Ministério da Saúde

FIOCRUZ
Fundação Oswaldo Cruz

ESCOLA NACIONAL DE SAÚDE PÚBLICA
SERGIO AROUCA
ENSP

"Usuários de Drogas Vivendo com HIV/AIDS: análise de fatores associados à sobrevida e à aderência ao tratamento"

por

Monica Siqueira Malta

Tese apresentada com vistas à obtenção do título de Doutor em Ciências na área de Saúde Pública.

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Esta tese, intitulada

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apresentada por

Monica Siqueira Malta

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RESUMO

Desde o advento da terapia antiretroviral de alta potência (HAART), desigualdades nas taxas de morbidade e da mortalidade secundárias ao HIV/AIDS têm sido observadas, particularmente em populações marginalizadas e minorias diversas, como usuários de drogas vivendo com HIV/AIDS (UD HIV+).

Buscando contribuir para esta questão, em um primeiro momento foi realizada uma revisão sistemática sobre aderência à HAART entre UD HIV+. De acordo com esta revisão, aderência mais alta à HAART foi encontrada entre UD HIV+ atendidos em serviços que oferecessem atenção integral, multidisciplinar, por exemplo, contando com tomadas de medicamentos supervisionadas (*directly observed therapy*-DOT) e/ou serviços que oferecessem em um mesmo contexto tratamento para a infecção pelo HIV e para a dependência química (co-localização).

Posteriormente realizamos uma meta-análise utilizando os mesmos estudos incluídos na revisão sistemática. Os estudos eram bastante heterogêneos (estatística $I^2 \geq$ 75%): mensuração de aderência através de métodos distintos (auto-relato, prontuários, dispositivos eletrônicos), utilização de pontos de corte para definir "aderência" diversos (75-100%), e adoção de diferentes desenhos de estudo (estudos seccionais, caso-controle ou longitudinais). 41 estudos foram incluídos, totalizando 15194 pacientes (11628 HIV+ UD, 76.5%), perfazendo uma aderência global de 60,3% (IC 95%: 52.9 – 67.4%). O desenho do estudo – principalmente quanto à estratégia e ao período de avaliação da aderência – se mostrou preditor independente da heterogeneidade inter-estudos observada. Dentre os estudos que avaliaram resultados clínicos associados à HAART, melhores resultados foram encontrados entre pacientes mais aderentes, aqueles em abstinência no momento (ou seja, ex-usuários), os que não apresentavam distúrbios psiquiátricos severos e que recebiam apoio psicossocial.

Em seguida realizamos uma análise da sobrevida de usuários de drogas injetáveis (UDI) vivendo com AIDS, diagnosticados entre 2000-2006, utilizando bases de dados nacionais. Entre os 28.426 pacientes incluídos no estudo (43% UDI; 57% HSH), 6777 (23,8%) morreram durante 87.792 pessoa-tempo de acompanhamento. No *baseline*, quando comparados com HSH, uma proporção menor de UDI estava recebendo HAART (24,3% *vs.* 31,2%; p<0.001), havia realizado pelo menos um exame de contagem de CD4 (44,1% *vs.* 56,9%; p<0.001) ou exame de carga viral (62,5% *vs.* 54,2%; p<0.001). Mesmo após a inclusão de termo de efeito aleatório por município e por estado de residência (fragilidade) no modelo multivariado escolhido, a mortalidade secundária à AIDS permaneceu maior em UDI (AHR: 1,94; 95% IC: 1,84 – 2,05).

Os resultados do estudo de sobrevida salientam o fato de que ineqüidades importantes ainda são observadas no acesso à HAART no Brasil, apesar do país possuir um dos programas de AIDS mais amplos entre os países em desenvolvimento e oferecer acesso gratuito e universal à HAART. Estas ineqüidades podem explicar a alta mortalidade identificada entre UDI quando comparados com HSH.

Os achados da revisão sistemática e da meta-análise sugerem que UD HIV+ podem alcançar níveis de aderência à HAART adequados, principalmente aqueles que têm acesso a serviços multidisciplinares, sintonizados às freqüentes comorbidades encontradas nesta população. Os estudos indicam que preocupações sobre a existência de uma aderência aquém da desejada entre UD HIV+ não estão baseados em evidências científicas disponíveis. Esforços para reduzir as desigualdades em saúde identificadas nesta população são claramente necessárias.

Palavras-chave: HIV, AIDS, uso de drogas, revisão sistemática, meta-análise, sobrevida, HAART

ABSTRACT

Since the advent of highly active antiretroviral therapy (HAART), widening disparities in AIDS-related morbidity and mortality have been observed, particularly among disadvantaged or marginalized populations, like drug users living with HIV/AIDS (DU HIV+).

Trying to contribute with this problem, initially we conducted a systematic review about adherence to HAART among HIV+ DU. Higher HAART adherence was found in patents receiving multidisciplinary care, particularly those being treated in structured settings (e.g. directly observed therapy) and/or in services providing on the same setting HIV and drug addiction treatment.

Secondly, we conducted a meta-analysis of the same studies included in our systematic review. Studies were highly heterogeneous (I^2 ≥75%): evaluation of adherence using distinct assessment methods (self-report, pharmacy records, MEMS-caps), different cut-offs to define optimal adherence (75-100%), and different study design (cross-sectional studies, randomized controlled trials and Nonrandomized longitudinal Design). Forty-one studies were considered, which analyzed 15194 patients (11628 HIV+ DU, 76.5%). Overall adherence was 60.3% (95% CI: 52.9-67,4%). Study design, particularly related to recall period and adherence measurement method, were independent predictors of inter-study heterogeneity. Among a sub-sample of studies evaluating clinical factors associated with HAART, better treatment outcomes were found among adherent patients, those under abstinence (i.e., former DU), those with less severe psychiatric conditions, and receiving psychosocial support.

And finally we conducted a survival analysis of HIV-positive injecting drug users (IDU), diagnosed between 2000-2006, using different Brazilian national databanks. Among 28,426 patients with complete data (43% IDU; 57% MSM), 6,777

(23.8%) died during 87,792 person-years of follow-up. At baseline, compared to MSM, IDU were significantly less likely to be receiving HAART (24.3% vs. 31.2%; p<0.001), to have ever conducted a CD4 count exam (44.1% vs. 56.9%; p<0.001) or HIV-1 RNA viral load determination (54.2% vs. 62.5%; p<0.001). After controlling for frailty effects, AIDS-related mortality remained higher in IDU than in MSM (AHR: 1.94; 95% CI: 1.84 - 2.05)

Survival analysis results emphasize that substantial inequalities in HAART access still remain in Brazil, despite the country universal and free access to HAART, one of the most comprehensive AIDS program in developing countries. Those inequalities may explain higher mortality among HIV-infected IDUs, compared to MSM in Brazil. Renewed efforts to reduce these health disparities are clearly needed

Findings from the systematic review and meta-analysis suggest that HIV-positive DU can achieve satisfactory levels of HAART adherence, particularly those who have access to multidisciplinary services, adequate to the frequent co-morbidities found within this population. Available evidence suggest that HIV+ DU tend to be inappropriately assumed to be less adherent and unlikely to achieve desirable treatment outcomes, when compared to their non-DU cohort, highlighting the need to expand access to HAART treatment for this population.

Keywords: HIV, AIDS, drug use, systematic review, meta-analysis, survival analysis, HAART

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LISTA DE ABREVIATURAS

AIDS	*Acquired Immune Deficiency Syndrome* (Síndrome da Imunodeficiência Adquirida – SIDA)
AOR	*Adjusted Odds Ration (Razão de chance ajustada)*
ART	*Antiretroviral Treatment* (Tratamento Antiretroviral)
ARV	Medicamentos Anti-retrovirais
CI	*Confidence Interval* (Intervalo de confiança)
DU	*Drug Users* (Usuários de Drogas)
HAART	*Highly Active Antiretroviral Therapy* (Terapia Antiretroviral de Alta Potência)
HCV	*Hepatitis C Virus* (Vírus da Hepatite C)
HIV	*Human Immuno - deficiency Virus* (Vírus da Imunodeficiência Humana)
HR	*Hazard ratio* (Razão de risco)
HSH	Homens que fazem sexo com homens
IDU	*Injection Drug Users* (Usuários de Drogas Injetáveis)
MEMS	*Medication Event Monitoring Systems* (Sistema de Monitoramento de Tomada de Medicação)
MeSH	*Medical Subject Headings (*indexadores de literatura biomédica)
MMT	*Methadone Maintenance Therapy* (Therapia de Manutenção com Metadona, utilizada em pacientes dependents de opiáceos)
MSM	*Men who have Sex with Men* (Homens que fazem sexo com homens)
OR	*Odds Ratio* (Razão de Chance)
PLWHA	*People Living with HIV/AIDS* (Pessoas Vivendo com HIV/AIDS)
PN DST/AIDS	Programa Nacional de AIDS do Ministério da Saúde
RCT	*Randomized Controled Trial* (Estudo de Caso controle)
SD	*Standard Deviation* (Desvio Padrão)
SICLOM	Sistema de Controle Logístico de Medicamentos do PN DST/AIDS
SIM	Sistema de Informações sobre Mortalidade
SINAN	Sistema de Informação de Agravos de Notificação
SISCEL	Sistema de Controle de Exames Laboratoriais do PN DST/AIDS
STI	*Sexually Transmitted Infections* (Infecções Sexualmente Transmissíveis)
SUS	Sistema Único de Saúde
UDI	Usuário de drogas injetáveis
UNAIDS	*Joint United Nations Programme on HIV/AIDS* (Programa Conjunto das Nações Unidas sobre HIV/AIDS)
VL	*Plasma Viral Load* (Carga viral plasmática)
WHO	*World Health Organization* (Organização Mundial da Saúde)

I. INTRODUÇÃO

"We build too many walls and not enough bridges."
Isaac Newton

I.a. Epidemia de HIV/AIDS no Brasil

Quase três décadas desde a identificação dos primeiros casos de pacientes infectados pelo HIV, a epidemia de AIDS representa um sério problema de saúde pública e não apresenta sinais de arrefecer em um futuro próximo. De acordo com estimativas recentes do Programa Conjunto das Nações Unidas em AIDS (UNAIDS), ao final de 2007 havia mais de 30 milhões de pessoas vivendo com HIV/AIDS (na sigla em inglês conhecida como *People Living with HIV/AIDS - PLWHA*), no mundo (UNAIDS/WHO, 2007). As estimativas brasileiras são de ~600.000 PLWHA, das quais aproximadamente 180.000 estão em tratamento e acompanhamento clínico/laboratorial gratuito através do Sistema Único de Saúde (SUS) (Ministério da Saúde, 2007). Avanços no tratamento para a infecção pelo HIV resultaram em importantes melhorias relativas à longevidade e à qualidade de vida de PLWHA nos países em desenvolvimento (Marins *et al.*, 2003). O Brasil representa um paradigma entre os países em desenvolvimento, por ter sido o primeiro a oferecer acesso universal e gratuito à terapia anti-retroviral e a exames para monitoramento da infecção pelo HIV, para todos os pacientes que tenham indicação clínica (Bastos *et al.*, 2001).

Imediatamente após a introdução da terapia antiretroviral de alta potência (HAART), alguns autores questionaram a factibilidade e a ética de ampliar o acesso à HAART nos países em desenvolvimento, principalmente devido ao receio de que populações empobrecidas e com pouca escolaridade apresentassem uma aderência aquém da necessária ao tratamento, o que poderia determinar a emergência e eventual transmissão de cepas virais multiresistentes à HAART (Popp & Fisher, 2002).

No entanto, em recente meta-análise, Mills *et al.* (2006) identificaram 58 estudos avaliando a aderência à HAART entre pacientes acompanhados na África sub-saariana e na América do Norte, concluindo que níveis mais elevados de aderência foram identificados nos estudos

conduzidos na África, e não na América do Norte. Pesquisas realizadas no Brasil, desde a introdução da HAART, também têm evidenciado que o acesso amplo à HAART não influenciou o surgimento e transmissão de cepas virais multiresistentes à HAART em níveis diferentes dos observados nos países desenvolvidos (Soares *et al.*, 2007).

Diversos estudos apontam que o acesso gratuito e universal à HAART no Brasil determinou: (a) aumento da qualidade de vida e sobrevida (Hacker *et al.*, 2004); e (b) minimização das perdas econômicas, em decorrência da diminuição de mortes relacionadas à AIDS, hospitalizações e realização de procedimentos clínico-laboratoriais de elevada complexidade e custo (Teixeira *et al.*, 2004; Gomes, 1999; Chequer *et al.*, 2002).

Por outro lado, estudos recentes apontam que as despesas nacionais com medicamentos anti-retrovirais (ARV) têm experimentado incrementos a cada ano, o que poderia comprometer a sustentabilidade da política brasileira de acesso universal ao tratamento em um futuro próximo (Nunn *et al.*, 2007; Grangeiro *et al.*, 2006).

Embora avaliações sobre a resposta brasileira à epidemia de AIDS sejam extremamente necessárias, não existe pesquisa realizada no Brasil, até o momento, que analise de forma abrangente e integrada os dados nacionais que compõem o sistema de monitoramento da epidemia de HIV/AIDS no país. Tais bases de dados contêm informações sobre todas as PLWHA notificadas ao Ministério da Saúde (aproximadamente 430.000), incluindo os aproximadamente 180.000 pacientes que recebem HAART gratuitamente através do SUS, e sua análise é de fundamental importância. A presente tese avaliou o impacto do acesso amplo à HAART no tempo de sobrevida de PLWHA, no contexto do primeiro país em desenvolvimento a oferecer HAART, monitoramento clínico e laboratorial de forma gratuita e universal – Brasil. A experiência brasileira está sendo acompanhada de perto por outros países em desenvolvimento, ONGs e agências financiadoras, com a intenção de desenvolver programas similares em outros locais; aspecto que torna o presente estudo oportuno e de importância crucial.

I.b. Acesso à terapia anti-retroviral no Brasil

Em 1996, o Brasil aprovou legislação que garante aos seus cidadãos vivendo com HIV/AIDS acesso gratuito e universal à terapia anti-retroviral através do SUS (Bastos *et al.*, 2001). Essa medida fez do Brasil um dos poucos países em desenvolvimento no mundo a oferecer HAART, e talvez o único a oferecer esses tratamentos de uma forma tão inclusiva e ampla. O Brasil foi capaz de estabelecer o acesso universal, em parte, a partir da produção de suas próprias versões genéricas de medicamentos ARV, reduzindo, com isso, os preços destes medicamentos em mais de 70 por cento (Nunn *et al.*, 2007; Ministério da Saúde, 2007).

Em recente estudo, Grangeiro *et al.* (2006) analisaram a evolução dos gastos do Ministério da Saúde com a aquisição de ARV, no período 1998 a 2005; e avaliaram a sustentabilidade desta política em médio prazo. Segundo os autores, as despesas brasileiras com medicamentos ARV aumentaram 66% em 2005, interrompendo uma tendência de redução observada no período 2000-2004. O estudo aponta que os principais fatores associados a esse aumento foram o enfraquecimento da indústria nacional de medicamentos genéricos e os resultados insatisfatórios dos processos de negociação com empresas farmacêuticas.

Buscando assegurar a sustentabilidade do Programa Nacional de AIDS (PN DST/AIDS), em maio de 2007, o presidente Luiz Inácio Lula da Silva assinou decreto autorizando o licenciamento compulsório do medicamento antiretroviral Efavirenz, fabricado pela Merck. Segundo o Governo, o alto custo do medicamento ameaçava a sustentabilidade do PN DST/AIDS. O Efavirenz é hoje utilizado por 75.000 das 180.000 PLWHA que recebem HAART através do SUS – a um custo unitário (por pílula) de US$ 1.59 para o Brasil, embora o mesmo medicamento seja vendido por US$ 0.65 para a Tailândia. Em paralelo às iniciativas buscando assegurar a sustentabilidade do programa de acesso universal à HAART no Brasil, faz-se necessário avaliar a eficácia dessa política, principalmente no que se refere ao impacto do acesso universal a este tratamento na sobrevida de PLWHA. O presente estudo objetiva suprir esta lacuna, utilizando como base de estudo dados de abrangência nacional.

I.c. Aderência ao tratamento para HIV entre usuários de drogas

O advento da HAART melhorou substancialmente o prognóstico e a qualidade de vida de pessoas vivendo com HIV/AIDS desde sua introdução, em 1996/7. No entanto, a eficácia do tratamento depende de uma constante aderência ao esquema terapêutico, um grande desafio para PLWHA (Altice *et al.*, 2001; Mannheimer *et al.*, 2005). Muitos dos esquemas terapêuticos são complexos, alguns contando com várias doses por dia, incluindo, por vezes, restrições alimentares, e podem determinar efeitos colaterais graves (Ferguson *et al.*, 2002). A aderência é necessária para alcançar a desejada supressão viral do HIV (Paterson *et al.*, 2000; Bangsberg *et al.*, 2000), para prevenir o surgimento de cepas virais multiresistentes (Bangsberg *et al.*, 2003) e a progressão da infecção rumo à síndrome clínica (AIDS) (Bangsberg *et al.*, 2001), com conseqüente evolução para óbito (Wood *et al.*, 2003).

Desigualdades no contexto das taxas de morbidade e da mortalidade secundárias ao HIV/AIDS têm sido observadas, principalmente devido a problemas relativos ao acesso à HAART e/ou retenção dos pacientes em terapia regular aquém do necessário à supressão viral e prevenção da falha terapêutica. Tais problemas têm sido mais freqüentes em populações marginalizadas e minorias diversas (Wood *et al.*, 2003a). Historicamente, os usuários de drogas vivendo com HIV têm apresentado não apenas acesso aquém do necessário à HAART (Bassetti *et al.*, 1999; Celentano *et al.*, 1998), mas tendência a iniciar a HAART em estágios mais avançados da infecção (Celentano et. al., 2001; Wang *et al.*, 2004). Estes problemas têm suscitado crescente preocupação, uma vez que o uso de drogas injetáveis é o principal *vetor* da transmissão do HIV em sete regiões do mundo, com destaque para a Europa central e leste e Sudeste da Ásia (UNAIDS/WHO, 2007). O uso de drogas não injetáveis constitui também um importante fator de risco para a infecção pelo HIV, devido ao comportamento sexual de alto risco nesta população (Inciardi & Surratt, 2001; Latkin *et al.*, 2001; Hacker *et al.*, 2005; Ferreira *et al.*, 2006).

Alguns profissionais de saúde referem preocupação em prescrever HAART para usuários de drogas, receando que uma possível melhora no quadro clínico possa favorecer o retorno a padrões

de comportamentos de risco vigentes anteriormente, além de recearem que a aderência aquém da necessária possa favorecer a emergência de resistência viral e a eventual transmissão de cepas virais resistentes (Wensing *et al.*, 2005; Vlahov & Celentano, 2006; Wainberg & Friedland, 1998). Além de problemas relativos à aderência, outros aspectos, como a existência de mutações virais pré-existentes (resistência primária, vide dados brasileiros em Maia Teixeira *et al.*, 2006) e a prescrição incorreta de medicamentos podem também influenciar tanto a supressão viral quanto a reconstituição do sistema auto-imune (Escoto-Delgadillo *et al.*, 2005; Maia Teixeira *et al.*, 2006).

Embora alguns estudos tenham identificado uma aderência mais baixa à HAART entre usuários de drogas "ativos" (Celentano *et al.*, 1998) e que a aderência experimente um declínio em períodos de recaída de uso de drogas (Lucas *et al.*, 2002), outros estudos identificaram que usuários de drogas vivendo com HIV, que têm acesso ao tratamento para dependência química e recebem apoio psicossocial, costumam alcançar os mesmos níveis de aderência encontrados entre PLWHA que nunca usaram drogas (Crystal *et al.*, 2001).

No entanto, as barreiras que podem comprometer a aderência à HAART entre usuários de drogas vivendo com HIV permanecem como uma questão a ser estudada de forma mais aprofundada. As preocupações com uma aderência aquém da necessária à supressão viral entre usuários de drogas vivendo com HIV são, de fato, justificáveis? A presente tese objetivou também avaliar de forma mais detalhada esta questão, realizando para tal uma revisão sistemática, seguida de meta-análise.

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II. OBJETIVOS

"Doubt is the father of invention." Galileo Galilei

OBJETIVO GERAL

Avaliar, através de diferentes estratégias metodológicas, o impacto da epidemia de HIV/AIDS e a aderência ao tratamento antiretroviral entre usuários de drogas.

OBJETIVOS ESPECÍFICOS

II.a. Realizar uma revisão sistemática seguida de meta-análise de artigos científicos, publicados em periódicos indexados, que tenham avaliado a aderência de usuários de drogas HIV-positivos à HAART. Partimos aqui do pressuposto de que a aderência à HAART na população de usuários de drogas seja diferenciada (frente às demais populações), e varie em função de características individuais (ex: idade na data do diagnóstico, comorbidades, níveis de CD4 e carga viral no início do tratamento) e em função de características do serviço de saúde (ex: acesso a suporte psicossocial, tratamento para dependência química).

II.b. Realizar um estudo de sobrevida de PLWHA do Brasil, comparando pacientes que tenham sido diagnosticados como casos de AIDS na chamada fase "pós-HAART tardia" (após 2000). Partimos aqui do pressuposto de que o uso de HAART e a disponibilidade de esquemas terapêuticos cada vez mais eficazes tenham influenciado os padrões de mortalidade entre PLWHA no Brasil ─ especialmente após 2000, quando o acesso amplo e universal já estava bem estabelecido no país como um todo. Porém, hipotetizamos também que o início da HAART seja diferenciado entre PLWHA infectadas em função de modalidades distintas de exposição (ou seja, pertencentes a diferentes categorias de exposição), tomando-se aqui como categorias de análise "homossexuais/bissexuais masculinos" vs. "usuários de drogas injetáveis", a despeito do acesso universal preconizado pelo Ministério da Saúde, fato que poderá contribuir para padrões de mortalidade diferenciados. O estudo objetivou identificar se os padrões de mortalidade entre PLWHA brasileiras variam em função das categorias de exposição sob análise, idade, raça, níveis de CD4 quando do início do tratamento e primeira contagem de carga viral.

III. RESULTADOS

"There's place and means for every man alive."
William Shakespeare

Breve descrição do formato adotado para apresentação dos resultados

Os objetivos propostos deram origem a três artigos. O artigo de revisão sistemática (*"Adherence to Antiretroviral Therapy for HIV/AIDS among Drug Users: A Systematic Review"*), que tematiza aspectos associados à aderência à HAART entre usuários de drogas, foi publicado na Revista *Addiction*, volume 103, páginas 1242–1257, publicação realizada em 2008.

A meta-análise realizada com base nos mesmos estudos incluídos na revisão sistemática (*"Adherence to Antiretroviral Therapy for HIV/AIDS among Drug Users: A Meta-analysis"*) foi submetida para publicação à Revista *AIDS and Behavior*, estando no momento de publicação da presente tese de doutorado, junho de 2008, em processo de avaliação.

A análise referente à sobrevida de usuários de drogas (*"Mortality among HIV-Infected Injecting Drug Users: A survival analysis of Universal Access to HIV-treatment in Brazil"*) está apresentada sob a forma de artigo, e será posteriormente submetida à revista indexada para publicação.

A metodologia empregada nos estudos encontra-se descrita em português no Anexo 1.

III.a ARTIGO 1

Adherence to Antiretroviral Therapy for HIV/AIDS among Drug Users: a Systematic Review*

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ABSTRACT

Context: Adherence to highly active antiretroviral therapy (HAART) is a key predictor of survival for HIV-infected persons. Suboptimal adherence among marginalized populations such as HIV-positive drug users could be associated with clinical failure and the emergence of viral resistance.

Objective: To conduct a systematic review of studies assessing adherence to HAART among HIV-positive drug users (DU) and identify factors associated with non-adherence to HIV treatment.

Data Sources: Seven electronic databases were searched for peer-reviewed papers published in English, French, Spanish or Portuguese, from 1996 to 2007.

Study Selection and Data Abstraction: Studies were excluded if they presented only qualitative data, were reviews themselves or assessed other populations without disaggregating data on DU. Findings on adherence were extracted and summarized.

Data Synthesis: Forty-one studies were considered, which studied a total of 15,194 patients, the majority of whom were HIV-positive DU (N=11,628, 76.5%). Twenty-two studies assessed adherence using patient self-reports, eight used pharmacy records, three used electronic monitoring (i.e. MEMS caps), six studies used a combination of patient self-report, clinical data and MEMS-caps, and two analyzed secondary data. Overall, active substance use was associated with poor adherence, as well as depression and low social support. Higher adherence was found in patents receiving care in structured settings (e.g., directly observed therapy) and/or drug addiction treatment (especially substitution therapy).

Conclusion: While lower than other populations – especially among users of stimulants, incarcerated DU and patients with psychiatric comorbidities - adherence to HAART among HIV-positive DU can be achieved. Better adherence was identified among those engaged in comprehensive services providing HIV and addiction treatment with psycho-social support.

Keywords: HIV, AIDS, adherence, drug use, review

INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has improved the health and quality of life of people living with HIV/AIDS (PLWHA), since its introduction in 1996/7. Treatment efficacy relies, however, on sustained adherence, which constitutes a challenge[1,2]. Most regimens are complex, with varying dosing schedules, dietary restrictions, and may cause serious adverse effects[3]. While some of the recent regimens have decreased pill burden and alleviated these problems, adherence is required for reliable viral suppression[4,5] and prevention of the emergence of resistant viruses[6], disease progression[7], and death[8].

Disparities in HIV-related mortality have been observed due to problems with access to highly active antiretroviral therapy (HAART) and/or poor retention in HIV-related treatment, particularly among disadvantaged or marginalized populations[9]. Historically, HIV-positive drug users (DU) have not only had suboptimal access to HAART[10,11], but tend to initiate HAART at more advanced stages of infection[12,13]. This raises concern since injection drug use is a major vector for HIV/AIDS transmission in seven of ten regions around the world[14]. Non-injecting DU are also at high risk for HIV infection due to high-risk sexual behaviors[15,16].

Some providers prescribing HAART to DU have been concerned that clinical improvement may lead to behavioral relapse, and that suboptimal adherence may favor the emergence of viral resistance and the transmission of drug-resistant HIV strains[17-19]. Beyond adherence, other factors such as pre-existing mutations and incorrectly prescribed drugs might influence both viral load reduction and/or the reconstitution of the immune system[20].

