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THIAGO SILVA TORRES

HIV E ENVELHECIMENTO: ESTUDOS EM UMA COORTE DE PACIENTES VIVENDO COM HIV/AIDS NO RIO DE JANEIRO

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HIV e Envelhecimento:
Estudos em uma coorte de pacientes vivendo com HIV/AIDS no Rio de Janeiro

THIAGO SILVA TORRES

Tese apresentada ao Curso de Pós-Graduação em Pesquisa Clínica em Doenças Infecciosas do Instituto de Pesquisa Clínica Evandro Chagas para obtenção do grau de Doutor

Orientadoras: Dra. Beatriz Gilda J. Grinsztejn

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"*Viver é envelhecer, nada mais"* (Simone de Beauvoir)

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RESUMO

Introdução: A introdução da terapia antirretroviral potente (HAART) durante os anos 90 foi crucial para o declínio das taxas de mortalidade e mortes relacionadas a síndrome da imunodeficiência adquirida (AIDS), tornando a infecção pelo vírus da imunodeficiência humana (HIV) uma condição crônica. Conseqüentemente, a população vivendo com HIV/AIDS está se tornando mais velha. Ademais, novas infecções em pessoas ≥ 50 anos vêm crescendo. **Objetivo**: Avaliar o impacto do envelhecimento em uma coorte de pacientes vivendo com HIV/AIDS na cidade do Rio de Janeiro. Seções de revisão da literatura, metodologia, resultados e discussão foram descritas na forma de três artigos científicos. **Primeiro Artigo**: Realizar uma revisão prática na literatura sobre HIV e envelhecimento. **Segundo Artigo**: Descrever o pefil imunológico, clínico e de comorbidades da coorte, estratificando os pacientes de acordo com a idade em 2008. Para as variáveis quantitativas o teste não-paramétrico de Cuzick foi utilizado, enquanto que para as variáveis categóricas foi utilizado o teste não-paramétrico de Cochran-Armitage para tendência. Para todos os testes foi considerado nível de significância de 5%. 2.307 pacientes foram incluídos; 1.023 (44,3%), 823 (35,7%), 352 (15,3%) e 109 (4,7%) dos pacientes tinham idade entre 18-39, 40-49, 50-59 ≥ 60 anos, respectivamente. Pacientes ≥ 40 anos apresentaram maior tendência a apresentar carga viral suprimida do que os mais jovens (18-39 anos) ($p<0.001$). Não foi observada diferença significativa no último exame de CD4 entre as faixas etárias, apesar dos pacientes ≥ 50 anos terem apresentado menor nadir de CD4 ($p<0.020$). Houve um aumento no número de comorbidades com a idade, e o mesmo perfil foi observado para a maioria das comorbidades, incluindo diabetes mellitus, dislipidemia, hipertensão, doenças cardiovasculares, disfunção erétil, HCV, disfunção renal e câncer não-relacionado a aids ($p<0.001$). **Terceiro Artigo**: Descrever a incidência de modificação ou descontinuação do primeiro esquema antirretroviral combinado (cART) provocado por toxicidade (TOX-MOD) durante o primeiro ano de tratamento estratificando por faixa etária. Taxa de incidência e intervalo de confiança (95% CI) de cada evento estratificado por faixa etária foram estimados usando o modelo quasipoisson. O modelo de Cox foi aplicado para estimar hazard ratio (HR) de TOX-MOD que ocorreram durante o primeiro ano de cART, sendo ajustado por sexo, classe de cART e ano de início de tratamento. Ao inciar cART, 957 (61,4%), 420(27,0%) e 181(11,6%) tinham idades entre <40, 40-49 e ≥50 anos, respectivamente; mediana de idade foi de 36 anos. 239 (15,3%) eventos que levaram a qualquer MOD durante o primeiro ano de cART foram observados; 228 (95,4%) destes eram relacionados a TOX-MOD, correspondendo em uma taxa de incidência de 16.6/100 pessoas-ano (95% CI: 14.6-18.9); probabilidade de TOX-MOD em 1 ano foi 14,6% (228/1.558). O modelo multivariável indicou que a taxa de incidência de TOX-MOD durante o primeiro ano de cART aumenta progressivamente com a idade, apesar de não ser estatisticamente significativa. **Conclusões**: Os resultados encontrados neste trabalho podem ser úteis para um plano nacional de manejo de indivíduos com 50 anos ou mais vivendo com HIV/AIDS, tanto para os que estão envelhecendo com a infecção, quanto para os novos casos diagnosticados em pessoas que já estão nesta faixa etária. **Palavras-chave**: 1. HIV. 2. Envelhecimento. 3. Terapia antirretroviral. 4. Comordidade 5. Toxicidade

Torres, TS. Rio de Janeiro, 2012. **HIV and Aging: Sudies in a HIV/AIDS Urban Cohort in Rio de Janeiro (Brazil)**. Tese [Doutorado em Pesquisa Clínica em Doenças Infecciosas] – Instituto de Pesquisa Clínica Evandro Chagas.

ABSTRACT

Introduction: The introduction of highly active antiretroviral therapy (HAART) during the 1990s was crucial to the decline in the rates of morbidity and death related to the acquired immunodeficiency syndrome (AIDS) and making human immunodeficiency virus (HIV) infection into a chronic condition. Consequently, the HIV/AIDS population is aging. In addition, new infections on people aging 50 or above are increasing. **Objective**: The aim of this thesis was to study the impact of aging in a HIV/AIDS Urban cohort in Rio de Janeiro (Brazil). State of art Review, Methodology, results and discussion of this thesis were described in three articles. **First Article**: A practical review about HIV and aging was performed. **Second Article**: Describe the immunological, clinical and comorbidity profile of the cohort, stratyfing patients according to age in 2008. For quantitative variables, Cuzick's non-parametric test was used. For categorical variables, the Cochran-Armitage non-parametric test for tendency was used. For all tests, the threshold for statistical significance was set at 5%. In 2008, 1,023 (44.3%), 823 (35.7%), 352 (15.3%) and 109 (4.7%) were aged 18-39, 40-49, 50-59 ≥ 60 years-old, respectively. Older and elderly patients (≥ 40 years) were more likely to have viral suppression than younger patients (18-39 years) ($p<0.001$). No significant difference in the latest CD4+ T lymphocyte count in the different age's strata was observed, although elderly patients (≥ 50 years) had lower CD4+ T lymphocyte nadir ($p<0.020$). The number of comorbidities increased with age and the same pattern was observed for the majority of the comorbidities, including diabetes mellitus, dyslipidemia, hypertension, cardiovascular diseases, erectile dysfunction, HCV, renal dysfunction and also for non-AIDS-related cancers ($p<0.001$). **Third Article**: Describe the incidence of modifying or discontinuing first combined antiretroviral regimen (cART) due to toxicity (TOX-MOD) during the first year of treatment, stratifying by age groups. Data from 1,558 antiretroviral-naïve patients who first received cART between 1996 and 2010 was collected. Incidence rate and confidence interval (95% CI) of each event stratified by age groups were estimated using Poisson model. Cox's proportional hazards regression was applied to estimate hazard ratio (HR) of overall TOX-MOD during the first year of cART. The model was also adjusted for sex, type of cART and year of treatment initiation. At cART initiation, 957 (61.4%), 420(27.0%) and 181(11.6%) were aged <40, 40-49 and ≥50 years, respectively; median age was 36 years. 239 (15.3%) events of any MOD within the first year of cART were observed; 228 (95.4%) of these were related to TOX-MOD, corresponding to an incidence rate of 16.6 per 100 PY (95% CI: 14.6-18.9); 1 year probability of TOX-MOD in 1 year was 14.6% (228/1,558). The multivariate model indicates that the incidence ratio of TOX-MOD during the first year of cART progressively increases with age, although not reaching statistical significance. **Conclusion**: Our results could be usefull for national guidelines about HIV and aging.

Keywords: 1. HIV. 2. Aging. 3. Antiretroviral therapy 4. Comorbidity 5. Toxicity

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LISTA DE ABREVIATURAS

3TC	Lamivudina
AIDS	Acquired Immunodeficiency Syndrome; Síndrome da Imunodeficiência Adquirida
ART/TAR	Antiretroviral Therapy / Terapia Antiretroviral
ARV	Antirretrovirais
ATV	Atazanavir
ATV/r	Atazanavir combinado com Ritonavir
BMI	Body Mass Index; Índice de Massa Corpórea
BZD	Benzodiazepinicos
cART	Combined antiretroviral treatment / Terapia antirretroviral combinada
CDC	US Centers for Disease Control
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CNS	Central Nervous System; Sistema Nervoso Central
CTL	Linfócitos CD8+ T citotóxicos
CVD	Cardiovascular Diseases; Doenças Cardiovasculares
D4T	Estavudina
DDI	Didanosina
ED	Disfunção Eréctil
EFV	Efavirenz
Fiocruz	Fundação Oswaldo Cruz
FTC	Entricitabina
GALT	Tecido Linfóide Associado ao Intestino
GFR	Glomerular Filtration Rate; Taxa de Filtração Glomerular
GI	Gastrintestinal; Trato Gastrintestinal
HAART	High Active Antiretroviral Therapy; Terapia Antiretroviral Altamente Ativa
HBV	Vírus da Hepatite B
HCV	Vírus da Hepatite C
HIV	Human Immunodeficiency Virus; Vírus da Imunodeficiência Humana
HPV	Papilomavirus Humano
HR	Hazard Ratio
IBGE	Instituto Brasileiro de Geografia e Estatística
IDU	Drug Injection User; Usuário de Drogas Injetáveis
IL-6	Interleucina 6
IPEC	Instituto de Pesquisa Clínica Evandro Chagas
LOP/r	Lopinavir combinado com Ritonavir
MI	Myocardial Infarction; Infarto do Miocárdio
MOD	Modificação ou Descontinuação da terapia antiretroviral
MS	Ministério da Saúde do Brasil
MSM/HSH	Men who have sex with men; Homens que fazem sexo com homens
NFV	Nelfinavir
NRTI	Inibidores da Transcriptase Reversa Análogos de Nucleosídeos
NNRTI	Inibidores da Transcriptase Reversa Não Análogos de Nucleosídeos
NVP	Nevirapina
PEP	Profilaxia Pós-exposição
PI	Inibidores da Protease
PLH/PVH	People Living with HIV/AIDS; Pessoas vivendo com HIV/AIDS
PN	Peripheral Neuropathy; Neuropatia Periférica
PrEP	Profilaxia Pré-exposição
P-Y	Pessoa-anos
TDF	Tenofovir
TOX-MOD	Modificação ou descontinuação da Terapia Antiretroviral causada por Toxicidade
UNAIDS	United Nations Programme on HIV/AIDS – Programa das Nações Unidas em HIV/AIDS
WHO/OMS	World Health Organization - Organização Mundial de Saúde
ZDV	Zidovudina

1 INTRODUÇÃO

Até 2025, espera-se uma elevação de cerca de 694 milhões no número de pessoas mais velhas no mundo. Nessa ocasião, haverá aproximadamente 2 bilhões de pessoas com idade igual ou superior a 60 anos no planeta, a maioria (80%) vivendo nos países em desenvolvimento (WHO, 2005). No Brasil, 20,6 milhões de pessoas encontram-se nesta faixa etária (IBGE, 2010) e estima-se que em 2030 esse número ultrapassará os 40 milhões (IBGE, 2007), o que poderá gerar um aumento substancial das despesas do governo com esta população. A expectativa de vida da população brasileira em 2030 será de 78,3 anos, sendo 81,9 anos para as mulheres (IBGE, 2007).

A partir da disponibilização da terapia antirretroviral altamente potente (HAART) em meados dos anos 90, a expectativa de vida das pessoas vivendo com HIV/AIDS (PVH) cresceu significativamente. A cobertura de terapia antirretroviral (TAR) no mundo aumentou de 7% em 2003 para 42% em 2008 (Lazarus, 2010). Cerca de 12 milhões de anos-vida foram adicionados no mundo entre 1996 e 2008 em função do maior acesso a HAART (Lazarus, 2010). A própria evolução da TAR vem favorecendo que pacientes diagnosticados em idades mais jovens sobrevivam até idade mais avançada, explicando em parte esta tendência ao envelhecimento na epidemia. Estima-se que em 2015 pessoas com idade igual ou superior a 50 anos corresponderão a 50% das PVH em tratamento clínico (Vance, 2010).

A Organização Mundial de Saúde (OMS) e a maioria dos clínicos e geriatras definem como “idoso” o indivíduo na população geral com 60 ou mais anos de idade. No caso das PVH, o Centers for Disease Control and Prevention (CDC) dos Estados Unidos considera “idoso” o indivíduo com 50 anos ou mais (CDC, 1998). O consenso brasileiro para TAR em adultos considera que a idade maior ou igual a 50 anos é um indicador para se iniciar TAR (Ministério da Saúde, 2008).

Na primeira década da epidemia de aids poucos casos entre pessoas de 50 anos ou mais de idade foram notificados. Desde então, observa-se um número crescente de casos nessa faixa etária. No Brasil, por exemplo, a incidência de aids nesta população dobrou entre 1996 e 2006 (Ministério da Saúde, 2011). Um dos possíveis fatores seria a introdução dos medicamentos contra disfunção erétil em 1998, o que gerou o prolongamento da atividade

sexual das pessoas mais velhas, as quais apresentam menor tendência em praticar sexo seguro quando comparados aos mais jovens (Schmid, 2009).

Entre os mais velhos, o diagnóstico da infecção pelo HIV tende a ser mais tardio, uma vez que certos sintomas podem ser confundidos com os de outras doenças comuns nesta população. Além disso, os profissionais de saúde muitas vezes não consideram os indíviduos mais velhos em risco de infecção pelo HIV.

Entre os já diagnosticados, a presença de morbidades associadas ao envelhecimento é um desafio. Condições crônicas associadas com o envelhecimento, tais como neoplasias não associadas a AIDS, doenças cardiovasculares e outras doenças de orgãos alvo, além das mortes associadas a estas condições, vem aumentando em coortes de HIV/AIDS no mundo (Belloso, 2010; Hasse, 2011; Friis-Moller, 2003; Vance, 2011).

Por fim, há uma maior suscetibilidade nas populações que envelhecem em apresentar toxicidades relacionadas a medicamentos e interações farmacológicas (Yuan, 2006). Em diversas coortes de HIV/AIDS verificou-se que o principal motivo que leva a troca ou modificação (MOD) do primeiro TAR está relacionado às toxicidades provocadas por antirretrovirais (ARVs) (Braithwaite, 2007; Dorrucci, 2001; Hänsel, 2001; Hart, 2007; Kumarasamy, 2006; Mocroft, 2001; Nakimulu-Mpungu, 2011; O'Brien, 2003; Teixeira, 2004; Vo, 2008). Estas toxicidades podem causar significante morbidade, baixa qualidade de vida, e pode ser importante barreira para adesão a TAR (Mocroft, 2005; van Roon, 1999), podendo acarretar em falha de tratamento e resistência viral (Monforte, 2000). Além disso, o envelhecimento tem considerável influência na farmacocinética dos medicamentos, podendo resultar em aumento da concentração dos ARVs, gerando um aumento no risco de toxicidades relacionadas a TAR (Kumarasamy, 2006) e aumento das taxas de MOD por toxicidade (Nakimulu-Mpungu, 2011).

O aumento da prevalência do HIV em grupos etários mais velhos não foi acompanhado pela criação de guias terapêuticos ou recomendações adequadas a esta população. Tendo em vista este cenário, estudos relacionados ao impacto do envelhecimento nas coortes de HIV/AIDS são de extrema importância para o nosso meio.

1.1 Objetivos

O tema central desta tese foi estudar o impacto do envelhecimento numa coorte de pacientes vivendo com HIV/AIDS. Os objetivos específicos foram: 1. Descrever as características da coorte de pacientes vivendo com HIV/AIDS do IPEC/Fiocruz, estratificando por faixas etárias no ano de 2008 (18-39, 40-49, 50-59 e ≥ 60 anos); 2. Descrever a taxa de incidência da modificação ou interrupção do primeiro esquema antiretroviral por toxicidade durante o primeiro ano de tratamento, estratificando pela idade no início do tratamento (18-29, 30-39, 40-49, 50-59 e ≥ 60 anos).

1.2 Estrutura da tese

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

1 – Aging with HIV: A Practical Review (Envelhecendo com HIV: Uma Revisão Prática).

2 - Aging with HIV: An Overview of an Urban Cohort in Rio de Janeiro (Brazil) Across Decades of Life (Envelhecendo com HIV: uma visão geral de uma coorte urbana no Rio de Janeiro (Brasil) ao longo das décadas de vida).

3 – Incidence rate of modifying or discontinuing first cART regimen due to toxicity during the first year of treatment stratified by age (Taxa de incidência da modificação ou interrupção do primeiro esquema antiretroviral em decorrência de toxicidade durante o primeiro ano de tratamento, de acordo com a idade).

2 Artigo 1

Título:

Aging with HIV: A Practical Review

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Abstract

The worldwide elderly population is expected to grow by an additional 694million people by 2025. By that time, there will be approximately 2 billion elderly people in the world, most of whom (80%) will be living in developing countries. Based on recent estimates, this population will number over 40 million in 2030 in Brazil and a consequent increase in governmental spending for this population can be expected. Since highly active antiretroviral therapy (HAART) became available in the mid-1990s, the life expectancy of people living with HIV (PLH) has increased significantly. Approximately 12 million life years were added to the world between 1996 and 2008 as a consequence of wider access to HAART. In Brazil, the incidence of AIDS among the population ≥50 years old doubled between 1996 and 2006. The development of antiretroviral therapy (ART) has allowed individuals diagnosed at a younger age to live longer, which partially explains the aging tendency associated with the HIV/AIDS epidemic. It is estimated that by 2015, subjects ≥50 years old will represent 50% of the PLH undergoing clinical treatment. This scenario presents some challenges, including the fact that the diagnosis of HIV tends to be delayed in older patients compared to younger patients because the symptoms of HIV can be confused with those of other common diseases among the elderly and also because healthcare professionals do not consider this population to be at high risk for HIV infection. In regard to the individuals diagnosed with HIV, a further challenge is presented by the morbidity normally associated with aging. Finally, the elderly also exhibit higher susceptibility to the toxic effects and pharmacological interactions of medications. The present article reviews the literature regarding the profile of HIV infection among individuals ≥50 years old focusing on practical features related to the clinical approach and long-term follow-up of this population.

