

AIDS cases and survival among injecting drug users in Sao Paulo State, Brazil*

Samuel Kilsztajn**

Erika de Souza Lopes**

Luciana Zilles Lima**

Patrícia Avanzini Ferreira da Rocha**

Sirlene Caminhada***

Ingrid Napoleão Cotta***

Artur Olhovetchi Kalichman***

Keywords: injecting drug use; HIV/AIDS; AIDS survival time; Sao Paulo, Brazil.

Abstract

Aims To estimate AIDS survival time among injecting drug users (IDU) compared to other exposure categories per Aids-case definition during the 1992-1995 and 1998-2001 periods in Sao Paulo State, Brazil.

Design, setting and participants Sao Paulo State 73923 AIDS cases diagnosed during the 1992-1995 and 1998-2001 periods for people aged 13 and older.

Measurements AIDS cases and mortality rate per AIDS case; Cox proportional hazards analysis; and Kaplan-Meier survival time (limited to 80 months for both periods of diagnosis).

Findings Heterosexual/females were diagnosed earlier than other exposure categories, followed by homosexual/males, heterosexual/males and IDU. Adjusted for period of diagnosis and Aids-case definition, as well as years of education and age at diagnosis, the hazard ratio for IDU was 1.27 (95% CI: 1.22 to 1.31). For sexual contact included patients diagnosed by asymptomatic Brazilian $CD4 < 350mm^3$ and death definitions, the estimated first quarter survival time improved from 2 months in 1992-1995 to 62 months in 1998-2001; taking into account only symptomatic Aids-case definitions (CDC/modified and/or Paho/Caracas) the improvement was from 4 months to 19 months. For IDU, taking into account only symptomatic Aids-case definition, the improvement was from 4 months to 9 months.

Conclusions The survival improvement in Sao Paulo State was due to the introduction of antiretroviral therapy with universal access; and to earlier diagnosis associated with the introduction in 1998 of $CD4 < 350mm^3$ Aids-case definition with superior sensitivity. IDU, specifically, were diagnosed later and presented the highest hazard ratio and the slightest survival time improvement.

* Trabalho apresentado no XV Encontro Nacional de Estudos Populacionais, ABEP, realizado em Caxambu - MG - Brasil, de 18 a 22 de setembro de 2006.

** Laboratório de Economia Social - LES/SP (skilmal@gmail.com).

*** Programa Estadual DST/AIDS - SES - São Paulo

AIDS cases and survival among injecting drug users in Sao Paulo State, Brazil *

Samuel Kilsztajn **

Erika de Souza Lopes**

Luciana Zilles Lima**

Patrícia Avanzini Ferreira da Rocha**

Sirlene Caminhada ***

Ingrid Napoleão Cotta***

Artur Olhovetchi Kalichman***

Introduction

Injecting drug users (IDU) have played an important role in the spread of HIV in Europe, United States and Latin America.^{1 2 3} Through 2003, IDU share of cumulative AIDS cases represented 40.7% in Europe,⁴ 33.6% in USA,⁵ and 32.1% in Sao Paulo State.⁶ Public health projects were implemented to eliminate needle sharing and to encourage extensive change in the health behaviour of IDU.^{7 8} Taking into account needle sharing and sexual partners, IDU was considered the most important HIV transmission group in Brazil, after sex workers.⁹

The introduction of highly active antiretroviral therapy brought about an expressive change in AIDS survival time and death incidence.¹⁰ Brazil provides universal access to antiretroviral treatment and the country adherence rate is similar to the rates obtained in developed countries.¹¹

Median survival was 5.1 months for Brazilian AIDS patients diagnosed in 1982-89¹² and 58 months for those diagnosed in 1996, after the introduction of antiretroviral treatment.¹³ However, study with AIDS patients diagnosed in 1992-1998 at Sao Paulo STD/AIDS Training and Referral Center showed that the improvement in survival time was lower for IDU than for other exposure categories.¹⁴

In 1998 Brazil introduced the $CD4 < 350mm^3$ Aids-case definition with superior sensitivity than the Paho/Caracas (and CDC/modified) Aids-case definition utilized since 1992.¹⁵ Therefore, the improvements in survival time since diagnosis might reflect both

* Trabalho apresentado no XV Encontro Nacional de Estudos Populacionais, ABEP, realizado em Caxambu - MG - Brasil, de 18 a 22 de setembro de 2006.