While some studies have found that adherence to HIV medication is lower among current drug users[11], or that adherence declines in periods of relapse[21], other studies have found that HIV-positive drug users who have access to drug abuse and mental health treatment, and particularly former drug users who are abstinent, can reach the same levels of adherence found among PLWHA who have never used illicit drugs[22]. However, the specific barriers that might jeopardize HIV-positive drug users' adherence to HAART remain to be further elucidated. Are concerns of poor

adherence to HAART among DU justified? To the best of our knowledge, no review has summarized the growing body of research on this topic. We conducted a systematic review of available data on HAART adherence among HIV-positive DU, and identified barriers and promoters associated with non-adherence among these studies.

METHODS

Inclusion and Exclusion Criteria

Only studies assessing adherence to HAART among DU as a primary outcome were included. Drug users were defined as those who have used any illicit drug (except cannabis) over the last 12 months. Studies had to have reported a given threshold/cut-off defining optimal adherence (e.g. 90% or 95%) and include multivariate analyses assessing correlates of adherence. Only studies conducting multivariate analysis were selected in order to control for confounding factors, something key in studies dealing with complex psychosocial phenomena – such as addiction and adherence.

Studies were excluded if they were exclusively based on qualitative data (due to the fact we aimed to carry out both a systematic review and a meta-analysis); were reviews themselves, were not published in English, Spanish or Portuguese; or assessed other populations without disaggregating DU from the overall sample. DU were defined herein as users of heroin, cocaine/*crack* or methamphetamine. Studies exclusively addressing alcohol users and/or cannabis smokers were not included.

Data Search

Search terms that reflect adherence (e.g., *adherence, compliance, pill counts*) or specific equipment used to measure adherence (e.g. Medication Event Monitoring Systems,[MEMS-caps] an electronic adherence monitoring system that uses a microchip in the prescription bottle-cap) were identified. Searches combined these terms with Medical Subject Headings [MeSH] for HIV and drug abuse. MEDLINE via PubMed, Cochrane CENTRAL, AIDSLINE, AMED, CINAHL,

TOXNET, SciELO, and Web of Science were searched from 1996 to February 29, 2008; except for AIDSLINE, which was searched from 1996 up to 2000, when the inclusion of new citations was discontinued.

Study Selection

Using a predefined protocol (available from the corresponding author on request), 2 investigators (MM, FIB), extracted the full text of peer-reviewed papers addressing adherence among HIV-positive DU and independently assessed their eligibility. After all potentially relevant peer-reviewed papers were identified, the two investigators met to achieve consensus.

Data Extraction

Data extraction was conducted using a standardized form. Data abstractors collected information about the country where the study was conducted, characteristics of the sample (age, sex, ethnicity) sample size, study design, measures of adherence, as well as other treatment outcomes such as viral load and CD4 count, when available. When more than one adherence measurement was used (e.g. MEMs cap and patient's self-report), data from all methods were collected and compared.

RESULTS

From the initial searches, 219 peer-reviewed papers were identified. Of these, there was perfect agreement between reviewers on the eligibility of 69 papers, with 150 papers not meeting the study inclusion criteria. In a second screening, thirteen studies were excluded because of their exclusive use of biological markers as outcomes (i.e. HIV-1 viral load and/or CD4 cell counts), instead of measuring adherence itself. Agreement between reviewers was also perfect on the second screening. A third screening excluded 15 studies, primarily because authors did not stratify results according to drug use status. Agreement on the last screening was close to perfect. We thus included 41 eligible reports for full data extraction.

Study Characteristics

Characteristics of the 41 selected studies were summarized in **Table 1**. In spite of searching for papers published in different languages, almost all identified studies were published in English (40/41). All were conducted in developed countries – the vast majority in North America (22 in the United States, 8 in Canada), and 11 in Europe (6 in France, 3 in Spain, 1 in Italy, and 1 in Ireland).

Two studies used secondary data from the U.S. Medicaid Program[22,23]. In New York, Turner and colleagues[23] had the largest sample among all selected studies (N=5,103). Crystal and colleagues[22] used data from the New Jersey Medicaid Program and evaluated 1,048 patients. Both studies were evaluated separately to avoid bias due to type-II errors. All other selected studies assessed primary data: 24 were longitudinal, four were randomized controlled trials and eleven were cross-sectional. The vast majority of selected studies evaluated HIV-positive injection drug users (IDU) and a few addressed a sub-sample of non-injecting drug users (**Table 1**).

Table 1. Characteristics of selected studies, 1999-2007.

				Characteristics of Study Population			
Source	**N**	**Country**	**Design (Period)**	**Population (%)**	**Age, y (range)**	**Female (%)**	**Ethnicity (%)**
Arnsten *et al.*, 2007	636	United States	RCT (2001-03)	IDU (100.0	>40 y: 63.0%	223 (35.0)	Non-Hispanic white: 43 (7.0) Non-Hispanic black: 412 (66.0) Hispanic: 124 (20.0) Non-Hispanic other: 42 (7.0)
Hinkin *et al.*, 2007	150	United States	Prospective cohort study (2001-05)	Current IDU: 102 (68.0)	41.3 (18-61)	26 (17.3)	African American 94 (62.6) White: 22 (14.6) Hispanic: 21 (14.0)
Palepu *et al.*, 2006	278	Canada	Prospective cohort study (1996-2003)	IDU: 276 (99.3) All HIV/HCV co-infected	Adherents 36 (32-42) Non-Adherents 35 (28-42)	Adherents 48 (37.2) Non-Adherents 70 (46.9)	Adherents Aboriginal: 41 (31.1) Non-Adherents Aboriginal: 41 (31.1)
Waldrop-Valverde et at., 2006	57	United States	Cross-sectional survey	IDU (100.0)	42.7 (±5.6)	13 (22.8)	African American: 51 (89.4)
Liu *et al.*, 2006	148	United States	Prospective cohort study (1999-2003)	Cocaine: 89 (61.0) Heroin: 39 (27.0) All DU[1] with history of child sexual abuse	40.0 (±8)	148 (100.0)	African American: 80 (54.0) Hispanic: 59 (39.8)
Knowlton *et al.*, 2006	466	United States	Cross sectional study (2001-04)	IDU (100.0) 91% current illicit drug users	43 (25-59)	159 (34.1)	Non-Hispanic black: 321 (68.8)
Waldrop-Valverde et at., 2005	58	United States	Cross sectional study NA	IDU (100.0)	Non-homeless: 42.7 (±5.9) Homeless: 43.4 (±4.4)	14 (24.1)	African American: 52 (89.6)
Haug *et al.*, 2005	78	United States	RCT (2001-2004)	78 patients under MMT*	Men: 42.9 (±7.95) Women: 45.4 (±7.62)	36 (46.1)	Non-white men: 21 (50.0) Non-white women:25 (69.4)
Kerr *et al.*, 2005	160	Canada	Prospective cohort study (2001-02)	IDU	39 (± 7.04)	69 (43.1)	NA
Martín *et al.*, 2005	100	Spain	Cross sectional study (2003)	IDU under MMT	37 (±5.32)	20 (20.0)	NA
Bouhnik *et al.*, 2005	243	France	Prospective cohort study (NA)	IDU	35 (NA)	68 (28.0)	NA
Martini *et al.*, 2004	214	Italy	Cross sectional study (1998)	Ex- DU: 154 (71.9)	Ex- DU: >34 (51.2%) DU: >34 (56.6%)	Ex- DU: 64 (41.5%) DU: 14 (23.3%)	NA
Sharpe *et al.*, 2004	1,196 (785 in Analysis)	United States	Cross sectional study (1997-2000)	Non DU: 448 (37.4) *Crack* users: 306 (25.6) Other drugs: 442 (36.9)	Non users: 38 (18-78) *Crack* users: 38.2 (20-59) Other drugs: 38.4 (18-70)	1196 (100)	African American: 1,196 (100)
Altice *et al.*, 2004	72 (62 in Analysis)	United States	RCT NA	IDU	42.1	23 (31.9)	African American: 43 (60.0) Hispanic: 13 (18.0) White: 16 (22.0)

Table 1. Characteristics of selected studies, 1999-2007 (cont.)

				Characteristics of Study Population			
Source	**N**	**Country**	**Design (Period)**	**Population (%)**	**Age, y (range)**	**Female (%)**	**Ethnicity (%)**
Purcell *et al.*, 2004	1161 (560 in Analysis)	United States	RCT (2001-03)	IDU (100.0)	42 (22-60)	426 (36.7)	African American: 740 (63.7) Hispanic: 201 (17.3)
Palepu *et al.*, 2004	349	United States	Prospective cohort study (1997-2001)	IDU (59%) Homeless (29%)	41.0	40(20.6)	Non-white: 121(62.4)
Palepu *et al.*, 2004a	1746	Canada	Prospective cohort study (1997-2002)	Incarcerated: 101 Non-Incarcerated:1,645 IDU/Ex-IDU: 395 Never-IDU: 1,351	Incarcerated: 34 (29-40) Non-incarcerated: 37 (32-44)	Incarcerated: 10 (9.9) Non-Incarcerated: 296 (17.9)	NA
Crisp *et al.*, 2004	137	United States	Cross sectional study (1999-2000)	112 (81.7%) smoke *crack* daily, last 7 days	39.7 (21-53)	37 (27.0)	African American: 137 (100)
Wood *et al.*, 2004	1,522	Canada	Prospective cohort study (1996-2002)	IDU::371 Never-IDU: 1,151	IDU: 38 (32-43) Never-IDU: 37 (32-44)	IDU: 86 (23.2) Never-IDU: 154 (13.4)	NA
Kerr *et al.*, 2004	108	Canada	Prospective cohort study (2001-2002)	IDU	39 (±7.1)	49 (45.4)	NA
Wood *et al.*, 2003b	1422	Canada	Prospective cohort study (1996-2000)	IDU: 359 (25.3) Never-IDU: 1063 (74.7)	Among IDU 37.6 (32.3-43.0)	Among IDU 85 (23.7)	NA
Clarke *et al.*, 2003	150	Ireland	Cross sectional Study (2000)	IDU	<19y - 1.3% 19-29 -36% >29 - 62.7%	63 (42.0)	NA
Turner *et al.*, 2003	5,073	United States	Retrospective cohort Study (NYS Medicaid Patients, 1997)	3,322 DU under addiction treatment	< 30 – 3.7% 30-39 – 38.0% 40-49 – 48.4% 50+ - 9.9%	1,122/5,103 (21.9)	NA
Palepu *et al.*, 2003	578	Canada	Prospective cohort study (1996-2000)	IDU: 78 (13) Ex-IDU: 96 (17) Never IDU: 404 (70)	38 (33-45)	NA	NA
Palepu *et al.*, 2003a	234	Canada	Prospective cohort study (1996-2000)	IDU: 128 (54.7) Injected cocaine/heroin on a daily basis	36 (30-42)	89 (38.0)	NA
Escobar *et al.*, 2003	283	Spain	Cross sectional Study (2000-2001)	Alcohol and/or drug use: 203 (71.7) IDU: 196 (69.3)	36 (25-72)	89 (31.4)	NA
Carrieri *et al.*, 2003	96	France	Prospective cohort study (1995-1998)	IDU	NA	30 (31.2)	NA
Wagner, 2003	82	United States	Prospective cohort study (1999-2002)	IDU	40 (±6)	NA	NA

Table 1. Characteristics of selected studies, 1999-2007 (cont.)

				Characteristics of Study Population			
Source	**N**	**Country**	**Design (Period)**	**Population (%)**	**Age, y (range)**	**Female (%)**	**Ethnicity (%)**
Arnsten *et al.*, 2002	85	United States	Prospective cohort study (1998-2000)	Active drug use during study: 32 (37.6)	42 (NA)	34 (40.0)	Hispanic: 51 (60.0) African American: 19 (22.3)
Bouhnik *et al.*, 2002	210	France	Prospective cohort study (1997-99)	Ex-IDU: 114 (54.3) IDU: 96 (45.7)	Ex-IDU: 33.3 IDU: 34.3	Ex-IDU: 33 (28.9) IDU: 28 (29.1)	NA
Duran *et al.*, 2001	57	France	Prospective cohort study (1995-99)	IDU (100.0)	NA	NA	NA
Lucas *et al.*, 2001	764 (558 in Analysis)	United States	Prospective cohort study (1998-99)	Ex-IDU: 376 (49.2) IDU: 199 (26.0) NIDU: 189 (24.7)	40 (35-45)	279 (37.0)	African American: 613 (80.0)
Altice *et al.*, 2001	205	United States (Prisions)	Cross-sectional survey (April-Oct, 1996)	Incarcerated population Ex-IDU (100.0)	36.2	98 (48.0)	Black: 84 (41.0) Hispanic 81 (40.0) White: 40 (19.0)
Arnsten *et al.*, 2001	67	United States	Prospective cohort study (1998-99)	Active drug use during study: 22 (32.8) MMT 64 (96.0)	43 (23-61)	26 (38.9)	African American: 16 (24.0) Hispanic: 40 (60.0) White: 8 (12.0)
McNabb *et al.*, 2001	40	United States	Prospective cohort study (Feb-Aug, 1999)	IDU	42 (26-51)	10 (25.0)	African American: 9 (22.5) Hispanic: 30 (75.0)
Crystal *et al.*, 2001	1,739[#]	United States	Prospective cohort Study (New Jersey Medicaid Patients, 1996-1998)	IDU: 1,048 (60.3%)	18-29: 14.4% 30-39: 49.4% 40-49: 30.1% >50: 6.1%	669 (38.5)	African American: 1,005 (58.1) Hispanic: 333 (19.3) White: 391 (22.6)
Pradier *et al.*, 2001	119	France	Prospective cohort study (1995-1998)	IDU	Age by ARV-drug group[§]: SQV: 34.0 (±4.7) IDV: 33.0 (±4.7) Other: 33.1 (± 3.4)	Male by ARV-drug group: SQV: 24 (57.1) IDV: 38 (71.7) Other: 16 (66.7)	NA
Avants *et al.*, 2001	42	United States	Prospective cohort study (period not available)	IDU	41.2 (±5.2	NA	NA
Moatti *et al.*, 2000	164	France	Prospective cohort study (1995-99)	Ex-IDU: 113 (68.9)	Non-adherent: 33.2 (±4.1) Adherent: 34.8 (±4.8)	52 (31.7)	NA
Roca *et al.*, 1999	133	Spain	Prospective cohort study (1997-1998)	IDU: 95 (71.0) Non-IDU: 38 (29.0)	Ex-IDU: 31.7 (±4.7) Non-IDU: 36.5 (±9.6)	Ex-IDU: 27 (28.4) Non-IDU: 15 (39.5)	NA
Gordillo *et al.*, 1999	366	Spain	Cross sectional study (1997-1998)	Former IDU: 97 (26.5) Current IDU: 65 (17.8) Non-IDU: 204 (55.7)	<32: 111 (30.3) 32-35: 79 (21.6) 35-40: 91 (24.9) >40: 85 (23.2)	87 (23.7)	Spanish: 342 (93.4) African: 6 (1.6) South-African: 5 (1.4) Others:13 (3.6)

DU – Drug Users (non necessarily injection drug users); *MMT – Methadone Maintenance Therapy; [#]Ethnicity data available only for 1,729 patients; [§] SQV: Saquinavir, IDV: Indinavir

Optimal Adherence Cut-offs

Twenty-two studies assessed adherence using patient self-reports, eight used pharmacy records on prescription refill compliance, three used MEMS-caps. Six studies used a combination of patient self-report, clinical data and MEMS-caps, and two analyzed secondary data.

Main results and adherence cut-offs adopted by selected studies are presented in **Table 2**. Eleven (26.8%) studies defined optimal adherence as 100% uptake of the prescribed doses. Eight studies (19.5%) assessed optimal adherence as greater than 95%, three as greater than 90%, eight as greater than 80%, and one study as greater than 75%. One study used two different cut-offs (90 and 100%). Three studies using MEMS-caps evaluated adherence as a continuous variable, and six studies used a combination of adherence measurements (e.g. self-report and pharmacy records).

Adherence was measured across various time periods, ranging from the previous day to the last 2.5 years. However, the majority of selected studies evaluated adherence using a time-frame which included the previous day up to the previous 15 days (19 studies; 46.3%); 3 studies evaluated adherence over a period of 1-2 months, and 2 studies used a 4-6 month time-frame. A few studies used an extended time-frame: 10 studies assessed adherence for a one year period, one study evaluated adherence over 2.5 years, 3 studies used a combination of days, weeks and months of recall. Time-frames were not clearly defined in three studies.

Table 2. Threshold of Measurement and adherence levels of selected studies, 1999-2007.

Source	Assessor	Threshold of Measurement	Period of Measurement	N Adherent (%)
Arnsten *et al.*, 2007	Patient (Self Report)	≥ 90; No. of pills taken/No pills prescribed	1 – 15 days (Previous day)	477 (75.0) Association w/adherence[1], Adjusted OR (95% CI) ↑ high school graduation: 1.57 (1.03-2.41) ↑ "ARV do not *eat*' methadone": 1.53 (1.00-2.36) ↑ no syringe/needle sharing: 2.30 (1.46-3.62) ↑ positive attitudes toward ARV: 2.04 (1.16-2.00) ↑ Higher self-efficacy for taking ARV: 2.13 (1.55-2.92) ↑ Higher sense of responsibility: 1.42 (1.04-1.93) ↓ Higher depressive symptoms: 0.74 (0.58-0.94)
Hinkin *et al.*, 2007	MEMS cap[2]	≥ 90; No. of pills taken/No pills prescribed	Previous 6 months	DU+: 63.6% (with positive urine analysis for drug use previous 2-3 days) DU-: 79.8% (with negative urine analysis)
Palepu *et al.*, 2006	Pharmacy records (refill compliance)	≥ 95; No. days patient receives HAART refills/No. days of medical follow-up	Previous 1 year of follow-up	129/278 (46.4) Association w/adherence, Adjusted OR (95% CI) ↑ IDU under MMT[3]: 1.52 (1.16-2.00) ↓ weekly heroin use: 0.52 (0.42-0.79)
Waldrop-Valverde et at., 2006	Patient (Self Report)	=100; No. of pills taken/No pills prescribed	1 – 15 days (Last 1 and 7 days)	Adherence past 7 days: 33 (57.8) Adherece preceeding day: 40 (70.1)
Liu *et al.*, 2006	Patient (Self Report)	=100 and ≥ 90; No. Doses taken/No. Doses prescribed	1 – 15 days (Last 1.2.3 and 14 days)	Adherence on 1, 2, 3 and 14 days: Adherence ≥ 90%: 88,90,92,73% Adherence=100%: 88.90.92.59%
Knowlton *et al.*, 2006	Patient (Self Report)	≥ 95; No. pills taken / No. pills prescribed	1 – 15 days (Last day)	350 (75.1) 239/350 (68.3) adherents with detectable HIV-VL[4] (p<.05)
Waldrop-Valverde et at., 2005	Patient (Self Report)	=100; No. pills taken / No. pills prescribed	1 – 15 days (Last day)	35 (60.3) Association w/ adherence ↑ Higher depression (p=.02)
Haug *et al.*, 2005	Patient (Self Report) and MEMS cap	=100; No pills taken/number pills prescribed	Self report: Previous day and previous 4 days on time adherence MEMS cap 4-weeks on-time adherence	Self-reported adherence: ♂ previous day: 76% ♀ previous day: 78% Average: 76.7% ♂ previous 2-4 days: 82% ♀ previous 2-4 days: 78% Average: 80.4% MEMs cap ♂ previous 4 weeks: 54% ♀ previous 4 weeks: 58% Average: 56.4%

Table 2. Threshold of Measurement and adherence levels of selected studies, 1999-2007 (cont.)

Source	Assessor	Threshold of Measurement	Period of Measurement	N Adherent (%)
Kerr *et al.*, 2005	Patient self-report and pharmacy records	=100; HAART discontinuation: (i) picked up at least one HAART prescription and (ii) reported HAART discontinuation for one month or over (confirmed by pharmacy dispensation records)	Discontinuation over a 1-year follow-up period	Discontinued HAART: 71 (44.4) Association w/ discontinuation: Incarceration: OR: 4.84, *p*= 0.022 Negative outcome expectations: OR: 1.41, *p*= 0.001 Adherence efficacy expectations: OR: 0.70, *p*= 0.003 Self-regulatory efficacy: OR: 0.86, *p*= 0.050
Martín *et al.*, 2005	Patient (Self Report)	=100 No. pills taken / No. pills prescribed	Previous day, week and month	61%, 58% and 43% (previous day, week and months respectively)
Bouhnik *et al.*, 2005	Patient (Self Report)	≥ 80%; No. pills taken / No. pills prescribed	1 – 15 days (Last 7 days)	Non-adherents Baseline: 31.0% Follow-up: 27.5% (5 years)
Martini *et al.*, 2004	Patient (Self Report)	No. error made (e.g. missing doses, interruption, changing time) High adherence: ≤ 2 Medium: 3-4 Low: ≥ 5	Previous 2 months	DU : 19/60 (31.6) Non-DU : 65/154 (42.3) Adherent DU vs. Non-DU (31.6% vs. 42.3%, p<.05)
Sharpe *et al.*, 2004	Patient (Self Report)	=100 No. pills taken / No. pills prescribed	NA	Overall adherence : 534/784 (68.0) Non-DU : 245/312 (78.5%) DU : 289/472 (61.2%) Non-crack-users: 63.5% *Crack*-users: 57.2% Association w/non-adherence, Adjusted OR (95% CI) ↓ *Crack* use; 0.37 (0.24–0.56) ↓ other drugs: 0.47 (0.36-0.68)
Altice *et al.*, 2004	MEMS-cap	> 75%; No pills taken / No pills prescribed	1 – 15 days (Last 3 days)	Baseline adherence: 25.0% Supervised doses: 76.2% Unsupervised doses: 50.0% Association w/ adherence ↑supervised vs. unsupervised pills administration (p<.0001)
Purcell *et al.*, 2004	Patient (Self Report)	=100 % of those who missed at east 1 dose	1 – 15 days (Last day)	420/560 (75.0)

Table 2. Threshold of Measurement and adherence levels of selected studies, 1999-2007 (cont.)

Source	Assessor	Threshold of Measurement	Period of Measurement	N Adherent (%)
Palepu t al., 2004	Patient (Self-Report)	≥ 95; No. of pills taken/No pills prescribed	Previous 30 days	146/194 (75.3)
Palepu *et al.*, 2004a	Pharmacy records (refill compliance)	=100; No days patient received HAART refills/No days of follow-up	1st year of therapy	Adherents: 1044 (59.8) Association w/ non-adherence, Adjusted OR (95% CI) ↑ incarceration: 2.40 (1.54-3.75) ↑ injection drug use: 1.49 (1.17-1.90)
Crisp *et al.*, 2004	Patient (Self Report)	=100; No pills taken / No pills prescribed	NA	Full compliance: 73/137 (53.3) 43/137 (31.3) compliant more than half the time
Wood *et al.*, 2004	Pharmacy records (refill compliance)	≥ 95; No days patient received HAART refills/No days of follow-up	1st year of therapy	IDU: 167 (45.0) Never-IDU: 722 (62.7)
Kerr *et al.*, 2004	Pharmacy records (refill compliance)	≥ 95; No days with filled prescription/No days under therapy	During one year of follow up	37 (34.3)
Wood *et al.*, 2003b	Patient (Self Report)	≥ 95; Non adherents: Received HAART for less than 95% of the follow-up period	1st year of therapy	160/359 (44.6)
Clarke *et al.*, 2003	Pharmacy records (refill compliance)	≥ 80; Pharmacy records demonstrate at least 80% rate of HAART refills	NA	55/85 (64.7)
Turner *et al.*, 2003	Pharmacy records (refill compliance)	≥ 95; No days with filled prescription/No days under therapy	During 1997 (1 year)	Overall: 1,141/5073 (22.5%) ♀ - 329/1,827 (18.0%) ♂ - 812/3,246 (25.0%)
Palepu *et al.*, 2003	Pharmacy records (refill compliance)	=100; No days patient received HAART refills/No days of follow-up	1st year of therapy	IDU: 76.9% Ex-IDU: 81.5% Non IDU: 91.6%
Palepu *et al.*, 2003a	Pharmacy records (refill compliance)	=100; No days patient received HAART refills/No days of follow-up	1st year of therapy	Overall: 167/234 (71.4%) 100/133 (75.2) IDU who achieved HIV viral suppression and were adherents 67/101 (66.3) IDU who did not achieve HIV viral suppression and were adherents

Table 2. Threshold of Measurement and adherence levels of selected studies, 1999-2007 (cont.)

Source	Assessor	Threshold of Measurement	Period of Measurement	N Adherent (%)
Escobar *et al.*, 2003	Pharmacy records (refill compliance)	≥ 95% No. of pills taken/No pills prescribed	Previous 4-6 months	Overall sample: 147/283 (51.9) Alcohol/drug users: 94/203 (46.3) IDU: 90/196 (45.9)
Carrieri *et al.*, 2003	Patient (Self Report)	≥ 80; No. of pills taken/No pills prescribed	1 – 15 days (Last 7 days)	74 (77.1%) Factors associated q/non-adherence: lack of stable relationship; active drug use, depression; anxiety.
Wagner, 2003	MEMS cap and Patient (Self Report)	Continuous variable No. MEMS cap openings/No prescribed doses	1 – 15 days (Last 14 days)	MEMs adherence: Average adherence: 74.4% ≥ 90% adherence: 39.0% ≥ 95% adherence: 25.6% Self-reported adherence: 86%
Arnsten *et al.*, 2002	MEMS cap	Continuous variable No. MEMS cap openings/No prescribed doses	Previous month	50.6%
Bouhnik *et al.*, 2002	Patient (Self Report)	≥ 80%; No. pills taken / No. pills prescribed	1 – 15 days (Last 7 days)	Ex-IDU: 74.6% IDU: 63.5%
Duran *et al.*, 2001	Patient (Self-Report)	≥ 80; No. of pills taken/No pills prescribed	1 – 15 days (Last 7 days)	39/57 (68.4)
Lucas *et al.*, 2001	Patient (Self-Report)	Non-adherence: > 2 missed doses	1 – 15 days (Last 2 weeks)	Non-adherents: 34% active IDU vs. 17% Ex-IDU vs. 24% non-IDU (p<.001, both comparisons)
Altice *et al.*, 2001	Patient (Self-Report)	≥ 80; No. of pills taken/No pills prescribed	1 – 15 days (Last 7 days)	137/164 (83.5) 62.4% ever self-discontinued HAART (118/189)
Arnsten *et al.*, 2001	MEMS cap and Patient (Self Report)	Continuous variable No. MEMS cap openings/No prescribed doses	1 – 15 days (Last day and 7 days)	Self reported adherence 1-day adherence: 79.1% (± 22.5) 1-week adherence: 78.1% (± 22.1) MEMS cap adherence 1-day adherence: 57.3% (± 31.9) 1-week adherence: 53.7% (± 33.9)
McNabb *et al.*, 2001	MEMS cap, Pill counts, and Patient (Self Report)	MEMS No. MEMS cap openings/No prescribed doses Pill counts and Self report No. pills taken / No. pills prescribed	MEMS and Pill counts: Previous 6 months Self report Previous1 and 2 days Previous 2 weeks	Self Reported Adherence: ≈ 100% Pill Count adherence: 79.8% (±26.0) MEMS cap adherence: 53.5% (± 28.7)

Table 2. Threshold of Measurement and adherence levels of selected studies, 1999-2007 (cont.)

