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EFETIVIDADE DOS ESQUEMAS ANTIRRETROVIRAIS DE PRIMEIRA E SEGUNDA LINHA UTILIZADOS NO TRATAMENTO DE PACIENTES COM HIV/AIDS NUMA COORTE URBANA NO RIO DE JANEIRO

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Efetividade dos esquemas antirretrovirais de primeira e segunda linha utilizados no tratamento de Pacientes com HIV/AIDS numa coorte urbana no Rio de Janeiro

SANDRA WAGNER CARDOSO

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: Prof[a] Dr[a] Beatriz Gilda J.Grinsztejn

Prof[a] Dr[a] Paula Mendes Luz

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“O trabalho agradável é o remédio da canseira”

(William Shakespeare)

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RESUMO

Introdução: O Brasil foi o primeiro país em desenvolvimento a implantar um programa de acesso universal ao tratamento antirretroviral (TAR) em larga escala, acarretando aumento da sobrevida da população vivendo com HIV/Aids, diminuição da incidência de infecções oportunistas e diminuição das hospitalizações. Contudo, dados sobre a efetividade dos esquemas terapêuticos de primeira e segunda linhas permanecem escassos em nosso meio. **Objetivo**: Estimar as taxas de efetividade dos esquemas antirretrovirais e fatores associados à resposta ao tratamento e sua durabilidade para TAR de primeira e segunda linhas na coorte de pacientes com HIV/Aids do IPEC-Fiocruz. **Primeiro Artigo:** Foi estimada a efetividade de TAR de primeira linha no IPEC-Fiocruz e os fatores sócio-demográficos, comportamentais, clínicos e estruturais associados à supressão viral foram avaliados. Os pontos de análises incluíram seis, 12 e 24 meses a partir do início do primeiro esquema TAR. Regressão Quasi-Poisson foi utilizada para quantificar os fatores associados com efetividade aos 12 e 24 meses. Entre janeiro de 2000 e junho de 2010, 1.311 pacientes iniciaram TAR de primeira linha, dos quais 987 (75%) utilizaram esquemas baseados em ITRNN. A efetividade foi de 77%, 76% e 68% aos seis, 12 e 24 meses, respectivamente. Fatores associados com supressão viral, definida como ter uma medida de carga viral $\leq$400 cópias/mL sem modificação/interrupção de classe, na análise multivariada em 12 meses foram maior escolaridade, início da TAR no calendário mais recente (2005-2010) e participação em estudo clínico; aos 24 meses nossos resultados sugerem que ser mais velho e usar esquemas baseados em ITRNN são fatores independentemente associados a melhor resposta. **Segundo Artigo**: Foram descritos os desfechos relacionados a TAR de segunda linha no IPEC-Fiocruz, assim como o tempo até a falha e os fatores associados. Análise de Kaplan Meier e teste de log-rank foram utilizados para estimar o tempo até a falha virológica e o modelo proporcional de Cox foi empregado para estimar a incidência de falha de esquemas de segunda linha. Entre janeiro de 2000 e dezembro de 2013, 386 (29,5%) pacientes da coorte iniciaram TAR de segunda linha; 135 (35,0%) estavam com carga viral indetectável e 234 (60,6%) com falha viral documentada ao iniciar segunda linha. A maioria (73%) dos pacientes iniciou segunda linha com esquemas baseados em IP-r. A probabilidade geral de falha aos 12, 24 e 36 meses foi de 26%, 41% e 48%, respectivamente. A incidência de falha de segunda linha entre os indivíduos com carga viral do HIV indetectável e detectável foi 5,7/1000 e 19/1000 pessoas-ano, respectivamente. Idade, grau de escolaridade e tipo de esquema de segunda linha foram independentemente associados com falha do esquema de segunda linha. **Conclusões:** As taxas de supressão viral de TAR de primeira linha em uma grande coorte clínica no Brasil, um país de renda média, com acesso gratuito ao tratamento, atingem patamares semelhantes a países ricos em recursos. No entanto, num tempo mediano menor que dois anos, cerca de um terço dos pacientes trocaram seus esquemas de primeira para segunda linha. Melhorias na atenção clínica básica, uso de esquemas com melhor perfil de toxicidade e um aumento no trabalho de adesão podem melhorar a efetividade destes esquemas e devem ser considerados como próximos passos para o programa de tratamento de HIV no Brasil, com foco especial nos pacientes mais jovens e com menor escolaridade.

Palavras-chave: 1. HIV. 2. AIDS. 3. Tratamento Antirretroviral. 4. Efetividade. 5. Coorte. 6. Rio de Janeiro. 7. Brasil.

Cardoso, SW. Rio de janeiro, 2014. **Effectiveness of first- and second-line antirretroviral therapy 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: Brazil was the first developing country to introduce a free access to antiretroviral therapy (cART) for all in need, leading to an increase in HIV/AIDS population survival and a decrease on the incidence of opportunistics infections and hospitalizations. Nevertheless, studies evaluating effectiveness of first and second line cART are still in scarce in our country**. Objective**: Evaluate first- and second-line cART effectiveness and factors correlated with response to treatment and its durability in HIV/AIDS IPEC-FIOCRUZ cohort. **First Article**: First-line cART effectiveness in IPEC-Fiocruz cohort was estimated and socio-demographic, behavioral, clinical and structural factors associated with virologic suppression were evaluated. Virologic suppression was accessed at 6, 12, and 24 months from cART initiation. Quasi-Poisson regression was used to quantify the association of factors with virologic suppression at 12 and 24 months. From January 2000 through June 2010, 1,311 patients started first-line cART; 987 (75%) patients used NNRTI-based regimens. Virologic suppression were achieved by 77%, 76% and 68% of patients at 6, 12 and 24 months, respectively. In multivariate analysis, factors associated with virologic suppression, defined as having a viral load measurement ≤400 copies/mL without drug class modification and/or discontinuation, at 12 months were higher formal education, starting cART more recently (2005-2010) and clinical trial participation; for the 24-month endpoint, older age and an NNRTI-based regimen were also independently associated with virologic suppression. **Second Article**: Second-line cART outcomes in IPEC-Fiocruz cohort were described, including time to failure as well as factors associated with treatment failure. Kaplan-Meier analyses and the log-rank test were used to assess time to virologic failure on second-line cART and Cox proportional hazards regression models were fit to estimate relative hazards and 95% confidence intervals of time to second cART virologic failure. From January 2000 through December 2013, 386 (29.5%) cohort patients started second-line cART; 135 (35.0%) with undetectable HIV RNA viral load and 234 (60.6%) with documented virologic failure. The majority of patients (73%) started cART with PI/r-based regimen. The overall probability of failure at 12, 24 and 36 months was 26%, 41% and 48% respectively. The incidence of second-line failure was 5.7/1000 person-years and 19/1000 person-years among those who started second line cART with an undetectable and a detectable HIV RNA viral load, respectively. Age, educational level and second-line cART anchor agent were independently associated with the incidence of second-line cART failure. **Conclusions**: Rates of virologic suppression on first-line ART achieved in a clinical cohort in Brazil, a middle-income country with free access to treatment, are similar to those reported in resource-rich settings. Nevertheless, in a median time lower than two years, one third of patients changed first-line cART to a second-line regimen. Primary medical care improve, use of antiretrovirals with the most favorable efficacy and safety profile, and adherence interventions may increase cART effectiveness and must be considered for HIV/Aids Programs in Brazil, especially among young and less educated population.

Keywords: 1. HIV. 2. AIDS. 3. Antiretroviral treatment. 4. Effectiveness. 5. Cohort study. 6. Rio de Janeiro. 7. Brazil.

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LISTA DE ABREVIATURAS

3TC	lamivudina
ACTG	*Aids Clinical Trials Group*
AIDS	(*Acquired Imunnodeficiency Syndrome*) síndrome da imunodeficiência adquirida
AR	antirretroviral(is)
ATV	atazanavir
AZT	zidovudina
cART	*(combination antiretroviral therapy) terapia antirretroviral combinada*
CV	carga viral
d4T	estavudina
ddI	didanosina
DNA	(*deoxyribonucleic acid*) ácido desoxirribonucleico
EFV	efavirenz
EUA	Estados Unidos da América
FTC	entricitabina
Fiocruz	Fundação Oswaldo Cruz
HAART	(*Highly Active Antiretroviral Therapy*) terapia antirretroviral altamente potente
HIV	(*Human Immunedeficiency Virus*) vírus da imunodeficiência humana
HSH/MSM	homens que fazem sexo com homens (*men who have sex with men*)
IC / CI	intervalo de confiança (confidence interval)
IQR	(*interquartile range*) amplitude inter-quartis
IP	inibidor(es) da protease
IP-r	inibidor de protease associado ao ritonavir
IPEC	Instituto de Pesquisa Clínica Evandro Chagas
ITRN	inibidor(es) da transcriptase reversa análogos de nucleosídeos

ITRNN	inibidor(es) da transcriptase reversa não-análogos de nucleosídeos
LPV-r	lopinavir associado ao ritonavir
MSF	*(Médecins Sans Frontières)* Médicos Sem Fronteiras
NVP	nevirapina
OMS/WHO	Organização Mundial de Saúde (*World Health Organization*)
RLS	resource-limited settings
RNA	(*ribonucleic acid*) ácido ribonucleico
RR	risco relativo (*relative risk*)
RTV	ritonavir
SUS	Sistema Único de Saúde
TAR/ART	terapia antirretroviral (*antiretroviral therapy*)
TAM	mutação nos análogos de timidina
TDF	tenofovir
UDI/IDU	usuário(s) de droga(s) injetável(is) (*injection drug users*)
UNAIDS	*Joint United Nations Programme on HIV/AIDS* – Programa Conjunto das Nações Unidas em HIV/AIDS

1 INTRODUÇÃO

Desde o início da epidemia de HIV/Aids, a resposta do Brasil tem sido imediata e inclusiva, focando tanto em ações de prevenção quanto de tratamento. Dentre os países em desenvolvimento, o Brasil continua o único o prover tratamento antirretroviral (TAR) universal e gratuito (Alves, 2012). Entretanto, mesmo após 18 anos de sua implementação, avaliações sobre o Programa Nacional de HIV/Aids ainda são limitadas. Atualmente, o Ministério da Saúde fornece TAR a aproximadamente 300 mil pacientes e este número tende a aumentar significativamente no futuro, visto que novas estratégias para a identificação precoce do HIV e a introdução de TAR precocemente após o diagnóstico tem se mostrado efetivas e seguras (Cohen, 2011; Grinsztejn, 2014).

Nos diferentes países do mundo, a utilização de TAR é norteada por diretrizes terapêuticas que vêm se modificando ao longo do tempo, incorporando novos medicamentos e estratégias de tratamento. Nos últimos anos, estas diretrizes passaram da recomendação de iniciar TAR para os pacientes assintomáticos com contagem de células T+ CD4 menor ou igual a 200células/mm^3 para menor ou igual a 350 células/mm^3. Atualmente a recomendação é de se iniciar com uma contagem de células CD4 menor ou igual a 500 células/mm^3 e orientação de estimular o tratamento para todos independentemente da contagem de CD4 (Brasil, 2013).

No Brasil, esquemas TAR iniciais (primeira linha) são compostos de duas classes de antirretrovirais (AR), geralmente dois inibidores da transcriptase reversa análogos de nucleosídeos (ITRN) associados a um inibidor da transcriptase reversa não-análogo de nucleosídeo (ITRNN) ou a um inibidor da protease (IP).

Embora as taxas de sucesso de TAR sejam elevadas, um tratamento de segunda linha deve ser introduzido em pacientes que apresentam falha virológica. Geralmente o esquema subsequente é baseado em IP potencializado por ritonavir (IP-r). Nos casos em que a TAR de primeira é baseada em IP, o esquema de segunda linha deve consistir em um IP de maior barreira genética associado a dois ITRN idealmente novos. Em situações críticas de perfil de resistência, a associação de um ITRNN ou uma nova classe de AR pode ser necessária (Brasil, 2013).

Os benefícios de TAR na população vivendo com HIV/Aids foram evidenciados pelo aumento da sobrevida (Guerreiro, 2002, Brasil, 2003; Marins, 2003; Campos, 2005; Grinsztejn, 2007), pela diminuição da incidência de infecções oportunistas e pela diminuição das hospitalizações (Brasil, 2003; Brigido, 2004). Contudo, interações medicamentosas, toxicidades relacionadas aos AR e falha viral precoce provocada pela resistência continuam como grandes entraves para o sucesso terapêutico.

A eficácia de TAR é invariavelmente avaliada em ensaios clínicos randomizados de curta duração em populações selecionadas. Estes estudos frequentemente excluem participantes com doenças oportunistas, histórico de uso abusivo de substâncias e comorbidades psiquiátricas (Fletcher, 2007). Assim, seus resultados não podem ser generalizados para os desfechos de longo prazo e para todos os indivíduos tratados. Indicadores de desfechos clínicos na população geral são importantes para guiar decisões bem como para medir a qualidade dos serviços de saúde fornecidos aos pacientes vivendo com HIV (Samaranayake, 2010).

Dados sobre a efetividade de TAR de primeira e segunda linhas permanecem escassos no Brasil. Conhecer, no contexto de coortes clínicas, as taxas de supressão viral, o ganho imunológico (aumento de células T+CD4), a influência da escolha de TAR inicial nos esquemas subsequentes e o perfil de resistência após falha terapêutica é fundamental para adequadas estratégias de tratamento.

Neste trabalho, as taxas de efetividade dos esquemas antirretrovirais de primeira e segunda linhas, além dos fatores associados à resposta ao tratamento e sua durabilidade foram avaliados na coorte de pacientes com HIV/Aids do Instituto de Pesquisa Clínica Evandro Chagas, Fundação Oswaldo Cruz (IPEC/Fiocruz).

Os resultados deste estudo poderão contribuir para o estabelecimento de condutas terapêuticas que permitam minimizar ou evitar a ocorrência de falha terapêutica, bem como para o melhor planejamento do cuidado para o paciente com infecção pelo HIV, da aquisição e distribuição de medicamentos e da previsão de necessidade de esquemas de terceira linha no país.

2 REVISÃO DA LITERATURA

2.1 Efetividade dos Esquemas Antirretrovirais de Primeira Linha

Muitos estudos avaliando a efetividade de TAR de primeira linha foram realizados na primeira década após a disponibilização da terapia antirretroviral altamente potente (HAART), a grande maioria avaliando coortes de países desenvolvidos onde o acesso ao tratamento era facilitado. Alguns estudos avaliaram pacientes em uso de HAART com IP e incluíram tanto pacientes virgens de TAR quanto pacientes previamente expostos a ITRN, sendo frequente a associação entre a resposta ao tratamento (definida como atingir carga viral indetectável) e o estágio clínico inicial. Uma menor chance de resposta para pacientes com doença mais avançada foi evidenciada, sendo que quanto mais avançada a imunodeficiência e mais elevada a carga viral do HIV no início do tratamento, menor a chance de resposta. (Mocroft, 1998; Ledergerber, 1999; Wit, 1999; Mocroft, 2000; Palella, 2002; Palella, 2003).