** Laboratório de Economia Social - LES/SP (skilmail@gmail.com).

*** Programa Estadual DST/AIDS - SES - São Paulo

antiretroviral treatment and earlier diagnosis (longer survival since diagnosis as a result of earlier diagnosis).

The objective of this paper is to estimate AIDS survival time among IDU compared to other exposure categories per Aids-case definition in Sao Paulo State during the 1992-1995 and 1998-2001 periods. Sao Paulo is the most industrialized state in Brazil, exhibits high-quality statistical records, contains 21.8% of the population, and reported 44.7% of the cumulative Brazilian AIDS cases diagnosed through 2001.¹⁶

Methods

This study utilized AIDS cases diagnosed during the 1992-1995 and 1998-2001 periods for people aged 13 and older reported by August 8, 2004 (Sao Paulo State STD/AIDS Program Database).

Six exposure categories were utilized: heterosexual/female; homosexual/male (and bisexual); heterosexual/male; IDU (with or without sexual risk behaviour); other (blood products, perinatal and occupational exposures); and undetermined exposure category.

Brazilian Aids-case definitions during the 1992-2001 period included CDC/modified; Paho/Caracas; $CD4 < 350/mm^3$; and death definition (the first three Aids-case definitions were reported solo or combined). For this study, AIDS cases were classified in three Aids-case definitions: asymptomatic (asymptomatic $CD4 < 350/mm^3$); symptomatic (CDC/modified and/or Paho/Caracas, with or without $CD4 < 350/mm^3$); and death definition.

Survival time was limited to 80 months for both periods of diagnosis (from January 1, 1992 to August 8, 1998 for 1992-1995 period; and from January 1, 1998 to August 8, 2004 for 1998-2001 period). AIDS cases and mortality rate per AIDS case were calculated for the two periods of diagnosis, six exposure categories and three Aids-case definitions.

The univariate and multivariate Cox proportional hazards models utilized the two periods, two Aids-case definitions (death definition was excluded by condition); four exposure categories (other and undetermined exposure categories were excluded); three categories for years of education (eight or more; under eight; and not reported); and three categories for age at diagnosis (13-24; 25-39; and 40 years or older). Other exposure category was excluded from the Cox proportional hazards models due to the low number of blood products, perinatal and occupational exposure AIDS cases; and undetermined exposure category was excluded because patients with short survival were not easily to be categorized and, by condition, exhibited high mortality rate per AIDS case.

Kaplan-Meier survival time (and log rank test) was calculated per period of diagnosis, exposure category and Aids-case definition.

Results

Up to August 8, 2004, Sao Paulo State STD/AIDS Program reported 34943 and 38980 AIDS cases diagnosed during respectively the 1992-1995 and 1998-2001 period for people aged 13 and older (Table 1). IDU represented 41.6% in 1992-1995 and 24.0% in 1998-2001 of the reported AIDS cases in Sao Paulo State (excluded undetermined exposure category).

Heterosexual/females were diagnosed earlier than other exposure categories, followed by homosexual/males, heterosexual/males and IDU. During the 1998-2001 period, although 45.7% heterosexual/females were reported by asymptomatic CD4 Aids-case definition, only 24.1% IDU were diagnosed by that criterion (Table 2). Mortality rate per AIDS case in 1998-2001 was 9.7% for asymptomatic CD4 Aids-case definition and 37.6% for symptomatic Aids-case definition (Table 3); and higher for IDU (39.2%) than for other exposure categories.

