The HIV-Brazil Cohort Study: Design, Methods and Participant Characteristics

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Abstract

Background: The HIV-Brazil Cohort Study was established to analyze the effectiveness of combination antiretroviral therapy (cART) and the impact of this treatment on morbidity, quality of life (QOL) and mortality. The study design, patients’ profiles and characteristics of cART initiation between 2003 and 2010 were described.

Methodology/Principal Findings: Since 2003, the HIV-Brazil Cohort has been following HIV-infected adults receiving cART at 26 public health care facilities, using routine clinical care data and self-reported QOL questionnaires. When not otherwise available, data are obtained from national information systems. The main outcomes of interest are diseases related or unrelated to HIV; suppression of viral replication; adverse events; virological, clinical and immunological failures; changes in the cART; and mortality. For the 5,061 patients who started cART between 2003 and 2010, the median follow-up time was 4.1 years (IQR 2.2–5.9 years) with an 83.4% retention rate. Patient profiles were characterized by a predominance of men (male/female ratio 1.7:1), with a mean age of 36.9 years (SD 9.9 years); 55.2% had been infected with HIV via heterosexual contact. The majority of patients (53.4%) initiated cART with a CD4+ T-cell count ≤200 cells/mm3. The medications most often used in the various treatment regimens were efavirenz (59.7%) and lopinavir/ritonavir (18.2%). The proportion of individuals achieving viral suppression within the first 12 months of cART use was 77.4% (95% CI 76.1–78.6). Nearly half (45.4%) of the patients presented HIV-related clinical manifestations after starting cART, and the AIDS mortality rate was 13.9 per 1,000 person-years.

Conclusions/Significance: Results from cART use in the daily practice of health services remain relatively unknown in low- and middle-income countries, and studies with the characteristics of the HIV-Brazil Cohort contribute to minimizing these shortcomings, given its scope and patient profile, which is similar to that of the AIDS epidemic in the country.

Introduction

In 1996, Brazil adopted a policy of universal access to combination antiretroviral therapy (cART), which was free of charge to human immunodeficiency virus (HIV)-infected individuals. Since then, immunological and virological treatment monitoring, as well as genotype-resistance testing for treatment failure management, have been incorporated into that policy. As of 2012, approximately 217,000 patients in Brazil were being treated with first-, second- or third-line antiretroviral therapy, including newer antiretroviral options for salvage therapy management, leading to an overall reduction in the morbidity and mortality associated with HIV infection [1–5].

In recent years, there has been a reduction in the magnitude of the impact that opportunistic diseases have had on morbidity and mortality in cART patients in Brazil, although there has been an increase in the incidence of complications unrelated to infection by HIV, such as cardiovascular events, impaired renal function, liver
disease and neoplasia [2,6–12]. These complications occur in the context of both long-term exposure to cART and the rapid demographic transition that is underway in Brazil, which has resulted in an increase in the number of HIV-infected people over the age of 50 [13].

The impact of the Brazilian policy has been the object of nationwide studies, mostly focused on mortality [9,10,14,15], the impact on the health system [1,5,16] and HIV resistance surveillance [17,18], as well as small studies with limited representativeness, evaluating the clinical aspects of HIV infection [0,11,19] and the use of cART [20–24]. However, to date, there have been no nationwide longitudinal studies providing a broader picture of the Brazilian HIV epidemic and the results of the national HIV policy.

Furthermore, recently, important changes have occurred in the use of cART therapy due to the proven efficacy of these drugs to reduce the risk of acquiring and transmitting HIV infection, as well as increased evidence that early initiation of cART has significant health benefits [25–30]. This new context has fuelled the debate regarding the feasibility of achieving effective control over the HIV/AIDS epidemic in the near future [31].

These circumstances increase the relevance of studies assessing the various dimensions of access to diagnosis and treatment of HIV infections; the efficacy and effectiveness of such treatment; and the impact of this treatment on morbidity, mortality, and QOL. Therefore, the HIV-Brazil Cohort Study was established to gather further knowledge on the context of the Brazilian epidemic and to generate scientific evidence to make informed decisions regarding the planning and implementation of public policies, taking into consideration the regional disparities, as well as the specificities of the Brazilian population and of the national health care system [32]. The aim of this paper is to present the design and scope of the HIV-Brazil Cohort Study and the profile and initial cART of enrolled patients.

