UNIVERSIDADE FEDERAL DO RIO GRANDE DO SU

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM EPIDEMIOLOGIA

TESE DE DOUTORADO

Mutações de Resistência Transmitida do Vírus da Imunodeficiência Humana aos Antirretrovirais: Prevalência e Impacto no Desfecho Virológico

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Orientadora: Prof. Dr. Carisi Anne Polanczyk

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Porto Alegre, Março de 2016.

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SUMÁRIO

LISTA DE ABREVIATURAS E SIGLAS

3TC lamivudina
ABC abacavir
APV amprenavir
ARV antirretroviral
ATV atazanavir
CRFs formas recombinantes circulantes
CV carga viral
d4T estavudina
DRM mutação de resistência adquirida
DRV darunavir
DTG dolutegravir
EFV efavirenz
ETR etravirina
EVT elvitegravir
FPV fosamprenavir
FV falha virológica
HAART terapêutica antirretroviral altamente efetiva
HIV vírus da imunodeficiência humana
IDV indinavir
IP inibidor de protease
ITRN inibidor da transcriptase reversa análogo de nucleosídeos ou nucleotídeos
ITRNN inibidor da transcriptase reversa não análogo de nucleosídeos
LPV lopinavir
MVC maraviroque
NFV nelfinavir
NVP nevirapina
OMS Organização Mundial da Saúde
PEP profilaxia pós-exposição
PrEP profilaxia pré-exposição
PR protease
RAL raltegravir

RNA ácido ribonucleico

RTV ritonavir

SQV saquinavir

T-20 enfuvirtida

TAM mutações dos análogos a timidina (AZT e d4T)

TARV terapia antirretroviral combinada

TDF tenofovir

TDR mutações de resistência transmitidas do HIV aos antirretrovirais

TPV tipranavir

TR transcriptase reversa

URF formas recombinantes únicas

VF virologic failure

VPN valor preditivo negativo

VPP valor preditivo positivo

ZAPS zona de alta pressão seletiva

ZDV zidovudina

RESUMO

Antecedentes: As mutações de resistência transmitida do vírus da imunodeficiência humana aos antirretrovirais (TDRM) podem afetar a efetividade da primeira linha dos esquemas empíricos da terapia antirretroviral (TARV). Acredita-se que sua prevalência esteja aumentando no mundo, porém não há resumo claro e conciso da prevalência das TDRM no Brasil e também não se conhece o impacto financeiro que a implantação do teste de genotipagem para detecção de TDRM causaria no sistema de saúde brasileiro.

Métodos: Foram realizadas buscas eletrônicas nas bases de dados Medline, Embase, Lilacs e Cochrane CENTRAL (até dezembro de 2015) para identificar estudos observacionais que relatam a prevalência de TDRM do HIV no Brasil e para identificar ensaios clínicos randomizados ou estudos observacionais para avaliar o risco de falha virológica (FV) entre pacientes portadores de HIV virgens de tratamento com e sem TDRM. Foi realizada metanálise de efeitos aleatórios das razões de risco (RR). A heterogeneidade foi avaliada pelo teste de inconsistência (I^2) e suas fontes foram investigadas em análise de sensibilidade de subgrupos na meta-análise quando adequado.

Para a realização do impacto orçamentário foi desenvolvida uma coorte simulada aberta através de um modelo de Markov. O modelo consistiu de 3 estados: (1) casos incidentes de HIV ("gerador de paciente" estado); (2) Teste de genotipagem e (estado onde ocorrem os custos) e (3) Saída do modelo (estado absortivo). A duração do ciclo foi de um mês e o horizonte de tempo foi de 5 anos. Não foram aplicados descontos. O número de indivíduos que entram no modelo por ciclo foi projetado a partir de um modelo de regressão derivado de uma série temporal de 10 anos de casos incidentes de HIV.

Resultados: Na revisão sistemática da prevalência, 58 estudos atenderam aos critérios de inclusão da revisão sistemática. Cinquenta e sete relataram TDRM para todas as principais classes de drogas e um foi limitado a inibidores da protease (IP). Apenas as mutações atualmente sob vigilância (Stanford, 2015) foram contabilizadas. A meta-análise revelou uma prevalência de TDRM de 8,9% (IC 95% 7,6 a 10,4) (I^2 = 10,6%), considerando mutação a qualquer classe de drogas. Os valores para TDRM específicas para NRTI, NNRTI e PI foram de 4,7% (IC 95% 3,7 a 5,9; I^2 = 0%); 3,7% (IC 95% 2,9 a 4,6; I^2 = 0%) e 2,8% (IC 95% 2,4 a 3,3; I2 = 0%), respectivamente. Entre os subgrupos, a prevalência de TDRM foi menor nos doadores de sangue (5,8%; 95% CI 3,8 a 12,2; I^2 = 13%) e maior em homens que fazem sexo com homens (16,9%; IC95% 10,9 a 25,3; I^2 = 0%) e em usuários de drogas injetáveis (13,7%; IC95% 10,3 a 18,1; I^2 = 0%). A região com a maior prevalência de TDRM foi a região Sudeste (11,2%; IC95% 9,2-18,6; I^2 = 8,6%).

No estudo do impacto das mutações de resistência transmitida do HIV aos antirretrovirais na resposta ao primeiro tratamento antirretroviral foram encontrados 28 estudos observacionais (23 de coorte e 5 estudos caso-controle) e nenhum ensaio clínico randomizado relatando taxas de FV entre pacientes portadores de HIV virgens de tratamento com e sem TDRM. O RR de FV para ter qualquer TDRM foi de 1,93 (IC 95% 1,44 a 2,59) em uma meta-análise de 21 estudos de coorte que forneceram informações suficientes (I^2 = 82%). Para NRTI, NNRTI e IP, as estimativas de RR em meta-análise foram de 2,58 (IC 95% 1,30 a 5,16); 4,20 (2,21 a 7,96) e 2,92 (1,20 a 7,10), respectivamente. A heterogeneidade diminuiu substancialmente para os subgrupos de classes de drogas (I^2 = 65%, 56% e 58%, respectivamente). A avaliação da qualidade

metodológica indicou ausência de ajuste abrangente para fatores de confusão em quatro dos 28 estudos e a análise do gráfico de funil indicou uma baixa probabilidade de viés de publicação.

As projeções do modelo de regressão linear para incidência anual esperada de HIV entre os anos de 2016 e 2020 variaram de 41022 a 42788 casos, respectivamente. Com 100% incorporação do teste de genótipagem para casos incidentes de HIV desde o início do modelo, o impacto orçamentário acumulado em 5 anos para este cenário foi estimado em R$ 108.244.403,3 (U$ 29.255.244,14).

Conclusão: A estimativa pontual para a prevalência geral de TDRM no Brasil é de 8,9%. Isto é comparável às taxas de prevalência observadas em outros países com elevada cobertura da TARV. As evidências disponíveis indicam que as TDRM aumentam o risco de falha virológica entre pacientes portadores de HIV virgens de tratamento. A aplicação universal do teste de genotipagem para casos incidentes de HIV resultaria em um aumento anual aproximado de 22 milhões de reais (5,9 milhões de dólares) para o sistema de saúde público brasileira.

Abstract

Background: HIV transmitted drug resistance mutations (TDRM) could impact the effectiveness of empirical first-line regimens of high active antiretroviral therapy (HAART). Its prevalence is thought to be increasing worldwide, however there is no clear and concise summary of TDRM prevalence in Brazil. Economic evaluations on HIV genotype test for detection of transmitted drug resistance mutations (TDRM) are scarce and the budget impact for the Brazilian public healthcare system has not been estimated.

Methods: We did electronic searches on Medline, Embase, Lilacs and Cochrane CENTRAL (up to December 2015) to identify observational studies reporting the prevalence of HIV TDRM in Brazil and to identify randomized clinical trials or observational studies reporting the risk of virologic failure (VF) among treatment naïve HIV patients with and without TDRM. To provide an updated summary prevalence measurement of TDRM among Brazilian treatment naïve adult HIV patients. We performed single-arm random effects meta-analyses of prevalence rates. Ninety-five percent confidence intervals (95% CI) were calculated. Heterogeneity was assessed by the inconsistency test (I^2) and its sources were investigated by subgroup and meta-analysis level sensitivity analyses whenever appropriate. To estimate the budget impact of universal HIV genotype test for incident HIV cases in 5 years in Brazil, we developed a Markov model open cohort. The model consisted of three states: (1) HIV incident cases ("patient generator" state); (2) Genotype test and (cost incurring state) and (3) Exit model (absorbing state). Cycle length was one month and time horizon was 5 years. No discounts were applied. The number of individuals entering the model per cycle

was projected from a regression model derived from a 10 years period time-series of HIV incident cases.

Results: Fifty-eight studies matched criteria to be included in the prevalence systematic review. Fifty-seven reported TDRM for all major drug classes and one was limited to protease inhibitor (PI) TDRM. Only major mutations currently under surveillance (Stanford, 2015) were accounted. Meta-analysis revealed a pooled TDRM prevalence of 8.9% (95% CI 7.6 to 10.4) (I^2= 10.6%), considering mutation to any drug class. For NRTI, NNRTI and PI specific TDRM figures were 4.7% (95% CI 3.7 to 5.9) (I^2= 0%), 3.7% (95% CI 2.9 to 4.6) (I^2= 0%) and 2.8% (95% CI 2.4 to 3.3; I^2= 0%), respectively. Among subgroups, TDRM prevalence was lower in blood donors (5.8%; 95% CI 3.8 to 8.8; I^2= 3.1%) and higher in men who had sex with men (16.9%; 95% CI 10.9 to 25.3; I^2= 0%) and injecting drug users (13.7%; 95% CI 10.3 to 18.1; I^2= 0%). The Brazilian territory with the highest TDRM prevalence was the Southeast region (10.9%; 95% CI 8.9 to 13.3; I^2= 9.8%).

In the study of the impact of HIV TDRM in response to the first antiretroviral treatment we found 28 observational studies (23 cohort, three case-cohort and two case-control studies) and no randomized clinical trial reporting VF rates among treatment naïve HIV patients with and without TDRM. RR of VF for having any TDRM was 1.93 (95% CI 1.44 to 2.59) in a meta-analysis of 21 cohort studies that provided sufficient information (I^2=82%). For NRTI, NNRTI and PI, meta-analysis RR estimates were 2.58 (95% CI 1.30 to 5.16), 4.2 (2.21 to 7.96) and 2.92 (1.2 to 7.10), respectively. Heterogeneity decreased substantially for drug class subgroup meta-analyses (I^2=65%, 56% and 58%, respectively). Quality assessment indicated absence of extensive adjustment to confounding in four out

of 28 studies and funnel plot analysis indicated a low probability of publication bias.

Linear model projections for expected annual incidence of HIV between years 2016 and 2020 varied from 41022 to 42788 cases, respectively. With 100% uptake of universal genotype test for incident cases of HIV from model start, annual budget impact estimates were: BRL 21,197,526.48 (USD 5,729,061.21) for 2016; BRL 21,420,723.6 (USD 5,789,384.75) for 2017; BRL 21,650,120.64 (USD 5,851,383.95) for 2018; BRL 21,873,317.76 (USD 5,911,707.50) for 2019 and BRL 22,102,714.8 (USD 5,973,706.70) for 2020. The accumulated 5-years budget impact for this scenario was estimated in BRL 108,244,403.3 (USD 29,255,244.14). Both deterministic and probabilistic sensitivity analyses were performed.

Conclusion: The point estimate for the overall prevalence of TDRM in Brazil is 8.9%. This is comparable to prevalence rates observed in other countries with high coverage of HAART. Available evidence indicates that TDRM increases the risk of VF among treatment naïve HIV patients. Universal HIV genotype test for incident HIV cases would result in an approximate annual increase of 22 million BRL (5.9 million USD) for the Brazilian public healthcare system.

1 APRESENTAÇÃO

O presente trabalho consiste na tese de doutorado intitulada “Mutações de Resistência Transmitida do Vírus da Imunodeficiência Humana aos Antirretrovirais: Prevalência e Impacto no Desfecho Virológico”, apresentada ao Programa de Pós-Graduação em epidemiologia da Universidade Federal do Rio Grande do Sul.

Para a avaliação da prevalência das mutações de resistência transmitida do vírus da imunodeficiência humana aos antirretrovirais no Brasil foi realizada uma revisão sistemática de estudos observacionais de prevalência. Para avaliação do impacto das mutações de resistência transmitida do vírus da imunodeficiência humana aos antirretrovirais no desfecho virológico foi realizada uma revisão sistemática de estudos observacionais de coorte. A avaliação do impacto orçamentário da implantação do teste de genotipagem para detecção das mutações de resistência transmitida do vírus da imunodeficiência humana aos antirretrovirais no Brasil foi realizada a partir do desenvolvimento de uma coorte simulada aberta através de um modelo de Markov.

O trabalho é apresentado em três partes, na ordem que segue:

- Introdução, Revisão da Literatura e Objetivos
- Artigos originais
- Conclusões e Considerações Finais

2 INTRODUÇÃO

A disponibilidade da terapia antirretroviral combinada (TARV) resultou em uma redução significativa da morbimortalidade associada à AIDS[1-4]. Entretanto, a disseminação da TARV levou a emergência de mutações de resistência aos antirretrovirais, documentada ainda nos anos 90 logo após a introdução da monoterapia com zidovudina[5, 6]. A supressão viral ineficiente durante a TARV é o principal fator para a seleção de variantes resistentes do HIV[7]. As cepas resistentes do vírus podem ser transmitidas a novos hospedeiros, fenômeno conhecido como transmissão de mutações de resistência do HIV (TDRM), podendo afetar negativamente o desfecho virológico do primeiro tratamento de pacientes virgens de tratamento[7, 8].

A Organização Mundial da Saúde (OMS), classifica as taxas prevalência de TDRM em baixa (>5%), moderada (5 to 15%) ou alta (>15%)[9]. Em países com alta renda, onde a TARV está disponível há mais tempo, a prevalência de TDRM varia de 8,8% a 17,5% na Europa, Estados Unidos, Japão e Australia[9, 10]. Contrastando com a prevalência observada em países de baixa renda que varia de baixa a moderada 2,8% to 7,6%[11]. No Brasil as taxas de prevalência de TDRM tem sido relatadas com variações desde baixa prevalência 3,8% até altas 18,2%[12, 13].

Em pacientes experimentados, o teste de genotipagem apresenta papel fundamental na escolha da nova terapia antirretroviral após a falha virológica[14, 15]. Entretanto, incertezas permanecem quanto ao risco de falha virológica relacionadas com TDRM em pacientes virgens de tratamento e a importância do teste do genótipo para orientar primeira TARV. Consensos internacionais recomendam o teste de genotipagem pré-tratamento do HIV para orientar a

escolha do esquema antirretroviral[16, 17]. No entanto, no Brasil esta orientação ainda não foi colocada em prática, pois se considera que os dados disponíveis na literatura não são conclusivos[18].

3 REVISÃO DA LITERATURA

3.2 Vírus da Imunodeficiência Humana – HIV

O vírus da imunodeficiência humana (HIV) foi isolado pela primeira vez em 1983 é um vírus da família *Retroviridae*, gênero *Lentivirus*[19]. Existem dois tipos de HIV, o HIV-1, mundialmente distribuído e o HIV-2, praticamente restrito ao oeste da África[20]. O HIV-1, é o responsável pela epidemia mundial, portanto, o mais estudado, já o HIV-2, parece ser menos infeccioso e apresentar progressão mais lenta da doença[20]. O HIV-1 é dividido em quatro grupos M (major), N, O e P. O grupo M é mundialmente distribuído, enquanto os grupos N, O e P estão restritos a África[20]. O Grupo M apresenta ao menos nove subtipos geneticamente distintos: A, B, C, D, F, G, H, J e k[20]. Além disso, os subtipos podem combinar material genético, resultando em formas recombinantes circulantes (CRFs)[20]. O subtipo B, predomina na Europa ocidental, nas Américas e na Austrália, no Brasil também é o subtipo predominante[20, 21]. Entretanto, na região sul se observa o predomínio do subtipo C, mais frequente na África e Índia[20, 22, 23].

3.2 Síndrome da Imunodeficiência Adquirida – AIDS

Em 1981 foram descritos os primeiros casos de imunodeficiência adquirida nos Estados Unidos[24]. A doença foi inicialmente associada a homens que fazem sexo com homens, usuários de drogas injetáveis, receptores de sangue e finalmente a população em geral[25].

A principal característica da infecção pelo HIV é o esgotamento progressivo de células T CD4 devido a redução da produção e aumento da destruição, levando a imunossupressão[20]. A imunodeficiência avançada

favorece a ocorrência de doenças oportunistas associadas a elevada morbi-mortalidade[26].

3.3 Epidemiologia da Infecção pelo HIV e da AIDS

Em 2014, 36,9 milhões de pessoas estavam vivendo com HIV em todo o mundo, dessas, 15,8 milhões tiveram acesso a TARV. Nesse mesmo ano, ocorreram 2 milhões novas infecções e 1,2 mortes relacionadas a AIDS[27].

No Brasil, a média anual de casos novos de AIDS é de 40,6 mil casos, a região com maior número de casos é a Sudeste, 17,0 mil; seguida da região Sul 8,6 e Nordeste, 8,2 mil[28]. Amazonas e Rio Grande do Sul apresentam as maiores taxas de detecção de AIDS, 39,2 e 38,3 casos para cada 100 mil habitantes, respectivamente[28]. Em 2014, aproximadamente 72 mil pessoas iniciaram a TARV, no mesmo ano, ocorreram 12.449 óbitos relacionados a AIDS 44,9% no Sudeste; 20,3% no Sul; 19,5% no Nordeste; 9,3% no Norte e 5,9% no Centro-Oeste[28].

3.4 Terapia Antirretroviral

A descoberta da zidovudina (AZT) em 1987 foi o marco do início da terapia antirretroviral. Sintetizada originalmente como quimioterápico, a droga demonstrou redução da mortalidade e doenças oportunistas[29]. Entretanto a maior avanço foi a introdução da terapia antirretroviral combinada (TARV) nos anos 90[1, 30]. A TARV deve resultar em máxima supressão viral para garantir redução da morbimortalidade associada à AIDS e da transmissão do HIV[31]. Além do impacto significativo na diminuição da morbimortalidade associada a infecção pelo HIV a TARV está associada a recuperação da função imunológica[1-4]. No

Brasil a TARV está disponível desde 1996 gratuita e universalmente distribuída[32]. Atualmente estão disponíveis em todo o mundo 25 antiretrovirais, distribuídos nas seguintes classes:

3.4.1 Inibidores da Transcriptase Reversa Análogos de Nucleosídeos e Inibidores da Transcriptase Reversa Análogos de Nucleotídeos

Os inibidores da transcriptase reversa nucleosídeos ou nucleotídeos (ITRN) são drogas que bloqueiam a enzima trancriptase reversa (TR) impedindo a síntese de DNA viral a partir do RNA[31]. São estruturalmente semelhantes aos nucleosídeos naturais: adenosina (a), guanosina (g), citosina (c) e timidina[33]. Durante o processo da transcrição reversa, os ITRNs substituem, de forma competitiva, os nucleosídeos verdadeiros[33]. São drogas análogas de nucleosídeos: zidovudina (AZT), didanosina (ddI), zalcitabina (ddC) – descontinuada, estavudina (d4T), lamivudina (3TC), abacavir (ABC), emtricitabina (FTC) – não disponível no Brasil e o análogo de nucleotídeo tenofovir (TDF)[31].

3.4.2 Inibidores da Transcriptase Reversa Não-Análogos de Nucleosídeos

O inibidores da transcriptase reversa não nucleosídeos (ITRNN), são inibidores não competitivos que se ligam em sítios específicos da enzima transcriptase reversa, reduzindo sua actividade. São representados por: nevirapina (NVP); delavirdina (DLV) - descontinuada e efavirenz (EFV)[31].

3.4.3 Inibidores da Protease

Esses farmacos inibem a enzima protease, impedindo que a cadeia de proteínas se divida e que elas exerçam as suas funções. Saquinavir (SQV), indinavir (IDV), ritonavir (RTV), nelfinavir (NFV) – descontinuado, ffosamprenavir (FPV), lopinavir/r (LPV), atazanavir (ATV), tipranavir (TPV) – não disponível no Brasil e Darunavir (DRV)[31].