Taxas de resposta terapêutica em torno de 50% foram encontradas por Mocroft e colaboradores (1998) (Canadá), entre pacientes virgens e não-virgens de tratamento, após 24 semanas do início de HAART. Entretanto, 15,5% desses pacientes voltavam a apresentar carga viral detectável seis meses após ter atingido carga viral indetectável pela primeira vez (falha viral). O risco de essa falha ocorrer foi menor entre aqueles que iniciaram TAR com níveis mais elevados de CD4 (RR, 0,73; IC 95%, 0,53 a 1,00; p=0,049) (Mocroft, 1998).

Na coorte suíça, 2.410 participantes com pelo menos quinze meses de acompanhamento após início de primeiro esquema HAART foram avaliados e a taxa global de pacientes com carga viral indetectável foi mais alta, 81,2% (Lampe, 2006), sendo próxima das taxas encontradas em ensaios clínicos (Ledergerber, 1999).

Mocroft e colaboradores (2000), avaliando pacientes ingleses iniciando o primeiro esquema HAART, encontraram, aos seis meses, 65% dos pacientes com carga viral indetectável e ganho de CD4 em torno de 50 células/mm^3 (Mocroft, 2000). Kitchen e colaboradores (2001) encontraram entre pacientes dos EUA que receberam pelo menos 115 semanas (aproximadamente 28 meses) de HAART taxa de supressão viral global de 69% (Kitchen, 2001).

Os poucos dados nacionais em relação à efetividade de TAR também datam, em sua maioria, da primeira década de disponibilização de HAART. Hofer e colaboradores (2004), avaliando pacientes em acompanhamento nos Centros Municipais de Saúde do Rio de janeiro e no Hospital-Escola São Francisco de Assis (HESFA-UFRJ), encontraram 53% de taxa de resposta completa (definida como redução de pelo menos 1 $\log_{10}$ na carga viral inicial associada a aumento de mais de 50 células/mm^3 na contagem de células T+ CD4 entre 6 e 12 meses) (Hofer, 2004).

Em estudo conduzido por Brigido e colaboradores (2004) numa coorte da Universidade de São Paulo composta por 148 pacientes foi evidenciado que, apesar da melhor resposta imunológica observada no grupo de pacientes com supressão viral (CV <500 cópias/mL nas duas últimas avaliações), aqueles com supressão apenas parcial (por ex. carga viral detectável, >500 cópias/mL, mas com supressão >1 $\log_{10}$ em pelo menos duas determinações e pelo menos 1 $\log_{10}$ abaixo do nível prévio) tiveram ganho significativo de células T+ CD4 ($p<0,013$) e diminuição do número de eventos definidores de AIDS ($p<0,001$) comparados aos que mantinham carga viral no mesmo patamar da inicial num período mediano de 5 anos. Os pacientes deste estudo receberam diferentes esquemas antirretrovirais e a maioria deles utilizou monoterapia e/ou terapia dupla antes de iniciar HAART (Brigido, 2004).

Tuboi e colaboradores (2005), em um estudo conduzido em Porto Alegre, avaliaram pacientes virgens de terapia e 72% apresentaram carga viral indetectável num intervalo de três a nove meses após iniciarem HAART. Para aqueles que iniciaram a terapia a partir de 1999, a não-adesão (auto-referida) a TAR mostrou-se um fator independentemente associado à falha viral (*odds ratio* 8,78, p=0,02), assim como escolaridade menor que cinco anos (*odds ratio* 6,05, p=0,05). De modo semelhante a Hofer e colaboradores (2004) os autores concluíram que as taxas de resposta viral entre pacientes atendidos em serviços públicos no Brasil eram comparáveis às dos países desenvolvidos (Tuboi, 2005). Grinsztejn e colaboradores (2007), em estudo que compara a resposta clínica à HAART em coortes do Rio de Janeiro (Brasil) e Baltimore (EUA), encontraram desfechos semelhantes (Grinsztejn, 2007).

Estudos longitudinais iniciais do uso clínico de HAART apontam para taxas de supressão viral aquém do ideal. No entanto, evidencia-se uma mudança evolutiva ao longo do tempo (Moore, 2005). Na coorte de Baltimore (EUA), Moore e colaboradores (2005), avaliando a taxa de supressão viral (CV < 400 cópias/mL) em dois períodos de tempo

diferentes, detectaram supressão que variou de 43% (1996) a 72,4% (2001-2002) aos seis meses de tratamento e de 60,1% (1996) a 79,9% (2001-2002) aos doze meses de tratamento. Estas diferenças se mostraram estatisticamente significativas em ambos os casos. Houve também melhora da resposta de células T+CD4 nos dois períodos avaliados. Entre 1996 e 2001-2002 observou-se um aumento importante do uso de ITRNN ou de IP com reforço farmacológico (*booster*) comparado ao uso de IP não potencializado. (Moore, 2005).

Lampe e colaboradores (2006), compilando dados retrospectivos da Europa e Canadá referentes ao risco de falha a partir do primeiro esquema terapêutico, encontraram falha viral mais frequentemente entre os pacientes usando IP sem reforço farmacológico de ritonavir (RTV), comparados àqueles utilizando esquemas contendo efavirenz (EFV) ou IP com reforço de RTV. No período de sete anos, o risco de falha viral inicial caiu pelo menos à metade, possivelmente devido à maior experiência clínica com os antirretrovirais e sua maior efetividade (Lampe, 2006).

Bartlett e colaboradores (2006) numa revisão sistemática sobre a eficácia da HAART, identificaram uma taxa de resposta superior para os esquemas contendo ITRNN ou IP reforçados com RTV quando comparados aos esquemas terapêuticos utilizando IP simples. Os estudos selecionados incluíram 13.147 pacientes em 85 braços independentes de tratamento. Após 48 semanas, 57% dos pacientes atingiram carga viral menor que 50 cópias/mL, contrastando com 47% encontrados em metanálise realizada anteriormente (Bartlett, 2001), sugerindo que esquemas mais efetivos foram disponibilizados desde então.

No Brasil, May e colaboradores (2007) encontraram desfechos menos favoráveis para aqueles que iniciaram HAART antes do ano 2000 (duas vezes mais chance de falha do tratamento) comparados aos que iniciaram mais recentemente. Isso foi atribuído à introdução do EFV e dos IP com o reforço farmacológico de RTV, e seu maior uso ao longo do tempo (May, 2007).

May e colaboradores (2007) avaliaram dados da colaboração entre grupo de coortes da Europa e América do Norte - ART-CC (*ARV Therapy Cohort Collaboration*) com redes regionais na África, América Latina e Ásia, envolvendo 42 países, totalizando 33.008 pacientes. Em todas as áreas, exceto no leste europeu, a combinação de primeira linha mais frequentemente prescrita incluiu dois ITRN com um ITRNN, utilizada para tratar 90% dos pacientes virgens de TAR. Entretanto, o número de primeiros esquemas possíveis variou de

59 na América do Norte, 47 na Europa e três na África e Ásia. As taxas de respostas foram similares entre as coortes, assim como as taxas de falha. As taxas de efetividade encontradas (carga viral < 400 cópias/mL aos seis meses de TAR) foram de 76% numa análise por intenção de continuar o tratamento (May, 2007).

Em um estudo conduzido no interior da África do Sul, Barth e colaboradores (2008) observaram efetividade após 12 meses de TAR de primeira linha em 55% dos indivíduos (Barth, 2008).

Em estudo prévio na coorte do IPEC/Fiocruz avaliando a incidência de modificações/interrupções do primeiro HAART, a principal razão encontrada para modificação/interrupção foi toxicidade aos AR. Entretanto, a falha terapêutica foi descrita como razão para troca em 19,6% (91/670) dos pacientes que iniciaram tratamento entre janeiro de 1996 e dezembro de 2006,correspondendo a uma taxa de incidência de 5,6 por 100 pessoas/ano (IC 95%: 4,5-7,0). O tempo médio de seguimento para troca por falha foi de 23,8 (IQR:13,5-36,1) meses. Nos modelos multivariados, um risco maior de modificação por falha foi observado entre aqueles que começaram HAART antes do ano 2000 e tinham contagem de linfócitos T+ CD4 menor do que 200 células/mm^3, enquanto que um menor risco foi observado entre os pacientes que iniciaram HAART como parte de um ensaio clínico e que utilizaram esquemas baseados em ITRNN (Cardoso, 2010).

Tendo em vista os estudos descritos anteriormente, pode-se afirmar que as taxas de resposta ao primeiro esquema de TAR são muito variáveis, especialmente em estudos de coorte. As taxas de sucesso em estudos realizados tanto em áreas ricas em recursos como áreas de recursos médios ou limitados podem variar de 45% até mais de 85%. Estas diferenças podem ser explicadas pelas diferentes definições de efetividade bem como pelo modo como a ausência de dados (*missing data*) e as perdas de seguimento são tratadas na análise. Observa-se, entretanto, alguma tendência a maiores percentuais de sucesso nos estudos mais recentes em comparação aos percentuais de sucesso encontrados nas décadas iniciais de HAART. Isso parece ter ocorrido na maioria dos casos, tanto em coortes como em ensaios clínicos, o que pode ser explicado pelo fato de os esquemas mais recentes serem mais toleráveis e potentes, menos exigentes em termos de restrição alimentar, além de exigirem um número consideravelmente menor de pílulas e da possibilidade de dose única diária (Mocroft, 2000; Ivers, 2005; Bartlett, 2006; Lampe, 2006; Fletcher, 2007; May, 2007; Barth, 2008;

Elliott, 2008; Fielding, 2008; Perez-Elias, 2009; Marconi, 2010; Samaranayake, 2010; Mugavero, 2011; Elzi, 2012; Fox, 2012; May, 2012; Taniguchi, 2013).

Diversos estudos verificaram que o primeiro esquema de TAR é o que tem maior chance de obter resposta viral supressiva sustentada (Ledergerber, 1999; Bini, 2000; Chen, 2003; O'Brien, 2003; Palella, 2003).

Palella e colaboradores (2002) avaliaram dados da coorte observacional, prospectiva, do estudo HOPS (*The HIV Outpatient Study*), envolvendo oito clínicas de atendimento nos EUA desde 1994. Os pacientes receberam em média 1,8 esquema de tratamento e o tempo mediano de permanência no primeiro esquema HAART foi de 11,8 meses, no segundo esquema de 7,4 meses e no terceiro, 7,2 meses. O primeiro esquema HAART apresentou maior chance de durabilidade (49%) quando comparado ao segundo (29,6%, p=0,013) ou ao terceiro ou mais esquemas (14,9%, p<0,0001) (Palella Jr, 2002).

Pesquisadores da coorte suíça acompanharam 1.402 pacientes e observaram que a chance de atingir carga viral indetectável após a primeira modificação de tratamento foi significativamente menor quando comparada à resposta ao esquema inicial. Aos 30 meses de acompanhamento, somente 40,0% dos pacientes virgens de terapia estavam com o mesmo esquema HAART inicial e mantinham carga viral indetectável (Ledergerber, 1999).

Nos EUA, Chen e colaboradores (2003) verificaram que a duração mediana de TAR de primeira linha foi de 1,6 ano, enquanto que a dos esquemas subsequentes foi consideravelmente mais curta (Chen, 2003).

No Reino Unido, em seis anos de tratamento, mais de 80% dos pacientes iniciaram um novo AR e cerca de um quarto iniciou uma nova classe (Phillips, 2005; Sabin, 2005).

2.2 Efetividade dos Esquemas Antirretrovirais de Segunda Linha

Estudos avaliando a efetividade de TAR de segunda linha vêm aumentando recentemente (Fox, 2010; Pujades-Rodriguez, 2010; Siripassorn, 2010; Kumarasamy, 2011; Win, 2011; Waters, 2012; Napravnik, 2013). Com a ampliação dos Programas Nacionais de HIV/Aids nos países em desenvolvimento, hoje um maior número de pacientes necessitam de

TAR de segunda linha. Atualmente, esquemas contendo IP são recomendados como opção após a falha de primeira linha nos guias de tratamento da maioria destes países (WHO, 2013).

Questões sobre o desenvolvimento de resistência ao primeiro esquema TAR têm preocupado tanto países em desenvolvimento (Boyd, 2007; Galarraga, 2007; Gallant, 2007; Sungkanuparph, 2007), como os desenvolvidos (Napravnik, 2013), devido ao monitoramento ineficaz da carga viral. A continuação de um esquema falhado está associada a um perfil complexo de mutações de resistência, como observado em diversos estudos (Hosseinipour, 2009; Orrell, 2009; Wallis, 2010).

Apenas 5% da TAR em países em desenvolvimento correspondem a tratamentos de segunda linha (WHO, 2013). Na América Latina e na região do Caribe, a porcentagem de indivíduos em uso de segunda linha é maior (27% dos pacientes, com uma taxa que varia de 4 a 43%) (PHO, 2013). Isto se deve em parte às características da região das Américas, onde os Programas Nacionais de HIV/Aids foram implementados ha mais tempo, com muitos pacientes iniciando TAR antes de 2000, assim como um acesso a mais opções de AR.

Nos estudos recentemente realizados nos países em desenvolvimento, verificou-se que a taxa de falha viral ao TAR de segunda linha é alta, estando associada à exposição prévia aos ARV e à baixa adesão (Egger, 2009; Pujades-Rodriguez, 2010; Ajose, 2012). Como o acesso a TAR de terceira linha ainda é muito restrito em diversos países, a identificação de resistência aos ARV torna-se crucial para muitos pacientes. Além disso, na maioria destes estudos os esquemas de primeira linha são quase que invariavelmente baseados em ITRNN e a segunda linha se restringe às combinações de ITRN reciclados com lopinavir/ritonavir (LPV-r) (Pujades-Rodriguez, 2010).

Ajose e colaboradores (2012) realizaram uma revisão sistemática com 19 estudos avaliando esquemas de segunda linha em Botswana, África do Sul, Malawi, Uganda, Tanzânia, Camboja, Tailândia e China. De um total de 2.035 pacientes, a proporção acumulada de adultos apresentando falha viral à segunda linha foi de 21,8%, 23,1%, 26,7% e 38,0% após 6, 12, 24 e 36 meses de TAR respectivamente (Ajose, 2012).

Egger e colaboradores (2009) avaliaram as trocas de esquemas de primeira linha baseados em ITRNN para esquemas de segunda linha baseados em IP em 17 programas de HIV/Aids na África, América Latina e Ásia. Havia monitoramento da imunodeficiência

através da avaliação da linfometria CD4 em todos os países e dez destes também dispunham de monitoramento de carga viral. Entre os 576 pacientes (2,9%) que modificaram para TAR de segunda linha, o tempo mediano para a troca foi de 16,3 meses (IQR 10,1–26,6 meses) nos programas com monitoramento de carga viral e 21,8 meses (IQR 14,0–21,8 meses) naqueles sem monitoramento ($p<0,001$). Também foi observada diferença significativa na mediana de contagem de CD4 entre os dois grupos ($p<0,001$). Os autores concluíram que o início de TAR de segunda linha tende a ocorrer mais precocemente e com taxas mais altas de CD4 nos países em desenvolvimento com acesso a carga viral (Egger, 2009).

Pujades-Rodriguez e colaboradores (2010) avaliaram a sobrevida de TAR de segunda linha em 27 programas financiados pelos Médicos Sem Fronteiras (MSF), em 13 países, totalizando 632 pacientes. A maioria dos pacientes iniciou TAR de segunda linha com LPV/r (71,8%) e 79,3% modificaram dois ITRN. Após 1 e 2 anos de acompanhamento, 12% e 28% dos pacientes, respectivamente, tiveram algum tipo de falha; 2% e 8% apresentaram falha imunológica e virológica, respectivamente. Ademais, 119 pacientes (18,8%) falharam após um tempo mediano de 11,9 meses (IQR 8,7-17,0 meses) e a taxa de morte 30 meses após o início de segundo esquema TAR foi de 44,2% (95%Cl 30,5-64,0) (Pujades-Rodriguez, 2010).

