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AVALIAÇÃO DA INCIDÊNCIA DE DOENÇAS OPORTUNISTAS NA COORTE DE PACIENTES INFECTADOS PELO HIV EM ACOMPANHAMENTO NO INSTITUTO DE PESQUISA CLÍNICA EVANDRO CHAGAS – IPEC/FIOCRUZ

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Dissertação apresentada ao Curso de Pós Graduação em Pesquisa Clínica em Doenças Infecciosas do Instituto de Pesquisa Clínica Evandro Chagas para obtenção do grau de Mestre.

Orientadoras: Profa. Dra. Paula Mendes Luz e Profa. Dra. Beatriz Gilda Jegerhorn Grinsztejn

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Dedico este trabalho a Rodrigo Amancio,

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RESUMO

Introdução: O advento da terapia antirretroviral de alta potência (ARTc) modificou dramaticamente a história natural de infecção pelo HIV. O aumento da sobrevida e qualidade de vida dos pacientes infectados pelo HIV foi acompanhado por um aumento gradual da ocorrência de doenças não diretamente relacionadas à Aids. No entanto, as doenças oportunistas persistem como uma das principais causas de morte e hospitalização nesta população. A ocorrência de doenças oportunistas na era pós-ARTc está na maior parte das vezes associada ao diagnóstico tardio e à falha virológica em pacientes em uso de cART. **Artigo 1:** Revisão sistemática sobre a incidência de doenças oportunistas e suas tendências temporais, comparando resultados publicados de países de alta renda e de países de baixa/média renda. Foi realizada busca sistemática de publicações sobre doenças oportunistas e infecção pelo HIV nas seguintes bases de dados: Pubmed, Web of Science, Lilacs e Google scholar. 37 publicações foram incluídas, sendo 25 estudos conduzidos em países de alta renda e 12 estudos conduzidos em países de baixa/média renda. **Conclusões:** Foi observada redução da taxas de incidência de doenças oportunistas tanto em países de alta quanto em países de baixa/média renda. A maior parte dos estudos é oriunda de países de alta renda. Não foram encontrados estudos brasileiros que reportassem taxas anuais de incidência de doenças oportunistas. **Artigo 2:**Estimar a incidência de doenças oportunistas na coorte de pacientes infectados pelo HIV do IPEC no período de 1987-2012, determinar variáveis associadas a incidência de doenças oportunistas na era pós-ARTc. 3.378 pacientes com idade superior a 18 anos foram incluídos, destes, 1.119 (33%) apresentaram doença oportunista durante o estudo. Os pacientes incluídos apresentavam uma idade média de 35 anos e mediana tempo de seguimento foi de 1279,5 dias. De 1987-1990 para 2009-2012 a taxa de incidência de doenças oportunistas diminuiu de 295.4/1000 pessoas-ano para 34.6/1000 pessoas-ano. A tuberculose foi a doença oportunista mais incidente na população do estudo. Os fatores associados a aumento da taxa incidência de doenças oportunistas na era pós cART foram: categoria de exposição "homem que faz sexo com homem" comparada à exposição heterossexual, maiores tempos desde o diagnóstico da infecção pelo HIV, carga viral HIV elevada, uso de profilaxia para PCP e presença de doenças oportunistas no momento inclusão. Último período do estudo, escolaridade >8 anos, CD4 >350 células/mm^3, uso de cART e isoniazida profilática foram associados à redução da taxa de incidência de doenças oportunistas. **Conclusões:** As taxas de incidência de doenças oportunistas diminuíram ao longo dos anos; Tuberculose permanece como a principal doença oportunista na população do estudo; Diagnóstico da infecção pelo HIV e início de acompanhamento tardios estão associados a aumento da incidência de doenças oportunistas na nossa população na era pós cART; O uso de cARTe de isoniazida profilática se associaram com a diminuição da incidência de doenças oportunistas.

Palavras chave: 1. HIV. 2. AIDS. 3. Incidência. 4. Infecções Oportunistas Relacionadas com a AIDS. 5. HAART.

Coelho, L. **Rio de Janeiro, 2013. Opportunistic illnesses incidence evaluation in IPEC cohort of HIV infected patients.** Dissertação [Mestrado em Pesquisa Clínica em Doenças Infecciosas] – Instituto de Pesquisa Clínica Evandro Chagas.

ABSTRACT

Introduction: The advent of highly active antiretroviral therapy (cART) dramatically changed the natural history of HIV infection . The gain in survival and quality of life of HIV-infected patients were accompanied by a gradual increase in incidence of diseases not directly related to AIDS. However, opportunistic illnesses remain the main cause of hospitalization and death in this population. The occurrence of opportunistic diseases in the post-cART era is mainly associated with late HIV diagnosis and linkage to care and to virological failure in cART experimented patients. **Article 1**: Systematic review of the incidence of opportunistic illnesses and their temporal trends, comparing published results of high-income and low/middle-income settings. We performed a systematic search of publications on opportunistic infections and HIV infection in the following databases: PubMed, Web of Science, Lilacs and Google scholar. 37 publications were included, 25 studies conducted in high-income settings and 12 studies in low/middle-income settings. **Conclusions**: We observed a reduction in the incidence rates of opportunistic diseases both in high and low/middle-income settings. Most of the studies are from high-income settings. No Brazilian studies were found that reported on annual incidence rates of opportunistic illnesses. **Article 2:** To estimate the incidence of opportunistic illnesses in the IPEC cohort of HIV-infected patients in the period of 1987-2012; to determine variables associated with the incidence of opportunistic illnesses in the post-cART. 3,378 patients aged 18 years or older were included, of whom 1,119 (33%) had an opportunistic illness during follow-up. Patients enrolled had a mean age of 35 years and median follow-up time of 1279.5 days. From 1987-1990 to 2009-2012 the incidence rate of opportunistic illnesses decreased from 295.4/1000 person-years to 34.6/1000 person-years. Tuberculosis was the most incident opportunistic illness in our cohort. The factors associated with increased incidence of opportunistic infections in the post cART era were: exposure category "men who has sex with men" compared to heterosexual exposure, longer time since HIV diagnosis, high HIV viral load at cohort entry, use of PCP prophylaxis and presence of opportunistic illness at enrollment. Most recent period of the study, higher educational level, CD4 counts> 350 cells/mm3, use of cART and isoniazid prophylaxis were associated with reduced incidence of opportunistic illnesses. **Conclusions**: The incidence rates of opportunistic illnesses decreased over the years; Tuberculosis remains the most incident opportunistic illness; Late HIV diagnosis and linkage to care were associated with increased incidence of opportunistic diseases in our population; Use of cART and isoniazid prophylaxis were associated with decreased incidence of opportunistic diseases.

Keywords: 1. HIV. 2. AIDS. 3. Incidence. 4. Opportunistic Illness. 5. HAART.

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LISTA DE ABREVIATURAS

ADI	AIDS defining illness
AIDS	Acquired Immunodeficiency Syndrome; Síndrome da Imunodeficiência Adquirida
aIRR	Adjusted incidence rates ratio; razão de taxas de incidência ajustada
ARTc	Combined antiretroviral treatment / Terapia antirretroviral combinada
ART	Highly Active Antiretroviral Therapy
AZT	Zidovudina
CDC	Centers for Disease Control and Prevention
CD4	CD4 + T cells; Linfócitos T CD4+
cIRR	Crude incidence rates ratio; razão de taxas de incidência bruta
CMV	Cytomegalovirus; Citomegalovirus
FDA	Food and Drug Administration
Fiocruz	Fundação Oswaldo Cruz
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatites B vírus; Vírus da Hepatite B
HCV	Hepatites C vírus; Vírus da Hepatite C
HIV	Human Immunodeficiency Virus; Vírus da Imunodeficiência Humana
IDU	Injection Drug User; Usuário de Drogas Injetáveis
ITRN	Inibidor da transcriptase reversa análogo de nucleosideo
ITRNN	Inibidor da transcriptase reversa não análogo de nucleosideo
IP	Inibidor da protease
IPEC	Instituto de Pesquisa Clínica Evandro Chagas
IRR	Incidence rates ratio; razão de taxas de incidência
MAC	*Mycobacterium avium* complex
MS	Ministério da Saúde do Brasil
MSM/HSH	Men who have sex with men; Homens que fazem sexo com homens
NTX	Cerebral toxoplasmosis; Toxoplasmose cerebral
PCP	*Pneumocystis carinii* pneumonia; *Pneumocystis jirovecii* Pneumonia
PY/PA	Persons-year; Pessoas-ano
TST	Tuberculin skin test; teste tuberculínico cutâneo
UNAIDS	United Nations Programme on HIV/AIDS; Programa das Nações Unidas em HIV/AIDS
WHO/OMS	World Health Organization; Organização Mundial de Saúde

1. INTRODUÇÃO

A primeira descrição na literatura da ocorrência de uma síndrome de imunodeficiência adquirida, sem etiologia conhecida, em homens que faziam sexo com homens (HSH), foi a partir de uma série de casos, em 1981, de pneumonia por *Pneumocystis carinii* (PCP, atualmente denominada *Pneumocystis jiroveci*) e Sarcoma de Kaposi (CDC, 1981; Hymes, 1981). Essa síndrome, que acometia em especial HSH, foi denominada *Gay Compromise Syndrome* (Brennan, 1982), porém, após relatos de casos semelhantes, em pacientes hemofílicos e usuários de drogas injetáveis (CDC, 1982, Haverkos, 1982) esta síndrome, não mais restrita à HSH, passou a ser denominada pelo *Center for Disease Control and Prevention* (CDC) Síndrome da Imunodeficiência Adquirida (SIDA; *Acquired Immunodeficiency Syndrome - AIDS*) (CDC, 1982).

Embora casos tenham sido relatados desde 1981, as primeiras descrições do agente etiológico, posteriormente denominado vírus da imunodeficiência humana (Human immunodeficiency virus - HIV) são de 1983 (Barre-Sinoussi, 1983; Gallo RC, 1984). Até 1985, quando o primeiro teste sorológico para diagnóstico de infecção pelo HIV foi aprovado pelo *Food and Drug Administration - FDA* (FDA, 1985), o diagnóstico da infecção pelo HIV/AIDS era baseado em critérios clínicos e epidemiológicos estabelecidos pelo CDC, e as doenças oportunistas que acometiam essa população eram denominadas doenças definidoras de AIDS (CDC, 1982).

Até 1987, quando a zidovudinda (AZT) foi aprovada pelo FDA para tratamento dos pacientes com AIDS (Fischl, 1987), as estratégias terapêuticas para pacientes infectados pelo HIV eram baseadas no tratamento de doenças oportunistas e no uso de profilaxias para algumas dessas doença, principalmente para PCP (Gordin, 1984; CDC, 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 inicio da década de 1990 (Moore, 1991, Grahan, 1992, Kaplan, 2000).

O marco histórico na epidemia do HIV acontece em 1996, com o advento da terapia antirretroviral combinada (*combined Antiretroviral Therapy* - cART), usualmente denominada HAART (*Highly Active Antiretroviral Therapy*). Esta estratégia terapêutica

consiste na associação de pelo menos três drogas antirretrovirais, de pelo menos duas classes diferentes, capazes de conferir controle da replicação virológica e aumento da contagem de células T CD4+. Os esquemas de cART usualmente prescritos associam inibidores da transcriptase reversa análogos de nucleosídeos, inibidores da transcriptase reversa não análogo de nucleosídeos, inibidores da protease e inibidores da integrase.

Com a implementação da cART, a incidência de doenças oportunistas foi reduzida de 2,6 a 12 vezes (Mocroft, 1999; Mocroft, 2000; San-Andres, 2003) e a taxa de mortalidade foi reduzida em quase 5 vezes (Hooshyar, 2007). Como conseqüência, foi observado aumento da sobrevida e melhora da qualidade de vida dos pacientes infectados pelo HIV (Buchacz, 2010; Long, 2008). Estudos conduzidos em países desenvolvidos estimaram que pacientes infectados pelo HIV em uso de cART, com carga viral persistentemente indetectável, e contagem de células CD4+ acima de 500/mm³ por mais de seis anos, apresentam a mesma chance de morte que a população geral (Lewden, 2007), com uma expectativa de vida que pode exceder 35 anos após o diagnóstico da infecção (Lohse, 2007), se aproximando da expectativa de vida da população geral (Hogg, 2013). O envelhecimento da população infectada pelo HIV se associou ao aumento da prevalência e incidência de doenças crônicas associadas ao envelhecimento tais como neoplasias, doenças cardiovasculares, doenças hepáticas e metabólicas (Pacheco, 2009).

A despeito do progresso obtido no diagnóstico, tratamento e manejo dos pacientes com HIV/AIDS, estima-se que mais de 35 milhões de pessoas estejam infectadas no mundo, e que, em 2012, 1,6 milhões de pessoas faleceram em decorrência da infecção pelo HIV (UNAIDS, 2013; WHO, 2013). A carga de doença pelo HIV é ainda mais importante nos países de baixa renda, nos quais a infecção pelo HIV representa a 2ª causa de morte na população geral (WHO, 2013). Além disso, as doenças oportunistas continuam representando uma das principais causas de morte e hospitalização nesta população, tanto em países de alta renda, como em países de baixa/média renda (Pacheco, 2009; Buchacz, 2010; Grinsztejn, 2013; Ribeiro, 2013). Os principais fatores associados à persistência da ocorrência de doenças oportunistas são o diagnóstico tardio da infecção pelo HIV e a imunossupressão relacionada à falha virológica em pacientes já experimentados em cART (Perbost, 2005).

O Brasil é um país de média renda, com acesso universal a cART desde 1996 (Ministério da Saúde, 1999), com uma baixa prevalência de infecção pelo HIV (0,6%) na população geral, e com um padrão de epidemia concentrada entre os homens que fazem sexo

com homens, profissionais do sexo e usuários de drogas injetáveis (Ministério da Saúde, 2012). Entretanto, embora cerca de 38.000 casos novos sejam diagnosticados anualmente (Ministério da Saúde, 2012), e o diagnóstico tardio permaneça uma característica da nossa epidemia (Cardoso, 2010), poucos estudos brasileiros informam sobre a tendência temporal das taxas de incidência de doenças oportunistas ao longo dos anos e o impacto da cART nas mesmas.

Conhecer a tendência temporal da incidência das doenças oportunistas é de fundamental importância para informar sobre a carga de doença e o perfil de morbidade da população infectada pelo HIV, além de permitir melhor planejamento das políticas de saúde e dos recursos destinados aos cuidados de saúde dos pacientes infectados pelo HIV.

Neste contexto, avaliamos a tendência temporal das taxas de incidência de doenças oportunistas em uma coorte de pacientes infectados pelo HIV no Rio de Janeiro, com acesso universal a cART, e determinamos os fatores associados à incidência de doença oportunista nessa população na era pós-cART.