Introduction

The worldwide elderly population is expected to grow by an additional 694 million people by 2025. By that time, there will be approximately 2 billion elderly people in the world, most of whom (80%) will be living in developing countries [1]. Brazil has one of the fastest ageing populations in the World [2]. In half a century (1960-2010), life expectancy of the Brazilian population increased by 25.4 years, having changed from 48.0 to 73.4 years [3]. There are currently 15.8 million people aged 60 years or older, and this number is expected to exceed 40 million by 2030 [4]. It is estimated that the government expenses with this population will increase from 38% to 68% considering the period from 2000 to 2050 [5]. Since 1998, the availability of drugs for the treatment of erectile dysfunction has extended the length of the active sex life. Moreover, older individuals have a lower tendency to practice safe sex than younger ones [6]. This situation may increase the elderly's risk of human immunodeficiency virus (HIV) infection. In addition, the availability of highly active antiretroviral therapy (HAART) since the mid-1990s has significantly increased the life expectancy of people living with HIV (PLH). The worldwide coverage of antiretroviral therapy (ART) increased from 7% in 2003 to 42% in 2008 [7]. Approximately 12 million life years were added to the world between 1996 and 2008 as a result of the wider access to HAART [7].

During the first decade of the acquired immunodeficiency syndrome (AIDS) epidemic, few cases in people 50 years old or older were reported. However, this number has been increasing steadily [7-11]. In Brazil, the incidence of AIDS in this age range doubled between 1996 and 2006 [8]. The advance of ART has increased the life expectancy of individuals diagnosed at a young age, which partially explains the aging tendency of the epidemic. It is estimated that by 2015, people aged 50 years old or older will represent 50% of the PLH undergoing clinical treatment [9]. This scenario presents some challenges, including the fact that the diagnosis of HIV tends to be delayed in older individuals, as some symptoms might be confused with those of other common diseases among the elderly and because healthcare professionals do not consider this population to be at high risk of HIV infection. In regard to the individuals already diagnosed with HIV, a further challenge is presented by the morbidity associated with aging. Finally, the elderly also exhibit higher susceptibility to the toxic effects and pharmacological interactions of medications.

The World Health Organization (WHO) and most general practitioners and geriatricians define “elderly” individuals as those aged 60 years old or older. With regard to PLH, the US Centers for Disease Control and Prevention (CDC) consider “elderly” individuals to be those aged 50 years old or older [12]. Having ≥ 50 years old is one of the indications to start HAART according to the Brazilian guideline for ART in adults [13]. The increased prevalence of HIV among older individuals has not been accompanied by the formulation of therapeutic guidelines or recommendations specific for this population.

Number of older individuals living with HIV/AIDS is increasing, as a result of a growing number of new HIV diagnoses among the elderly as well as the increased survival as a result of better management. Very scarce data is available about elderly individuals with HIV/AIDS in our setting. These data are important not only to serve as guidance for the development of national policies and management guidelines targeting this population but also to guide other low and middle income countries on the several aspects of a reality they will face very soon.

The aim of the present article is to review the literature regarding the profile of HIV infection among individuals ≥ 50 years old by focusing on the practical aspects of the clinical approach and long-term follow-up of this population.

Epidemiological data

According to the CDC, individuals aged ≥ 50 years represented 15% of the newly diagnosed HIV cases, 24% of PLH, 29% of people diagnosed with AIDS, and 35% of the deaths caused by AIDS in the USA in 2005 [11]. In Western Europe, 12.9% of the new HIV cases reported in 2007 involved individuals aged ≥ 50 years, which is higher than the rate of 3.7% found in Eastern Europe. In Central Europe, the ratio of new cases among the elderly to new cases in younger individuals was approximately 1:10 [7].

The epidemiological data available for this population in Latin America are limited. In Peru, the HIV/AIDS epidemic mostly affects young people, as 41% of the cases correspond to individuals between the ages of 25 and 34 [14]. The latest WHO bulletin does not stratify adult cases by age range and does not highlight aging as a specific topic for this epidemic [15].

In Brazil, a total of 608,230 cases of AIDS were reported between 1980 and June of 2011; of these, 64,500 (10.6%) corresponded to individuals older than 50 years, most of whom were male (65.0%). The data from this time period show an increase in the AIDS incidence rates among individuals older than 50 years. Among individuals older than 60 years, 10,915 male and 5,923 female cases were reported [8]. Data provided by the Health Ministry show an increase of 100% in the incidence of AIDS in this population between 2000 and 2010. Comparison of age distribution between PLH (age on AIDS diagnostic) and general population during 2010 in Brazil is shown on Figure 1. Percentage of individuals in Brazilian General Population decreases with age while for PLH in Brazil the majority of cases are diagnosed on age strata between 20-49 years old.

Biology of aging

The notion of aging is almost as simple as it is challenging. Over time physical fitness (vision, hearing, and mobility), external appearance (wrinkles and hair loss), and mental agility (efficiency in the retention and processing of new and old information) decline. Although aging is unavoidable, its progression is variable. Performance parameters include the vital capacity of key organs such as the heart, brain, and kidneys. Most body systems exhibit a considerable reserve capacity, such that disease-free aging imposes few constraints on organ function. Generally, organ function is expected to decline by 1% each year beginning at the age of 25 [16].

The criteria for and definitions of aging vary so widely among geriatricians, researchers, and governmental agencies that there is not even a consensus regarding the “cutoff point” for defining “old age.” For the general population, individuals aged 60 – 75 years are considered candidates for monitoring/intervention, and this limit falls to 50 years old in PLH [12].

Chronological age is the measurement of the years of life since birth. The speed of aging depends on genetic factors, whereas environmental, biological, and lifestyle-related factors also influence the biological or phenotypic age. Senescence, i.e., the increase in the chronological age of a population of predominantly indivisible cells in culture, is an

essentially biological definition of aging and is considered to be a natural process. In contrast, senility corresponds to aging under pathological circumstances.

Genetic factors – the role of telomeres

All chromosomes of eukaryotic cells include a structure known as the telomere (from the Greek, *telos*, end, and *meros*, part), which is a marker of cellular division. Telomeres are a kind of "cap" that protect the ends of chromosomes and consist of proteins and noncoding DNA. Their function is to maintain the structural stability of chromosomes. Under normal aging conditions, the telomeres shorten at each cell division until the cell totally or partially loses its ability to divide, leading to disease and death. Telomeres play the role of a biological clock. The synthesis of telomeres occurs at the end of DNA replication by the action of the enzyme telomerase, which is a reverse transcriptase, and telomerase activity depends on the activation of a specific gene that is not activated ("turned on") in all cells.

The role of telomeres in CD4+ T-cell depletion and in the clonal replication of these cells during HIV infection was described in 1966 [17]. In HIV+ individuals, the length of telomeres is similar to that of non-infected elderly individuals, which might indicate a predisposition to premature aging. This finding might explain the presence of abnormalities common to the elderly in HIV+ younger individuals, such as low numbers of CD4+ T cells and decreased thymus activity. The physiopathology of aging in PLH with or without prolonged ART is still poorly understood. The use of thymidine analogs appears to induce telomere shortening [18].

The oxidative stress that occurs in natural aging seems to favor the replication of HIV, and the presence of HIV, in turn, appears to accelerate the natural aging process. Factors involved in the progressive loss of the vital (reserve) capacity of the bodily systems in PLH, leading to organ failure, reduced cognitive functions, disease, and death include: the presence of comorbidities; viral hepatitis coinfection; alcohol abuse, tobacco, or other drugs; microbial translocation; and chronic immune dysfunction, in addition to the toxicity of ARV agents and other drugs used concomitantly [19].

Effects of HIV infection and aging on immunity

By itself, aging is associated with complex changes in the immune system that increase susceptibility to infections and autoimmune and neoplastic diseases and reduce the response to active immunization [20]. During the natural progression of HIV infection, the immune system is chronically and progressively impaired. HIV infection and normal aging exert many similar effects on the immune system. For example, the T-cell population, particularly in the gastrointestinal tract, is strongly affected by both HIV and aging, as are nearly all aspects of immunity [21].

B cells and antibody production

Aging and HIV infection can also affect immunological memory. HIV infection is associated with an increased activation of naïve B cells, which persists even during the use of HAART [21]. Some examples of the B-cell dysfunction that occurs in both PLH and older adults include the increased risk of severe bacterial infections with pathogens such as *Streptococcus pneumoniae* and the reduced ability of polysaccharide antigens to activate B cells, demonstrated by a poor response to the pneumococcal vaccine both in terms of the production of efficacious antibodies as well as clinical protection [22].

T-cell function

The number of naïve T cells (CD4+ and CD8+) decreases with age and HIV infection, and this can also influence the effect of ART [22]. The number of such cells is as low in PLH as in non-infected individuals 20 to 30 years older. The T cells become less responsive, are less able to proliferate, and exhibit alterations in the signaling receptors and surface markers, including a loss of CD28 expression [23]. These changes result in an increase of the Th-2 cells and simultaneous decrease of the Th-1 cells. Consequently, the levels of interleukin-2 (IL-2), which is produced by Th-1 cells, decreases as a result of aging; this phenomenon represents one of the most common cytokine alterations observed in immunosenescence.

The number of cytotoxic CD8+ T lymphocytes (CTL) increases in HIV infection in both young and old individuals [24]. The memory T cells express surface CD28, which stimulates cell division in the presence of antigens. “Old” memory cells tend to lose CD28 expression and thus multiply less than younger cells upon antigen exposure [25].

During chronic HIV infection, the repeated expansion of the CD8+ T cell population leads to a loss of CD27 and CD28 by the T cells, resulting in a predominance of lymphocytes that lack the receptors needed for co-stimulation and efficient antigen presentation. Eventually, the cells attain replicative senescence (exhaustion), which is characterized by shorter telomeres, low telomerase activity, and the increased production of pro-inflammatory cytokines. A high proportion of CD8+ CD28 CTL is predictive of early mortality [19] and rapid progression to AIDS among PLH [23], although a causal relationship has not yet been established.

The immune function of the mucous membranes is severely impaired by HIV infection. Independently of the route of infection, HIV replicates more intensely and the CD4+ T cell population is exhausted much more quickly in the gut-associated lymphoid tissue (GALT) than in the peripheral blood. This reduction in the number of CD4+ T cells in the GALT does not recover after the onset of HAART as it does in the peripheral blood. The effects of aging on the GALT are still poorly understood. The consequences of T-cell senescence are profound, and the ability to control chronic viral infections is lost.

Age and risk of HIV infection

New cases of HIV infection among individuals ≥ 50 years old have been reported. The CDC estimated that approximately 7,000 new cases of HIV infection occurred in this population in the USA in 2009 [11]. According to an American report with 3,000 individuals aged 57-85 years old, many older people are sexually active on a regular basis (73%, 53% and 26% for 57-64, 65-74 and 75-85 years old, respectively) [26]. In another study conducted in the USA, 20 to 30% of men and women in their 80s reported being sexually active [27]. Therefore, risky sexual behaviors of individuals’ ≥ 50 years of age must be addressed. In a study conducted in London (UK) older HIV+ MSM (men who have sex with men) are just as likely to report unsafe sex as younger HIV+ MSM [28]. On contrary, a study conducted in the

US with HIV+ women verified that condom use decreased with age while lubrificant use increased with age [29]. Older individuals, particularly heterosexuals, might not have an accurate understanding of their risk for HIV, most likely as a function of the typical features of AIDS at the onset of the epidemic, when AIDS occurred mostly in young homosexual men. Many heterosexual individuals ≥ 50 years are single, have no stable partners, are divorced or widowed, and have active sexual lives, often involving partners who are also unaware of the need to practice safe sex. There seems to be reluctance on the part of both older heterosexual men and women to use condoms. Certainly, unwanted pregnancy is not a concern among individuals of this age range, and men with erectile dysfunction might be particularly unlikely to accept condoms [26]. Biological mucosa modifications like low estrogen levels causing decreased lubrication might favor the production of mucosal lesions that increase the risk of HIV transmission, also, similarly, biological changes in the anal mucosa make it susceptible to lesions that also facilitate the transmission of HIV [30]. The strategies for behavioral interventions aimed at promoting the use of condoms among the elderly population must be reassessed. In addition, more recently investigated preventive strategies, such as the treatment of positive partners of serodiscordant couples and pre-exposure (PrEP) and post-exposure (PEP) prophylaxis, need to be assessed because this population might have less access to or may not be targeted for such preventative strategies.

Life expectancy and HIV infection

The survival estimates for PLH for the period corresponding to the introduction of HAART (1996 to 2005) were approximately two-thirds of the life expectancy of the general population [31]. Since that time, there have been advances in treatment, including wider access to ART and increased knowledge regarding issues such as the prevention of cardiovascular disease (CVD) and the control of metabolic diseases in HIV+ individuals. The life expectancy of HIV+ individuals is influenced by social and demographic factors in addition to their level of immunosuppression. For example, the length of time the CD4+ T-cell count is below 100 cells/mm^3 might be an important predictor of death [32]. Nevertheless, the current life expectancy of patients starting HAART early and thus achieving normal CD4+ counts sooner might be very similar to that of the general population [33].

HAART and aging

Two different scenarios must be taken into account with regard to HAART and aging. One situation involves HIV diagnosis in an individual ≥ 50 years old, and the other involves individuals who have lived with HIV for many years (chronic cases) with complications typically not expected for a given age range. PLH include those of all age ranges and may therefore be exposed to different durations of infection and different degrees of toxicity associated with the long-term use of ART. Therefore, the ART outcome among HIV+ patients starting treatment after age 50 must be thoroughly understood in addition to the impact of ARV drugs on the cardiovascular and metabolic disorders that can be expected in aging people with HIV. Interruptions or modification of ARV regimens are often needed in such patients to minimize drug interactions or toxicity. In addition, more thorough or frequent assessments might be needed in the surveillance of associated morbidities and preventive interventions during the follow-up care of elderly individuals with HIV.

Clinical outcomes

In general, the clinical manifestations of immunodeficiency appear late in the course of HIV infection. However, in most cases, diagnosis is established only after the immune system has been strongly affected and CD4+ T-cell count is less than 200 cells/mm^3. Older people are diagnosed at more advanced stages of HIV infection than younger individuals [34]. This delayed diagnosis might partially explain some studies' findings of poorer clinical outcomes, including shorter intervals between the identification of HIV, the AIDS diagnosis and reduced survival times [7], in elderly patients than in younger patients. Healthcare professionals do not seem overly concerned with the possibility of HIV infection in older individuals, possibly because older people are less likely than younger ones to be considered sexually active or intravenous drug users. In addition, many of the symptoms of HIV infection might be confused with signs of natural aging, such as weight loss, fatigue, and cognitive or visual problems [35]. The older patients themselves also may not suspect that they have been infected by HIV. Most individuals diagnosed with HIV after age 60 never suspected that they were infected before they were tested [36].

Studies conducted in the pre-HAART era found an association between old age and the risk of death among HIV infected individuals [37]. At the beginning of the HAART era, access to ART was identified as the only factor associated with survival in patients older than 50 years [38]. ART efficacy improvement have been correlated with longer life expectancy among individuals with HIV infection, and it is estimated that 50% of the currently treated population will reach age ≥ 60 years old in 2015 [39].

Early mortality

Early mortality risk after the HIV infection diagnosis increases with age. A CDC survey on 12-, 24-, and 36-month survival after diagnosis showed that mortality was substantially higher among the older patients at all three time points assessed [40]. A study comparing early mortality between the cities of Rio de Janeiro and Baltimore also found a higher risk of death among the elderly (hazard ratio (HR) 1.03; p=0.03) [41].

Immune response to HAART and viral suppression

In terms of the CD4+ T cell count improvement and viral suppression at different age ranges, most studies found that older people can achieve success rates similar to younger individuals given adherence to HAART [42, 43]. Greenbaum et al. found that the average time to attain the first undetectable viral load (VL) was lower among patients ≥ 50 years old than patients ≤ 40 years old (3.2 vs. 4.4 months; p=0.001). This difference was more significant when HAART included one protease inhibitor (PI) [44].

Nevertheless, the immune recovery rate can be slower and less robust among older patients. Data from the NA-ACCORD cohort study showed that the probability of recovering the CD4+ T-cell count (an increase of at least 100 cells/mm^3 over the first two years of ART) decreased with age [45]. Low treatment compliance does not seem to explain these outcomes because older patients exhibit better adherence than younger patients and have a lower risk of viral rebound [46].

Selection of ART regimens

When deciding upon an ART regimen, it is recommended that patient's lifestyle be taken into account. Age is also an important factor for the selection of ART. Nucleoside analogs are strongly associated with mitochondrial toxicity, and zidovudine (ZDV) causes bone marrow suppression. Older patients might exhibit reduced renal function and loss of bone mass in addition to depression and cognitive disorders. There is more information regarding aging patients with HIV infection that have been exposed to ART for long periods of time than information regarding how to treat an old HIV+ patient recently diagnosed. Moreover, the choice to start treatment for individuals who have a diagnosis in the age groups above 50-60 years is probably something new for most clinicians. As the proportion of older patients starting treatment increases, studies assessing the efficacy and tolerability of regimens for this particular population are needed.

Tolerability to ART

Due to the greater need for concomitant medications in older patients, elderly HIV+ patients are expected to have poorer tolerability to ART, higher toxicity, and more numerous drug interactions. However, there are currently few data regarding these aspects [47]. In the Swiss cohort, older patients tended to use more concomitant medications than younger patients and also exhibited higher risks of drug interactions, which were mostly related to the effects of ART on the action of the concomitant medications. The toxic effects most commonly described were associated with gastrointestinal intolerance, followed by central nervous system disorders, hepatotoxicity, and dyslipidemia [48].