Em uma coorte da Tailândia (2010), 95 pacientes com falha virológica ao primeiro esquema TAR foram acompanhados. Após 6, 12, 24 e 36 meses de segundo esquema TAR, 67%, 62%, 84% e 90% dos pacientes atingiram carga viral indetectável (HIV-1 RNA< 50 cópias/mL), respectivamente (Win, 2011).

Em um estudo transversal na Índia (2012), 107 pacientes que falharam o primeiro esquema TAR e que receberam IP-r como segunda linha por 6 meses foram avaliados entre 2008 e 2009. Setenta e sete (72%) apresentavam carga viral detectável, com mediana de 5.450 cópias/mL (IQR 169-1997), além de 73% apresentarem pelo menos uma mutação para a classe IP (Saravanan, 2012).

Em um estudo de coorte da África do Sul (2012), 1.668 pacientes que iniciaram e falharam o primeiro esquema TAR entre 2003 e 2008 foram incluídos. Após 12 meses, a incidência acumulada de troca de esquema, ressupressão viral e morte foram de 16,9%, 13,2% e 4,6%, respectivamente. Em um modelo ajustado, observou-se que a troca foi mais frequente na terceira visita ou na subsequente após a falha, em visitas ocorrendo em 2008 vs. 2003-2007 e em pacientes com alta carga viral e baixa contagem de células T+ CD4 (Johnston, 2012).

Em outro estudo conduzido na África do Sul (2012) foram identificados retrospectivamente 43/322 pacientes que falharam no segundo esquema TAR com IP, sendo o tempo mediano do início do segundo esquema TAR até a falha virológica de 10 meses. Verificou-se também que 67% destes indivíduos apresentavam vírus selvagem e nestes casos intervenções para melhorar a adesão poderiam aumentar o tempo de tratamento de segundo esquema (Levison, 2012).

Sigaloff e colaboradores (2012) avaliaram 243 pacientes que trocaram para segundo esquema TAR com IP/r após falha virológica entre 2007 e 2009 em 13 centros de pesquisa na África. Um total de 13,9% de falhas de segundo esquema TAR foi observado após 12 meses de acompanhamento. No modelo multivariado, risco de falha virológica foi aumentado para pacientes com adesão menor que 95% em 30 dias de e reduzido para aqueles com maior idade (Sigaloff, 2012).

Em coortes de países desenvolvidos, dados sobre efetividade de esquemas de segunda linha são escassos. Napravnik e colaboradores avaliaram desfechos de segunda linha num estudo de coorte multicêntrico nos EUA entre pacientes que iniciaram primeira linha e na sequência segunda linha de TAR entre 1996 e 2010. A taxa de falha viral entre os pacientes que iniciaram esquema de segunda linha com carga viral detectável (> 400 cópias/mL) foi de 17% aos seis meses de seu início. Uma baixa contagem de células CD4+ ao iniciar TAR de segunda linha foi associada a maior risco de falha viral. As taxas de falha foram menores no calendário mais recente (2008 a 2010, comparado com 1996 a 1998) e a a classe de AR na qual o esquema foi baseado não se mostrou independentemente associada ao desfecho (Napravnik, 2013).

Em um estudo realizado na coorte CHIC do Reino Unido (2012) foram avaliados 470 pacientes que iniciaram primeiro esquema TAR com ITRNN e modificaram para um esquema baseado em IP/r. Foi observada falha de segundo esquema em 10,9% e 13% dos indivíduos após 48 e 96 semanas, respectivamente. Na análise multivariada, ser heterossexual e apresentar carga viral detectável foram considerados independentemente associados à falha virológica, enquanto que um alto valor de células T CD4+ foi protetor (Waters, 2012).

Poucos estudos referentes à TAR de segunda linha no Brasil foram encontrados na literatura, nenhum deles avaliando efetividade. Lorenzana e colaboradores (2012) realizaram uma análise simulando custo-efetividade para implementação do uso da genotipagem como

ferramenta de escolha do esquema terapêutico em ensaio clínico de terceira linha planejado para áreas de recursos limitados (Lorenzana, 2012). Pinheiro e colaboradores avaliam o custo dos AR, incluindo de medicamentos genéricos (Pinheiro Edos, 2008). Schechter e colaboradores (2007) realizaram um estudo de estratégia do uso de monoterapia com LPV como segundo esquema (Schechter, 2007).

2.3 Resistência aos antirretrovirais

O uso inadequado dos antirretrovirais permite que a replicação viral ocorra na presença de níveis séricos dos medicamentos aquém do ideal, favorecendo a seleção de vírus resistente. Inúmeros fatores estão envolvidos no desenvolvimento de falha terapêutica, incluindo falta de potência da combinação utilizada, má adesão à TAR e aquisição da infecção com transmissão de vírus resistentes, resultando em uma supressão incompleta da replicação viral (Cane, 2005).

Uma das consequências mais expressivas da falha viral é a seleção de cepas virais contendo mutações associadas à resistência aos medicamentos em uso. Estudos observacionais demonstraram que a manutenção de esquemas em falha estava associada ao acúmulo de mutações e desenvolvimento de resistência a classes inteiras de AR. Como resultado de todo este processo, a falha virológica foi significativamente associada ao desenvolvimento de condições oportunistas e ao óbito (Hatano, 2006).

Considerados atualmente padrão ouro no cuidado dos pacientes com infecção pelo HIV que apresentam falha terapêutica no que concerne a guiar a escolha do esquema subsequente, os testes de resistência vem sendo utilizados na condução, interpretação e estratificação dos resultados dos principais estudos envolvendo novas drogas.

O vírus HIV-1 apresenta uma grande diversidade genética à custa de erros introduzidos durante a síntese do DNA viral a partir do RNA. Ele pode ser classificado em três grupos (M,N e O), sendo o grupo M classificado em nove subtipos (A, B, C, D, F, G, H, J e K) e 43 formas recombinantes (CRFs), estas mais prevalentes na Ásia e África. Os subtipos A e F podem se subdividir em quatro e dois sub-subtipos respectivamente: A1, A2, A3, A4, F1 e F2 (Robertson, 2000).

Nos últimos anos muitos estudos foram publicados com a finalidade de descrever as mutações encontradas na primeira falha ao esquema TAR avaliando o impacto destas mutações em esquemas de resgate. A grande maioria das publicações é do continente Africano com pacientes em falha a esquemas baseados em dois ITRN e um ITRNN, conforme se preconiza nos guias terapêuticos daqueles países.

Em 2012, foi publicado estudo realizado em seis países africanos, onde 142 participantes com carga viral > 1000cp/ml após 12 meses de TAR foram incluídos para realização de teste de genotipagem de forma retrospectiva. Os esquemas de primeira linha utilizados eram baseados em ITRNN (EFV ou NVP). A presença de pelo menos uma mutação associada à resistência foi identificada em 70% dos pacientes. Em aproximadamente 50% havia resistência a duas classes. O perfil mutacional mostrou o predomínio da M184V e uma frequência significativa de K65R (12%), especialmente nos pacientes fazendo uso de d4T (15%) ou TDF (27%). A seleção de TAM foi identificada menos frequentemente (8,5%). Em relação aos não análogos, o predomínio foi de K103N (28,9%), Y181C (15,5%) e G190A (14,1%) (Hamers, 2012).

Na Europa, dois importantes estudos foram realizados. O primeiro foi publicado por von Wyl e colaboradores abordando o perfil mutacional na primeira falha na coorte suíça. Este estudo teve 109 participantes que vinham em uso de esquemas de primeira linha contendo não análogos (EFV) e IP com *booster* (LPV/r e ATV/r). A mutação mais frequente para todos os grupos de tratamento foi a M184V. O aparecimento de TAM foi pouco frequente e mais observada no grupo que usou zidovudina (ZDV)/lamivudina (3TC)/efavirenz (EFV). As mutações para a classe dos IP foram muito poucas, não comprometendo esta classe (von Wyl, 2012).

O segundo foi realizado na Itália, com maior número de participantes (300). Neste estudo foram utilizados apenas ITRNN associados a análogos timidínicos e não timidínicos. Foi evidenciada maior prevalência da mutação 184V e 103N. As mutações K65R e 115F só apareceram no grupo que usou análogos não timidínicos (Santoro, 2013).

Em 2008, foi publicada revisão sistemática abordando a resistência à primeira linha de TAR por Gupta et al (Gupta, 2008). Esta revisão mostra uma maior prevalência das mutações M184Ve K65R nos pacientes que tiveram falha virológica com esquemas baseados em não análogos (35,3% e 5,3%, respectivamente), quando comparado com esquemas baseados em IP (21% e 0%, respectivamente). Foi demonstrado também uma maior frequência de resistência

à terceira droga (53% vs 0,9%) e um maior percentual de pacientes que apresentaram uma ou mais TAM (1,5% vs 0,6%) no grupo que fez uso de ITRNN em comparação com o grupo que usou IP. Além disso, foi evidenciado que a prevalência de resistência na população tratada foi pequena, apesar das taxas de falha viral encontradas terem sido superiores a 10%. Isso foi justificado pela alta taxa de genotipagens sem mutações de resistência, isto é mostrando vírus selvagens.

No Brasil poucos estudos foram realizados para avaliar o perfil de resistência à TAR de primeira linha. Diferente dos países africanos, o Brasil apresenta como subtipo mais prevalente de HIV-1 o B, que pode levar a perfis mutacionais diferentes na seleção de cepas resistentes. Além disso, a monitorização virológica no nosso país, por ser mais amplamente disponível do que no continente africano, pode modificar o perfil mutacional selecionado após a primeira falha.

3 OBJETIVOS

Objetivo principal:

Determinar as taxas de efetividade dos esquemas antirretrovirais de primeira e segunda linhas na coorte de pacientes com HIV/Aids do Instituto de Pesquisa Clínica Evandro Chagas – Fiocruz (IPEC / Fiocruz) no período de 2000 a 2013.

Objetivos secundários:

- Determinar os fatores associados à resposta ao tratamento e a durabilidade de TAR de primeira e segunda linha;

- Comparar durabilidade da TAR de segunda linha entre os pacientes que iniciaram TAR com carga viral detectável ou indetectável;

- Descrever o perfil genotípico por ocasião da falha de primeira e segunda linhas.

4 ESTRUTURA DA TESE

Os capítulos de metodologia, resultados e discussão foram apresentados na forma de dois artigos:

1 – Effectiveness of first-line antirretroviral therapy in the IPEC cohort, Rio de Janeiro, Brazil (Efetividade do tratamento antirretroviral de primeira linha na coorte do IPEC, Rio de Janeiro, Brasil).

2 –Outcomes of second-line combination antirretroviral therapy for HIV-infected patients from Rio de Janeiro, Brazil (Desfechos de combinações de antirretrovirais de segunda linha em pacientes infectados pelo HIV no Rio de Janeiro, Brasil).

5 PRIMEIRO ARTIGO

Título:

Effectiveness of first-line antirretroviral therapy in the IPEC cohort, Rio de Janeiro, Brazil (Efetividade do tratamento antirretroviral de primeira linha na coorte do IPEC, Rio de Janeiro, Brasil).

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Background

Since the beginning of the HIV/AIDS epidemic, Brazil's response has been both timely and inclusive, addressing prevention as well as treatment. A noteworthy moment was the decision to provide highly active antiretroviral therapy (ART) for all patients in need in 1996. With over 15 years of universal access to ART and almost 300,000 patients receiving ART, Brazil's HIV treatment program stands alone in its universal coverage of all in need compared to other middle-income or resource-limited countries [1]. Despite the enormous publicity it has received, evaluations of Brazil's HIV treatment program are limited. Studies have indicated that morbidity and mortality from HIV infection has fallen since the introduction of ART [2-4]. However, studies evaluating the impact of ART in suppressing HIV viral load, i.e. its effectiveness within the routine care provided through the public health system (the Unified Health System) of Brazil are scarce.

The efficacy of new drugs is assessed in short-term randomized clinical trials usually conducted in selected populations which frequently exclude participants with concurrent opportunistic diseases, substance abuse and/or psychiatric comorbidities [5]. As such, results from clinical trials are often not generalizable to all treated individuals who might be part of a clinical cohort or to longer-term outcomes [6]. Understanding ART effectiveness within the routine care setting is crucial to guide the evolution of the Brazilian HIV Treatment program. In this study, we evaluated first-line ART effectiveness for patients starting therapy from 2000 to 2010, as well as the factors that correlate with virologic suppression in a large urban cohort in Rio de Janeiro, Brazil.

Methods

The IPEC Clinical Cohort

This study was conducted at the Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation (IPEC/ FIOCRUZ), one of the largest infectious disease research centers in Brazil, where care has been provided to HIV/AIDS patients since the beginning of the AIDS epidemic in Brazil in 1986. An observational, longitudinal, clinical database is maintained on patients receiving primary and specialized outpatient and inpatient HIV care at the clinic; it

includes socio-demographic, behavioral, clinical and therapeutic information. Details of the HIV/AIDS clinical cohort can be found elsewhere [7, 8]. The IPEC Institutional Review Board reviewed and approved this study.

Study population and definitions

All patients who started first-line ART between January 1, 2000 and June 30, 2010 were included and follow-up information included data through September 30, 2011. ART was defined as two nucleoside reverse transcriptase inhibitors (NRTI) in combination with one non-nucleoside reverse transcriptase inhibitor (NNRTI) or one protease inhibitor (PI). Drug class modification and/or discontinuation were defined based on the class of a particular drug. A patient who started a first-line NNRTI-based regimen, for example, was assumed to have modified and/or discontinued the regimen if it was changed to a PI-based regimen or if the NNRTI was discontinued. NRTI modifications and/or discontinuations were not considered.

First-line ART effectiveness

First-line ART effectiveness was defined as having HIV viral load ≤ 400 copies/mL and no drug class modification and/or discontinuation. Deaths from AIDS-related causes were considered as failures. Because the limit of detection of viral load assays used throughout the study period varied from ≤400 copies/mL to ≤50 copies/mL, we used the ≤400 copies/mL threshold for the entire study period for consistency.

We examined virologic outcomes at 6, 12, and 24 months from first-line ART initiation. Window periods were defined for each time point as 5-9 months, 9-15 months, and 21-27 months, respectively. Within each window, the viral load measurement occurring closest to the target time point (either before or after) was chosen. Drug class modification and/or discontinuations were evaluated for the entire period from the start of first-line ART until the upper limit of each window period.

Missing Data

The IPEC Cohort has a validated algorithm for identification of deaths which has been previously described [8, 9]. In addition, since IPEC provides outpatient and inpatient care, as well as a multidisciplinary team including a cadre of clinical specialties coupled with pharmaceutical care, the rate of loss-to-follow-up is low (4.1/100 person-years). Absence of laboratory measurements is most frequently a result of insufficient infrastructure to support the CD4/viral load monitoring needed for all patients on ART. As such, we evaluated the impact of missing viral load measurements on first-line ART effectiveness by examining both best and worst-case scenarios. In the best case scenario, missing viral load data were assumed as suppression. Alternatively, in the worst-case scenario, missing viral loads were imputed as failures.

