Ministério da Saúde
FIOCRUZ
Fundação Oswaldo Cruz

ESCOLA NACIONAL DE SAÚDE PÚBLICA
SERGIO AROUCA
ENSP

Lara Esteves Coelho

# Hospitalizações e readmissão hospitalar em 30 dias na coorte de pacientes infectados pelo HIV do Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz), no período de 2007 a 2013.

Rio de Janeiro
2016

Lara Esteves Coelho

# Hospitalizações e readmissão hospitalar em 30 dias na coorte de pacientes infectados pelo HIV do Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz), no período de 2007 a 2013.

Tese apresentada ao Programa de Pós-graduação em Epidemiologia em Saúde Pública da Escola Nacional de Saúde Pública Sergio Arouca, na Fundação Oswaldo Cruz, como requisito parcial para obtenção do título de Doutor em Ciências.

Orientadora: Profa. Dra. Paula Mendes Luz

Rio de Janeiro

2016

Catalogação na fonte
Fundação Oswaldo Cruz
Instituto de Comunicação e Informação Científica e Tecnológica
Biblioteca de Saúde Pública

C672h Coelho, Lara Esteves
Hospitalizações e readmissão hospitalar em 30 dias na coorte de pacientes infectados pelo HIV do Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz), no período de 2007 a 2013. / Lara Esteves Coelho. -- 2016.
108 f. : tab.

Orientadora: Paula Mendes Luz.
Tese (Doutorado) – Fundação Oswaldo Cruz, Escola Nacional de Saúde Pública Sergio Arouca, Rio de Janeiro, 2016.

1. HIV. 2. Hospitalização. 3. Readmissão do Paciente. 4. Tempo de Internação. 5. Mortalidade Hospitalar. I. Título.

CDD – 22.ed. – 614.5993

Lara Esteves Coelho

# Hospitalizações e readmissão hospitalar em 30 dias na coorte de pacientes infectados pelo HIV do Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz), no período de 2007 a 2013.

Tese apresentada ao Programa de Pós-graduação em Epidemiologia em Saúde Pública da Escola Nacional de Saúde Pública Sergio Arouca, na Fundação Oswaldo Cruz, como requisito parcial para obtenção do título de Doutor em Ciências.

Aprovada em 28 de novembro de 2016.

Banca Examinadora:

Prof. Dr. Antônio Guilherme Pacheco
PROCC/FIOCRUZ

Prof. Dr. Francisco Inácio Pinkusfeld Monteiro Bastos
ICICT/FIOCRUZ

Prof. Dr. Fernando Augusto Bozza
INI/FIOCRUZ

Profa. Dra. Sandra Wagner Cardoso
INI/FIOCRUZ

Profa. Dra. Paula Mendes Luz (orientadora)
INI/FIOCRUZ

Rio de Janeiro

2016

Dedico este trabalho a Rodrigo Amâncio.

## AGRADECIMENTOS

Aos meus pais, Cida e Carlos, e a minha irmã, Bruna, pelo apoio irrestrito.

À minha orientadora, Profª. Paula Mendes Luz, pelos ensinamentos e pela paciência ao longo de todos esses anos.

A Profª Beatriz Grinztejn e Profª Valdilea Veloso pela contribuição intelectual na idealização desse projeto.

A Dra. Sandra Wagner por todo apoio durante a realização dessa tese.

A Dra. Sayonara Ribeiro, importante colaboradora deste projeto.

A toda equipe do banco de dados da Coorte do INI, Ronaldo Ismerio Moreira, Mario Sergio Pereira, Flaviana Victoriano, sempre prontos a ajudar.

A Priscila Lara que auxilio na revisão das hospitalizações.

Ao Dr. Andre Japiassu (Laboratório de Pesquisa Clínica em Terapia Intensiva do INI/FIOCRUZ) que contribui na execução desse projeto.

Aos membros da banca, Profª Sandra Wagner Cardoso, Prof. Fernando Augusto Bozza, Prof. Francisco Inácio Pinkusfeld Monteiro Bastos, Prof. Dr. Antônio Guilherme Pacheco, Prof. Andre Japiassu.

## RESUMO

**Introdução:** A despeito do progresso obtido com a introdução da terapia antirretroviral de alta potência, pacientes infectados pelo HIV apresentam elevadas taxas de hospitalização e risco aumentado de readmissão em 30 dias, quando comparados à população geral. **Artigo 1:** Avaliação das taxas de hospitalização, tempo de internação e mortalidade hospitalar dos pacientes infectados pelo HIV da coorte do Instituto Nacional de Infectologia (INI/Fiocruz), 2000-2013. Foram incluídos 3991 pacientes, somando 1861 hospitalizações (taxa de hospitalização de 10,44/100 pessoas-ano). As taxas de hospitalização, o tempo de internação e a mortalidade hospitalar diminuíram ao longo dos anos. **Conclusões:** A tendência temporal de diminuição das taxas de hospitalização acoplada à inversão das causas (causas não relacionadas a Aids superando as causas Aids no último período do estudo) apontam para modificações no padrão de morbidade dos pacientes infectados pelo HIV. Essas mudanças sugerem um desafio para os serviços de saúde que tratam de pacientes infectados pelo HIV, já que estes precisam estar preparados para o atendimento de pacientes doenças crônicas não diretamente relacionadas ao HIV. **Artigo 2**: Revisão sistemática e metanálise sobre readmissão em pacientes infectados pelo HIV. Sete publicações foram incluídas na revisão sistemática e 5 na metanálise. A taxa de readmissão em 30 dias agregada foi de 19%. Modelos de meta-regressão foram limitados pelo baixo número de estudos e análises de subgrupos não explicaram a heterogeneidade encontrada. **Conclusões:** O desfecho readmissão em 30 dias em pacientes infectados pelo HIV é pouco explorado e novos estudos são necessários para elucidar o efeito de variáveis relacionadas ao HIV/Aids no risco de readmissão. **Artigo 3:** Taxas de readmissão em 30 dias foram estimadas para os pacientes infectados pelo HIV da coorte do INI/Fiocruz no período de 2007-2013. Modelos de Cox foram utilizados para avaliar fatores associados com o risco de readmissão em 30 dias. A taxa de readmissão foi estimada em 14%. Consulta médica precoce pós alta, hospitalizações em anos mais recentes e uso de terapia antirretroviral reduziram o risco de readmissão. Hospitalização por Aids, CD4 baixo, infecção pelo HIV há mais de 10 anos e alta hospitalar à revelia aumentaram o risco de readmissão. **Conclusão:** Diagnóstico precoce da infecção pelo HIV e início precoce de terapia antirretroviral, combinados com consulta médica pós alta podem reduzir as taxas de readmissão em 30 dias em nossa população.



**Palavras-chave:** HIV, hospitalização, readmissão hospitalar, tempo de internação, mortalidade hospitalar.

## ABSTRACT

**Introduction**: Despite the progress achieved with the introduction of highly active antiretroviral therapy, HIV-infected patients have higher rates of hospitalization and increased risk of readmission within 30 days when compared to the general population. **Article 1:** Evaluation of hospitalization rates, length of stay and in-hospital mortality in HIV infected patients from Instituto Nacional de Infectologia (INI/Fiocruz), from 2007 until 2013. Among the 3991 patients included, 1861 hospitalizations occurred (hospitalization rate of 10.44 / 100 person-years). Hospitalization rates, length of stay and in-hospital mortality decreased over the years. **Conclusion:** Hospitalization rates were reduced during the study and non-AIDS related hospitalizations surpassed AIDS related ones in the last years of observation period. This shift represents a challenge for HIV in-patient care, since the presence of multiple chronic conditions complexity the clinical management of HIV infected patients. **Article 2:** Systematic review and meta-analysis on readmission in patients with HIV infection. Seven publications were included in the systematic review and 5 in the meta-analysis. The pooled 30-day readmission rate was 19%. Meta-regression models were limited by the small number of studies and subgroup analyzes did not explain the heterogeneity found. **Conclusions:** 30-day readmission in HIV-infected patients is still poorly explored, and further studies are needed to elucidate the role of HIV specific variables on the risk of readmission. **Article 3:** 30-day readmission rates were estimated for HIV-infected patients in the INI/Fiocruz cohort in the period 2007-2013. Predictors of readmission were evaluated trough Cox regression models. 30-day readmission rate was 14%. Early medical visit post discharge, admissions in the most recent calendar years and use of antiretroviral therapy reduced the risk of readmission. Hospitalization for AIDS, lower CD4, HIV infection for more than 10 years, and discharge in absentia increased risk of readmission. **Conclusion:** Early HIV diagnosis and early antiretroviral initiation, combined with a post-discharge medical visit can reduce 30-day readmission risk in our population.



**Keywords:** HIV, hospitalization, readmission, length of stay, in-hospital mortality.

## LISTA DE ILUSTRAÇÕES

**Artigo 2**



**Artigo 3**

## LISTA DE TABELAS

## LISTA DE ABREVIATURAS

| | |
|---|---|
| Aids/AIDS | Síndrome da Imunodeficiência Adquirida*; Acquired Immunodeficiency Syndrome* |
| aHR | Razão de risco ajustada*; Adjusted hazard ratio*; |
| ART/cART | Terapia antirretroviral combinada; *Combined antiretroviral treatment* |
| CDC | *Centers for Disease Control and Prevention* |
| CCASAnet | *Caribbean, Central and South America network for HIV epidemiology* |
| CD4 | *CD4 + T cells*; Linfócitos T CD4+ |
| CID-10/ICD-10 | Classificação Internacional de Doenças - 10ª edição; *10th Edition of the International Classification of Disease* |
| CNPq | Conselho Nacional de Desenvolvimento Científico e Tecnológico; |
| CoDe | *Coding of Death in HIV* |
| CVD | Doença cardiovascular; *Cardiovascular disease* |
| CTI/ICU | Centro de terapia intensiva; *Intensive care unit* |
| ENSP | Escola Nacional de Saúde Pública Sérgio Arouca |
| EUA/USA | Estados Unidos da América; *United States of America*; |
| FAPERJ | Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro; |
| Fiocruz/FIOCRUZ | Fundação Oswaldo Cruz |
| HCV | Vírus da Hepatite C; *Hepatites C virus* |
| HI | Hospitalização índice |
| HIV | Vírus da Imunodeficiência Humana; *Human Immunodeficiency Virus* |
| HIVRN | *HIV Research Network* |
| HOPS | *HIV Outpatient Study* |
| IC/CI | Intervalo de confiança; *confidence interval* |
| IDU | Usuário de Drogas Injetáveis; *Injection drug users* |
| leDEA | *International Epidemiologic Databases to Evaluate AIDS* |
| INI | Instituto Nacional de Infectologia Evandro Chagas |
| IPEC | Instituto de Pesquisa Clínica Evandro Chagas |
| IQR | Intervalo interquatil*; Interquartile range* |

| | |
|---|---|
| IRIS | Síndrome inflamatória de reconstituição imune*; Immune reconstitution inflammatory syndrome* |
| IRR | Razão de taxas de incidência; *Incidence rates ratio* |
| LOS | Tempo de internação*; length of stay* |
| MSM | Homens que fazem sexo com homens; *Men who have sex with men* |
| NIH | *National Institutes of Heath* |
| PRISMA | *Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement* |
| PY | Pessoas-ano; *Person-years* |
| SD | Desvio padrão*; Standard deviation* |
| uHR | Razão de risco não ajustada*; Unadjusted hazard ratio*; |

**SUMÁRIO**

# 1 INTRODUÇÃO

A síndrome da imunodeficiência adquirida (*Acquired Immunodeficiency Syndrome* - Aids) foi descrita em 1981, a partir de uma série de casos de pneumonia por *Pneumocystis jirovecci* e de Sarcoma de Kaposi acometendo homens que faziam sexo com homens nos Estados Unidos da América (EUA) (CENTER FOR DISEASES CONTROL, 1981; HYMES et al., 1981). Trinta anos após seus primeiros casos, o HIV/Aids ainda figura como uma das principais causas de morte no mundo, sendo responsável por 1,1 milhão de mortes somente no ano de 2015 (UNAIDS, 2016). Atualmente, 36,7 milhões de pessoas estão infectadas pelo HIV no mundo e 2,1 milhões de novos casos foram identificados somente no último ano (UNAIDS, 2016). No Brasil, do início da epidemia até o ano de 2015, foram identificados 798.366 casos de Aids e 290.929 óbitos relacionados ao HIV/Aids (MINISTÉRIO DA SAÚDE, 2015). A prevalência de Aids na população geral é baixa (0,39%) (MINISTÉRIO DA SAÚDE, 2015), no entanto a epidemia HIV/Aids no Brasil se caracteriza por ser uma epidemia concentrada, com elevada prevalência em alguns subgrupos populacionais como usuários de drogas (23,1%), homens que fazem sexo com homens (13,6%) e mulheres profissionais do sexo (6,2%) (MALTA et al., 2010).

Do início da epidemia, até 1987, quando a zidovudinda (AZT) foi aprovada pela agência norte-americana *Food and Drug Administration* (FDA, órgão responsável pela aprovação e controle de medicamentos) para tratamento dos pacientes com Aids (FISCHL et al., 1987), as estratégias terapêuticas para pacientes infectados pelo HIV eram baseadas no tratamento de doenças oportunistas e no uso de profilaxias para algumas dessas doenças (GORDIN et al., 1984; CENTERS FOR DISEASES CONTROL, 1989). O uso de profilaxias para doenças oportunistas, o melhor manejo clínico dos pacientes infectados pelo HIV e o uso de drogas antirretrovirais resultaram em diminuição significativa da morbimortalidade dos pacientes com HIV/AIDS a partir do início da década de 1990 (MOORE et al., 1991; GRAHAN et al., 1992; KAPLAN et al., 2000).

O ano de 1996 foi um marco histórico na epidemia de HIV/Aids. Nesse ano, a agência norte-americana *Food and Drug Administration* (órgão responsável pela aprovação e controle de medicamentos) aprovou o uso dos primeiros inibidores da protease (saquinavir, indinavir e ritonavir) e da nevirapina (primeiro inibidor não nucleosídeo da transcriptase reversa), resultando no advento da terapia antirretroviral de alta potência (ART). Como resultado, pela primeira vez na

história da epidemia, em 1996 foi observado declínio no número de novos casos de Aids nos EUA (CENTER FOR DISEASES CONTROL, 2001).

No Brasil, a ART foi disponibilizada de forma gratuita e universal pelo Ministério da Saúde a partir de 1996. As indicações do uso de ART em pacientes infectados pelo HIV evoluíram desde sua introdução, e desde 2013, o Ministério da Saúde Brasileiro adotou a estratégia de recomendar ART para todos os indivíduos infectados pelo HIV a despeito de suas contagens de linfócitos CD4 (*test and treat strategy*) (MINISTÉRIO DA SAÚDE, 2013). Apesar da recomendação "universal" de ART, no ano de 2014, somente 83% dos indivíduos infectados pelo HIV no Brasil tinham conhecimento do seu status sorológico e somente 52% estavam em uso de ART (MINISTÉRIO DA SAÚDE, 2015).

A introdução e o uso difundido da ART resultaram em redução da incidência de doenças oportunistas e da mortalidade dos indivíduos infectados pelo HIV (BUCHACZ et al., 2010; MOCROFT et al., 2000; PALELLA JR et al., 2006). Como consequência, foi observado aumento da expectativa de vida, envelhecimento e aumento da incidência e prevalência de doenças crônicas nessa população (BUCHACZ et al., 2010; LONG et al., 2008; PACHECO et al., 2009).

A redução da incidência de doenças oportunistas foi observada tanto em países de alta renda quanto em países de baixa renda (BUCHACZ et al., 2010; ROJANAWIWAT et al., 2011). Na coorte multicêntrica EuroSIDA (que inclui 51 centros na Europa e Israel), a taxa de incidência de doenças oportunistas foi reduzida de 30,7/100 pessoas-ano em 1994 para 2,5/100 pessoas-ano em 1998 (MOCROFT et al., 2000). No Brasil, estudo conduzido na coorte do Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz) observou uma redução da incidência de doenças oportunistas de 29,5/100 pessoas-ano em 1987-1990 para 3,5/100 pessoas-ano em 2009-2012 (COELHO et al., 2014).

As taxas de mortalidade também diminuíram significativamente após a introdução da ART em países de alta e baixa renda (BRAITSTEIN et al., 2006; PACHECO et al., 2009; PALELLA et al., 1998). Na coorte multicêntrica *HIV Outpatient Study* (HOPS), que inclui 9 centros nos EUA, a taxa de mortalidade dos pacientes infectados pelo HIV foi reduzida de 29,4/100 pessoas-ano em 1995 para 8,8/100 pessoas-ano em 1997 (PALELLA et al., 1998). Nessa mesma coorte, a taxa de mortalidade se manteve em queda até os anos mais recentes (7/100 pessoas-ano em 1996 *versus* 1,3/100 pessoas-ano em 2004) (PALELLA JR et al., 2006). No Brasil, na coorte do INI/Fiocruz, a

taxa de mortalidade da população infectada pelo HIV foi reduzida de 9,19/100 pessoas-ano no período de 1986-1991 para 1,35/100 pessoas-ano em 2007-2009 (GRINSZTEJN et al., 2013). Outro estudo brasileiro, que incluiu somente homens que fazem sexo com homens, observou que as taxas de mortalidade diminuíram ao longo dos anos que seguiram a introdução da ART, e indivíduos diagnosticados com Aids no período de 2005-2008 tiveram um risco de morte 50% inferior do que aqueles diagnosticados em 1998-2001 (*hazard ratio*: 0,51, intervalo de confiança de 95% [IC95%]: 0,48-0,55) (MALTA et al., 2015).

Assim, ao diminuir a incidência de doenças oportunistas e a mortalidade (principalmente por doenças relacionadas à Aids), a ART permitiu que a população infectada pelo HIV envelhecesse e experimentasse uma mudança no seu perfil de morbimortalidade. Em estudo multicêntrico conduzido na França no período de 1997-2005 demonstrou-se que indivíduos infectados pelo HIV em uso de ART, com carga viral persistentemente indetectável e contagem de CD4 acima de 500/mm³ por mais de seis anos, apresentam a mesma chance de morte que a população geral (LEWDEN et al., 2007). Esse resultado foi corroborado por estudo conduzido na coorte dinamarquesa, de base populacional (*Danish HIV Cohort Study*), no período de 1995-2005, que estimou sobrevida mediana superior a 35 anos para adultos jovens diagnosticados com a infecção pelo HIV no período pós ART (LOHSE et al., 2007). O incremento da expectativa de vida da população infectada foi acompanhado por aumento da prevalência de doenças crônicas associadas ao envelhecimento destes indivíduos (CARDOSO et al., 2013). Indivíduos infectados pelo HIV apresentam risco aumentado (e mais precoce, em relação à população geral) de desenvolver doenças cardiovasculares, neoplasias não associadas à Aids, osteoporose, demência, fibrose e cirrose hepáticas, insuficiência renal e doenças hematológicas (NEGIN et al., 2012). Esse fenômeno tem reflexo nas estatísticas de mortalidade e, nos últimos anos, tem sido observado na população infectada pelo HIV uma tendência de inversão das causas de óbito, com aumento da proporção de óbitos por doenças não relacionadas ao HIV e redução dos óbitos por doenças oportunistas (ANTIRETROVIRAL THERAPY COHORT COLLABORATION., 2010; PACHECO et al., 2009).

## HOSPITALIZAÇÕES NA POPULAÇÃO INFECTADA PELO HIV

A introdução da ART foi associada à redução das taxas de hospitalização de pacientes infectados pelo HIV. Dados do *Cornell Medical Center* (Nova York, EUA) mostram uma redução superior à 50% nas taxas de hospitalização da população infectada pelo HIV após a introdução da ART, de 60,4/100 pessoas-ano em 1995 para 28,8/100 pessoas-ano em 1997 (PAUL et al., 1999). Na coorte HOPS, essa taxa foi reduzida de 24,6/100 pessoas-ano em 1994 para 11,5/100 pessoas-ano em 2005 (BUCHACZ et al., 2008). O impacto da ART nas hospitalizações também foi evidenciado em países de baixa renda. Em estudo conduzido na África subsaariana (*Africa Centre population-based cohort*) no período de 2009-2012, o uso de ART se relacionou com redução na taxa de hospitalização de 12,8/100 pessoas-ano para 8,2/100 pessoas-ano (HONTELEZ et al., 2016).

A redução da incidência de doenças oportunistas foi acompanhada por diminuição de hospitalizações por essas causas. Estudo da coorte HOPS demonstrou que, as infecções oportunistas respondiam por 31% das hospitalizações no período de 1994-1996 e por somente 9,5% em 2003-2005, com taxas de hospitalização de 7,59/100 pessoas-ano e 0,97/100 pessoas-ano, respectivamente (BUCHACZ et al., 2008). Por outro lado, o envelhecimento da população infectada pelo HIV e o aumento da prevalência de doenças crônicas (HASSE et al., 2011) se associou ao aumento gradual das hospitalizações por doenças não relacionadas ao HIV/Aids (BERRY et al., 2012; BUCHACZ et al., 2008; CRUM-CIANFLONE et al., 2010). Essa tendência fica evidente no estudo de Berry e colaboradores com pacientes da coorte multicêntrica HIV *Research Network (*HIVRN, que inclui 12 centros no EUA) no período de 2001-2008. Os autores mostraram que enquanto a taxa de hospitalização por doenças relacionadas a Aids foi reduzida na ordem de 0,89 por ano (razão de taxas de incidência, IC95%: 0,87-0,91), a taxa de hospitalização por doenças cardiovasculares teve um incremento anual de 1,07 (IC95%: 1,03-1,11). Outro achado relevante nesse estudo foi que as infecções não relacionadas à Aids representaram a principal causa de hospitalização (BERRY et al., 2012).

Ford e colaboradores conduziram uma metanálise que agregou dados de 106 diferentes coortes de pacientes infectados pelo HIV, publicados entre 2007 e 2015. Nessa metanálise, as doenças relacionadas à Aids foram responsáveis por 46% das hospitalizações em adultos infectados pelo HIV (IC95%: 40%-53%), seguida pelas infecções bacterianas (com 31% das hospitalizações, IC95%: 20%-42%). No entanto, foi observada ampla variação geográfica das principais causas de hospitalização. Enquanto que em países do oeste do Pacífico, do leste do Mediterrâneo, do oeste

da Ásia e da África, as hospitalizações por Aids representavam a principal causa de hospitalização (com 79%, 68%, 66%, 63% das hospitalizações, respectivamente) nos países da Europa (31%), Américas do Norte (28%) e Sul (40%) essa proporção é significativamente menor. Nessas ultimas regiões, as hospitalizações por doenças bacterianas assumem posição de destaque representando 27%, 27% e 57% das hospitalizações, respectivamente (FORD et al., 2015).

Além da redução das taxas de hospitalização e da modificação nas causas de hospitalização, a introdução da ART também teve impacto em desfechos hospitalares como tempo de internação (tempo de permanência hospitalar) e mortalidade hospitalar.

Em relação ao tempo de internação, estudo das hospitalizações na coorte EuroSIDA demonstrou redução da mediana de tempo de internação de 12 dias em 1995 para 5 dias em 2003 (MOCROFT et al., 2004). No Brasil, Casseb e colaboradores utilizando dados de internação do Hospital Emilio Ribas em São Paulo reportaram redução do tempo médio de internação de 33 dias em 1996 (CASSEB et al., 1999) para 16 dias em 1999 (CASSEB et al., 2001). Ademais, foi demonstrado que hospitalizações por doenças relacionadas à Aids estão associadas a maiores tempos de internação. Em estudo que compreendeu os períodos pré e pós ART (1995-2003), Krentz e colaboradores (Calgary, Canadá) mostraram que hospitalizações por doenças relacionadas à Aids eram comparativamente mais longas do que aquelas por doenças não relacionadas à Aids (médias de 8 e 4 dias, respectivamente) (KRENTZ; DEAN; GILL, 2006). Posteriormente Berry e colaboradores em seu estudo com hospitalizações na coorte HIVRN (período de 2001-2008) descreveram achado semelhante. O tempo médio de internação por doenças relacionadas foi de 10,4 dias enquanto outras causas de hospitalização, como infecções não relacionadas a Aids e doenças cardiovasculares, tiveram média de 7,3 e 5,9 dias de internação, respectivamente (BERRY et al., 2012).

A partir dos anos 2000, a tendência dos tempos de internação foi de estabilização ou de queda menos pronunciada. Estudo português, de abrangência nacional, reportou pequena tendência de redução dos tempos internação no período de 2000-2010 (mediana de 12 dias em 2000 e 10 dias em 2010, coeficiente de regressão linear de -0,200 [IC95%: -0.296, -0.104]) (CATUMBELA et al., 2015). Por outro lado, Yehia e colaboradores utilizando dados da coorte HIVRN observaram tempos de internação estável nos anos de 2002 e 2007 (médias de 6,84 e 6,89 dias, respectivamente) (YEHIA et al., 2010).

A mortalidade hospitalar também foi significativamente reduzida após a introdução da ART. Estudo que incluiu 12.183 hospitalizações de pacientes infectados pelo HIV no *Yale-New Haven Hospital* (Connecticut, EUA) no período de 1995-2011 observou redução na fração de hospitalizações que resultou em morte (mortalidade hospitalar) de 6,2% em 1995 para 1,5% em 2011 (COWELL et al., 2015). Kim e colaboradores estudaram 9.101 hospitalizações no período 2004-2008 no S*aint Luke's-Roosevelt Hospital Center* (Nova York, EUA) e estimaram uma mortalidade hospitalar de 2.6% (KIM et al., 2013). As diferenças regionais de mortalidade hospitalar também foram descritas na metanálise de Ford e colaboradores, com estudos de 106 coortes publicados entre 2007-2015. A mortalidade hospitalar agregada foi de 20% (IC95%: 18%-23%), sendo maior nos estudos de países africanos (31%, IC95% 7-37%). Nesse metanálise, a mortalidade hospitalar de hospitalizações por doenças relacionadas à Aids foi de 57% (IC95%: 46-68%) enquanto que as doenças bacterianas (segunda causa de hospitalização) resultaram em uma mortalidade hospitalar de 23% (IC95%: 17%-30%) (FORD et al., 2015).

Faz-se relevante observar que os tempos médios de internação hospitalar e a mortalidade hospitalar descritos para a população infectada pelo HIV no Brasil no período pós ART, descritos na Tabela 1, se mantem consideravelmente superiores àqueles descritos para países de alta renda (BERRY et al., 2012; COWELL et al., 2015; HELLINGER, 2007; KIM et al., 2013; MOCROFT et al., 2004; YEHIA et al., 2010).