**Methods**

**Cohort Sites**

There are 13 sites participating in the study, involving 26 public health facilities in 11 cities across four of the five regions of the country (Figure 1). The facilities were selected based on convenience, by region and city of location, the availability of information on the clinical follow-up and use of cART, and the existing infrastructure to conduct studies of this nature. The cities in which these facilities are located (Table 1) were chosen because they are representative of the diversity of the epidemiological profile of AIDS in Brazil [33] and account for 28% of all AIDS cases diagnosed in the country. Information regarding epidemiological surveillance derived by the Ministry of Health (Table 1) shows that, in 6 of the 11 cities, the incidence of AIDS cases is progressively increasing, having risen by an average of 30.7% from 2001 to 2010; in 7 of the cities, heterosexual transmission is the predominant route of HIV infection (in >60% of cases); and 6 of the cities are located in lower-income regions of the country (North or Northeast).

The number of patients under treatment at the participating sites ranged from 519 (at the Jaboatão de Guararapes Municipal Specialised Outreach Clinic) to 34,932 (within the São Paulo Municipal Network), with 7 of the 13 sites being responsible for treating more than half of the AIDS cases identified in their municipalities. Across the 13 sites, the mean ratio of outpatients to inpatients (at 6 sites) and home care services (at 4 sites). $18 years of age $18 years of age.
The questionnaire is applied at follow-up initiation and every 12 months after the initiation of cART. Information about the treatment facilities, as well as the appropriateness and quality of the participant’s enrollment and data collection procedures, are obtained periodicaly through an electronic form completed at the sites.

The main outcomes of interest are the occurrence of diseases related or unrelated to HIV; suppression of viral replication (viral load <400 copies/ml [2003 to 2006] and <50 copies/ml [after 2007]); antiretroviral treatment modifications (initial or subsequent regimen); treatment failure (virological, clinical or immunological failure); adverse events; and death. Clinical and epidemiological data were collected for the entire clinical follow-up period, including socio-demographic data; HIV transmission category; use of illicit drugs, alcohol and tobacco; individual or family history of metabolic disorders, hypertension or cardiovascular disease; AIDS-related and non-AIDS-related manifestations; initial and subsequent cART regimens used for prophylaxis and treatment; occurrence of adverse events related to the use of cART, prophylaxis for opportunistic diseases and vaccines; CD4, viral load and genotyping results, as well as safety laboratory tests for cART monitoring; and mortality.

Data–notably, demographic data, CD4+ T-cell counts, viral load and mortality data–were systematically checked across the national information systems.

Censoring Criteria

Individuals were censored in case of loss of clinical follow-up, relocation for follow-up in another clinical setting or death. To check the status of patients in the cohort, those categorized as lost to clinical follow-up were traced in the national information systems managed by the Brazilian National Ministry of Health: the National CD4+/CD8+ T Lymphocyte Count and Viral Load Network Laboratory Test Control System (for CD4+ T-cell counts and viral loads); the National System for the Logistic Control of Medications (for information regarding the dispensing of cART); and the National Mortality Information System (for mortality data). The screening was conducted annually, through electronic matching, checking for perfect combinations of key fields (patient’s name, mother’s name and date of birth). Patients not located through this procedure were then investigated using an alphabetically sorted list.