1.1 Objetivos

O tema central dessa dissertação foi estudar o comportamento das taxas de incidência de doenças oportunistas na coorte do IPEC/Fiocruz ao longo dos anos. Os objetivos específicos foram:

1. Estimar as taxas de incidência de cada doença oportunista específica em 8 períodos definidos *a priori* (1987-1990; 1991-1993; 1994-1996; 1997-1999; 2000-2002; 2003-2005; 2006-2008; 2009-2012);

2. Definir fatores associados ao desenvolvimento de doenças oportunistas na era pós-cART.

1.2 Estrutura da dissertação:

Os capítulos de revisão da literatura, metodologia, resultados e discussão foram apresentados na forma de 2 artigos.

1- Trends in overall opportunistic illnesses, *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis and *Mycobacterium avium* complex incidence rates over the 30 years of the HIV epidemic: a systematic review (Tendências das taxas de incidência de doenças oportunistas em geral, pneumonia por *Pneumocystis jirovecii*, toxoplasmose cerebral e complexo *Mycobacterium avium* ao longo dos 30 anos de epidemia de HIV: uma revisão sistemática).

2- Trends on AIDS-defining Opportunistic Illnesses incidence over 25 years in Brazil and risk factors in the post cART era (Tendências da incidência de doenças oportunistas definidoras de AIDS em 25 anos no Brasil e os fatores de risco associados na era pós-cART).

2 Artigo 1

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Trends in overall opportunistic illnesses, *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis and *Mycobacterium avium* complex incidence rates over the 30 years of the HIV epidemic: a systematic review

Abstract

Background: The natural history of HIV infection has changed dramatically after the introduction of highly active antiretroviral therapy. Currently, opportunistic illnesses still represent a major cause of death and hospitalization in this population. In this study, we review the trends in opportunistic illnesses incidence rates and compare the results observed in high-income settings with that for low/middle-income settings, with special attention given to studies from Brazil. **Methods:** We systematically searched Pubmed, Web of Science, Lilacs and Google scholar for publications on HIV associated opportunistic illness. Studies reporting rates based on person-time for all opportunistic illness and/or the three opportunistic infections of interest namely *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis, and *Mycobacterium avium* complex were included. **Results:** Significant reductions in the incidence rates were demonstrated for opportunistic illnesses overall and also for specific opportunistic infections included in the present study, both in high and low/middle-income settings. Out of the thirty seven studies included in the present review, almost 70% were from high-income settings. All the studies conducted in low/middle-income settings were single center studies and four were from Brazil. We found no study from Brazil that reports annual incidence rates of opportunistic illnesses. **Conclusions:** Opportunistic illnesses remain an important public health problem. To better guide health policies in low/middle-income settings, multicenter cohort studies should be encouraged. Studies from Brazil are urgently needed to assess the current burden of opportunistic illnesses in our population and to support the planning of HIV/AIDS health care services organization.

Trends in overall opportunistic illnesses, *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis and *Mycobacterium avium* complex incidence rates over the 30 years of the HIV epidemic: a systematic review

Introduction

The natural history of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) has changed dramatically since the onset of the epidemic in the 1980s. The landmark of this process was the introduction of highly active antiretroviral therapy (ART) in 1996. Despite the progress made in the treatment and control of HIV infection, HIV/AIDS persists as one of the main causes of death in the world, affecting individuals from both high-income and low-income settings[1]. In addition, although an increase in non-AIDS associated morbidity and mortality has been observed, opportunistic infections remain a major cause of hospitalization and death in people living with HIV/AIDS in high and low-income settings[2-4].

Currently, in the post-ART period, opportunistic illnesses are mainly related with late diagnosis and/or presentation to care, non-adherence to ART and HIV resistance to antiretroviral drugs[2, 5]. Late diagnosis and/or presentation to care is one of the most challenging aspects of the HIV epidemic. In Brazil, 34% of the patients still present with an opportunistic illness at the moment of ART initiation 6. Furthermore, non-adherence to ART results in virologic failure and disease progression. Factors associated with non-adherence, such as low education level, young age, unemployment, alcoholism and use of illicit drugs represent an important social-economic problem, in particular for low-income settings[7, 8]. And finally, multidrug resistance to antiretroviral drugs is a consequence of HIV exposure to ART, particularly in settings where non-adherence prevails[9].

In this study, we review the trends in opportunistic illnesses incidence rates and compare the results observed in high-income settings (HIS) with that for low/middle income settings (LMIS), with special attention given to studies from Brazil. We evaluate the impact that ART has had in three specific opportunistic infections of particular importance to Brazil and contrast the patterns in the countries evaluated.

Search strategy and selection criteria

Publications related to AIDS-associated opportunistic illnesses incidence were identified by systematically searching in Pubmed, Web of Science, Lilacs and Google scholar. Publications were restricted to the following languages: English, Portuguese, and Spanish. The databases were searched for studies published until January 2013 using the following search terms and Boolean operators, for matches under any field: (incidence) AND (HIV OR human immunodeficiency virus) AND (AIDS-defining illness OR opportunistic infection OR opportunistic disease OR AIDS-related opportunistic infection OR AIDS-related opportunistic illness). For the Lilacs database, search terms were translated into Portuguese language and separate searches with each term were conducted. Titles and available abstracts were scanned for relevance identifying papers requiring further consideration. Bibliographies of relevant articles were also checked. Inclusion criteria consisted in (1) presence of a person-time denominator and (2) results for all opportunistic illness and/or the three opportunistic infections of interest, namely*: Pneumocystis carinii* pneumonia (PCP), cerebral toxoplasmosis (NTX) and *Mycobacterium avium* complex (MAC). Exclusion criteria included: (1) results given only for hospitalization and/or severe diseases, (2) results given relative terms only (that is, as incidence rate ratios, odds ratios or relative risks), (3) results given only for Immune Reconstitution Inflammatory Syndrome (IRIS), and (4) results that aggregate death and opportunistic infections in one outcome. The results, inclusion and exclusion criteria are shown in Figure 1.

Results

Thirty seven publications met the study's criteria, 25 from HIS and 12 studies from LMIS (Figure 1). Out of the 12 studies from LMIS, four were from Latin America, specifically from Brazil. Results from these studies are summarized in the next sections giving incidence rates in 100 person-years (100PY) format.

Opportunistic Illnesses

Table 1 summarizes the findings for the incidence rate of opportunistic illnesses from 1984 to 2010 in HIS and LMIS. Depending of the study, incidence rates were found to be from 12.3 to 2.3 times lower in the post-ART period compared to the pre-ART period.

In HIS, a multicenter study conducted in the United States using data from the HIV Outpatient Study (HOPS) cohort with no CD4+cell count restriction of the study population reported that the incidence rate of opportunistic illnesses decreased from 9.24/100PY in pre-ART period to 1.66/100PY in post-ART period[2]. A more striking result was reported for the Eurosida cohort, an European multicenter cohort that included only patients with CD4+ cell counts less than 500 cells/mm3 where the incidence rate of opportunistic illnesses decreased from 30.7/100PY in the pre-ART period to 2.5/100PY in the post-ART period[10]. Similarly, a study from Spain that included patients with CD4+ cell counts of less than 500 cells/mm3 reported significant decreases in the incidence rate of opportunistic illnesses, which went from 43.2/100PY to 14.6/100PY, in the pre and post-ART periods, respectively[11]. Others studies conducted in HIS can be found in Table 1, including results from England, Canada, Switzerland and Germany.

In LMIS, in a study from Thailand with no CD4+ cell count restriction of the study population, the incidence rate of opportunistic illnesses decreased from 19.1/100PY in the absence of ART to 8.2/100PY after ART use[12]. A study conducted in São Paulo in the period of 1986 to 1997 also with no CD4+ cell count restriction of the study population reported an incidence rate of opportunistic illnesses of 12.24/100PY in what can be assumed to be a pre-ART period[13]. Another study conducted with the same population during the period from 1987 to 2002 estimated a lower incidence rate of opportunistic illnesses, of 4.6/100PY[14]. A study from Rio de Janeiro, that included only patients with CD4+ counts of less than 100 cells/mm3 in the period of 1997 to 1999, found an incidence rate of opportunistic illness of 29/100PY in what can be assumed to be the post-ART period[15]. Others studies conducted in LMIS can be found in Table 1 and include results from South Africa, Ivory Coast, Senegal and Poland.

Pneumocystis carinii pneumonia

Table 2 summarizes the findings for PCP incidence rate from 1982 to 2008 in HIS and LMIS. Depending of the study, incidence rates were found to be from 15.6 to 2.0 times lower in the post-ART period compared to the pre-ART period.

In HIS, a study conducted in one center in England included all HIV-infected individuals and showed that the incidence rate of PCP decreased from 9.1/100PY in the pre-

ART period (before 1992) to 1.9/100PY in the post-ART period (in 1997)[16]. An even more dramatic result was reported in a study from San Francisco, United States, that used surveillance data of the HIV-infected population from that city and showed that the incidence rate of PCP dropped from 9.5/100PY in pre-ART period (1993-1995) to 0.85/100PY in post-ART period (2001-2008)[17]. Others studies conducted in HIS can be found in Table 2, including results from France, Spain, Switzerland and Germany.

In LMIS, a study from Taiwan that included all HIV-infected individuals estimated that the incidence rate of PCP decreased from 70.5/100PY in the pre-ART period (1995) to 9.2/100PY in the post-ART period (1999)[18]. In addition, a study from Thailand that, again, included all HIV-infected reported that the incidence rate of PCP decreased from 4.7/100PY in the absence of ART to 0.3/100PY after ART use[12]. Other studies conducted in LMIS can be found in Table 2 and include results from South Africa and Poland. Unfortunately, we found no study from Brazil.

Cerebral toxoplasmosis

Table 3 summarizes the findings for NXT incidence rate from 1985 to 2010 in HIS and LMIS. Depending of the study, incidence rates were found to be from 8.0 to 1.2 times lower in the post-ART period compared to the pre-ART period.

In HIS, a multicenter cohort (Multicenter AIDS Cohort Study – MACS) of HIV-infected men who have sex with men from the United States reported that the incidence rate of NTX decreased from 0.54/100PY in pre-ART period (1990-1992) to 0.22/100PY in post-ART period (1996-1998)[19]. Data of the Swiss cohort (multicenter cohort), confirmed this trend showing that the incidence rate of NTX among HIV-infected individuals who started antiretroviral therapy between 1995 and 1997 decreased from 1.45/100PY before ART use to 0.18 after ART use[20]. Also in HIS, in a multicenter study from United Kingdom conducted among HIV-infected individuals reported that the incidence rate of NTX decreased from 0.32/100PY in the pre-ART period (1996-1997) to 0.04 in the post-ART period (1006-2007)[21]. Others studies conducted in HIS can be found in Table 3, including results from England, France, Spain, Switzerland and Germany.

In LMIS, a study from Thailand that included all HIV-infected patients estimated that the incidence rate of NTX decreased from 1.2/100PY in the absence of ART to 1.0/100PY

after ART use[12]. Data from LMIS also include a study from South Africa, with no CD4+ cell count restriction of the study population, with an incidence rate of NTX of 0.15/100PY in period of 1992 to 200022. Again, we unfortunately did not find any study from Brazil.

Mycobacterium avium complex disease

Table 4 summarizes the findings for MAC incidence rate from 1985 to 2008 in HIS and LMIS. Depending of the study, incidence rates were found to be from 25.8 to 2.4 times lower in the post-ART period compared to the pre-ART period.

In HIS, a surveillance study from San Francisco (United States), with no CD4+ cell count restriction of the study population, reported that the incidence rate of MAC decreased from 8.52/100PY in pre-ART period (1993-1995) to 0.32 in post-ART period (2001-2008)[17]. A one center study from Spain, that included only patients with CD4+ counts less than 500 cells/mm3, reported that the incidence rate of MAC decreased from 2.9/100PY in pre-ART period (1992) to 0.6/100PY in post-ART period (1997)[11]. In addition, data from the Swiss Cohort for patients with CD4+ counts less than 50 cells/mm3, showed that the incidence rate of MAC decreased from 8.8/100PY in pre-ART period (1990-1996) to 1.4/100PY in post-ART period (1997-1999)[23]. Others studies conducted in HIS can be found in Table 4, including results from England, France, Spain, Switzerland and Germany.

In LMIS, two studies from Africa and one from Brazil report incidence rates of MAC. A study from South Africa, with no CD4+ cell count restriction of the study population reported an incidence rate of 0.4/100PY for the period of 1992 to 2000[22]. Another study, from Ivory Coast for all HIV-infected found an incidence rate of 1.85/100PY for the period of 1992 to 2002[24]. The study from Brazil, conducted from 1997 to 1999 among patients with CD4+ cell counts less than 100 cells/mm3 reported no cases of disseminated MAC[25].

Discussion

Through a systematic review of the literature, we have shown that the incidence of opportunistic illnesses decreased over the 30 years of the HIV epidemic, markedly after ART availability. The significant reduction in the incidence rates was demonstrated for opportunistic illnesses overall and also for specific opportunistic infections, namely, PCP,

NXT and MAC. In addition, the decreasing trends were shown for both HIS and LMIS where ART was made available. This result is extremely positive as it shows that opportunistic illnesses can be controlled while also pointing to a persistent challenge, that of the diagnosis of HIV infection. Indeed, in order to control opportunistic illnesses, HIV infection status must be known and earlier linkage to care needs to be facilitated. That is, a higher uptake of HIV testing with direct linkage to care of those found to be HIV-infected is urgently needed.

We found that the magnitude of the incidence rates and of the reduction of these rates as a function of ART varied between the studies. Indeed, it is well known that there are geographical differences in the incidence of opportunistic illnesses[26]. Other reasons for the differences in the baseline rates might include the different study populations, including different socio-demographic subgroups evaluated in a specific study, for example, the MACS cohort that focuses on men who have sex men[27], as well as different inclusion criteria where some studies included all HIV-infected individuals while others restricted the study population to individuals with specific CD4 cell counts, for example, including only those with CD4+ cell count of less then 100 cells/mm3[15]. Moreover, different study definitions with respect to the diseases chosen to be included in any given study might have further contributed to the disparate results.

Out of the thirty seven studies included in the present review, almost 70% were from HIS. From the twelve studies from LMIS, four studies were from Brazil[13-15, 25]. These studies reported incidence rates for opportunistic illnesses for the entire study period included in the respective study and not annual rates that could allow us to evaluate the temporal trends in the incidence. Also, only one study from Brazil reported separately on the incidence rate of MAC. However, this study reported no cases of the disease, a finding that could be due to the small sample size and/or short follow-up. For the others important diseases that define the AIDS epidemic, namely, PCP, NXT, no studies from Brazil were found. Furthermore, all are single center cohort studies, two from São Paulo (Hospital das Clínicas, Faculdade de Medicina da Universidade de São Paulo) and two from Rio de Janeiro (Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz). We believe that the description of the trends in the incidence rate of opportunistic illnesses is of fundamental value to health care providers to guide clinical decision making and policy makers to define priorities for care and prevention of opportunistic infections.