3.4.4 Inibidores da Entrada

Inibidores de Fusão

O complexo glicoproteína do envelope (env) é responsável pela entrada do vírus da imunodeficiência humana tipo 1 (HIV - 1) em células , mediando a ligação de células e subsequente fusão da membrana alvo . Env é composto por três subunidades gp120 que medeiam a ligação do receptor e do co-receptor e três subunidades gp41 responsáveis pela fusão de membrana . A Enfuvirtida (T20) impede que a fusão da membrana competitivamente se ligando a gp41 e bloqueando a formação da estrutura de pós- fusão[34].

Antagonistas do CCR5

O maraviroc e vicriviroc são antagonistas do co-receptor CCR5 atua bloqueando esse correceptor na superfície dos linfocitos T CD4, evitando a entrada do HIV na célula[35].

3.4.5 Inibidores da Integrase

Após a entrada do HIV na célula e transcrição no citoplasma, o DNA viral é transportado para o núcleo da célula onde ocorrera a integração com o genoma celular catalizado pela enzima integrase do HIV. Os inibidores da integrase inibem a replicação viral, bloqueando a integração do DNA viral com o DNA celular. São representantes dessa classe: raltegravir, elvitegravir e dolutegravir[31].

3.5 Resistência aos Antirretrovirais

A resistência aos antirretrovirais é a principal causa de falha virológica[36, 37]. É classificada em resistência transmitida (TDRM) ou primária e resistência adquirida (DRM) ou secundária[7]. A TDRM é observada em pacientes virgens de tratamento e se deve a transmissão de uma variante resistente do HIV[7]. Já a DRM se deve ao desenvolvimento de resistência em indivíduos sob TARV, em decorrência da pressão de seleção exercida pela medicação antirretroviral[7].

3.5.1 Resistência Adquirida aos Antirretrovirais

A DRM tem sido descrita desde os anos 90, após a introdução da monoterapia com AZT[5, 6]. O impacto da presença de resistência secundária na falha virológica e imunológica e na morbimortalidade associada ao HIV está bem estabelecido[5]. Pacientes com resistência secundária apresentam maior risco de progressão para doenças definidoras de AIDS e morte[5]. Também está evidente o importante papel dos testes de genotipagem ou fenotipagem na escolha do esquema antirretroviral após a falha virológica, pacientes que tem a TARV guiada pelo teste tem maior chance de sucesso virológico[14, 15].

3.5.2 Resistência Transmitida

A resistência transmitida também tem sido descrita desde os anos 90[38, 39]. A TDRM é considerada um problema de saúde pública, pois sua presença pode impactar na resposta aos esquemas antirretrovirais de primeira linha. A OMS define os níveis de prevalência TRDM em baixa (>5%), moderada (5 to 15%) ou alta (>15%)[9].

Em países com renda elevada, onde a TARV está disponível a mais tempo, as taxas de prevalência variam de moderada a alta. Os níveis variam de 8,8% a 17,5% na Europa, Estados Unidos, Japão e Austrália[9, 10], contrastando com as taxas de prevalência observadas em países de baixa renda, especialmente na África, onde a prevalência varia de baixa a moderada 2,8% a 7,6%[9]. Uma tendência de aumento da prevalência de TDRM tem sido reportada neste último grupo[9, 40]. Enquanto uma tendência de estabilização ou mesmo redução tem sido apontada em países com TARV já estabelecida[41, 42].

No Brasil os relatos sobre a prevalência de TDRM são conflitantes e não há uma vigilância estruturada com orienta a OMS. As taxas no país, variam de baixas 3,8% a altas 18,2%[12, 13]. Em geral, é aceito que a prevalência de TDRM no Brasil é intermediária entre 11 e 12%[43].

Um estudo mostrou que pacientes com mutações de resistência tiveram mais relações sexuais desprotegidas quando comparados aqueles sem mutações. Dessa forma, expuseram mais seus parceiros a transmissão do HIV e a transmissão de cepas com mutações de resistência[44].

Se acredita que a presença de TDRM impactem negativamente no desfecho do primeiro tratamento antirretroviral de pacientes virgens de tratamento. Dessa forma, a não identificação de mutações de resistência e o

início do tratamento antirretroviral empírico poderiam comprometer a eficácia do primeiro esquema antirretroviral aumentando o risco de falha virológica[7, 8].

Enquanto alguns estudos não encontraram diferença de resposta virológica entre pacientes com TDRM ou vírus selvagem[45, 46], outros demonstraram maior proporção de falha virológica em pacientes com TDRM apesar da terapia plenamente ativa[47]. Dois estudos avaliaram o impacto do teste de genotipagem como guia da TARV: um deles encontrou eficácia semelhante da TARV em pacientes com virus selvagem ou TDRM[46], e o outro identificou que pacientes com TDRM apresentaram maior risco de falha virológica, mesmo com o tratamento guiado pelo teste de genotipagem[47].

Além disso, a genotipagem convencional detecta populações virais que estejam presentes em proporções superiores a 25 ou 30%, estudos tem demonstrado que a presença de populações virais minoritárias, identificadas por métodos ultrassensíveis capaz de detectar populações virais em proporções inferiores a 1%, podem aumentar o risco de falha virológica [36, 48]. Portanto, esses pacientes não teriam sido identificados pelo teste de genotipagem convencional.

3.5.3 Mutações de resistência

As mutações de resistência levam a alterações que impedem, alteram ou anulam a ligação dos ITRNs, ITRNNs ou IPs ao HIV, diminuindo ou inativando a ação desses fármacos[33].

A resistência aos ITRNs pode ocorrer através de dois mecanismos: as mutações resultam em um aumento na capacidade da TR do HIV-1 em discriminar entre o ITRN e o nucleosídeo verdadeiro, levando a uma incorporação preferencial do nuceosídeo natural ou as mutações aumentam a

capacidade da enzima em eliminar o ITRN incorporado ao final da cadeia impedindo seu alongamento[33]. As mutações análogas da timidina (TAMs) são mutações não polimórficas selecionadas pelos análogos da timidina AZT e d4T que reduzem a suscetibilidade dos IRTNs favorecendo sua eliminação[49]. As mutações M41L, D67N, K70R, L210W, T215Y/F and K219Q/E são TAMs clássicas[49]. A mutação M184V/I é uma mutação não-TAM induzida pelo 3TC ou FTC que reduz a suscetibilidade a esses fármacos, aumentando a suscetibilidade ao AZT, d4T e TDF[49]. K65R, K70E, L74V/I, Y115F são outras mutações não-TAM também associadas a redução de suscetibilidade de fármacos ITRNs[49]. As mutações T69*ins* (inserção) e Q151M, geralmente em combinação com outras mutações, causam resistência a múltiplos ITRNs[49].

As mutações de resistência aos ITRNNs atuam promovendo uma alteração estrutural na TR impedindo a ligação desses fármacos[33]. As mutações L100I, K101E/P, K103N/S, V106A/M, E138 A/G/K/Q, Y181C/I/V, Y188L/C/H, G190A/S/E e M230L são mutações com relevância clínica associadas a redução da suscetibilidade ou da resposta virológica aos ITRNNs[50].

As mutações selecionadas pelos IPs levam a uma alteração na conformação tridimensional da protease resultando em diminuição do tempo de ligação dos IPs à protease favorecendo a ligação das poliproteínas virais no sítio ativo da enzima e diminuição do tempo de clivagem da cadeia de proteínas pela protease[33]. As mutações D30N, V32I, L33F, M46I/L, I47V/A, G48V/M, I50L/V, I54V/T/A/L/M, L76V, V82A/T/F/S, I84V, N88S E L90M são mutações com relevância clínica associadas a redução da suscetibilidade AOS IPs[51].

3.5.4 Testes de resistência

Os testes de resistência para detecção de mutações do HIV podem ser fenotípicos ou genotípicos[52]. Os testes de fenotipagem medem a concentração inibitória necessária para inibir o crescimento do HIV in vitro, medem diretamente a suscetibilidade a drogas antirretrovirais[52]. Enquanto os testes de genotipagem detectam a presença de mutações específicas do HIV[52].

Os testes de fenotipagem apresentam uma medida direta da resistência viral, são mais fáceis de interpretar, apresentando resultados quantitativos para a perda da suscetibilidade[52]. Entretanto, são tecnicamente mais complexos, mais caros e mais demorados[52]. Os testes de genotipagem apresentam menor custo e tempo de execução, mas apresentam menor sensibilidade para variantes minoritárias do HIV (<20%)[52]. A determinação da resistência é indireta, sendo complexa quando múltiplas mutações estão presentes[52].

A fenotipagem virtual é uma forma de interpretação que correlaciona os resultados da genotipagem com um banco virtual de resultados de fenotipagem e parece apresentar resultados comparáveis à fenotipagem convencional[53].

Os métodos convencionais de detecção de mutações de resistência falham em detectar variantes minoritárias que podem impactar na resposta ao HAART[36, 54]. Metodologias ultrassensíveis tem sido desenvolvidas, capazes de detectar frequências tão baixas quanto 1%[55]. No entanto, essas metodologias são experimentais e ainda não estão disponíveis para o uso rotineiro[33].

3.5.5 Vigilância das Mutações de Resistência transmitida do HIV aos antirretrovirais

A Organização Mundial da Saúde propõe que seja realizada uma vigilância nacional das mutações de resistência transmitida[56]. O objetivo dessa vigilância é conhecer a prevalência dessas mutações de resistência para determinar o esquema de primeira linha mais adequado da TARV assim como o esquema para as profilaxias pré e pós-exposição (PrEP e PEP)[56]. Uma lista de mutações é definida para que essa vigilância seja comparável entre os países. São levados em consideração mutações que causam ou contribuem para a resistência a antirretrovirais, mutações que não ocorreram como polimorfismos na ausência de terapia e que a lista seja aplicável a todos os subtipos do Grupo M[57]. A última atualização da lista mutações para vigilância foi feita em 2009, 93 mutações foram incluídas, 34 mutações de resistência aos ITRN, 19 aos IRTNN e 40 aos IP[58]. As mutações selecionados aos ITRN são: M41L, K65R, D67N/G/E, T69D/ins (inserção), K70R/E, L74V/I, V75M/T/A/S, F77L, Y115F, F116Y, Q151M, M184V/I, L210W, T215Y/F/S/C/D/E/I/V e K219Q/E/N/R; aos ITRNN: L100I, K101E/P, K103N/S, V106A/M, V179F, Y181C/I/V, Y188L/C/H, G190A/S/E, P225H e M230L e aos IP: L23I, L24I, D30N, V32I, M46I/L, I47V/A, G48V/M, I50V/L, F53F/Y, I54V/L/M/T/A/S, G73S/T/C/A, L76V, V82A/T/S/F/L/C/M, N83D, I84V/A/C, I85V, N88D/S, L90M[58, 59].

3.6 Análise de impacto orçamentário de tecnologias da saúde

A análise de impacto orçamentário pode ser definida como a avaliação das consequências financeiras advindas da adoção de uma nova tecnologia (intervenção) em saúde, dentro de um determinado cenário de saúde com

recursos finitos[60, 61]. Diferentemente das análises de custo-efetividade, onde usualmente se compara o efeito na relação custo-benefício da substituição de uma tecnologia por outra, na análise de impacto orçamentário é estimado o impacto econômico da incorporação (ou remoção) uma nova intervenção considerando-se o conjunto das tecnologias disponíveis para o problema de saúde em análise, incluindo os custos da nova intervenção em si, custos de co-intervenções, movimento de recursos associados às opções terapêuticas em uso e possíveis realocações de recursos para os casos em que a inclusão de uma nova tecnologia possa resultar em economias ao sistema de saúde[60, 62-65].

O principal papel deste tipo de estudo é a previsão do impacto financeiro da adoção de determinada tecnologia. Para tanto, integra os seguintes elementos: (1) o gasto atual com uma dada condição de saúde, (2) a fração de indivíduos elegível para a nova intervenção, (3) os custos diretos da nova intervenção e (4) o grau de inserção da mesma após sua incorporação. Desta forma, a AIO se constitui em uma ferramenta fundamental para os gestores do orçamento da saúde pública e suplementar, auxiliando a previsão orçamentária em um intervalo de tempo definido[61].

3.7 Conclusões da Revisão da Literatura

O Brasil não tem uma vigilância estruturada das TDRM e a prevalência dessas mutações relatadas em estudos observacionais varia de baixa a alta. O papel das TDRM na resposta ao primeiro tratamento antirretroviral ainda não está claro, embora haja uma tendência de acreditar que a presença de mutações de resistência aumente o risco de falha virológica. Além disso, a eficácia do teste de genotipagem pré-tratamento no HIV não está estabelecida, os estudos disponíveis não permitem concluir se a TARV guiada pelo teste tem melhor resultado do que o tratamento empírico. Além disso, estudos que utilizaram metodologia ultrassensível, tem mostrado que o teste de genotipagem convencional tem falhado em detectar populações minoritária que podem impactar na resposta a TARV. Não há consenso se o teste de genotipagem pré-tratamento do HIV deve ser implantado e também não se conhece o impacto financeiro que isso causaria ao sistema de saúde.

4 OBJETIVOS

- Estimar a prevalência das mutações de resistência transmitida do HIV aos antirretrovirais no Brasil.

- Estimar o impacto das mutações de resistência transmitida do HIV aos antirretrovirais na falha virológica do primeiro esquema antirretroviral.

- Estimar o impacto do uso do teste de genotipagem do HIV na prevenção de falha virológica do primeiro esquema antirretroviral.

- Estimar o impacto financeiro da implantação do teste de genotipagem pré-tratamento do HIV.

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6 Artigo 1

PREVALENCE OF HUMAN IMMUNODEFICIENCY VIRUS TRANSMITTED DRUG RESISTANCE IN BRAZIL: A SYSTEMATIC REVIEW AND META-ANALYSIS

Prevalência das Mutações de Resistência Transmitida do Vírus da Imunodeficiência Humana aos Antirretrovirais no Brasil: uma revisão sistemática e metanálise.

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PREVALENCE OF HUMAN IMMUNODEFICIENCY VIRUS TRANSMITTED DRUG RESISTANCE IN BRAZIL: A SYSTEMATIC REVIEW AND META-ANALYSIS

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ABSTRACT

Background: HIV transmitted drug resistance mutations (TDRM) could impact the effectiveness of empirical first-line regimens of high active antiretroviral therapy (HAART). Its prevalence is thought to be increasing worldwide, however there is no clear and concise summary of TDRM prevalence in Brazil.

Methods: This systematic review of literature aimed at providing an updated summary prevalence measurement of TDRM among Brazilian treatment naïve adult HIV patients. We did electronic searches on Medline, Embase, Lilacs and Cochrane CENTRAL (up to December 2015) to identify observational studies reporting the prevalence of HIV TDRM in Brazil. We performed single-arm random effects meta-analyses of prevalence rates. Ninety-five percent confidence intervals (95% CI) were calculated. Heterogeneity was assessed by the inconsistency test (I^2) and its sources were investigated by subgroup and meta-analysis level sensitivity analyses whenever appropriate.

Results: Among the 736 records identified in the initial electronic search, 58 studies matched criteria to be included in this systematic review. Fifty-seven reported TDRM for all major drug classes and one was limited to protease inhibitor (PI) TDRM. Only major mutations currently under surveillance (Stanford, 2015) were accounted. Meta-analysis revealed a pooled TDRM prevalence of 8.9% (95% CI 7.6 to 10.4) (I^2= 10.6%), considering mutation to any drug class. For NRTI, NNRTI and PI specific TDRM figures were 4.7% (95% CI 3.7 to 5.9) (I^2= 0%), 3.7% (95% CI 2.9 to 4.6) (I^2= 0%) and 2.8% (95% CI 2.4 to 3.3; I^2= 0%), respectively. Among subgroups, TDRM prevalence was lower in blood donors

(5.8%; 95% CI 3.8 to 8.8; I^2= 3.1%) and higher in men who had sex with men (16.9%; 95% CI 10.9 to 25.3; I^2= 0%) and injecting drug users (13.7%; 95% CI 10.3 to 18.1; I^2= 0%). The Brazilian territory with the highest TDRM prevalence was the Southeast region (10.9%; 95% CI 8.9 to 13.3; I^2= 9.8%).

Conclusion: The point estimate for the overall prevalence of TDRM in Brazil is 8.9%. This is comparable to prevalence rates observed in other countries with high coverage of HAART. The clinical relevance of this finding is still a subject to be researched.

INTRODUCTION

Transmitted drug resistance mutations (TDRM) results from infection with an HIV-1 strain containing one or more resistance associated mutations. It is believed that TDRM negatively impacts antiretroviral treatment, delaying immunologic and virologic responses. This could increase the risk of virologic failure[1-3].

According to the World Heath Organization (WHO), TDRM prevalence rates for each drug class is categorized as low (>5%), moderate (5 to 15%) or high (>15%)[4]. In high-income countries, where highly active antiretroviral therapy (HAART) has been available for a longer time, prevalence rates are moderate to high. Reported levels range from 8.8% to 17.5% in Europe, United States, Japan and Australia[5, 6]. This contrasts with prevalence rates observed in low-income countries, especially in Africa, where reported figures are in the low to moderate range, varying from 2.8% to 7.6%[7]. A tendency for increase in TDRM prevalence rate has been reported for this latter group[6, 8].

Reports on TDRM prevalence rate in Brazil are conflicting, ranging from as low as 3.8% to as high as 18.2%[9, 10]. It is generally accepted that TDRM prevalence in Brazil is at the moderate WHO level, with a countrywide point estimate between 11 and 12%[11]. Previous systematic reviews have provided prevalence estimates for Latin American countries, including Brazil[12]. However, no study has addressed specifically the question of TDRM prevalence in Brazil with sufficient detail to report and analyze summary estimates organized by country territories and subgroups of patients.

The objective of this study is to report updated TDRM prevalence rates in Brazil and to provide a clear and concise summary of reported prevalence rates by country territory and by subgroups of patients. To do so, we conducted a systematic review of literature with single-arm meta-analysis.

METHODS

Search Strategy

We conducted a systematic review of literature to identify observational studies reporting the prevalence of HIV transmitted drug resistance in Brazil. Literature search was conducted in Medline, Embase, Lilacs and Cochrane CENTRAL (up to December 2015). The following medical subject headings (MeSH) and text word combinations were used: Acquired Immunodeficiency Syndrome, HIV infection, antiretroviral therapy, highly active antiretroviral therapy (HAART), genotype. No filters for study design were used. A complete description of search strategy is provided (appendix I).

Eligibility criteria

We included clinical studies reporting TDRM in treatment-naive adult subjects submitted to HIV genotyping. Additionally, we limited the inclusion to studies reporting major resistance mutations. We excluded studies on pediatric patients or in pregnant women. Studies reporting only minority resistance mutations were excluded as well. There was no restriction as to study period or number of patients. There was no language restriction.

Study selection

Records identified by the literature searches were scrutinized in two phases. All studies were initially scanned for relevance by title and abstract. Studies that could not be excluded according to our eligibility criteria in the abstract review had their full text retrieved for further evaluation. Study selection

was independently performed by two investigators (C.G.R. and A.F.A.S.). Disagreements were solved by consensus.

Data extraction

Two reviewers independently abstracted data from included articles (C.G.R. and A.F.A.S.). Disagreements were resolved by consensus and, if necessary, with the opinion of a third reviewer (C.A.P.). Abstracted information comprised: study design, patient population characteristics, study state and city, publication year, data collection period, HIV subtypes, duration of HIV infection, type of genotype test, genotype test interpretation (Stanford or IAS-USA), proportion of patients with TDRM in general and proportion of patients with drug class specific TDRM (NRTI, NNRTI and PI). Data on mutations have been standardized through the World Health Organization 2009 list of mutations for surveillance of transmitted drug resistant HIV strains[13].

Statistical analysis

We performed random-effects single-arm meta-analyses of prevalence rates in the software Comprehensive Meta-Analysis Software (CMA version 3). Heterogeneity between studies was assessed by inconsistency test (I^2) and its sources were investigated by subgroup and meta-analysis level sensitivity analyses whenever appropriate. Ninety five percent confidence intervals (95% CI) were calculated.

RESULTS

The initial search identified 736 records, with 25 duplicates. Titles an abstracts were analyzed from 711; 91 were selected for full-text review; 58 articles met the eligibility criteria and were included (figure 1). Table 1 presents the characteristics of the included studies. One study presented result only for PI mutations and wasn't included in the global TDRM analysis[14]. Thirty-five studies were sampled from general population[9-11, 14-45], eleven were from voluntary counseling and testing centers (VCTs)[46-55], four were from blood donors (datasets from blood banks)[56-59], three were from Injecting drug users[60-62], two were from men who had sex with men (MSM)[63, 64], one from women[65], one from prisoners and one from multiple sampling sources[66] (VCTs, antenatal clinics, army soldiers and AIDS clinics). Regarding geographic location, twenty-five studies were from the Southeast region[10, 14, 15, 17-23, 26, 31, 35, 36, 40, 51, 53, 55-58, 60, 64, 66, 67], ten from the South region[24, 27, 33, 38, 39, 44, 48, 52, 54, 68], nine were from the Northeast region[9, 16, 25, 28, 42, 43, 61, 65, 69], four from the Midwest region[29, 32, 37, 47] and two from North region[30, 34]. Eight were from multiple regions[11, 41, 45, 46, 59, 62, 63, 70]. Subtype B was the most frequent subtype in most studies.