Loss of follow-up was defined as an absence of patient contact with the health care center for more than 12 months (i.e., no consultations, no CD4 or viral load exams performed, no records related to ARV refills in the clinical records) and the non-identification of the patient in the national information systems, as described above, up to July 2011. Patients were classified as having
Table 1. Characteristics of the AIDS epidemic, sites involved and patient-selection process in the HIV-Brazil Cohort Study.

| REGION /City/Site | Incidence Rate^a (%) | Increase^b | Heterosexual contact | Other sexual contact | IDU | N per center^d | % of Municipality^e | Diagnostic | Home care | Hospitalization | In-house laboratory | Pharmacy | P/Ph. ratio | Interval between follow-up visits (months) | Absentee outreach | Phase | Criteria |
|-------------------|----------------------|-----------|----------------------|---------------------|-----|----------------|---------------------|------------|-----------|----------------|-------------------|----------|-----------|------------------------------------------|------------------|-------|----------|
| NORTH             |                      |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
| Manaus            | 42.1                 | 68.1      | 67.8                 | 25                  | 2.7 | 5249          | 91–100             | Yes        | No        | Yes            | Yes               | 404      | 3         | No                                       | 1st Universal^g  |       |           |
| Tropical Medicine Foundation | | | | | | | | | | | | | | | | | |
| Belém              | 35.0                 | 24.6      | 65.1                 | 26.8                | 4.9 | 3950          | 51–90              | Yes        | Yes       | No             | No                 | 263      | 3         | No                                       | 1st Universal^g  |       |           |
| UREDIPE           | 15.1                 | 11.0      | 52.5                 | 28.8                | –   | 725           | 91–100             | Yes        | Yes       | No             | Yes               | 145      | 3         | Yes                                      | 1st Universal^g  |       |           |
| Santarém          | 25.1                 | 3.9       | 70                   | 25.5                | 1.6 | 1300          | ≥20                 | No         | No        | Yes            | Yes               | 217      | 4         | No                                       | 2nd Universal^g  |       |           |
| Municipal STF     | 23.5                 | 14.6      | 59                   | 29.8                | 6.9 | 1600          | ≥20                 | Yes        | No        | Yes            | Yes               | 200      | 4         | No                                       | 1st Sample        |       |           |
| Recife            | 28.1                 | 0.1       | 67.7                 | 28.3                | 1.6 | 10597         | 51–90              | Yes        | No        | No             | Yes               | 706      | 6         | No                                       | 1st Sample        |       |           |
| SFPE              |                      |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
| Jaboatão de Guararapes | 25.1             | 3.9       | 70                   | 25.5                | 1.6 | 519           | 51–90              | Yes        | No        | No             | No                 | 260      | 3         | Yes                                      | 2nd Universal^g  |       |           |
| Municipal STF     | 23.5                 | 14.6      | 59                   | 29.8                | 6.9 | 1600          | ≥20                 | Yes        | No        | Yes            | Yes               | 200      | 4         | No                                       | 1st Sample        |       |           |
| Salvador          | 23.5                 | 14.6      | 59                   | 29.8                | 6.9 | 1600          | ≥20                 | Yes        | No        | Yes            | Yes               | 200      | 4         | No                                       | 1st Sample        |       |           |
| HUPES             | 10597                | 51–90     | Yes                   | No                   | Yes | Yes            | Yes                   | Yes        | No        | Yes            | Yes               | 706      | 6         | Yes                                      | 1st Sample        |       |           |
| SOUTHEAST         |                      |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
| Rio de Janeiro    | 36.1                 | 34924.9   | 60.5                 | 35.2                | 2.5 | 3000          | ≥20                 | No         | No        | Yes            | Yes               | 250      | 3         | Yes                                      | 1st Sample        |       |           |
| IPEC              |                      |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
| Belo Horizonte    | 22.5                 | –11.1     | 53.4                 | 39.9                | 4.5 | 3680          | 51–90              | No         | No        | Yes            | Yes               | 245      | 3         | No                                       | 1st Sample        |       |           |
| UFMG              |                      |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
| São Paulo         | 25.3                 | –25.1     | 58                   | 32.7                | 6.1 | 5000          | ≥20                 | Yes        | Yes       | Yes            | Yes               | 77       | 3         | Yes                                      | 1st Universal^g  |       |           |
| CRT-SESSP         | 34932                | 51–90     | Yes                   | No                   | No | No             | Yes                   | Yes        | No        | Yes            | No                 | 354      | 4         | No                                       | 1st Sample        |       |           |
| Municipal Network^h |                    |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
| São José Rio Preto | 31.9                | –31.1     | 70.7                 | 22.6                | 5.4 | 1228          | ≥20                 | Yes        | Yes       | No             | No                 | 307      | 4         | Yes                                      | 1st Universal^g  |       |           |
| Municipal STF     |                      |           |                      |                     |     |                |                     |            |           |                |                   |          |           |                                          |                  |       |           |
Table 1. Cont.

