The first ten years: achievements and challenges of the Brazilian program of universal access to HIV/AIDS comprehensive management and care, 1996-2006

Os primeiros dez anos: conquistas e desafios do programa brasileiro de acesso ao manejo e cuidado integral do HIV/AIDS no Brasil, 1996-2006

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Abstract

A review was carried out of papers published between 1996 and 2006, documenting the introduction of highly active anti-retroviral therapy (HAART) in Brazil. Papers indexed in the MEDLINE and SciELO databases were retrieved using different combinations of keywords related to the management and care of AIDS in the post-HAART era: opportunistic diseases and co-infections, adherence to therapy, survival in the pre- and post-HAART eras, adverse events and side-effects, emergence and possible transmission of resistant viral strains, metabolic and cardiovascular disorders, and issues related to access to care and equity. The review documents the dramatic changes in HIV/AIDS disease progression in the post-HAART era, including an increase in survival and quality of life and a pronounced decrease in the episodes of opportunistic diseases. Notwithstanding such major achievements, new challenges have emerged, including slow evolving co-infections (such as hepatitis C, metabolic and cardiovascular disorders), the emergence of viral resistance, with consequences at the individual level (virological failure) and the community level (primary/secondary resistance at the population level), and impacts on the cost of new therapeutic regimens.

Acquired Immunodeficiency Syndrome; Highly Active Antiretroviral Therapy; Survivorship

Introduction

The year 2006 marked two milestones in the fight against HIV/AIDS in Brazil – the 10-year anniversary of both the availability of highly active antiretroviral therapy (HAART) and the passage of a Brazilian federal law establishing universal access to antiretroviral (ARV) therapy.

In November 1996, the Brazilian government issued *Law n°. 9,313*, which guarantees access to ARV therapy to every Brazilian citizen living with AIDS, at no cost at the point of delivery [1]. This legislation constituted the successful culmination of a long series of treatment access initiatives, spearheaded by people living with AIDS and other community leaders, in cooperation with a committed group of civil servants [2].

The legislation was executed via a comprehensive initiative, which provides antiretroviral medicines, performs CD4 cell counts and viral load testing, and, in the case of clinical/virologic failure, conducts viral genotyping [3]. This initiative constitutes the world's most comprehensive access to ARV treatment program in a middle-income country. As of June 2005, approximately 161,000 HIV-infected individuals in Brazil were currently taking HAART [4].

Past studies have assessed the Brazilian initiative, and documented the overall success of the so-called "Brazilian model", which includes the domestic production of generic medicines, integration of voluntary testing and counseling

with treatment and care, and delivery of medicines through a network of public facilities [2].

The purpose of the current review, however, is slightly different – to assess the minute but essential details of daily practices encountered in implementing universal access to ARV therapy. Through a review of the available clinical and public health evidence on the management and care of HIV/AIDS in Brazil, answers are sought the following questions: (1) Did post-HAART survival increase in different contexts in a country plagued by deep social inequality? (2) How is Brazil addressing the challenges posed by adherence to long-term complex drug regimens? (3) Is viral resistance a major challenge? (4) Does HAART decrease morbidity associated with AIDS? and (5) Do adverse reactions and other morbid conditions associated with HAART (e.g., lipodystrophy) represent a relevant problem and barrier toward better clinical outcomes?

As the popular adage goes "the devil is in the details". Ten years after the adoption of its seminal law, it is time for Brazilian health professionals and policy makers to look back and face whether the devils challenging its program of universal access have been tamed, or not, in order to fix the previous errors and move forward.

Methods

Papers published in peer-reviewed journals were retrieved from PubMed, using the combinations of keywords as follows: "adherence+Brazil", "survival+Brazil", "opportunistic diseases+Brazil"/"opportunistic infections+Brazil", "coinfections+Brazil" (with subsequent exploration of HPV and HCV co-infections), "cancer+Brazil"/"neoplasia+Brazil", "cardiovascular disorders+Brazil", "lipodystrophy+Brazil", "neurological diseases+Brazil", and "HAART+adverse reactions+Brazil", always using the subset "AIDS" as a filter. The search was primarily restricted to articles published during the period 1996-2006. A search was also done of the Latin American database SciELO, using the correspondent Portuguese/Spanish keywords (as well as the same English words/expressions listed above). Searches were updated as of September 2006.