As estatísticas de hospitalização de pacientes infectados pelo HIV no Brasil, obtidas através da plataforma Datasus (que inclui internações hospitalares no Sistema Único de Saúde), demonstram que o tempo médio de internação hospitalar no período de 2008-2015 variou entre 17,7 e 18,2 dias. Esses tempos são mais próximos àquele observado por encontrados por Lewden e colaboradores em estudo multicêntrico africano (IeDEA *West Africa collaboration*) conduzido em 2010 que incluiu 823 internações de pacientes infectados pelo HIV, recém diagnosticados, em Benin, Burkina Faso, Costa do Marfim, Mali e Senegal. Nesse estudo, a mediana de tempo de internação hospitalar foi de 13 dias (intervalo interquartil 7-22 dias) (LEWDEN et al., 2014).

Em relação à mortalidade hospitalar de pacientes infectados pelo HIV no Brasil (Tabela 1), observamos que esta variou entre 13,97% em 2008 e 11,98% em 2015. Estas estimativas são inferiores aos 20% de mortalidade hospitalar agregada estimada na metanálise de Ford e colaboradores (FORD et al., 2015) e aos 38% de mortalidade hospitalar reportado por Lewden e

colaboradores na África (LEWDEN et al., 2014), porém são consideravelmente superiores aos 1,5% e 2,6% observados em estudos norte-americanos (COWELL et al., 2015; KIM et al., 2013).

Em conjunto, esses dados (tempo de internação e mortalidade hospitalar) sugerem a existência de fatores estruturais relacionados a peculiaridades próprias dos sistemas de saúde que expliquem (pelo menos em parte) essa discrepância nos desfechos hospitalares observados entre países de alta *versus* média e baixa rendas.

**Tabela 1. Casos de Aids, número de hospitalizações, tempo de internação e mortalidade hospitalar no Brasil, 2008-2015.**

| Ano | Casos de Aids | Internações hospitalares | Total de dias de internação | Média de dias por internação | Total de óbitos hospitalares | Mortalidade hospitalar (%) |
|---|---|---|---|---|---|---|
| **2008** | 39.855 | 31.768 | 560.815 | 17,7 | 4427 | 13,97 |
| **2009** | 39.751 | 35.955 | 641.957 | 17,9 | 4958 | 13,82 |
| **2010** | 39.226 | 36.323 | 653.082 | 18,1 | 4963 | 13,75 |
| **2011** | 41.199 | 36.627 | 618.705 | 17,1 | 4505 | 12,42 |
| **2012** | 40.904 | 36.553 | 641.186 | 17,9 | 4329 | 12,05 |
| **2013** | 41.814 | 37.905 | 676.678 | 18,2 | 4433 | 11,94 |
| **2014** | 39.951 | 36.346 | 649.228 | 18,2 | 4267 | 11,98 |
| **2015** | 15.181 | 34.228 | 597.279 | 17,9 | 4283 | 12,86 |
| **Total** | 297.881 | 285.705 | 5.038.930 | 17,9 | 36165 | 12,83 |

Fonte: Datasus (SIH/SUS); Boletim Epidemiológico HIV/Aids (Ministério da Saúde, 2015)

Diante do exposto, podemos concluir que as taxas de hospitalizações, os tempos de internação e a mortalidade hospitalar foram significativamente reduzidos após a introdução da ART. Não obstante, as taxas de hospitalização dos pacientes infectados pelo HIV ainda persistem elevadas, e consomem parcela importante dos custos de assistência à saúde da população infectada pelo HIV. Evidenciou-se ainda que, na era pós ART, os tempos de internação e a mortalidade hospitalar parecem divergir amplamente quando comparamos países de alta *versus* média e baixa rendas, apontando para a necessidade de condução de estudos de desfechos hospitalares nesses últimos.

O tópico a seguir discorrerá acerca de outro desfecho hospitalar relevante e que tem sido cada vez mais utilizado para avaliação de qualidade da assistência à saúde, na população geral e em populações específicas (incluindo pacientes infectados pelo HIV), a readmissão hospitalar precoce (mais especificamente, a readmissão hospitalar em 30 dias).

## READMISSÃO HOSPITALAR EM 30 DIAS

A taxa de readmissão em 30 dias é definida como a proporção de hospitalizações, denominadas hospitalizações índices, que são seguidas por uma readmissão hospitalar num período inferior a 30 dias após a alta hospitalar. Apesar de se tratar de uma fração, a nomenclatura taxa é usualmente aplicada na literatura que trata desse desfecho.

A readmissão hospitalar precoce representa tanto um problema clínico quanto um problema financeiro e, segundo dados norte-americanos, no ano de 2013, 13,9% das internações foram seguidas por uma readmissão em 30 dias (BARRET et al., 2015). O custo das readmissões é elevado (em geral uma readmissão supera em 5% a 30% o custo de uma internação índice) (BARRET et al., 2015) e somente no ano de 2011, foram gastos nos EUA 41,3 milhões de dólares em cerca de 3,3 milhões de readmissões (HINES et al., 2014).

Pacientes portadores de doenças crônicas como insuficiência cardíaca, doença arterial coronariana e doença pulmonar obstrutiva crônica apresentam taxas de readmissão em 30 dias superiores àquelas da população geral (DESAI; STEVENSON, 2012; DHARMARAJAN et al., 2013; ELIXHAUSER; AU; PODULKA, 2011). No contexto dos pacientes infectados pelo HIV, fatores como ocorrência de doenças oportunistas, efeitos adversos da ART, polifarmácia e a elevada prevalência de doenças crônicas poderiam justificar um maior risco de readmissão hospitalar em 30 dias quando comparados à população geral. De fato, estudo de base nacional conduzido nos EUA, que incluiu 6.441.695 hospitalizações índices, observou que as taxas de readmissão em 30 dias de pacientes HIV positivos superam àquelas observadas em pacientes não infectados pelo HIV (19,7% *versus* 11,2%) e que, mesmo após controlar por variáveis demográficas e clínicas, a infecção pelo HIV foi associada a um risco 50% maior de readmissão (*Odds ratio* ajustado: 1,50 [IC95%: 1,46-1,54]) (BERRY et al., 2015).

Readmissões em 30 dias podem resultar de infecções nosocomiais, alta hospitalar prematura, falha na assistência hospitalar (incluindo não reconciliação medicamentosa, falhas de comunicação entre profissionais, pacientes, cuidadores e médicos ambulatoriais), falha nos cuidados de transição (entre hospital e serviços ambulatoriais), falha nos cuidados pós alta hospitalar e progressão de doenças crônicas (GOLDFIELD et al., 2008). Por estar associado a eventos hospitalares, e também à transição hospital-ambulatório, pode-se considerar que as readmissões em 30 dias reflitam a performance da assistência à saúde de uma maneira mais geral e não somente restrita ao ambiente hospitalar (HANSEN et al., 2011).

Estima-se que na população geral, aproximadamente 30% das readmissões possam ser evitadas, e estas são consideradas como eventos potencialmente preveníveis (VAN WALRAVEN et al., 2011). Essa denominação é aplicada quando a causa da readmissão está relacionada com a causa da hospitalização índice ou é uma complicação desta (GOLDFIELD et al., 2008). No contexto dos pacientes infectados pelo HIV, a fração de readmissões potencialmente preveníveis parece ser ainda maior. Nijhawan e colaboradores em estudo com pacientes infectados pelo HIV hospitalizados no *Parkland Health and Hospital* no ano de 2011 e identificaram que 53% das readmissões poderiam ser classificadas como eventos potencialmente preveníveis (NIJHAWAN et al., 2015). Nesse estudo ainda, o não uso de ART esteve associado a um aumento de 6 vezes na chance de ocorrência de uma readmissão potencialmente prevenível (*Odds ratio* 5.9, p-valor < 0.01) (NIJHAWAN et al., 2015).

## 2 JUSTIFICATIVA

O HIV/Aids ainda representa um grave problema de saúde pública no Brasil e no mundo, e as mudanças no perfil de morbimortalidade dessa população precisam ser acompanhadas e mensuradas, pois fornecem informações vitais para a elaboração de políticas de saúde e protocolos de tratamento. Em particular, o estudo da morbimortalidade hospitalar é de fundamental importância pelos seguintes aspectos: 1) A despeito do progresso obtido com a ART, pacientes infectados pelo HIV continuam apresentando elevadas taxas de hospitalização (BACHHUBER; SOUTHERN, 2014); 2) Alterações nas taxas de hospitalização são mais sensíveis do que alterações nas taxas de mortalidade para mensuração de efeitos relacionados a mudanças de protocolos de tratamento e políticas de saúde (BACHHUBER; SOUTHERN, 2014); 3) Hospitalizações consomem uma parcela importante dos gastos em saúde associados ao tratamento pacientes infectados pelo HIV(BOZZETTE et al., 2001; LONG et al., 2016; NOSYK et al., 2015); 4) Readmissões hospitalares estão relacionados com aumento da morbimortalidade dos pacientes e dos gastos em saúde (JENCKS; WILLIAMS; COLEMAN, 2009); 5) Readmissões em 30 dias parecem ser mais frequentes em pacientes infectados pelo HIV do que na população geral (BERRY et al., 2015); 6) A taxa de readmissão em 30 dias é um indicador amplamente utilizado para avaliação da qualidade da assistência à saúde (JENCKS; WILLIAMS; COLEMAN, 2009); 7) Estudos que avaliam as taxas de readmissão hospitalar em 30 dias em pacientes infectados pelo HIV são escassos e até a presente data não encontramos nenhum estudo publicado em revista cientifica que reporte esse desfecho em pacientes infectados pelo HIV em países de média e baixa renda.

# 3 OBJETIVOS

## 3.1 OBJETIVO GERAL

Estudar as hospitalizações e as readmissões hospitalares em 30 dias em pacientes infectados pelo HIV na era pós ART.

Essa tese foi desenvolvida e será apresentada na forma de 3 artigos. Seus objetivos específicos serão descritos no âmbito de cada artigo, conforme descrição no tópico a seguir.

## 3.2 OBJETIVOS ESPECÍFICOS

**a) Artigo 1: Taxas de hospitalização, tempo de internação e mortalidade hospitalar na coorte de pacientes infectados pelo HIV hospitalizados no Hospital Evandro Chagas da Fundação Oswaldo Cruz no período de 2007-2013, Rio de Janeiro, Brasil.**

Os objetivos desse estudo foram:

1) Estimar as taxas anuais de hospitalização, geral e estratificada por diagnóstico de hospitalização: Aids *versus* não Aids;
2) Avaliar a tendência das taxas de hospitalização ao longo dos anos;
3) Estimar o tempo de internação hospitalar por ano, geral e estratificado por diagnóstico de hospitalização: Aids *versus* não Aids;
4) Avaliar a tendência dos tempos de internação hospitalar ao longo dos anos;
5) Estimar a mortalidade hospitalar anual, geral e estratificada por diagnóstico de hospitalização: Aids *versus* não Aids;
6) Avaliar a tendência da mortalidade hospitalar ao longo dos anos.

**b) Artigo 2: Readmissão em 30 dias em pacientes infectados pelo HIV na era pós ART: revisão sistemática e metanálise.**

Os objetivos desse estudo foram:

1) Comparar as taxas de readmissão em 30 dias reportadas em diferentes populações;
2) Calcular uma taxa de readmissão em 30 dias agregada (metanálise);

3) Identificar os preditores de readmissão em 30 dias em cada estudo (individualmente);
4) Identificar os preditores de readmissão em 30 dias através de modelos de meta regressão (estudos agregados).

**c) Artigo 3: Taxa de readmissão em 30 dias na coorte de pacientes infectados pelo HIV hospitalizados no Hospital Evandro Chagas da Fundação Oswaldo Cruz no período de 2007-2013, Rio de Janeiro, Brasil**

Os objetivos desse estudo foram:

1) Estimar a taxa de readmissão hospitalar em 30 dias;
2) Avaliar os fatores sócio demográficos, clínicos e assistenciais associados à readmissão em 30 dias;
3) Comparar os resultados encontrados com os disponíveis na literatura.

# 4 METODOLOGIA

## 4.1 ARTIGO 1: TAXAS DE HOSPITALIZAÇÃO, TEMPO DE INTERNAÇÃO E MORTALIDADE HOSPITALAR NA COORTE DE PACIENTES INFECTADOS PELO HIV HOSPITALIZADOS NO HOSPITAL EVANDRO CHAGAS DA FUNDAÇÃO OSWALDO CRUZ NO PERÍODO DE 2007-2013, RIO DE JANEIRO, BRASIL.

A descrição completa dos métodos utilizados nesse estudo encontra-se no corpo do artigo número 1 apresentado na seção da tese intitulada Resultados.

O INI é um centro de referência nacional para o tratamento de doenças infecciosas e desde 1986 é um centro de referência para o tratamento de pacientes infectados pelo HIV. No estado do Rio de Janeiro, o programa de Aids do INI é um dos maiores a oferecer cuidados primários, secundários e terciários à pacientes infectados pelo HIV, e conta atualmente com cerca de 3700 pacientes ativos.

A estrutura assistencial do INI é composta por um serviço ambulatorial multidisciplinar (incluindo infectologia, cardiologia, endocrinologia, psiquiatria, hematologia, oftalmologia, gastrenterologia, psicologia, nutrição entre outros), um serviço de pronto-atendimento para os pacientes cadastrados no INI, um hospital dia para administração de quimioterapia e medicações parenterais intermitentes, e um serviço de internação hospitalar especializado em doenças infecciosas (Hospital Evandro Chagas que conta com 24 leitos de enfermaria e um centro de terapia intensiva com 4 leitos).

Desde 1998, uma base de dados longitudinal dos pacientes em acompanhamento é mantida, e periodicamente atualizada com informações extraídas dos prontuários médicos, por equipe treinada. Os procedimentos da coorte já foram descritos e resultados publicados (GRINSZTEJN et al., 2009, 2013; MOREIRA et al., 2011; RIBEIRO et al., 2014). Concisamente, a base de dados conta com: informações sócio demográficas; exames laboratoriais (incluindo histórico de exames de CD4 e carga viral, sorologia para hepatites virais entre outros); informações sobre ART (data de início e término de cada esquema terapêutico utilizado); informações sobre comorbidades, incluindo doenças oportunistas e doenças crônicas (hipertensão arterial, diabetes entre outras); informações sobre hospitalizações (datas de admissão, alta hospitalar, tipo de alta hospitalar). Auditorias interna e externa dos dados coletados são realizadas periodicamente.

Informações vitais dos participantes da coorte são periodicamente confrontadas com dados do Sistema de Informação de Mortalidade do Estado do Rio de Janeiro através de um algoritmo validado (PACHECO et al., 2008). Os óbitos da coorte são revistos e classificados de acordo com o protocolo *Coding of Death in HIV* (CoDe) (KOWALSKA et al., 2011).

Para este estudo foram incluídos pacientes infectados pelo HIV, com pelo menos 18 anos de idade, incluídos na coorte do INI/Fiocruz desde 01 de janeiro de 1985 até 01 de dezembro de 2013 e que estavam em acompanhamento após 01 janeiro de 2007 (isto é, não morreram antes dessa data e compareceram a pelo menos uma visita clínica após essa data). As hospitalizações no Hospital Evandro Chagas que ocorreram no período de 01 de janeiro de 2007 até 31 de dezembro de 2013 foram incluídas nesse estudo. A escolha do período do estudo (a partir de 2007) foi relacionada com a abertura do Centro de Terapia Intensiva do Hospital Evandro Chagas que ocorreu nos últimos meses de 2006, com o objetivo tornar o suporte assistencial hospitalar comparável ao longo dos anos do estudo.

Os relatórios de alta hospitalar foram revistos para classificação da causa de hospitalização (Aids *versus* não Aids). Todos os diagnósticos listados no resumo de alta foram classificados de acordo com a Classificação Internacional de Doenças – 10ª edição (CID-10) (WORLD HEALTH ORGANIZATION, 2011) em 24 categorias independentes (Apêndice A). A causa primária de hospitalização foi definida a partir de uma classificação hierárquica dos CIDs listados na seguinte ordem: doenças definidoras de Aids, neoplasias não relacionadas à Aids, doenças cardiovasculares, infecções bacterianas, infecções fúngicas, infecções virais, infecções parasitarias, doenças do aparelho digestivo, doenças renais, doença respiratória, doenças neurológicas, doenças endócrinas, doenças hematológicas, doenças psiquiátricas, hepatites virais, hepatite não viral, doenças dermatológicas, doenças reumatológicas, trauma, doenças ginecológicas, toxicidades, outras, sinais e sintomas.

As taxas de hospitalização foram calculadas por 1000 pessoas-ano. Modelos de regressão de Poisson foram utilizados para avaliação de tendência das taxas de hospitalização ao longo do período do estudo. Os tempos de internação foram calculados por subtração da data de admissão da data de alta hospitalar e posteriormente acrescido de 1 dia. A mortalidade hospitalar foi definida pela razão entre o número de hospitalizações que terminaram em óbito dividido pelo número total de hospitalizações. Modelos de regressão linear e regressão logística foram utilizados para

avaliação da tendência dos tempos de permanência hospitalar e da mortalidade hospitalar, respectivamente.

Este artigo foi aceito para publicação no *Brazilian Journal of Infectious Diseases* (carta de aceite – Apêndice B).

## 4.2 ARTIGO 2: READMISSÃO EM 30 DIAS EM PACIENTES INFECTADOS PELO HIV NA ERA PÓS ART: REVISÃO SISTEMÁTICA E METANÁLISE.

A descrição completa dos métodos desse estudo está presente no Artigo 2 na seção da tese intitulada Resultados.

Resumidamente, foi conduzida uma busca sistemática nas bases de dados *Medline* via *Pubmed*, *Scopus* e *Web of Science*, incluindo o período de 01 de janeiro de 1996 até 02 de dezembro de 2014, por estudos que reportavam taxas de readmissão hospitalar em 30 dias em pacientes infectados pelo HIV.

Os artigos incluídos tiveram sua qualidade avaliada através da escala adaptada de *New-Castle-Otawa* para estudos observacionais. A taxa agrupada de readmissão hospitalar em 30 dias foi calculada utilizando o método de Mantel-Haenszel e meta-regressões foram conduzidas para avaliar fatores associados à readmissão.

Este estudo foi retirado de submissão por sugestão da banca de qualificação. Será realizada atualização da busca, para inclusão de estudos publicados após 02 de dezembro de 2014, além de objetivarmos a inclusão do estudo original, apresentado como artigo 3.

## 4.3 ARTIGO 3: TAXA DE READMISSÃO EM 30 DIAS NA COORTE DE PACIENTES INFECTADOS PELO HIV HOSPITALIZADOS NO HOSPITAL EVANDRO CHAGAS DA FUNDAÇÃO OSWALDO CRUZ NO PERÍODO DE 2007-2013, RIO DE JANEIRO, BRASIL

A descrição completa dos métodos desse estudo está presente no Artigo 3 na seção da tese intitulada Resultados.

A população desse estudo é a mesma apresentada no item 4.1. O desfecho avaliado nesse estudo foi a taxa de readmissão hospitalar em 30 dias.

Readmissão em 30 dias foi definida como qualquer readmissão hospitalar que segue uma hospitalização índice num período de até 30 dias após a alta. Hospitalização índice foi definida como: 1º) a primeira hospitalização experimentada pelo paciente durante o período do estudo; e/ou 2º) qualquer hospitalização que ocorra após 30 dias de uma hospitalização anterior. Foram excluídas as potenciais hospitalizações índices que ocorreram no primeiro (anterior a 01 fevereiro 2007) e último meses da série temporal (posterior a 30 novembro 2013). No primeiro mês por não termos como definir se aquela era uma hospitalização índice ou uma readmissão e, no último mês por não permitir um seguimento mínimo de 30 dias para análise de readmissão. Nos casos em que uma hospitalização índice foi seguida por uma cadeia de múltiplas readmissões, cada uma com intervalos inferiores a 30 dias (sendo que a amplitude global da cadeia pode exceder 30 dias), todas as readmissões incluídas na cadeia não foram consideradas como hospitalização índice.

A taxa de readmissão em 30 dias foi calculada como o número de readmissões hospitalares em 30 dias dividido pelo número de altas hospitalares. Para clarificação, apesar de se tratar de uma fração, convencionalmente tem sido denominada taxa e para fins de consistência com as publicações disponíveis seguiremos com essa nomenclatura.

Modelos de regressão Cox foram usados para avaliação de preditores de readmissão em 30 dias. Para tanto, o início do seguimento de cada paciente foi definido como data da alta da hospitalização índice e o término do seguimento foi dado pela data de readmissão, data de óbito ou censura (definida como data da alta hospitalização índice acrescida de 30 dias), o que acontecer primeiro. Apesar de óbito ocorrendo em 30 dias após a alta poder ser tratado como um desfecho competitivo, essa abordagem não foi utilizada devido ao baixo número de eventos observados.

Resíduos de Schoenfeld foram usados para avaliar a premissa de proporcionalidade dos riscos. Observamos que a variável dicotômica "consulta médica pós alta" violou a premissa de proporcionalidade. Dessa forma, um novo modelo foi construído, e a variável "consulta médica pós alta" foi incluída como uma variável tempo-dependente, consequentemente, o seguimento dos pacientes que tiveram consulta médica pós alta foi divido em dois tempos: antes e após a consulta médica.

As seguintes variáveis independentes foram avaliadas nesse estudo: variáveis categóricas: sexo; raça (branca e não branca); escolaridade ("até 9 anos de educação formal" vs. "mais de 9 anos de educação formal"); categoria de exposição ao HIV (categorizada hierarquicamente em uso de drogas injetáveis, homem que faz sexo com homem, transmissão heterossexual, acidente

material biológico, transmissão vertical e outros); hospitalização por doença definidora de Aids, uso de ART antes da hospitalização índice; permanência em terapia intensiva na hospitalização índice; tipo de alta hospitalar referente a hospitalização índice (alta médica formal, alta à revelia - *against medical advice*, transferência para outro hospital); consulta médica pós alta (em até 30 dias após a alta). Variáveis quantitativas: idade na admissão da hospitalização índice, tempo de diagnóstico do HIV (estimado como o tempo decorrido entre primeiro teste anti-HIV positivo documentado e a data de admissão hospitalização índice), contagem de linfócitos T CD4+ e carga viral do HIV na hospitalização índice (período que engloba os 180 dias anteriores e 30 dias após a admissão), tempo de permanência hospitalar da hospitalização índice.

Este artigo encontra-se submetido ao *Journal of Acquired Immune Deficiency Syndromes*.

## 5 ASPECTOS ÉTICOS

O presente estudo (artigo empíricos desenvolvidos nessa tese) foi submetido e aprovado pelo Comitê de Ética em Pesquisa da Escola Nacional de Saúde Pública Sergio Arouca (CAAE 57135616.0.0000.5240) (Anexo A).

Estudos observacionais realizados com a coorte de pacientes infectados pelo HIV do INI/Fiocruz estão contidos no "Estudo Longitudinal da História Natural da Infecção pelo HIV em pacientes acompanhados no IPEC-FIOCRUZ", aprovado pelo Comitê de Ética em Pesquisa do Instituto Nacional de Infectologia Evandro Chagas (CAAE 0032.0.009.000-10) (Anexo B).

## 6 RESULTADOS

A seção de resultados será apresentada na forma de três artigos, conforme descrito nas seções Objetivos e Métodos.

**Artigo 1:** Taxas de hospitalização, tempo de internação e mortalidade hospitalar em uma coorte de pacientes infectados pelo HIV no Rio de Janeiro, Brasil. (*Hospitalizations rates, length of stay and in-hospital mortality in a cohort of HIV infected patients from Rio de Janeiro, Brazil.)*

**Artigo 2:** Readmissão em 30 dias em pacientes infectados pelo HIV na era pós ART: revisão sistemática e metanálise. (*30-day readmissions among HIV infected patients in the post cART era: a systematic review and meta-analysis.)*

**Artigo 2:** Taxas de readmissão em 30 dias em uma coorte de pacientes infectados pelo HIV no Rio de Janeiro, Brasil. (*30-day readmission rates in an HIV-infected cohort from Rio de Janeiro, Brazil.)*

6.1 ARTIGO 1

# Hospitalizations rates, length of stay and in-hospital mortality in a cohort of HIV infected patients from Rio de Janeiro, Brazil.

Lara E. Coelho, Sayonara R. Ribeiro, Valdilea G. Veloso, Beatriz Grinsztejn, Paula M. Luz

Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ, Rio de Janeiro, Brazil

Corresponding author: Lara E. Coelho, MD, MSc
Email: lara.coelho@ini.fiocruz.br
Address: Instituto Nacional de Infectologia Evandro Chagas (INI), FIOCRUZ, Av Brasil 4365, Manguinhos, Rio de Janeiro, RJ, Brazil. Zip code: 21045-900.

Keywords: HIV, hospitalization, length of stay, in-hospital mortality

**Abstract**

In this study, we evaluated trends in hospitalization rates, length of stay and in-hospital mortality in a cohort of HIV infected patients in Rio de Janeiro, Brazil, from 2007 until 2013. Among the 3,991 included patients, 1861 hospitalizations occurred (hospitalization rate of 10.44/100 person-years, 95% confidence interval [CI] 9.98-10.93/100 person-years). Hospitalization rates decreased annually (per year incidence rate ratio 0.92, 95%CI 0.89-0.95) as well as length of stay (median of 15 days in 2007 *vs.* 11 days in 2013, p-value for trend <0.001) and in-hospital mortality (13.4% in 2007 to 8.1% in 2013, p-value for trend = 0.053). We showed that, in a middle-income setting, hospitalizations rates are decreasing over time and that non-AIDS hospitalizations are currently more frequent than AIDS related ones. Notwithstanding, compared with high-income settings, our results show longer length of stay and high in-hospital mortality. Further studies addressing these outcomes are needed to provide information that may guide protocols and interventions to reduce health-care costs and in-hospital mortality.

## Introduction

Combination antiretroviral therapy (ART) has led to a reduction in the rates of hospitalizations among HIV-infected patients[1,2]. The immunological improvement and the gain in life expectancy achieved with ART also modified causes of hospitalizations, and, in most recent years, non-AIDS events surpassed AIDS-related ones as the main cause of hospitalization in high income settings[2–4]. Simultaneously, duration of hospitalizations (i.e. length of stay) and in-hospital mortality[1,5], among HIV-infected patients decreased over time. Nevertheless, in late ART era, the study of hospitalizations, length of stay and in-hospital mortality are needed since they provide updated information on morbidity and health care utilization among HIV infected patients, which are essential to evaluate health care provision, guide health policies and project its associated costs. In this study, we sought to evaluate trends in hospitalization rates, length of stay and in-hospital mortality in a cohort of HIV infected patients in Rio de Janeiro, from 2007 until 2013.

## Methods

Instituto Nacional de Infectologia Evandro Chagas (INI, formerly known as Instituto de Pesquisa Clínica Evandro Chagas/IPEC) is a reference center for research and care of HIV infected patients, in Rio de Janeiro, Brazil, since 1986. INI provides primary, specialty and tertiary care for HIV infected patients and it is comprised by an outpatient facility, an emergency department, a day-clinic and an inpatient care unit (comprising an intensive care unit), all funded by Brazilian National Health System. Patients followed at INI have free-of charge access to all its facilities. A longitudinal database maintains in-hospital and outpatient clinical information on patients receiveing HIV care. Cohort procedures and results are published eslwhere[6,7].