Immunologic response

We examined CD4 counts 6, 12, and 24 months from ART initiation. Window periods were, as for viral loads, defined for each time point as 5-9 months, 9-15 months, and 21-27 months. Within each window, the CD4 count occurring closest to the target time point (either before or after) was chosen.

Statistical Analyses

First-line ART effectiveness was calculated as the probability (95% CI) of viral suppression at 6, 12 and 24 months after ART initiation. The impact of socio-demographic, behavioral, clinical and structural factors on virologic suppression at 12 and 24 months was estimated using a quasi-Poisson regression model; this corrected for variance estimation and allowed for the estimation of relative risks. The final adjusted model included variables found to be significant at a threshold p-value of 0.05, as well as factors known to be clinically relevant or that were shown to modify the effect of a covariate in the adjusted model. We also examined the impact of missing viral load measurements on the multivariate model by re-estimating the parameters of the final model assuming the worst-case and best-case scenarios. R software version 2.15.2 (www.r-project.org) was used for all statistical analyses.

Results

Study population

From January 2000 through June 2010, 1,311 patients started first-line ART; 40% were ≥40 years old (Table 1). Among men, men who have sex with men (MSM) predominated as the HIV risk exposure category; 9.8% of the study population reported injection drug use (IDU) or other modes of HIV risk exposure. Half of the cohort had over 8 years of education. Sixty-four percent of the patients had three years or less since their first positive HIV test; 494 (37.7%) had a pre-treatment CD4 count ≤200 cells/μL (overall median 222/μL, IQR:105-322 cells/μL), and 466 (35.5%) had a pre-treatment viral load >100,000 copies/mL. The majority of patients started a first-line NNRTI-based regimen (987, 75.3%). Seventy percent of patients started their first-line regimens in the calendar period 2005-2010. Just over one-third of patients started first-line ART within a clinical trial conducted at IPEC.

Among the 987 patients who started an NNRTI-based regimen, efavirenz (EFV) was used by 93.3% (921/987); the most frequent EFV-based combination was zidovudine (AZT) + lamivudine (3TC) + EFV (590/921, 64.1%), followed by tenofovir (TDF) + 3TC + EFV or TDF + emtricitabine (FTC) + EFV (252/921, 27.4%). Among the 324 patients who started a PI-containing regimen, the majority used a boosted PI (197, 60.8%). The most frequent boosted PI was ritonavir-boosted lopinavir LPV/r (93/197, 47.2%) followed by ritonavir-boosted atazanavir ATV/r (62/197, 31.4%). Among those who started a non-boosted PI regimen (39.2%, 127/324), 65.4% (83/127) started with ATV. The frequency of boosted PI prescriptions was 47.8% (54/113) for the calendar years 2000-04 and 67.7% (143/211) for 2005-10.

First-line ART effectiveness

Overall first-line ART effectiveness, inclusive only of those with viral load data, was 76.9%, 76.1% and 67.9% at 6, 12 and 24 months (Table 2, top section). When assuming the best-case scenario including all patients, ART effectiveness increased to 82.8%, 80.8% and 77.0% at 6, 12 and 24 months. Inclusive of all patients, the worse-case scenario produced ART effectiveness rates of 57.5%, 61.2% and 48.6% at 6, 12 and 24 months. First-line ART effectiveness at each time point was consistently higher for those using an NNRTI-based regimen compared to a PI-based regimen (Table 2, middle section). Increased effectiveness

was also observed for those who started first-line ART in 2005-2010 compared to those who started in 2000-2004 (Table 2, bottom section).

CD4 counts

Median CD4 counts for the entire cohort significantly increased with the progression of the time points evaluated (Figure 1). At baseline, the median CD4 count was 221/µL whereas at 6, 12 and 24 months, it was 338/µL, 375/µL and 448/µL. These improvements correspond to a median CD4 count increase from baseline of 107/µL, 151/µL and 242/µL at 6, 12, and 24 months.

Factors associated with virologic suppression

In the adjusted model for the 12-month endpoint, gender/risk category, education, calendar year of ART initiation and participation in a clinical trial all remained independently associated with virologic suppression (Table 3). Compared to heterosexual men, women were less likely to be virologically suppressed (RR 0.90 95% CI 0.82-0.99). Having over eight years of formal education resulted in improved virologic suppression (RR 1.13 95% CI 1.03-1.24), compared to less than four years of formal education. Increased virologic suppression was also associated with starting ART in 2005-2010 (RR 1.25 95% CI 1.15-1.35) compared to starting in 2000-2004. Participation in a clinical trial versus not was associated with increased virologic suppression (RR 1.08 95% CI 1.01-1.16).

In the adjusted model for the 24-month endpoint, age, gender/risk category, education, type of ART regimen, calendar year of ART initiation, and clinical trial participation remained independently associated with virologic suppression (Table 3). Virologic suppression was associated with older age (RR for ≥40 years old 1.12 95% CI 1.00-1.26, compared to < 30 years old), and with MSM risk behavior (RR 1.11 95% CI 0.98-1.27, borderline significance compared to heterosexual men). Again, women compared to heterosexual men were less likely to be virologically suppressed, although this estimate did not reach statistical significance. Virologic suppression remained associated with first-line NNTRI-based regimen (RR 1.17 95% CI 1.05-1.31, compared to PI-based regimen), calendar

year 2005-10 (RR 1.14 95% CI 1.03-1.27, compared to 2000-2004), and participation in a clinical trial (RR 1.12 95% CI 1.02-1.23).

For the 12-month adjusted model, the magnitude of the relative risks changed minimally when assuming either the best or worst case scenarios (Table 4). For the 24-month endpoint, if missing data were assumed as success, the magnitude of the relative risks decreased for all variables. In contrast, if missing data were assumed as failures, there was a slight increase in the magnitude of the relative risk of most variables in the adjusted model. Despite these differences, the direction of the association of each variable with the outcome remained the same.

Discussion

In this large cohort study of HIV-infected patients in Rio de Janeiro, Brazil, we estimated ART effectiveness for 1311 patients who were cared for between 2000 and 2010, and demonstrated that levels of virologic suppression similar to those seen in the literature can be achieved in a middle-income country where ART is provided universally and free of charge.

We estimated ART effectiveness at 6 months to be 77% among patients with viral load results and no drug class modification and/or discontinuation. Using an intent-to-continue-treatment approach, that is, a less stringent criterion compared to that of the present study, the ART-CC cohort reported an estimate of 76% of undetectable viral load 6 months after ART initiation [10]. For the 12-month time point, our estimate of 61% for ART effectiveness when assuming missing data equals failure is consistent with that reported in a systematic review of clinical trials and cohort studies that employed the same approach to evaluating first-line ART efficacy (57-66% [11-13]). In line with our results, Barth et al, in a study conducted in rural South Africa, found 55% effectiveness using the same intent-to-treat approach [14]. It is important to take into account the calendar period, the stringency of study definitions and the availability of one pill once-daily regimens, all factors that could partially explain diverging suppression rates in other cohort studies when compared to our findings [5, 6, 10, 11, 13-23].

We showed in a stratified analysis that ART effectiveness was higher for NNRTI-based regimens. These findings corroborate results from clinical trials and cohort studies that

demonstrate greater effectiveness of NNRTI-based regimens, in particular, of efavirenz-based regimens [11, 19, 24]. In the adjusted analysis, however, the NNRTI-based regimen was found to be independently associated with virologic suppression solely at the 24-month endpoint; as such, when other factors were included the regimens were not different. LPV/r was the most frequently prescribed PI, as recommended in the Brazilian HIV Treatment Guidelines, which may explain the poorer outcomes observed with PI-based regimens, as opposed to the comparable effectiveness shown in AIDS Clinical Trials Group (ACTG5202), when boosted atazanavir was the PI comparator [25]. Of note, 39% of the patients in our cohort who started a PI-based regimen started on a non-boosted PI, of which 65% were atazanavir-based. It is well known that drug regimens including non-boosted PIs have poorer outcomes compared to other ART strategies [26]. The ACTG A5175 PEARLS trial, which was conducted in both high-income and low-middle-income settings, found non-boosted atazanavir to be inferior to efavirenz-based regimens [27]. Thus, the use of non-boosted PI-based regimens could partially explain the differences in ART effectiveness between our study and these trial findings.

Our study covered a time span of 11 years which allowed us to evaluate ART effectiveness in two periods, namely 2000-2004 and 2005-2010. Both the crude estimates and the adjusted analyses showed that the more recent calendar period was associated with increased ART effectiveness. This finding most likely results from the availability, more recently, of regimens with improved drug combinations, drugs with better tolerability and dosing convenience and, as a result, improved treatment adherence [28].

We found that clinical trial participation was independently associated with virologic suppression at 12 and 24 months from start of ART, corroborating other published results [29, 30]. Notably, in contrast to routine care, clinical trial participants are more intensively followed, adherence to study visits and drugs is monitored, drug toxicities are closely sought, and access to medical appointments is facilitated. For the time points evaluated in this study, clinical trial participants had significantly fewer missing viral load measurements. We believe that these results highlight the need to enhance patients' routine care within Brazil's Unified Health System in order to improve ART effectiveness. That is, given that clinical trial participants are not specifically selected based on how well they will adhere to study protocol, our results show that the enhanced patient care provided within the scope of a clinical trial may help improve the effectiveness of the Ministry of Health's universal access to free ART. A comparative analysis of the procedures carried out in routine care versus the clinical trial

setting could shed light into the most important aspects of trial participation that lead to increased ART effectiveness. Further studies are also needed to evaluate the long-term benefits of clinical trial participation, given that at the end of the trials patients are fully incorporated into routine care.

We found three socio-demographic and behavioral factors to be independently associated with increased ART effectiveness: older age, higher education level, and MSM HIV risk exposure. Regarding older age, our findings corroborate results from other cohort studies that have found increased ART effectiveness among older individuals [31, 32]. Likewise, improved virologic response among those with more years of formal education has also been reported in studies from both Brazil and the United States [33, 34]. Older age and higher education are likely correlated with a better understanding of the importance and value of ART and, consequently, better treatment adherence [35, 36]. We also found that MSM, compared to heterosexual men, had increased ART effectiveness. In our study population, MSM was linked to higher education, as 69% of the MSM reported > 8 years of formal education while only 38% of the women and heterosexual men reported this same level of education. In the multivariate model for the 12-month endpoint, women were found to have decreased ART effectiveness. In other studies that considered ART discontinuations as failures, men showed improved ART outcomes when compared to women [37]. Moreover, several clinical trials [38] and observational studies [7, 39, 40] have described a higher frequency of ART-related adverse events among women compared to men. In our cohort, we have previously reported that the hazard of ART modification or discontinuation for women is 1.67 times the hazard for men within the first year of treatment [7]. Taken together, these findings reinforce that high adherence is critical for optimal ART outcomes [41]. For Brazil, this highlights the need to focus adherence interventions among young, less educated heterosexual men and women, and to address specific issues particularly among women including ART tolerability and competing priorities such as child bearing/caretaker.

Our study has several limitations. One is the substantial fraction of missing viral load measurements. We addressed this limitation by conducting sensitivity analyses which allowed us to generate upper and lower limits for the ART effectiveness estimates. We also evaluated the impact of the missing viral loads on the adjusted analysis by modeling both best- and worst-case scenarios. These modeling exercises generated results which are similar to those obtained when the missing data were excluded. In contrast, CD4 counts were not imputed and

did suffer from a somewhat smaller degree of missing data, and therefore care is needed when extrapolating from these results.

In summary, we have shown that rates of effectiveness on first-line ART achieved in a clinical cohort in Brazil, a middle-income country with free access to treatment, is similar to that reported in many resource-rich settings. We have also shown that the strongest determinants of virologic suppression were participation in a clinical trial and starting treatment in the most recent calendar period (2005-2010). Together, these results lend evidence to the fact that enhanced clinical care and improved drugs increase the effect of ART. As the main goal of ART is to suppress viral load and allow for immune recovery, which consequently decreases AIDS-associated morbidity and mortality, enhanced clinical care and improved drugs could also lead to improved clinical outcomes. As such, this analysis highlights the next steps for improving Brazil's response to the HIV/AIDS epidemic; this response must include clinical care of increased quality, improved lab capacity for reliably timed measurements, and incorporation of drugs that are better tolerated and thereby more effective.

Authors contributions:

SWC contributed to the conception and design of the study, acquired the data, and drafted the manuscript. PML contributed to the conception and design of the study, and drafted the manuscript. LV contributed to the conception and design of the study, and performed the statistical analysis. TT and LC acquired and revised the data. KAF participated in the study's design, discussed the results, helped to draft and revise the manuscript for important intellectual content. VGV participated in the study's design and coordination and helped to draft the manuscript. RPW participated in the study's design, discussed the results, helped to draft and revise the manuscript for important intellectual content. BG contributed to the conception and design of the study, coordinated efforts, drafted and revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Table 1: Baseline socio-demographic, behavioral, clinical and structural characteristics at first-line antiretroviral therapy (ART) initiation (IPEC Clinical Cohort, 2000 to 2010). Unless otherwise stated, number (percentages) are shown.

Total	**1311**
Age	
Mean (SD)	37.1 (9.9)
< 30	355 (27.1)
30-39	446 (34.0)
≥ 40	510 (38.9)
Race	
Non-white	621 (47.4)
White	690 (52.6)
Gender/Risk category [a]	
Women	432 (33.0)
Heterosexual men	327 (24.9)
MSM	423 (32.3)
IDU/Other	129 (9.8)
Years of formal education	
< 4	277 (21.1)
4-8	380 (29.0)
> 8	654 (49.9)
Years since HIV+ test	
<= 3	836 (63.8)
> 3	475 (36.2)
Pre-treatment CD4 count/µL [b]	
Mean (SD)	233 (184)
<= 200	494 (37.7)
201-350	392 (29.9)
> 350	208 (15.9)
Missing	217 (16.6)
Pre-treatment HIV viral load copies/mL [c]	
<= 100000	532 (40.6)
> 100000	466 (35.5)
Missing	313 (23.9)
Concurrent AIDS defining illness [d]	
No	1013 (77.3)
Yes	298 (22.7)
Hepatitis B/C co-infection [e]	
No	1270 (96.9)
Yes	41 (3.1)
ART regimen [f]	
PI-based	324 (24.7)
NNRTI-based	987 (75.3)
Calendar year of ART initiation	
2000-2004	392 (29.9)
2005-2009	919 (70.1)
Started ART in clinical trial	
No	856 (65.3)
Yes	455 (34.7)

SD: standard deviation, HIV: human immunodeficiency virus, PI: protease inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor

[a] Gender and reported mode of HIV exposure were categorized jointly into women, men who have sex with men (MSM), heterosexual men, and injection drug users (IDU, men and women) and other reported modes of HIV exposure (men and women). Individuals reporting both injection drug use and other modes of HIV exposure were categorized as IDU.

[b] Measurement closest to the date of start of ART up to 30 days after.

[c] Measurement closest to the date of start of ART up to 7 days after.

[d] Defined as the presence of any Centers for Disease Control and Prevention (CDC) 1993 disease from 90 days prior to up to 30 days after start of ART.

[e] Defined as having diagnosed Hepatitis B or C chronic infection at the start of ART.

[f] Patients starting Integrase inhibitor-based regimens were too few and thus excluded (7 individuals with start of ART in 2010).