| REGION /City/Site | Incidence Rate (%) | Increaseb | Heterosexual contact | Other sexual contact | IDU | N per center | % of Municipality | Patients | Services offered | Interval between follow-up visits (months) | Absentee outreach | Phase | Criteria |
|-------------------|---------------------|------------|----------------------|----------------------|-----|--------------|-------------------|----------|------------------|------------------------------------------|-------------------|--------|----------|
| SOUTH             |                     |            |                      |                      |     |              |                   |          |                  |                                          |                   |        |          |
| Porto Alegre      | 100.4               | 6.7        | 68.6                 | 16                   | 11.7| 2281         | ≈20               | Yes      | No               | 456                                      | 6                 | 1st    | Universal |

Data Source: Features of AIDS by site: Data of the municipalities where the sites belonging to the study, with information from the National Epidemiological Surveillance System are; Characteristics of the centers: self-administered questionnaire by the manager of the service within the HIV- Brazil Cohort Study.

Abbreviations: Het., heterosexual; IDU, injection drug use; P./Ph., patient/physician; UREDIPE, Unidade de Referência Especializada em Doenc¸as Infecciosas e Parasitárias Especiais (Referral Center Specializing in Specific Infectious and Parasitic Diseases); STF, specialized treatment facility; UFPE, Universidade Federal de Pernambuco (Federal University of Pernambuco); HUPES, Hospital Universitário Professor Edgard Santos (Professor Edgard Santos University Hospital); CEDAP, Centro Estadual Especializado em Diagnostico, Assistência e Pesquisa (State Center Specializing in Diagnosis, Treatment and Research); IPEC, Instituto Evandro Chagas (Evandro Chagas Institute); UFMG, Universidade Federal de Minas Gerais (Federal University of Minas Gerais); CRT-SEESP, Centro de Referência e Treinamento em DST e AIDS, Secretaria de Estado da Saúde de São Paulo (São Paulo State Department of Health STD/AIDS Referral and Training Center).

1Per 100,000 population (2006-2010).
22001-2005 vs. 2006-2010.
3In relation to the total number of cases reported between 2006 and 2010.
4Proportion of the AIDS cases identified in the municipalities served by the facility.
5Patients who meet the inclusion criteria between the total number of patients in the clinic follow-up sites.
6Fourteen health care facilities affiliated with the City of São Paulo municipality.

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### Table 2. Characteristics of the patients and AIDS cases reported to the Brazilian Ministry of Health.