The present study included HIV-infected adults (≥18 years of age at cohort enrollment) , enrolled in the INI cohort between 01 January 1986 and 01 December 2013, who were alive and in active care (at least one medical visit) after 01 January 2007. Follow-up started on 01 January 2007 or the date of cohort enrollment, whichever occurred last, and it ended on 31 December 2013, date of death or last clinical visit (medical visit, CD4, HIV viral load or any blood exam) whichever occurred first. Lost to follow-up was defined as not having a clinical visit after 01 January 2013 for those known not to be deceased. Information regarding vital status was exhaustedly checked using the patients' medical charts and by linkage with the Rio de Janeiro Mortality database (up to 31 December 2013) using a previously validated algorithm[8].

The primary cause of a hospitalization was inferred from discharge reports. All diagnoses listed in the discharge report were classified using the 10th Edition of the International Classification of Disease (ICD-10), into 24 different categories[9]. Since some ICD-10 codes could be allocated to several categories, we considered a hierarchical classification protocol with a decreasing order of priority as follows: AIDS-events, non-AIDS malignancies, infections and then systemic events[9]. To determine the primary cause of a hospitalization, the one or more ICD-10 codes listed in the discharge reports were hierarchically classified as follows: AIDS-defining diseases, non-AIDS cancer, cardiovascular disease, bacterial infections, fungal infections, viral infections, parasitic infections, digestive diseases, renal diseases, respiratory diseases, neurologic diseases, endocrine diseases, hematological diseases, psychiatric diseases, viral hepatitis, non-viral hepatitis, dermatological diseases, rheumatologic diseases, trauma, gynecologic disease, toxicities, others and sings and symptoms.

Socio-demographic and clinical features were compared among included patients by study period (2007-2009, 2010-2011, 2012-2013) using Kruskal-Wallis test for continuous variables and

Chi-square for categorical variables. Annual hospitalization rates, defined as the number of hospitalizations divided by the person-years of follow-up, were calculated per 100 person-years (PY); Poisson regression models were used to estimate trends in hospitalization rates. Length of stay (LOS) was calculated by subtracting hospital admission date from date of discharge and adding 1; linear regression models were used to estimate trends in LOS. In-hospital mortality, defined as the number of hospitalizations that ended in death divided by the total number hospitalizations, were calculated; logistic regression models were used to estimate trends in in-hospital mortality.

**Results**

A total of 3,991 patients, enrolled from June 1986 until November 2013, were followed from 01 January 2007 until 31 December 2013, accounting for 17,822 PY of follow-up. One hundred and eighty nine patients (4.7%) were deemed loss to follow up, yielding a loss to follow up rate of rate of 1.06/100 PY. The study population aged slightly through the years and the proportion of patients with 60 years or more increased from 5.1% in 2007-2009 to 7.1% in 2012-2013 (p-value <0.001, Table 1). Likewise, the median CD4 counts (419 cells/mm$^3$ in 2007-2009 to 542 cells/mm$^3$ in 2012-2013, p-value <0.001), the proportion of patients using ART (80.9% in 2007-2009 vs. 90.8% in 2012-2013, p-value <0.001) and the proportion of patients with a HIV viral load under 400 copies/mL (54% in 2007-2009 vs. 69.5% in 2012-2013, p-value<0.001) significantly increased through the years.

**Table 1. Study population characteristics by study periods.**

| | 2007-2009 (N=2639) | 2010-2011 (N=3117) | 2012-2013 (N=3605) | p-value |
|---|---|---|---|---|
| **Sex** | | | | 0.678 |
| **Male** | 1699 (64.4) | 2020 (64.8) | 2359 (65.4) | |
| **Female** | 940 (35.6) | 1097 (35.2) | 1246 (34.6) | |
| **Age in years**[a] | | | | |
| **median(IQR)** | 41.7 (34.1,48.6) | 42 (34.2,49.4) | 42.5 (34.5,50.5) | 0.004 |
| **≤30** | 372 (14.1) | 414 (13.3) | 466 (12.9) | < 0.001 |
| **31-40** | 807 (30.6) | 925 (29.7) | 1051 (29.2) | |
| **41-50** | 885 (33.5) | 1065 (34.2) | 1124 (31.2) | |
| **51-60** | 440 (16.7) | 525 (16.8) | 709 (19.7) | |
| **>60** | 135 (5.1) | 188 (6) | 255 (7.1) | |
| **Race / ethnicity** | | | | |
| **White** | 1454 (55.1) | 1619 (51.9) | 1807 (50.1) | < 0.001 |
| **Non White** | 1185 (44.9) | 1498 (48.1) | 1798 (49.9) | |
| **Educational level** | | | | 0.075 |
| **Up to 9 years** | 1340 (50.8) | 1555 (49.9) | 1730 (48) | |
| **More than 9** | 1299 (49.2) | 1562 (50.1) | 1875 (52) | |
| **HIV exposure** | | | | 0.028 |
| **Heterosexual** | 1420 (53.8) | 1636 (52.5) | 1830 (50.8) | |
| **MSM** | 948 (35.9) | 1146 (36.8) | 1363 (37.8) | |
| **IDU** | 52 (2) | 50 (1.6) | 47 (1.3) | |
| **Other/unknown** | 219 (8.3) | 285 (9.1) | 365 (10.1) | |
| **Chronic hepatites** | 169 (6.4) | 188 (6) | 198 (5.5) | 0.308 |
| **Chronic hepatites** | 278 (10.5) | 301 (9.7) | 309 (8.6) | 0.03 |
| **CD4 count (cells/mm$^3$)**[d] | | | | |
| **median(IQR)** | 419 (254,616) | 532 (336,772) | 542 (358,775) | < 0.001 |
| **>500** | 970 (36.8) | 1664 (53.4) | 1924 (53.4) | < 0.001 |
| **500-351** | 581 (22) | 554 (17.8) | 676 (18.8) | |
| **<=350** | 996 (37.7) | 801 (25.7) | 831 (23.1) | |
| **missing** | 92 (3.5) | 98 (3.1) | 174 (4.8) | |
| **HIV viral load (copies/mL)** [d] | | | | < 0.001 |
| **≤400** | 1424 (54) | 2050 (65.8) | 2504 (69.5) | |
| **>400** | 1073 (40.7) | 952 (30.5) | 956 (26.5) | |
| **missing** | 142 (5.4) | 115 (3.7) | 145 (4) | |
| **ART use**[e] | 2136 (80.9) | 2687 (86.2) | 3273 (90.8) | < 0.001 |

MSM: Men who have sex with men; IDU: Injectable drug use; ART: combination antiretroviral therapy;
[a] Age at the end of each period.
[b] Defined as having a positive HBsAg antigen.
[c] Defined as having a positive anti-HCV serology.
[d] The closest result to the midpoint of each period.
[e] Defined as ART start before end of each period.

During the study period, 1861 hospitalizations occurred, yielding an overall hospitalization rate of 10.44/100 PY (95% confidence interval [CI] 9.98-10.93/100 PY). Hospitalization rates decreased annually (from 10.52/100 PY in 2007to 7.28/100 PY in 2013, per year incidence rate ratio [IRR] 0.92, 95%CI 0.89-0.95) mainly due to a decrease of AIDS-related hospitalizations (from 5.17/100 PY in 2007 to 2.78/100 PY in 2013, per year IRR 0.88, 95%CI 0.84-0.92). Non-AIDS related hospitalization also decreased with a borderline significant trend (from 5.34/100 PY in 2007 to 4.49/100 PY in 2013, per year IRR 0.96, 95%CI 0.92-1.00) (Table 2). Moreover, throughout the years the proportion of non-AIDS related hospitalizations gradually increased and accounted for the majority of the hospitalizations in the last three years of the study period. Bacterial infections (53.4%, n=507), cardiovascular diseases (18.6%, n=177) and viral infections (10.3%, n=98) represented the three most common causes on non-AIDS hospitalizations during the study.

Following the trends of hospitalization rates, the overall LOS decreased significantly over the study period (median of 15 days in 2007 *vs.* 11 days in 2013, p-value for trend <0.001) as well as the LOS of non AIDS-related hospitalizations (median of 11 days in 2007 *vs.* 8 days in 2013, p-value for trend=0.038) and of AIDS-related hospitalizations (median of 19 days in 2007 *vs.* 16 days in 2013, p-value for trend=0.036). Overall, in-hospital mortality decreased during the study period (from 13.4% in 2007 to 8.1% in 2013, per calendar year increase odds ratio 0.92, 95%CI 0.85-1.00) and as well in-hospital mortality of non-AIDS related hospitalizations (from 14.7% in 2007 to 5.6% in 2013, per calendar year increase odds ratio 0.84, 95%CI 0.74-0.96). AIDS related hospitalizations' in-hospital mortality remained stable throughout the study period and, overall, it was 1.66 times higher than non-AIDS related hospitalizations' in-hospital mortality (11.6% *vs.* 7.0%, Chi-square test p-value <0.001) (Table 2).

**Table 2. Number of hospitalization, hospitalization rates and length of stay, and in-hospital mortality, stratified into AIDS- and non-AIDS-related causes by year, 2007-2013, INI cohort.**

| | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 | 2013 | Total | Test for trend** |
|---|---|---|---|---|---|---|---|---|---|
| **Person-years** | 1,778 | 2,057 | 2,336 | 2,556 | 2,825 | 3,040 | 3,229 | 17,822 | |
| **Hospitalizations, N (%)** | | | | | | | | | |
| **All causes** | 187 | 284 | 290 | 274 | 320 | 271 | 235 | 1861 | |
| **AIDS-related *** | 92 (49.2) | 152 (53.5) | 157 (54.1) | 148 (54.0) | 144 (45.0) | 128 (47.2) | 90 (38.3) | 911 (49) | <0.001[a] |
| **Non-AIDS related** | 95 (50.8) | 132 (46.5) | 133 (45.9) | 126 (46.0) | 176 (55.0) | 143 (52.8) | 145 (61.7) | 950 (51) | <0.001[a] |
| **Hospitalizations, rate/100PY (95% CI)** | | | | | | | | | |
| **All causes** | 10.52 (9.11, 12.14) | 13.80 (12. 29, 15.51) | 12.42 (11.07, 13.93) | 10.72 (9.52, 12.07) | 11.33 (10.15, 12.64) | 8.91 (7.91, 10.04) | 7.28 (6.40, 8.27) | 10.40 (9.98, 10.93) | 0.92 (0.89-0.95)[b] |
| **AIDS-related *** | 5.17 (4.22, 6.35) | 7.39 (6.30, 8.66) | 6.72 (5.75, 7.86) | 5.79 (4.93, 6.80) | 5.10 (4.33, 6.00) | 4.21 (3.54, 5.01) | 2.78 (2.27, 3.43) | 5.11 (4.79, 5.45) | 0.88 (0.84-0.92)[b] |
| **Non-AIDS related** | 5.34 (4.37, 6.53) | 6.42 (5.41, 7.61) | 5.69 (4.80, 6.75) | 4.93 (4.14, 5.88) | 6.23 (5.37, 7.22) | 4.70 (3.99, 5.54) | 4.49 (3.81, 5.28) | 5.33 (5.00, 5.68) | 0.96 (0.92-1.00)[b] |
| **Length of stay, median (IQR)** | | | | | | | | | |
| **All causes** | 15 (8, 25) | 15 (8, 27) | 14 (8, 26) | 15 (7, 26) | 12 (7, 21) | 12 (6, 21) | 11 (7, 20) | 13 (7, 23) | -1.00 (-1.54--0.47)[c] |
| **AIDS-related *** | 19 (12, 31.2) | 19 (11, 30.2) | 19 (11, 33) | 21 (10, 36) | 18 (11, 31) | 15 (9, 26) | 16 (9, 25) | 18 (11, 31) | -0.92 (-1.78--0.06)[c] |
| **Non-AIDS related** | 11 (7, 22) | 9 (6, 19) | 10 (6, 16) | 9 (5, 17) | 8 (5, 14) | 8 (5, 16) | 8 (5, 16) | 9 (6, 16) | -0.65 (-1.26--0.04)[c] |
| **In-hospital mortality, N (%)** | | | | | | | | | |
| **All causes** | 25 (13.4) | 24 (8.5) | 30 (10.3) | 25 (9.1) | 19 (5.9) | 30 (11.1) | 19 (8.1) | 172 (9.2) | 0.92 (0.85-1.00)[d] |
| **AIDS-related *** | 11 (12) | 13 (8.6) | 22 (14) | 19 (12.8) | 9 (6.3) | 21 (16.4) | 11 (12.2) | 106 (11.6) | 1.00 (0.90-1.12)[d] |
| **Non-AIDS related** | 14 (14.7) | 11 (8.3) | 8 (6.0) | 6 (4.8) | 10 (5.7) | 9 (6.3) | 8 (5.6) | 66 (6.9) | 0.84 (0.74-0.96)[d] |

PY: person-years, 95% CI: 95% confidence interval, IQR: inter-quartile range

* Defined as presenting any AIDS event (CDC, 1994) during hospitalization

** Chi-squared test for trend in proportions; Poisson regression for hospitalization rates; Linear regression coefficient for length of stay; Odds ratio for in-hospital mortality.

[a] P-value estimated using Chi-squared test for trend in proportions

[b] Per calendar year increase, incidence rate ratio and 95% confidence interval estimated using Poisson regression

[c] Per calendar year increase, linear coefficient and 95% confidence interval estimated using linear regression

[d] Per calendar year increase, odds ratio and 95% confidence interval, estimated using logistic regression.

## Discussion

In this study, we have shown that among HIV-infected patients living in a middle-income setting in a late ART era, hospitalization rates have decreased through the years, mostly due to a decrease in the rate of AIDS related hospitalizations. Consequently, non-AIDS hospitalizations became more common than AIDS related ones in the last three years of the study period. Decreases in hospitalization rates in late ART era have been described for both high- [4] and middle-income settings[10]. This shift in hospitalizations causes (from AIDS related to non AIDS related) follows the reduction in AIDS-defining diseases incidence[11] and mortality[12] already demonstrated in our cohort, highlighting an increased relevance of non-communicable events among HIV infected patients. Changes in the study population characteristics through the study period likely contributed to this scenario. Our results show that, over time, the cohort population aged, while CD4 counts, the proportion of virologic suppressed patients and ART use among patients increased.

LOS also decreased throughout the study though it remained high mainly due to AIDS related hospitalizations. Overall, our estimated median LOS (13 days) surpasses the one reported for a US multicentric HIV study (median of 5 days)[13] but is closer to that reported by a national Portuguese study (median 11 days)[14]. And, similarly to other studies[13],[15] we found that hospitalizations due to AIDS were associated with longer LOS (median of 9 *vs.* 18 days for non-AIDS and AIDS-related hospitalizations, respectively).

In-hospital mortality also decreased over study period, although AIDS-related hospitalization' in-hospital mortality remained quite stable through the years. In-hospital mortality was almost two times higher in AIDS-related hospitalizations than in non-AIDS-related hospitalizations. The overall 9.2% in-hospital mortality rate found in our study is higher than a previous report from tertiary hospital in New York that estimated a 2.6% mortality rate

between 2004 and 2008[16], but is smaller than the one observed by Akinkuotu et al. in Malawi (24%)[17].

Disparities in hospitalization rates, LOS and in-hospital mortality among the studies (particularly, when comparing high- *vs.* low- and middle-income settings) can be explained by several factors that range from hospital structure, hospital setting, type of health care system as well as by the burden of diseases, in particular of AIDS-defining diseases. In this context, tuberculosis burden might play a key role. In high burden settings, tuberculosis is a leading cause of hospitalizations among HIV infected patients and is related to high in-hospital mortality (24.9% in a meta-analysis including 66 studies)[18]. In addition, tuberculosis is also associated with longer LOS both among the general and the HIV-infected population[19,20]. In our casuistic, tuberculosis accounted for 43% of all AIDS related hospitalizations and yielded an in-hospital mortality of 10.9% (data not shown). Additionally, LOS of tuberculosis related hospitalization is significantly longer than non-tuberculosis hospitalizations' (median of 18 days *vs.* 12 days, respectively, Chi-square p-value <0.001, data not shown).

There are several limitations that need to be highlighted in the present study. First, our study casuistic is from a single cohort that has access to an outpatient as well as an infectious diseases hospital located in Rio de Janeiro, and our results may not reflect those for other HIV populations in Brazil. Second, although patients have a free of charge access to Evandro Chagas hospital we cannot rule out the possibility of hospitalizations in other hospitals within the city, implying that our rates may be somewhat underestimated. Finally, Evandro Chagas hospitalizations are restricted to non-surgical and non-obstetrics procedures, and therefore our rates do not represent the entire sort of events that can happen to an HIV infected patient.

In summary, we demonstrated that, in a middle-income setting, hospitalizations rates are decreasing over time and that non-AIDS hospitalizations are currently more frequent

than AIDS related ones. We also showed that in our setting we still struggle with long LOS and high in-hospital mortality. Studies addressing predictors of LOS and in-hospital mortality, mainly in low- and middle-income settings are needed and will be of utmost importance to guide health policies and assistance protocols in order to reduce health costs and in-hospital mortality.

## References


1. Mocroft A., d'Arminio Monforte A., Kirk O., et al. Changes in hospital admissions across Europe: 1995–2003. Results from the EuroSIDA study. HIV Med. 2004;5(6):437–47.

2. Buchacz K., Baker RK., Moorman AC., et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994–2005. Aids. 2008;22(11):1345–54.

3. Crum-Cianflone NF., Grandits G., Echols S., et al. Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? J Acquir Immune Defic Syndr 1999. 2010;54(3):248–57.

4. Berry SA., Fleishman JA., Moore RD., Gebo KA. Trends in Reasons for Hospitalization in a Multisite United States Cohort of Persons Living With HIV, 2001–2008: JAIDS J Acquir Immune Defic Syndr. 2012;59(4):368–75. Doi: 10.1097/QAI.0b013e318246b862.

5. Krentz HB., Dean S., Gill MJ. Longitudinal assessment (1995–2003) of hospitalizations of HIV-infected patients within a geographical population in Canada. HIV Med. 2006;7(7):457–66.

6. Grinsztejn B., Veloso VG., Friedman RK., et al. Early mortality and cause of deaths in patients using HAART in Brazil and the United States: AIDS. 2009;23(16):2107–14. Doi: 10.1097/QAD.0b013e32832ec494.

7. Moreira RI., Luz PM., Struchiner CJ., et al. Immune Status at Presentation for HIV Clinical Care in Rio de Janeiro and Baltimore: JAIDS J Acquir Immune Defic Syndr. 2011;57:S171–8. Doi: 10.1097/QAI.0b013e31821e9d59.

8. Pacheco AG., Saraceni V., Tuboi SH., et al. Validation of a Hierarchical Deterministic Record-Linkage Algorithm Using Data From 2 Different Cohorts of Human Immunodeficiency Virus-Infected Persons and Mortality Databases in Brazil. Am J Epidemiol. 2008;168(11):1326–32. Doi: 10.1093/aje/kwn249.

9. Ribeiro SR., Luz PM., Campos DP., et al. Incidence and determinants of severe morbidity among HIV-infected patients from Rio de Janeiro, Brazil, 2000–2010. Antivir Ther. 2014;19(4):387–97. Doi: 10.3851/IMP2716.

10. Hontelez JAC., Tanser FC., Naidu KK., Pillay D., Bärnighausen T. The Effect of Antiretroviral Treatment on Health Care Utilization in Rural South Africa: A Population-Based Cohort Study. PLOS ONE. 2016;11(7):e0158015. Doi: 10.1371/journal.pone.0158015.

11. Coelho L., Cardoso SW., Amancio RT., et al. Trends in AIDS-Defining Opportunistic Illnesses Incidence over 25 Years in Rio de Janeiro, Brazil. PLoS ONE. 2014;9(6):e98666. Doi: 10.1371/journal.pone.0098666.

12. Grinsztejn B., Luz PM., Pacheco AG., et al. Changing Mortality Profile among HIV-Infected Patients in Rio de Janeiro, Brazil: Shifting from AIDS to Non-AIDS Related Conditions in the HAART Era. PLoS ONE. 2013;8(4):e59768. Doi: 10.1371/journal.pone.0059768.

13. Berry SA., Fleishman JA., Yehia BR., et al. Thirty-day hospital readmission rate among adults living with HIV: AIDS. 2013;27(13):2059–68. Doi: 10.1097/QAD.0b013e3283623d5f.

14. Catumbela E., Freitas A., Lopes F., et al. HIV disease burden, cost, and length of stay in Portuguese hospitals from 2000 to 2010: a cross-sectional study. BMC Health Serv Res. 2015;15(1). Doi: 10.1186/s12913-015-0801-8.

15. Long LC., Fox MP., Sauls C., Evans D., Sanne I., Rosen SB. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. PLOS ONE. 2016;11(2):e0148546. Doi: 10.1371/journal.pone.0148546.

16. Kim JH., Psevdos G., Gonzalez E., Singh S., Kilayko MC., Sharp V. All-cause mortality in hospitalized HIV-infected patients at an acute tertiary care hospital with a comprehensive outpatient HIV care program in New York City in the era of highly active antiretroviral therapy (HAART). Infection. 2013;41(2):545–51. Doi: 10.1007/s15010-012-0386-7.

17. Akinkuotu A., Roemer E., Richardson A., et al. In-hospital mortality rates and HIV: a medical ward review, Lilongwe, Malawi. Int J STD AIDS. 2011;22(8):465–70. Doi: 10.1258/ijsa.2011.011021.

18. Ford N., Matteelli A., Shubber Z., et al. TB as a cause of hospitalization and in-hospital mortality among people living with HIV worldwide: a systematic review and meta-analysis. J Int AIDS Soc. 2016;19(1). Doi: 10.7448/IAS.19.1.20714.

19. Holmquist L., Russo, A., Elixhauser, A. Tuberculosis Stays in U.S. Hospitals, 2006. HCUP Statistical Brief #60 Agency for Healthcare Research and Quality. 2008.

20. Gonçalves MJF., Ferreira AA. Factors Associated with Length of Hospital Stay among HIV Positive and HIV Negative Patients with Tuberculosis in Brazil. PLoS ONE. 2013;8(4):e60487. Doi: 10.1371/journal.pone.0060487.

6.2 ARTIGO 2

**30-day readmissions among HIV infected patients in the post cART era: a systematic review and meta-analysis**

Lara E. Coelho[1§*], Eliane P. Mendonça[2*], Beatriz Grinsztejn[1*], Valdilea G. Veloso[1*], Paula M. Luz[1*]

[1] Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ, Rio de Janeiro, Brazil

[2] Escola Nacional de Saúde Pública Sergio Arouca, FIOCRUZ, Rio de Janeiro, Brazil

LEC: lara.coelho@ini.fiocruz.br

EPM: eliane.mendonca@posgrad.ensp.fiocruz.br

BG: gbeatriz@ini.fiocruz.br

VGV: valdilea.veloso@ini.fiocruz.br

PML: paula.luz@ini.fiocruz.br

[§]Corresponding author:

Instituto de Nacional de Infectologia Evandro Chagas

Fundação Oswaldo Cruz

Avenida Brasil 4365, Manguinhos, Rio de Janeiro

CEP: 21045-900, Rio de Janeiro, Brasil

Tel/Fax: +55 21 22707064

Email: lara.coelho@ini.fiocruz.br

Keywords: meta-analysis, HIV, hospitalization, readmission, healthcare utilization, length of stay, antiretroviral therapy.

**Abstract**

**Background:** Thirty-day readmissions is a benchmark indicator of the quality of hospital care while also consuming an important share of health expenditures. The knowledge of population sub-groups and/or disease-specific factors associated with increased 30-day readmission allow for better allocation of efforts and attention possibly reducing readmissions, inpatient costs, and hospital-related morbidity. The aim of this study was to evaluate 30-day readmission rates among HIV infected patients as well as the socio-demographic and clinical factors that could be related to an increased risk of 30-day readmission.

**Methods:** A systematic review of the literature coupled with a meta-analysis of the studies that reported on 30-day readmissions of HIV-infected patients was conducted using PRISMA guidelines.

**Results:** Seven studies met inclusion criteria (reported on HIV patients' readmissions), five of which were included in the 30-day readmission meta-analysis (accounting for 8,252 HIV infected patients, 15,334 index hospitalizations and 3,057 30-day readmissions). The pooled 30-day readmission rate was 19% (95% CI 0.14%-0.25%), with high statistical heterogeneity observed among the included studies (I-squared= 94% and p-value <0.0001). Subgroup analysis and bivariate meta-regressions using demographic and clinical variables did not explain the heterogeneity among the studies.

**Conclusions:** This study reveals the lack of studies addressing 30-day readmissions among HIV-infected patients who have experienced an important shift in their morbidity and mortality profile particularly in the last 15 years. The role of HIV/AIDS specific variables (such as immune status, combination antiretroviral therapy use, and virological suppression) as well as the impact of causes of index hospitalization (AIDS-related vs. non-AIDS related) on the 30-day readmission rates remain to be elucidated and confirmed with further evidence.

## Introduction

The 30-day hospital readmission defines a subsequent hospital admission to a hospital within 30 days of discharge, and it can be associated with hospital-acquired infections, sub-optimal inpatient care, premature discharge, failure to coordinate and reconcile medications, inadequate communication among hospital personnel, patients, caregivers, and community based clinicians, insufficient outpatient care and poor planning for care transitions, and severe progressive illness[1,2]. An analysis of 30-day hospital readmission in the United States Medicare fee-for-service program showed that readmissions are frequent, consume an important share of health expenditures and can be used as indicator of the quality and performance of not only a hospital but of an entire health care system[2]. Moreover, almost 30% of the 30-day hospital readmissions are classified as potentially preventable, which means in general that the cause of the readmission is related to the cause of the index hospitalization[3].

Prior studies have addressed whether individuals presenting with specific diseases (such as acute myocardial infarction, heart failure, or pneumonia) have higher rates of readmissions than the ones observed for general population [4–6]. Establishing the most at risk population as well as the predictors of readmission for specific populations would allow the implementation of interventions that decrease the risk of readmission. Few studies have addressed hospital readmissions in HIV-infected individuals.

There are multiple reasons to think that they might have higher risk of readmission than the general population given the occurrence of opportunistic illnesses and toxicities related to antiretroviral therapy. Additionally, non-AIDS related co-morbidities are also observed at increased frequency among HIV-infected individuals, including cardiovascular diseases, cancer, kidney and liver diseases, neurocognitive disorders, and osteopenia/osteoporosis [7,8]. In fact, a recent study in demonstrated that HIV infection is associated 50% increase in the risk of readmission compared with non HIV-infected individuals[9].

In order to evaluate the readmission rates among HIV infected patients as well as the socio-demographic and clinical factors that could be related to an increased risk of 30-day readmission we undertook a systematic review of the literature coupled with a meta-analysis of the included studies. To ensure optimal reporting of included studies, we followed the standards suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement, the PRISMA guidelines[10].