There is little information regarding the reasons to change ART in the elderly population. Among 95 patients aged ≥ 50 years in the IPEC/Fiocruz cohort starting their first HAART regimen between January 1996 and December 2008, 59% modified or discontinued (MOD) the first regimen (28.1/100 individuals per year of follow-up); the mean time to MOD was 12 months, and the main reasons for MOD were therapeutic failure (14%), toxicity during the first year of HAART (11%), and long-term toxicity (6%). The incidence of MOD was significantly higher among patients who started HAART with CD4+ T-cell counts < 100

cells/mm^3 (HR 1.97; 95% confidence interval (CI) 1.08-3.61) [49]. In a German cohort, a change of regimen was more common among the patients aged ≥ 50 years [50].

Adherence, Resistance and Drug Interactions

Some studies found a higher adherence to ART among patients ≥ 50 years compared to younger patients [46, 51].

Data regarding the resistance profile in therapeutic failure among elderly patients are scarce, as are data on primary resistance and age. In a German cohort, no difference was found in the transmission of resistance between the older and younger patients [50]. In an Italian cohort, increased age was independently associated with a higher likelihood of primary resistance [52].

Older patients tend to have more comorbidities, fall ill more often, and pharmacological intervention is frequently needed, with a consequent high risk of drug interactions. Older HIV+ patients use more medications for CVD, gastrointestinal, and hormonal problems than younger patients, whose use of these medications matches that of the general population [48]. In the Swiss cohort, age was one of the risk factors associated with increased drug interactions [53].

Non-AIDS-defining illnesses associated with HIV

HAART reduced AIDS-related morbidity and mortality; however, the death rate among HIV+ individuals attributed to non-AIDS-defining illnesses, including liver, lung, cardiovascular, and neoplastic diseases, increased [54]. Many such illnesses correlate with HIV after adjustment for well-established demographic and behavioral risk factors. Some examples include myocardial infarction, thrombosis, and stroke; bone diseases, including osteoporosis and avascular necrosis; neoplasias caused by infectious agents such as human papillomavirus (HPV)-related anal cancer; and neoplasias not caused by infectious agents, such as lung cancer; chronic obstructive pulmonary disease, dementia, liver fibrosis progressing into cirrhosis, and hepatoma; hematologic diseases such as anemia and

thrombocytopenia; and kidney dysfunction, including terminal failure [54]. Chronic immunosuppression has been associated with many such conditions in large cohort studies, where low CD4+ T-cell counts are predictive of death by non-AIDS-defining outcomes. The incidence of such conditions is higher among people ≥ 50 years [23].

Some authors have disputed the correlation between HIV/HAART and the early appearance of comorbidities based on the predominance of retrospective analyses among these studies and the lack of sufficient data regarding well-established risk factors such as smoking, abuse of alcohol and recreational drugs, socioeconomic status, and concomitant medications [55].

Malignancies

The higher incidence of malignancies in PLH is related to the chronic oncogenic effect of some viral infections but is not necessarily related to aging. Nevertheless, some important aspects related to HIV, age, and the incidence of neoplasias are still controversial, such as whether HIV leads to the early occurrence of cancer, whether the high incidence of some malignancies among PLH is a consequence of accelerated aging, and whether all patients should be treated with HAART upon diagnosis of HIV infection to achieve steady viral suppression and maintain immunity close to its normal status. Also, it is unclear whether avoiding severe immunodeficiency alone reduces the risk of HIV-related malignancies [56].

The predictive factors of non-AIDS-defining malignancies include age, (the risk rate doubles per ten years of age increase); the most recent low CD4+ T-cell count; a history of smoking and hepatitis B (HBV) coinfection [57]. HAART is protective against AIDS-defining malignancies but does not seem to protect against non-AIDS-defining malignancies [57]. Some studies have shown that since HAART was introduced, non-AIDS-defining malignancies have been diagnosed earlier in HIV/AIDS patients [57, 58]. PLH might also be at a higher risk of cancer due to peculiarities of their lifestyle, particularly smoking and the use of alcohol [56].

As the HIV+ population ages while exhibiting persistent alterations of the immune system, an increasing number of malignancies can be expected over time. Lung, anal, and liver cancer, as well as Hodgkin’s lymphoma, represent the main contributions to this

increase. In the United States, the incidence of breast, colon, and prostate cancer is lower among HIV+ individuals than among the general population; this may be because the HIV+ individuals had not reached a sufficient age to develop such malignancies or to some protective effect related to HIV [56].

In any case, the prevention and early treatment of neoplasias in PLH must be included in public health follow-up strategies and therapeutic guidelines targeting the elderly population.

Frailty

Frailty is a pathologic aging syndrome, the mechanism of which is unknown, that leads to unfavorable outcomes such as hospitalization, disability, and death [59]. Increased free radical levels, mitochondrial dysfunction, and cytokines might activate inflammatory pathways, leading to this condition. The levels of C-reactive protein, d-dimer, fibrinogen, and IL-6 are increased in older individuals with the frailty phenotype [60]. Similarly, HIV infection and ART toxicity activate the inflammatory mechanisms associated with frailty [59]. There is no universal definition of “frailty” for patients with HIV/AIDS; in the general population, a frailty phenotype is established when at least three of the following traits are present: exhaustion, slow walking speed, low levels of physical activity, weakness, and weight loss [60]. HIV infection seems to accelerate the development of frailty, even when the patient exhibits viral suppression under HAART. In addition to HIV, frailty has also been associated with age, the female gender, a low level of schooling, being single, the abuse of non-prescription drugs, and depressive symptoms. Table 1 describes an algorithm for the calculation of frailty that can be applied to patients.

Fat, metabolic, hormonal disorders and cardiovascular disease

HIV infection is associated with a higher risk of metabolic disorders such as insulin resistance, pro-atherogenic lipid profiles, and alterations of the subcutaneous and visceral body fat distribution (lipodystrophy). Such disorders might contribute to the higher risk of CVD associated with HIV and ART [61]. Some cross-sectional studies have found an

increased risk of metabolic and hormonal disorders, including osteopenia, hypogonadism, diabetes mellitus, and dyslipidemia [62, 63]. In the Swiss cohort, a higher proportion of non-AIDS comorbidities and multiple morbidities such as diabetes mellitus and CVD were observed among older individuals [64].

The earliest cohort studies associated HIV infection and exposure to ART with a risk of coronary disease and myocardial infarction (MI). Subsequently, Friis-Moller et al. found that the risk of MI was more strongly associated with pre-established risk factors such as advanced age [65]. Nevertheless, the correlation among HIV infection, inflammation, and cardiovascular risk has not yet been fully elucidated [66]. HIV infection, prolonged ART, and aging are known to contribute to lipoatrophy and metabolic disorders [67]. In the American VACS cohort, the risk of MI was twice as high among the HIV+ than the non-infected individuals, even after adjusting for established risk factors such as age, race, hypertension, diabetes mellitus, hypercholesterolemia, smoking, infection with hepatitis C virus (HCV), kidney disease, body mass index (BMI), and history of cocaine and alcohol abuse. However, the age at which MI occurred did not differ significantly among the older individuals, regardless of HIV status [68].

Renal function

Renal function is reduced in both elderly and PLH, leading to an impaired elimination of drugs and an increased risk of toxicity and mortality associated with CVD [69]. Although the survival of PLH with terminal kidney disease has improved since the introduction of HAART, its incidence has not changed [69]. The survival rates of elderly patients undergoing dialysis are low, and a delay in the initiation of dialysis is associated with even greater morbidity and mortality. It is not yet known whether the control of arterial pressure and glycemia might delay the progression of kidney disease in HIV+ patients as it does in the general population [69].

Liver disease

Liver disease is an important cause of death among PLH, surpassed only by opportunistic infections. Morbidity and mortality due to liver disease are up to 4-fold higher among the elderly than among young adults. In addition, the liver volume, blood flow, drug metabolism, and regenerative capacity decrease with age. Age is also associated with hepatocellular carcinoma. The progression of HCV into cirrhosis is accelerated in HIV+ patients [70].

Cognitive impairment and HIV

The natural history of HIV infection is changing, and factors associated with advanced age will become an important modulator of its clinical outcomes, particularly dementia. Historically, there was no need to consider the potential contribution of age-related neurodegenerative diseases such as Alzheimer's to cognitive disorders among PLH because HIV primarily affected young individuals, whose life expectancy was then low. With the advance of HAART, there is an increased likelihood that young and middle-aged HIV+ individuals will develop premature neurodegenerative disorders that could directly impact their ability to work and reduce their quality of life [71]. Increased longevity under conditions of chronic HIV-mediated inflammation combined with the secondary effects of HAART might significantly contribute to the increased risk of early cerebral aging and cognitive loss. Although the incidence of HIV-related dementia decreased after HAART was introduced, several studies reported a correlation between old age and an increased risk of HIV-associated dementia as the initial AIDS-defining illness [32].

Smoking

The well-established risks of smoking are considered greater among PLH, as these risks may be enhanced by the chronic inflammation associated with HIV, even among individuals with appropriate viral suppression. Associated questions include whether PLH smokers are at a higher risk of lung cancer or other malignancies as well as cardiovascular complications compared to smokers in general population. As PLH are aging, their risk for all

age-related diseases, including malignancies, will increase. The impact of being a smoker among HIV+ individuals who are aging needs to be established, once the prevalence of smokers among PLH is high, ranging from 50 to 70% [72].

Vitamin D deficiency

Although the rates of vitamin D deficiency are high among PLH [73, 74] little is known about the benefits of vitamin D supplements in metabolic disorders other than those involving the bones. The available data are controversial and non-standardized. In addition, the ideal replacement and maintenance regimes for PLH are not known. It is also important to highlight that bone diseases, depression and cognitive impairments can be associated with both aging and vitamin D deficiency. Therefore, controlled trials assessing both the success of vitamin D replacement and its benefits are needed.

Bone mass loss

HIV causes chronic activation of T cells and increases the production of pro-inflammatory cytokines, which increase the activity of osteoclasts, and these alterations persist despite effective ART and viral suppression [75]. The current understanding of bone metabolism in the aging HIV/AIDS population is limited, and the sparse longitudinal data available show conflicting results [76]. Despite the currently limited understanding of the factors associated with bone mineral reduction, the assessment of risk factors for bone loss is needed to reduce the morbidity of osteopenia and osteoporosis in the HIV+ aging population.

Women with HIV/AIDS and menopause

A study conducted in Germany found that women reported more age-related complaints (such as mood swings and impaired mobility) than men, and 80% of the women believed that they were aging prematurely, compared to 18% of men ($p<0.001$) [77]. Early menopause seems to be related to HIV-induced immunodeficiency and is more common among women with low CD4+ T-cell counts. Risk factors described and established for the

general female population, such as African descent and a history of intravenous drug use, have been associated with early menopause among HIV+ women [78]. In turn, early menopause influences the overall health of women and might be associated with reduced sexual function and depressive symptoms in addition to increased cardiovascular risk and skeletal health issues. Recently, higher rates of bone mass loss were found in the spine and forearms of postmenopausal HIV+ women compared to non-infected women, independent of stable ART [79]. The loss of bone mass is likely to increase the risk of fractures in this population. Therefore, stratification of risk by means of bone densitometry and research on secondary causes of osteoporosis and its appropriate treatment in all postmenopausal HIV+ women seems justified. The usefulness of such assessments in younger women has not yet been established.

Routine measures that should be incorporated into the preventive care and health maintenance of older individuals living with HIV/AIDS

Regular physical exercise is extremely important to the quality of life of PLH, especially older individuals. A study performed in São Paulo, Brazil, found that resistance training increased the strength of older patients and allowed them to achieve the same level of performance as the healthy control patients, even when their initial clinical profile was worse [80].

In addition to physical exercise, other healthy habits such as eating a balanced diet; controlling the blood pressure; treating diabetes and dyslipidemia; and abstaining from smoking, alcohol, and drugs, must be strongly encouraged in PLH, particularly among the older. Routine measures applied to the general population that should be incorporated into the preventive care and health maintenance of PLH are described in Table 2.

Conclusion

Health care and prevention guidelines tailored to elderly HIV+ individuals are needed. The higher prevalence of comorbidities, polipharmacy, drug interactions and end organ disease in this patient population requires a multidisciplinary approach. Longitudinal studies

are needed to assess the actual impact of HIV on aging and vice versa. In addition, HIV prevention strategies targeted to older adults should be considered.

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Figure 1. Comparison of age distribution between people living with HIV-AIDS (PLH) and general population (BRPOP) in Brazil (2010).

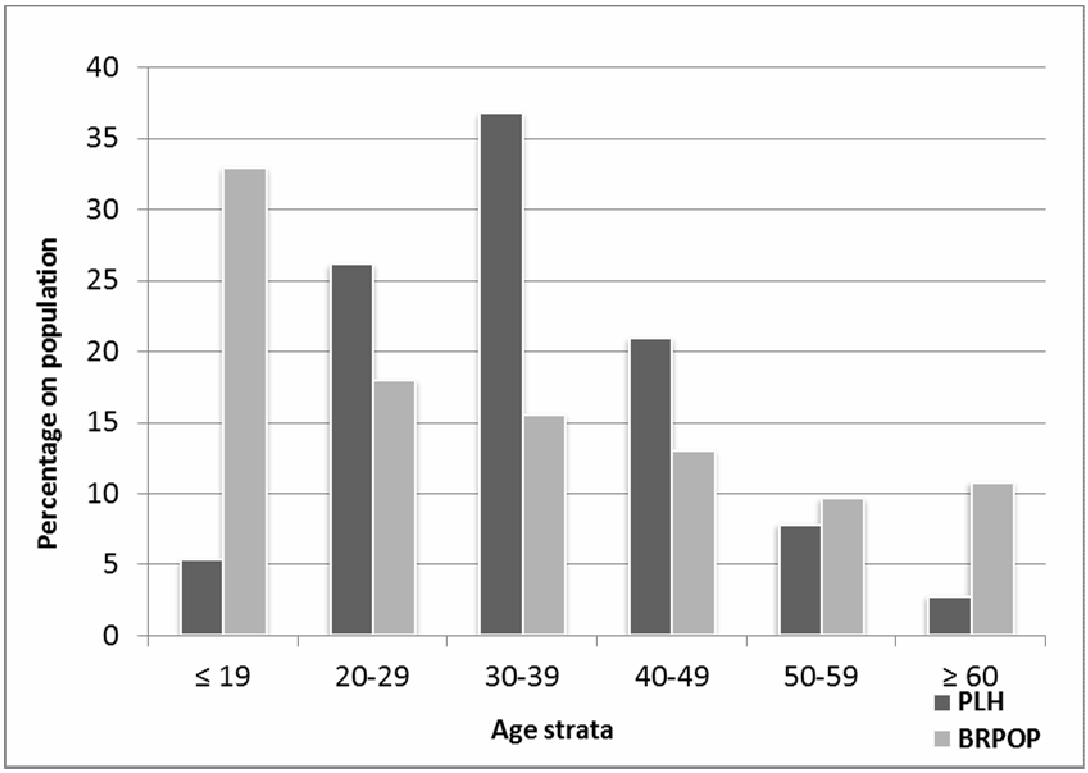

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Table 1. Frailty Calculation

Criteria	Definition	Positive
Unintentional weight loss	≥ 5% of previous body weight OR > 4.5Kg of body weight loss in the last year.	---
Low physical activity	Health limits vigorous activities such as running, lifting heavy objects or participating in strenuous sports. **OPTIONS:** **(1) NOT AT ALL;** **(2) YES, LIMITED A LITTLE;** **(3) YES, LIMITED A LOT.**	**(3) YES, LIMITED A LOT.**
Low Resistance / Exhaustion	In the last week, how often the patient felt that everything s/he did was an effort OR s/he could not 'get going'. **OPTIONS:** **(0) RARELY (< 1 DAY);** **(1) SOME OF THE TIME (1-2 DAYS);** **(2) OCCASIONALLY (3-4 DAYS);** **(3) MOST OF THE TIME (5-7 DAYS).**	**(2) OCCASIONALLY (3-4 DAYS) OR** **(3) MOST OF THE TIME (5-7 DAYS).**
Serial Strength Test	Highest pressure strength (dynamometer Jamar = 3 attempts)	**20% WEAKER STRATIFIED BY SEX AND BMI.**
Slow walking time	Time to walk 4m in an usual place.	**20% SLOWER BY SEX AND MEDIUM HEIGHT**
FRAILTY	**POSITIVE FOR 3 OR MORE CRITERIA (PRE-FRAILTY: 1-2; NORMAL: 0)**	

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Table 2. Routine measures used in the general population that must be incorporated into the preventive care and health maintenance of patients living with HIV/AIDS (PLH).