| Variable                                      | 2003–2010 | HIV-Brazil Cohort | Reported Cases of AIDS* |
|-----------------------------------------------|-----------|-------------------|-------------------------|
|                                               | (N)       | (%)               | (N)                    | (%)                     |
| Brazil (nationwide)                           | 5061      | 100.0             | 156391                 | 100.0                   |
| Region                                        |           |                   |                        |                         |
| North                                         | 1366      | 27.0              | 13159                  | 8.4                     |
| Northeast                                     | 576       | 11.4              | 29448                  | 18.8                    |
| Southeast                                     | 2300      | 45.4              | 74277                  | 47.9                    |
| South                                         | 819       | 16.2              | 39505                  | 25.3                    |
| No data available                             | –         | –                 | 2                      | 0.0                     |
| Gender                                        |           |                   |                        |                         |
| Male                                          | 3208      | 63.4              | 95952                  | 61.4                    |
| Female                                        | 1853      | 36.6              | 60425                  | 38.6                    |
| No data available                             | –         | –                 | 14                     | 0.0                     |
| Male/female ratio                             | 1.7       | –                 | 1.7                    | 1.6                     |
| Age group (years)                             |           |                   |                        |                         |
| 18 to 25                                      | 543       | 10.7              | 17708                  | 11.3                    |
| 26 to 30                                      | 925       | 18.3              | 25289                  | 16.2                    |
| 31 to 35                                      | 1030      | 20.4              | 28067                  | 17.9                    |
| 36 to 40                                      | 915       | 18.1              | 26240                  | 16.8                    |
| 41 to 45                                      | 711       | 14.0              | 22231                  | 14.2                    |
| 46 to 50                                      | 460       | 9.1               | 15588                  | 10.0                    |
| 51 to 90                                      | 475       | 9.4               | 21241                  | 13.6                    |
| No data available                             | 2         | 0.0               | 27                     | 0.0                     |
| Age (in years), mean (SD)                     | 36.9 (9.9) | 37.9 (10.8)       |                         |                         |
| Exposure Category                             |           |                   |                        |                         |
| Heterosexual transmission                     | 2792      | 55.2              | 66165                  | 60.0                    |
| Homosexual transmission                       | 859       | 17.0              | 14408                  | 13.1                    |
| Bisexual transmission                         | 334       | 6.6               | 6074                   | 5.5                     |
| Unspecified sexual transmissionb              | 203       | 4.0               | –                      | –                       |
| Injection drug use                            | 183       | 3.6               | 5838                   | 5.3                     |
| Transfusion of blood or blood products        | 87        | 1.7               | 117                    | 0.1                     |
| Vertical transmission                         | 18        | 0.4               | 348                    | 0.3                     |
| No data available                             | 585       | 11.6              | 17323                  | 15.7                    |
| Pre-cART use of cocaineb                      |           |                   |                        |                         |
| No                                            | 4318      | 85.3              | –                      | –                       |
| Yes                                           | 743       | 14.7              | –                      | –                       |
| Lowest CD4+ T-cell count (cells/mm³)b         |           |                   |                        |                         |
| >350                                          | 241       | 4.8               | –                      | –                       |
| 200 ≤ 350                                     | 1587      | 31.4              | –                      | –                       |
| ≤200                                          | 2704      | 53.4              | –                      | –                       |
| No data available                             | 529       | 10.5              | –                      | –                       |
| Nadir CD4+ T-cell count (cells/mm³), mean (SD)b | 177.5 (121.7) | –       | –                      | –                       |
| Clinical manifestation at the initiation of cARTb |           |                   |                        |                         |
| None                                          | 2062      | 40.7              | –                      | –                       |
| Signs and symptoms                            | 1620      | 32.0              | –                      | –                       |
| Associated diseases                           | 1379      | 27.2              | –                      | –                       |
| Initial regimen, by drug classb               |           |                   |                        |                         |
| 2NRTIs+1NNRTI                                 | 3247      | 64.2              | –                      | –                       |
| 2NRTIs+PI/r                                   | 1220      | 24.1              | –                      | –                       |
been relocated for follow-up in another clinical setting when relocations were noted in the clinical record or when the patients were identified in the information systems as performing their CD4+ T-cell count, viral load determination or ART dispensation elsewhere after the date of the last entry in the clinical record. AIDS-related deaths were defined as those in which the official record listed AIDS as being the underlying cause of death.
### Table 3. Descriptive analysis of loss of follow-up\(^a\) in the HIV-Brazil Cohort Study.