## Material and Methods

### *Eligibility criteria*

The literature search was opened to all studies reporting on hospital readmission rates in HIV-infected populations. Publications reporting only on rehabilitation and/or psychiatric causes of hospitalization were not included.

### *Search of studies*

We performed a bibliographic search of MEDLINE via PubMed, Scopus and Web of Science electronic databases. We did not apply any restriction to publication status. Publications were restricted to the following languages: English, Spanish, French and Portuguese. We filtered for publications dated after 1996 and the last search was run on 02 December 2014. We used the following search strategy: (HIV OR AIDS) AND (readmission, hospital[MeSH Terms] OR "hospital readmission"). We also hand-searched the reference lists of all included articles to ensure a comprehensive coverage.

### *Study selection*

An initial screening was conducted by reading titles and abstracts. If doubts about the fulfillment of inclusion criteria still remained, the full text of paper was assessed. This stage was performed by one review author (LEC). When in doubt, a second author (PML) was consulted.

### *Data extraction*

We developed a data extraction sheet including the most relevant information about the samples and study design. Two authors (LEC and PML) independently extracted data form the selected publications. Disagreements were solved by discussion between these two reviewers. We extracted information from each selected study including: (i) characteristics of the participants/index hospitalization (e.g. age, gender, CD4+ T lymphocyte counts, length of stay); (ii) characteristics of the study (e.g. year, setting, source population, sample size); (iii) outcome measurement (30-day hospital readmission rate).

### *Methodological quality of individual studies*

To assess the quality of selected studies, we adapted the Newcastle-Ottawa scale (NOS)[10] for cohort studies. We graphically represented the quality using the Review Manager (RevMan) software adapting the graphs of risk of bias proposed in Higgins & Green[11]. This entire section was conducted by two authors working together (LEC and EPM), and disagreements were solved by consensus.

***Statistical analysis***

30-day readmissions rates were computed for each one of the included studies by dividing the number of hospital readmissions within 30 days by the number of index hospitalizations discharges. Because normal distribution is required for the pooling of data, logit transformation of the rates and their standard errors were calculated[12]. Pooled 30-day readmission rates were calculated using the Mantel-Haenszel method[13] assuming a fixed-effects model and the DerSimonian-Laird method[14] assuming a random-effects model. Heterogeneity between studies was initially evaluated by visual inspection of forest-plots. Statistical significance of heterogeneity was assessed by Q-test whilst the proportion of true heterogeneity to total variance was calculated by the Higgins I2 statistic[15].

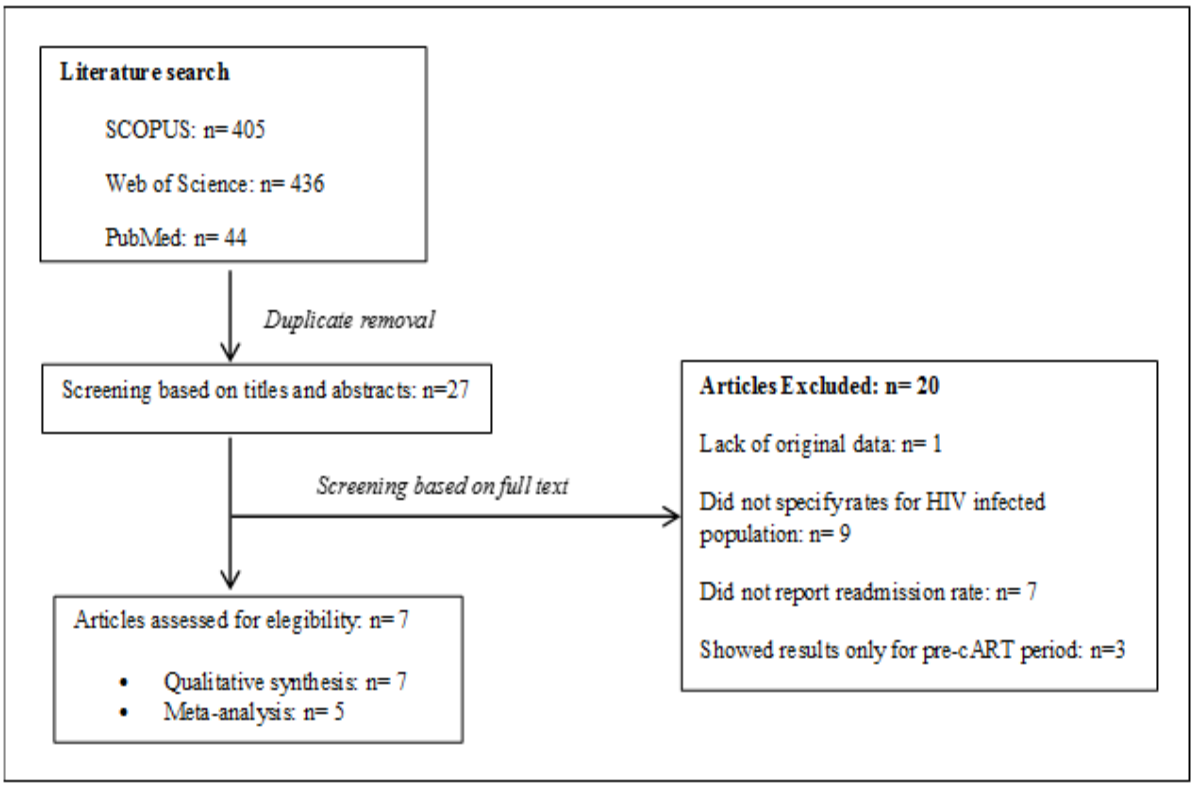
Subgroup analyses were performed according to studies' characteristics. We adjusted models of meta-regression including variables related to participants' and hospitalizations' characteristics aiming to identify possible sources of heterogeneity among the studies. Means and standard deviations (SD) of the continuous variables distributions were used for the meta-regression models. Authors from studies reporting only medians, first and third quartiles were e-mailed and asked for means and SD of their data. When the attempted contact did not yield a response, we estimated the mean and SD based on the median, first and third quartiles, and sample size, as proposed by Wan et al. 2014[16]. We also conducted post-hoc sensitivity analyses to evaluate the impact of removing/including studies on the pooled measures. Data was analyzed using R (version 3.0.3) software, library meta.

**Results**

A total of 405, 436 and 44 studies were found in SCOPUS, Web of Science and PubMed electronic databases, respectively. After duplicates were removed, a first screening based on titles and abstracts identified 27 articles as potentially relevant. We assessed the full text of these 27 papers and 20 were excluded based on the following exclusion criteria: lack of original

data (n=1); did not specify rates for HIV infected population (n=9); did not report readmission rate (n=7); showed results only for the pre-cART period (n=3). No additional studies were identified by hand-searching the reference section of the included studies. The flow diagram of study selection is depicted in Fig 1.

**Figure 1. Flow diagram of literature search for systematic review.**




***Studies characteristics***

Seven publications were included in the systematic review, five of which included only HIV-infected patients[17–21] while two of them assessed a more general population[22,23]. The outcome of interest, 30-day readmission rate among HIV-infected patients, was available in five studies and, therefore, these were included in the meta-analysis.

Of the five studies selected for meta-analysis, four were published in English and one in Spanish. The years of publication ranged from 2000 to 2013. Three articles were from United

States of America (USA), one from Canada and one from Spain. Detailed characteristics of included studies in the systematic review are presented in Table 1.

**Table 1: Characteristics and results of the studies included in the systematic review (n=7).**

| First author, year | Setting / Study design | Selection of study participants | Outcome and independent variables | Design-specific sources of bias (selection bias, loss to follow-up) | Index hospitalization discharges | Readmission (N, %) |
|---|---|---|---|---|---|---|
| **Anis, 2002** | Vancouver, Canada / cohort | All HIV-positive patients admitted to St. Paul's Hospital, from Apr. 1, 1997 to Mar. 1, 1999, who survived to discharge.<br>No exclusion criteria. | Outcome variable: Hospital readmission stratified as follows: within 30 days; within 30 days with the same or related diagnosis; within 1 year.<br>Independent variables: type of discharge (against medical advice *vs.* formal discharge), age, sex, housing status (homeless or not), injection drug use status and severity of underlying HIV disease. | Did not identify who died after discharge (were no longer at risk for readmission) or those who readmitted to another hospital. | 981 | 147 (14.98%) |
| **Barba-Martin, 2000** | Madrid, Spain / cohort | All patients hospitalized at the Internal Medicine service at Hospital Severo Ochoa de Leganés, between Jan. 1, 1997, and Dec. 21, 1997.<br>No exclusion criteria. | Outcome variable: 30-day readmission.<br>Independent variables: diagnostic category for the index hospitalization. | Did not identify who died after discharge (were no longer at risk for readmission) or those who readmitted to another hospital. | 128 | 19 (14.84%) |
| **Berry, 2013** | HIV Research Network, 11 cities in the U.S. / cohort | HIV infected patients from 9 sites of HIVRN, six of them had data from 2005-2010 and three had only 2010 data.<br>Exclusion criteria: hospitalizations of patients not in active care (n=1042), hospitalizations for clinical trials (n=87), for rehabilitation (n=32), with illogical dates (n=9). | Outcome variable: 30-day readmission<br>Independent variables: year of index hospitalization, geographic region, age, gender, race/ethnicity, injection drug use (IDU, either alone or in combination with other HIV risk factors), CD4 cell count, HIV RNA less than 400 copies/ml, antiretroviral use at discharge, length of stay, primary insurance, diagnostic category for index hospitalization, and outpatient follow-up. | Did not identify who died after discharge (were no longer at risk for readmission). Reports a 91% of same hospital readmission in HIVRN sites. | 11651 | 2252 (19.33%) |
| **Chew, 2007** | San Francisco, U.S. / cohort | HIV infected patients (≥18 years) admitted to the Internal Medicine or Family Practice inpatient services at San Francisco General Hospital with the diagnosis of community acquired pneumonia, from Nov. 2005 to Jul., 2006.<br>Exclusion criteria: medical chart not available, not HIV-infected, | Outcome variable: survival at 30 days.<br>Secondary outcomes: length of stay, ICU admission, survival on discharge, and 30-day readmission.<br>Independent variables: age, CD4 count, viral load, prior opportunistic diseases (including bacterial pneumonia), use of ART or prophylactic antibiotics at time of admission, use of alcohol, tobacco, or | Did not identify who died after discharge (were no longer at risk for readmission) or those who readmitted to another hospital. | 98 | 16 (16.33%) |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | concomitant treatment for pneumocystis pneumonia or tuberculosis, no evidence of an infiltrate on chest imaging within 48 h of admission, recently hospitalized (< 10 days), or if the admitting team did not feel the patient had community acquired pneumonia. | illicit drugs, pneumococcal vaccination history, housing status, comorbid psychiatric disease, baseline cognitive impairment, blood and sputum culture results, PORT score components, length of stay, intensive care unit (ICU) admission, discharge condition and discharge housing status. | | | |
| **Hsieh, 2008** | Baltimore, U.S. / cohort | All patients aged ≥18 years with documented fever of ≥100.4ºF, self-reported injection drug use in < 3 months, and ability to provide informed consent, from 1998 to 2004, who were admitted to The Johns Hopkins Hospital Emergency Department.<br>Exclusion criteria: admission to the intensive care unit, belonging to the hospital HIV specialty care service (which admits patients only to a distinct inpatient unit), discharge or transfer from the emergency department, or left the emergency department against medical advice. | Outcome variables: length of stay and readmission within 90-days.<br>Independent variables: age, sex, race, CD4 cell counts, HIV RNA viral load, chronic hepatitis C virus and hepatitis B virus infection, diabetes, blood and skin and soft tissue culture results, length of hospital stay. | Did not identify who died after discharge (were no longer at risk for readmission) or those who readmitted to another hospital. Reports that 25% of the patients declined to participate. | 82 | 34 (41.46%)[a] |
| **Nijhawan, 2012** | Dallas, U.S. / cohort | HIV-infected patients hospitalized on the internal medicine service from Mar.1, 2006 to Nov. 30, 2008 at Parkland Memorial Hospital<br>No exclusion criteria. | Outcome variables: 30-day readmission and 30-day mortality.<br>Independent variables: HIV/AIDS severity, laboratory test results, mental health history, antiretroviral therapy, socio-demographic informations, social instability, health-risk behavior (eg, history of confirmed cocaine, opiate use during the past year), adherence measures (eg, history of missed clinical appointments and leaving against medical advice), and prior acute health care utilization (hospitalizations and emergency department visits), a composite neighborhood measure of social "disadvantagedness". | Used data linkage to identify any readmission to 70 acute care hospitals in the North of Texas. Active searched for deaths after discharge through Social Security Death Index. | 2476 | 623 (25.16%) |

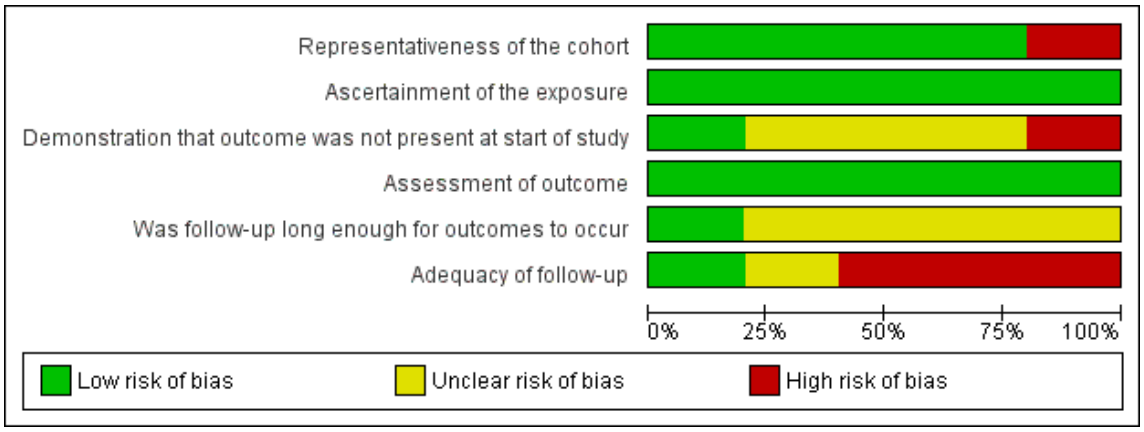
| | | | | | | |
|---|---|---|---|---|---|---|
| **Palepu, 2003** | Vancouver, Canada / case-control | HIV-infected patients hospitalized with *Pneumocystis jiroveci* pneumonia or bacterial pneumonia, at St. Paul hospital from Jan.1, 1997 to Dec. 1, 1997. No exclusion criteria. | Outcome variable: readmission within 14-days. Independent variables: sex, ethnicity, injection drug use, CD4 counts, advanced of HIV/AIDS disease, type of discharge (against medical advice *vs.* formal discharge), hospitalization in the prior 6-months, month of hospitalization, antiretroviral therapy, neighborhood. Cases were defined as HIV-infected patients with *Pneumocystis jiroveci* pneumonia or bacterial pneumonia with a hospital readmission within 14-days; while controls were defined as HIV-infected patients with *Pneumocystis jiroveci* pneumonia or bacterial pneumonia with no readmission within 14-days. | Did not identify who died after discharge (were no longer at risk for readmission) or those who readmitted to another hospital. | 1311 | 216 (16.5%)[b] |

[a] 90-day readmission rate
[b] 14-day readmission rate

***Methodological quality of individual studies and sensitivity analysis***

Fig 2 shows the assessment of the methodological quality of the included publications. According to New Castle-Otawa scale, three domains (Selection, Comparability and Outcome) should be evaluated in order to assess the quality of a study. For the purpose of this review, since the study population of the included studies were all classified as exposed (which is to say that they all had been hospitalized), the Comparability domain was not applicable.

**Figure 2. Assessment of the methodological quality of the studies included in the meta-analysis.**



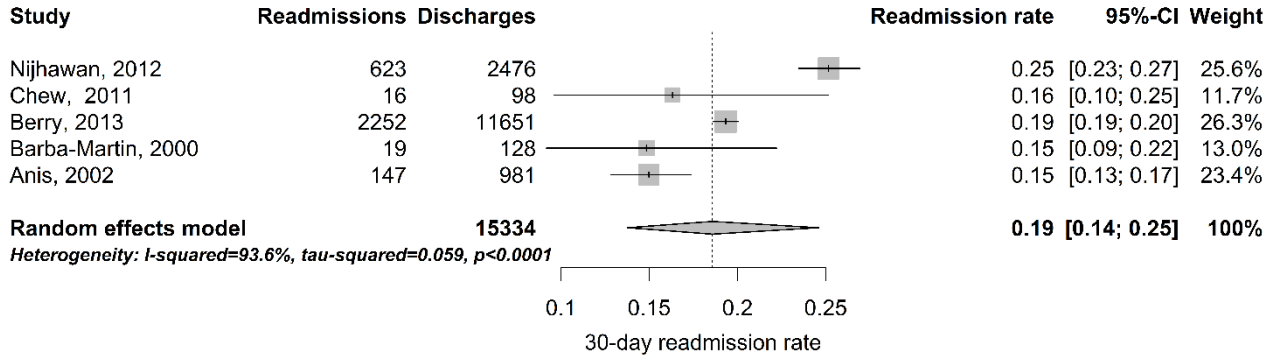

Regarding the Selection domain, one study was negatively evaluated on the representativeness of the hospitalized HIV-infected population[21] because its population was restricted to HIV-infected patients diagnosed with community acquired pneumonia. We carried out a sensitivity analysis to evaluate the impact of removing this study on the pooled measure and since no important changes were observed, we decided to keep the study in all analyses. All studies used secure records to assess the ascertainment of exposure (index hospitalization), therefore, they were all positively scored in this domain. Most of the studies did not inform if they checked the 30-day time frame prior to study initiation (to rule out if the hospitalization being considered as index was not indeed a readmission) and were considered as having an unclear risk of bias in demonstrating that the outcome was not present at start of the study. As for outcome ascertainment, all studies were deemed to have used secure records to assess the outcome (30-day readmission). Most of studies did not report on a minimum of 30-day follow-up of patients discharged at the last month of the study period and were considered as having

unclear risk of bias in the follow-up time. Regarding the adequacy of follow-up (30 days after discharge), it was established that in order to have a low risk of bias studies should report on active search or data linkage to identify readmission to other hospitals or deaths. Most of the studies did not report on those active searches and were considered as having a high risk of bias in the adequacy of follow-up category.

***Pooled measure: Readmission rate within 30-days***

In total, 8,252 HIV infected patients from the 5 studies included in the meta-analysis had an index hospitalization. These individuals accounted for 15,334 index hospitalizations and 3,057 30-day readmissions. The 30-day readmission rates ranged from 15% to 25%, with a median of 16% and a mean of 18%. The highest 30-day readmission rate (25%) was observed in the study of Nijhawan et al.[20] with HIV infected patients in Dallas, USA, during the years of 2006 and 2008. The lowest rate was observed in the study of Barba-Martin et al. (15%) [22], with HIV infected patients in Madrid, Spain, during the year of 1997. The pooled 30-day readmission rate was 19% (95% CI 0.14%-0.25%), with high statistical heterogeneity observed among the included studies (I-squared= 94% and p-value <0.0001) (Fig 3).

**Figure 3. Forest plot showing summary estimates and pooled 30-day readmission rates from 5 studies included in the meta-analysis.**




Heterogeneity among the publications included in the meta-analysis were explored through subgroup analysis and meta-regression models. Meta-analysis stratified by type of hospitalization (all hospitalizations vs. hospitalization for community-acquired pneumonia), by

number of study sites (multicentric vs. only one center), by last year of the study (prior to 2005 and 2005 or after) did not explain the observed heterogeneity (data not shown). The same result was obtained in bivariate meta-regression models fitted by age, gender, previous AIDS diagnosis, cART use prior to index hospitalization and length of stay (LOS) of index hospitalization with none of these factors being able to explain the heterogeneity (Table 2). Models exploring the role of race, injection drug use, type of discharge (formal or against medical advice) and CD4+ T lymphocyte counts were not performed because data were not available in most of the studies.

**Table 2. Demographics and clinical characteristics of the studies included in the meta-analysis and meta-regression analyses.**

| Author, year | Age, mean (SD) | % Males | % Non-white | % IDU | Previous AIDS diagnosis (%) | cART use[b] (%) | Length of stay in days, mean (SD) | CD4 counts, cells/mm$^3$, mean (SD) | Discharge against medical advice[d] (%) |
|---|---|---|---|---|---|---|---|---|---|
| **Anis, 2002** | 38.3 (8.2) | 78.3 | Not available | 45.7% | 36.2 | Not available | 10.2 (12.4) | Not available | 13 |
| **Barba-Martin, 2000** | 34.3* | Not available | Not available | Not available | Not available | Not available | 11.8* | Not available | Not available |
| **Berry, 2013[a]** | 46.5 (0.3) | 68.6 | 74.8 | 28.1% | Not available | 61.3[c] | 4.9 (0.4) | 261 (26.9) | Not available |
| **Chew, 2011** | 45.4 (7.4) | 69.6 | Not available | Not available | 80 | 43.1 | 5.7 (2.0) | 318* | Not available |
| **Nijhawan, 2012** | 43 (9.4) | 73.4 | 75.4 | Not available | 24.8 | 45.1 | 7 (9.8) | Not available | 5.6 |
| **Meta-regression coefficients (95% CI)** | **0.03 (-0.06, 0.12)** | **-1.86 (-20.9, 17.2)** | **Not applicable** | **Not applicable** | **-0,69 (-14.7, 13.4)** | **-0.55 (-32.8, 31.7)** | **-0.05 (-0.20, 0.10)** | **Not applicable** | **Not applicable** |
| **$R^2$** | **0%** | **0%** | **Not applicable** | **Not applicable** | **13.15%** | **0%** | **0%** | **Not applicable** | **Not applicable** |

IDU: injection drug users; cART: combination antiretroviral therapy; SD: standard deviation; CI: confidence interval; $R^2$: amount of heterogeneity accounted for by the variable.

*Standard deviations not informed.

[a] Means and standard deviations obtained from medians and interquartile ranges and then rearranged ("Index Hospitalizations without 30-day readmission" and "Index Hospitalizations with 30-day readmission") to obtain overall values

[b] Prior to index hospitalization

[c] Information extracted from the subgroup "Discharged on cART after being admitted on cART"

[d] Index hospitalization related discharge

***Predictors for 30-day readmission***

The assessment of predictors of 30-day readmission among HIV infected through meta-regression models of the aggregate studies' variables failed due to the small number of studies included and non-uniform independent variables explored by the studies individually (Table 2). Predictors analysis performed within the individual studies were then compared for consistency.

Three studies reported on HIV/AIDS related variables and the risk of 30-day readmission. Berry et al.[19] showed that CD4+ T lymphocyte counts below 50 cells/mm³ in the year of index hospitalization was associated with 30-day readmission (Odds Ratio [OR] 1.80, IQR: 1.53-2.11) and that HIV viral load and cART use were not found to be associated with 30-day readmission. Chew et al.[21] addressed hospital admissions by community-acquired pneumonia and did not find an association between CD4+ T lymphocyte counts (the closest one to the index hospitalization, 12 months prior or 6 months after) or use of cART with 30-day readmission risk. Nijhawan et al.[20] found that 30-day readmission was associated with history of AIDS defining illness (OR 1.32, IQR 1.02, 1.69) and with CD4+ T lymphocyte counts below 92 cells/mm3 (OR 1.30, IQR 1.04, 1.63). The association between LOS and 30-day readmission was evaluated in two studies[19,20], and in both of them, bivariate analysis showed that longer LOS was associated with increased risk of 30-day readmission. However, in adjusted models, this association remained significant only in one study (9 days or longer OR 1.77, IQR 1.53, 2.04)[19]. Associations between age, gender, race with 30-day readmissions were provided in two studies without any significant effect[19,20], also no significant effect was found for injection drug use[19].

**Discussion**

The present systematic review and meta-analysis brought together readmission estimates for HIV infected patients found in a limited number of publications, all from high income settings. This study reveals the lack of studies addressing this relevant outcome among HIV-infected patients who have experienced an important shift in their morbidity and mortality profile, particularly in the last 15 years. As HIV evolves into a chronic disease, the knowledge of hospital related morbidity patterns in this population will be of great value to adequately address and plan HIV care. Thirty-day readmissions is already a benchmark indicator of the quality of hospital care for the general population[1,24] and we believe it may prove of value for guiding and evaluating

HIV care. Additionally, the knowledge of factors associated with readmission in this particular population can help focus efforts and attention on the most at risk patients and/or conditions possibly reducing readmissions, inpatient costs, and hospital-related morbidity among HIV infected patients.

The pooling of the 30-day readmission rates yielded an overall 30-day readmission rate of 19% (95% CI 14%-25%), which is higher than the 13.9% estimated for general US population in 2013 [26]. Although, in our theoretical framework we had speculated that severe immunodeficiency, use of cART, and hospitalizations due to AIDS-related illnesses could be associated with 30-day readmission among HIV infected patients, in our pooled analysis we failed to identify predictors associated with 30-day readmission. It is worth noting, though, that the failure to detect an association could be due to the small number of studies available for our meta-analysis.

Severe immunodeficiency is associated with risk of hospitalization among HIV infected patients. Two studies included in the meta-analysis found increased risk of 30-day readmissions for patients with low CD4+ T lymphocyte counts[19,20] and with history of AIDS defining illness[20]. A recent meta-analysis found that among HIV infected patients almost half of the hospitalizations worldwide are due to AIDS-related diseases[26], notably in middle and low-income settings. Unfortunately, in this review, we were not able to explore the cause of the index hospitalization and its relationship with 30-day readmission risk because this variable was only available for one study (that reported on increased risk of 30-day readmission associated with an AIDS-related index hospitalization)[19]. Future studies are needed to address this plausible link.

Use of cART has been shown to reduce the risk of hospitalization[27] and death[28] but the impact of cART use on 30-day readmissions remains unclear. Berry et al.[19] hypothesized that the use of cART at discharge from the index hospitalization (among those who started cART during the index hospitalization) could increase the 30-day readmission risk because of cART-related toxicities or immune reconstitution inflammatory syndrome (IRIS) which are both more frequent in the early months of cART use. However, after adjusting for other covariates including CD4+ T lymphocyte count, cART use was no longer statistically associated with increased risk of 30-day readmission. Nijhawan et al.[20] also explored the effect of cART use on 30-day readmission risk using a different theoretic model. The aim of their analysis was to estimate the effect of using cART 30 days prior to the index hospitalization on the 30-day readmission risk. Similarly to the results described above, it was found in the unadjusted analysis that those who started cART 30 days prior

to the index hospitalization were at increased risk of 30-day readmission although this finding was not sustained in the adjusted analysis. These two studies, coupled with those that evaluated overall hospitalizations among HIV infected patients[29,30] suggests that the association of cART use with 30-day readmission might be complex meriting further proof of evidence. Consistent use of cART restores HIV-infected patients' immunity likely lowering their risk of 30-day readmission. In contrast, for those who started cART recently, the risk of drug toxicities and of IRIS might contribute for a higher risk of 30-day readmission. Finally, starting cART during a hospitalization when other co-morbid conditions might be present, including opportunistic illnesses, increases the risk of toxicities, drug interactions and IRIS[31–33] and might also be associated with an increased risk of 30-day readmission.