Source	Assessor	Threshold of Measurement	Period of Measurement	N Adherent (%)
Crystal *et al.*, 2001	Pharmacy records (refill compliance)	Proportion (0-1.0); No days on PI/NNRTI drugs/No days from first prescription to the end of study	~2.5 years of follow-up (March 1996 – Dec 1998)	IDU: 0.66 Non-IDU: 0.68 (Non-statistically significant)
Pradier *et al.*, 2001	Patient (Self Report)	=100%; No. pills taken/No pills prescribed	1 – 15 days (Last 7 days)	85 (71.4)
Avants *et al.*, 2001	Patient (Self Report)	≥ 80; No. pills taken / No. pills prescribed	1 – 15 days (Last 7 days)	Non-adherents: 15 (35.7) Non-adherence associated w/: low education, high viral load, low fluid intelligence, depression, low cognitive function (p's<0.01)
Moatti *et al.*, 2000	Patient (Self Report)	≥ 80; No. pills taken / No. pills prescribed	1 – 15 days (Last 7 days)	107 (65.2)
Roca *et al.*, 1999	Patient (Self Report) and Medical Charts	Adequate Adherence: (i) patients kept the appointments; (ii) > 80% of prescribed doses; (iii) HIV-RNA level at least 1.5 $\log_{10}$ below pre-treatment level Inadequate Adherence: (i) or (ii) were not met. Indeterminate Adherence: (i) and (ii) were met, but condition (iii) was not.	Previous 1 year of follow-up	43/133 (32.3) IDU: 26/95 (27.4) Non IDU: 17/38 (44.7)
Gordillo *et al.*, 1999	Patient (Self Report)	> 90%; No. pills taken / No. pills prescribed	1 – 15 days (Last 7 days)	IDU: 134/204 (65.7) Non-IDU: 77/162 (47.5) Non IDU vs. IDU adherence: AOR: 2.05, 95%CI: 1.28-3.29

1. ↑ - Positive association; ↓ - Negative association
2. MEMS cap - Medication Event Monitoring System
3. MMT - Methadone Maintenance Treatment
4. VL – Plasma Viral Load

Major study findings

Adherence Assessment: Longitudinal Studies vs. Randomized Controlled Trials

Longitudinal studies using MEMS-caps were roughly comparable. Arnsten *et al.*[24] found an overall monthly adherence of 51.0% among IDU, while another study conducted by the same group[25] reported an adherence of 57.3% for the day before evaluation and 53.4% for the previous week. Wagner and colleagues[26] reported an average electronically monitored adherence of 74% over a two-week period among 81 IDU, with 39% of participants having at least 90% adherence. Two studies used MEMS-caps to evaluate adherence over a period of six months. McNabb and collaborators[27] reported an adherence level of 53.5%, while a recent study[28] found a higher adherence for both active drug users (63.6%) and former drug users (79.8%), using the same time-frame.

Two studies used MEMS-caps to evaluate adherence in the context of randomized controlled trials (RCT). Altice *et al.* [29] found a significantly higher adherence level among those receiving directly administered HAART compared to those self-administering their HAART (76.2% vs. 49.9%; $p<0.0001$). Haug *et al.* [30] found an overall adherence of 54.0% among men and 58.0% among women, after a 4-week observation period. A recent study conducted by the INSPIRE Study Team[31] used self-reported adherence in the context of a RCT, with an overall adherence of 75.0%.

Purcell and colleagues[32] found one of the highest total (100%) adherence levels: 75.0%. Comprehensive management, as well as the strict eligibility criteria and the willingness to join an intensive intervention study such as this RCT might have contributed for these auspicious findings.

Adherence Assessment: MEMS cap, pharmacy refill and self-report

A few longitudinal studies compared adherence measured by MEMS-caps and self-report. Overall, self-report tended to overestimate adherence compared to MEMS-caps[25,26,27,30]. For instance, Arnsten and collaborators[25] reported a mean self-reported 1-day adherence of 79%, but 57% when measured by MEMS-caps.

Two longitudinal studies conducted in Canada, by Palepu and colleagues[33,34], found very similar results using data from pharmacy refill compliance, although evaluating different drug-using populations. The first study was implemented in a province-wide Drug Treatment Program in British Columbia, while the second was developed in the context of a cohort study of IDU. These studies found that 76.9% vs. 75.2% of the participants were 100% adherent to their scheduled pharmacy refills after 12-months. A third study conducted in Ireland found that 64.7% of 85 IDU attending a reference center in Dublin, Ireland, refilled their antiretroviral medications at least 80% of the time[35]. Lower compliance to pharmacy refills was found in a study conducted with HIV/HCV co-infected DU from Canada: 46.4%[36].

Self-reported adherence tended to be higher than the other adherence measurements used. One of the highest self-reported adherence levels was found in a cross-sectional assessment of an incarcerated population – 83.5%[2]. Knowlton and colleagues[37] found that 75.0% of participants took at least 95% of prescribed pills on the day before assessment. Palepu *et al.* [38] found a similar adherence over the previous 30 days (75.2%). One study found that 60.3% of patients were 100% adherent to ARTs prescribed the previous day[39]. Another study by the same group found an adherence of 70.1% on previous day and 57.8% on previous 7-days[40]. A slightly higher adherence was found by Sharpe and colleagues[41], in a study conducted among black women

(68.0%). Although the overall adherence was higher, the authors found lower proportions of adherence between non-DU, users of other drugs and *crack*-cocaine users, with 78.5%, 63.5%, and 57.2%, respectively.

Liu and collaborators[42] conducted another study exclusively with women, where all participants had a history of child sexual abuse and drug addiction. Interestingly, this study found the highest self-reported adherence. The proportion of participants with adherence ≥ 90% were 88%, 90%, 92%, and 73%, for 1, 2, 3, and 14 days, respectively. The proportion of participants who were 100% adherent to HAART were 88%, 90%, 92%, and 59%, for 1, 2, 3 and 14 days, respectively[42]. According to the authors, self-reported medication adherence tended to overestimate patients' true adherence levels by as much as 10-20%.

Roca *et al.* [43] defined as adherent patients those who kept all medical appointments, took at least 80% of prescribed doses, and had an HIV-RNA level at least 1.5 $\log_{10}$ below pre-treatment level. With a median follow-up of 12 months, 32% of the patients showed optimal adherence in all clinical appointments (27% IDU and 32% non-IDU). The use of a synthetic indicator (combining self-reported adherence, compliance with medical appointments and viral load suppression) may have influenced the findings.

Facilitators of HAART adherence among HIV-positive DU

Studies showed that major facilitators of HAART adherence among HIV-positive DU are access to drug abuse treatment, mainly substitution therapy for opiate dependence, psychological characteristics, and access to mental health treatment among those in need.

Palepu and col.[36] found that methadone maintenance therapy (MMT) was positively associated with optimal adherence (Adjusted Odds Ratio [AOR] 1.52, 95% Confidence Interval

[CI] 1.16-2.00). Findings from the MANIF 2000 Study Group, in France, also underscored the importance of substitution therapy in reducing drug injection behaviors and improving adherence to HAART. Moatti *et al.*[44] showed that IDU receiving buprenorphine maintenance therapy reached higher levels of adherence (78.1%) than IDU who had stopped injecting drugs for more than 6 months, but were out of maintenance therapy (65.5%). Other studies conducted by the same group suggest that once under substitution therapy, patients follow a structured daily routine, a possible reason for higher adherence among this population[44-49].

Liu and collaborators[42] identified that participants with adherence levels over 90% reported significantly higher self-esteem (20.4 vs. 18.2; $p<0.05$) and adherence self-efficacy (24.1 vs. 19.9; $p<0.001$) than those with adherence less than 90%; similar findings were identified using a 100% adherence cut-off.

In the New York Medicaid sample[23], women with depression who were receiving both psychiatric care and antidepressants had higher adherence than those receiving psychiatric care alone (AOR: 1.92; 95% CI: 1.00-3.68). Among those without a diagnosis of depression, drug treatment was found to be associated with better adherence among men ($p<0.001$), but not among women.

According to a study conducted by Arnsten and colleagues[31], good adherence was associated with being a high-school graduate, not believing that antiretrovirals have a counteractive effect on methadone, not sharing or lending drug injection equipment with HIV-negative or unknown status partners, and the following psychosocial characteristics: positive attitudes toward HIV medicines, greater self-efficacy for taking medicines as prescribed, sense of responsibility for protecting others from HIV, and fewer depressive symptoms.

Barriers to HAART adherence among HIV-positive DU

Significant barriers to HAART adherence reported among HIV-positive DUs were related to psychological problems, and active drug use. Kerr and colleagues[50] evaluated the underlying reasons for HAART discontinuation among IDU in Vancouver, Canada, where 44% discontinued HAART during a 1 year follow-up period. The major factor associated with HAART discontinuation was recent incarceration (OR=4.84, p=0.022). A second study carried out in Vancouver[51] also documented incarceration as a major barrier for optimal adherence.

Psychological problems were found to be associated with poor adherence by different studies. According to Kerr *et al.*[52], negative outcome expectations were inversely associated with adherence (OR=0.8; 95%CI: 0.7-0.9). Similar findings were identified by a study conducted in Spain with IDU receiving MMT[53]. Another study conducted in Spain[54] found that non-adherent patients were more likely to present higher rates of anxiety. Gordillo and collaborators[55] also found higher adherence levels among participants who were not depressed and had good social support (OR: 1.86; 95% CI: 0.98-3.53). Findings from the MANIF 2000 Study Group highlight the role of depression and others psychiatric problems as barriers to optimal adherence[44,46-49].

Active drug use has been consistently found to be associated with non-adherence. Crisp and colleagues[56] conducted a study with African-American active *crack* cocaine users. The study identified that 53.3% self-reported full compliance with their physicians' recommendations; while one-third (31.3%) reported they were compliant more than a half of the time. Another study conducted with active IDU found similar rates of self-reported non-adherence in the previous 2 weeks: 44%[57]. The study conducted by Martini and colleagues[58] also found fewer

high-compliant patients among active DU when compared to non-drug users: 31.6% vs. 42.3% ($p<0.05$).

According to the study conducted by Crystal and collaborators[22], conducted with beneficiaries from the New Jersey Medicaid Program, IDU experienced longer delays in initiating HAART than did non-IDU. However, once the treatment was initiated, IDU were as adherent to treatment as non-IDU.

DISCUSSION

We identified 41 studies assessing adherence to HAART among HIV-positive drug users. Although these studies used heterogeneous cut-offs, different measures and various study designs, most found that HIV-positive drug users had moderate levels of adherence to HAART. Most papers suggest that the adherence to HAART among HIV-positive drug users can be similar to those found among other PLWHA, once proper timing to initiate treatment is followed, comorbidities are properly managed and treated, psychosocial support is provided, and drug treatment, particularly substitution therapy is instituted.

The selected studies bring understanding to the complex inter-relationship of drug addiction, HIV-infection and adherence to HAART. The high prevalence of comorbid medical conditions and social disadvantages identified by the studies suggest the need for drug treatment, case-management, medical services, and psychosocial support to optimize adherence. Several studies documented that once HIV-positive drug users have access to the necessary support, they are able to adhere to ARV regimens and hence experience treatment benefits.

Overall, most studies which found higher adherence were carried out among DU receiving HAART in structured settings, particularly those engaged in integrated services

offering both addiction treatment and psychosocial support[32] and/or directly observed therapy (DOT) [29,59]. For instance, one of the highest self-reported adherence levels was found in a cross-sectional assessment of an incarcerated population – 83.5%[2]. According to the authors, possible reasons for the high acceptance of and adherence to HAART among these patients might include the drug-free environment, the availability of HIV specialists, and the lack of concern that "street drugs" will interfere with the therapeutic benefits of ART[2]. Patients receiving methadone maintenance therapy (or alternatively, buprenorphine maintenance therapy) also presented higher levels of adherence than out-of-treatment opiate users. The literature suggests that these patients significantly reduced their drug using habits and attained a more stable living style that promoted better adherence to HAART[35,43]. These findings suggest that the extent to which one's daily life is routinized constitutes a key factor to improve adherence[60].

Illicit stimulant use represents a key challenge for optimal adherence[24,28,41]. The study by Hinkin and collaborators[28] found that stimulant users were seven times more likely to have less than optimal adherence than non-stimulant users and had a more precipitous decline in adherence over a 6-month period than did non-users. Unfortunately, one of the most worrisome aspects of the link between substance abuse and HIV is the absence of effective prevention and treatment interventions for cocaine and other stimulant users – particularly an effective pharmacotherapy for stimulant abuse[61-63].

Several studies highlighted the role of social/structural factors on HAART adherence. According to some studies, the importance of the patient-provider relationship and communication supports the need for low-threshold/user-friendly health care delivery systems, targeted to the specific needs of HIV-positive DU[37,56,64]. According to Knowlton and colleagues[37], besides the role of a positive patient-provider relationship, the access to social

support and ancillary services is also pivotal in effective HAART access and adherence among HIV-positive active DU. Social instability (e.g. unemployment, history of incarceration, homelessness) was associated with poor HAART adherence[34,39,49]. These findings underscore a major role of social support in effective and long-term HAART adherence in this population.

The use of HAART by HIV-positive DU remains a complex medical, social and legal issue. Relative to other at-risk populations, active DU initiate HAART at a more advanced stage of infection compared to other populations[12,13]. Frequently, the prescription of HAART by physicians tends to be influenced not only by decreasing CD4 cell counts and increasing HIV-RNA levels, but also by the anticipated adherence levels, which can compromise enrollment of DU into treatment[65].

This review has several limitations. We aimed to reduce reviewer bias by conducting abstraction independently, in parallel. However, we did not conduct our review on the so-called 'gray literature' (e.g. non-peer reviewed manuscripts), and therefore publication bias could not be avoided. Qualitative studies were not included in our analysis, since our aim was to conduct both a systematic and a meta-analysis. However, qualitative studies might bring additional understanding to the complex interplay of drug addiction, comorbidities, HAART adherence, and different psychosocial and contextual factors, and should be evaluated by future studies. This review was not able to evaluate possible relationships between different regimen characteristics and adherence (e.g. putative higher adherence among patients under best-tolerated regimens and/or regimens with less pill burden), since this information was rarely available among the identified studies. Finally, it is possible that our conclusions might be overestimating patients adherence levels, mainly due to the fact that half of selected studies relied only on self-reported adherence – a measure known to overestimate patients' true adherence levels.

Different interpretations of what constitutes optimal adherence made between-study comparisons difficult. We were unable to identify studies conducted in developing countries, making it difficult to generalize our findings to those settings. Finally, our review relied on the information reported in peer-reviewed scientific publications, the vast majority of them published in English. Therefore, these findings are unlikely to represent the treatment experience of a high proportion of HIV-positive individuals living in other contexts, such as Russia and Eastern Europe, where the HIV epidemic is mainly driven by drug using populations and access to HAART is uneven[14].

Evidence-based studies on barriers and facilitators to adherence among HIV-positive DU have been very scarce in developing countries. This is of great concern given that the largest HIV epidemics among DU have taken place in recent years in developing/transitional countries. In the coming decades, PLWHA from developing countries will constitute a growing proportion of the world's HAART recipients as treatment access expands.

While there is significant reluctance among medical care providers to deliver HAART to DU, the evidence supporting this decision is limited[18,66]. The reviewed studies highlight that in a context of a non-coercive, comprehensive HIV management and care patients traditionally marginalized by the health care system can access, accept and are able to adhere to complex therapeutic regimens. Since HIV-positive DU are frequently involved in high-risk social networks, by providing effective treatment and significantly reducing their HIV load and hence their infectivity, it is possible to reduce sexual and parenteral transmission of HIV to the broader community. Overcoming stigma and discrimination towards HIV-positive DU, and improving the quality and efficacy of available treatment/care are essential for optimal treatment for this population.

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III.b ARTIGO 2

Adherence to Antiretroviral Therapy for HIV/AIDS among Drug Users: A Meta-analysis**

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ABSTRACT

We conducted a meta-analysis of studies assessing adherence to HAART among HIV+ drug users, followed by a qualitative analysis of treatment outcomes associated with adherence among this population. Random-effects meta-analysis was performed to summarize adherence; and between-study heterogeneity was examined using multivariable mixed-effects models. We evaluated 41 studies, including 15,194 patients in our analysis. The overall adherence was 0.60 (95% CI:0.53-0.67). Study design, particularly related to timeframe used to measure adherence, was an independent predictor of inter-study heterogeneity. Better HIV treatment outcomes were found among former DU, those with less severe psychiatric conditions, those receiving opioid substitution therapy and/or psychosocial support. Patients initiating HAART with lower viral load and higher CD4 counts, and those without co-infections (e.g. HCV) also had better treatment outcomes. Once proper management is provided, data suggest that HIV-positive DU can achieve satisfactory levels of HAART adherence, HIV viral suppression and immune reconstitution. Available evidence does not justify refusal/protracted access to HIV-treatment for HIV-positive drug users.

Keywords: HIV, AIDS, adherence, drug use, meta-analysis

INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has improved the health and quality of life of many people living with HIV/AIDS (PLWHA) since its introduction in 1996/7. HAART significantly improves the prognosis of HIV-infected persons, reducing HIV viral load, increasing CD4+ cell levels, delaying progression to AIDS and reducing mortality (Egger et al., 2002). Adherence to antiretroviral therapy is closely tied to HIV viral suppression and CD4 cell count response (Wood et al., 2003, 2004, 2004a) and is a key predictor of antiretroviral success and survival (Hogg et al., 1998; Palella et al., 1998).

Reduced HIV viral load may be important for reducing HIV transmission, and as such, the availability of HAART may be an important addition to the arsenal of HIV prevention strategies (Quinn et al., 2000). However, since the advent of HAART, widening disparities in health outcomes among HIV-seropositive populations indicate the urgent need to elucidate factors facilitating and impeding effective HAART use within vulnerable populations, particularly among disadvantaged or marginalized populations (Mills et al., 2006; Wood et al., 2003a).

Previous studies have found that active drug users had inferior adherence, resulting in poorer virologic and immunologic outcomes to HAART, compared to former and non-drug users (Lucas et al., 2001; Palepu et al., 2003a). Furthermore, compared to patients remaining free of substance abuse, individuals who switched from non-use to active substance abuse were more likely to experience worsening antiretroviral therapy adherence, less frequent HIV-1 RNA suppression, and lower CD4 cell increases (Lucas et al., 2002). Conversely, switching from substance abuse to non-use was strongly associated with improvements in antiretroviral therapy use and adherence, and HIV-1 treatment outcomes, compared to subjects with persistent

substance abuse (Lucas et al., 2002). However, other studies have found that HIV-positive drug users who have access to drug abuse and mental health treatment, and particularly former drug users who are abstinent, can reach the same levels of adherence found among PLWHA who have never used illicit drugs (Crystal et al., 2001). The specific barriers that might jeopardize HIV-positive drug users' adherence to HAART remain to be fully elucidated.

Drug users (DU) living with HIV/AIDS have often experienced suboptimal access to HAART (Bassetti et al., 1999; Celentano et al., 1998; Strathdee et al., 1998), and tend to initiate HAART at more advanced stages of infection (Celentano et al., 2001; Wang et al., 2004). This raises concern, as injection drug use is a major vector for HIV/AIDS transmission in seven of 10 regions around the world (WHO/UNAIDS, 2007). Non-injecting DU are also at high risk for HIV infection due to high-risk sexual behaviors (Inciardi and Surratt et al., 2001; Latkin et al., 2001).

In the past years, the number of PLWHA increased substantially in East and Central Asia, as well as in Eastern Europe, where nearly two thirds of HIV infections (62%) are attributed to injection drug use. In highly populated countries such as China and India, injection drug use is also a major component of local HIV/AIDS epidemics (WHO/UNAIDS, 2007).

Some providers prescribing HAART to DU have been concerned that clinical improvement may lead to behavioral relapse, and that suboptimal adherence may favor the emergence of viral resistance and the transmission of drug-resistant HIV strains (Vlahov and Celentano, 2006; Wainberg and Friedland, 1998; Wensing et al., 2005). Beyond adherence, other factors such as pre-existing mutations and incorrectly prescribed drugs might influence both viral load reduction and/or the reconstitution of the immune system (Escoto-Delgadillo et al., 2005).

Optimizing the benefits of HAART among DU constitutes a major public health concern, and the specific barriers that might jeopardize HIV-positive drug users' adherence to HAART remain to be further elucidated. A former paper by our group reviewed such issues, summarizing the main barriers and facilitators of adherence among this population (Malta et al., 2008).

In this meta-analysis, we synthesize the available scientific literature, presenting a pooled measurement of adherence among HIV-positive DU accounting for between-study heterogeneity. In addition, we also summarize factors associated with optimal HIV viral suppression and/or immunological reconstitution among the subset of studies that examined those treatment outcomes.

METHODS

In planning the systematic review and meta-analysis, we reviewed standard guidelines to conduct and report meta-analysis studies. Statements developed by the Consolidated Standards of Reporting Trials – CONSORT (Altman et al., 2001; Moher et al., 2001), the Quality of Reporting of Meta-analyses – QUOROM (Moher et al., 2000), the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group (Stroup et al., 2000), and the Transparent Reporting of Evaluations with Nonrandomized Designs – TREND (Des Jarlais et al., 2004) were thoroughly reviewed. The MOOSE recommendations were used to conduct and report the meta-analysis as it was found to be the most appropriate for the current study, while the TREND checklist (Version 1.0) was used as a guide for data abstraction.

Search Strategy

Search strategies were developed using systematic automated and manual search strategies (Lyles *et al.*, 2006). First, we conducted a comprehensive automated search of five electronic bibliographic databases — including MEDLINE via PubMed, Cochrane CENTRAL, AIDSLINE, AMED, CINAHL, TOXNET, SciELO, and ISI-Web of Science were searched from 1996 to February 29, 2008; except for AIDSLINE, which was searched from 1996 up to 2000, when the inclusion of new citations was discontinued. This search combined standardized search terms (keywords and medical subject heading terms) that reflect key domains: (a) HIV/AIDS, (b) compliance (i.e., adherence, compliance, directly observed therapy), (c) addiction (i.e., substance abuse, substance dependence), and (d) target population (i.e., PLWHA). Citations that intersect all four domains were downloaded into the study database.

To reduce publication bias and gaps in the automated search, we implemented four supplementary search strategies to identify additional studies. First, we searched the published conference abstracts from national and international HIV/AIDS and STD conferences using the same domains as the automated search. Second we searched the National Institutes of Health's Computer Retrieval of Information on Scientific Projects (CRISP) database (http://crisp.cit.nih.gov) to identify principal investigators working in the field of HIV/AIDS and/or drug addiction. Third we contacted authors of all selected papers and principal investigators to obtain unpublished manuscripts and upcoming publications. And finally, we reviewed the reference lists of all selected studies for additional citations. All studies identified through these procedures that meet our eligible criteria were entered into the study database.

To be included in the review, studies had to evaluate adherence to HAART as the primary outcome, report a given cut-off to define optimal adherence (e.g. 90% or 95%) or evaluate

adherence as a continuous outcome, include multivariable analyses to assess correlates of adherence and present data stratifying participants according to history of drug use (drug users vs. never drug users), or evaluate only current/former drug users on their studies. Further details are available elsewhere (Malta et al., 2008).

Study Selection and Data Extraction

Using a predefined protocol, 2 investigators (MM, FIB) extracted data from peer-reviewed papers addressing adherence among HIV-positive DU and independently assessed their eligibility. Using standardized coding forms, each selected paper was coded for study characteristics (study date, location, study design [RCT, cross-sectional, or non-RCT longitudinal studies], timeframe used to measure adherence [previous day to previous two weeks, two weeks to six months, more than six months], recruitment setting, and method for adherence measurement [MEMs cap - Medication Events Monitoring System, self report or pharmacy records]), participant characteristics (age, gender, race/ethnicity, percent who use/used alcohol and/or illicit drugs), treatment outcomes (clinical and/or immunological outcomes [HIV-1 viral load and CD4 count] and factors associated with better HIV-treatment response).

When more than one adherence measurement was used (e.g. MEMs cap [Medication Events Monitoring System] and patient's self-report), data from all methods were collected. For those studies, we calculated an average adherence estimate, using information collected with all different methods. For studies measuring adherence as a continuous variable, adherence was defined as the mean percentage of the doses taken at the study period (i.e., average adherence measured as a continuous outcome of 80%, within a sample size of 100, would be entered into

the database as 80 adherent participants/100 participants). For studies measuring adherence as a discrete variable, the estimate included in our analysis refer to the percentage of patients rated as adherent, according to the cut-off and adherence measurement method adopted by each study. After all potentially relevant studies were identified and data abstracted, the two investigators met to achieve consensus regarding eligibility.

Statistical Analysis

Standard meta-analytic methods were used (Cooper and Hedges; 1994; Lipsey and Wilson, 2001). A random-effects model for aggregating individual effect sizes was used, because it provides a more conservative estimate than a fixed-effects model of variance and generates more accurate inferences since this approach recognizes studies as a sample of all potential studies and incorporates between-study variability on the overall pooled estimation (Hedges and Vevea, 1998; van Houwelingen et al., 2002). Thresholds for adherence were considered as greater than or equal to the cutoff levels used on each study, and the raw proportion of adherence reported by each study was used to pool the overall proportion, using the DerSimonian-Laird random-effects method (Fleiss, 1993; DerSimonian, 1986).