In the univariate analysis, the hazard ratio for IDU compared to heterosexual/female was 2.03 (Table 4). The hazard ratio for IDU remained at the same level (2.03) when adjusted for years of education and age at diagnosis. Adjusted for period of diagnosis and Aids-case definition, as well as years of education and age at diagnosis, the hazard ratio for IDU was reduced to 1.27 (95% CI: 1.22 to 1.31).

Figure 1 shows the Kaplan-Meier survival time functions for 1992-1995 and 1998-2001 symptomatic Aids-case definition (CDC/modified and/or Paho/Caracas); 1998-2001 asymptomatic $CD4 < 350mm^3$ Aids-case definition; and 1998-2001/both symptomatic and asymptomatic Aids-case definitions. Figure 2 shows the Kaplan-Meier survival time functions per exposure category for 1992-1995 and 1998-2001 symptomatic Aids-case definition.

The median survival time for patients diagnosed in 1998-2001 was not calculable due to the expressive improvement in survival time. Even the first quarter was not calculable for asymptomatic Aids-case definition (Figure 1).

For the total AIDS cases excluded death definition (Figure 1 and Table 5), the estimated first quarter survival improved from 4 months in 1992-1995 to 37 months in 1998-2001. Taking into account only symptomatic Aids-case definition (e.g. excluded

asymptomatic and death definition) the improvement was from 4 months in 1992-1995 to 10 months in 1998-2001.

For the total AIDS cases excluded death definition and undetermined exposure category (Table 5), the estimated first quarter survival improved from 4 months in 1992-1995 to 50 months in 1998-2001. Taking into account only symptomatic Aids-case definition the improvement was from 4 months in 1992-1995 to 14 months in 1998-2001.

For sexual contact included death definition, the estimated first quarter survival time improved from 2 months in 1992-1995 to 62 months in 1998-2001; taking into account only symptomatic Aids-case definition the improvement was from 4 months to 19 months. For IDU included death definition, the estimated first quarter survival time improved from 2 months in 1992-1995 to 10 months in 1998-2001; taking into account only symptomatic Aids-case definition the improvement was from 4 months to 9 months.

Discussion

Heterosexual/females were diagnosed earlier among other exposure categories and presented lower mortality rate per AIDS case, followed by homosexual/males, heterosexual/males and IDU. Brazilian women are known to frequent health care clinics more regularly than men; and Sao Paulo State exhibits high rate of antenatal HIV testing to reduce perinatal infection.¹⁷

In the univariate analysis, the hazard ratio for IDU compared to heterosexual/female attained 2.03. Although IDU have the lowest socio-economic status among Brazilians living with AIDS,¹⁸ the hazard ratio for IDU remained at the same level when adjusted for years of education (that is a proxy of income in Sao Paulo State) and age at diagnosis. The hazard ratio for IDU was reduced only when adjusted for period of diagnosis and Aids-case definition, as well as years of education and age at diagnosis.

Period of diagnosis and Aids-case definition were very strong predictors of survival in the multivariate Cox proportional hazards model. Period of diagnosis reflects the introduction of antiretroviral therapy, since survival time was limited to 80 months for both periods. Aids-case definition reflects the difference in stage and time of the disease progression concerning patients diagnosed by CDC/modified and/or Paho/Caracas and patients diagnosed by the asymptomatic Brazilian Aids-case definition ($CD4 < 350mm^3$).

CD4 T lymphocytes count is one of the laboratory markers most closely correlated with the HIV disease progression.¹⁹ If a patient diagnosed by the asymptomatic CD4 Aids-

case definition with $CD4=349/mm^3$ survives three years longer than a patient diagnosed by CDC/modified and/or Paho/Caracas with $CD4=90/mm^3$, those three years cannot be considered additional survival since the natural history median survival time between $CD4=349$ and $CD=90$ is estimated at three years and the total survival time since primary infection would be the same for both patients.