Comorbidity	Risk Factors	Preventive Measures
Anal cancer	• Infection by human papillomavirus (HPV)	• The anti-HPV recommendations are currently the same as those established for the general population and might have a future impact; however, recommendations specifically for the HIV-infected population are still being established, and several strategies are currently being studied. Screening for anal cancer prevents invasive cancer by means of the identification and removal of precancerous lesions (high-grade anal intraepithelial neoplasia – HGAIN) before their progression. Initial screening tests usually include a digital rectal examination, visual inspection, and anal cytology. When abnormal, patients are referred for high-resolution anoscopy and biopsy of lesions suspected of HGAIN. HGAIN areas are removed by ablation to reduce the risk of progression into anal cancer. Cost-effectiveness studies of these strategies are currently being conducted.
Arterial hypertension	• Gender: until menopause, women are more protected • Race: Afro-descendants exhibit higher risk than Caucasians • Familial history • Sedentarism • Obesity • Contraceptives (women aged > 35 years old) • Smoking • Use of alcohol • Nutritional habits (high salt consumption) • Low socioeconomic level	• Pre-hypertension (systolic arterial pressure - SAP = 120-139 mmHg or diastolic arterial pressure - DAP = 80-89 mmHg): Increased attention to lifestyle habits such as eating a healthy diet and exercising regularly. • Hypertension stage I (SAP = 140-159 mmHg or DAP = 90-99 mmHg): thiazide diuretics. Also consider the use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium-channel blockers, or a combination of these. • Hypertension stage II (SAP ≥ 160 mmHg or DAP ≥ 100 mmHg): combination of 2 anti-hypertensive agents

Breast cancer	• Personal or familial history of breast cancer • No children • Significant exposure to x-rays • Early menarche • Late menopause • High socioeconomic class • First pregnancy after age 30 • Fat-rich diet • Prolonged use of oral contraception (disputed)	• Clinical and self-examinations • Refer to gynecologist for periodical assessment • Mammography • Ultrasound
Cancer of the respiratory system (lung, throat, larynx)	• Familial history • Smoking	• Lung cancer screening; early assessment when symptoms are present • Smoking cessation • Preliminary data suggest that thorax computed tomography with low radiation doses might be beneficial, but further studies are needed.
Cardiovascular disease and stroke	• Smoking • Sedentarism • Dyslipidemia • Menopause (women) • Glucose intolerance • Familial history • Obesity (BMI > 30 Kg/m^2) • Abdominal obesity (men > 94 cm, women > 80 cm)	• 1^{st} step – assess CVD risk: Framingham scale • Use of aspirin (dose according to coronary disease risk calculated by Framingham score) • Control of blood pressure • Control of cholesterol • Smoking cessation • Control of diabetes and prediabetes • Aerobic physical exercise (30 min, 3-5 days/week) • Balanced diet to maintain healthy body weight: fruits, vegetables, whole grains,

	• Metabolic syndrome • HIV infection appeared as an independent risk factor; however, risk increases when CD4+ count is low and VL is persistently high (loss of virologic control).	fiber-rich foodstuffs, fish (especially oily fish twice a week) • Restrict saturated fat to < 7% of daily intake, trans fat to 1%, and cholesterol to < 300 mg/day. • Reduce consumption of sodas and foodstuffs containing added sugar. • Choose and prepare foodstuffs with little salt. • Use alcohol moderately.
Colon/bowel cancer	• Familial history of colorectal cancer • Diet high in fat and meat and low in calcium • Obesity • Sedentarism • Inflammatory bowel disease	• Colonoscopy; screening starting at age 50 is recommended for the general population • Smoking cessation
Dementia/Alzheimer's disease	• Familial history	• Cognitive exercises • Dementia after stroke: lifestyle changes, including regular physical exercise, a balanced diet, and the control of high blood pressure and diabetes mellitus • Alzheimer's disease: no prevention is available
Diabetes Mellitus Normal glycemia: < 100 mg/dL fasting or < 140 mg/dL 2 hours after intake of 75 g of dextrose Prediabetes: 100-120 mg/dl fasting or 140-200 mg/dL after dextrose Diabetes Mellitus: fasting glycemia ≥ 126 mg/dL, > 200 mg/dL after dextrose or casual glycemia, or > 200 mg/dL when symptoms are present	• Age equal to or older than 45 years (HIV non-infected individuals) • Familial history • Sedentarism • Low high-density lipoprotein (HDL-c) or increased triglyceride levels • Arterial hypertension • Coronary disease	• Diet control/planning • Physical exercise • Weight loss • Restricted use of alcohol • Glycemic control • Smoking cessation • Avoid pancreas-damaging medications (cortisone, thiazide diuretics).

	• Previous gestational diabetes • Children with birth weights higher than 4 kg, repetitive abortions, children dying during the first days of life • Use of medications that increase glucose (cortisone, thiazide diuretics, beta-blockers) • HIV-infected patients using ART exhibit a fourfold higher risk.	• Pharmacological treatment: metformin is the first choice and might be associated with sulfonylureas • Insulin might be needed as an adjuvant of oral drugs or as a second choice because it improves insulin resistance and has possible effects on the lipids and body composition. Risk of hypoglycemia • More complex cases must be referred to specialists.
Dyslipidemia	Types of dyslipidemia: • Isolated hypercholesterolemia: low-density lipoprotein - LDL-C ≥ 160 mg/dL • Isolated hypertriglyceridemia: TG ≥ 150 mg/dL • Mixed hyperlipidemia: LDL-C ≥ 160 mg/dL and TG ≥ 150 mg/dL simultaneously • Low HDL: isolated reduction of HDL-C (< 40 mg/dL in males and < 50 mg/dL in females) or associated with increased LDL-C or TG	• Changes in lifestyle: regular physical exercise, weight loss, smoking cessation, nutritional therapy • Isolated hypercholesterolemia: statins (LDL-C reduction; lower TG reduction; slight HDL-C increase); ezetimibe (combined with a statin). Use cautiously in patients using ART due to the risk of interactions. Simvastatin and lovastatin cannot be used due to interaction with ART. • Mixed hyperlipidemia (increased cholesterol, LDL-C and TG): fibrates (bezafibrate, ciprofibrate, fenofibrate, and gemfibrozil). Caution is needed due to interaction with ART; nicotinic acid; omega-3 fatty acids. • Elderly: attention to secondary causes of dyslipidemia, mainly hypothyroidism, diabetes mellitus, and chronic kidney failure
Hepatitis A (HAV)	• Intake of contaminated water • Lack of basic sanitation	• Personal hygiene (intake of treated water, washing hands, avoiding foodstuffs of unknown origin) • Basic sanitation: (sewage, septic tanks) • Laboratory test for HAV markers (anti-HAV IgM and anti-HAV IgG) • Vaccination: schedule for susceptible individuals (non-reagent HAV IgG serology) – 2 doses (at 0 and 6-12 months or 0 and 6-18 months). Not included in the Handbook for CRIE – Health Ministry (Brazil) • Lower response to vaccine in individuals with CD4+ < 200

Hepatitis B (HBV)	• Multiple sexual partners • Healthcare professionals • Patients undergoing hemodialysis • Injection drug use	• Use of condoms • Universal precautions with biological materials • Laboratory tests for HBV markers (HbsAg, anti-HBs, anti-HBc IgM, anti-HBc) • Vaccination: 4 double-dose applications (at 0, 1, 2, and 6 months) • Butantan (Brazil)**:** Up to 18 years old: 1 mL; ≥ 19 years old: 2 mL • Lower response to vaccine in cases of advanced immunodeficiency, patients with detectable viral load, and those with transiently increased viral load. Measurement of anti-Hbs is recommended (4-6 weeks after the last vaccine dose) because revaccination might be needed.
Hepatitis C (HCV)	• Multiple sexual partners • Injection drug and inhalants use	• Use of condoms • Universal precautions with biological materials • Not sharing needles and other tools used in the preparation and consumption of injectable drugs and inhalants (straws) • Laboratory tests for HCV markers (anti-HCV)
Liver cancer	• Alcoholism • HCV and HBV coinfection	• Careful monitoring of patients with chronic HBV and HCV infection; treatment when indicated, periodic assessment of the liver function, viral load, and possibly alpha-fetoprotein
Menopause/andropause	---	• Hormonal replacement
Metabolic syndrome	**Characterized by** • Glucose ≥ 100 mg/dL • Triglycerides ≥ 150 mg/dL	• Diet • Regular physical exercise • Lipid profile

	• Blood pressure ≥ 130/85 mmHg • HDL cholesterol < 50 mg/dL (men) or < 40 mg/dL (women) • Abdominal circumference > 80 cm (women) and > 94 cm (men)	• BMI reduction to 18.5 kg/m^2 – 24.9 kg/m^2
Osteopenia/Osteoporosis	• Female gender (menopause) • Smoking • Low calcium intake • Vitamin D deficiency • Vitamin A excess • Sedentarism • High caffeine intake • High salt consumption • Immobilization • Falls • Alcohol (more than 3 drinks/day) • Low BMI Osteoporosis is diagnosed by means of BMD measurements using dual-energy x-ray absorptiometry (DXA) of the hips and lumbar spine. The measurements are expressed as g/cm2 for the same age and gender (Z score) and for same-gender young adults (T score). The WHO defines osteoporosis as a T score ≤ -2.5, which does not apply to women before menopause, men younger than 50 years old, and children. In such cases, the diagnosis is based on ≤ -2.0, which means BMD below the 'normal' BMD expected for age and gender, suggesting the need to investigate pathological causes.	• Calcium intake: women > 50 years old = 1,200 mg/day (supplements: 600 mg of elemental calcium + 200 IU or 400 IU of cholecalciferol) • Vitamin D: adults > 50 years old = 800-1,000 IU/day of vitamin D3 (cod liver oil, fortified milk, egg yolk, fresh salmon, canned tuna, canned sardine) • Exercises that increase muscle strength against gravity (bodybuilding, local exercises, etc.) • Prevention of falls • Smoking cessation • Avoid excessive alcohol consumption. • Avoid the use of steroids and proton-pump inhibitors. • Pharmacological treatment: - Antiresorptive agents: bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid); selective estrogen receptor modulators (raloxifene); hormonal therapy - Bone forming or anabolic: teriparatide - Bone forming/antiresorptive: strontium ranelate The use of calcium and bisphosphonates is recommended in cases of fractures or BMD T score < 2.5 standard deviations.

Prostate cancer	• Familial history • Afro-descendants • Fat-rich diet	• Prostate assessment (digital rectal exam - DRE) • Assessment of the blood prostate-specific agent (PSA) levels • Transrectal ultrasound • Diet low in fat and high in protein, fruits, vegetables, and legumes • The American Urological Association recommends PSA and DRE in asymptomatic men 40 years old or older when the life expectancy is greater than 10 years. This recommendation is currently being updated. • The American Cancer Society recommends that men at average risk be given information starting at age 50 and black men and those with familial history of prostate cancer at age 45. • The American College of Preventive Medicine recommends that general practitioners discuss the potential benefits and risks of PSA screening with men aged 50 years or older while taking the patients' preferences into account and making individual screening decisions. • Guidelines for HIV-infected patients are being established. Earlier prostate cancer screening based on an HIV diagnosis does not show patent advantages.
Renal function	• Age • Diabetes • CVD • Deficient nutrition • HIV: directly or indirectly causes several types of kidney disorders such as nephropathy, thrombotic microangiopathy,	• Verify the glomerular filtration rate (GFR): ***Grade 1***: Kidney alterations with normal or increased GFR; GFR > 90 mL/min/1.73 m^2 ***Grade 2***: Kidney alterations with slightly decreased GFR; GFR = 30-59 mL/min/1.73 m^2 ***Grade 3***: Moderate reduction of GFR; GFR = 30-59 mL/min/1.73 m^2 ***Grade 4***: Severe reduction of GFR; GFR = 15-29 mL/min/1.73 m^2 ***Grade 5***: Kidney failure; GFR < 15 mL/min/1.73 m^2 (or under dialysis) • Avoid combinations of nephrotoxic drugs.

	immune-mediated glomerulonephritis • Some ART agents might cause or exacerbate pre-existing nephropathy.	• Smoking and alcoholism cessation and a healthy diet • Treat dyslipidemia and diabetes. • Adjust dose of medications when needed.
Skin cancer	• Light skin	• Use of sun protection • Avoidance of excessive sun exposure
Uterine cancer	• Social factors (low socioeconomic class) • Habits (poor hygiene; prolonged use of oral contraceptives) • Sexual activity and pregnancy before age 18 • Smoking (directly related with the number of cigarettes) • Infection by HPV and herpes virus type 2 (HSV-2) • Multiple sexual partners	• Annual preventive cervical cancer exam (Papanicolaou, Pap) • For cervical cancer screening, the Pap smear must be performed during anogenital examination after the diagnosis of HIV, with a second Pap smear six months later and then once a year when the results are normal. • Colposcopy in indicated cases: whenever Pap is abnormal • HPV testing as a cervical cancer screening method in HIV-infected women might also be efficacious.
Vaccination	Vaccination decisions depend on the clinical and vaccination history of patients. The response to vaccines is better in patients with CD4+ > 350 cells/mm^3. Assess the best time to vaccinate the patient, but do not delay the onset of vaccination in high-risk patients. Inactivated vaccines have no restrictions in immunodeficient individuals. Attenuated vaccines must only be used when the potential benefit outweighs the risk and only in patients with CD4+ > 200 cells/$mm^{3.}$ Some vaccines might transiently increase the viral load without clinical consequences. It is recommended to vaccinate during the intervals between viral load tests.	• Inactivated DT: Basic schedule: 3 doses (at 0, 2, and 4 months; booster: 1 dose every 10 years) • Influenza: 1 dose every year • Pneumococcus (*Streptococcus pneumoniae*) – inactivated pneumo 23-valent: 1 intramuscular or subcutaneous dose with a single booster 5 years later; vaccination reduces the risk of pneumonia and invasive disease • Attenuated varicella: susceptible adults with CD4+ > 200 cells/mm^3: 2 doses with a 4-8-week interval • HPV: tetravalent (HPV 16, 18, 6, 11) – ideally, vaccinate both males and females between the ages of 9 and 26 (3 doses: 0, 2, and 6 months). Not available in the Brazilian public health network, and its cost is high. Use is safe in HIV-infected individuals; however, cost-effectiveness studies must be performed in this

		population. • Attenuated yellow fever: upon travelling to risk area. When CD4+ > 200 cells/mm^3: 1 dose every 10 years

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3 Artigo 2

Título:

Aging with HIV: An Overview of an Urban Cohort in Rio de Janeiro (Brazil) Across Decades of Life

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Abstract

The introduction of highly active antiretroviral therapy (HAART) during the 1990s was crucial to the decline in the rates of morbidity and death related to the acquired immunodeficiency syndrome (AIDS) and turned human immunodeficiency virus (HIV) infection into a chronic condition. Consequently, the HIV/AIDS population is becoming older. The aim of this study was to describe the immunological, clinical and comorbidity profile of an urban cohort of patients with HIV/AIDS followed up at Instituto de Pesquisa Clinica Evandro Chagas, Oswaldo Cruz Foundation (IPEC/FIOCRUZ) in Rio de Janeiro, Brazil. Retrospective data from 2,307 patients during January 1st, 2008 and December 31st, 2008 (n=2,307) were collected. For continuous variables, Cuzick's non-parametric test was used. For categorical variables, the Cochran-Armitage non-parametric test for tendency was used. For all tests, the threshold for statistical significance was set at 5%. In 2008, 1,023 (44.3%), 823 (35.7%), 352 (15.3%) and 109 (4.7%) were aged 18-39, 40-49, 50-59 ≥ 60 years-old, respectively. Older and elderly patients (≥ 40 years) were more likely to have viral suppression than younger patients (18-39 years) ($p<0.001$). No significant difference in the latest CD4+ T lymphocyte count in the different age's strata was observed, although elderly patients (≥ 50 years) had lower CD4+ T lymphocyte nadir ($p<0.020$). The number of comorbidities increased with age and the same pattern was observed for the majority of the comorbidities, including diabetes mellitus, dyslipidemia, hypertension, cardiovascular diseases, erectile dysfunction, HCV, renal dysfunction and also for non-AIDS-related cancers ($p<0.001$). With the survival increase associated to successful ART and with the increasing new infections among elderly group, the burden associated to the diagnostics and treatment of the non-AIDS related HIV comorbidities will grow. Longitudinal studies on the impact of aging on the HIV/AIDS population are still necessary, especially in resource-limited countries.

Introduction

Worldwide, life expectancies have been increasing over the last several decades, even in developing countries, leading to a greater number of individuals ≥ 60 years. There will be approximately 2 billion individuals ≥ 60 years in the world by 2025, the majority of whom (80%) will reside in developing countries [1]. According to the Brazilian Institute of Geography and Statistics (IBGE), 97% of the Brazilian population at the beginning of the 20th century was younger than 59 years; currently, 15.8 million Brazilians are at least 60 years old, and it is estimated that this number will increase to more than 40 million by 2030. It is estimated that by 2030 the life expectancy of the Brazilian population will be 78.3 years, 81.9 years for women [2].

The introduction of highly active antiretroviral therapy (HAART) during the 1990s was crucial to reduce HIV related morbidity and mortality rates turning HIV infection into a chronic condition. ART global coverage has significantly grown in the latest years, with 11.7 million life-years added to the world between 1996 and 2008 [3]. Consequently, the HIV/AIDS population is becoming older. The World Health Organization (WHO) and the majority of geriatricians define “elderly” as a person aged ≥ 60 years. However, the American Centers for Disease Control and Prevention (CDC) considers a patient with HIV/AIDS ≥ 50 years-old to be elderly due to the impacts of HIV and antiretroviral therapy (ART) on aging [4]. According to the Brazilian Ministry of Health, among the 608,230 cases of HIV/AIDS notified up to June 2011; 64,560 (10.6%) were in the elderly (≥ 50 years) [5].

Chronic conditions associated with aging, such as non-AIDS-defining malignancies, cardiovascular disease and other end-organ disease and deaths attributable to these conditions have also increased in HIV/AIDS cohorts [6-9].

The aim of this study was to describe the immunological, clinical and comorbidity profile across age of an urban cohort of patients with HIV/AIDS followed up at a referral center for HIV care and research in Rio de Janeiro, Brazil, in 2008.

Materials and Methods

Description of the clinical cohort and study population

This study was conducted at Instituto de Pesquisa Clinica Evandro Chagas, Oswaldo Cruz Foundation (IPEC/FIOCRUZ), where care has been provided to HIV/AIDS patients since 1986. An observational, longitudinal, clinical database has been maintained on patients receiving primary HIV care in the clinic. Data are updated regularly using outpatient and inpatient clinical documentation, laboratory testing results, and pharmacy records. Trained abstractors record all this information onto standardized forms for processing. Details of the methodology have been previously described [10].

For this cross sectional study, we included retrospective data from all patients over 18 years of age who have had at least one follow-up appointment (clinical visit, lab exams, antiretroviral (ARV) reload, social assistance interview) between January 1st, 2008 and December 31st, 2008 (n=2,307). This study was approved by IPEC/FIOCRUZ ethics committee.

Study definitions

Age in 2008 was the variable of interest across all analyses. Patients were stratified as 18-39 years ("younger patients"), 40-49 years ("older patients"); 50-59 years and ≥ 60 years ("elderly"), according to CDC criteria [4]. Other variables used to describe our cohort included demographic, clinical and treatment related characteristics.

