ANÁLISE ECOLÓGICA MULTINÍVEL DOS CASOS DE AIDS NOS MUNICÍPIOS BRASILEIROS

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Resumo:

A epidemia de AIDS no Brasil vem se disseminando dos maiores centros urbanos para municípios de médio e pequeno porte, onde a disponibilização e monitoramento de intervenções preventivas e tratamento constituem desafios relevantes. Os usuários de drogas injetáveis (UDI) desempenham um papel relevante na epidemia de HIV/AIDS no Brasil e em diversos outros países. Os UDI funcionariam como uma "ponte" na disseminação do HIV para outras populações, por estarem duplamente expostos à transmissão parenteral e sexual e devido à sua estreita interação com não-usuários.

A importância dos determinantes econômicos e sociais vem sendo reconhecida, e têm recebido atenção em estudos epidemiológicos relativos à distribuição e determinantes da dinâmica do HIV e demais infecções sexualmente transmissíveis. Considerando a grande heterogeneidade da epidemia brasileira, as desigualdades sociais, as desigualdades no acesso e infra-estrutura médica nas diferentes regiões do Brasil, faz-se oportuno identificar indicadores relacionados aos diferenciais de magnitude e extensão da epidemia de AIDS nos diferentes municípios brasileiros, ao longo do tempo.

A análise dos casos de AIDS registrados entre UDI nos municípios brasileiros (1984 - 2000) identificou os indicadores "número de médicos por habitante" e "distância-padrão da capital do respectivo estado" como associados à taxa de incidência de AIDS entre UDI, evidenciando que os casos de AIDS entre UDI parecem se concentrar em municípios mais ricos e bem equipados. Na análise dos casos de AIDS registrados entre heterossexuais nos municípios da região Sul do país os indicadores "Índice de Desenvolvimento Humano" (IDH) e a "Proporção de moradores que tem acesso a instalações sanitárias" se mostraram inversamente associados à taxa de AIDS entre heterossexuais. A taxa de incidência de AIDS entre UDI se mostrou positivamente associada à taxa de AIDS entre heterossexuais. Os achados demonstram a importância do papel da desigualdade/pobreza e o papel dos UDI como uma "população-ponte" na disseminação do HIV/AIDS nos municípios do Sul do Brasil. Esses resultados refletem a tendência de "pauperização" e "interiorização" da epidemia no Brasil. Políticas públicas devem ser direcionadas de acordo com as especificidades sociais e regionais, especialmente num país de vasta dimensão e marcado pelos contrastes sociais, como o Brasil.

Palavras-chave: HIV/AIDS; Usuários de drogas injetáveis; Indicadores municipais; Modelo multinível; Brasil.

Abstract:

The AIDS epidemic in Brazil has been spreading from the largest urban centers to smaller and medium-size municipalities, where the implementation and monitoring of treatment and prevention strategies constitute an important challenge. Injecting drug users (IDUs) play a relevant role in Brazilian HIV/AIDS epidemic. In many different countries IDUs may function as a "bridging population", contributing to the spread of HIV to other populations, due to their double exposure to sexual and parenteral risks and their strong interaction with non-drug users.

The importance of socioeconomic determinants has been recognized by epidemiologic studies addressing the diffusion patterns and dynamics of HIV and others sexually transmitted infections. The heterogeneity of the Brazilian epidemic and the deep social inequalities and striking inequalities in terms of access to health services and availability of health professionals make the identification and analysis of a comprehensive set of indicators a key effort. Brazilian policy-makers should use sound information in their attempt to monitor the scope and magnitude of the AIDS epidemic across the vast network of Brazilian municipalities, over time. The analysis of AIDS cases notified among IDUs in Brazilian municipalities from 1986 to 2000 found that the "Number of physicians per inhabitant" and the "Standard distance to the state's capital" were associated with the AIDS incidence rate among IDUs. AIDS cases among IDUs cluster in richer and better equipped municipalities. In the analysis of AIDS cases registered among heterosexuals in southern municipalities the following indicators were found to be inversely associated with AIDS incidence rate: "Human Development Index" (HDI) and "Ratio of residents who have access to sanitary installations". AIDS incidence rate among IDUs was found to be positively associated with AIDS incidence rate among heterosexuals. These findings show that social inequality/poverty and bridging from injection drug users to non-drug users foster the spread of HIV/AIDS Brazilian southern municipalities. Our findings reflect the "impoverishment" and "interiorization" of the Brazilian AIDS epidemic. Public policies should be tailored to regional and social specificities in a multifarious and complex epidemic, especially in a country with vast dimension and striking social contrasts such as Brazil.

Key-words: HIV/AIDS; Injection drug users; Social indicators; Multilevel modeling; Brazil.

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1- Introdução

1.1- A epidemia de HIV/AIDS e a "Era HAART"

Segundo informações da UNAIDS, em 2004, aproximadamente 5 milhões de pessoas foram infectadas pelo HIV, o maior número de infectados em um único ano desde o início da epidemia. O número de pessoas vivendo com HIV continua crescendo, com 40 milhões de pessoas, em todo o mundo, em 2004. Nesse mesmo ano, quase 3 milhões de pessoas morreram devido a complicações da síndrome clínica (AIDS).UNAIDS, 2005[1].

De acordo com o último relatório do programa '3 by 5' (iniciativa global da Organização Mundial de Saúde e UNAIDS para disponibilizar terapia antiretroviral a 3 milhões de pessoas com HIV/AIDS nos países em desenvolvimento até o final de 2005), nos países em desenvolvimento, 1 milhão de pessoas infectadas pelo HIV estão recebendo terapia antiretroviral, o que representa apenas 15% daqueles que necessitam de tratamento (UNAIDS, 2005) [1].

A epidemia afeta de maneira substancialmente heterogênea as diversas regiões geográficas (países, sociedades e comunidades). Além do marcante contraste no âmbito da disseminação do HIV nos diferentes contextos, preocupa a profunda iniqüidade no tocante à oferta de terapias antiretrovirais de alta potência (HAART − sigla em inglês), raras ou inexistentes exatamente nas regiões onde a epidemia vem afetando mais profundamente a saúde pública e a própria dinâmica social e econômica, como na África subsaariana.

Mesmo em um contexto de oferta universal e gratuita da terapia, foram encontradas evidências de que o baixo nível sócio-econômico está associado a uma menor sobrevida de pacientes com HIV/AIDS. Uma análise recente concluiu que esse fato poderia estar sendo confundido em função da desigualdade referente ao acesso efetivo ao tratamento, de acordo com o nível sócio-econômico (Wood et al., 2002)[2].

O acesso universal à HAART é condição necessária mas não suficiente para o sucesso do tratamento para os pacientes e para a saúde pública como um todo. A aderência ao tratamento é de fundamental importância.

Para os indivíduos vivendo com HIV/AIDS, uma aderência aquém da desejada pode levar à falha terapêutica, deterioração do sistema imunológico e/ou o aparecimento de cepas virais multi-resistentes do HIV. Ao nível populacional, a não aderência à HAART pode também levar a um aumento das taxas de infectividade entre pessoas vivendo com HIV/AIDS, e, potencialmente, a um aumento das taxas de transmissão de cepas virais

multi-resistentes do HIV (de Ronde et al., 2001)[3], determinando uma maior morbidade e mortalidade.

O aumento da sobrevida entre indivíduos infectados pelo HIV que utilizam HAART (fato documentado em diferentes países, inclusive no Brasil ─ Marins et al., 2003[4]) resulta no aumento do número de pessoas vivendo com HIV/AIDS e vem determinando mudanças no padrão de morbi-mortalidade por AIDS.

Ao aumentar a sobrevida e a qualidade de vida das pessoas vivendo com HIV/AIDS configura-se uma "recomposição" na dinâmica do HIV em uma dada comunidade, com um novo balanço do *pool* de infectados *versus* suscetíveis e uma redefinição das redes sociais, com o retorno à vida sexual ativa e ao eventual uso compartilhado de drogas injetáveis de indivíduos antes gravemente adoecidos ou que nem chegariam a sobreviver por mais do que alguns meses após o aparecimento da síndrome clínica (Boily et al., 2005) [5].

Além desses fenômenos, de dimensão propriamente populacional e ecológica, explorados em detalhe em publicações recentes (Boily et al., 2004[6]; Boily et al., 2005[5]), existem fortes evidências no sentido de um "otimismo" vinculado à HAART, com uma crescente despreocupação dos indivíduos com a gravidade clínica da infecção, descuido com a prevenção e banalização da relevância e do impacto da própria epidemia (Van de Ven et al., 2002)[7].

Existem evidências na literatura de que crenças "otimistas" ou percepções sobre a redução de infectividade e/ou susceptibilidade ao HIV devido à existência da HAART estariam associadas a um aumento da freqüência de comportamentos sexuais menos seguros (Remien & Smith, 2000)[8].

A maioria dos países desenvolvidos vem registrando declínio substancial na mortalidade por AIDS após 1996, coincidindo com o período de disponibilização da HAART (Hickman et al., 1999[9]; Pezzotti et al., 1999[10]). Entretanto, os benefícios da terapia não têm sido homogeneamente observados entre os diferentes estratos populacionais, segundo raça, sexo e classe sócio-econômica (Fordyce et al, 2002)[11].

O acesso à terapia é mínimo ou ausente para a maioria da população de infectados no mundo. Igualmente preocupante é o fato de que, nos países desenvolvidos, a epidemia afeta basicamente populações marginalizadas, sem acesso a serviços médicos e informações que poderiam protegê-los contra o HIV/AIDS.

Foi observado que, mesmo em países desenvolvidos, que dispõem de acesso gratuito à HAART, como Espanha e Canadá, os padrões de mortalidade por AIDS são

diferenciados (no sentido de óbitos mais precoces) nas regiões menos providas e em pacientes com nível educacional e socioeconômico mais baixo (revisado por Antunes et al., 2005)[12].

Estudo realizado no município de São Paulo referente aos óbitos por AIDS, no período de 1994 a 2002, procurou analisar as correlações entre os coeficientes de mortalidade por AIDS e os índices de inclusão/exclusão social em homens e mulheres, com idades entre 25 a 49 anos. Observou-se que os distritos do município de São Paulo com os maiores coeficientes de mortalidade coincidiam com os municípios com maiores proporções de mulheres chefes de família/analfabetas. Esse resultado poderia estar refletindo as tendências da epidemia, que vem se expandindo entre a população de menor escolaridade e do sexo feminino, uma pior resposta à terapia entre os segmentos mais pobres e marginalizados, ou uma combinação de ambos (Farias et al., 2005)[13].

1.2- A epidemia de HIV/AIDS no Brasil

Desde o início da epidemia (década de 80) até 2004, foram notificados pelo Ministério da Saúde 362.364 casos de AIDS no país. Embora em patamares elevados, a incidência apresenta tendência de estabilidade, se considerados os últimos anos da série histórica, e declínio, se compararmos o final de década de 90 com o início da presente década. A região sudeste apresentou uma redução na taxa de incidência de AIDS em 2003 (comparada com a taxa em 1998, ressalvando-se a necessidade de corrigir o atraso de notificação ─ Barbosa & Struchiner, 2002[14]). Nas demais regiões, observa-se uma estabilidade ou mesmo incremento da taxa de incidência em anos recentes, como na região sul (MS, 2005)[15]. Como a região sudeste concentra mais de 60% dos casos registrados em todo o país, o cômputo global sinaliza um declínio (MS, 2005) [15].

Os casos masculinos entre usuários de drogas injetáveis (UDI) vêm decrescendo em anos recentes, ao passo que os casos registrados entre homo/bissexuais mantiveram-se estabilizados (ou em declínio, a depender da região) e os casos devido à transmissão heterossexual apresentam tendência crescente. Os casos devidos à transfusão de sangue e hemoderivados têm, hoje, um papel residual. A epidemia vem atingindo de maneira especialmente relevante os indivíduos com menor escolaridade (MS, 2005) [15].

Atualmente, cerca de 158 mil pacientes recebem terapia antiretroviral no país (UNAIDS, 2005) [16] . Em novembro de 1996, a lei federal brasileira n° 9.313 estabeleceu o acesso livre e gratuito à terapia antiretroviral para todos os cidadãos brasileiros vivendo com

HIV/AIDS (MS 2000)[17], tornando o Brasil o primeiro (e, à época, único) país em desenvolvimento a oferecer HAART através de um sistema público de saúde, com cobertura universal.

O Brasil representa, no contexto da pandemia, um caso único, dada a magnitude e diversidade regional da sua epidemia, os seus imensos contrastes sociais e a condição de único país em desenvolvimento com uma epidemia desta magnitude a contar com um programa plenamente instalado de acesso universal à terapia antiretroviral.

Entretanto, o Brasil apresenta uma distribuição desigual de acesso à infra-estrutura médica e de saúde e saneamento de um modo geral. A distribuição dos serviços e profissionais de saúde nas diferentes regiões do país é heterogênea, com uma maior concentração nas regiões e estados economicamente mais desenvolvidos (Petersen et al., no prelo) [18].

Desigualdades econômicas, diversidades geográficas e as dimensões continentais do país dificultam a resposta brasileira frente à epidemia de HIV/AIDS. O acesso universal à terapia se concretizou rapidamente nas maiores regiões metropolitanas do país servidas por sistemas de saúde locais bem desenvolvidos, mas, em função da grande dispersão da população na região norte, por exemplo, persistem barreiras relevantes no acesso ao tratamento naquela região (Petersen et al., no prelo) [18].

A epidemia de AIDS no Brasil vem se disseminando dos maiores centros urbanos para municípios de médio e pequeno porte, onde a distribuição, aderência e monitoramento do tratamento constituem desafios relevantes (Antunes et al., 2005) [12].

As desigualdades de acesso de diferentes segmentos da população podem ser pronunciadas quando novos programas de saúde são implementados, beneficiando inicialmente aqueles com melhores condições socioeconômicas, e se estendendo mais tardiamente aos segmentos mais carentes da população. Nesse sentido, a HAART pode ter, em certa medida, aprofundado desigualdades socioeconômicas pré-existentes, de um modo geral e na sua inter-relação com a dinâmica da AIDS no Brasil, uma vez que os pacientes de diferentes estratos sociais têm acesso desigual ao tratamento (Antunes et al., 2005) [12].

O fato do acesso universal à HAART existir em um país como o Brasil, com profundas desigualdades de renda, oferece a oportunidade de avaliar questões importantes visando assegurar a qualidade da assistência e serviços, assim como a oferta de serviços voltados para a prevenção. Estes aspectos têm de ser avaliados em diversos contextos sócio-culturais e econômicos, que diferem daqueles vigentes nos Estados Unidos e Europa,

onde a maioria esmagadora das pesquisas referentes a estas questões tem sido desenvolvida até o presente momento.

O declínio heterogêneo da mortalidade e da incidência da AIDS leva à formulação de múltiplas hipóteses, como as diferenças referentes ao estágio clínico, quando da demanda por cuidados médicos, entre diferentes subpopulações, a predominância de certos modos de transmissão em determinadas regiões, acesso diferencial à informação, prevenção e serviços médicos, além de desigualdades na qualidade do tratamento e aderência (Fonseca & Barreira, 2000) [19].

No entanto, o declínio da incidência da AIDS não pode ser atribuído à introdução da HAART, pois os casos notificados anualmente referem-se a infecções ocorridas em anos muito anteriores à disponibilização da HAART. Além disso, ainda não é possível prever qual será o real impacto da HAART sobre a incidência em função da reconfiguração da dinâmica do HIV, devido ao aumento da sobrevida e conseqüente aumento do número de infectados, aumento da freqüência de comportamentos menos seguros (em função de "crenças otimistas"), em contraposição à redução da infectividade (Boily et al., 2004) [6].

Um artigo recente discute os possíveis impactos da HAART sobre a dinâmica da transmissão sexual do HIV. O trabalho sugere que um declínio dos comportamentos sexuais de risco tenha ocorrido ao nível populacional no início da epidemia devido, ao menos em parte, ao fato de que a mortalidade e a morbidade (adoecimento grave) atingiram especialmente o grupo de indivíduos que apresentava comportamentos de maior risco. Com isso, teria havido uma redução ao nível dos comportamentos de risco dos indivíduos, em função da redução da disponibilidade de parceiros para estes indivíduos que apresentavam comportamentos de maior risco. Com a introdução da HAART, o grupo de indivíduos com comportamentos de maior risco se recompõe, devido aos benefícios da HAART, que prolongam a sobrevida e reduzem substancialmente a morbidade. Conseqüentemente, esses indivíduos puderam retomar seus padrões comportamentais de risco iniciais, determinando, com isso, um incremento das taxas de infecções sexualmente transmissíveis, como observado em homossexuais masculinos de países industrializados onde a HAART é amplamente disponível (Boily et al., 2005)[5].

Poucos estudos analisaram a mortalidade por AIDS no Brasil após a disponibilização da HAART, e estão habitualmente restritos a um determinado estado ou região.

Um estudo analisou a sobrevida entre adultos vivendo com AIDS, antes e após a introdução da HAART, em 1996, selecionando aleatoriamente casos de 18 cidades e 7 estados, representando, *grosso modo*, as regiões brasileiras, e apresentando resultados agregados para o país como um todo (Marins et al., 2003)[4]. O estudo evidenciou um aumento substancial da sobrevida após a introdução da HAART (Marins et al., 2003)[4].

Uma análise ecológica realizada com as dados de incidência do SINAN (Sistema de Informação de Agravos de Notificação) e mortalidade do SIM (Sistema de Informação de Mortalidade) por AIDS no Brasil, no período de 1984 a 2000, por sexo e região, mostra que, para ambos os sexos e nas diferentes regiões brasileiras, a taxa de mortalidade declinou após a introdução da HAART (1996), embora a incidência continue crescendo em algumas regiões (como na região Sul) ou oscilando entre a estabilidade e discreto decréscimo em outras (Hacker et al., 2004)[20], o que varia em função de que anos são incluídos na série histórica (os dados do MS abrangem anos mais recentes, mas, por isso mesmo, estão sujeitos ao viés decorrente do atraso da notificação).

Em um contexto de inegável redução da prevalência e incidência das infecções oportunistas (Mayer et al., 2003)[21], surgem novas questões centrais à clínica e saúde pública no âmbito do HIV/AIDS, como a dimensão ecológica do impacto da HAART em um contexto de profundas desigualdades sociais e de acesso aos cuidados de saúde, como o que se observa no Brasil, e o acesso à terapia de populações marginalizadas e estigmatizadas, como os usuários de drogas injetáveis (UDI), à HAART.

