive patients include lack of time, resources, which may affect patient adherence to treatment [100]. Promoting multidisciplinary adherence teams and training of providers in adherence counselling techniques are other healthcare-related factors that may lead to improved patient adherence [18, 96, 101].

Several studies had shown that complexity of treatment and drug side-effects are factors negatively associated with adherence [18, 92]. It is recognized that HAART regimens had evolved from multiple drugs to nowadays once-daily and more potent regimens [4, 102]. A recent meta-analysis showed that adherence was modestly higher with once-daily regimens than with twice-daily regimens, while other studies not included also showed higher adherence among subjects receiving once-daily regimens [102, 103]. Even though some questions remain about the impact of once-daily regimens on adherence to HAART, simpler regimens are recommended and physicians should evaluate if switching to an equally effective regimen with fewer drugs or lower pill burden will improve patient adherence and treatment outcomes [15, 18].

Adverse effects are still frequent among the available antiretroviral drugs, even for newer options [102]. Patients may experience several problems, ranging from transient problems, mainly gastrointestinal effects such as diarrhoea and nausea, to longer-lasting effects such as lipodystrophy and neuropathy [18, 102]. Adverse effects that occur early during the treatment

were identified as the main reason for drug switches in the first year of HAART, and strong predictors of non-adherence [18]. On the other hand, lipodystrophy is a frequent problem among subjects on HAART and its physical manifestations may lead patients to abandon treatment [18]. Hence, guidelines recommend switching antiretroviral drugs when adverse effects occur, to prevent non-adherence and emergence of drug resistance [15].

In summary, patient adherence to antiretroviral treatment is a main determinant of its success and high levels are required to avoid drug resistances. We have described several factors that are known to influence adherence, which depends on both psychosocial conditions and treatment-related characteristics.

Patient-tailored interventions and regimens with improved tolerance are required to improve long-term outcomes for those HIV-infected subjects at risk of adherence failure [96]. Due to the impact of clinical context and healthcare system in adherence, evaluating adherence and its determinants and how to define goals in a given setting may enable the design of more effective interventions [4].

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I.3.

Epidemiology of HIV/AIDS infection in Portugal: an update of disperse information

- The Global and European context of the HIV/AIDS epidemics

In recent years, the HIV infection epidemic appears to have stabilized [1]. The annual number of new HIV/AIDS cases reported has been declining since the late 1990s (Figure I.3.1). The UNAIDS estimated that 2.6 million people became newly infected with HIV during 2009. This figure represents a fallen by 19% since 1999 and 21% since 1997, the year in which it was observed the higher number of new infections worldwide. Moreover, the use of antiretroviral therapy over the past few years has resulted in fewer AIDS cases and AIDS-related deaths (Figure I.3.1), which were observed earlier in the WHO health region of North America and Western and Central Europe (Figure I.3.2). With the reduction of the AIDS mortality rate, the number of people living with HIV/AIDS worldwide has increased [1].

At the European level, a total of 53 427 HIV/AIDS new cases were reported in 2009, by 49 out of the 53 countries of the WHO European region, resulting in a rate of 8.5 per 100 000 population (12.2% aged 15-24 years, 34.7% females) [2]. However, there are epidemiological differences regarding the HIV infection geographical distribution, among the three geographical areas in WHO European region (Figure I.3.3): the East European region reported a higher number of HIV new diagnosis with a rising trend, while the Western and Central European areas reported lower rates. With respect to 2009 data from 21 Western European countries, a total of 24 703 newly diagnosed HIV cases were reported, with a rate of 6.7 per 100 000 population.

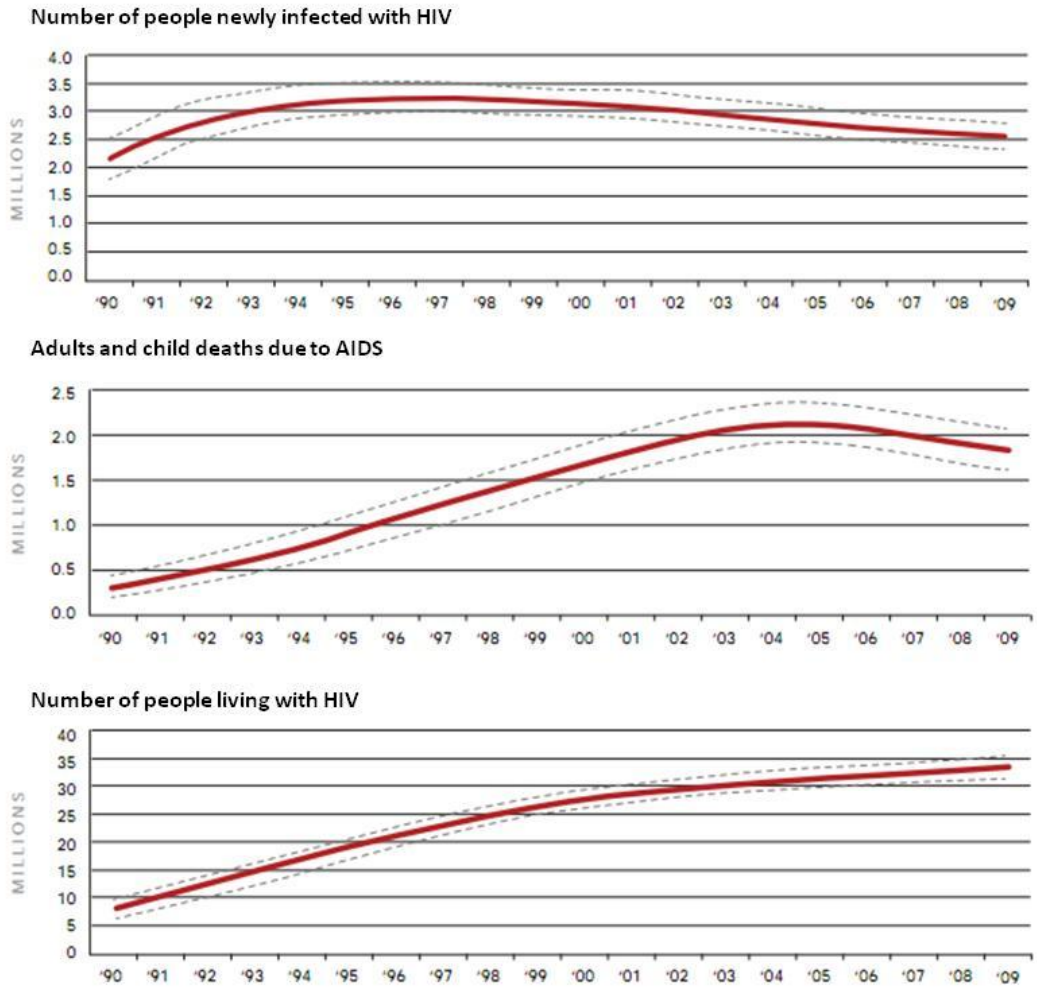

Figure I.3.1. Global HIV trends, 1990 to 2009. Dotted lines represent minimal and maximal ranges; solid lines represent the best estimate (reprinted from [1])

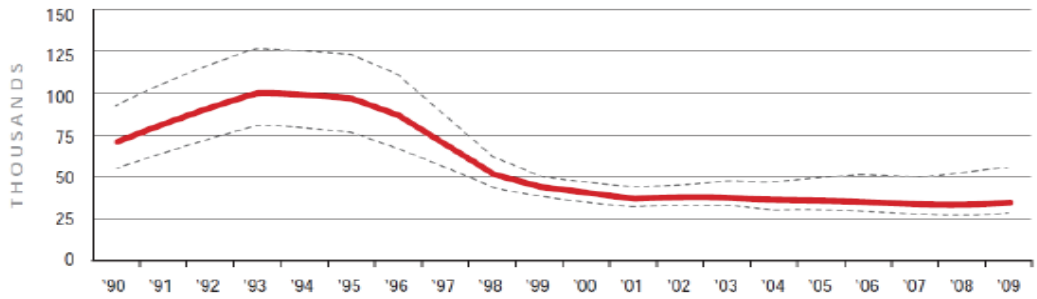

Figure I.3.2. Trend of AIDS-related deaths, in the WHO health region *North America and Western and Central Europe*; dotted lines represent minimal and maximal ranges; solid lines represent the best estimate (reprinted from [1]).

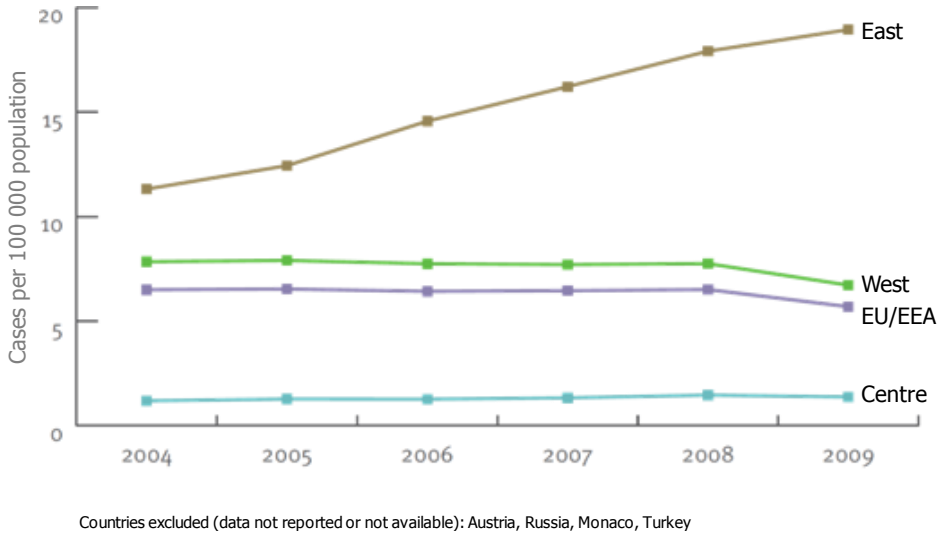

Figure I.3.3. HIV infection new diagnosis in the three geographical areas of the WHO European Region and the EU/EEA, over the period 2004–09

Also in the West Europe, 40% of the HIV cases were acquired through heterosexual contact (n=9 960 cases). However, when cases originating from countries with generalised epidemics are excluded (n=3 721 cases), this proportion decreases to 25% [2]. The trends of HIV infection by transmission routes is identical as for the EU/EEA region, presented in Figure I.3.4.

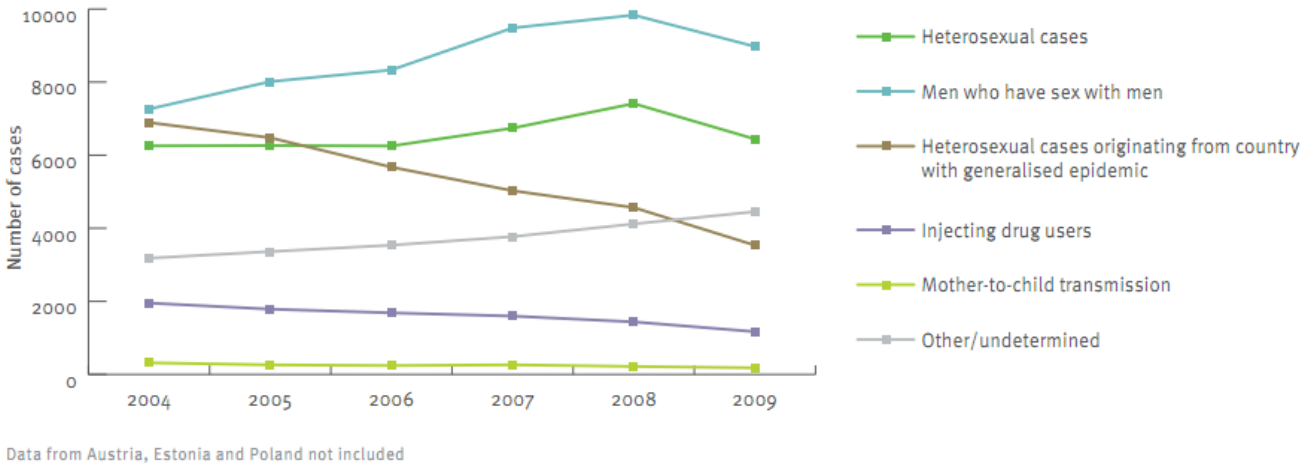

Figure I.3.4. Number of HIV infection cases reported by transmission route and origin in EU/EEA countries, over the period 2004–2009 (reprinted from [**2**]).

Regarding AIDS cases, the 2009 data reported a total of 4 650 cases of AIDS diagnosed in 27 EU/EEA countries (no data from Austria or Sweden), which represents a rate of 1.0 cases per 100 000 population, higher among men (1.4 per 100 000) than women (0.5 per 100 000). The highest AIDS rates were reported by Latvia (4.3 per 100 000; n=96), Estonia (2.8 per 100 000; n=38), Portugal (2.8 per 100 000; n=297), and Spain (2.3 per 100 000; n=1037) [2].

- Epidemiology of HIV/AIDS infection in Portugal

Portugal presents one of the highest rates of new HIV cases among the countries within Western and Central Europe region [2]. Taking into consideration the reporting delay for HIV/AIDS diagnoses, the estimated 2009 rate of HIV new infections in Portugal was 15.3 per 100 000 population, from which 463 were estimated to be AIDS cases [2].

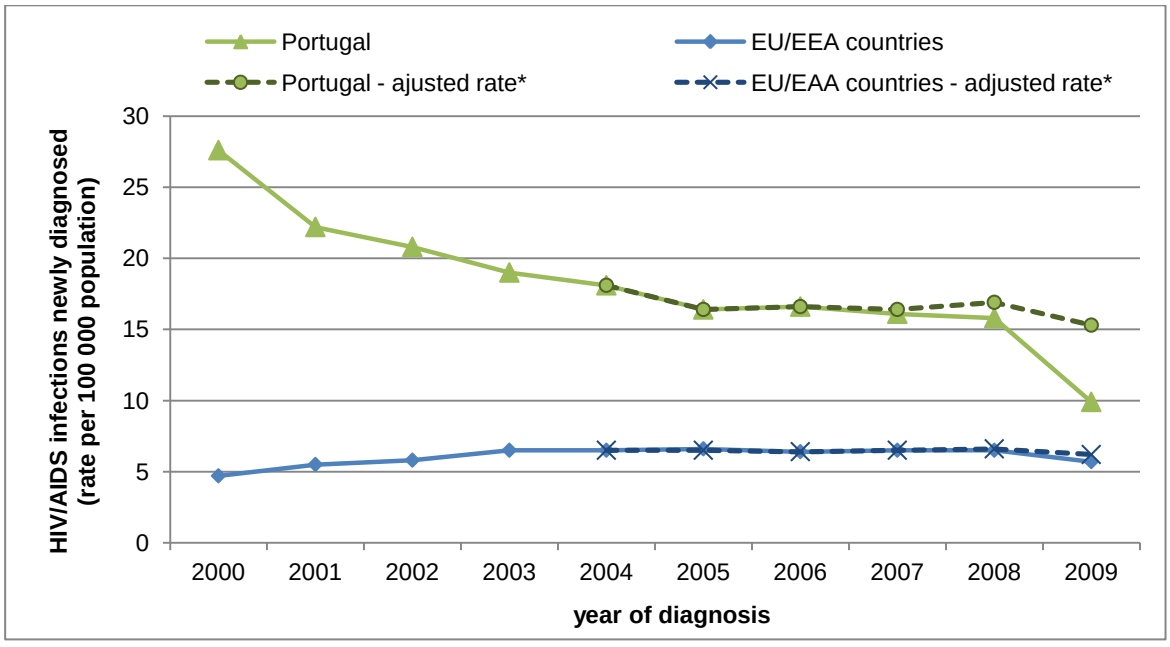

Figure I.3.5. EU/EEA and Portuguese trends of new HIV/AIDS cases diagnosed (rate per 100 000 population), by year of diagnosis and over the period 2000-2009. *rates were adjusted to account for the reporting delay, which refers to the time between HIV/AIDS diagnosis and its report at national level [**2**].

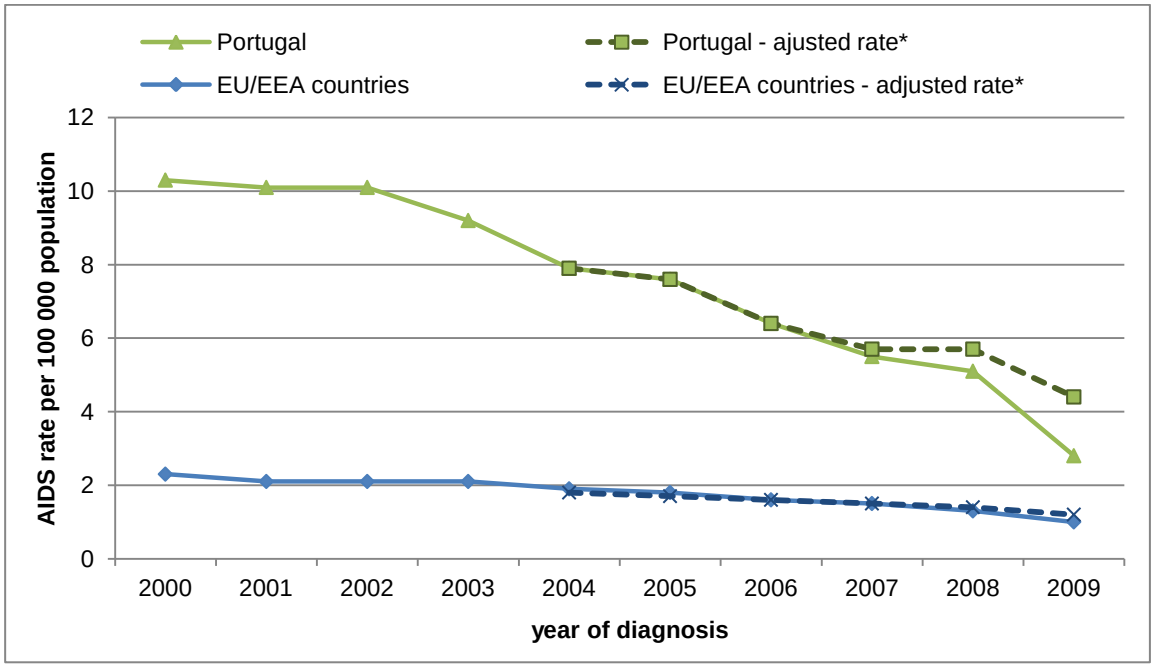

Figure I.3.6. EU/EEA and Portuguese trends of AIDS rates at the time of HIV/AIDS diagnosis (rate per 100 000 population), by year of diagnosis and over the period 2000-2009. *rates were adjusted to account for the reporting delay, which refers to the time between HIV/AIDS diagnosis and its report at national level [2].

Alongside with a high rate of newly diagnosed infections, there are more Portuguese individuals living with HIV/AIDS infection nowadays. The 2010 UNAIDS Report on the global AIDS epidemic indicated that the 2009 adult Portuguese prevalence of HIV/AIDS infection was 0.6% [lower-higher estimates: 0.4-0.7] for ages between 15 and 49 years, and that 42 000 individuals over 15 years were living with HIV/AIDS infection [1]. This prevalence estimate was higher than the remaining Western and Central European countries and higher than the average of 0.2% for this WHO region. In fact, Portugal was the only western and central European country that showed an increase in HIV prevalence estimates: in 2001, the prevalence rate was 0.5% [0.4-0.6], while the regional mean was 0.2% [0.2-0.2] as in 2009. No information on HIV progression to AIDS regarding the Portuguese reality was found. When considering AIDS mortality, the European HIV surveillance system reports that

the number of AIDS deaths in Portugal is decreasing in the period 2004-2009, as shown in Figure I.3.7 [1, 2]. However, we also found that the National Institute of Statistics (INE) reported higher absolute numbers of deaths due to HIV-related disease (Figure I.3.7) and that the decrease seems to be lower when compared to the one reported in the surveillance system [3].

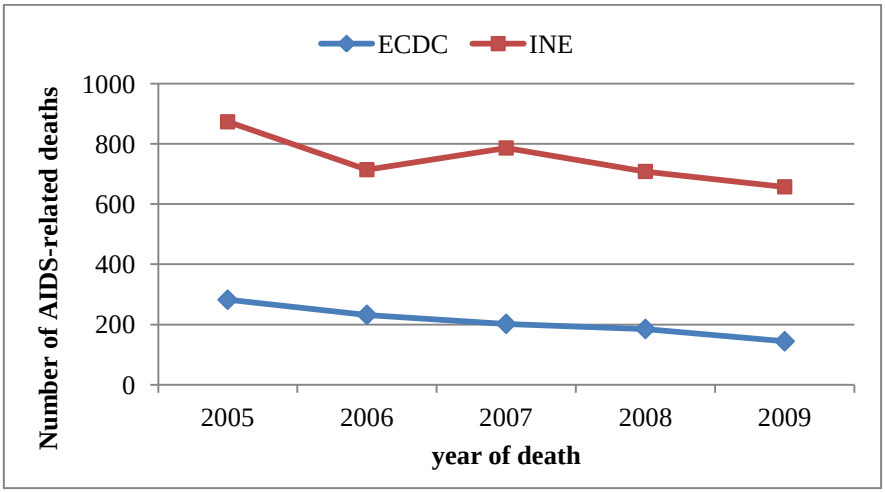

Figure I.3.7. Number of AIDS-related deaths reported in Portugal, over the period from 2005 until 2009.

The observed differences in the absolute numbers of AIDS-related deaths reported by each source may be explained by the use of different notification systems and different definitions. The HIV/AIDS national surveillance system, which provides data to the European surveillance system, is based on case notifications sent by physicians to a national centre. Since 2005, notification is mandatory at diagnosis and whenever there is a change in infection status. Deaths among confirmed AIDS cases should also be notified [4]. However, a 2009 evaluation of the national HIV surveillance system revealed that its acceptability was relatively low and that reporting of deaths (as well as changes in infection status) were seen as problematic, which may explain the observed underreporting [4].

Furthermore, this evaluation also focused on timeliness of reporting and completeness of information, among other characteristics. Timeliness was measured in terms of number of days between the diagnosis as reported by the physician and reception of notification at the centre. From 2005 to 2008, the average delay for diagnosed cases was 168 days, with the majority (≈71%) being reported until six months after the diagnosis. For the same period and regarding completeness of information, 13 of 20 variables included in the analysis had no incompletes, while "date of death" had 90.5% incompletes, a finding which the report justifies as related to better care and treatment available to patients [4]. However, this may also be seen as an indicator of underreporting which, alongside with the reporting delay, may result in a smaller rate of AIDS related deaths reported by this source.

The INE is responsible for the Portuguese general mortality registry, based on medical death certificates, also mandatory for all population. Regarding the HIV/AIDS infection, INE consider all deaths due to AIDS or other HIV-related disease as the underlying cause (ICD-10 code B20-24), a broader definition than the one used in the HIV surveillance system since it includes deaths in non-AIDS HIV cases [5]. Thus, general mortality rates seem to be more accurate and useful for the assessment of HIV-related deaths than HIV surveillance data [5]. When considering data from Eurostat, the statistical office of the European Union, we found that Portugal presents a 2009 death rate due to AIDS (HIV-disease) of 5.8 per 100 000 inhabitants, the highest among the 27 EU countries (Figure I.3.8) [6].