Strengths and limitations to the present study are worth mentioning. Through a systematic review conducted in four databases we found the epidemiological studies that reported on the incidence rate of opportunistic illnesses. We restricted the studies to those reporting on rates (and not overall numbers or frequencies) since this epidemiological parameter is adjusted for population size and time under risk thus allowing for comparisons between studies. Though not a limitation of our study design and approach, the lack of studies from LMIS implies that we cannot adequately describe the patterns of incidence in these settings. In addition, the few studies found should also not be understood as representative of entire countries as they report from one center only. Finally, the different methodologies applied by the studies, such as inclusion criteria and diseases included for example, limited the comparisons.

In conclusion, the incidence rate of opportunistic illnesses has decreased over time mainly due to the availability of highly effective, safe and well tolerated ART. However, a public health challenge remains for future years. Public health policies focusing on earlier HIV diagnosis and linkage to care, adherence and retention programs, and surveillance of HIV multidrug resistance in populations should be developed and implemented with the goal of improving the quality of life and reducing morbid-mortality among HIV-infected individuals. To better understand the nuances of the epidemiology of opportunistic illnesses in LMIS, multicenter cohort studies should be encouraged. Finally, it is clear that studies from Brazil are urgently needed to assess the current burden of opportunistic illnesses in order to support the planning of HIV/AIDS health care services organization.

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Figure 1: Search strategy and papers selection flowchart.

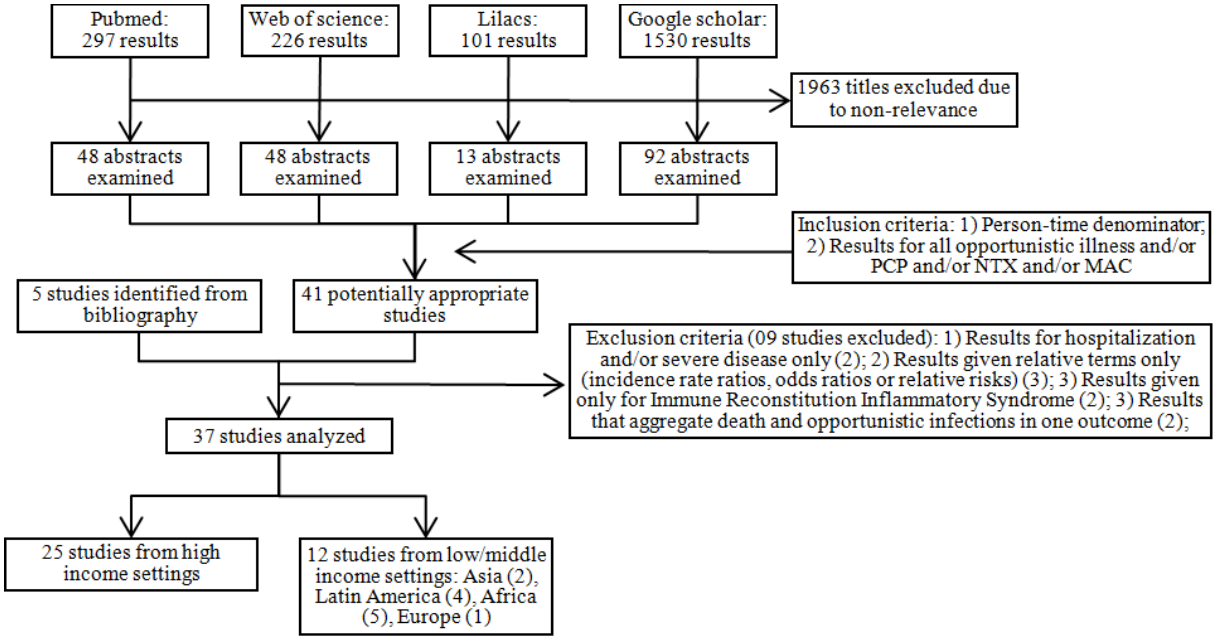

Table 1: Incidence rates for opportunistic illnesses among HIV-infected individuals from high and low/middle-income settings.

First author, year, journal	Setting and cohort (when applicable)	Time period evaluated	Incidence rate estimate	Notes
High-income Settings				
Cain, 2009, American Journal of Epidemiology	Baltimore, Pittsburgh, Chicago and Los Angeles, US, MACS cohort	1984[a] to April 2007	Entire period: 5.23/100 PY; Before 1996: 7.53/100PY; After1996: 2.19/100 PY	Patient inclusion criteria: no CD4 criteria, MSM only; Disease definition: CDC 1993, considers only the first ADI after cohort enrollment
Mocroft, 1999, Journal of Acquired Immune Deficiency Syndromes	London, UK, Royal Free Centre for HIV Medicine	1987[a] to 1998[a]	Before 1992: 27,4/100 PY; 1992-93: 16,8/100 PY; 1994: 17,9/100PY; 1995: 19.3/100 PY; 1996: 16,7/100 PY; 1997: 6,9/100 PY	Patient inclusion criteria: no CD4 criteria; Disease definition: CDC 1993, considers only the first ADI after cohort enrollment
San-Andres, 2003, Clinical Infectious Diseases	Madrid, Spain, University Hospital	January 1989 to 1997[a]	1989-91: 36.4/100 PY; 1992: 43.2/100 PY; 1993: 39.0/100 PY; 1994: 32.4/100 PY; 1995: 32.0/100 PY; 1996: 30.9/100 PY; 1997: 14.6/100 PY	Patient inclusion criteria: CD4 less than 500 cells/mm3 or previous AIDS diagnosis; Disease definition: not clearly stated, likely considers all ADI[b] episodes after cohort enrollment
Charurat, 2004, Journal of Women's Health	4 states in US and Puerto Rico, WITS Cohort	December 1989 to June 2002	Before feb/1994: 4.52/100PY; mar/1994 to jul/1996: 5.09/100PY; After aug/1996: 1.22/100PY	Patient inclusion criteria: no CD4 criteria, only women without previous diagnosis of AIDS; Disease definition: CDC 1993; considers only the first ADI after cohort enrollment
Kaplan, 2000, Clinical Infectious Diseases	10 US cities, Adults/Adolescents Spectrum of HIV Disease (ASD) Study	1992[a] to September 1999	1996 to 1998: 16/100PY[c]	Patient inclusion criteria: no CD4 criteria; Disease definition: not clearly stated, likely considers all ADI[d] episodes after cohort enrollment
Forrest, 1998, Clinical Infectious Diseases	British Columbia, Canada, British Columbia Center for Excellence in HIV/AIDS	January 1994 to December 1996	1994: 8/100PY; 1996: 2.2/100PY	Patient inclusion criteria: no CD4 criteria, included only patients in use of antiretroviral drugs; Disease definition: CDC 1993, considers only the first ADI after cohort enrollment.
Mocroft, 2000, Lancet	51 centers in Europe, Eurosida cohort	May 1994 to spring 1999[a]	1994: 30.7/100PY; 1998: 2.5/100PY[c]	Patient inclusion criteria: CD4<500 cells/mm3; Disease definition: CDC 1993, considers the first ADI after cohort enrollment
Buchacz, 2010, AIDS	12 centers in US, HOPS cohort	January 1994 to December 2007	1994-97: 9.24/100 PY; 1998-2002: 2.96/100 PY; 2003-2007: 1.66/100 PY	Patient inclusion criteria: no CD4 criteria; Disease definition: CDC 1993[e]; considers only the first ADI after cohort enrollment
Lerdeberger, 1999, Journal of the American Medical Association	7 centers in Switzerland, Swiss HIV Cohort Study	September 1995 to March 1999	Before to ART use: 15.1/100PY; after ART use: 3.57/100PY	Patient inclusion criteria: no CD4 criteria, included patients who started ART between September 1995 and December 1997. Disease definition: CDC 1993, considers only the first ADI after cohort enrollment
Wohl, 2003, Aids Patient Care and STDs	10 US cities, ASD cohort	1996[a] to 2000[a]	US born: 21.0/100PY; Mexican born: 16.6/100PY; Central American born: 13.9/100PY	Patient inclusion criteria: no CD4 criteria; included US born Latinos, Mexican born Latinos and Central American Latinos. Disease definition: not clear stated, apparently included all ADI presented in the study period.

Plettenberg, 2011, Infection	Germany, KompNet cohort	1996[a] to2010[f]	Group 1: 1.38/100PY; Group 2: 0.78/100PY	Patient inclusion criteria: patients who started antiretroviral treatment[g]. Disease definition: included the first episode of an ADIafter antiretroviral therapy.
Low/Middle-income Settings				
Fonseca, 1999, International Journal of Epidemiology	São Paulo, Brazil, University of São Paulo	1986[a] to June 1997	12.24/100PY (converted from 10.2/1000PM)	Patient inclusion criteria: asymptomatic patients; Disease definition: CDC 1987, modified to include pulmonary tuberculosis as an AIDS defining-condition, considers only the first ADI after cohort enrollment
Casseb, 2003, AIDS Patient care and STDs	São Paulo, Brazil, University of São Paulo	October 1987 to Febrary 2002	4.6/100PY (converted from 3.84/1000PM)	Patient inclusion criteria: asymptomatic patients; Disease definition: CDC 1987, considers only the first ADI after cohort enrollment
Badri, 2005, The Southern African Journal of HIV Medicine	Cape Town, South Africa, Cape Town AIDS Cohort (CTAC)	1992[a] to December 2000	21.34/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: WHO 1990, considers all ADI episodes after cohort enrollment
Losina, 2007, Antiviral Therapy	Abidjan, Ivory Coast, Cotrimo CI ANRS 059 and Cotrame ANRS1203	1996[a] to July 2003	Cotrimoxazole alone: CD4 less than 50cells/mm^3: 20.17/100PY; CD4 above 200 cells/mm^3: 3.54/100PY; Cotrimoxazole plus ART (0-6months): CD4 less 50cells/mm^3: 20.22/100PY, CD4>200 cells/mm^3: 2.79/100PY; Cotrimoxazole plus ART (>6months): CD4<50cells/mm^3: 6.84/100PY, CD4>200 cells/mm^3: 1.68/100PY	Patient inclusion: Patients participating in Cotrimo ANRS and Cotrame ANRS studies. Disease definition: considers only the first ADI[h] presented in each period[i] of study. Results were stratified by use of cotrimoxazole prophylaxis, ART and CD4 counts.
Gadelha, 2002, Journal of the Institute of Tropical Medicine of São Paulo	Rio de Janeiro, Brazil, IPEC cohort	September 1997 to December 1999	29/100PY[j]	Patient inclusion criteria: at least one CD4<100 cells/mm^3, included patients who started ART between September 1995 and December 1997. Disease definition: CDC 1993, considers the first ADI after cohort enrollment
De Beaudrap, 2010, BMC Infectious Diseases	Senegal, Initative Sénégalaise d'Acèss aux médicaments Antiretroviraux[k]	August 1998 to April 2008	First year after ART initiation: 20.5/100PY. Over the fourth year after ART initiation: 4.3/100PY	Patient inclusion criteria: no CD4 criteria. Disease definition: CDC 1993, considered the first episode of each ADI presented after ART initiation. Results were stratified by timing of ART use
Podlasin, 2006, Infection	10 centers in Poland	2000[a] to 2002[a]	Total: 2.4/100PY; 2000: 6,8/100 PY; 2001: 6.5/100 PY; 2002: 4,8/100 PY	Patient inclusion criteria: none; Disease definition: CDC 1993, not clearly stated, likely considers all ADI after cohort enrollment
Rojanawiwat, 2011, International Health	Lampang, Thailand, Governmental Referral Hospital[l]	July 2000 to October 2004	Prior to ART: 19.1/100 PY; After ART use: 8.2/100 PY	Patient inclusion criteria: no CD4 criteria; Disease definition: included the first episode of all ADI[m] presented by the patient

ADI: AIDS defining illness; CDC: Centers for Disease Control; CMV: cytomegalovirus; MAC: *Mycobacterium avium* complex; MSM: men who have sex with men; PCP: *Pneumocystis carinii* pneumonia.

[a] Month not specified

[b] Does not specify the criteria used for ADI, the results include: Esophageal candidiasis,PCP, tuberculosis, wasting syndrome, cerebral toxoplasmosis, Kaposi's sarcoma, AIDS dementia complex, progressive multifocal leukoencephalopathy, primary brain lymphoma, CMV disease,MAC, non-Hodgkin lymphoma, cryptosporidiosis, recurrent pneumonia, cryptococcosis, chronic herpes simplex, invasive cervical cancer.

[c] Results for other years shown in Figure format only, thus not reported here.

[d] Diseases included: PCP, disseminated MAC, cerebral toxoplasmosis, Kaposi's sarcoma, CMV retinitis, esophageal candidiasis, cryptococcosis.
[e] Excluded diseases: recurrent pneumonia, *Salmonella* septicemia and wasting syndrome
[f] Time inferred from information contained in the text;
[g] Patients were separated into two groups: Group 1: patients who started ART with CD4 between 250 and 349 cells/mm^3; Group 2: patients who started ART with CD4 between 350 and 450 cells/mm^3
[h] Diseases included: Severe bacterial infections (Pneumonia, enteritis, bacteremia, invasive urogenital infection), malaria, cerebral toxoplasmosis, isosporosis, PCP, extrapulmonar cryptococosis, esophageal candidiasis, tuberculosis, MAC, other WHO clinical stage 3 and 4.
[i] In the first period (until December 1998), patients received cotrimoxazole prophylaxis. In the second period (after December 1998) patients received ART plus cotrimoxazole prophylaxis (the later period was separated in the first 6 months after ART initiation and after 6 months of ART initiation).
[j] Data from de prospective period;
[k] Antiretroviral drugs available for free since December 2003.
[l] In 2002 the government introduced the co-formulation stavudine, lamivudine and nevirapine (on a pilot basis). The use of this medication gradually increased especially after 2004.
[m] Does not specify the criteria used for ADI, the results include: tuberculosis, PCP, cryptococcal meningitis, penicilliosis, esophageal candidiasis, herpes zoster, cerebral toxoplasmosis, CMV retinitis.

Table 2: Incidence rate for *Pneumocystis carinii* pneumonia among HIV-infected individuals from high and low/middle-income settings.