Several studies have found that longer LOS was associated increased risk of 30-day readmission[2,34,35]. In contrast, concerns have been raised regarding policies favoring reductions in LOS stating that this could lead to an increase in 30-day readmission if patients were to be discharged prematurely. Indeed, these speculations were raised after some studies showed trends of shorter duration of index hospitalizations and increased trends in hospital readmission[36–38]. For the HIV infected population, prior studies have found that HIV infected patients have longer LOS than non HIV patients[39] and that hospitalizations due to AIDS-related diseases are associated with longer LOS[26]. Nonetheless, the association between longer LOS and 30-day readmission in HIV-infected patients was evaluated only by two studies and found to be statistically significant only in one of them[19].

In this meta-analysis we were not able to explore the role of causes of hospitalization and 30-day readmission due to the lack of information provided in the studies. An interesting aspect of studying causes of index hospitalization and causes of readmissions is to estimate the proportion of readmission that could be considered potentially preventable[40]. Previous studies have shown that the proportion of potentially preventable readmission varies widely ranging from 5% to 79%, and a meta-analysis of the aggregate estimates generate a unweighted median of 27% [3]. This variation among study's estimates appears to correlate with factors that span multiple levels including the individual and the hospital level as well as with the methodology applied by each study[3,41]. In addition, specific underlying diseases, such as cardiovascular diseases, seem to be related to the risk of a potential preventable readmission[41]. The knowledge of potential preventable readmissions in HIV infected populations is scarce, but a recent publication estimated

53% of the 30-day readmissions occurring in a large urban hospital were potentially preventable. The authors also explored the factors associated with potentially preventable 30-day readmissions and found that "not receiving cART" the main predictor of these events (adjusted OR 5.9, 95%CI 2.4,14.8)[42]. This new evidence corroborates the potential impact of cART use in preventing 30-day readmission especially in regards to the potentially preventable fraction of 30-day readmissions. It is worth mentioning that this last publication also reported on 30-day readmission rates among HIV-infected individuals, which was found to be quite similar to that reported in this study (19% of 30-day readmissions rate). Unfortunately, the study was not included in our meta-analysis because its publication date occurred after our last search date.

There are limitations to our study that should be acknowledged. Due to the small number of studies found and the high heterogeneity observed among them caution is essential when interpreting the results of this meta-analysis. In particular, the high heterogeneity observed among studies prevented us from detecting publication bias[11]. Our ability to evaluate predictors of 30-day readmission was also limited by the small sample and by the fact that reporting on associated factors was not consistent across studies. Additionally, it is worth noting that none of the included studies reported data from middle or low-income settings. Several publications have shown that important differences exist between high- and low-middle income settings concerning rates and causes of hospitalizations among HIV-infected patients[27]. These differences could influence readmission rates as well as their predictors.

## Conclusion

This review and meta-analysis pooled together the available data on 30-day readmission among HIV infected patients in the post-cART era, and revealed that only a small number of studies have addressed readmissions in this population. The estimated pooled 30-day readmission rate among HIV infected patients is similar to the ones observed in general population. On the other hand, the role of HIV/AIDS specific variables (such as immune status, cART use, and virological suppression) as well as the impact of causes of index hospitalization (AIDS-related vs. non-AIDS related) on the 30-day readmission risk remains to be elucidated and confirmed with further evidence.

## Competing interests

Authors have no competing interests to declare.

## Acknowledgements

BG and PML acknowledge funding from the National Council of Technological and Scientific Development (CNPq) and the Research Funding Agency of the State of Rio de Janeiro (FAPERJ). We wish to thank all authors of potentially eligible and included studies who responded to our emails and those who supplied us with additional data and information.

## Authors' contributions

LEC conceived of the study and participated in its design and coordination, and drafted the manuscript. PML, BG, VGV participated in its design and drafted the manuscript. EPM helped with statistical analysis and drafted the manuscript. All authors have given final approval of the version to be published and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

## References


1. Berenson RA, Paulus RA, Kalman NS. Medicare's readmissions-reduction program--a positive alternative. N Engl J Med. 2012;366: 1364–1366. doi:10.1056/NEJMp1201268

2. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360: 1418–1428.

3. van Walraven C, Bennett C, Jennings A, Austin PC, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. CMAJ Can Med Assoc J J Assoc Medicale Can. 2011;183. doi:10.1503/cmaj.101860

4. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Hospital readmission performance and patterns of readmission: retrospective cohort study of Medicare admissions. BMJ. 2013;347: f6571–f6571. doi:10.1136/bmj.f6571

5. Krumholz HM, Lin Z, Keenan PS, Chen J, Ross JS, Drye EE, et al. Relationship Between Hospital Readmission and Mortality Rates for Patients Hospitalized With Acute Myocardial Infarction, Heart Failure, or Pneumonia. JAMA. 2013;309: 587. doi:10.1001/jama.2013.333

6. Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, et al. Statistical models and patient predictors of readmission for heart failure: a systematic review. Arch Intern Med. 2008;168: 1371–1386.

7. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. The Lancet. 2013;382: 1525–1533. doi:10.1016/S0140-6736(13)61809-7

8. Castilho JL, Luz PM, Shepherd BE, Turner M, Ribeiro SR, Bebawy SS, et al. HIV and cancer: a comparative retrospective study of Brazilian and U.S. clinical cohorts. Infect Agent Cancer. 2015;10. doi:10.1186/1750-9378-10-4

9. Berry S, Fleishman J, Moore R, Gebo K. Thirty-day hospital readmissions for adults with and without HIV infection: HIV readmissions. HIV Med. 2015; n/a–n/a. doi:10.1111/hiv.12287

10. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009;62. doi:10.1016/j.jclinepi.2009.06.006

11. G. Wells , B Shea, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

12. Higgins JPT, Green S, Cochrane Collaboration, editors. Cochrane handbook for systematic reviews of interventions. Chichester, England ; Hoboken, NJ: Wiley-Blackwell; 2008.

13. Wilson, David B LMW. Practical meta-analysis. California: Sage Publications; 2001.

14. MANTEL N, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22: 719–748.

15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7: 177–188.

16. Borenstein M, editor. Introduction to meta-analysis. Chichester, U.K: John Wiley & Sons; 2009.

17. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. 2014;14: 135.

18. Anis AH, Sun H, Guh DP, Palepu A, Schechter MT, O'Shaughnessy MV. Leaving hospital against medical advice among HIV-positive patients. Can Med Assoc J. 2002;167: 633–637.

19. Palepu A, Sun H, Kuyper L, Schechter MT, O'Shaughnessy MV, Anis AH. Predictors of Early Hospital Readmission in HIV-infected Patients with Pneumonia. J Gen Intern Med. 2003;18: 242–247.

20. Berry SA, Fleishman JA, Yehia BR, Korthuis PT, Agwu AL, Moore RD, et al. Thirty-day hospital readmission rate among adults living with HIV: AIDS. 2013;27: 2059–2068. doi:10.1097/QAD.0b013e3283623d5f

21. Nijhawan AE, Clark C, Kaplan R, Moore B, Halm EA, Amarasingham R. An electronic medical record-based model to predict 30-day risk of readmission and death among HIV-infected inpatients. JAIDS J Acquir Immune Defic Syndr. 2012;61: 349–358.

22. Chew KW, Yen IH, Li JZ, Winston LG. Predictors of Pneumonia Severity in HIV-Infected Adults Admitted to an Urban Public Hospital. AIDS Patient Care STDs. 2011;25: 273–277. doi:10.1089/apc.2010.0365

23. Barba Martin R, Marco Martinez J, Plaza Canteli S, Gomez Rodrigo J, de la Riva I, Cervero Jimenez M, et al. [Retrospective study of early readmissions at an internal medicine service]. Rev Clin Esp. 2000;200: 252–256.

24. Hsieh Y-H, Rothman RE, Bartlett JG, Yang S, Kelen GD. HIV seropositivity predicts longer duration of stay and rehospitalization among nonbacteremic febrile injection drug users with skin and soft tissue infections. JAIDS J Acquir Immune Defic Syndr. 2008;49: 398–405.

25. Axon RN, Williams MV. Hospital readmission as an accountability measure. JAMA. 2011;305: 504–505. doi:10.1001/jama.2011.72

26. Barret ML, Wier LM, Jiang J, Steiner CA. All-Cause Readmissions by Payer and Age, 2009–2013. Agency Healthc Res Qual HCUP Stat Brief 199. 2015;

27. Ford N, Shubber Z, Meintjes G, Grinsztejn B, Eholie S, Mills EJ, et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. Lancet HIV. 2015; doi:10.1016/S2352-3018(15)00137-X

28. Luz PM, Bruyand M, Ribeiro S, Bonnet F, Moreira RI, Hessamfar M, et al. AIDS and non-AIDS severe morbidity associated with hospitalizations among HIV-infected patients in two regions with universal access to care and antiretroviral therapy, France and Brazil, 2000–2008: hospital-based cohort studies. BMC Infect Dis. 2014;14: 278.

29. Grinsztejn B, Luz PM, Pacheco AG, Santos DVG, Velasque L, Moreira RI, et al. Changing Mortality Profile among HIV-Infected Patients in Rio de Janeiro, Brazil: Shifting from AIDS to Non-AIDS Related Conditions in the HAART Era. Yazdanpanah Y, editor. PLoS ONE. 2013;8: e59768. doi:10.1371/journal.pone.0059768

30. Crum-Cianflone NF, Grandits G, Echols S, Ganesan A, Landrum M, Weintrob A, et al. Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? J Acquir Immune Defic Syndr 1999. 2010;54: 248–257.

31. Gebo KA, Diener-West M, Moore RD. Hospitalization rates in an urban cohort after the introduction of highly active antiretroviral therapy. J Acquir Immune Defic Syndr 1999. 2001;27: 143–152.

32. Maartens G, Decloedt E, Cohen K. Effectiveness and safety of antiretrovirals with rifampicin: crucial issues for high-burden countries. Antivir Ther. 2009;14: 1039–1043. doi:10.3851/IMP1455

33. Grant PM, Zolopa AR. When to Start ART in the Setting of Acute AIDS-Related Opportunistic Infections: The Time Is Now! Curr HIV/AIDS Rep. 2012;9: 251–258. doi:10.1007/s11904-012-0126-8

34. Müller M, Wandel S, Colebunders R, Attia S, Furrer H, Egger M, et al. Immune reconstitution inflammatory syndrome in patients starting antiretroviral therapy for HIV infection: a systematic review and meta-analysis. Lancet Infect Dis. 2010;10: 251–261.

35. Hasan O, Meltzer DO, Shaykevich SA, Bell CM, Kaboli PJ, Auerbach AD, et al. Hospital readmission in general medicine patients: a prediction model. J Gen Intern Med. 2010;25: 211–219. doi:10.1007/s11606-009-1196-1

36. van Walraven C, Dhalla IA, Bell C, Etchells E, Stiell IG, Zarnke K, et al. Derivation and validation of an index to predict early death or unplanned readmission after discharge from hospital to the community. Can Med Assoc J. 2010;182: 551–557. doi:10.1503/cmaj.091117

37. Baker DW, Einstadter D, Husak SS, Cebul RD. Trends in postdischarge mortality and readmissions: has length of stay declined too far? Arch Intern Med. 2004;164: 538–544.

38. Kociol RD, Lopes RD, Clare R, Thomas L, Mehta RH, Kaul P, et al. International variation in and factors associated with hospital readmission after myocardial infarction. JAMA. 2012;307: 66–74.

39. Bueno H, Ross JS, Wang Y, et al. Trends in length of stay and short-term outcomes among medicare patients hospitalized for heart failure, 1993-2006. JAMA. 2010;303: 2141–2147. doi:10.1001/jama.2010.748

40. Krentz HB, Dean S, Gill MJ. Longitudinal assessment (1995–2003) of hospitalizations of HIV-infected patients within a geographical population in Canada. HIV Med. 2006;7: 457–466.

41. Goldfield NI, McCullough EC, Hughes JS, Tang AM, Eastman B, Rawlins LK, et al. Identifying potentially preventable readmissions. Health Care Financ Rev. 2008;30: 75.

42. Vest JR, Gamm LD, Oxford BA, Gonzalez MI, Slawson KM. Determinants of preventable readmissions in the United States: a systematic review. Implement Sci. 2010;5: 88.

43. Nijhawan AE, Kitchell E, Etherton SS, Duarte P, Halm EA, Jain MK. Half of 30-Day Hospital Readmissions Among HIV-Infected Patients Are Potentially Preventable. AIDS Patient Care STDs. 2015;29: 465–473. doi:10.1089/apc.2015.0096

6.3 ARTIGO 3

**30-day readmission rates in an HIV-infected cohort from Rio de Janeiro, Brazil**

Lara E. Coelho[§1], Sayonara R. Ribeiro[1], Andre M. Japiassu[1], Ronaldo I. Moreira[1], Priscila C. Lara[1], Valdilea G. Veloso[1], Beatriz Grinsztejn B[1], Paula M. Luz[1]

Instituto Nacional de Infectologia Evandro Chagas, FIOCRUZ, Rio de Janeiro, Brazil

[§]Corresponding author: Lara Coelho, MD, MSc

Email: lara.coelho@ini.fiocruz.br

Address: Instituto Nacional de Infectologia Evandro Chagas (INI), FIOCRUZ, Av Brasil 4365, Manguinhos, Rio de Janeiro, RJ, Brazil. Zip code: 21045-900.

Keywords: HIV, hospitalization, readmission, healthcare utilization, length of stay, antiretroviral therapy

**Abstract**

**Introduction:** The 30-day readmission rate is an indicator of the quality of hospital care and transition to the outpatient setting. HIV infection might increase the risk of readmission though estimates of 30-day readmission rates are unavailable among HIV infected individuals living in middle/low income settings. Additionally, factors that may increase readmission risk in HIV infected populations are poorly understood.

**Methods:** 30-day readmission rates were estimated for HIV-infected adults from the Instituto Nacional de Infectologia Evandro Chagas/Fiocruz cohort in Rio de Janeiro, Brazil, from January 2007 to December 2013. Cox regression models were used to evaluate factors associated with the risk of 30-day readmission.

**Results:** Between January 2007 and December 2013, 3991 patients were followed and 1861 hospitalizations were observed. The estimated 30-day readmission rate was 14% (95% confidence interval 12.3%-15.9%). Attending a medical visit within 30 days after discharge (aHR 0.74, p=0.057), being hospitalized in more recent calendar years (aHR 0.87, p=0.002) and the use of antiretroviral therapy (adjusted hazard ratio [aHR] 0.76, p=0.16) reduced the risk of 30-day readmission. In contrast, hospitalization due to AIDS-defining diseases (aHR 1.62, p=0.015), having a CD4 count ≤ 50 cells/mm³ (aHR 1.63, p=0.053), time since HIV diagnosis longer than 10 years (aHR 1.65, p=0.036) and leaving hospital against medical advice (aHR 2.78, p=0.022) increased the risk of 30-day readmission.

**Conclusions:** Our results suggest that preventing immune deterioration, through early HIV diagnosis and prompt antiretroviral therapy initiation, coupled with an early medical visit post-discharge could reduce 30-day readmissions in our population.

## Introduction

Hospital readmission within 30 days of discharge, i.e. 30-day readmission, has been increasingly proposed as an indicator of the quality of hospital care and of transition care to the outpatient setting[1]. Between hospitals comparisons, adjusted for patients' characteristics and for the community within which a hospital is located[2], can help identify institutions with worse performance allowing for adoption/reviewing of clinical protocols to improve hospital care[3]. Economically, 30-day readmissions are expensive and consume a great share of health designated expenditures[4]. Altogether, studies have suggested that the keeping of 30-day readmission rates within the expected average values can result in a win-win scenario: improvement in hospital quality and efficiency allowing for better allocation of health expenditures.

In the United States, all-cause 30-day readmission rates in the general population is estimated at 14%[5]. Additionally, of the overall 30-day readmissions, 30% are thought to be potentially preventable events[6]. Several chronic medical conditions have been associated with high 30-day readmission rates with HIV being recently included among these conditions[7–9]. A recent study conducted in the United States showed a 1.5-fold increase in the risk of readmission for HIV infected patients compared to their non-HIV infected counterparts[9]. Moreover, among HIV infected patients, the proportion of potentially preventable readmissions is suggested to be even higher, reaching 53%[10].

The study of 30-day readmission rates and its predictors among HIV infected patients can provide relevant information to guide monitoring of hospital quality and transition of care with the goal of reducing morbidity of the HIV infected population. To the best of our knowledge, studies addressing 30-day readmission rates and its determinants in HIV infected populations are restricted to high-income settings[9–16] and the findings likely do not reflect low- to middle-income settings due to dissimilarities in infectious diseases burden as well as differences in the provision and structure of health care. In this study, we sought to 1) estimate 30-day readmissions rates among HIV patients living in a middle-income setting and 2) identify patient- and health care-level factors that were associated with higher risk of 30-day readmission among HIV infected patients from a cohort in Rio de Janeiro, Brazil, during the period of 2007-2013.

## Methods

### Study site and population

Since 1986, Instituto Nacional de Infectologia Evandro Chagas of Fundacao Oswaldo Cruz (INI/FIOCRUZ) has been a national reference center for infectious diseases care, research and training, being one of the largest providers of primary, specialty, and tertiary care for HIV infected individuals in Rio de Janeiro State. INI comprises an Infectious Disease tertiary hospital, Evandro Chagas Hospital, a day clinic (for chemotherapy and other parenteral drugs administration), an outpatient clinic and an emergency service, all funded by the Brazilian national health system (known as Sistema Único de Saúde). All HIV infected patients followed in the INI cohort have free-of-charge access to INI's facilities as well as to antiretroviral treatment and other medications (such as opportunistic infections prophylaxis, Kaposi sarcoma chemotherapy, and diabetes, hypertension medications, etc.) provided by the Brazilian national health system. A longitudinal, periodically updated, observational clinical database has been maintained on patients receiving HIV care at INI. The database includes socio-demographic, laboratory, clinical, and therapeutic information abstracted from the medical records by trained staff. Additionally, dates of admission and discharge to Evandro Chagas Hospital are also included in the database along with discharge diagnoses and summary. Cohort procedures have been described and results published[17–19].

For the present study, the study population included adult (≥18 years of age at cohort enrollment) HIV infected patients, enrolled in the INI cohort between 01 January 1985 and 01 December 2013, who were alive after 01 January 2007 and in active care (at least one medical visit after 01 January 2007).

### Outcome definition

Index hospitalizations were defined as: 1) the first hospitalization in the study period or any hospitalization occurring >30 days after the most recent previous hospitalization, and 2) for which there was a live discharge. Hospitalizations occurring from 01 January 2007 (or from date of cohort enrollment for those enrolled after this date) until 31 December 2013 were considered. Patients were not censored after a hospitalization such that all hospitalization events during the years 2007-2013 were included. The only exceptions were the exclusion of hospitalizations (1) with admission

date prior to 01 February 2007 because of the need to observe 30 days before a potential index hospitalization, and (2) with discharge date after 30 November 2013 because of the need to observed 30 days after a discharge for potential 30-day readmissions. Hospital readmissions occurring within 30 days of an index hospitalization discharge were defined as 30-day readmissions. When a "chain" of multiple readmissions with less than 30-day intervals each followed an index hospitalization, all readmissions in the chain were excluded from being an index hospitalization. 30-day readmission rate was calculated by dividing the number of 30-day readmissions by the number of index hospitalizations.

**Independent variables**

Socio-demographic and clinical variables were evaluated for association with 30-day readmission risk. Lymphocytes T CD4+ and HIV viral load closest to index hospitalization were selected on a timeframe of 180 days before and 30 days after the hospital admission date. Use of antiretroviral therapy (ART) before index hospitalization was used as a dichotomous variable. Since we do not have information on adherence, after ART first prescription, participants were defined as on ART. Time since first HIV positive serologic test was calculated as the difference between date of admission and date of the first positive HIV test. Type of hospitalization discharge was based on discharge reports and categorized as follows: according to medical advice, against medical advice, transfer to another hospital facility and unknown. Length of stay (LOS) was calculated by subtracting hospital admission date from date of discharge and adding 1. Use of intensive care unit (ICU) (yes/no) was used as a proxy for the severity of the patient's clinical condition. Early transition from hospital to outpatient care was evaluated through the presence of a medical visit within 30-days of index hospitalization discharge or before readmission for those readmitted within 30-days.

Hospitalization discharge reports were reviewed and all the diagnoses listed in the discharge report were classified using the 10$^{th}$ Edition of the International Classification of Disease (ICD-10), into 24 different categories[18]. Since some ICD-10 codes could be allocated to several categories, we considered a hierarchical classification scheme with a decreasing order of priority as follows: AIDS-events, non-AIDS malignancies, infections and then systemic events[18]. Subsequently, to determine the primary cause of a hospitalization, the one or more ICD-10 codes listed in the

discharge reports were hierarchically classified as follows: AIDS-defining diseases, non-AIDS malignancies, cardiovascular disease, bacterial infections, fungal infections, viral infections, parasitic infection, digestive diseases, renal diseases, respiratory diseases, neurologic diseases, endocrine diseases, hematological diseases, psychiatric diseases, viral hepatitis, non-viral hepatitis, dermatological diseases, rheumatologic diseases, trauma, gynecologic disease, toxicities, others and sings and symptoms.

### Statistical analysis

The evaluation of the factors associated with 30-day readmission risk was performed using Cox extended regression models (accounting for clusters within patients). Patient's follow-up started on the day of discharge from the index hospitalization and ended at the readmission date, date of death or 30 days after index discharge, whichever occurred first. Variables with p-value below 0.10 in the unadjusted analysis were included in the adjusted model in order to explore their effects after adjusting for all potential confounding. Proportional hazards assumption were tested using Schoenfeld residuals. The dichotomous variable "medical visit within 30-day of discharge" violated this assumption and was included in the model as a time-dependent variable such that a patient's follow up time was split into before and after the medical visit for those who attended a medical visit within 30-days of discharge. R (version 3.0.3) and library "survival" were used for the analyses.

### Ethical considerations

This study was approved by the ethics committee of the INI (CAAE 0032.0.009.000-10) and was conducted according to the principles expressed in the Declaration of Helsinki. All patient records/information were de-identified prior to analysis.

## Results

During the study period, from the 3991 included patients, 3014 were never hospitalized while 977 had at least one hospitalization during the study period. In total, 1861 hospitalization events occurred: 1442 were considered index hospitalizations, 202 were 30-day readmissions, and 16

index hospitalizations were followed by death after discharge (without readmission) (Figure 1). Thirty-day readmission rate was estimated as 14.0% (95% confidence interval [CI] 12.3%-15.9%). The three most frequent causes of index hospitalizations were AIDS-defining diseases (688/1442, 47.7%), bacterial infections (289/1442, 20.0%), and cardiovascular diseases (117/1442, 8.1%) (Figure 2). 30-day readmission rate among AIDS-defining diseases index hospitalizations reached 18.8% (95% CI 15.9%-21.9%) which is higher than the overall rate. The highest readmission rate was observed for endocrine diseases (20.0%, 95% CI 3.5%-55.8%) which comprised only 0.7% (n=10) of the index hospitalizations (Figure 2). Among the 202 readmissions, the most frequent cause of hospitalization was an AIDS-defining diseases (129/202, 63.9%) and the second most frequent cause was bacterial infections (36/202, 17.8%).

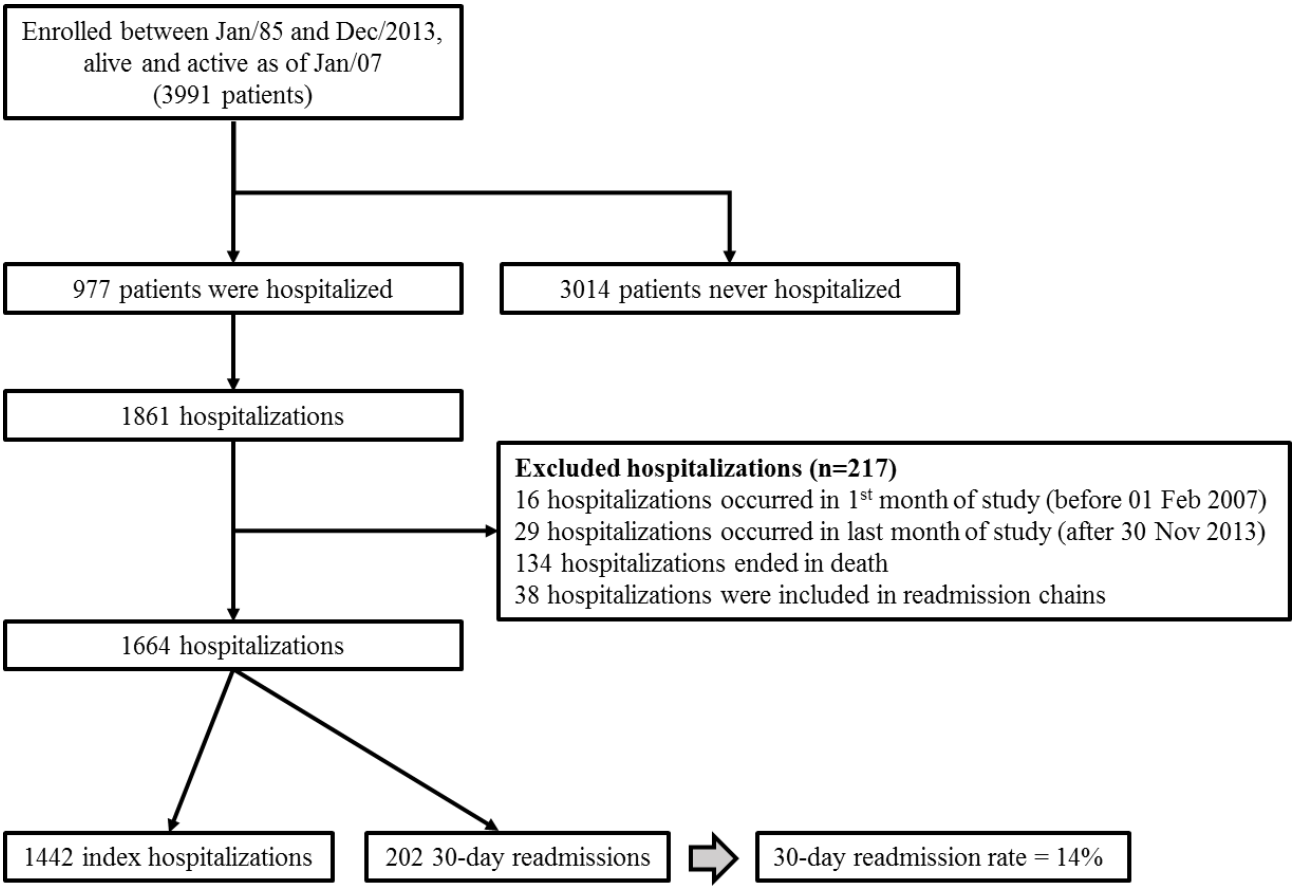



**Figure 1. Patients and hospitalizations.** Flowchart showing patient selection, total number of hospitalizations, hospitalization exclusion criteria and 30-day readmission rate.