1.3- A epidemia do HIV/AIDS entre UDI

Os UDI desempenham um papel relevante na epidemia de HIV/AIDS no Brasil e em diversos outros países. Os UDI "funcionam" como uma "ponte" na disseminação do HIV para outras populações, estando duplamente expostos à transmissão parenteral e sexual. A maioria dos UDI é do sexo masculino, e freqüentemente são parceiros de mulheres que não são usuárias de drogas injetáveis, estando envolvidos em relações onde o uso de preservativos é inconsistente, contribuindo também para a transmissão vertical do HIV, através da infecção de suas parceiras sexuais (Friedman & Aral, 2001)[22].

Em diferentes países foi verificada interação entre populações de UDI e outras populações. A relação sexual desprotegida (sem o uso de condom) entre usuários e não-usuários é o fator responsável pela interação da epidemia nessas duas populações (Williams et al., 2003)[23].

O uso inconsistente de preservativos entre UDI é reportado em diferentes contextos (Sherman & Latkin 2000[24]; Hacker et al., 2005[25]; Pechansky et al., 2005[26]). Artigos recentes têm demonstrado o papel dos comportamentos sexuais de risco na transmissão do HIV entre UDI e seus parceiros não-usuários (Flom et al., 2001[27]; Strathdee & Sherman 2001[28]**;** Hacker et al., 2005[29]; Williams et al., 2005[30]).

A epidemia do HIV/AIDS entre UDI no Brasil seguia, em seu início, as principais rotas de tráfico da cocaína, da fronteira oeste (próxima às áreas de produção de coca e refino de cocaína dos países andinos, como Bolívia e Colômbia) aos principais portos localizados na costa da região sudeste (Barcellos & Bastos, 1996)[31].

Mais recentemente, o tráfico e o consumo de cocaína e a disseminação do HIV e outras infecções de transmissão sangüínea vêm-se mostrando especialmente relevantes no litoral sul, com epidemias extensas e de propagação acelerada do HIV entre UDI, especialmente em alguns municípios localizados no litoral de Santa Catarina e Rio Grande do Sul (Bastos, 2000) [32].

Apesar do declínio da epidemia de HIV/AIDS entre UDI, observado em praticamente todas as regiões do país (exceção feita ao sul do Brasil), através de diferentes indicadores, como prevalência, incidência (de AIDS e de HIV, esta última estimada através da utilização de algoritmos de testagem com testes em duplicata ─ sensíveis/menos sensíveis ─, ver detalhes em Teixeira et al., 2004[33]), além da redução da freqüência de injeção (especialmente entre os novos injetadores – Hacker et al., 2005[29]), paralelamente ao declínio observado para outras infecções de transmissão parenteral como a hepatite C, e, em certa medida, a hepatite B (Bastos et al., 2005)[34], essa população experimenta subepidemias contrastantes em diferentes regiões brasileiras (Szwarcwald et al., 2000[35]; Bastos et al., 2002[36]).

A prevalência do HIV entre UDI apresenta grande variação geográfica (tanto entre diferentes países, como entre diferentes regiões de um mesmo país). Essas diferenças geográficas marcantes das epidemias entre UDI refletem a interação complexa de vários fatores, incluindo padrões de uso de drogas, número de usuários de drogas em cada contexto, práticas de injeção e prevalências de fundo para o HIV e demais infecções de transmissão sexual e sangüínea ("background prevalences") (Hamers et al.,1997) [37].

1.4- Os Sistemas de Informação em AIDS

Os sistemas de informações de estatísticas vitais, relacionadas à morbidade e mortalidade, constituem uma importante fonte de informação, ainda que, com freqüência, pouco valorizada, devido aos possíveis problemas de qualidade dessas informações (Lessa, 2000)[38].

A intensificação do uso de grandes bancos de dados referentes a notificações de casos, óbitos e operação de serviços de saúde tem sido acompanhada pela preocupação com a qualidade destes dados. A confiabilidade dos dados oficiais vem sendo objeto de interesse em nosso meio e trabalhos vêm sendo realizados para verificar a fidedignidade dessas informações (Mathias & Soboll, 1998)[39].

Desde 1973, o Instituto Brasileiro de Geografia e Estatística (IBGE) coleta dados de estatísticas vitais, a partir das informações enviadas pelos Cartórios de Registro Civil. Em 1976, o Ministério da Saúde implantou o Sistema de Informações sobre Mortalidade (SIM) com o objetivo de coletar estatísticas de mortalidade por causas, já que a causa de morte não era, até então, informada nos registros civis. A coleta das informações passou a ser realizada através da declaração de óbito, seguindo o modelo internacional recomendado pela Organização Mundial de Saúde (OMS).

O Sistema de informações sobre Mortalidade fornece informações a partir das declarações de óbito coletadas pelas Secretarias Estaduais de Saúde. A Base de Dados nacional gerada é administrada pelo CENEPI (Centro Nacional de Epidemiologia), em cooperação com o DATASUS (Departamento de Informação e Informática do SUS).

O Sistema Nacional de Agravos de Notificação (SINAN) é o sistema oficial de registro de morbidade do Brasil. O SINAN registra dados sobre agravos de notificação compulsória em todo o território nacional, a fim de fornecer informações para a análise do perfil de morbidade vigente.

O sistema é operacionalizado a partir da unidade de saúde, e a coleta dos dados é feita utilizando-se ficha de notificação padronizada. Algumas deficiências referentes à abrangência e qualidade dos dados devem-se a erros de diagnóstico, descuido para com a obrigatoriedade da notificação, erros de coleta e digitação.

Um dos problemas encontrados nos bancos de dados de sistemas de informações em saúde é a subnotificação. A subnotificação das doenças de notificação obrigatória não é problema encontrado apenas no Brasil, mas em todo o mundo. Alternativas têm sido

procuradas, como a busca ativa de casos em registros médicos, papeletas hospitalares e declarações de óbito (Oliveira, 2000)[40].

A subnotificação dos casos de AIDS, além de se traduzir em estimativas errôneas da magnitude da epidemia, prejudica a implementação de ações preventivas, bem como a alocação ótima de recursos, a dispensação de medicamentos e a distribuição de preservativos (Bessa Ferreira & Portela, 1999) [41].

Outro problema relacionado aos sistemas de informação refere-se à cobertura dos registros. De acordo com fontes oficiais, a cobertura dos registros de mortalidade no Brasil que era de 86,3%, em 1990, passou a ser de 81,7%, em 1998. Quando os dados são desagregados por estado, observam-se grandes variações na cobertura (Volochko, 2003) [42].

O atraso de notificação constitui-se num outro problema referente aos sistemas de informação, correspondendo ao tempo decorrido entre o diagnóstico do caso e sua efetiva notificação (Barbosa & Struchiner, 2002)[14]. Esse atraso pode ainda ser diferencial segundo categorial de exposição (Barbosa & Struchiner,1998) [43].

Alguns trabalhos avaliaram a subnotificação dos casos de AIDS no Brasil (Lemos & Valente, 2001[44]; Bessa Ferreira & Portela, 1999[41]; Oliveira, 2000[40]; Oliveira et al., 2004[45]).

Para o estado do Rio de Janeiro, no período de 1991 a 1995, o subregistro encontrado para o SINAN a partir dos óbitos notificados no SIM foi de 51,9%. As análises evidenciaram que as mulheres apresentavam maior chance de não terem sido notificadas, se comparadas aos homens. Os analfabetos apresentavam chance 2 vezes maior de não terem sido notificados, se comparados aos indivíduos com nível universitário. Os óbitos ocorridos em unidades de saúde privadas foram menos freqüentemente notificados, frente àqueles ocorridos em unidades públicas (OR=2,58). Os óbitos ocorridos na capital foram menos freqüentemente notificados do que aqueles ocorridos nos demais municípios do estado (OR=2,20) (Lemos et al., 2001)[44].

Ainda neste estudo, verificou-se que o percentual de óbitos que não haviam sido notificados se reduziu ao longo do período, sendo de 59,7%, em 1991, e de 45,2%, em 1995. Essa tendência foi observada para ambos os sexos (Lemos et al., 2001)[44].

Considerando as internações registradas no município do Rio de Janeiro no ano de 1996, evidenciou-se que 42,7% eram referentes a casos não notificados ao SINAN. O trabalho mostrou que a subnotificação é maior para os pacientes menores de 13 anos, entre os pacientes atendidos em hospitais municipais, quando comparados aos de hospitais universitários e federais (Bessa Ferreira & Portela, 1999)[41].

Em relação aos casos de AIDS em adultos do município de Belo Horizonte, registrados no período de 1995-1996, a subnotificação dos casos de AIDS foi de 46,37%, conforme verificado através do método de captura-recaptura, considerando-se o SINAN como sistema oficial de registro de agravos, com a utilização adicional do SIM e do SIH (Oliveira, 2000) [40].

Também utilizando o método de captura e recaptura e as fontes de informação do SINAN e SIH, evidenciou-se uma subnotificação de 24% em Florianópolis, 45% em Uberaba, 55% em Niterói, 56% no Rio de Janeiro, 60% em Belo Horizonte e 65% em Uberlândia, para o ano de 2001 (Oliveira et al., 2004) [45].

Outros trabalhos avaliam o registro de diferentes variáveis na notificação. O trabalho de Cassano et al. (2000)[46] analisou o registro da variável "ocupação" no SINAN no ano de 1995, encontrando-se um percentual de 10,5% dos casos no Brasil com ocupação ignorada. Esse percentual variou conforme região geográfica, sendo de 3,5% no Norte, 9,0% no Nordeste, 9,3% no Sudeste, 14,9% no Sul e 18,7% na região Centro-oeste. Em relação à qualidade da informação, verificou-se certa imprecisão, que poderia afetar o cálculo dos coeficientes por ocupação. Pode-se observar que enquanto 2,8% dos casos do sexo masculino foram classificados na categoria "outras ocupações ou ocupações mal-definidas"; no sexo feminino este percentual correspondeu a 5,4%.

Tomazelli et al. (2003)[47], analisando a distribuição dos casos de AIDS em mulheres no município do Rio de Janeiro, de 1982 a 1997, encontraram uma proporção elevada de casos com escolaridade ignorada. A qualidade da informação referente à escolaridade foi um pouco melhor para os homens (23,5% dos casos com informação ignorada) do que para as mulheres (26,5% dos casos com informação ignorada). Observou-se tendência de melhoria no preenchimento desta informação no decorrer do período avaliado.

Trabalhos têm sido realizados para a correção do atraso de notificação dos casos de AIDS. Vários métodos tem sido utilizados, oferecendo estimativas mais precisas do número de casos de AIDS, necessárias para o monitoramento da epidemia, alocação de recursos e avaliação de campanhas preventivas (Barbosa & Struchiner, 2002[14]; Barbosa & Struchiner, 1998[43]).

A qualidade da informação constitui um indicador da qualidade de assistência e, indiretamente, da condição sócio-econômica dos casos, sendo, em geral, de pior qualidade em locais com menor infra-estrutura, que concentram populações mais pobres (Tomazelli et

al., 2003)[47]. Esforços devem ser continuamente empreendidos no sentido de aprimorar tanto a qualidade da assistência, como dos sistemas de informação em saúde no Brasil.

Apesar das limitações discutidas, diversos trabalhos têm sido desenvolvidos a partir dos dados do SIM e SINAN (Szwarcwald et al., 2000[35]; Bastos et al., 2002[36]; Hacker et al., 2004[20]; Farias et al., 2005[13]), contribuindo para a formulação de hipóteses a serem testadas em estudos subseqüentes. As implicações das limitações aqui mencionadas sobre as análises que serão realizadas no âmbito da presente tese serão discutidas. Em que pesem as deficiências constatadas, reiteramos nossa aposta na relevância de estudos ecológicos, únicos capazes de abarcar, de uma forma sintética, os dados referentes a um país de dimensões continentais e elemento essencial à formulação de políticas públicas de maior abrangência.

1.5- Analisando a dimensão ecológica

A epidemiologia dos fatores de risco individuais tem sido o paradigma dominante nas últimas décadas, com foco nos comportamentos e exposições individuais. Nos últimos anos, porém, a epidemiologia social, área da epidemiologia que estuda a distribuição social e determinantes sociais de saúde, tem-se tornado proeminente e incorporado novas ferramentas de análise (Boerma & Wier, 2005)[48].

Apesar da epidemiologia moderna focalizar prioritariamente fatores de risco e comportamentos individuais, os determinantes fundamentais de saúde, ao nível populacional, estão relacionados a fatores sociais, econômicos e ambientais. O contexto social (demográfico, econômico e político) influencia a epidemiologia dos diferentes agravos à saúde e modula comportamentos individuais que afetam a saúde populacional (Adimora & Schoenbach, 2005)[49].

O termo "contexto social" se refere a fatores demográficos, socioeconômicos, macroeconômicos, sócio-políticos e ambientais. Características econômicas e demográficas e outros aspectos estruturais das sociedades, supra-individuais, exercem um importante papel de modulação sobre as variáveis epidemiológicas e os comportamentos individuais, incluindo comportamentos sexuais, transmissão de infecções sexualmente transmissíveis e outros agravos à saúde (Adimora & Schoenbach, 2005)[49].

A importância dos determinantes econômicos e sociais vem sendo reconhecida, e variáveis contextuais têm recebido maior atenção em estudos epidemiológicos relativos à

distribuição e determinantes da dinâmica do HIV e outras infecções sexualmente transmissíveis (Boerma & Wier, 2005)[48].

Estudos que abordam as diferenças referentes a diversos agravos em saúde entre diferentes cidades sugerem que fatores inter e intra-urbanos (por exemplo, segregação residencial) desempenham um importante papel na saúde coletiva, indicando que é a multiplicidade e interação de fatores em diferentes níveis que determinam a saúde das populações urbanas (Galea et al., 2005)[50].

Cliff et al. (1998)[51] mostram que, para diferentes doenças infecciosas com longo período de incubação, a distribuição se mostra distinta em função das características geográficas e econômicas das cidades, e que quanto maior o período de incubação da doença maior a variação da forma da distribuição das doenças de uma cidade para outra. Tal fato é especialmente relevante na epidemia de HIV/AIDS, onde o período de tempo que vai da infecção à emergência da síndrome clínica ultrapassa, hoje (a partir das intervenções profiláticas), uma década (Artzrouni, 2004)[52].

Apesar dos muitos trabalhos realizados para elucidar os mecanismos de transmissão do HIV entre os indivíduos, relativamente poucos trabalhos têm sido realizados sobre a dinâmica de transmissão ao nível populacional (Wallace & Wallace, 1995) [53].

Discute-se que, embora o desenvolvimento de cada doença seja um fenômeno biológico individual, é possível que para diversas, se não todas, doenças estes determinantes não possam ser inteiramente operacionalizados apenas ao nível individual (Diez-Roux, 1998)[54]. Em se tratando de doenças infecciosas, a dimensão ecológica é indispensável, pois a determinação é, inevitavelmente, individual e coletiva (Halloran & Struchiner, 1995)[55].

Tem sido enfatizada a necessidade de investigar o papel da dimensão propriamente ecológica dos contextos socioeconômicos na distribuição dos fatores de risco e de articular as conexões entre as ações individuais e o contexto social no qual essas ações têm lugar (Diez-Roux, 1998)[54].

Infelizmente pouca atenção tem sido dada aos determinantes meso- e macro-sociais dos comportamentos de risco (sexual e parenteral) na disseminação do HIV. Fatores contextuais associados a comportamentos de risco para o HIV incluem fatores estruturais, como a disponibilidade de serviços, normas e atitudes sociais, vulnerabilidade social (por exemplo, nível socioeconômico da região/local de residência) e características do ambiente físico (por exemplo, qualidade da moradia) (Galea et al., 2003)[56].

No contexto da disseminação do HIV, múltiplos comportamentos de risco, incluindo uso de drogas e comportamentos sexuais, determinam as probabilidades de transmissão do vírus, ressaltando a importância de se considerar o contexto e sua influência sobre os comportamentos sexuais e de uso de drogas (Galea et al., 2003)[56].

Considerando a grande heterogeneidade da epidemia brasileira, as desigualdades sociais, as desigualdades no acesso à infra-estrutura médica e distribuição dos serviços e profissionais de saúde nas diferentes regiões do Brasil, faz-se oportuno identificar indicadores relacionados aos diferenciais de magnitude e extensão da epidemia de AIDS nos diferentes municípios brasileiros, ao longo do tempo, considerando ainda os diferentes padrões regionais da epidemia, controlando-se as possíveis interações e confundimentos, através de estratégias estatísticas que dêem conta da estrutura de correlação espaço-temporal.

Para isso, técnicas estatísticas apropriadas devem ser empregadas, como a modelagem multinível, que considera a estrutura de correlação entre observações em diferentes níveis hierárquicos.

2-Objetivo geral

Análise ecológica dos casos de AIDS registrados pelo Sistema de Informação de Agravos de Notificação (SINAN), no período de 1984 a 2000, considerando como unidade de análise os municípios brasileiros. Indicadores municipais referentes à educação, habitação, renda, saúde, desenvolvimento humano, e população urbana serão usados como variáveis explicativas. A relação entre a incidência dos casos de AIDS e indicadores municipais será avaliada para as categorias de exposição "heterossexual" e "UDI".

2.1- Objetivos específicos

- Revisar a literatura a respeito da epidemia de AIDS e o consumo de drogas ilícitas na América do Sul, com o propósito de sistematizar os principais determinantes meso- e macro-sociais na determinação da epidemia nesta população;

- Analisar os casos de AIDS registrados entre UDI, no período de 1984 a 2000, nos municípios brasileiros, considerando indicadores municipais como variáveis explicativas;

- Analisar os casos de AIDS registrados entre heterossexuais, no período de 1984 a 2000, nos municípios da região sul do Brasil, considerando indicadores municipais e casos de AIDS entre UDI como variáveis explicativas;

3 - Resultados

Os objetivos propostos deram origem a três artigos. O artigo de revisão ("HIV/AIDS and Drug Consumption in South America and the Caribbean: Reviewing Epidemiological Evidence and Initiatives Aimed at Curbing the Epidemic"), que tematiza a disseminação do HIV/AIDS entre usuários de drogas na América Latina, foi publicado na *Revista Pan-americana de Saúde Pública* no seu número especial de outubro/novembro de 2005 (artigo 1).

A análise referente aos casos de AIDS notificados segundo a categoria de exposição UDI (artigo 2), foi aceita para publicação, sob a forma de artigo ("Reconstructing the AIDS epidemic among Brazilian injection drug users"), nos *Cadernos de Saúde Pública*, com publicação prevista para o número 3 do corrente ano (2006).

A análise referente aos casos entre heterossexuais nos municípios do sul (artigo 3) está apresentada sob a forma de artigo, e será posteriormente submetida à revista indexada para publicação.