First author, year, journal	Setting and cohort (when applicable)	Time period evaluated	Incidence rate estimate	Notes
High-income Settings				
Mocroft, 1998, Archives of Internal Medicine	London, England, Chelsea and Westminster Hospital and The Royal Free Hospital	1982[a] to July 1995	6.22/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers only first episode after cohort enrollment
Bacellar,1994, Journal of Infectious Diseases	Baltimore, Pittsburgh, Chicago and Los Angeles, US, MACS cohort	1985[a] to 1993[a]	No antiretroviral nor PCP prophylaxis: 3.1/100PY; Only antiretroviral: 1.8/100PY; Antiretroviral and PCP prophylaxis: 2.4/100PY	Patient inclusion criteria: CD4 < 100 cells/mm^3, MSM only; Disease definition: considers only the first episode after cohort enrollment. Results stratified by use of antiretroviral[b] and/or PCP prophylaxis
Yazdanpanah, 2001, International Journal of Epidemiology	France, Tourcoing and Aquitaine cohorts	January 1987 to December 1995	>500 cells/mm^3: 0.4/100PY; 301-500 cells/mm^3: 0.5/100PY; 201-300cells/mm^3: 1.6/100PY; 101-200 cells/mm^3: 3.1/100PY; 51-100 cells/mm^3: 6.7/100PY; >50 cells/mm^3: 11.4/100PY;	Patient exclusion criteria: patients in use of antiretroviral therapy other than zidovudine monotheray and prophylaxis; patients with less than 3 CD4 counts; patients with prior PCP diagnosis or PCP diagnosis in the first cohort visit and those in use of PCP prophylaxis. Disease definition: only the first case after cohort enrollment. Results stratified by CD4 counts.
Mocroft, 1999, Journal of Acquired Immune Deficiency Syndromes	London, England, Royal Free Centre for HIV Medicine	1987[a] to 1998[a]	Before 1992: 9.1/100 PY; 1992-93: 5.3 /100 PY; 1994: 3.5/100 PY; 1995: 6.4/100 PY; 1996: 4.0/100 PY; 1997: 1.9/100 PY	Patient inclusion criteria: no CD4 criteria; Disease definition: only first ADI was considered after cohort enrollment
Moore, 1996, Annals of Internal Medicine	Baltimore, US, Johns Hopkins Clinical Cohort	July 1989 to April 1995	8.9/100PY	Patient inclusion criteria: CD4<300 cells/mm3; Disease definition: only first episode considered after cohort enrollment
San-Andres, 2003, Clinical Infectious Diseases	Madrid, Spain, University Hospital	January 1989 to 1997[a]	1989-91: 5.5/100 PY; 1992: 5.4/100 PY; 1993: 3.5/100 PY; 1994: 3.4/100 PY; 1995: 3.0/100 PY; 1996: 3.3/100 PY; 1997: 0.6/100PY	Patient inclusion criteria: CD4<500 cells/mm3 or previous diagnosis of an ADI; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Charurat, 2004, Journal of Women's Health	4 states in US and Puerto Rico, WITS Cohort	December 1989 to June 2002	Before February 1994: 0.44/100PY; March 1994 to July 1996: 0.86/100PY After August 1996: 0.42/100PY	Patient inclusion criteria: no CD4 criteria, women only, without previous diagnosis of AIDS; Disease definition: only first episode considered after cohort enrollment

Moorman, 1998, Journal of Acquired Immune Deficiency Syndromes	8 US cities, HOPS cohort	January 1992 to June 1996	4.6/100PY	Patient inclusion criteria: patients in use of PCP prophylaxis for at least 3 months[c]; Disease definition: all episodes considered after cohort enrollment
Brodt, 1997, AIDS	Frankfurt, Germany, Frankfurt AIDS Cohort	January 1992 to March 1997	1992: 17.8/100PY; 1993: 18.2/100PY; 1994: 16.3/100PY; 1995: 9.9/100PY; 1996: 6.4/100PY	Patient inclusion criteria: CD4<200 cells/mm3, MSM only; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Kaplan, 2000, Clinical Infectious Diseases	10 US cities, Adults/Adolescents Spectrum of HIV Disease (ASD) Study	1992[a] to September 1999	1996-98: 4.7/100PY[d]	Patient inclusion criteria: no CD4 criteria; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Schwarcz, 2013, AIDS	San Francisco, US, SFDHP	January 1993 to December 2008	1993-1995: 9.5/100PY; 1996-2000: 2.15/100PY; 2001-2008: 0.84/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers only the first episode after cohort enrollment
Ledergerber, 1999, Journal of the American Medical Association	7 centers in Switzerland, Swiss HIV Cohort Study	September 1995 to March 1999	Before ART use: 2.35/100PY, after ART use: 0.22/100PY	Patient inclusion criteria: no CD4 criteria, patients who started ART between September 1995 and December 1997. Disease definition: only first episode considered after cohort enrollment
Mocroft, 2000, Lancet	51 centers in Europe, Eurosida cohort	December 1995 to spring 1999[a]	Non-ART regimens: 2.3/100PY; ARTregimens: 0.5/100PY	Patient inclusion criteria: CD4<500 cells/mm3; Disease definition: considers the first episode after cohort enrollment
Wohl, 2003, Aids Patient Care and STDs	10 US cities, ASD cohort	1996[a] to 2000[a]	US born: 3.6/100PY; Mexican born: 2.7/100PY; Central American born: 1.3/100PY	Patient inclusion criteria: no CD4 criteria; included US born Latinos, Mexican born Latinos and Central American Latinos. Disease definition: not clear stated, apparently included all episodes presented in the study period.
Low/Middle-income Settings				
Badri, 2005, The Southern African Journal of HIV Medicine	Cape Town, South Africa, Cape Town AIDS Cohort (CTAC)	1992[a] to December 2000	1.19/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment.
Hung, 2000, AIDS	Taiwan, National Taiwan University Hospital	June 1994 to June 1999	1995: 70.5/100PY; 1999: 9.2/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers only the first episode after cohort enrollment
Holmes, 2006, Journal of Acquired Immune Deficiency Syndromes	Cape Town, South Africa, University of Cape Town cohort	1994[a] to 2000[a]	CD4<50: 8.1/100PY; CD4 51-200: 0.6/100PY; CD4 201-350: 0.3/100PY;	Patient inclusion criteria: patients with at least two CD4 cell counts; Disease definition: WHO stage III and IV,

			CD4>350: 0	considers only first episode considered after cohort enrollment. Results were stratified by CD4.
Podlasin, 2006, Infection	10 centers in Poland	2000[a] to 2002[a]	2000: 0.89/100PY; 2001: 0.82/100PY; 2002: 0.5/100PY	Patient inclusion criteria: none; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Rojanawiwat, 2011, International Health	Lampang, Thailand, Governmental Referral Hospital[e]	July 2000 to October 2004	Prior toART: 4.7/100PY; After H ART use: 0.3/100PY	Patient inclusion criteria: none; Disease definition: not clearly stated, likely considers the first episode after cohort enrollment

ADI: AIDS defining illness; ART: Highly Active Antiretroviral Therapy; MSM: men who have sex with men; PCP: *Pneumocytis carinii* pneumonia.

[a] Month not specified

[b] Zidovudine, didanosine or both.

[c] PCP prophylaxis was prescribed for patients with CD4 count less than 200 cells/mm^3 or considered at risk by their clinicians (even if CD4>200 cells/mm^3)

[d] Results for other years shown in Figure format only, thus not reported here.

[e] In 2002 the government introduced the co-formulation stavudine, lamivudine and nevirapine (on a pilot basis). The use of this medication gradually increased especially after 2004.

Table 3: Incidence rates for cerebral toxoplasmosis among HIV-infected individuals from high and low/middle-income settings.

First author, year, journal	Setting and cohort (when applicable)	Time period evaluated	Incidence rate estimate	Notes
High-income Settings				
Bacellar, 1994, Journal of Infectious Diseases	Baltimore, Pittsburgh, Chicago and Los Angeles, US, MACS cohort	1985[a] to 1993[a]	No antiretroviral nor PCP prophylaxis: 6.9/100PY; Only antiretroviral: 6.0/100PY; Antiretroviral and PCP prophylaxis: 14.8/100PY	Patient inclusion criteria: CD4<100 cells/mm^3, MSM only; Disease definition: considers only the first episode after cohort enrollment. Results stratified by use of antiretroviral[b] and/or PCP prophylaxis
Yazdanpanah, 2001, International Journal of Epidemiology	France, Tourcoing and Aquitaine cohorts	January 1987 to December 1995	>500 cells/mm^3: 0.1/100PY; 301-500 cells/mm^3: 0.6/100PY; 201-300cells/mm^3: 1.1/100PY; 101-200 cells/mm^3: 2.0/100PY; 51-100 cells/mm^3: 3.9/100PY; >50 cells/mm^3: 12.6/100PY;	Patient exclusion criteria:patients in use of antiretroviral therapy other than zidovudine monotheray and prophylaxis; patients with less than 3 CD4 counts; patients with prior NTX diagnosis or with NTX diagnosis in the first cohort visit and those in use of NTX prophylaxis. Disease definition: only the first case after cohort enrollment. Results stratified by CD4 counts.
Moore, 1996, Annals of Internal Medicine	Baltimore, US, Johns Hopkins Clinical Cohort	July 1989 to April 1995	2.3/100PY	Patient inclusion criteria: CD4<300 cells/mm3; Disease definition: considers only the first episode after cohort enrollment
San-Andres, 2003, Clinical Infectious Diseases	Madrid, Spain, University Hospital	January 1989 to 1997[a]	1989-91: 2.1/100PY, 1992: 2.9/100PY, 1993: 2.4/100PY, 1994: 0.8/100PY, 1995: 1.1/100PY, 1996: 1.0/100PY, 1997: 1.8/100PY	Patient inclusion criteria: CD4<500 cells/mm3 or previous diagnosis of AIDS; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Sacktor, 2001, Neurology	Baltimore, Pittsburgh, Chicago and Los Angeles, US, MACS cohort	January 1990 to December 1998	1990-92: 0.54/100PY, 1993-95: 0.38/100PY, 1996-98: 0.22/100PY	Patient inclusion criteria: no CD4 criteria, MSM only; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Brodt, 1997, AIDS	Frankfurt, Germany, Frankfurt AIDS Cohort	January 1992 to March 1997	1992: 10.6/100PY, 1993: 6.1/100PY, 1994: 3.9/100PY, 1995: 4.0/100PY, 1996: 2.6/100PY	Patient inclusion criteria: CD4<200 cells/mm3, MSM only; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Ledergerber, 1999, Journal of the American Medical Association	7 centers in Switzerland, Swiss HIV Cohort Study	September 1995 to March 1999	Before ART use: 1.45/100PY, after ART use: 0.18/100PY	Patient inclusion criteria: no CD4 criteria, patients who started ART between September 1995 and December 1997. Disease definition: considers only the first episode after cohort enrollment
Wohl, 2003, Aids Patient Care and STDs	10 US cities, ASD cohort	1996[a] to 2000[a]	US born: 0; Mexican born: 0.5/100PY; Central American born:	Patient inclusion criteria: no CD4 criteria; included US born Latinos, Mexican born Latinos

			0.7/100PY	and Central American Latinos. Disease definition: not clear stated, likely considers all episodes presented in the study period.
Garvey, 2011, European Journal of Neurology	10 UK HIV centers, CHIC (UK Collaborative HIV Cohort)	January 1996 to December 2007	Total: 0.12/100PY; 1996-97: 0.32/100PY, 1998-99: 0.11/100PY, 2000-01: 0.15/100PY, 2002-03: 0.11/100PY, 2004-05: 0.09/100PY, 2006-07: 0.04/100PY	Patient inclusion criteria: none; Disease definition: considers only the first episode after cohort enrollment
Riveiro-Barciela, 2013, HIV medicine	Barcelona, Spain	January 2000 to December 2010	2000 to June 2005: 0.32/100PY; July 2005 to 2010: 0.11/100PY	Patient inclusion criteria: none; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Low/Middle-income Settings				
Badri, 2005, The Southern African Journal of HIV Medicine	Cape Town, South Africa, Cape Town AIDS Cohort (CTAC)	1992[a] to December 2000	0.15/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment.
Holmes, 2006, Journal of Acquired Immune Deficiency Syndromes	Cape Town, South Africa, University of Cape Town cohort	1994[a] to 2000[a]	CD4<50: 1.2/100PY; CD4 51-200: 0; CD4 201-350: 0; CD4>350: 0	Patient inclusion criteria: patients with at least two CD4 cell counts; Disease definition: WHO stage III and IV; considers only first episode after cohort enrollment. Results were stratified by CD4.
Rojanawiwat, 2011, International Health	Lampang, Thailand, Governmental Referral Hospital[c]	July 2000 to October 2004	Before ART use: 1.2/100PY, After ART use: 1.0/100PY	Patient inclusion criteria: none; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment

ART: Highly Active Antiretroviral Therapy; MSM: men who have sex with men; NTX: Cerebral toxoplasmosis; PCP: *Pneumocytis carinii* pneumonia.
[a] Month not specified.
[b] Zidovudine, didanosine or both.
[c] In 2002 the government introduced the co-formulation stavudine, lamivudine and nevirapine (on a pilot basis). The use of this medication gradually increased especially after 2004.

Table 4: Incidence rate of *Mycobacterium avium* complex among HIV-infected individuals from high and low/middle-income settings.

First author, year, journal	Setting and cohort (when applicable)	Time period evaluated	Incidence rate estimate	Notes
High-income Settings				
Bacellar, 1994, Journal of Infectious Diseases	Baltimore, Pittsburgh, Chicago and Los Angeles, US, MACS cohort	1985[a] to 1993[a]	No antiretroviral nor PCP prophylaxis: 6.9/100PY; Only antiretroviral: 6.0/100PY; Antiretroviral and PCP prophylaxis: 14.8/100PY	Patient inclusion criteria: CD4<100 cells/mm^3, MSM only; Disease definition: CDC 1993; considers only the first episode of each ADI after cohort enrollment. Results stratified by use of antiretroviral[b] and/or PCP prophylaxis
Chaisson, 1992, American review of respiratory disease	Multicenter observational cohort in US	April 1987 to 1990[c]	8.6/100PY	Patient inclusion criteria: patients with AIDS diagnoses defined by PCP, an opportunistic disease other than PCP and CD4<250cells/mm^3, or AIDS related complex and CD4<250 cells/mm^3; Disease definition: not clearly stated, likely considers only the first episodes after cohort enrollment
Yazdanpanah, 2001, International Journal of Epidemiology	France, Tourcoing and Aquitaine cohorts	January 1987 to December 1995	>500 cells/mm^3: 0.0/100PY; 301-500 cells/mm^3: 0.2/100PY; 201-300cells/mm^3: 0.3/100PY; 101-200 cells/mm^3: 1.0/100PY; 51-100 cells/mm^3: 1.9/100PY; >50 cells/mm^3: 9.5/100PY;	Patient exclusion criteria: patients in use of antiretroviral therapy other than zidovudine monotheray and prophylaxis; patients with less than 3 CD4 counts; excluded patients with prior MAC diagnosis or with MAC diagnosis in the first cohort visit and those in use of MAC prophylaxis. Disease definition: considers only the first case after cohort enrollment. Results stratified by CD4 counts
Mocroft, 1999, Journal of Acquired Immune Deficiency Syndromes	London, England, Royal Free Centre for HIV Medicine	1987[c] to 1998[c]	Before 1992: 1.1/100PY, 1992-93: 3.8/100PY, 1994: 4.1/100PY, 1995: 4.1 /100PY, 1996: 2.7/100PY, 1997: 1.0/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers only the first episode after cohort enrollment
Moore, 1996, Annals of Internal Medicine	Baltimore, US, Johns Hopkins Clinical Cohort	July 1989 to April 1995	7.4/100PY	Patient inclusion criteria: CD4<300 cells/mm3; Disease definition: considers only the first episode after cohort enrollment
San-Andres, 2003, Clinical Infectious Diseases	Madrid, Spain, University Hospital	January 1989 to 1997[c]	1989-91: 1.5/100PY, 1992: 2.9/100PY, 1993: 1.5/100PY, 1994: 1.1/100PY, 1995: 1.9/100PY, 1996: 2.5/100PY, 1997: 0.6/100PY	Patient inclusion criteria: CD4<500 cells/mm3 or previous diagnosis AIDS; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Charurat, 2004, Journal of	4 states in US and Puerto Rico, WITS Cohort	December 1989 to June 2002	Before February 1994: 0.32/100PY; March	Patient inclusion criteria: no CD4 criteria, women only, without