| Characteristics                  | HIV-Brazil Cohort | Loss of follow-up | 95% CI of the proportion | Rate of follow up loss (1000 PY) |
|----------------------------------|-------------------|-------------------|---------------------------|---------------------------------|
|                                  | N                 | N (%)             | Minimum                   | Maximum                         |
| **Gender**                       |                   |                   |                           |                                 |
| Male                             | 3208              | 147               | 4.6                       | 3.9                             |
| Female                           | 1853              | 59                | 3.2                       | 2.5                             |
| **Sexual Orientation\(^b\)**     |                   |                   |                           |                                 |
| Homosexual                       | 906               | 20                | 2.2                       | 1.4                             |
| Bisexual                         | 374               | 21                | 5.6                       | 3.7                             |
| Heterosexual                     | 2983              | 113               | 3.8                       | 3.2                             |
| **Age group (years)\(^b\)**      |                   |                   |                           |                                 |
| 18 to 25                         | 543               | 30                | 5.5                       | 3.9                             |
| 26 to 30                         | 925               | 56                | 6.1                       | 4.7                             |
| 31 to 35                         | 1030              | 43                | 4.2                       | 3.1                             |
| 36 to 40                         | 915               | 27                | 3.0                       | 2.0                             |
| 41 to 45                         | 711               | 30                | 4.2                       | 3.0                             |
| 46 to 50                         | 460               | 6                 | 1.3                       | 0.6                             |
| 51 to 90                         | 475               | 12                | 2.5                       | 1.5                             |
| **Region**                       |                   |                   |                           |                                 |
| North                            | 1366              | 105               | 7.7                       | 6.4                             |
| Northeast                        | 576               | 25                | 4.3                       | 3.0                             |
| Southeast                        | 2300              | 63                | 2.7                       | 2.1                             |
| South                            | 819               | 13                | 1.6                       | 1.3                             |
| **Pre-cART clinical manifestation** |                 |                   |                           |                                 |
| None                             | 2062              | 84                | 4.1                       | 3.3                             |
| Signs and symptoms               | 1620              | 70                | 4.3                       | 3.4                             |
| Associated disease               | 1379              | 52                | 3.8                       | 2.9                             |
| **Post-cART clinical manifestation** |                |                   |                           |                                 |
| None                             | 2762              | 131               | 4.7                       | 4.0                             |
| Signs and symptoms               | 1311              | 38                | 2.9                       | 2.1                             |
| Associated disease               | 988               | 37                | 3.7                       | 2.7                             |
| **Pre-cART use of cocaine**      |                   |                   |                           |                                 |
| Yes                              | 4318              | 170               | 3.9                       | 3.4                             |
| No                               | 743               | 36                | 4.8                       | 3.5                             |
| **Lowest CD4+ T-cell count (mm\(^+\))\(^b\)** | | | | |
| >350                             | 241               | 10                | 4.1                       | 2.2                             |
| 200 \(\leq 350\)                | 1587              | 69                | 4.3                       | 3.4                             |
| \(\leq 200\)                    | 2704              | 97                | 3.6                       | 2.9                             |

Abbreviation: PY, person-years.
\(^a\)Maximum follow-up time of 8.8 years.
\(^b\)Not included are 798 individuals with unknown transmission categories, 2 with unknown ages and 529 without a CD4–T exam prior to cART initiation.

### Availability of Data

Proposals from external researchers to use our data are encouraged and welcomed, and requests will be analyzed by the Cohort Steering Committee that is composed of the Cohort Principal Investigators. The use of data pertaining to the individual sites is restricted to the sites themselves. In all circumstances, the confidentiality of each participant’s related data must be preserved.

### Ethics Statement

This protocol was approved by the Institutional Review Boards (IRB) of the participating sites (Comité de Ética em Pesquisa da Secretaria Municipal de Saúde de São Paulo, Comitê de Ética do Centro de Referência e Treinamento DST/AIDS, Comitê de Ética em Pesquisa do Instituto de Pesquisa Clínica Evandro Chagas da Fundação Oswaldo Cruz, Comitê de Ética na Pesquisa em Saúde da Escola de Saúde Pública da Secretaria de Estado da Saúde do Rio Grande do Sul, Comitê de Ética em Pesquisa da Maternidade Climério de Oliveira da Universidade Federal da Bahia and Comissão de Ética para Análise de Projetos de Pesquisa do...
respectively. In the 2009–2010 period, there was an increase in the vir/ritonavir (AZT with a nadir CD4+ of 200 cells/mm3, and the CD4+ T-cell count at cART initiation was 206 (41% of the 5,061 cohort patients) were lost to follow-up, 345 (6.8%) were censored due to transfer from the health care centers where they were being followed in the cohort, and 297 (5.7%) had died. Therefore, the retention rate was 83.4%, with 20,593.9 person-years (PY) of observation.