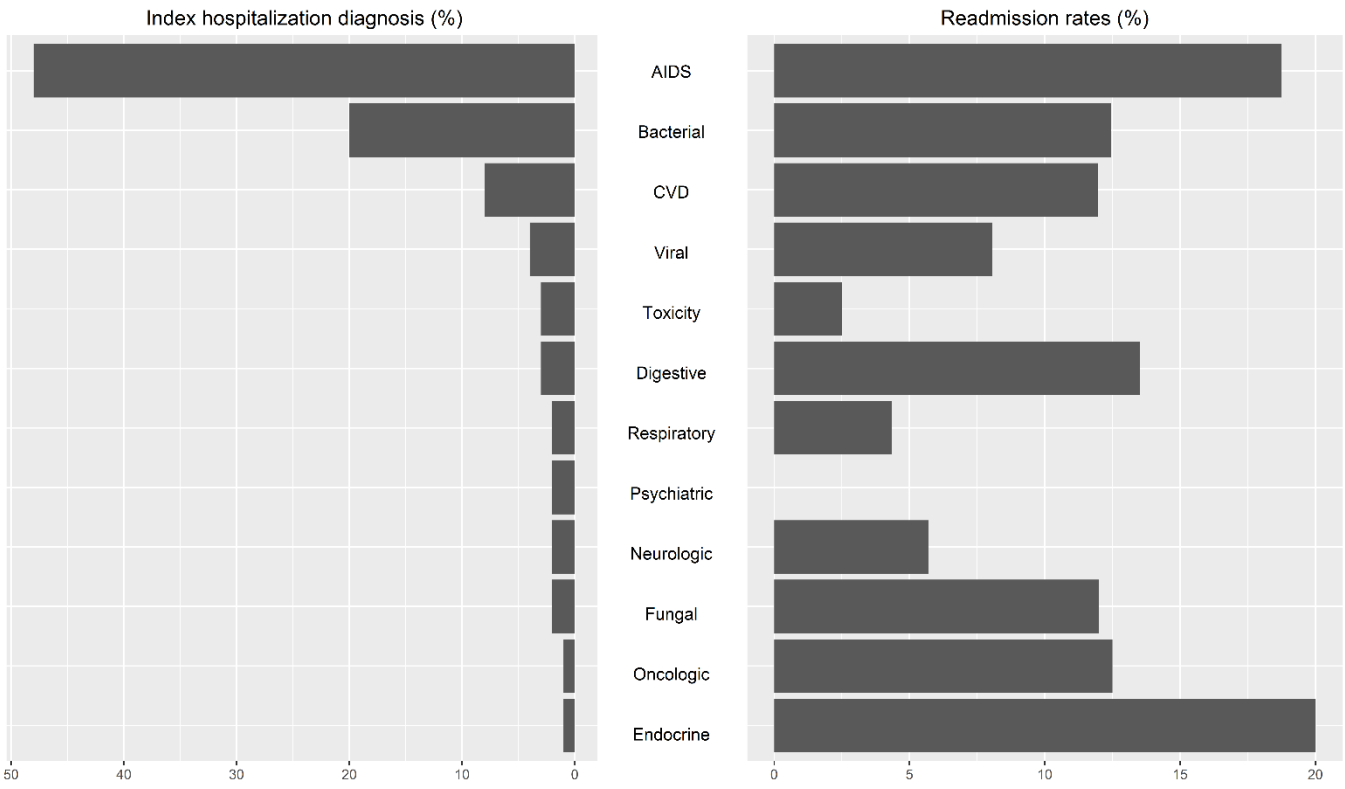



**Figure 2. Index hospitalizations causes and 30-day readmission rates per diagnosis.** Left panel shows proportion of index hospitalizations by cause of hospitalization. Right panel shows readmissions rate by index hospitalization cause. CVD: cardiovascular diseases.

Patients' characteristics at the moment of the index hospitalization admission (stratified by yes/no 30-day readmission), as well as the unadjusted hazard ratios (cHR) are shown in Table 1. Compared to patients not readmitted, those who were readmitted were more likely to have recent (≤30 days) HIV diagnosis (14.9% *vs.* 8.5% among non-readmitted, Chi-squared p-value=0.019), AIDS-defining diseases as the cause of index hospitalizations (63.9% vs. 45.1% among non-readmitted, Chi-squared p-value<0.001) and lower CD4 counts (median 118 cells/mm³ *vs.* 191 cells/mm³ among non-readmitted, Wilcoxon Rank-Sum test p-value<0.0001). On the other hand, patients who were readmitted were less likely to have ART use prior to index hospitalization (66.3% *vs.* 76.3% among non-readmitted, Chi-squared p-value=0.003) and to attend a medical visit within 30 days after index discharge (37.6% vs. 74.7% among non-readmitted, Chi-squared p-value<0.001). Moreover, index hospitalizations that were followed by 30-day readmissions had longer LOS

(median 16 days *vs.* 12 days among non-readmitted, Wilcoxon Rank-Sum test p-value<0.001), had higher frequency of ICU stay (15.3% vs. 9.4% among non-readmitted, Chi-squared p-value=0.015), and more likely ended with a discharge against medical advice (5.4% *vs.* 2.5% among non-readmitted, Chi-squared p-value=0.029).

In unadjusted models, recent HIV diagnosis (≤30 days), hospitalizations due to AIDS-defining diseases, CD4 counts bellow 200 cells/mm³, LOS longer than 21 days, ICU stay and discharge against medical advice significantly increased the risk of 30-day readmission. On the other hand, ART use prior to index hospitalization, being hospitalized in most recent calendar years and attending medical visit within 30 days after discharge protected against 30-day readmission (though this last variable had a p-value=0.072) (Table 1).

**Table 1. Socio-demographic and clinical characteristics and unadjusted hazard ratios (95% confidence interval) for patients who hospitalized stratified by readmission, INI cohort.**

| | Index hospitalizations | 30-day readmission | | |
|---|---|---|---|---|
| | Total (N = 1442) | No (N = 1240[a]) | Yes (N = 202) | Unadjusted models uHR (95% CI) |
| **Sex at birth** | | | | |
| **Male** | 932 (64.6) | 802 (64.7) | 130 (64.4) | ref |
| **Female** | 510 (35.4) | 438 (35.3) | 72 (35.6) | 1.02 (0.75, 1.37) |
| **Age* (years) median (IQR)** | 39.9 (33.2,47.1) | 40 (33.3,47.2) | 38.8 (32.2,46.7) | 0.99 (.098, 1.01) |
| **<30 years** | 233 (16.2) | 195 (15.7) | 38 (18.8) | ref |
| **30-39 years** | 496 (34.4) | 428 (34.5) | 68 (33.7) | 0.85 (0.57, 1.27) |
| **40-49 years** | 447 (31) | 388 (31.3) | 59 (29.2) | 0.81 (0.54, 1.22) |
| **≥50 years** | 266 (18.4) | 229 (18.5) | 37 (18.3) | 0.87 (0.55, 1.36) |
| **Race / ethnicity** | | | | |
| **White** | 616 (42.7) | 536 (43.2) | 80 (39.6) | ref |
| **Non White** | 826 (57.3) | 704 (56.8) | 122 (60.4) | 1.16 (0.87, 1.56) |
| **Educational level** | | | | |
| **Up to 9 years** | 1026 (71.2) | 878 (70.8) | 148 (73.3) | ref |
| **More than 9 years** | 416 (28.8) | 362 (29.2) | 54 (26.7) | 0.88 (0.64, 1.22) |
| **HIV exposure category** | | | | |
| **Heterosexual** | 900 (62.4) | 782 (63.1) | 118 (58.4) | ref |
| **MSM** | 446 (30.9) | 381 (30.7) | 65 (32.2) | 1.11 (0.82, 1.52) |
| **IDU** | 46 (3.2) | 36 (2.9) | 10 (5) | 1.76 (0.88, 3.51) |
| **Other/unknown** | 50 (3.5) | 41 (3.3) | 9 (4.5) | 1.45 (0.71, 2.94) |
| **Time since HIV diagnosis (years)*** | 5.4 (0.8,11.3) | 5.4 (0.9,11.3) | 4.6 (0.3,11.3) | |
| **≤30 days** | 136 (9.4) | 106 (8.5) | 30 (14.9) | **2.16 (1.32, 3.55)** |
| **31-365 days** | 257 (17.8) | 218 (17.6) | 39 (19.3) | 1.42 (0.88, 2.29) |
| **1-5 years** | 305 (21.2) | 272 (21.9) | 33 (16.3) | ref |
| **5-10 years** | 294 (20.4) | 260 (21) | 34 (16.8) | 1.07 (0.68, 1.69) |
| **>10 years** | 450 (31.2) | 384 (31) | 66 (32.7) | 1.38 (0.89, 2.14) |
| **AIDS-defining disease hospitalization*** | | | | |
| **No** | 754 (52.3) | 681 (54.9) | 73 (36.1) | ref |
| **Yes** | 688 (47.7) | 559 (45.1) | 129 (63.9) | **2.03 (1.49, 2.76)** |
| **CD4* (cells/mm$^3$) median (IQR)** | 177 (56,395) | 191 (62,414) | 118 (32,257) | |
| **>350** | 360 (25) | 327 (26.4) | 33 (16.3) | ref |
| **201-350** | 222 (15.4) | 198 (16) | 24 (11.9) | 1.18 (0.69, 2.01) |
| **51-200** | 391 (27.1) | 328 (26.5) | 63 (31.2) | **1.87 (1.20, 2.91)** |
| **≤50** | 283 (19.6) | 223 (18) | 60 (29.7) | **2.51 (1.61, 3.92)** |
| **Missing** | 186 (12.9) | 164 (13.2) | 22 (10.9) | 1.36 (0.80, 2.31) |
| **HIV viral load* (copies/mL)** | | | | |
| **≤400** | 499 (34.6) | 436 (35.2) | 63 (31.2) | ref |
| **>400** | 699 (48.5) | 597 (48.1) | 102 (50.5) | 1.16 (0.85, 1.60) |
| **Missing** | 244 (16.9) | 207 (16.7) | 37 (18.3) | 1.19 (0.79, 1.79) |
| **ART use prior to hospitalization*** | | | | |
| **No** | 362 (25.1) | 294 (23.7) | 68 (33.7) | ref |
| **Yes** | 1080 (74.9) | 946 (76.3) | 134 (66.3) | **0.64 (0.47, 0.87)** |
| **Length of stay, median (IQR)*** | 12 (7,22) | 12 (7,22) | 16 (8,28) | |
| **≤7 days** | 12 (7,22) | 364 (29.4) | 45 (22.3) | ref |
| **8-14 days** | 409 (28.4) | 356 (28.7) | 50 (24.8) | 1.12 (0.75, 1.67) |
| **15-21 days** | 406 (28.2) | 198 (16) | 34 (16.8) | 1.35 (0.86, 2.12) |
| **>21 days** | 232 (16.1) | 322 (26) | 73 (36.1) | **1.74 (1.19, 2.54)** |
| **Type of discharge*** | | | | |
| **Medical discharge** | 1300 (90.2) | 1128 (91) | 172 (85.1) | ref |

| | | | | |
|---|---|---|---|---|
| **Against medical advice** | 42 (2.9) | 31 (2.5) | 11 (5.4) | **2.35 (1.25, 4.42)** |
| **Transfer** | 33 (2.3) | 25 (2) | 8 (4) | 1.87 (0.98, 3.59) |
| **Unknown** | 67 (4.6) | 56 (4.5) | 11 (5.4) | 1.25 (0.68, 2.30) |
| **ICU admission*** | 148 (10.3) | 117 (9.4) | 31 (15.3) | **1.68 (1.14, 2.48)** |
| **Medical visit within 30 days after discharge[b]** | 1002 (69.5) | 926 (74.7) | 76 (37.6) | 0.75 (0.55, 1.03) |
| **Year of hospitalization** | | | | **0.87 (0.81, 0.94)[c]** |
| **2007** | 126 (8.7) | 101 (8.1) | 25 (12.4) | |
| **2008** | 217 (15) | 177 (14.3) | 40 (19.8) | |
| **2009** | 226 (15.7) | 196 (15.8) | 30 (14.9) | |
| **2010** | 211 (14.6) | 170 (13.7) | 41 (20.3) | |
| **2011** | 268 (18.6) | 241 (19.4) | 27 (13.4) | |
| **2012** | 220 (15.3) | 198 (16) | 22 (10.9) | |
| **2013** | 174 (12.1) | 157 (12.7) | 17 (8.4) | |

MSM: Men who have sex with men; IDU: Injectable drug use; ART: combination antiretroviral therapy; ICU: intensive care unit; uHR: unadjusted hazard ratio.

* Refers to index hospitalization or index hospitalization admission date.

[a] Includes 16 patients who died within 30 days (without been readmitted)

[b] Defined as a medical visit before end of follow-up or readmission, for those who readmitted.

[c] Tested in Poisson regression model as a continuous variable.

The final adjusted model is shown in Figure 3. Comparing the effects of the independent variables in the unadjusted and adjusted models, we found that after adjusting for covariates, the protective effect of attending a medical visit within 30 days of discharge remained similar but it gained statistical significance (adjusted hazard ratio [aHR] 0.75, p-value=0.057). Being hospitalized in most recent years also remained significant in the adjusted models (aHR 0.89, p-value=0.002). The protective effect of ART use prior to hospitalization observed in the unadjusted model was attenuated but remained protective after controlling for covariates (aHR 0.76, p-value = 0.164). On the other hand, index hospitalization due to AIDS-defining diseases (aHR 1.62, p-value = 0.015), having a CD4 count $\leq$ 50 cells/mm$^3$ (aHR 1.63, p-value = 0.053), and leaving the hospital against medical advice (aHR 2.78, p-value = 0.002) increased the risk of 30-day readmission. Additionally, after adjusting for covariates, having HIV diagnosis for 10 or more years also increased the risk of 30-day readmission (aHR 1.62, p-value= 0.036).

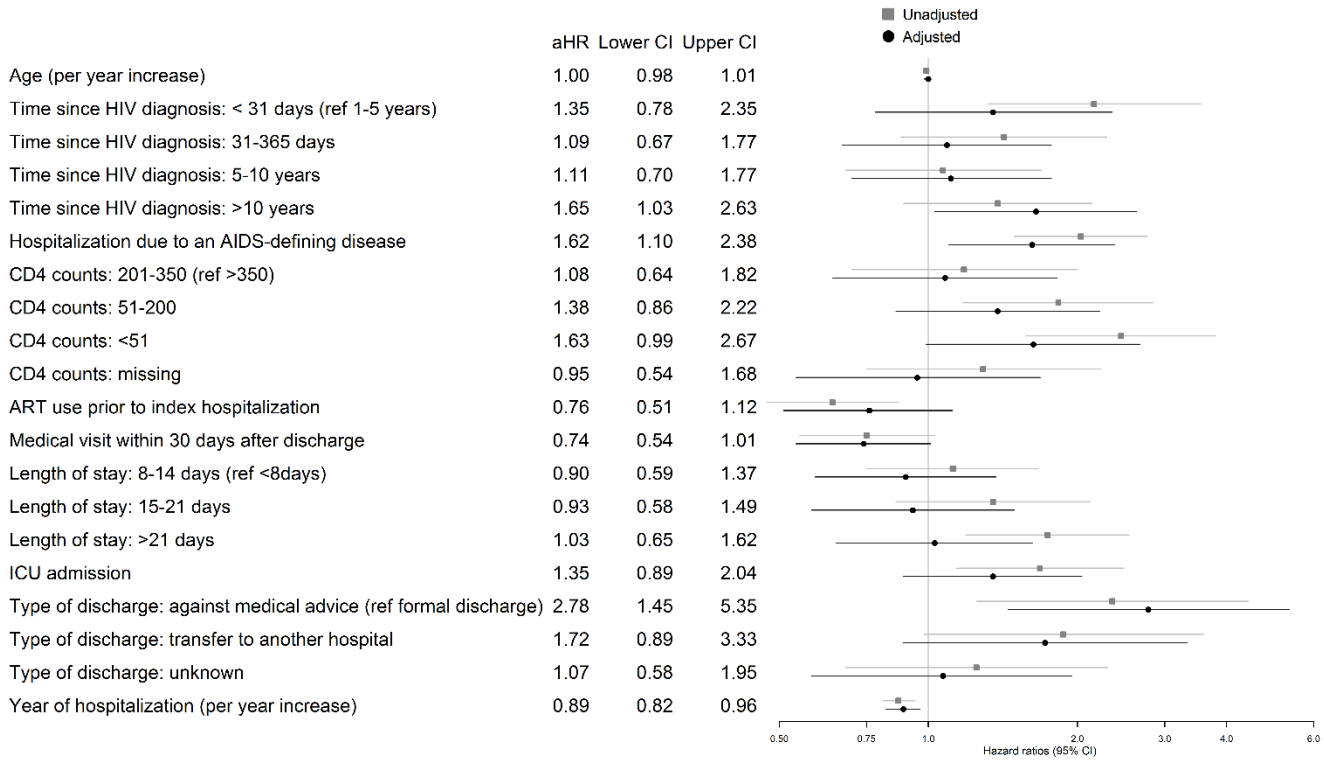



**Figure 3. Adjusted extended Cox regression model.** Hazard ratios and 95% confidence intervals for 30-day readmission.

## Discussion

In the present study, we have estimated the 30-day readmission rate for an HIV infected cohort followed in Rio de Janeiro, Brazil. Our estimated 14% readmission rate is lower than the rates reported for HIV infected patients in high-income settings. Nijhawan et al. estimated a 25% readmission rate in Dallas, US[16], Berry at al. reported 19% readmission rate for the HIV Research Network (HIVRN, which includes 12 sites in the US) [15], and a US national report (using data from Healthcare Cost and Utilization Project) found a readmission rate of 20% for HIV infected patients[9]. The reasons for the disparate readmission rates likely include patient, hospital and health care system as well as community characteristics[2] beyond those that we have been able to address. Nonetheless, patient-level characteristics shown to increase the risk of readmission, such as those indicative of advanced disease, were similar among ours and the previous studies,

highlighting sub-populations for whom efforts could be targeted. Moreover, our results shed light on the benefits of an early post-discharge medical visit in preventing readmission.

In our casuistic, attending an early post-discharge medical visit reduced the risk of 30-day readmission by 25%. Over the study period, 75% of the patients who were not readmitted had attended a medical visit within 30 days of discharge compared to 38% of those who were eventually readmitted. These results concord with a previously described protective effect of careful transitioning to the outpatient setting on reducing the risk of readmission among patients with other chronic conditions[20–23]. Additionally, it might indicate a better post discharge support system (i.e family and social support) that has also been associated with lower risk of hospital readmission [22,24]. Interestingly, among HIV-infected patients, only one study reported on this association and found no link between early transition to outpatient care and 30-day readmission[15]. Unfortunately, although no association between outpatient visit and 30-day readmission was found, frequencies of outpatient visits among those who did and did not readmit were not available preventing us from better exploring this difference. Thus, although our results are consistent with previous studies that included patients with other chronic diseases, confirmatory studies are needed to provide more reliable information on the effect of attending an outpatient visit on 30-day readmission rates for the HIV infected population.

Our findings corroborate results reported by Berry et al and Nijhawan et al[15,16] by showing that an index hospital admission due to AIDS-defining disease and lower CD4 counts were associated with an increased risk of readmission. These findings highlight the impact that advanced chronic diseases[25,26], in our case, advanced HIV disease, has on 30-day readmission risk. To focus clinical efforts in this severely ill sub-population seems feasible given they represent only a small fraction of patients under follow-up. For the present cohort, this sub-population would amount to approximately 15% of the patients under follow-up as only 588 patients had an AIDS-defining disease or poor immune function at index hospitalization out of 3991 patients under follow-up. Importantly, we also found that ART use prior to the index hospitalization reduced the risk of 30-day readmission. In fact, when we stratified ART use into recent start (≤30 days) or not (more than 30 days of use prior to index hospitalization admission) we did not find an increased risk of readmission associated with recent ART start that could be linked to Immune Reconstitution Inflammatory Syndrome and/or acute toxic events (data not shown). Similarly, both Berry et al and

Nijhawan et al explored this possible risk association (recent ART and readmission risk) and neither found an association[15,16]. Taken together, these findings suggest that early ART use for all HIV-infected patients might not only prevent HIV disease progression and HIV transmission but may as well reduce 30-day readmission.

Another interesting finding from our study was the fact that long term HIV infected patients, i.e. those diagnosed for 10 or more years, were at higher risk of 30-day readmissions after controlling for all other covariates (including age). We can speculate on some plausible explanations for this finding. First, it is possible that some chronically HIV infected patients, likely heavily ART experienced, are presenting with multidrug HIV resistance and disease progression, leading to increased risk of readmission. This hypothesis is supported by the fact that although 94.2% of those patients had used ART prior to index hospitalization, less than half (47%) had a viral load < 400 copies/mL (data not shown). Another possible reason would be the fact that HIV chronic infection leads to persistent inflammation and immune activation which is associated with increased risk of cardiovascular disease, cancer and other non-AIDS related events[27,28]. Corroborating this hypothesis, we found that index hospitalizations among patients with HIV diagnosis for 10 or more years were less likely to be due to an AIDS defining disease (29% vs. 47% among all index hospitalizations), and that the readmission rate for digestive diseases index hospitalizations surpassed the one for AIDS-defining diseases index hospitalizations (23.8% vs. 21.4%) highlighting the importance of non-AIDS events on the risk of readmission for this particular population subset. In summary, a multicausal pathway that encompasses aging, higher prevalence of non-communicable diseases, ART failure seems to be a more plausible explanation for the increased readmission risk observed among HIV long term infected patients.

Additionally, our results show that patients who left the hospital against medical advice had a two-fold higher risk of 30-day readmission. Indeed, discharge against medical advice had already been associated with increased risk of 30-day readmission in the general population and among those with HIV[12,29]. Specifically, among HIV infected patients, leaving hospital against medical advice led to a 5-fold increased odds of 30-day readmission for a related diagnosis and was associated with longer LOS (compared to those who had been formally discharged) [12].

Altogether, interventions focusing on reducing such discharges are needed to improve patients' health and reduce unnecessary costs with readmissions.

AIDS-defining diseases were the main cause of index hospitalizations comprising almost half of all admissions, followed by bacterial infections. Endocrine diseases had the highest readmission rate in our study population, a finding that results from the very small number of index hospitalizations (i.e. small denominator) while AIDS-defining diseases led to the second highest readmission rate. These findings are somewhat different from those observed in previous studies. In the HIVRN population, non-AIDS infections were the main cause of index hospitalizations, and the highest 30-day readmission rate was observed for oncologic index hospitalizations, with the second highest 30-day readmission rate for an AIDS-defining disease index hospitalization[15]. Nijhawan et al also found AIDS-defining diseases as the main cause of index hospitalizations but the oncologic hospitalizations led the 30-day readmission rates and AIDS-related diseases came in fifth [16]. Several factors can explain these differences in the rating of the causes of index hospitalizations and readmissions. Foremost, the burden of AIDS diseases in the context of hospitalizations is quite different between our study population and HIVRN population. In our population, the proportion of index hospitalizations due to AIDS-defining diseases was 5-fold higher than that observed for the HIVRN population (47.7% vs. 9.6%) [15] likely driving the ranking for both index hospitalizations and readmissions. Additionally, differences in the burden of cancer among our study population and HIV-infected populations from high-income settings might explain some of these disparities. A recent study compared the incidence of cancer (AIDS and non-AIDS defining) between HIV infected patients from INI cohort and Vanderbilt Comprehensive Care Clinic cohort (Nashville, US) and showed significant differences on the incidence of cancer between these two HIV-infected populations[30]. They showed that the incidence of AIDS defining cancer was higher in INI than in Vanderbilt, mainly driven by Kaposi sarcoma incidence (almost three times higher in INI). On the other hand, non-AIDS defining cancer incidence was higher in Vanderbilt than in INI, and the most incident cancer types were also different (anal cancer in INI vs. lung cancer in Vanderbilt). It is worthwhile mentioning that although INI provides treatment of Kaposi sarcoma, mostly administrated in a day clinic (including monitoring and management of potential side effects such as leukopenia), all other oncologic and chemotherapy-relate hospitalization are referred to another facility and thus not included in this

casuistic. Altogether, the findings regarding oncologic admissions and readmissions should be compared with care to other published results.

Overall, the median LOS of index hospitalizations (12 days) surpasses the one reported for the HIVRN population (median of 5 days)[15] and the one reported by Nijhawan et al (mean 7 days) [16] but is closer to a national HIV-infected Portuguese estimate (median 11 days)[31]. And similarly to Berry et al[15], we found that compared with other causes, hospitalizations due to AIDS defining diseases were associated with longer LOS (median of 18 vs. 9 days for AIDS and non-AIDS related hospitalizations, respectively, data not shown). Differences in hospital structure, hospital setting and health system level factors could be the sources of such disparities. For the purpose of comparison with Brazilian data, we searched publicly available databases that provide mean LOS and found that overall the mean LOS estimated for the state of Rio de Janeiro in the period of 2008-2015 was 9 days, while, for the same period, the national mean was 7 days revealing the high heterogeneity that exists when it comes to hospital outcomes even within Brazil[32].

There are several limitations that need to be highlighted in the present study, some of which were already addressed throughout this discussion. First, the comparison of readmission rates in our setting with that reported in the United States and other countries must be made cautiously since there are innumerous hospital and health systems level factors that can influence this outcome. Second, our study casuistic is from a single cohort that has access to an outpatient clinic as well as an infectious diseases hospital located in Rio de Janeiro, hence our results may not reflect those for other HIV populations in Brazil. And finally, hospitalizations at Evandro Chagas hospital are restricted to non-surgical and non-obstetrics procedures, and, as mentioned earlier, oncologic hospitalizations (except for Kaposi sarcoma) are mainly referred to an oncological hospital and therefore our rates do not represent the entire sort of events that can happen to an HIV infected patient.

In summary, we found that the 30-day readmission rate in our HIV infected cohort of patients was 14%. To our knowledge, ours is the first study to estimate and address 30-day readmission among HIV infected individuals in Brazil and, as such, provides a benchmark until more comprehensive data is available for the country. We also showed that attending an early medical visit after discharge had an important effect on preventing readmissions; this finding could be used to

create/modify transition protocols to reduce readmission rates in the future. Finally, we demonstrated that variables that indicated advanced HIV (i.e. hospitalizations due to AIDS-defining diseases and low CD4 counts) increased the risk of readmission and that ART reduced this risk, thus indicating early HIV diagnosis and prompt ART start as strategies that could reduce 30-day readmissions.