In addition, official documents, such as government reports and guidelines were retrieved from the website of the Brazilian National STD/AIDS Program, Brazilian Ministry of Health (http://www.aids.gov.br).

A recent article by the present research group [5] reviewed published data on viral resistance from Brazil. To update this review, a search of MEDLINE was done, using the combination of keywords as follows: "resistance+Brazil" and "mutation+Brazil", again within the subset "AIDS", but restricted to 2006 (i.e., articles not included in the previous review).

Results

Post-HAART survival in different regional contexts

The main study findings regarding survival in the pre- and post-HAART eras in Brazil are presented in Table 1. Figure 1 shows the geographical location of the cities where the studies were carried out. The first study to document the survival of adult patients living with AIDS in Brazil was published in 1992 and summarizes data from a national sample of 2,135 patients [6]. The study found a low median survival time of 5.1 months after AIDS diagnosis, much shorter than the corresponding median survival for patients under follow-up in developed countries in that period (1982-1989). No significant differences were observed between men and women, but younger patients were found to live longer than their older counterparts [6]. Similarly unfavorable results were found by Santos et al. [7], analyzing survival data from AIDS cases followed up in a referral center in Porto Alegre, Rio Grande do Sul State, between 1986-1991. The authors documented uneven access to ARVs in the period and a low median survival time of 5 months.

Survival data from 1989-1992 were analyzed by a retrospective cohort study, carried out in a referral center from Belo Horizonte, Minas Gerais State. Using the criteria of the Centers for Disease Control and Prevention (CDC 1992) [8], patients living with HIV/AIDS were classified as "infected with HIV without AIDS" and "AIDS cases". The former group had a median survival time of 17.8 months whereas AIDS cases had a median survival of 14.3 months. The lack of AZT use, advanced disease when patients entered treatment, and an uneven follow up (defined as outpatient visits greater than 6 months apart) were found to be independent predictors of shorter survival. To the best of our knowledge, this was the first paper published in Brazil to assess the use of ARVs (then restricted to monotherapy with AZT), timely engagement into treatment, and regular follow up, as key predictors of a better clinical prognosis [9].

Another study [10] carried out in Santos, São Paulo State, in 1989-1990 estimated survival probabilities of people living with HIV/AIDS. The authors found that 51.7 and 38.8% of the AIDS cases followed up in a network of local facilities

Table 1

Studies assessing survival in the pre- and post-HAART (antiretroviral therapy) eras. Brazil: Macro-regions, States and cities, 1982-2003.