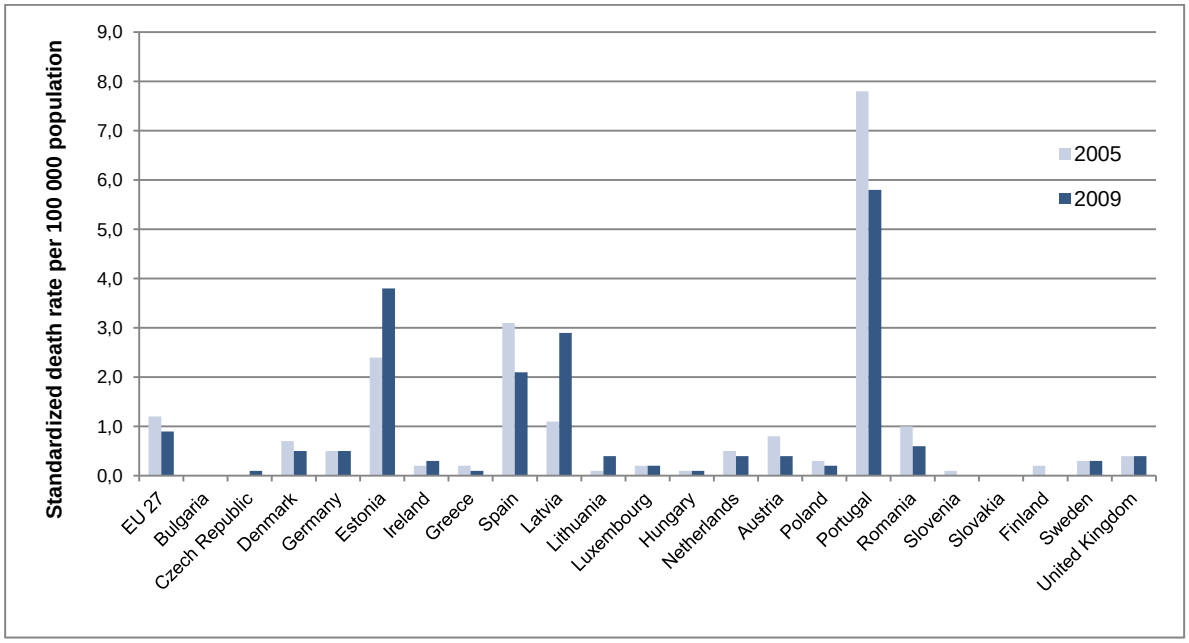

Figure I.3.8. AIDS (HIV disease ICD10 B20-24) mortality rates in EU* in 2005 and 2009. *no 2009 data for Belgium, France, Italy, Cyprus, Malta. Source: Eurostat [**6**]

The high prevalence of HIV infection and rate of AIDS newly diagnosed cases, as well as the high rate of HIV-related mortality, place a challenge to the Portuguese National Health System [7]. It reflects the need for a stronger prevention programme and early HIV detection strategies, but also the need for a sustainable treatment response, regarding the continuity of its delivery within an efficient and effective HIV/AIDS clinical management [1]. Similar to the reported global trends, Portuguese expenditure on HIV treatment has increased over the last decade [1, 4]. In fact, recent data from INFARMED showed an increase of 11.2% in the overall expenditure related to drugs prescribed for HIV/AIDS treatment, when comparing the 2011 and 2010 homologous periods January-September. In the first semester of 2011, antiretroviral medication accounted already for near 158M€, 20.6% of the total expenditure with medication dispensed in Portuguese hospitals (758M€) [8]. However, it is important to note that this value may be underestimated due to the number of reporting hospitals. Figure

I.3.9 and Figure I.3.10 show the evolution of expenditure related to antiviral medication and individual antiretroviral drugs, based on the available data from INFARMED reports of drug use in Portuguese hospitals (www.infarmed.pt). Figure I.3.9 also shows the estimates reported by IMS Health (Portugal) and CNSida [9], higher than those reported by INFARMED.

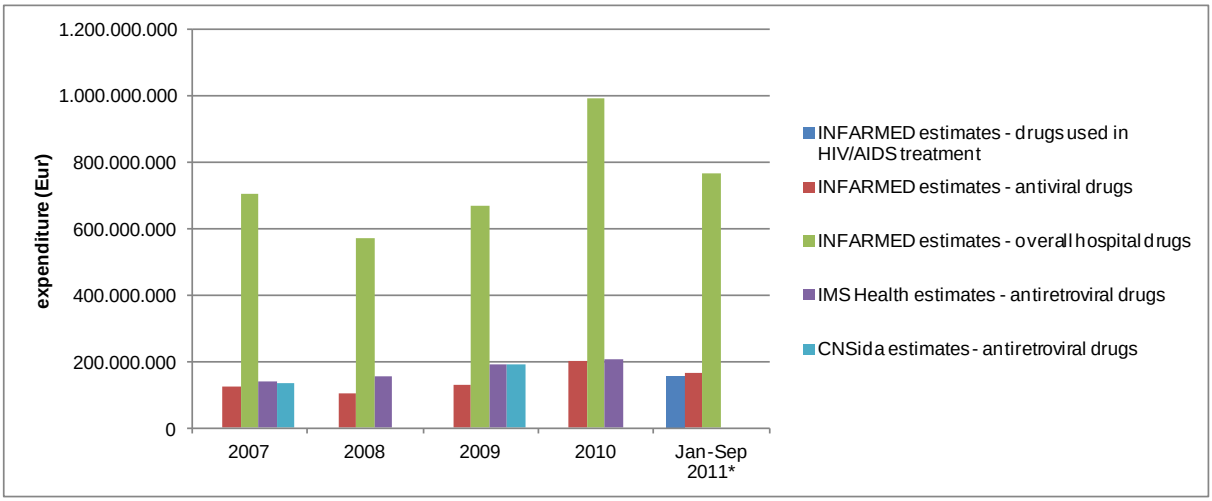

Figure I.3.9. Estimates of expenditures with antiviral drugs and overall hospital drugs (INFARMED), and with antiretroviral drugs (IMS Health and CNSida), from 2007 to September 2011. *estimates from the last available report from INFARMED.

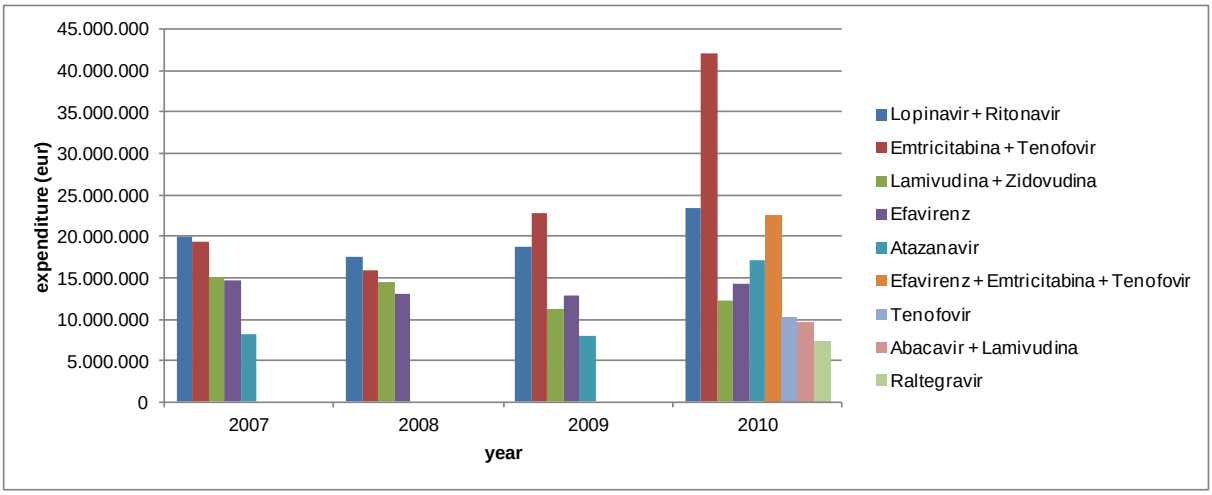

Figure I.3.10. Trends in expenditure (eur) with individual antiretroviral drugs or associations, over the period 2007-2010. Source: INFARMED

Differences among sources might result from the different methods for collecting data. In the INFARMED approach, each hospital provide monthly uploads of data on drug sales and consumption, enabling a closer monitoring of medication consumption [10]. However, since hospitals might provide further data corrections, it is possible that the expenditures estimates presented in each report might be modified in further ones [8]. CNSida obtains its data by asking each hospital to fulfil an annual questionnaire, designed specifically for the HIV/AIDS care indicators. However, it might be biased due to refusals and to the type of hospitals that voluntarily collaborate.

When considering the number of HIV-infected adults receiving antiretroviral treatment in Portugal, the available data is unclear. The UNAIDS reports that 18 107 individuals were receiving antiretroviral treatment in 2009, an increase of 32% when comparing to the 12 366 individuals reported in December 2008 [1]. However, a recent national report showed a higher number of subjects receiving antiretroviral treatment: 22 418 individuals in 2009 [9]. Another national report also indicated a total number of 22 380 for the same calendar year [11]. Differences might be due to reporting delays, refusal rate and missing information from the Portuguese hospitals. Table I.3.1 shows that more hospitals have reported the number of subjects that were receiving antiretroviral treatment in 2009 (n=33) than for 2007 year (n=22), and similar differences were found for other variables. The type and dimension of the hospitals that have fulfilled the questionnaire are also relevant. For instance, *Centro Hospitalar Lisboa Central* did not accounted for the 2007 estimates although subjects were still being followed at that time: 1 223 and 1 846 subjects followed at that unit were on HAART in 2005 and 2009 years, respectively (Table I.3.2).

Table I.3.1. Main HIV indicators (CNSida) and number of Portuguese reporting hospitals, for the years 2006, 2007 and 2009 [9].

	2006		2007		2009	
	Number of reporting hospitals	Total **(min-max)**	Number of reporting hospitals	Total **(min-max)**	Number of reporting hospitals	Total **(min-max)**
HIV-infected subjects followed-up in the hospital	21	16 522 (74-2557)	23	18 500 (86-2622)	28	22 816 (11-3000)
AIDS subjects followed-up in the hospital	11	1 461 (9-508)	14	2 235 (11-516)	18	4 560 (0-1675)
Subjects that had abandoned medical appointments	12	899 (2-404)	14	901 (2-416)	19	809 (0-229)
Hospitalizations due to HIV infection	23	2 875 (7-423)	23	3 018 (14-398)	32	3 400 (0-508)
Subjects that were hospitalized due to HIV infection	22	2 112 (7-318)	22	2 146 (9-370)	30	2595 (0-430)
AIDS-related deaths among subjects followed-up in the hospital	13	96 (0-25)	15	122 (0-40)	25	255 (0-36)
AIDS-related deaths during hospitalizations of subjects followed-up in the hospital	18	144 (0-35)	19	163 (0-42)	28	244 (0-36)
AIDS-related deaths during hospitalizations of subjects who were not followed-up in the hospital	18	70 (0-11)	19	89 (0-19)	26	125 (0-37)
Subjects receiving antiretroviral treatment	**21**	**13 406 (48-2234)**	**22**	**15 042 (58-2302)**	**33**	**22 418 (11-2476)**
Subjects initiating antiretroviral treatment	16	834 (10-204)	21	1 370 (5-251)	30	1 936 (0-174)
TB cases among HIV-infected subjects	18	364 (1-70)	19	332 (0-75)	26	343 (0-52)

Table I.3.2. Number of subjects receiving antiretroviral treatment, for each hospital unit with more than 400 HIV-infected subjects on treatment, in the years 2005 and 2009 [9, 12].

Hospital Units	**Portuguese Health Region**	**number of patients receiving antiretroviral treatment**	
		2005 year	***2009 year***
Centro Hospitalar Barreiro/Montijo	LVT	–	490
Centro Hospitalar de Cascais	LVT	661	1 098
Centro Hospitalar de Coimbra	Centre	428	660
Centro Hospitalar de Setúbal	LVT	996	830
Centro Hospitalar de Vila Nova de Gaia	North	584	851
Centro Hospitalar do Porto	North	–	546
Centro Hospitalar Lisboa Central	LVT	1 223	1 846
Centro Hospitalar Lisboa Norte	LVT	2 460	2 138
Centro Hospitalar Lisboa Ocidental	LVT	1 615	1 794
Hospitais da Universidade de Coimbra	Centre	604	860
Hospital Curry Cabral	LVT	1 846	2 574
Hospital de Joaquim Urbano	North	1 398	1 676

Hospital Units	Portuguese Health Region	number of patients receiving antiretroviral treatment	
		2005 year	*2009 year*
Hospital de São João	North	1 292	1 602
Hospital Distrital de Faro	Algarve	497	732
Hospital Distrital de Santarém	LVT	–	406
Hospital Fernando da Fonseca	LVT	1 006	1 615
Hospital Garcia de Orta	LVT	1 011	1 463
Unidade Local de Saúde de Matosinhos	North	438	593

LVT = Lisbon and Tagus Valley Health Region

The incompleteness and the lack of updated information on HIV infection and treatment is recognized [11]. Data regarding antiretroviral drug use and patient adherence to treatment is also dispersed and bias may be present with the use of different definitions and measures.

- What is already known about patient adherence to HAART in Portugal?

In Portugal, there have been some single-centre studies addressing patient adherence to HAART. Table I.3.3 summarizes the studies that to our knowledge have been conducted as of 2011. This was retrieved from the reference lists of master and doctoral thesis and from other available publications, such as conference abstracts.

Table I.3.3. Summary of Portuguese studies regarding patient adherence to HAART.

Author *publication*	Hospital *study period*	Inclusion criteria	n	% men	Age (y)	Measure of adherence	% adherence	Ref
Aragão (2009)	Cascais (2002 - 2008)	• Aged ≥14 y • Naïve	1 333 (naïve: 193)	65 (naïve : 65)	40.1 ± 0.9	Pharmacy refill (overall adherence level)	86 95%CI: [83.8;87.9]	*13*
Margalho (2010)	HUC (*)	• HIV+, asymptomatic • Followed-up at outpatient clinic • Prescribed to antiretrovirals ≥ 30 days • Portuguese nationality • Literacy level sufficient to answer to the questionnaire	81	49.4	38.7 ± 10.9	Self-report (question)	45.7	*14*

Author *publication*	Hospital *study period*	Inclusion criteria	n	% men	Age (y)	Measure of adherence	% adherence	Ref
		• Exclusion of subjects in prison and with active psychological symptoms, dementia or other cognitive conditions, and drug consumption						
Reis (2007)	Joaquim Urbano (2006 – 2007)	• Aged >18 y • HIV+ • Prescribed to antiretrovirals ≥ 3 months • Informed consent • Followed-up regularly at outpatient clinic • Exclusion of subjects hospitalized during recruitment	125	80	39.9 ± 9.8	Pharmacy refill (overall adherence level) *Self-report (CEAT)**	91.1±15.8 (≈33.6 ≥95%)	*15* *16* *17*
Margalho (2007)	HUC (*)	• HIV+ • Recruited at Psychology appointment • Followed-up at outpatient clinic • Exclusion of subjects in prison and with active psychological symptoms	100	73	38.2 ± 10.3	Self-report (question)	73.1	*18*
Gonçalves (2007)	HSM (*)	• HIV+ • Informed consent • Followed-up at outpatient clinic	210	66	-	Self-report (AACTG)	75.7	*19* *20*
Ventura (2006)	Joaquim Urbano (2002-2003)	• HIV+ • Naïve • Informed consent • Followed-up at outpatient clinic • One year of treatment	134	70.1	38.0 ± 11.4	Pharmacy refill - overall adherence level	86.9 (68.7 ≥95%)	*21*
Marin (2002)	Portimão (2000-2002)	• HIV+ • Followed-up at outpatient clinic • With more than one refill	206 (more than one refill: 187)	67.5	*	Pharmacy refill (irregular)	regular: 67.9	*22*
Neto (2003)	Cascais (1999, 2000)	*	1999: 369 2000: 473	*	*	Pharmacy refill (*)	1999: 42% 2000: 60%	

** data not available*

Several measures of adherence were used, including self-report questionnaires, pharmacy-based measures and electronic monitoring, and this heterogeneity of measures makes the studies' comparison difficult.

For instance, Margalho *et al.* study showed that, among patients followed in *Hospitais Universitários de Coimbra* in 2007, 93 out of 100 were prescribed to HAART and 68 (73.1%) were adherent [14]. Gonçalves *et al.* indicated a non-adherence prevalence of 22.3% in a 2004 study conducted in *Hospital de Santa Maria* [19]. Both studies included small sample sizes and had measured adherence by patient self-report, but each one used different questions. Gonçalves *et al.* study also identified as main reasons for non-adherence the following: "simply forgot" (11.5%), "impact in daily routine" (7.6%), "feeling well" (8.1%), "having problems with taking medication in some occasions" (6.2%) and "being busy" (6.2%) [19, 20]. Reis *et al.* conducted a validation study of an adherence questionnaire (CEAT), in a sample of 125 subjects followed at *Hospital Joaquim Urbano* [15, 16]. In this study, the authors reported that overall adherence level, based on pharmacy refills, was 91.1±15.8%, although only a third of the subjects had adherence levels ≥95% [17]. Having psychological symptoms, poor pharmacy refill adherence and experience of adverse reactions were conditions identified as non-adherence predictors [15, 17].

Using pharmacy refills, Aragão *et al.* found a mean adherence level of 86% for the first regimen among the naïve patients followed at *Centro Hospitalar de Cascais* between 2002 and 2008 [13]. Ventura *et al.* reported a similar mean adherence level of 86.9% in *Hospital Joaquim Urbano*, with a non-adherence estimate (e.g., subjects with adherence level <90%) of 31.3% for the first year on antiretroviral treatment, between 2002 and 2003 [21]. Additionally, this study also described some adherence determinants, namely, sex, place of residency, clinical status of the HIV infection, CD4 cell count increase and viral load at the end of follow-up, hospitalizations and number of skipped medical appointments [21].

These studies included only persistent subjects for a one year period. Since the non-persistent patients were not included, there may have been an underestimation of non-adherence: the 2010 UNAIDS report indicates that the 2009 percentage of Portuguese adults known to be on treatment 12 months after initiation was 84% [1].

Previous studies, using also pharmacy-based measures, reported similar adherence levels. A study conducted in *Hospital de Portimão* showed that, from 206 subjects followed between July 2000 and June 2002, 146 subjects (70.5%) were still receiving treatment at the end of the study period, while 39 (19%) had dropped-out from the medical appointments. Also, from the 187 subjects with more than one pharmacy refill, 60 were classified as irregular (e.g., presented more than one medication gap with length superior to one month) [22]. In the *Hospital de Cascais*, a 1999 study reported a mean adherence level of 42% for 369 subjects receiving antiretroviral treatment, while a 2000 study in the same hospital and with the same methodology showed an increase in the mean adherence level to 60%, for 473 subjects under treatment [21].

Recently, CNSida has developed a national registry to support the clinical activities related to the HIV/AIDS infection. This registry (SI.VIDA) aims to collect some clinical variables such as viral load, CD4+ cell count over time, antiretroviral regimens used and adherence to therapy of HIV infected subjects [11]. For now, a feasibility study was conducted in three health units – *Hospital de São João, Hospital Egas Moniz* and H*ospital Distrital de Faro* – and concluded in May 2010. It is expected that, in the future, more Portuguese information about the HIV/AIDS infection may become available.

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Chapter II

Study Objectives

The study aims to characterize patient non-adherence to antiretroviral treatment among HIV-1 infected adult subjects followed up at the HIV outpatient clinic from *Hospital de Santa Maria* (Lisbon, Portugal), a university tertiary central hospital and the largest hospital in Portugal.

Specific aims were:

1) to provide a characterization of the pattern of HAART prescription and non-adherence, over the period from 2005 to 2008 calendar year (*Section IV.1.*);

2) to verify which factors may be associated to non-adherence to HAART (Section IV.2.); and

3) to evaluate the completeness of the clinical and pharmacy records, according to the study variables (Chapter V).

Chapter III

Study Design & Methods

- Study design and Eligibility criteria

Observational cohort study, conducted at the HIV outpatient clinic of the *Hospital de Santa Maria* with a retrospective data collection of HIV-infected adults followed up at the clinic and having at least one antiretroviral refill between 01-01-2005 and 31-12-2008.

Other eligibility criteria were defined as having:

- started antiretroviral treatment at HSM clinic when aged ≥ 18 years;
- at least 2 medical appointments during the same period;
- no participation in clinical trials;
- antiretroviral drugs prescribed for HIV-1 treatment, with the exclusion of post-exposure prophylactic treatment and other regimens besides HAART.

Subjects were excluded if (or censored at date of being) arrested, under a social institution care or dependent of a third person for taking medication. Subjects were also censored at the date of death or at the date of the last medical appointment before moving to a different hospital.

- Sampling

To assess how many subjects had at least one antiretroviral refill between 01-01-2005 and 31-12-2008, we asked for the collaboration of HSM Pharmacy for a list with all refills of solid forms of ARV that took place during this period and were initially prescribed by the physicians at the HIV outpatient clinic. Simple randomization (with R software) was then

used to select the potential participants. The eligibility criteria were assessed when retrieving the hand-written clinical record, for each subject.

The sample size of the pilot study was calculated based in the initial assumptions for the ATAR-VIH project (see Annex III). In the retrospective phase of the pilot study, we also assumed an exclusion rate of 37%. Hence, from 320 subjects randomly selected, we aimed to include 200 subjects that would enable a precision estimate ±7% (α=.05) of the true frequency of overall non-adherence to HAART during the 2005-2008 period. Assuming a statistical power of 80%, and non-adherence as a dichotomous variable, we expected to detect relative risks ≥1.8 or more for different risk factors, when non-adherence rate among controls was 0.3.

- Study variables

Adherence was assessed as compliance (or quality of execution – see ***Chapter I.2***) and assessed with the pharmacy-based measures *Medication Possession Ratio* (MPR) and *medication GAPs*. Treatment modifications were defined as any change at both HAART regimens or at individual drugs and included structured or unstructured treatment interruptions. Sociodemographic characteristics and clinical variables related to HIV/AIDS infection (e.g., viral load, CD4 and CD8 cell counts, opportunistic infections and comorbidities) were also retrieved from hand-written clinical records, as well as the physician notes on reasons for HAART modifications and evaluation of patient adherence. Information from adverse effects, genotyping resistance test information, and TDM was also collected. Annex IV shows the conceptual model with the variables collected.

- Data collection process

From May to October, 2010, 3 medical students and a pharmacist collected data from the subjects' clinical records. A specific form was used to retrieve information (Annex V). In the period before 2005, we retrieved only information about the first medical visit, the first visit with prescription of antiretrovirals and the following ones when treatment modifications occurred. After year 2005, we collected data from all visits, until December 2009. Latter, the collected information was registered in an electronic (Microsoft Access®) database. Pharmacy refills data were downloaded from the electronic registry of the HSM Pharmaceutical Services into a Microsoft Excel® file.

- Data validation and statistical analysis

The information registered at the electronic database was validated for specific variables (viral load, CD4 cell count, HAART modifications and HAART regimens) in 30% of the forms, selected by a random process. Regarding HAART use, we assumed that information from pharmacy database about medication (name, dose, refill dates, number of pills dispensed) was more accurate and complete. Statistical analysis plan was defined for each specific aim. We estimate 95% confidence intervals for parameters of interest and adopted a 5% significance level for all statistical hypotheses tests. Analyses were conducted by using R software.