The improvement in survival since diagnosis reflects both antiretroviral treatment and earlier diagnosis (longer survival since diagnosis as a result of earlier diagnosis). The estimated survival improvement from 1992-1995 for symptomatic Aids-case definition to 1998-2001 for both asymptomatic and symptomatic Aids-case definitions includes two components (Figure 1): the first, from 1992-1995/symptomatic to 1998-2001/symptomatic, reflects antiretroviral treatment; the second, from 1998-2001/symptomatic to 1998-2001/both Aids-case definitions, reflects both antiretroviral therapy and longer survival since diagnosis as a result of earlier diagnosis.

For the total AIDS cases, excluded undetermined exposure category, the estimated first quarter survival improvement from 4 to 14 months was due to the introduction of antiretroviral therapy; and the survival time improvement from 14 to 50 months was due both to antiretroviral therapy and to earlier diagnosis associated with the introduction of the $CD4<350mm^3$ Aids-case definition with superior sensitivity in 1998.

During the 1992-1995 period, before the introduction of antiretroviral treatment, the survival time for IDU was similar to other exposure categories. The introduction of antiretroviral treatment improved AIDS survival time for all exposure categories but the improvement was lower for IDU than for sexual contact categories. The first quarter survival, including death definition, improved from 2 to 10 months for IDU and from 2 to 62 months for sexual contact categories.

Those results are consistent with the study at Sao Paulo STD/AIDS Training and Referral Center which observed that IDU had less access to antiretroviral treatment and fewer visits to the Center, and concluded that health policies must develop special strategies to guarantee IDU access to earlier HIV testing, access and adherence to antiretroviral treatment.

Injecting drug users, which exhibited the highest mortality rate per AIDS case and the highest hazard ratio among the exposure categories, also exhibited the shortest survival time among AIDS patients. According to the results of this study, injecting drug users show worse progress even when diagnosed at the same stage/time as other exposure categories; and, additionally, were diagnosed later and had less opportunity to benefit from health services.

The results for Sao Paulo are also consistent with studies for other regions that revealed that survival time for patients with AIDS was extended with the use of antiretroviral treatment but the gains were lower for IDU compared to non-IDU patients.²⁰ There are many barriers to enrolment in drug abuse treatment²¹; antiretroviral treatment seems to be delayed for IDU and the health-care systems are not always adapted to their lifestyles²²; and IDU are known to miss medical appointments and discontinue their follow-up.²³ Those facts should be taking into account for public health policies among injecting drug users living with HIV/AIDS.

Acknowledgments

We are grateful to Manuela Santos Nunes do Carmo (LES/PUCSP), Maria Inês Baptistella Nemes (FMUSP), Rosa de Alencar Souza, Denise E. Lotufo, Ângela Tayra, Leda Fátima Jamal and Marcia Neves Moreira (CRT-DST/AIDS-SP) for their contribution; Sao Paulo State STD/AIDS Program for providing the AIDS Database; and PUCSP and CNPq for the support.

Table 4 - Cox proportional hazards models - Sao Paulo State

Covariates	Univariate	Multivariate
	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Period of diagnosis		
1998-2001	1.00	1.00
1992-1995	3.89 (3.78 to 4.00)	2.66 (2.58 to 2.74)
AIDS-case definition		
Asymptomatic CD4<350/mm ³	1.00	1.00
CDC/modified and/or Paho/Caracas	8.56 (8.04 to 9.10)	4.84 (4.53 to 5.16)
Exposure category		
Heterosexual/female	1.00	1.00
Homosexual/male	1.43 (1.37 to 1.48)	1.08 (1.04 to 1.13)
Heterosexual/male	1.34 (1.28 to 1.39)	1.11 (1.07 to 1.16)
Injecting drug use*	2.03 (1.96 to 2.10)	1.27 (1.22 to 1.31)
Years of education		
8 or more	1.00	1.00
Under 8	1.24 (1.20 to 1.28)	1.25 (1.21 to 1.29)
Not reported (15%)	1.36 (1.30 to 1.42)	1.17 (1.12 to 1.22)
Age at diagnosis (years)		
13 to 24	1.00	1.00
25 to 39	0.93 (0.89 to 0.96)	1.10 (1.06 to 1.14)
40 or older	0.96 (0.92 to 1.00)	1.31 (1.25 to 1.37)

Source: CRT-DST/AIDS-SP (2005). Data reported by August 8, 2004.