Funnel plot analysis was conducted to evaluate risk of publication bias. Funnel plot of standard error (as a measurement of sample size) and log odds ratio (as a measurement of prevalence) was asymmetrical among smaller studies, which suggests that publication bias might be present. Reasons for not publishing observational studies are less understood than clinical trials meta-analysis, but the absence of small studies with large prevalence estimates

suggests that there might exist small studies with large prevalence measurements that were kept unpublished.

We did not perform adjustments for publication bias because 47 out of 59 studies formed a symmetrical cloud at the upper part of the forest plot, indicating that the possibility of publication bias among larger studies was lower.

Meta-analysis: prevalence of TDRM to any drug class

Meta-analysis from all 57 studies that reported TDRM to any drug class has shown a prevalence of 8.9% (95% CI 7.6 to 10.4) (I^2= 10.6%) to global TDRM (figure 3). Drug class specific pooled TDRM prevalence estimates were 4.7% (95% CI 3.7 to 5.9) (I^2= 0%) for NRTI (figure 4); 3.7% (95% CI 2.9 to 4.6) (I^2= 0%) for NNRTI (figure 5); and 2.8% (95% CI 2.4 to 3.3) (I^2= 0%) to PI (figure 6).

Meta-analysis: studies grouped by clinical setting

In the meta-analysis by clinical setting (table 2), general population presented pooled prevalence rates of 8.6%; 4.5%; 3.8% and 2.7%, respectively to global, NRTI, NNRTI and PI TDRM. Population from voluntary counseling and testing center presented pooled prevalence rates of 8.6%; 4.5%; 3.8% and 2.7%, respectively to global, NRTI, NNRTI and PI TDRM. Blood donors presented pooled prevalence rates of 5.8%; 4.2%; 0.9% and 1.3%, respectively to global, NRTI, NNRTI and PI TDRM. Injecting drug users presented prevalence rates of 13.7%; 9.4%; 3.4% and 3.7%, respectively to global, NRTI, NNRTI and PI TDRM. MSM presented prevalence rates of 16.9%; 11.5%; 5.6% and 4.6%, respectively to global, NRTI, NNRTI and PI TDRM.

Meta-analysis: studies grouped by Brazilian regions

In the meta-analysis by regions (table 3), Southeast region presented prevalence rates of 10.9%; 6.1%; 4.4% and 3.3%, respectively to global, NRTI, NNRTI and PI TDRM. South region presented prevalence rates of 7.3%; 3.2%; 3.0% and 1.8%, respectively to global, NRTI, NNRTI and PI TDRM. Northeast region presented prevalence rates of 8.7%; 4.2%; 3.3% and 2.6%, respectively to global, NRTI, NNRTI and PI TDRM. Midwest region presented prevalence rates of 7.5%; 4.9%; 2.5% and 1.9%, respectively to global, NRTI, NNRTI and PI TDRM. North region presented prevalence rates of 4.2%; 2.0%; 3.0% and 1.2%, respectively to global, NRTI, NNRTI and PI TDRM.

Meta-analysis by time period

In the meta analysis by period (table 4), prevalence rates for the 1989 to 2004 period were 8.1%; 5.0%; 1.9% and 2.6% respectively to global, NRTI, NNRTI and PI TDRM. Prevalence rates for the 2005 to 2009 period were 8.7%; 4.2%; 4.7% and 2.7 respectively to global, NRTI, NNRTI and PI TDRM. The prevalence rates for the 2010 to 2015 period were 9.7%; 4.7%; 3.7% and 2.8 respectively to global, NRTI, NNRTI and PI TDRM.

DISCUSSION

This systematic review presents valid pooled estimates of HIV-1 TDRM prevalence for the Brazilian population. Fifty-nine studies were identified, covering all Brazilian territories and a broad range of clinical scenarios and subgroups of patients. We have demonstrated that the pooled all-time prevalence of TDRM to any drug class in Brazil is 8.9%, a number in the intermediate range of the WHO TDRM prevalence rate classification. Individual antiretroviral class analysis shows low level of resistance for all classes. Heterogeneity was low and it could be explained by geographic location, time expanse covered and differences in the clinical settings where TDRM were detected[5, 7, 8].

Analysis by geographic region demonstrated intermediate level (5 to 15%) of TDRM for all regions, except for the North region, which presented low level of resistance (4.2%). However, pooled estimates for regional levels of TDRM should be taken with caution, since the Southeast region is overrepresented and the North region is underrepresented, generating a wide confidence interval.

Meta-analysis of patient subgroups (clinical context) has found a disproportionate higher prevalence of TDRM among men who have sex with men (MSM) and injection drug users (IDUs). These findings are in accordance with previous published studies that have identified a greater prevalence of TDRM in those groups [71, 72].

Our point estimate of 8.9% for HIV-1 TDRM prevalence rate in Brazil resulted from the pooling of all 58 studies, spanning a 15 years period. Yet, meta-analysis limited to studies from the current era of HIV treatment (2010 to 2015) resulted in a point estimate of 9.7%, not too far off. Prevalence rates for the other

time periods (8.1% for 1989 to 2004 and 8.7% for 2005 to 2009) are relatively stable, with slow increase over time. Drug class specific TDRM also seems relatively stable along time, with an apparent tendency for reduction in NRTI and NNRTI (table 4).

One of the main strengths of the present work is that it is simple and clear, providing pooled estimates readily applicable from established meta-analytic techniques. Methodological transparency permits scrutiny and appreciation by the scientific community, which leads to an increased external validity of our findings.

This contrasts with the systematic review by Coelho et al that have estimated pooled prevalence rates for Latin America and Caribbean, including Brazil[12]. There are a number of issues with their approach to generating meta-analytic estimates of HIV-1 TDRM in Brazil. First and foremost: the method used to generate pooled prevalence estimates along time, an auto-regressive moving average model, though theoretically valid, lacks the transparency of more traditional meta-analytic approaches[12]. This is critical to an appraisal of their work, as they have found a worrying steep increase in TDRM prevalence "projections", from 7.3% (80% CI=1.0-13.6) in 2012 to 15.3% (95% CI=5.6-25.0) in 2013 and impressive 20.6% (95% CI=10.7-30.6) in 2014. These figures are likely to be overestimating true prevalence rates once they are compared to the rest of the world. No country has ever had TDRM prevalence estimates greater than 20%, the highest estimate being from Australia, with 17% and TDRM prevalence rates in countries with established HAART programs tend to remain relatively stable or decrease over time, with no steep increase once those programs have been successfully implemented[6, 73, 74]. There are still another

problems with their work. Literature search was limited to MEDLINE (Pubmed), with no supplementary search in other databases such as EMBASE, CENTRAL or LILACS, the latter specialized in literature from Latin America and Caribbean and they have not identified seven studies relevant to the research question that had been published within their search time frame (seven other have been published after July 2014).

We acknowledge some limitations in the present systematic review. First, we have only accounted for currently relevant major resistance mutations (Stanford classification, 2015), thus resistance mutations that were relevant in the past (but not in the present) have not been included in prevalence estimates. Second, we have not included minority mutations variants, as their reporting was inconsistent among identified studies and their clinical significance is controversial. Third, funnel plot indicates risk for publications bias. Yet it is unlikely that missing studies would modify substantially meta-analysis results because the bulk of evidence is symmetrically arranged in a cloud of studies with bigger sample sizes on the upper part of the funnel plot. Fourth, some subgroups were underrepresented (for example, North region), generating very imprecise estimates of pooled prevalence rates. Finally, selection bias may be at play in the primary studies, resulting in overestimation of prevalence rates (patients with higher probability of TDRM might have a higher probability of being submitted to primary HIV genotype test). Pre-treatment genotyping in Brazil is restricted to a few indications and the country does not adopt the TDRM surveillance recommended by WHO[75]. This results in selection of patients at higher risk for TDRM to be tested. This phenomenon has been described previously, as in a recent study that showed low frequency of pre-treatment genotype test in South

America (1.8%) and greater likelihood of pre-treatment testing in white ethnicity and MSM[5].

In conclusion, all time prevalence of HIV-1 TDRM in Brazil was estimated at 8.9% and current prevalence at 9.7%. Those are not negligible amounts. Future research and public health policies should be directed at monitoring TDRM prevalence trends and relation to clinically relevant outcomes. Sampling of future studies should include sufficient participants from regions and subgroups underrepresented in published literature to improve external validity and precision of prevalence estimates.

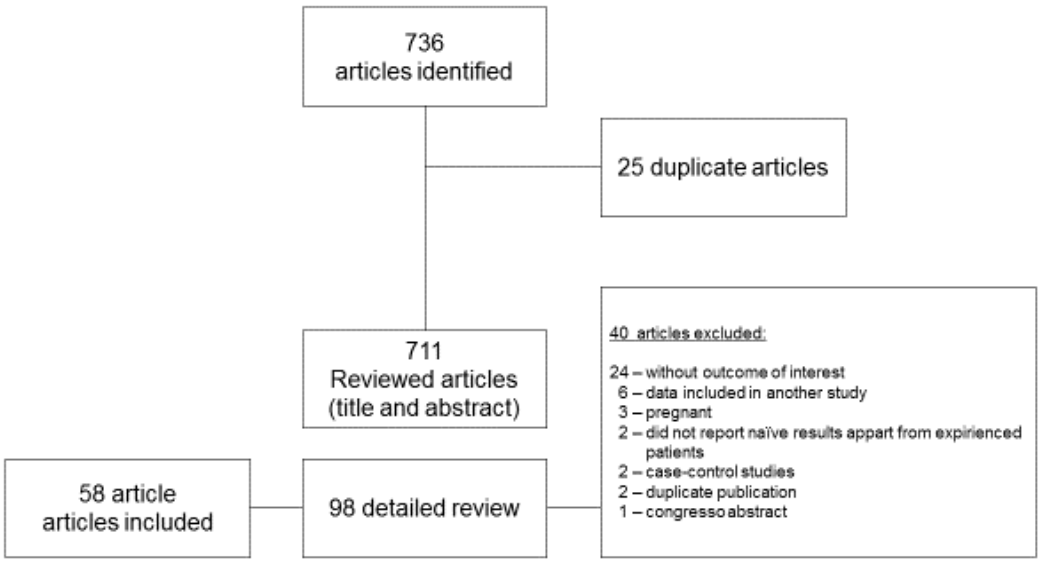


Figure 1 - Flowchart diagram

Table 1 – Studies Characteristics

Author, sample collection period	Publication year	N	State	Population	Male sex n (%)	Age Median (range)	MSM n (%)	Recent infection	Subtype B n (%)
Dumans, 1989-2005	2009	290	RJ	General	NI	NI	NI	NI	211 (74.4)
Maia Teixeira, 1994-2001	2006	65	RJ	IDU	NI	NI	NI	NI	45 (62.2)
Brites, 1995-1997	2001	40	BA	General	NI	NI	NI	NI	NI
Brindeiro, 1996	1999	32	RJ, SP	Blood donors	NI	NI	NI	NI	23 (71.9)
Couto-Fernandez, 1996-2009	2010	294	RJ	VCT, antenatal clinics, army soldiers and AIDS clinics	NI	NI	NI	0	NI
Tupinambas, 1996-2012	2013	64	MG	MSM	64 (100)	30.6† (19-54)	64 (100)	64 (100)	44 (68.8)
Brigido, 1997	2005	33	SP	General	30 (90.9)	recent infection 29 (25–35) chronic infection 35 (30–37)	19‡ (73.1)	26 (78.8)	NI
Pilcher, 1997	1999	42	ES	General	NI	NI	NI	NI	NI
Barreto, 1998- 2002	2006	341	SP	Blood donors	NI	NI	NI	NI	277 (81.2)
Dumans, 1998	2002	49	RJ	Blood donors	NI	NI	NI	NI	41 (83.7)
Eyer-Silva, 1999-2005	2005	27	RJ	General	12 (44)	27 (20-57)	NI	NI	27 (100)
Sucupira, 1999-2000	2007	90	SP	VCT	NI	NI	NI	25 (27.8)	49 (54.4)
Varella, 1999-2001	2007	71	RJ	General	47 (69.2)	NI	NI	20 (28.2)	60 (84.5)
Gonsalez, 2000-2006	2007	123	SP	General	89 (72.4)	37¥ (± 12)	NI	0	101 (82.1)
Pires, 2000-2002	2004	56	RJ	General	45 (80.4)	NI	NI	NI	39 (69.6)

Sá-Ferreira, 2000-2004	2007	74	AM, BA, MG, PE, RJ, SP	Blood donors	NI	NI	NI	NI	62 (83.8)
Brindeiro, 2001	2003	409	RS, PR, SP, RJ, MS,PA , BA, CE	VCT	225 (55.0)	30.7¥ (±9.1)	NI	0	122 (29.8)
Soares, 2001	2003	112	RS, PR, SP, RJ, MS	VCT	61 (54.5)	31 (15-60)	NI	112 (100)	57 (50.9)
Alcalde, 2002-2010	2012	211	SP	General	NI	NI	NI	NI	167 (79.1)
De medeiros, 2002-2003	2006	84	PE		54 (64.3)	35 (18-80)	35 (41.7)	NI	61 (72.6)
Sanabani, 2002	2011	101	SP	General	91 (90.1)	31 (18-56)	80 (79.2)	101 (100)	81 (80.2)
Soares, 2002	2005	25	RS	General	NI	NI	NI	NI	NI
Sucupira, 2002-2007	2009	174	SP	VCT	NI	NI	NI	174 (100)	NI
Diaz, 2003-2004	2008	56	SP	General	NI	37	NI	NI	44 (78.6)
Brigido, 2004-2006	2007	204	RS, SC	General	112 (54.9)	33 (16.2)	NI	NI	59 (28.9)
Eyer-Silva, 2004-2006	2008	50	RJ	General	NI	NI	NI	NI	NI
Rodrigues, 2004	2006	76	RS	VCT	65 (85.5)	31 (40.8)	10 (13.2)	NI	35 (46.1)
De Paula Ferreira, 2005-2006	2008	57	PR	VCT	43 (75.4)	NI	32 (56.1)	17 (29.8)	31 (54.4)
Pfrimer, 2005-2008	2013	82	GO	VCT	57 (69.5)	36 (± 12)	NI	14 (17.1)	69 (84,1)
Santos, 2005-2008	2011	205	RS	General	116 (56.5)	35.4 (±11.7)	18 (8.8)	205 (100)	45 (22.0)
Velasco-de-Castro, 2005-2007	2014	246	RJ	VCT	130 (52.8)	NI	51 (20.7)	144 (58.5)	192 (78.0)
De Medeiros, 2006-2007	2011	99	RS	General	54 (53.5)	(19-56)	NI	NI	26 (26.2)

De Sa-Filho, 2006-2008	2009	33	SP	General	NI	NI	NI	NI	22 (66.7)
Cardoso, 2007-2008	2009	97	GO	General	66 (68)	32 (15-71)	25 (25.8)	16 (16.5)	78 (80.4)
Cavalcanti, 2007-2009	2012	130	CE	VCT	69 (53.1)	(31-50)	21 (16.2)	25 (23.1)	74 (56.9)
Inocencio, 2007-2008	2009	210	SP, RJ, BA, RS, DF, PA	General	95 (45.2)	36¥ (± 8)	NI	210 (100)	153 (72.9)
Monteiro-Cunha, 2007	2011	7	BA	Women	0	NI	NI	NI	NI
Sprinz, 2007	2009	387	BA, DF, MG, PR, RJ, RS, SC, SP	General	265 (68.5)	36 (15-66)	173 (44.7)	NI	264 (68.2)
Arruda, 2008-2009	2011	63	CE	General	56 (88.9)	30 (1-67)	41 (65.1)	NI	NI
Bermudez-Aza, 2008-2009	2011	44	AM, PE, BA, MS, MG, RJ, SP, PR, SC	MSM	44 (100)	29.1€	44 (100)	NI	B (66,8%)
Carvalho, 2008-2009	2011	52	TO	General	31 (59.6)	30 (14-65)	9 (17.3)	NI	41 (78.8)
Da Silveira, 2008-2010	2012	49	MS	General	30 (61.2)	36 (19–64)	33 (67.3)	NI	32 (65.3)
Ferreira, 2008-2009	2011	92	MT	General	54	36 (12-65)	MSM 7	NI	66 (71.7)
Ferreira*,2008-2009	2013	225	SP	VCT	161	34 (29–40)	120	NI	180 (80.0)
Graf, 2008-2009	2011	82	SC	General	40	37, 8 (± 10)	18	NI	11 (13.4)
Couto-Fernandez, 2009-2012	2013	159	RJ	General	NI	NI	NI	NI	127 (79.9)
De Moraes Soares, 2009-2010	2014	329	AM, BA, DF, RJ,	General	227 (69.0)	39 (18-76)	NI	NI	86 (26.1)

			RS, SC, SP						
Gaspareto, 2009	2012	48	PR	General	36 (75.0)	35 (15-61)	12 (25.0)	NI	19 (39.6)
Guimaraes, 2009	2015	128	SP	IDU	NI	NI	NI	19 (14.8)	66 (51.6)
Prellwitz, 2009	2013	31	RS	Inmates	31 (100)	NI	NI	NI	NI
Moura, 2011-2012	2015	89	PI	General	45 (50.6)	34 (18-20)	22 (24.7)	NI	77 (88.5)
Guimaraes, 2012-2014	2015	186	SP	General	141 (75.8)	31 (25–38)	92 (49.5)	NI	132 (71.0)
Moura, 2012	2015	106	MA, PI	General	48 (45.3)	31 (18-72)	19 (17.9)	NI	86 (81.1)
Dos Anjos Silva, 2013-2014	2015	95	AP	General	62 (65.5)	33 (15-72)	NI	NI	72 (78.3)
Dudley, 1998-2003	2012	50	SP	General	NI	NI	NI	NI	NI
Pessoa, 2013-2014	2014	24	PE	General	NI	NI	NI	NI	NI
Grinberg, 2015	2015	76	SC	VCT	NI	NI	38 (45.8)	38 (45.8)	18 (23.7)
Oliveira-Filho, 2015	2015	107	PI	IDU	NI	NI	NI	NI	90 (84.1)

† mean (range), ¥ mean (standard deviation), € mean
‡ information only for recent infection
AP, Amapá; AM, Amazona; BA, Bahia; CE, Ceará; DF, Distrito Federal; ES, Espirito Santo; GO, Goias; MA, Maranhão; MS, Mato Grosso do Sul; MT, Mato Grosso; MG, Minas Gerais; PA, Pará; PR, Paraná, PE, Pernambuco; PI, Piauí; RJ, Rio de Janeiro; RS, Rio Grande do Sul; SC, Santa Catarina; SP, São Paulo; TO, Tocantins
IDU, Injecting drug users; VCT, voluntary counseling and testing center