Table 2: Effectiveness of first-line antiretroviral therapy at 6, 12, and 24 months from start of antiretroviral therapy (ART) stratified by regimen and calendar year.

		6 months	12 months	24 months
Overall		**N (%)**	**N (%)**	**N (%)**
	For patients with HIV VL	754/980 (76.9)	802/1054 (76.1)	637/938 (67.9)
	Best-case scenario [a]	1085/1311 (82.8)	1059/1311 (80.8)	1010/1311 (77.0)
	Worst-case scenario [b]	754/1311 (57.5)	802/1311 (61.2)	637/1311 (48.6)
Stratified by type of ART regimen				
NNRTI-based				
	For patients with HIV VL	583/740 (78.8)	603/784 (76.9)	503/711 (70.7)
	Best-case scenario	830/987 (84.1)	806/987 (81.7)	779/987 (78.9)
	Worst-case scenario	583/987 (59.1)	603/987 (61.1)	503/987 (51.0)
PI-based				
	For patients with HIV VL	171/240 (71.3)	199/270 (73.7)	134/227 (59.0)
	Best-case scenario	255/324 (78.7)	253/324 (78.1)	231/324 (71.3)
	Worst-case scenario	171/324 (52.8)	199/324 (61.4)	134/324 (41.4)
Stratified by calendar year of ART initiation				
2000-2004				
	For patients with HIV VL	157/252 (62.3)	188/297 (63.3)	171/287 (59.6)
	Best-case scenario	297/392 (75.8)	283/392 (72.2)	276/392 (70.4)
	Worst-case scenario	157/392 (40.1)	188/392 (48.0)	171/392 (43.6)
2005-2010				
	For patients with HIV VL	597/728 (82.0)	614/757 (81.1)	466/651 (71.6)
	Best-case scenario	788/919 (85.7)	776/919 (84.4)	734/919 (79.9)
	Worst-case scenario	597/919 (65.0)	614/919 (66.8)	466/919 (50.7)

HIV: human immunodeficiency virus, VL: viral load, PI: protease inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor

[a] Best-case scenario assumes missing viral load data as suppression

[b] Worst-case scenario assumes missing viral loads data as failures.

Table 3: Unadjusted and adjusted relative risks (95% confidence intervals) for first-line antiretroviral therapy effectiveness at 12 and 24 months (IPEC cohort, 2000 to 2010).

	12 months		24 months	
	Unadjusted	**Adjusted**	**Unadjusted**	**Adjusted**
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
Age				
< 30	Ref.		Ref.	Ref.
30-39	0.99 (0.91, 1.08)		1.05 (0.93, 1.18)	1.06 (0.94, 1.19)
>= 40	1.04 (0.95, 1.13)		1.09 (0.98, 1.22)	1.12 (1.00, 1.26)
Race				
Non-white	Ref.		Ref.	
White	1.07 (1.00, 1.14)		1.05 (0.97, 1.15)	
Gender/Risk category [a]				
Women	0.89 (0.82, 0.98)	0.90 (0.82, 0.99)	0.92 (0.82, 1.03)	0.94 (0.84, 1.06)
Heterosexual men	Ref.	Ref.	Ref.	Ref.
MSM	1.05 (0.97, 1.15)	1.02 (0.93, 1.12)	1.11 (0.99, 1.25)	1.11 (0.98, 1.25)
IDU/Other	1.02 (0.90, 1.16)	1.02 (0.89, 1.16)	0.93 (0.78, 1.11)	0.95 (0.79, 1.13)
Education				
< 4 years	Ref.	Ref.	Ref.	Ref.
4-8 years	1.06 (0.96, 1.17)	1.07 (0.96, 1.18)	1.12 (0.98, 1.28)	1.13 (0.99, 1.29)
> 8 years	1.16 (1.06, 1.27)	1.13 (1.03, 1.24)	1.17 (1.04, 1.32)	1.14 (1, 1.29)
Years since HIV+ test				
<= 3	Ref.		Ref.	
> 3	0.97 (0.90, 1.04)		0.94 (0.86, 1.03)	
Baseline CD4 cell count [b]				
<= 200	Ref.		Ref.	
201-350	1.05 (0.97, 1.14)		1.01 (0.91, 1.12)	
> 350	1.09 (0.99, 1.20)		1.11 (0.97, 1.26)	
Missing	0.92 (0.83, 1.03)		1.01 (0.88, 1.15)	
Baseline HIV viral load [c]				
<= 100000	Ref.		Ref.	
> 100000	1.00 (0.93, 1.08)		1.03 (0.93, 1.14)	
Missing	0.95 (0.87, 1.04)		0.99 (0.88, 1.11)	
Concurrent ADI [d]				
No	Ref.		Ref.	
Yes	1.06 (0.98, 1.16)		1.06 (0.95, 1.18)	
Hepatitis B/C co-infection [e]				
No	Ref.		Ref.	
Yes	1.16 (0.95, 1.43)		1.07 (0.83, 1.39)	
Initial ART regimen [f]				
PI-based	Ref.		Ref.	Ref.
NNRTI-based	1.04 (0.96, 1.13)		1.20 (1.08, 1.34)	1.17 (1.05, 1.31)
Calendar year of ART initiation				
2005-2010	1.28 (1.18, 1.39)	1.25 (1.15, 1.35)	1.20 (1.09, 1.33)	1.14 (1.03, 1.27)
2000-2004	Ref.	Ref.	Ref.	Ref.
Started ART in clinical trial				
No	Ref.	Ref.	Ref.	Ref.
Yes	1.10 (1.03, 1.18)	1.08 (1.01, 1.16)	1.14 (1.04, 1.25)	1.12 (1.02, 1.23)

HIV: human immunodeficiency virus, VL: viral load, PI: protease inhibitor, NNRTI: non-nucleoside reverse transcriptase inhibitor

[a] Gender and reported mode of HIV exposure were categorized jointly into women, men who have sex with men (MSM), heterosexual men, and injection drug users (IDU, men and women) and other reported modes of HIV exposure (men and women). Individuals reporting both injection drug use and other modes of HIV exposure were categorized into IDU.

[b] Measurement closest to the date of start of ART up to 30 days after.

[c] Measurement closest to the date of start of ART up to 7 days after.

[d] Defined as the presence of any Centers for Disease Control and Prevention (CDC) 1993 ADI at 90 days prior to up to 30 days after start of ART.

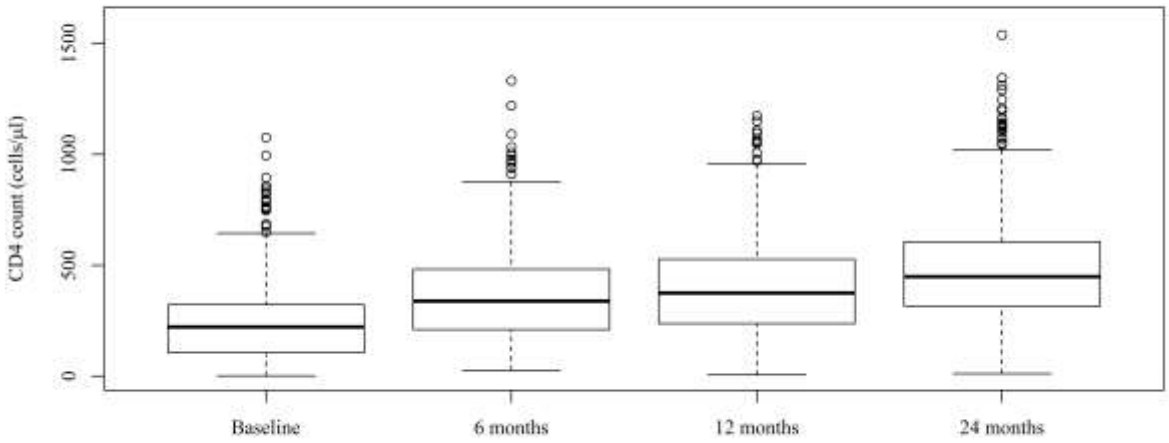
[e] Defined as having diagnosed Hepatitis B or C chronic infection at the start of ART.

[f] Patients starting Integrase inhibitor-based regimens were too few and thus excluded (7 individuals with start of ART in 2010).

Table 4: Adjusted relative risks (95% confidence intervals) for first-line antiretroviral (ART) effectiveness at 12 and 24 months when assuming best-case (missing as success) and worst-case scenarios (missing as failure) (IPEC cohort, 2000 to 2010).

	12 months			24 months		
	RR (95%CI)	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**	**RR (95%CI)**
	Missing excluded	**Missing = Success**	**Missing = Failure**	**Missing excluded**	**Missing = Success**	**Missing = Failure**
Age						
< 30				Ref.	Ref.	Ref.
30-39				1.06 (0.94, 1.19)	1.01 (0.94, 1.09)	1.15 (0.99, 1.33)
>= 40				1.12 (1.00, 1.26)	1.04 (0.97, 1.13)	1.24 (1.07, 1.44)
Gender/Risk category						
Women	0.90 (0.82, 0.99)	0.93 (0.87, 1.00)	0.87 (0.77, 0.98)	0.94 (0.84, 1.06)	0.94 (0.87, 1.02)	0.98 (0.84, 1.14)
Heterosexual men	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
MSM	1.02 (0.93, 1.12)	1.03 (0.96, 1.11)	0.98 (0.87, 1.10)	1.11 (0.98, 1.25)	1.08 (0.99, 1.17)	1.05 (0.90, 1.22)
IDU/Other	1.02 (0.89, 1.16)	1.03 (0.94, 1.14)	0.89 (0.75, 1.05)	0.95 (0.79, 1.13)	0.97 (0.87, 1.09)	0.87 (0.70, 1.09)
Education						
< 4 years	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
4-8 years	1.07 (0.96, 1.18)	1.05 (0.97, 1.13)	1.05 (0.93, 1.20)	1.13 (0.99, 1.29)	1.06 (0.98, 1.16)	1.18 (1.00, 1.39)
> 8 years	1.13 (1.03, 1.24)	1.08 (1.01, 1.17)	1.16 (1.03, 1.30)	1.14 (1.00, 1.29)	1.07 (0.99, 1.16)	1.21 (1.03, 1.41)
Initial ART regimen						
PI-based				Ref.	Ref.	Ref.
NNRTI-based				1.17 (1.05, 1.31)	1.09 (1.02, 1.17)	1.21 (1.05, 1.39)
Calendar year of ART initiation						
2005-2009	1.25 (1.15, 1.35)	1.14 (1.08, 1.22)	1.34 (1.21, 1.49)	1.14 (1.03, 1.27)	1.11 (1.03, 1.19)	1.08 (0.95, 1.23)
2000-2004	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Started ART in clinical trial						
No	Ref.	Ref.	Ref.	Ref.	Ref.	Ref.
Yes	1.08 (1.01, 1.16)	1.05 (0.99, 1.11)	1.10 (1.00, 1.21)	1.12 (1.02, 1.23)	1.04 (0.98, 1.11)	1.24 (1.10, 1.39)

Figure 1: Box plot of CD4 count distribution at baseline and 6, 12, and 24 months after antiretroviral therapy initiation. Pair-wise comparisons of baseline measurement with 6-, 12-, and 24-month time points indicate statistically significant differences (Wilcoxon paired test).



6 SEGUNDO ARTIGO

Título:

Outcomes of second-line combination antirretroviral therapy for HIV-infected patients from Rio de Janeiro, Brazil

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Introduction

Globally, studies addressing second-line combination antiretroviral (cART) virologic, immunologic and clinical outcomes have become increasingly common in recent years [1-5]. Resource-limited setting shave expanded their HIV/AIDS treatment programs leading to an increasing number of patients in need of second-line cART. Currently, boosted protease inhibitors (PI)-containing regimens are the recommended option after first-line cART failure for patients treated in the public sector in most resource-limited settings[6]. Given the first-line cART usually available in resource-limited settings, concerns over the development of resistance to second-line cART in developing countries have been raised, particularly in the absence of (or in the presence of insufficient) viral load monitoring [7,8]. Indeed, the emergence of drug resistance has been a major threat to the sustained effectiveness of cART in resource-rich settings [9] and the continuation of a failing regimen may be associated with more complex mutation patterns, as observed in several studies [10-12]. A critical assessment of the outcomes of second-line cART in resource-limited settings is timely as treatment programs are relatively new or maturing and monitoring strategies are still inadequate[13,14].

Second-line cART accounts for less than5% of total antiretroviral treatments in RLS[15]. In Latin America and the Caribbean region, the percentage of individuals receiving second-line cART is higher than that reported in other resource-limited settings (27% of the patients, ranging from 4 to 43%, are receiving second-line regimens compared with 0.05% in other regions of the developing world[16]. This may in part be due to specific characteristics of the Americas Region, such as the age of national programs, with many patients starting cART before 2000, as well as with an access to a broader options of drugs. In 1996, Brazil was the first middle-income country to implement a universal access cART while also providing immunologic and virologic monitoring and resistance testing after first-line failure. Currently, over three hundred thousand patients are under cART, using first, second, third-line and salvage regimens, and roughly 30,000 patients initiate treatment yearly. Nevertheless, no data is available on second-line treatment outcomes within the routine care provided through the public health system. Although third-line and salvage regimens, including drugs from new classes such as raltegravir and maraviroc, as well as darunavir and etravirine are available, such regimens are even more complex and still highly costly. As such, a greater understanding of factors associated to second-line cART outcomes in our setting is critical to

guide the evolution of the Brazilian HIV Treatment Program, as well as to maximize the durability of these regimens, preventing disease progression and reducing long-term AIDS-related mortality. Accordingly, this study describes second-line cART outcomes in a large urban cohort from Rio de Janeiro, Brazil, including time to failure as well as factors associated with treatment failure.

Methods

Description of the clinical cohort

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. IPEC is one of the largest infectious diseases research centers in Brazil, where over five thousand HIV infected patients have been treated since the beginning of the AIDS epidemic. An observational, longitudinal, clinical database is maintained on patients receiving primary and specialized HIV care at the clinic. Details and results of the HIV/AIDS Clinical Cohort can be found elsewhere [17]. The IPEC Institutional Review Board reviewed and approved the study and patients provided written informed consent.

Study population and definitions

For this study we included all patients who started first-line cART between January 01, 2000 and June 30, 2010. Follow-up information included data up to December 30 2013. The included patients had to be at least 18 years old at cohort enrollment. Patients must have initiated a first-line cART followed by a second-line cART regimen.

First- and second-line cART regimens were defined as two or more nucleoside reverse transcriptase inhibitors (NRTI) plus an anchor agent [i.e., a nonnucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI)]. Patients were treated according to the Brazilian antiretroviral treatment guideline that recommend as a preferred first-line cART a regimen based on NNRTIs though PI-based regimens can also be prescribed. In

contrast, second-line cART, according to the guideline, should be PI-based though NNRTI-based regimens can also alternatively be prescribed [18].

Second-line cART was defined for individuals who either failed first-line cART (HIV RNA viral load measurement >400 copies/mL after 5 months of initiating first-line cART) and subsequently changed their regimen class and/or drug, depending on the class of the first-line cART as detailed below, or for patients who had not failed their first-line cART but changed their regimen class and/or drug, depending on the class of the first-line cART as detailed below.