- Ethical and legal aspects

The pilot study was authorized by the HSM Ethics Committee and the National Data Protection Authority (see Annex I and II). The retrospective phase did not require any informed consent for the data collection, since this process involved only health professionals and medical students under a confidentiality contract under the physicians' supervision. Subjects were coded with a unique non-identifying number. The database has protected access. Also, only grouped data will be presented and published. No financial gratifications were given to the study participants, and this study has no commercial aims. The HSM Ethics Committee recognized the public health relevance of the study.

In ***Chapter IV Results***, we detail more information about the definition of variables and statistical analysis applied to each specific aim, as well as a discussion of its results. The ***Chapter V General Discussion & Conclusions*** presents an overall discussion of results and study limitations.

Chapter IV

Results

IV.1.

Antiretroviral Prescription and Adherence in a Portuguese Cohort of HIV-1 infected subjects: an overall analysis of changes over the years 2005 - 2008

Abstract

Objectives: To evaluate the trends in adherence to antiretroviral treatment (ART), in a cohort of HIV-1 infected adults, and to characterize the HAART prescription pattern over the period 2005-2008.

Methods: A sample was randomly selected from the total of HIV-1 adult infected subjects, followed up at a Portuguese hospital HIV outpatient clinic and that had at least one antiretroviral refill between 01-01-2005 and 31-12-2008. Medication possession ratio (MPR) was determined using a fixed 12- or 6-month period. Non-adherence was defined as MPR<95%. HAART prescription was analyzed according to regimens, within each antiretroviral class, and regarding fixed-dose combinations.

Results: A total of 186 subjects were included, 78.5% treatment-experienced at baseline. Over the period 2005-2008, we found a significant increase in the proportion of subjects with MPR<95% from 12.3% in 2005 to 25.9% 2008, that was usually higher among injection drug users (IDU) and subjects with depression/anxiety. The proportion of subjects with at least one registry of detectable viral load had significantly decreased from 43.5 in the first semester of 2005 to 29.2% in the second semester of 2008 (P=0.01). No significant differences were observed in the HAART regimens use along the study period. The two usual options were 2 NRTIs and a NNRTI or a PI. The use of fixed-dose combinations had significantly increased from 54.8 to 77.7% (P<0.001), mainly due to emtricitabine/tenofovir association.

Conclusions: Non-adherence increased over the period 2005-2008, being higher among IDU and subjects with depression/anxiety, as well as during second calendar semesters. The prescription pattern seemed to be in accordance with guidelines for the treatment of HIV infection, including the use of fixed-dose combinations.

Keywords: HIV/AIDS infection; patient adherence; antiretroviral treatment.

Background

The prescription of Highly Active Antiretroviral Therapy (HAART) has been changing over the years [1]. For the period 2005-2008, new drugs and fixed-dose combinations (e.g. emtricitabine/tenofovir) became available, while some were withdrew (e.g. nelfinavir) [2, 3, 4]. Besides the increase of antiretroviral agents and combination options, other factors had changed that might have an impact on the clinical progression of HIV/AIDS infection. For instance, the detection of HIV RNA viral load was possible for values below the 40 copies/ml, while guidelines now recommend to start treatment when Lymphocyte T CD4 cell count <350/µl. Treatment is also recommended in some circumstances such as HIV-associated kidney disease / neurocognitive impairment or Hodgkin's lymphoma, even if CD4 count is higher than 350/µl [1, 5, 6].

At an individual level, high levels of adherence are required to achieve the best response to treatment, preventing drug resistances and reducing disease progression and death [7, 8, 9]. Even though there is a need to better definition of the minimum cut-off for HAART adherence, especially for more recently approved drugs, it is usually accepted that adherence should be higher than 95% in order to achieve the highest treatment efficiency [9, 10, 11]. Moreover, longitudinal evaluations are recommended to address adherence to HAART as a dynamic process [12].

It is widely recognized that knowledge on which HAART is used for treatment of HIV infection may provide useful information for clinical evaluation with regard to safety and effectiveness and also for design cost-effectiveness strategies to improve standard care [13]. In fact, drug utilization studies may be used to promote appropriate drug use through education and other interventions, since "without a knowledge of how drugs are being

prescribed and used, it is difficult to initiate a discussion on rational drug use or to suggest measures to improve prescribing habits" [14].

Although drug utilization studies usually rely on large samples and administrative claims, in some contexts (such as the Portuguese one) it may be impossible to directly link aggregate data about medication with information about patient's demographic and clinical characterization. Another issue of concern is the level of record keeping, since computerized clinical databases may not be available for research purposes. In these cases, other data sources should be considered and an option could be collecting local data from patients' clinical records and pharmacy registries [14]. To our knowledge, there are no published studies that describe the trends for the prescription of antiretroviral agents and adherence, using the same time window (2005-2008), although this has been done at marketing level and for previous time periods, some including pre-HAART information [13]

In this study, we aim to evaluate the trends in adherence to HAART in a Portuguese cohort of HIV-1 infected adults receiving treatment over the period 2005-2008. For each semester, we specifically aim to determine the prevalence of adherence, based on medication possession ratio (MPR) ≥95%, and the proportion of individuals with detectable viral load. In addition, the study aims to characterize the patterns of antiretroviral prescription treatment.

Methods

Study design and participants

Data were retrospectively collected from pharmacy and outpatient clinic registries, for the *Prevalence and determinants of patient adherence to ART and regimen modification in a Portuguese cohort of HIV-infected adults* (ATAR-VIH) study. This study was authorized by

the Ethics Committee of the *Hospital de Santa Maria* (Lisbon, Portugal), and by the Portuguese Data Protection Authority.

A sample of 320 subjects that had at least one ART refill between January 2005 and December 2008 was randomly selected from a total of 2861 HIV-1 adult infected subjects, followed up at the HIV outpatient clinic of *Hospital de Santa Maria* (HSM, Lisbon, Portugal), the largest Portuguese hospital.. Sample size calculation assumed an exclusion rate of 35%, a non-adherence prevalence of 50%, and that the final inclusion of 200 subjects would enable a precision estimate ± 7% (α=.05) of the true frequency of overall non-adherence to ART during this period. HSM is a university tertiary central hospital and, since 2005, one of the two hospitals following the largest number of HIV-infected subjects in Portugal [15].

Inclusion criteria were defined as having started ART for HIV-1 infection at HSM clinic when aged ≥ 18 years-, and had at least 2 medical appointments between 01-01-2005 and 31-12-2008, with no participation on clinical trials. HIV post-exposure prophylactic treatment and antiretroviral regimens other than HAART were excluded. Subjects were censored at the date of death or date of being arrested, being in a social institution or dependent of a third person for taking medication. Baseline was the date of the first medical appointment during the study period.

ART prescription and adherence definition

The pattern of overall ART usage for each semester was assessed by considering the first subjects' prescription in that period. ART regimens were classified into nucleoside reverse

transcriptase inhibitor (NRTI) plus protease inhibitor (PI), NRTI plus non-nucleoside reverse transcriptase inhibitor (NNRTI), only NNRTI-containing regimen, PI and NNRTI-containing regimen, regimens with 4 antiretroviral drugs and other regimens. We also characterized the ART prescription pattern within each antiretroviral class, i.e. PI, NRTIs and NNRTIs, and the proportion of subjects receiving ART in fixed-dose combinations.

Adherence was assessed as compliance and evaluated from the pharmacy refill registry for the study time window and for specific index antiretroviral drug, defined as the PI or, if not applicable, the NNRTI or abacavir/tenofovir [16,17]. The pharmacy registry included the refills ordered by physicians from the Outpatient Clinic and registered between 01-01-2005 and 31-12-2008.

For adherence assessment, we determined MPR using a fixed 12- and 6-month period. In the 6-month assessment, MPR was defined as the number of days for which prescribed HAART was available for each calendar semester from January 2005 until December 2008, divided by number of days of each period (Figure IV.1.1).

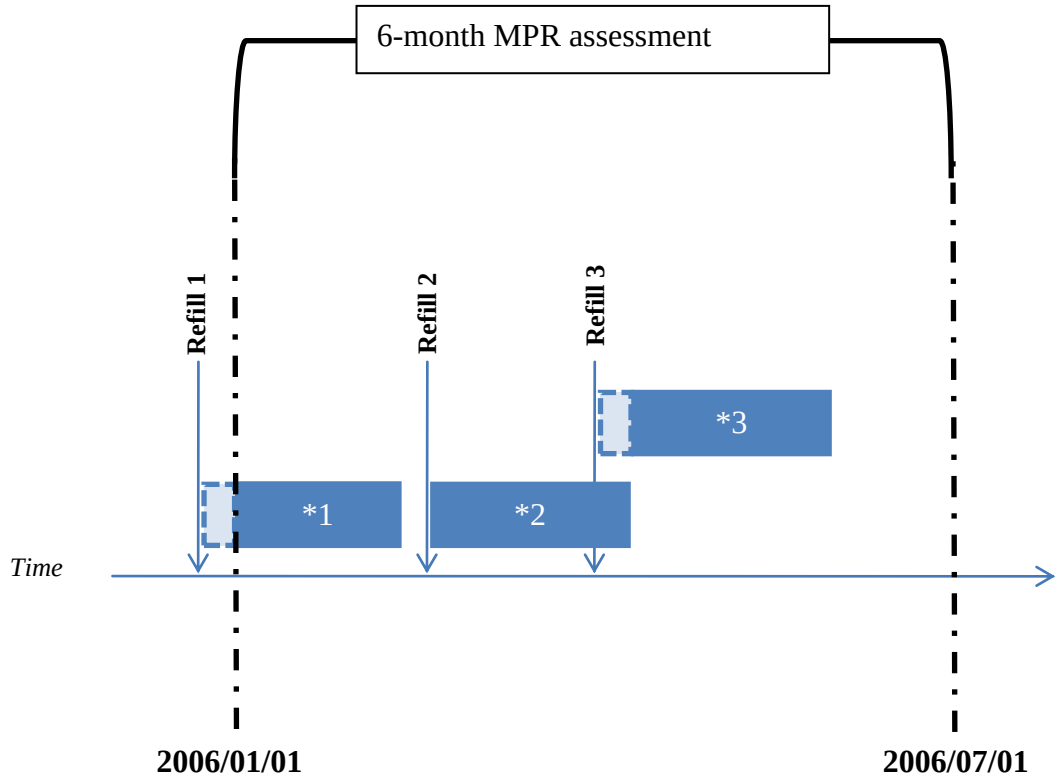

Figure IV.1.1. Scheme for the calculation 6-month Medication Possession Ratio. MPR is determined by assessing the total number of days with ART available (*periods) from all refills occurring in each semester, divided by total number of days for the semester. Leftover medication from previous semester was taken into account when determining MPR [18].

In order to avoid an overestimation of non-adherence, we corrected the MPR denominator for first calendar semester of 2005, so it included only the number of days between the first refill and 30th June. The same correction was assumed for the ART-naïve subjects in the subsequent semesters. The annual MPR assessment was performed similarly, for each calendar year over the study period. Number of pills prescribed per day was calculated based on the recommended daily dosage, according to the guidelines, and confirmed with the information from the clinical records. In case of overlapping refills, we assumed that HAART was taken

sequentially and accounted for the leftovers when estimating adherence [16,18]. At the end of each semester, subjects were classified as adherents if MPR ≥ 95%.

Variables related to adherence and clinical outcomes

Information from hand-written clinical records was retrieved and linked to pharmacy registry, by using the patients' individual number at HSM. Collected variables included sex, age and race, mode of HIV transmission, date of HIV-1 diagnosis and any physician annotation of intravenous drug use (IDU) behaviour (current or past). Depression/anxiety was defined as having a physician annotation of the diagnosis of depression or anxiety, or prescription of antidepressants (ATC code N06A) or anxiolytics (ATC code N05B). Treatment-related variables were time on HAART, number of ART changes, hospitalizations and number of medical appointments (visits) per subject, during the study period. ART discontinuation was based on physician annotation or, when the patient had no visit, in the calendar semester.

Laboratorial data on HIV plasma viral load and CD4+ T-cell counts were also collected from the clinical records, for each visit over the study period. The proportion of subjects with at least one detectable viral load was evaluated at each semester. The detection limit was ≥40 copies/ml, with the exception of the first semester of 2005, were the limit was ≥50 copies/ml (due to equipment limitations). We also evaluated the proportion of subjects with CD4 cell count < 350 or < 200 cells/μl.

Statistical analysis

Descriptive statistics were used for the sample characterization at baseline. 95% confidence intervals (CI) were calculated for MPR estimates and proportion of detectable viral load and CD4 cell count, assuming a binomial distribution. A χ^2 test for linear trend was used to assess temporal differences within each variable. Statistical analysis was performed with R software

(www.r-project.org), and a 5% significance level was adopted for all statistical hypotheses tests, with exclusion of missing data.

Results

Participant characteristics

A total of 186 subjects were included in this study. The remaining 134 were excluded due to having started ART in other hospital (n=42), participation in clinical trials (n=34), had less than 2 medical appointments during the study period (n=14), being in a prophylactic or a non-HAART regimen (n=13), missing clinical records (n=9), starting HAART when arrested or depending on another person for medication intake (n=6), not being followed up in the outpatient clinic (n=6), had only one ART refill in the study period (n=3) or presented HIV-2 infection (n=4).

At baseline, with regard to demographic characteristics, subjects were on average 39.7 ± 9.5 years old, and the majority were male (63.4%) and Caucasian (78.6%). The 186 subjects had a median time of 43.5 months since HIV infection diagnosis (IQR 14.8-91.0 months). Acquisition of HIV infection was due to heterosexual intercourse for 50.3% of subjects, while injection drug use (IDU) and men having sex with men (MSM) were the modes of acquisition for 23.2% and 19.2%, respectively. Other modes of transmission, including occupational exposure and subjects with more than one possible mode, accounted for 7.3% of the cases. The characteristics of study' participants are presented in Table IV.1.1, for each semester in the period from January 2005 to December 2008. Regarding ART experience, the sample is mainly constituted by prevalent users. A total of 21.5% of subjects were treatment-naïve at baseline, and the proportion of ART-naïve subjects significantly decreased over time.

Adherence evaluation

For the period 2005-2008, medication possession ratio (MPR) was high, with median annual MPR being 100% in each year (Figure IV.1.2). However, a significant increase in the proportion of non-adherent subjects was observed, with MPR <95% (Table IV.1.2). In 2008, non-adherence had a prevalence of 25.9%.

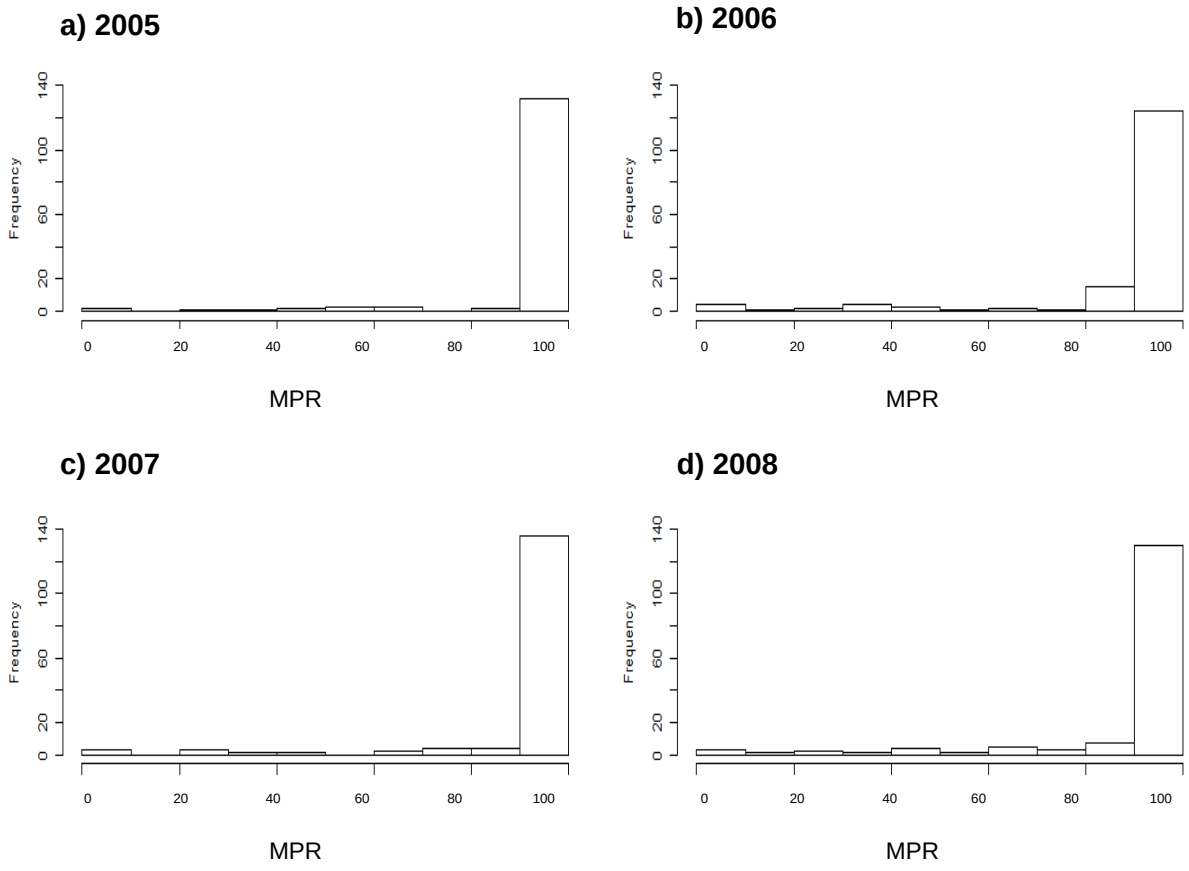

Figure IV.1.2. Histograms of medication possession ratio (MPR) annual estimates, over the period from 2005 to 2008.

Table IV.1. Characteristics of the study cohort, for each semester from 2005-2008 period

	2005 S1	2005 S2	2006 S1	2006 S2	2007 S1	2007 S2	2008 S1	2008 S2	*P**
Number of subjects	125	142	148	149	148	151	149	146	--
Number of person-months	3.8	5.5	5.8	5.8	5.9	5.8	5.9	5.9	--
MPR < 95%, %	7.2	12.7	17.6	24.2	15.5	11.9	6.7	24.5	0.14
[95% CI]	[3.5;13.6]	[7.9;19.6]	[12.0;24.9]	[17.7;32.0]	[10.3;22.6]	[7.4;18.4]	[3.4;12.3]	[17.9;32.4]	
Detectable Viral load [(a)], %	43.5	36.5	31.6	30.6	29.5	34.0	28.3	29.2	**0.01**
[95% CI]	[34.8;52.7]	[28.6;45.2]	[23.9;40.3]	[23.3;38.9]	[22.5;37.6]	[26.6;42.2]	[21.3;36.5]	[22.0;37.4]	
CD4 < 350 cell/µL [(b)], %	37.3	36.7	37.6	30.8	32.9	29.3	27.8	30.6	**0.03**
[95% CI]	[29.0;46.4]	[28.9;45.3]	[29.5;46.4]	[23.5;39.1]	[25.5;41.1]	[22.3;37.4]	[20.8;36.0]	[23.3;38.9]	
CD4 < 200 cell/µL [(b)], %	11.9	13.7	17.3	14.7	18.1	16.0	13.9	12.5	0.94
[95% CI]	[7.0;19.2]	[8.6;20.8]	[11.5;25.0]	[9.5;21.8]	[12.5;25.5]	[10.7;23.1]	[8.9;20.9]	[7.8;19.3]	
Months since HIV diagnosis [(c)],	55.0	61.0	65.0	62.5	67.0	71.0	80.0	83.0	--
median (IQR)	(28.0-94.0)	(32.0-100.0)	(35.5 - 106.0)	(39.0 - 109.8)	(39.0 - 115.0)	(43.8 - 121.0)	(50.0 - 127.0)	(54.3 - 125.8)	
Months on HAART, median	45.2	49.3	51.1	51.2	55.8	61.6	67.7	73.6	--
(IQR)	(21.4;74.6)	(20.0;80.5)	(21.8;85.9)	(26.2;88.0)	(29.6;93.7)	(30.0;99.5)	(37.2;105.6)	(42.6;111.9)	
Started with non-HAART, %	26.4	26.1	26.4	24.8	23.0	23.2	22.1	20.5	0.12
Antiretroviral naïve, %	5.9	5.6	2.9	4.7	2.6	1.3	2.6	2.0	**0.01**
ART regimen, %									
2 NRTIs + NNRTI	49.6	50.0	52.0	51.7	53.4	51.0	49.0	50.0	0.92
2 NRTIs + PI	40.0	37.3	35.1	34.9	34.5	35.8	38.3	39.7	0.88
3 NNRTIs	3.2	2.8	2.7	4.0	3.4	4.6	4.0	3.4	0.52
PI and NNRTI–based regimens	1.6	2.8	2.0	1.3	1.4	1.3	1.3	1.4	0.41
4 antiretroviral drugs	4.8	4.2	4.1	3.4	4.1	3.3	3.4	2.7	0.33
Others	0.8	2.8	4.1	4.7	3.4	4.0	4.0	2.7	0.41

Table IV.1.1. Characteristics of the study cohort, for each semester from 2005-2008 period

	2005 S1	2005 S2	2006 S1	2006 S2	2007 S1	2007S2	2008 S1	2008 S2	*P* *
ART discontinuation	2.4	4.2	4.7	2.7	0.7	3.3	2.0	1.4	0.14
ART associations, %	48.8	50.0	48.6	56.4	63.5	65.6	61.7	74.0	**< 0.001**
ART changes, %	16.9	11.8	11.5	11.5	16.6	10.5	7.2	10.9	0.06
Hospitalizations, %	3.2	4.9	2.0	7.4	4.1	3.3	5.4	4.1	0.71
Visits per subject, mean ± SD	2.0 ± 1.4	1.7 ± 1.1	1.8 ± 1.1	1.7 ± 1.4	2.0 ± 1.1	1.9 ± 1.2	1.8 ± 1.1	1.9 ± 1.2	0.87
Past or current IDU, %	27.6	28.9	29.1	26.2	26.4	26.5	28.2	28.8	0.99
Past or current D/A, %	40.0	41.5	40.5	38.9	39.9	38.4	38.9	39.0	0.63
Male, %	64.8	63.4	63.5	61.7	60.8	60.9	63.1	62.6	0.84
Age, mean ± SD	41.2 ± 9.8	40.5 ± 9.5	41.1 ± 9.2	40.9 ± 9.4	41.6 ± 9.1	41.5 ± 9.3	42.6 ± 9.4	42.3 ± 9.4	--
Caucasian [(d)], %	81.3	81.3	81.4	80.0	78.9	76.9	77.6	75.9	0.15
Risk group HIV infection [(e)], %									
Heterosexual contact	45.0	44.4	46.1	51.1	51.4	51.7	49.3	51.4	0.10
Men having Sex with Men	23.3	22.2	20.6	19.8	19.3	18.9	19.7	18.6	0.36
IDU	23.3	25.2	25.5	22.0	22.1	21.7	22.2	22.9	0.65
Other	8.4	8.2	7.8	7.1	7.2	7.7	8.5	7.1	0.98

* p-value of the χ^2 test for trend (α=0.05). (a) % subjects with at least one medical appointment (visit) with detectable viral load. (b) % subjects with at least one medical appointment (visit) with CD4 cell count <350 or <200/µl. (c) missing information per semester ranges from 12 to 14% of the subjects. (d) missing information per semester ranges from 22 to 27% of the subjects. (e) missing information per semester ranges from 5 to 8% of the subjects. NRTI, Nucleoside Reverse Transcriptase Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; PI, Protease Inhibitor; IQR, Interquartile Range; ART, Antiretroviral therapy; HAART, Highly active antiretroviral therapy, defined as any regimen containing

Table IV.1.2. Medication Possession Ratio annual estimates, over the period from 2005 to 2008

	2005	**2006**	**2007**	**2008**	***P****
Number of subjects	146	157	154	157	
MPR < 95%, %	12.3	24.8	14.9	25.9	**0.03**
[95% CI]	[7.7;19.0]	[18.4;32.5]	[9.9;21.8]	[19.5;33.6]	

* p-value of the χ^2 test for trend (α=0.05). MPR, medication possession ratio (%). CI, confidence interval.