For "years HIV-infection", we considered the period between the first HIV positive test available and 31 December 2008.

"Viral suppression" was defined as viral load less than 400 HIV RNA copies/µL at all available viral load assessments performed during 2008. For "Last CD4 cells/µL" the last

CD4+ T lymphocyte count available in 2008 was considered while for “Nadir CD4 cells/µL” all historical CD4 results available until 31 December 2008 were considered.

For “Era of starting antiretroviral therapy (ART)”, we classified patients who started using mono/dual (one or two ARV only) or highly active antiretroviral therapy (HAART). To classify “ART-naïve” and “current HAART regimen” only year 2008 information was considered. We have also accessed the number of patients on use of new ARV (etravirine, enfurvitide, raltegravir and darunavir).

For “Comorbidities” (diabetes mellitus, dyslipidemia, hypertension, depression and erectile dysfunction) we considered the cases under specific drug intervention during the year 2008. Data was collected from medical prescriptions and medical charts. For “cardiovascular diseases” other than hypertension, reports of cardiac arrhythmia, heart failure, coronary disease, ischemic heart disease, peripheral vascular insufficiency and stroke were considered. For Hepatitis B (HBV), we considered all patients with a positive HBV surface antigen (HbsAg) exam. For Hepatitis C (HCV), we considered all patients with an anti-HCV positive exam.

“Renal dysfunction” was defined as a glomerular filtration rate (GFR) lower than 60 mL/min calculated by the CKD-EPI for all patient who had a creatinine result in 2008 (n=1,971; 85.4%). Patients with hospitalization history within 6 months interval of the creatinine result were excluded to avoid bias with acute renal disease (n=37; 1.6%).

For “AIDS defining illness”, “AIDS-defining cancer” and “non-AIDS-defining cancer” all diagnostic until 2008 were considered. We used the Centers of Disease Control (CDC, 1993) definition for to consider “AIDS defining illness”.

Statistical Analysis

Statistical comparison of quantitative variables across decade of life was accessed by the Cuzick’s non-parametric test for trend. For categorical variables, the Cochran-Armitage

non-parametric test for trend was used. For all tests, the threshold for statistical significance was set at 5%. Analyses were done using R-software (version 2.14.2).

Results

Demographic data

Selected demographic values distributed according to the decade of life are summarized in Table 1. A total of 2,307 patients were included in this analysis. From those, 1,023 (44.3%) were 18-39 years, 823 (35.7%) were 40-49 years, 352 (15.3%) were 50-59 years, and 109 (4.7%) were ≥ 60 years. Each age category had more male (overall average of 63.6%) and white (overall average of 57.2%) patients.

The proportion of MSM and of non-whites significantly fluctuated over age groups ($p=0.021$ and $p<0.001$, respectively). MSM Transmission Group was less frequent among elderly (49.3% for 50-59 years; 53.2% for ≥ 60 years).

There were no statistically significant differences in years of education and enrollment in an ART clinical trial among the age groups.

Treatment and Clinical Status

HIV treatment and clinical status distributed according to the decades of life are depicted in Table 1. The median age at HIV diagnosis and the duration in years of HIV infection significant increased ($p<0.001$) with age. Consequently, other variables related to ART use (e.g. number of years on ART, use of mono/dual therapy, use of PI-based regimen, use of new ARV) also increased with age, while the proportion of ARV-naïve patients significantly decreased with age ($p<0.001$).

We found a higher proportion of viral suppression among older and elderly patients ($p<0.001$). There was no significant difference in the latest CD4+ T lymphocyte count in the different age's strata. However, older and elderly patients had lower CD4+ T lymphocyte nadir ($p<0.020$).

Comorbidities, Smoking Status and Other Characteristics

The number of comorbidities increased with age (Figure 1). The same pattern was observed for the majority of the comorbidities, including diabetes mellitus, dyslipidemia, hypertension, cardiovascular diseases, erectile dysfunction, HCV, renal dysfunction and also for non-AIDS-related cancers ($p<0.001$) (Table 2).

Depression was observed in 14.3%, 18.8%, 23.3% and 19.3% of individuals aged 18-39 years, 40-49 years, 50-59 years and ≥ 60 years, respectively ($p<0.001$). Use of anxiolytics was observed in 15.0%, 20.8%, 23.9% and 14.7% for the groups aged 18-39 years, 40-49 years, 50-59 years and ≥ 60 years, respectively ($p=0.005$). For AIDS-defining illnesses, there was a higher proportion of these complications among older and elderly patients (58.1% and 56.0%, respectively) compared to younger (44.6%; $p<0.001$). There was no significant difference in the proportion of patients with HBV and AIDS-related cancers among the different age groups.

Overall, 27.0% (507 individuals) were current smokers. There was no significant difference on current smoking status by age strata. However, only 9.8% of patients aged ≥ 60 years were current smokers, whereas values for patients aged 18-39 years, 40-49 years and 50-59 years were 27.8%, 27.4% and 28.5%, respectively. A higher proportion of elderly patients had quit smoking ($p<0.001$), and a greater proportion of patients who never smoked was found in the younger (55.3%) and ≥ 60 years (48.8%) age strata ($p< 0.001$).

Among women in different age strata we found no differences in hormone use (either for contraception or replacement therapy). Menopause was observed in 1.0%, 22.7%, 79.2% and 100% of individuals aged 18-39 years, 40-49 years, 50-59 years and ≥ 60 years, respectively ($p<0.001$). Overall, 24.5% of women had undergone menopause.

Discussion

Our results show that there are important variations in several aspects related to HIV infection across the life decades.

Demographic and clinical parameters varied with age in our cohort. Individuals considered elderly (≥ 50 years) comprised 20% of our cohort, which is low when compared to this proportion in cohorts from resource rich countries. In the Swiss cohort, for instance, 26% of individuals were 50-64 years old, and 5% were ≥ 65 years old [7]. We found a men to women HIV infection ratio of 1.7, which is equal to the ratio observed in the overall Brazilian HIV population and in Rio de Janeiro State [5], but lower than cohorts in developed countries [9, 11].

Whites were more prevalent in all age groups. Nevertheless, the difference between whites and non-whites was higher among older and elderly individuals. This is in accordance with the trends of the Brazilian epidemic, if we assume the race as a proxy of social strata [5].

Elderly men (≥ 50 years) reported less MSM exposure as HIV risk category when compared to younger and older men. The same results have been observed in other studies in Spain and the USA [11, 12]. This may be related to the fact that elderly individuals may not be comfortable with reporting MSM sexual practices. It has been reported that men at this age are more prone to having sex with multiple partners or to not using condoms [13], therefore behavioral interventions to promote condom use and other prevention strategies should be evaluated in this population.

Elderly individuals had a longer duration of HIV infection compared with younger patients (10.1 years and 10.9 years for patients aged 50-59 years and ≥ 60 years, respectively). These values were lower than in the Swiss cohort (15.7 years for ages 50-64 years and 18.2 years for ages ≥ 65 years) [7]. Elderly patients (≥ 50 years) in our cohort were infected younger and are aging, whereas new HIV infections in older individuals are rarer, especially among those patients aged ≥ 60 years. These findings suggest that our study population actually is aging with HIV.

Elderly patients had slightly higher median last CD4+ T lymphocyte counts, although this difference was not statistically significant. This finding could be attributed to a survival bias in older patients with higher CD4+ T lymphocyte counts, or could be a merely reflection of HIV viral replication control after HAART introduction [14]. As observed in other cohorts, we found a higher proportion of older and elderly patients who achieved virological responses with HAART when compared with younger patients [7, 11, 15], and this could be attributed to better adherence to ART [16]. In a study conducted in the US, elderly patients were more likely to achieve superior virological responses within 1 year of HAART, but adjustment for adherence attenuated this finding [17]. Unfortunately we don't have structured adherence evaluations for our patient population.

Late presentation in HIV infection is common. Diagnosis is usually done when the immunological system is already compromised and median values of CD4+ T lymphocyte counts are lower than 200 cels/mm^3 [18]. Elderly individuals are frequently diagnosed even later than younger patients [19, 20], and this is reflected in the lower CD4+ T lymphocyte nadir that we observed among elderly patients in our cohort. Other studies in this population have also observed low CD4+ T lymphocyte nadir [21] as well as worse clinical outcomes including a shorter time between HIV identification, AIDS diagnosis, and survival time [15]. This may be related to the lower level of suspicious of the HIV diagnosis among older adults [19].

Because older patients have longer durations of HIV infection, it was expected that this population would be on ART for a longer period of time. According to the Brazilian guidelines, NNRTI based HAART should be preferred as the first-line regimen, and PI regimens as second-line and salvage regimens [22]. This could explain the higher prevalence of younger individuals on NNRTI while among older and elderly patients PI-based regimens were more widely used. This was also observed for the use of new drugs (enfurvitide, raltegravir, etravirine and darunavir), although their overall use is still low among all age groups. This could be attributed to the fact that these new drugs can only be used as salvage regimens according to Brazilian ART guidelines [22].

The prevalence of current smokers in our cohort was higher than for the Brazilian general population (27.0% vs. 15.5%) [23].The prevalence of smoking is usually higher in HIV

patients than in the HIV-negative population. Patients aged ≥ 60 years had the lowest prevalence of current smoking (9.76%), probably due to the fact that many of those older past smokers have already quit smoking. The same profile has been observed in other cohorts from resource rich countries [7, 14].

Consistent with the literature, 74.3% of our patients ≥ 60 years and 61.4% of patients aged 50-59 had at least one comorbidity [24, 25]. In the Brazilian general population, 65.0% of individuals aged 50-64 years and 79.1% aged ≥ 65 years have at least one chronic disease [26]. Results from a recent study conducted in Italy showed that the prevalence of 2 or more comorbidities in HIV patients aged 40 years was similar to a control group of HIV-negative patients aged 55 years, which may be translated as premature aging by 15 years [27].

The prevalence of diabetes mellitus in Brazilians aged ≥ 18 years is 5.2% [2], and the current estimated prevalence in the world population is 4.1% [28]. These rates are greater than the overall diabetes prevalence (1.6%) in our cohort but similar to the rate observed in the elderly group. The prevalence of diabetes mellitus among HIV-infected patients on ART in a cohort from the US (median age of 48 years) has been reported to be more than 4-fold higher than in seronegative control groups [29]. It is important to highlight that our study was mostly comprised by a larger proportion of younger people. Moreover, we have used a strict definition for diabetes in our study, as we only considered as having diabetes those patients who were using specific treatment.

As expected, an association between age and dyslipidemia was observed in our study, with a prevalence of 23% for those patients aged 50-59 years, similar to the observed for patients in use of lipid-lowering agents aged 50-65 years in the Swiss Cohort [7].

Hypertension was detected in 11.9% of all patients in our study, which is similar to the prevalence of hypertension controlled by antihypertensive agents in the Brazilian general population (14.8%) [30]. Comparing the age groups, the prevalence was 30.3% for patients aged ≥ 60 years and 21.6% for patients aged 50-59 years whereas it was 5.6% and 13.2% among those patients aged 18-39 and 40-49, respectively. These data are comparable to a HIV/AIDS cohort from the US [31].

Patients with HIV/AIDS have a higher risk of cardiovascular disease (CVD) in the long-term [8]. In our cohort, there was a higher prevalence of CVD among elderly patients (15,9% and 27,5%, for 50-59 and ≥ 60 years, respectively) compared with younger patients, which is higher than the observed for the Brazilian general population (8.5% and 15.9%, for 50-64 and ≥ 65 years, respectively) [32] and higher than HIV/AIDS cohorts from Spain (13%) [11] and Italy (16%) [27]. It is important to note that the prevalence of tobacco use in our cohort is high, increasing the risk of CVD. Assessment of risk factors followed by targeted interventions for risk reduction are critical steps for CVD prevention in this patient population.

Glomerular filtration rates (GFR) usually decrease with age, and individuals over 60 years have 20-30% lower GFR than those younger than 50 years [33]. The prevalence of GFR < 60 ml/min in our population was 3.9%, higher than observed in the UK CHIC cohort (2.0%) [34]. As expected, there was a significant difference in the proportion of reduced GFR among patients ≥ 60 years (20.8%) and 50-59 years (6.6%) when compared to younger patients (1.5%; $p<0.0001$), consistent with what was observed in other cohorts [9, 11]. Earlier ART initiation, renal toxicity monitoring and appropriate comorbidity management are key measures to preserve a heath renal function among the HIV/AIDS patients who are getting older.

The prevalence of depression in our cohort was higher than the worldwide prevalence (17.5% vs. 4.10%) but lower than that observed in other HIV cohort studies in other countries, which varied from 20% to 79% depending on the population studied, the duration of the study and the parameters used to define depression [35, 36]. This may be related to the fact that we have only considered as having depression those patients who were using antidepressants, and we may therefore have excluded patients with milder clinical presentations. We observed a high proportion of depression among the older and elderly. A similar profile was observed in the Swiss cohort, although in other cohorts the prevalence of depression was higher only among those patients aged ≥ 60 years [37]. The same pattern was observed for the use of anxiolytics (BZD); 18% of our population regularly used one BZD, which is similar to the observed in a cross-sectional survey of 2,932 HIV-infected patients in France (16%) [38] and much higher than the observed for the overall Brazilian population (5.6%) [39]. This highlights the additional burden related to HIV infection and its impact on the quality of life of people living with HIV/AIDS [40].

In various studies, when compared to the general population, elderly patients with HIV/AIDS had a relative risk of 1.3 for all non-AIDS-defining cancers, especially those related to chronic infections (HPV-anal cancer, Epstein Barr-Hodgkin's disease, and hepatitis band C-liver cancer) [41, 42]. Cancer prevalence in our study was higher among patients aged ≥ 60 years compared with patients aged 50-59 years (5.5% vs. 2.3%) but lower than that observed in the literature for elderly (13%) [11]. The most frequently diagnosed cancers in our cohort were skin (37.5%), rectum/anal (18.7%), breast and uterus (9.4% each), lung and stomach (6.2% each), larynx, intestine, prostate and renal (3.1% each). In the USA AIDS population, aproximately 50% of the estimated non-AIDS-defining cancers (n = 9645) were cases of lung cancer, anal cancer, liver cancer, and Hodgkin lymphoma, which are known to occur more frequently among people with HIV [43]. In the Swiss cohort, the most frequent cancers were lung (10.3%), prostate (7.1%), and skin (5.6%) [7]. The fact that Brazil is a tropical country and our Institution is located in a beach town could explain the high proportion of skin cancers, which are probably related to non-protected solar exposure. Anal cancer is one of the most common cancers affecting individuals infected with HIV. In a study involving 13 cohorts from North America, anal cancer rates were substantially higher for HIV-infected MSM, other men, and women compared with HIV-uninfected individuals [44].

Prevalence of erectile dysfunction (ED) among patients ≥ 60 years and patients aged 50-59 years (10.5% and 8.3%) could have been underestimated due to the absence of free ED drugs available at our hospital, patients failing to report ED drug use, or even the lack of information on ED reported by health professionals. However, these results are in agreement with a previous study from São Paulo (Brazil) with general population, where 12.3% of patients aged ≥ 60 years and 6.7% of patients aged 50-59 years reported complete ED [45]. In a MSM cohort in California, it was verified that HIV-positive MSM with advanced disease had significantly increased odds of erectile dysfunction when compared to HIV-negative men while HIV-positive MSM with no evidence of AIDS appeared to have a slightly (but statistically insignificant) increase in odds of ED relative to HIV-negative MSM [46]. These prevalences are higher than those found in our study, probably because they were based on questionnaires responded by the patients, and not on the report of the use of medications targeting ED.

We have observed a high prevalence of menopause among women between the ages of 40-49 years (22.7%), in accordance with data reported by the Women's Interagency HIV Study who found that median age for menopause was 47.7 years-old [47]. In the general population, the median age at menopause is 51 years [48]. HIV-infected women tend to reach menopause younger, with an average age of 46 years [49]. De Pommerol and colleagues observed that average age was 49 years and identified an association with earlier menopause in women with more advanced immunossupression, defined as lymphocyte T CD4+ counts < 200 cells/mm^3 [50].

It is important to highlight that the lifestyle of people living with HIV can be different inside the HIV context itself and also when compared to the general population. Moreover, the impact of the traditional risk factors may also differ both among distinct groups of people living with HIV, as in the general population. These differences may affect the frequency and the outcomes of the different comorbidities. Finally, these differences can be crucial to define better strategies for the prevention, early identification and treatment of the comorbidities.

In summary, we have observed a higher prevalence of Non-AIDS comorbidities, particularly cardiovascular disease, dyslipidemia, renal disease, depression and non-AIDS-defining malignancies among elderly patients. Our data also suggest that menopause may occur earlier among HIV infected women, as observed in other cohorts. Of note, due to the cross sectional design of our study, causal associations cannot be inferred. Moreover, the retrospective nature of the work, and the lack of more detailed information in medical charts/database on some specific aspects of medication use are potential causes of underestimation of some events such as ED and depression.

With the survival increase associated to successful ART, coupled with the higher numbers of new HIV infections among this age group, the burden associated to the diagnostics and treatment of non-AIDS related HIV comorbidities will grow substantially. These results point out the importance of a comprehensive approach in the clinical management of the HIV population, including risk factors reduction and preventive screening procedures. Longitudinal studies on the impact of aging on the HIV/AIDS population are necessary, especially in resource-limited countries.

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Figura 1. Number of comorbidities of HIV/AIDS patients from IPEC/FIOCRUZ cohort, Rio de Janeiro, Brazil, stratified by age in 2008.