A metodologia empregada encontra-se descrita no anexo 1.

ARTIGO 1

Human immunodeficiency virus, AIDS and drug consumption in South America and the Caribbean: epidemiological evidence and initiatives to curb the epidemic

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Synopsis

The paper reviews data on drug use in relation to the spread of human immunodeficiency virus and AIDS in South America and the Caribbean. Information was gathered by thoroughly reviewing major bibliographic databanks, web sites of international institutions and regional networks working with substance misuse or human immunodeficiency virus and AIDS, and abstracts from conferences and meetings. Although some gaps remain, a growing body of evidence documents the significant role of injected cocaine in the Brazilian and Southern Cone epidemics. The Caribbean and the Andean areas have thus far been spared in large part from the spread of injection drug use and its consequences, but the situation has been changing in Southern Cone countries towards a higher prevalence of harmful injection habits. Additional challenges have been posed by the increasing availability of heroin in the Andean Area and the abuse of crack cocaine and its impact on the sexual transmission of human immunodeficiency virus in many cities. Harm reduction strategies have been established in most areas of Brazil and are gaining momentum in Argentina. Other countries in the region still face serious limitations due to restrictive legislation and lack of broader support. Greater participation of Latin American and Caribbean countries in research protocols and continued debate on both successful and failed experiences should be encouraged in order to minimize existing barriers to the full adoption of effective measures to curb the human immunodeficiency virus and AIDS epidemic in this region.

Key words South America; Caribbean; drug use; cocaine, human immunodeficiency virus; AIDS.

Sinopsis

O presente artigo revisa dados sobre o uso de drogas ilícitas relacionado à disseminação do HIV/AIDS na América do Sul e Caribe Foram revisadas informações dos principais bancos de dados bibliográficos, páginas da *internet* de instituições e redes regionais, bem como resumos de conferências e encontros científicos. A despeito de algumas lacunas, um crescente número de evidências documenta o importante papel do uso de cocaína injetável na epidemia brasileira e no cone sul. Nas regiões caribenha e andina, até então poupadas de uma disseminação mais extensa do uso de drogas injetáveis e suas conseqüências, essa situação vem se alterando recentemente, devido à elevada prevalência do hábito de injetar. Outros desafios surgem a partir da crescente disponibilidade da heroína em áreas andinas e do abuso de *crack* e seus impactos sobre a transmissão sexual do HIV em muitas cidades da região. Estratégias de redução de danos foram estabelecidas em diversas áreas brasileiras e, recentemente, na Argentina. Em outros países da região ainda persistem sérias limitações, em função da legislação restritiva e ausência de apoios de maior monta. A crescente participação dos países da região nos protocolos de pesquisa e o contínuo debate sobre experiências bem sucedidas e fracassadas devem estimular os esforços de minimizar as barreiras existentes na adoção de medidas efetivas para conter a epidemia de HIV/AIDS na América do Sul e Caribe.

INTRODUCTION

Epidemiological studies addressing the intertwined epidemics of injection drug use, human immunodeficiency virus (HIV) and AIDS in South America and the Caribbean are still fragmentary. Health professionals and policy makers face great difficulties in assessing the initiatives aimed at curbing the spread of HIV in different countries of the region (1) and providing management and care to HIV-infected drug users (2).

Given these obstacles, a remarkable achievement has been the inclusion of South American cities in large, multicenter studies such as those sponsored by the World Health Organization (WHO). Efforts to better understand the patterns of illicit drug abuse and risk behaviors for HIV and AIDS (hereafter HIV/AIDS) in South America began with a multicenter study sponsored by the WHO in 1989-1990, the WHO Drug Injection Study Phase I, which was conducted in 13 cities including Rio de Janeiro and Santos, Brazil. This study was the largest international project of its kind at that time. Apart from the wealth of data collected in each of the participating cities, the study contributed significantly toward developing research methods, informing national policies, establishing international collaborative networks and placing drug injection, HIV and related health policy issues on international and local agendas (1).

The WHO Drug Injection Study Phase I resulted in recommendations to develop methods for rapid assessment, focus on "new" HIV epidemics and other health consequences of injection drug use (such as hepatitis B and C, and overdoses) and to narrow the gap between research and the development of policies and interventions. These recommendations shaped the design of the WHO Drug Injection Study Phase II, which was implemented in 2000. The study involved 14 cities in 13 countries, including four cities in South America: Rosario City (Argentina), Santos and Rio de Janeiro (Brazil), and Bogotá (Colombia). Results from the WHO Phase II study pointed to the importance of harm reduction interventions targeted for injection drug users (IDUs), and helped to strengthen low-threshold approaches targeted for IDUs in Brazil, Argentina and Colombia (1, 3–6).

By thoroughly reviewing data from WHO studies, major databases and nonindexed literature in English, Spanish and Portuguese, we were able to discern major epidemiological trends and identify achievements and drawbacks in the field of prevention.

METHODS

This paper reviews a large body of information that was gathered from different sources. Emphasis has been placed on peer-reviewed papers, posters and oral presentations from major conferences and nonindexed manuscripts and reports.

Two major electronic databanks, one international (Medline, www.ncbi.nlm.nih.gov) and one regional (Scielo, Scientific Electronic Library Online, www.scielo.br) were thoroughly explored, using key words such as "AIDS/HIV," "drug use," "Latin America," "South America," and "Caribbean," the name of each of the countries in the region, and key words in Spanish and Portuguese for the SciELO database.

Other major data sources and websites we searched were SIDALAC (Regional AIDS Initiative for Latin America and Caribbean, www.sidalac.org.mx); UNAIDS (Joint United Nations Programme on HIV/AIDS, www.unaids.org); IRHA (International Harm Reduction Association, www.ihra.net), and its official journal *The International Journal of Drug Policy*; WHO (www.who.int); and RELARD (Rede Latino-Americana de Redução de Danos/Latin-America Harm Reduction Network, www.relard.net).

To examine recent studies, we reviewed abstracts from the 15th International Conference on the Reduction of Drug Related Harm (2004 April 20-24, Melbourne, Australia) in the abstract book, as well as abstracts from the 14th International AIDS Conference (2002 July 7-17, Barcelona, Spain), available at www.aids2002.com.

Finally, information about survey studies was retrieved from the US Census Bureau web site (http://www.census.gov/). Additional information was obtained from personal contacts and networks, and the private library and files of the senior author (FIB).

We devoted particular attention to papers published in peer-reviewed journals. Additional information was considered reliable when data were extracted from surveys carried out with appropriate methods (i.e., appropriate recruitment and HIV testing and proper use of epidemiological and statistical tools), as described in the survey's abstract or in compliance with the criteria of the sponsoring or coordinating institutions (e.g., PAHO, the Brazilian Ministry of Health, etc.).

Given the current status of information in South America and the Caribbean in the field of HIV/AIDS among drug users, it was impossible to carry out a systematic review in accordance with rigorous rules such as those of the Cochrane Library (http://www.update-software.com/publications/cochrane/).

Despite the undeniable limitations related to the relative lack of information due to deficiencies in accessibility and dissemination, preliminary efforts to amass widely dispersed information are pivotal for improving local health information systems, guiding future research, and fostering innovative, evidence-based interventions.

RESULTS

Epidemiological evidence

Overview

The dynamics of HIV/AIDS in South America and the Caribbean has been remarkably heterogeneous. Countries such as Bolivia (Andean Area), Paraguay (Southern Cone) and most countries from the Central American isthmus have been relatively spared by the epidemic so far. On the other hand, the AIDS epidemic has spread extensively in highly populated countries such as Brazil and Argentina, and especially in some small countries such as Haiti, the Bahamas and French Guiana (7).

The role of IDUs and crack cocaine users in the HIV/AIDS dynamics in these regions is quite distinct. In countries where injection drug use has been extensive, such as Brazil and Argentina, there are clear regional patterns, which are described in detail for Brazil. In other countries where the consumption of drugs through injection remains uncommon, HIV transmission occurs predominantly through sexual transmission. In many Caribbean countries the use of illicit drugs such as crack and powder cocaine is frequently linked to the spread of HIV through unprotected sexual intercourse and the sex trade (8).

Because of the very heterogeneous dynamic of HIV/AIDS and the distinct role of injection drug users, as well as the striking socioeconomic and cultural contrasts in South and Central America and the Caribbean, the results are presented here according to a rough geographical division into four areas: The Caribbean and Central America, Brazil, the Southern Cone, and the Andean Area. Information from different HIV seroprevalence surveys and data about the proportional number of AIDS cases among IDUs in some areas of the region are presented in Tables 1 and 2, respectively.

TABLE 1. Selected HIV seroprevalence surveys of injection drug users in South America and the Caribbean, 1988-2005

Country	City	Year	Seroprevalence (%)	Reference
Argentina	Not specified	1988	27.0	47
Argentina	Buenos Aires	1995	80.0	47
Argentina	Rosario	1998-1999	55.0	48
Argentina	Buenos Aires	2001	46.0	74[a]
Brazil	Itajai	1998	78.0	27
		2000-2001	31.0	
Brazil	Porto Alegre	1998	48.5	27
		2000-2001	64.3	
Brazil	Santos	1991-1992	63.0	3
		1994-1996	65.0	
		1999	42.0	
Brazil	Rio de Janeiro	1990s	25.0	32
Brazil	Rio de Janeiro	2000-2001	8.0	6
Colombia	Bogota	1999	<2.0	5
Nicaragua	Managua	Not specified	6.0	14
Peru	Part of a national survey	1994-4995	13.0	75[a]
Uruguay	Not specified	1991-1992	76.5	76[a]
Uruguay	Montevideo	1997	24.4	77[a]

[a]Additional reference not discussed in the text

TABLE 2. Proportional number of AIDS cases among injection drug users in some areas of South America and the Caribbean, 1987-2003

Area	Year	(%)	Reference
Costa Rica and the Bahamas	To 2001[a]	<1.0	7
Brazil	To 2003[a]	22.9 (men) 11.9 (women)	20
Southern Cone	Late 1990s	29.0	27
Argentina	1987	10.0	44
	1989	23.0	
	1991	40.0	
	1993	44.0	
Argentina	To 2001[a]	42.0	46
Uruguay	2001-2003	25.0	45
Chile	To 2001[a]	05.0	4

[a]Accumulated AIDS cases among injection drug users

The Caribbean and Central America

Although located in the geographic space of the Caribbean and Central America, Puerto Rico has a unique drug scene. The conspicuous presence of injected cocaine is strongly associated with the local HIV/AIDS epidemic. Because of its socioeconomic situation, cultural background, and close ties to the United States, its regional pattern of IDU-associated HIV infection is more similar to that of the continental USA than to the patterns in South or Central America or the Caribbean. This similarity was clearly shown in a study of Puerto Rican injection drug users who were interviewed in New York and Puerto Rico. Strong similarities in influences on high-risk behaviors were found in both settings (9). In the same vein, molecular epidemiology findings have convincingly shown that the continental USA and Puerto Rico have been affected by a common epidemic, indicating infection by a shared HIV-1 strain. This pattern may be due to continuous human traffic or (a less likely explanation) may indicate a similar evolution of a common source virus (10). For the reasons mentioned above, data from Puerto Rico will not be reviewed in detail in the present paper.

For decades the Caribbean has been a traditional transshipment route for cocaine from Andean coca-producing countries to the markets of North America and Europe. Since the 1970 and 1980s, the Caribbean drug scene has been noted for widespread cultivation and consumption of cannabis (a key component of the Rastafarian culture) and the incidental use of cocaine. However, since the end of the 1980s, crack cocaine has become popular in many Caribbean islands in the French Caribbean (11) and the Bahamas (12). Similar increases in cocaine consumption (by smoking, inhaling or both) appear to be occurring in Central America (13).

According to the available literature and anecdotal reports, the injection of cocaine is still rare throughout the Caribbean, and presently has no meaningful role in the dynamics of the regional HIV/AIDS subepidemics. However, the role of crack and its close relationship to the sex trade has contributed to the spread of HIV through heterosexual transmission (8, 12).

The drug scene seems to be changing in the Central American isthmus in recent years. The relevance of the shared injection of illicit drugs (especially cocaine) has been increasing in the AIDS epidemic in Nicaragua (7). Preliminary data from a cross-sectional study were presented at the 2000 Latin American AIDS Forum (14). The 50 drug users

interviewed for the study reported cocaine use amidst other miscellaneous psychoactive substances. Although cocaine has most often been snorted or smoked, the habit of injecting cocaine was found to be quite prevalent in this small sample of polydrug users, with 50% of them reporting having ever injected cocaine. The point prevalence of HIV infection was found to be 6.0% and should be evaluated further in larger samples (14).

According to recent data compiled by UNAIDS, the role of injection drug users is still negligible in Costa Rica and the Bahamas, accounting for less than 1% of the AIDS cases reported as of December 2001 (7).

Brazil

Several studies (15–18) have shown that Brazil, because of its continental size and marked social and cultural heterogeneity, harbors many different HIV subepidemics. Injection drug users, however, have thus far had a negligible role in the AIDS epidemic in the less industrialized areas in northeastern Brazil, with the exception of the state of Bahia (19), the southernmost state in this region.

Among adults (persons 14 years of age or older in the Brazilian National AIDS Register SINAN-AIDS), 22.9% of all cases of AIDS in men reported to the Brazilian Ministry of Health as of the end of 2003 were IDUs. The figures are substantially lower for women, among whom this proportion corresponds to 11.9% of all female cases reported in the same period (20). However, IDUs have played a central role in the HIV/AIDS subepidemic in the industrialized southeast, especially in São Paulo state, and, more recently, along the southern coast from São Paulo to the southern border of Brazil (18).

In its beginnings, the IDU-associated HIV/AIDS epidemic in Brazil broadly followed the main cocaine transshipment routes from the western border to the main coastal ports in the southeast (16, 18). A similar phenomenon was described for heroin routes in Asia (21). The transshipment cocaine routes—linking the west and the south/southeast of the country—benefited from the best Brazilian highway network.

As shown by Kalichman (22), Grangeiro (23), and Fonseca and Castilho (24), IDUs are concentrated in the richest socioeconomic regions of Brazil, but the vast majority of them belong to the poorer and less educated strata of Brazilian society. Injection drug users live mainly in the impoverished areas ringing Brazil's richest cities such as São Paulo City (23).

International research indicates that IDUs are a very mobile population (25), which often has a dramatic impact on the spread of blood-borne pathogens. A unique example is the occurrence of two outbreaks of secondary malaria among IDUs in São Paulo state, which had been free of malaria for decades. These outbreaks were attributed to the migration of IDUs from distant areas in the country (i.e., the Amazonian basin and tropical rainforest) where malaria is still endemic. Most of these IDUs were co-infected with HIV (26).

Cocaine trafficking, cocaine consumption and the spread of HIV and other blood-borne infections became the hallmark of the Brazilian southern coastal subepidemics in the late 1990s, with explosive IDU-related HIV epidemics in some municipalities located along the coast of the states of Santa Catarina and Rio Grande do Sul (18). In some municipalities in this coastal strip over 50% of all AIDS cases have been reported among IDUs (20). This high incidence rate explains at least part of the rapid, sustained spread of HIV in the south, which affects a large number of women (most of them partners of IDUs) and their children, and contributes to the slower decline in AIDS-related deaths in comparison to other regions of Brazil (18).

An analysis of two surveys (1998 and 2000-2001) of IDUs from the two southern municipalities of Itajaí and Porto Alegre found that the prevalence of HIV increased in Porto Alegre, the southernmost metropolitan area of Brazil, from 48.5% to 64.3%, whereas it declined in Itajaí from 78.0% to 31.0%, where the epidemic became established earlier (27). In contrast to recent findings from southern municipalities, the epidemic has been diminishing in the southeast since the second half of the 1990s, after a substantial increase in the late 1980s (3, 6, 28). Data from two recent incidence studies corroborated inferences from serial seroprevalence surveys and ecological analyses. Whereas the incidence of HIV among cocaine users was found to be 5.3 per 100 person-years at risk in a cohort study in Porto Alegre (29), it was estimated to be 0.71 in a sample of cocaine users of similar characteristics in São Paulo (30).

In the Santos Metropolitan Region of São Paulo State, three cross-sectional studies of IDUs have been conducted. The seroprevalence of HIV was 63% from 1991 through 1992, 65% from 1994 through 1996, and 42% in 1999 (3). Analyses with space-time diffusion models documented that the spread of HIV among IDUs in the state of São Paulo followed a localized growth pattern, and thus suggested that the very rapid spread of HIV

among IDUs in this state, especially at the end of the 1980s, was subsequently overtaken by a larger secondary spread of heterosexually acquired infections (31).

Rio de Janeiro, the second largest Brazilian city and port, has a lively drug scene where cocaine is consumed typically by snorting. Interestingly, its HIV/AIDS epidemic has not been strongly influenced by the rather small population of IDUs. As reported elsewhere (32), HIV seroprevalence rates among IDUs in Rio de Janeiro had been high by international standards (approximately 25%) in the early 1990s, but never reached the catastrophic level observed in Santos (33). Over the years AIDS cases attributed to IDUs have comprised no more than 6% of all cases reported in Rio de Janeiro, and are currently decreasing.

A series of papers by our group highlight the auspicious finding of an apparent decline in new HIV infections among IDUs from Rio de Janeiro (6, 28, 34). Using a sensitive/less sensitive HIV testing algorithm, we did not find a single new infection in the blood samples from IDUs collected between 1994-1996 (34) and estimated HIV seroincidence as 0.76% for IDUs recruited in 2000-2001 (28). The prevalence of HIV was found to be substantially lower (~8%) in the 2000-2001 survey (WHO Phase II Study) than in previous surveys (32), and low injecting frequencies have been observed among new injectors (6).

Recent data from Salvador, Bahia have also pointed to a substantial decline in the prevalence of HIV among IDUs (35). Some studies have highlighted the high prevalence of sexual risk behaviors and HIV infection rates among crack users such as impoverished commercial sex workers from São Paulo (36), or among gay men enrolled in a cohort study in Rio de Janeiro (37). Our provisional conclusion is that Brazilian cities harboring mature (i.e., prone to saturation) HIV epidemics in their IDU population, in which prevention programs have been fully implemented (as in Rio de Janeiro, Santos, and Salvador), seem to be experiencing a substantial decline of their AIDS epidemic among IDUs.

A key aspect addressed by Brazilian research has been the transition between routes of cocaine self-administration (38, 39). As shown by these two Brazilian studies, cocaine transitions are very common and take place in different directions. Transition may occur from riskier modes of administration to safer ones, and vice versa, and can include spontaneous abstinence periods as well as frequent relapses. A study undertaken in São Paulo in 1996-1997 found that 87% of the patients began using cocaine by snorting and 74% subsequently underwent a transition of route, with 68% switching to smoking and 20% to injecting.