Situation at August 8, 1998 for 1992-1995 period; and August 8, 2004 for 1998-2001 period.

n = 54971 (30029 alive, 24942 death). Excludes 1064 unknown and 251 inconsistent situation; 11476 death definition; and 6161 other and undetermined exposure categories.

* Hazard ratio for drugs adjusted for years of education and age at diagnosis: 2.03 (1.96 to 2.10).

Table 5 - Estimated first quarter survival time per exposure category (Kaplan-Meier) - Sao Paulo State

Exposure category	1992-1995		1998-2001			
	Sy**	Total***	As*	Sy**	As*+Sy**	Total***
	Months					
Sexual contact	4	2	-	19	-	62
Heterosexual/female	5	2	-	21	-	-
Homosexual/male	5	2	-	23	-	64
Heterosexual/male	4	2	-	16	52	36
Injecting drug use	4	2	-	9	17	10
Subtotal (a)	4	2	-	14	50	34
Undetermined (b)	1	0	-	1	1	0
Total (a+b)	4	0	-	10	37	5
<i>n</i> (total)	27513	34648	11902	21217	33119	37960
Events (deaths)	19393	26035	1151	7921	9072	13913

Source: CRT-DST/AIDS-SP (2005). Data reported by August 8, 2004.

Situation at August 8, 1998 for 1992-1995 period; and August 8, 2004 for 1998-2001 period.

Excludes 1064 unknown and 251 inconsistent situation. Subtotal and total exposure categories includes 744 blood products, perinatal and occupational exposure. Log rank (Mantel-Cox) sig. = 0.000.

* Asymptomatic CD4<350/mm³ Aids-case definition.