The I^2 index was calculated as a measure of the overall variation in adherence that was attributable to between-study heterogeneity (Higgins and Thompson, 2002; Higgins et al., 2003). According to recent reviews, the I^2 index assesses not only heterogeneity in meta-analysis but also the extent of that heterogeneity, it should be a more advisable procedure than the Q test in assessing whether there is true heterogeneity among the studies in a meta-analysis. Experts have demonstrated that the I^2 index exhibit higher power with a larger number of studies (>20), with

an average sample size higher than 80 individuals (Huedo-Medina et al., 2006). We anticipated large heterogeneity considering the varied populations, the different thresholds used in the definition of optimal adherence, and distinct timeframes used in the assessment of adherence. According to standard meta-analysis guidelines, when observational studies are pooled, heterogeneity of populations (e.g. US vs. international studies), design (e.g. case-control vs. cohort studies), and outcome (e.g. different studies yielding different relative risks that cannot be accounted for by sampling variation) is expected (Berlin, 1995; Stroup et al., 2000)

Researchers have used a variety of timeframes to measure adherence, including 1, 3, 7 days, 2 weeks, 1 month or more than 1 month. Shorter time frames have the potential benefit of more accurate recall for those studies based on self-report. The widely used Aids Clinical Trials Group (ACTG) adherence instrument employs a 4-day recall period (Chesney et al. 2000). However, recent studies have suggested that 1-month recall periods may be more accurate than 3- or 7-day periods (Lu et al., 2008). Trying to further contribute to this discussion, we aggregated studies according to their timeframes into three subgroups: from 1-14 days, 2 weeks-6 months, and 1-2.5 years (no selected study used a time frame between 6 months and one year).

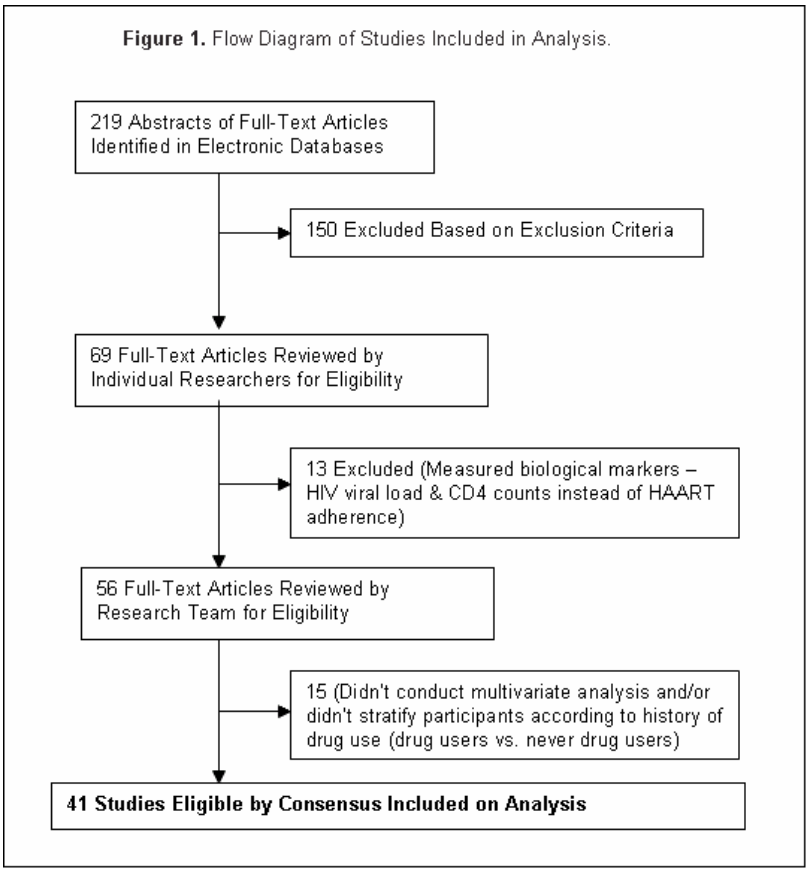
One forest plot was drawn for all 41 studies and additional figures were created according to those timeframes. Forest plots illustrate the individual study proportion, its 95% confidence intervals (CI) and the overall DerSimonian-Laird pooled estimate.

A mixed-effects meta-regression model was used to asses the underlying reasons for between-study heterogeneity, whereby each study overall proportion was transformed to their logit value. The logit transformation (logistic function) allows for calculation because the values are normally distributed in contrast with probability scores, which range from 0 to 1 (Viechtbauer, 2007).

Results from univariate analysis with a *p*-value ≤ 0.20 were included in the multivariable analysis. The following covariates were included in the meta-regression multivariable model: timeframe (last day to last two weeks, last two weeks to last six months, last one year to last 2.5 years), most frequently abused drug in the study sample (heroin, crack/cocaine, heroin and crack/cocaine vs. abstinence), method of assessment for adherence (self-report, pharmacy records, MEMS-caps), and adherence cut-off (>80%). Analyses were conducted using Stata version 10.0 (StataCorp, 2005) and R version 2.6.2 (R Core Development Team, 2004). Graphics were generated using StatsDirect version 2.5.2 (StatsDirect, 2007).

RESULTS

Study Characteristics



Forty-one studies meeting inclusion/exclusion criteria were identified **(Figure 1)**. Approximately half of selected studies assessed adherence using patient self-reports, while the remainder used a broad range of measurements (e.g. pharmacy records, MEMS-caps, secondary data). Studies used heterogeneous cut-offs to define optimal adherence (range: 75-100%). The 41 studies enrolled a mean of 370 patients (range: 40-5073; SD: 815). The 23 studies which used self-reported adherence enrolled a mean of 224 patients (range: 42-636; SD: 181.8), while 11 studies which evaluated adherence through pharmacy records and/or pill counts enrolled a mean of 862 patients (range: 85-5073; SD: 1486.5). The 7 studies which evaluated adherence using MEMS-caps or a combination of self-report and clinical data enrolled a mean of 81 patients (range: 40-150; SD: 34.2). We were unable to identify studies conducted in developing countries.

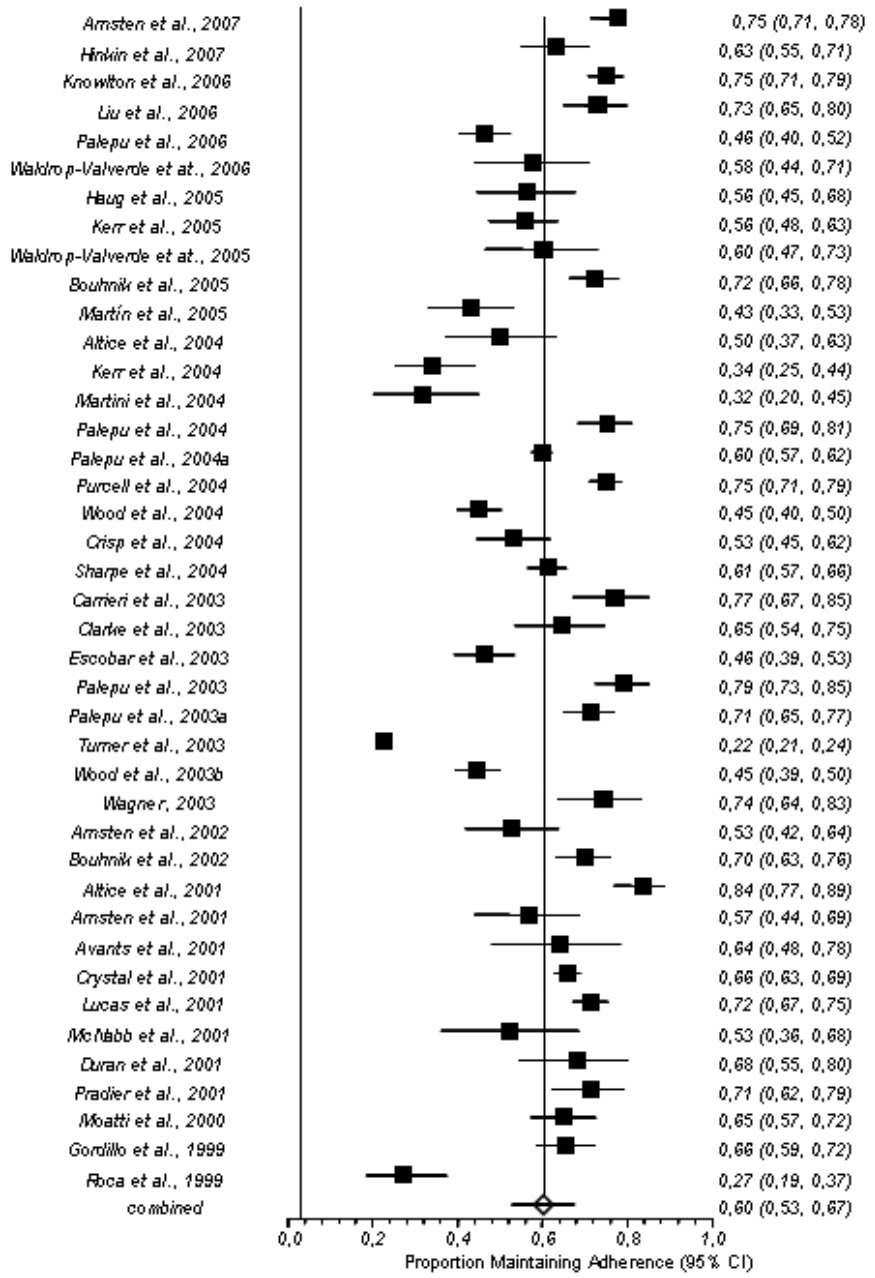
Eleven studies defined optimal antiretroviral adherence as 100% uptake of the prescribed doses (Crisp et al., 2004; Haug et al., 2005; Martin et al., 2005; Palepu et al., 2003, 2003a, 2004; Pradier et al., 2001; Purcell et al., 2004; Sharpe et al., 2004; Waldrop-Valverde and Valverde, 2005; Waldrop-Valverde et al., 2006). Eight studies assessed optimal adherence as greater than 95% (Escobar et al., 2003; Kerr et al., 2004; Knowlton et al., 2006; Palepu et al., 2004, 2006; Turner et al., 2003; Wood et al., 2003, 2004). Three studies used adherence greater than 90% (Arnsten et al., 2007; Gordillo et al., 1999; Hinkin et al., 2007); eight as greater than 80% (Altice et al., 2001; Avants et al., 2001; Bouhnik et al., 2002, 2005; Carrieri et al., 2003; Clarke et al., 2003; Duran et al., 2001; Moatti et al., 2000); and one study as greater than 75% of prescribed medicines (Altice et al., 2004). One study used two different cut-offs – 90 and 100% (Liu et al., 2006). Three studies using MEMS-caps evaluated adherence as a continuous variable (Arnsten et al., 2001, 2002; Wagner, 2003); and 6 studies used a combination of adherence measurements,

e.g. self-report and MEMS-caps (Crystal et al., 2001; Kerr et al., 2005; Lucas et al., 2001; Martini et al., 2004; McNabb et al., 2001; Roca et al., 1999).

Meta-Analysis

The combined pooled adherence across 41 studies (N=15,194) was 0.60 (95% CI: 0.53–0.67, **Figure 2**). Due to the large between-study heterogeneity (I^2:98.7%), we conducted subgroup analyses, re-calculating the pooled adherence according to their timeframes: studies with a timeframe ≤ 2 weeks (19 studies, N=3,944); between 2 weeks and six months (11 studies, N=3,156); and studies with timeframes greater than one year (11 studies, N=8,094). The pooled estimate for the shortest period was higher (0.70; 95% CI: 0.67–0.73, I^2: 70.1% **Figure 3a**), than the pooled estimated for the intermediate period (0.54, 95% CI: 0.49–0.59, I^2:79.0%, **Figure 3b**). The group using a timeframe larger than one year had the lowest pooled adherence estimates (0.52; 95% CI: 0.36–0.67, I^2: 99.2%, **Figure 3c**).

Figure 2. Pooled Proportion of all HIV+ DU Adhering to Antiretroviral Therapy*



*The combined data marker indicates the DerSimmonian-Laird combined proportion

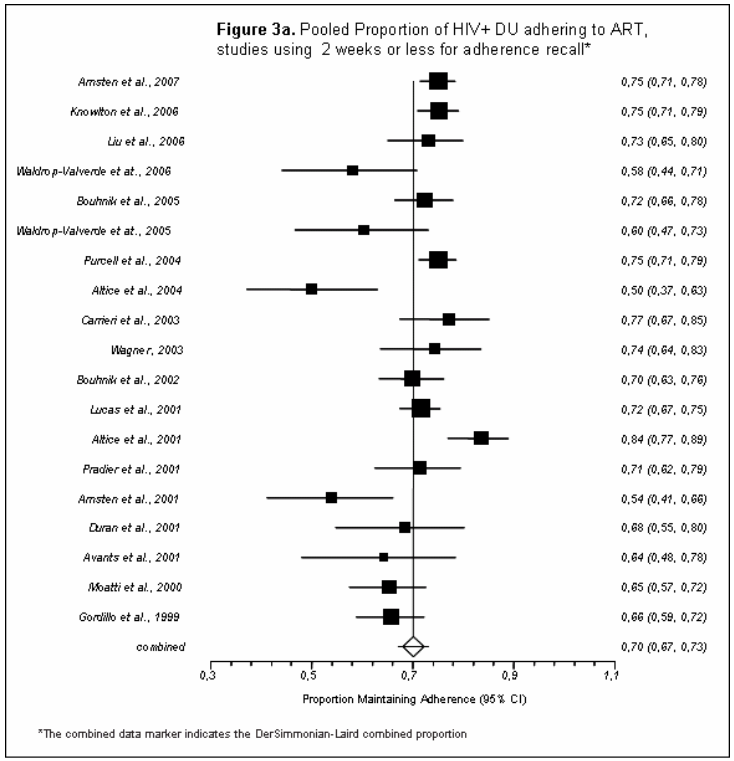


Figure 3a. Pooled Proportion of HIV+ DU adhering to ART, studies using 2 weeks or less for adherence recall*
Amsten et al., 2007 0,75 (0,71, 0,78)
Knowlton et al., 2006 0,75 (0,71, 0,79)
Liu et al., 2006 0,73 (0,65, 0,80)
Waldrop-Valverde et al., 2006 0,58 (0,44, 0,71)
Bouhnik et al., 2005 0,72 (0,66, 0,78)
Waldrop-Valverde et al., 2005 0,60 (0,47, 0,73)
Purcell et al., 2004 0,75 (0,71, 0,79)
Altice et al., 2004 0,50 (0,37, 0,63)
Carrieri et al., 2003 0,77 (0,67, 0,85)
Wagner, 2003 0,74 (0,64, 0,83)
Bouhnik et al., 2002 0,70 (0,63, 0,76)
Lucas et al., 2001 0,72 (0,67, 0,75)
Altice et al., 2001 0,84 (0,77, 0,89)
Pradier et al., 2001 0,71 (0,62, 0,79)
Amsten et al., 2001 0,54 (0,41, 0,66)
Duran et al., 2001 0,68 (0,55, 0,80)
Avants et al., 2001 0,64 (0,48, 0,78)
Moatti et al., 2000 0,65 (0,57, 0,72)
Gordillo et al., 1999 0,66 (0,59, 0,72)
combined 0,70 (0,67, 0,73)
0,3 0,5 0,7 0,9 1,1
Proportion Maintaining Adherence (95% CI)
*The combined data marker indicates the DerSimmonian-Laird combined proportion

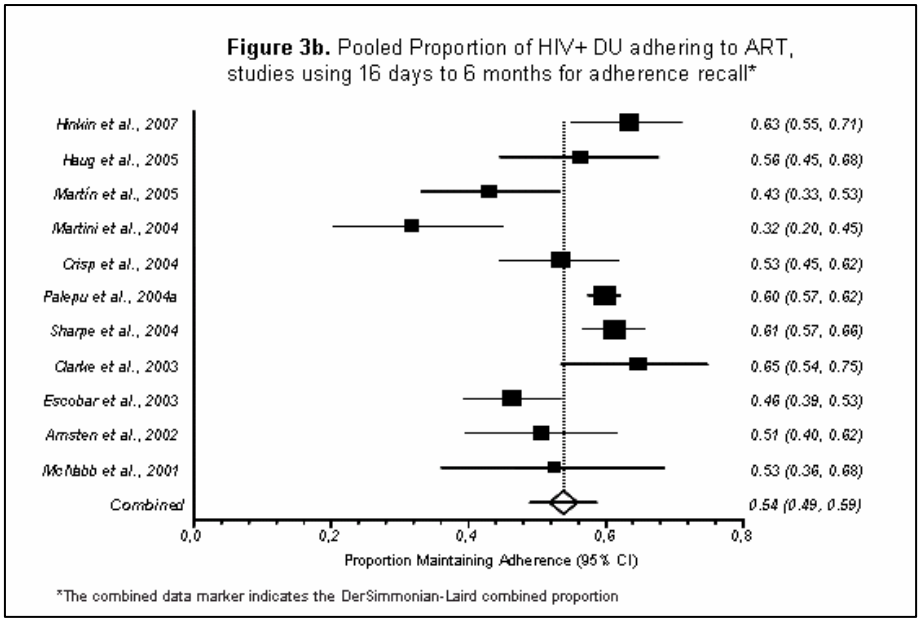


Figure 3b. Pooled Proportion of HIV+ DU adhering to ART, studies using 16 days to 6 months for adherence recall*
Hinkin et al., 2007 0.63 (0.55, 0.71)
Haug et al., 2005 0.56 (0.45, 0.68)
Martín et al., 2005 0.43 (0.33, 0.53)
Martini et al., 2004 0.32 (0.20, 0.45)
Crisp et al., 2004 0.53 (0.45, 0.62)
Palepu et al., 2004a 0.60 (0.57, 0.62)
Sharpe et al., 2004 0.61 (0.57, 0.66)
Clarke et al., 2003 0.65 (0.54, 0.75)
Escobar et al., 2003 0.46 (0.39, 0.53)
Amsten et al., 2002 0.51 (0.40, 0.62)
McNabb et al., 2001 0.53 (0.36, 0.68)
Combined 0.54 (0.49, 0.59)
0,0 0,2 0,4 0,6 0,8
Proportion Maintaining Adherence (95% CI)
*The combined data marker indicates the DerSimmonian-Laird combined proportion

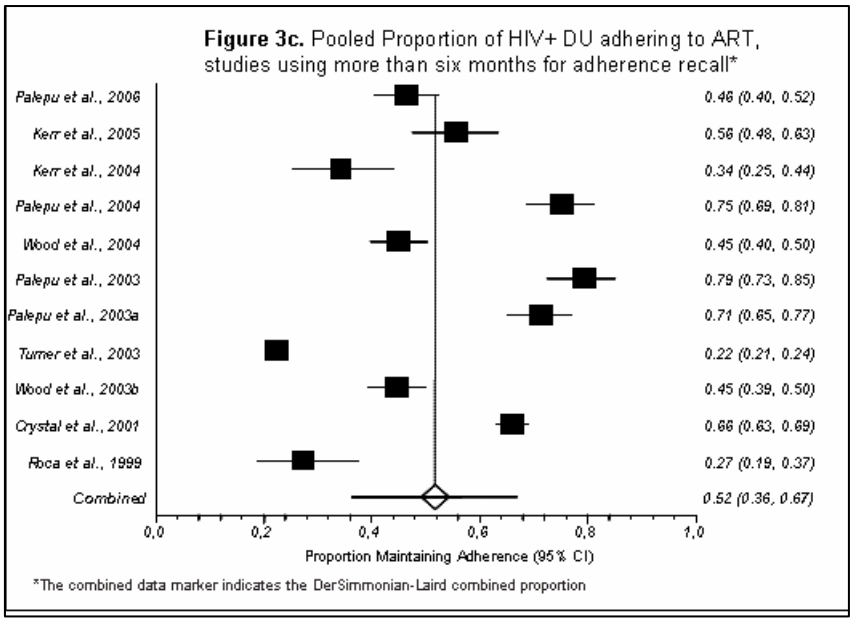


Figure 3c. Pooled Proportion of HIV+ DU adhering to ART, studies using more than six months for adherence recall*
Palepu et al., 2006 0.46 (0.40, 0.52)
Kerr et al., 2005 0.56 (0.48, 0.63)
Kerr et al., 2004 0.34 (0.25, 0.44)
Palepu et al., 2004 0.75 (0.69, 0.81)
Wood et al., 2004 0.45 (0.40, 0.50)
Palepu et al., 2003 0.79 (0.73, 0.85)
Palepu et al., 2003a 0.71 (0.65, 0.77)
Turner et al., 2003 0.22 (0.21, 0.24)
Wood et al., 2003b 0.45 (0.39, 0.50)
Crystal et al., 2001 0.66 (0.63, 0.69)
Roca et al., 1999 0.27 (0.19, 0.37)
Combined 0.52 (0.36, 0.67)
0,0 0,2 0,4 0,6 0,8 1,0
Proportion Maintaining Adherence (95% CI)
*The combined data marker indicates the DerSimmonian-Laird combined proportion

A meta-regression model (**Table 1**) was fitted to evaluate major predictors of the between-studies heterogeneity, including the following four covariates: timeframes (≤ 2 weeks, 2 weeks to 6 months, 1 year or more); substance used by the study population (heroin, crack/cocaine, heroin and crack/cocaine vs. abstinence); type of measurement (MEMS-caps, self-report, pharmacy records), and adherence cut-off equal or higher than 80%. Free or paid HAART was not included in the multivariable analysis since this covariate didn't reach the established significance level in the univariate analysis (p-value ≤ 0.20). After adjustment, only the recall period remained associated with the between-study heterogeneity (p-value ≤ 0.05).

When compared to studies using the shorter timeframe (≤ 2 weeks) studies using a larger recall period had an adherence around 50% lower. For studies using a timeframe between 2 weeks-6 months, the adjusted odds ratio (AOR) was 0.51 (95% CI: 0.31-0.83), while for studies using a timeframe higher than one year, AOR was 0.46 (95% CI: 0.26-0.84).

Table 1. Covariates associated with "between-studies" heterogeneity according to multivariable logistic regression.

Variable		OR (95%CI)	AOR (95%CI)
Recall			
	Last day – 15 days	1.00	1.00
	16 days – 6 months	0.50 (0.33 to 0.76)	0.50 (0.31 to 0.83)**
	Over 6 months	0.47 (0.31 to 0.71)	0.46 (0.25 to 0.84)**
Drug used			
	Heroin and cocaine	1.00	1.00
	Heroin	1.35 (0.77 to 2.38)	0.90 (0.51 to 1.59)
	Crack/cocaine	1.21 (0.56 to 2.60)	1.14 (0.54 to 2.39)
	Abstinence	3.61 (0.98 to 13.19)	2.14 (0.65 to 7.02)
Measurement			
	Self report	1.00	1.00
	Pharmacy records	0.64 (0.40 to 1.00)	1.07 (0.61 to 1.91)
	MEMS-cap	0.74 (0.43 to 1.29)	1.05 (0.59 to 1.87)
Adherence cut-off (>80%)		1.61 (0.98 to 2.67)	1.49 (0.88 to 2.51)
Adherence cut-off (>90%)		0.93 (0.61 to 1.41)	--------
Adherence cut-off (>95%)		0.79 (0.53 to 1.18)	--------
Adherence cut-off (=100%)		1.14 (0.73 to 1.77)	--------
Paying for treatment		1.13 (0.76 to 1.70)	--------

Abbreviations: CI – Confidence Interval; OR – Odds Ratio; AOR – Adjusted Odds Ratio; MEMS – Medication Events Monitoring System.
** p-value ≤0.05

Treatment Outcomes

Twenty of the 41 studies evaluated HAART clinical outcomes (Arnsten et al., 2001, 2002; Avants et al., 2001; Bouhnik et al., 2005; Carrieri et al., 2003; Duran et al., 2001; Knowlton et al., 2006; Lucas et al., 2001; McNabb et al., 2001; Moatti et al., 2000; Palepu et al., 2003, 2003a, 2004, 2004a, 2006; Pradier et al., 2001; Roca et al., 1999; Waldrop-Valverde et at., 2006; Wood et al., 2003a, 2004) (**Table 2**).

Arnsten and colleagues (2001) compared electronically monitoring with self-reported adherence, and conducted a further evaluation of the impact of adherence on HIV-viral load. According to the authors, both self-reported and MEMS-Caps adherence were correlated with HIV viral load (r=0.43-0.60), but MEMS-Caps was found to have a better sensitivity, compared to self-report.

Active drug use was identified by some authors as a barrier for better clinical outcomes (Arnsten et al., 2002; Lucas et al., 2001; Palepu et al., 2003; Wood et al., 2004). Arnsten et al. (2002) identified active drug use (especially cocaine use) as a stronger predictor for poor adherence and, in turn, failure to achieve/maintain better clinical outcomes over time. Another study from Baltimore, US, reported that active drug use was strongly associated with underutilization of HAART, non-adherence, and poorer responses to therapy, whereas former drug users and non-drug users had comparable outcomes (Lucas et al., 2001).

Substitution therapy for opiate dependence was independently associated with HIV-1 RNA suppression according to several studies (Avants et al., 2001; Duran et al., 2001; Lucas et al., 2001; Moatti et al., 2000; Palepu et al., 2006). According to Palepu et al. (2006), methadone maintenance therapy (MMT) was associated with both HIV-1 RNA suppression (AOR:1.34; 95% CI:1.00-1.79) and CD4 cell count increase (AOR: 1.58; 95% CI:1.26-1.99).

Table 2. Treatment outcomes for 20 studies with available data, 1999-2006.