The largest proportion of patient loss (104, 50.4%) was observed in the first year of cohort follow-up, with reductions over time. The loss to follow-up rate ranged from 19.8 per 1,000 PY in the first 12 months to 1.1 per 1,000 PY after the sixth year of observation, with an overall loss rate of 10.1 per 1,000 PY. The greatest risk of loss (Table 3) was observed for the health care centers located in the less developed regions (21.3 per 1,000 PY [North] and 10.9 per 1,000 PY [Northeast]), among young patients (18 to 25 years [14.0 per 1,000 PY] and 26 to 30 years [15.6 per 1,000 PY]), bisexuals (13.8 per 1,000 PY), those with no clinical manifestations after cART initiation (12.6 per 1,000 PY) and those with no history of cocaine use before cART initiation (12.1 per 1,000 PY).

### Characteristic of the Initial Treatment

Information on the pre-cART immunological status is available for 89.6% of the patients, who presented with a mean and median nadir CD4+ T-cell count of 177.5 cells/mm3 (SD 121.7 cells/mm3) and 169.0 cells/mm3 (IQR 75.0–250.0 cells/mm3), respectively. These values remained stable over the years evaluated (p<0.001; p<0.99). The majority of patients (53.4%) initiated cART with a nadir CD4+ T-cell count ≤200 cells/mm3, and the CD4+ T-cell count at cART initiation was ≤350 cells/mm3 in 84.0% of the sample.

The initial treatment regimens prescribed were in line with the current recommendations of the Brazilian National Ministry of Health [36], and 26 cases (of the 5,061 cases) were identified in which inappropriate regimens were prescribed. Among the initial treatments, regimens involving non-nucleoside analogue reverse transcriptase inhibitors, boosted protease inhibitors and protease inhibitors without booster were prescribed for 64.2%, 24.1% and 10.1% of the patients, respectively. In 48.1% of the 5,061 cases, the first-line treatment regimen prescribed was zidovudine+lamivudine+efavirenz (AZT+3TC+EFZ), whereas AZT+3TC+lopinavir/ritonavir (AZT+3TC+LPV/r) and AZT+3TC+atazanavir/ritonavir (AZT+3TC+ATV/r) were used in 14.3% and 4.6%, respectively. In the 2009–2010 period, there was an increase in the number of cases in which tenofovir was prescribed, (11.6% in 2010).

The median number of regimens used per patient was 1 (IQR 1–2; mean 1.3), and the mean duration of the first-line regimens was 30.4 months (95% CI 29.7–31.2). The number of individuals achieving viral suppression (VL <400 copies/ml [2003 to 2006] and <50 copies/ml [after 2007]) within the first 12 months after cART initiation was 77.4% (95% CI 76.1–78.6). During the 6.5 years of observation, 80.2% (95% CI 87.2–89.1) of the patients achieved viral suppression at some point after cART initiation.

The lowest rates of viral suppression in the first year of cART were observed in individuals aged between 18 and 29 years (66.2%), in transmission category infection drug use (73.7%), with cocaine use before treatment (74.1%), in service areas with lower economic development (North and Northeast regions, 61.3% 73.3%) and showing no adverse ARV events (85.2%).

Nearly half (45.4%) of the patients presented with HIV-related clinical manifestations after starting cART, and the most frequent were oral candidiasis and tuberculosis. The AIDS mortality rate for the period evaluated was 13.9 per 1,000 PY.

### Discussion

The HIV-Brazil Cohort Study, with a long follow-up period and a significant number of observations, is an important asset to increase the availability of data on the countrywide outcomes of the National AIDS Program related to cART in public health care services. A special feature of our cohort is that HIV-infected individuals in Brazil have been exposed to a broad array of antiretroviral drugs–21 antiretroviral drugs of all classes (including 10 generic drugs) used in first-, second- and third-line treatment regimens [4]–for a longer period than patients from other resource-limited settings. Consequently, the results obtained from this cohort might be predictive of the effects that the longer-term use of cART will have in other middle- or low-income countries, where the regimens currently in use in Brazil have yet to be widely applied.

The characteristics of the HIV-Brazil Cohort Study facilitates analyses of the short-, medium- and long-term impact of using antiretroviral drugs in the context of the routine care of patients at publicly funded health care centers, providing complementary evidence to that obtained through clinical efficacy trials. The evidence obtained from the analyses performed in this cohort will enable field evaluations and further improvement of the national public health policies [37].