When considering semester analysis (Table IV.1.1), we found that the proportion of subjects with MPR <95% in the first calendar semesters of the study period were always lower than the proportion observed in the second ones. The 2008 second semester showed the highest proportion of non-adherent subjects (24.5%).

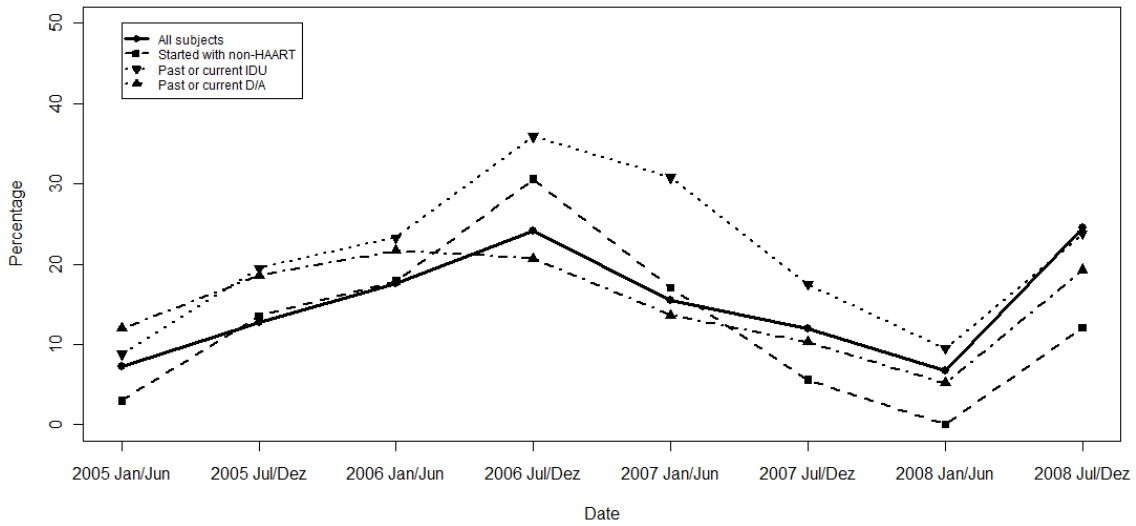

Figure IV.1.3. Prevalence of non-adherence, defined as MPR<95%, for each semester from 2005-2008 period. In all cases, p-values for linear trend were >.05. IDU, Injection Drug Use. D/A, depression/anxiety. Started with non-HAART, when the first antiretroviral treatment was with mono or dual antiretroviral therapy.

Adherence was also evaluated for different subgroups (Figure IV.1.3). A higher proportion of non-adherent subjects was observed among those with past or current IDU and among those that had past or current information of depression or anxiety. Subjects that had started ART in monotherapy or with a dual combination of antiretroviral drugs usually showed inferior estimates of non-adherence, with exception of the 2006 second semester.

HAART regimens and prescription of antiretroviral drugs

No significant differences were observed in the HAART regimens adopted at the HIV outpatient clinic, during the study period (Table IV.1.1). The two most usual options were regimens with 2 NRTIs plus 1 NNRTI or with 2 NRTIs plus PI. When considering individual antiretroviral agents, there was an increase in the number of subjects using atazanavir and fosamprenavir among the NRTIs and abacavir among NNRTIs (Figure IV.1.4).

A significant increase was observed in the proportion of subjects using ART associations (p-value <0.001). As shown in Figure IV.1.4, this is mainly due to the emtricitabine / tenofovir association and to the slight increase of the abacavir / lamivudine. There was a decrease in the proportion of subjects presenting at least one ART change during each semester.

Virological and immunological control

Over the study period, it was observed a significant decrease of the proportion of subjects with at least one registry of detectable HIV RNA viral load. In the 2008 second semester, 29.2% of the subjects presented detectable viral load. A similar decrease was observed for the proportion of subjects with at least one registry of CD4 cell count < 350 cell/µl. No trend was observed when CD4 inferior limit was set at < 200 cell/µl.

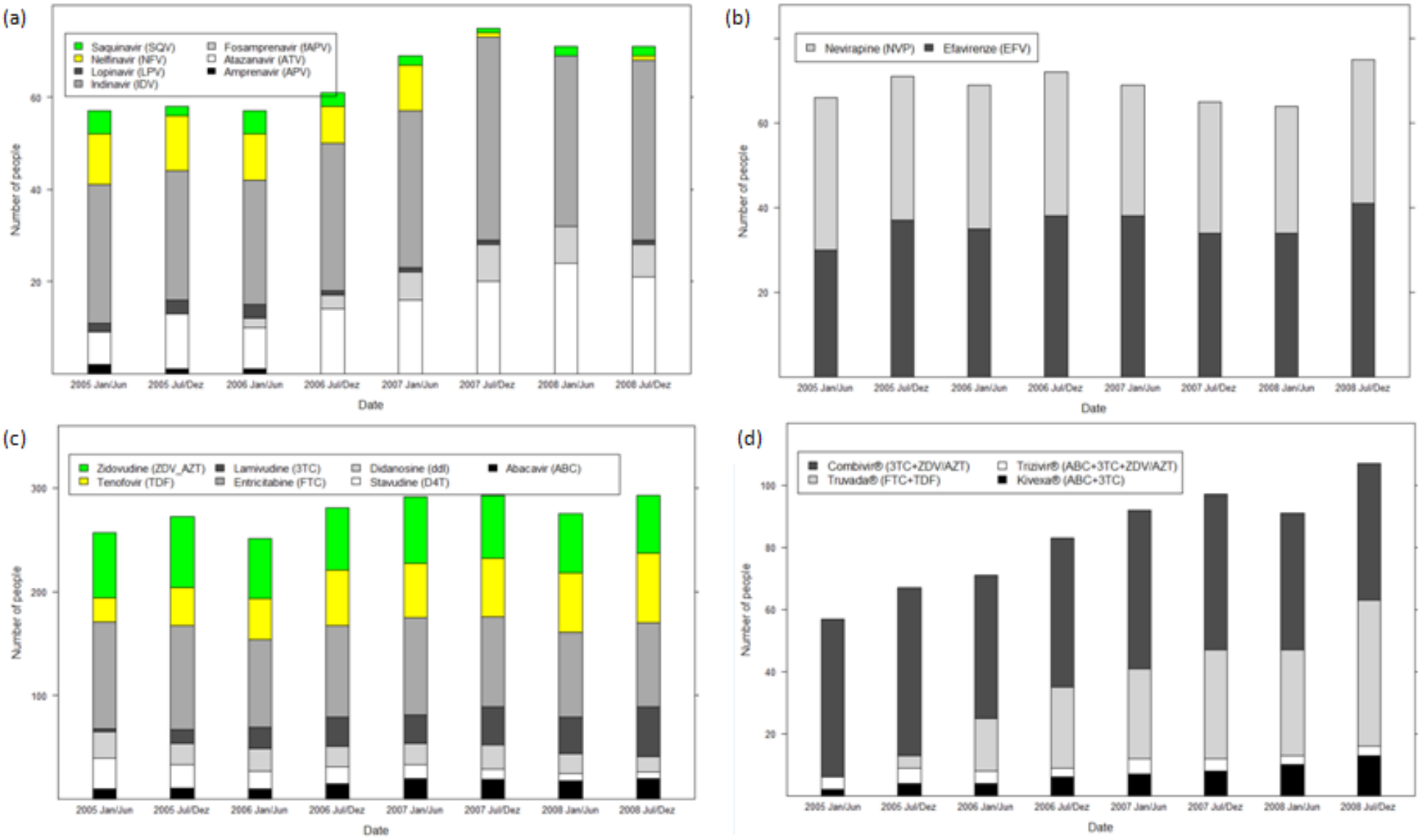

Figure V.1.4. Number of subjects prescribed to each antiretroviral drug [a) NRTIs, b) NNRTIs, c) PIs], and combinations [d)] at the first prescription of each semester.

Discussion

Adherence to HAART was high among the subjects followed at the outpatient clinic of HSM, but there seems to be an increase in the prevalence of non-adherence to treatment. The 2008 overall data revealed that a quarter of the subjects were non-adherent. These findings are inferior to the ones reviewed in a recent meta-analysis, in which the prevalence of adherence ≥90% to ART was estimated to be 62% worldwide, and 61% (95%CI 58-64%) for the 52 observed groups from Western Europe countries [7]. Some explanations could explain this difference. Firstly, the included studies were performed between 1999 and 2009, a larger period of time than the one observed in our study, and it has been described that earlier PI-based regimens presented a worst tolerability profile [12]. Secondly, different groups were included in the analysis, namely hospitalized and institutionalized patients and the IDU was the most common (44.4%) mode of HIV acquisition. Our study included only subjects followed at ambulatory care level, and the majority acquired HIV infection through heterosexual contact. Similar to our study results, subjects with past or current IDU seem to have a higher prevalence of non-adherence [7]. Another aspect is that our study included only those subjects that had at least 2 medical appointments from January 2005 until December 2008, which may lead to an overestimation of adherence to HAART (since we exclude those with only one visit to the outpatient clinic).

Some of these aspects are also present when we compare our study results with other Portuguese studies. For instance, Aragão *et al*. found an adherence level of 86% for the first regimen among the naïve patients followed at Centro Hospitalar de Cascais (Portugal) between 2002 and 2008, using also a pharmacy-based measure of adherence [19]. However, it is difficult to compare our study results with this finding, since only naïve subjects were included and several studies have indicated that non-adherence was higher in the first year of

treatment. On the other hand, Aragão *et al*. included only subjects that had persisted in treatment, which usually leads to an underestimation of non-adherence: the 2010 UNAIDS report indicates that 84% of Portuguese adult subjects were still receiving ART 12 months after initiation [19, 20].

The 6-month analysis of adherence aimed the assessment of eventual temporal patterns of non-adherence. We have found that non-adherence was more prevalent in the second semesters, which may be related to the inclusion of the holiday seasons during these periods. Since ART refill usually covers one-month periods, this finding suggests that medication should be available for a larger period (e.g. 2 months) and that adherence during holidays should be reinforced by the physician.

The 2006 and 2008 calendar years seemed to have a higher prevalence of non-adherence. A larger time window should be considered to confirm the bi-annual pattern, since this trend was not observed in other variables that could explain the observed differences, such as regimen changes, average of medical appointments per subject or number of hospitalizations. In addition, as MPR was equally assessed in every semester and took into account the leftovers from previous periods, we do not expect that this pattern could result from bias in the adherence evaluation. The exception is made for the 2005 first semester, in which we were not able to account for previous leftover and, thus, non-adherence could have been overestimated. Moreover, this method' limitation does not explain the trend.

Similar to other studies, our findings show that non-adherence is higher among subjects that had past or current IDU or had depression / anxiety disorders [12, 21]. Nevertheless, the overall prevalence of non-adherence in the 2008 second semester was similar to the one observed for the subgroup of past or current IDU and higher than that of the group with

depression / anxiety registry. This may highlight that other adherence' determinants were more relevant in 2008.

Regarding HAART prescription during this period, we found no significant change at regimen level. The most frequently prescribed regimens included a dual NRTI component plus a third agent, NNRTI or PI, in line with the actual guidelines on the treatment of HIV infection [5, 22]. At individual drug level, there was a slight increase in the use of abacavir and lamivudine, which probably reflects the need for using an alternative regimen (compared to tenofovir/emtricitabine one) for prevalent HAART users.

There was a marked increase in the use of fixed-dose antiretroviral combinations, which seems mainly related to the availability of tenofovir/emtricitabine option. Since there was no relevant increase in the number of users for these two NRTIs, the increase of its combination reflects the clinical practice to simplify the prescribed regimens. Simplification is a strong recommendation for adherence improvement [6, 11, 22]. Although, in our study, we cannot evaluate if this simplification resulted from previous non-adherence, we are now conducting a prospective study that addresses the possible reasons for HAART changes (ongoing research). On the other hand, the increase of non-adherence raises the question of whether this could be a consequence of the combination use and, if so, the need to evaluate the economic impact of non-adherence with these usually more expensive options.

Non-adherence is pointed out as a major determinant of virological control. However, our study shows a significant decrease in the proportion of subjects with detectable viral load, across the study period. When considering immunological data, a similar decrease was observed in subjects with CD4 cell count less than 350/µl. Two explanations are possible. Firstly, the fact that our cohort is mainly constituted by ART-experienced users and secondly, that recent studies had shown that adherence seem to be less related to viral load after viral

suppression is achieved and maintained [23, 24]. Lima *et al*. found that, among 1305 individuals who achieved initial viral suppression, 21% presented a subsequent virological rebound. However, the risk of virological rebound decreased with longer duration (in years) of initial viral suppression (OR, 0.37; 95% CI, 0.32 to 0.42) [23]. Another hypothesis is that the effectiveness of newer antiretroviral agents may be reasonable for adherence levels inferior to 95% [25, 26]. In fact, this cut-off was based in older studies that only considered PIs as antiretroviral agents, while other studies showed that sustained viral suppression was also obtained by subjects on NNRTI-based regimens who had adherence rates lower than 95% [27, 28]. It seems less probable that the decrease of detectable viral load may be related to the decrease in the number of ART-naïve subjects, since we did not consider the first medical appointment with ART prescription (at which viral load is always detectable). The significant decrease in ART-naïve subjects may reflect the decreasing trend in the Portuguese incidence of the HIV infection: 16.4 (2005) to 15.8 (2008) per 100 000 population [29].

Study limitations

Adherence and antiretroviral prescription were presented as aggregate data, according to calendar semester or year. This approach provided overall information of the actual clinical practice that, however, had to be more comprehensively analyzed. For instance, in this study, we did not link the prescription of ART with subjects' stage of HIV infection or their history of comorbidities and other clinical conditions. Data collection from hand-written clinical records was necessary due to the absence of electronic databases that could be linked to pharmacy claims information. Actually, this was the main reason why our study had a smaller sample size when compared to others with similar aims [12, 13]. Furthermore, clinical records missed information about other demographic characteristics that might be related to

adherence (e.g. professional status and familiar support). Another study limitation derives from using a pharmacy-based measure to assess adherence: when using ART refill data, we are assuming that all refilled medication will be actually taken by the subjects. This is an already recognized problem and results in the overestimation of actual adherence [18].

Practice implications and conclusion

Although our sample may not be representative of the total Portuguese population under HAART, this study provides a good description of recent clinical practice and reinforces the need for addressing barriers to adherence. The prescription pattern seems to be in accordance with guidelines for the treatment of HIV/AIDS infection, including the use of fixed-dose combinations as a way to simplify HAART regimens. Furthermore, physicians should continue to promote adherence among IDU and subjects with depression / anxiety, and during holiday seasons.

Several questions were raised from this analysis, such as the assessment of the relationship between adherence and HIV clinical outcomes, and the identification of adherence determinants in nowadays practice. Further studies, with larger datasets and more comprehensive information at individual level, are required to address these questions, and to characterize the impact of the increased use of fixed-dose combinations.

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IV.2.

Determinants, pattern and outcomes of non-adherence to HAART in a Portuguese cohort of HIV-1 infected subjects

Abstract

Objectives: To identify the determinants of non-adherence to HAART during 2008, to characterize frequency and duration of medication gaps and to verify the association of non-adherence with immunological and virological outcomes, among HIV-1 infected adults.

Methods: A sample was randomly selected from the HIV-1 adult infected subjects followed up at a HIV outpatient clinic of the largest Portuguese hospital and having at least one HAART refill between 01-01-2005 and 31-12-2008. Average adherence was determined as medication possession ratio (MPR), and non-adherence was defined as MPR<95%. Detectable viral load (>40 copies/ml) and CD4 cell count <350/µl in 100% of recorded measurements per subject and throughout follow-up were also analyzed.

Results: A total of 157 subjects were included in the analysis, 4.5% were HAART-naïve at baseline, 74.1% of the subjects had MPR≥95%. Having periods >12 months without medical appointments previous to baseline and 3 or less years of HAART experience were significantly associated to non-adherence. The majority (81.6%) of the non-adherent subjects had more than one medication gap with length < 30 days. It was observed a significant decrease in the proportion of subjects with CD4 <350/µl and viral load >40copies/ml with the increase of the average adherence. Time on HAART and AIDS classification at diagnosis seemed also to be related to virological and immunological outcomes.

Conclusions: Subjects with less time with HAART experience and those that had already abandon medical appointments for a period>12 months are more likely non-adherents. Lower to moderate average adherence levels and shorter HAART gaps are frequent among HIV-1 infected adults.

Keywords: HIV/AIDS infection; patient adherence; antiretroviral treatment; pharmacy refill.

Background

The relation between the success of highly active antiretroviral therapy (HAART) and adherence has been well documented [1, 2]. Although some studies have shown that virological failure and emergence of drug resistance is not always directly associated with patient non-adherence to treatment [3, 4], this is still a major determinant of clinical success, with impact at healthcare utilization and costs [5, 6].

Using a pharmacy-refill measure of adherence, we have found that 25.9% of the HIV-1 infected adults followed at ambulatory level during 2008 had a medication possession ratio (MPR) <95%. This unpublished data revealed a significant increase of non-adherence among a random sample of subjects followed up at the HIV outpatient clinic from *Hospital de Santa Maria* (HSM, Lisbon, Portugal), a university tertiary central hospital, the largest in Portugal, which followed around 2000 HIV-infected subjects under antiretroviral treatment in 2009 [7]. These findings are similar to the results of a recent meta-analysis, which reported that the average adherence rate of ≥90% is 62% worldwide, and reinforces the need for addressing barriers to adherence by identifying its associated factors [2, 8].

The main determinants of adherence to HAART have been already described, including treatment-, infection-, health system- related variables that may influence medication intake [9, 10]. However, it has been highlighted the need to perform local assessment of adherence determinants and to update this information for newer antiretroviral options [11].

Adherence is a dynamic and complex behaviour [9, 12]. The pattern of drug use and moment of therapy at which missed doses occur may also affect the level of adherence required to maintain viral suppression. Some studies on structured intermittent therapy had shown that HIV-infected subjects experienced no virological rebound, and it has been suggested that a

higher adherence is essential at the beginning of HAART, while lower adherence may be tolerated after viral suppression has been achieved and sustained for a certain length of time[4, 12, 13]. Thus, it seems relevant to address the pattern of non-adherence to HAART alongside with its determinants, in order to achieve better effectiveness of the available regimens [2].

Our study aimed to identify the determinants of non-adherence to HAART during 2008 and to describe how frequent it is for a subject to be without antiretroviral medication, and for how many days, in a sample of HAART-naïve or experienced HIV-1 infected adults. We also aimed to study the association of non-adherence with immunological and virological outcomes.

Methods

Study design and participants

Data was retrospectively collected for the *Prevalence and determinants of patient adherence to antiretroviral treatment and regimen modification in a Portuguese cohort of HIV-infected adults* (ATAR-VIH) study. This is an ongoing observational longitudinal study, that aims to determine the prevalence and determinants of non-adherence to HAART and it is being conducted on HIV-1 adult subjects followed up at the HIV outpatient clinic from HSM. A sample of 320 subjects was randomly selected from a total of 2861 HIV infected subjects who had antiretroviral refills between January 2005 and December 2008. Sample size assumed an exclusion rate of 35%, a non-adherence prevalence of 50%, and that the final inclusion of 200 subjects would enable a precision estimate ± 7% of the true frequency of non-adherence to

HAART (α=.05), during the period from January 2005 until December 2008. The ATAR-VIH study was authorized by the Ethics Committee of the *Hospital de Santa Maria* (Lisbon, Portugal), and by the Portuguese Data Protection Authority.

With this analysis, we aim to evaluate the main non-adherence determinants for the 2008 year. We included subjects with HIV-1 infection that had started antiretroviral treatment at HSM clinic when aged ≥ 18 years, that had at least two medical appointments during 2005-2008 period and at least one medical appointment and 2 pharmacy refills during year 2008 (study period), with no participation on clinical trials. Baseline data were retrieved from the last medical appointment with HAART prescription before January 1st, 2008. Subjects were followed up until last visit before 31-12-2008 or censored at date of death or date of being arrested, under a social institution care or being dependent of a third person for taking medication.

Adherence definition and measure

Adherence was assessed from the pharmacy registry that included the refills between 01-01-2005 and 31-12-2008, and for specific index antiretroviral drug, defined as the protease inhibitor or, if not applicable, the non-nucleoside reverse transcriptase inhibitor or abacavir/tenofovir [14, 15]. We defined the number of days with available medication between each contiguous refill as (pills dispensed/pills prescribed per day) for the index drug. Pills prescribed per day were calculated based on the recommended daily dosage, and confirmed with the information available from the clinical records. In case of overlapping refills, we assumed that HAART was taken sequentially and accounted for the leftovers when estimating adherence [14, 16].

According to the study aims, two measures of adherence were considered:

1) For the overall compliance evaluation, we determined individual medication possession ratio (MPR) using a fixed 12-month period, defined as the number of days for which prescribed medication was available from January until December 2008, divided by 366 days and expressed as percentage (Figure IV.2.1). When considering HAART-naïve subjects, denominator was corrected to include only the number of days between the first refill and December, 31st. MPR assumed leftovers from 2007 and was truncated at 100%. A cut-off of ≥ 95% was assumed as good adherence, in accordance with the international guidelines on HIV infection management[1, 17, 18].

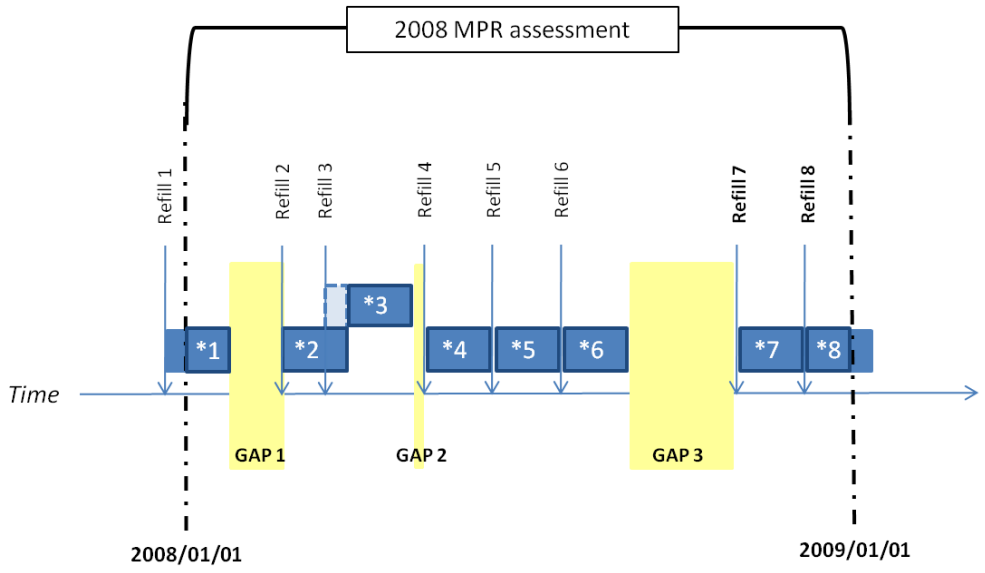

Figure IV.2.1. Schematic representation of the assessment of medication possession ratio (MPR) and medication GAP, during 2008 year. MPR were determined as the total number of days with ART available (*periods) from all refills occurring in 2008, divided by 366 days. Medication GAPs were identified as number of days without available ART, between refills. Leftover medication from previous refills was taken into account in both MPR and GAP assessment.