Many cocaine transitions are toward routes associated with a higher dependency potential and increased HIV risk behaviors (38). A recent qualitative study in São Paulo found changes in the administration of cocaine in two directions: abandonment of injecting in favor of sniffing and smoking, and the increasing use of crack cocaine in younger and lower-income groups (40).

The Southern Cone

Of the subregions of South America and the Caribbean, the Southern Cone together with Brazil has reported the largest number of AIDS cases among IDUs. Injection drug use accounted for 29% of all reported AIDS cases in the Southern Cone in the late 1990s (41).

The impact of the Mercosul free trade zone on Southern Cone commerce and the mobilization of people between and within countries in the Southern Cone and southern Brazil has been immense, and has increased in recent years. The trade agreement has had an undeniable impact on the flow of all commodities. Despite the efforts to control transshipment of illicit commodities such as drugs, weapons, and ammunitions, illicit commerce will continue to challenge customs officials and police agencies in the years to come with expanding criminal networks, money laundering, and the growing availability of illicit drugs. Those responsible for formulating and implementing public policies and those health professionals who deal with drug users and HIV/AIDS must address the renewed challenges of very dynamic drug scenes.

Argentina. The role of IDUs in Argentina's HIV/AIDS epidemic increased substantially from the mid to late 1990s, following a pattern similar to South European countries where IDU is the most important exposure category (42). Argentina's IDU subepidemic is chronologically delayed relative to Brazil. The first AIDS case in an IDU was reported in Brazil in 1983 (23), but did not occur in Argentina until 1985 (43). Unlike Brazil, where the proportion of AIDS cases attributable to IDUs reached a plateau of 20%-21% at the beginning of the 1990s and then declined (with the exception of the southern coast), AIDS cases among IDUs in Argentina increased steadily until the mid-1990s (from 10% of all AIDS cases in 1987 to 23% in 1989, 40% in 1991 and 44% in 1993). Argentina's IDU subepidemic plateaued in the second half of the 1990s (44), but still represents more than 40% of all AIDS cases in the country (45).

As of March 2001, approximately 130 000 people were living with HIV/AIDS in Argentina. From the roughly 20 000 AIDS cases reported among adults (those aged 13 years old or more) up until 2001, 42% of the total and 46% of the cases in men were IDUs (45). The national AIDS incidence rate in 2000 was 48.9 per million (46).

A review of 22 studies carried out between 1987 and 1999 found HIV prevalence rates that ranged from 27% (a study carried out in 1988) to 80% (a study conducted in 1995) among IDUs. This finding suggested an increase in HIV infection rates during that period, although this conclusion should be interpreted with caution in light of the heterogeneous nature of the sources and study designs (47).

A study in Rosario City in 1998-1999 with the Rapid Assessment and Response methodology developed by WHO pointed to disquietingly high levels of HIV infection (point prevalence of 55.0%) and serious deficiencies in terms of medical and psychological support for drug-related psychosocial harm and HIV/AIDS. Frequencies of needle sharing remained unacceptably high (70%) in this population, which consisted mainly of cocaine injectors (48).

Another study carried out in Buenos Aires in 2000-2001 interviewed and tested street-recruited IDUs for different blood-borne infections. The results yielded an HIV seroprevalence of 44.3%. Only 6.5% of the HIV-infected IDUs were not co-infected with other viruses; 88.3% of them were co-infected with hepatitis C virus (HCV) and 68.6% with hepatitis B virus (HBV) (49). A survey carried out in four different regions of Argentina (Córdoba, Rosário, Mar del Plata, and Buenos Aires) corroborated these findings, and reinforced the disquieting picture of high levels of sharing of injection equipment and high rates of HIV infection among IDUs from all four sites (50).

In Argentina and Brazil, IDUs have played a central role in the impoverishment of the AIDS epidemic, combining the vulnerability of marginalized and underserved populations with the negative impact of a wide-ranging economic crisis and political turmoil. Most new AIDS cases in Argentina, as in Brazil, have been reported among people living in poor communities who have received less formal education and have higher unemployment levels. It is in this stratum that harmful drug usage patterns are commonly found (51). The ecological analyses were corroborated by a recent study of 174 HIV-positive heterosexuals living in Buenos Aires in 1999 (52). The study points to high levels of drug injection (41.5% of the men interviewed reported having injected illicit drugs),

frequent sharing of injection equipment (over 90% among those who reported having ever injected), and a high prevalence of unprotected sex, sexually transmitted and blood-borne infections among those with an IDU history. An association was found between reported exchanges of sex for money, drugs or food and the use of illegal drugs. The self-injection of illicit drugs was found to be highly prevalent among men from lower educational strata (52).

Uruguay and Paraguay. In Uruguay and Paraguay, the pattern of the HIV/AIDS epidemic among IDUs broadly follows that of Argentina, although in both countries, and in particular Paraguay, the epidemic has evolved more slowly than in Argentina and Brazil (53). The spread of HIV among IDUs in Paraguay has been slower, probably because of the smaller size of their high-risk IDU populations and the smaller number of inhabitants in general. However, its role as a transshipment route seems to be increasing along with the numbers of heavy drug users or polydrug users (54). In both countries the current drug scene combines "traditional" patterns of drug use, e.g., over-the-counter psychopharmacological drugs, cannabis products and inhalants (which are of particular concern in Uruguay) (55), with the relatively new habits of injecting cocaine and smoking crack (56).

More recently, very high HIV infection rates have been reported in Uruguayan IDUs, with rising infection rates in their noninjecting sexual partners and children. In 2003, 25% of all new AIDS cases were reported among IDUs, and 45% of these cases occurred among individuals aged 15-24 years (45). Further analyses pointed to an even more worrisome picture. Among those aged 15-19 years, infections among IDUs accounted for 81% of all AIDS cases in this age bracket (57). Precocious initiation into illicit drug use was corroborated by an empirical study in Montevideo in 1995-1996, which showed that most people started using drugs between the ages of 10 and 14 years (56).

The pattern of drug use in Uruguay has changed, with a steady increase in the number of drug-using women and a tendency for illicit drug use to commence at very young ages. Of special concern is the increasing number of HIV infections among pregnant women and the newborns of drug-injecting mothers (58).

The Andean Area

The availability of coca and its derivatives such as cocaine powder and coca paste is not the only factor that determines its abuse. As observed for different regions of Brazil

(18), drug-using scenes tend to be distinct from one another since they represent a combination of different derivatives and consumption habits. In the Andean Area, powdered cocaine is widely available but injection is still rare. In these countries the traditional habit of chewing coca leaf has coexisted, especially after the 1980s, with the smoking of raw coca paste and *bazuco* (a blend of coca and marihuana/tobacco leaves) in socially disadvantaged strata, and the inhaling of cocaine powder among the middle and higher social strata. However, the former clearly predominates in rural areas and the latter in larger cities (59).

In the late 1990s a decline in the use of smoked coca paste and an increase in the availability of heroin and powder cocaine were observed in Colombia. This trend is believed to be due in part to the renewed strategies of drug cartels, which serve to increase the availability of low-quality water-soluble drugs (60, 61). After 12 years of the Colombian epidemic without a single recorded case of AIDS among IDUs (1983-1995), 33 new cases of AIDS were reported among IDUs in 1996-1997 (61).

The changing nature of the Bogotá (Colombia) drug scene was first reported by Ross et al. (62) on the basis of data from an intervention project carried out in the downtown Bogotá area. The authors studied a group of polydrug users, some of them injectors with high levels of needle and syringe sharing. Risky sexual practices, including unprotected sex among multiple sexual partners and frequent engagement in commercial sex work, were common among study participants (62).

More recently a comprehensive study was carried out in Bogotá (5) as part of a WHO Multicenter Study. The Colombian study consisted of two complementary components: 1) a rapid assessment and response component and a survey to obtain sociodemographic and behavioral data, and 2) determination of the seroprevalence of HIV, HBV and HCV). This study documented a dynamic drug scene with a sizeable proportion of people recently engaged in the habit of injecting cocaine, alcohol and heroin. Although the interviewees—most of them polydrug users—reported low injection frequencies and the seroprevalence of HIV, HBV and HCV was low (below 2%), high frequencies of direct and indirect sharing of drug injection paraphernalia and unprotected sex were evident (5).

Within the context of the increasing availability of heroin (which has thus far been too expensive for most consumers), the abundance of cheap cocaine, and the virtual absence of prevention and treatment programs other than those oriented toward strict

abstinence, one may expect an increase in the number of injectors and in infection rates among them and their sexual partners. Concerted efforts should be implemented to avert an escalation in hazardous polydrug use and drug injection, and to forestall the consequent spread of HIV/AIDS and viral hepatitis.

Bolivia has one of the lowest HIV prevalence rates in the Andean Region, with IDUs playing a negligible role (less than 3% of reported AIDS cases) in the local HIV/AIDS dynamics thus far (7). In Peru, comprehensive surveys found fewer than 150 active IDUs among a sample of 141 000 individuals (63). Recent data compiled by UNAIDS corroborated these findings, and showed that IDUs play no relevant role in the Peruvian subepidemic (7). Ecuadorian data point to an incipient AIDS epidemic in which the role of IDUs is still negligible (7). Data are scant for Chile, where IDUs contributed to 5% of all AIDS cases reported up to 2001 (4).

However, the pattern has been changing in Venezuela. Although the Venezuelan AIDS epidemic is still limited in scope (7), recent findings from molecular epidemiology studies point to a putative bridging phenomenon between Venezuela and the Caribbean AIDS subepidemic (64). The extent to which this bridging phenomenon will affect the Venezuelan epidemic, and the role of the small population of Venezuelan IDUs in the epidemic in the years to come, are unknown and should be explored in future studies.

Efforts to curb the HIV/AIDS epidemic: drug policies and prevention in South America

In 2000 the HIV Prevention among Injecting Drug Users in the Southern Cone regional project was launched, with the participation of national AIDS programs and nongovernmental organizations (NGOs) from Paraguay, Uruguay, Argentina and Brazil. The main goal of this initiative was to involve policy makers, NGOs and community-based organizations in the development of better interventions targeted at drug users and their networks, to address the growing HIV/AIDS epidemic (4).

Prevention initiatives in the Southern Cone and Andean Area

Most South American countries still base their drug policies on a low-tolerance- and "drug-free"-oriented approach (4). Until the mid 1990s, strategies that aimed to reduce

drug-related harm, such as syringe exchange programs (SEPs), were usually irregular and narrowly-focused, and did not scale up (65). Since the late 1990s, however, successful prevention efforts targeting injection and noninjection drug users have been developed in the region. Syringe exchange programs as well as other outreach initiatives implemented by governments, NGOs and community-based organizations have been targeting IDUs, with Brazil and Argentina taking the lead in South America (3, 71).

Networking has made a fundamental contribution to recent Latin American drug policy reforms and the implementation of harm-reduction strategies. The Latin American Harm-Reduction Network (RELARD), founded in 1998, seeks to consolidate regional cooperation and increase local capacity for harm reduction. Cooperation between RELARD and national and international organizations has supported training, fundraising, information circulation, and harm-reduction efforts (66, 67).

Chile. Chile has developed a rapid assessment and response study and educational activities for different communities, including IDUs. Until now, however, there have been no programs to provide sterile materials to IDUs, and no harm reduction projects have been implemented (4).

Colombia. A rapid assessment and intervention study in downtown Bogotá, Colombia explored patterns of drug use and risk behaviors related to overdose, crime, violence, sexually transmitted infections and HIV/AIDS among drug users who frequent the "Calle 19" (19th Street) neighborhood. In this study drug users and dealers were interviewed, and health promotion activities and harm reduction strategies were implemented. According to participants, the violence related to drug dealing and to police harassment was perceived as more dangerous than the sexual and health risks of taking drugs. Lack of health insurance limited participant access to health care and drug-dependence treatment. The project identified and worked closely with peer leaders, who conducted peer-education activities and engaged at-risk individuals in treatment and care. The partnership between study staff and community leaders helped create better bridges between at-risk individuals and health interventions, thus contributing to a reduction in HIV/AIDS risk behaviors (62).

Uruguay. In Uruguay the vast majority of drug treatment centers are private and strictly oriented toward abstinence (57). In 2001 the NGO Instituto de Investigación y Desarrollo Social (IDES) organized an intervention program that targeted injection and noninjection

drug users and their sexual partners who frequented a high-risk neighborhood. The intervention provided training, information materials and condoms, but did not provide injection paraphernalia, since there is no legal support for this activity in Uruguay. Until now Uruguay has not provided sterile syringes and needles to IDUs, although the IDU population accessed by researches is growing. Interventions so far have been aimed at the general drug-using population (57).

Paraguay. Paraguay does not provide sterile materials to IDUs and no harm-reduction projects have been initiated (45), although some interventions have accessed several IDUs. For example, the NGO PREVER study of this population demonstrated a prevalence of HIV of 15% and frequent high-risk injection practices (4).

Prevention initiatives in Argentina and Brazil

Argentina. In Argentina there are no comprehensive public policies and public health services for IDUs which might influence the high HIV/AIDS incidence in this population (68). Despite the clear HIV/AIDS epidemic among IDUs, Argentina still lacks large-scale harm-reduction programs at a national, state, and local level (69).

The prevailing drug policy in Argentina is based on abstinence. Starting in the mid-1970s drug possession has been punishable by law. Military dictatorship during the 1970s and 1980s strongly influenced interventions and policies related to the reeducation and rehabilitation of drug users; during this period drug-dependence treatment was the responsibility of psychiatric hospitals and prisons.

Since the mid-1980s, nongovernmental rehabilitation centers have piloted alternative treatment approaches based mainly on therapeutic community models. During the mid-1980s criminal punishments for drug possession were revised, so that if the holder could show that drugs were intended for personal use only, he or she might be required to complete compulsory treatment without incarceration.

However, harm-reduction initiatives have been implemented only in the two largest cities in Argentina, Rosario and Buenos Aires (48), where the distribution of sterile injection equipment began in 1999 (68). The NGO Intercambios in Buenos Aires carried out a rapid assessment and response study and organized several community interventions targeted at injection drug users (70). This study provided support for local

initiatives aiming to reduce drug-related harm, and led to the first needle exchange program in Argentina (71).

Brazil. Because of its relevant socioeconomic role in South America and the scope of its HIV/AIDS epidemic, the reformulation of Brazilian HIV/AIDS prevention policies has had a significant impact upon activities in most countries of South America. The first SEP in South America began in Salvador, Bahia, in 1994 (72). According to the Brazilian Ministry of Health, there are over 200 harm-reduction projects in operation in different regions of Brazil (73). These initiatives are supported by a consortium involving the Brazilian Ministry of Health, the World Bank, the United Nations International Drug Control Program (UNDCP) and other international agencies. No other South American country except Argentina has officially endorsed SEPs.

Despite funding restrictions and a lack of managerial expertise in most SEPs, support for harm-reduction initiatives including SEPs is growing in Brazil. Advocacy activities and lobbying have helped to pass several state laws that permit the implementation of SEPs and similar activities, and additional legislative reforms are under negotiation, including a federal bill to regulate SEPs and harm-reduction activities in general. Although federal drug policies still prohibit SEPs, local laws have eased repressive conditions faced by local activists and outreach workers, thereby improving the stability of such initiatives in several Brazilian states (72, 73).

Regional and national networks function as forums for ideas and practical experiences with respect to SEPs and other harm-reduction initiatives. In Brazil there are two national harm-reduction associations—the Brazilian Harm Reduction Association (ABORDA) and the Brazilian Harm Reduction Network (REDUC)—in addition to several local networks. Support from international agencies such as UNAIDS and the World Bank has been necessary to introduce and sustain SEPs in Brazil. The task in the future will be to expand these programs and develop a framework for the integrated evaluation of these initiatives from the onset (72).

CONCLUSIONS

Accelerated globalization has made drug trafficking a worldwide challenge. Traditional habits of psychoactive substance use, such as chewing coca leaves or drinking coca tea—a common part of the social customs and mores of small communities—have been replaced by modern patterns of drug consumption. Frequently, different patterns of drug abuse overlap, creating extensive, intertwined illicit drug markets and a legion of polydrug users. The habit of injecting illicit drugs is on the rise in the South American and Caribbean regions and worldwide.

The growing interconnection between regions and populations has also contributed to the accelerated spread of HIV worldwide, making the AIDS pandemic one of the greatest challenges of our contemporary world. Although prejudices toward drug users and entrenched myths of national immunity to the double challenge of drug use and HIV/AIDS still persist, the present review clearly documents that most countries in the region have been affected by the dissemination of the harmful consequences of drug consumption, including HIV/AIDS.

Global and local drug policies still run counter to scientific evidence in many different contexts. This has substantially delayed and limited the scope of initiatives that could avert or ameliorate the adverse consequences associated with drug use, minimize human suffering, and contain the rising costs associated with the management of HIV/AIDS, viral hepatitis, overdose, and many other problems.

There is no excuse for further delay or hesitation. South America and the Caribbean must scale up their initiatives to curb the spread of HIV/AIDS, take advantage of improved local scientific evidence, subject any project and program to continuous monitoring and scrutiny, and adopt the best international scientific standards.

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ARTIGO 2

Reconstructing the AIDS epidemic among Brazilian injection drug users
Reconstruindo a epidemia de AIDS entre usuários de drogas injetáveis brasileiros

Título corrido: AIDS among IDUs in Brazil

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Abstract (**176 words**)

The HIV/AIDS epidemic among injection drug users (IDUs) in Brazil has been unique in terms of temporal and geographical contrasts. This analysis explores these through the use of multilevel modeling. Standardized AIDS incidence rates among IDUs for Brazilian municipalities, 1986-2000 were used as the dependent variable, with a set of social indicators as independent variabes (covariates). In some states of the North/Northeast, the epidemic among IDUs has been incipient. The Sao Paulo epidemic extended to reach a network of municipalities, most of them located far away from the capital. More recently, on a smaller scale, a similar extension has been observed in southernmost states. Both "number of physicians per inhabitant" and "standard distance to the state's capital" were found to be associated with the AIDS incidence. AIDS cases among IDUs appeared to cluster in richer, more developed municipalities. The relative weight of such extensive dissemination in key, heavy-populated, states prevails upon the Brazilian IDUs epidemic, defining a center-western-southeastern stripe of richer middle-sized municipalities and, more recently, a southern stripe of municipalities deeply affected by the epidemic in this population.