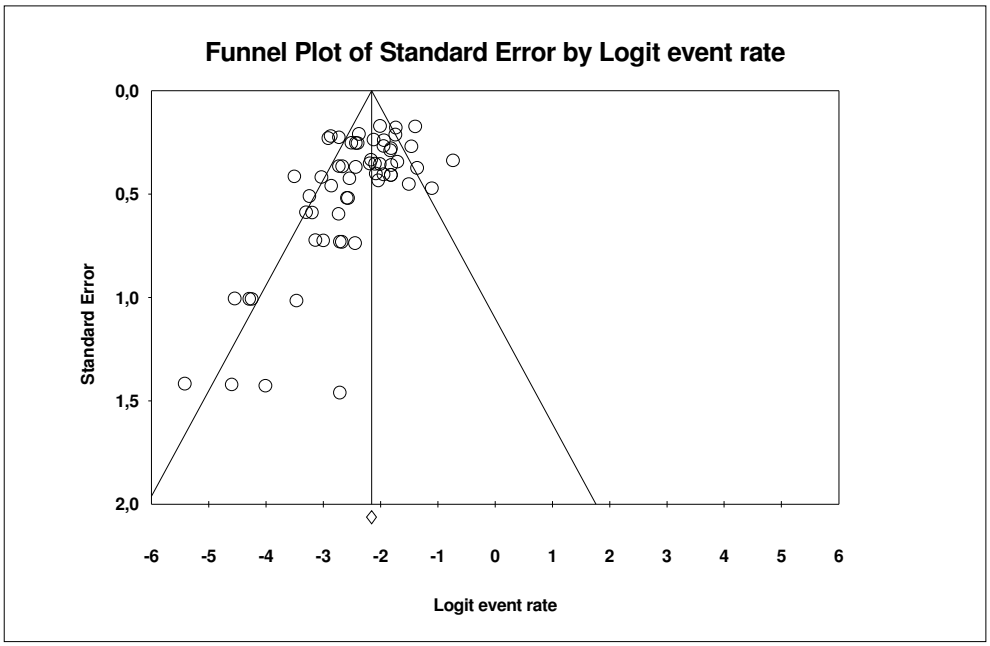
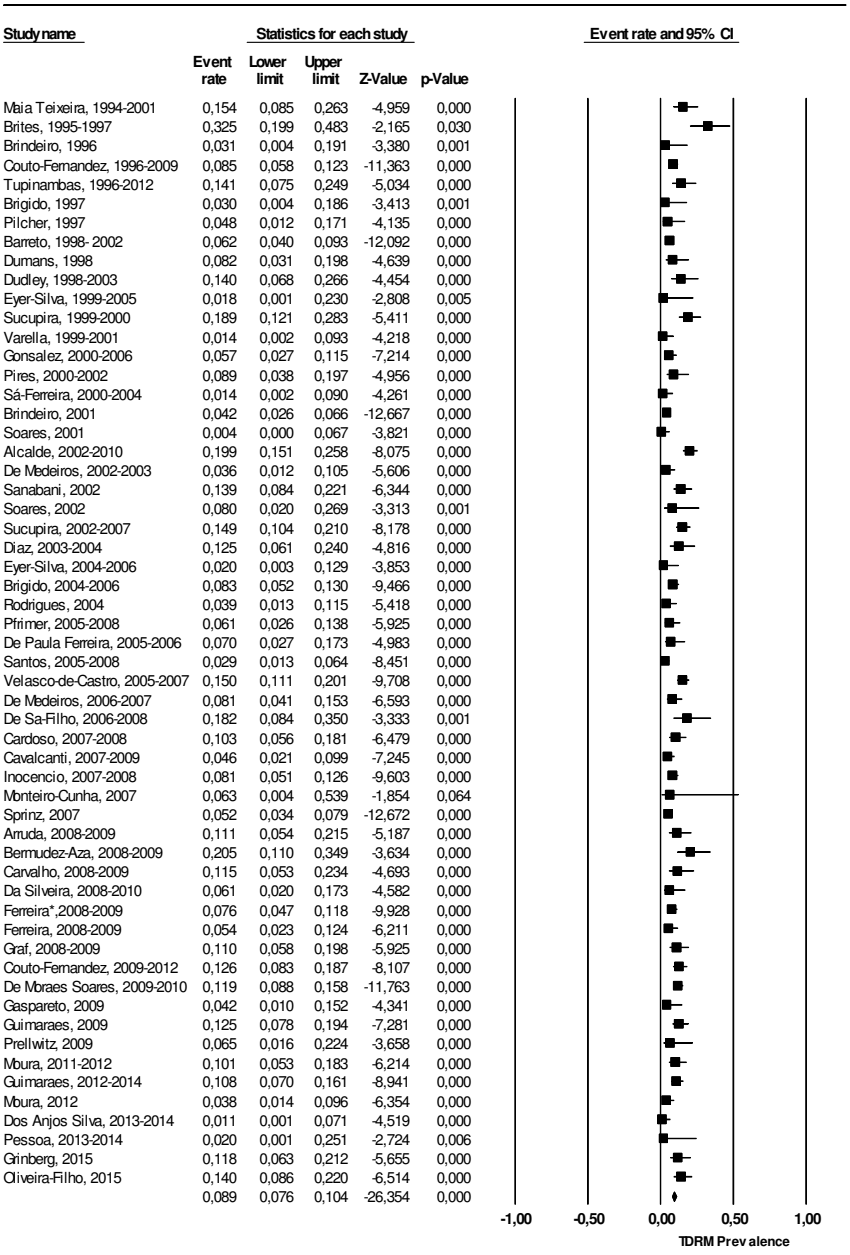
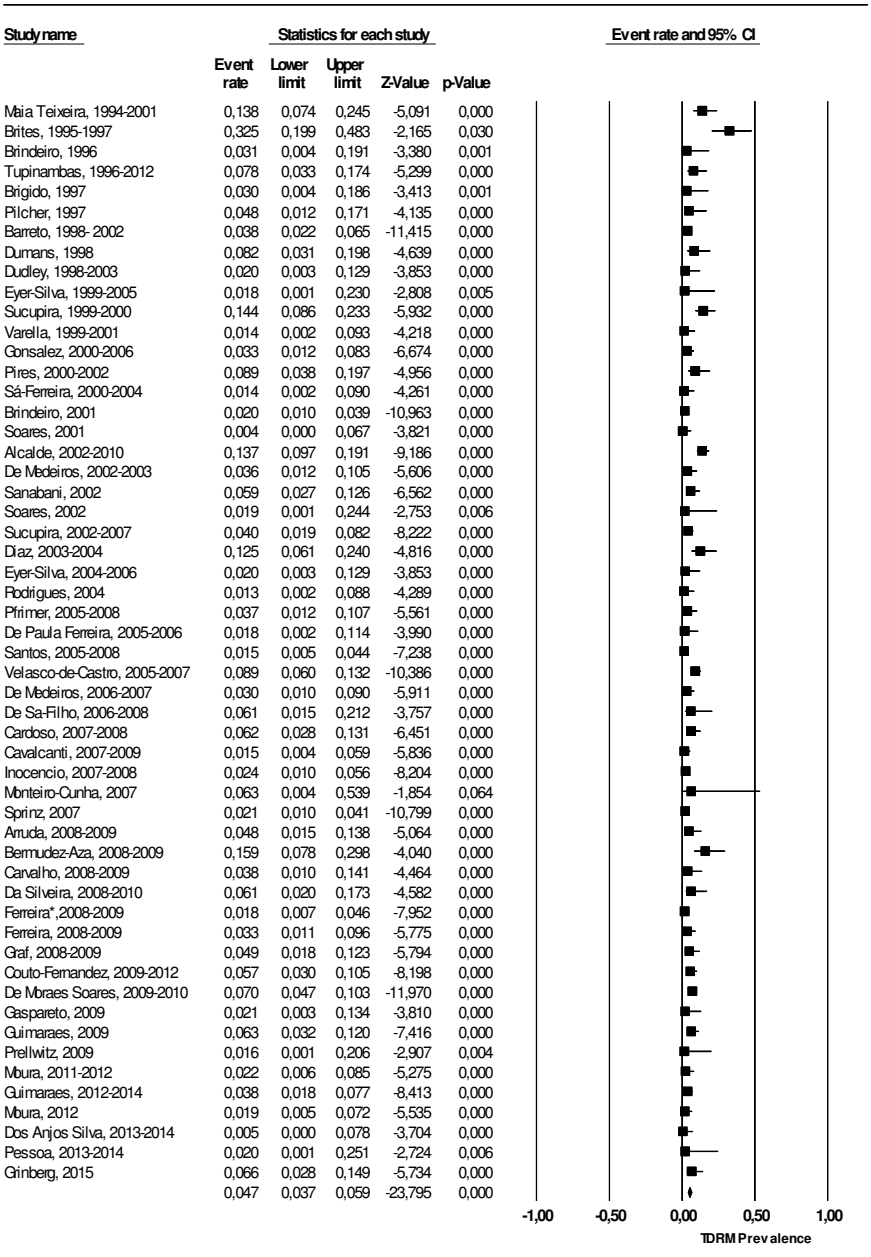


Figure 2 - Funnel plot distribution



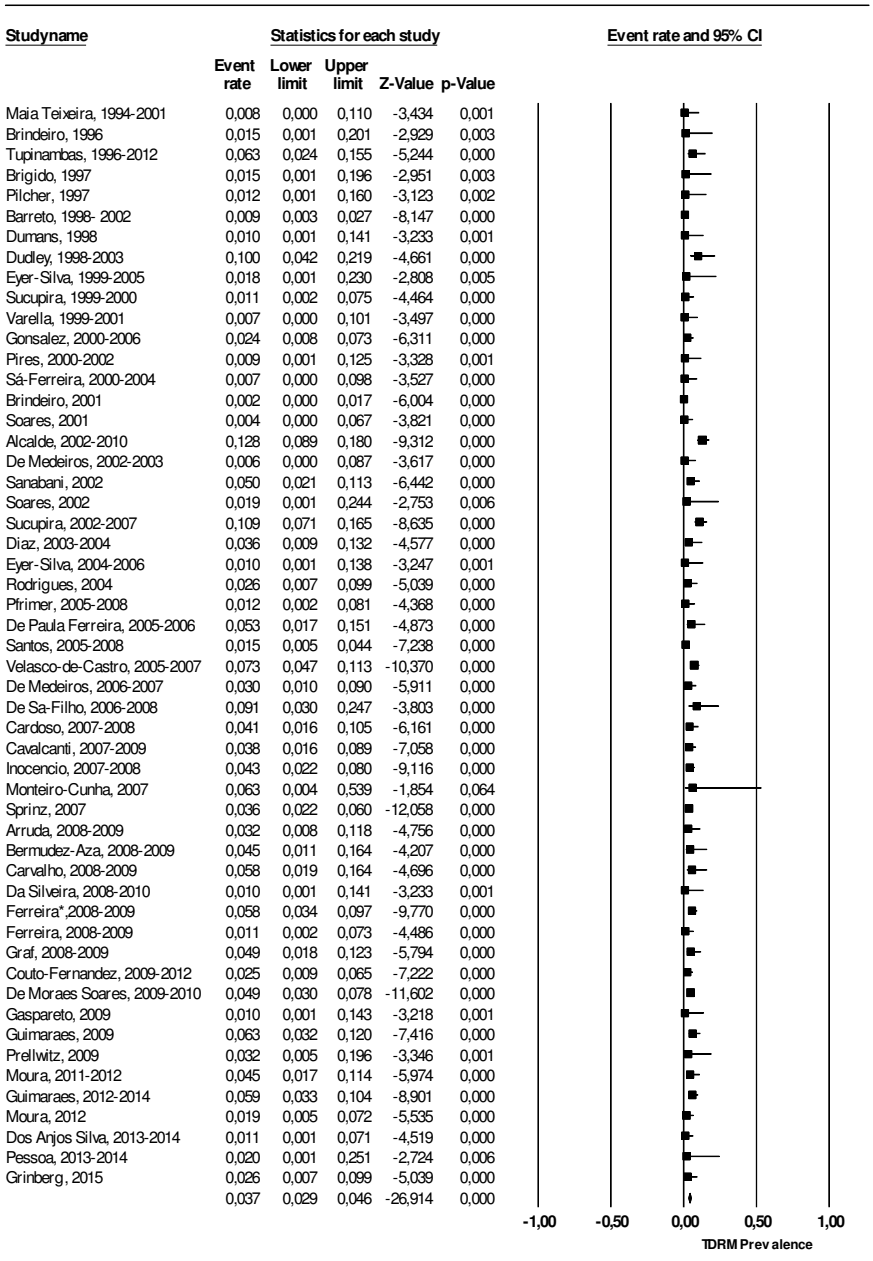
Meta Analysis

Figure 3 – Forest Plot for Global TDRM



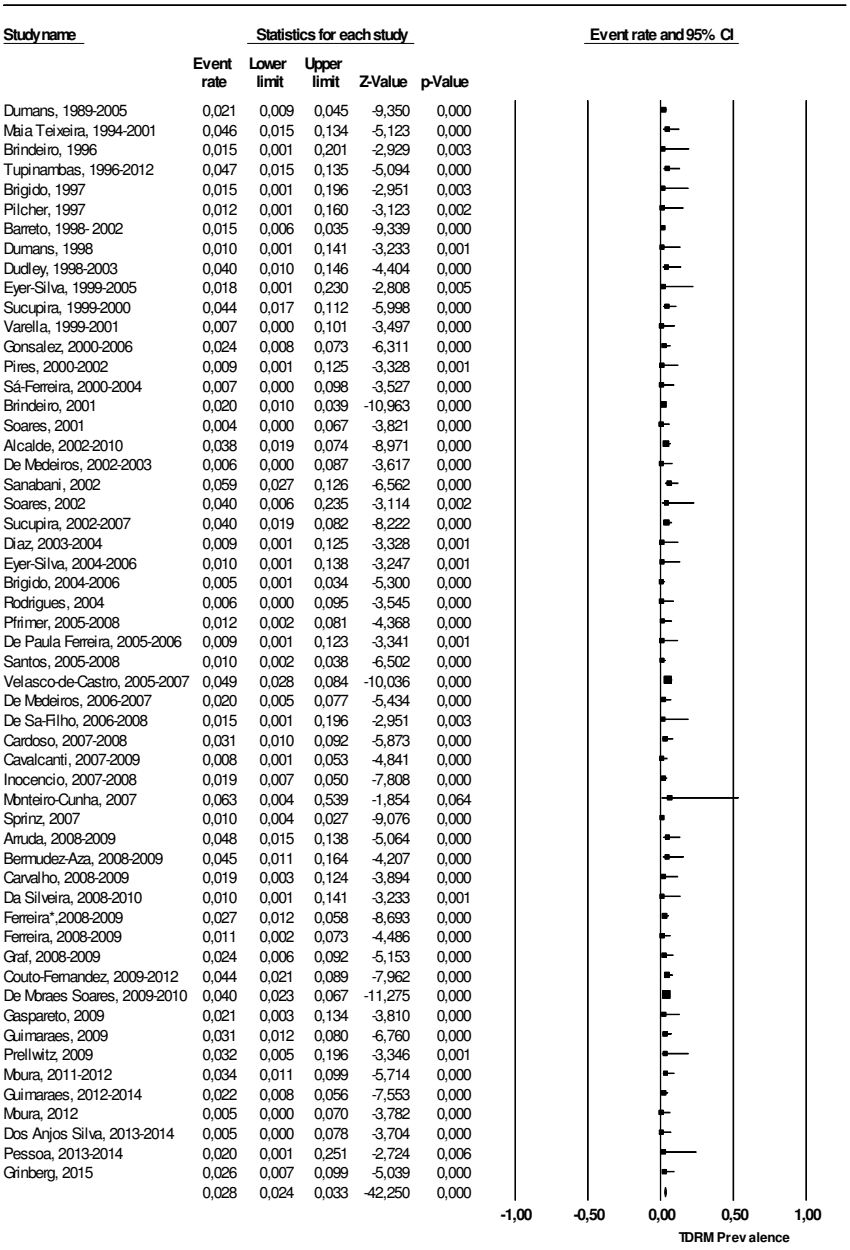
Meta Analysis

Figure 4- Forest Plot NRTI



Meta Analysis

Figure 5 - Forest Plot NNRTI



Meta Analysis

Figure 6 – Forest Plot PI

Table 2 - Meta Analysis by Populations Groups

Population	Number of Studies	Global TDRM	NRTI TDRM	NNRTI TDRM	PI TDRM
General population	35	8.6% (95% CI 7.0 to 10.7) (I^2= 8.9%)	4.5% (95% CI 3.2 to 6.1) (I^2= 0%)	3.8% (95% CI 2.8 to 5.0) (I^2= 0%)	2.7% (95% CI 2.1 to 3.3) (I^2= 0%)
Voluntary counseling and testing centers	11	8.3% (95% CI 5.5 to 12.2) (I^2= 13%)	3.6% (95% CI 2.0 to 6.4) (I^2= 0%)	3.7% (95% CI 2.2 to 6.2) (I^2= 26.1%)	2.8% (95% CI 2.0 to 4.1) (I^2= 0%)
Blood donors	4	5.8% (95% CI 3.8 to 8.8) (I^2= 3.1%)	4.2% (95% CI 2.5 to 7.0) (I^2= 0.8%)	0.9% (95% CI 0.4 to 2.3) (I^2= 0%)	1.3% (95% CI 0.6 to 2.9) (I^2= 0%)
Injecting drug users	3	13.7% (95% CI 10.3 to 18.1) (I^2= 0%)	9.4% (95% CI 4.2 to 19.7) (I^2= 0%)	3.4% (95% CI 0.5 to 19.6) (I^2= 0%)	3.7% (95% CI 1.8 to 7.5) (I^2= 0%)
Men sex with men	2	16.9% (95% CI 10.9 to 25.3) (I^2= 0%)	11.5% (95% CI 5.6 to 22.2) (I^2= 0%)	5.6% (95% CI 2.5 to 11.9) (I^2= 0%)	4.6% (95% CI 1.9 to 10.6) (I^2= 0%)
Total*	58	8.9% (95% CI 7.6 to 10.4) (I^2= 10.6%)	4.7% (95% CI 3.7 to 5.9) (I^2= 0%)	3.7% (95% CI 2.9 to 4.6) (I^2= 0%)	2.8% (95% CI 2.4 to 3.3) (I^2= 0%)

* three studies were not included in the analyzes by population : one about women , one about inmates and one about multiple populations

Table 3 - Meta Analysis by Region

Population	Number of Studies	Global TDRM	NRTI TDRM	NNRTI TDRM	PI TDRM
Southeast	25	10.9% (95% CI 8.9 to 13.3) (I^2= 9.8%)	6.1% (95% CI 4.6 to 8.1) (I^2= 0%)	4.4% (95% CI 3.1 to 6.3) (I^2= 4.7%)	3.3% (95% CI 2.7 to 4.1) (I^2= 0%)
South	10	7.3% (95% CI 5.5 to 9.7) (I^2= 0%)	3.2% (95% CI 2.1 to 5.0) (I^2= 0%)	3.0% (95% CI 1.9 to 4.7) (I^2= 0%)	1.8% (95% CI 1.0 to 3.0) (I^2= 0%)
Northeast	9	8.7% (95% CI 4.8 to 15.2) (I^2= 0%)	4.2% (95% CI 1.3 to12.5) (I^2= 0%)	3.3% (95% CI 2.0 to 5.4) (I^2= 0%)	2.6% (95% CI 1.4 to 4.9) (I^2= 0%)
Midwest	4	7.5% (95% CI 5.0 to 11.0) (I^2= 0%)	4.9% (95% CI 3.0 to 7.9) (I^2= 0%)	2.5% (95% CI 1.2 to 5.3) (I^2= 0%)	1.9% (95% CI 0.8 to 4.4) (I^2= 0%)
North	2	4.2% (95% CI 0.4 to 33.4) (I^2= 0%)	2.0% (95% CI 0.3 to11.8) (I^2= 0%)	3.0% (95% CI 0.6 to 14.1) (I^2= 0%)	1.2% (95% CI 0.3 to 5.9) (I^2= 0%)
Total*	58	8.9% (95% CI 7.6 to 10.4) (I^2= 10.6%)	4.7% (95% CI 3.7 to 5.9) (I^2= 0%)	3.7% (95% CI 2.9 to 4.6) (I^2= 0%)	2.8% (95% CI 2.4 to 3.3) (I^2= 0%)

* eight studies were not included in the analyzes by region because they were from multiple regions

Table 4- Meta Analysis by Period

Population	Number of Studies	Global TDRM	NRTI TDRM	NNRTI TDRM	PI TDRM
1989-2004	24	8.1% (95% CI 5.9 to 11.0) (I^2= 14.2%)	5.0% (95% CI 3.2 to 7.8) (I^2= 0%)	1.9% (95% CI 1.1 to 3.5) (I^2= 0%)	2.6% (95% CI 2.0 to 3.4) (I^2= 0%)
2005-2009	24	8.7% (95% CI 7.1 to 10.6) (I^2= 0%)	4.2% (95% CI 3.1 to 5.6) (I^2= 0%)	4.7% (95% CI 3.9 to 5.6) (I^2= 0%)	2.7% (95% CI 2.1 to 3.5) (I^2= 0%)
2010-2015	8	9.7% (95% CI 6.9 to 13.5) (I^2= 31.4%)	4.1% (95% CI 2.7 to 6.1) (I^2= 1.6%)	3.7% (95% CI 2.5 to 5.6) (I^2= 0%)	2.9% (95% CI 1.8 to 4.6) (I^2= 0%)
Total*	58	8.9% (95% CI 7.6 to 10.4) (I^2= 10.6%)	4.7% (95% CI 3.7 to 5.9) (I^2= 0%)	3.7% (95% CI 2.9 to 4.6) (I^2= 0%)	2.8% (95% CI 2.4 to 3.3) (I^2= 0%)

* two studies were not included in the analyzes by period because they had very long period (1996 to 2012 and 2002 to 2010)

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Appendix I

Search strategy:

EMBASE **HIV** 'acquired immune deficiency syndrome'/exp OR 'acquired immune deficiency syndrome' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' **DRUG RESISTANCE** 'drug resistance'/exp **BRAZIL** 'brazil'/exp AND 'drug resistance'/exp
PUBMED **HIV** ("Acquired Immunodeficiency Syndrome"[Mesh] OR "Immunologic Deficiency Syndrome, Acquired" OR "AcquiredImmune Deficiency Syndrome" OR "Acquired Immuno-DeficiencySyndrome" OR "Acquired Immuno Deficiency Syndrome" OR "Acquired Immuno-Deficiency Syndromes" OR "Immuno-Deficiency Syndrome, Acquired" OR "Immuno-Deficiency Syndromes,Acquired" OR "Syndrome, Acquired Immuno-Deficiency" OR"Syndromes, Acquired Immuno-Deficiency" OR "ImmunodeficiencySyndrome, Acquired" OR "Acquired Immunodeficiency Syndromes"

OR "Immunodeficiency Syndromes, Acquired" OR "Syndrome, Acquired Immunodeficiency" OR "Syndromes, AcquiredImmunodeficiency" OR "AIDS" OR "SIDA" OR "HIV Infections"[Mesh] OR "HIV Infections" OR "HIV Infection" OR "Infection, HIV"

OR "Infections, HIV" OR "HTLV-III-LAV Infections" OR "HTLV III LAVInfections" OR "HTLV-III-LAV Infection" OR "Infection, HTLV-III-LAV"OR "Infections, HTLV-III-LAV" OR "T-Lymphotropic Virus Type IIIInfections, Human" OR "T Lymphotropic Virus Type III Infections,Human" OR "HTLV-III Infections" OR "HTLV III Infections" OR"HTLV-III Infection" OR "Infection, HTLV-III" OR "Infections, HTLV-III")

DRUG RESISTANCE

("drug resistance"[Mesh] OR "drug resistance" OR "resistance")

BRASIL

("Brazil" [Mesh] OR "brasil" OR "brazil" OR brazil)

COCHRANE

HIV/AIDS

MeSH descriptor: [HIV] explode all trees OR HIV:ti,ab,kw (Word variations have been searched) OR AIDS

BRAZIL

MeSH descriptor: [Brazil] explode all trees

ARTIGO 1 - RESUMO EM PORTUGUÊS

Antecedentes: As mutações do HIV de resistência transmitidas a drogas (TDRM) podem afetar a efetividade da primeira linha dos esquemas empíricos da terapia anti-retroviral (TARV). Acredita-se que sua prevalência esteja aumentando no mundo, porém não há resumo claro e conciso da prevalência das TDRM no Brasil.