2) Among those subjects that presented MPR <95%, we assessed the existence of single-interval periods for which there was an insufficient refill of medication, by retrieving individual medication gaps (GAP), i.e. the number of days between the expected end date of a refill and the start date of the following one (Figure IV.2.1).

Factors associated with non-adherence

Hand-written clinical records were analysed to obtain laboratorial data and information about adherence determinants, after being linked to pharmacy registry, through the subjects' individual number at HSM [9, 10]. Figure IV.2.2 presents the collected variables, such as gender and age at baseline, injection drug use (IDU) behaviour (past or current), hospitalizations prior to 2008 year, time since HIV-1 diagnosis at baseline (in years), viral load and CD4 cell count and prevalence of co-morbidities. Psychiatric treatment was defined as diagnosis of depression or anxiety, or taking antidepressants (ATC code N06A) or anxiolytics (ATC code N05B). Treatment-related factors included time on HAART at baseline, number of previous antiretroviral regimens at baseline and HAART changes during the study period.

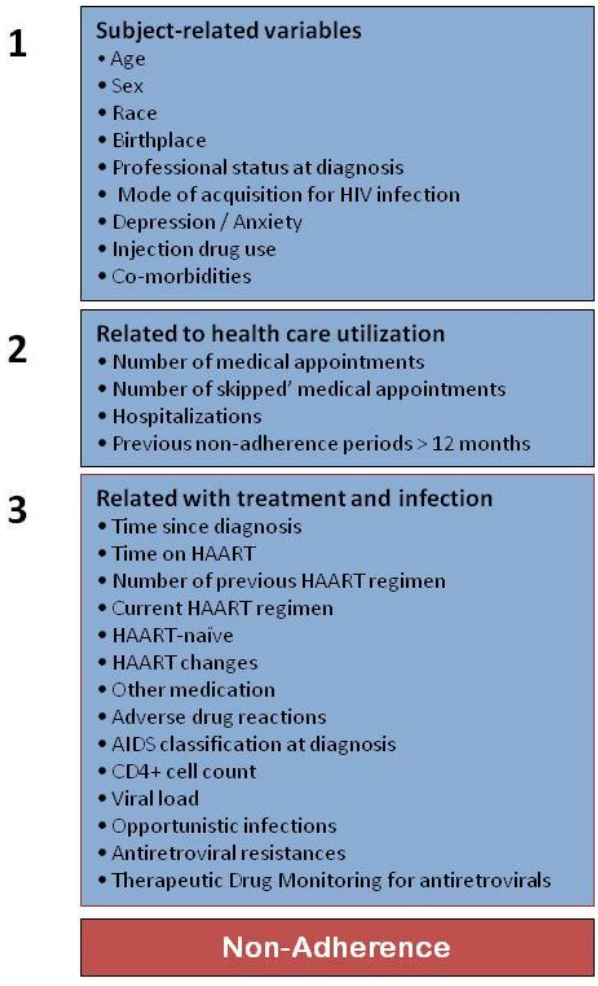

Figure IV.2.2. Variables related to subject (group 1), to health care utilization (group 2) and related to treatment and infection (group 3).

Statistical analysis

Descriptive statistics were used for the sample characterization at baseline and to analyse frequency and duration of GAPs. For the estimates of the proportion of subjects with MPR<95%, detectable viral load and CD4 cell count <350/µl, 95% confidence intervals (CI) were determined assuming a binomial distribution. All statistical analysis was performed with R software, version 2.12.1 (www.r-project.org).

Based on variables described as potential determinants of non-adherence (Figure IV.2.2), we aimed to verify if variables related to subject (group 1), health system (group 2) and treatment and infection related variables (group 3) were significantly associated with non-adherence. Assuming non-adherence as a dichotomised variable, we compared adherent (MPR ≥95%) *vs.* non-adherent groups through χ^2 (or Fisher's exact test) or Mann-Whitney test, for categorical or continuous variables, respectively. We specifically evaluated possible differences in the proportion of subjects with at least one clinical record of CD4 cell count < 350/µl or detectable viral load (>40 copies/ml), for different adherence levels, by using χ^2 test. A 5% significance level was adopted for all statistical hypotheses tests.

A multivariate logistic unconditional regression model was performed in order to identify predictors of non-adherence. Factors were entered into the regression model if they were found by univariate analysis to be significantly or marginally associated ($P \leq 0.15$) [19, 20]. A stepwise procedure was used to select variables to be included in each model. A variable was omitted if the p-value for the likelihood ratio test was less than 0.05 [21]. Estimates of the odds ratio (OR) and 95% CI were calculated for collected variables. Hosmer-Lemeshow test and Receiver Operating Characteristic (ROC) curves were used to assess the validity of the final model.

Results

Participants

As shown in Figure IV.2.3, a total of 157 subjects were included in the analysis. The cohort baseline characteristics are presented in Table IV.2.1.

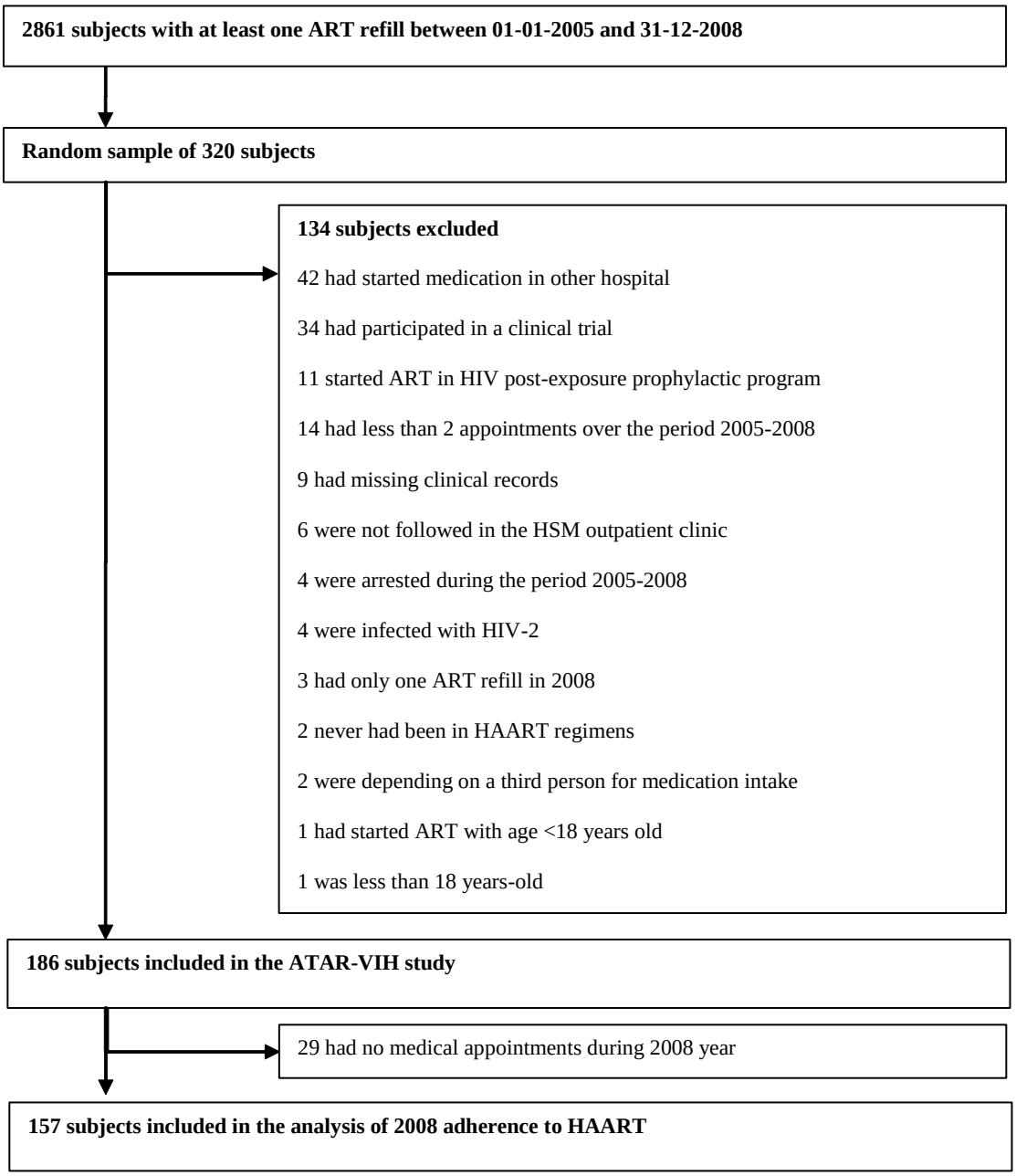

Figure IV.2.3. Study flowchart.

Table IV.2.1. Characteristics of the study cohort, at baseline

	(n=157)
Male, %	63.7
Age, mean±SD (years)	42.3±9.2
Race, %	
Caucasian	77.4
Black	18.5
Other race	0.04
missing information, n (%)	33 (21.0)
Birthplace, %	
Portugal	63.9
Angola	10.9
Cape Verde	9.6
Mozambique	7.2
Guinea-Bissau	4.8
Other	3.6
missing information, n (%)	74 (47.1)
Professional status at diagnosis, % ‡	
Employed	66.4
Unemployed	21.4
Retired	4.6
Housewife	3.8
Student	3.0
Other	0.8
missing information, n (%)	26 (16.6)
Mode of acquisition for HIV infection, %	
Heterosexual contact	47.8
Injection Drug Use	21.6
Men having Sex with Men	18.5
Other risk group	7.6
missing information, n (%)	7 (4.5)
Past or current IDU, %	26.8
Co-morbidities, %	44.6
Past or current Depression/Anxiety, %	38.2
AIDS classification at diagnosis, %	
Non-AIDS	53.7
AIDS	46.3
missing information, n (%)	62 (39.5)

	(n=157)
AIDS classification at baseline, %	
Non-AIDS	62.1
AIDS	37.9
missing information, n (%)	12 (7.6)
Detectable viral load [(a)], %	24.2
Detectable viral load 12 months before baseline, %	22.9
CD4 count < 350 cells/µl [(b)], %	26.8
CD4 count < 350 cells/µl 12 months before baseline, %	24.3
Opportunistic infections [(c)], %	44.6
HAART-naïve, %	4.5
Age when starting HAART, mean±SD (years)	36.88 ± 9.3
Started ART with non-HAART regimens, %	22.3
No. of HAART regimens, median (IQR) †	1.0 (1.0-2.0)
Time on HAART, median (IQR) (months)	65.6 (33.2-110.5)
Time since HIV diagnosis, median (IQR) (months)	84.0 (60.0-132.0)
missing information, n (%)	4 (2.5)
HAART regimen, %	
2 NRTIs + NNRTI	47.1
2 NRTIs + PI	39.5
3 NNRTIs	3.8
4 antiretroviral drugs	3.8
Other regimens	5.7
Skipped medical appointments [(d)], %	24.2
Hospitalized [(e)], %	28.0
Previous periods >12 months without medical appointments [(f)], %	9.6
Other medication, %	37.0
Adverse drug reactions [(g)], %	49.0
Antiretroviral resistances, %	14.2
Therapeutic Drug Monitoring over 2008 year, %	7.6

† Number of different HAART regimens at baseline, including the current one. ‡ Professional status as registered in the subjects' first medical appointment. Considering the clinical history previous to baseline, table shows % of subjects with at least one (a) medical appointment with detectable viral load, (b) medical appointment with CD4 cell count <350/µl, (c) opportunistic infection, (d) skipped medical appointment, (e) hospitalization, (f) one previous period of at least 12 months without medical appointments and (g) one adverse drug reaction. NRTI, Nucleoside Reverse Transcriptase Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; PI, Protease Inhibitor; IQR, Interquartile Range; SD, Standard Deviation; ART, Antiretroviral therapy; HAART, Highly active antiretroviral therapy, defined as any regimen containing three or more antiretroviral medications or containing a NNRTI and a PI; IDU, Injection Drug Use.

Regarding treatment's experience, the median time on HAART was 65.6 (IQR: 33.2-110.5) months, 22.3% had started treatment with non-HAART regimens and only 4.5 % were HAART-naïve at baseline. The mean number of days of study participation was 215.9 ± 87.9, with a total of 1410 refills (9.0±3.3; mean±SD, refills per subject). The MPR estimates ranged from 0.1 to 100% (median 100%, IQR: 94.4-100.0%), with 74.1% of the subjects presenting MPR≥95%.

Factors associated with non-adherence (MPR<95%)

Table IV.2.2 presents the univariate analysis of factors related to non-adherence, defined as MPR<95%. Among variables related to subject characteristics, we found that age and co-morbidities were significantly associated to non-adherence. Regarding age, younger subjects (aged ≤35years-old) were more likely to be non-adherent (OR 3.14), when compared to subjects older than 45 years. Having a previous record of at least one co-morbidity was also associated to non-adherence (OR 2.65). In group 2 (variables related to health care utilization), only the number of previous medical appointments at baseline was significantly associated to non-adherence. Subjects with ≤8 medical appointments had a higher probability of being non-adherent (OR 3.94). When considering the variables related to treatment and HIV infection (group 3), time since diagnosis of HIV infection, time on HAART, being HAART-naïve, the number of previous ART regimens (including non-HAART options) and having at least one record of detectable viral load previous to baseline were also significantly associated to non-adherence. Subjects with less time since diagnosis and HAART beginning had higher probability of being non-adherent (OR 4.33 and 4.77, respectively), as well as those that were HAART-naïve or were in their first HAART regimen (OR 4.67 and 2.90,

respectively). A previous experience of detectable viral load was also associated to non-adherence (OR 2.74).

Table IV.2.2. Univariate analysis of determinants of non-adherence, according to baseline information

Variable	% subjects MPR≥95%	% subjects MPR<95%	p-value	Univariate OR	95% CI
Group 1: Subject-related variables					
Male			0.57		
No	26.1	10.2		1.00	
Yes	48.4	15.3		0.81	0.36 - 1.83
Age (years)			**0.01***		
Older than 45	23.6	7.0		1.00	
36 – 45	38.8	7.0		0.61	0.22 - 1.72
35 or younger	12.1	11.5		3.14	1.14 - 9.03
Age when starting HAART (years)			**0.16***		
Older than 40	22.3	7.0		1.00	
31 – 40	40.1	7.7		0.61	0.22 - 1.70
30 or younger	14.0	8.9		2.01	0.70 – 5.88
Mode of acquisition for HIV infection			0.84*		
Heterosexual contact	35.0	12.7		1.00	
Injection Drug Use	13.4	5.1		1.05	0.34 - 2.97
Men having Sex with Men	16.6	5.1		0.85	0.28 - 2.35
Other	5.1	2.5		1.37	0.27 - 5.83
Past or current IDU			0.54		
No	53.5	19.8		1.00	
Yes	21.0	5.7		0.74	0.28 - 1.81
Past or current Depression/Anxiety			0.45		
No	44.6	17.2		1.00	
Yes	29.9	8.3		0.72	0.31 - 1-62
Co-morbidities			**0.01**		
No	45.8	9.6		1.00	
Yes	28.7	15.9		2.65	1.20 - 6.03
Group 2: Related to health care system					
Number of medical appointments (2005 – 2008)			**0.01***		
More than 16	19.1	5.1		1.00	
9 – 16	47.1	11.5		0.91	0.33 - 2.70
8 or less	8.3	8.9		3.94	1.20 - 13.87
Number of medical appointments (12 months before baseline)			0.10		
More than 4	15.9	2.6		1.00	
3 – 4	45.2	14.0		1.93	0.57 - 8.44
2 or less	15.3	7.0		2.82	0.71 - 13.85

Variable	% subjects MPR≥95%	% subjects MPR<95%	p-value	Univariate OR	95% CI
Mean number of medical appointments per subject's year of HAART experience			**< 0.01***		
More than 3	19.7	12.1		1.00	
3 or less	56.7	11.5		0.33	0.14 – 0.76
Skipped medical appointments			0.83		
No	56.1	19.7		1.00	
Yes	18.5	5.7		0.88	0.33 - 2.19
Hospitalizations			1.00		
No	53.5	18.5		1.00	
Yes	21.0	7.0		0.96	0.39 - 2.28
Previous periods >12 months without medical appointments			0.12		
No	70.7	19.8		1.00	
Yes	5.7	3.8		2.37	0.64 - 8.15
Group 3: Related with treatment and infection					
Time since diagnosis (years)			**< 0.01***		
More than 10	23.6	3.8		1.00	
6 – 10	31.2	8.3		1.62	0.52 - 5.74
5 or less	17.8	12.7		4.33	1.44 - 14.99
Time on HAART (years)			**< 0.01***		
More than 7	33.8	4.5		1.00	
4 - 7	27.4	6.4		1.75	0.55 - 5.92
3 or less	15.3	12.7		6.19	2.16 - 19.79
Number of pills/day			0.71		
More than 4	32.5	12.1		1.00	
4 or less	42.0	13.4		0.85	0.39 - 1.88
HAART-naïve			**0.05**		
No	74.5	21.0		1.00	
Yes	1.9	2.5		4.67	0.75 - 33.44
Number of previous HAART regimen †			**0.01**		
More than 1 regimen	31.8	4.5		1.00	
1 regimen	44.6	19.1		3.04	1.19 - 8.87
Current ART regimen			0.65*		
2 NRTIs + NNRTI	35.7	11.5		1.00	
2 NRTIs + PI	31.2	8.3		0.83	0.33 - 1.99
3 NRTIs	2.5	1.3		1.55	0.12 - 11.86
4 antiretroviral drugs	2.5	1.3		1.55	0.12 - 11.86
Other regimens	5.1	0.6		0.39	0.01 - 3.28
ART changes			0.10		
No	36.9	16.6		1.00	
Yes	37.6	8.9		0.53	0.23 - 1.18

Variable	% subjects MPR≥95%	% subjects MPR<95%	p-value	Univariate OR	95% CI
Other medication			0.09		
No	43.9	19.1		1.00	
Yes	30.6	6.4		0.48	0.19 - 1.13
Adverse drug reactions			0.20		
No	35.7	15.3		1.00	
Yes	38.8	10.2		0.61	0.27 - 1.34
Antiretroviral resistances			0.58		
No	66.9	19.7		1.00	
Yes	9.6	3.8		1.35	0.40 - 4.09
Therapeutic Drug Monitoring over 2008 year			0.73		
No	70.0	22.3		1.00	
Yes	6.4	1.3		0.63	0.06 - 3.17
AIDS classification at diagnosis			0.64		
Non-AIDS	39.0	14.7		1.00	
AIDS	35.8	10.5		0.78	0.27 - 2.18
Previous LyT CD4+ cell count			0.12		
< 350 cell/µl	16.6	8.3		1.00	
≥ 350 cell/µl	54.1	13.4		0.50	0.20 - 1.24
12 months before baseline LyT CD4+ cell count			0.81		
< 350 cell/µl	18.4	5.9		1.00	
≥ 350 cell/µl	59.5	16.2		0.85	0.31 - 2.48
Previous viral load			**0.02**		
Non-detectable	56.7	13.4		1.00	
Detectable	14.6	9.6		2.74	1.12 - 6.63
12 months before baseline viral load			0.81		
Non-detectable	59.3	17.8		1.00	
Detectable	18.5	4.4		0.80	0.24 - 2.32
Opportunistic infections			0.36		
No	39.5	15.9		1.00	
Yes	35.0	9.6		0.67	0.30 - 1.49

*Qui-square test for trend. †Number of different HAART regimens at baseline, including the current one. OR, odds ratio estimate; CI, confidence interval; NRTI, Nucleoside Reverse Transcriptase Inhibitor; NNRTI, Non-Nucleoside Reverse Transcriptase Inhibitor; PI, Protease Inhibitor; ART, Antiretroviral therapy; HAART, Highly active antiretroviral therapy, defined as any regimen containing three or more antiretroviral medications or containing a NNRTI and a PI; IDU, Injection Drug Use.

Table IV.2.3 shows the logistic regression model and the OR estimates. Adjusting for the variables that presented P≥0.15 in the univariate analysis, having periods of at least 12 months without medical appointments previous to baseline and 3 or less years of HAART experience

remained as significantly associated to non-adherence. The final model was considered adequate according to the Hosmer-Lemeshow test (statistic value =6.9, P=0.547). The ROC curves returned an area under the curve of 0.801, with a sensitivity of 80.0% and a specificity of 74.3%.

Frequency and length of medication GAPs

For non-adherent subjects (MPR<95%), we have analysed the frequency and length of medication GAPs. As shown in Figure IV.2.4, 18.4 % of the non-adherent subjects had only one GAP, whereas 71.1 % had less than 4 GAPs (median 2.5, IQR: 2.0-4.0). The majority (81.5%) of the observed GAPs had lengths <50 days, and 68.9 % were <30 days. The distribution of GAPs per subject confirmed that 81.6% of the non-adherent subjects had more than one GAP with length <30 days.

Table IV.2.3. Adjusted associations for non-adherence.