Patients who started a first-line NNRTI-based regimen were assumed to have changed to second-line cART if a PI-based regimen was started. Alternatively, patients who started a first-line PI-based regimen were assumed to have changed to second-line cART if either a NNRTI-based regimen was started or there was a change of the PI drug used. Changes in the NRTI backbone, that is, in any or all NRTIs alone, were not considered as changes from first to second-line cART. Also, the addition of ritonavir to a PI-based first-line regimen was not considered as a change from first to second line cART.

Start of follow-up is given by the start date of the second-line cART. The definition of virologic failure for second-line cART was conditional on the HIV-1 RNA level at the start of the second-line cART regimen. For patients with an HIV RNA of >400 copies/ml at the start of second-line cART, virologic failure was defined as an HIV RNA level of >400 copies/ml after 5 months of start of second-line cART. For patients with an HIV RNA of <400 copies/ml at the start of second-line cART, virologic failure was defined as an HIV RNA >400 copies/ml after 2 months of start of second-line cART. Two scenarios were defined as virologic failure while on second line cART: a single HIV-1 RNA >400 copies/mL followed by a regimen class modification as well as having two consecutive HIV-1 RNA >400 copies/mL regardless if a regimen class modification had occurred or not. A single HIV-1 RNA >400 copies/mL followed by a subsequent HIV-1 RNA of <400 copies/mL with no regimen class modification was considered a blip. Deaths from AIDS-related causes were defined as virologic failures while deaths from non-AIDS-related causes were defined as censored observations. Censoring was also applied in two situations. First, patients who did not fail assuming the definitions above were censored at the date of the last viral load plus six months. Second, patients who did not have a an HIV-1 RNA result or any documented change in regimen class were censored after the grace periods described above (patients with an HIV

RNA of > 400 copies/ml at the start of second-line cART were censored at 5 months and patients with an HIV RNA of < 400 copies/ml at the start of second-line cART were censored at 2 months). The limit of detection of viral load assays used throughout the study period varied from < 400 to < 50 copies/ml. For consistency, we have used the <400 copies/ml threshold for the entire study period.

Statistical analysis

Basic bivariate contrasts included performing the Pearson's Chi-square test for categorical variables and the Mann-Whitney rank sum test for continuous variables. Kaplan-Meier analyses and the log-rank test were used to assess time to virologic failure on second-line cART overall and stratified by virologic suppression at the start of second-line cART and by regimen change. Cox proportional hazards regression models were fit to estimate relative hazards and 95% confidence intervals of time to second cART virologic failure. To verify the proportionality assumption in Cox's model, we tested the correlation between survival time and Shoenfeld's standardized residuals. R software version 3.0.3 (www.r-project.org) was used for all statistical analyses.

Results

Among the 1,311 patients who started first-line cART a total of 386 patients (29.5%) initiated second-line cART. Most patients used a first-line NNRTI-based regimen (n=243; 63%) while 143 (37%) used a PI-based regimen, 51% (74/143) of these a non-boosted PI. First-line effectiveness for our cohort of patients has been previously described[19].

Out of 386 patients who started second-line cART, one hundred and thirty five patients (35.0%) switched from their first-line to second-line cART when their HIV RNA was undetectable, and 234 patients (60.6%) initiated second-line cART after documented virologic failure (Table 1). Seventeen patients (4.4%) did not have an HIV RNA result available before second-line cART initiation. Reasons for changing first-line cART were available for 382

patients. Thirty-one percent (121/382) were found to have changed cART due to toxicities, 41% and 26% among the undetectable and detectable groups, respectively.

At second line cART initiation, median age was 38 years [interquartile range (IQR): 31-45 years], 59% were male and half were non-white (Table 1). The majority (59%) of patients had less than 8 years of formal education and the median time since first HIV+ test was 3.3 years. Overall, median CD4 cell count at second-line cART initiation was 260 cells/mm^3 (IQR: 145-425 cell/mm^3). The median CD4 count was significantly different for patients starting second-line cART undetectable [412 cells/mm^3 (IQR: 240-617)] compared to those starting second-line cART after documented virologic failure [230 cells/mm^3 (IQR: 118-322.5)] ($p < 0.01$, Table 1). The median HIV RNA at the time of second-line for those with virologic failure was 4.4 $\log_{10}$ copies/mL (IQR: 3.8-5.0$\log_{10}$ copies/mL).

Most anchor drug changes were either a modification from NNRTI- or PI-based regimens to a boosted PI-based regimen (73%) and to a much smaller extent from a PI/PI-r to an NNRTI (19%). Overall, 296 patients (82%) used a PI-based second-line cART out of which the majority (269/296, 91%) used a ritonavir-boosted PI (PI-r). Lopinavir/r was used by 46% (135/296) and ATV/r by 37% (111/296). The most frequently used NRTI backbones were: AZT/3TC (197/369, 53%) and 3TC/TDF or FTC/TDF (114/369, 31%). For patients initiating second-line cART undetectable, the most frequent switches were from NNRTI-based to a boosted PI-based cART (37%) followed by PI/PI-r to NNRTI-based (31%) and PI/PI-r to PI/PI-r (22%). For patients who initiated second-line cART detectable, the most frequent modification was from NNRTI to a boosted PI-based (65%) cART (Table 1).

HIV genotyping results at first line cART failure were available for 39% (91/234) of patients who started second-line cART with a detectable viral load. A genotyping result yielding wild type virus was found in 7.7% (7/91) of patients. Overall, M184V was the most prevalent mutation (59/91; 65%); K65R was identified in 38% of patients using TDF (8/21) all of which were using an NNRTI based cART regimen. At least one primary PI mutation was found for 75% (6/8) and 55% (5/9) of patients using PI and PI-r cART based regimens. Among those patients using a NNRTI based regimen, the most prevalent NNRTI mutation was K103N (43/74; 58%) (Figure 1).

Overall, the median survival time from first-line cART to second-line cART was 20.1 months (95% CI 17.1-22.6). The median survival time for patients who initiated second-line

cART undetectable was 20.3 months (95% 16.7-24.2) and for those who initiated cART detectable was 20.8 months (18.4-23.1). The Kaplan-Meier plot of the survival time is given in Figure 2; log-rank test indicated that the curves were not significantly different (p=0.58).

Among the 386 patients who started second-line cART (corresponding to 1,232.6 person-years of follow-up), 13 patients died during follow-up due to AIDS related causes (5 and 6 deaths in the undetectable and detectable groups). The overall incidence of second-line failure (defined as a HIV RNA>400 copies/mL or an AIDS related death) was 12/1000 person-years (95%CI 10-14/1000 person-years). The incidence of second-line failure was 5.7/1000 person-years (95%CI 4.2-7.7/1000 person-years) and 19/1000 person-years (95% CI 16-23/1000 person-years) among those who started second line cART with an undetectable and a detectable HIV RNA (incidence rate ratio for detectable compared to undetectable of 3.4, p<0.0001).The overall probability of failure at 12, 24 and 36 months was 26%,41% and48%respectively. For the undetectable group, 12-, 24- and 36-months probability of failure was 15%, 23% and 30% while for the detectable group, 12-, 24- and 36-months probability of failure was 34%, 55% and 62%.

Overall, the median survival time from second-line cART to virologic failure was 40.0 months (95% CI 30.4-52.2). The median survival time from second-line cART initiation to failure was significantly different between the two groups (log-rank test p<0.01, Figure 3). For patients who started second-line cART undetectable, the median survival time was 113.6 months (lower bound of the 95%CI 82.4 months, upper bound could not be calculated) and for those who started second-line cART detectable the median survival time was 19.8 months (95% CI:15.7-28.6 months).Overall, the median survival time from second-line cART initiation to failure stratified by anchor drug was significantly different (log-rank test p=0.002, Figure 4). The median survival time from second-line cART initiation to failure stratified by anchor drug was also significantly different for the undetectable group (log-rank test p<0.002). In contrast, for the detectable group, the median survival time from second-line cART initiation to failure stratified by anchor drug was not significantly different (log-rank test p=0.70). No differences were observed in the median survival time from second-line cART to AIDS related deaths (25.2 months [95% CI:10.1-50.8months] and 23.4 months [95% CI:12.1-40.2] for the detectable and undetectable groups, respectively [log rank test p=0.22]).

The hazard ratios (HR) for second-line cART failure overall (adjusted for detectable viral load level), and stratified by group according to HIV RNA level at second cART

initiation (detectable and undetectable) are shown in Table 2. Overall, age, level of education and second cART anchor drug were independently associated with the incidence of second line ART failure. The relative hazard of failure when second cART was initiated between 30-39 years old and ≥40years compared to starting at a younger age was 0.56 (95% CI 0.39-0.81) and 0.53 (95% CI 0.37-0.75), respectively. A higher hazard of failure was observed among patients with less than 8 years of formal education compared to those with more than 8 years (HR 1.50, 95%CI 1.1-2.0) and among those who switched from an NNRTI to a non-boosted PI compared to those who switched from NNRTI to a boosted PI (HR 1.73, 95%CI 1.07-2.79).

For patients who initiated second-line cART with an undetectable HIV RNA, age, second-line cART anchor agent and first-line cART duration were independently associated with the incidence of second-line cART failure (Table 2). A protective effect was observed for older age, with a lower HR for those individuals older than 40 years when compared to those younger than 30 years at second-line cART initiation (HR 0.44 95%CI 0.22-090), as well as for switching either from PI/PI-r to NNRTI (HR0.40 95%CI0.18-0.85) and PI/PI-r to PI-r (HR0.39 95%CI0.15-0.96) when compared to switching from a NNRTI to a PI-r based regimen. The longer the patient remained on first-line cART, the lower was the hazard for second-line cART failure, with a 3% decrease in the hazard of failure for each additional month on first line cART. Toxicity as the reason for changing first-line cART was not associated with an increased incidence of second-line cART failure.

For patients who initiated second-line cART with a detectable HIV RNA, age and level of education were independently associated with the incidence of second-line cART failure. Again, a protective pattern was found for older age when compared to younger individuals and for higher education when compared to those with less years of education (Table 2). Whilst not significant, a higher hazard of failure was observed for patients initiating second line cART with an HIV RNA level between 10,001-100,000 copies/ml, when compared to those with HIV RNA levels <10,000 copies/ml (p=0.06). Time from first-line cART failure to second-line cART initiation and toxicity as the reason for changing first-line cART were not associated with the incidence of second-line cART failure.

Resistance Profile

Resistance testing results were available for 23% (43/187) of patients at second-line cART virologic failure. Overall, 32.5% (14/43) of the genotyping results yielded no resistance mutations (wild type virus), and this was higher among those patients using a boosted PI cART regimen (12/30; 40%). More than 3 TAMS were identified in 11.6% (5/43). At least one primary PI mutation was identified in 75% (3/4) of patients using an unboosted PI cART based regimen (D30N, I50L and 46V), and 10% (3/30) among those using a PI-r cART regimen (47V, 82A and 90M) (Figure 5).

Discussion

Our results show that outcomes from start of second-line cART were significantly different for patients who started second-line cART with an undetectable HIV RNA compared to a detectable HIV RNA. The median survival time from second-line cART to failure was significantly higher for those who started with an undetectable HIV RNA compared to those with a detectable HIV RNA. In addition, the incidence of second-line failure was 3.4 times higher for those with a detectable viral load and the probabilities of failure at 12, 24 and 36 months were consistently higher for this group. Finally, in the multivariate model including the entire population, having a detectable HIV RNA increased the hazard of failure by almost three-fold. Taken together, these results clearly point to differences in outcomes as a function of an individual's HIV RNA at start of second-line cART which is in agreement with the findings from a multicenter study with a similar design [20].

We found that more than half of our study population (60%) started second-line cART after a documented virologic failure. The median second-line cART survival time in this group (20 months) was consistent with that observed in an US multicenter study [20] but longer than the observed in two large studies from resource-limited settings [3,21]. The virologic failure probability increased over time from 34% at 12 months to 62% at 36 months, again higher than those described in other studies from resource-limited settings [22]. Although the great majority of second-line cART regimens in our cohort (80%) and in those from other resource-limited studies were lopinavir/r based, differences in cohort size, study

definitions, first-line cART duration, as well as demographic, immunological and clinical profile of the study population may have contributed the disparate results.

We also found that the median time from first- to second-line cART was not significantly different among those who started second-line cART undetectable compared to those who started with a detectable HIV RNA, suggesting that concurrent reasons to change first-line cART occurred overtime which included toxicities in addition to virologic failure. In fact, a higher proportion of patients who switched to second-line cART while having HIV RNA undetectable did so due to toxicities (41% and 26% among the undetectable and detectable groups, respectively). A somewhat surprising finding was that the median survival time of second-line cART was significantly longer than that of first-line cART (40 months for second-line compared to 20 months for first-line). Again, this may result from a high proportion of first-line cART changes due to toxicities. In previous analyses we have shown that toxicities were the driving force for first-line cART modifications and/or interruptions which were highly incident in our cohort especially during the first year of cART [23].

Given that an undetectable HIV RNA can be taken as surrogate marker for treatment response and possibly good adherence and no viral resistance, it was expected that patients starting second-line cART undetectable would show improved outcomes. Indeed, non-adherence to therapy has been shown to be one of the strongest predictors of cART failure [24,25]. In this group, the median second-line cART survival time was 113 months, two-fold higher than the 50 months median survival time found in a multicenter study from the United States [20]. Differences in socio-demographic characteristics, adherence pattern and regimen tolerability may explain the better outcomes shown in our study. Also, in our cohort, only 2% were IDUs, while up to 24.2% were IDUs in the US cohort [20]. Moreover, our study participants initiated cART on or after the year 2000 when friendlier regimens were increasingly available.

As for socio-demographic factors impacting second-line cART outcomes, our results suggest that older age and higher education were associated with a decreased hazard of failure. For this sample population, age older than 30 years at start of second-line cART significantly decreased the hazard of failure in the overall population and also in the sub-group analysis that considered patients with detectable and undetectable HIV RNA at second-line cART start. In a recent analysis of first-line cART conducted by our group, both factors were also found to impact treatment effectiveness [19] and a higher proportion of viral

suppression was detected for older/elderly patients [26]. In agreement, a protective effect of older age was also observed in other cohorts both in resource-rich and resource-limited settings [27,28]. Older age and higher education are likely correlated with a better understanding of the importance and value of cART and, consequently, better treatment adherence [29]. These results are worrisome given the current epidemiological scenario of the Brazilian AIDS epidemic which shows an increase of AIDS cases among the younger and less educated [18]. The structural nature of these factors implies that strategies needed hamper the growing epidemic will become more complex and will likely be harder implementing a broader scale within the public health system.

The clinical factors impacting second-line cART failure varied as a function of the sub-group of patients. The overall multivariate model clearly indicated that having a detectable HIV RNA at the start of second-line cART increased the hazard of failure by almost three-fold. In addition, for both the overall population and for the sub-group with an undetectable HIV RNA, our results show that the anchor drug changes from first-line to second-line cART can impact the hazard of second-line cART. We found that patients changing from an NNRTI-based regimen to an unboosted PI-based regimen had increased hazard of failure of second-line cART when compared to those changing to a boosted-PI-based regimen. In contrast, patients were protected from failure if changes were from unboosted or boosted PI-based regimens to either NNRTI-based regimens or a boosted PI-based regimen. In accordance, unboosted PI regimens are no longer an option in contemporary treatment guidelines [6,18]. The multivariate analysis for the sub-group of patients with an undetectable viral load at start of second-line cART also showed that as the duration of first-line cART increases the incidence of second-line cART failure decreases which can be interpreted as being due to a good treatment adherence which was first evidenced during first-line cART and possibly extends to second-line. In contrast, for the sub-group of patients with a detectable viral load, the HIV RNA level at start of second-line cART led to an increased hazard of failure with borderline significance. Indeed, HIV RNA>100,000 copies/mL is well known to be associated with higher risk of first-line cART virologic failure [30-32], and second-line cART failure [33,34]. The even higher risk among patients with intermediate HIV RNA level at second-line cART initiation could suggest that this group had more irregular treatment adherence and, consequently, more viral resistance.