Source	Major Treatment Outcomes
Palepu et al., 2006	Factors associated with HIV-1 RNA suppression: MMT[1] (AOR[2] 1.34; 95% CI 1.00–1.79), ≥95%HAART[3] adherence (AOR2.86; 95% CI 2.19–3.75) Older age, per 10 years (AOR1.47; 95% CI 1.13–1.91) Time on HAART (AOR 1.08; 95% CI 1.02–1.14) Factors associated with CD4 cell count rise: MMT (AOR 1.58; 95% CI 1.26–1.99), ≥95% HAART adherence (AOR 1.42; 95% CI 1.13–1.78) Baseline CD4 cell count (AOR 1.27; 95% CI 1.18–1.36)
Waldrop-Valverde et at., 2006	IDU[4] ≥95% adherents to HAART vs. IDU <95% adherents to HAART (previous day adherence): **Lower** mean HIV RNA log-transformed copies (ml): 8.7 (±2.5) vs. 10.0 (±2.16); p=0.047 **No differences** in mean CD4 log-transformed cell counts (mm^3): 5.3 (± 1.2) vs. 5.2 (± 1.2); p=0.839
Knowlton et al., 2006	239/350 (68.3%) adherents patients had detectable HIV-1 viral load (p<0.05) Factors associated with HIV-1 RNA suppression:: CD4 count >200: AOR:2.75, 95% CI: 1.63-4.63 (p<0.001) High social support: AOR: 4.86, 95% CI: 1.08-21.93 (p<0.05) Better patient x provider communication: AOR: 1.57, 95% CI: 1.01-2.45 (p<0.05) Stable housing: AOR: 3.67, 95% CI: 1.04-13.04 (p<0.05)
Bouhnik et al., 2005	HIV clinical progression faster for non-adherents at baseline: adherents vs. non-adherents (log-rank test, p=0.02) HIV clinical progression faster for non-adherents during follow-up: adherents vs. non-adherents (Cox model, $p<10^{-3}$) HIV clinical progression faster for depressive patients at baseline: adherents vs. non-adherents (log-rank test, $p<10^{-3}$) HIV clinical progression faster for depressive patients during follow-up: adherents vs. non-adherents (Cox model, $p<10^{-3}$)

[1] MMT – Methadone Maintenance Therapy
[2] AOR – Adjusted Odds Ratio
[3] HAART – Highly Active Antiretroviral Therapy
[4] IDU – Injection Drug Users

Table 2. Treatment outcomes for 20 studies with available data, 1999-2006 (cont.)

Source	Major Treatment Outcomes
Palepu t al., 2004	Factors **negatively** associated with HIV-1 RNA suppression: History of incarceration within 12 months of initiating HAART: AHR[5]: 0.68; 95% CI: 0.51–0.89; History of drug injection: AHR: 0.79; 95% CI: 0.69–0.91; Two nucleosides + PI **vs** two nucleosides + NNRTI (AHR: 0.77; 95% CI: 0.69–0.87; Higher baseline HIV-1 RNA: AHR: 0.66; 95% CI: 0.62–0.70 Factors **positively** associated with HIV-1 RNA suppression: Higher adherence to HAART: AHR: 1.38; 95% CI: 1.34–1.42 Among participants incarcerated in the first year of starting HAART, the time spent in jail was positively associated with HIV-1 RNA suppression: HR: 1.06; 95% CI: 1.02–1.10
Palepu et al., 2004a	Achieved HIV-1 RNA suppression: 1,318 (76.9%) Factors associated HIV-1 RNA suppression: No history of incarceration: 96% vs. 89% (p<0.001) Older age: 37 vs. 36 years (p<0.001) Higher median adherence: 100% vs. 58% (p<0.001) Higher physician HIV-related experience: 59 vs. 38 (p=0.002) Male gender (p<0.001) Never IDU (p<0.001)
Wood et al., 2004	CD4 cell count response (probability of first CD4 cell count gain of : ≥ cells/mm3 from baseline) Patients with history of injection drug use had lower CD4 response rates (log-rank: p<0.05) Among patients with adherence ≥ 95%, no statistical difference was found between IDU and Never-IDU (log-rank: p=0.349)
Wood et al., 2003	Cumulative suppression of HIV viral load **among all participants**, after 12 months of HAART: Non-IDU vs. IDU: 70.8% vs. 51.4% (log-rank: p<0.001) Cumulative suppression of HIV viral load **among participants ≥ 95% adherents**, after 12 months of HAART: **Similar** between non-IDU vs. IDU: log-rank, p=0.12 HIV viral load suppression in multivariate model (adjusted for adherence, sex, age, PI use, baseline CD4 & HIV viral load and date of therapy initiation): **Similar** between non-IDU vs. IDU: Adjusted RH: 0.9, 95% CI 0.7-1.0 Cumulative HIV RNA rebound rate, **among all participants who achieved viral suppression**: Non-IDU vs. IDU: 23.8% vs. 34.7 (log-rank, p<0.001) Cumulative HIV RNA rebound rate, among **participants ≥ 95% adherents** who achieved viral suppression: **Similar** between non-IDU and IDU: log-rank, p=0.12 Rates of HIV rebound in multivariate model (adjusted for adherence, sex, age, PI use, baseline CD4 & HIV viral load and date of therapy initiation): **Similar** between non-IDU vs. IDU: Adjusted RH: 1.3, 95% CI 1.0-1.6

[5] AHR - Adjusted Hazards Ratio

Table 2. Treatment outcomes for 20 studies with available data, 1999-2006 (cont.)

Source	Major Treatment Outcomes
Palepu et al., 2003	Factors associated with HIV-1 RNA suppression, former and non-IDU: Adherence to HAART, per 10%: AOR: 1.33, 95% CI: 1.14– 1.55; Lower baseline HIV-1 RNA: AOR: 2.16, 95% CI: 1.18–4.18; Two nucleosides plus NNRTI versus two nucleosides plus PI: AOR: 4.67, 95% CI: 1.55–14.1; Months on therapy: AOR: 1.11, 95% CI: 1.07– 1.15 Factors associated with HIV-1 RNA suppression, active drug users: Lower baseline HIV-1 RNA: AOR: 4.85, 95% CI: 1.34–17.5; Two nucleosides plus NNRTI versus two nucleosides plus PI: AOR: 7.19, 95% CI: 1.46–35.7; Months on therapy: AOR: 1.13, 95% CI: 1.06–1.20
Palepu et al., 2003a	Factors **negatively** associated with HIV-1 RNA suppression: Alcohol use (AOR: 0.32; 95% CI 0.13–0.81) and incarceration (AOR 0.22; 95% CI 0.09–0.58) in the 6 months prior to initiating antiretroviral therapy. Factors **positively** associated with HIV-1 RNA suppression: Adherence (AOR 1.27; 95% CI 1.06–1.51); lower baseline HIV-1 RNA (AOR 1.30; 95% CI 1.01–1.66); highly active antiretroviral therapy (AOR 4.10; 95% CI 1.56–10.6); months on therapy (AOR 1.1; 95% CI 1.06–1.14).
Carrieri et al., 2003	Undetectable HIV viral load, IDU adherents vs. IDU non-adherents (< 500 copies/ml): 56.8% vs. 36.3% (p=0.09)
Arnsten et al., 2002	Viral load suppression (< 500 copies/ml), six-months of study: Active cocaine users (yes vs. no): 13% vs. 46% (p=0.005) Alcohol or drug use to cope with problems (yes vs. no): 19% vs. 44% (p=0.03) Best predictive model for achieving viral load suppression included: No active cocaine use: OR: 6.3 (p=0.005) Male gender: OR: 3.4 (p=0.04) Less antiretroviral experience: OR: 0.7 for each additional medication (p=0.03)
Duran et al., 2001	Median viral load, last visit: Non-adherent 3.80 $\log_{10}$ copies/ml, IQR: 2.60–5.04 Adherents patients: 2.30 $\log_{10}$ copies/ml, IQR: 2.30–3.64 Strictly adherent: 2.30 $\log_{10}$ copies/ml, IQR: 2.30–3.45, Mann–Whitney test (p = 0.001) Proportion of patients with undetectable viral load, last visit: Non-adherent (22.2%), vs. adherent (69.2%) vs. 'strictly adherent' (73.1%); χ^2 test (p = 0.002) Median CD4 cell counts, last visit: Non-adherent: 403 cells/mm^3, IQR: 218–534 Adherents: 446 cells/mm^3, IQR: 355–517 Strictly adherents: 518 cells/mm^3, IQR: 389–655 Mann–Whitney test (p = 0.06)

Table 2. Treatment outcomes for 20 studies with available data, 1999-2006 (cont.)

Source	Major Treatment Outcomes
Lucas et al., 2001	Active drug use status was correlated with lower virologic and immunologic response to HAART. Median HIV-1 RNA reduction: Active drug users 0.8 $\log_{10}$ copies/ml **vs.** 1.7 in nonusers and 1.6 in former users ($p < 0.001$, both comparisons) Median $CD4^+$ lymphocyte count increase: Active drug users 65 cells/mm^3 **vs.** 116 in nonusers and 122 in former users ($p = 0.003$ both comparisons) Prevalence of patients achieving undetectable HIV viral load (<400 copies/ml): 32% of active drug users **vs.** 46% of nonusers **vs.** 44% of former users ($p = 0.02$ both comparisons).
Arnsten et al., 2001	Both self-reported and MEMS caps adherence were highly correlated with HIV viral load ($p<0.001$) 79% of subjects with MEMS caps adherence ≥ 90% achieved viral load suppression (<500 copies/ml) 62% of subjects with 1 week self reported adherence ≥ 90% achieved viral load suppression (<500 copies/ml) Viral load suppression if MEMS caps adherence > 90%: AOR: 12.3, 95% CI: 2.8-52.6 (p=0.0008) Viral load suppression if self-reported adherence > 90%: AOR: 8.2, 95% CI: 2.5-27.0 (p=0.0006) Multivariate models including adherence, antiretroviral experience, CD4 counts as predictors of viral load suppression < 500 copies/ml: For 1 day self reported adherence, 10 % adherence increase was associated with AOR=1.98; 95% CI: 1.19-3.32 (p=0.009) of achieving viral load < 500 copies/ml For 1 day MEMS caps adherence, 10 % adherence increase was associated with AOR=1.46; 95% CI: 1.18-1.82 (p=0.006) of achieving viral load < 500 copies/ml
McNabb et al., 2001	After 3 months of follow-up, MEMs cap adherence was associated with virologic success (p=0.0231); Subjects with stable, undetectable or decreasing virus load had better rates of adherence (70%-80%) than those subjects with stable virus load >400 copies/ml or an increasing virus load (27% - 51%)
Pradier et al., 2001	PI Adherence and Plasma HIV-1 RNA viral load G1 – participants w/detectable viral load and decreased ≤ 0.5 log of plasma HIV viral load: 17 (56.7%) were 100% adherents G2 – participants w/detectable viral load and decreased > 0.5 log of plasma HIV viral load: 22 (64.7%) were 100% adherents G3 – participants w/ undetectable viral load and decreased <2.3 log of plasma HIV viral load: 46 (83.6%) were 100% adherents (p=0.02, G1 vs. G2 vs. G3) Mean increase in CD4+ count/mm3 G1 – participants w/detectable viral load and decreased ≤ 0.5 log of plasma HIV viral load: **3.2 ±106** G2 – participants w/detectable viral load and decreased > 0.5 log of plasma HIV viral load: **143 ± 147** G3 – participants w/ undetectable viral load and decreased <2.3 log of plasma HIV viral load: **123±160** (p=0.0002, G1 vs. G2 vs. G3)
Avants et al., 2001	Ratio of missed prescriptions decreased during methadone stabilization: Week 1: 0.24 (±0.32) Week 3: 0.11 (± 0.22) Week 2: 0.13 (±0.24) Week 4: 0.13 (±0.25)

Table 2. Treatment outcomes for 20 studies with available data, 1999-2006 (cont.)

Source	Major Treatment Outcomes
Moatti et al., 2000	Median viral load, non-adherent vs. adherents patients: 3.9 $\log_{10}$ copies/ml **vs.** 2.7 $\log_{10}$ copies/ml (p= 0.008). Median decrease in viral load before and after HAART initiation, non-adherent vs. adherents patients: -0.53 $\log_{10}$ copies/ml **vs.** -1.04 $\log_{10}$ copies/ml (p=0.025). Percentage of patients with undetectable viral load or with a viral load decrease higher than 1 $\log_{10,}$ non-adherent vs. adherents patients: 40.3% **vs.** 57.0% (p=0.04). Median increase of CD4 cell counts among non-adherent vs. adherents patients: 46 x 10^6/l **vs.** 80 x 10^6/l (p= 0.82).
Roca et al., 1999	Virological efficacy was reached in > 40% of patients of both groups in all visits (IDU and non-IDUS) After 6 months of treatment: 35 (43%) participants presented a CD4 cell count increase >100 x 10^6/l 47 (58%) participants achieved undetectable HIV RNA (≤200 copies/ml) CD4 cell count and HIV RNA responses were similar in both groups. No differences were observed in immunological, virological or clinical efficacy between IDU and non-IDU.

Psychiatric conditions, particularly depression, were found to be associated with poorer response to HAART. Bouhnik et al. (2005) found that besides non-adherence, having a high score of depressive symptoms following HAART initiation was highly associated with HIV clinical progression (HR: 5.3; 95% CI: 2.2-13.0; $p<10^{-3}$).

In some studies, low socioeconomic status indicators were also associated with poorer clinical and virologic response among HIV-positive DU receiving HAART. Those studies identified access to social support and stable housing as key aspects to achieve/maintain both HAART adherence and viral suppression (Avants et al., 2001; Carrieri et al., 2003; Knowlton et al., 2006; Lucas et al., 2001; Palepu et al., 2006, 2003, 2004, 2004a; Wood et al., 2003).

Characteristics directly related to the class of antiretroviral drugs (two nucleosides + protease inhibitor vs. non-nucleoside reverse transcriptase inhibitors), time on HAART (more experienced vs. less experienced patients), and levels of viral load/CD4 cells counts in the moment of HAART initiation were also identified as cofactors independently associated with viral suppression and immune reconstitution (Knowlton et al., 2006; Palepu et al., 2006, 2004a, 2003).

DISCUSSION

Findings from this meta-analysis suggest that adherence to HAART among HIV-positive drug users' falls within the range observed among PLWHA in general: our combined proportion indicates an overall adherence of 60%. However, the strong heterogeneity among different studies jeopardizes the effort to standardize the assessment of adherence and to derive from the results evidence-based guidelines about how adherence should be measured in this population and how to improve it using clearly defined strategies and methods.

A recent meta-analysis evaluating 31 studies measuring adherence to HAART among adult PLWHA from North America (17573 patients total) indicated a pooled estimate of 55% (95% C.I. 49%-62%), slightly lower than the one identified by our study (Mills et al., 2006). Non-adherence

to HAART in adult populations has ranged from 33%–88%, depending on the methods by which adherence is defined and evaluated (Friedland and Williams, 1999). A recent paper by Bangsberg (2006) found that viral suppression and better clinical outcomes was common among patients with a 54%-100% mean adherence level, if the patient was using non-nucleoside reverse-transcriptase-inhibitor regimens instead of unboosted protease inhibitor regimens, known to be partially suppressive. Although perfect adherence is an important goal, viral suppression and better clinical outcomes are possible with moderate adherence to potent regimens, such as those levels identified by our study.

Evidence-based studies on barriers and facilitators to adherence among HIV-positive DU have been very scarce, particularly in developing countries. This is of great concern given that the largest AIDS epidemics among DU have taking place in recent years in developing/transitional countries, such as Eastern Europe, as well as South east, South and Central Asia. Over the coming decades, PLWHA from developing countries will constitute a growing proportion of the World's HAART recipients as treatment roll-out progresses.

A few studies have compared self-reported HAART adherence with more objective indicators, such as MEMS caps. Our meta-analysis found that studies using shorter timeframes were more homogeneous among HIV-positive drug users from disenfranchised communities. A recent report compared self-reported and MEMS adherence among HIV-positive patients and found less overestimation of self-reported adherence with a 1-month recall period than with 3- or 7-day recall periods among participants with higher socioeconomic status – 94% had finished high school (Lu et al., 2008). There is no consensus yet about the more accurate measurement of HAART adherence among HIV-positive patients (Arnsten et al., 2001; Chesney, 2006; Pearson et al., 2007; Simoni et al., 2007).

Clinical guidelines for the management of HIV-positive drug users favor the use of shorter timeframes to evaluate their adherence to HAART, following, for instance, the widely used AIDS

Clinical Trials Group (ACTG) adherence instruments, that employs a 4-day recall period (Chesney et al., 2000; New York State Department of Health, 2005).

One must observe that long-term adherence is particularly challenging, since adherence often fluctuates (Carrieri et al., 2003a) and may decrease over time (Howard et al., 2002; Parruti et al., 2006; Pearson et al., 2007a; Pinheiro et al., 2002). The HIV Epidemiology Research Study (HERS) found that adherence rates declined from 64% at 1 month to 45% at 6 months after initiation of HAART (Arnsten et al., 2001) Although Parruti *et al.* (2006) found that adherence remained fairly stable up to 24 months of follow-up, adherence then declined about 5% every 6 months thereafter. Therefore, the identified differences in our study, related to short versus long-term adherence may represent a true decrease of adherence over time. Further studies are needed to clarify this issue in this specific population.

Most studies reporting higher adherence were carried out among DU receiving HAART in structured settings, particularly those offering both addiction treatment and psychosocial support (Purcell et al., 2004) and/or directly observed therapy (Altice et al., 2004; Smith-Rohrberg et al., 2006). In particular, DU engaged in opioid substitution therapy significantly reduce their drug using habits, have better adherence to HAART, and usually achieve the expected HIV-1 RNA suppression and CD4 cell count response to HAART (Clarke et al., 2003; Moatti et al., 2000; Palepu et al., 2006). These findings suggest that the extent to which one's daily life is routinized and stabilized constitutes a key factor to improve adherence and, as a consequence, might improve responses to HIV treatment among DU (Wagner, 2003).

Although opioid substitution therapy may foster HAART adherence among people who use heroin and other opioids, illicit stimulant use remains a key problem. The use of cocaine among people receiving HAART is of special concern. The vast majority of reviewed studies have also shown that active alcohol abuse (Palepu et al., 2003) and/or illicit drugs in general (Hinkin et al., 2007; Lucas et al., 2001; Martini et al., 2004; Palepu et al., 2006, 2004a; Sharpe et al., 2004) are associated with lower adherence to HAART. HIV-positive active cocaine users may seek treatment with

considerable delay, initiating HAART in more advanced disease stages (Cofrancesco et al., 2008; Martín-Sánchez et al., 2002), which, in turn, will decrease its effectiveness. Patients co-infected with HCV and other STIs may also have worse clinical outcomes (Miller et al., 2005; Vissoci Reiche et al., 2008).

We identified a high degree of between-study heterogeneity in adherence estimates, since selected studies used heterogeneous cut-offs to define optimal adherence (range: 75-100%), assessed adherence through different measurements, used different recall periods, and collected data in a variety of research centers and clinical settings. Due to this high degree of heterogeneity, which was not completely explained either by sub-groups analysis or by meta-regression, our pooled results need to be viewed with caution. The exclusion criteria for our analysis may have limited the generalizability of our study findings. However, another recent meta-analysis on adherence to HAART has also identified a large heterogeneity between studies – I^2: 98.4 (Mills et al., 2006). We can hypothesize that heterogeneity between studies will remain an issue for further studies in this field and should be the object of concerted efforts toward standardization. Multicenter studies and especially cross-cultural studies are sorely needed.

This meta-analysis has other limitations. We aimed to reduce reviewer bias by conducting abstraction independently, in parallel. We cannot, however, know to what extent we may miss important topics or to what extent reporting bias of the original report may have contributed to wrong conclusions. Reporting bias, particularly in studies relying only on self-report may have limited our ability to accurately identify the actual levels of adherence to HAART among HIV-positive DU. Different interpretations of what constitutes optimal adherence made comparisons between studies difficult, if not impossible.

We were unable to identify studies conducted in developing countries, making it impossible to generalize our findings to those settings. Our review relies on information reported in peer-reviewed scientific publications of studies conducted in developed countries, which did not represent those

DU living in specific contexts, such as Eastern Europe, where the AIDS epidemic is mainly driven by drug using population and access to HAART is uneven (WHO/UNAIDS, 2007).

While there is significant reluctance among medical care providers to deliver HAART to DU, the evidence supporting this decision is limited (Aceijas et al., 2006; Vlahov and Celentano, 2006; Malta et al., 2008). Overcoming stigma and discrimination towards HIV-positive DU, and improving the quality and efficacy of HIV care and management is necessary to achieve optimal clinical outcomes for this marginalized population. Much has to be done in terms of a comprehensive monitoring of adherence, including the standardization of methods, timeframes and the very covariates to be explored as predictors and or confounders.

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III.c ARTIGO 3

Mortality among HIV-Infected Injecting Drug Users versus Men who Have Sex with Men: A survival analysis Assessing the Impact of Universal Access to Antiretroviral Treatment in Brazil

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ABSTRACT

Background: HIV-positive injecting drug users (IDUs) appear to benefit less than other populations from highly active antiretroviral therapy (HAART), often due to suboptimal access and/or adherence. Brazil accounts for around 70% of all IDUs receiving HAART in low/middle income countries. We assessed impact of HAART availability/access on AIDS-related mortality among IDUs versus men who have sex with men (MSM)

Methods: Data were merged from four different national information systems (SINAN [AIDS Cases], SICLOM [patients under treatment], and SISCEL [laboratory monitoring], SIM [*Mortality Information System*), using probabilistic linkage. Women were not included on the analysis, since they corresponded to <3% of the IDU cases, and would bias comparisons with male homosexuals/bisexuals. Cox regression was used to assess impact of HAART availability/access on AIDS-related mortality among IDU versus MSM who received AIDS diagnoses from 2000-2006, adjusting for demographic, clinical, and behavioral covariates and controlling for spatially-correlated survival data by the inclusion of a frailty effect

Results: Among 28,426 patients with complete data (43% IDU; 57% MSM), 6,777 (23.8%) died during 87,792 person-years of follow-up. At baseline, compared to MSM, IDU were significantly less likely to be receiving HAART (24.3% vs. 31.2%; $p<0.001$), to have ever had a CD4 count (44.1% vs. 56.9%; $p<0.001$) or HIV-1 RNA viral load determination (54.2% vs. 62.5%; $p<0.001$). After controlling for frailty effects, AIDS-related mortality remained higher in IDU than in MSM (AHR: 1.94; 95% CI: 1.84 - 2.05)

Conclusions: Despite universal access at no cost at the point of delivery to HAART, substantial inequalities remain, which may explain higher mortality among HIV-infected IDUs, compared to MSM in Brazil. Renewed efforts to reduce these health disparities are clearly needed

Keywords: AIDS, Survival analysis, Injecting drug users (IDU), Men who have sex with men (MSM), Antiretroviral therapy, Health inequalities, Brazil.

INTRODUCTION

Since its introduction in 1996, highly active antiretroviral therapy (HAART) has demonstrated great efficacy in reducing morbidity and mortality associated with HIV infection in both high- (Couzigou et al., 2007) and middle-income countries (Marins et al., 2003). HAART significantly improves the prognosis of HIV-infected persons by reducing HIV viral load, increasing CD4+ cell levels and delaying progression to AIDS, ultimately reducing mortality rates (Egger et al., 2002). Since reduced HIV viral load appears to be important for reducing HIV transmission (Quinn et al., 2000), increasing availability and adherence to HAART has also gained attention as a potential HIV prevention strategy (Montaner et al., 2006).

However, since the advent of HAART, inequalities in health outcomes among people living with AIDS have been reported in several high-income countries such as the United States, Spain, and France (Levine et al., 2007; Harper & Lynch, 2007; Dray-Spira et al., 2007); as well as middle and low income countries such as Brazil and Uganda (Braga et al., 2007; Hacker et al., 2004; Kiguba et al., 2007). A high proportion of AIDS deaths in the developed world are due to poor access to therapy among disadvantaged/marginalized populations (Wood et al., 2003a).

Disparities in HIV-related mortality might be due to problems with access to HAART and retention in treatment among specific subpopulations that traditionally have less than optimal access to health care, among them drug users (Fein, 1995; Aceijas et al., 2006). Compared with other populations living with HIV/AIDS, injecting drug users (IDU) usually have lower utilization and adherence to HAART and are more likely to experience virologic failure, contributing to their more rapid progression to HIV disease (Palepu et al., 2003; Celentano et al., 2001; Poundstone et al., 2001). Studies in the United States indicate that IDU tend to initiate HAART at a more advanced stage of HIV infection compared to other populations (Celentano et al., 2001; Wang et al., 2004). In a Swiss study, Bassetti et al. (1999) found that 25% of patients eligible for treatment according to international guidelines did not receive treatment and that IDU were two times more likely to not

receive any antiretroviral (ARV) prescription compared to men who have sex with men (MSM). Mocroft et al. (1999) found that among 6,645 people living with HIV/AIDS, IDU were half as likely to be receiving HAART at recruitment compared with MSM. Similarly, during follow-up, IDU were at a 27% reduced "risk" of starting HAART, after adjusting for other factors.

The active use of drugs, especially of stimulants (e.g. cocaine and meta-amphetamine), the low quality of HIV/AIDS treatment services, the absence of mental health care and substance abuse management (especially methadone substitution therapy), and incarceration/detention of drug users could contribute towards delays or interruptions in HAART use among IDUs (Vlahov & Celentano, 2006; Malta et al., in press).

Brazil was the first middle-income country to provide full access to HAART, laboratory monitoring and clinical care at no cost at the point of delivery to any eligible patient, since 1996 (Bastos et al., 2001). As of June 2007, approximately 180,000 patients were under HAART in Brazil (BMoH, 2007). Brazil's program of universal access to HAART is the most comprehensive initiative implemented so far in a middle-income country, worldwide (Bastos et al., 2008). The country provides treatment and care to the largest number of HIV+ IDU outside high-income countries (Aceijas et al, 2006).

In spite of having implemented free and universal access to HAART in 1996, until nowadays no evaluation has ever been conducted using longitudinal information of all PLWHA under treatment and care through public health facilities in the country. A recent small study analyzed data from 170 patients (68 IDU) from Brazil, aiming to compare the utilization of HIV-related healthcare by IDU and other populations (Melo et al., 2006). According to this study, IDU, as compared to non-IDU, were less likely to receive ARV prescriptions and requests for CD4 lymphocyte and viral load counts. The healthcare utilization increased in calendar-year in the non-IDU group, parallel to the implementation of the Brazilian health policy of universal access to HIV-treatment, but this favorable trend was not observed among IDU.

Herein, we report differences in survival from AIDS diagnosis by transmission risk category, within the unique Brazilian setting. The study evaluated all patients receiving treatment in the country between 2000 and 2006, therefore avoiding selection bias present in other studies that only include partial experience of the entire population living with AIDS.