Variable	β	OR	95% CI	p-value
(Intercept)	-3.35	0.04	(0.00 - 0.26)	< 0.01
Co-morbidities				
No				
Yes	0.68	1.95	(0.76 - 4.89)	0.15
Mean number of medical appointments per subject's year of HAART experience				
More than 3				
3 or less	0.86	2.37	(0.68 – 8.24)	0.17
Previous non-adherence periods > 12 months				
No				
Yes	1.96	7.14	(1.71 – 29.78)	**0.01**
Viral load				
Non-detectable				
Detectable	0.59	1.80	(0.70 - 4.64)	0.22
Time on HAART (years)				
More than 7				
5 – 7	0.44	1.55	(0.45 – 5.30)	0.48
4 or less	2.11	8.26	(1.89 – 36.08)	**0.01**
Age (years)				
Older than 45				
36 – 45	-1.18	0.31	(0.10 – 0.99)	**0.05**
35 or younger	0.51	1.67	(0.54 – 5.15)	0.37
Number of previous HAART regimen				
More than 1 regimen				
1 regimen	0.50	1.65	(0.55 – 4.95)	0.37

OR, odds ratio estimate; CI, confidence interval; ART, Antiretroviral therapy

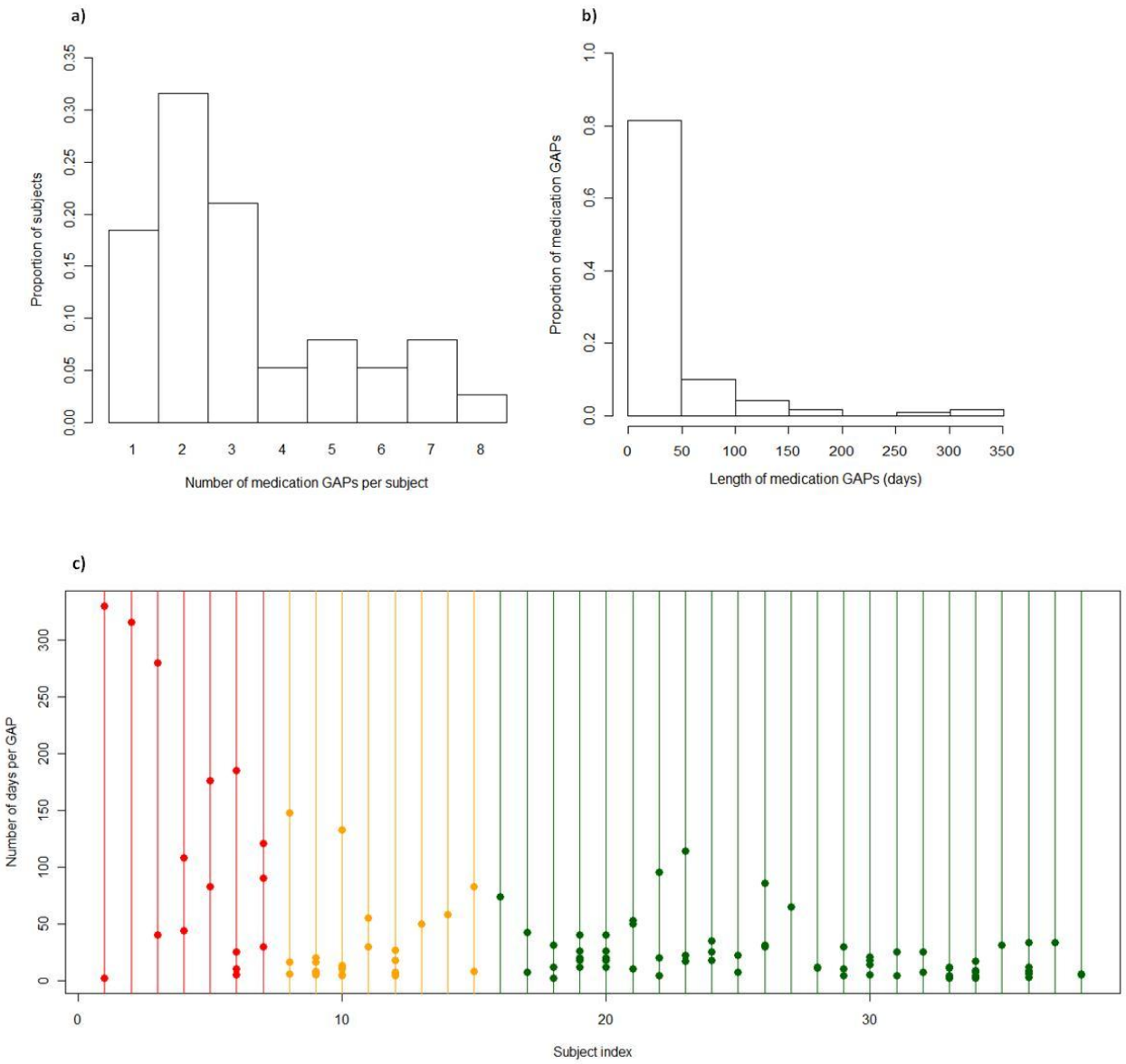

Figure IV.2.4. Distribution of medication GAPs, observed for the non-adherent subjects (MPR<95%) over 2008: frequency of GAPs per subject (a); frequency of the lengths of all observed GAPs; d) number and length of observed GAPs, for each non-adherent subject, according to MPR%

[0-50[(red), [50-75[(yellow), and [75,95[(green).

Association of average non-adherence with immunological and virological outcomes

We identified a statistically significant (P<0.001) decrease in the proportion of subjects with at least one 2008 record of CD4 cell count <350/µl across different adherence levels. In fact, this proportion was 85.7% among the subjects with MPR<50%, decreasing to 57.1% for subjects with MPR between 50 and 74% and to 22.1% for those with MPR≥75% (Figure IV.2.5). A statistically significant (P=0.008) decrease was also observed for the proportion of subjects with detectable viral load, though this proportion was similar in the less adherent levels: 57.1% among the subjects with MPR<50% and MPR 50-74%, while only 22.4% had detectable viral load when MPR≥75% (Figure IV.2.5). No statistically significant differences were observed between adherence level 75-95% and ≥95%, for both outcomes.

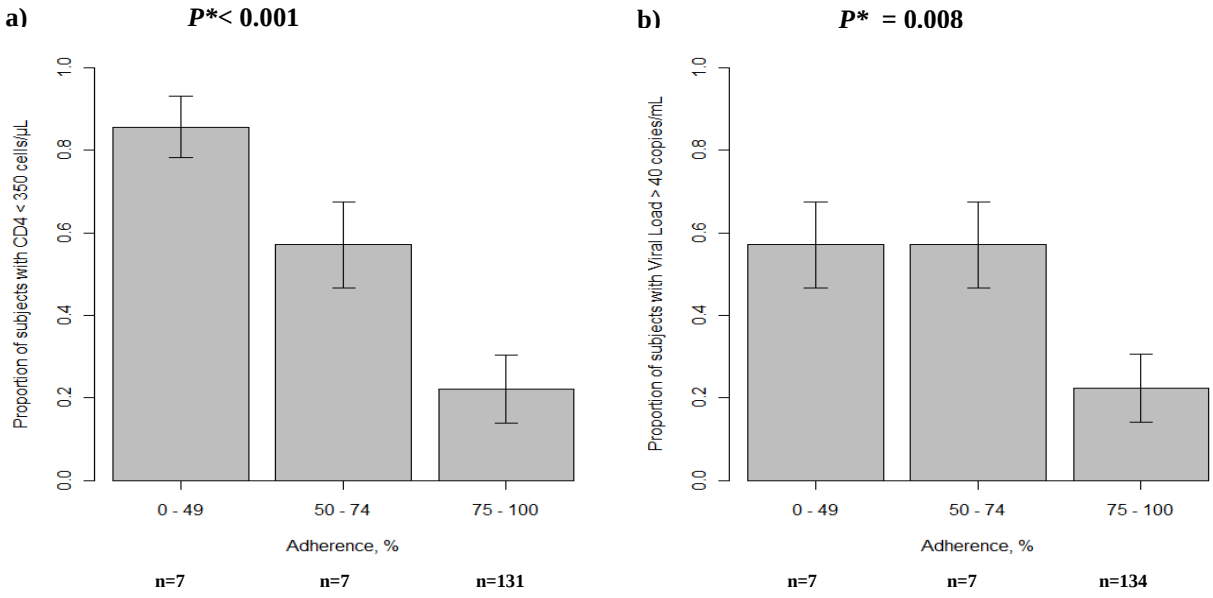

Figure IV.2.5. Proportion of subjects with at least one record of CD4 cell count <350/µl (a) or detectable viral load (b), for different adherence' levels, over 2008. No statistically significant differences were observed between adherence level 75-95% and ≥95%, for both outcomes. The error bars represent 95% CIs around the estimate of the respective proportions, assuming a binomial probability distribution and using the sample sizes listed. P*, p-value for the χ^2 test for trend.

The decrease in the proportion of subjects with CD4 cell count <350/µl was also observed across different adherence levels, within time strata after HAART initiation (Figure IV.2.6) and according to HIV infection status (AIDS vs. non-AIDS) at diagnosis (Figure IV.2.7). The decrease seemed to be more evident among the subjects with 3 or more years on HAART when comparing to subjects with less time on HAART, as well as among non-AIDS subjects when comparing to those presenting AIDS at the moment of HIV infection diagnosis.

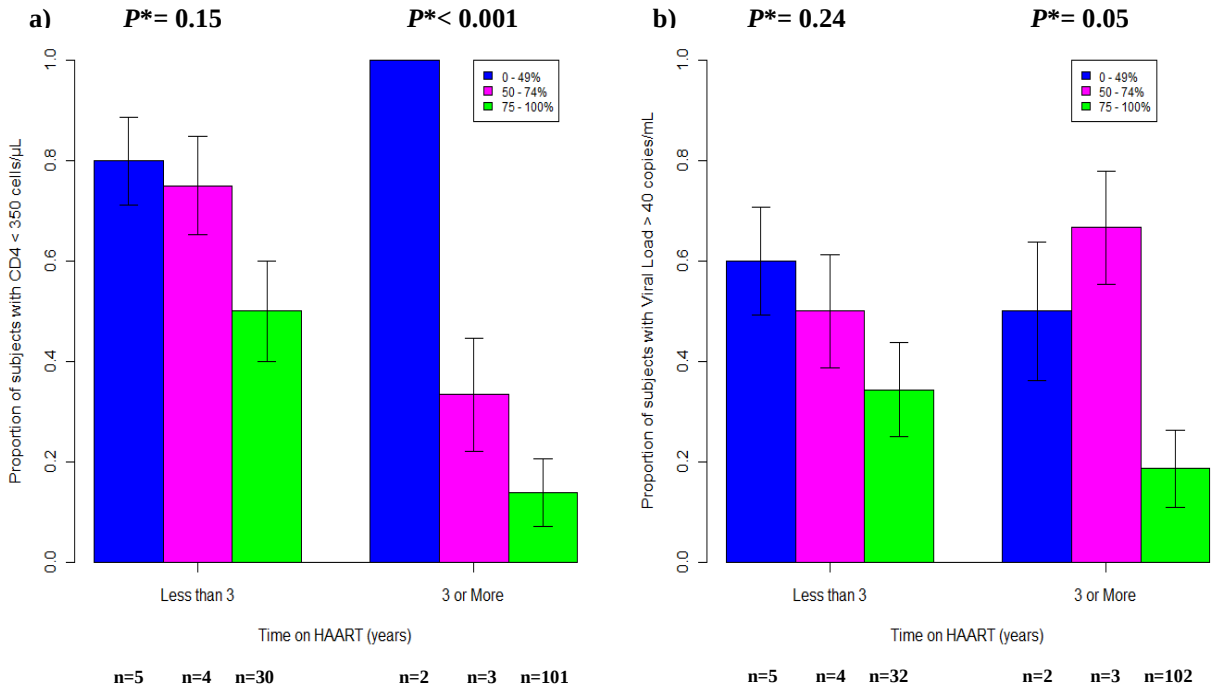

Figure IV.2.6. Proportion of subjects with at least one record of CD4 cell count <350/µl (a) or detectable viral load (b) over 2008, for different adherence' levels and according to *time on HAART*. No statistically significant differences were observed between adherence level 75-95% and ≥95%, for both outcomes. The error bars represent 95% CIs around the estimate of the respective proportions, assuming a binomial probability distribution and using the sample sizes listed. P*, p-value for the χ^2 test for trend.

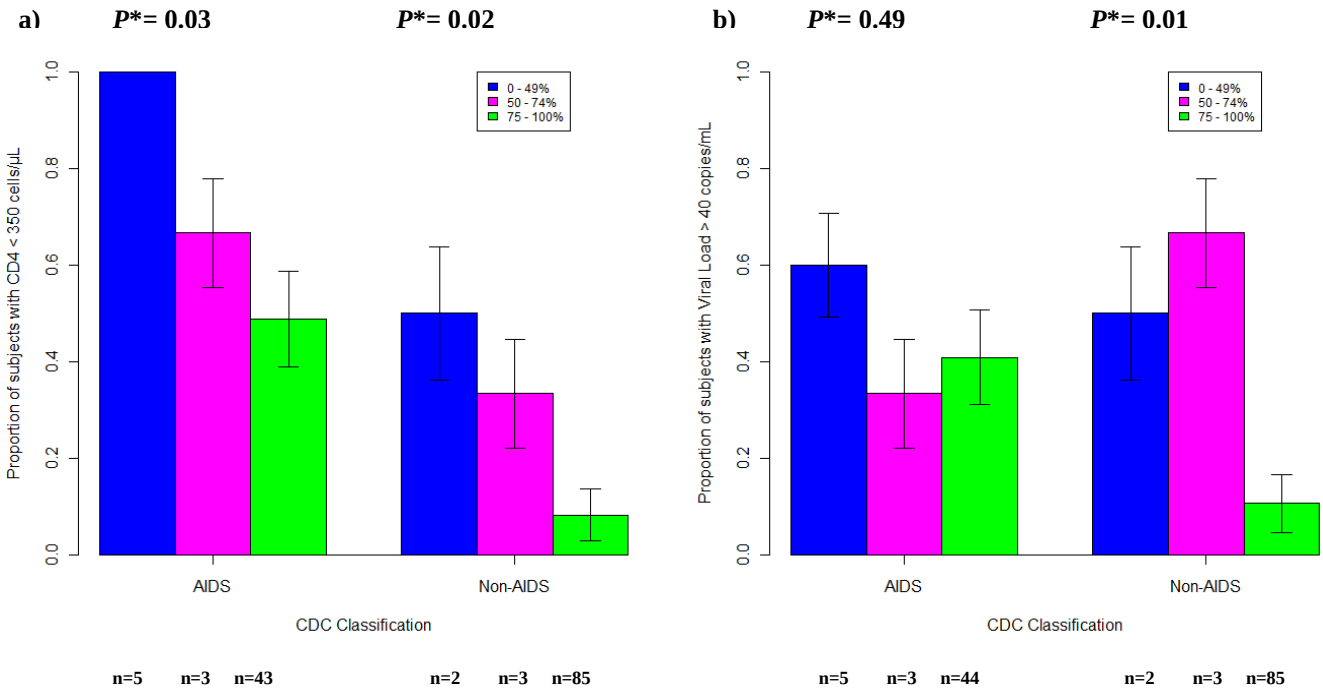

Figure IV.2.7. Proportion of subjects with at least one record of CD4 cell count <350/µl (a) or detectable viral load (b) over 2008, for different adherence' levels and according to *HIV infection status (AIDS vs. non-AIDS) at diagnosis*. No statistically significant differences were observed between adherence level 75-95% and ≥95%, for both outcomes. The error bars represent 95% CIs around the estimate of the respective proportions, assuming a binomial probability distribution and using the sample sizes listed. P, p-value for the χ^2 test for trend.

Regarding the proportion of subjects with detectable viral load, a linear decrease (with higher adherence' levels) was only identified among the subjects with less than 3 years on HAART, even if not statistically significant (Figure IV.2.6). Subjects with MPR 50-75% had higher proportions of detectable viral load among those with 3 or more years of HAART experience (Figure IV.2.6), as well as among non-AIDS subjects (Figure IV.2.7). We did not observe a significant pattern for detectable viral load distribution across the different adherence' levels, among AIDS subjects (Figure IV.2.7).

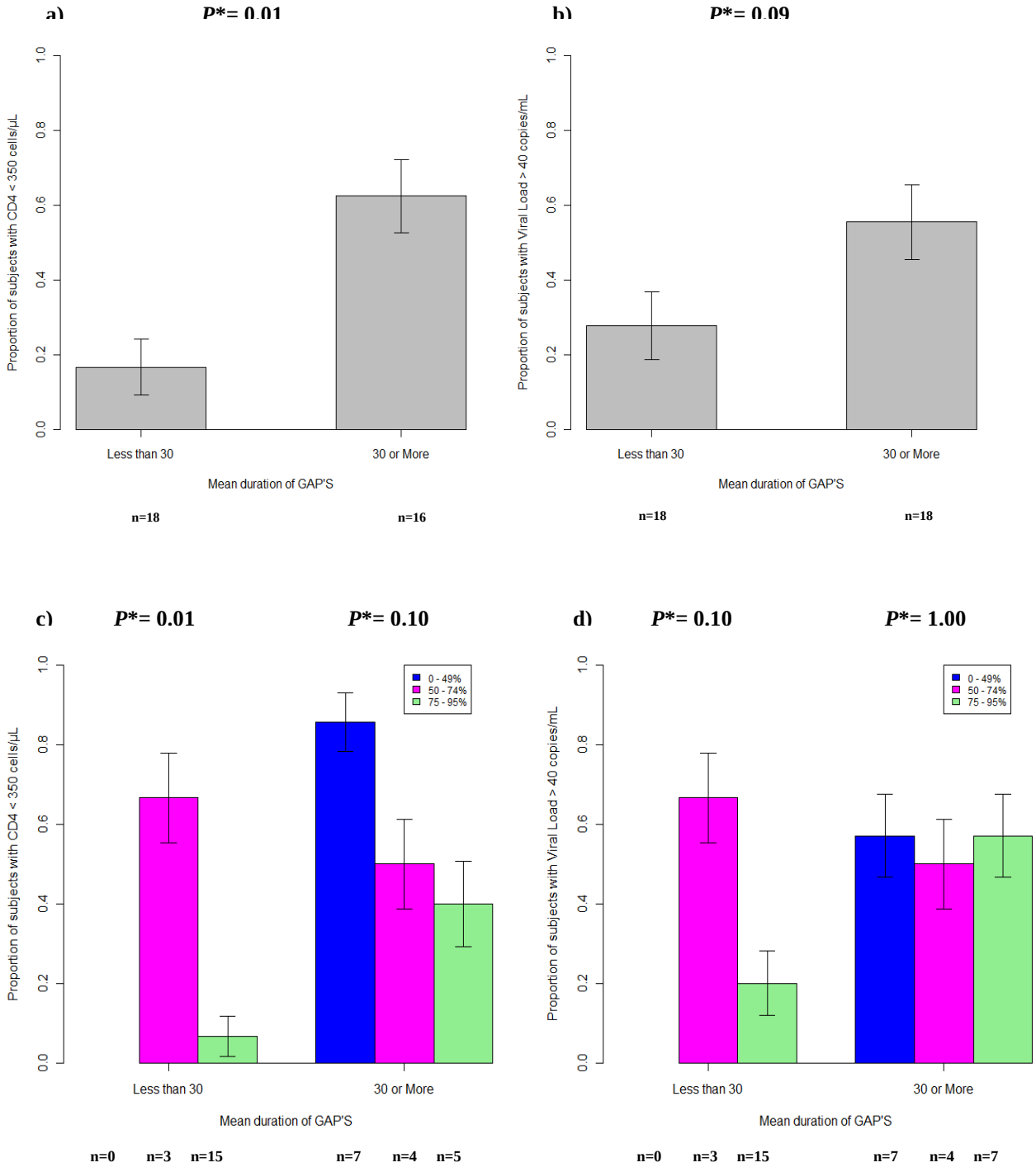

Figure IV.2.8. Proportion of non-adherent subjects (MPR<95%) with at least one record of CD4 cell count <350/µl or detectable viral load over 2008, according to the mean duration of observed medication GAPs [a) and b), respectively], and considering different levels of non-adherence [c) and d), respectively]. The error bars represent 95% CIs around the estimate of the respective proportions, assuming a binomial probability distribution and using the sample sizes listed. P, p-value for the χ^2 test for trend.

Medication GAPs and immunological and virological outcomes

Among the non-adherent subjects (MPR<95%), we identified a higher proportion of subjects with at least one record of CD4 cell count <350/µl or detectable viral load, for those subjects with a mean duration of observed medication GAPs superior to 30 days (Figure IV.2.8). For subjects with GAP>30days, strata of MPR<50% had a higher proportion of subjects with CD4<350/µl. No significant differences were observed across MPR levels, for the proportion of subjects with detectable viral load, and there were no subjects with GAP<30days and MPR<50%.

Discussion

Adherence to antiretroviral treatment is a multifactorial behaviour and dependent on a given clinical and cultural setting [2, 9]. Our study results support earlier findings, showing identification of non-adherence determinants among variables related to subject characteristics, to health care system and to HIV infection and its treatment. Non-adherence complexity is also a result from different patterns of non-adherence [9, 22]. We observed that it ranged from short and repeated periods without medication to longer periods, with different impact on both immunological and virological outcomes.

Non-adherence to HAART is more likely among recent HAART users but also for subjects that had a previous 12-month period without a medical appointment.

It is recognized that the association between socio-demographic factors and adherence to HAART is unclear [9, 23]. In our cohort, younger subjects were more likely to be non-

adherent, as reported by other studies [20, 24, 25], but this association was less evident when adjusting for other variables. Nonetheless, having less than 3 years of treatment experience, which includes subjects that initiated HAART or were in their first regimen at baseline, remained significantly associated to non-adherence. Thus, our results reinforce the need for a closer follow-up at the beginning of HAART, as recommended by national and international guidelines [26, 27].

Having abandoned medical appointments for a 12-month period was another factor associated to non-adherence, and probably related to previous record of detectable viral load after HAART initiation. Other studies have also showed that non-adherence to HAART medications seems not to be a random event, since subjects reporting non-adherence were more likely to continue to be non-adherent between consecutive visits [28, 29]. These findings suggest that attention should be paid to subjects with more HAART experience, in order to prevent repeated non-adherence periods. Adherence to HAART must be assessed frequently, alongside with other factors such as beliefs about medication and social support that may also impact non-adherence [9, 30, 31]. In Portugal, a prospective study is now being conducted to evaluate the association of these variables, not registered in clinical records, with HAART use among our study population.

Short and repeated medication GAPs are frequent among non-adherent subjects.

There are several pharmacy-based measures of adherence to medication [16]. The assessment of medication GAPs allows a characterization of how frequent it is for a subject to be without medication, while MPR assessment may dilute periods of undersupply of medication [32]. In

our study cohort and during the 2008 year, near 71% of the non-adherent subjects experienced 1 to 3 periods without HAART, and medication GAPs with a length <50 days were frequent. However, several patterns of non-adherence were observed. In fact, most of study subjects had repeated periods of less than 30 days without medication, that resulted in moderate to high adherence levels (MPR>50%), while others presented longer periods without HAART and lower adherence levels. Using electronic monitoring of adherence, Parienti *et al.* also found a higher variability of periods without medication among lower average adherence rates [22, 33]. Compared to electronic monitoring, the pharmacy refill monitoring does not enable a complete characterization of HAART interruption patterns [22] but further studies should assess its validity as it may provide earlier information to promote adherence, while being more feasible in clinical practice and resource-poor settings [34].

Non-adherence is associated with lower CD4 count and detectable viral load, but other factors should also be taken into account when evaluation HAART outcomes.

Our study results showed a significant decrease in the proportion of subjects that had CD4 count <350/µl and in the proportion of those having viral load >40 copies/ml, when increasing the average (MPR) adherence to HAART. A dose-response relationship between adherence and viral suppression has been well described in previous studies, for HAART regimens PI- or NNRTI-based [20, 35]. We also have found no significant differences regarding both outcomes, when comparing average adherence between 75 to 94% with the recommend level of ≥95%. Furthermore, there seem to be no differences on the probability of having detectable viral load in the less adherent levels (<50% and 50-75%) and the linear decrease observed among subjects with less than 3 years of HAART experience was marginally significant. Besides our study small sample size, other possible explanation is that more than 50% of our

study subjects were receiving a NNRTI-based regimen, for which it has been pointed out that viral suppression is possible with adherence levels <95% [35, 36]. The higher NNRTI "forgiveability" was showed by clinical trials and observational data and it is mainly due to their antiretroviral potency and long plasma drug half-lives [37], and may result in a less evident dose-response effect than the one described for PI-based regimens [36].

We also found that subjects with MPR 50-75% and 3 or more years of HAART experience or classified as non-AIDS at the moment of HIV diagnosis, seem to have a higher probability of presenting detectable viral load. The finding that more experienced subjects may have higher probability of virological failure is not supported by previous studies and should be confirmed in a larger study sample since it may indicate the presence of antiretroviral resistances [3, 36]. We have collected data about resistance when it was mentioned in the clinical records, but an active assessment would enable a better characterization of this determinant of treatment failure. Hence, even though viral suppression may be possible with moderate levels of adherence, physicians should continue to promote the highest level of adherence possible [36, 37].