Reference	Period	Region	City/State	Sample size	Measure	Survival
Chequer et al. [6]	1982-1989	Brazil (national databank)	-	2,135	Median survival (time from diagnosis to death)	5.1 months
Marins et al. [12]	1982-1996	Brazil (national databank)	-	3,930	Median survival (time from diagnosis to death); proportion of survivors	1982-1989: 5.1 months, 32% survived > 1 year and 21% > 2 years; 1995: 18 months, 60% survived > 1year and 45% > 2 years; 1996: 58 months, 72% survived > 1 year and 63% > 2 years
Matida et al. [21]	1983-1998	Brazil	10 Brazilian cities (children)	914	Median survival (time from diagnosis to death); proportion of survivors	Before 1988: 20 months; 1988-1992: 24 months; 1993-1994: 50 months; 1997-1998: +75% survived > 4 years
Acurcio et al. [9]	1989-1992	Southeast	Belo Horizonte/ MG	291	Median survival (time from diagnosis to death)	14.3 months (overall); 17.8 months (non-symptomatic patients); 10.4 months (symptomatic patients)
Santoro-Lopes et al. [11]	1991-1995	Southeast	Rio de Janeiro/RJ	124	Median survival (time from diagnosis to death)	Men: 20.4 months; women: 11 months
Signorini et al. [13]	1995-2002	Southeast	Rio de Janeiro/RJ	1,420	Median survival (time from diagnosis to death); proportion of survivors	1995: 35 months; 1996: 68 months; 1995: +75% survived > 14 months; 1998: +75% survived > 46 months
Gadelha et al. [14]	1997-1999	Southeast	Rio de Janeiro/RJ	79	Average and median survival (time from diagnosis to death)	Average: 84 months; median: 96 months
Campos et al. [15]	1986-2003	Southeast	Rio de Janeiro/RJ	1,415	Proportion of survivors	75% survived > 22 months
Henriques et al. [10]	1989-1990	Southeast	Santos/SP	1,056	Proportion of survivors	Cases: 51.7% (6 months after diagnosis) and 38.8% (12 months after diagnosis); non-symptomatic: 97.2% (6 months after diagnosis) and 95% (12 months after diagnosis)
Menesia et al. [16]	1986-1997	Southeast	Ribeirão Preto/SP	1,231	Median survival (time from diagnosis to death)	1986-1990: 12 months; 1991-1995: 9 months; 1996-1997: 29 months
Guerreiro et al. [17]	1986-1998	Northeast	Fortaleza/CE	502	Median survival (time from diagnosis to death)	25 months
Brites et al. [18]	1989-1999	Northeast	Salvador/BA	198	Average and median survival (time from diagnosis to death)	Average: ≈ 81 months; median: ≈ 100 months; co-infected with HTLV-1- average: 62 months and median: 79 months

Brazilian states: MG – Minas Gerais; RJ – Rio de Janeiro; SP – São Paulo, CE – Ceará; BA – Bahia.

were alive 6 and 12 months after been diagnosed with AIDS, respectively.

Findings from the early 1990s document an increase in the median survival time of patients living with AIDS, primarily due to the progresses of therapy during that period (then basically restricted to dual therapy). The paper by Santoro-Lopes et al. [11] analyzed data from patients followed up in a referral center in the city of Rio de Janeiro in 1991-1995, and observed a significant difference between median survival times for men (20.4 months) and women (11.0 months), even after controlling for clinical and laboratory covariates. Most papers published thereafter

Figure 1

Brazil and South America, major geographic divisions, and cities where studies cited in the text were carried out.

Source: Laboratório de Geoprocessamento, Departamento de Informações para a Saúde, Instituto de Comunicação e de Informação Científica e Tecnológica em Saúde, Fundação Oswaldo Cruz [Geoprocessing Laboratory, Health Information Department, Institute for Communication and Scientific and Technological Information in Health, Oswaldo Cruz Foundation].

did not confirm such findings, but rather found roughly similar median survival times for men and women living with AIDS.

HAART represented a breakthrough in terms of much longer survival after the diagnosis of AIDS. A paper by Marins et al. [12] documents the dramatic increase in survival time, using data from 3,930 randomly selected patients from the national AIDS cases database. For those patients diagnosed in 1982-1989, the median survival was 5.1 months (as found by Chequer et al. [6]). On the other hand, the median survival was much longer for those patients diagnosed in 1995 (18 months) and substantially longer (58 months) for those patients diagnosed in 1996 who started their ARV therapy with HAART. Indeed, HAART use was the sole independent predictor of longer survival for those patients.

Different studies analyzing data from referral centers from different regions and localities have broadly corroborated the national findings from Marins et al. [12]. A study [13] covering patients under ARV therapy from 1995 to 2002 in a hospital and outpatient unit in the city of Rio de Janeiro, found median survival times of 35 and 68 months for those patients entering treatment in 1995 and 1996, respectively. In the most recent years under analysis (from 1998 on), median survival was no longer a valid measure since most people remained alive at the end of the follow up period (75% of the patients lived for more than 46 months). Two other studies, carried out in another referral center in the city of Rio de Janeiro, documented substantial increases of survival in the late 1990s and the present decade. For those patients entering treatment in 1997-1999 the median survival time was 96 months [14]. The most recent analysis carried out in the same facility [15] could not calculate median survival since the vast majority of patients entering treatment in the late 1990s, and the present decade, were still alive.