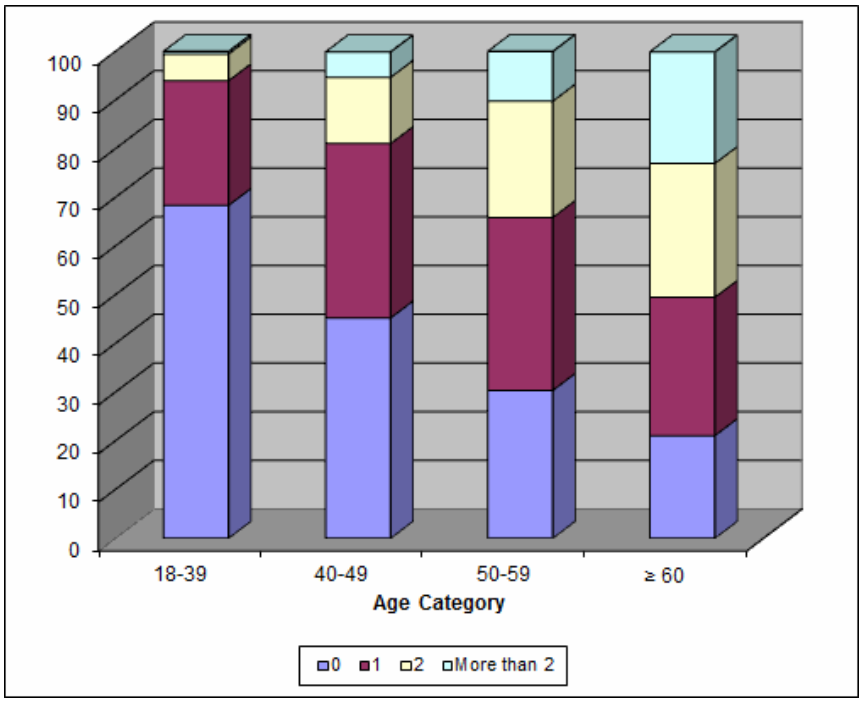

Tabela 1. Demographics, HIV Treatment and Clinical Status of HIV/AIDS patients from IPEC/FIOCRUZ cohort, Rio de Janeiro, Brazil, stratified by age in 2008.

Variable	18-39 (n = 1,023)	40-49 (n = 823)	50-59 (n = 352)	≥ 60 (n = 109)	Total (n=2,307)	p-value
Sex: Men, n (%)	631 (61.7)	542 (65.9)	228 (64.8)	67 (61.5)	1,468 (63.6)	0.335
HIV transmission group: MSM[*1]	331 (60.7)	301 (63.6)	101 (49.3)	33 (53.2)	766 (59.6)	0.021
Race: Non-white	473 (46.4)	334 (40.6)	134 (38.1)	44 (40.4)	985 (42.8)	0.004
Education: < 4 years, n (%)	264 (25.8)	171 (20.8)	93 (26.6)	42 (38.5)	570 (24.7)	0.150
ART clinical trial enrolment, n (%)	447 (44.3)	347 (43.1)	148 (43.1)	35 (33.6)	977 (43.2)	0.129
Age at HIV diagnosis, years mean (SD) median (IQR)	27.3 (5.9) 27.4 (23.7-31.4)	35.9 (6.1) 36.0 (31.5-40.6)	44.2 (6.5) 44.0 (39.4-49.1)	55.1 (7.1) 54.3 (50.4-59.7)	34.3 (9.8) 33.1 (27.3-40.2)	< 0.001
Years HIV-infection mean (SD) median (IQR)	5.2 (4.4) 3.5 (1.9-8.0)	9.1 (5.7) 8.8 (3.8-13.5)	10.1 (5.8) 10.2 (4.9-15.3)	10.9 (5.6) 11.5 (7.1-15.4)	7.6 (5.6) 6.9 (2.6-11.7)	< 0.001
Viral suppression, n (%)	472 (50.4)	458 (61.6)	194 (60.6)	59 (57.3)	1,183 (56.2)	< 0.001
Last CD4 cells/µL mean (SD) median (IQR)	477 (378) 425 (298-605)	491 (299) 437 (299-624)	590 (1372) 464 (287-657)	497 (309) 460(279-690)	501 (620) 436 (294-622)	0.490
Nadir CD4 cells/µL mean (SD) median (IQR)	243 (205) 220 (84-333)	197 (181) 163 (76-298)	191 (168) 160 (61-279)	188 (148) 169 (77-272)	217 (190) 184 (73-302)	< 0.020
ART-naïve, n (%)	251 (24.5)	93 (11.3)	32 (9.1)	5 (4.6)	381 (16.5)	< 0.001
Years on ART mean (SD) median (IQR)	4.6 (4.1) 3.0 (1.1-7.7)	7.4 (4.7) 7.8 (2.7-11.5)	8.5 (4.9) 9.5 (4.2-12.4)	8.8 (5.0) 9.8 (3.9-12.5)	6.5 (4.8) 6.4 (1.8-10.8)	< 0.001
Age at ART start, years, median (IQR)	28.5 (25.0-32.6)	37.2 (33.3-41.7)	45.4 (41.2-49.7)	56.7 (51.8-60.8)	35.4 (29.5-42.4)	< 0.001
Era of starting ART, n (%)						
HAART	599 (78.2)	468 (65.1)	189 (59.2)	55 (53.4)	1,311 (68.7)	< 0.001
Mono/Dual	167 (21.8)	251 (34.9)	130 (40.7)	48 (46.6)	596 (31.2)	
Current HAART Regimen, n (%)						
NNRTI	400 (51.8)	299 (41.0)	122 (38.1)	32 (30.8)	853 (44.3)	
PI	330 (42.7)	374 (51.2)	180 (56.2)	62 (59.6)	946 (49.1)	0.097
Others	42 (5.4)	57 (7.8)	18 (5.6)	10 (9.6)	127 (6.6)	
Use of new ARV, n (%)						
Etravirine	10 (1.0)	28 (3.4)	8 (2.3)	5 (4.6)	51 (2.2)	0.003
Enfurvitide	9 (0.9)	28 (3.4)	14 (4.0)	3 (2.7)	54 (2.3)	0.001
Raltegravir	15 (1.5)	19 (2.3)	10 (2.8)	4 (3.7)	48 (2.1)	0.036
Darunavir	34 (3.3)	75 (9.1)	28 (7.9)	12 (11.0)	149 (6.5)	< 0.001

SD = Standard deviation; IQR = Interquartile range; *1 only men were considered.
Missing data: Race (5); Years of education (3); ART clinical trial enrolment (45); Viral suppression (203); Era of starting ART (19).

Tabela 2. Distribution of Smoking Status, Comorbidities, Polipharmacy and Other Characteristics of HIV/AIDS patients from IPEC/FIOCRUZ cohort, Rio de Janeiro, Brazil, stratified by age in 2008.

Variable	18-39 (n = 1,023)	40-49 (n = 823)	50-59 (n = 352)	≥ 60 (n = 109)	Total (n=2,307)	p-value
Smoking Status, nr. (%)						
Current	226 (27.8)	187 (27.4)	86 (28.5)	8 (9.8)	507 (27.0)	0.067
Quit	137 (16.8)	209 (30.6)	125 (41.4)	33 (40.2)	504 (26.8)	< 0.001
Never	450 (55.3)	285 (41.8)	90 (29.8)	40 (48.8)	865 (46.0)	< 0.001
Comorbidities and Polipharmacy, nr. (%)						
Diabetes mellitus	2 (0.2)	14 (1.7)	15 (4.3)	5 (4.6)	36 (1.6)	< 0.001
Dyslipidemia	49 (4.8)	139 (16.9)	81 (23.0)	32 (29.4)	301 (13.0)	< 0.001
Hypertension	57 (5.6)	109 (13.2)	76 (21.6)	33 (30.3)	275 (11.9)	< 0.001
Cardiovascular diseases	42 (4.1)	73 (8.8)	56 (15.9)	30 (27.5)	201 (8.7)	< 0.001
Estimated Glomerular Filtration Rate (CKD-EPI < 60ml/min)	13 (1.5)	26 (3.6)	20 (6.6)	20 (20.8)	79 (3.9)	< 0.001
Median CKD-EPI, ml/min (IQR)	120.1 (108.7-133.7)	107.8 (95.0-120.2)	100.1 (85.2-111.0)	92.0 (67.5-102.0)	111.3 (97.4-124.5)	< 0.001
Hepatitis B	29 (2.9)	25 (3.1)	9 (2.6)	2 (1.9)	65 (2.9)	0.580
Hepatitis C	26 (2.6)	53(6.6)	42(12.1)	13 (12.1)	134(6.0)	< 0.001
Depression	146 (14.3)	155 (18.8)	82 (23.3)	21 (19.3)	404 (17.5)	< 0.001
Use of Anxyolitics, nr. (%)	154 (15.0)	171 (20.8)	84 (23.9)	16 (14.7)	425(18.4)	0.005
Non-AIDS-defining Cancers	6 (0.6)	15 (1.8)	8 (2.3)	6 (5.5)	35 (1.5)	< 0.001
Erectile Disfunction *[1]	11 (1.8)	32 (5.8)	19 (8.3)	7 (10.4)	69 (4.7)	< 0.001
Use of Female Hormones, nr. (%) *[2]	71 (18.2)	32 (11.5)	18 (14.6)	4 (9.5)	125 (15.0)	0.053
Other Characteristics, nr. (%)						
Menopause, nr. (%) *[2]	4 (1.0)	63 (22.7)	95 (79.2)	42 (100)	204 (24.5)	< 0.001
AIDS-defining Cancers, nr. (%)	21 (2.0)	38 (4.6)	12 (3.4)	3 (2.7)	74 (3.2)	0.115
AIDS-defining illness, nr. (%)	456 (44.6)	478 (58.1)	197 (56.0)	61 (56.0)	1192 (51.7)	< 0.001
Death, nr. (%)	15 (1.5)	13 (1.6)	5 (1.4)	5 (4.6)	38 (1.6%)	0.158

SD = Standard deviation; IQR = Interquartile range
*1 only men were considered; *2 only women were considered
Missing data: Cardiovascular Diseases (8); Estimated Glomerular Filtration Rate (305), Smoking Satatus (427), Hepatitis B (67), Hepatitis C (70).

4 Artigo 3

Título:

Incidence rate of modifying or discontinuing first cART regimen due to toxicity during the first year of treatment stratified by age

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Situação do Manuscrito:

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Abstract

Toxicity is the most frequently reported reason for modifying or discontinuing (MOD) first cART regimens, and it can cause significant morbidity, poor quality of life and also can be an important barrier to adherence, ultimately resulting in treatment failure and viral resistance. Elderly patients with HIV/AIDS (≥50years) may have a different profile in terms of treatment modification due to the higher incidence of comorbidities and polypharmacy. The aim of this study was to describe the incidence of MOD first cART regimen due to toxicity (TOX-MOD) during the first year of treatment at the IPEC-Fiocruz HIV/AIDS cohort, Rio de Janeiro, Brazil, stratified by age. Demographic, clinical and treatment characteristics from antiretroviral-naïve patients who first received cART between Jan/1996-Dec/2010 were collected. Incidence rate and confidence interval of each event were estimated using quasipoisson model. To estimate hazard ratio of TOX-MOD during the first year of cART Cox's proportional hazards regression was applied. 1,558 patients were included; 957(61.4%), 420(27.0%) and 181(11.6%) were aged <40, 40-49 and ≥50years, respectively. 239(15.3%) events that led to any MOD within the first year of treatment were observed; 228(95.4%) of these were TOX-MOD, corresponding to an incidence rate of 16.6/100PY(95%CI:14.6-18.9). The most frequent TOX-MOD during first cART regimen were hematologic (59;26.3%), CNS (47;20.9%), rash (42;19.1%) and GI (38;16.7%). In multivariate analysis, incidence ratio of TOX-MOD during the first year of cART progressively increases with age, albeit not reaching statistical significance. This profile was maintained after adjusting the model by sex, cART regimen and year of cART initiation. These results are important because not only patients are living longer and aging with HIV, but also new diagnoses are occurring among the elderly. Prospective studies are needed to evaluate the safety profile of first line cART on elderly individuals, especially in resource-limited countries, where initial regimens are mostly NNRTI-based.

Key Words

HIV; AIDS; antiretroviral treatment; HAART; cART; toxicity; elderly

Introduction

The introduction of highly active antiretroviral therapy (HAART) during the 1990s was crucial to reduce HIV related morbidity and mortality rates turning HIV infection into a chronic condition. In Brazil, where HAART has been universally available for more than 15 years, prolonged survival has been shown [1,2]. Currently, with more than 220,000 patients receiving combined antiretroviral therapy (cART), Brazil is in a unique position to evaluate treatment outcomes of cART in the context of developing countries.

Several studies from developed and developing countries have investigated the rates and reasons for modification or discontinuation of the first cART regimen, and their results indicate that up to 69% of patients may modify their regimen over time; 25% to 44% of them in the first 12 months of treatment [3-19]. The most frequently reported reason for modifying first cART was treatment-associated toxicity [5-8, 10, 12-13, 17, 19-24] that can cause significant morbidity, poor quality of life and also can be an important barrier to adherence [16, 25], ultimately resulting in treatment failure and viral resistance [26]. We have previously described that, in our cohort, toxicity was the main reason for modifying or discontinuing first HAART regimen [5].

Elderly patients with HIV/AIDS (≥50 years old) may have a different profile in terms of treatment modification due to the higher incidence of comorbidities and polypharmacy [27]. Also, the general characteristics of aging may have considerable influence on the pharmacokinetics of medications. These changes can result in increased antiretroviral (ARV) concentrations, which may lead to a higher risk of related toxicity [28] and increased rates of treatment modifications related to toxicities [29].

This study describes the incidence of modifying or discontinuing (MOD) first cART regimen due to toxicity during the first year of treatment in the IPEC- Fiocruz HIV/AIDS cohort for patients who started cART in five different age groups (18-29, 30-39, 40-49, 50-59, ≥60 years).

Materials and methods

Ethics

IPEC/Fiocruz Ethics Committee (IRB 00004170) has approved this study (060/2010). This is a cohort study with data collected from patients' charts retrospectively. The IRB approved the written consent exemption and the confidentiality agreement.

Description of the clinical cohort and study population

This study was conducted at the Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation (IPEC/FIOCRUZ) where care has been provided to HIV/AIDS patients since 1986. A longitudinal observational clinical database has been maintained on patients receiving HIV care at IPEC. Cohort procedures have been described and results published [30-32]. Briefly, data are updated regularly using outpatient and inpatient clinical documentation and laboratory testing results. Prescription of antiretroviral therapy (drug, dates of use, and dose) is documented by the medical provider and support staff in the clinical records. Trained abstractors record the information onto standardized forms for processing.

For this study, we included data from 1,558 antiretroviral (ART)-naïve patients who first received cART between January 1996 and December 2010, with follow-up through August 2011. The IPEC Institutional Review Board has reviewed and approved the study.

Study definitions

Age at HAART initiation was the variable of interest across all analyses. Patients were stratified as 18-29 years and 30-39 years ("younger"), 40-49 years ("older"); 50-59 years and ≥ 60 years ("elderly"). "Elderly" was defined according to CDC definition for HIV/AIDS

patients [33]. Other variables used to describe our cohort included demographic, clinical and treatment related characteristics.

HIV exposure categories were presented as: heterosexual (women and men separately); men who have sex with men (MSM); injecting drug users (IDU) and others (not specified). Race was grouped as white and non-white. Schooling was stratified in (≤ 4 years; 5-8 years; 9-11 years; > 11 years. Starting cART while participating in an ART naive clinical trial, baseline CD4+ T lymphocyte count (cells/μL), baseline HIV viral load (log_{10}copies/mL) and AIDS-defining disease history were also accessed.

cART was defined as two NRTIs in combination with at least one PI or one NNRTI. Patients were grouped according to the year of cART initiation before and after year 2004, when new, less toxic and friendlier ARV options became available. First cART regimens were defined as PI-based regimen, NNRTI-based regimen and others. PI-based regimen that used ritonavir (RTV) as booster and the most frequent first cART regimens were also accessed.

cART discontinuation due to toxicity during the first year of treatment was defined as treatment interruption caused by any ARV-related toxicity with no documented regimen resumed within 2 months of interruption. cART modification due to toxicity was defined as a toxicity driven substitution of at least one ARV in the regimen. ARV dosage adjustments were not considered as modifications.

For this study, we have only accessed toxicity related to cART modifications or discontinuations (TOX-MOD) that occurred during the first year after treatment initiation. The type and date of TOX-MOD were defined as given in the medical chart, and were grouped as follows: hematologic (anemia, thrombocytopenia, leukopenia, pancytopenia, plaquetopenia), central nervous system (CNS) (neuropsiquiatric manifestation, e.g. alucinations, vertigo, insomnia, nightmares, depression, phobia), peripheral neuropathy (PN), rash, gastrointestinal (GI) (nausea, vomiting, diarrhea), liver (liver enzymes increase, hyperbilirubinemia, jaundice), renal (creatinine clearence decrease, serum creatinine increase, proteinuria, lithiasis, acute renal failure) and metabolic (dyslipidemia and lipodystrophy).

Statistical analysis

Our outcomes of interest were overall toxicity and the most frequent toxicities during the first year after treatment initiation that had led to cART MOD grouped as described above. We estimated the incidence rate and confidence interval (95% CI) of each event stratified by age groups (18-29, 30-39, 40-49, 50-59, ≥60 years) using quasipoisson model and reported it as the number of occurrences per 100 persons-years (PY). Daths and MOD related to other reasons during the first year of ART were censored at the time of their occurrence. Patients who did not MOD their first ART were censored at one year after cART initiation.

Cox's proportional hazards regression was applied to estimate the hazard ratio (HR) of overall TOX-MOD during the first year of cART. The model was also adjusted by toxicity risk factors previously identified (sex, type of regimen and year of treatment initiation) [5]. The proportional hazard assumption was tested by Schoenfeld residuals analysis.

We used the statistical software R, version 2.14.1 (www.r-project.org) for all statistical analyses.

Results

Demographic Data and Treatment Characteristics

Selected demographic values and treatment characteristics distributed according to the decade of life are summarized in Table 1. A total of 1,558 ART naïve patients were included in this analysis. At cART initiation, 957 (61.4%) were younger (< 40 years), 420 (27.0%) were older (40-49 years) and 181 (11.6%) were elderly (≥ 50 years). The median age was 36 years [interquartile range (IQR): 29-43].