Women's Health			1994 to July 1996: 0.23/100PY; After August 1996: 0.12/100PY	previous diagnosis of AIDS; Disease definition: considers only the first episode after cohort enrollment[d]
Rossi, 2001, Swiss Medical Weekly	7 centers in Switzerland, Swiss HIV Cohort Study	January 1990 to December 1999	Overall: 5.8/100PY, 1990-96: 8.8/100PY, 1997-99: 1.4/100PY	Patient inclusion criteria: CD4<50 cells/mm3; Disease definition: considers only the first episode after cohort enrollment
Brodt, 1997, AIDS	Frankfurt, Germany, Frankfurt AIDS Cohort	January 1992 to March 1997	1992: 4.5/100PY; 1993: 6.1/100PY; 1994: 6.6/100PY; 1995: 5.4/100PY; 1996: 2.8/100PY;	Patient inclusion criteria: CD4<200 cells/mm3, MSM only; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Kaplan, 2000, Clinical Infectious Diseases	10 US cities, Adults/Adolescents Spectrum of HIV Disease (ASD) Study	1992[c] to September 1999	1996-98: 3.4/100PY[e]	Patient inclusion criteria: no CD4 criteria; Disease definition: not clearly stated, likely considers all episodes after cohort enrollment
Schwarcz, 2013, AIDS	San Francisco, US, SFDHP	January 1993 to December 2008	1993-1995:8.52/100PY; 1996-2000: 1.34/100PY; 2001-2008: 0.32/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers only the first episode after cohort enrollment
Kirk, 2000, American Journal of Respiratory and Critical Care Medicine	17 European countries, EuroSIDA Cohort	May 1994 to February 1999	1.38/100 PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers only the first episode after cohort enrollment
Mocroft, 2000, Lancet	51 centers in Europe, Eurosida cohort	May 1994 to spring 1999[c]	Non-ART regimens: 2.3/100PY; ART regimens: 0.5/100PY	Patient inclusion criteria: CD4<500 cells/mm3; Disease definition: considers only the first episode after cohort enrollment
Baril, 2000, AIDS	Paris, France, Pitié-Salpêtrière Hospital	January 1995 to December 1997	January 1996 to June 1996: 13.4/100PY; July 1996 to December 1997: 2.6/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: considers the first episode after cohort enrollment
Ledergerber, 1999, Journal of the American Medical Association	7 centers in Switzerland, Swiss HIV Cohort Study	September 1995 to March 1999	Before ART use: 1.79/100PY; after ART use: 0.76/100PY	Patient inclusion criteria: no CD4 criteria, patients who started ART between September 1995 and December 1997. Disease definition: considers only the first episode after cohort enrollment[d]
Wohl, 2003, Aids Patient Care and STDs	10 US cities, ASD cohort	1996[c] to 2000[c]	US born: 1.8/100PY; Mexican born: 1.1/100PY; Central American born: 0.4/100PY	Patient inclusion criteria: no CD4 criteria; included US born Latinos, Mexican born Latinos and Central American Latinos. Disease definition: not clear stated, apparently included all OI presented in the study period.
Low/Middle-income Settings				
Badri, 2005, The Southern African Journal of HIV Medicine	Cape Town, South Africa, Cape Town AIDS Cohort (CTAC)	1992[c] to December 2000	0.40/100PY	Patient inclusion criteria: no CD4 criteria; Disease definition: disseminated atypical mycobacteria; likely considers all episodes after cohort enrollment.
Bonard, 2004,	Ivory Coast, Cotrame	1992[c] to October	1.85/100PY	Patient inclusion criteria: no CD4

AIDS	ANRS 1203	2002	criteria; Disease definition: considers only the first episode after cohort enrollment[d]
Gadelha, 2002, The Brazilian Journal of Infectious Diseases	Rio de Janeiro, Brazil, IPEC cohort	September 1997 to December 1999	0 Patient inclusion criteria: CD4<100 cells/mm^3; Excluded patients under MAC treatment or prophylaxis. Disease definition: considers only the first episode presented in the study period.

ART: Highly Active Antiretroviral Therapy; MAC: *Mycbacterium avium* complex; MSM: men who have sex with men; PCP: *Pneumocystis carinii* pneumonia.

[a] Time inferred from information contained in the text;

[b] Zidovudine, didanosine or both

[c] Month not specified;

[d] Classify as *Mycobacterium* non *tuberculosis*

[e] Results for other years shown in Figure format only, thus not reported here;

3 Artigo 2

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Situação do manuscrito:

Finalizado, a ser submetido.

AIDS-defining Opportunistic Illnesses Incidence over 25 years in Brazil and risk factors in the post combination antiretroviral therapy era

Abstract

Objectives: To assess the temporal trends in the incidence of AIDS-defining opportunistic illnesses in a middle-income setting, and evaluate the risk factors associated with its incidence in the post combination antiretroviral therapy (cART) era. **Methods:** HIV infected patients aged 18 years or more at cohort entry were included in this analysis. We calculated incidence rates per 1000 persons-years (PY) of observation for the first opportunistic illness (OI) presented after cohort enrollment, during 1987-2012. Poisson regression models were fitted to estimate the association of socio-demographic, behavioral and clinical factors with the incidence of AIDS-defining opportunistic illnesses (OI) in post cART era. **Results:** A total of 3378 patients were included, 1119 (33%) patients presented an OI during follow up. Median age at enrollment was 35 years and median follow-up time was 1280 days (3.5 years). From 1987-1990 to 2009-2012 the incidence rate of OI dropped from 295.4/1000 PY to 34.6/1000 PY ($p<0.001$). Tuberculosis, esophageal candidiasis, cerebral toxoplasmosis, *Pneumocystis jirovecii* pneumonia and were the most incident OIs during the study period. Tuberculosis incidence was highest for all periods except for 1987-90. Final multivariate model indicated that several factors were independently associated with OI incidence. HIV risk exposure categories (men who have sex with men and compared to heterosexual transmission), baseline low CD4 cell count and high viral load, opportunistic illness at enrollment and use of *Pneumocystis jirovecii* pneumonia prophylaxis were associated with increased incidence while, higher level of education, use of cART, use of isoniazid prophylaxis were independently associated with a decreased incidence of OI. **Conclusions:** Our results show that even in the post cART era, late presentation, characterized by immunosuppression, high viral load and OI diagnosis were associated with a higher incidence of OI highlighting the need to properly and timely treat those who still reach care late. Our results also show the protective effect of cART on OI incidence corroborating the need to promptly start treatment. Of particular relevance was the protective effect of isoniazid prophylaxis on OI incidence even after adjusting for covariates. This finding poses the question of how of isoniazid prophylaxis can be related to the immunological status of HIV infected patients. Whether if controlling latent tuberculosis and its inflammation, isoniazid prophylaxis can partially restore the immunological function. This is a hypothesis that should be carefully evaluated in future studies.

AIDS-defining Opportunistic Illnesses Incidence over 25 years in Brazil and risk factors in the post combination antiretroviral therapy era

Introduction

Major advances have been achieved in the management and treatment of HIV infected patients. As a result the incidence and morbimortality of opportunistic illnesses has dramatically declined in the years that followed combination antiretroviral therapy (cART) introduction[1, 2]. Nonetheless, opportunist illnesses (OI) still represent a major cause of death and hospitalization in HIV infected patients, both in high income and low income settings[3-6]. In the post cART era, the factors associated with OI occurrence are mainly related to late presentation and linkage to care and to treatment failure[4, 7].Late diagnosis and difficulties in access to health care are a major challenge in current HIV/AIDS epidemic, and more than a third of HIV infected patients start treatment with advanced disease, both in high and low-middle income settings[7-9]. Furthermore, non-adherence to antiretroviral therapy and emergence of multidrug resistance are associated with the occurrence of opportunistic illnesses in cART experimented patients[10].

OI incidence rates can vary significantly between settings[11]. The high burden of tropical infectious diseases and tuberculosis observed in middle-low income settings can be associated with a higher incidence of specific OIs[12, 13]. One prominent example is tuberculosis with only 22 countries located in Africa, Asia and Latin America being responsible for more than 80% of all cases worldwide[12].

Brazil is a middle-income country where publically funded with universal access to cART, laboratory monitoring and OI prophylaxis and treatment are provided since 1996[14]. And Brazil still struggles with a high prevalence of infectious diseases, mainly tuberculosis, which may contribute to a higher incidence of AIDS related infections among treated HIV-infected patients [15, 16]. Yet, few studies have evaluated trends in the incidence of OI in our setting.

We examine rates and patterns of OIs incidence and risk factors associated with OI occurrence in post cART era, in urban clinical cohort in Rio de Janeiro, Brazil, from 1987 until 2012, with special attention to tuberculosis incidence rates and the impact of tuberculosis prophylaxis on tuberculosis and others opportunistic illnesses incidence rates.

Patients and Methods

Study population

Evandro Chagas Clinical Research Institute (IPEC/Fiocruz) is a reference center for treatment of HIV infected patients, in Rio de Janeiro, Brazil. As of June 2013, over 5,000 patients have been cared for at IPEC. A longitudinal observational clinical database has been maintained on patients receiving HIV care at IPEC since 1986. Cohort procedures have been described and results published[8, 17, 18]. The database includes socio-demographic, behavioral, laboratory, clinical, and therapeutic information abstracted from the medical records and is updated periodically by trained staff.

For this study we included all patients 18 years of age or older at cohort entry, who were followed for a period of at least 60 days from 1 January 1987 to 31 December 2012. The start of the observation period was defined based on the first medical appointment in IPEC. Follow-up ended at date of the first opportunistic illness for those who presented with an OI during follow-up. For the patients who never experienced an opportunistic illness during follow-up, the end of follow-up was defined as the date of the last clinic visit, the date of death or study closure, whichever occurred first.

Database validation

To assess the quality of the opportunistic illnesses diagnoses present in the IPEC longitudinal database, we performed a clinical validation of diagnoses by direct comparison of database with chart review. Ten percent of the patients who presented an opportunistic illness during follow-up (n=118 patients) were randomly selected for chart review and validation of the first and concomitant opportunistic illnesses, that is, those occurring within 30 days of the date of the first opportunistic illnesses.

A trained HIV medical specialist used two criteria to validate the diagnoses. The first, which classified diagnoses into certain, probable and possible, took into consideration all forms of complementary exams, including radiological, microbiological and hystopatological, in addition to medical prescriptions. This criterion had already been used by our team in other study[3]. The second criterion was built based on the case definition for HIV-related diseases established by the WHO[19]. According to it the diagnoses were either classified as definitive or clinical.

The validation showed that 95% of the opportunistic illnesses diagnosis were confirmed using either criteria. Out of the confirmed diagnosis, 49% were classified as certain using the first criterion, and 56% were classified as definitive according to second (WHO) criterion.

Outcome measures

The outcome of interest was the occurrence of the first opportunistic illness after cohort enrollment. Prevalent diagnosis at or up to 30 days of the date of cohort enrollment were excluded from the incidence rate calculation.

The opportunistic illnesses included in the analysis were those in the CDC 1993 definition, namely tuberculosis, esophageal candidiasis, toxoplasmosis cerebral, *Pneumocystis jirovecii* pneumonia (PCP), herpes simplex virus, cytomegalovirus disease (other than liver, spleen or nodes), extrapulmonar cryptococcosis, Kaposi sarcoma, crypstosporidiosis, isosporosis, non tuberculosis mycobacterium disease, disseminated histoplasmosis, non Hodgkin lymphoma. We excluded from the analysis the following opportunistic illnesses: HIV associated encephalopathy, recurrent bacterial pneumonia, *salmonella* septicemia and wasting syndrome. The reasons for excluding these diseases were disease-specific, namely the low number of cases in the case of salmonella septicemia, the difficultly in establishing a diagnosis of recurrence in the case of bacterial pneumonia, and the subjective nature of the diagnosis criteria in the case of HIV associated encephalopathy and wasting syndrome.

Statistical Methods

We estimate the incidence rate of the first opportunistic illness in each calendar period. Eight calendar periods were defined a priori as follows: 1987-1999, 1991-1993, 1994-1996, 1997-1999, 2000-2002, 2003-2005, 2006-2008 and 2009-2012.

The incidence rate of an opportunistic illness was defined as the ratio between the number of cases of a specific illness and the number of person-years at risk during that period. Person-years at risk were calculated for each patient as the sum of days at risk by period. Rates were calculated by 1000 person-years with respective 95% confidence intervals (CI) using a Poisson distribution. For the group of patients enrolled on or after January 01 1997, generalized estimating equations models with robust standard errors were used to estimate incidence rate ratios for the following outcomes: opportunistic illnesses and the four most

frequent illnesses namely tuberculosis, esophageal candidiasis, cerebral toxoplasmosis, and PCP. Unadjusted analyses were performed and all variables found to be significantly associated with the outcome at the threshold level of 0.2 were included in the initial multivariate model. The final multivariate model was reached by progressively removing variables not significantly associated with the outcome at the threshold level of 0.05, one at a time, until a parsimonious model was achieved that contained only the significant terms.

Independent variables tested in the models included age, sex, race/ethnicity, educational level, presumed HIV risk exposure group, time since HIV diagnosis up to cohort enrollment, baseline CD4 cell count and HIV viral load defined as those occurring 180 days before or 30 days after cohort enrollment, nadir of CD4 cell count, presence of an opportunistic infection at cohort enrollment (6 months prior to up to 30 days after enrollment), and use of antiretroviral therapy and PCP, *Mycobacterium avium* (MAC), and isoniazid prophylaxis as time dependent variables.

Antiretroviral therapy was classified into mono, dual or combined therapy based on at least a 60-days period under treatment. This minimum amount of exposure to antiretroviral was defined so as to avoid a possible increase in OI incidence in this first 60 days of treatment that could be related to Immune Reconstitution Inflammatory Syndrome. The use PCP, MAC and isoniazid prophylaxis were defined based on at least a 30-days period under treatment.