Key-words: AIDS; Brazil; Injection drug users (IDUs); multilevel analysis; social dimensions of the AIDS epidemic

Resumo (179 palavras)

A epidemia de HIV/AIDS entre usuários de drogas injetáveis (UDI) apresenta, no Brasil, contrastes temporais e geográficos. Esta análise explora estas complexidades, com o emprego de modelagem multinível. As taxas padronizadas de incidência de AIDS em UDI para os municípios brasileiros (período 1986-2000) foram consideradas como variável-dependente, e um conjunto de indicadores sociais como covariáveis. Em alguns estados do Norte e Nordeste a epidemia é incipiente entre UDI, enquanto a epidemia paulista atinge uma rede de municípios, a maioria deles distantes da capital. Mais recentemente, e em menor escala, disseminação análoga foi observada nos estados mais meridionais. As covariáveis "número de médicos por habitante" e "distância-padrão da capital do respectivo estado" se mostraram associadas à variável-dependente. Os casos de AIDS entre UDI parecem se concentrar em municípios mais ricos e bem equipados. O peso relativo desta disseminação extensa em estados-chave, populosos, prevalece sobre o conjunto da epidemia brasileira, definindo uma faixa que se estende do Centro-Oeste ao Sudeste, com municípios mais ricos, de médio porte, e, mais recentemente, uma faixa sul de municípios substancialmente afetados pela epidemia entre UDI.

Palavras-chave: AIDS; Brasil; Usuários de drogas injetáveis (UDI); análise multinível; dimensão social da epidemia de AIDS

Introduction

Currently in its third decade, the HIV/AIDS pandemic has progressed unabated in many different regions of the world[1]. The contrasts between relatively spared and deeply affected regions and communities have been widening, both in terms of epidemic size and trajectory, and the scale and availability of preventive and treatment interventions[1]

These contrasts have been particularly marked among injection drug users (IDUs). Stigmatized and criminalized in almost all countries, IDUs have been affected by extremely rapid epidemics, in places as diverse as Bangkok, Thailand[2], Ho Chi Minh City, Vietnam[3], southern provinces of China[4], and in different settings in Eastern Europe[5,6]. On the other hand, epidemics among IDUs have been prevented in some contexts[7] and reversed in some others, such as New York in recent years[8].

Proximate risk factors for IDU-associated transmission such as injecting practices, are determined largely by broader social, cultural, political and legal dimensions' influences on individual behaviour[9,10]. Location -specific patterns of drug use, and their interaction with drug availability, purity, methods of drug production, and trafficking routes[10,11] are particularly important.

HIV infection rates among IDUs consequently show considerable geographic variation across and within countries reflecting variation in the risk environment as well as the timing and extent of implementation of comprehensive prevention strategies[7]. Most programs and projects aiming to reduce drug-related harm still face political opposition and experience serious operational difficulties in many communities and countries[12]. More recently, with the introduction of highly active antiretroviral therapy (HAART) in developed countries (and a small number of developing countries, striking differences have been observed in terms of rates of progression of human immunodeficiency virus (HIV) infection within IDU populations and between IDUs and other populations, due to differences in the spectrum of HIV-related illnesses, prevalence of different co-infections, access to health care, and adherence to HAART[13,14].

Owing to its size and economic and social heterogeneity, Brazil's HIV/AIDS epidemics among IDUs have been very variable in size and trajectory in different regions, states, and municipalities[15,16].

In this paper we seek to describe the geographical variation in the size and trajectories of the AIDS epidemics in Brazil and to investigate the role of structural determinants in explaining these variations using routinely collected data broken down to

the level of municipalities. These data describe: a) numbers of new cases of AIDS among IDUs in different years between 1986 and 2000 and b) measures of socioeconomic and structural environment (SSE) areas. We have used a multilevel modeling strategy which incorporates temporal information available at the municipality and state level, and which partially overcomes the limitations of former analyses, using geoprocessing[15,16].

Methods

Data

Data describing reporting of new AIDS cases among UDIs for each year between 1986 and 2000 were obtained from the Brazilian AIDS Cases Databank (SINAN-AIDS), for the period 1986-2000.

We classified cases as belonging to the "injection drug users" exposure category follows the hierarchical classification approach proposed by UNAIDS (1999) In this approach injection drug users are classified under this broad category, even if included in additional exposure categories (i.e., categories 11, 14, 15, 21, 24, 25, 31, 34, 35, 40, 41, 42, 61, 64, 65 & 67, as defined by SINAN-AIDS, Brazilian Ministry of Health). We double-checked this information with the variable: "ever used injectable drugs [for non-therapeutic purposes]", from SINAN-AIDS. We found an agreement of approximately 98% between the two definitions, and thus adopted UNAIDS standard classification.

We calculated rates of new AIDS cases (where HIV infection was acquired through IDU) for those Brazilian municipalities which had registered at least 15 cases of AIDS among 15-69 years old, in this period. This yielded 255 out of 5,507 Brazilian municipalities, from 23 states (of a total of 27 Brazilian states). Demographic data for each municipality were downloaded from the Department of Information of the National Health System's site (DATASUS) (www.datasus.gov.br). In order to standardize the effect of the age structures of the different municipal populations, we calculated the directly standardized registration rate by age groups (15 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 69), using the Brazilian population for the year 2000 as the reference population.

A set of socioeconomic and structural indicators which might be associated with the variability of the standardized rates of AIDS cases among IDUs was constructed for, using 1991 and 2000 census data, and from a comprehensive inter-census assessment of educational indicators carried out in 1996. This included: adult literacy rate; proportion of persons older than 15 years old who completed 8 years of education; proportion of residents with a) full water provision; b) with municipal garbage collection service, and c) access to sewage systems, were used as indicators for housing standards. "Per capita income" and "the Gini coefficent" were used to assess income and income inequality. In relation to social vulnerability and health infra-structure, we used two indicators: the proportion of households headed by women with children younger than 15 years old; and the number of physicians per inhabitant. We used the Human Development Index (HDI) as a composite

index that measures average achievement in three basic aspects of human development: longevity, knowledge, and standard of living (available at www.undp.org). To describe population dispersion we used the proportion of urban population for each municipality and the distance (in km) from each municipality to the respective state's capital were also explored in the analyses.

Indicators for education, water provision, sewage, and garbage collection were downloaded from the abovementioned DATASUS site. All other indicators were downloaded from the Brazilian site of the United Nations Development Programme (PNUD-Brasil) (http://www.pnud.org.br).

Analysis

Because the data structure gives a) multiple observations on single units of analysis and b) natural geographically determined hierarchy of observations (municipality / state), a multi-level model was used in order to take into account a) correlation within units in AIDS incidence over time, and b) correlation of AIDS incidence between different municipalities, and states. We considered time as the first level, corresponding to the 15 years period (1986-2000) under analysis, municipalities as the second level (255), and Brazilian states (23) as the third level.

Logged AIDS standardized incidence rates among IDUs were used as the response variable in order to provide a better approximation to the linear function and normal distribution. MlwiN (Multilevel Models Project Institute of Education) software, version 2.0, was used for all analyses.

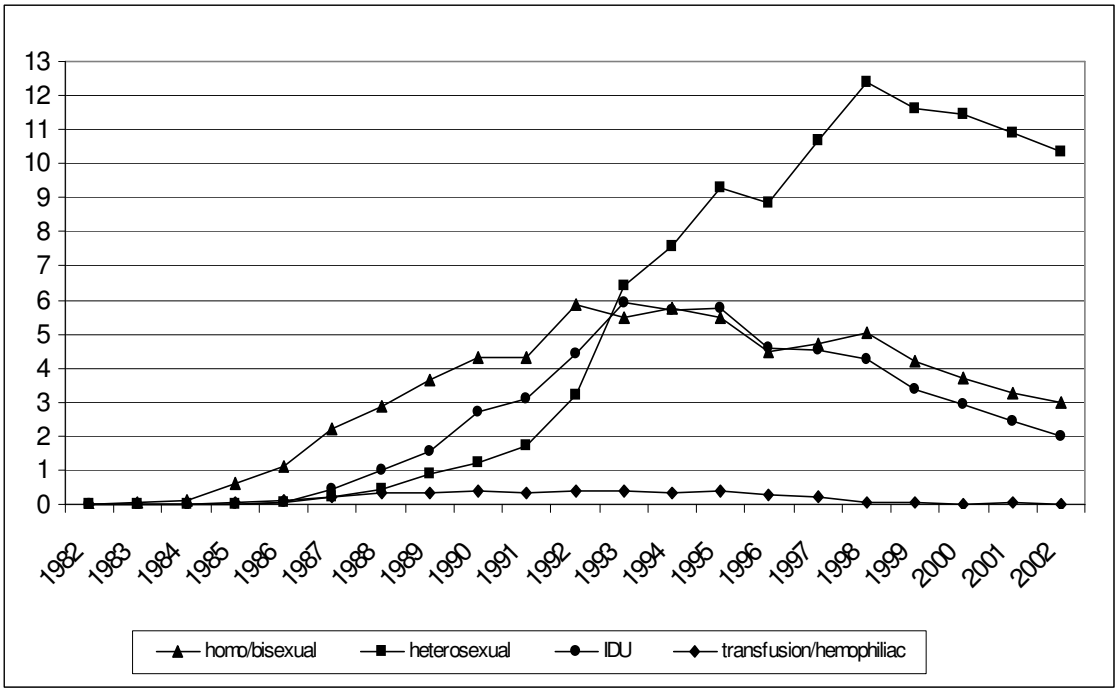
In order to assess colinearity, a correlation matrix including all covariates was constructed.

The analyses were performed in two steps, starting with univariate analyses. Those variables shown to be associated with the outcome, considering a significance level of 5% were included in the multivariate analysis. Covariates were then selected using a backward stepwise procedure, based on maximum likelihood ratio test. Residual analyses were carried out to evaluate the underlying assumptions of the multilevel model.

Results

Before presenting the results of the multilevel model, we briefly illustrate the distribution of AIDS cases for Brazil, 1980-2002. Figure 1 shows the distribution of AIDS cases according to exposure categories among population older than 13 years old.

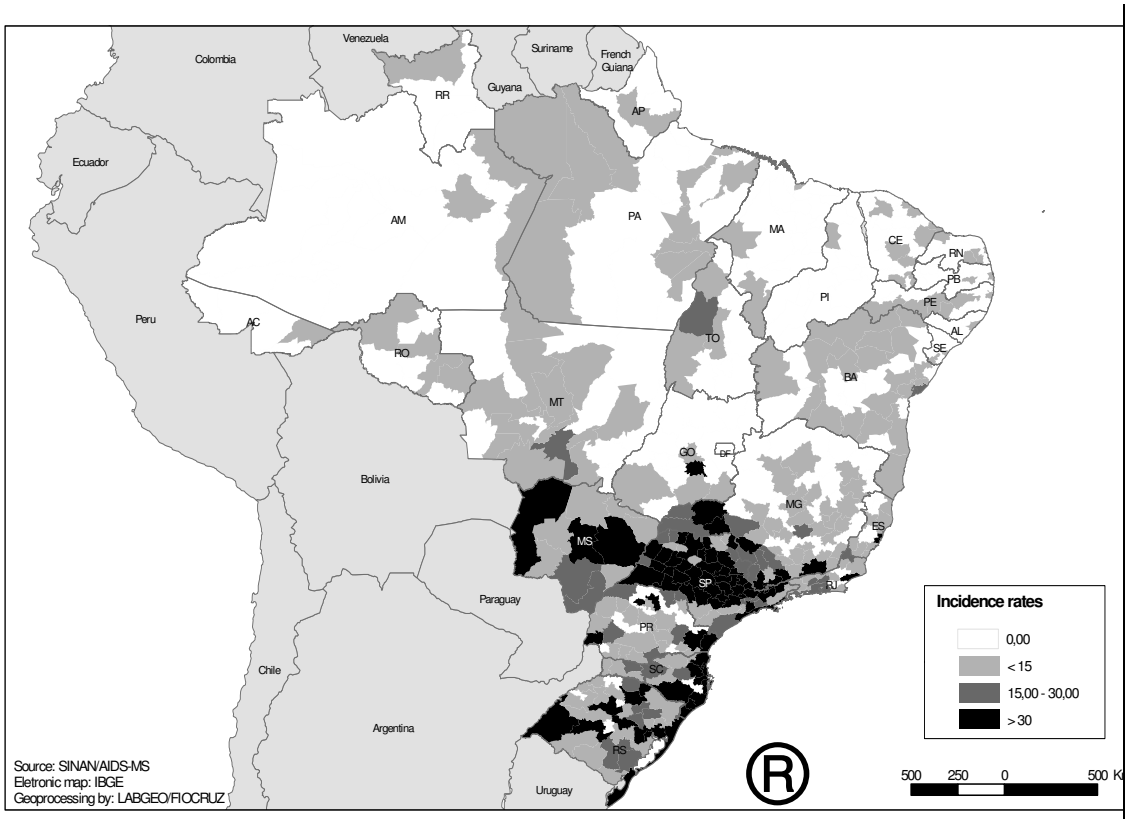
Figure 1: AIDS incidence rate (per 100,000 inhabitants) by exposure categories among population older than 13 years old. Brazil, 1982-2002



As depicted in Figure 1, the proportion of IDUs among AIDS cases increased in the late-1980s, reached a peak in early 1990s, and declined thereafter, with substantial increase of cases acquired through heterosexual transmission.

We also illustrate the spatial distribution of AIDS cases among IDUs across the different Brazilian regions, using the AIDS accumulated rates, for 1984-2000. In order to improve the representation, we smoothed the rates according to the Brazilian micro-regions, as defined by the National Institute for Geography and Statistics (IBGE) (Figure 2).

Figure 2: AIDS incidence cumulate rate (per 100,000 inhabitants) among UDIs. Brazil, 1984-2000.



As expected, "Per capita income" and indicators for education showed a strong correlation with HDI (data not shown), because the HDI contains these in its composition.. Therefore, only the HDI was included in the intermediate models. The indicators related to sewage infra-structure, garbage collection, and the proportion of population living in urban areas did not explain variations in AIDS cases across municipalities in the univariate analyses and were excluded from further analyses.

Therefore, the final model is formed by an intercept (allowed to vary across the 3 levels: states, municipalities, years), a parameter describing the effect of the variable "time" (with random effects at the level of municipality and state), a parameter referred to "time squared" (with random effects at the level of municipality and state), and by the variables "number of physicians per inhabitant" and "standard distance to the state's capital" defined

at the level of the municipality. The model coefficient estimates for the selected variables and their respective standard errors are presented in Table 1.

Table 1: Coefficient and confidence interval of variables of the final multilevel model.

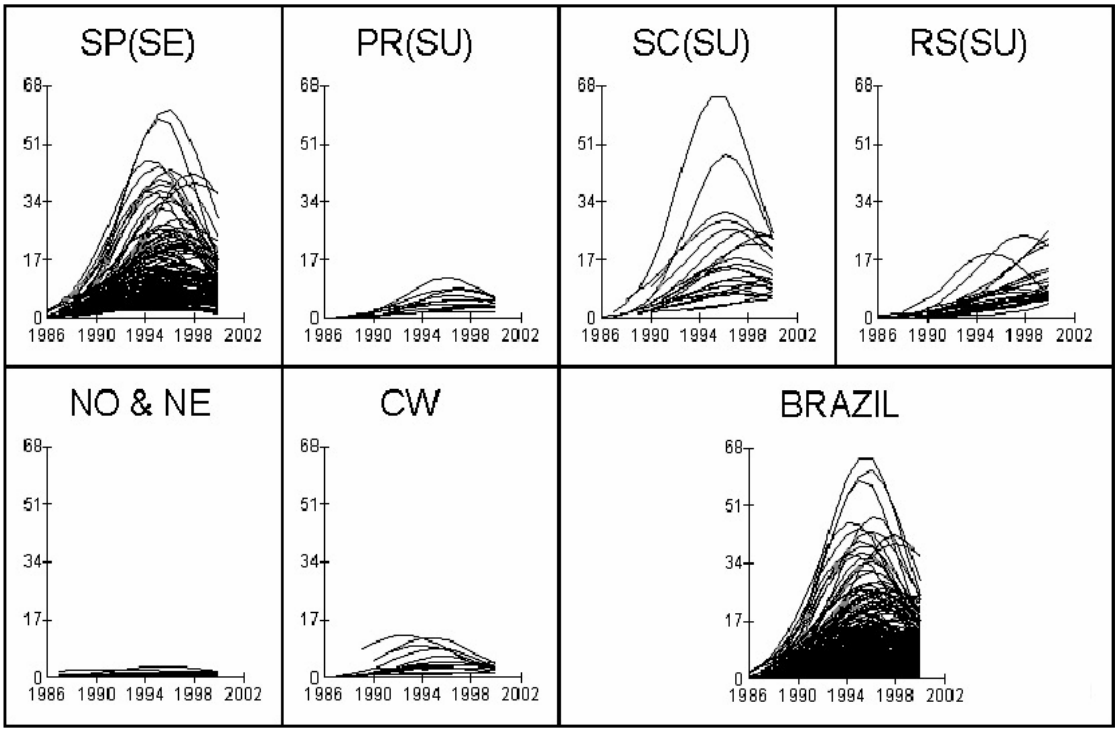
Variables	**Coefficient**	**CI (95%)**
Fixed part		
Constant	-1.343	(-1.741;-0.945)
Time	0.452	(0.395;0.509)
$Time^2$	-0.022	(-0.024;-0.020)
Distance to the state's capital*	0.001	(0.001;0.002)
Number of physicians per inhabitant*	0.076	(0.005;0.147)
Constant		
State	0.533	(0.086;0.980)
Municipality	0.987	(0.644;1.330)
Year	0.318	(0.298;0.338)
Time		
State	0.003	(0.001;0.005)
Municipality	0.086	(0.061;0.111)
$Time^2$		
Municipality	0.001	(0.001;0.001)

*indicators were centered at their respective mean values

Figure 3 presents the predicted standardized rates, based on the estimated parameters, for each municipality and state. An average line was imposed on each graphic, assuming no effect at the municipality level. States from the North (NO) and Northeast (NE) present lowest rates and the smallest number of municipalities reporting AIDS cases among IDUs, basically restricted to their respective capital or main metropolitan area. In the Center-West (CW), rates were found to be higher and in some states, such as Goiás (GO) and Mato Grosso do Sul (MS), AIDS cases were spread across different municipalities. States located in the South (SU) and Southeast (SE) contained the municipalities with the highest rates, especially in São Paulo state (SP) and Santa Catarina (SC). In these, AIDS cases among IDUs had been registered in municipalities located across the whole state territory, and were not confined to major urban concentrations.

In some municipalities including from Santa Catarina (SC) and Rio Grande do Sul (RS), Brazil's southernmost states, the AIDS incidence rates appear to be increasing. In Santa Catarina, the most affected municipalities comprise Laguna, Joinville, Blumenau, Jaraguá do Sul, and Lages. In Rio Grande do Sul, the incidence has been increasing in all municipalities, with the single exception of Porto Alegre (state's capital) and Passo Fundo, were incidence rates seem to be stabilized.