Each age category had more male (overall average of 67.2%), and the number of white individuals decreased with age (54.1% for 18-29 years and 30.6% for ≥ 60 years; $p<0.0043$). HIV exposure categories significantly fluctuated over age groups ($p<0.001$). Considering only men, the proportion of MSM was: 48.4%, 39.7%, 41.2%, 19.3% and 18.3% for 18-29 years, 30-39 years, 40-49 years, 50-59 years and ≥60 years, respectively ($p<0.0001$). Elderly patients had less years of education (≤ 4 years) than younger and older patients (14.5% for 18-29 years and 51.4% for ≥ 60 years; $p<0.0001$). There was no statistically significant difference on ART clinical trial participation among the age groups.

At the time of cART initiation, 430 (27.6%) patients had already presented at least one AIDS-defining disease, and the frequency increased with age, except for patients ≥60 years ($p=0.0247$). Baseline CD4+ T lymphocyte count significant decrease with age (248 cells/μL for 18-29 years and 150 cells/μL for ≥ 60 years; $p=0.016$), while there was no significant difference on baseline HIV viral load among the age groups.

The majority of patients started cART after 2004 (overall average 68.2%); as well as the majority of patients started first cART with a NNTRI-based regimen (1,088; 69.8%) and there were no statistically significant differences among age groups neither for the calendar year nor for the regimen. 243 (56.4%) of patients on a PI-based regimen used RTV as booster, and it significantly increased with age (17.0% for 18-29 years and 30.0% for ≥ 60 years; $p<0.0001$).

The most frequent first cART regimens stratified by age are depicted on Table 2. A combination of zidovudine (ZDV) + lamivudine (3TC) + efavirenz (EFV) was used by two fifths of the study population (628, 40.3%). Nevirapine (NVP) was used in 3.8% of cART regimens. Comparing ITRN use along the calendar year, TDF use increased after 2004, while d4T, ddI and ABC use decreased. A continuous increase on ZDV and 3TC use was observed from 1996 to 2010.

TOX-MOD during the first year of ART

Patients were followed for a total of 1,369 person-years (PY), from ART initiation up to one year of treatment or up to any MOD that occurred within the first year of treatment. A total of 239 (15.3%) events that led to any MOD within the first year of treatment were observed; 228 (95.4%) of these were related to toxicity (TOX-MOD), corresponding to an incidence rate of 16.6 per 100 PY (95% CI: 14.6-18.9). The median time from ART initiation to TOX-MOD during the first year of ART was 1.46 months (IQR: 0.5-4.0). The overall probability of TOX-MOD in the first year of ART was 14.6% (228/1,558). Almost half of the patients who presented TOX-MOD were in use of ZDV + 3TC + EFV.

The most frequent toxicity events associated with MOD during first cART regimen were hematologic (59/228; 26.3%), CNS (47/228; 20.9%), rash (42/228; 19.1%) and GI (38/228; 16.7%) (Figure 1). The great majority of the hematologic events were anemia (48, 81.4%), followed by leucopenia (6; 10.3%). For the GI events, the most common were nausea and vomiting (25; 65.8%), gastrointestinal intolerance (7; 18.4%) and diarrhea (4; 10.5%).

Frequency and incidence of TOX-MOD increased with age (Table 3). For younger patients overall frequency of TOX-MOD was 12.0% and 14.4% (18-29 and 30-39 years, respectively) while for older and elderly patients an increase of 2% and 3% per decade of age were observed, respectively. The incidence rate of TOX-MOD for patients aged 18-29 years was 13.4 per 100 PY (95% CI: 10.1-17.6) while for patients aged 50-59 years and ≥60 years was 19.4 per 100 PY (95% CI: 13.0-29.0) and 22.8 per 100 PY (95% CI: 10.9-47.8), respectively. Stratifying by age groups, both frequency and incidence increased with age for

most of toxicities, and this increase is more pronounced from 40-49 years above. In contrast, the incidence rate of TOX-MOD by gastrointestinal events was much higher among patients aged 30-39 years (44.0 per 100 PY (95% CI: 28.4-68.2). Frequency of liver, renal, PN and metabolic toxicities was low in this study.

The results from the multivariate model (Cox's proportional hazards regression) show that the incidence ratio of TOX-MOD during the first year of cART progressively increases with age, albeit not reaching statistical significance. This profile was maintained after adjusting for sex, cART regimen and year of cART initiation: HR 1.18(95% CI: 0.82-1.68) for 30-39 years; HR 1.41(95% CI: 0.97-2.03) for 40-49 years; HR 1.42(95% CI: 0.87-2.30) for 50-59 years; HR 1.61(95% CI: 0.73-3.55) for ≥ 60 years (Table 4). No violation of Schoenfeld proportional hazard assumption was found.

Discussion

Our results provide important insights into the toxicities that led to first line cART MOD during the first year of treatment as a funtion of age at cART initiation among patients followed at a clinical research institute in a middle income country. Roughly 95% of the MOD the first ART regimen were related to toxicity. Hematologic, CNS , rash and GI were the most frequently reported causes of TOX-MOD. These results are important because not only patients are living longer and aging with HIV, but also new diagnoses are occurring among the elderly [34-36].

In a previous assessment on the incidence of MOD of first cART regimen in our cohort, evaluating 670 patients who started cART between 1996 and 2006, toxicities within the first year of treatment were observed in 26.7%, corresponding to an incidence rate of 24 per 100 PY (95% CI: 20.0-28.0), much higher than the observed in this study (14.6%). This difference can be attributed to the larger number of patients in our cohort who started therapy after 2006, when the use of friendlier, less toxic NRTIs and PIs have dramatically increased, when compared to the initial HAART period until 2006. The same profile of TOX-MOD during the first year of treatment was found in the Caribbean, Central and South America Network for HIV Research (CCASAnet) cohort, with adverse events prompting ART regimen change in 14.4% of patients initiating a HAART regimen, among six of the seven participating clinical sites. Similar to what was found in our cohort, in this multicenter Latin America cohort, hematologic events, 70% of which anemia, were the most frequently observed toxicity [6].

Until very recently in 2012, the Brazilian ARV guidelines preferential option for first cART regimen was composed by ZDV + 3TC + EFV [37]. This may explain the toxicity profile observed, with hematologic and GI events as the most commonly reported, probably associated with ZDV, and CNS and rash events, commonly related to EFV.

The high use of LPV/r and ATV/r as second options for first-line regimen can also explain the high frequency of GI toxicities. However, these observations are based on previous studies, as this study focused on the overall incidence of toxicities stratified by age rather than class-related (NRTI, NNRTI, PI) or even ARV-related toxicities. The use of PI with booster

increased with age and no association with calendar year was identified. We saw that at the time of cART initiation, almost 30% of our patient population had already presented at least one AIDS-defining disease, and this frequency increased with age. Furthermore, CD4+ T lymphocyte depletion significantly increased with age. It is well known that clinicians tended to prescribe more PI-based regimens for individuals with more advanced immunosuppression, and this may have had an impact on the ARV prescription pattern in our cohort. It could also be the case that patients and their providers could have feared EFV related CNS toxicity among older individuals, and thus PI-based regimens were more prescribed among these patients.

A high incidence of CNS related toxicities on individuals aged 18-29 years (42.5 per 100PY; 95% CI: 25.6-70.4) when compared to those aged 30-39 years (22.0/100PY; 95% CI: 11.8-40.9) was observed. Although data on the use of recreational drugs was not available for our cohort, the higher reported use of such drugs among young HIV-infected individuals could be contributing to this finding [38]. Further studies on this topic should be encouraged.

Metabolic, liver, renal and PN related toxicities are more common on the long term, and this could explain the low frequency observed up to 1 year of cART, which precluded us to compare the frequency and incidence differences of these events among the age groups.

In the multivariate model adjusted for sex, first cART regimen and calendar year of cART initiation, the hazard ratio for TOX-MOD increased with age, although this effect did not reach statistical significance. The limited number of patients on the elderly group, especially ≥ 60 years, could have influenced these results.

Increased risk of toxicity related to cART among elderly individuals was previously observed [39-41]. However, very limited data comparing TOX-MOD of first cART among different age groups is available, and the few comparisons available [42-44] were done between 2 major age groups only (< 50 years and ≥50 years, elderly). Moreover, no previous analysis neither from Latin America nor from developing countries from other regions was found. In a study from the Italian Cohort Naïve Antiretrovirals (ICoNA) a significantly higher risk of TOX-MOD on elderly was observed, and this difference in the significance may be attributed to the higher number of elderly in comparison with our population (< 50 years,

n=4818; ≥ 50 years, n=399) [42]. In a cohort from France, TOX-MOD of first cART regimens was independently associated with age and occurs at earlier stages of treatment in individuals ≥50 years. Consistent with our findings, a higher frequency of CNS and hematologic events on elderly people was observed [43].

Other authors have also studied the impact of age on TOX-MOD but due to the different methodology and definitions applied, comparisons are difficult. In a study from the UK, MOD for reasons other than virological failure during the first year of cART was higher in those aged < 30 years and ≥ 50 years. Although TOX-MOD was not studied separately, a higher frequency of laboratory abnormalities among the elderly population, specially a decrease in hemoglobin count, could be associated with this finding [44].

Recently published results from the PEARLS study have shown that a regimen composed by tenofovir (TDF) + emtricitabine (FTC) + EFV has shown a better safety profile than ZDV + 3TC + EFV, with less hematologic and CNS related toxicities, and can be a potentially better regimen for the elderly individuals [45].

Elderly individuals are prone to develop other clinical conditions typical of an aging population, and the medications used to treat such comorbidities may interact with ARV drugs leading to a higher incidence of toxicity. As elderly individuals have been shown to be more adherent to therapy [46] toxicities may also be more frequent given the higher cumulative exposure to the drugs.

Our study has limitations. The retrospective nature of the data collection process implies that biases may have influenced our results. Moreover, we did not evaluate the patient's adherence level and have not collected data of toxicities to cART that did not result in MOD.

Prospective studies are needed to evaluate the safety profile of first line cART on elderly individuals, especially in resource-limited countries, where initial regimens are mostly NNRTI based.

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Figure 1. TOX-MOD of first cART within the first year of treatment stratified by age.

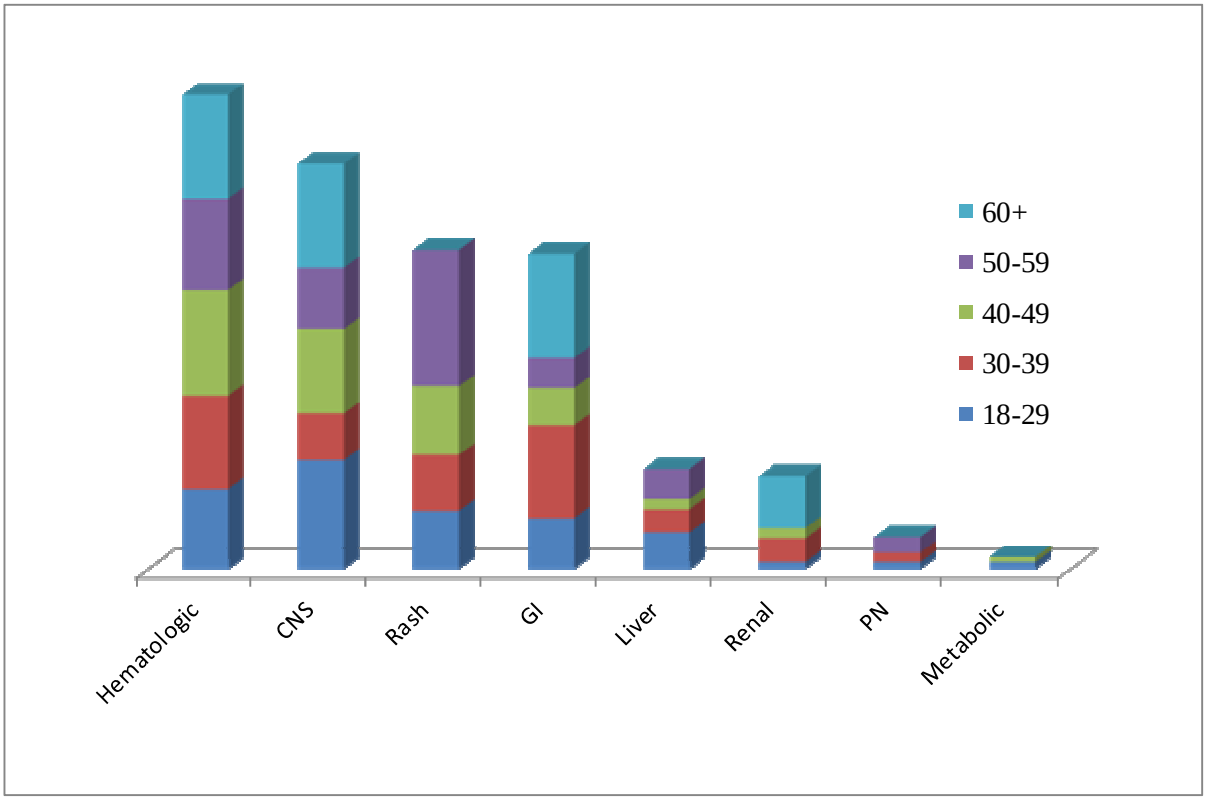

Table 1. Demographics, Clinical and HIV Treatment Characteristics for individuals at IPEC - Fiocruz HIV/AIDS cohort stratified by age at cART initiation.

Variable	Younger		Older	Elderly		Total	p-value
	18-29	30-39	40-49	50-59	≥ 60		
Patients, nr. (%)	417 (26.7)	540 (34.6)	420 (26.9)	145 (9.3)	36 (2.3)	1,558	0.0077
Men (%)	285 (68.3)	358 (66.3)	294 (70.0)	88 (60.7)	22 (61.1)	1,047 (67.2)	0.2545
HIV Exposure Categories, nr. (%)							
Heterosexual (Women)	117 (30.5)	161 (33.1)	104 (28.0)	47 (37.9)	10 (33.3)	439 (28.2)	<0.001
Heterosexual (Men)	72 (18.8)	108 (22.2)	89 (23.9)	45 (36.3)	13 (43.3)	327 (31.2)	
MSM	138 (35.9)	142 (29.2)	121 (32.5)	17 (13.7)	4 (13.3)	422 (40.3)	
IDU	2 (0.5)	3 (0.6)	3 (0.8)	0	0	8 (0.6)	
Others	55 (14.3)	72 (14.8)	55 (14.8)	15 (12.1)	3 (10.0)	200 (14.3)	
Race, nr. (%): White	225 (54.1)	318 (59.1)	243 (58.0)	72 (49.7)	11 (30.6)	869 (55.8)	0.0043
Schooling, nr. (%)							
≤4	60 (14.5)	119 (22.2)	81 (19.4)	46 (31.7)	18 (51.4)	324 (20.8)	< 0.001
5-8	102 (24.6)	164 (30.6)	128 (30.7)	36 (24.8)	4 (11.4)	434 (27.8)	
9-11	184 (44.3)	173 (32.3)	126 (30.2)	38 (26.2)	8 (22.9)	529 (33.9)	
>11	69 (16.6)	80 (14.9)	82 (19.7)	25 (17.2)	5 (14.3)	261 (16.7)	
Baseline CD4+ T lymphocyte count (cells/μL) median (IQR)	248 (137-339)	216 (96-313)	203 (94-320)	206 (116-294)	150 (86-254)	222 (105-322)	0.016
Baseline HIV Viral Load (log_{10}copies/mL) median (IQR)	4.8 (4.2-5.4)	5.0 (4.4-5.5)	5.0 (4.3-5.5)	4.9 (4.4-5.4)	5.1 (4.5-5.7)	5.0 (4.3-5.5)	0.144
History of AIDS-defining disease	94 (23.0)	148 (27.7)	132 (32.3)	48 (33.3)	8 (23.5)	430 (27.6)	0.0247
ART clinical trial participation	146 (35.1)	179 (33.1)	123 (29.5)	41 (28.5)	6 (17.1)	495 (31.8)	0.1016
Year of cART initiation							
> 2004	287 (68.8)	349 (64.6)	293 (69.8)	108 (74.5)	25 (69.4)	1062 (68.2)	0.1724
≤ 2004	130 (31.2)	191 (35.4)	127 (30.2)	37 (25.5)	11 (30.6)	496 (31.8)	
First cART							
NNRTI	289 (69.8)	381 (71.3)	292 (70.5)	105 (72.4)	21 (58.3)	1,088 (69.8)	0.7515
PI	121 (29.2)	145 (27.2)	114 (27.5)	37 (25.5)	14 (38.9)	431 (27.7)	
Others	4 (1.0)	8 (1.5)	8 (1.9)	3 (2.1)	1 (2.8)	24 (1.5)	
PI with booster (RTV)	71 (17.0)	71 (13.1)	72 (17.1)	30 (16.7)	9 (30.0)	243 (15.6)	< 0.001

IQR = Interquartile range

Table 2. Most Frequent First cART regimens at IPEC - Fiocruz HIV/AIDS cohort.

First cART regimens	Younger		Older	Elderly		Total n=1,558
	18-29 n=417 (26.7%)	30-39 n=540 (34.6%)	40-49 n=420 (26.9%)	50-59 n=145 (9.3%)	≥ 60 n=36 (2.3%)	
ZDV + 3TC + EFV	151 (36.1)	218 (40.4)	173 (41.2)	74 (51.0)	12 (33.3)	628 (40.3%)
TDF + 3TC + EFV	50 (12.0)	50 (9.3)	49 (11.7)	10 (6.9)	4 (11.1)	163 (10.5%)
FTC + TDF + EFV	40 (9.6)	50 (9.3)	33 (7.9)	12 (8.3)	0	135 (8.7%)
ZDV + 3TC + LOP/r	15 (3.6)	19 (3.5)	23 (5.5)	5 (3.4)	3 (8.3)	65 (4.2%)
TDF + 3TC + ATV/r	15 (3.6)	14 (2.6)	13 (3.1)	1 (0.7)	1 (2.8)	44 (2.8%)
ZDV + 3TC + NFV	6 (1.4)	21 (3.9)	13(3.1)	1(0.7)	0	41 (2.6%)
d4T + 3TC + EFV	9 (2.1)	18 (3.3)	8 (1.9)	3 (2.1)	3 (8.3)	41 (2.6%)
FTC + ddI + ATV	10 (2.4)	10 (1.8)	10 (2.4)	4 (2.8)	1 (2.8)	35 (2.3%)

3TC=lamivudine; ATV/r=atazanavir/ritonavir; d4T=stavudine; ddI=didanosine; EFV=efavirenz; FTC=emtricitabine; LOP/r=lopinavir/ritonavir; NFV=nelfinavir; TDF=tenofovir; ZDV=zidovudine.