Another study, carried out in Ribeirão Preto, São Paulo State [16], documented a substantial, but less pronounced increase, of the median survival time, vis-à-vis the national study [12], and the studies carried out in Rio de Janeiro [13,15]. Data abstracted from the city database pointed to a median survival of approximately 29 months for those patients diagnosed with AIDS in 1996-1997.

Data are relatively scarce for the less industrialized regions of Brazil, far from the southeastern-southern main metropolitan areas. Two available studies [17,18] conducted long-term follow up of patients over both the pre and post-HAART eras, and documented two relevant issues that the national and southeastern studies did not make evident. First, in a study conducted in Fortaleza, Ceará State [17], the median survival time for patients under follow up from 1986 to 1998 was approximately 25 months, but, unlike the abovementioned studies, low educational level was found to be an independent predictor of poorer survival one year after AIDS diagnosis. Second, the findings from a study [18] carried out in Salvador, Bahia State, a region where HTLV infection is relatively prevalent among the general population [19] and quite prevalent (≈20%) among people living with HIV/AIDS, contributed to the debate regarding whether HIV/HTLV co-infection accelerates the course of HIV disease [20]. The authors conducted follow up between 1989 and 1999 and found that coinfection with HTLV was associated with shorter survival times, with a median survival of approximately 79 months for patients coinfected with HIV and HTLV compared with approximately 100 months for patients not coinfected with HTLV.

Studies on the impact of mono and dual ARV therapy and HAART on the survival of pediatric patients were virtually absent in the Brazilian literature in the 1980s and 1990s. However, a recent comprehensive survival analysis of pediatric AIDS cases was published in 2004 [21]. The authors merged data on 914 children from 10 Brazilian cities, who acquired HIV infection due to mother-to-child transmission in 1983-1998. The progress of ARV therapy determined a progressive increase in the median survival time for these children, from 20 months for those diagnosed before 1988, to 24 months for those diagnosed in 1988-1992, to 50 months for those diagnosed in 1993-1994. Most children from the latter cohort had access to HAART when they were aged 2-3 years old, which resulted in more than doubling their median survival time, compared with those children for whom the benefits of HAART arrived too late.

Despite some minor differences between major metropolitan areas and smaller cities, the overall findings point to the pronounced effect of HAART in improving survival for both adult and pediatric HIV/AIDS patients in Brazil.

The challenges posed by non-adherence to HAART

Optimal adherence is a key precondition for the success of HAART [22]. The reasons for less than optimal adherence are complex and are reviewed in detail elsewhere [23,24]. Brazil's literature on adherence has been growing in recent years, but is still far from comprehensive in terms of exploring the interplay of individual and contextual factors.

Table 2

Studies assessing adherence to HAART (antiretroviral therapy) regimen. Brazil: Macro-regions, States and cities, 1982-2003.