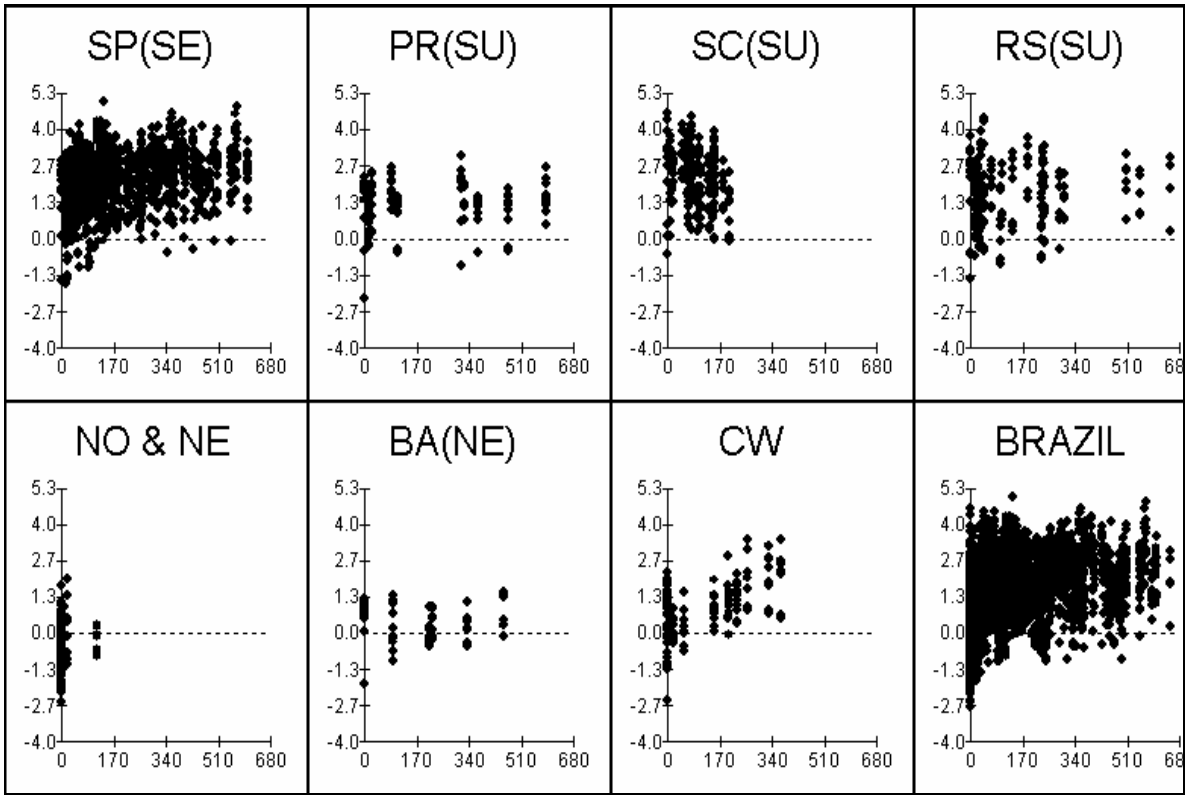
Figure 3: Predicted AIDS incidence standardized rates, 1986-2000



To further explore effect of municipalitiy's distance from the state's capital, we carried additional analyses. The distance to the state's capital (km) of each municipality is plotted against the logged standardized AIDS incidence rate in Figure 4, with states, ordered from the left to the right, from the top to the bottom, according to Brazilian regional geography.

In some states, especially in the North and Northeast, AIDS cases are located very near to the state's capital or have been registered exclusively in the capital. As mentioned before, such findings contrast with those for municipalities located in the Center-West, and especially for those located in the industrialized regions in the South and Southeast. Since approximately 74% of cases registered among IDUs are located in the states of São Paulo (southeast) and Rio Grande do Sul (south), the overall effect on the Brazilian epidemic in this population is strongly influenced by those states and their respective regions.

Figure 4: Neperian logarithm of standardized rate *versus* Standard distance to the state's capital (km), 1986-2000



Discussion

Previous analyses carried out at different levels of aggregation have suggested an apparent paradox: that while there is a strong concentration of AIDS cases among IDUs in the richest and most industrialized areas of Brazil, (the south and southeast); the vast majority IDUs registered as AIDS cases registered are from to the poorest strata of Brazilian society[12], one of the most socially unequal societies in the world[18]. The present analysis offers additional insight, exploring the interplay of determinants situated at the meso and macro-level.

At its outset the AIDS epidemic among Brazilian IDUs followed the main trafficking routes of cocaine, from the west (bordering coca/cocaine producing areas) to the mains ports located in the southeastern coast[15,16]. Through visual inspection, it is possible to identify a strip of high HIV incidence running from the Center-West to the Southeast, crossing the richest municipalities of São Paulo, probably reflecting the better transportation networks, and opportunities to traffickers to sell the cocaine en route to export points[15,16]

In recent years, AIDS incidence among IDUs has stabilized or declined in those municipalities affected early by the epidemic. This may be reflecting saturation, spontaneous behavior change, or the effects of preventive programs. The effectiveness of the latter has been demonstrated by many different research studies carried out among IDUs using different indicators and outcomes, such as HIV prevalence and incidence, risk behaviors and prevalence of different blood-borne infections[19-24].

However, no such stabilization or decline has been observed in the southern region. Our findings show that current trends for the northernmost state of the southern region – Paraná –, roughly follows the patterns described for São Paulo and the other southeastern states in the early years of the epidemic. On the other hand, our findings suggest that the epidemic has been spreading among IDUs from some municipalities of Santa Catarina and most municipalities of Rio Grande do Sul, Brazil's southernmost states. These states have been deeply affected by the epidemic since the middle-1980s and in many municipalities the epidemic has progressed unabated in the late 1990s.

Our findings, for AIDS incidence (which reflect epidemics of HIV transmission occurring several years earlier) are also supported and extended by individual-level studies, documenting persistent high HIV infection rates in southern municipalities[25,26]. The major difference between our findings (based on AIDS data) and those of studies reporting HIV

infection rates in the late 1990s-2000 is found in relation to Porto Alegre, the capital city of Rio Grande do Sul. In Porto Alegre, a decline in incidence is suggested by our analyses, in contrast to the disquieting increase among IDUs, recruited in the local communities in 1998 and 2000[26] and a high HIV incidence among non-injection heavy cocaine users from a cohort followed-up from 1996 to 1998[25]. It should be noted, however, that both our findings and inferences are based on non-random samples of hard-to-reach populations should be viewed with caution. Considering the non-commensurability of studies carried-out at the individual and ecological levels, we may hypothesize that a new wave of HIV transmission took place in the late 1990s among IDUs from Porto Alegre, yet to be captured by AIDS surveillance.

In a country with deep social contrasts, we explored the relationship between a comprehensive set of social inequality indicators and the spread of AIDS among Brazilian IDUs. Since health services may also be important; and given the persistent geographical unbalance of the Brazilian Health System we also used the number of physicians per inhabitant, in our analysis. Such heterogeneities impose some limitations to the analyses carried out in the present paper.

Despite the efforts to implement health policies to drive universalization of access to health care27, Brazil still maintains an unfair distribution of financial resources among regions, and delivery of health care services remains extremely unequal across the country28. Physicians are still concentrated in the bigger and better served urban centers.

In this sense, AIDS cases among IDUs may concentrate in richer and better equipped municipalities, where higher average incomes and concentrations of IDUs may foster the establishment of drug smuggling and consuming networks[29]. This collective phenomenon can take place despite the fact individual IDUs belong to dispossessed and marginalized strata[30].

In several European countries HIV prevalence among IDU shows considerable variation between and within countries[9]. The late upsurge of drug consumption and AIDS cases among injection drug users in Portugal in the context of trends in other southern European countries[31] illustrates well how richer and more developed societies may be affected by increased access to illicit drugs and to the harms associated with drug injection[32]. Further, the complex interplay of globalization, social change, drug trafficking and consumption, and increasing social inequality is dramatically illustrated by the fast and extensive spread of HIV/AIDS among Eastern European IDUs[5,31,33].

We found that AIDS occurrence among IDUs is significantly and positively correlated with higher distances from metropolitan areas. This could be viewed as an apparent paradox, since in the vast majority of Brazilian states AIDS cases in this population are restricted to the main metropolitan areas, if not to the state's capital itself. Additional analyses showed, however, that specific and contrasting geographical patterns can be discerned in different states.

Whereas in some states of the North and Northeast the epidemic among IDUs could be accurately described as incipient, the São Paulo epidemic has reached an extensive network of large, middle-size and small municipalities, most of them located far away from the capital. More recently and on a smaller scale similar epidemiological phenomena have been observed in the southern states.

It is difficult to provide conclusive explanations for the geographical variation in levels and trends in AIDS cases in Brazil. While, our findings must be cautiously interpreted they do suggest the need for different policy and intervention responses. Targeting incipient epidemics will be the priority in some regions while consolidating activities and promoting epidemic reversal will be the priority where mature epidemics have have stabilized. Most challenging of all will be controlling epidemics that are far from being curbed, such as those prevailing in the south.

Brazilian regional heterogeneity in both differential under-reporting and report delay may have significantly biased our findings. Published work in Brazil has sought to address report delay and suggest ways to correct it[34], and we have minimized this bias in our analyses by the deliberate exclusion of the last 4 years from analysis. However, to the best of our knowledge no published paper has addressed differential under-reporting which is likely to result from the variable reliability of local and regional health information systems. We have not, therefore, been able to mitigate bias from this source.

The triangulation of data from ecological and person-based analyses may provide Brazilian policy-makers with important information to inform the development of sound and culturally-sensitive interventions. Despite the usual limitations of secondary data, the major Brazilian databanks provide an important resource for the exploration of epidemic trajectories at different levels of geographical aggregation informing the tailoring of location specific responses which should complement nationwide analysis.

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ARTIGO 3

Social Inequality and Bridging Between Injection Drug Users and the General Population May Explain Unabated Spread of HIV in Southern Brazil

Introduction

The AIDS epidemic in Brazil commenced in the early 1980s and since then has passed many different phases and presented different regional patterns (Petersen et al., 2006; Hacker et al., 2006). As of June 2005, 371,827 AIDS cases have been reported in Brazil. AIDS incidence declines and remained stable thereafter, with 17.2 AIDS cases per 100,000, in 2004 (BMoH, 2005).

Initially, gay and bisexual men, mainly from higher and middle social ranks, were deeply affected, as well as recipients of blood and blood derivates (Lowndes et al., 2000; Petersen et al., 2006). Since the middle-1980s AIDS cases among injection drug users (IDUs) have been registered under a fast pace in the late 1980s/early 1990s, with a substantial decline thereafter (BMoH, 2005). Such decline has been observed in all Brazilian macro-regions, exception made to the southern region, especially in its southernmost states, Santa Catarina and Rio Grande do Sul (Hacker et al., 2006).

In recent years, the subepidemics in the two most populous and industrialized Brazilian regions ─ the southeastern and southern macro-regions ─, have been following opposed patterns. Whereas the epidemic has been consistently declining in the southeast, it has been progressing unabated in the south, both among injection drug users and heterosexuals (i.e. among both specific at-risk groups and the general population) (BMoH, 2005).

Much has been debated worldwide on the role of IDUs as a bridging population, contributing to the spread of HIV and other sexually transmitted infections and blood-borne pathogens to the so-called general population (Qian et al., 2005; Williams et al., 2003).

Inconsistent use of condoms among injection drug users and their sexual partners have been reported in different contexts (Sherman & Latkin 2000; Hacker et al., 2005; Pechansky et al., 2005). Recent papers have highlighted the often disregarded central role of sexual risky behaviors in the transmission of HIV among injection drug users (Flom et al., 2001; Strathdee & Sherman 2003**;** Hacker et al., 2005) and between them and their non-injecting sexual partners (Williams et al., 2005).

A recent paper by our research group assessed the association of socio-economic and structural indicators and AIDS incidence among injection drug users from different Brazilian macro-regions (Hacker et al., 2006). This paper made evident the deep heterogeneity of the Brazilian AIDS subepidemics among IDUs. The epidemic in this specific population has been declining in the southeastern region. On the other hand, the role of injection drug users in the northern and northeastern subepidemics has been negligible, whereas in the southernmost states IDUs have been hardly hit by HIV/AIDS (BMoH, 2005; Hacker et al., 2006).

The present paper focuses on the Brazilian southern subepidemic in order to better understand its dynamics, taking in consideration both its structural determinants as well as the putative role injection drug users may have as a bridging population to the general population.

Methods

Our basic dataset was composed by AIDS cases due to heterosexual transmission (i.e. those defined as belonging to exposure category "heterosexual transmission", corresponding to SINAN codes 30 and 36), registered among population aged 15 to 69 years old living in 288 southern municipalities, i.e. living in the southern states of Paraná (PR), Santa Catarina (SC) and Rio Grande do Sul (RS), downloaded from the National AIDS Notification System (SINAN-AIDS) for the period 1986-2000.

The earliest years of the epidemic were excluded from analysis in order to avoid unstable rates due to the small number of cases and more recent years were excluded because of case report delay (Barbosa & Struchiner, 2002). More seriously than the overall case report delay, former analyses by the same authors pointed out to differential delays for AIDS cases from different exposure categories (Barbosa & Struchiner, 1998), a especially relevant caveat considering the purposes of the present analysis. Anyway, available strategies to correct reporting delays eventuate from analyses related to the former DOS-based SINAN, replaced by a brand new Windows-based SINAN in the current decade (BMoH, 2005).

In order to standardize the effect of the age and sex structures of the different municipal populations, we calculated the directly standardized registration rate by age groups (15 to 19, 20 to 29, 30 to 39, 40 to 49, 50 to 59, and 60 to 69) and sex, using the Brazilian population for the year 2000 as the reference population.

A set of socioeconomic and structural indicators which might be associated with the variability of the standardized rates of AIDS cases among heterosexuals was constructed for, using 1991 and 2000 census data, and from a comprehensive inter-census assessment of educational indicators carried out in 1996. This included: adult literacy rate; proportion of persons older than 15 years old who completed 8 years of education; proportion of residents with a) full water provision; b) with municipal garbage collection service, and c) access to sewage systems, were used as indicators for housing standards. "Per capita income" and "the Gini coefficent" were used to assess income and income inequality. In relation to social vulnerability and health infra-structure, we used two indicators: the proportion of households headed by women with children younger than 15 years old; and the number of physicians per inhabitant. We used the Human Development Index (HDI) as a composite index that measures average achievement in three basic aspects of human development: longevity, knowledge, and standard of living (available at www.undp.org). To describe population dispersion we used the proportion of urban population for each municipality.

Indicators for education, water provision, sewage, and garbage collection were downloaded from the abovementioned DATASUS site. All other indicators were downloaded from the Brazilian site of the United Nations Development Programme (PNUD-Brasil) (http://www.pnud.org.br).

Another covariate entered in the multivariate models was the rate of AIDS cases among IDUs. This variable was further categorized using the median rate (1.08 cases per 1000 inhabitants) as the cut-point. The reference category was formed by values below the median.

In order to assess colinearity between indicators, correlation coefficients were calculated. Because the data structure allows for multiple observations of single units of analysis and due to the natural geographical hierarchy of observations (municipality/state), a hierarchical multi-level model was used, being the years the first level and municipalities the second level.

The linear multilevel model was constructed with a constant term with random effects to the first and second levels and two dummies variables were used to control the effects of the states, considering the state of Santa Catarina (the state with the greatest number of municipalities where increasing incidence AIDS rates have been registered at the end of the period ─ BMoH, 2005) as the reference category. In this model we allowed the

effect of time to be different depending on the municipality, i.e., time was included simultaneously as a fixed and a random parameter. Logged AIDS standardized incidence rate among heterosexuals was used as the response variable in order to provide a better approximation to the linear function and normal distribution. MlwiN (Multilevel Models Project Institute of Education) software, version 1.1 was used for all analyses.

The municipalities' indicators were introduced as covariates. Each term was included in the model and its significance level was verified, interaction terms between indicators were also tested. Variables with a significance level of 5% were maintained in the model.

The results were presented as both thematic maps, using standard digital maps, information merged from the IBGE sociodemographic databank and information on AIDS entered into the multilevel model, and a table summarizing the main findings of the multilevel model.

Results

In the bivariate analysis the following variables were shown to be associated with the outcome: "AIDS rate among IDUs", "Human Development Index", "Proportion of residents who have access to sanitary installations", "Proportion of households headed by women with children younger than 15 years old", and "Proportion of urban population".

Interaction terms between "HDI", "Proportion of urban population" and "Proportion of residents who have access to sanitary installations" were tested in pairs of hypothetical interactions.

In the final multivariate model (table 1) the following variables were found to be associated with the logged AIDS standardized incidence rate (among heterosexuals): "AIDS rate among IDUs", "Human Development Index" (HDI) and "Ratio of residents who have access to sanitary installations". The two latter indicators are referred to year 2000 and showed to be inversely associated with the outcome, i.e. the greatest proportion of residents with access to sanitary installations and the highest the HDI the lowest the AIDS incidence among heterosexuals in a given municipality.

Table 1 - Coefficient and standard deviation of the variables of the final multilevel model.

Variables	Coefficient (SD)
Fixed Part	
Constant	-2.204(1.125)
Time	0.032(0.008)
State (SC=reference)	
RS	-0.187(0.112)
PR	-0.357(0.140)
AIDS rate among UDI	
Above median value	0.183(0.043)
HDI	-6.491(1.388)
Sanitary installations	-0.016(0.003)
Random Part	
Constant	
Municipality	1.507(0.215)
Coefficient	
Time	0.007(0.001)

The AIDS rate among IDUs was found to be positively and significantly associated with the logged AIDS standardized incidence rate among heterosexuals, after controlling for different social and structural indicators.

The dummy covariate related to the three southern states (Paraná, Santa Catarina and Rio Grande do Sul) pointed out a smaller effect on the logged AIDS standardized incidence rate among heterosexuals in Rio Grande do Sul vis-à-vis Santa Catarina. Such effect is even smaller when the state of Paraná is compared to Santa Catarina.

The visual inspection of the thematic maps (Figures 1, 2 and 3) helps to understand the model's findings in context. Figure 1 illustrates HDI indexes for the southern municipalities under analysis. Although HDI indexes for the southern region are relatively high vis-à-vis overall Brazilian indexes (data not shown), there is a relevant variation between such indexes. There is a spatial overlapping between municipalities with lower HDIs and areas where the epidemic among both heterosexuals and IDUs has been spreading unabated in the period under observation (Figure 1).