**Competing interests**

The authors declare no competing interests.

**Acknowledgements and funding**

PML and BG acknowledge funding from the National Council of Technological and Scientific Development (CNPq) and the Research Funding Agency of the State of Rio de Janeiro (FAPERJ). This work was supported in part by the NIH-funded Caribbean, Central and South America network for HIV epidemiology (CCASAnet), a member cohort of the International Epidemiologic Databases to Evaluate AIDS (leDEA) (U01AI069923).

**Authors' contributions**

LEC and PML conceived the study, performed the analyses, and drafted the manuscript. LEC, SRR and PCL reviewed hospitalizations' discharge summaries and followed the protocol for assigning ICD-10 codes/causes to all hospitalizations. AMJ and RIM were in charge of obtaining and reviewing patient data and were responsible for data harmonization. BG and VGV contributed to the study's design and were involved in revising the manuscript for important intellectual content. All authors read and approved the final manuscript.

## References


1. Hansen LO, Young RS, Hinami K, Leung A, Williams MV. Interventions to reduce 30-day rehospitalization: a systematic review. Ann Intern Med. 2011;155: 520–528.

2. Joynt KE, Jha AK. Thirty-day readmissions--truth and consequences. N Engl J Med. 2012;366: 1366–1369. doi:10.1056/NEJMp1201598

3. Dharmarajan K, Hsieh AF, Lin Z, Bueno H, Ross JS, Horwitz LI, et al. Hospital readmission performance and patterns of readmission: retrospective cohort study of Medicare admissions. BMJ. 2013;347: f6571–f6571. doi:10.1136/bmj.f6571

4. Jencks SF, Williams MV, Coleman EA. Rehospitalizations among patients in the Medicare fee-for-service program. N Engl J Med. 2009;360: 1418–1428.

5. Barret ML, Wier LM, Jiang J, Steiner CA. All-Cause Readmissions by Payer and Age, 2009–2013. Agency Healthc Res Qual HCUP Stat Brief 199. 2015;

6. van Walraven C, Bennett C, Jennings A, Austin PC, Forster AJ. Proportion of hospital readmissions deemed avoidable: a systematic review. CMAJ Can Med Assoc J J Assoc Medicale Can. 2011;183. doi:10.1503/cmaj.101860

7. Ross JS, Mulvey GK, Stauffer B, Patlolla V, Bernheim SM, Keenan PS, et al. Statistical models and patient predictors of readmission for heart failure: a systematic review. Arch Intern Med. 2008;168: 1371–1386.

8. Mannino DM, Thomashow B. Reducing COPD readmissions: great promise but big problems. Chest. 2015;147: 1199–1201. doi:10.1378/chest.15-0380

9. Berry S, Fleishman J, Moore R, Gebo K. Thirty-day hospital readmissions for adults with and without HIV infection: HIV readmissions. HIV Med. 2015; n/a–n/a. doi:10.1111/hiv.12287

10. Nijhawan AE, Kitchell E, Etherton SS, Duarte P, Halm EA, Jain MK. Half of 30-Day Hospital Readmissions Among HIV-Infected Patients Are Potentially Preventable. AIDS Patient Care STDs. 2015;29: 465–473. doi:10.1089/apc.2015.0096

11. Barba Martin R, Marco Martinez J, Plaza Canteli S, Gomez Rodrigo J, de la Riva I, Cervero Jimenez M, et al. [Retrospective study of early readmissions at an internal medicine service]. Rev Clin Esp. 2000;200: 252–256.

12. Anis AH, Sun H, Guh DP, Palepu A, Schechter MT, O'Shaughnessy MV. Leaving hospital against medical advice among HIV-positive patients. Can Med Assoc J. 2002;167: 633–637.

13. Chew KW, Yen IH, Li JZ, Winston LG. Predictors of Pneumonia Severity in HIV-Infected Adults Admitted to an Urban Public Hospital. AIDS Patient Care STDs. 2011;25: 273–277. doi:10.1089/apc.2010.0365

14. Hsieh Y-H, Rothman RE, Bartlett JG, Yang S, Kelen GD. HIV seropositivity predicts longer duration of stay and rehospitalization among nonbacteremic febrile injection drug users with skin and soft tissue infections. JAIDS J Acquir Immune Defic Syndr. 2008;49: 398–405.

15. Berry SA, Fleishman JA, Yehia BR, Korthuis PT, Agwu AL, Moore RD, et al. Thirty-day hospital readmission rate among adults living with HIV: AIDS. 2013;27: 2059–2068. doi:10.1097/QAD.0b013e3283623d5f

16. Nijhawan AE, Clark C, Kaplan R, Moore B, Halm EA, Amarasingham R. An electronic medical record-based model to predict 30-day risk of readmission and death among HIV-infected inpatients. JAIDS J Acquir Immune Defic Syndr. 2012;61: 349–358.

17. Grinsztejn B, Veloso VG, Friedman RK, Moreira RI, Luz PM, Campos DP, et al. Early mortality and cause of deaths in patients using HAART in Brazil and the United States: AIDS. 2009;23: 2107–2114. doi:10.1097/QAD.0b013e32832ec494

18. Ribeiro SR, Luz PM, Campos DP, Moreira RI, Coelho L, Japiassu A, et al. Incidence and determinants of severe morbidity among HIV-infected patients from Rio de Janeiro, Brazil, 2000–2010. Antivir Ther. 2014;19: 387–397. doi:10.3851/IMP2716

19. Grinsztejn B, Luz PM, Pacheco AG, Santos DVG, Velasque L, Moreira RI, et al. Changing Mortality Profile among HIV-Infected Patients in Rio de Janeiro, Brazil: Shifting from AIDS to Non-AIDS Related Conditions in the HAART Era. Yazdanpanah Y, editor. PLoS ONE. 2013;8: e59768. doi:10.1371/journal.pone.0059768

20. Coleman EA, Parry C, Chalmers S, Min S. The care transitions intervention: results of a randomized controlled trial. Arch Intern Med. 2006;166: 1822–1828.

21. Peikes D, Chen A, Schore J, Brown R. Effects of care coordination on hospitalization, quality of care, and health care expenditures among Medicare beneficiaries: 15 randomized trials. Jama. 2009;301: 603–618.

22. Sharma G, Kuo Y-F, Freeman JL, Zhang DD, Goodwin JS. Outpatient follow-up visit and 30-day emergency department visit and readmission in patients hospitalized for chronic obstructive pulmonary disease. Arch Intern Med. 2010;170: 1664–1670.

23. Chen H, Tisminetzky M, Lapane KL, Yarzebski J, Person SD, Kiefe CI, et al. Decade-Long Trends in 30-Day Rehospitalization Rates After Acute Myocardial Infarction. J Am Heart Assoc. 2015;4: e002291. doi:10.1161/JAHA.115.002291

24. Arbaje AI, Wolff JL, Yu Q, Powe NR, Anderson GF, Boult C. Postdischarge environmental and socioeconomic factors and the likelihood of early hospital readmission among community-dwelling Medicare beneficiaries. The Gerontologist. 2008;48: 495–504.

25. Berry CE, Kalhan R. Chronic Obstructive Pulmonary Disease Rehospitalization. A Big Problem that Now Needs Solutions. Ann Am Thorac Soc. 2015;12: 1741–1742. doi:10.1513/AnnalsATS.201510-687ED

26. Desai AS, Stevenson LW. Rehospitalization for Heart Failure: Predict or Prevent? Circulation. 2012;126: 501–506. doi:10.1161/CIRCULATIONAHA.112.125435

27. Erlandson KM, Campbell TB. Inflammation in Chronic HIV Infection: What Can We Do? J Infect Dis. 2015;212: 339–342. doi:10.1093/infdis/jiv007

28. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. The Lancet. 2013;382: 1525–1533. doi:10.1016/S0140-6736(13)61809-7

29. Glasgow JM, Vaughn-Sarrazin M, Kaboli PJ. Leaving Against Medical Advice (AMA): Risk of 30-Day Mortality and Hospital Readmission. J Gen Intern Med. 2010;25: 926–929. doi:10.1007/s11606-010-1371-4

30. Castilho JL, Luz PM, Shepherd BE, Turner M, Ribeiro SR, Bebawy SS, et al. HIV and cancer: a comparative retrospective study of Brazilian and U.S. clinical cohorts. Infect Agent Cancer. 2015;10. doi:10.1186/1750-9378-10-4

31. Catumbela E, Freitas A, Lopes F, Mendoza M del CT, Costa C, Sarmento A, et al. HIV disease burden, cost, and length of stay in Portuguese hospitals from 2000 to 2010: a cross-sectional study. BMC Health Serv Res. 2015;15. doi:10.1186/s12913-015-0801-8

32. Ministério da Saúde. Departamento de informática do SUS (DATASUS). Sistema de Informações Hospitalares do SUS (SIH/SUS). Brasil. Link: www.datasus.gov.br. Access date: 02/02/2016.

# 7 CONCLUSÕES E RECOMENDAÇÕES

A tendência temporal de redução das taxas de hospitalização observada nos pacientes infectados pelo HIV foi acompanhada por alteração progressiva das causas de hospitalização, e as hospitalizações por doenças não relacionadas a Aids superaram as hospitalizações por Aids nos anos mais recentes. Essa observação vai ao encontro da mudança no perfil de morbidade já descrito para a população infectada pelo HIV na era pós ART. A evidência de que as doenças não relacionadas à Aids representam nos últimos anos do estudo a principal causa de internação sugere um desafio para os serviços assistências que tratam de pacientes infectados pelo HIV, já que estes devem estar preparados para o atendimento de pacientes com múltiplas comorbidades crônicas e de manejo clínico mais complexo.

Os tempos de internação e a mortalidade hospitalar no Hospital Evandro Chagas (INI/Fiocruz) diminuíram ao longo dos anos, mas permanecem elevados quando comparados aqueles reportados por países de alta renda. Melhor compreensão dos fatores (demográficos, socioeconômicos, clínicos e assistenciais) associados ao prolongado tempo de internação e à alta mortalidade hospitalar são necessários.

Poucos estudos publicados avaliam o desfecho taxa de readmissão em 30 dias em pacientes infectados pelo HIV. A taxa de readmissão em pacientes infectados pelo HIV agregada (estimada na metanálise) é superior àquela reportada para a população geral. O baixo número de estudos identificados limitou a identificação de preditores de readmissão utilizando modelos de meta-regressão.

A taxa de readmissão hospitalar em 30 dias de pacientes infectados pelo HIV no Hospital Evandro Chagas foi similar àquela observada em países de alta renda. A

identificação dos fatores associados ao risco de readmissão permite verificar a existência de uma subpopulação de alto risco de readmissão (ou seja, aqueles hospitalizados por doenças relacionadas à Aids, com CD4 abaixo de 200 células/mm³ e sem uso prévio de ART). A identificação de grupos de sob maior risco possibilita individualização de conduta assistencial e intensificação de cuidados de transição nessa subpopulação.

O efeito protetor da ART no risco de readmissão corrobora com a estratégia de início precoce de tratamento. Novos estudos, incluindo hospitalizações posteriores a 2013, poderão verificar se ocorrerá uma redução das taxas de hospitalização em decorrência da mudança no protocolo de tratamento dos pacientes infectados pelo HIV (devido ao início precoce de ART, preconizado pelo Ministério da Saúde desde 2013 – *test and treat strategy*). A melhora da transição hospital-ambulatório (através de consulta médica precoce) pode reduzir as taxas de readmissão hospitalar. Protocolos de transição podem ser implementados como rotina assistencial no INI/Fiocruz (especialmente para os indivíduos com outros fatores de risco para readmissão precoce).

Status funcional (na hospitalização índice) e rede de suporte social estão associadas a readmissão em 30 dias na população geral, no entanto essa associação em indivíduos infectados pelo HIV ainda não foi estudada. Sugerimos padronização de medidas de status funcional em hospitalizações de pacientes infectados pelo HIV, bem como melhor caracterização de rede de suporte social para melhor compreensão dos fatores relacionados à readmissão em 30 dias nessa população.

Sugere-se o monitoramento das taxas de readmissão em 30 dias como um instrumento de avaliação longitudinal da assistência à saúde. Este trabalho contribui com evidências para a criação e modificação de protocolos assistenciais (com foco em cuidados

de transição), e a manutenção da monitorização das taxas de readmissão poderá informar sobre a efetividade dessas intervenções.

## REFERÊNCIAS


ANTIRETROVIRAL THERAPY COHORT COLLABORATION. Causes of Death in HIV- 1–Infected Patients Treated with Antiretroviral Therapy, 1996–2006: Collaborative Analysis of 13 HIV Cohort Studies. **Clinical Infectious Diseases**, v. 50, n. 10, p. 1387–1396, 15 maio 2010.

BACHHUBER, M. A.; SOUTHERN, W. N. Hospitalization rates of people living with HIV in the United States, 2009. **Public Health Reports (Washington, D.C.: 1974)**, v. 129, n. 2, p. 178–186, abr. 2014.

BARRET, M. L. et al. All-Cause Readmissions by Payer and Age, 2009–2013. **Agency for Healthcare Research and Quality. HCUP Statistical Brief #199**, 2015.

BERRY, S. et al. Thirty-day hospital readmissions for adults with and without HIV infection: HIV readmissions. **HIV Medicine**, p. n/a–n/a, ago. 2015.

BERRY, S. A. et al. Trends in reasons for hospitalization in a multisite United States cohort of persons living with HIV, 2001-2008. **Journal of acquired immune deficiency syndromes (1999)**, v. 59, n. 4, p. 368–375, 1 abr. 2012.

BOZZETTE, S. A. et al. Expenditures for the Care of HIV-Infected Patients in the Era of Highly Active Antiretroviral Therapy. **New England Journal of Medicine**, v. 344, n. 11, p. 817–823, 15 mar. 2001.

BRAITSTEIN, P. et al. Mortality of HIV-1-infected patients in the first year of antiretroviral therapy: comparison between low-income and high-income countries. **The Lancet**, v. 367, n. 9513, p. 817–824, mar. 2006.

BUCHACZ, K. et al. Rates of hospitalizations and associated diagnoses in a large multisite cohort of HIV patients in the United States, 1994–2005. **Aids**, v. 22, n. 11, p. 1345–1354, 2008.

BUCHACZ, K. et al. AIDS-defining opportunistic illnesses in US patients, 1994–2007: a cohort study: **AIDS**, v. 24, n. 10, p. 1549–1559, jun. 2010.

CARDOSO, S. W. et al. Aging with HIV: a practical review. **The Brazilian Journal of Infectious Diseases**, v. 17, n. 4, p. 464–479, jul. 2013.

CASSEB, J. et al. Decreasing Mortality and Morbidity in Adult AIDS Patients from 1995 to 1997 in São Paulo, Brazil. **AIDS Patient Care and STDs**, v. 13, n. 4, p. 213–214, abr. 1999.

CASSEB, J. et al. Lack of Prior Antiretroviral Therapy Is Associated with Increased Mortality Among Hospitalized Patients with AIDS in São Paulo, Brazil. **AIDS Patient Care and STDs**, v. 15, n. 5, p. 271–275, maio 2001.

CATUMBELA, E. et al. HIV disease burden, cost, and length of stay in Portuguese hospitals from 2000 to 2010: a cross-sectional study. **BMC Health Services Research**, v. 15, n. 1, dez. 2015.

CENTER FOR DISEASES CONTROL. Kaposi's Sarcoma and Pneumocystis Pneumonia Among Homossexual Men - New York City and California. 1981.

CENTERS FOR DISEASE CONTROL. Guidelines for Prophylaxis Against Pneumocystis carinii Pneumonia for Persons Infected with Human Immunodeficiency Virus. **MMWR**. v. 38, n. S-5, p. 1-9, 1989.

CENTER FOR DISEASES CONTROL. HIV and AIDS --- United States, 1981--2000. **MMWR**, v. 50, n. 21, p. 430–4, 2001.

COELHO, L. et al. Trends in AIDS-Defining Opportunistic Illnesses Incidence over 25 Years in Rio de Janeiro, Brazil. **PLoS ONE**, v. 9, n. 6, p. e98666, 5 jun. 2014.

COWELL, A. et al. Trends in hospital deaths among human immunodeficiency virus-infected patients during the antiretroviral therapy era, 1995 to 2011: Hospital Deaths Among HIV Patients. **Journal of Hospital Medicine**, v. 10, n. 9, p. 608–614, set. 2015.

CRUM-CIANFLONE, N. F. et al. Trends and causes of hospitalizations among HIV-infected persons during the late HAART era: what is the impact of CD4 counts and HAART use? **Journal of Acquired Immune Deficiency Syndromes (1999)**, v. 54, n. 3, p. 248–257, jul. 2010.

DESAI, A. S.; STEVENSON, L. W. Rehospitalization for Heart Failure: Predict or Prevent? **Circulation**, v. 126, n. 4, p. 501–506, 24 jul. 2012.

DHARMARAJAN, K. et al. Hospital readmission performance and patterns of readmission: retrospective cohort study of Medicare admissions. **BMJ**, v. 347, n. nov19 23, p. f6571–f6571, 20 nov. 2013.

ELIXHAUSER, A.; AU, D. H.; PODULKA, J. Readmissions for chronic obstructive pulmonary disease, 2008. **Agency for Healthcare Research and Quality. HCUP Statistical Brief #121,** 2011.

FISCHL M, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. **New England Journal of Medicine**. v. 317, n. 4, p. 185-91, 1987.

FORD, N. et al. Causes of hospital admission among people living with HIV worldwide: a systematic review and meta-analysis. **The Lancet HIV**, ago. 2015.

GOLDFIELD, N. I. et al. Identifying potentially preventable readmissions. **Health care financing review**, v. 30, n. 1, p. 75, 2008.

GORDIN FM, et al. Adverse reactions to trimethoprim-sulfamethoxazole in patients with the acquired immunodeficiency syndrome. **Annals of Internal Medicine**, v. 100, p. 495-9, 1984.

GRAHAM N, et al. The effects on survival of early treatment of immunodeficiency vírus infection. **New England Journal of Medicine**. v. 326, n. 12, p. 1037-10-42, 1992.

GRINSZTEJN, B. et al. Early mortality and cause of deaths in patients using HAART in Brazil and the United States: **AIDS**, v. 23, n. 16, p. 2107–2114, out. 2009.

GRINSZTEJN, B. et al. Changing Mortality Profile among HIV-Infected Patients in Rio de Janeiro, Brazil: Shifting from AIDS to Non-AIDS Related Conditions in the HAART Era. **PLoS ONE**, v. 8, n. 4, p. e59768, 5 abr. 2013.

HANSEN, L. O. et al. Interventions to reduce 30-day rehospitalization: a systematic review. **Annals of internal medicine**, v. 155, n. 8, p. 520–528, 2011.

HASSE, B. et al. Morbidity and Aging in HIV-Infected Persons: The Swiss HIV Cohort Study. **Clinical Infectious Diseases**, v. 53, n. 11, p. 1130–1139, 1 dez. 2011.

HELLINGER, F. J. The changing pattern of hospital care for persons living with HIV: 2000 through 2004. **JAIDS Journal of Acquired Immune Deficiency Syndromes**, v. 45, n. 2, p. 239–246, 2007.

HINES, A. L. et al. Conditions with the largest number of adult hospital readmissions by payer, 2011. 2014.

HONTELEZ, J. A. C. et al. The Effect of Antiretroviral Treatment on Health Care Utilization in Rural South Africa: A Population-Based Cohort Study. **PLOS ONE**, v. 11, n. 7, p. e0158015, 6 jul. 2016.

HYMES, K. et al. KAPOSI'S SARCOMA IN HOMOSEXUAL MEN—A REPORT OF EIGHT CASES. **The Lancet**, v. 318, n. 8247, p. 598–600, set. 1981.

JENCKS, S. F.; WILLIAMS, M. V.; COLEMAN, E. A. Rehospitalizations among patients in the Medicare fee-for-service program. **New England Journal of Medicine**, v. 360, n. 14, p. 1418–1428, 2009.

KAPLAN JE, et al. Epidemiology of Human Immunodeficiency Virus–Associated Opportunistic Infections in the United States in the Era of Highly Active Antiretroviral Therapy. **Clinical Infectious Diseases**. v. 30, p. S5-14, 2000.

KIM, J. H. et al. All-cause mortality in hospitalized HIV-infected patients at an acute tertiary care hospital with a comprehensive outpatient HIV care program in New York City in the era of highly active antiretroviral therapy (HAART). **Infection**, v. 41, n. 2, p. 545–551, abr. 2013.

KOWALSKA, J. D. et al. The Coding Causes of Death in HIV (CoDe) Project: Initial Results and Evaluation of Methodology. **Epidemiology**, v. 22, n. 4, p. 516–523, jul. 2011.

KRENTZ, H. B.; DEAN, S.; GILL, M. J. Longitudinal assessment (1995–2003) of hospitalizations of HIV-infected patients within a geographical population in Canada. **HIV medicine**, v. 7, n. 7, p. 457–466, 2006.

LEWDEN, C. et al. HIV-infected adults with a CD4 cell count greater than 500 cells/mm3 on long-term combination antiretroviral therapy reach same mortality rates as the general population. **Journal of acquired immune deficiency syndromes (1999)**, v. 46, n. 1, p. 72–77, 1 set. 2007.

LOHSE, N. et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. **Annals of Internal Medicine**, v. 146, n. 2, p. 87–95, 16 jan. 2007.

LONG, J. L. et al. Incidence and outcomes of malignancy in the HAART era in an urban cohort of HIV-infected individuals: **AIDS**, v. 22, n. 4, p. 489–496, fev. 2008.

LONG, L. C. et al. The High Cost of HIV-Positive Inpatient Care at an Urban Hospital in Johannesburg, South Africa. **PLOS ONE**, v. 11, n. 2, p. e0148546, 17 fev. 2016.

MALTA, M. et al. HIV prevalence among female sex workers, drug users and men who have sex with men in Brazil: a systematic review and meta-analysis. **BMC Public Health**, v. 10, n. 1, p. 1, 2010.

MALTA, M. et al. Improvement of HAART in Brazil, 1998–2008: a nationwide assessment of survival times after AIDS diagnosis among men who have sex with men. **BMC Public Health**, v. 15, n. 1, p. 226, 2015.

MINISTÉRIO DA SAÚDE. PROTOCOLO CLÍNICO E DIRETRIZES TERAPÊUTICAS PARA MANEJO DA INFECÇÃO PELO HIV EM ADULTOS. 2013. Available at: http://conitec.gov.br/images/Protocolos/PCDT_Manejo-HIV-Adultos_2013.pdf. Acess date: 22/08/2016. 2013.

MINISTÉRIO DA SAÚDE. **Boletim Epidemiologico HIV AIDS**, 2015. Disponível em: <http://www.aids.gov.br/sites/default/files/anexos/publicacao/2015/58534/boletim_aids_11_2015_web_pdf_19105.pdf>. Acesso em: 10 out. 2016

MOCROFT, A. et al. AIDS across Europe, 1994–98: the EuroSIDA study. **The Lancet**, v. 356, n. 9226, p. 291–296, 2000.

MOCROFT, A. et al. Changes in hospital admissions across Europe: 1995–2003. Results from the EuroSIDA study. **HIV medicine**, v. 5, n. 6, p. 437–447, 2004.

MOORE RA, et al.. Zidovudine and the natural history of the Acquired Immunodeficiency Syndrome. **New England Journal of Medicine.** v. 324, n. 20, p. 1412-1416, 1991.

MOREIRA, R. I. et al. Immune Status at Presentation for HIV Clinical Care in Rio de Janeiro and Baltimore: **JAIDS Journal of Acquired Immune Deficiency Syndromes**, v. 57, p. S171–S178, ago. 2011.

NEGIN, J. et al. Prevalence of HIV and chronic comorbidities among older adults: **AIDS**, v. 26, p. S55–S63, jul. 2012.

NIJHAWAN, A. E. et al. Half of 30-Day Hospital Readmissions Among HIV-Infected Patients Are Potentially Preventable. **AIDS Patient Care and STDs**, v. 29, n. 9, p. 465–473, set. 2015.

NOSYK, B. et al. Costs of Health Resource Utilization Among HIV-Positive Individuals in British Columbia, Canada: Results From a Population-Level Study. **PharmacoEconomics**, v. 33, n. 3, p. 243–253, mar. 2015.

PACHECO, A. G. et al. Validation of a Hierarchical Deterministic Record-Linkage Algorithm Using Data From 2 Different Cohorts of Human Immunodeficiency Virus-Infected Persons and Mortality Databases in Brazil. **American Journal of Epidemiology**, v. 168, n. 11, p. 1326–1332, 15 out. 2008.

PACHECO, A. G. et al. Temporal Changes in Causes of Death Among HIV-Infected Patients in the HAART Era in Rio de Janeiro, Brazil: **JAIDS Journal of Acquired Immune Deficiency Syndromes**, v. 51, n. 5, p. 624–630, ago. 2009.

PALELLA, F. J. et al. Declining Morbidity and Mortality among Patients with Advanced Human Immunodeficiency Virus Infection. **New England Journal of Medicine**, v. 338, n. 13, p. 853–860, 26 mar. 1998.

PALELLA JR, F. J. et al. Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. **JAIDS Journal of Acquired Immune Deficiency Syndromes**, v. 43, n. 1, p. 27–34, 2006.

PAUL, S. et al. The impact of potent antiretroviral therapy on the characteristics of hospitalized patients with HIV infection. **AIDS (London, England)**, v. 13, n. 3, p. 415–418, 25 fev. 1999.

RIBEIRO, S. R. et al. Incidence and determinants of severe morbidity among HIV-infected patients from Rio de Janeiro, Brazil, 2000–2010. **Antiviral Therapy**, v. 19, n. 4, p. 387–397, 2014.

ROJANAWIWAT, A. et al. Impact of the National Access to Antiretroviral Program on the incidence of opportunistic infections in Thailand. **International Health**, v. 3, n. 2, p. 101–107, jun. 2011.

UNAIDS. **Global AIDS Update - 2016**, 2016. Disponível em: <http://www.unaids.org/sites/default/files/media_asset/global-AIDS-update-2016_en.pdf>. Acesso em: 10 out. 2016

VAN WALRAVEN, C. et al. Proportion of hospital readmissions deemed avoidable: a systematic review. **CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne**, v. 183, n. 7, 19 abr. 2011.

WORLD HEALTH ORGANIZATION. **ICD-10: International statistical classification of diseases and related health problems.** Geneva: [s.n.].

YEHIA, B. R. et al. Inpatient Health Services Utilization Among HIV-Infected Adult Patients in Care 2002-2007: **JAIDS Journal of Acquired Immune Deficiency Syndromes**, v. 53, n. 3, p. 397–404, mar. 2010.