Reference	Period	Region	City/State	Study design	Sample size	Measure	Adherence
Nemes et al. [26]	2003	Brazil (network of health units, all over the country)	-	Cross-sectional	1,972	Number of pills taken/prescribed (last 3 days)	75% (ingested ≥ 95% pills prescribed)
Brigido et al. [27]	Post-HAART (50 months of follow-up; no period specified)	Southeast	São Paulo /SP	Cohort	168	"Regular": all doses all days, tolerating timing of ±2 hours of intake; "quasi-regular": missing up to 4 doses or 1 full day during a month; "irregular": all other regimens	"Regular": 41%; "quasi-regular": 19%; "irregular": 29%
Barroso et al. [28]	1996-1998	Southeast	Rio de Janeiro/RJ	Cohort	93 men	Number of days that medications where not taken (last 30 days)	52% (no missing day after 1 month); 57% (no missing day after 2 or 3 months) ; 39% (no missing day after 6 months)
Hofer et al. [29]	Post-HAART (not specified)	Southeast	Rio de Janeiro/RJ	Cross-sectional	211	Number of pills taken/ prescribed (last 3 days)	Average proportion of pills ingested: 81%
Lignani Junior et al. [30]	1999	Southeast	Belo Horizonte /MG	Cross-sectional	120	Number of pills taken/ prescribed	74% (ingested ≥ 90% pills prescribed)
Bonolo et al. [31]	2001-2003	Southeast	Belo Horizonte /MG	Cohort	306	Number of pills taken/ prescribed (last 3 days)	Accumulated incidence of non-adherence (ingestion of less than 95% of prescribed doses): 36.9%
Gupta et al. [33]	-	Southeast	Vitória/ES	Cross-sectional	56	Compliance score (sum of the self-rating for adherence (0 to 6 = never miss to always miss/abandonment); last dose missed (0 to 4 = never to today); and frequency of missed treatment due to each of twenty possible reasons (0 to 3 = never miss to frequently miss).	Mean compliance score; currently on home-care program patients: 4.0; previously on home-care program patients: 6.76; only on outpatient unit: 13.05
Pinheiro et al. [34]	1998-2000	South	Pelotas/RS	Cross-sectional	195	Number of pills taken/ prescribed (last 48 hours)	56.9% (ingested ≥ 95% pills prescribed)
Carvalho et al. [37]	1999-2000	Center-West	Brasília/DF	Cross-sectional	150	Number of pills taken/ prescribed	76% (ingested ≥ 95% pills prescribed); 83.2% (ingested ≥ 80% pills prescribed)

Brazilian states: SP – São Paulo; RJ – Rio de Janeiro; MG – Minas Gerais; ES – Espírito Santo; RS – Rio Grande do Sul; DF – Federal District.

Table 2 summarizes the main findings from adherence studies carried out in Brazil. One of the caveats of the different studies is the diverse ways adherence is conceptualized and measured, as well as a lack of definition about what levels of adherence should be considered "optimal" [25]. Such discrepancies in terms of what is being measured and how it is being measured may explain the variation observed, with a range of 52 to 83% of patients considered "adherent" to ARV therapy [26,27,28,29,30,31,32,33,34,35,36,37].

A large study of 60 health units from 7 different Brazilian States, carried out in 2003, found that 75% of HIV/AIDS patients adhered to their treatment regimen (adherence defined as having taken 95% of prescribed pills in the previous 3 days). Lower educational level, younger age, and a higher burden of pills to be taken every day, were found to be independently associated with poorer adherence [26].

Patients followed at a referral center in the city of São Paulo in the late 1990s were ranked as "regular" (see Table 2 for definitions), "semi-regular", or "irregular" with respect to adherence to HAART. "Regular" adherence was reported by 41% patients, "quasi-regular adherence" was reported by 19%, and "irregular" adherence was reported by the remaining 29%. Irregular adherence was independently associated with forgetfulness, intolerance, alcohol consumption, and misunderstanding of prescriptions [27].

Among patients followed by a referral center in the city of Rio de Janeiro between 1996 and 1998, 52% patients reported a 100% adherence one month after starting HAART and this increased to 57% after the third month of HAART. However, by the sixth month, optimal adherence had decreased to 39%. Optimal adherence was found to be associated with both blood and seminal HIV RNA suppression [28]. The same research group carried out a second cross-sectional study of five public health units in Rio de Janeiro and found an overall optimal adherence of 81% [29].

A research group from the city of Belo Horizonte carried out a study in a local referral center using two complementary measures of adherence: self-reports and pharmacy checks. Using a cut-off of 90% for the proportion of pills taken in the last three days, 74% were considered adherent, versus 76.5% using the pharmacy checks, indicating good agreement of the measurement strategies. A poorer adherence, as measured by both strategies, was independently associated with lower educational level [30].