Figure 2 depicts the accumulated AIDS incidence among IDUs (1986-2000), per 1,000 inhabitants for each municipality. There is a clear concentration of AIDS cases among IDUs along the coastal line, especially in the harbor areas and municipalities located nearby, such as Paranaguá (PR), São Francisco do Sul (SC), Itajaí (SC), Imbituba (SC), Laguna (SC), Rio Grande (RS), and Pelotas (RS), where AIDS cases among heterosexuals concentrate as well. High accumulated rates can be also found in municipalities located close to international frontiers (with Argentina and Uruguay), such as Uruguaiana (RS) and São Borja (RS).

Figure 3 illustrates accumulated AIDS incidence rates among heterosexuals (men and women, 1986-2000), per 1,000 inhabitants for each municipality. Besides the aforementioned concentration in the port municipalities, where IDUs also cluster, there is a relevant concentration in nearby coastal municipalities such as Pontal do Paraná (PR), Joinville (SC), Florianópolis (SC, capital city), Tubarão (SC). In the state of Rio Grande do Sul, the municipalities of Torres, Três Cachoeiras e Rio Grande, located in or close to the coastal line concentrate AIDS cases in this population.

AIDS cases among heterosexuals present a more diffuse geographic pattern compared to cases registered among IDUs, with an additional concentration in the metropolitan areas around the capitals of the states of Rio Grande do Sul (Porto Alegre) and Paraná (Curitiba). AIDS cases among heterosexuals cluster as well around the main highways, as depicted in Figure 3.

Discussion

Both HDI and the "Proportion of residents who have access to sanitary installations" were found to be inversely associated with AIDS rates. These findings may reflect the "impoverishment" of the epidemic in Brazil, i.e. the progressive spread of the epidemic toward dispossessed communities (Szwarcwald et al., 2001) and individuals belonging to poor social strata, as expressed by the proportional increase of AIDS cases among people with a lower educational background (Fonseca et al., 2002) and unemployed and/or working in low-paid occupations (Fonseca et al., 2003), and its specific patterning in southern Brazil.

Such process of impoverishment seems to be especially relevant in the Brazilian south, a region originally inhabited by European migrants (especially Germans and Italians), that nowadays compose a vast (for Brazilian standards) affluent middle-class,

amidst a growing population of impoverished peasants and low-paid/unemployed urban dwellers. Former studies carried out at the individual level documented the high infection rates of both HIV and Human T cell lymphotropic viruses type 1 and 2 (Morimoto et al., 2005) among impoverished social strata in municipalities from the state of Paraná.

The maps permit to triangulate the findings from the model, putting them in the context of Brazilian geography and demographics. There is a clear overlap between areas where the epidemic has been affecting IDUs and heterosexuals, and between such areas and the municipalities which score poorly on the human development index. The key role of port cities and other municipalities located in the southern coastal line highlighted by the present analysis confirms the findings of a former analysis employing geoprocessing techniques and targeting the dynamic of AIDS among IDUs (Bastos et al., 2002).

A vast literature (Victoria et al., 1992; Cesar et al., 1997; Victoria &Vaughan, 1997; Barros et al., 2001; Lima et al., 1999) documents the somber effects of poverty and social inequality in southern Brazil on a variety of medical conditions and social problems.

The different studies carried out in southern Brazil point out a combined effect of absolute deprivation and social inequality on adverse health standards, as discussed in the international literature (Marmot, 2003).

Our findings seem to reflect the trend of Brazilian epidemic to spread not only toward impoverished communities, but also toward middle-sized and smaller municipalities (Petersen et al., 2006). The combined effects of these two overarching tendencies make the middle-sized and small municipalities with lower human development standards and worse infra-structure particularly vulnerable.

Meso- and macro- social and economic determinants, individual behaviors and small networks interaction patterns have been explored as predictors of HIV/AIDS by the international literature. Broad social and economic determinants, largely disregarded by most literature have been reassessed by recent publications (Boerma & Wier, 2005; Rhodes et al., 2005).

The interplay of determinants at the level of individuals, their networks and the society at large is especially relevant among injection drug users, due to the complex inter-relationship of individual behaviors and communities in the frame of a powerful illicit market, ruled by contradictory policies and plagued by structural violence (Galea et al., 2003; Rhodes et al., 2005).

Most injection drug users do not fit to the stereotype of isolated individuals living in secluded places, but indeed partner with non-injecting mates and interact with their respective communities. Due to their especially vulnerability to blood-borne infections they may function as a bridge to the general population respecting HIV and other blood-borne pathogens (Williams et al., 2003; Williams et al., 2005).

In a former study carried out in a network of southern centers for HIV testing and counseling, the partnership with IDUs was found to be a key risk factor for HIV infection (Barcellos et al., 2003).

In sum, the present study, profiting from hierarchical multi-level modeling documents the combined role of social inequality/poverty and bridging from injection drug users on the unabated spread of HIV/AIDS in Brazilian southern municipalities.

Ecological studies, on one hand, are essential to catch the broad picture, never assessed before in the Brazilian south. On the other hand, they miss details to be explored by individual-level studies. Besides the usual limitations found in the analysis of secondary data, the present study did not explore a key biological variable ─ HIV diversity.

HIV is characterized by its extraordinary genetic diversity. Such diversity may be associated with differential spread of HIV across specific populations and the clustering of given subtypes in social and geographic contexts. (Salemi et al., 2005). Unlike all other Brazilian regions, where B subtype predominates, HIV C subtype infections are exquisitely prevalent in southern Brazil and have been on the rise in recent years (Soares et al., 2003; Soares et al., 2005).

The recent study by Salemi et al. (2005) hypothesizes HIV subtypes B and C have different epidemic potentials, what may explain why the Brazilian southern subepidemic, driven by HIV C subtype, has been spreading unabated whereas the southeastern subepidemic, driven by B subtype infections, has been on decline. Much probably the complex interplay of virological, individual and social determinants explains the unique epidemic trends observed in southern Brazil.

Our study refines previous analysis showing the pivotal role of injection drug users in southern Brazil. The present study extends former conclusions, exploring the putative bridging from IDUs toward the general population, at the ecological level, and highlighted an additional dimension ─ the role of social inequality/absolute deprivation (impossible to disentangle in the current analysis).

Public policies must be tailored to regional and social specificities. The full integration of studies carried out at the level of individuals, communities and broad geographic areas is pivotal in a multifarious and complex epidemic such as the ongoing HIV/AIDS epidemic, especially in a country with vast dimension and striking social contrasts such as Brazil. The present study brought new insights to the challenge posed by the unabated spread of HIV/AIDS in southern Brazil, a region where the undeniable achievements of the Brazilian AIDS Program did not materialize yet.

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Figure 1: HDI of selected municipalities, South region, Brazil, 2000

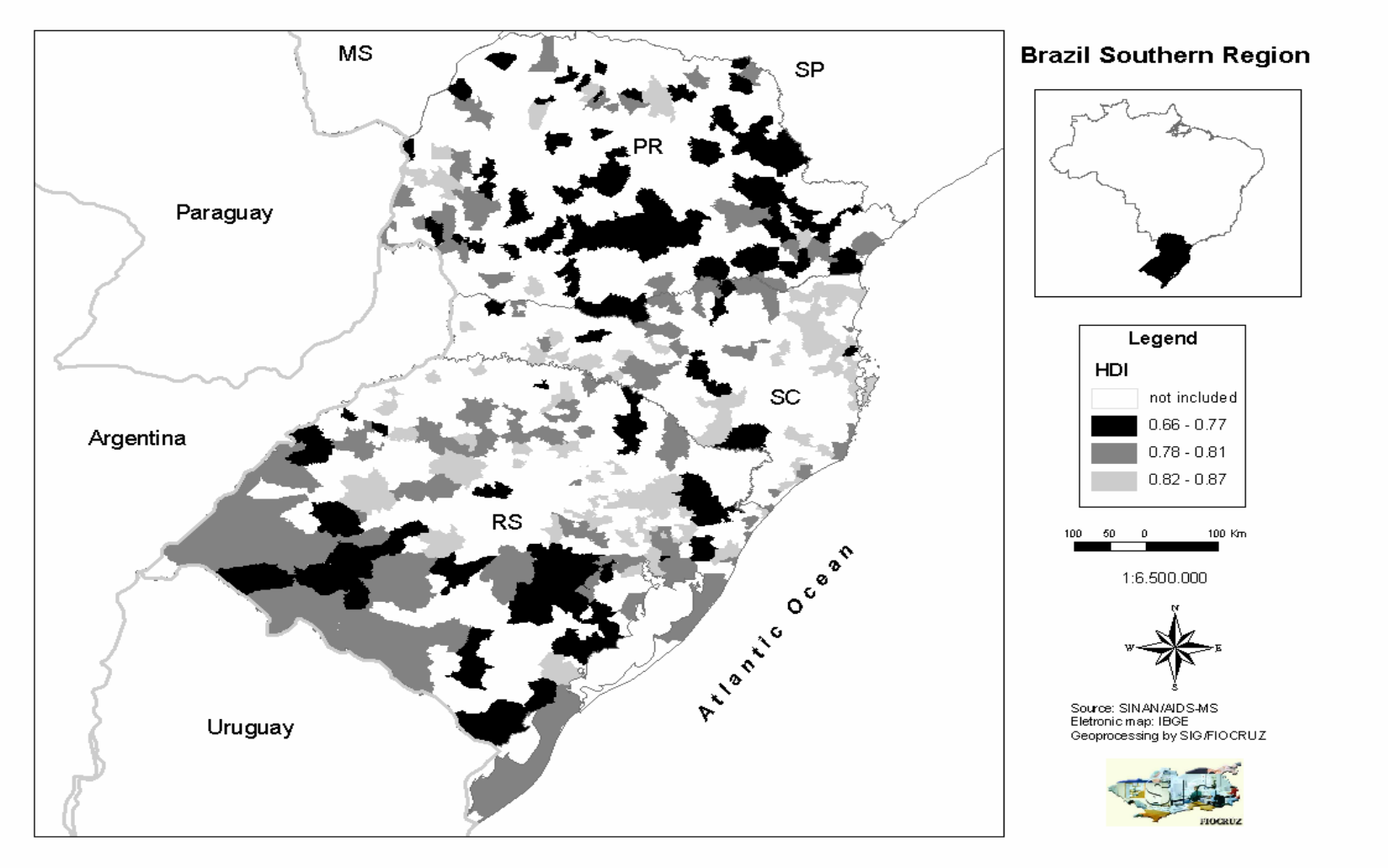


Figure 2: Accumulated AIDS incidence rate (per 1,000 inhabitants) among UDIs in South region, Brazil, 1986-2000.

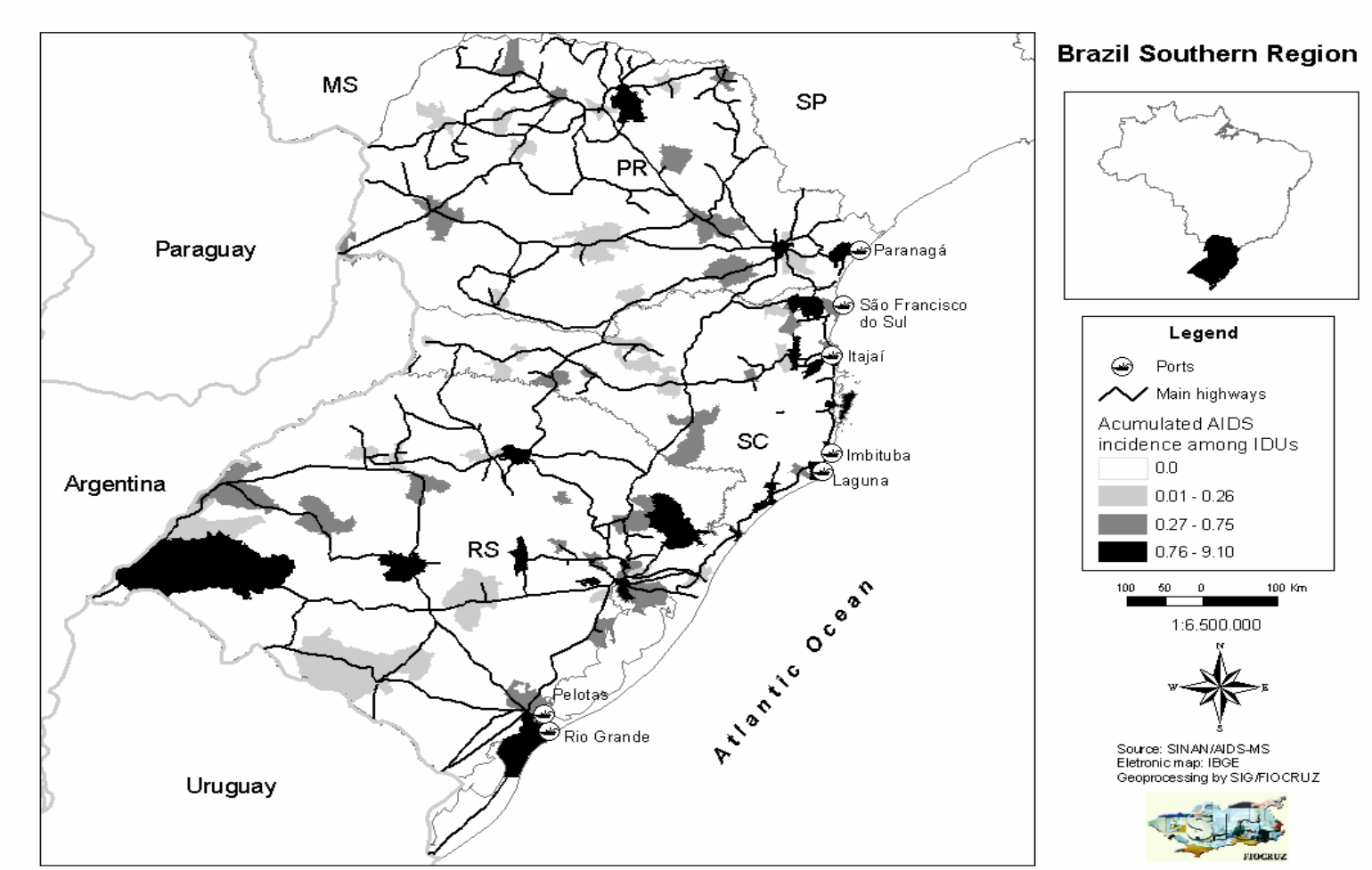
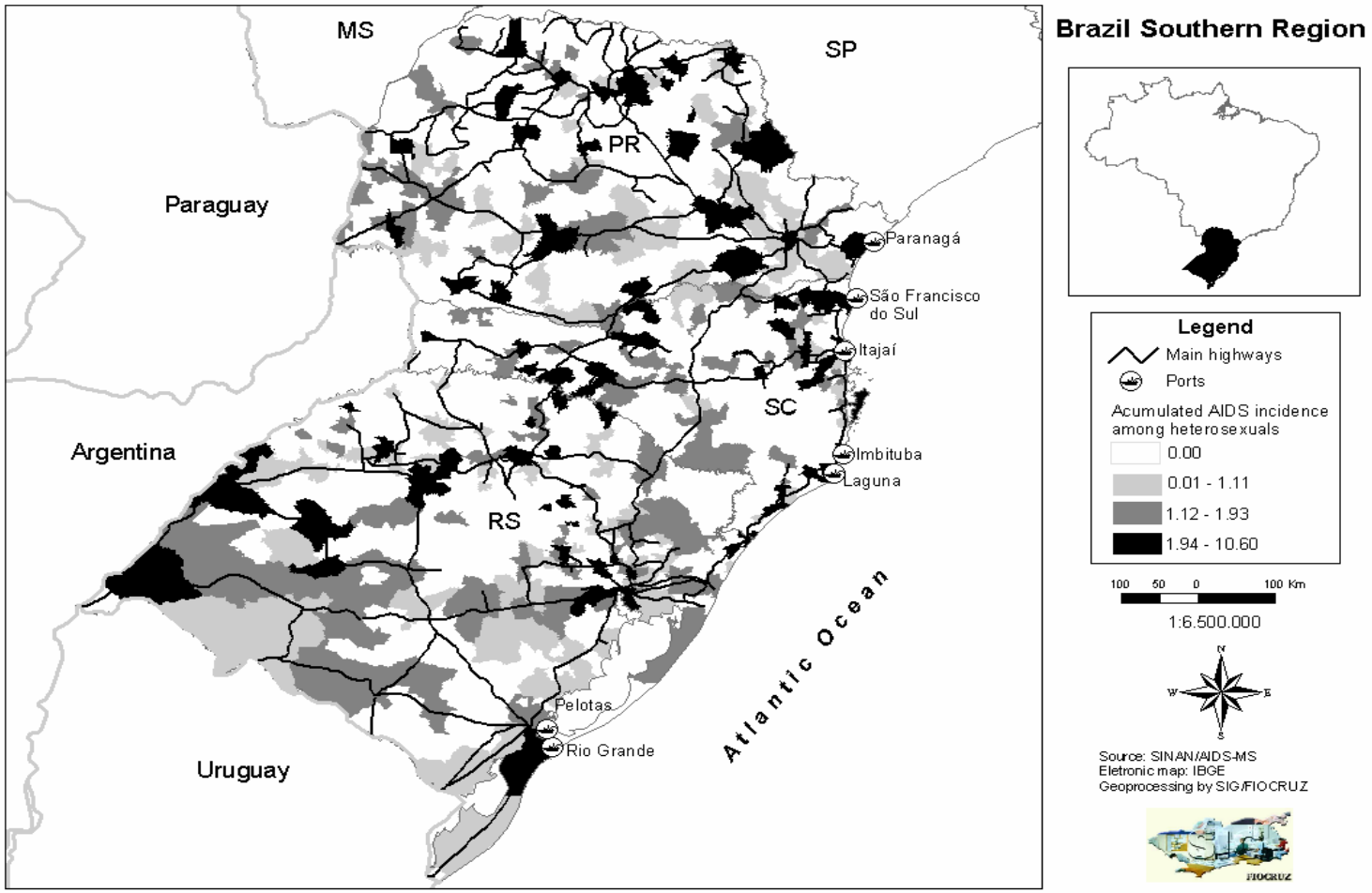


Figure 3: Accumulated AIDS incidence rate (per 1,000 inhabitants) among heterosexuals, South region, Brazil, 1986-2000.