Although HIV genotyping tests are available in Brazil through the Public Health System since 2001, only 39% of the patients had a resistance test performed after first line virologic failure and before starting second-line cART. Also a small number of patients (23%) who developed second-line cART virologic failure had a resistance testing performed at second-line failure. Several issues such as insufficient laboratory infrastructure, long intervals to receive the genotyping results, technical limitations related to the viral load threshold for viral amplification (initially 5,000 copies/mL, only recently changed to 1,000 copies/mL), among others, may explain the small number of tests performed. Of note, although our numbers are very small, it is important to highlight the number of genotyping results yielding wild type virus among patients using a PI-r cART regimen at second-line virologic failure. Although boosted PI cART regimens have a higher genetic barrier against resistance [35, 36], it is well known that poorer adherence may happen more frequently with this drug class, as a consequence of the worse tolerability profile, especially with lopinavir/r, the most frequently used boosted-PI in our cohort.

Finally, we found that the majority of changes in anchor drug from first- to second-line cART were from an NNRTI-based to a boosted-PI-regimen which is in agreement with the Brazilian Treatment Guideline as well as to the WHO's guidelines [6, 18] This pattern has also been observed in both developed [20, 33] and in developing countries [3, 21, 22, 27, 37-40]. In contrast, our overall median CD4 count at second-line cART initiation of 230 cells/mm3 (IQR 118-322 cells/mm3) was higher than the observed in other resource-limited settings, where the majority of patients staring second line cART had <200 cells/mm3 [22, 27, 37, 40]. A probable explanation for this finding is the availability of virologic monitoring in Brazil, available since 1997, leading to earlier diagnosis of treatment failure and thus protecting patients from progressive immunodeficiency.

Our study has strengths and limitations. A major strength of our study is its large time span, covering 13 years of cART, in a cohort of HIV-infected patients from a middle-income country that provides universal access to treatment. In this scenario we were able to study outcomes of second-line cART with detailed socio-demographic, laboratory and treatment data. To the best of our knowledge, this is the first study of second-line cART outcomes in Brazil and, in the international literature, possibly one of the few studies that longitudinally evaluated outcomes of second-line cART. Lack of adherence data is a major limitation of our study. Despite this pitfall, given the availability of HIV RNA measurements, we were capable

of using an undetectable HIV RNA as a proxy for treatment adherence which allowed us to discuss important findings with respect to second-line cART. That said, specific treatment adherence measures are needed to study its impact as well as to allow for adherence interventions to be carried out. Current WHO guidelines recommend that patients presenting with failure should be subject to adherence support interventions, after which a second viral load test should be performed prior to deciding on a regimen change [6]. We were not able to use two consecutive HIV RNA measurements as a definition of virologic failure which would have been more consistent. Instead, we used the definition that was feasible (1 measurement) and this could have led to some misclassification of patients as failures when in fact this would not have been confirmed. In addition, beyond study definitions, the reality of having only one measurement available implies that physicians are also making decisions to change regimens based on only one measurement, meaning that patients might be unnecessarily being subject to treatment changes. Studies have shown that individuals on first-line cART viral failure experienced re-suppression without switching [41]. To explore these speculations additional studies are needed.

Achieving sustained viral suppression is the target for any cART irrespective if it is the first-line or subsequent treatment regimens. The need for lifelong antiretroviral therapy for HIV infection argues for the use of subsequent regimens with the most favorable efficacy and safety profile, ideally including drug classes without super-imposable resistance patterns. We have shown that in a middle-income country with universal access to cART, having a detectable HIV RNA at the start of second-line cART negatively impacts second-line outcomes and that structural factors such as younger age and lower education level can also negatively impact second-line cART outcomes. Although third-line cARTs such as darunavir, etravirine, raltegravir and maraviroc are available in Brazil, the costs associated with these drugs are significantly higher, and treatment regimens frequently include a larger number of pills, adding further complexity to treatment management. As such, tailored interventions targeting the young, the less educated and the less adherent are critically to guarantee the benefits of second-line cART.

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Table 1: Demographic and clinical characteristics at second-line cART initiation stratified by HIV-1 RNA level, IPEC cohort, 2000-2013.

			HIV-1 RNA level		
		Overall	**Undetectable**	**Detectable**	**p-value**
N (%)*		369	135	234	
Age					
	Median (IQR)	38.3 (31.8-45.2)	38.7 (30.4-45.4)	37.9 (31.9-45.2)	0.93
	≤30	78 (21.1)	33 (24.4)	45 (19.2)	0.27
	30-39	127 (34.4)	40 (29.6)	87 (37.2)	
	≥40	164 (44.4)	62 (45.9)	102 (43.6)	
Gender					0.78
	Female	151 (40.9)	57 (42.2)	94 (40.2)	
	Male	218 (59.1)	78 (57.8)	140 (59.8)	
Race					0.05
	Non White	185 (50.1)	58 (43.0)	127 (54.3)	
	White	184 (49.9)	77 (57.0)	107 (45.7)	
Gender/HIV exposure					0.28
	Heterosexual Men	110 (28.5)	36 (26.7)	70 (30.7)	
	Women	127 (33.0)	50 (37.0)	71 (31.1)	
	MSM	97 (25.0)	38 (28.1)	57 (25.0)	
	IDU	9 (2.5)	4 (3.0)	5 (2.2)	
	Other	37 (10.0)	7 (5.2)	25 (11.0)	
Education					0.11
	≤ 8 years	219 (59.5)	72 (53.7)	147 (62.8)	
	> 8 years	149 (41.5)	62 (46.3)	87 (37.2)	
Years since first HIV+ test					0.80
	Median (IQR)	3.3 (1.8-5.8)	3.1 (1.7-5.8)	3.4 (1.9-5.7)	
CD4 cell count, cells/mm3					<0.01
	Median (IQR)	260 (145, 425)	412 (239, 617)	230 (118, 322)	
	≤200	110 (34.3)	19 (15.6)	91 (45.7)	
	201-350	96 (29.9)	31 (25.4)	65 (32.7)	
	>350	115 (35.8)	72 (59)	43 (21.6)	
HIV-1 RNA level, log10 copies/ml*					
	Median (IQR)	N/A	N/A	4.4 (3.8-5.0)	-
	≤400	135 (36.6)	135 (100.0)	N/A	-
	401-10,000	83 (22.5)	N/A	83 (35.5)	
	10,001-100,000	97 (26.3)	N/A	97 (41.5)	
	>100,000	54 (14.6)	N/A	54 (23.0)	
Change in anchor drug from 1st to 2nd line					<0.01
	NNRTI to PI-r	204 (55.3)	50 (37)	154 (65.8)	
	NNRTI to PI	27 (7.3)	13 (9.6)	14 (6)	
	PI/PI-r to NNRTI	73 (19.8)	42 (31.1)	31 (13.2)	
	PI/PI-r to PI/PI-r	65 (17.6)	30 (22.2)	35 (15)	
Calendar year					0.97
	2000-2006	154 (41.7)	57 (42.2)	97 (41.5)	
	2007-2013	215 (58.3)	78 (57.8)	137 (58.5)	
Days from 1st line failure to 2nd line initiation					-
	Median (IQR)	N/A	N/A	173 (0.0-606)	

*17 patients did not have an HIV RNA result prior to starting second-line cART

HIV: human immunodeficiency virus; MSM: men who have sex with men; IDU: injection drug user; ART: antiretroviral therapy

Gender and reported mode of HIV exposure were categorized jointly into women, heterosexual men, MSM, IDU (men and women) and other reported modes of HIV exposure (men and women). Individuals reporting both IDU and other modes of HIV exposure were categorized into IDU.
Education was self-reported and based on the number of years of formal education.
CD4 cell count was defined as the CD4 cell count closest to the date of start the second line cART up to 30 days after.
HIV viral load was defined as the HIV viral load closest to the date of start second line cART up to 7 days after.
Days from failure of first-line cART to start of second-line cART was assumed to be zero if patients started second-line cART without virologic failure.

Table 2: Adjusted hazard ratios and 95% confidence intervals as estimated by Cox proportional hazards regression for second-line cART failure overall and stratified by HIV RNA level at time of second-line cART initiation, IPEC cohort, 2000-2013.

		Overall*	**Undetectable**	**Detectable**
Age				
	<30 years	Ref.	Ref.	Ref.
	30-39 years	0.56 (0.39-0.81)	0.75 (0.34-1.70)	0.54 (0.35-0.83)
	≥40 years	0.53 (0.37-0.75)	0.44 (0.22-0.90)	0.58 (0.38-0.89)
Education				
	>8 years	Ref.		Ref.
	≤8 years	1.50 (1.11-2.04)		1.44 (1.01-2.03)
HIV RNA at second-line cART initiation				
	Undetectable	Ref.		
	Detectable	2.70 (1.90-3.82)		
HIV-1 RNA level, copies/ml (median, IQR)				
	401-10,000			Ref.
	10,001-100,000			1.42 (0.98-2.06)
	>100,000			1.09 (0.70-1.70)
Second-line cART anchor agent				
	NNRTI-PI/r	Ref.	Ref.	
	NNRTI-PI	1.73 (1.07-2.79)	1.19 (0.53-2.70)	
	PI/PI/r-NNRTI	0.81 (0.53-1.23)	0.40 (0.18-0.85)	
	PI/PI/r-PI/PI-r	0.77 (0.51-1.17)	0.39 (0.15-0.96)	
Time from first-line to second-line initiation				
	Per 1 month increase		0.97 (0.95-0.99)	

Figure 1: First-line resistance profile, IPEC cohort, 2000-2010; A – TAMS according to the anchor drug; B: Primary PI Mutations; C: Primary NNRTI Mutations.

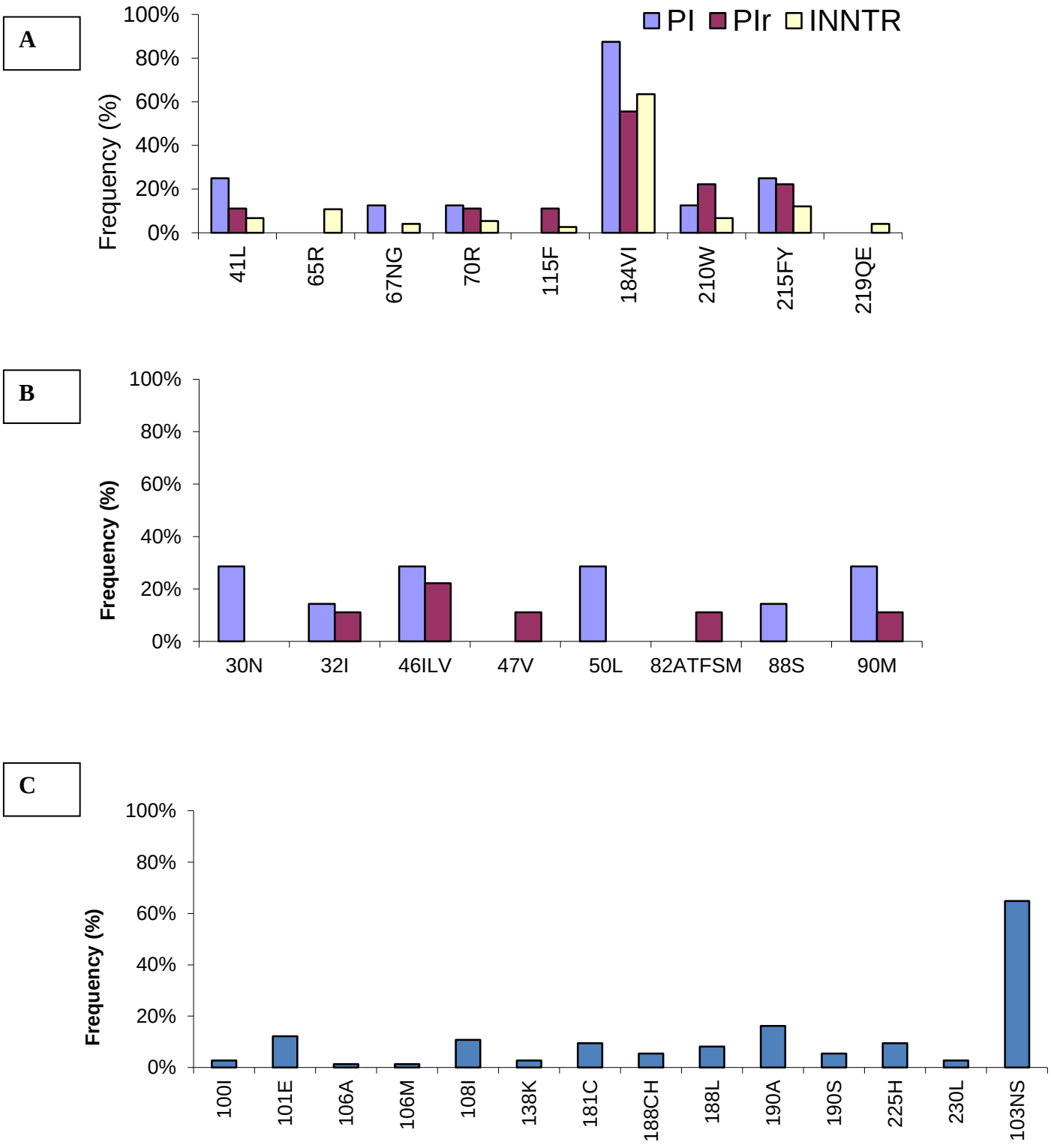


Figure 2: Time from first-line cART initiation to second-line cART initiation stratified by HIV RNA level at time of second-line cART initiation, IPEC cohort, 2000-2013. Log-rank test indicated that curves were not significantly different (p=0.58).