It has been described that the risk of immunological failure diminishes with a longer HAART experience and is associated with higher pre-treatment CD4 cell count, ongoing viral replication, and intravenous drug use [38]. Our study results also indicate that subjects with 3 or more years of HAART experience had a lower probability of presenting CD4 count <350cell/µl, with a significant dose-response effect related to average adherence levels. However, we found that subjects presenting higher CD4 count at diagnosis (and classified as

non-AIDS) had also lower probability of having CD4 count <350cell/µl. Some possible hypotheses are that 1) subjects presenting AIDS at diagnosis had more difficulty in achieving and maintaining CD4 count ≥350cell/µl, due to a lower baseline cell count (<200cells/µl) or to the presence of opportunistic diseases, 2) non-AIDS subjects have a higher CD4 cell count that decreases linearly with lower adherence level but remains higher than the mentioned threshold, 3) previous findings had promoted a change in clinical practice that placed subjects with higher CD4 count under a closer follow-up by the physicians, and that 4) the nowadays earlier beginning of HAART (in some cases, even when CD4 count is >500cell/µl) had lead to a stronger protection of immunological failure among non-AIDS subjects [27]. Further studies are required to confirm this hypothesis.

HAART gaps and immunological and virological outcomes

Similar to other studies, we have found that non-adherent subjects (MPR<95%) having HAART gaps with a mean length ≥30days had more probability of presenting worse immunological outcomes. In fact, a previous study also showed that subjects with gap ≥30days had less gain in CD4 count (80.7 cells/µl less) than those without gaps [34]. Additionally, when assessing the impact on CD4 count of both average adherence and duration of HAART gap, we observed that having a mean duration of gaps ≥30days is a relevant condition for presenting CD4 <350 cells/µl, since differences across average adherence levels were marginally significant. On the other hand, average adherence seems to be more relevant when subjects had a mean duration of gaps <30days. A possible explanation is that CD4 changes to values less than 350 cell/µl require lower levels of HAART exposition that may occur with single longer periods or from cumulative shorter medication gaps.

Regarding virological outcomes, the difference among non-adherent subjects having HAART gaps with a mean length ≥30 or <30 days was marginally significant. This finding may be due to lack of power, since previous studies showed that longer HAART gaps are associated with higher probability of having detectable viral load, for different antiretroviral regimens [22, 33]. Nevertheless, our study results also indicate that subjects with mean duration of HAART gap ≥30 days had identical probability of showing detectable viral load across different average adherence levels.

Medication gaps seem to have a different impact in immunological and virological outcomes, a finding that was already discussed in other studies and that is related to the causal relationship between adherence, virological failure and immunological decline [38]. Our results support Bisson *et al.* recommendation for the inclusion of pharmacy-based measures of adherence as predictors of virological failure in resource-poor settings, besides CD4 count [39]. The identification of HAART gaps may prevent virological failure, enabling adherence interventions aiming to prolong time on first-line of HAART, while CD4 count monitoring only detects virological failure after it has already occurred [39].

Study limitations

A first limitation is related to the lack of power to evaluate possible associations between adherence and its determinants and outcomes. This is particularly relevant during the logistic regression analysis, which resulted in a final model that is adequate and explains non-adherence determinants despite the fact that several variables had lost their statistical significance. The small sample size may also lead to spurious associations when comparing the immunological and virological outcomes for different adherence levels and a third

variable. Nevertheless, several findings are in accordance with previous studies, supporting their validity.

Secondly, adherence was assessed through pharmacy-based measures, which assumes that subjects will take their medication once it is available after a refill. This may result in an overestimation of adherence to HAART because subjects may not take all of their refilled medication. Even so, pharmacy records correlate well with electronic monitoring, drug resistance, viral suppression or rebound, and survival, and we may assume that patients would not continue to refill a prescription without intending to adhere to HAART [35]. Underestimation of adherence is less likely to occur since Portuguese subjects receive HAART only from the pharmacy at the hospital at which they are followed. We also included leftovers from previous refills, resulting in a more conservative estimation of non-adherence. However, we were unable to correct MPR and HAART gaps assessment with information regarding hospitalizations during 2008 as well as treatment interruptions due to clinical decision that may have resulted in underestimation of HAART adherence.

Another limitation is that adherence data and virological or immunological outcomes were presented only in aggregate form, and we have not assessed individual adherence as a time-dependent variable. As a result, reverse causation is possible and subjects who experience poor outcomes related to virological failure may subsequently stop taking HAART.

Confounding by indication may also be present. Although our cohort was largely HAART experienced, NNRTI-based regimens may have been selected as first option to reduce the risk of non-adherence and promote a better viral suppression at moderate adherence levels. This may explain why being HAART-naïve was a variable not included in the final model.

Finally, our study reflects the current situation of the present heterogeneous patient population in a country with universal access to care, at hospital care level. Hence, the study design implied that subjects had to survive until 2008 and a selection bias may be present with an overestimation of adherence.

Clinical implications

Our study results actualize information about adherence to HAART and its determinants, suggesting that two groups of HIV-1 infected subjects should have more frequent evaluations of non-adherence: subjects with less HAART experience and those that had already abandon medical appointments for a period>12 months. It also shows that viral load is not a good proxy of non-adherence, especially in some situations such as when subjects had more than 3 years of HAART experience, and that CD4 count is less susceptible to change due to shorter periods of non-adherence. In this manner, pharmacy-based measures may be useful to identify subjects with lower to moderate average adherence levels and shorter HAART gaps, enabling the use of targeted interventions to promote the higher levels of adherence to medication.

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Chapter V

General Discussion & Future Research

V.1.

Overall discussion of study results

Antiretroviral treatment has undergone considerable changes in the last decade, with more options being available nowadays. Guidelines on HIV infection management recommend early starting of treatment and closer medical follow-up in order to assess drug resistance and toxicity, as well as to maintain patient's adherence to treatment.

Adherence to treatment is not a new issue, with physicians reporting this problem since the time of Hippocrates [1]. The impact of adherence has been well demonstrated in the HIV/AIDS infection. Adherence to antiretroviral regimens was associated with virological, immunological and clinical outcomes, as well as drug resistance and healthcare utilization and costs. In fact, adherence to HAART is recognized as an essential component of treatment success and high levels (>90% or >95%) are required.

There have been some studies conducted in Portuguese hospitals, regarding adherence to antiretroviral treatment. The reported prevalence rates of patient adherence ranged from 46 to 91%, due to different settings, study population and adherence measures. In fact, quantitative assessment of adherence remains a challenge and several measures were defined, but there are no "gold standard" to evaluate adherence and all measures show some limitations.

Nevertheless, the study of patient adherence and its determinants is essential to define effective intervention strategies in order to promote a better use of antiretroviral drugs. This is particularly relevant in the Portuguese reality, due to a high rate of new HIV infection among Western and Central European region countries, the increasing prevalence of this condition,

the high AIDS-related mortality and the public expenditure with antiretroviral treatment. In a time of limited resources, it is relevant to identify which patients are at increased risk of non-adherence, as potential target groups for preventive strategies.

We aimed to characterize patient non-adherence to antiretroviral treatment among HIV-1 infected adult subjects followed up at the HIV outpatient clinic from *Hospital de Santa Maria* (Lisbon, Portugal), a university tertiary central hospital and the largest hospital in Portugal.
Over the period 2005-2008, we have observed an increase in the prevalence of non-adherence to HAART, from 12.3% in 2005 to 25.9% in 2008. This finding contrasts with the ones from a similar Spanish study, that showed a decrease from of non-adherence from 23.7% in 2005 to 20.7% in 2008 [2]. Furthermore, the observed increase of non-adherence seemed to be related to an increase of the proportion of subjects with moderate adherence (MPR 75-95%), which may explain the decrease in the proportion of subjects with detectable viral load. In fact, previous studies have found that to NNRTI-based regimens, which were prescribed to most of our study subjects, could lead to viral suppression with adherence levels lower than 95%. However, moderate levels of adherence may trigger drug resistance. Therefore, the achievement and maintenance of high adherence levels should be promoted by healthcare providers, especially among IDU, subjects with depression/anxiety conditions and during holiday seasons.

IDUs are usually referred as a risk group for non-adherence to treatment, namely active substance abusers [3, 4]. Although some studies have shown that history of drug use [5, 6] or IDU as a source of acquisition of HIV infection [7] were unrelated to adherence, others have found lower levels of adherence to HAART among IDUs, leading to lower virological

response rates [4, 8]. Our study results also showed that IDUs had a mean non-adherence rate higher than the mean from all subjects. Although we were unable to distinguish between former and current IDUs, these findings suggest that healthcare providers should promote adherence strategies for these subjects, by addressing the patient's concerns about the medications and raising awareness of possible side effects [3].

Depression and anxiety are described as predictors of non-adherence, since they may reduce motivation and ability to take medication as prescribed [3]. Although we were unable to verify if depression/anxiety were associated with non-adherence, the proportion of subjects with MPR<95% was higher among those subjects with these conditions. Hence, physicians should assess a diagnosis of depression and provide closer monitoring of adherence is suggested [5].

An interesting finding was that mean adherence level was lower in the second calendar semesters. A possible explanation is that skipping medical appointments and medication refills are more likely to happen during holiday seasons (in Portugal, summer vacations usually take place during July-September months). Thus, healthcare providers may prevent non-adherence by prescribing for more than one month, alongside with the assessment of patient barriers to take HAART during this period.

Evaluation of non-adherence determinants was incomplete when assessing adherence to HAART through calendar years. On the other hand, we have observed a decrease in the proportion of detectable viral load over years, even though non-adherence has increased. Hence, we aimed to evaluate determinants and patterns of non-adherence for those subjects

prescribed to HAART during 2008, and to verify its impact in terms of virological and immunological outcomes, at individual level.

We have found HAART low-experienced subjects and those skipping medical appointments for a period >12 months to be more likely non-adherents. It has been well described that HAART-naïve subjects are more likely to be non-adherent during the first year of treatment [9]. Our study results suggest that subjects who had already experienced non-adherence – to treatment and medical appointments – were also at increased risk of becoming non-adherent for a second time. Although recent guidelines mention that adherence should be evaluated in the presence of virological failure, our findings support the European 2011 recommendation, to monitor adherence barriers in each medical appointment [10]. Other healthcare providers – including pharmacists at the moment of medication refill – should also assess and promote adherence [3, 11].

We have confirmed that subjects with high adherence to HAART were less prone to have detectable viral loads and CD4 counts <350/µl, but time on HAART and AIDS classification at diagnosis were also related to virological and immunological outcomes. Patient adherence, time on HAART, CD4 count at diagnosis and resistances are major determinants of clinical outcomes. However, further studies are required to describe the interactions between these factors in clinical outcomes of long-term treated subjects.

Non-adherence complexity is also a result of its different patterns [12]. We observed that non-adherence ranged from short but repeated periods to fewer but longer periods without medication. Among non-adherent subjects (MPR<95%), those with medication gaps with a

mean length ≥30 days were at higher risk of worse immunological outcomes, even though no significant differences were observed when considering viral suppression. This finding may be due to the relationship between adherence, virological failure and immunological decline [13]. Since virological outcomes are more susceptible to shorter periods of non-adherence that immunological decline, the identification of HAART gaps may be used to prevent virological failure, enabling adherence interventions to prolong time on first-line of HAART [14].

- Completeness of the clinical and pharmacy records

An important limitation of retrospective studies is the quality of data. When considering completeness of clinical hand-written records, we have found that several socio-demographic variables had a large proportion of missing information. Table V.1.1 summarizes the missing information for main study variables, in 2008.

These findings may not reflect the physicians' lack of information regarding each patient condition. However, records are important for quality assessment as well as for clinical studies [15]. The introduction of electronic medical records, integrated or not with surveillance systems, may result in better management of HIV/AIDS infection [16].

The pharmacy records are used for administrative purposes and seem to be more complete, while only intake frequency was not registered over the period 2005-2008. The integration of electronic prescription may prevent introduction limitations at the moment of medication dispensing.

Table V.1.1. Missing information (number of subjects and percentage) for study variables at baseline, for the total of 157 participants followed in 2008.

	n (%)
Gender	0 (0.0)
Age	0 (0.0)
Race	**33 (21.0)**
Birthplace	**74 (47.1)**
Professional status at diagnosis ‡	**26 (16.6)**
Mode of acquisition for HIV infection	7 (4.5)
Past or current IDU, %	*
Co-morbidities, %	*
Past or current Depression/Anxiety, %	*
AIDS classification at diagnosis	**62 (39.5)**
AIDS classification at baseline	12 (7.6)
Detectable viral load [(a)]	9 (5.7)
CD4 count < 350 cells/µl [(b)]	12 (7.6)
Opportunistic infections [(c)], %	*
HAART-naïve, %	*
Time on HAART	0 (0.0)
Started ART with non-HAART regimens	*
Time since HIV diagnosis	4 (2.5)
Skipped medical appointments [(d)], %	*
Hospitalized [(e)], %	*
Previous non-adherence periods > 12 months [(f)], %	*
Other medication, %	*
Adverse drug reactions [(g)], %	*
Antiretroviral resistances, %	*
Therapeutic Drug Monitoring over 2008 year, %	*

* Variables for which the absence of information may also be explained by the subjects not presenting these conditions (see Table IV.2.1. for more information). ‡ Professional status as registered in the subjects' first medical appointment. Considering the clinical history previous to baseline, table shows % of subjects with missing information regarding the presence of at least one (a) medical appointment with detectable viral load, (b) medical appointment with CD4 cell count <350/µl, (c) opportunistic infections, (d) skipped medical appointment, (e) hospitalization, (f) one previous non-adherence period > 12 months and (g) one adverse drug reaction. ART, Antiretroviral therapy; HAART, Highly active antiretroviral therapy, defined as any regimen containing three or more antiretroviral medications or containing a NNRTI and a PI; IDU, Injection Drug Use.

- Study limitations

Study limitations have already been discussed. They are mainly related to the small sample size when comparing to published studies, and to the procedure of collecting data from hand-written clinical records. In fact, it is difficult to obtain clinical data from large datasets of HIV-infected subjects in Portugal, since there is no electronic database available. Hopefully, the registry that is now being developed by CNSida will enable more research in the future.

Other study limitation is related to the use of pharmacy-based measures. As discussed previously, when using ART refill data, we must assume that all refilled medication will be actually taken by the subjects, which may result in adherence overestimation. Another limitation is that we have not assessed individual adherence as a time-dependent variable, which may lead to reverse causation since subjects who experience poor outcomes related to virological failure may subsequently stop taking HAART. Other main limitations are due to the cohort design, such as the possibility of confounding by indication related to the selection of NNRTI-based regimens as first option (to reduce the risk of non-adherence) and the possible selection bias related to the inclusion of subjects that had survived until 2008.

- Main conclusions and clinical implications

We can summarize the main clinical implications of the study as follows:

- Adherence should be promoted among IDU and subjects with depression / anxiety, and during holiday seasons.

- Subjects with less HAART experience and those that had already abandon medical appointments for a period >12 months should be subject to a close monitoring of adherence to antiretroviral drugs and its barriers.
- Viral load is not a good proxy of non-adherence especially when subjects had more than 3 years of HAART experience, and pharmacy-based measures may enable the identification of subjects at risk of non-adherence and consequent drug resistance.

- Future research

As future research, we propose a national study on patient adherence to HAART and with the assessment of its determinants. Although we expect that the national registry being now developed by CNSida may provide more information on HIV infection management, our project results show that several variables that will not be collected in this registry are potentially associated to non-adherence. Hence, we propose a national multicentre cohort study with HIV-1 infected subjects receiving HAART.

With the ATAR-VIH project, we aim to identify the prevalence and determinants of patient non-adherence, and to provide comparative information to support health planning regarding HAART utilization and HIV infection management in Portugal. The study will also enable a better evaluation of adherence dynamic, with the characterization of HAART modifications, its associated factors and its relation with patient adherence, as well as a better understanding of the relationship between adherence and progression of HIV/AIDS, confirming the 95%

adherence level assumed as the ideal or retrieving information for some parameters usually incorporated into pharmacoeconomic models.

It is true that cohort studies are demanding, expensive and prone to irregular dropout or attrition [17, 18]. Nevertheless, HIV/AIDS infection-specific cohorts are epidemiological tools that enable the evaluation of effectiveness, beneficial/adverse effects and resistance profile for different HAART regimens; research in social determinants of HIV infection and management, in population groups such as injection-drug users, migrants, women and older subjects, and comparison of clinical outcomes and associated factors between subjects with a long experience on HAART and naïve patients. A cohort study also promotes translational research, e.g. regarding pharmacological or virus-host interaction mechanisms [17, 19], and a way to assess the impact of policy measures at local and national level, regarding HIV/AIDS management [20, 21]. In this context, the ATAR-VIH project may also provide an opportunity to promote a national network of clinical and epidemiological researchers in HIV/AIDS infection and HAART utilization.

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prospectiva do estudo, e a constante disponibilidade das administrativas Ana, Marina e Sandra, fundamentais para a recolha retrospectiva de dados. Aos utentes que se encontram a participar na fase prospectiva, sem os quais não seria possível o estudo.

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De uma forma especial, agradeço ao Mestre Rui Simões pela análise de dados, à Dr.ª Francisca Silva e Dr.ª Susana Froes pela essencial colaboração na recolha de dados na fase prospectiva. Aos alunos e estagiários que abraçaram este projecto como seu, nomeadamente Andreia Leite, J. Alexandre Freitas, Mª Emília Pereira, Rita Martins, Violeta Nogueira, João Costa, Raquel Simões, pelo entusiamo contagiante e pela confiança e exigência.

À Mestre Carla Torre, pela grande amizade, dedicação e disponibilidade, ao longo de todo o projecto e no cuidado da revisão e da discussão dos dados apresentados.

Ao Professor Doutor J. Pereira Miguel, director do Instituto de Medicina Preventiva, e ao Prof. Doutor Evangelista Rocha, coordenador da Unidade de Epidemiologia, pelo acolhimento deste projecto. À Dr.ª Violeta Alarcão, Dr. Filipe Miranda e aos restantes colegas na Unidade de Epidemiologia, por todo o apoio demonstrado.

À Fundação Merck, Sharp & Dohme (Portugal), na pessoa do seu Presidente Professor Doutor Virgílio Durão, pelo apoio financeiro concedido ao estudo, sem implicações no desenho do mesmo e análise dos dados apresentados.

A todos cujo nome não mencionei mas que contribuíram para este projecto.

À minha família, aos meus amigos.

But what is your final goal, you may ask. That goal will become clearer, will emerge slowly but surely, much as the draft turns into the sketch and the sketch into the painting through the serious work done on it, through the elaboration of the original vague idea and through the consolidation of the first fleeting and passing thought.

Vincent to Theo van Gogh, July 1880

Ao meu irmão

Aos meus pais

Annexes

Annex I

Authorization from the HSM Ethics Committee

CENTRO HOSPITALAR LISBOA NORTE, EPE — HOSPITAL DE SANTA MARIA — Hospital Pulido Valente

Exma. Senhora
Dra. Milene Fernandes
Unidade de Epidemiologia
Instituto de Medicina Preventiva
Faculdade de Medicina de Lisboa
Edifício Egas Moniz

Lisboa, 2 de Fevereiro de 2010

Assunto: Adenda ao estudo **"ATAR-VIH - Adesão à Terapêutica Anti-Retrovírica em doentes seropositivos para o VIH: prevalência e factores associados"**

Pela presente informamos que o projecto citado em epígrafe obteve, na reunião realizada em 27 de Janeiro de 2010, parecer favorável da Comissão de Ética, sendo a sua realização de interesse público pela actualidade e pertinência do tema na área abordada.

Salientamos que iniciado o ano de 2010, foi decidido na primeira reunião plenária, ao abrigo e no âmbito das competências da Comissão, esta ser semestralmente actualizada em relação ao desenvolvimento dos estudos favoravelmente avaliados e informada da data de conclusão dos mesmos que deverá ser acompanhada de um relatório final.

Com os melhores cumprimentos,

O Presidente da Comissão de Ética para a Saúde

Prof. Doutor João Lobo Antunes

COMISSÃO DE ÉTICA
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Annex II

Authorization from the National Data Protection Authority

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Processo n.º 1496/2010

AUTORIZAÇÃO N.º 1207 **/2010**

A AIDFM – Associação para a Investigação e Desenvolvimento da Faculdade de Medicina de Lisboa notificou à CNPD um tratamento de dados pessoais com a finalidade de elaborar um estudo para avaliar a prevalência e factores associados à adesão à terapêutica antiretrovírica, pelos doentes seropositivos para o vírus de imunodeficiência humana (HIV) - Estudo ATAR VIH.

O estudo terá uma componente retrospectiva e uma componente prospectiva.

Serão incluídos no estudo os doentes com a patologia que frequentam a consulta dos centros participantes. O médico assistente, investigador no estudo, solicitará consentimento informado, cuja declaração deverá ser arquivada no processo clínico do doente.

Os dados serão recolhidos num caderno de recolha de dados em formato papel.

No "caderno de recolha de dados" não há identificação nominal do titular, sendo aposto um código de doente. A chave desta codificação só pode ser conhecida do profissional de saúde participante.

Os destinatários deverão ser ainda informados sobre a natureza facultativa da sua participação e garantida confidencialidade no tratamento da informação.

A CNPD já se pronunciou na sua Deliberação n.º 227 /2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correcto cumprimento da Lei de Protecção de Dados, bem como as condições gerais aplicáveis ao tratamento de dados pessoais para esta finalidade.

A informação tratada é recolhida de forma lícita (art.º 5º, n.º1 al. a) da Lei 67/98), para finalidades determinadas, explícitas e legítimas (cf. al. b) do mesmo artigo) e não é excessiva.

No que concerne à recolha e tratamento do dado raça, o responsável pelo tratamento justifica a sua necessidade do seguinte modo: *"A raça/etnia é um elemento fundamental na descrição demográfica das populações estudadas, como a idade ou o sexo. A não inclusão desta variável*

no nosso estudo irá condicionar, por um lado a possibilidade de comparação com estudos internacionais e por outro poderá colocar dificuldades acrescidas de aceitação dos nossos dados em publicações internacionais. O relatório da OMS sobre a adesão à terapêutica (2003) refere que, para a terapêutica anti-retrovírica, a adesão tem sido reportada como inferior para indivíduos de raça negra sem que os dados sejam consistentes. Contudo, existem diferenças no perfil de segurança e eficácia associadas a diferenças étnicas, o que pode justificar diferenças na escolha do regime terapêutico. As recomendações portuguesas para o tratamento da Infecção VIH/SIDA (2009) mencionam que "uma percentagem significativa dos doentes, sob terapêutica uniformizada, apresenta níveis sub-terapêuticos dos fármacos utilizados, possivelmente relacionados com as diferenças étnicas, sexuais ou de massa corporal". ".

O fundamento de legitimidade é o consentimento expresso do titular dos dados.

Assim, tendo em atenção o disposto nas disposições combinadas dos artigos 28º, n º1, alínea a) e 30º da Lei n.º 67/98, de 26 de Outubro, e as condições e limites fixados na referida Deliberação, que se dão aqui por reproduzidos e que fundamentam esta decisão, autoriza-se o tratamento de dados pessoais nos seguintes termos:

Responsável pelo tratamento: AIDFM – Associação para a Investigação e Desenvolvimento da Faculdade de Medicina de Lisboa

Finalidade: estudo para avaliar a prevalência e factores associados à adesão à terapêutica antiretrovírica, pelos doentes seropositivos para o vírus de imunodeficiência humana (HIV) - Estudo ATAR VIH.