Table 3. Incidence rate of TOX-MOD on first cART regimen at IPEC - Fiocruz HIV/AIDS cohort stratified by age at cART initiation.

MOD	Younger				Older		Elderly				Total n=1,558	
	18-29 years n=417 (26.7%)		30-39 years n=540 (34.6%)		40-49 years n=420 (26.9%)		50-59 years n=145 (9.3%)		≥60 years n=36 (2.3%)			
	n(%)	Rate/100 PY	n(%)	Rate/100 PY	n(%)	Rate/100 PY	n(%)	Rate/100 PY	n(%)	Rate/100 PY	n(%)	Rate/100 PY
Overall Toxicity	50(12.0)	13.4(10.1-17.6)	78(14.4)	16.4(13.2-20.5)	69(16.4)	18.8(14.9-23.9)	24(19.2)	19.4(13.0-29.0)	7(23.3)	22.8(10.9-47.8)	228(14.6)	16.6(14.6-18.9)
Hematologic	11(2.6)	31.1(17.2-56.2)	20(3.7)	44.0(28.4-68.2)	20(4.8)	58.2(37.5-90.1)	6(4.1)	50.6(22.7-112.5)	2(5.6)	66.6(16.7-266.4)	59(3.8)	4.3(3.3-5.6)
CNS	15(3.6)	42.5(25.6-70.4)	10(1.8)	22.0(11.8-40.9)	16(3.8)	46.5(28.5-75.9)	4(2.7)	33.7(12.6-89.8)	2(5.6)	66.6(16.7-266.4)	47(3.0)	3.4(2.6-4.6)
Rash	8(1.9)	22.6(11.3-45.3)	12(2.2)	26.4(15.0-46.5)	13(3.1)	37.8(22.0-65.1)	9(6.2)	75.8(39.4-145.7)	0	0	42(2.7)	3.1(2.3-4.2)
Gastrointestinal	7(1.7)	19.8(9.4-41.6)	20(3.7)	44.0(28.4-68.2)	7(1.7)	20.4(9.7-42.7)	2(1.4)	16.8(4.2-67.4)	2(5.6)	16.8(4.2-67.4)	38(2.4)	2.8(2.0-3.8)
Liver	5(1.2)	14.1(5.9-34.0)	5(0.9)	11.0(4.6-26.4)	2(0.5)	5.8(1.4-23.2)	2(1.4)	16.8(4.2-67.4)	0	0	14(0.9)	1.0(0.6-1.7)
Renal	1(0.2)	2.8(0.4-20.1)	5(0.9)	11.0(4.6-26.4)	2(0.5)	5.8(1.4-23.2)	0	0	1(2.8)	33.3(4.7-236.5)	9(0.6)	0.7(0.3-1.3)
Metabolic	1(0.2)	2.8(0.4-20.1)	0	0	1(0.2)	2.9(0.4-20.6)	0	0	0	0	2(0.1)	0.1(0.04-0.58)
Peripheral Neuropathy	1(0.2)	2.8(0.4-20.1)	2(0.4)	4.4(1.1-17.6)	0	0	1(0.7)	8.4(1.2-59.8)	0	0	4(0.2)	0.3(0.1-0.8)

Table 4. Hazard Ratio (HR) and 95% Confidence Interval (95% CI) estimated by Cox proportional hazards regression of TOX-MOD on first cART at IPEC- Fiocruz HIV/AIDS cohort stratified by age at cART start.

Age Category	Unadjustuded		Adjusting for sex, first cART regimen and year of ART initiation	
	HR (95% CI)	p-value	HR (95% CI)	p-value
18-29 years	1	-	1	-
30-39 years	1.22 (0.86-1.75)	0.26	1.18 (0.82-1.68)	0.36
40-49 years	1.39 (0.96-2.00)	0.07	1.41 (0.97-2.03)	0.06
50-59 years	1.43 (0.88-2.33)	0.14	1.42 (0.87-2.30)	0.16
≥ 60 years	1.66 (0.75-3.67)	0.20	1.61 (0.73-3.55)	0.23

5 CONCLUSÕES

Nos três artigos aqui apresentados, trabalharam-se questões relacionadas ao impacto do envelhecimento na coorte de pacientes vivendo com HIV/AIDS do IPEC/FIOCRUZ. Nossos resultados permitem concluir que:

1- A proporção de pacientes ≥ 50 anos é menor que a de outras coortes de HIV/AIDS no mundo.

2- O aumento da população ≥ 50 anos está mais relacionado ao aumento da sobrevida dos pacientes do que com novos casos de infecção pelo HIV, visto que não houve variação de novos casos nesta faixa etária ao longo do ano-calendário.

3- Homens ≥ 50 anos reportaram menor exposição ao HIV através de sexo com outros homens (HSH), devido provavelmente ao medo do estigma.

4- Não foi verificada diferença estatisticamente significativa na média do número de células CD4 nas faixas etárias estudadas. Este resultado pode ser atribuido ao viés de sobrevida dos pacientes mais velhos com maior CD4 ou ao controle da carga viral com introdução de HAART.

5- O número de pacientes com carga viral indectável aumenta com a idade, devido provavelmente a uma melhor adesão a HAART pelos indivíduos nesta faixa etária.

6- Pacientes ≥ 50 anos apresentaram menor taxa de nadir de CD4, o que reflete em um maior tempo entre a infecção pelo HIV e o seu diagnóstico em comparação com os mais novos. Isso reflete uma menor suspeita da infecção pelo HIV entre os mais velhos tanto pelos pacientes quanto pelos profissionais de saúde.

7- Comorbidades não associadas à AIDS tendem a aumentar com a idade, principalmente doenças cardiovasculares, dislipidemia, doença renal, depressão e neoplasias não relacionadas a AIDS.

8- Menopausa ocorreu precocemente nas mulheres da coorte do IPEC quando comparadas à população geral.

9- A troca ou descontinuação do primeiro esquema antiretroviral por toxicidade no primeiro ano de tratamento tende a aumentar quanto maior a idade no início do tratamento. Contudo, esta diferença não foi estatisticamente significativa.

Poucos trabalhos avaliando o impacto do envelhecimento na população vivendo com HIV/AIDS no Brasil foram encontrados na literatura. Desta forma, os resultados deste trabalho podem ser úteis para um plano nacional de manejo de indivíduos ≥ 50 anos vivendo com HIV/AIDS, tanto para os que estão envelhecendo com a infecção, quanto para os novos casos diagnosticados em pessoas que já estão nesta faixa etária.

Além da importância em âmbito nacional, os dados deste trabalho podem ser úteis para outros países em desenvolvimento, principalmente na América Latina, onde o perfil da população se assemelha ao Brasil, além do esquema antiorretroviral inicial preconizado também ser baseado em inibidores da transcriptase reversa não análogos de nucleosídeos.

6 RECOMENDAÇÕES E DESDOBRAMENTOS

Recomenda-se que manuais e guias específicos para indivíduos ≥ 50 anos vivendo com HIV/AIDS sejam elaborados e para isso os resultados aqui apresentados são de grande valia. Ademais, campanhas para testagem e tratamento nesta população devem ser consideradas.

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ANEXO I

Carta de aprovação do CEP do IPEC/Fiocruz

Ministério da Saúde

FIOCRUZ
Fundação Oswaldo Cruz
Instituto de Pesquisa Clínica Evandro Chagas

I P E C

Comitê de Ética em Pesquisa

PARECER CONSUBSTANCIADO – 060/2010

Protocolo 0059.0.009.000-10

1. Identificação:
Título do Projeto: "HIV e Envelhecimento".
Pesquisador Responsável: Beatriz Grinsztejn.
Doutorando: Thiago Silva Torres.
Instituição Responsável: Instituto de Pesquisa Clínica Evandro Chagas/FIOCRUZ.
Data de Apresentação ao CEP: 28/10/2010.

2. Sumário:
Visa a estudar o impacto do envelhecimento no tratamento antirretroviral numa coorte urbana de pacientes com HIV/AIDS. Tem como objetivos específicos: a) Descrever a coorte de pacientes infectados pelo HIV do IPEC/Fiocruz a partir da distribuição dos pacientes ao longo de cada década de vida (18-29, 30-39, 40-49, 50-59 e ≥ 60 anos); b) Descrever as características clínicas, laboratoriais e a prevalência de comorbidades nessa coorte; c) Descrever a razão de modificação ou interrupção dos esquemas HAART, comparando os pacientes com idade igual ou superior a 50 anos com os pacientes com idade igual ou inferior a 40 anos; d) Analisar a incidência de toxicidades que levaram a interrupção ou troca de esquemas HAART, comparando os pacientes com idade igual ou superior a 50 anos com os pacientes com idade igual ou inferior a 40 anos. Este é um estudo de coorte, retrospectivo, descritivo, realizado num único centro de pesquisa, baseado na revisão do banco de dados e dos prontuários médicos de pacientes com HIV/Aids incluídos na coorte do Instituto de Pesquisa Clínica Evandro Chagas (IPEC/Fiocruz). A população do estudo será composta de pacientes com HIV/AIDS idade ≥ 50 anos acompanhados no ambulatório do IPEC com diagnóstico de infecção pelo HIV que iniciaram terapia antirretroviral potente (HAART) entre janeiro de 1996 e dezembro de 2008. Atualmente encontram-se cadastrados, no IPEC, dados de cerca de 4000 pacientes com HIV/AIDS. Desse total, cerca de 2380 encontram-se em acompanhamento ativo e cerca de 480 tem idade ≥ 50 anos.

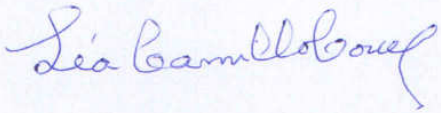
3. Observações Gerais: (Atendendo à Resolução CNS 196/96).
Projeto com delineamento adequado. Em substituição ao Termo de Consentimento Livre e Esclarecido foi elaborado um Termo de Compromisso, no qual o pesquisador responsável assegura que as informações obtidas serão de caráter confidencial e serão utilizadas apenas para fins científicos. Por se tratar de análise de dados secundários, a realização deste projeto não terá custos significativos.

4. Diligências:
Não houve.

5. Parecer: APROVADO.

Data da Reunião: 13 de dezembro de 2010.

Assinatura do Coordenador:



Dr.ª Léa Camillo-Coura
Coordenadora do Comitê
de Ética em Pesquisa
IPEC / FIOCRUZ

ANEXO II

E-mail com confirmação para a publicação do artigo “Aging with HIV: A Practical Review” no periódico “Brazilian Journal of Infectious Diseases.”

De: "Carlos Brites" <crbrites@gmail.com>
Data: 20 de novembro de 2012 22:25:55 BRST

Para: gbeatriz@ipec.fiocruz.br
Assunto: Your Submission

Ms. Ref. No.: BJID-D-12-00448R1

Title: Aging with HIV: A Practical Review
Brazilian Journal of Infectious Diseases

Dear Dr Beatriz Grinsztejn,

I am pleased to inform you that your paper "Aging with HIV: A Practical 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:

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ANEXO III

E-mail com confirmação para a publicação do artigo “Aging with HIV: An Overview of an Urban Cohort in Rio de Janeiro (Brazil) Across Decades of Life” no periódico “Brazilian Journal of Infectious Diseases.”

De: "Carlos Brites" <crbrites@gmail.com>
Data: 23 de outubro de 2012 19:17:50 BRST
Para: gbeatriz@ipec.fiocruz.br
Assunto: Your Submission

Ms. Ref. No.: BJID-D-12-00382R1

Title: Aging with HIV: An Overview of an Urban Cohort in Rio de Janeiro (Brazil) Across Decades of Life
Brazilian Journal of Infectious Diseases

Dear Dr Beatriz Grinsztejn,

I am pleased to inform you that your paper "Aging with HIV: An Overview of an Urban Cohort in Rio de Janeiro (Brazil) Across Decades of Life" 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:

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ANEXO IV

E-mail com confirmação da publicação do artigo “Incidence rate of modifying or discontinuing first cART regimen due to toxicity during the first year of treatment stratified by age” no periódico “PLOS ONE.”

From: PLOS ONE <plosone@plos.org>
Date: 2012/11/7
Subject: Submission Confirmation for Incidence rate of modifying or discontinuing first cART regimen due to toxicity during the first year of treatment stratified by age
To: "Beatriz G. J. Grinsztejn" <beatriz.grinsztejn@gmail.com>

Dear Médica Pesquisadora Grinsztejn,

Your submission entitled "Incidence rate of modifying or discontinuing first cART regimen due to toxicity during the first year of treatment stratified by age" has been received by PLOS ONE. You will be able to check on the progress of your paper by logging on to Editorial Manager as an author. The URL is http://pone.edmgr.com/.

Your manuscript will be given a reference number once an Editor has been assigned.

Thank you for submitting your work to this journal.

Kind regards,

PLOS ONE

ANEXO V

Análise para verificar o pressuposto de proporcionalidade do modelo de Cox, artigo "Incidence rate of modifying or discontinuing first cART regimen due to toxicity during the first year of treatment stratified by age."

Resultado da análise de correlação do resíduo de Schoenfeld com o tempo:

	rho	chisq	p
Idade 30-39	-0.0553	0.685	0.4080
Idade 40-49	0.0438	0.432	0.5108
Idade 50-59	-0.0716	1.146	0.2844
Idade >=60	0.0379	0.322	0.5704
SEXO	0.0633	0.900	0.3429
Classe HAART	-0.1101	2.707	0.0999
Ano de Inicio HAART	0.0544	0.652	0.4195
GLOBAL	NA	9.105	0.2452

Para nenhuma variável ajustada no modelo houve violação do pressuposto de proporcionalidade

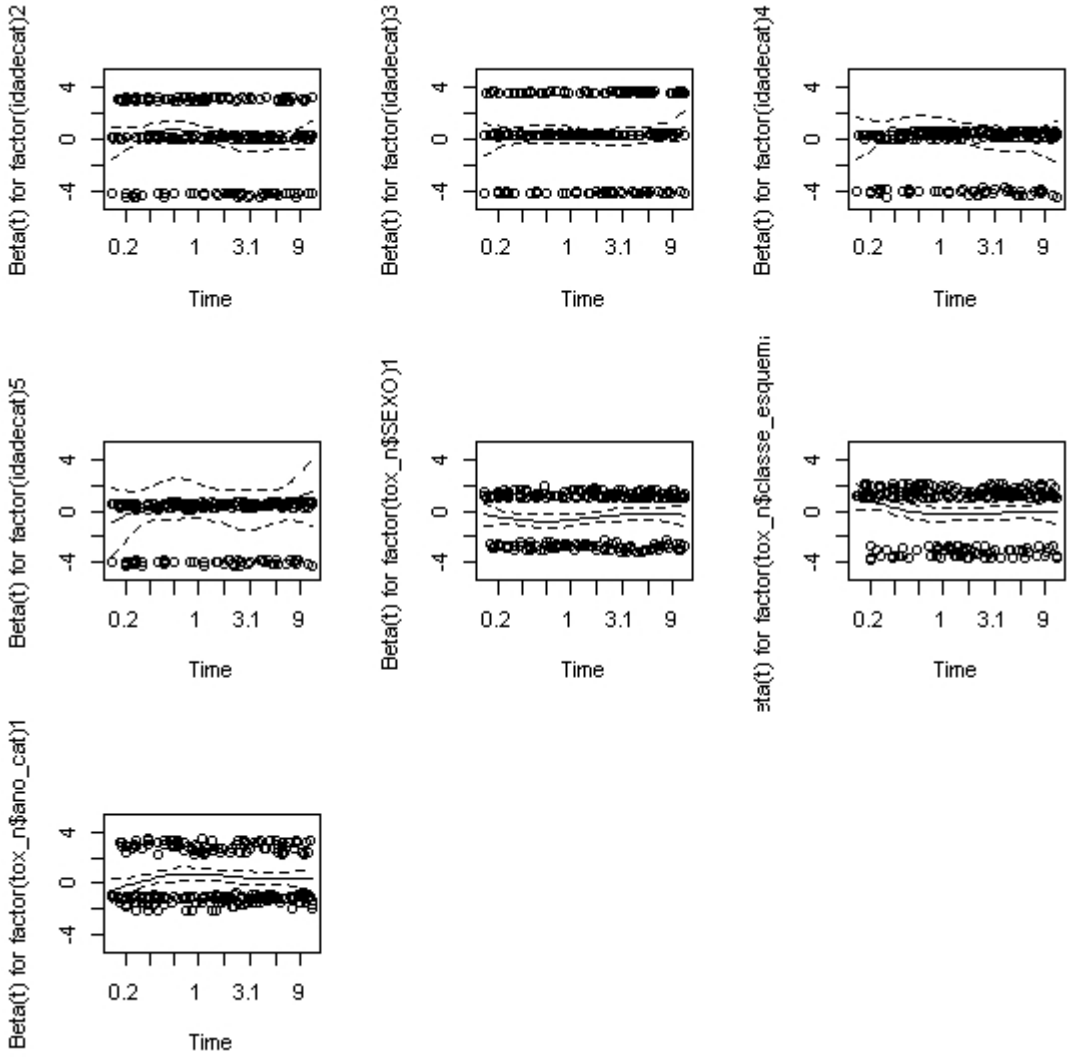

Figura. Resíduos de Schoenfeld das variáveis ajustadas no modelo.