Métodos: Revisão sistemática da literatura para produzir um resumo atualizado das estimativas de prevalência das TDRM entre pacientes com HIV, adultos, virgens de tratamento, no Brasil. Realizamos buscas eletrônicas nas bases de dados Medline, Embase, Lilacs e Cochrane (até dezembro de 2015) para identificar estudos observacionais que relatam a prevalência de TDRM ao HIV no Brasil. Foi realizada uma metanálise de único braço utilizando modelo dos efeitos aleatórios para obter (RR). Os intervalos de confiança de 95% foram calculados. A heterogeneidade foi avaliada pelo teste de inconsistência (I^2) e suas fontes foram investigadas em análises de sensibilidade de subgrupos de estudos sempre que adequado.

Resultados: Entre os 736 registros identificados na busca eletrônica inicial, 58 estudos atenderam aos critérios de inclusão da revisão sistemática. Cinquenta e sete relataram TDRM para todas as principais classes de drogas e um foi limitado a inibidores da protease (IP). Apenas as principais mutações atualmente sob vigilância (Stanford, 2015) foram contabilizadas. A meta-análise revelou uma prevalência de MRTD de 8,9% (IC 95% 7,6-10,4) (I^2 = 10,6%), considerando mutação a qualquer classe de drogas. Os valores para TDRM específicas para NRTI, NNRTI e PI foram de 4,7% (IC 95% 3,7 a 5,9; I^2 = 0%), 3,7% (IC 95% 2,9 a 4,6; I^2 = 0%) e 2,8% (IC 95% 2,4 a 3,3; $I^2$2 = 0%),

respectivamente. Entre os subgrupos, a prevalência de MRTD foi menor nos doadores de sangue (5,8%; 95% CI 3,8 a 8,8; I^2 = 13%) e maior em homens que fazem sexo com homens (16,9%; IC95% 10,9-25,3; I^2 = 0%) e em usuários de drogas injetáveis (13,7%; IC95% 10,3-18,1; I^2 = 0%). A região com a maior prevalência de TDRM foi a região Sudeste (10,9%; IC95% 8,9 a 13,3; I^2 = 9,8%).

Conclusão: A estimativa pontual para a prevalência geral de MRTD no Brasil é de 8,9%. Isto é comparável às taxas de prevalência observadas em outros países com elevada cobertura da TARV. A relevância clínica deste achado ainda é um assunto a ser pesquisado.

7 ARTIGO 2

Impact of HIV-1 transmitted drug resistance mutations on response to first antiretroviral treatment: a systematic review and meta-analysis

Impacto das mutações de resistência transmitidas do HIV-1 aos antirrtrovirais na resposta ao primeiro tratamento antirretroviral: uma revisão sistemática e metanálise.

Carina Guedes Ramos, Doutoranda em Epidemiologia pela UFRGS

Orientadora: Profª. Carisi Anne Polanczyk

Co-Orientador: Prof. Ricardo de Souza Kuchenbecker

UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL (UFRGS)

A ser enviado para publicação.

Impact of HIV-1 transmitted drug resistance mutations on response to first antiretroviral treatment: a systematic review and meta-analysis

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March, 2016

ABSTRACT

Background: HIV drug resistance mutations are associated with increased risk of virologic failure (VF) among treatment experienced patients but uncertainty remains regarding the risk related to transmitted drug resistance mutations (TDRM) in treatment naïve patients.

Methods: We did electronic searches on Medline, Embase and Cochrane CENTRAL (up to December 2015) to identify randomized clinical trials or observational studies reporting the risk of VF among treatment naïve HIV patients with and without TDRM. Risk of bias was assessed with the Newcastle-Ottawa Scale. We performed random-effects meta-analyses of risk ratios (RR). Heterogeneity was assessed by the inconsistency test (I^2) and its sources were investigated by subgroup and meta-analysis level sensitivity analyses whenever appropriate.

Results: We found 28 observational studies (23 cohort, three case-cohort and two case-control studies) and no randomized clinical trial reporting VF rates among treatment naïve HIV patients with and without TDRM. RR of VF for having any TDRM was 1.93 (95% CI 1.44 to 2.59) in a meta-analysis of 21 cohort studies that provided sufficient information (I^2=82%). For NRTI, NNRTI and PI, meta-analysis RR estimates were 2.58 (95% CI 1.30 to 5.16), 4.2 (2.21 to 7.96) and 2.92 (1.2 to 7.10), respectively. Heterogeneity decreased substantially for drug class subgroup meta-analyses (I^2=65%, 56% and 58%, respectively). Quality assessment indicated absence of extensive adjustment to confounding in four out of 28 studies and funnel plot analysis indicated a low probability of publication bias.

Conclusion: Available evidence indicates that TDRM increases the risk of virologic failure among treatment naïve HIV patients.

INTRODUCTION

The availability of highly active antiretroviral therapy (HAART) has significantly improved HIV disease morbidity and mortality[1-4]. However, its widespread use has lead to the emergence of antiretroviral drug resistance, which is associated to poorer health outcomes among patients on HIV treatment[5].

In addition to that, transmission of HIV variants with drug resistance mutations is believed to adversely affect health outcomes of treatment naïve individuals, primarily infected with these mutated variants, a phenomenon known as transmitted drug resistance mutations (TDRM). This causes concern because unidentified TDRM could impact the first antiretroviral treatment effectiveness if initiated on an empirical basis, increasing the risk of virologic failure (VF)[6, 7]. The prevalence of TDRM has been assessed in different contexts and ranges between 10% to 17% in Europe, United States, Japan and Australia[8].

In treatment experienced patients, HIV genotype test plays a crucial role in the choice of a new therapeutic regimen after VF[5, 9]. Nevertheless, uncertainty remains regarding VF risk related to TDRM in treatment naïve patients and the role of genotype test to guide first HAART.

Both observational and experimental studies have assessed the impact of TDRM on the risk of VF whether being their primary research question or as a secondary outcome. To or knowledge, no systematic review or meta-analysis has provided a clear and concise summary of available evidence thus far.

The objective of the present study was to estimate the impact of HAART guided by HIV genotype test on the virologic outcome of first antiretroviral treatment and evaluate de impact of TDRM on virological outcome. To do so, we

performed a systematic review of literature with meta-analysis of clinical studies measuring the effect of TDRM on the risk of VF.

METHODS

Search Strategy

We conducted a systematic review of literature to identify clinical trials or observational studies comparing VF rates among treatment-naïve HIV patients that were submitted to HIV genotyping for TDRM detection prior to HAART initiation. Literature search was conducted in Medline, Embase and Cochrane CENTRAL (up to December 2015). The following medical subject headings (MeSH) and text word combinations were used: Acquired Immunodeficiency Syndrome, HIV infection, antiretroviral therapy, highly active antiretroviral therapy (HAART), genotype. No filters for study design were used. A complete description of search strategy is provided in appendix I.

Eligibility criteria

We included clinical trials or observational studies reporting VF rates among HIV treatment-naive adult subjects submitted to HIV genotyping for TDRM detection prior to HAART initiation. Additionally, we limited the inclusion to studies reporting bulk resistance mutations. We excluded studies on pediatric patients or in pregnant women. Studies reporting only minority resistance mutations were excluded as well. There was no restriction as to study duration or number of patients. There was no language restriction.

Study selection

Records identified by the literature searches were scrutinized in two phases. All studies were initially scanned for relevance by title and abstract. Studies that could not be excluded according to our eligibility criteria in the abstract review had their full text retrieved for further evaluation. Study selection was independently performed by two investigators (C.G.R. and A.F.A.S.). Disagreements were solved by consensus.

Data extraction and quality assessment

Two reviewers independently abstracted data from included articles (C.G.R. and A.F.A.S.). Disagreements were resolved by consensus and, if necessary, with the opinion of a third reviewer (C.A.P.). Abstracted information comprised: study design, patient population characteristics, study country, publication year, data collection period, HIV subtypes, duration of HIV infection, type of genotype test, genotype test interpretation (Stanford or IAS-USA), duration of follow-up, viral load cutoff for VF definition, treatment regimens, proportion of patients with TDRM in general, proportion of patients with drug class specific TDRM (NRTI, NNRTI and PI) and virologic failure rates. Risk of bias was assessed with the Newcastle-Ottawa Scale[10].

Statistical analysis

We performed random effect meta-analysis of risk ratios to estimate summary effect of having TDRM resistance mutations on the risk of virologic failure among treatment naive HIV patients. Risk ratio was chosen as the effect size estimator considering the elevated frequency of events (≥ 10% in most

studies). In this case, OR estimates would have lead to risk overestimation. Meta-analyses were performed for global and class-specific TDRM (NRTI, NNRTI and PI).

Heterogeneity between studies was assessed with the I^2 statistic as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity. Sources of heterogeneity were investigated by subgroup and meta-analysis level sensitivity analyses whenever appropriate. We did no data imputation and studies with missing data were excluded from quantitative synthesis. Meta-analysis was carried out in Review Manager 5.3.5 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2015).

RESULTS

Initial literature search retrieved 4948 records. After removal of 400 duplicate records and inclusion of articles indentified by handsearch of included articles reference list, 4558 studies had their titles an abstracts screened; 77 were selected to full-text review; 28 articles met the eligibility criteria and were included in the systematic review[7, 11-38]. Study flowchart is presented in **figure 1.**

There were no randomized clinical trials. Thirteen studies were prospective cohorts, ten were retrospective cohorts, three were case-cohort and two were case-control. Median of follow up was 48 (14-144) weeks. A summary of included studies characteristics is presented in **table 1.**

Case definition was virologic failure in four out of five case-control and case-cohort studies[32-34, 36]. In the remainder, case was defined as presence of TDRM[35]. Twenty-one studies directly evaluated the impact of TDRM on virologic failure[7, 11-16, 18, 19, 21-34, 36-38], but in only three of those genotype test results were used to guide initial HAART regimen[12, 15, 19].

With respect to study quality assessment, studies were considered of fair quality according to the items evaluated in the Newcastle-Ottawa Scale. In general, cohort studies were better rated than case-control and case-cohort studies (**tables 2 and 3**). The case-control and case-cohort were not included in the meta-analysis because either the exposition (TDRM) or the outcome (VF) presented artificial frequencies due to the nature of these research designs. Analysis of funnel plot revealed a symmetric distribution of the included studies (**figure 2**). Twenty-one cohort studies presented TDRM results for conventional genotype test in general and were included in the meta-analysis of the global

TDRM (**figure 3**). This resulted in a summary RR of 1.93 (95% CI 1.44 to 2.59), with high heterogeneity (I^2=82%). There was statistically significant difference on the risk of virologic failure for global TDRM.

Summary RR associated to class-specific TDRM were estimated. NRTI, NNRTI and PI, meta-analysis RR estimates were 1.58 (95% CI 1.30 to 5.16), 4.20 (2.21 to 7.96) and 2.92 (1.20 to 7.10), respectively. Heterogeneity was lower in the meta-analyses by antiretroviral class (Chi^2= 20.24; I^2 = 65%), (Chi^2= 13.54; I^2 = 56%) and (Chi^2= 11.99; I^2 = 58%), respectively, for NRTI (**figure 4**), NNRTI (**figure 5**) and PI (**figure 6**). Statistically significant differences were observed on VF for class-related TDRM.

We performed meta-analysis level sensitive analysis. Studies were grouped by: (1) data gathering year, as both treatment regimens and prevalent TDRM have changed during the 15 years time-span covered by the available evidence; (2) by quality assessment scores; and (3) by recent versus chronic HIV infection. No subgroup analysis was able to significantly decrease the observed heterogeneity.

DISCUSSION

To our knowledge, this is the first systematic review with meta-analysis to address the impact of TDRM on VF for treatment naïve HIV patients. We pooled the risk of virological failure among HIV patients according to the presence of TDRM identified prior to treatment initiation. Wittkop et al[11], performed a systematic review without meta-analysis, restrict to the 2006 to 2011 period with no conclusive results: four studies showed no significant association between presence of TDRM and time to virological suppression or proportions of patients with VF between groups with or without TDRM and six studies showed poorer virological response in patients with TDRM or a significantly higher time to virological suppression in patients with TDRM.

Available evidence is insufficient to directly assess the effectiveness of HIV genotyping test for choosing first anti-retroviral regimen. The ideal study to answer this research question would have been a clinical trial in which treatment naïve HIV patients with indication for HAART were randomized to either genotype test oriented first-regimen or empirical (guideline oriented) first-regimen, with no knowledge of baseline genotyping results. Three of the identified observational studies had HAART guided by genotype test and they reported conflicting findings. In two of them, no difference on VF or time to virological suppression was found between patients with wild-type virus and patients with TDRM when treatment was genotype-test oriented[15, 19], and the remaining study found that patients with TDRM had an increased incidence of VF despite genotype-test oriented therapy[12].

Main meta-analysis results indicate that TDRM increase the risk of virologic failure among treatment naïve HIV patients. Our results, suggest that the widespread use of genotype test to direct the initial treatment of HIV could lead to better virological outcomes of initial HAART in patients with TDRM. However, presence of low-frequency mutations, which are not identified by conventional genotyping, have been implicated with poorer virological outcomes even in patients with full HAART[39-43].

The high heterogeneity that was observed for global TDRM meta-analysis limits the extrapolation of calculated summary effect estimate. Heterogeneity was partially explained by the inclusion of TDRM to any drug class in the main analysis. Nevertheless, class-specific meta-analyses still retained intermediate levels of heterogeneity. Residual heterogeneity could be explained by distinct levels of control for potential confounders among included studies, such as baseline viral load or CD4 count. Furthermore, the differences in antiretroviral treatment regimens employed in the different study settings could impact treatment outcomes and increase heterogeneity. To some extend, this issues were assessed in a set of sensitivity analyses with no change in study results.

This systematic review presents some limitations that deserve to be mentioned. First, some of the identified studies reported VF rates among patients with and without TDRM as a secondary outcome, and might be underpowered to measure this outcome. Second, the time expanse among the identified studies (more than 12 years) might account for some of the observed heterogeneity. In fact, the extremely significant progresses in HAART regimens for HIV treatment could limit the pooling of data and account for some heterogeneity. This was

assessed in a sensitivity analysis, with no change in our findings. Third, inherently to systematic reviews of observational studies, risk might be overestimated due to confounding.

TDRM remains a controversial topic. Our meta-analysis results suggests that presence of TDRM impact negatively on virological outcome and that this could be minimized by HAART guided by genotype testing. However, the role of drug resistant low-frequency variants is still poorly understood. These minorities could be confounders in evaluation of HAART failure because they could be present in patients with TDRM or in patients with wild-virus by conventional genotype test.

CONCLUSION

Meta-analysis of available evidence demonstrate that the presence of TDRM increases the risk of VF to first ARV regimen. This finding supports the adoption of genotype test prior to first ARV regimen. The impact of conventional genotype test guiding first HAART on virological response could be better evaluated in a randomized controlled trial.