The socio-demographic profile of the HIV-Brazil Cohort Study is similar to that represented by the cases of AIDS in adults reported to the Brazilian National Ministry of Health between 2003 and 2010 (Table 2). The two groups are also comparable in terms of the HIV transmission category and region of origin, although, proportionally, the HIV-Brazil Cohort Study included fewer individuals treated in the southern region of the country, resulting in a smaller representation of injection drug users.

The quality assessment of the data collected showed a satisfactory degree of completeness of the information for essential variables (Table 2). A lack of CD4+ T-cell counts prior to the initiation of cART was observed in 1 of 10 patients and was probably related to clinical decisions not to request this testing if the patient had a concomitant opportunistic infection at the time of cART initiation or during hospitalization. The epidemiological characteristics of individuals without baseline information on CD4+ T-cell count, such as gender, age and transmission category, did not differ (p<0.05) from the other patients included in the cohort. Although the analysis of outcomes directly related to the
CD4+ T-cell count showed few significant variations when excluding individuals without baseline information on CD4+ T-cell count, the mortality rate rose from 13.9 to 14.2 per 1,000 PY.

An important aspect to be highlighted is the relatively low rate of loss of follow-up, similar to what is observed in high-income countries, middle- and low-income countries. Therefore, the lowest rates of loss of follow up [38,39]. The greater accuracy of this information was obtained through the linkage with national health information systems databases. These databases have high rates of coverage, gathering data from all HIV-infected patients linked to care and receiving ART nationwide, as well as the overall mortality data in the country [14]. Consequently, patients classified as lost to follow-up in the cohort have a high possibility of still being alive even without appearing for the clinical follow-up or are using cART from some other health service in the country.

The analysis presented in this article aims to outline the scope and potential use of the information derived from the HIV-Brazil Cohort Study. First-line non-nucleoside reverse-transcriptase-based regimens were the most prescribed first-line cART in Brazil and resulted in high levels of viral suppression in the first year of treatment, comparable to single-site observational studies [20,23,24,40]. This finding has reinforced the assumption that the use of cART in Brazilian health services has achieved results similar to other low- and middle-income countries [41–42].

The majority of patients presented with severe immunodeficiency (CD4+ T-cell counts ≤200 cells/mm³) or AIDS-related diseases at cART initiation. This finding was higher than the results of previously reported studies that reviewed the clinical and epidemiological profile of AIDS-related deaths in Brazil in the first two years of cART [14]. Consequently, a higher proportion of late-onset cART in HIV-Brazil Cohort Study might have been caused by the loss of clinical follow-up before the initial prescription of cART.

It is also noteworthy that the mean CD4+ T-cell count at the beginning of cART did not show a trend of increase over time, indicating the urgent need for increased access to earlier HIV diagnosis and linkage to care countrywide, considering the fact that Brazil has a concentrated epidemic in social sectors with a high degree of stigma and a pattern of service use that is more restricted than in the general population [32,33].

Another important aspect is the fact that the worst results were observed in regions with the lowest economic development levels in the country, indicating that the reduced ability of these regions to obtain optimal results from the therapies available for AIDS may lead to an increase in the health inequalities existing in the country through increase HIV incidence and HIV-associated mortality.

The study design, characteristics of patients included and the initiation of cART presented in this paper show the scope of investigation conducted by the HIV-Brazil Cohort Study, which is the main initiative to analyze the effects of cART use in public health services in the country. Thus, the results shown herein and those yet to be produced can contribute to advancing the knowledge generated from clinical trials, particularly considering the context of medium- and low-income countries, which in recent years have greatly expanded their programs to access cART. This is important in the formulation of better health policies for the needs of people living with HIV in resource-constrained situations.

Author Contributions

Conceived and designed the experiments: AG MME RAS AOK VV. Performed the experiments: RAS AOK VV NTB CB BG. Analyzed the data: AG MME AJFC EAC. Wrote the paper: AG MME AJFC RAS AOK VV NTB CB BG.

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