** Symptomatic Aids-case definition (CDC/modified and/or Paho/Caracas).

*** Includes death definition.

Figure 1 - AIDS survival by period of diagnosis and Aids-case definition

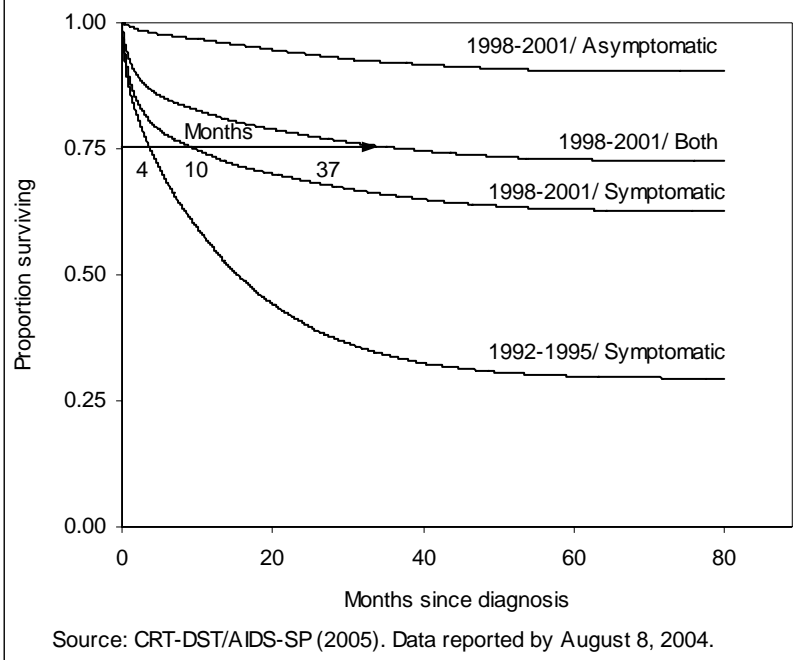
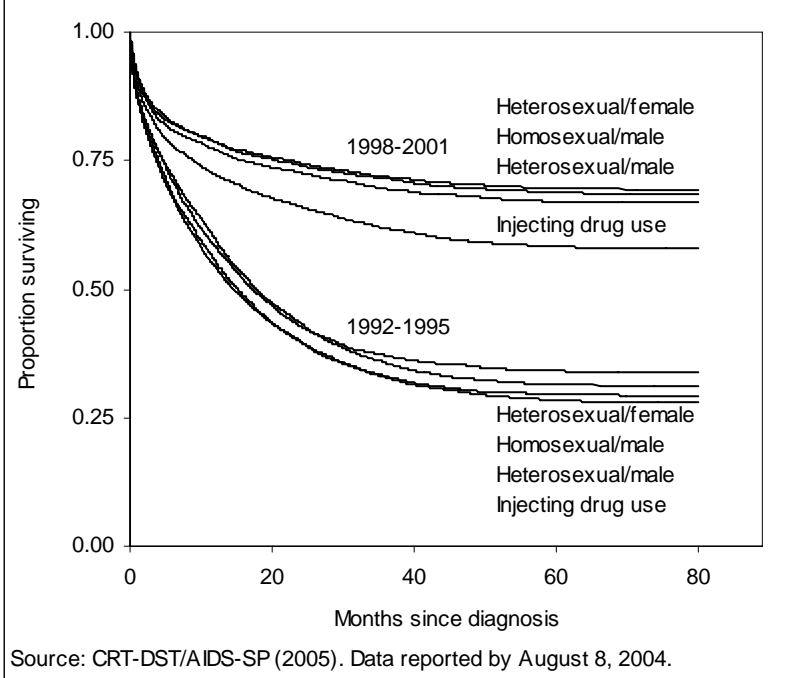


Figure 2 - Symptomatic AIDS survival by period and exposure category



Reference

- ¹ Hamers FF, Batter V, Downs AM, Alix J, Cazein F, Brunet JB. The HIV epidemic associated with injecting drug use in Europe: geographic and time trends. *AIDS* 1997;11(11):1365-74.
- ² Rockwell R, Deren S, Goldstein MF, Friedman SR, Des Jarlais DC. Trends in the AIDS epidemic among New York City's injecting drug users: localized or citywide? *J Urban Health* 2002;79(1):136-46.
- ³ Rodriguez CM, Marques LF, Touze G. HIV and injecting drug use in Latin America. *AIDS* 2002;16(Suppl 3):S34-41.
- ⁴ EuroHIV. *HIV/AIDS surveillance in Europe: end-year report 2003 (70)*. Saint-Maurice: Institut de Veille Sanitaire, 2004.
http://www.eurohiv.org/reports/report_70/pdf/report_eurohiv_70.pdf [May 22, 2005].
- ⁵ USA. Centers for Disease Control and Prevention (CDC). *AIDS cases by exposure category*. Atlanta: CDC, 2005. <http://www.cdc.gov/hiv/stats.htm#exposure> [May 22, 2005].
- ⁶ Brazil. Sao Paulo State STD/AIDS Program. *AIDS database (reported by August 8, 2004)*. Sao Paulo: CRT-DST/AIDS-SP, 2005.
- ⁷ Stimson GV. AIDS and injecting drug use in the United Kingdom, 1987-1993: the policy response and the prevention of the epidemic. *Soc Sci Med* 1995;41(5):699-716.
- ⁸ Houweling H, Wiessing LG, Hamers FF, Termorshuizen F, Gill ON, Sprenger MJ. An age-period-cohort analysis of 50,875 AIDS cases among injecting drug users in Europe. *Int J Epidemiol* 1999;28(6):1141-8.
- ⁹ Novaes HMD, Luna EJA, Goldbaum M, Kilsztajn S, Rossbach A, Carneiro JR. *The potential demand for an HIV/AIDS vaccine in Brazil*. New York: World Bank 2002 (Policy Research Working Paper 2940). <http://econ.worldbank.org/view.php?type=5&id=22734> [May 19, 2005].
- ¹⁰ Mocroft A, Brettle R, Kirk O, Blaxhult A, Parkin JM, Antunes F, Francioli P, D'Arminio Monforte A, Fox Z, Lundgren JD; EuroSIDA study group. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS* 2002;16(12):1663-71.
- ¹¹ Nemes MI, Carvalho HB, Souza MF. Antiretroviral therapy adherence in Brazil. *AIDS* 2004;18(Suppl 3):S15-20.