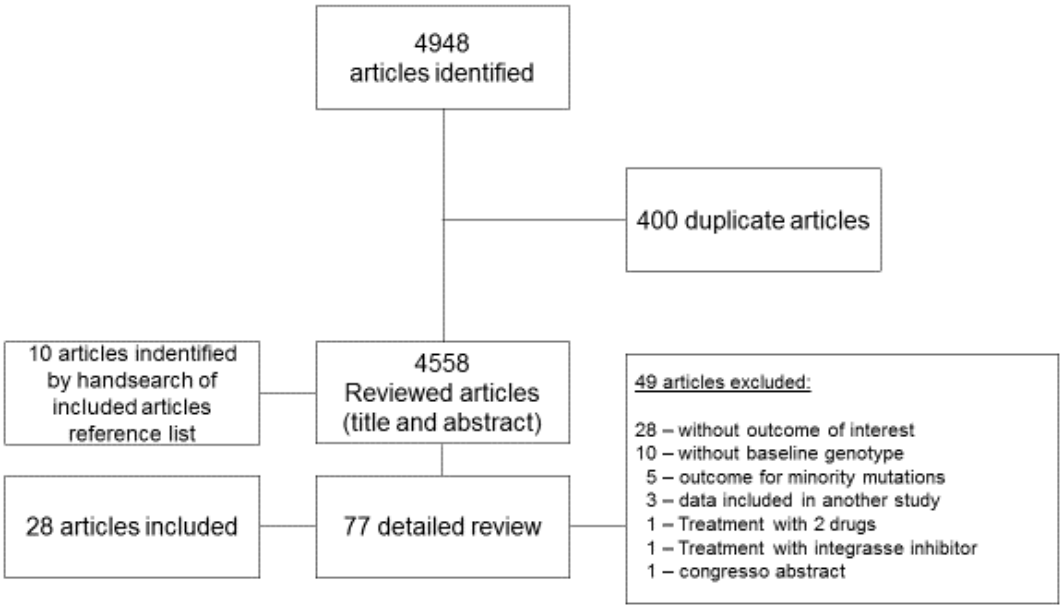

Figure 1 - Flowchart of study selection

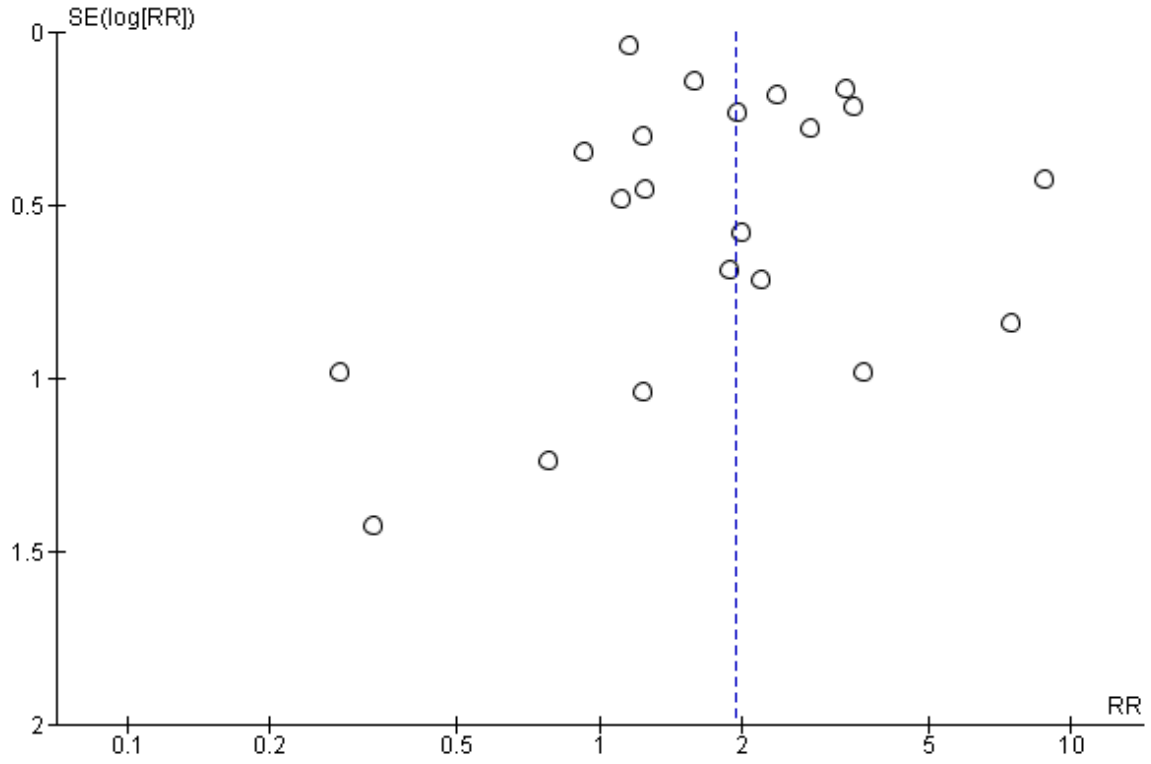

Figure 2 - Funnel plot distribution

Table 1 - Characteristics of studies included in the systematic review

Autor, year	Study design	Country	N	CD4 (cell/mm^3)*	HIV-1 RNA (log_{10} copies/mL)*	Technique	Interpretation	Follow-up (weeks)	Virologic failure (copies/mL)	Treatment
Balotta, 2000	Retrospective cohort	Italy	11	520 (344-746)	5.1 (3.7-6.1)	Genotype, phenotype	NI	24	≥ 200	ZDV/3TC/SQV or ZDV/3TC/IDV
Tamalet, 2000	Prospective cohort	France	46	564 ± 231**	5.35 ± 1.09	Genotype	IAS-USA	24	≥ 20	2 NRTI and 1 PI
Perno, 2001	Retrospective cohort	Italy	248	232 (1-1186)	4.9 (2.7-6.6)	Genotype	NI	24	> 500	2 NNRT: 3TC, d4T, ddC, ddI, ZDV and 1 IP: IDV, NFV, RTV, SQV
Grant, 2002	Prospective cohort	United States	141	511 (383-601)	40,900 (6697-156,496)¥	Genotype	NI	24	≥ 500	2 NRTIs and 1 NNRTI or 2 NRTI and 1 PI
Ferrer, 2003	Retrospective cohort study nested in a randomized clinical trial	Spain and Argentina	91	346# (10-777)	4.8# (3.3-6.2)	Genotype, phenotype	NI	48	≥ 200	ZDV/3TC/NVP versus ZDV/3TC/NFV
Harrigan, 2003	Retrospective cohort	Canada	262	320 (175-460)	4.8 (4.3-5.2)	Genotype	NI	48	≥ 400	Most common: d4T/3TC/NVP; d4T/ddI/NVP; ZDV/ddI/NVP
Oette, 2006	Prospective cohort	Germany	231	178 ±167**	171.205 ± 271.799**,†	Genotype	NI	48	≥50	2 NRTI: ZDV,3TC, d4T, ABC plus 1 NNRTI: EFZ, NVP or 1 IP: ATV-r, IDV-r, SQV-r, LPV-r
Shet, 2006	Prospective cohort	United States	76	NI	NI	Genotype	IAS-USA	29	≥50	HAART
Borroto-Esoda, 2007	Retrospective cohort study nested in a randomized clinical trial	Canada, United States, Porto Rico, Argentina, Brazil, Chile, Mexico, France, Germany , United King	546	314 (5-1317)***	5.0 (3.6-5.9)***	Genotype, phenotype	DeGruttola, 2000	48	two consecutive viral load values above > 400 or never achieving ≤ 400	FTC or d4T plus ddI and EFZ
Chaix, 2007	Prospective cohort	France	359	480 (353-736)	5,2 (4.3-5.9)	Genotype	2006 French ANRS algorithm	24	≥400	2 NRTI and 1 NNRTI OR 2 NRTI AND 1 PI
Kuritzkes, 2008	Case-cohort	United States	342	NI	NI	Genotype	Stanford	16	2 consecutive measurements of HIV-1 RNA level ≥ 200	ZDV/3TC/ EFZ VERSUS ZDV/3TC/ABC/ EFZ
Margot, 2009	Retrospective cohort study nested in a randomized clinical trial	United States	509	NI	NI	Genotype, phenotype	IAS-USA	144	≥400	FTC/TDF/EFV OU 3TC/ZDV/EFV

Strang, 2009	Case-control	United Kingdom	93	NI	NI	Genotype	NI	24	≥50	2NRTI + NVP ou EFZ
Bansi, 2010	Prospective cohort	United Kingdom	935	218 (148-299)	5 (4.5-5.5)	Genotype and sensitive real-time PCR	Stanford	48	≥50	NRTIs in combination with either 1 NNRTI, 1 or 2 PIs or another NRTI
Ross, 2010	Retrospective cohort study nested in a randomized clinical trial	United States	106	NI	NI	Genotype and clonal analysis	IAS-USA	48	≥400	TDF/FTC plus FPV-r or ATV-r
Bartmeyer, 2010	Prospective cohort	Germany	78	NI	NI	Phenotype	Stanford	48	> 500	2 NRTIs and 1 NNRTI or 2 NRTI and 1 RTV boosted PI
Wittkop, 2011	Prospective cohort	Europe	10056	218 (124–310)	5 (4·4–5·4)	Genotype	WHO	48	two consecutive viral loads > 500	2 NRTIs and 1 NNRTI or 2 NRTI and 1 RTV boosted PI
Hamers, 2012	Prospective cohort	Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe	1991	NI	NI	Genotype	IAS-USA	48	≥400	2 NRTIs (ABC, d4T, TDF, ZDV) and 1 NNRTI (EFZ or NVP)
Gagliani, 2011	Case-control	Brazil	80	286#	4.9#	Genotype	NI	48	≥50	2 NRTI (ZDV, 3TC, d4T, ddI) plus 1 NNRTI (EFZ or NVP) or (1 IP (IDV, IDV-r, NFV)
Lai, 2012	Case-cohort	Taiwan	136	118# (34-340)	5,2# (4,5-5,9)	Genotype	Stanford	24	≥200	2 NRTI (ZDV, ABC, 3TC, d4T, ddI) plus 1 NNRTI (EFZ ou NVP) or 1 IP (ATV, LPV-r, NFV)
Taniguchi, 2012	Retrospective cohort	EUA	611	308 (99-467)	4,6 (4.0-5.1)	Genotype	WHO	48	≥400	2 NRTI + 1 NNRTI ou 2 NRTI + 1 PI
Rusine, 2013	Retrospective cohort	Ruanda	109	215 (129-278)	4.8 (4.2-5.2)	Genotype	WHO	48	≥1000	2 NRTI + 1 NNRTI or 3 NRTI
Geretti, 2014	Retrospective cohort study nested in a randomized clinical trial	Austria, Denmark, France, Germany, Great Britain, Hungary, Italy, Israel, Romania, Russia, Spain, Switzerland	153	296# (74-722)	4.8# (3.6-6.6)	Genotype and ultra-deep RTsequencing	NI	48	>1000	2 NRTI: ZDV, ABC, TDF, FTC plus NNRTI: EFZ OU ETR
Lee, 2014	Prospective cohort	Uganda	74	60 (12-136)	5.5 (4.9-5.8)	Genotype	Stanford	24	>400	2 NRTIs and 1 NNRTI
Knyphausen, 2014	Prospective cohort	Germany	323	473 (350–642)	5.3 (4.5–5.9)	Genotype	Stanford	48	≥ 500	2 NRTIs (3TC, ABC, d4T, DDI, FTC, TDF, ZDV and 1 NNRTI (EFV, ETR, NVP OR

										RPV) or 2 NRTI and one PI (DRV, FPV, LPV/r,
Kantor, 2015	Case-cohort	Brazil, Haiti, India, Malawi, Peru, South Africa, Thailand, United States, and Zimbabwe	466	151*** (2-298)	5.0*** (2.6-5.9)	Genotype	WHO	14	2 consecutive >1000	EFZ/ZDV/3TC or ATV/ddI/FTC or EFV/FTC/TDF
Li, 2015	Prospective cohort	China	429	177# (65-276)	4.6# (3.8-5.1)	Genotype	STANFORD	96	2 consecutive >1000 after viral suppression or 1 >1000 after viral suppression and treatment change to second-line	3TC/NVP plus ZDV/d4T or d4Tfollowed by ZDV at week 24.
Shet, 2015	Prospective cohort	Índia	587	192** ±109	NI	Genotype	WHO	24	>400	ZDV or d4T plus 3TC and 1 NNRTI (EFZ or NVP)

3TC, lamivudine; ABC, abacavir; ATV, atazanavir; d4T, stavudine; DRV, darunavir; ddC, zalcitabine; ddI, didanosine; EFZ, efavirenz; ETR, etravirine; FTC, emtricitabine; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; NVP, nevirapine; RPV, rilpivirine; RTV, ritonavir; -r, ritonavir (booster); SQV, saquinavir; TDF, tenofovir; ZDV, zidovodine;
ANRS – National Agency for AIDS Research
WHO – World Health Organization
Stanford – HIV Drug Resistance Database, Stanford University
IAS-USA – International Antiviral Society - USA

* median (range)
** mean ± standard deviation
*** mean (range)
# median (range) copies per Ml
¥ copies/mL

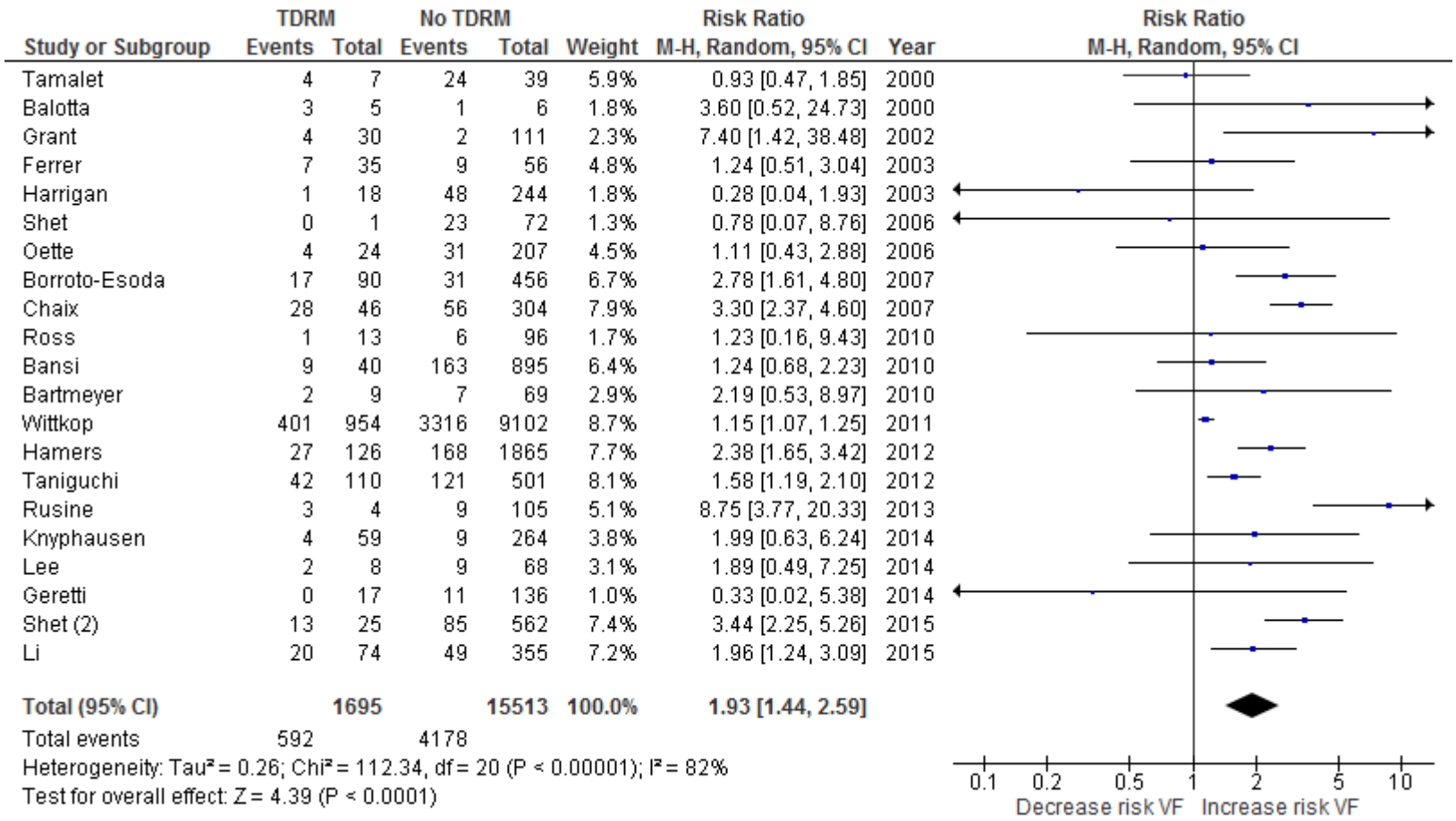

Figure 3 - Relative Risk of Virologic Failure for Global TDRM

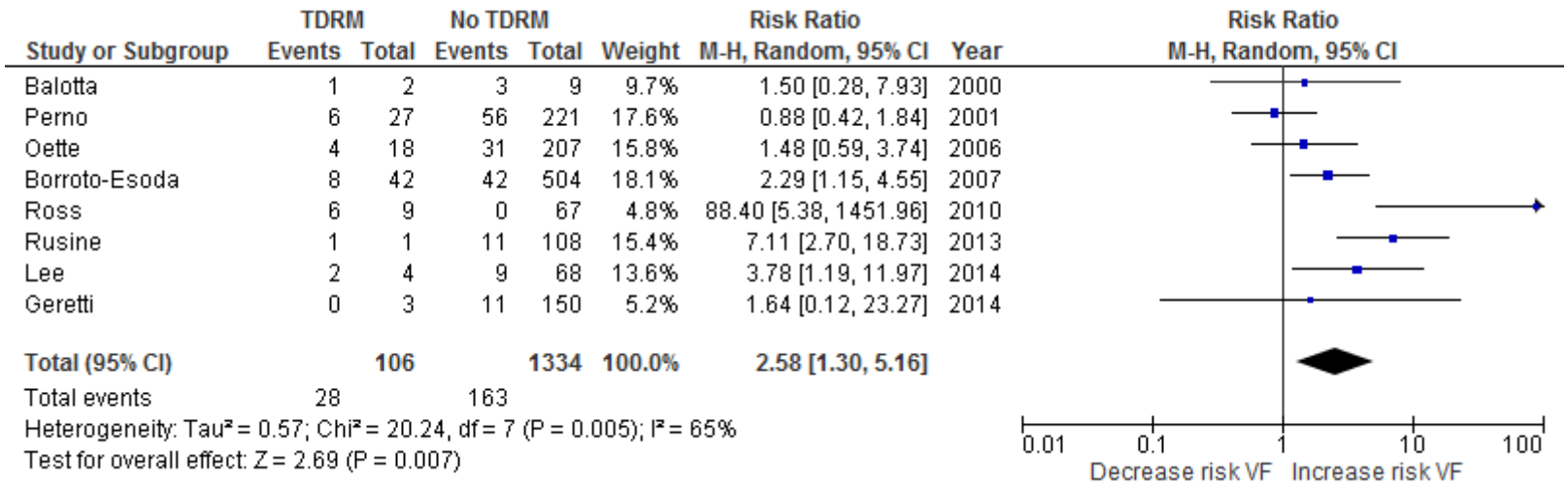

Figure 4 - Relative Risk of Virologic Failure for NRTI TDRM

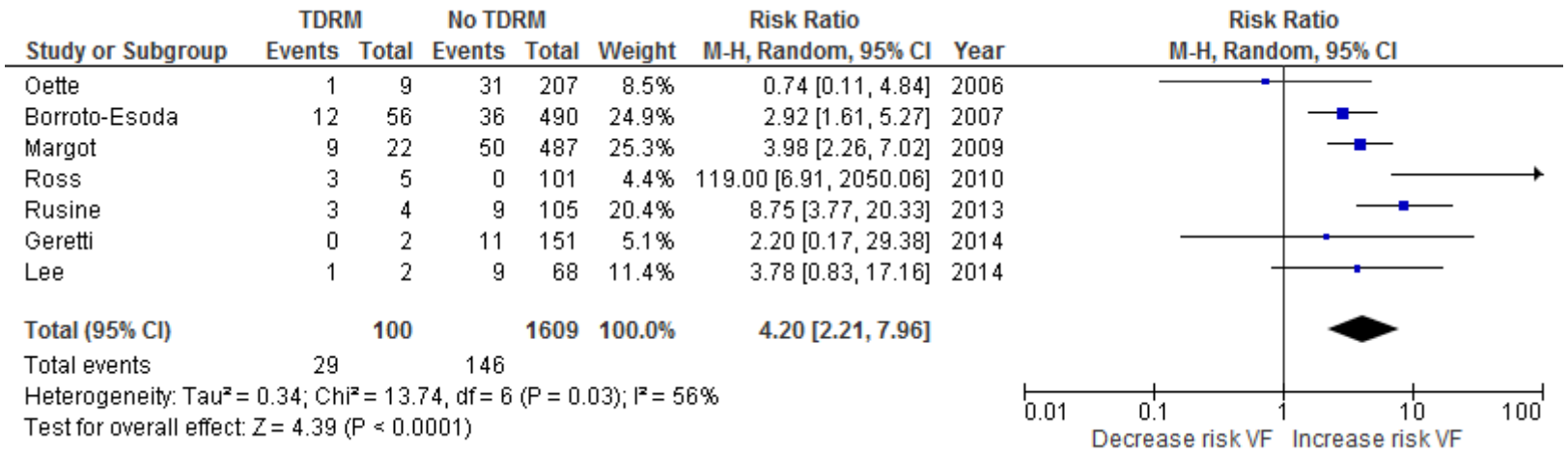

Figure 5 - Relative Risk of Virologic Failure for NNRTI TDRM

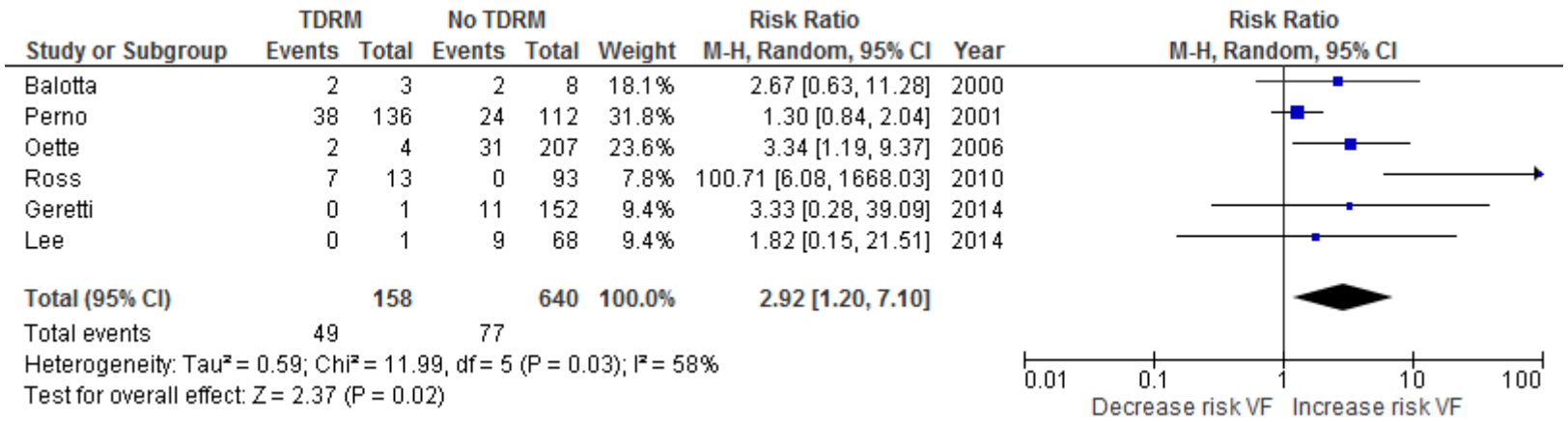

Figura 6 - Relative Risk of Virologic Failure for PI TDRM

Table 2 - Quality of evidence assessment - Newcastle-Ottawa Scale for Cohort studies