Another study carried out in two referral centers in the city of Belo Horizonte in 2001-2003, estimated incidence of non-adherence using a Cox proportional hazards model. Using an adherence cut-off of 95% for the last three days, the cumulative incidence of non-adherence was found to be 36.9%, with declining proportions of non-adherence as patients progressed from the first (57.5%), to the second (31%), to the third (11.5%) follow-up visit. Unemployment, use of alcohol, high pill burden (> 12), three or more adverse reactions, a switch to more complex regimens, and a longer time between HIV test and the first prescription were found to be independently associated with non-adherence [31]. The same research group published another study using similar techniques to measure adherence, but focused on initial adherence, in order to evaluate cost-effectiveness of HAART in this population. The point prevalence of adherence in the initial phase of ARV therapy was 79.7% [32].

In the city of Vitória, Espírito Santo State, the adherence of patients with special needs was assessed in three groups of patients: those currently followed by a home-care service, those formerly served by a home-care service (now attending the outpatient unit), and those exclusively followed by the outpatient unit. Adherence was significantly higher among those currently served by a homecare service, compared with those currently attending the outpatient unit [33].

Patients followed by a health unit in the city of Pelotas, Rio Grande do Sul State, in 1998-2002 were found to have a relatively low (56.9%) adherence to HAART, as measured by self-reporting about pills taken in the last two days, and a cut-off of 95%. Self-efficacy and a lower number of daily doses were found to be associated with a better adherence [34]. In a companion paper [35], the authors suggest adherence could be maximized by regimens with a lower number of doses, with no compulsory fasting, and with fewer adverse effects.

In another study, carried out in a referral center located in the city of Porto Alegre, virologic failure (viral load ≥ 400 copies/µl) was documented in 28% of 454 patients under followup between 1996-2004, with a high correlation to self-reported non-adherence [36].

In Brasilia, Brazil's federal capital located in the central-west, high levels of adherence (76% with a 95% cut-off) were reported among 150 patients attending a day-hospital service. Lower adherence levels were found to be associated with illicit drug use and lower family income [37].

A study carried out in Rio Grande do Norte State, addressed the complementary issue of treatment interruption among patients under follow-up in two health services, in 1999-2002. Approximately 35% patients discontinued their treatment, mainly due to psychiatric problems, abuse of illicit drugs, and low educational level [38].

Despite a thorough search, no published study has used electronic drug monitoring to measure adherence to HAART in Brazil. The heterogeneities in terms of defining what constitutes optimal adherence and how to measure it do not permit discernment of patterns over time. Notwithstanding, adherence levels observed in Brazil do not appear to differ substantially from those reported by other studies carried out worldwide [39].

Updating the challenges of viral resistance

Although providing HAART offers unquestionable benefit to the individual, there remains concern that distribution of therapy in poorly monitored situations may result in the dissemination of viral variants that are resistant to ARVs. A recent article [5] examined viral resistance data from Brazil.

Available data from Brazil show that ARV therapy can be delivered in a resource-limited setting without resulting in widespread transmission of a resistant virus. The prevalence of secondary resistance in Brazil is high (up to 77.9%), but the levels of transmitted resistance in Brazil remains comparable to that observed in Europe and the United States [40,41]. The available data showed that resistance has not yet become a greater problem in Brazil than in richer countries.

The most recent papers, partially or totally unavailable at the time the Petersen et al. [5] paper was written, do not show any major discrepancies with the previous findings. Drug resistance mutations were evaluated in antiretroviral-naive intravenous drug users (IDUs) in the city of Rio de Janeiro at two time points (pre- and post-HAART). Genotypic analysis revealed the presence of protease (PR) primary mutations in 7.9% of the post-HAART group, and a high frequency of secondary mutations (84.2%). In the pre-HAART group, a higher frequency of reverse transcriptase (RT) mutations was observed (22.2%) and no PR primary mutations were found [42].

Findings on drug resistance mutations in antiretroviral-naive city of São Paulo blood donors with recently acquired or established HIV-1 infections were recently published. The proportion of resistant strains was 12.7% among recently infected individuals, compared with 5% among those with long-standing infections. The prevalence of drug-resistant mutations among newly diagnosed persons in the city of São Paulo is low, and similar to what has been described in Europe and the United States [43].

Among HIV seropositive users at a voluntary counseling and testing site in the city of Porto Alegre, principal ARV resistance mutations were observed in 3% of the sample [44].