Results

A total of 3378 patients, met the inclusion criteria and were included in this analysis out of which 1119 (33%) presented an OI during follow-up. Several characteristics were significantly different between the groups who did and did not develop an OI during follow-up (Table 1). Patients who developed an OI during follow-up were less educated, and more likely to report MSM or IDU as their risk exposure category. Also, a greater proportion of those who developed an OI during follow-up had <1 year since HIV diagnosis, OI at enrollment, and hepatitis C co-infection. As for their immune status, these patients were also more severely immunosuppressed as indicated by their baseline and nadir CD4 cell counts. A significantly higher proportion of patients who did not develop an OI during follow-up used isoniazid prophylaxis and cART. Follow-up time was 4 times longer for those who did not develop an OI while death was 7 times more frequent among those who developed an OI during follow-up.

Trends in Rates of Opportunistic Illnesses

During the study period, the incidence rates of OIs decreased by almost 9 times from 295/1000PY in 1987-1990 to 34/1000PY in 2009-2012 (Figure 1). Incidence rates for specific OIs also significantly decreased during the study period (Table 2). PCP had the most expressive decline in incidence rates (30-fold decrease), from 87/1000PY in 1987-1990 to 2.8/1000PY in 2009-2012 ($p<0.001$), followed by cerebral toxoplasmosis (11-fold decrease), from 43.6/1000PY in 1987-1990 to 4.0/1000PY in 2009-2012 ($p<0.001$). Tuberculosis, esophageal candidiasis, cerebral toxoplasmosis, PCP and cutaneous *Herpes simplex* were the most incident OIs in the cohort (Table 2).

Predictors of Opportunistic Illnesses Incidence in post-cART era

The adjusted model indicates that, in post cART era, the most recent calendar period, 2009-2012 (aIRR 0.42 CI95% 0.27-0.64, compared to 1987-90), nine or more years of school (aIRR 0.66 CI95% 0.54-0.8, compared to up to 8 years), baseline CD4 cell counts above 350/mm^3 (aIRR 0.43 CI95% 0.29-0.64, compared to <50/mm^3), CD4 nadir counts above 350 cells/mm^3 (aIRR 0.44, CI95% 0.3-0.66, compared to <50/mm^3), use of cART (aIRR 0.2 CI95%0.16, 0.25) and of isoniazid prophylaxis (aIRR 0.28, CI95% 0.15-0.52) were independently associated with a lower incidence of OI (Table 3). When compared to heterosexual exposure, MSM exposure (aIRR 1.37, CI95% 1.12-1.67) was associated with a higher incidence of OI. In addition, time since HIV diagnosis greater than 5 years (aIRR 1.63, CI95% 1.27-2,07, compared to <1 year), missing nadir CD4 cell count (aIRR 8.81 CI95% 5.58-13.91), HIV viral load at baseline above 100,000 copies/mL (aIRR 2.09, CI95%1.25-3.48, compared to <400 copies/mL), presence of OI at enrollment (aIRR 2.08, CI95% 1.68-2.58) and use of PCP prophylaxis (aIRR 2.95, CI95% 2.36-3.68) were associated with higher incidence of OI (Table 3).

The adjusted model for the four most incident OIs (tuberculosis, esophageal candidiasis, cerebral toxoplasmosis, and PCP) are given in Table 3. For tuberculosis, most recent calendar period, female sex, higher education, baseline CD4 cell count >350/mm^3, use of cART and isoniazid propylaxis were associated with a lower incidence. On the other hand, non-white race/ethnicity, use of PCP prophylaxis were associated with a higher incidence of tuberculosis. The final model of esophageal candidiasis showed that higher education and

cART use were associated with a decreased incidence, while time since HIV diagnosis greater than 5 years, PCP and MAC prophylaxis, and presence of an OI at enrollment were associated with an increased incidence. In the analysis of cerebral toxoplasmosis higher education, higher baseline CD4 cell count, use of cART and isoniazid prophylaxis were associated with decreased incidence. In contrast, use of PCP prophylaxis and presence of an OI at enrollment were associated with increased incidence of cerebral toxoplasmosis. Finally, for PCP, most recent calendar period, higher baseline CD4 cell counts and use of cART and isoniazid prophylaxis were associated with decreased incidence, while presence of an OI at enrollment and PCP prophylaxis increased the incidence. Of note is the fact that missing nadir CD4 cell count significantly increased the incidence of all studied illnesses. A more detailed evaluation of the subgroup of patients with missing nadir CD4 cell counts showed that these patients had shorter follow-up (median 75.1 days vs. 1362 days, $p<0.001$), lower use of cART (15.2% vs. 76.6%, $p<0.001$), and higher mortality (25% vs. 7%, $p<0.001$) than those with at least one CD4 cell count before end of follow-up.

Discussion

In this study, we have shown that the incidence rates of OI decreased over the years, with a trend of reduction that began even before cART was made universally available in Brazil. These results are in agreement with those reported from others cohorts and most likely reflect improvements in the general care of HIV infected patients in addition to the use of specific OI preventive measures as well as mono and dual antiretroviral therapy[2, 20, 21]. The 80% reduction in OI incidence associated with the use of cART is similar to those reported in high-income settings[20], but for specific OIs, the reduction in incidence resulting from cART use observed in our cohort was even greater than that previously published from high income settings[22]. The most incident OIs in our casuistic (tuberculosis, esophageal candidiasis, cerebral toxoplasmosis and PCP) are also the most frequent OI reported in other studies from high-income and low-income settings[4, 23, 24].

We found that in post cART era, advanced HIV clinical stage at baseline, characterized in our study by low CD4 cell count, high viral load, and presence of OI at enrollment were associated with increased OI incidence. Similar results were reported from cohort studies from Europe and United States[22, 25, 26]. These findings suggest that late presentation is still a challenge and highlights the need to improve earlier HIV diagnosis, effective linkage to care and prompt antiretroviral treatment initiation. A sub-group of patients

for which late presentation likely occurred are those with a missing nadir CD4 cell count which was associated with a significantly higher OI incidence. Patients with a missing nadir CD4 cell count had shorter follow-up, decreased use of cART and higher mortality indicating late and poor linkage to the health care system. Finally, the use of PCP prophylaxis was found to increase OI incidence which may be a result of selection bias given that this prophylaxis is indicated for patients with CD4 counts under 200 cells/mm^3 [27, 28].

Tuberculosis represents the most incident OI in our cohort, with an incidence rate that is currently two-fold higher than the second most incident OI, esophageal candidiasis (12.54/1000PY vs. 6.08/1000PY). The 85% reduction observed in tuberculosis incidence rate over the years (1991-1993 *vs.* 2009-2012) is similar to the incidence rate variation observed in multiple cohorts[4, 29-31], in both high-income and low-income settings. In a meta-analysis, the summary estimate of tuberculosis risk reduction associated with the use of ART across all CD4 counts was 67% (CI 95% 61–73)[32]. Randomized clinical trials such as the Cipra HAITI study and the HPTN 052 also showed a 50% reduction in tuberculosis incidence after ART initiation among individuals with CD4 cell counts higher than 250 and 350 respectively[33, 34].

HIV and tuberculosis co-infection is a huge challenge for countries with high tuberculosis prevalence, as Brazil, and, in these settings, tuberculosis is an important cause of severe morbidity[3] and the main cause of death of HIV infected individuals[5, 12, 35, 36]. Unlike others OI, tuberculosis can occur in a HIV-infected patient independently of the immunodeficiency severity[29] and the risk of developing tuberculosis is 20 to 37 times higher in HIV infected persons than in those without HIV infection[37]. Our results corroborate these findings, as CD4 cell counts and presence of OI at enrollment (an indicator of HIV clinical stage) were not associated with tuberculosis incidence. As expected, the use isoniazid prophylaxis was independently protective against tuberculosis. Previous studies have already shown the protective effect of isoniazid prophylaxis on tuberculosis incidence, independently of cART use[30, 38, 39], particularly for those patients with positive tuberculin skin test (TST)[40]. Despite the fact that a meta-analysis did not find a reduction in tuberculosis incidence in TST negative patients[38], considering the high risk of false-negative results (up to 66%) in HIV infected patients[41] and operational barriers related to TST implementation and realization, the WHO recommends that in resource-constrained settings TST should not be a requirement for initiating isoniazid prophylaxis[37]. In contrast, Brazilian guidelines recommend isoniazid prophylaxis only for TST positive patients. Given that operational barriers also prevail in our setting it is possible that patients that used isoniazid prophylaxis may represent a subgroup of patients that are better adapted to all HIV/medical care system. Another explanation would be

that patients with a positive TST have higher probability of having a CD4 >200 cells/mm^3 thus making the use of isoniazid prophylaxis more common among less immunodeficient patients. However this later explanation does seems less plausible in our study since the protective effect of isoniazid prophylaxis was adjusted by baseline and nadir CD4 cell counts.

A surprising finding was that the use of isoniazid prophylaxis is associated with reduction in OI incidence, as well as with the incidence of PCP and cerebral toxoplasmosis. To our knowledge, no other study has reported a protective effect of isoniazid prophylaxis against opportunistic illnesses other than tuberculosis. Although, some studies reported improvement in HIV infected patient's survival and delayed HIV disease progression associated with use of isoniazid prophylaxis [40, 42, 43], the effect on specific illnesses was not evaluated. Latent tuberculosis prevalence is estimated to occur in 2 billion persons worldwide[12] and the role played by latent tuberculosis in HIV infected patients has been already described. Latent tuberculosis leads to HIV replication and accelerates HIV disease progression[44, 45]. Following this rationale, isoniazid prophylaxis can reduce tuberculosis associated inflammation and deleterious influence over HIV immunodeficiency[43], and the impact observed with isoniazid prophylaxis on others OIs could be explained by this effect.

There are limitations and strengths to our study that should be considered. First, the clinical database for the cohort is based in chart-abstracted information and thus subject to errors in the process of collecting the data from the medical charts. To examine the degree of this limitation, a clinical database validation and chart review was performed and great consistence (95%) between the database and original medical charts was found. Second, since we have no information on adherence, we assumed that every cART and prophylaxis prescription were correctly used and could have overestimated their use. That said the protective effect of both cART and isoniazid prophylaxis would only be enhanced if individuals with poor adherence were removed. And finally, underestimation of opportunistic illnesses as a consequence of an outside medical visit or hospitalization might have happened. However, IPEC provides general multidisciplinary care including inpatient care and intensive care free of charge with an emergency entrance available and therefore the likelihood that they resort to IPEC in case of illness is high.

In conclusion, all opportunistic illnesses incidence rates decreased over the years but still occur in an unacceptable frequency. Late presentation to care is strongly associated with the incidence OI in post cART era. Although there is no doubt about the protective effect of cART on OI incidence, a significant proportion of patients do not benefit from this intervention either because HIV diagnosis occurs later in the infection or because, even with a

previous HIV diagnosis, they are not properly linked to the health care system. Tuberculosis and HIV co-infection represent a challenge for the health care professional and policy makers. Isoniazid prophylaxis is effective but is not broadly used in HIV infected patients. Whether it should be provided despite of TST is a matter or great discussion that takes into account the risk of emergency of multidrug resistance tuberculosis, potential side effects associated with isoniazid and cost-effectiveness evaluation of this intervention.

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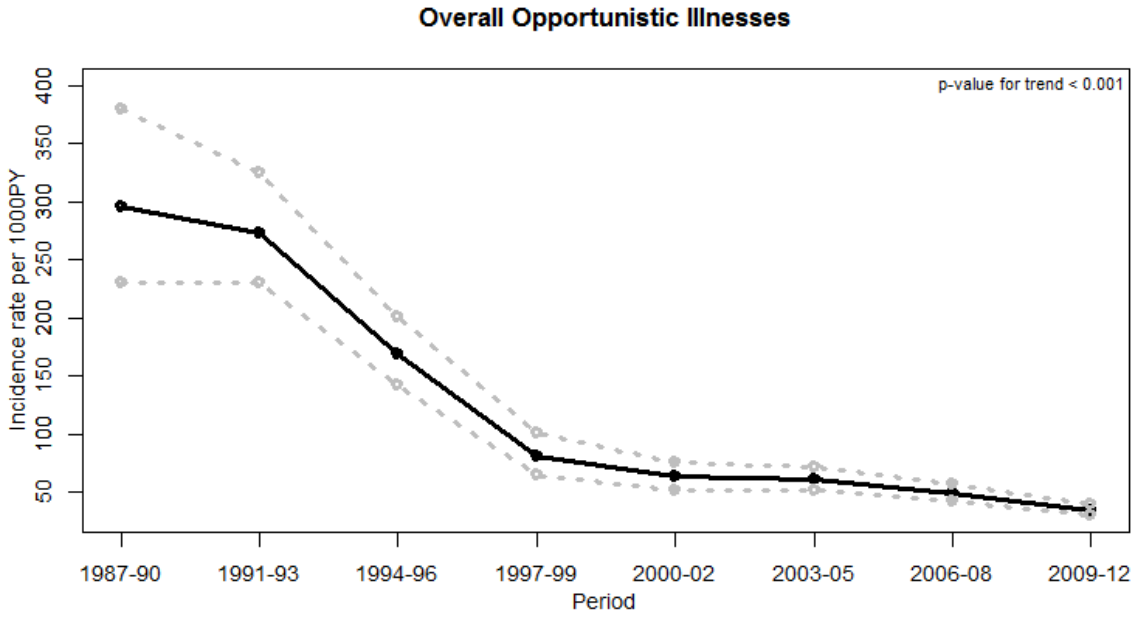

Figure 1: Trends in opportunistic illnesses incidence rates, IPEC cohort, 1987-2012.

Table 1: Characteristics of patients included in analyses of opportunistic illnesses incidence rates, IPEC cohort, 1987-2012.