-
- ¹² Chequer P, Hearst N, Hudes ES, Castilho E, Rutherford G, Loures L, Rodrigues L. Determinants of survival in adult Brazilian AIDS patients, 1982-1989. The Brazilian State AIDS Program Co-Ordinators. *AID* 1992;6:483-7.
- ¹³ Marins JR, Jamal LF, Chen SY, Barros MB, Hudes ES, Barbosa AA, Chequer P, Teixeira PR, Hearst N. Dramatic improvement in survival among adult Brazilian AIDS patients. *AIDS* 2003;17:1675-82.
- ¹⁴ Kalichman AO, Gianna MC, Bueno SM, Basso CR, Ruiz EAC, Tayra A, Santos NJS, Holcman MM. Survival among AIDS patients by situations before and after HAART availability at STD/AIDS training and referral center, Sao Paulo, Brazil. *The XV International AIDS Conference*. Bangkok: IAS; 2004 (Abstract no. MoOrD1088 and oral presentation). http://www.iasociety.org/ejias/show.asp?abstract_id=2168854 [25may05].
- ¹⁵ Kilsztajn S. AIDS-case definition and trends in AIDS cases: S.Paulo, Brazil, 1980-98. *Rev Bras Epidemiol* 2001;4:96-104.
- ¹⁶ Brazil. Programa Nacional de DST/AIDS. *Casos por ano de diagnostico segundo UF: residência*. http://www.aids.gov.br/tabnet_aids.htm [May 18, 2005].
- ¹⁷ Souza Junior PR, Szwarcwald CL, Barbosa Junior A, Carvalho MF, Castilho EA. HIV infection during pregnancy: the Sentinel Surveillance Project, Brazil, 2002. *Rev. Saúde Pública* 2004;38:764-72.
- ¹⁸ Fonseca MG, Travassos C, Bastos FI, Silva Ndo V, Szwarcwald CL. Social distribution of AIDS in Brazil, according to labor market participation, occupation and socioeconomic status of cases from 1987 to 1998. *Cad Saude Publica* 2003;19(5):1351-63.
- ¹⁹ Pantaleo G, Graziosi C, Fauci AS. The immunopathogenesis of human immunodeficiency virus infection. *New Eng J Med* 1993;328:327-35.
- ²⁰ Poundstone KE, Chaisson RE, Moore RD. Differences in HIV disease progression by injecting drug use and by sex in the era of highly active antiretroviral therapy. *AIDS* 2001;15(9):1115-23.
- ²¹ Appel PW, Ellison AA, Jansky HK, Oldak R. Barriers to enrollment in drug abuse treatment and suggestions for reducing them: opinions of drug injecting street outreach clients and other system stakeholders. *Am J Drug Alcohol Abuse* 2004;30(1):129-53.
- ²² Carre N, Prins M, Meyer L, Brette RP, Robertson JR, McArdle H, Goldberg DJ, Zangerle R, Coutinho RA, van den Hoek A. Has the rate of progression to AIDS changed in recent years? *AIDS* 1997;11(13):1611-8.

²³ Arici C, Ripamonti D, Maggiolo F, Rizzi M, Finazzi MG, Pezzotti P, Suter F. Factors associated with the failure of HIV-positive persons to return for scheduled medical visits. *HIV Clin Trials* 2002;3(1):52-7.