Does HAART decrease morbidity (including opportunistic infections, neoplasms, and co-infections) associated with AIDS?

A cohort study of participants from 10 American cities enrolled in the HIV outpatient study (1996-2004) evaluated recent trends in mortality and morbidity among mostly HAART-treated persons. The substantial increase in survival allowed chronic underlying co-morbid conditions, or risks for such conditions, to become relevant, particularly liver disease (e.g. chronic hepatitis B and C), hypertension, diabetes, cardiovascular illness, pulmonary disease, and non-AIDS malignancies. Non-traditionally HIV-related conditions are more likely to figure prominently in the risk for death and disease among patients under HAART [45].

AIDS-associated opportunistic infections declined substantially in Brazil in the post-HAART era. Brazilian national data from 1980-1999 [46] revealed a statistically significant decline in all opportunistic infections/AIDS-associated cancers evaluated (including candidiasis, tuberculosis, *Pneumocystis carinii* (nowadays, *Pneumocystis jirovecci*) pneumonia, neurotoxoplasmosis, Kaposi sarcoma, cryptococcal meningitis, and protozoa infections).

A previous review by our group showed that tropical diseases among HIV-infected individuals have declined in Brazil because of HAART, despite the spread of HIV toward remote regions of Brazil where major endemic diseases, such as malaria, Chagas disease, and leishmaniasis, are prevalent [47].

Recent research from a referral centre in the city of Belo Horizonte has revealed a substantial change in the frequency of associated diseases among patients living with AIDS before and after HAART (1989-2000). There was an increase in the prevalence of tuberculosis and toxoplasmosis, with a decrease in Kaposi's sarcoma, histoplasmosis, and cryptococcosis. Overall, with the exception of cerebral toxoplasmosis, a smaller proportion of opportunistic conditions related to severe immunosuppression have been observed in the post-HAART group [48].

Various papers [49,50] have documented a dramatic decline of *Mycobacterium avium* complex infection in the post-HAART era in Brazil, as reported elsewhere [51]. To a lesser extent, co-infections with *Mycobacterium tuberculosis* declined as well [52], but remain as a major cause of morbidity and mortality of Brazilian AIDS patients [53].

The combined impact of universal access to HAART and the systematic adoption of directly observed therapy (DOT) for tuberculosis seems a promising strategy to curb the still unaccept-

able levels of HIV/tuberculosis co-infection in Brazil [54]. Recent papers have pointed to a substantial decline of tuberculosis co-infection, and a growing number of people living with AIDS with no sign of any opportunistic infection in the post-HAART era. Unfortunately, such encouraging findings are not observed across different social strata; HIV/tuberculosis still disproportionately affects those with lower educational levels [55].

Recent papers from southern Brazil [56,57] highlighted that dermatoses are still a relevant problem among AIDS patients. Although less relevant than in the pre-HAART era, infectious dermatoses remain a major cause of morbidity among this population, with a recent increase in cutaneous reactions to various ARVs. Cutaneous neoplasms, especially Kaposi's sarcoma, have been rarer in recent years, but still affect a minority of AIDS patients [56].

As patients with AIDS live longer due to HAART, infections with a protracted course, such as hepatitis C virus (HCV) infection, have the necessary time to evolve toward full liver disease, as cirrhosis and/or liver cancer [45]. The Brazilian literature on HIV/HCV has been deficient in the longitudinal evaluation of coinfected patients and published studies have been limited to a series of cases analyzed from a cross-sectional perspective or over short time periods.

HIV/HCV coinfection seems to be particularly relevant in settings such as in the city of Santos, Sao Paulo State, Brazil's biggest harbor city, formerly affected by a substantial epidemic among its relatively large population of IDUs [58]. In a cross-sectional analysis of a cohort of patients from Santos, HCV co-infection was relatively prevalent among patients with AIDS (36.2%) and extremely common among those with an IDU history (84.8%) [59].