Categoria de Dados pessoais tratados: código do doente, dados sócio-demográficos (idade, sexo, nacionalidade, naturalidade, raça, escolaridade, agregado familiar, situação profissional actual, profissão, caracterização da infecção por VIH (via de transmissão mais provável, ano provável da infecção, ano do diagnóstico, tipo de vírus, sintomatologia, co-infecções, infecções oportunistas, co-morbilidades), caracterização terapêutica (alterações, terapêutica, dose, posologia, motivo), outra medicação, caracterização de parâmetros clínicos (estádio, carga viral, contagem de linfócitos, efeitos adversos, TDM, resistências), recomendações médicas e seguimento no hospital em causa.

Entidades a quem podem ser comunicados: Não há.

Formas de exercício do direito de acesso e rectificação: junto do médico assistente.

Interconexões de tratamentos: Não há.

Transferências de dados para países terceiros: Não há

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

Prazo de conservação: o código do titular deve ser destruído um mês após o fim do estudo.

Dos termos e condições fixados na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 22 de Março de 2010

Ana Roque, Luís Paiva de Andrade, Vasco Almeida, Helena Delgado António (Relatora), Carlos Campos Lobo, Luis Barroso

Luis Lingnau da Silveira (Presidente)

Annex III

the ATAR-VIH national project – sampling process

Sampling

A multistage cluster sampling approach will be conducted, similar to previous studies [1]. Information regarding the total number of HIV-1 infected subjects followed at each Portuguese hospital at December 31, 2011 will be asked to the CNSida or, if unavailable, to each Portuguese hospital. This data will update the most recently available official information, regarding the number of hospitals following more than 200 HIV-infected subjects under HAART.

Moreover, a feasibility evaluation will be conducted, with a survey among the directors of the infectious diseases' departments (or internal medicine, when applicable), from the Portuguese hospitals, aiming for an overall characterization of the clinical practice and research experience. For a random sample of 10 Portuguese hospitals following more than 200 HIV-infected subjects on HAART, each director of the infectious diseases' department will be invited to the study. Replacement of refusing hospitals will be allowed. In the selected hospitals, physicians will be asked to participate in the study. Their participation consists in the identification of eligible patients to be enrolled in a 2-month period and the filling in of a form related to the participants' clinical visits.

Sample size

According to official data, 18 093 subjects were receiving HAART in 2005. We assumed that the true prevalence of non-adherence to HAART was 50% and that the precision of the estimate of non-adherence prevalence was to be ± 5% (α=.05) of the true frequency of non-adherence to HAART. Hence, we defined a total sample size of 373 subjects at 12-month evaluation, considering the formula:

$$\boxed{d = Z\sqrt{\{[P(1-P)(N-n)]/[n(N-1)]\}}}$$

Assuming a 40% refusal rate, we defined that invitation should be made to at least 530 eligible subjects. Then, we stratified the sample size assuming the participation of 10 out of the 24 hospitals following more than 200 subjects on HAART, in 2005. To define an estimate for the sample size needed in HSM, we assumed the worst scenario in which, after random selection, the remaining 9 hospitals were those having fewer subjects on HAART, thus increasing the strata in HSM (Table III.1).

Given a statistical power of 80%, and assuming non-adherence as a dichotomous variable, it will be possible to detect relative risks of 1.5 or more for different risk factors, when non-adherence rate among controls is 0.4. Also, with this sample size, we will be able to detect differences of viral load means of adherents vs. non-adherents. For instance, assuming a standard deviation of 150 copies within each group, if the true difference in the groups' means is 50, we will need to study 142 subjects per group to be able to reject the null hypothesis that the population means of the experimental and control groups are equal (power=0.8, α=0.05). This sample size will allow multivariate models, even more as repeated measures will be taken. Assuming that lost to follow-up could be up to 20% per year, the sample size will be increased by 30%. Therefore, the final sample size should be 490 subjects. We should invite

640 eligible subjects, assuming a 30% refusal rate. To find how many patients should participate by study centre, we will have a stratified approach that takes into account the total number of HIV-infected subjects receiving HAART from that centre.

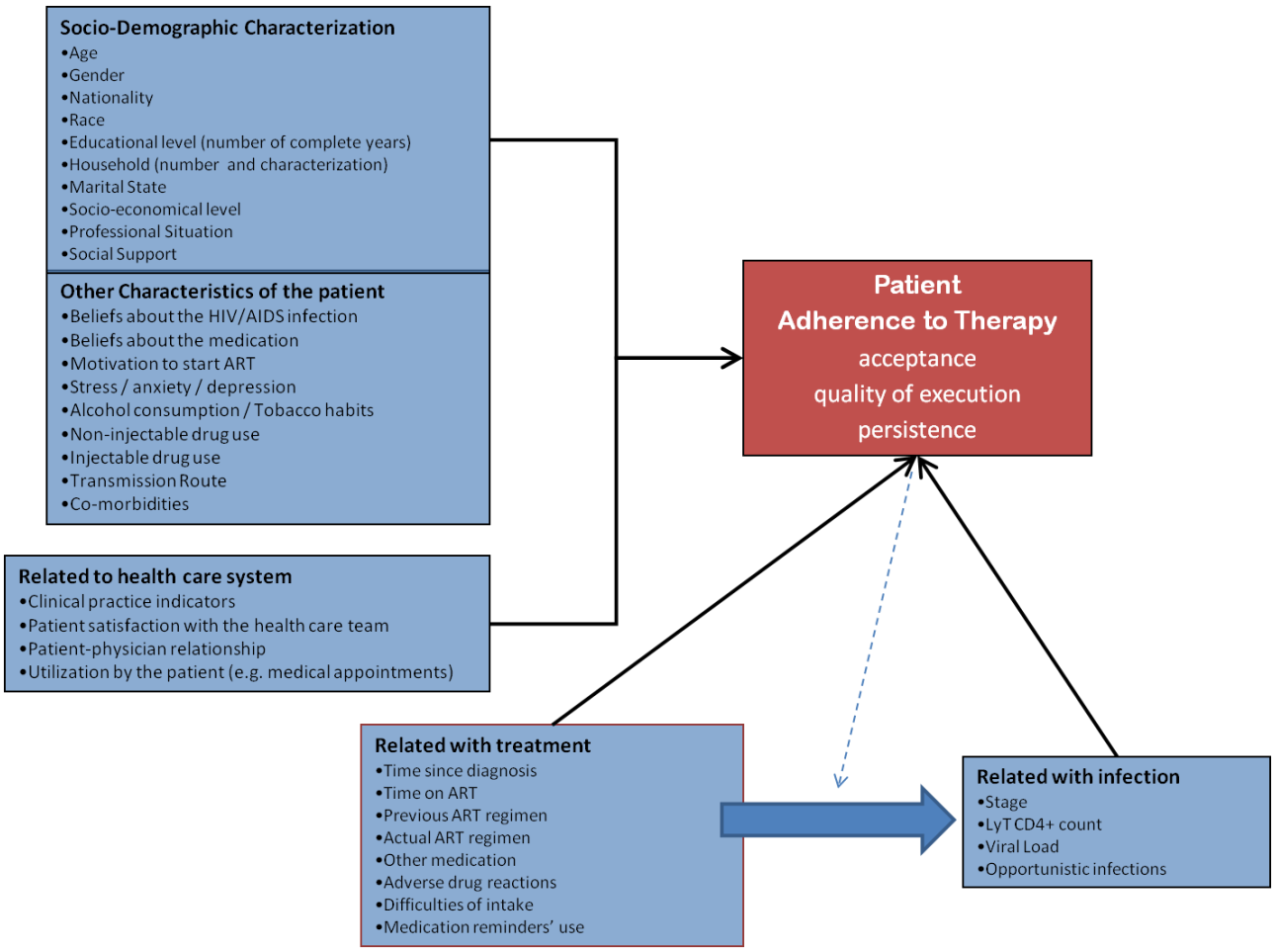
Table III.1. Initial sampling estimates for the ATAR-VIH-study.

	n	n+40%	
1	**124**	**199**	Hospital Santa Maria, EPE
2	**0**	0	Hospital Curry Cabral
3	**100**	159	Centro Hospitalar Lisboa Ocidental
4	**86**	138	Hospital de Joaquim Urbano
5	**0**	0	Hospital São João, EPE
6	**0**	0	Centro Hospitalar Lisboa Central
7	**62**	100	Hospital Garcia de Orta
8	**0**	0	Hospital Fernando Fonseca
9	**41**	65	Centro Hospitalar de Cascais
10	**37**	60	Hospitais da Universidade de Coimbra
11	**0**	0	Centro Hospitalar de Vila Nova de Gaia
12	**61**	98	Hospital de São Bernardo / Centro Hospitalar de Setúbal, EPE
13	**36**	57	Hospital Pulido Valente
14	**0**	0	Hospital Distrital de Faro
15	**0**	0	Unidade Local de Saúde de Matosinhos
16	**26**	42	Centro Hospitalar de Coimbra
17	**26**	42	Hospital Nossa Senhora do Rosário, EPE
18	**0**	0	Hospital Geral de Santo António, EPE
19	**0**	0	Hospital Distrital de Santarém, EPE
20	**0**	0	Centro Hospitalar Barlavento Algarvio, EPE
21	**0**	0	Hospital S. Marcos
22	**0**	0	Hospital Nossa Senhora da Oliveira, EPE
23	**0**	0	Centro Hospitalar Médio Tejo, EPE
24	**0**	0	Centro Hospitalar das Caldas da Rainha
Total	**373**	**596**	

11. Frankel MR, Shapiro MF, Duan N, Morton SC, Berry SH, Brown J, Burnam MA, Cohn SE, Goldman DP, Mccaffrey DF, Smith SM, Clair AS, Tebow JF, Bozzette SA.: **National probability samples in studies of low-prevalence diseases. Part II : designing and implementing the HIV Cost and Services Utilization Study sample**. *Health Services Research* 1999, **34**: 969-992.

Annex IV

Conceptual Model of the ATAR-VIH project



Study conceptual model (adapted from Sabaté E, ed: **Adherence to long-term therapies: evidence for action**. *World Health Organization*; 2003). Patient adherence to HAART is a multidimensional behaviour, as the associated factors may be related to patient characteristics, to health care access and utilization, with antiretroviral regimens or with the HIV/AIDS infection aspects. The ATAR-VIH will evaluate the major determinants of adherence to HAART, for the Portuguese context (black lines), and the impact of non-adherence on effectiveness of HAART regimens (dotted line).

Annex V

Clinical Data Collection Form (retrospective phase)

Formulário para Recolha Retrospectiva de Dados - Processo Clínico

CÓDIGO PARTICIPANTE: _____ **DATA DE HOJE:** ____ ____ 2010 **PREENCHIDO POR:**_____
(letra de máquina) *dia* *mês* *(iniciais)*

Verificação de Elegibilidade		**Sim**	**Não**
No início da Terapêutica Anti-Retrovírica (TAR), o participante…			
a. é seguido no Hospital de Dia de Infecciologia?	***(se não, excluir)***	☐	☐
b. iniciou a TAR num outro hospital que não o HSM?	***(se sim, excluir)***	☐	☐
c. iniciou a TAR em programa de toma sob observação directa?	***(se sim, excluir)***	☐	☐
d. participou em algum ensaio clínico?	***(se sim, excluir)***	☐	☐
e. estava detido quando iniciou a TAR?	***(se sim, excluir)***	☐	☐
f. estava numa instituição social quando iniciou a TAR?	***(se sim, excluir)***	☐	☐
g. tem pelo menos 2 consultas registadas entre 1 Janeiro 2005 e 31 Dezembro 2009?	***(se não, excluir)***	☐	☐
h. depende de outras pessoas para tomar a medicação ? *(incapacidade cognitiva grave ou física para tomar a medicação)*	***(se sim, excluir)***	☐	☐
Desde o início da TAR e até 31 Dezembro de 2009, o participante…			
i. mudou de hospital desde o início da TAR?	***(se sim, registar todos os dados até evento e a data do evento ____mês / ____ano)***	☐	☐
j. passou a cumprir a TAR num programa de toma sob observação directa?	***(se sim, registar todos os dados até evento e a data do evento ____mês / ____ano)***	☐	☐
k. foi detido?	***(se sim, registar todos os dados até evento e a data do evento ____mês / ____ano)***	☐	☐
l. ficou sob o cuidado de uma instituição social?	***(se sim, registar todos os dados até evento e a data do evento ____mês / ____ano)***	☐	☐
m. passou a depender de outras pessoas para tomar a medicação ?*(incapacidade cognitiva grave ou física para tomar a medicação)*	***(se sim, registar todos os dados até evento e a data do evento ____mês / ____ano)***	☐	☐

Dados Sócio-Demográficos (de acordo com última informação registada)

1.1 Sexo ☐ Masculino ☐ Feminino **1.2 Ano de Nascimento**_____ ☐ sem informação (s/ info)

2.Naturalidade: **País** _____ **Distrito** _____ **Etnia** _____ ☐ s/ info

a. Se não nasceu em Portugal, há quantos anos reside em Portugal? _____ **anos** ☐ s/ info

3.Nacionalidade: _____ ☐ s/ info

No início da TAR:

4.Residência:
Distrito _____ Concelho _____ ☐ s/ info

5.Morava sozinho: ☐ Sim ☐ Não ☐ s/ info

a.Se não mora sozinho quais as pessoas com quem mora (marido/mulher, parceiro, filhos, etc.) ☐ s/ info

i. _____ **ii.** _____

iii. _____ **iv.** _____

6.Situação Profissional: ☐ s/ info

a. Empregado ☐ profissão? _____ ☐ s/ info
b. Desempregado ☐ última profissão? _____ ☐ s/ info
c. Reformado ☐ última profissão? _____ ☐ s/ info
d. Estudante ☐
e. Doméstico ☐

Alteração ou outra informação ao longo do processo:

Data: (DD / MM / AAAA)	**Alteração:**

Dados Clínicos Gerais

1.Data de diagnóstico da infecção VIH/SIDA: ____ / _____ (MM / AAAA) [ou há ____ anos] ☐ s/ info

2.Ano provável de infecção: _____ ☐ s/ info

3.Infecção por: ☐ VIH-1 ☐ VIH-2 ☐ VIH-1 e VIH-2 ☐ s/ info

4.Categoria de transmissão: ☐ s/ info ou

a. Toxicodependência IV ☐ b. Sexual: Homossexual ☐
c. Transfusão ☐ d. Sexual: Heterossexual ☐
e. Acidente de trabalho ☐ f. Desconhecido ☐
g. Outro ☐ Qual? _____

1ª consulta registada e 1ª consulta com TAR prescrita		
Nesta consulta há registo sobre:	**1ª Consulta registada __/__/__**	**1ª Consulta com TAR prescrita __/__/__**
Estadio CDC?	Sim ☐ Não ☐ **A** **B** **C** **1** **2** **3**	Sim ☐ Não ☐ **A** **B** **C** **1** **2** **3**
CD4+ / CD8+?	Sim ☐ Não ☐ células/mm3 Data:	Sim ☐ Não ☐ células/mm3 Data:
Carga Viral?	Sim ☐ Não ☐ cps/mL Data:	Sim ☐ Não ☐ cps/mL Data:
Infecções oportunistas?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Neoplasias?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Co-morbilidades?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Consumos de drogas?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Terapêutica AR? Nome / Dose / Posologia *Nota:* indicar as associações fixas na mesma linha		Sim ☐ Não ☐ 1. 2. 3. 4.
Outra Medicação prescrita? Nome / Dose / Posologia	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.
Outra Medicação conhecida? Nome / Dose / Posologia	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.
Comentários sobre a adesão à terapêutica?		Sim ☐ Não ☐ Qual?_____
Recomendações sobre a adesão à terapêutica?		Sim ☐ Não ☐ Qual?_____
Pedida avaliação de Resistências?	Sim ☐ Não ☐ Resultado:_____ Data:	Sim ☐ Não ☐ Resultado:_____ Data:
Observações sobre o Registo da Consulta		

Informação registada desde 1ª consulta com TAR prescrita até 1 Janeiro 2005 (quando aplicável)

	Número	Datas
Total de consultas		
Faltas		
Extra-consultas		
Internamentos		
Ausências superiores a 1 ano		
Só para receituário		

Informação registada desde 1 Janeiro 2005 até 31 de Dezembro de 2009

	Número	Datas
Total de consultas		
Faltas		
Extra-consultas		
Internamentos		
Ausências superiores a 1 ano		
Só para receituário		

Comentários

Como classifica a facilidade em ler a informação do processo clínico:

1. ☐ muito fácil
2. ☐ fácil
3. ☐ nem fácil nem difícil
4. ☐ difícil
5. ☐ muito difícil

É necessário consultar o médico assistente? ☐ Sim

motivo?_____

☐ Não

Outras notas

Sobre as consultas em que está registada mudança de TAR, preencher a tabela seguinte:

Nesta consulta há registo sobre:	__/__/__ (dd/mm/aa)	__/__/__ (dd/mm/aa)	__/__/__ (dd/mm/aa)	__/__/__ (dd/mm/aa)
Data da Consulta anterior?	__/__/__ CD4+/CD8+: _____ células/mm3 Carga Viral: _____ cps/mL	__/__/__ CD4+/CD8+: _____ células/mm3 Carga Viral: _____ cps/mL	__/__/__ CD4+/CD8+: _____ células/mm3 Carga Viral: _____ cps/mL	__/__/__ CD4+/CD8+: _____ células/mm3 Carga Viral: _____ cps/mL
Motivo da mudança de regime?	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____
Nova Terapêutica AR? Nome / Dose / Posologia *Nota:* indicar as associações fixas na mesma linha	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.	1. 2. 3. 4.
Notas sobre a Medicação?				
Comentários sobre a adesão à terapêutica?	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____
Recomendações sobre a adesão à terapêutica?	Sim ☐ Não ☐ Qual?_____ _____ _____	Sim ☐ Não ☐ Qual?_____ _____ _____	Sim ☐ Não ☐ Qual?_____ _____ _____	Sim ☐ Não ☐ Qual?_____ _____ _____
TDM?	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Qual?_____	Sim ☐ Não ☐ Qual?_____	Sim ☐ Não ☐ Qual?_____
Pedido resistência?	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Qual?_____	Sim ☐ Não ☐ Qual?_____	Sim ☐ Não ☐ Qual?_____
Eeitos adversos?	Sim ☐ Não ☐ Quais?_____	Sim ☐ Não ☐ Quais?_____	Sim ☐ Não ☐ Quais?_____	Sim ☐ Não ☐ Quais?_____
Estadio CDC	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐
	A **B** **C**	**A** **B** **C**	**A** **B** **C**	**A** **B** **C**
	1	**1**	**1**	**1**
	2	**2**	**2**	**2**
	3	**3**	**3**	**3**
CD4+ / CD8+?	Sim ☐ Não ☐ _____ cél/mm^3 Data:	Sim ☐ Não ☐ _____ cél/mm^3 Data:	Sim ☐ Não ☐ _____ cél/mm^3 Data:	Sim ☐ Não ☐ _____ cél/mm^3 Data:
Carga Viral?	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐

Nesta consulta há registo sobre:	__/__/__ (dd/mm/aa)	__/__/__ (dd/mm/aa)	__/__/__ (dd/mm/aa)	__/__/__ (dd/mm/aa)
	_____ cps/mL Data:	_____ cps/mL Data:	_____ cps/mL Data:	_____ cps/mL Data:
Infecções oportunistas?	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐
Neoplasias?	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐
Co-morbilidades?	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐
Consumos de drogas?	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ _____ Nenhuma ☐
Observações sobre o Registo da Consulta				

Informação registada desde 1 Janeiro 2005 até 31 Dezembro 2009				
Nesta consulta há registo sobre:	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __
Estadio CDC?	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐
	A **B** **C**	**A** **B** **C**	**A** **B** **C**	**A** **B** **C**
	1	**1**	**1**	**1**
	2	**2**	**2**	**2**
	3	**3**	**3**	**3**
CD4+ / CD8+?	Sim ☐ Não ☐ células/mm3 Data:	Sim ☐ Não ☐ células/mm3 Data:	Sim ☐ Não ☐ células/mm3 Data:	Sim ☐ Não ☐ células/mm3 Data:
Carga Viral?	Sim ☐ Não ☐ cps/mL Data:	Sim ☐ Não ☐ cps/mL Data:	Sim ☐ Não ☐ cps/mL Data:	Sim ☐ Não ☐ cps/mL Data:
Infecções oportunistas?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Neoplasias?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Co-morbilidades?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Mudança terapêutica?	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐	Sim ☐ Não ☐
Motivo da mudança de regime?	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____
Terapêutica AR? Nome / Dose / Posologia *Nota:* indicar as associações fixas na mesma linha	Sim ☐ Não ☐ 1. 2. 3. 4.	Sim ☐ Não ☐ 1. 2. 3. 4.	Sim ☐ Não ☐ 1. 2. 3. 4.	Sim ☐ Não ☐ 1. 2. 3. 4.

Informação registada desde 1 Janeiro 2005 até 31 Dezembro 2009				
Nesta consulta há registo sobre:	__ / __ / __	__ / __ / __	__ / __ / __	__ / __ / __
Outra Medicação prescrita? Nome / Dose / Posologia	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.
Outra Medicação conhecida? Nome / Dose / Posologia	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.	Sim ☐ Não ☐ 1. 2. 3.
De efeitos adversos?	Sim ☐ Não ☐ Quais?_____	Sim ☐ Não ☐ Quais?_____	Sim ☐ Não ☐ Quais?_____	Sim ☐ Não ☐ Quais?_____
Notas sobre a Medicação				
Há registo de comentários sobre a adesão à terapêutica?	Sim ☐ Não ☐ Qual?_____ _____ _____	Sim ☐ Não ☐ Qual?_____ _____ _____	Sim ☐ Não ☐ Qual?_____ _____ _____	Sim ☐ Não ☐ Qual?_____ _____ _____
Existem recomendações sobre a adesão à terapêutica?	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____	Sim ☐ Não ☐ Qual?_____ _____
TDM?	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Resultado?_____
De pedido de resistência?	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Resultado?_____	Sim ☐ Não ☐ Resultado?_____
Consumos de drogas?	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐	Sim ☐ Não ☐ Qual?_____ Nenhuma ☐
Observações sobre o Registo da Consulta				

Annex VI

Evaluation of patient adherence to HAART and regimen modification, in a Portuguese cohort of HIV-1 infected adults: the ATAR-VIH project protocol

Summary

Background: HIV/AIDS infection requires continuous promotion of patient adherence to antiretroviral treatment. This is a complex behaviour determined by factors related to the patient characteristics, HIV/AIDS progression, HAART complexity and tolerability, and health services organization. The ATAR-VIH project aims to determine the prevalence of patient non-adherence to HAART, as well as to study and model potential determinants of medication adherence dynamic.

Design: The study is an observational, multicentre cohort (study) with a prospective 18-month follow-up of HIV1-positive subjects. Eligible subjects are required to have a treated HIV1 infection, age ≥18 years-old when starting HAART, and no previous participation on a clinical trial. The study will have a multistage cluster sampling approach, with the systematic recruitment of subjects from a random sample of Portuguese hospitals following more than 200 HIV-infected subjects on HAART. The overall sample size is 490 subjects, assuming a 30% refusal rate, and an estimate of non-adherence prevalence of 50%. Clinical records will be reviewed, and questionnaires will be applied to both patients and their physicians, at defined moments. All data will be further assembled in a central electronic database. Analysis includes logistic regression models, and Cox's regression model, to evaluate determinants of compliance and persistence on HAART.

Discussion: With the ATAR-VIH study, we aim to provide comparative information to support health planning regarding HAART utilization and HIV infection management.

Keywords: HIV/AIDS infection; patient adherence; regimen modification; antiretroviral