METHODS

This study utilizes four databanks comprising different longitudinal information of all PLWHA under treatment and care through the public health system from Brazil (**Table 1**). These databanks contain the core information of Brazil's surveillance system, and are specified as follows: sociodemographic information on AIDS cases (SINAN); data from exams conducted in public laboratories, particularly TCD4+/TCD8 lymphocyte counting and HIV viral load (SISCEL), information about monthly ARV refills and therapeutic regimen changes over time (SICLOM), and the date and cause/s of death (SIM). Data from the entire population of PLWHA with diagnosis between 2000 and 2006, whose transmission category was injecting drug use or homo/bisexual contact were extracted from those databanks and merged.

Table 1. Description of Databanks included on the present study.

Databank	Description	Available Period
SINAN-AIDS	*Brazilian AIDS Cases Databank* - Confirmed AIDS case, with demographic information and exposure category, independent of patient been under treatment and care through the public or private health system.	**1984-2006**
SISCEL	*Laboratory Control System* – Information from a public network of laboratories conducting TCD4+/TCD8 lymphocyte counting, and HIV viral load; with information of successive exams performed by all PLWHA under laboratorial follow-up through the public health system.	**1996-2006**
SICLOM	*Drug Control System* – System that controls the distribution of antiretroviral (ARV) medication through public health services, with information on monthly ARV refills and ARV schemes for all PLWHA receiving ARV through the public health system.	**1996-2006**
SIM	*National Mortality Information System* – Information on all deaths registered (date and cause/s of death)	**2000-2006**

Databanks linkage

In Brazil, although private health insurance covers costs with laboratorial exams, accredited physicians and hospitals, it does not cover costs with medications. Therefore, although affluent PLWHA usually look for private physicians and laboratories, the vast majority of those patients also receive their antiretroviral (ARV) drugs through the public health system. Consequently, those patients tend to be notified on SICLOM and SINAN databanks, although are rarely found on SISCEL.

On the other hand, highly vulnerable populations such as IDU usually have less than optimal access to health care, including lower access to successive laboratory follow-up and ARV refills. Therefore, one might hypothesize that the majority of Brazilian IDU living with HIV/AIDS might tend to be more efficiently and rapidly included on SINAN-AIDS and SIM than on SISCEL and SICLOM databanks.

Since differential information is found in each databank, comprehensive analyses must use data from all databanks. As a first step, we standardized the different databanks, in order to have exactly the same variable names, lengths and format throughout all databanks. An identification key was created for each patient, therefore permitting his unique identification in the different databanks.

The National AIDS Program is in charge of the management of three of the abovementioned databanks (SINAN-AIDS, SISCEL, and SICLOM). The merging of such databanks originated a new databank, comprising sociodemographic information and information on exposure category (SINAN-AIDS), successive laboratorial exams (SISCEL), monthly refill of ARV medication and ARV therapeutic regimens changes (SICLOM).

In a subsequent step, we performed the linkage of this merged databank with information from the National Mortality System (SIM). SIM identifies each death through the patient full name, his mother's name, and cause(s) of death, but lacks alphanumeric identifiers. Due to this reason, we linked the merged AIDS databank with SIM using the Recklink 3.0 software (Camargo & Coeli,

2000), a software for databank linkage based on the probabilistic record linkage technique (Grannis et al., 2003; Cook et al., 2001).

We linked the mortality databank with information on ~7 millions deaths from January 1, 2000 to August 31, 2006 with the merged AIDS databank. Through its standardizing algorithm, Reclink 3.0 allows common variables (patient name, date of birth, and mother's name) to be blocked with the objective to identify, with a priori defined probabilities, if the records linked belong to the same individual.

After the linkage, we obtained a comprehensive databank with information on PLWHA under treatment through the Brazilian public health system, aged 18 years or older and with a confirmed AIDS diagnostic. Participants were included if they were diagnosed between January 1, 2000 and August 31, 2006 and if their most probable route of HIV infection was IDU or male homosexual contact.

Patients whose most probable route of HIV infection was heterosexual contact were not included, because our major aim was to analyze differences in survival from AIDS diagnosis between a population known to have higher rates of initiation and maintenance into HAART (MSM) with a population known to have the lowest rates of initiating HAART, worldwide: IDU. Females were not included on the analysis, since they corresponded to less than 3% of the IDU AIDS cases.

The final databank comprised the following covariates: date of birth, most probable route of HIV infection, ethnicity, date of AIDS diagnosis, dates of initiation of HAART, CD4 counts and viral load values in successive visits (with the corresponding dates), and cause(s) and date of death.

Statistical analyses

Descriptive analyses of sociodemographic characteristics and clinical parameters for MSM and IDU were carried out using frequency distributions, and the respective means and standard

deviations. Survival of incident AIDS was assessed in patients whose date of AIDS diagnosis was between January 1, 2000 and August 31, 2006.

The primary endpoint was mortality from AIDS-related causes during the follow-up period. Survival was calculated as the time elapsed from date of AIDS diagnosis until the date of AIDS-related death (or censoring). All other deaths were censored on the date of death, and individuals who stayed alive were censored at the end of data collection period (August 31, 2006). Since analyses were based on secondary data, we did not have access to information on clinical visits; therefore we were not able to calculate losses to follow-up.

Kaplan-Meier curves were fitted in order to compare probabilities of survival according to selected covariates (e.g., baseline HIV viral load, transmission risk category), using the log-rank test. The Cox proportional hazard regression model (Cox, 1972) was used to examine covariates associated with survival among the following: age at AIDS diagnosis, HIV exposure category (IDU vs. MSM), first CD4 lymphocyte count, HAART uptake, first HIV-RNA viral load exam, and ethnicity. The likelihood ratio test was used to define the variables to be entered in the Cox models, adjusting for potential confounders and testing for effect modification. We used the likelihood ratio test to get *p* values, and the assumption of proportionality was evaluated through the examination of Schoenfeld residuals (Schoenfeld, 1982).

Unobserved individual heterogeneity or frailty (Clayton, 1978; Hougaard, 2000) was taken into account. Hazard rates are strongly influenced by selection effects operating in the population (e.g. higher availability of reference centers in a given locality), and individuals surviving up to a certain time will on average be less frail than the original population (Aalen, 1994; Carvalho et al., 2005).

With 8.5 million square kilometers and 185 million inhabitants, Brazil is the largest and most populous country in Latin America, and faces deep health and socioeconomic differences within each region. Therefore, in an attempt to account for the heterogeneity between different Brazilian regions and, within each region, differences between states and municipalities, analyses

were repeated with the introduction of a random effect term, in order to assess the potential association between survival times within a cluster – state or municipality of residency – using gamma-distributed frailty (Naskar et al., 2005).

Analyses were performed in R (version 2.6.0; R Core Development Team, 2004). To estimate confidence intervals for Cox's proportional hazards models, robust methods were used, and maximum penalized likelihood estimation was used to estimate frailty models.

RESULTS

Characteristics of the patients

A total of 28,426 patients were included in the study. Of these, 43% were IDU and the overall mean age at AIDS diagnosis was 34.8 (SD:8.5). Ethnicity and mean age were similar when comparing IDU and MSM. Although all patients had a confirmed AIDS diagnosis, only 28.3% were actually receiving HAART in the beginning of the period under study (Table 2).

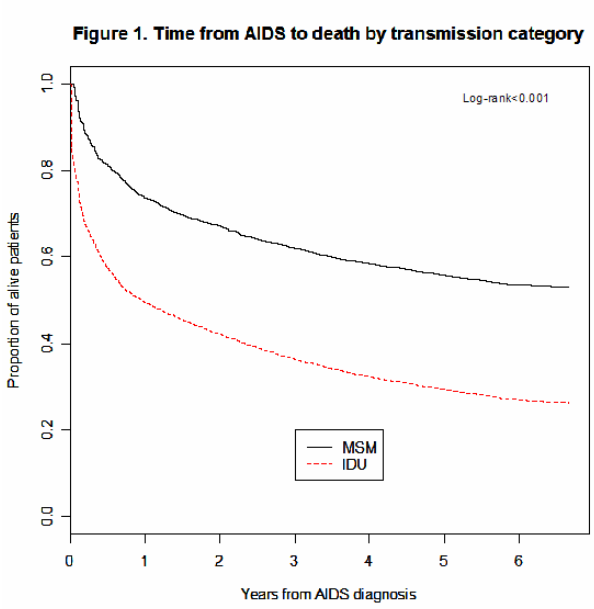
The overall median survival was 2.45 years, and during the follow-up period, 6,777 (23.8%) patients were known to have died from AIDS-related deaths. The proportion of deaths was 2.4 times higher among IDU than among MSM (33.1% vs. 16.8%; $p<0.0001$) (Table 2). Patients who actually accessed the accredited health units had better survival rates (versus those who did not enroll into treatment), and overall, IDU had a lower utilization of treatment and care than MSM. Compared to MSM, IDU were significantly less likely to be receiving HAART at recruitment (24.3% vs. 31.2%; $p<0.001$), less likely to have ever performed at least one CD4 count (44.1% vs. 56.9%; $p<0.001$), and less likely to have ever had at least one HIV-1 RNA viral load determination (62.5% vs. 54.2%; $p<0.001$). Among those who had conducted at least one CD4 and HIV-1 RNA viral load exam, IDU had lower mean CD4 (277.3 vs. 309.2; $p=0.000$), but similar HIV-1 RNA viral load counts: 3.94 vs. 4.05 $\log_{10}$ copies/ml (compared to MSM) (Table 2).

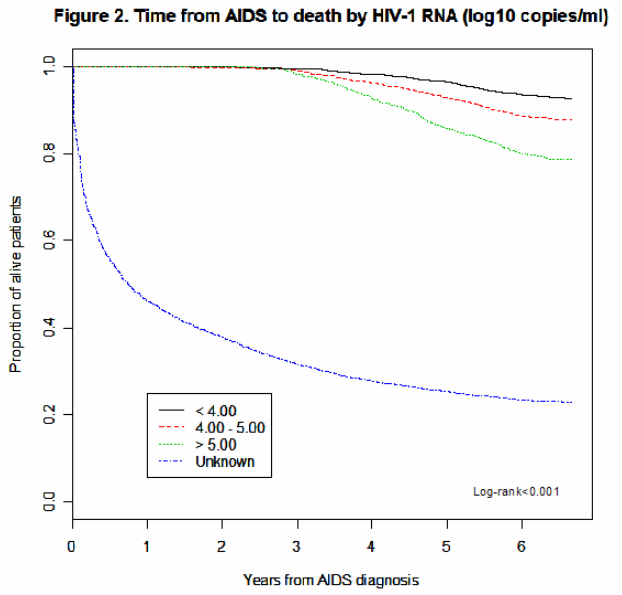
Table 2. Sociodemographic and clinical characteristics of patients included on the study, according to transmission category (n=28,426).

			Transmission category	
		Total	***Male homosexual contact***	***Injecting drug use***
Subjects (N, %)		28,426	16,195 (57.0)	12,231 (43.0)
Age at diagnosis				
	Mean ± SD	34.8 ± 8.5	35.3 ± 9.1	34.2 ± 7.4
	Range	18 – 89	18 – 89	18 - 81
Ethnicity				
	Caucasian	10,433 (36.7)	5,620 (34.7)	4,813 (39.4)
	Mulatto (mixed white and black)	3,915 (13.8)	2,625 (16.2)	1,290 (10.5)
	Black	1,657 (5.8)	838 (5.2)	819 (6.7)
	Others (Asian, Indigenous...)	118 (0.4)	75 (0.5)	43 (0.4)
	Unspecified	12,303 (43.3)	7,037 (43.5)	5,266 (43.1)
HAART[a] uptake (N, %)				
	Never received HAART	20,395 (71.7)	11,138 (68.8)	9,257 (75.7)
	Received (or is still under) HAART	8,031 (28.3)	5,057 (31.2)	2,974 (24.3)
Deaths[c]		6,777 (23.8)	2,727 (16.8)	4,050 (33.1)
Have ever done at least one CD4 exam				
	No	13,822 (48.6)	6,984 (43.1)	6,838 (55.9)
	Yes	14,604 (51.4)	9,211 (56.9)	5,393 (44.1)
CD4 lymphocytes (first exam available)[d]				
	Mean ± SD	297.4 ± 213.4	309.2 ± 217.2	277.3 ± 205.2
	Range	1 – 1,778	1 – 1,758	1 – 1,778
Have ever done at least one HIV-1 RNA Viral load exam				
	No	16,424 (57.8)	8,775 (54.2)	7,649 (62.5)
	Yes	12,002 (42.2)	7,420(45.8)	4,582 (37.5)
HIV RNA in plasma, $\log_{10}$ copies/ml (first exam available)[e]				
	Mean ± SD	4.01 ± 1.17	4.05 ± 1.16	3.94 ± 1.18
	Range	1.70 – 6.85	1.70 – 6.85	1.70 – 6.80

[a] Highly Active Antiretroviral Therapy
[b] Persons-year
[c] All causes of death
[d] Among those who have done at least one CD4 exam
[e] Among those who have done at least one Viral load exam

As shown by Kaplan-Meier curves, IDU had statistically significant lower survival since AIDS diagnosis, when compared to MSM (Figure 1). Survival since AIDS diagnosis was lower among those who had never had an HIV-1 RNA viral load determination, followed by those with first HIV-1 RNA test >5.00 log_{10} copies/ml, those with results between 4.00 and 5.00 log_{10} copies/ml, and patients with HIV-1 RNA bellow 4.00 log_{10} copies/ml (Figure 2). Patients with unknown first CD4 cells count (e.g. those who have never conducted at least one CD4 count exam during the study period) had the worst survival following AIDS diagnosis, followed by those with CD4 counts bellow 200 cells/mm^3, and those with CD4 counts higher than 200 cells/mm^3.





Predictors of survival

In univariate analysis, exposure category was a strong predictor of survival: risk of death for IDU was roughly 2 times higher than that of MSM (HR 1.96; 95% CI: 1.86 – 2.06). Predictors of longer survival included HAART uptake (HR 0.14 95% CI: 0.13 – 0.16) and CD4 counts above 350 cells/mm^3 at AIDS diagnosis (HR 0.24; 95% CI: 0.20 – 0.27). Patients with an HIV-RNA viral load greater than 5log_{10} copies/ml at AIDS diagnosis had a higher risk of death (HR 3.77; 95% CI: 3.25 – 4.37). Non-white patients had also a higher risk of death, when compared to white patients: HR 1.32; 95% CI: 1.23 – 1.41 (Table 3).

In multivariate analysis, the increased risk of death observed in IDU compared to MSM in the univariate analyses persisted (HR: 1.77; 95% CI: 1.68 – 1.88). As expected, biological predictors such as higher CD4 cells counts and lower viral load remained a strong predictor of survival, as well as HAART uptake (Table 3).

Table 3. Hazard ratios of mortality according to baseline variables among IDU and MSM diagnosed with AIDS from 2000-2006 in Brazil.

	Unadjusted	Adjusted[#]
	HR (95%CI)[a]	HR (95%CI)
Predictor		
Exposure category		
MSM[b]	1.00	1.00
IDU[c]	1.96 (1.86 – 2.06)**	1.77 (1.68 – 1.86)**
Age (per year of increase)	1.02 (1.01 – 1.02)**	1.02 (1.02 – 1.03)**
Ethnicity		
White	1.00	1.00
Non-white	1.32 (1.23 – 1.41)***	1.39 (1.30 – 1.49)**
Unknown	0.63 (0.59 – 0.67)**	0.64 (0.60 – 0.68)**
HAART uptake after AIDS diagnosis		
No	1.00	1.00
Yes	0.14 (0.13 – 0.16)**	0.52 (0.46 – 0.58)**
CD4 cell count at diagnosis ($x10^6$/l)		
<200	1.00	1.00
200-350	0.27 (0.23 – 0.31)***	0.31 (0.26 – 0.37)**
>350	0.24 (0.20 – 0.27)**	0.30 (0.26 – 0.35)**
Unknown	3.11 (2.86 – 3.37)**	2.23 (1.99 – 2.50)**
HIV-1 RNA (log_{10} copies/ml)		
<4.00	1.00	1.00
4.00-5.00	1.91 (1.64 – 2.22)***	1.48 (1.27 – 1.72)***
>5.00	3.77 (3.25 – 4.37)**	2.44 (2.10 – 2.84)**
Unknown	7.29 (6.52 – 8.16)**	1.67 (1.46 – 1.92)***

[a] Hazard Ratio (95% Confidence Interval); [b] Men who have sex with men; [c] Injection Drug Users; [d] Highly Active Antiretroviral Therapy; [e] Antiretroviral Therapy; ***p*-value=0.0000; ****p*-value<0.001
[#]Cox proportional hazards model adjusted for all variables listed in the table.

On multivariate Cox frailty regression, accounting for a random effect due to the place of residence (Table 4), the increased risk of death observed in IDU, when compared to MSM, was higher than the estimates found in our multivariate model (HR: 1.94; 95% CI: 1.84 – 2.05). Both CD4 cells counts and viral load remained significantly predictors of survival, as well as HAART uptake. Non-white participants had a higher risk of death (HR: 1.29; 95% CI: 1.20 – 1.38), versus whites. As expected, older participants had a slightly higher risk of death (HR: 1.02; 95% CI: 1.02 – 1.03 per year increase). The same patterns were observed on multivariate Cox frailty regression, accounting for a random effect due to the municipality of residence, although with a slightly smaller variance. The estimated frailty variance was statistically significantly different from zero on both

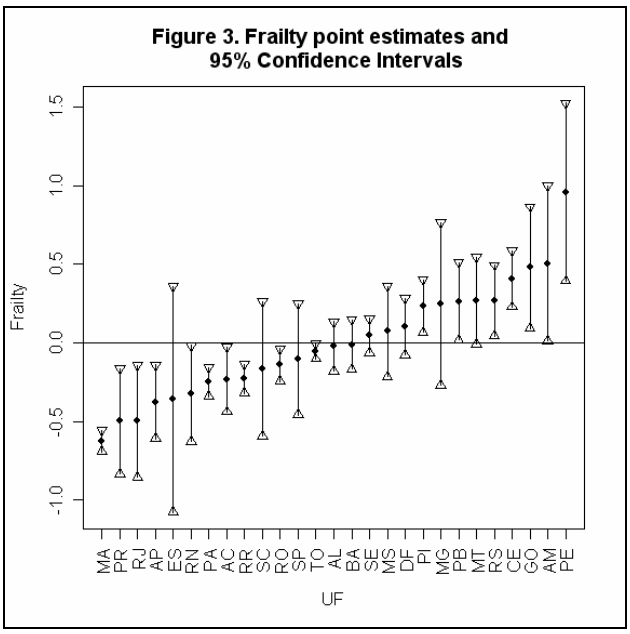
analyses, suggesting that the risk of death after AIDS diagnosis was heterogeneous among subjects living in different states and municipalities (Table 4).

Table 4. Hazard ratios of mortality according to baseline variables among IDU and MSM diagnosed with AIDS from 2000-2006 in Brazil, adjusted by state or municipality frailty effect.

	Frailty: State of Residence[#]	**Frailty: Municipality of Residence**[#]
Predictor	**HR (95%CI)** [a]	**HR (95%CI)**
Exposure category		
MSM[b]	1.00	1.00
IDU[c]	1.94 (1.84 – 2.05)***	1.87 (1.77 – 1.98)***
Age (per year of increase)	1.02 (1.02 – 1.03)***	1.02 (1.02 – 1.03)***
Ethnicity		
White	1.00	1.00
Non-white	1.29 (1.20 – 1.38)***	1.34 (1.25 – 1.45) ***
Unknown	0.56 (0.52 – 0.59)***	0.56 (0.52 – 0.59) ***
HAART uptake after AIDS diagnosis		
No	1.00	1.00
Yes	0.50 (0.44 – 0.56)***	0.48 (0.42 – 0.53) ***
CD4 cell count at diagnosis ($x10^6$/l)		
<200	1.00	1.00
200-350	0.31 (0.26 – 0.36)***	0.30 (0.26 – 0.35) ***
>350	0.30 (0.26 – 0.36)***	0.30 (0.26 – 0.35) ***
Unknown	2.39 (2.13 – 2.68)***	2.65 (2.35 – 2.99) ***
HIV-1 RNA (log_{10} copies/ml)		
<4.00	1.00	1.00
4.00-5.00	1.44 (1.23 – 1.67)***	1.47 (1.26 – 1.72) ***
>5.00	2.39 (2.05 – 2.77)**	2.46 (2.11 – 2.87) ***
Unknown	1.67 (1.46 – 1.91)***	1.71 (1.49 – 1.96) ***
Estimated frailty variance	0.57***	0.50***

[a] Hazard Ratio (95% Confidence Interval)
[b] Men who have sex with men
[c] Injection Drug Users
[d] Highly Active Antiretroviral Therapy
[e] Antiretroviral Therapy
****p*-value=0.0000
[#]Cox proportional hazards model adjusted for all variables listed in the table.

The visual inspection of frailty graphs suggests that the largest frailty effects were found in the larger states located in the Rain Forest region (e.g. Amazon - AM), in the states located in the Northeast region, Brazil's poorest region, and in the largest and most heterogeneous state of the Southeast region (Minas Gerais – MG). On the other hand, the smallest states of the North region (e.g. Roraima – RR, Rondonia - RO, and Tocantins – TO) accounted for the smallest frailty effect. Industrialized areas from the Southern (Parana – PR, Santa Catarina - SC) and Southeastern regions (Sao Paulo – SP & Rio de Janeiro – RJ) also presented small frailty effects (Figure 3).



DISCUSSION

This is the first study in Brazil to conduct survival analyzes with a large and representative population of PLWHA using data from all Brazilian AIDS surveillance databanks.

MSM were selected as the comparison group because several studies have already demonstrated the increased survival and better access to health care among MSM, particularly when compared to IDU, a highly marginalized population (Rodríguez-Arenas et al., 2006; Blades et al., 2007; Kirk & Vlahov, 2007).

Previous survival analyses conducted with Brazilian AIDS National Data have found a substantial increase in survival time over the years, particularly among patients diagnosed after 1996, when free and universal access was instituted in Brazil (Marins et al., 2003). But our study went a step further, analyzing for the first time data from all patients under treatment in Brazil after HAART was widely available in the country, with specific analyses for different exposure categories (IDU and MSM).

The study made evident a significant increase in survival after AIDS diagnosis, observed among patients belonging to both exposure categories: the overall median survival was 2.45 years for those patients diagnosed in the late post-HAART era (after 2000). In a previous study conducted

with national data median survival times were as follows: 5 months for cases diagnosed in the 1980s, 18 months for those diagnosed in 1995, and 58 months for those diagnosed in 1996 (Marins et al., 2003). The increased survival observed underscores the dramatic benefit of providing universal access to HAART to both MSM and IDU, and emphasizes the need for treatment roll-out in developing countries.

However, our analysis also illustrates that deep inequalities remain, even in the context of free and universal access to HAART. IDU living with AIDS had a lower probability of receiving HAART, lower CD4 counts and higher HIV-1 viral loads when presenting to health care facilities, and subsequently had higher mortality rates when compared to MSM. Even for patients diagnosed after 2000, when HAART and correspondent monitoring were available in every single corner of Brazil, IDU still had a higher mortality rate: almost one and a half times higher than MSM, after adjusting for confounders. These disparities may be attributed to key problems already identified among this population: lower uptake of HAART (Aceijas et al., 2006); lower adherence to HAART in the absence of additional psychosocial support, mental health care, and substance abuse treatment (Malta et al., 2008); initiation of HAART at more advanced stages of disease (Vlahov & Celentano, 2006).

The higher mortality rate we observed among IDU has already been described in Brazil (Cardoso et al., 2006) and high-income countries with universal access to HAART (Rodríguez-Arenas et al., 2006; Wood et al., 2006). As expected, CD4 count and viral load measurements at AIDS diagnosis were strong determinants of survival (Wood et al., 2003; Hogg et al., 2001).

In the present study, having received HAART was also associated with a clear survival advantage after AIDS diagnosis; however, given the design and nature of the analysis used, it is not possible to rule out selection bias due to differential indication of treatment, as those patients who are prescribed HAART might be those with a greater a priori probability of survival. Additional modeling analyses are needed to separate these entangled effects.

This study is highly representative in terms of its broad geographic scope, however, its external validity might be limited by the fact that a not measurable fraction of people living with AIDS may not access the network of accredited health units due to traveling costs or other marginal costs (e.g. losses secondary to unexpected work leaves or the need to care of young children) may be underrepresented.

Another limitation of our study is the unavailability of information on other covariates that may influence health and survival and which may vary over time, such as active drug use and engagement in drug addiction treatment. We were unable to examine other structural factors, such as the access to private health insurance, quality of care, or health-related behavior (e.g. HAART adherence) that may account for these disparities on an individual and/or at population level. Differences in outcomes among different populations might result from biases and/or confounders not accounted for in our model.

Around 40-50% of our sample had never had a CD4 count and/or an HIV viral load exam performed through the public health system, what could be either mean they have been performing their exams through private laboratories (usually reimbursed by private insurances) or did not perform such exams at all. However, the Kaplan-Meier curves for those with unknown initial CD4 or HIV viral load is significantly lower that for those with available results, reinforcing the supposition that an important percentage of those with unknown information might be really out of any care.

Universal access to ARV therapy was established by Brazilian Federal Law on November, 1996. However, a key finding from our study is that around 70% of patients with a confirmed AIDS diagnosis were not receiving HAART in the beginning of the study. A partial explanation for this incongruence, besides the protracted introduction of HAART or the interruption of treatment before the effective introduction of HAART (Rodrigues et al., 2003), is that SICLOM (the databank summarizing information on patients under HAART) has a less than optimal coverage, therefore under-reporting patients who are actually under treatment. Recent reports, assessing information

from 2007 up to early 2008, document that SICLOM has a coverage of approximately 70%, i.e. roughly 30% of HAART dispensing units are not yet fully integrated to such electronic database and much probably still follow-up patients using manual spreadsheets to monitor medicine dispensing (Bastos et al., 2001; BMoH, 2008).

Perhaps the greatest limitation of our analysis is the lack of information on treatment course and clinical events, such as the type of initial ART regimen and changes in therapeutic regimens over time. Recent studies have found that better immunological, virological and clinical outcomes are associated with non-nucleoside reverse-transcriptase-inhibitor regimens instead of unboosted protease inhibitor regimens, which are known to be only partially suppressive (Bangsberg, 2006). Information on treatment interruptions due to the development of medication side-effects (Pádua et al., 2006), or the development of a concurrent illness was also not available.