**APÊNDICE A**

**Distribuição de códigos da Classificação Internacional de Doenças 10ª edição (CID-10) em 24 grupos de doenças.**

| Grupo | Códigos da CID-10 |
|---|---|
| **Aids** | A07.2, A07.3, A15.0, A15, A15.1, A15.2, A15.3, A15.4, A15.5, A15.6, A15.9, A16, A16.0, A16.3, A16.5, A17.0, A17, A17.8, A18, A18.1, A18.2, A18.3, A18.4, A18.8, A19, A19.0, A19.1, A19.9, A31, A31.0, A31.2, A31.8, A31.9, A81.2, B21.0, B21.0, B21.2, B21.8, B22.0, B22.2, B25.8, B25.9, B39.9, B39, B39.3, B45.1, B45.7, B45.9, B58.2, B59, C46, C83.7, C85, C85.1, C85.9, G05.1 |
| **Infecções bacterianas (não Aids)** | A01.0, A02.0, A02.1, A04.7, A09, A09.0, A09.9, A27.9, A30.9, A40.3, A41, A41.0, A41.1, A41.2, A41.5, A41.8, A41.9, A43.9, A44, A44.9, A46, A48.1, A49.0, A49, A49.8, A51.3, A51.5, A52.1, A52.7, A54.4, A54.8, A55, B00.5, B95.6, B96.4, D70, D73.3, E06.6, G00.1, G00.9, G07, H01.0, H10.0, H19.2, H66.0, H66.4, H66.9, H70.0, H70.1, I30.9, I33.0, J01, J01.0, J01.4, J06.8, J13, J15, J15.0, J15.1, J15.6, J15.9, J22, J32, J32.8, J85, J85.2, J86, J86.9, K61.0, K65, K65.0, K81.0, L02, L02.0, L02.4, L02.8, L02.9, L03, L03.0, L04, L03.1, L03.2, L03.8, L03.9, L08, L08.0, L08.9, M00.9, M46.1, M60.0, M60.8, M68.0, M86, M86.0, M86.4, N15.1, N30, N30.0, N30.8, N30.9, N34.1, N39.0, N41.0, N45, N73.8, N75.1, N73.9, R57.2, T84.5 |
| **Cardiovasculares** | G08, G90.0, G93.1, I05.1, I05.9, I10, I11.0, I20, I20.0, I20.9, I21, I21.9, I24.8, I24.9, I25, I25.2, I25.5, I26.9, I27.0, I27, I27.9, I31.9, I35.0, I35.1, I40, I42, I42.0, I42.9, I47.1, I48, I49.9, I50, I50.0, I50.1, I51.8, I60.9, I61, I61.9, I62.0, I63, I63.9, I64, I70.1, I71.4, I73.9, I74.3, I74.9, I80.0, I80.9, I81, I82.8, I82.9, I83.1, I87.1, J81, Q21.9, R57.0, R57.1 |
| **Dermatológicas** | L21.1, L28.2, L51.1, L51.2, L52, L59.8, L89, T88.6, T88.7 |
| **Digestivas** | I85.0, I89.8, K11.1, K20, K21, K21.0, K22.1, K22.6, K22.2, K23, K23.8, K25, K25.9, K26, K29, K29.0, K29.1, K29.4, K35, K51, K51.0, K52.1, K52.9, K56.1, K56.6, K60.0, K63.1, K64, K74, K76, K76.1, K76.6, K80.0, K80.2, K81, K85, K85.0, K85.1, K86.1, K86.3, K90.0, K92, K92.1, K92.2, Q44.6, R10.0, R50.9, T85.5, Y43.9 |
| **Endócrinas** | E03.9, E05, E10, E11, E11.8, E14, E20.9, E23.2, E24.9, E27, E27.4, E43, E78, E78.2, E78.9, E83.9, E87.2 |
| **Infecções fúngicas (não Aids)** | B35, B37, B37.0, B37.7, B37.8, B38.8, B41.7, B41.9, B42.7, B42.8, B42.9, B44, B44.0, B44.1, B45.0, B47, J17.2 |
| **Ginecológicas** | N76, N77.0, N92, N92.4 |
| **Hematológicas** | C84.4, C96.1, D18.0, D46.4, D56.9, D57.0, D59, D59.9, D61.1, D61.9, D64.9, D69.3, D69.4, D69.6, D70, D72, D74.8 |
| **Neoplasias não-Aids** | C00, C16.9, C18.2, C20, C22.0, C22.9, C32.9, C34, C34.1, C34.2, C34.9, C44, C50, C50.9, C53, C56, C64, C71, C71.9, C78, C79, C79.9, C81.9, C84.5, C95, D02.2, D06 |

| | |
|---|---|
| **Neurológicas** | F01, F02.4, F03, G03.2, G11.1, G40, G40.2, G40.5, G40.9, G43, G43.3, G43.9, G45, G45.9, G51, G51.0, G53,0, G54.0, G55.1, G61, G61.9, G62.9, G83.9, G91, G91.1, G91.9, G93.4, G95.8, G96.0, G98, H81.9, H83.0, I62.9, M51.1, M54.1, S06.5 |
| **Hepatites não virais** | K70.1, K72.0, K72, K72.9, K74.6, K75.4 |
| **Oftalmológicas** | H13, H20, H30.1, H32, H44, H54.0 |
| **Outras** | B21.2, B23, B23.0, B23.1, B23.2, B23.8, D53.9, D89.1, E80.2, E87.5, M62.8, M80, R65, S83, T65.2, Y40, Y40.7, Y41.5, Y84.8, Y84.9, Z93.1, Z91.8, |
| **Parasitarias (não Aids)** | A06.0, A07.1, B50, B55.0, B55.1, B55.2, B56, B57.2, B58.0, B65.9, B78.0, B78.7, B87, B87.0, K23.1 |
| **Psiquiatricas** | F06.9, F10, F10.5, F13.0, F14, F14.0, F14.3, F14.5, F19, F19.5, F20, F20.0, F24, F31.9, F32.2, F32, F32.3, F32.9, F33.2, F33.3, F44, F48.8, F50.5, F60, F60.4, F70, F99, Z91.5 |
| **Renais** | N03, N04, N10, N13.2, N17, N17.0, N17.8, N17.9, N18, N18.0, N18.3, N18.4, N18.5, N18.9, N19, N20, N20.0, N20.1, N20.9, Y43.9 |
| **Respiratorias** | B90.9, E84.9, D86.0, J01.9, J20.9, J32.9, J44.1, J44.9, J45.9, J47, J80, J84.1, J84.9, J90, J91, J93.0, J93, J93.1, J93.8, J93.9, J95.5, J96.0, J98.4, S27.0 |
| **Reumatológicas** | M02.9, M19, M19.9, M31, M48, M89.0, M93 |
| **Sinais e sintomas** | A68, B23.1, B23.8, D72.1, D89.3, E46, E86, E87.6, G44, I89, I95, K12.0, K66.8, M54.5, M79.6, R04.2, R06.8, R07.2, R11, R17, R18, R20.2, R32, R41, R44, R45.1, R47.1, R50, R50.9, R51, R56, R57.9, R59, R59.0, R59.1, R59.9, R64 |
| **Toxicidade** | D59.9, D64.2, D64.9, D70, E79.0, F32.3, G62.0, G62.9, I02.9, I42.7, K29.1, K71.0, K71.2, K85.3, M13.0, N14.1, R55, T88.7, Y41.1, Y43.9 |
| **Trauma** | S02.2, S02.6, S07, S09.9, S32, S32.5, S36.0, S72.0, S72.7, X76 |
| **Infecções virais viral (não Aids)** | A08.4, A60, A60.0, A60.1, A85.8, A86, A87.9, A90, A91, B00.1, B00.2, B00.4, B00.5, B00.8, B00.9, B02, B02.1, B02.3, B02.7, B02.8, B02.9, B05.2, B05.9, B08.1, B97.6, G02.0, G04.9, G83.9, H19.1, I51.4, J10.0, K52.9, L03.9, Z22.6 |
| **Hepatites virais** | B16.9, B17.1, B18.0, B18.1, B18.2, B18.3 |

**APÊNDICE B**

**Carta de aceite para publicação.**

## Your Submission

**Carlos Brites** <crbrites@gmail.com> 13 de outubro de 2016 22:30
Para: lara.coelho@ini.fiocruz.br, laraesteves@gmail.com

Ms. Ref. No.: BJID-D-16-00566
Title: Hospitalizations rates, length of stay and in-hospital mortality in a cohort of HIV infected patients from Rio de Janeiro, Brazil.
Brazilian Journal of Infectious Diseases

Dear Mrs. Lara Esteves Coelho,

I am pleased to inform you that your paper "Hospitalizations rates, length of stay and in-hospital mortality in a cohort of HIV infected patients from Rio de Janeiro, Brazil." has been accepted for publication in Brazilian Journal of Infectious Diseases.

Below are comments from the editor and reviewers.

Thank you for submitting your work to Brazilian Journal of Infectious Diseases.

Yours sincerely,

Carlos Brites
Editor-in-Chief
Brazilian Journal of Infectious Diseases

**ANEXO A**

ESCOLA NACIONAL DE SAÚDE PÚBLICA SERGIO AROUCA - ENSP/ FIOCRUZ

## PARECER CONSUBSTANCIADO DO CEP

**DADOS DO PROJETO DE PESQUISA**

**Título da Pesquisa:** TAXAS DE READMISSÃO HOSPITALAR EM 30 DIAS NA COORTE DE PACIENTES INFECTADOS PELO HIV DO INSTITUTO NACIONAL DE INFECTOLOGIA EVANDRO CHAGAS - INI/FIOCRUZ, NO PERÍODO DE 2007 A 2013

**Pesquisador:** Lara Esteves Coelho

**Área Temática:**

**Versão:** 1

**CAAE:** 57135616.0.0000.5240

**Instituição Proponente:** FUNDACAO OSWALDO CRUZ

**Patrocinador Principal:** Financiamento Próprio

**DADOS DO PARECER**

**Número do Parecer:** 1.629.865

**Apresentação do Projeto:**

Trata-se de projeto de doutorado da aluna Lara Esteves Coelho do Programa de Pós-graduação Stricto Sensu em Epidemiologia e Saúde Pública, sob a orientação da Professora Paula Mendes Luz, intitulado "Taxas de Readmissão Hospitalar em 30 dias na Coorte de Pacientes Infectados pelo HIV do Instituto Nacional de Infectologia Evandro Chagas – INI/FIOCRUZ, no período de 2007 a 20013", qualificado em 02/06/2016. O orçamento do projeto é de R$ R$ 214,00, com financiamento próprio.

Resumo:

"Introdução: A taxa de readmissão em 30 dias é um indicador internacionalmente usado para avaliação da qualidade da assistência hospitalar. Comparado à população geral, pacientes infectados pelo HIV tem maior risco de readmissão em 30 dias. Existe uma lacuna na literatura no que se refere às taxas de readmissão, bem como seus preditores em países de baixa e média rendas. Objetivo primário: Avaliar as taxas de readmissão hospitalar em 30 dias e os fatores preditores de readmissão hospitalar em 30 dias em uma coorte de pacientes infectados pelo HIV no município do Rio de Janeiro, Brasil. Metodologia: A população do estudo será composta por pacientes infectados pelo HIV em acompanhamento na coorte do Instituto Nacional de Infectologia

**Endereço:** Rua Leopoldo Bulhões, 1480 - Térreo
**Bairro:** Manguinhos **CEP:** 21.041-210
**UF:** RJ **Município:** RIO DE JANEIRO
**Telefone:** (21)2598-2863 **Fax:** (21)2598-2863 **E-mail:** cep@ensp.fiocruz.br

Evandro Chagas (INI/Fiocruz). As hospitalizações no Hospital Evandro Chagas (INI/Fiocruz) que ocorreram no período de 01/jan/2007 até 31/dez/2013 serão incluídas. As taxas de readmissão serão calculadas e modelo de regressão de Cox será utilizado para avaliação de preditores de risco de readmissão em 30 dias."

Hipótese:

"A taxa de readmissão em pacientes infectados pelo HIV, em uma coorte no Rio de Janeiro, deve ser semelhantes àquelas descritas para países de alta renda. Os fatores relacionados à progressão da imunodeficiência (como presença de doença definidora de AIDS e baixas contagens de linfócitos T CD4+) devem se relacionar com aumento do risco de readmissão em 30 dias. Por outro lado, o uso de terapia antirretroviral deve atuar como fator de proteção contra readmissões."

Metodologia Proposta:

"A população do estudo será constituída por pacientes infectados pelo HIV com idade superior 18 anos em acompanhamento na coorte do Instituto Nacional de Infectologia Evandro Chagas (INI/Fiocruz). Hospitalizações no Hospital Evandro Chagas (hospital de referência para internação dos pacientes da coorte INI) que aconteceram no período de 01 janeiro 2007 a 31 dezembro 2013 serão analisadas. O INI é um centro de referência nacional para o tratamento de doenças infecciosas e desde 1986 é um centro de referência para o tratamento e pesquisa de pacientes infectados pelo HIV. No estado do Rio de Janeiro, o programa de AIDS do INI é um dos maiores a oferecer cuidados primários e terciários à pacientes infectados pelo HIV, e conta atualmente com cerca de 4000 pacientes ativos. Uma base de dados longitudinal é mantida referentes aos pacientes em acompanhamento no serviço (projeto "Estudo Longitudinal da História Natural da Infecção pelo HIV em pacientes acompanhados no IPECFIOCRUZ", aprovado pelo Comitê de Ética em Pesquisa do INI, CAAE 0032.0.009.000-10).Todas as nformações contidas nesta base de dados estão anonimizadas e todos estudos envolvendo os participantes desta coorte seguem os princípios expressos na Declaração de Helsinki.

Concisamente, a base de dados conta com informações sócio demográficas, laboratoriais, terapêuticas, ambulatoriais e hospitalares, essas informações são obtidas dos prontuários médicos por pessoas treinadas e atualizadas periodicamente.Os procedimentos da coorte já foram descritos e resultados publicados (6,31–33). Readmissão em 30 dias será definida como qualquer readmissão hospitalar que segue uma hospitalização índice num período de até 30 dias após a alta.Hospitalização índice (HI) foi definida como: 1º) a primeira hospitalização experimentada pelo

paciente durante o período do estudo e/ou qualquer hospitalização que ocorra após 30 dias de uma hospitalização anterior; e 2º) que os pacientes sobrevivam a esta hospitalização (recebam alta "vivos"). Serão excluídas as potenciais HI que ocorreram no primeiro (anteriores a 01 fevereiro 2007) e último meses da série temporal (posteriores a 30 novembro 2013). No primeiro mês por não termos como definir se aquela era uma HI ou uma readmissão e, no último mês por não permitir um seguimento mínimo de 30 dias para análise de readmissão. Nos casos em que uma HI foi seguida por uma cadeia de múltiplas readmissões, cada um com intervalos inferiores a 30 dias (sendo que a amplitude global da cadeia pode exceder 30 dias), todas as readmissões incluídas na cadeia não foram consideradas como HI."

Metodologia de Análise de Dados:

"Modelos de regressão Cox serão usados para avaliação de preditores de readmissão em 30 dias. Para tanto, o inicio do seguimento de cada paciente será definido como data da alta da hospitalização índice e o termino do seguimento será dado pela data de readmissão, data de óbito ou censura (definida como data da alta hospitalização índice acrescida de 30 dias), o que acontecer primeiro. Resíduos de Schoenfeld serão usados

para avaliar a premissa de proporcionalidade dos riscos.

Variáveis:

a)Variáveis categóricas: sexo; raça (branca e não branca); escolaridade ("até 9 anos de educação formal" vs. "mais de 9 anos de educação formal"); categoria de exposição ao HIV (categorizada hierarquicamente em uso de drogas injetáveis, homem que faz sexo com homem, transmissão heterossexual, acidente material biológico, transmissão vertical e outros); hospitalização por doença definidora de AIDS (CDC 1994), uso de terapia antirretroviral antes da hospitalização índice; permanência em terapia intensiva na hospitalização índice; tipo de alta hospitalar referente a hospitalização índice (alta médica formal, alta à revelia - against medical advice, transferência para outro hospital, óbito hospitalar); consulta médica pós alta (em até 30 dias após a alta).

b)Variáveis quantitativas: idade na admissão da hospitalização índice, tempo de diagnóstico do HIV (estimado como o tempo decorrido entre primeiro teste anti-HIV positivo documentado e a data de admissão hospitalização índice), contagem de linfócitos T CD4+ e carga viral do HIV na hospitalização índice (janela que engloba os 180 dias anteriores e 30 dias após a admissão), tempo de permanência hospitalar da hospitalização índice (calculado como a diferença entre a data de alta e a data de admissão e acrescido 1). ART foi definida como uso concomitante de pelo menos 3 drogas antirretrovirais de pelo menos

duas classes diferentes. Os esquemas usualmente prescritos associam dois análogos de nucleosídeo e um não análogo ou dois análogos de nucleosídeo e um inibidor de protease."

Desfecho Primário:
"A taxa de readmissão em 30 dias será calculada como o número de readmissões hospitalares em 30 dias".

Tamanho da Amostra no Brasil: 3.991

**Objetivo da Pesquisa:**
"Avaliar as taxas de readmissão hospitalar em 30 dias e os fatores preditores de readmissão hospitalar em 30 dias em uma coorte de pacientes infectados pelo HIV no município do Rio de Janeiro, Brasil."

**Avaliação dos Riscos e Benefícios:**
Segundo a pesquisadora:

"Riscos:
Trata-se de um estudo observacional, não existindo intervenções que impliquem em risco aos participantes. Todas as informações contidas na base de dados da coorte do INI estão anonimizadas e todos estudos envolvendo os participantes desta coorte seguem os princípios expressos na Declaração de Helsinki.

Benefícios:
Os beneficios obtidos com esse estudo envolvem o melhor entendimento da qualidade da assistencia hospitalar prestada aos pacientes infectados pelo HIV internados no Hospital Evandro Chagas (INI/Fiocruz) e poderá fornecer informação que permitam elaboração e melhora dos protocolos assistenciais."

**Comentários e Considerações sobre a Pesquisa:**
O protocolo de pesquisa apresenta todos os elementos necessários e adequados à apreciação ética.

**Considerações sobre os Termos de apresentação obrigatória:**

Apresentou:

- Projeto de Pesquisa na íntegra;
- Folha de Rosto gerada pela Plataforma Brasil assinada pelo pesquisador responsável;
- Formulário de encaminhamento assinado pela orientadora;
- TCUD - Termo de Compromisso de Uso de Dados - assinado pela pesquisadora responsável;
- Termo de autorização assinado e datado para fornecimento de banco de dados para uso na pesquisa em questão.

**Recomendações:**

Vide item "Conclusões ou Pendências e Lista de Inadequações".

**Conclusões ou Pendências e Lista de Inadequações:**

Projeto sem pendências ou inadequações.

**Considerações Finais a critério do CEP:**

ATENÇÃO: ***CASO OCORRA ALGUMA ALTERAÇÃO NO FINANCIAMENTO DO PROJETO ORA APRESENTADO (ALTERAÇÃO DE PATROCINADOR, COPATROCÍNIO, MODIFICAÇÃO NO ORÇAMENTO), O PESQUISADOR TEM A RESPONSABILIDADE DE SUBMETER UMA EMENDA AO CEP SOLICITANDO AS ALTERAÇÕES NECESSÁRIAS. A NOVA FOLHA DE ROSTO A SER GERADA DEVERÁ SER ASSINADA NOS CAMPOS PERTINENTES E ENTREGUE A VIA ORIGINAL NO CEP. ATENTAR PARA A NECESSIDADE DE ATUALIZAÇÃO DO CRONOGRAMA DA PESQUISA.***

* Em atendimento ao subitem II.19 da Resolução CNS nº 466/2012, cabe ao pesquisador responsável pelo presente estudo elaborar e apresentar relatório final "[...] após o encerramento da pesquisa, totalizando seus resultados". O relatório deve ser enviado ao CEP pela Plataforma Brasil em forma de "notificação". O modelo de relatório que deve ser seguido se encontra disponível em www.ensp.fiocruz.br/etica.

* Qualquer necessidade de modificação no curso do projeto deverá ser submetida à apreciação do

CEP, como emenda. Deve-se aguardar parecer favorável do CEP antes de efetuar a modificação.

* Justificar fundamentadamente, caso haja necessidade de interrupção do projeto ou a não publicação dos resultados.

**Este parecer foi elaborado baseado nos documentos abaixo relacionados:**

| Tipo Documento | Arquivo | Postagem | Autor | Situaçã |
|---|---|---|---|---|
| Informações Básicas do Projeto | PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_734989.pdf | 17/06/2016 15:01:34 | | Aceit |
| Outros | tcud.pdf | 17/06/2016 15:01:17 | Lara Esteves Coelho | Aceit |
| Outros | formularioencaminhamento.pdf | 17/06/2016 15:00:04 | Lara Esteves Coelho | Aceit |
| Projeto Detalhado / Brochura Investigador | PROJETODOUTORADOCEP.docx | 13/06/2016 16:59:30 | Lara Esteves Coelho | Aceit |
| Folha de Rosto | folharosto.pdf | 10/06/2016 17:36:15 | Lara Esteves Coelho | Aceit |
| Outros | Aprovacao.pdf | 09/06/2016 13:31:41 | Lara Esteves Coelho | Aceit |
| Outros | autorizacao.pdf | 09/06/2016 13:31:00 | Lara Esteves Coelho | Aceit |
| Outros | FolhaRosto_LaraEstevesCoelho.pdf | 09/07/2016 20:55:03 | Carla Lourenço Tavares de Andrade | Aceit |

**Situação do Parecer:**
Aprovado

**Necessita Apreciação da CONEP:**
Não

RIO DE JANEIRO, 09 de Julho de 2016

**Assinado por:**
**Carla Lourenço Tavares de Andrade**
**(Coordenador)**

**Endereço:** Rua Leopoldo Bulhões, 1480 - Térreo
**Bairro:** Manguinhos **CEP:** 21.041-210
**UF:** RJ **Município:** RIO DE JANEIRO
**Telefone:** (21)2598-2863 **Fax:** (21)2598-2863 **E-mail:** cep@ensp.fiocruz.br

**ANEXO B**



Ministério da Saúde

FIOCRUZ
Fundação Oswaldo Cruz
Instituto de Pesquisa Clínica Evandro Chagas

I P E C

**Comitê de Ética em Pesquisa**

## PARECER CONSUBSTANCIADO – 043/2010

**Protocolo 0032.0.009.000-10**

**1. Identificação:**
**Título do Projeto:** "Estudo Longitudinal da História Natural da Infecção pelo HIV em pacientes acompanhados no IPEC-FIOCRUZ".
**Pesquisador Responsável:** Beatriz Grinsztejn.
**Instituição Responsável:** Instituto de Pesquisa Clínica Evandro Chagas/FIOCRUZ.
**Data de Apresentação ao CEP:** 30/07/2010.

**2. Sumário:**
Trata-se de um estudo de coorte, retrospectivo, entre os pacientes acompanhados no IPEC a partir de janeiro de 1986. Tem como objetivos: a) Avaliar a resposta a terapia antirretroviral e subsequente e seus preditores no contexto de uma coorte urbana de apcientes infectados pelo HIV/AIDS em acompanhamento num serviço de referência, o Instituto de Pesquisa Clínica Evandro-IPEC/Fiocruz, que iniciaram o uso de terapia antirretroviral potente (HAART); b) Caracterizar o perfil dos eventos não associados ao HIV/AIDS, tais como eventos cardiovasculares, renais, hepáticos, neoplasias, ósseos, metabólicos entre outros, estimar sua incidência e fatores de risco nos períodos pré e pós disponibilização de terapia antirretroviral potente no Brasil; c) Descrever as causas de morte nessa coorte, analisando o risco competitivo das difrerentes causas de morte envolvidas; d) Estudar o diagnóstico tardio da infecção pelo HIV: seus preditores e impacto do diagnóstico tardio na sobrevida; e) Estimar a frequencia de eventos graves e que motivaram a troca de medicamentos/esquemas terapêuticos relacionados à toxicidade dos ARV, os fatores associados à sua ocorrência nesta coorte de pacientes com HIV/AIDS acompanhados no IPEC/Fiocruz; f) Estimar a prevalência de toxicidadfe de curto e longo prazo nessa coorte; g) Estimar as taxas de interrupção e modificação dos esquemas HAART inicial e subsequentementes e seus fatores associados; h) Estabelecer o tempo até a modificação ou interrupção do primeiro esquema e dos esuqemas HAART subsequentes nestes pacientes; i) Estudar o processo de senescência nos indivíduos infectados pelo HIV e suas repercussões no perfil de morbimortalidade, no tratamento antirretroviral e consumo de serviço de saúde; j) Estudar a efetividade dos esquemas HAART na coorte de pacientes com idade igual ou superior a 50 anos acompanhados no IPEC/Fiocruz; k) Estudar a tolerabiliodade e segurança dos esquemas HAART na coorte de pacientes com idade igual ou superior a 50 anos acompanhados no IPEC/Fiocruz; l) Acessar o perfil de morbimortalidade na coorte de pacientes com igual ou superior a 50 anos acompanhados no IPEC/Fiocruz; m) Estudar o consumo de serviços hospitalares e ambulatoriais dessa população de pacinets. Os dados serão obtidos através da base de dados da coorte de pacientes com HIV/AIDS do IPEC/Fiocruz e sempre que necessário através da revisão dos prontuários. Para o cálculo da freqüência absoluta e relativa das doenças indicativas presentes na definição do caso de AIDS, as análises serão realizadas para o período como um todo (1986 até 2009 podendo se estender posteriormente em novas revisões), e para cada um dos períodos específicos: 1986-1990; 1991-1995 e 1996-2005, 2006-2009, que correspondem às eras de ausência de terapia antirretroviral; instituição da monoterapia e terapia dupla; instituição da terapia potente

"Estudo Longitudinal da História Natural da Infecção pelo HIV em pacientes acompanhados no IPEC-FIOCRUZ".

(HAART) e períodos subseqüentes englobando importantes modificações nas rotinas de tratamento.

**3. Observações Gerais: (Atendendo à Resolução CNS 196/96).**
Projeto com delineamento adequado. Para os pacientes em acompanhamento ativo na coorte ou iniciando acompanhamento será aplicado Termo de Consentimento Livre e Esclarecido, elaborado em linguagem acessível ao sujeito de pesquisa. Para os pacientes cujo acompanhamento resultou em perda de seguimento ou óbito, para os quais não será possível a utilização de TCLE, foi confeccionado um Termo de Confidencialidade para que seja assegurado que as informações obtidas serão de caráter confidencial e serão utilizadas apenas para fins científicos. Os atendimentos ambulatoriais e os exames laboratoriais de rotina e para diagnóstico serão realizados de acordo com o preconizado para cortejo de portadores de HIV no IPEC, sem custo adicional.

**4. Diligências:**
Não houve.

**5. Parecer: APROVADO.**

**Data da Reunião: 13 de setembro de 2010.**

**Assinatura do Coordenador:**

Dr.ª Léa Camillo-Coutinho
Coordenadora do Comitê de Ética em Pesquisa