Conclusões:

Ao revisarmos a literatura referente à disseminação do HIV/AIDS entre usuários de drogas na América Latina pudemos observar que, apesar de algumas lacunas, um crescente número de evidências documenta o importante papel do uso de cocaína injetável na epidemia brasileira e no Cone Sul. Estratégias de redução de danos foram estabelecidas em diversas localidades brasileiras e, mais recentemente, na Argentina. Em outros países da região ainda persistem sérias limitações no âmbito da prevenção, em função da legislação restritiva e ausência de apoios efetivos à plena implementação de ações preventivas e acesso restrito aos cuidados e tratamento.

A crescente participação dos países da região em protocolos de pesquisa (alguns deles multicêntricos) e o contínuo debate sobre experiências bem-sucedidas e fracassadas devem estimular os esforços de minimizar as barreiras postas à adoção de medidas efetivas para conter a epidemia de HIV/AIDS entre UDI e conseqüentemente na população como um todo.

A abordagem multinível utilizada nos dois artigos empíricos permitiu analisar um grande número de municípios brasileiros com observações repetidas, no período sob estudo. Apesar das limitações discutidas no âmbito da Introdução e dos próprios artigos, os bancos de dados nacionais constituem uma importante fonte de informações sobre a epidemia em diferentes níveis de agregação geográfica.

A epidemia de AIDS entre UDI se mostrou associada ao indicador "número de médicos por habitantes". Esse resultado pode estar refletindo o fato de que melhores condições e melhor infra-estrutura de serviços de saúde (incluindo a maior disponibilidade de profissionais de saúde) caracterizam os centros urbanos de porte grande e médio, locais onde se concentram os UDI. Possivelmente, existem diferenciais intra-urbanos na distribuição desta população, com uma maior concentração de UDI em áreas que contam com uma infra-estrutura sócio-econômica mais precária. No entanto, este efeito não é observável a partir de análises que tomam o município como unidade mínima de agregação.

Nas regiões Norte e Nordeste, os casos de AIDS apresentaram-se concentrados nas capitais ou em municípios próximos à capital, e são observadas, de um modo geral, as menores taxas de incidência de AIDS. Na região Centro-oeste e, principalmente, nas regiões Sul e Sudeste (onde se observam as maiores taxas de incidência), os casos se mostraram localizados em municípios distribuídos ao longo de todo o território da

respectiva Unidade da Federação, não se concentrando apenas em áreas próximas das capitais, refletindo, muito provavelmente, a tendência de interiorização da epidemia.

O IDH e a "proporção de residentes com acesso a instalações sanitárias" foram indicadores que se apresentaram inversamente associados à taxa de incidência de AIDS entre heterossexuais, nos municípios do sul do Brasil. Esses resultados também podem estar refletindo a tendência de "empobrecimento" (ou "pauperização") da epidemia, ou seja, a tendência da expansão da epidemia em comunidades e indivíduos de estratos sociais menos favorecidos. A relação entre a taxa de AIDS entre heterossexuais e a taxa de AIDS entre UDI evidencia a relevância do papel dos UDI na epidemia com um todo, provavelmente enquanto "ponte" de uma epidemia inicialmente concentrada em populações particularmente vulneráveis rumo a assim denominada "população geral".

Com base nos resultados encontrados e dada a expressiva variação geográfica e social da epidemia de AIDS no Brasil, sugere-se que diferentes estratégias e políticas devem ser adotadas nas ações preventivas, com claras especificidades regionais e sociais, colocando-se o duplo desafio de controlar a epidemia em regiões onde ela se apresenta em expansão, como na região sul do país, e evitar sua disseminação em regiões onde ela ainda é pouco relevante em populações específicas (como a população de UDI na região Nordeste, com exceção do estado da Bahia).

A combinação e integração de análises desenvolvidas ao nível de indivíduos, redes sociais, comunidades e regiões de maior abrangência geográfica se mostra essencial à adequada compreensão de uma epidemia cuja determinação é múltipla e complexa.

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ANEXO 1

Metodologia

Descrição das variáveis empregadas nas análises:

A primeira análise desenvolvida no âmbito da presente tese (artigo 2) é referente aos casos de AIDS entre usuários de drogas injetáveis (UDI), registrados nos municípios brasileiros, para o período de 1986 a 2000, minimizando-se, assim, a instabilidade das taxas nos anos iniciais da epidemia e as conseqüências do atraso da notificação em anos recentes (Barbosa & Struchiner, 2002).

A base de dados utilizada apresenta estrutura hierárquica devido não somente ao aninhamento de áreas geográficas, estado/município, mas também às medidas repetidas relativas aos casos de AIDS entre usuários de drogas injetáveis ao longo do período considerado. Por isso, um modelo hierárquico/multinível linear com três níveis foi utilizado, considerando como variável-resposta a taxa padronizada de incidência de casos de AIDS entre UDI (definidos como casos pertencentes às categorias de números 11,14,15,21,24,25,31,34,35,40,41,42,61,64,65 e 67 do SINAN, ou seja, compreendendo a categoria de exposição simples "usuário de drogas injetáveis" e diferentes categorias de exposição múltipla que incluem os "usuários de drogas injetáveis") nos municípios e como variáveis explicativas diferentes indicadores municipais referentes a características sócio-econômicas e de infra-estrutura destes municípios. Neste modelo, o primeiro nível se refere aos anos do período sob análise, o segundo nível é composto pelos municípios e o terceiro nível é referente às unidades da federação.

A taxa de incidência de AIDS foi padronizada por idade, segundo as faixas etárias de 15 a 19, 20 a 29, 30 a 39, 40 a 49, 50 a 59, e 60 a 69. Foi utilizada a padronização direta, considerando a população brasileira no ano de 2000 como população de referência.

Os dados relativos à população dos municípios e da população do Brasil foram obtidas na página da *internet* do DATASUS (www.datasus.gov.br), disponibilizados pelo Instituto Brasileiro de Geografia e Estatística (IBGE).

Os indicadores municipais estão disponíveis somente para os anos de realização do censo (realizados pelo IBGE a cada 10 anos), portanto para o período de 1986 a 2000, há disponibilidade dos indicadores para apenas dois anos, 1991 (quando o censo foi excepcionalmente realizado com atraso) e 2000. No ano de 1996, foi realizada uma contagem da população, que possibilitou a utilização de dois indicadores referentes ao

nível de escolaridade da população:proporção de alfabetizados na faixa etária de 15 a 69 anos e proporção de indivíduos acima de 15 anos com até 4 e com até 8 anos de estudo, em 1996.

A proporção de moradores (em todas as faixas etárias), que dispõem de abastecimento de água proveniente de rede geral, a proporção de moradores que têm o lixo coletado por serviços de limpeza ou em caçamba de serviço de limpeza, e a proporção de moradores que têm acesso a instalações sanitárias (rede geral) foram utilizadas como indicadores de qualidade de moradia e acesso a serviços essenciais de higiene.

A renda *per capita* e o Índice de Gini (que mede o grau de desigualdade existente na distribuição de indivíduos segundo a renda domiciliar *per capita*; variando de 0, quando não há desigualdade, a 1, quando a desigualdade é máxima) foram utilizados como indicadores de renda.

Como indicador de desenvolvimento humano foi utilizado o IDH (índice de desenvolvimento humano). O IDH é obtido pela média aritmética simples de três subíndices, referentes à longevidade, educação e renda. A proporção de população urbana foi utilizada como um indicador da distribuição da população na área do município.

Os indicadores municipais de alfabetização, escolaridade, abastecimento de água, instalações sanitárias e coleta de lixo foram obtidos no *site* do DATASUS, disponibilizados pelo IBGE.

Os indicadores de renda, vulnerabilidade, desenvolvimento humano e população foram obtidos através do *site* do Programa das Nações Unidas para o Desenvolvimento.

A segunda análise proposta (sistematizada no terceiro artigo que integra a presente tese) diz respeito aos casos de AIDS referentes à categoria de exposição heterossexual nos municípios da região sul, a única região do país onde a tendência da epidemia é de crescimento, no período sob análise (enquanto nas demais a tendência é de declínio ou estabilização). A região sul também é a região onde a epidemia entre UDI é mais relevante no contexto da subepidemia regional. Por isso, além dos indicadores municipais, uma variável referente à magnitude da epidemia de AIDS entre UDI foi incluída na análise com potencial variável explicativa. Como variável-resposta foi utilizada a taxa de AIDS entre heterossexuais (definidos como casos pertencentes às categorias de números 30 e 36 do SINAN), padronizada por sexo e idade. Os grupos etários considerados foram os mesmos utilizados na análise anterior, assim como a população de referência considerada foi igualmente a população brasileira referente ao ano de 2000.

Modelos Multiníveis:

Em diversas áreas de investigação, é possível observar estruturas hierárquicas nos dados. Um exemplo clássico de estrutura hierárquica é dado pela relação entre indivíduo e sociedade, onde indivíduos pertencentes a mesma sociedade tendem a ter atitudes mais semelhantes. Neste contexto, o efeito da "sociedade" deve ser levado em conta na explicação dos desfechos individuais, tendo em vista que ele cria uma dependência entre as observações.

A estrutura hierárquica é intrínseca aos dados longitudinais, onde as medidas repetidas, geralmente correlacionadas, constituem o primeiro nível de análise.

As abordagens clássicas de modelos de regressão estão baseadas no pressuposto de que as observações são independentes, ignorando assim qualquer tipo de estrutura hierárquica dos dados. A análise de dados com estrutura hierárquica geralmente envolve a avaliação do efeito de variáveis de ambos os níveis (indivíduo e sociedade). Há ainda o interesse de se quantificar o efeito da unidade de segundo nível sobre o desfecho de interesse. Assumindo-se que a base de dado tenha estrutura de hierárquica com dois níveis, indivíduo e área geográfica, o efeito da área na aplicação de um modelo de regressão pode ser mensurado por meio da inclusão de (k-1) variáveis dummies no modelo, onde k é o número de áreas geográficas sob investigação. No entanto, essa abordagem não permite a inclusão de características das áreas geográficas, pois essas variáveis sempre poderão ser expressas como combinação linear das dummies representando as áreas geográficas. A inclusão de dummies no modelo, quando há muitas unidades de segundo nível, resulta em perdas significativas de graus de liberdade tornando o modelo ineficiente. Além disso, a correlação entre as observações resulta na subestimação dos erros-padrão dos parâmetros tornando os testes estatísticos muito liberais (Snijders e Bosker, 1999; Goldstein, 1995).

Esses problemas são resolvidos por meio da implementação de modelos hierárquicos ou multiníveis, onde as variáveis dummies referentes às unidades de segundo nível são substituídas por um efeito aleatório que fica definido pelos parâmetros da distribuição de probabilidade a ele atribuída. É comum assumir que este efeito aleatório possui distribuição Normal com média zero e variância a ser estimada, fazendo com que,

apenas um parâmetro extra seja incorporado pelo modelo. Desta forma, pode-se inferir o efeito das unidades de segundo nível, a partir da variabilidade entre essas unidades, assim como analisar o efeito de suas características. Outro aspecto importante, é a possibilidade de se decompor a variabilidade total dos dados em variância do primeiro e segundo nível e assim calcular o que é denominado de coeficiente de correlação intraclasse que mede o quanto da variabilidade total dos dados é explicada pelas unidades de segundo-nível (Bryk e Raudenbush, 1992; Snijders e Bosker, 1999; Goldstein, 1995).

Os modelos multinível ou hierárquicos são também bastante utilizados na análise de medidas repetidas ou dados longitudinais, onde as unidades do primeiro nível se referem às medidas repetidas referentes a cada unidade do segundo nível. A contribuição dos modelos multinível à análise de dados repetidos provém da flexibilidade de se trabalhar com dados não-balanceados, isto é, que ocorrem em circunstâncias em que as unidades do segundo nível não apresentem o mesmo número de medidas repetidas ou tenham sido medidas em diferentes pontos do tempo.

Por todos esses motivos, na última década, o interesse pelos modelos estatísticos multinível tem crescido na área da saúde pública (Bingenheimer & Raundenbush, 2004). Esses modelos têm sido freqüentemente empregados em estudos de eventos de saúde cuja determinação ocorre em múltiplos níveis, considerando a maneira complexa como cada covariável etiológica em diferentes níveis pode interagir, determinando diferentes padrões de variação nos desfechos de saúde (Bingenheimer & Raundenbush, 2004).

Formulação do modelo

Modelos multiníveis procuram incorporar a dependência entre observações decorrentes da estrutura hierárquica dos dados. Nesse tipo de análise, a variabilidade total pode ser decomposta entre os diferentes níveis de agregação.

Modelos multiníveis podem ser classificados como de intercepto e coeficientes aleatórios. Modelos multiníveis de interceptos aleatórios são aqueles nos quais apenas o intercepto depende da unidade de segundo nível. Modelos com coeficientes aleatórios permitem que as covariáveis de primeiro nível possam ter efeitos diferenciados dependendo da unidade de segundo nível. O presente texto limita-se a apresentar os pontos básicos do modelo de regressão linear multinível.

Seja um modelo multinível com dois níveis e apenas uma variável explicativa:

$$Y_{ij} = \beta_{0j} + \beta_{1j} X_{ij} + R_{ij} \qquad (1)$$

onde:

Y_{ij} se refere a i-ésima observação j-ésimo grupo. Assume-se que há J unidades de segundo nível (j=1...J) e n_j observações em cada uma dessas unidades.

X_{ij} é a variável explicativa do modelo

R_{ij} é o resíduo do primeiro nível.

O intercepto β_{0j} e o coeficiente de inclinação β_{1j} são grupo-dependente. Esses coeficientes podem ser decompostos em duas partes, uma que representa o coeficiente médio e outra que representa o desvio em relação a cada grupo:

$$\begin{aligned} \beta_{0j} &= \gamma_{00} + U_{0j} \\ \beta_{1j} &= \gamma_{10} + U_{1j} \end{aligned} \qquad (2)$$

U_{0j} e U_{1j} são efeitos aleatórios com média zero e desvio-padrão σ^2_{u0} e σ^2_{u1} respectivamente. Assume-se também que o resíduo do primeiro nível, R_{ij}, é normalmente distribuídos com média zero e variância σ^2_r.

Quando β_{1j} é igual a β_1, isto é, o efeito da variável explicativa é o mesmo em todos os grupos, o modelo multinível é denominado de intercepto aleatório. Neste caso, susbstituindo-se o intercepto apresentado em (2) na equação (1) temos que:

$$Y_{ij} = \gamma_{00} + \gamma_{10} X_{ij} + U_{0j} + R_{ij} \qquad (3)$$

Cabe ressaltar que o efeito aleatório associado ao intercepto substitui as variáveis dummies que deveriam ser incluídas no modelo, representando as unidades de segundo nível.

A variância total é dada pela soma da varibilidade do primeiro e do segundo nível ($\sigma^2_{u0} + \sigma^2_r$). Pode-se mostrar que a correlação entre observações dentro do mesmo grupo é

dada por σ^2_{u0}. Sendo assim, definimos uma estatística de grande importância nos modelos multiníveis, que é o coeficiente de correlação intraclasse, definido como a proporção da variabilidade total atribuída ao segundo nível:

$$\rho = \frac{\sigma^2_{u0}}{\sigma^2_{u0} + \sigma^2_r} \qquad (4)$$

Permitindo-se que o efeito da variável explicativa seja grupo-dependente, obtemos o modelo multinível com coeficiente aleatório, cuja equação é obtida substituindo-se, na equação (1), o intercepto e coeficiente descritos na equação (2):

$$Y_{ij} = \gamma_{00} + \gamma_{10} X_{ij} + U_{0j} + U_{1j} X_{ij} + R_{ij} \qquad (5)$$

O termo $U_{1j}x_{ij}$ atua como uma interação entre a covariável e a unidades que compõem o segundo nível. Neste tipo de modelo, é difícil se calcular o coeficiente de correlação intraclasse, pois tanto a variância total quanto a covariância dentro do grupo dependem da covariável.

Essa formulação pode ser estendida para três ou mais níveis:

$$Y_{ijk} = \beta_{0jk} + \beta_{1jk} X_{ijk} + R_{ijk} \qquad (6)$$

onde:

i se refere a i = 1, ... , n observações do primeiro nível
j se refere a j = 1, ... , J observações do segundo nível
k se refere a k = 1, ... , K observações do terceiro nível

O intercepto β_{0jk} e o coeficiente de inclinação β_{1jk} podem ser decompostos em três partes, uma que representa o coeficiente médio, outra que representa o desvio em relação a cada agrupamento no segundo nível e outra que representa o desvio em relação a cada agrupamento do terceiro nível:

$$\beta_{0jk} = \gamma_{00} + U_{0j} + V_{0k}$$
$$\beta_{1jk} = \gamma_{10} + U_{1j} + V_{1k} \qquad (7)$$

Substituindo (7) em (6), temos:

$$Y_{ijk} = \gamma_{00} + \gamma_{10} X_{ijk} + U_{1j} X_{ijk} + V_{1k} X_{ijk} + U_{0j} + V_{0k} + R_{ijk} \qquad (8)$$

onde:

V_{0k} e V_{1k} se referem à parte aleatória do terceiro nível

U_{0j} e U_{1j} se referem à parte aleatória do segundo nível

R_{ijk} se refere ao resíduo do primeiro nível.

Em relação à estimação dos parâmetros, existem dois métodos principais de estimação: estimação de máxima verossimilhança (ML - *Maximum Likelihood*) e máxima verossimilhança restrita (REML - *Restricted Maximum Likelihood*).

No Método da Verossimilhança Restrita, a estimativa da variância dos efeitos aleatórios leva em conta a perda de graus de liberdade resultante da estimação dos parâmetros fixos. Sendo assim, a comparação entre modelos só pode ser feita quando a parte fixa é idêntica (Pinheiro e Bates, 2000). Neste estudo utilizou-se, para estimação dos parâmetros, o método de Mínimos Quadrados Generalizados Iterativo (Iterative Generalized Least Squares), proposto por Goldstein (1986), que produz resultados semelhantes ao da Máxima Verossimilhança e possui também uma variante que permite que a estimativa dos efeitos aleatórios levem em consideração a perda de graus de liberdade pela inclusão dos parâmetros fixos. Este procedimento de estimação é o que está disponível no software MlwiN, utilizado nas análises implementadas neste estudo.

Esses dois métodos, REML e ML, diferem pouco com relação à estimação dos coeficientes de regressão, mas diferem em relação à estimação dos componentes da variância.

O REML leva em consideração a perda dos graus de liberdade resultante da estimação dos parâmetros da regressão. No ML a estimativa dos componentes da variância ficam subestimados, pois não levam em conta a perda desses graus de liberdade. Essa diferença entre os métodos de estimação pode ser importante, especialmente quando o número de grupos é reduzido. Para um número grande grupos (acima de 30) a diferença entre o ML E REML é irrelevante.

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