Our analysis attempted to account for the heterogeneity between different Brazilian regions and, within each region, for the differences between different states and municipalities. The results of these analyses suggest that the mortality risks did vary between subjects living in different states and/or different municipalities.

The visual analysis of frailty suggests that largest frailty effect was found in states located in larger semi-urban and rural areas and/or in the poorest regions of Brazil In those regions, AIDS mortality might be influenced by structural factors related to the place of residence, beyond individual level factors (e.g. less availability of specialized services, great distances from residence to AIDS services). Yet even after these adjustments, the analyses followed the same general trends of a significantly increased risk of death among IDU compared to MSM. However, the significant frailty variance suggests the need to include the analysis of structural variables and/or to conduct multilevel analyses in future studies.

Strengths of this study include the assessment of a large and representative study population, yielding relatively precise estimates and the use of probabilistic linkage procedures to create a merged national databank with broad information on different aspects of AIDS management and

care. The chance to double-check every information using different sources and the use of multivariate modeling with a random effects component represent additional strengths.

In summary, among the patients who access Brazil's network of over 600 ARV dispensing units IDU had a lower uptake of HAART, accessed care at more advanced stages of HIV infection, and, as a result, had higher mortality rates following AIDS diagnosis. These substantial inequalities pose a major challenge in the context of free and universal access to HAART and health care in general. There is a pressing need to improve access and adherence of drug users to HAART, taking into account their frequent comorbidities, such as the abuse of alcohol and mental conditions, the co-infection with hepatitis C, as well as social disadvantage.

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IV. CONCLUSÕES

"We must become the change we want to see."
Mahatma Gandhi

Desde o advento da HAART, a morbidade e mortalidade associadas à AIDS experimentaram redução significativa, nos países que oferecem este tratamento a pessoas vivendo com HIV/AIDS. No entanto, de acordo com nossa análise de sobrevida, o benefício associado à HAART não tem tido o mesmo impacto, quando comparamos pessoas vivendo com HIV/AIDS infectadas através do uso de drogas injetáveis com pacientes infectados através de contato homo/bissexual, apesar do acesso gratuito e universal à HAART preconizado pelo Ministério da Saúde. O artigo que apresenta a análise de sobrevida aponta que a mortalidade secundária à AIDS permanece mais elevada entre pacientes infectados através do uso de drogas, quando comparados com pacientes infectados através de relações homo/bisexuais. Diversos aspectos parecem contribuir para um impacto da HAART aquém do esperado na mortalidade de usuários de drogas, entre os quais sobressaltam o acesso tardio à HAART. Este benefício aquém do esperado parece estar associado a uma ampla gama de questões, incluindo a maior freqüência de óbitos associados a outras causas, acesso sub-ótimo ao acompanhamento clínico e laboratorial e apresentação tardia aos serviços de saúde, muitas das vezes apresentando quadros clínicos de grande deficiência imunológica.

Dúvidas relacionadas a uma possível existência de padrões específicos de progressão do HIV e mortalidade secundária à AIDS entre usuários de drogas injetáveis, quando comparados com outros grupos de pacientes, e incertezas quanto ao impacto do uso continuado de substâncias psicoativas na progressão da doença têm sido levantadas desde o início da epidemia de AIDS. Antes do advento da HAART, a mortalidade entre usuários de drogas vivendo com HIV/AIDS já era sabidamente maior do que em outros grupos de pacientes, principalmente devido a altas taxas de mortalidade secundárias a outras causas, em particular óbitos por causas externas e, em menor

magnitude, óbitos associados a outras infecções ou doenças crônicas mais prevalentes entre usuários de drogas, tais como as Hepatites virais e cirrose hepática, endocardites e trombo-embolias (Prins, 1998).

A evidência sumarizada nos artigos de revisão sistemática e meta-análise indicam que usuários de drogas se beneficiam da terapia antiretroviral e podem apresentar níveis de aderência à HAART semelhantes aos encontrados em outros grupos de pacientes vivendo com HIV/AIDS. A aderência é um aspecto chave para prevenir a falha terapêutica à HAART e conseqüente morbidade e mortalidade aumentadas. De acordo com a revisão realizada, o uso continuado de substâncias psicoativas, em particular da cocaína e o consumo abusivo de álcool estão associados a uma aderência aquém da esperada à HAART, enquanto entre ex-usuários de drogas, o principal fator associado à aderência sub-ótima tende a ser uma maior vulnerabilidade social. Entre usuários de drogas em tratamento para dependência química, particularmente aqueles engajados em programas de substituição da heroína com metadona ou buprenorfina, a aderência à HAART tende a ser significativamente mais elevada do que a encontrada em usuários de drogas ativos e ex-usuários de drogas. Programas de substituição facilitam a estabilização do paciente e seu manejo clínico, influenciando de forma positiva sua recuperação. Estes programas e, de forma menos pronunciada, tratamentos baseados em psicoterapia e acompanhamento psiquiátrico para dependentes de cocaína, costumam contribuir de forma importante para uma melhor aderência destes pacientes à HAART. Este aspecto se dá pelo fato do tratamento para dependência química permitir um acompanhamento mais regular do paciente, facilitando o manejo de recaídas e a referência do paciente a serviços de saúde diversos ao longo do tratamento.

A evidência científica atualmente disponível, relatada nos artigos de revisão sistemática e meta-análise, sugere de forma veemente a importância e eficácia de oferecer tratamentos mais inclusivos e adequados às necessidades e especificidades desta população, particularmente no que se refere ao oferecimento em conjunto de tratamento para dependência química e para a infecção pelo HIV.

No entanto, na maioria dos países o tratamento para dependência química e para a infecção pelo HIV são frequentemente oferecidos em serviços de saúde distintos, sendo uma exceção a oferta de serviços includentes e multi-facetados em um único local. A natureza crônica e a freqüência de recaídas associadas à dependência química, na qual se alternam padrões de uso abusivo, uso controlado e abstinência, com períodos de maior ou menor aderência a diferentes tratamentos em saúde dificultam análises mais adequadas sobre a complexa inter-relação entre dependência química, infecção pelo HIV e aderência à HAART

Na complexa inter-relação entre uso de drogas e contextos desfavoráveis de vida, na maioria das vezes, não é possível distinguir o papel específico de fatores contextuais e individuais, não sendo tão pouco possível apontar qualquer direcionalidade de associações identificadas pelos estudos de revisão, meta-análise e sobrevida apresentados. Estudos com desenho longitudinal poderão responder, de forma mais adequada, às questões ora levantadas.

Uma vez que a dependência química e a infecção pelo HIV são condições coexistentes e com características de cronicidade, a integração de tratamento para ambos os agravos é fundamental e premente, para que possamos responder de forma mais adequada a esta dupla carga de doença, a qual sobrecarrega não só o indivíduo e sua família, mas também as ações em saúde pública voltadas para usuários de drogas vivendo com HIV/AIDS.

"Only a life lived for others is a life worth while."
Albert Einstein

ANEXOS

I. Metodologia utilizada na revisão sistemática e meta-análise: Descrição das etapas

I.1 - *Objetivo da busca bibliográfica*

Identificar artigos científicos publicados em revistas indexadas que apresentem estudos avaliando a aderência de usuários de drogas à terapia antiretroviral de alta potência (HAART).

I.2 - *Etapas iniciais*

Para elaborar os procedimentos a serem utilizados na condução e posterior descrição dos resultados da revisão sistemática e meta-análise, foram revisadas as seguintes normas internacionais para realização e descrição de revisões sistemáticas e meta-análises:

- *Consolidated Standards of Reporting Trials* – CONSORT (Altman et al., 2001; Moher et al., 2001)
- *Quality of Reporting of Meta-analyses* – QUOROM (Moher et al., 2000)
- *Meta-analysis of Observational Studies in Epidemiology* – MOOSE (Stroup et al., 2000),
- *Transparent Reporting of Evaluations with Nonrandomized Designs* – TREND (Des Jarlais et al., 2004).

As normas organizadas pelos grupos "CONSORT" e "QUOROM" foram elaboradas especificamente para revisões sistemáticas baseadas em estudos do tipo caso-controle (*Randomized Controlled Trials* – RCT), enquanto as normas elaboradas pelo grupo "MOOSE" e "TREND" foram organizadas visando nortear a elaboração e descrição de revisões sistemáticas que incluam estudos observacionais.

Após proceder a uma cuidadosa revisão, o modelo "MOOSE" foi adotado para elaboração e descrição da revisão sistemática e meta-análise, enquanto o checklist elaborado pela equipe do "TREND", versão 1.0, foi utilizado como base para a elaboração do instrumento para extração de dados, por serem mais adequadas ao nosso estudo.

I.3 - *Busca Bibliográfica*

O processo de busca bibliográfica foi elaborado em duas etapas, uma etapa inicial de busca automatizada e uma etapa posterior de busca manual (Lyles *et al.*, 2006). Inicialmente, descritores (termos indexadores) relacionados à aderência, em inglês, foram identificados (ex: *adherence, compliance, pill counts, Medication Event Monitoring System* [MEMS]). A busca automatizada combinou estes termos com indexadores de literatura biomédica utilizados em *sites* de busca bibliográfica da área (em inglês, *Medical Subject Headings* – MeSH) para HIV, AIDS e dependência ou abuso de drogas. As buscas foram realizadas nos principais indexadores internacionais de literatura biomédica, a saber: MEDLINE via PubMed, Cochrane CENTRAL, AIDSLINE, AMED, CINAHL, TOXNET, e ISI *Web of Science*. As buscas foram realizadas para o período compreendido entre Janeiro de 1996 e Fevereiro de 2008, com exceção para o *site* AIDSLINE, no qual as buscas foram realizadas para o período compreendido entre 1996-2000 (ano no qual a inclusão de novas citações foi descontinuado).

Objetivando reduzir possíveis vieses da busca eletrônica, procedemos posteriormente a uma busca bibliográfica manual, a qual contemplou as seguintes etapas:

1. Busca de resumos apresentados em conferências nacionais e internacionais sobre HIV/AIDS e/ou dependência química, utilizando os mesmos termos indexadores utilizados na busca automatizada;

2. Busca de pesquisadores que trabalhem em pesquisas relacionadas com HIV/AIDS e/ou dependência química. Pesquisadores internacionais foram buscados através da base de dados do *National Institutes of Health*, intitulada *Computer Retrieval of Information on Scientific Projects* (CRISP) (http://crisp.cit.nih.gov). Pesquisadores nacionais foram identificados através da Plataforma Lattes do Conselho Nacional de Desenvolvimento Científico e Tecnológico – CNPq (http://lattes.cnpq.br/);

3. Contato com todos os pesquisadores identificados e autores de artigos/resumos de congressos selecionados, objetivando obter cópias de trabalhos no prelo;

4. Revisão da bibliografia citada em todos os artigos selecionados, buscando identificar estudos elegíveis adicionais.

I.4 - *Critérios de Inclusão e Exclusão adotados*

Apenas estudos avaliando a aderência de usuários de drogas ao tratamento anti-retroviral como desfecho principal foram incluídos. Para ser selecionado, o estudo deveria apresentar o ponto de corte adotado na definição de aderência utilizada no estudo (ex: "foram considerados aderentes pacientes que tomaram pelo menos 90% das pílulas prescritas durante a última semana") ou ter avaliado a aderência como variável contínua, incluir análises multivariadas para avaliar preditores de aderência e apresentar os dados estratificando participantes de acordo com o uso de substâncias ilícitas (usuários de drogas vs. não usuários de drogas) ou ter avaliado apenas usuários atuais e ex-usuários de drogas.

Estudos foram excluídos caso apresentassem exclusivamente dados qualitativos, fossem revisões, ou tivessem avaliado a aderência à ART em outros segmentos populacionais (sem que apresentassem os resultados estratificados para usuários de drogas). Usuários de drogas foram definidos como usuários de heroína, cocaína, *crack* ou meta-anfetaminas. Estudos avaliando exclusivamente usuários de álcool e/ou maconha foram excluídos, assim como estudos com menos de 30 participantes.

I.5 - *Seleção dos estudos*

Utilizando um protocolo pré-definido, dois pesquisadores extraíram o texto completo dos artigos científicos identificados como elegíveis. A avaliação da elegibilidade de cada estudo e a extração das informações se deu de forma independente, objetivando com isso minimizar possíveis vícios de observação. Após a identificação de todos os artigos considerados como relevantes para o estudo, os dois pesquisadores responsáveis pela extração se reuniram, visando buscar um consenso com relação aos artigos que deveriam ser incluídos no estudo.

I.6 - *Extração dos dados*

A extração dos dados foi realizada utilizando um formulário padronizado (apresentado a seguir). Este formulário facilitou a coleta sistemática de informações sobre o país no qual o estudo foi realizado, características da amostra (sexo, raça, idade), tamanho da amostra, período e desenho do estudo, medidas utilizadas para mensurar a aderência, proporção de pacientes aderentes, ponto de corte utilizado para mensurar aderência, assim como covariáveis associadas à aderência, tais como o aumento da contagem de células CD4 e a diminuição da carga viral para o HIV, ao longo do período de acompanhamento – quando estes dados estivessem disponíveis. Quando mais de uma forma de mensurar a aderência foram utilizadas (ex: MEMS-cap e auto-relato), dados sobre todos os métodos foram coletados.

Quando mais de um método para mensurar a aderência foi utilizado (ex: MEMs cap e auto-relato), dados relativos à proporção de pacientes aderentes mensurados por cada um dos métodos foram extraídos. Para estes estudos, foi calculada a proporção de aderência média, utilizando todas as informações disponíveis. Esta estratégia foi adotada pelo fato de não existir, até o momento, um consenso na literatura científica sobre a existência de um método para mensurar a aderência que possa ser considerado como "padrão-ouro" (Pearson et a., 2007). Para estudos que mensuraram aderência como variável contínua, calculamos uma percentagem média de pacientes aderentes utilizando os dados disponíveis (ex: para um estudo que tivesse mensurado aderência como 0.80, em uma amostra de 100 pacientes, esta informação teria sido incluída no banco de dados como 80 pacientes aderentes, em uma amostra de 100 pacientes). E para estudos que avaliaram aderência como uma variável discreta, utilizando apenas uma forma de mensuração, a estimative incluída em nosso banco de dados refere-se ao percentual de pacientes considerados aderentes no estudo, de acordo com o ponto de corte utilizado pelos autores.

I.7 - ***Meta-análise***

Foram utilizados métodos padronizados para realização da meta-análise (Cooper & Hedges, 1994; Lipsey & Wilson, 2001). Utilizou-se um modelo de efeitos mistos para agregar efeitos individuais de cada estudo, pois este tipo de modelagem fornece uma estimativa mais conservadora da variância entre estudos, quando comparado aos modelos de efeitos fixos. Modelos de efeitos mistos também permitem obter inferências mais acuradas, além de possibilitarem ajustar o modelo final com relação a uma possível heterogeneidade entre as populações incluídas nos diferentes estudos (Hedges & Vevea, 1998; van Houwelingen *et al.*, 2002).

O ponto de corte para aderência adotado na meta-análise foi aquele utilizado em cada estudo e a proporção de aderência referida em cada estudo foi utilizada para calcular a proporção geral de pacientes aderentes em todos os estudos incluídos, por meio do método de efeitos aleatórios de DerSimonian-Lair (Fleiss, 1993; DerSimonian, 1986). Este método reconhece cada estudo como uma amostra de todos os estudos em potencial que poderiam ter sido incluídos na análise, além de incorporar a variabilidade inter-estudos na estimativa total da proporção de aderência.

A estatística I^2 foi calculada como uma forma de mensurar a variação total da aderência que seria atribuível à heterogeneidade entre-estudos (Higgins & Thompson, 2002; Higgins *et al.*, 2003). Conforme antecipado, foi identificada uma grande heterogeneidade entre-estudos, considerando as diferentes populações estudadas, diversas formas de definir aderência e a duração de estudos diferenciados que costumam para utilizados ao mensurar aderência.

Gráficos em formato de árvore (*forest plots*, na expressão em inglês) foram gerados, de modo a facilitar a visualização das proporções identificadas em cada estudo, o intervalo de confiança de 95% para cada estimativa pontual e a estimativa global de aderência, utilizando a estimativa de DerSimonian-Lair.

Devido à grande variabilidade identificada entre os diferentes estudos, referente às estimativas de pacientes aderentes ($I^2 \geq 75\%$), tentou-se, inicialmente, agregar os estudos em três

grupos menores, de acordo com o tempo utilizado para mensurar a aderência, objetivando com isso encontrar grupos menores que fossem mais homogêneos. Os grupos foram elaborados de acordo com os seguintes critérios:

Grupo 1: Período de lembrança entre o último dia e as últimas duas semanas;

Grupo 2: Período de lembrança entre os últimos 15 dias e os últimos 6 meses

Grupo 3: Período de lembrança entre o último ano e os últimos 2,5 anos (ressalta-se que nenhum estudo utilizou como tempo de mensuração o período compreendido entre 6 meses e um ano)

Como a heterogeneidade inter-estudos se manteve elevada, mesmo após a subdivisão dos estudos selecionados em grupos menores, realizamos uma meta-regressão, objetivando identificar os fatores mais estreitamente associados a esta grande heterogeneidade entre-estudos observada.

Para realizar a meta-regressão, a variável dependente (proporção de participantes aderentes de cada estudo - r/n) foi transformada em seu logito. A transformação logito costuma permitir um cálculo estatisticamente mais adequado, uma vez que os valores do log são distribuídos de forma normal (ao contrário de escores probabilísticos), variando entre 0 e 1 (Viechtbauer, 2006).

Inicialmente, procedeu-se à análise univariada, tendo por variável dependente o logito da proporção de participantes aderentes de cada estudo, e por variáveis independentes: período de lembrança – *recall* (aderência entre o último dia e as últimas duas semanas; aderência entre os últimos 15 dias e os últimos 6 meses; aderência nos últimos 6 meses ou mais); substância ilícita mais comumente consumida pela população estudada (heroína e cocaína, apenas de heroína, cocaína e *crack*; abstinência durante todo o período do estudo); método de mensuração da aderência (auto-relato, dados de prontuários/farmácia, MEMS-cap); ponto de corte de 80% para mensurar aderência; ponto de corte de 90% para mensurar aderência; ponto de corte de 95% para mensurar aderência; ponto de corte de 100% para mensurar aderência e se o paciente pagou ou não para receber ART.

Variáveis com p-valor ≤0,20 na análise univariada foram incluídas na análise multivariada. As seguintes covariáveis foram incluídas no modelo multivariado de meta-regressão: período de *recall*, substância ilícita mais comumente consumida pela população estudada; método de mensuração da aderência e ponto de corte de 80% para mensurar a aderência.

As analises foram realizadas utilizando os seguintes pacotes estatísticos: StatsDirect versão 2.5.2 (StatsDirect Ltd, 2007), R versão 2.6.2 (R Core Development Team, 2004) e Stata versão 10.0 (StataCorp, 2005).

II. Metodologia utilizada na revisão sistemática e meta-análise: Avaliação da Heterogeneidade entre-estudos

A forma mais freqüente para avaliar a presença de heterogeneidade em meta-análises tem sido a utilização da estatística **Q**, proposta por Cochran (1954). Nesta estatística a hipótese nula é de que os efeitos reais identificados em cada estudo são iguais ($\mathbf{H_0: \theta_1 = \theta_2 = ... = \theta_k}$, onde os $\mathbf{\theta_i}$**'s**, são os efeitos (RR, OR) identificados nos estudos correspondentes **i** = 1 a **k**, e a hipótese alternativa de que o efeito de pelo menos um dos estudos (θ_i) seja diferente dos outros. A estatística **Q** é gerada pela rotina meta (Sharp & Sterne, 1997, 1998, 1998a) do Stata e apresenta uma distribuição χ^2 em **k** -1 graus de liberdade sob $\mathbf{H_0}$. O fato de não rejeitar a hipótese de homogeneidade geralmente leva à adoção de modelos com efeitos fixos para cada estudo, pois assume-se que os efeitos de cada estudo diferem apenas devido a erros amostrais. Por outro lado, ao ser rejeitada a hipótese de homogeneidade, tende-se a adotar um modelo de efeitos aleatórios que inclui tanto a heterogeneidade dentro de cada estudo e entre os diferentes estudos. Um problema identificado na utilização da estatística Q é o fato de que este teste possui pouco poder para detectar a heterogeneidade entre estudos, quando a meta-análise inclui um número pequeno de estudos e poder muito acentuado para detectar uma variabilidade mínima quando muitos estudos são incluídos na meta-análise (Higgins et al., 2003). Com isso, um resultado não significativo para a estatística Q, quando um pequeno número de estudos tenha sido incluído na meta-análise, pode levar à errônea adoção do modelo de efeitos fixos, apesar de existir heterogeneidade entre estudos, e vice-versa. Além deste problema, a estatística Q não informa a extensão da heterogeneidade real, apenas apresenta sua significância estatística, impedindo com isso uma decisão mais embasada.

Testes baseados apenas em significância estatística para avaliar heterogeneidade costumam ter baixo poder, por dependerem do número e da precisão das estimativas dos estudos. Por esse motivo, decidimos avaliar a heterogeneidade através da utilização da estatística **H** e do índice $\mathbf{I^2}$ propostas recentemente por Higgins & Thompson (2002). A estatística **H** pode ser interpretada

como a razão entre os tamanhos dos intervalos de confiança (IC) obtidos pelo método de efeitos aleatórios e pelo método de efeitos fixos. O índice $\mathbf{I^2}$ descreve a percentagem da variabilidade total que é devida à heterogeneidade (variação entre-estudo). Deste modo, pode-se quantificar o grau de heterogeneidade na Meta-análise. Para esta quantificação, Higgins & Thompson (2002), sugerem que valores de **H** inferiores a 1,2 representariam heterogeneidade leve, valores intermediários entre 1,2 e 1,5, heterogeneidade moderada e, superiores a 1,5, um elevado grau de heterogeneidade. No entanto, estes autores ressaltam o fato de que nenhuma regra universal pode ser definida, e que especificidades de cada estudo e o conhecimento dos pesquisadores acerca do tema estudado devem ser sempre consideradas ao decidir se existe realmente heterogeneidade entre-estudos. Em relação ao índice $\mathbf{I^2}$, valores inferiores a 25% representariam heterogeneidade leve, valores intermediários de 25% a 50% heterogeneidade moderada e, superiores a 75%, um elevado grau de heterogeneidade. De acordo com Higgins & Thompson (2002), uma vantagem do índice $\mathbf{I^2}$ é o fato de que os índices $\mathbf{I^2}$ obtidos através de meta-análises que tenham utilizado diferentes números de estudos e diferentes efeitos são diretamente comparáveis, tornando o impacto e a possibilidade de comparação entre a meta-análise ora realizada e futuras meta-análises que venham a ser publicadas sobre aderência à HAART fatores que influenciaram fortemente nossa decisão em utilizar o índice $\mathbf{I^2}$.

A fórmula abaixo, proposta por Higgins & Thompson (2002) foi utilizada para cálculo da estatística $\mathbf{H^2}$ com o auxílio do programa Stata (StataCorp, 2005):

$\mathbf{H^2 = Q/(k - 1)}$ (onde **Q** é a estatística χ^2 e **k** é o número de estudos)

(caso $\mathbf{Q \leq k - 1}$, atribui-se a **H** o valor unitário, ou seja, $\mathbf{H = 1}$)

Para o cálculo de $\mathbf{I^2}$, foi utilizada a fórmula abaixo, proposta por Takkouche et al. (1999).

$$\mathbf{I^2 = (H^2 - 1) / H^2}$$

Por fim, e ainda levando em conta o baixo poder estatístico do teste Q, a literatura (Sutton et al., 2000) recomenda que seja realizada uma análise exploratória gráfica. Portanto avaliamos também os gráficos (*forest plots*) gerados pela rotina meta (Sharp & Sterne, 1997, 1998, 1998a) do programa Stata (StataCorp, 2005). A posição das estimativas pontuais de efeito, assim como a superposição dos IC foram utilizadas para avaliar a heterogeneidade entre os estudos.

Tabela A.1 - Modelo Básico Utilizado Para Extração de Dados

Fonte	**País**	**Características da amostra**	**N**	**Período do estudo**	**Pagamento pelo tratamento**	**Desenho do estudo**	**Medidas de mensuração**	**Aderência**	**Covariáveis associadas à aderência**
autores, ano		Sexo Raça Idade...			S/N	Survey Caso-controle Coorte	MEMS Auto-relato Arquivo de farmácia	% aderentes entre UD Ponto de corte Período de *recall*	

IV. Metodologia utilizada na análise de sobrevida

IV.1 - *Critérios de inclusão de casos notificados*

Para o presente estudo, foram considerados todos os casos de AIDS notificados entre adultos (18 anos ou mais), entre 01 de janeiro de 2000 e 30 de junho de 2006, nas diferentes bases de dados nacionais, cujas categorias de notificação tenham sido "usuário de drogas injetáveis" (UDI) ou "homossexuais" (HSH). A utilização de bancos de dados nacionais evita viéses comumente encontrados em estudos de base hospitalar ou realizados com amostras de conveniência, os quais só incluem uma parcela da população de pessoas vivendo com HIV/AIDS. O estudo incluiu um total de 28.426 pacientes.

Usuários de drogas injetáveis foram definidos como casos pertencentes à categoria de exposição simples "UDI" e diferentes categorias de exposição múltipla, que incluem os UDI (ex: heterossexual/UDI, bissexual/UDI, homossexual/UDI, etc. Ao todo foram incluídos os seguintes códigos do SINAN-AIDS como casos ocorridos em UDI: 11, 14, 15, 21, 24, 25, 31, 34, 35, 40, 41, 42, 61, 64, 65 e 67), totalizando 12.231 pacientes. Homossexuais foram definidos como casos pertencentes à categoria de exposição simples homossexual, bissexual e diferentes categorias de exposição múltipla que incluem estas práticas sexuais, exceto UDI (ex: Homossexual/hemofílico, bissexual/hemofílico etc. Ao todo foram incluídos os seguintes códigos do SINAN-AIDS como casos ocorridos entre homo/bissexuais: 10, 12, 13, 20, 22, 23, 62, 63), totalizando 16.195 pacientes.

Apenas casos do sexo masculino foram incluídos na análise, uma vez que o percentual de mulheres notificadas na categoria de notificação UDI representa menos de 3% do total de casos.