Cohort Studies									
	Selection				Comparability **	Outcome			Total
Author	Representativeness of the exposed cohort	Selection of the non exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	
Balotta, 2000	YES	YES	YES	YES	NO	YES	YES	YES	7
Tamalet, 2000'	YES	YES	YES	YES	YES*	YES	YES	YES	8
Perno , 2001	YES	YES	YES	YES	YES**	YES	YES	YES	9
Grant, 2002	YES	YES	YES	YES	YES*	YES	YES	YES	8
Ferrer, 2003	YES	YES	YES	YES	YES*	YES	YES	YES	8
Harrigan, 2003	YES	YES	YES	YES	YES**	YES	YES	YES	9
Oette, 2006	YES	YES	YES	YES	YES**	YES	YES	NO	8
Shet, 2006	YES	YES	YES	YES	YES*	YES	YES	YES	8
Borroto-Esoda, 2007	YES	YES	YES	YES	YES**	YES	YES	YES	9
Chaix, 2007	YES	YES	YES	YES	YES*	YES	YES	YES	8
Margot, 2009	YES	YES	YES	YES	NO	YES	YES	YES	7
Bansi, 2010	YES	YES	YES	YES	YES**	YES	YES	YES	9
Ross, 2010	YES	YES	YES	YES	NO	YES	YES	YES	7
Bartmeyer, 2010	YES	YES	YES	YES	YES*	YES	YES	YES	8
Wittkop	YES	YES	YES	YES	YES*	YES	YES	YES	8
Hamers, 2012	YES'	YES	YES	YES	YES*	YES	YES	YES	8
Taniguchi, 2012	YES	YES	YES	YES	YES**	YES	YES	YES	9

Rusine, 2013	YES	YES	YES	YES	YES**	YES	YES	YES	9
Geretti, 2014	YES	YES	YES	YES	NO	YES	YES	YES	7
Lee, 2014	YES	YES	YES	YES	YES*	YES	YES	YES	8
Knyphausen, 2014	YES	YES	YES	YES	YES*	YES	YES	YES	8
Li, 2015	YES	YES	YES	YES	YES**	YES	YES	YES	9
Shet, 2015	YES	YES	YES	YES	YES**	YES	YES	YES	9

Table 3 - Quality of evidence assessment - Newcastle-Ottawa Scale for Case-Control Studies

Author, year	Selection				Comparability **	Outcome			Total
	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
Kuritzkes†, 2008	YES	YES	NO	YES	YES*	YES	YES	YES	7
Strang, 2009	YES	NO	YES	YES	YES*	YES	YES	NO	6
Gagliani, 2011	NO	NO	NO	YES	NO	YES	YES	YES	4
Lai†, 2012	YES	YES	YES	YES	YES**	YES	YES	YES	9
Kantor†, 2015	YES	YES	YES	YES	YES*	YES	YES	YES	8

† Case-cohort study

Comparability ** 1(*) or 2(**) stars can be allotted in this category.

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Appendix I

Search strategy:

EMBASE **HIV** 'acquired immune deficiency syndrome'/exp OR 'acquired immune deficiency syndrome' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' **HIV TREATMENT** 'anti human immunodeficiency virus agent'/exp OR 'highly active antiretroviral therapy'/exp OR 'RNA directed DNA polymerase'/exp OR 'Human immunodeficiency virus proteinase inhibitor'/exp **DRUG RESISTANCE** 'drug resistance'/exp **GENOTYPE** 'genotyping technique'/exp OR 'genotype'/exp
PUBMED **HIV**

("Acquired Immunodeficiency Syndrome"[Mesh] OR "Immunologic Deficiency Syndrome, Acquired" OR "AcquiredImmune Deficiency Syndrome" OR "Acquired Immuno-DeficiencySyndrome" OR "Acquired Immuno Deficiency Syndrome" OR "Acquired Immuno-Deficiency Syndromes" OR "Immuno-Deficiency Syndrome, Acquired" OR "Immuno-Deficiency Syndromes,Acquired" OR "Syndrome, Acquired Immuno-Deficiency" OR"Syndromes, Acquired Immuno-Deficiency" OR "ImmunodeficiencySyndrome, Acquired" OR "Acquired Immunodeficiency Syndromes"

OR "Immunodeficiency Syndromes, Acquired" OR "Syndrome, Acquired Immunodeficiency" OR "Syndromes, AcquiredImmunodeficiency" OR "AIDS" OR "SIDA" OR "HIV Infections"[Mesh] OR "HIV Infections" OR "HIV Infection" OR "Infection, HIV"

OR "Infections, HIV" OR "HTLV-III-LAV Infections" OR "HTLV III LAVInfections" OR "HTLV-III-LAV Infection" OR "Infection, HTLV-III-LAV"OR "Infections, HTLV-III-LAV" OR "T-Lymphotropic Virus Type IIIInfections, Human" OR "T Lymphotropic Virus Type III Infections,Human" OR "HTLV-III Infections" OR "HTLV III Infections" OR"HTLV-III Infection" OR "Infection, HTLV-III" OR "Infections, HTLV-III")

HIV TREATMENT

("Anti-HIV Agents"[Mesh] OR "Antiretroviral Therapy, Highly Active"[Mesh] OR "HIV Reverse Transcriptase"[Mesh] OR "HIV Fusion Inhibitors"[Mesh] OR "HIV

Integrase Inhibitors"[Mesh] OR "HIV Protease Inhibitors"[Mesh] OR "Anti-HIV Agents" OR “Agents, Anti-HIV” OR “Anti HIV Agents” OR “Anti-HIV Drugs” OR “Anti HIV Drugs” OR “Drugs, Anti-HIV” OR “AIDS Drugs” OR “Drugs, AIDS” OR “Anti-AIDS Agents” OR “Agents, Anti-AIDS” OR “Anti AIDS Agents” OR “Anti-AIDS Drugs” OR “Anti AIDS Drugs” OR “Drugs, Anti-AIDS” OR "Antiretroviral Therapy, Highly Active" OR “Highly Active Antiretroviral Therapy” OR “HAART” OR "HIV Reverse Transcriptase" OR "Transcriptase, HIV Reverse" OR "Reverse Transcriptase, Human Immunodeficiency Virus" OR "Reverse Transcriptase, HIV" OR "HIV Fusion Inhibitors" OR "Fusion Inhibitors, HIV" OR "HIV Cell Fusion Inhibitors" OR "HIV Entry Inhibitors" OR "Entry Inhibitors, HIV" OR "HIV Integrase Inhibitors" OR "Integrase Inhibitors, HIV" OR "Inhibitors, HIV Integrase" OR "Inhibitors, HIV Protease" OR "HIV Protease Inhibitors" OR "Protease Inhibitors, HIV")

GENOTYPE

("Genotyping Techniques"[Mesh] OR "Genotyping Technique" OR "Technique, Genotyping" OR "Techniques, Genotyping" OR "Genotype Assignment Methodology" OR "Assignment Methodologies, Genotype" OR "Assignment Methodology, Genotype" OR "Genotype Assignment Methodologies" OR "Methodologies, Genotype Assignment" OR "Methodology, Genotype Assignment" OR "Genotype Calling Methods" OR "Calling Method, Genotype" OR "Calling Methods, Genotype" OR "Genotype Calling Method" OR "Method,

Genotype Calling" OR "Methods, Genotype Calling" OR "Genotype Determination Methods" OR "Determination Method, Genotype" OR "Determination Methods, Genotype" OR "Genotype Determination Method" OR "Method, Genotype Determination" OR "Methods, Genotype Determination" OR "Genotype"[Mesh] OR "Genotypes" OR "HIV genotyping test" OR "HIV genotype test" OR "HIV genotyping" OR "HIV genotype" OR "HIV resistance")

COCHRANE

HIV/AIDS

MeSH descriptor: [HIV] explode all trees OR HIV:ti,ab,kw (Word variations have been searched) OR AIDS

HIV TREATMENT

MeSH descriptor: [Antiretroviral Therapy, Highly Active] explode all trees OR Highly Active Antiretroviral Therapy

DRUG RESISTANCE

[Drug Resistance] explode all trees OR drug resistance

GENOTYPE

MeSH descriptor: [Genotype] explode all trees OR genotype

Artigo 2 - Resumo em Português

Antecedentes: As mutações de resistência do HIV estão associadas com risco aumentado de falha virológica (FV) entre pacientes previamente tratados, mas ainda existe incerteza sobre o risco relacionado com mutações transmissíveis de resistência a fármacos (MTRF) em pacientes virgens de tratamento.

Métodos: Foram realizadas buscas eletrônicas nas bases de dados Medline, Embase e Cochrane CENTRAL (até dezembro de 2015) para identificar ensaios clínicos randomizados ou estudos observacionais que relataram o risco de FV entre pacientes portadores de HIV virgens de tratamento com e sem MTRF. O risco de viéses foi avaliado com a escala de Newcastle-Ottawa. Realizamos metanálise de efeitos aleatórios das razões de risco (RR). A heterogeneidade foi avaliada pelo teste de inconsistência (I^2) e suas fontes foram investigadas em análise de sensibilidade de subgrupos na meta-análise quando adequado.

Resultados: Foram encontrados 28 estudos observacionais (23 de coorte, três caso-coorte e dois caso-controle) e nenhum ensaio clínico randomizado relatando taxas de FV entre pacientes portadores de HIV virgens de tratamento com e sem TDRM. O RR de FV para ter qualquer TDRM foi de 1,93 (95% CI 1,44 a 2,59) em uma meta-análise de 21 estudos de coorte que forneceram informações suficientes (I^2 = 82%). Para NRTI, NNRTI e IP, as estimativas de RR em meta-análise foram de 2,58 (95% CI 1,30 a 5,16); 4,2 (2,21 a 7,96) e 2,92 (1,20 a 7,10), respectivamente. A heterogeneidade diminuiu substancialmente para os subgrupos de classes de drogas (I^2=65%, 56% e 58%, respectivamente). A avaliação da

qualidade metodológica indicou ausência de ajuste abrangente para fatores de confusão em quatro dos 28 estudos e a análise do gráfico de funil indicou uma baixa probabilidade de viés de publicação.

Conclusão: As evidências disponíveis indicam que as TDRM aumentam o risco de falha virológica em pacientes HIV virgens de tratamento.

8 ARTIGO 3

HIV Genotype Test for Treatment Naïve Patients: A Markov Model Based Budget Impact Analysis

Teste de genotipagem do vírus HIV para pacientes virgens de tratamento: uma análise de impacto orçamentário baseada em um modelo de Markov

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HIV Genotype Test for Treatment Naïve Patients: A Markov Model Based Budget Impact Analysis

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March, 2016

ABSTRACT

Background: Economic evaluations on HIV genotype test for detection of transmitted drug resistance mutations (TDRM) are scarce and the budget impact for the Brazilian public healthcare system hasn't been estimated.

Objective: To estimate the budget impact of universal HIV genotype test for incident HIV cases in 5 years in Brazil.

Methods: We developed a Markov model open cohort. The model consisted of 3 states: (1) HIV incident cases ("patient generator" state); (2) Genotype test and (cost incurring state) and (3) Exit model (absorbing state). Cycle length was one month and time horizon was 5 years. No discounts were applied. The number of individuals entering the model per cycle was projected from a regression model derived from a 10 years period time-series of HIV incident cases.

Results: Linear model projections for expected annual incidence of HIV between years 2016 and 2020 varied from 41022 to 42788 cases, respectively. With 100% uptake of universal genotype test for incident cases of HIV from model start, annual budget impact estimates were: BRL 21,197,526.48 (USD 5,729,061.21) for 2016; BRL 21,420,723.6 (USD 5,789,384.75) for 2017; BRL 21,650,120.64 (USD 5,851,383.95) for 2018; BRL 21,873,317.76 (USD 5,911,707.50) for 2019 and BRL 22,102,714.8 (USD 5,973,706.70) for 2020. The accumulated 5-years budget impact for this scenario was estimated in BRL 108,244,403.3 (USD 29,255,244.14). Both deterministic and probabilistic sensitivity analyses were performed.

Conclusion: Universal HIV genotype test for incident HIV cases would result in an approximate annual increase of 22 million BRL (5.9 million USD) for the Brazilian public healthcare system.

Keywords: HIV, Transmitted drug resistance mutation, budget impact, Markov model

INTRODUCTION

Transmitted drug resistance mutations (TDRM) results from infection with an HIV-1 strain containing one or more resistance associated mutations. It is believed that TDRM negatively impacts antiretroviral treatment, delaying immunologic and virologic responses. This could increase the risk of virologic failure[1-3].

Reports on TDRM prevalence rates are conflicting. Figures for Brazil range from as low as 3.8% to as high as 18.2%. It is generally accepted that TDRM prevalence in Brazil is at the moderate level (5 to15%) according to the the World Heath Organization classification[4-6].

Currently, the Brazilian public healthcare system offers genotype test only at virologic failure. However, the perception of an increasing prevalence of TDRM has prompted physicians and healthcare system administrators to consider the incorporation of universal HIV genotype test for incident HIV cases in order to direct initial antiretroviral regimen[7, 8].

Economic evaluations on HIV genotype test for detection of TDRM are scarce. A cost-effectiveness analysis devised for the Brazilian healthcare system has found that a genotype-test oriented strategy for the first antiretroviral regimen is likely to be marginally more effective than an empirical treatment strategy, resulting in net cost savings in a lifetime time horizon[9]. However, budget impact for the Brazilian public healthcare system has not been estimated. Evaluation of affordability is critical for the implementation of new health technologies and strategies[10].

The objective of this study is to estimate the budget impact of universal HIV genotype test for incident HIV cases in 5 years in Brazil. To do so, we developed a Markov model simulated open cohort with target population projections based on actual data.

METHODS

Markov Cohort

We developed a Markov simulated open cohort as base model for budget impact and cost-effectiveness calculations. An open simulated cohort estimates the exact absolute number of individuals in each state and each cycle, while allowing entrance and exiting of individuals in certain parts of the model, as oppose to closed cohorts, that predicts proportions of a fixed number of individuals in each state per cycle, with no entrance or exiting points[10, 11].

The model consisted of 3 states: (1) HIV incident cases ("patient generator" state); (2) Genotype test and (3) Exit model (absorbing state). Cycle length was one month and time horizon was 5 years. Model begun with incident population size projected for the year 2016. The model was set up to accept incongruent probabilities in the "patient generator" state (i.e. probabilities that summed up to values greater than1). This was done to permit the creation of a limited number of simulated individuals per cycle. Model structure is presented in **Figure 1**.

Each cycle, a number of simulated individuals with recently diagnosed HIV infection entered the model in state (1) HIV incident cases. Number of individuals entering the model per cycle was calculated from a regression model derived from a 10 years period time-series of HIV incident cases. Details on the regression model are provided below. Incoming individuals had a probability of being submitted to HIV genotype test (100% in the base case and a variable proportion in analyses that accounted for technology uptake curve). Tested individuals were sent to state (2)

"Genotype test" in next cycle, where cost of genotype test was incurred. All individuals where then sent to the absorbing state "Exit model". Model was developed in Treeage Pro 2015 (TreeAge Software, Inc). **Table 1** presents sources for model inputs.

Linear regression model

Projected incidence of HIV for the years 2016 to 2020 were obtained from a linear regression model. A time-series of HIV incidence from 2004 to 2013 was used to estimate a linear regression equation to allow projections of future incidence[12]. At the time of model development, data from years 2014 and 2015 were not available. Modeled equation coefficients were statistically significant. Durbin Watson test showed absence of statistically significant auto-correlation. Calculated r^2 was 0.69. The equation to linearly predict annual incidence of HIV (absolute number of new cases), with the year 2004 as the time-index 1 of the time-series is presented in **Box 1**.

Box 1 - Linear regression model equation to predict annual incidence of HIV in Brazil (absolute number of new cases).

$$PAI = 35315{,}333 + 439{,}576 \times YTI$$

PAI: predicted annual incidence (predicted number of new cases for a given year)

YTI: year time-index (2004 is time-index 1)

Budget impact analysis

Determinants of budget impact in our model were: (1) target-population size; (2) genotype test cost; (3) proportion of target population being submitted to genotype test over time (technology uptake curve). Budget impact was estimated in a 5-years time horizon (2016 to 2020). Current scenario assumed no budget allocated to genotype test for recently diagnosed treatment naïve HIV patients. Alternative scenario assumed universal genotype testing for recently diagnosed treatment naïve HIV patients. Thus, any cost of providing genotype test for this group of patients is the incremental budget impact. Sources of information for the BIA are presented in **Table 2**.

Size of target population

Target population consisted of model output of projected incident cases of HIV infection per month[12]. Both deterministic and probabilistic calculations were made from regression equation coefficients in base-case and sensitivity analyses, respectivelly.

Costs

The only cost considered in the present model was the cost of genotype test, which was set to BRL 516.66 (USD 139.64) in the main analysis. This was the price of test acquisition in 2015 by the Brazilian Ministry of Health as reported in publicly available reports[13]. All other costs were assumed to be the same irrespective of simulated scenarios.

Technology uptake curve

As we found no reliable source of information to estimate the technology uptake curve, we have arbitrated three possible scenarios for uptake curve: in the base case, there is no uptake curve, and a 100% utilization rate is assumed from cycle 1. Alternative uptake curves were assessed in a sensitivity analysis[10].

Sensitivity analysis

To assess robustness of budget impact estimates, we performed deterministic and probabilistic sensitivity analyses. Uncertainties on incident population size and costs were assessed in Monte Carlo simulations (2nd order), with 100.000 iterations. For population size, it was assumed a normal distribution of regression equation coefficients. Mean and standard deviation derived from the linear model. For costs, a triangular distribution was used. Lower bound derived from inflation-adjusted acquisition prices of genotype test by the Brazilian government in 2002, and upper bound originated from the cost-effectiveness analysis reported by Luz et al (2015)[9, 14].

For the budget impact calculations, alternative uptake curves were tested in a deterministic way. First, we assumed an initial uptake of 60% in the first year, with 10% increases per year, reaching 100% uptake in the fifth year. Second, we tested a linear uptake curve with 0% utilization in first cycle and 100% utilization in the fifth year.

RESULTS

Linear model projections for expected annual incidence of HIV between years 2016 and 2020 varied from 41022 to 42788 cases, respectively. A comparison of observed and predicted annual HIV incidence is presented in **Table 3**.

Base-case budget impact estimates are presented for 3 hypothetical uptake curves: 100% from cycle one, linear progression from 60 to 100% uptake in five years and linear progression from o to 100% uptake in 5 years. With 100% uptake of universal genotype test for incident cases of HIV, annual undiscounted budget impact estimates are the following: BRL 21,197,526.48 (USD 5,729,061.21) for 2016; BRL21,420,723.6 (USD 5,789,384.75) for 2017; BRL 21,650,120.64 (USD 5,851,383.95) for 2018; BRL 21,873,317.76 (USD 5,911,707.50) for 2019 and BRL 22,102,714.8 (USD 5,973,706.70) for 2020. The accumulated 5-years budget impact for this scenario was estimated in BRL 108,244,403.3 (USD 29,255,244.14).

Accumulated 5-years budget impact for initial 60% and 0% technology uptake scenarios were estimated in BRL 90,681,657.4 (USD 24,508,556.0) and BRL 64,337,538.58 (USD 17,388,523.94), respectively. Budget impact projections for base-case scenarios are presented in **Table 4**.

A probabilistic sensitivity analysis that simultaneously varied size of target population and alternative genotype test cost estimated the 95% CI for cumulative 5-years budget impact to be from BRL 80,283,367.66 (USD 21,698,207.48) to BRL 178,047,356.5 (USD 48,120,907.16). Median value was BRL 119,621,904.6 (USD

32,330,244.49). **Figure 2** presents expected values for this analysis. **Table 5** presents the full range of sensitivity analyses performed.