	No OI N=2659 (%)	**Developed OI** N=1119(%)	**Total** N=3778(%)	**P-value**
Follow-up in days (median, IQR)	1644 (722, 2804.5)	370 (93,1280.5)	1279.5 (391,2400)	< 0.001
Age at enrollment (median, IQR)	34.7 (28.5, 42.2)	35.2 (29.2, 41.7)	34.9 (28.6, 42.1)	0.342
18-29 years	843 (31.7)	317 (28.3)	1160 (30.7)	0.016
30-39 years	964 (36.3)	458 (40.9)	1422 (37.6)	
40-49 years	595 (22.4)	256 (22.9)	851 (22.5)	
50+ years	257 (9.7)	88 (7.9)	345 (9.1)	
Male sex	1736 (65.3)	778 (69.5)	2514 (66.5)	0.013
Race/Ethnicity				0.188
White	1369 (51.8)	604 (54.2)	1973 (52.5)	
Non white	1276 (48.2)	511 (45.8)	1787 (47.5)	
Education level				< 0.001
0-8 years	1258 (47.7)	637 (57.8)	1895 (50.7)	
9+ years	1379 (52.3)	466 (42.2)	1845 (49.3)	
HIV risk group				< 0.001
Heterossexual	1339 (50.4)	520 (46.5)	1859 (49.2)	
MSM	996 (37.5)	446 (39.9)	1442 (38.2)	
IDU	33 (1.2)	50 (4.5)	83 (2.2)	
Other/Unknown	291 (10.9)	103 (9.2)	394 (10.4)	
Time since HIV diagnosis				
Median days(IQR)	86 (16,611.5)	61 (1,381)	79 (13,533.2)	< 0.001
<1 year	1875 (70.5)	835 (74.6)	2710 (71.7)	0.037
1-5 years	387 (14.6)	142 (12.7)	529 (14)	
5+ years	397 (14.9)	142 (12.7)	539 (14.3)	
OI at enrollment	518 (19.5)	366 (32.7)	884 (23.4)	< 0.001
Hepatitis C co-infection				< 0.001
Yes	195 (7.3)	116 (10.4)	311 (8.2)	
No	2262 (85.1)	667 (59.6)	2929 (77.5)	
Missing	202 (7.6)	336 (30)	538 (14.2)	
Hepatitis B co-infection				<0.001
Yes	137 (5.2)	60 (5.4)	197 (5.2)	
No	2070 (77.8)	717 (64.1)	2787 (73.8)	
Missing	452 (17)	342 (30.6)	794 (21)	
CD4 nadir (median, IQR)	225 (104, 335)	110 (39, 235.8)	198 (78,316)	< 0.001
0-49 cells/mm^3	357 (13.4)	248 (22.2)	605 (16)	< 0.001
50-199 cells/mm^3	785 (29.5)	340 (30.4)	1125 (29.8)	
200-349 cells/mm^3	856 (32.2)	168 (15)	1024 (27.1)	
350+ cells/mm^3	595 (22.4)	86 (7.7)	681 (18)	
Missing	66 (2.5)	277 (24.8)	343 (9.1)	
Baseline CD4 (median, IQR)	331 (144, 550.5)	161 (45.5, 357)	290 (108, 516)	< 0.001
0-49 cells/mm^3	188 (7.1)	127 (11.3)	315 (8.3)	< 0.001
50-199 cells/mm^3	383 (14.4)	152 (13.6)	535 (14.2)	
200-349 cells/mm^3	354 (13.3)	84 (7.5)	438 (11.6)	
350+ cells/mm^3	867 (32.6)	127 (11.3)	994 (26.3)	
Missing	867 (32.6)	629 (56.2)	1496 (39.6)	
Baseline VL (median, IQR)	23578 (2877,126413)	92000 (19710,350000)	32038 (4670,157011)	< 0.001
0-399 copies/ mm^3	225 (8.5)	20 (1.8)	245 (6.5)	
400-4,999 copies/ mm^3	172 (6.5)	22 (2)	194 (5.1)	< 0.001
5,000-99,999 copies/ mm^3	562 (21.1)	141 (12.6)	703 (18.6)	
100,000+ copies/ mm^3	386 (14.5)	166 (14.8)	552 (14.6)	
Missing	1314 (49.4)	770 (68.8)	2084 (55.2)	
PCP prophylaxis				<0.001
Yes	1452 (54.6)	587 (52.5)	2039 (54)	
No	1207 (45.4)	532 (47.5)	1739 (46)	
Isoniazid prophylaxis				<0.001
Yes	419 (15.8)	65 (5.8)	484 (12.8)	
No	2240 (84.2)	1054 (94.2)	3294 (87.2)	
MAC prophylaxis				0.538
Yes	190 (7.1)	73 (6.5)	263 (7)	
No	2469 (92.9)	1046 (93.5)	3515 (93)	
ART Monotherapy				< 0.001
Yes	21 (0.8)	102 (9.1)	123 (3.3)	
No	2638 (99.2)	1017 (90.9)	3655 (96.7)	
ART Dual therapy				< 0.001

Yes	26 (1)	55 (4.9)	81 (2.1)	
No	2633 (99)	1064 (95.1)	3697 (97.9)	
cART				< 0.001
Yes	2132 (80.2)	406 (36.3)	2538 (67.2)	
No	527 (19.8)	713 (63.7)	1240 (32.8)	
Time on cART(days) median(IQR)	1787.5 (826.8,3699)	1186 (478.5,2340.5)	1682.5 (760.5,3364)	< 0.001
Time until cART(days) median(IQR)	63 (6,495)	32.5 (-494.5,281.8)	57 (0,471)	< 0.001
Death	149 (5.6)	458 (40.9)	607 (16.1)	< 0.001

OI: opportunistic illness; MSM: men who had sex with men; IDU: injection drug users; VL: viral load; PCP: *Pneumocystis jirovecii* pneumonia; MAC:*Mycobacterium avium* complex; ART: antiretroviral therapy; cART: combined antiretroviral therapy.

Table 2: First opportunistic illness after enrollment in IPEC cohort, absolute numbers and incidence rates per 1000 person-years for 1987-2012 and by calendar period.

	1987-2012		1987-1990		1991-1993		1994-1996		1997-1999		2000-2002		2003-2005		2006-2008		2009-2012		p-value for trend*
Person-years	18,137		206		483		780		1,047		1,694		2,317		3,877		7,735		
	n	IR	n	IR	n	IR	n	IR	n	IR	n	IR	n	IR	n	IR	N	IR	
Tuberculosis	336	18.53	12	58.12	39	80.80	33	42.32	29	27.71	37	21.85	32	13.81	57	14.70	97	12.54	<0.01
Esophageal candidiasis	155	8.55	7	33.90	7	14.50	11	14.11	10	9.55	10	5.90	20	8.63	43	11.09	47	6.08	<0.01
Toxoplasmosis cerebral	143	7.88	9	43.59	18	37.29	14	17.95	14	13.38	11	6.50	21	9.07	25	6.45	31	4.01	<0.01
Pneumocystis carinii pneumonia	140	7.72	18	87.18	25	51.79	15	19.24	7	6.69	8	4.72	21	9.07	24	6.19	22	2.84	<0.01
Herpes simplex virus	64	3.53	4	19.37	3	6.22	1	1.28	6	5.73	18	10.63	5	2.16	11	2.84	16	2.07	<0.01
Cytomegalovirus	58	3.20	1	4.84	10	20.72	13	16.67	2	1.91	7	4.13	7	3.02	6	1.55	12	1.55	<0.01
Extrapulmonar cryptococcosis	52	2.87	1	4.84	7	14.50	5	6.41	7	6.69	6	3.54	6	2.59	8	2.06	12	1.55	<0.01
Kaposi Sarcoma	45	2.48	2	9.69	8	16.57	8	10.26	3	2.87	1	0.59	10	4.32	4	1.03	9	1.16	<0.01
Crypstosporidiosis	31	1.71	2	9.69	4	8.29	17	21.80	0	0.00	1	0.59	3	1.30	2	0.52	2	0.26	-
Isosporosis	30	1.65	3	14.53	9	18.65	4	5.13	2	1.91	2	1.18	2	0.86	4	1.03	4	0.52	-
Non tuberculosis mycobacterium	26	1.43	0	0.00	0	0.00	7	8.98	2	1.91	3	1.77	7	3.02	4	1.03	3	0.39	-
Disseminated histoplasmosis	15	0.83	1	4.84	1	2.07	3	3.85	1	0.96	1	0.59	1	0.43	2	0.52	5	0.65	-
Non-Hodgkin lymphoma	14	0.77	1	4.84	0	0.00	1	1.28	2	1.91	1	0.59	2	0.86	1	0.26	6	0.78	-

Diseases with less than 10 cases reported during the study period are not shown (progressive multifocal leukoencephalopathy n=8, invasive cervical cancer n=1, coccidioidomycosis n=1).

*Trend was tested for all illnesses with 40 cases of more during the study period.

Table3: Crude and adjusted Incidence Rates Ratio (IRR) for variables associated with opportunistic illnesses in post cART era, patients enrolled after 01 January 1997, IPEC/Fiocruz (n=3096 patients).

	OI cIRR (IC95%)	OI aIRR (IC95%)	TB aRR (IC95%)	CAN aIRR IC95%)	TOXO aIRR(IC95%)*	PCP aIRR (IC95%)*
Study period						
1997 – 1999	reference	reference	reference			reference
2000 – 2002	**0.62 (0.42, 0.91)**	0.82 (0.51, 1.31)	0.77 (0.37, 1.58)			0.6 (0.17, 2.08)
2003 – 2005	**0.52 (0.36, 0.75)**	0.81 (0.52, 1.27)	0.56 (0.27, 1.15)			1.06 (0.33, 3.45)
2006 – 2008	**0.41 (0.28, 0.58)**	0.67 (0.43, 1.03)	0.64 (0.32, 1.27)			0.69 (0.22, 2.21)
2009 – 2012	**0.28 (0.2, 0.4)**	**0.42 (0.27, 0.64)**	**0.49 (0.25, 0.95)**			**0.29 (0.09, 0.92)**
Age at enrollment						
18-29years	reference					
30-39 years	1.21 (0.99, 1.48)					
40-49 years	1.17 (0.93, 1.47)					
50+ years	1.29 (0.96, 1.75)					
Male sex	reference		reference			
Female sex	**0.79 (0.67, 0.94)**		**0.61 (0.45, 0.83)**			
White race	reference		reference			
Non White race	**1.4 (1.19, 1.64)**		**1.59 (1.19, 2.12)**			
School years (0-8)	reference	reference	reference	reference	reference	
School years (9+)	**0.58 (0.49, 0.68)**	**0.66 (0.54, 0.8)**	**0.6 (0.44, 0.82)**	**0.52 (0.34, 0.8)**	**0.56 (0.35, 0.9)**	
HIV risk group						
Heterossexual	reference	reference				
MSM	1.09 (0.92, 1.31)	**1.37 (1.12, 1.67)**				
IDU	**2.23 (1.17, 4.25)**	1.88 (0.96, 3.7)				
Other/Unkown	**1.35 (1.02, 1.77)**	1.03 (0.74, 1.43)				
Time since HIV diagnosis						
<1 year	reference	reference		reference		
1-5 years	0.99 (0.79, 1.25)	1.14 (0.88, 1.46)		1.52 (0.9, 2.58)		
5+ years	**1.32 (1.07, 1.63)**	**1.63 (1.27, 2.07**)		**2.4 (1.45, 3.97)**		
CD4 counts nadir (cells/mm^3)						
<50	reference	reference	reference	reference	reference	reference
50-199	**0.49 (0.4, 0.61)**	**0.7 (0.52, 0.94)**	1.47 (0.8, 2.69)	0.82 (0.41, 1.64)	**0.41 (0.24, 0.71)**	**0.47 (0.26, 0.85)**
200-349	**0.25 (0.2, 0.32)**	**0.46 (0.33, 0.64)**	1.07 (0.56, 2.05)	0.56 (0.25, 1.26)	**0.21 (0.1, 0.44)**	**0.23 (0.1, 0.5)**
350+	**0.26 (0.19, 0.35)**	**0.43 (0.29, 0.64)**	0.77 (0.37, 1.64)	0.55 (0.22, 1.36)	**0.25 (0.1, 0.64)**	**0.27 (0.1, 0.73)**
Missing	**13.49 (8.72, 20.8)**	**8.81 (5.58, 13.91)**	**17.16 (7.74, 38.01)**	**13.19 (4.73, 36.74)**	**5.8 (2.44, 13.79)**	**5.31 (1.89, 14.93)**
Baseline CD4 counts (cells/mm^3)						
<50	reference	reference	reference	reference		
50-199	**0.44 (0.33, 0.58)**	0.72 (0.49, 1.07)	0.5 (0.23, 1.09)	0.8 (0.35, 1.8)		
200-349	**0.28 (0.2, 0.39)**	0.71 (0.46, 1.09)	0.56 (0.25, 1.25)	0.69 (0.28, 1.71)		
350+	**0.18 (0.13, 0.23)**	**0.55 (0.36, 0.84)**	**0.38 (0.17, 0.86)**	0.51 (0.2, 1.32)		
Missing	**0.4 (0.3, 0.51)**	**0.5 (0.33, 0.76)**	0.47 (0.22, 1.02)	**0.38 (0.16, 0.93)**		
Baseline Viral Load (copies/mm^3)						
<400	reference	reference				
400-4999	1.17 (0.64, 2.15)	1.23 (0.67, 2.27)				
5000-99999	**2.3 (1.43, 3.69)**	**1.85 (1.13, 3.04)**				
100000+	**3.78 (2.36, 6.07)**	**2.09 (1.25, 3.48)**				
Missing	**2.66 (1.69, 4.18)**	**2.08 (1.26, 3.44)**				
No ARTc	reference	reference	reference	reference	reference	reference
ARTc	**0.37 (0.31, 0.43)**	**0.2 (0.16, 0.25)**	**0.23 (0.16, 0.33)**	**0.18 (0.1, 0.33)**	**0.24 (0.13, 0.42)**	**0.2 (0.1, 0.37)**
PCP prophylaxis						
No	reference	reference	reference	reference	reference	reference
Yes	**2.12 (1.8, 2.51)**	**2.95 (2.36, 3.68)**	**2.75 (1.91, 3.96)**	**2.57 (1.45, 4.58)**	**3.47 (1.98, 6.09)**	**2.67 (1.44, 4.94)**
Isoniazid prophylaxis						
No	reference	reference	reference		reference	reference
Yes	**0.22 (0.12, 0.39)**	**0.28 (0.15, 0.52)**	**0.27 (0.1, 0.73)**		**0 (0, 0)**[a]	**0 (0, 0)**[a]
MAC prophylaxis						
No	reference			reference		
Yes	**2.69 (2.01, 3.59)**			2**.54 (1.25, 5.14)**		
OI at enrollment						
No	reference	reference		reference	reference	reference
Yes	**3.15 (2.64, 3.74)**	**2.08 (1.68, 2.58)**		**2.56 (1.6, 4.1)**	**2.74 (1.66, 4.51)**	**2.44 (1.42, 4.22)**

OI: opportunistic illnesses, TB: tuberculosis; CAND: esophageal candidiasis. TOXO: cerebral toxoplasmosis; PCP *Pneumocystis jirovecii pneumonia*, cIRR: crude Incidence Rates Ratio; aIRR: adjusted Incidence Rates Ratio; MSM: men who had sex with men; IDU: injection drug users; VL: viral load; MAC: Mycobacterium avium complex; cART: combined antiretroviral therapy; OI: opportunistic illness.

* Baseline viral load not included in the model since no patient who present PCP or TOXO had viral load under 400 copies/mm3.

[a] aIRR equal zero since no patient who presented PCP or TOXO had TB prophylaxis prescribed.

4 CONCLUSÕES

Nos dois artigos apresentados nesta dissertação, foram estudadas as taxas de incidência de doenças oportunistas nos pacientes infectados pelo HIV, suas tendências no decorrer dos anos, o impacto da cART nessas taxas e os fatores associados à incidência de doenças oportunistas na era pós-cART. Nossos resultados permitem concluir que:

1- As taxas de incidência de doenças oportunistas diminuíram ao longo dos anos, principalmente após a introdução da cART, e essa redução nas taxas foram observadas tanto em países de alta renda quanto em países de baixa/média renda;

2- Os estudos que avaliam a incidência de doenças oportunistas são em sua maioria oriundos de países de alta renda. Em relação ao Brasil, existe uma deficiência de dados relativo ao comportamento das doenças oportunistas ao longo dos anos e o impacto da cART nas taxas de incidência dessas doenças;

3- As taxas de incidência de doença oportunistas na coorte de pacientes infectados pelo HIV do IPEC/Fiocruz, tiveram um comportamento semelhante àquele observados em outros estudos, com importante redução após a introdução da cART;

4- A tuberculose representa em nossa coorte a doença oportunista mais incidente;

5- Diagnóstico tardio da infecção pelo HIV está associado ao aumento da incidência de doenças oportunistas na nossa população;

6- O uso de isoniazida profilática mostrou-se associado à diminuição da incidência de doenças oportunistas, não somente tuberculose, na população do estudo.