IV.2 - *Descrição das Bases de Dados*

Em 1993, o Ministério da Saúde implantou o Sistema Nacional de Agravos de Notificação – SINAN, como ferramenta de coleta e processamento de dados dos agravos de notificação compulsória em todo o território nacional. A AIDS tornou-se uma doença de notificação compulsória em 1986.

SINAN-AIDS: Sistema alimentado a partir da notificação de casos confirmados de AIDS, seguindo-se os critérios de definição de casos definidos pelo Ministério da Saúde (Ministério da Saúde, 2006).

SISCEL (Sistema de Controle de Exames Laboratoriais): Sistema que contempla o registro de todos os indivíduos HIV-positivos em acompanhamento laboratorial através do SUS, contando com informações sobre quantificação da carga viral do HIV, contagem de linfócitos T CD4+/CD8+.

SICLOM (Sistema de Controle Logístico de Medicamentos): Registro da dispensação mensal de medicamentos ARV através do SUS, trocas medicamentosas etc.

SIM (Sistema de Informações sobre Mortalidade): Registros oriundos das declarações de óbito.

IV.3 - *Relacionamento entre os diferentes bancos de dados (Linkage)*

As diferentes bases de dados foram integradas através de um processo de relacionamento (*linkage*). Até onde é de nosso conhecimento, a elaboração de uma base de dados única a partir destes diferentes sistemas de informação ainda não foi realizada no Brasil. Análises utilizando estas bases integradas possibilitam uma melhor avaliação do impacto da oferta gratuita e universal de HAART no Brasil, por utilizarem todos os pacientes notificados em âmbito nacional.

Foram utilizados, no relacionamento entre as diferentes bases de dados, procedimentos probabilísticos realizados com auxílio do aplicativo Reclink® versão 3.0 (Camargo Jr. & Coeli, 2002). Tais procedimentos utilizam campos comuns das diferentes bases de dados (ex: nome do paciente, nome da mãe), objetivando com isso identificar, com probabilidades pré-estabelecidas, se os registros pareados pertencem ao mesmo indivíduo. Tais procedimentos permitiram recuperar informações acerca do acompanhamento laboratorial, medicamentoso, categoria de exposição e informações sobre óbitos de todas as PLWHA em acompanhamento através do SUS notificadas durante o período estudado. Os registros resultantes deste *linkage* foram analisados de acordo com o critério de confirmação de casos de AIDS em adultos adotado pelo PN DST/AIDS: indivíduos com 13 anos ou mais registrados no SISCEL/SICLOM que apresentam contagem de linfócitos T-CD4+ abaixo de 350 células/mm^3 (Ministério da Saúde, 2006)

IV.4 - *Análise de sobrevida*

Inicialmente, foi realizada uma análise univariada, com a utilização da técnica não-paramétrica de Kaplan-Meier, de modo a visualizar as curvas de sobrevida dos dois segmentos populacionais. A seguir, foi utilizada modelagem semiparamétrica, com o uso do modelo de riscos proporcionais de Cox (Cox & Oakes, 1984; Carvalho *et al.*, 2005). A premissa de risco relativo constante no tempo foi avaliada por meio da análise de resíduos de Schoenfeld. Utilizando-se o método de Kaplan-Meier, foram geradas curvas de sobrevida gerais e curvas específicas, de acordo com sexo, idade, ano de diagnóstico, categoria de exposição e valor da 1ª contagem de CD4 (abaixo de 100, 100-199; 200-349; 350-499; 500 ou acima). Possíveis diferenças nas curvas de sobrevida foram testadas através do teste de logaritmo de escores (*log-rank*).

Modelos multivariados de sobrevida foram ajustados para pacientes notificados como casos de AIDS nas duas categorias de exposição a serem estudadas (usuários de drogas injetáveis e homossexuais); de forma a identificar as covariáveis de maior relevância na sobrevida destes pacientes. A determinação do efeito independente entre covariáveis selecionadas e o tempo de sobrevida foi avaliado por meio do modelo de riscos proporcionais de Cox estendido. A modelagem foi iniciada com todas as variáveis que se mostraram significativamente associadas ao desfecho na análise univariada ("modelo cheio ou saturado"), seguida da exclusão seqüencial, de acordo com a relevância de cada uma delas para os modelos sucessivamente ajustados. Com o objetivo de avaliar-se a relevância de cada variável na modelagem, utilizou-se o teste de Wald. O pressuposto de riscos proporcionais foi verificado através da avaliação dos resíduos de Schoenfeld do modelo escolhido.

Em seguida, procedeu-se à inclusão de um termo de efeito aleatório (fragilidade) no modelo de Cox anteriormente estimado. As taxas de risco (*harzard rates*) podem ser altamente influenciadas por vícios de seleção que ocorrem no nível populacional (ex: maior disponibilidade de centros de referência em determinado município), e indivíduos que sobrevivem um período maior de tempo tendem a ser menos *frágeis* do que o restante da população (Aalen, 1994; Carvalho *et al.*, 2005). Objetivando levar em conta a grande heterogeneidade existente entre as diferentes regiões do

Brasil e, entre estas regiões, entre os diferentes estados e municípios, as análises multivariadas foram repetidas. Para avaliar um possível viés de sobrevida (ou fragilidade), um termo de efeito aleatório foi incluído no modelo multivariado escolhido no passo anterior. A inclusão deste termo objetivou estudar a associação entre tempo de sobrevida em determinado cluster – estado ou município de residência – utilizando a distribuição gamma de fragilidade (Naskar *et al.*, 2005).

As análises de sobrevida foram realizadas utilizando o *software* R versão 2.5.0 (R Core Development Team, 2004).

V. Descrição adicional do banco de dados e modelos de Cox utilizados no trabalho

Tabela A.2 – Variaveis incluidas nos modelos de Cox estendido

Variavel	Descrição
T_INI	Data do diagnostico de AIDS
T_FIN	Data do óbito ou fim do estudo
STATUS	Censura; óbito por qualquer causa
CD4_CAT2	Primeira contagem de CD4 (<200; 200-350;>350;Unknown)
HAART_S	Inicio de HAART("Never received HAART"; "Received (or is still under) HAART")
LOG_1	Primeiro exame de carga viral para HIV, em $\log_{10}$ (<4.00; 4.00-5.00; >5.00; Unknown)
HIERARF	Categoria de exposição (MSM- men who have sex with men; IDU – injection drug user)
RACA2	Raça (White; Non-white, Unspecified)
IDADE	Idade na data do diagnostico

V.1 - Descrição dos modelos de Cox testados, utilizando processo de contagem e tempo em anos.

```
y<-Surv((dados$T_INI/365.25), ((dados$T_FIN+1)/365.25), dados$STATUS)

anova(mod1,mod1,mod3,mod4,mod5,mod6,mod7,test="Chisq")
Analysis of Deviance Table

Model 1: y ~ 1
Model 2: y ~ CD4_CAT2
Model 3: y ~ CD4_CAT2 + HAART_S
Model 4: y ~ CD4_CAT2 + HAART_S + LOG_1
Model 5: y ~ CD4_CAT2 + HAART_S + LOG_1 + HIERARF
Model 6: y ~ CD4_CAT2 + HAART_S + LOG_1 + HIERARF + RACA2
Model 7: y ~ CD4_CAT2 + HAART_S + LOG_1 + HIERARF + RACA2 + IDADE
  Resid. Df Resid. Dev    Df Deviance  P(>|Chi|)
1     28426     126637
2     28423     121656     3     4982          0
3     28422     121450     1      205  1.537e-46
4     28419     121305     3      145  3.080e-31
5     28418     120797     1      508 1.438e-112
6     28416     120265     2      532 2.655e-116
7     28415     120043     1      222  3.679e-50
```

Modelo escolhido para Cox estendido:

y ~ CD4_CAT2 + HAART_S + LOG_1 + HIERARF + RACA2 + IDADE

V.2 - nclusão de termo aleatório no modelo escolhido: fragilidade por estado de residência

```
mod.frag<-
coxph(y~CD4_CAT2+HAART_S+LOG_1+HIERARF+RACA2+IDADE+frailty(UFRES,method="aic",di
st="gauss"),data=dados,x=T)
summary(mod.frag)
Call:
coxph(formula = y ~ CD4_CAT2 + HAART_S + LOG_1 + HIERARF + RACA2 + IDADE +
frailty(UFRES, method = "aic", dist = "gauss"), data = dados, x = T)

  n= 28426
                          coef    se(coef) se2     Chisq DF   p
CD4_CAT2[T.200-350]       -1.1792 0.08311  0.08311 201.3  1.0 0.0e+00
CD4_CAT2[T.> 350]         -1.1910 0.08052  0.08052 218.8  1.0 0.0e+00
CD4_CAT2[T.Unknown]        0.8708 0.05943  0.05942 214.7  1.0 0.0e+00
HAART_S[T.Received (or is -0.6937 0.05853  0.05852 140.4  1.0 0.0e+00
LOG_1[T.4.00 - 5.00]       0.3627 0.07827  0.07827  21.5  1.0 3.6e-06
LOG_1[T.> 5.00]            0.8701 0.07692  0.07691 128.0  1.0 0.0e+00
LOG_1[T.Unknown]           0.5120 0.06931  0.06931  54.6  1.0 1.5e-13
HIERARF[T.IDU]             0.6651 0.02758  0.02754 581.6  1.0 0.0e+00
RACA2[T.Non-white]         0.2527 0.03706  0.03701  46.5  1.0 9.2e-12
RACA2[T.Unspecified]      -0.5854 0.03049  0.03048 368.6  1.0 0.0e+00
IDADE                      0.0221 0.00142  0.00142 242.4  1.0 0.0e+00
frailty(UFRES, method = "                          476.4 25.7 0.0e+00

                          exp(coef) exp(-coef) lower .95 upper .95
CD4_CAT2[T.200-350]           0.308      3.252     0.261     0.362
CD4_CAT2[T.> 350]             0.304      3.290     0.260     0.356
CD4_CAT2[T.Unknown]           2.389      0.419     2.126     2.684
HAART_S[T.Received (or is     0.500      2.001     0.446     0.560
LOG_1[T.4.00 - 5.00]          1.437      0.696     1.233     1.675
LOG_1[T.> 5.00]               2.387      0.419     2.053     2.776
LOG_1[T.Unknown]              1.669      0.599     1.457     1.911
HIERARF[T.IDU]                1.945      0.514     1.842     2.053
RACA2[T.Non-white]            1.287      0.777     1.197     1.384
RACA2[T.Unspecified]          0.557      1.796     0.525     0.591
IDADE                         1.022      0.978     1.020     1.025

Iterations: 3 outer, 12 Newton-Raphson
     Variance of random effect= 0.55
Degrees of freedom for terms=  3.0  1.0  3.0  1.0  2.0  1.0 25.7
Rsquare= 0.219   (max possible= 0.988 )
Likelihood ratio test= 7011  on 36.7 df,   p=0
Wald test            = 4373  on 36.7 df,   p=0
```

V.3 - Inclusão de termo aleatório no modelo escolhido: fragilidade por município de residência

```
mod.frag.1<-
coxph(y~CD4_CAT2+HAART_S+LOG_1+HIERARF+RACA2+IDADE+frailty(MUNIC_RE,method="aic"
,dist="gauss"),data=dados,x=T)
summary(mod.frag.1)
Call:
coxph(formula = y ~ CD4_CAT2 + HAART_S + LOG_1 + HIERARF + RACA2 + IDADE +
frailty(MUNIC_RE), data = dados, x = T)

  n= 28426
                           coef    se(coef) se2     Chisq  DF  p
CD4_CAT2[T.200-350]       -1.1983 0.08365  0.08336  205.2   1 0.0e+00
CD4_CAT2[T.> 350]         -1.1937 0.08117  0.08086  216.3   1 0.0e+00
CD4_CAT2[T.Unknown]        0.9755 0.06043  0.05985  260.6   1 0.0e+00
HAART_S[T.Received (or is -0.7430 0.05943  0.05892  156.3   1 0.0e+00
LOG_1[T.4.00 - 5.00]       0.3870 0.07919  0.07873   23.9   1 1.0e-06
LOG_1[T.> 5.00]            0.9004 0.07820  0.07764  132.6   1 0.0e+00
LOG_1[T.Unknown]           0.5359 0.07050  0.07004   57.8   1 2.9e-14
HIERARF[T.IDU]             0.6257 0.02841  0.02786  485.0   1 0.0e+00
RACA2[T.Non-white]         0.2947 0.03803  0.03734   60.1   1 9.2e-15
RACA2[T.Unspecified]      -0.5846 0.03200  0.03151  333.7   1 0.0e+00
IDADE                      0.0238 0.00148  0.00146  260.5   1 0.0e+00
frailty(MUNIC_RE)                                  2398.3 521 0.0e+00

                          exp(coef) exp(-coef) lower .95 upper .95
CD4_CAT2[T.200-350]           0.302      3.315     0.256     0.355
CD4_CAT2[T.> 350]             0.303      3.299     0.259     0.355
CD4_CAT2[T.Unknown]           2.653      0.377     2.356     2.986
HAART_S[T.Received (or is     0.476      2.102     0.423     0.534
LOG_1[T.4.00 - 5.00]          1.473      0.679     1.261     1.720
LOG_1[T.> 5.00]               2.461      0.406     2.111     2.868
LOG_1[T.Unknown]              1.709      0.585     1.488     1.962
HIERARF[T.IDU]                1.870      0.535     1.768     1.977
RACA2[T.Non-white]            1.343      0.745     1.246     1.447
RACA2[T.Unspecified]          0.557      1.794     0.523     0.593
IDADE                         1.024      0.976     1.021     1.027

Iterations: 10 outer, 61 Newton-Raphson
     Variance of random effect= 0.504   I-likelihood = -59643.8
Degrees of freedom for terms=   3.0   1.0   3.0   1.0   1.9   1.0 521.2
Rsquare= 0.265   (max possible= 0.988 )
Likelihood ratio test= 8756  on 532 df,   p=0
Wald test            = 4543  on 532 df,   p=0
```

VI. Análise do ajuste do modelo de Cox selecionado

Para analisar o ajuste do modelo multivariado de Cox escolhido, foram analisados os resíduo s de Schoenfeld. Esta análise objetiva avaliar se o pressuposto de que o efeito de uma covariável é sempre o mesmo durante todo o tempo de observação foi violado (Carvalho et al., 2005). O estudo dos resíduos de Schoenfeld permite estimar a proporcionalidade do risco ao longo do tempo dos preditores inseridos em modelos de risco proporcionais de Cox. Estes resíduos são definidos como a diferença entre os valores das covariáveis do individuo 'i' e a média ponderada das covariáveis x do grupo sob risco no tempo ti. Ou seja, o resíduo de Schoenfeld é a diferença entre os valores observados e os valores esperados de covariáveis de um indivíduo, de acordo com a fórmula:

$$r_i(\beta) = x_i - \frac{\sum_{j \in R(t_i)} x_j \exp(x_j \beta)}{\sum_{j \in R(t_i)} \exp(x_j \beta)}$$

Na qual:
***j* representa cada indivíduo**
***i* (*i*=1,...,m) o índice dos tempos observados de eventos.**

O gráfico dos resíduos são plotados versus o tempo, e podem estar dispostos em escala linear, logarítmica ou a raiz quadrada e revelaram desvios do postulado de riscos proporcionais. Assim, testa-se se o comportamento da covariável é constante ao longo do tempo. A interpretações dos resíduos de Schoenfeld e as estatísticas rho, quiquadrado e o *p*-valor, estas três últimas provenientes da saída do comando 'cox.zph' do pacote estatístico R, prestam-se a avaliar o comportamento da variável inserida no modelo quanto à observância do pressuposto de proporcionalidade de risco.

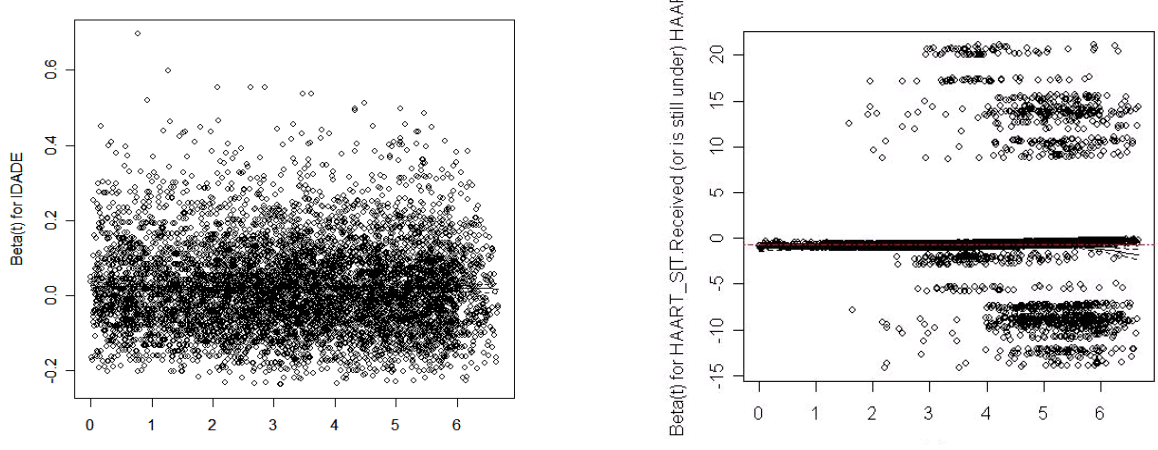
Tabela A.3 - Estatísticas relacionadas à análise do pressuposto de proporcionalidade de risco no modelo multivariado de Cox escolhido

	Rho	**χ^2**	**p-valor**
CD4 (200-350)	-0,00424	0,124	0,7250000
CD4 (> 350)	0,02251	3,481	0,0621000
CD4 (Desconhecido)	-0,13010	144,164	0
HAART (iniciou HAART após diagnóstico de AIDS)	0,00672	0,328	0,5670000
Carga Viral para HIV Log_{10}(4.00 - 5.00)	-0,01254	1,062	0,3030000
Carga Viral para HIV Log_{10}(> 5.00)	-0,03154	6,681	0,0097400
Carga Viral para HIV (Desconhecida)	-0,05762	23,146	0,0000015
UDI	0,04663	14,683	0,0001270
Raça (Não-brancos)	0,01071	0,775	0,3790000
Raça (Desconhecida)	-0,14690	131,120	0
IDADE	-0.00682	0.319	0,5720000
GLOBAL	NA	992.977	0

Ao analisar os valores de rho para cada variável, avaliados em conjunto com os valores da estatística quiquadrado e o p-valor, nota-se que nenhuma categoria das variáveis incluídas no modelo escolhido apresenta violação ao pressuposto de proporcionalidade do modelo de Cox. A análise visual dos resíduos de Shoenfeld para cada uma das covariáveis incluídas no modelo multivariado de Cox escolhido segue-se abaixo, com uma breve interpretação de cada gráfico.

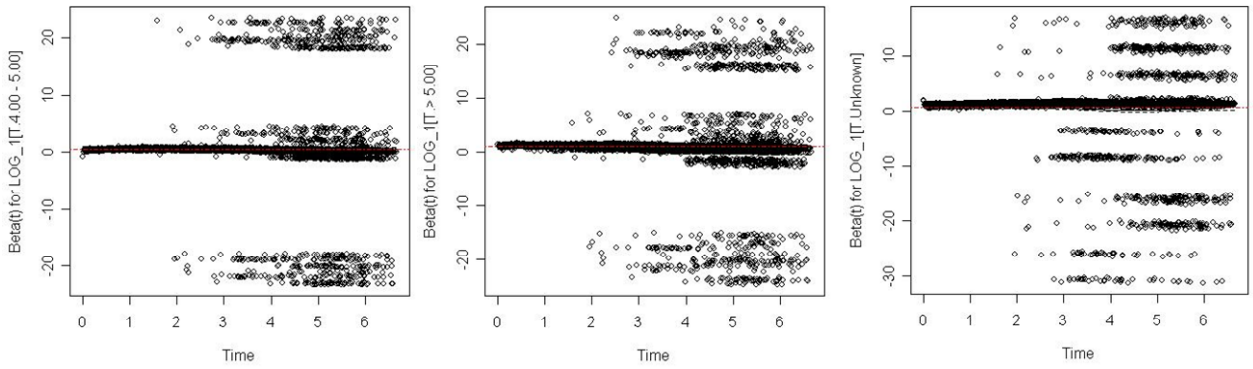
Com relação às covariáveis "idade" (na data do diagnóstico de AIDS) e "HAART" ('Nunca utilizou HAART' vs. 'Utilizou ou ainda está em uso de HAART') não foi observada nenhuma tendência, conforme a visualização dos gráficos abaixo:

Gráfico A.1 – Resíduos de Schoenfeld das variáveis "idade" e "HAART"



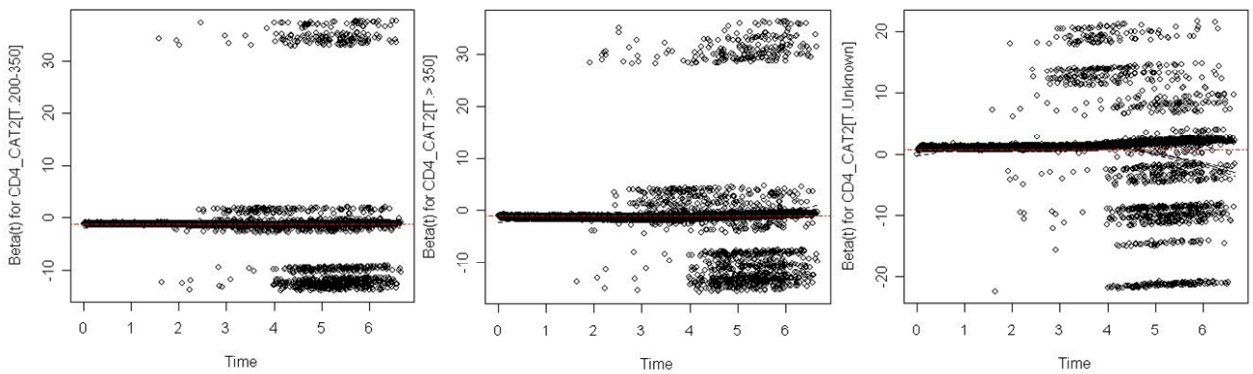
Com relação às categorias de Log_{10} da Carga Viral, após a análise visual dos gráficos também não foi observada nenhuma tendência ao longo do tempo, análise consistente com os resultados apresentados na Tabela 1.

Gráfico A.2 – Resíduos de Schoenfeld da variável Log_{10} da Carga Vira (4.00-5.00; >5.00; desconhecida)



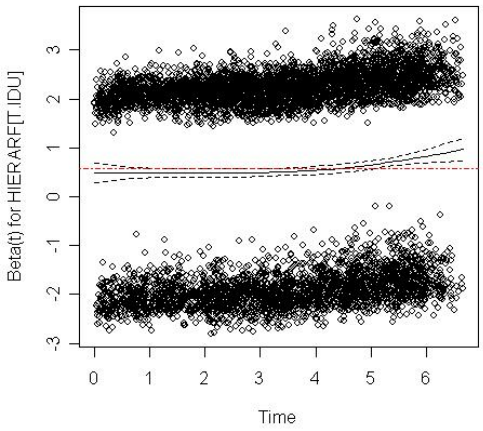
Com relação à covariável "primeira mensuração de CD4 após o diagnóstico de AIDS", apenas o efeito da categoria "Contagem de CD4 desconhecida" apresenta modificação visível ao longo do tempo – decrescente (terceira figura). Ou seja, parece que o número de pacientes que nunca fizeram um exame de contagem de CD4 vai diminuindo ao longo do tempo, resultados concistentes com os valores da estatística quiquadrado e p-valor apresentados para esta categoria (Tabela 1). No entanto, decidimos não realizar nenhuma transformação nesta variável, pois as outras categorias da mesma variável não apresentavam tendência nenhuma.

Gráfico A.3 – Resíduos de Schoenfeld da variável 1ª Contagem de CD4 (200-350; >350; desconhecida)



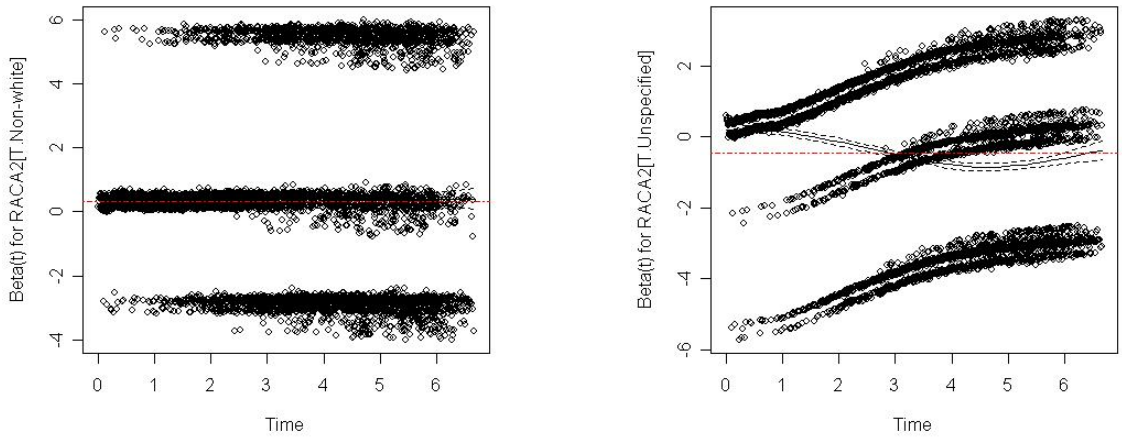
Após a análise visual do gráfico, é possível percebermos que efeito da categoria de exposição UDI parece ser um pouco diferente apenas no final do período. Esta categoria apresenta o maior valor de rho apresentado, no entanto este ainda é um valor pequeno (0,046), portanto decidimos não realizar nenhuma transformação nesta variável.

Gráfico A.4 – Resíduos de Schoenfeld da Categoria de exposição UDI



Com relação à variável raça, apenas o efeito da categoria "Raça desconhecida" no final do período de observação parece ser diferente do início do período, tendo efeito oscilatório, e as curvas do intervalo de confiança não incluem o zero. Estes resultados são concistentes com os valores da estatística quiquadrado e p-valor apresentados para esta categoria (Tabela 1). No entanto, decidimos não realizar nenhuma transformação nesta variável, pois as outras categorias da mesma variável não apresentavam tendência nenhuma.

Gráfico A.5 – Resíduos de Schoenfeld da variável Raça ("Não Brancos" e "Raça desconhecida")



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