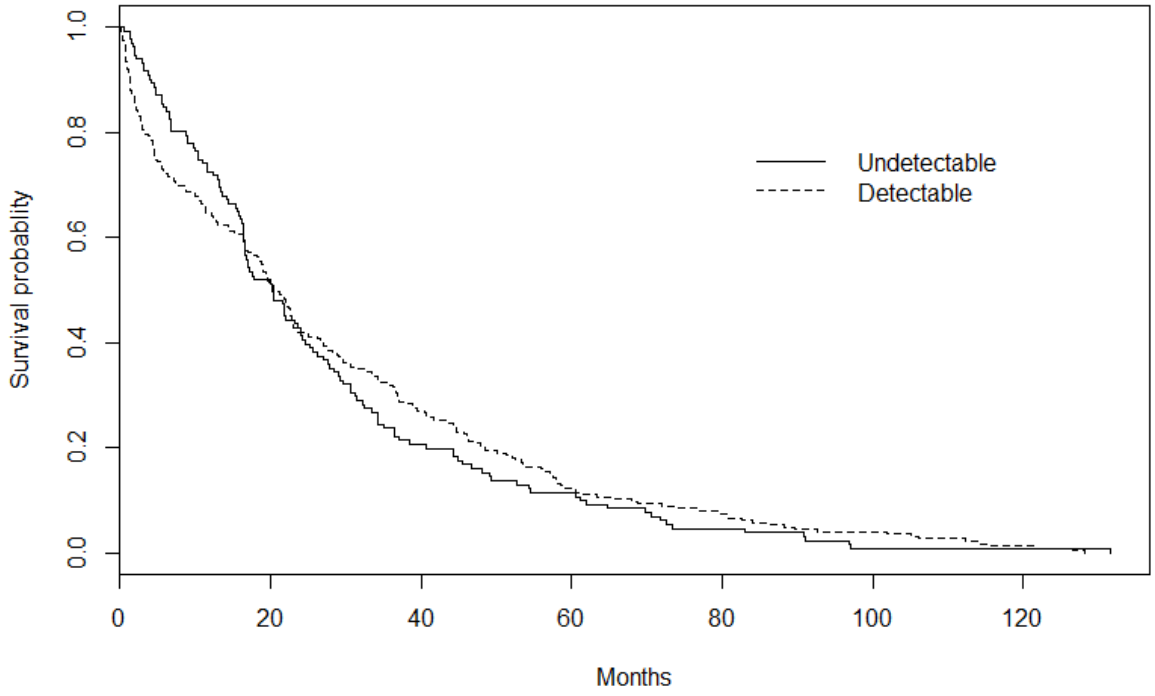


Figure 3: Time from second-line cART initiation to virologic failure stratified by HIV RNA level at time of second-line cART initiation, IPEC cohort, 2000-2013. Log-rank test indicated that curves were significantly different ($p<0.01$).

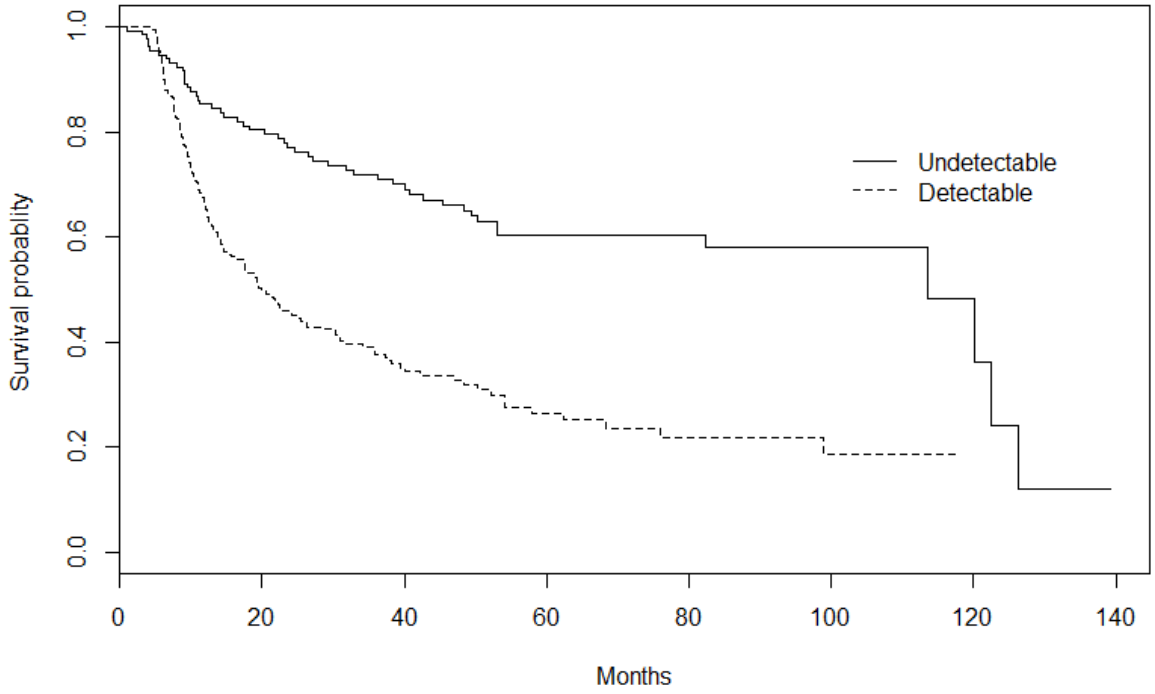


Figure 4: Time from second-line cART initiation to virologic failure stratified by anchor drug received for all patients (top, log-rank test p=0.002), the sub-group of patients with an undetectable viral load (middle, log-rank test p<0.002), and the sub-group of patients with detectable viral load (bottom, log-rank test p=0.70), IPEC cohort, 2000-2013.

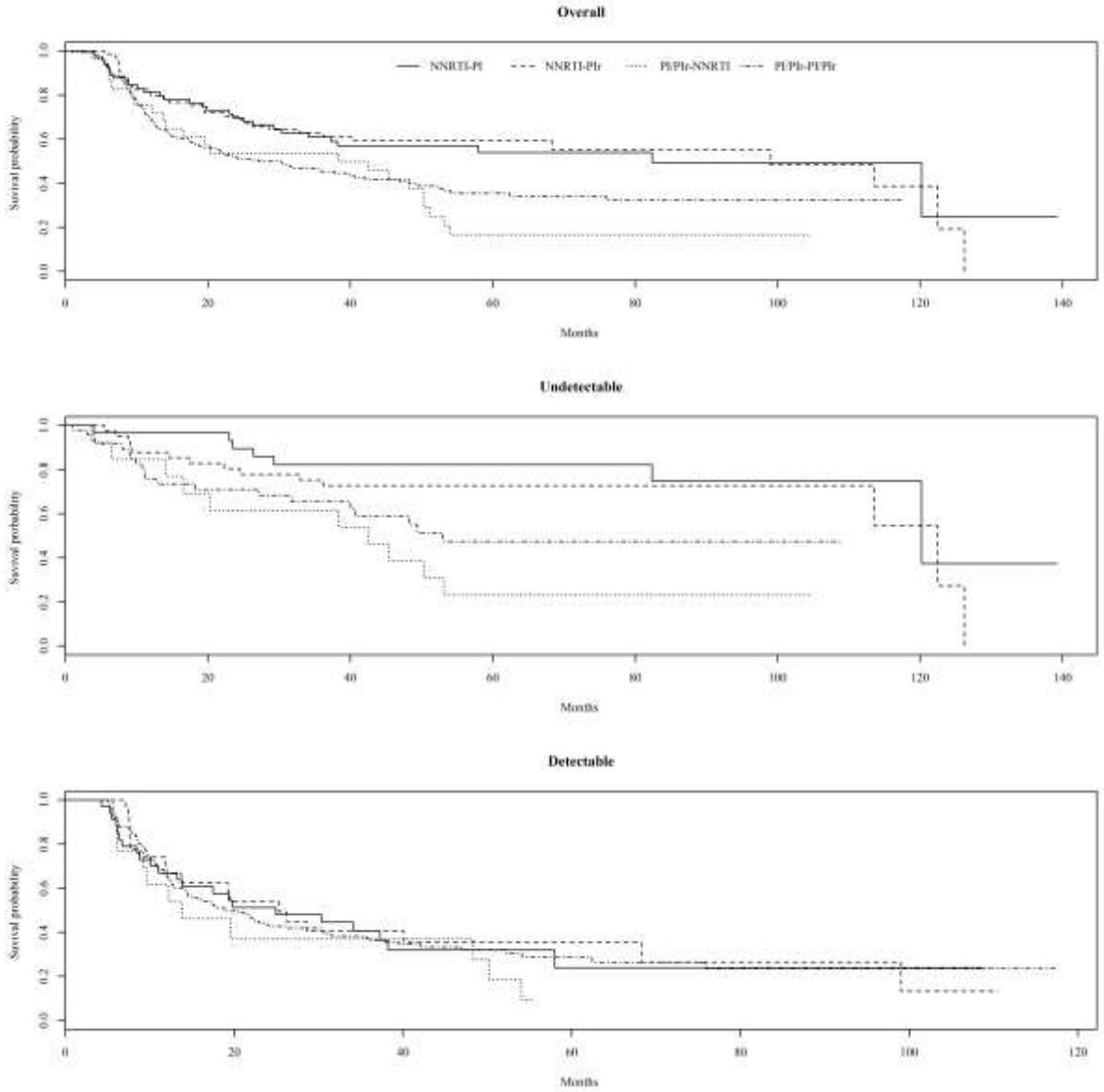
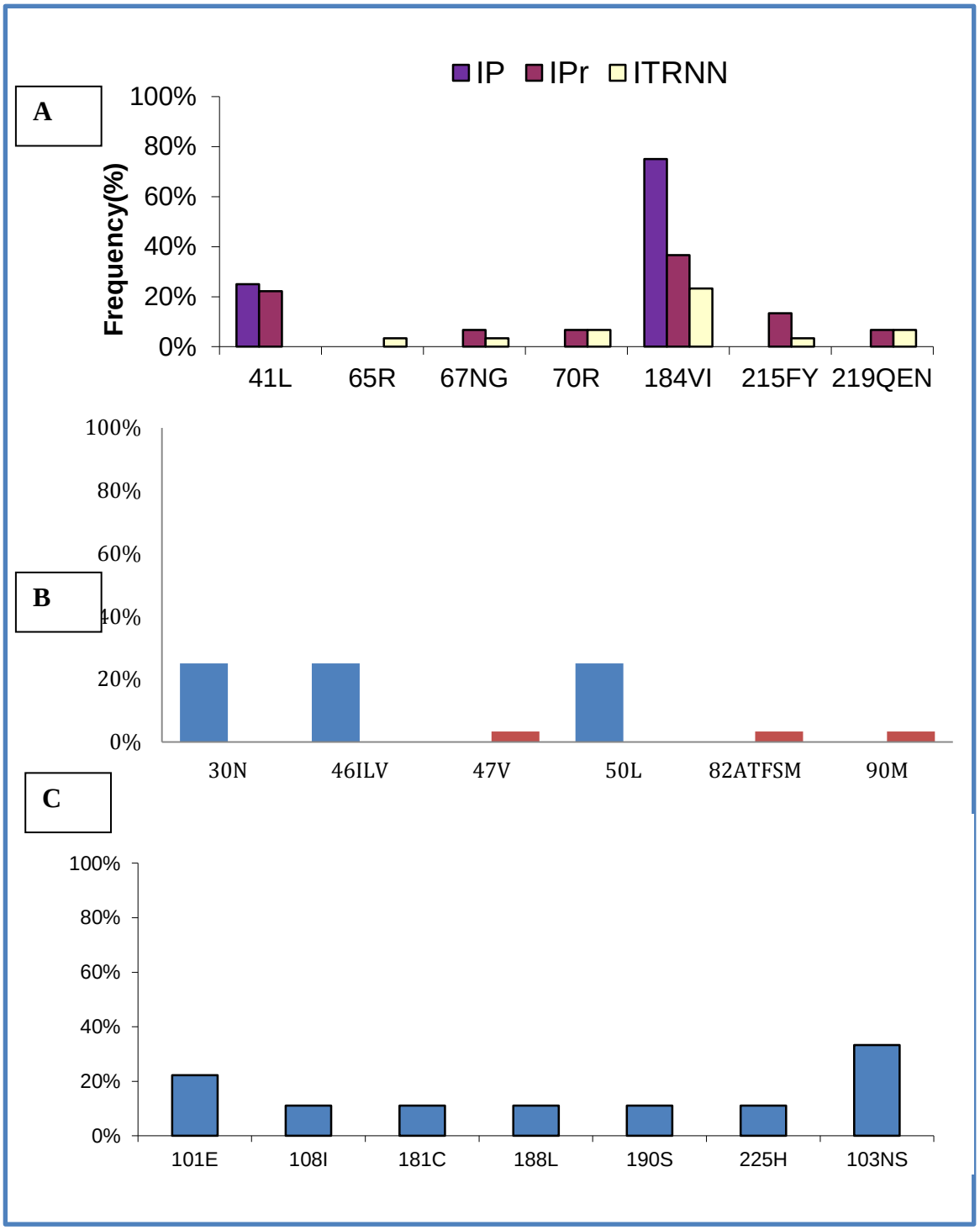


Figure 5: Second-line resistance profile: A: TAMS according to the anchor drug, B: Primary PI Mutations; C: Primary NNRTI Mutations



7 CONCLUSÕES

Neste trabalho estudamos a efetividade de esquemas de tratamento antirretroviral de primeira e segunda linhas na coorte de pacientes vivendo com HIV/AIDS do IPEC/FIOCRUZ. Nossos resultados permitem concluir que:

1- A efetividade dos esquemas de primeira linha aos seis, 12 e aos 24 meses foi respectivamente de 77%, 76% e 68%. Estas taxas são semelhantes às encontradas em outras coortes tanto em países desenvolvidos quanto em desenvolvimento.

2- Aos 24 meses a efetividade dos esquemas de primeira linha baseados em ITRNN foi superior quando comparada a dos esquemas baseados em IP.

3- Início da TAR no calendário mais recente (2005-2010) e participação em ensaio clínico foram fatores associados à maior efetividade de esquemas de primeira linha.

4- Em comparação com os homens mulheres apresentaram menor efetividade aos 12 meses para esquemas de primeira linha.

5- O tempo mediano para a troca de esquemas de primeira linha, não foi significativamente diferente entre os grupos com carga viral indetectável e detectável.

6- A incidência de falha de segunda linha foi 3,4 vezes maior entre os pacientes que iniciaram segunda-linha com carga viral detectável quando comparados aos que iniciaram com carga viral indetectável e o impacto da carga viral detectável foi confirmado na análise multivariada como fator independentemente associado a falha de esquemas de segunda linha.

7- Pacientes mais jovens e aqueles com menor nível de escolaridade apresentaram menor efetividade para esquemas de primeira linha e maior risco de falha virológica para esquemas de segunda linha.

8- Apesar da disponibilidade dos testes de resistência, a maior parte das trocas de esquemas de primeira e segunda linha entre pacientes apresentando falha virológica foi realizada sem o embasamento de um resultado de genotipagem.

9- O perfil genotípico encontrado entre aqueles que tiveram um teste de resistência realizado foi compatível como esperado para os esquemas em uso no momento de sua realização. Genotipagens sem evidência de resistência (vírus selvagem) foram mais freqüentes entre pacientes usando esquemas de segunda linha em comparação com primeira linha, especialmente IP-r.

8 CONSIDERAÇÕES FINAIS E RECOMENDAÇÕES

Os dados deste trabalho poderão ser úteis para melhor compreensão dos diferentes perfis de resposta ao tratamento e para a definição de rotinas mais adequadas aos pacientes recebendo TAR em nosso meio. A maioria dos pacientes em primeira linha irá utilizar esquemas baseados em ITRNN conforme a recomendação do protocolo de tratamento brasileiro. Identificamos neste estudo que estes esquemas foram efetivos.

Os pacientes mais jovens e os com menor escolaridade devem ser priorizados para estratégias de adesão tanto para esquemas de primeira linha como para esquemas subsequentes, com maior numero de comprimidos e de maior custo. As estratégias de adesão e cuidado intensivo com monitoramento de toxicidades devem particularmente ser aplicadas às mulheres no primeiro ano de tratamento.

A genotipagem que é uma ferramenta reconhecidamente efetiva precisa ter sua utilização ampliada em nosso meio para guiar as decisões sobre a composição dos esquemas terapêuticos desde a primeira falha.

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