5 RECOMENDAÇÕES E DESDOBRAMENTOS

Em nosso estudo, avaliamos a tendência temporal das taxas de incidência de doenças oportunistas em uma coorte de pacientes infectados pelo HIV no Brasil. O conhecimento da carga imposta pelas doenças oportunistas na população infectada pelo HIV é de fundamental importância para o planejamento das políticas públicas e dos recursos destinados aos cuidados de saúde desses pacientes.

Embora, os atuais esquemas antirretrovirais disponíveis universalmente no Brasil sejam eficazes e bem toleráveis, o diagnóstico tardio da infecção pelo HIV não permite que uma grande parcela de pacientes se beneficie dos efeitos protetores da cART. Grandes avanços foram feitos no tratamento dos pacientes com HIV, embora seja ainda um desafio ampliar o alcance desses avanços a um número maior de indivíduos. Programas de incentivo à testagem para o HIV e acolhimento dos pacientes infectados nos serviços de saúde devem ser implementados e ampliados no sentido de diminuir a morbimortalidade associada ao HIV/AIDS.

Em lugares de alta prevalência de tuberculose, como a cidade do Rio de Janeiro, a co-infecção HIV-tuberculose se mantém como um desafio para os profissionais e gestores de saúde. A utilização de isoniazida profilática reduz o risco de tuberculose em pacientes infectados pelo HIV, mas no Brasil seu uso está atrelado à realização de TST, e considerando todas dificuldades de operacionais na implementação e realização de TST, a profilaxia de isoniazida é subutilizada. Dessa forma. a ampliação do uso da isoniazida de acordo com as recomendações da Organização Mundial da Saúde deveria ser considerada nas áreas de alta endemicidade de tuberculose no Brasil.

O efeito protetor da isoniazida na incidência de outras doenças oportunistas, que não a tuberculose, reforça a importância do uso de isoniazida profilática em pacientes infectados pelo HIV em locais de alta prevalência de tuberculose. A associação do uso de uso de isoniazida profilática e a redução da incidência de doenças oportunistas deve ser melhor estudada.

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ANEXO I

Declaração de aprovação pelo CEP do IPEC/Fiocruz.

Ministério da Saúde

FIOCRUZ
Fundação Oswaldo Cruz
Instituto de Pesquisa Clínica Evandro Chagas

IPEC

Rio de Janeiro, 23 de outubro de 2012.

DECLARAÇÃO

O projeto **"Avaliação da incidência de doenças oportunistas na coorte de pacientes HIV positivos acompanhados no Instituto de Pesquisa Clínica Evandro Chagas – IPEC/Fiocruz**, dissertação de mestrado de Lara Esteves Coelho, orientada pela Dra. Paula Mendes Luz, submetido a este Comitê em 24/09/2012, trata-se de um subprojeto do projeto **"Estudo Longitudinal da História Natural da Infecção pelo HIV acompanhados no IPEC-FIOCRUZ"**, aprovado por este Comitê em 13/09/2010, CAAE 0032.0.009.000-10, Parecer 043/2010, sendo pesquisadora responsável a Dra. Beatriz Grinsztejn.

Declaramos que este Comitê o apreciou e o aprova na presente data.

Atenciosamente,

Drª Léa Ferreira Camillo-Coura
Coordenadora do Comitê
de Ética em Pesquisa
Mat. SIAPE 003709620
IPEC / FIOCRUZ

VL

ANEXO II

E-mail com confirmação para publicação do artigo “Trends in overall opportunistic illnesses, *Pneumocystis carinii* pneumonia, cerebral toxoplasmosis and *Mycobacterium avium* complex incidence rates over the 30 years of the HIV epidemic: a systematic review” no periódico *Brazilian Journal of Infectious Diseases.*

Carlos Brites <crbrites@gmail.com> 12 de outubro de 2013 12:54
Para: lara.coelho@ipec.fiocruz.br, laraesteves@gmail.com

Ms. Ref. No.: BJID-D-13-00431R1
Title: Trends in overall opportunistic illnesses, Pneumocystis carinii pneumonia, cerebral toxoplasmosis and Mycobacterium avium complex incidence rates over the 30 years of the HIV epidemic: a systematic review
Brazilian Journal of Infectious Diseases

Dear Mrs. Lara Coelho,

I am pleased to inform you that your paper "Trends in overall opportunistic illnesses, Pneumocystis carinii pneumonia, cerebral toxoplasmosis and Mycobacterium avium complex incidence rates over the 30 years of the HIV epidemic: a systematic review" 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

Comments from the editors and reviewers:

ANEXO III:

Doenças oportunistas definidas pelo CDC, 1992

Candidíase de brônquios, traquéia e pulmões
Candidiase esofageana
Câncer cervical invasivo
Coccidioidomicose disseminada ou extrapulmonar
Criptococose extrapulmonar
Criptosporidiose intestinal crônica (duração superior a 1 mês)
Doença por Citomegalovírus (excluindo fígado, baço e linfonodos)
Retinite por Citomegalovírus (com comprometimento visual)
Encefalopatia associada ao HIV
Herpes simplex (ulcera com duração superior há 1 mês, bronquite, pneumonite, esofagite)
Histoplasmose disseminada ou extrapulmonar
Isosporíase crônica intestinal (duração superior a 1 mês)
Sarcoma de Kaposi
Linfoma de Burkitt
Linfoma imunoblástico
Linfoma primário de Sistema Nervoso Central
Mycobacterium avium complex, *M. Kansasii* (disseminado ou extrapulmonar)
Mycobacterium tuberculosis
Outras espécies de *Mycobacterium* (disseminado ou extrapulmonar)
Pneumonia por *Pneumocystis carinii*
Pneumonia recorrente
Leucoencefalopatia multifocal progressiva
Sepse por *Salmonella* (recorrente)
Síndrome consuptiva
Toxoplasmose cerebral

ANEXO IV:

Critérios de definição de eventos clínicos em pacientes HIV positivos

DEFINIÇÃO DO EVENTO

A - Presença de pelo menos 1 dos seguintes:

- O diagnóstico é baseado no relato patológico do evento (e estabelece o diagnóstico);

Por exemplo:
- Histopatológico para o diagnóstico de câncer
- Culturas positivas para diagnóstico de infecção bacteriana.
- Alterações de ECG típicas para diagnóstico de IAM.
- TC de crânio para diagnóstico de AVC

- O diagnóstico é claramente citado em notas de consulta, resumos/relatos de internação e relatórios de autopsia.

- Ou, o diagnóstico é usualmente baseado em exame clínico e questionários, e está claramente citado no prontuário médico.

Por exemplo:
- Doenças psiquiátricas
- Caquexia
- Encefalopatia pelo HIV

B- Na ausência de critérios para A.

- Forte suspeita clínica corroborada por testes biológicos ou exames de imagem.

Por exemplo:

- Tomografia de tórax com imagem sugestiva de CA pulmão porém sem confirmação histopatológica.

- Radiografia de tórax com imagem sugestiva de infecção pulmonar porém sem confirmação bacteriológica, mas com leucocitose no hemograma.

- Ou o diagnóstico é citado como provável em notas de consulta, resumos/relatos de internação e relatórios de autopsia.

- Ou tratamento específico para a doença é prescrito.

Por exemplo:
- Drogas anti-diabetes para o diagnóstico de diabetes mellitus

C – Na ausência de A ou B

- O diagnóstico é baseado em exame clínico mas não é realizado exame complementar posteriormente para confirmar ao diagnóstico.

Por exemplo, diagnóstico de Sarcoma de Kaposi baseado em inspeção visual porém não confirmado por realização de biópsia.

Se **A**: o diagnóstico é de **Certeza**.
Se **B**: o diagnóstico é **Provável**.
Se **C**: o diagnóstico é **Possível**.
Na **ausência** de A ou B ou C o evento **não deve ser considerado**.

ANEXO V:

Critérios da definição de doenças oportunistas em pacientes HIV positivos (WHO, 2007)

DEFINIÇÃO DO EVENTO

Evento	Diagnóstico Clínico	Diagnóstico Definitivo
Tuberculose Pulmonar	Sintomas com duração superior a 2-3 semanas: tosse, hemoptise, falta de ar, dor no peito, perda ponderal, febre, sudorese noturna. Associado à: Escarro com BAAR positivo Ou RX tórax sugestivo (infiltrado, cavitação, fibrose..)	Cultura com isolamento de M. tuberculosis em escarro ou histológico.
Tuberculose extrapulmonar	Febre, sudorese noturna, fraqueza e perda ponderal . Evidencia de acometimento extrapulmonar (pleural, pericárdio, peritone, meninges, linfonodos, ossos)	Cultura com isolamento de M. tuberculosis de sítios extrapulmonares. RX com infiltrado micronodular (miliar) + cultura de escarro;
Pneumonia por *Pneumocystis*	Dispnéia, tosse seca (de inicio há 3 meses), taquipnéia e febre. Associado à: Rx tórax com infiltrado intersisticial difuso bilateral E: Ausência de evidencia de pneumonia bacteriana; Ausculta pulmonar com creptações bilaterais com ou sem hipoventilação.	Citologia ou imunofluorescência positiva de escarro induzido, lavado broncoalveolar ou histológico de pulmão.
Herpes simplex virus - orolabial, genital ou anuretal com duraçao superior a 1 mês; ou visceral	Ulcerações dolorosas e progressivas; lesões causadas por recorrências de HSV, com duração superior a 1 mês. História previa de episódios de herpes. Herpes visceral requer diagnóstico definitivo.	Cultura, PCR-DNA positivos ou citologia e histologia compatíveis.
Candidíase esofageana	Dor retroesternal ou disfagia associados a candidiase oral.	Endoscopia digestiva alta ou broncoscopia com visualização macroscópia. Ou, microscopia e histológico.
Sarcoma de Kaposi	Lesões típicas (manchas, placas, nódulos), rosadas ou violáceas em pele ou orofaringe.	Lesão macroscopia observada em endocopia, boncoscopia. Histopatológico.
CMV (exceto fígado, baço, linfonodos)	Retinite: diagnosticado por profissional experiente.	Histopatológico ou PCR-DNA
Toxoplasmose de SNC	Sinal neurológico focal compatível com doença intracraniana, redução do nível de consciência; Associado à: Resposta clínica após 10 dias de tratamento.	Sorologia positiva para toxoplasma e Lesões com efeito de massa em exames de imagem do SNC (TC ou RNM)
Criptococose pulmonar (incluindo meningite)	Meningite: inicio usualmente subagudo de febre, cefaléial, meningismo, confusão mental, alteração comportamento. Associado à: Resposta ao tratamento específico.	Isolamento de Cryptococcus neoformans de sítios extrapulmonares ou antígeno positivo em sangue ou liquor.
Micobacteriose disseminada (não-tuberculosis)	Não há diagnóstico presuntivo	Indetificação de mycobacteria em fezes, sangue, outros fluidos ou tecidos, excluindo pulmão.
Leuncoencefalopaia multifocal progressiva	Não há diagnóstico presuntivo	Disordem progressiva de SNC(disfunção cognitiva, alteração de marcha e fala, perda visual, fraqueza, paralisia de pares cranianos) Associada à: Neuroimagem: lesões hipodensas de substancia branca Ou

		PCR para JC no liquor.
Criptosporidiose (diarréia > 1mês)	Não há diagnóstico presuntivo	Identificação microscópica de cistos nas fezes
Isosporíase crônica (diarréia > 1mês)	Não há diagnóstico presuntivo	Identificação de Isospora em fezes
Micoses disseminadas (coccidiomicose ou histoplasmose)	Não há diagnóstico presuntivo	Histológico, detecção de antígeno ou cultura de espécimes clínicos ou sangue.
Linfoma (cerebral ou não-Hodgkin)	Não há diagnóstico presuntivo	Histopatológico. Para tumores de SNC, neuroimagem.
Carcinoma cervical invasivo	Não há diagnóstico presuntivo	Histológico ou citológico

APÊNDICE I:

Ficha 1: Coleta de dados dos prontuários para validação(baseada na definição de eventos clínicos)

Prontuário |___|___|___|___|___| Data preenchimento|___|___|.|___|___|.|___|___|___|___|

Iniciais |___|___|___|___|___|

Data da doença |___|___|.|___|___|.|___|___|___|___|

Doença oportunista |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0
Se confirmado, qual o grau de certeza (veja abaixo)? |___|
A=1 B=2 C=3

Existiram doenças oportunistas concomitantes (período de 30 dias)? |___|
Sim=1 Não= 0

Se sim, quantas (incluindo a primeira)? |___|

Doença oportunista 2: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0
Se confirmado, qual o grau de certeza (veja abaixo)? |___|
A=1 B=2 C=3

Doença oportunista 3: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0
Se confirmado, qual o grau de certeza (veja abaixo)? |___|
A=1 B=2 C=3

Doença oportunista 4: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0
Se confirmado, qual o grau de certeza (veja abaixo)? |___|
A=1 B=2 C=3

Doença oportunista 5: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0
Se confirmado, qual o grau de certeza (veja abaixo)? |___|
A=1 B=2 C=3

APÊNDICE II:

Ficha 1: Coleta de dados dos prontuários para validação(baseada na definição da OMS)

Prontuário |___|___|___|___|___| Data preenchimento|___|___|.|___|___|.|___|___|___|___|

Iniciais |___|___|___|___|___|

Data da doença |___|___|.|___|___|.|___|___|___|___|

Doença oportunista |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0

Se confirmado, qual o tipo de diagnóstico (veja abaixo)? |___|
Clínico=1 Definitivo=2

Existiram doenças oportunistas concomitantes (período de 30 dias)? |___|
Sim=1 Não= 0

Se sim, quantas (incluindo a primeira)? |___|

Doença oportunista 2: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0

Se confirmado, qual o tipo de diagnóstico (veja abaixo)? |___|
Clínico=1 Definitivo=2

Doença oportunista 3: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0

Se confirmado, qual o tipo de diagnóstico (veja abaixo)? |___|
Clínico=1 Definitivo=2

Doença oportunista 4: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0

Se confirmado, qual o tipo de diagnóstico (veja abaixo)? |___|
Clínico=1 Definitivo=2

Doença oportunista 5: |___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|___|

A ocorrência da doença foi confirmada (veja definição de caso)? |___|
Sim=1 Não= 0
Se confirmado, qual o tipo de diagnóstico (veja abaixo)? |___|
Clínico=1 Definitivo=2