DISCUSSION

We presented a Markov model based budget impact analysis for universal genotype test of new HIV cases under Brazilian public healthcare system perspective. To our knowledge, there are no published Markov model budget impact analyses on the current research question. This type of model was chosen due to its flexibility in terms of sensitivity analysis[10].

Budget impact analysis has gained recognition as an important and necessary step on economic evaluation of health technologies. In some circumstances, with demonstration of effectiveness and safety in line with healthcare policy decisions, full economic evaluations such as cost-effectiveness and cost-utility might not be required, and financial planning takes precedence over economic efficiency[10, 15, 16].

That might be the case with universal genotype test to for TDRM screening among incident cases of HIV infection. Virologic failure has long been accepted as an appropriate intermediate endpoint to hard endpoints related to HIV infection such as occurrence of opportunistic infections and death. Genotype test for detection of secondary (acquired) drug resistance mutations among patients who underwent virologic failure is currently regarded standard of care in the choice of a next anti-retroviral regimen. With a growing prevalence of TDRM, it is a next logic step to implement universal genotype test for newly diagnosed treatment naïve HIV patients. In theory, this would result in lower rates of virologic failures to the first antiretroviral regimen[17, 18].

As we found no source to estimate reliably the technology uptake curve, base case results were presented for 3 hypothetical uptake curves: 100% from cycle one, linear progression from 60 to 100% uptake in five years and linear progression from o to 100% uptake in 5 years. Assuming universal HIV genotype test to incident cases of HIV would be a mandatory public health policy, and considering the successful cases of implementation of many mandatory HIV policies by Brazilian government in the recent past, we believe a figure close to 100% uptake curve from the beginning of such a healthcare program is the likeliest scenario to occur.

In the base-case, we estimated an increase of approximately 22 million Brazilian Reais (5.9 million Dollars) in annual budget would be required to implement universal genotype test for incident HIV cases. Though this is not a negligible amount, it is likely to be affordable at present in comparison to other investments reported in the Brazilian 2012-2015 National Healthcare Plan[19].

We believe actual budget impact tends to be lower than our base-case estimate because Brazilian Ministry of Health was able to negotiate a lower price for genotype test in the past (year 2002), and universal TDRM screening would result in larger and more predictable purchases, which could drive prices down in future negotiations with suppliers.

The present budget impact analysis has some limitations that deserve mention. First, budget impact estimates rely on a linear projection of expected target-population size as a function of time. Though the linear model is mathematically valid, other factors could come to play in future years that could change current HIV incidence projections, such as effective large scale HIV

prevention programs or even HIV vaccination programs. Second, it is assumed current Brazilian infrastructure of specialized laboratories would be able to handle the increased demand for HIV genotype tests, thus only direct cost of genotype test acquisition were considered. Though this is probably true, budget impact might increase if additional infrastructure investments are required to process this new burden of genotype tests. This was partially assessed on probabilistic cost sensitivity analysis, with an upper bound cost of BRL 851 (USD 230). Finally, we didn't account for possible savings derived from universal HIV genotyping, as healthcare system costs as a whole would tend to decrease with the expected reduction of virologic failures from TDRM detection to guide initial ARV treatment. Such cascade and indirect consequences of universal incident HIV genotyping are very complex to predict and are beyond the scope of the present budget impact analysis[10].

In conclusion, universal HIV genotype test for incident HIV cases would result in an accumulated 5-years budget impact of BRL 108,244,403.3 (USD 29,255,244.14). Current laboratory infrastructure capability and the potential to attain lower prices in large and consistent purchases are sources of uncertainties on budget impact estimates.

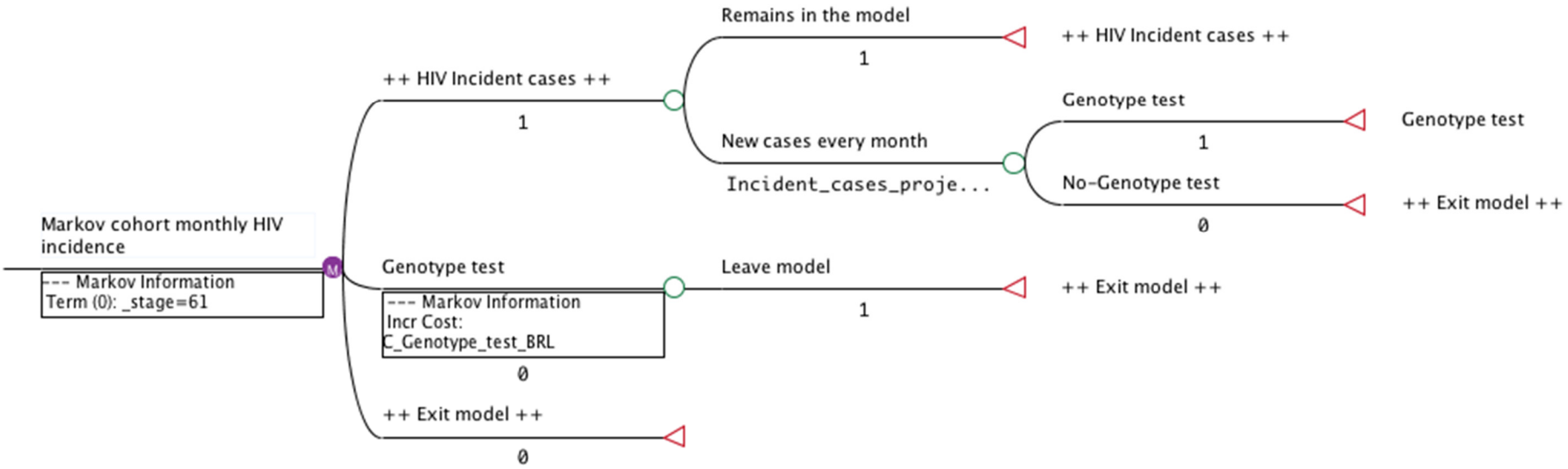

Figure 1 - Markov model for budget impact analysis of primary HIV transmitted drug resistance genotype test

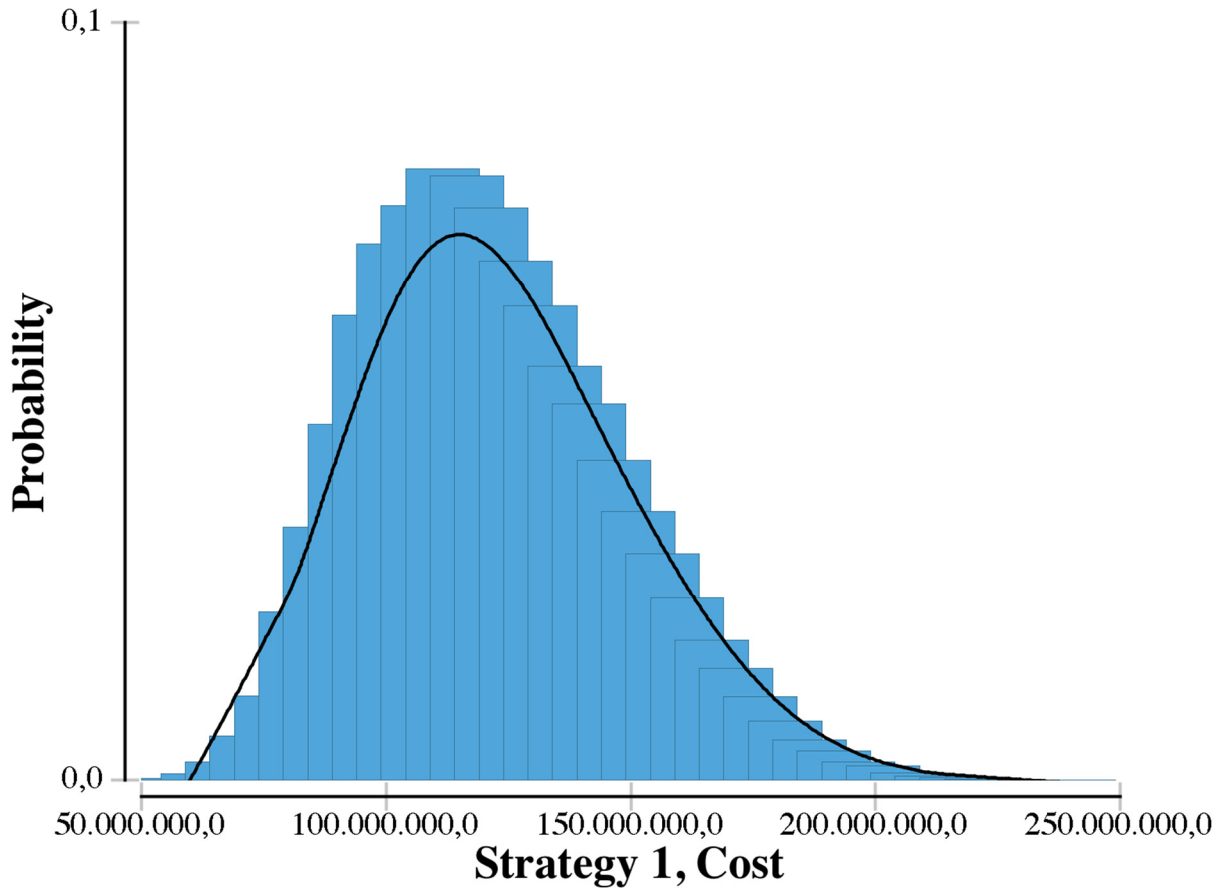

Figure 2 - Histogram of Monte Carlo simulation probabilistic sensitivity analysis with simultaneous variation of size of target population and genotype test cost, 100.000 iterations.

Table 1 - Model assumptions for budget impact analysis of primary HIV transmitted drug resistance genotype test

Model assumption	Base-case BIA
Target condition	HIV bearing primary resistance mutation to anti-retroviral drugs
Technology	Genotype test major mutation
Perspective	Brazilian public healthcare system (SUS)
Time horizon	5 years (2016 to 2020)
Adjustment for inflation	No
Discounting	No
Method to estimate size of target population	Epidemiological method: Regression model from Brazilian surveillance system time-series (DATASUS)
Model type	Open cohort Markov simulation
Cycle length	1 month
Rate of technology uptake	100% from the start
Comparisons	Current scenario: no genotype test available to patients with HIV prior to first anti-retroviral treatment Alternative scenario: genotype test available to all patients with HIV prior to first anti-retroviral treatment (at diagnosis)

BIA, budget impact analysis; SUS, Unified Healthcare System (Brazilian public healthcare system)

Table 2 - Model parameters for base-case and sensitivity analyses

Parameter	Base case	Sensitivity analysis	Source
Monthly incidence of HIV (absolute number of new cases)	Deterministic projection from time-series derived regression equation. Incident cases per month, per year: 2016: 3419 2017: 3455 2018: 3492 2019: 3528 2020: 3565	Probabilistic projections for regression equation coefficients (normal distribution) y = ND_B0 + ND_B1 * Stage converted to years, starting at stage 145 (year 2016) (See explanatory note below)	For the base-case, incident cases were estimated from a linear regression model developed from a 10 years (2004-2013) time-series of new cases (DATASUS) Sensitivity analysis figures are probabilistic projections from regression equation coefficients.
Technology uptake curve	100% uptake from cycle 1.	Uptake curve 1: 60,70,80,90 and 100% for years 2016 to 2020, respectively. Uptake curve 2: linear progression from 0 to 100% uptake from year 2016 to 2020.	Arbitrary definition
Cost of genotype test	BRL 516.66 USD 139.64	BRL 393.51 - 851 USD 106.24 - 230	Base case: Brazilian Ministry of Health investment report 2015 Lower bound for sensitivity analysis: inflation-adjusted cost from Brazilian Ministry of Health genotype test acquisition of 2002 Upper bound: Luz et al, 2015.

Note: Equation for probabilistic prediction of the absolute number of new cases per month, starting at month 144 (this corresponds to the end of year 12 (year 2015) of prediction model, thus estimates start at year 2016: y= {ND_B0[35315.333; 2042.287] + ND_B1[438.576; 329.14567] x [(_stage+144)/12]}/12

BRL, Brazilian Real (R$); USD, Unite States Dollar (U$); ND, normal distribution [mean; standard deviation]; ND_B0, normal distribution for regression equation B0 coefficient; ND_B1, normal distribution for regression equation B1 coefficient.

Table 3 - Linear regression model projected annual incidence of HIV and comparison with observed incidence

Year	Observed number of HIV cases in adults (>15 years old)*	Projected from linear regression model annual number of incident cases of HIV**	Prediction error
2004	36268	35754	-514
2005	36320	36193	-127
2006	35298	36632	+1334
2007	36137	37071	+934
2008	38793	37510	-1283
2009	38446	37949	-497
2010	37934	38388	+454
2011	40005	38827	-1178
2012	39279	39266	-13
2013	38850	39705	+855
2014	-	40144	-
2015	-	40583	-
2016	-	41022	-
2017	-	41461	-
2018	-	41900	-
2019	-	42339	-
2020	-	42778	-

* Source: DATASUS, absolute number of new cases of persons infected with HIV between 2004 and 2013.
** Linear regression model derived from the DATASUS time series of new HIV cases between 2004 and 2013, with projections from 2014 to 2020.

Table 4 - Results of base-case budget impact analysis for universal genotype test for projected incident cases of HIV infection in Brazil (5 years time horizon, undiscounted)

Model Assumptions			Expected value					
Scenario	**HIV incidence**	**Genotype test cost**	**2016**	**2017**	**2018**	**2019**	**2020**	**Cumulative 5 year BI**
Base-case 100% uptake curve	Deterministic projection from regression equation	BRL 516.66 USD 139.64	BRL 21,197,526.48 USD 5,729,061.21	BRL 21,420,723.6 USD 5,789,384.75	BRL 21,650,120.64 USD 5,851,383.95	BRL 21,873,317.76 USD 5,911,707.50	BRL 22,102,714.8 USD 5,973,706.70	BRL 108,244,403.3 USD 29,255,244.14
Base-case 60 to 100% uptake curve	Deterministic projection from regression equation	BRL 516.66 USD 139.64	BRL 13,601,746.16 USD 3,676,147.61	BRL 15,976,289.69 USD 4,317,916.13	BRL 18,312,393.71 USD 4949295.59	BRL 20,688,513.05 USD 5591490.01	BRL 22,102,714.8 USD 5,973,706.70	BRL 90,681,657.4 USD 24,508,556.0
Base-case 0 to 100% uptake curve	Deterministic projection from regression equation	BRL 516.66 USD 139.64	BRL 2208075.675 USD 596777.21	BRL 7,809,638.813 USD 2,110,713.19	BRL 13,305,803.31 USD 3,596,163.05	BRL 18,911,305.98 USD 5,111,163.77	BRL 22,102,714.8 USD 5,973,706.70	BRL 64,337,538.58 USD 17,388,523.94

BRL, Brazilian Real; USD, United States Dollar; BI, budget impact.

Table 5 - Probabilistic sensitivity analyses on cumulative 5 years budget impact analysis for universal genotype test for projected incident cases of HIV infection in Brazil (undiscounted, 100% technology uptake from model start)

Model Assumptions			Expected value					
Scenario	**HIV Incidence**	**Genotype test cost**	**Minimum**	**2.5% CI**	**97.5% CI**	**Maximum**	**Mean**	**Median**
4-Sensitivity Analysis population size	Probabilistic projection from regression equation (normal distribution of equation coefficients)	BRL 516.66 USD 139.64	BRL 46,655,734.87 USD 12,609,658.07	BRL 81,339,143.87 USD 12,609,658.07	BRL 133,647,059.7 USD 36,120,826.95	BRL 162,088,578.1 USD 43,807,723.81	BRL 107,533,579,.7 USD 29,063,129.65	BRL107,570,290.7 USD 29,073,051.54
Sensitivity Analysis cost	Deterministic projection from regression equation	Triangular distribution BRL 393.51 -516.66 - 851 USD 106.24 - 139 - 230	BRL 82,534,977.39 USD 22,306,750.65	BRL 90,250,601.51 USD 24,392,054.46	BRL 165,300,896.4 USD 44,675,917.95	BRL 178,120,018.9 USD 48,140,545.65	BRL 122930,572.5 USD 33,224,479.05	BRL 120,265,477.5 USD 32,504,183.11
5-Probabilistic Sensitivity analysis Population Size	Probabilistic projection from regression equation (normal distribution of equation coeficients)	Triangular distribution BRL 393.51 -516.66 - 851 USD 106.24 - 139 - 230	BRL 49,814,238.29 USD 13,463,307.65	BRL 80,283,367.66 USD 21,698,207.48	BRL 178,047,356.5 USD 48,120,907.16	BRL 242,916,064.9 USD 65,652,990.51	BRL 122,423,863.6 USD 33,087,530.7	BRL 119,621,904.6 USD 32,330,244.49

BRL Brazilian Real; USD, United States Dollar; CI, confidence interval.

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Artigo 3 - Resumo em português

Antecedentes: Escassas são as avaliações econômicas do teste de genotipagem do HIV para a detecção de mutações de resistência transmissíveis (MRT), e o impacto orçamento para o sistema de saúde público brasileiro não foi estimado.

Objetivo: Estimar o impacto orçamentário da aplicação universal do teste de genotipagem do HIV para casos de HIV incidentes, em 5 anos, no Brasil.

Métodos: Foi desenvolvido uma coorte simulada aberta através de um modelo de Markov. O modelo consistiu de 3 estados: (1) casos incidentes de HIV ("gerador de paciente" estado); (2) Teste de genotipagem e (estado onde ocorrem os custos) e (3) Saída do modelo (estado absortivo). A duração do ciclo foi de um mês e o horizonte de tempo foi de 5 anos. Não foram aplicados descontos. O número de indivíduos que entram no modelo por ciclo foi projetado a partir de um modelo de regressão derivado de uma série temporal de 10 anos de casos incidentes de HIV.

Resultados: As projeções do modelo de regressão linear para incidência anual esperada de HIV entre os anos de 2016 e 2020 variaram de 41022 a 42788 casos, respectivamente. Com 100% incorporação do de teste de genótipagem para casos incidentes de HIV desde o início do modelo, as estimativas anuais de impacto orçamentário foram: R$ 21.197.526,48 (U$ 5.729.061,21) para 2016; R$ 21.420.723,6 (U$ 5.789.384,75) para 2017; R$ 21.650.120,64 (U$ 5.851.383,95)

para 2018; R$ 21.873.317,76 (U$ 5.911.707,50) para 2019 e R$ 22.102.714,8 (U$ 5.973.706,70) para 2020. O impacto orçamentário acumulado em 5 anos para este cenário foi estimado em R$ 108.244.403,3 (U$ 29.255.244,14). Tanto análise de sensibilidade determinística quanto probabilística foram realizadas.

Conclusão: A aplicação universal do teste de genotipagem para casos incidentes de HIV resultaria em um aumento anual aproximado de 22 milhões de reais (5,9 milhões de dólares) para o sistema de saúde público brasileira.

Palavras-Chave: HIV, mutação transmitida de resistência a drogas, impacto orçamentário, modelo de Markov

9 CONSIDERAÇÕES FINAIS

A presente tese investigou o impacto das mutações de resistência transmitidas do vírus HIV aos antirretrovirais no risco de falha virológica. Previamente ao trabalho atual, uma elevada incerteza sobre essa relação existia, embora o pensamento dominante na comunidade científica fosse o de que a presença de TDRM estaria associada a um maior risco de desfechos adversos, inclusive a uma maior falha virológica. Com mais de 15000 pacientes estudados nos 21 estudos de coorte incluídos na metanálise principal, pode-se agora afirmar que a presença de TDRM aumenta risco de falha virológica. Essa constatação reforça a necessidade de avaliar a adotação da genotipagem do vírus HIV em larga-escala entre pacientes que ainda não iniciaram o seu primeiro esquema antirretroviral.

A prevalência das TDRM no Brasil foi melhor quantificada e tendências de subgrupos de pacientes foram melhor compreendidas como resultado da revisão sistemática de prevalências que foi empreendida na presente tese. O resultado do impacto orçamentário mostrou que a aplicação universal do teste de genotipagem para casos incidentes de HIV resultaria em um aumento anual aproximado de 22 milhões de reais (5,9 milhões de dólares) para o sistema de saúde público brasileiro.

O conjunto das informações aqui levantadas e organizadas não corresponde a um simples exercício acadêmico. Trata-se de informações com elevada

relevância para fim do planejamento de políticas de saúde pública. Cabe-nos fazer essas informações serem incluídas nas tomadas de decisão dos gestores do sistema de saúde, a começar pela publicação dos estudos.

Com a presente tese, esperamos ter proporcionado uma pequena, porém relevante contribuição para a luta contra a epidemia do vírus HIV no Brasil e no mundo.