Another major source of concern in the post-HAART era in Brazil has been the co-infection of HIV and human papillomavirus (HPV). HPV infection is relatively prevalent in the Brazilian general population [60], and especially prevalent and aggressive among women living with HIV/AIDS [61,62,63,64,65]. HIV infection may increase the oncogenicity of high-risk HPV types and the activation of low risk types, with higher rates of squamous intraepithelial lesions (SIL), and uterine cancer, over time [63,66].

Neurological diseases continue to be a relatively frequent complication of HIV/AIDS in Brazil. Central nervous system infections, as opportunistic infections in general, declined substantially in the post-HAART era. Notwithstanding, some infections such as cerebral toxoplasmosis, *Cryptococcus neoformans* meningitis, HIV encephalitis, and central nervous system tuberculosis are still relatively common [67,68,69,70], sometimes as an AIDS-defining disease of people living with HIV or a first manifestation of immunodeficiency among patients previously unaware of their serostatus [71]. A distinctive characteristic of neurological complications of HIV infection in Brazil is the much lower incidence of progressive multifocal leukoencephalopathy compared with developed countries, probably due to local characteristics of human polyomavirus JC (JCV) isolates and/or their interaction with co-circulating HIV strains [69].

Worldwide, AIDS-associated cancers have been dramatically changing over the years, both due to changes in the profile of individuals at risk in different periods of the epidemic and the impact of HAART. As the proportion of new AIDS cases among gay men declined in Brazil and increased among women, incidence of Kaposi's sarcoma declined dramatically since, for unclear reasons, women seem to be relatively protected from the full development of Kaposi's sarcoma, even when they are infected by the human herpesvirus-8 [72]. But owing to the major epidemiological changes that took place in Brazil, in parallel with the continuous reformulation of ARV therapies, it may be impossible to disentangle the specific impact of the changing profile of at-risk populations over time from the impact of mono, dual, and HAART therapy on Kaposi's sarcoma.

On the other hand, other malignancies, especially malignant lymphoma and cervical cancer, have been increasingly important causes of morbidity and mortality in AIDS patients as patients live longer [65,73,74] .

Overall, the incidence of many opportunistic infections, neoplasms, and other causes of AIDS-related morbidity have decreased in the post-HAART in Brazil. Nonetheless, many of these causes of morbidity still affect a substantial proportion of AIDS patients and remain a major cause of morbidity and mortality among Brazilian HIV/AIDS patients.

Adverse reactions and other morbid conditions associated with HAART

Adverse reactions to HAART can be a major obstacle toward optimal adherence, particularly when patients are initiating therapy. Data from patients from two public health units in the city of Belo Horizonte [75] found that 34.5% of patients presented at least one adverse reaction to HAART, most of which were mild reactions such as nausea and vomiting, but sometimes serious enough to require changes to the therapeutic regimen or even its discontinuation. The authors pointed to a

complex relationship between adverse reactions and adherence, with less than optimal adherence contributing to a higher prevalence of adverse reactions which, in turn, further compromise adherence. Among other factors, adverse reactions have been found to be associated with regimens containing nevirapine and indinavir or indinavir/ritonavir combinations.

Lipodystrophy currently is a major concern among patients under HAART, especially among those using protease inhibitors [76,77]. Such issues are yet to be explored in detail in Brazil.

A cross-sectional study conducted in 2001 at a reference unit in the city of São Paulo showed that 64.3% of patients perceived that they had experienced central fat gain and peripheral fat loss after initiating HAART. Whereas central fat gain was associated with the use of protease inhibitors, peripheral fat loss was found to be associated with the use of stavudine and less than optimal adherence [78]. Another study carried out in the city of São Paulo performed an anthropometric assessment of HIV-infected patients and healthy controls, finding signs of lipodistrophy in the upper limbs among AIDS patients, especially those treated with protease inhibitors [79].

A recent pilot study conducted in the city of Porto Alegre showed aerobic exercise and a low-lipid diet increased the functional capacity of HIV-infected individuals with lipodystrophy and dyslipidemia, but did not improve their plasma lipid levels after 12 weeks [80].

Lipodystrophy, as well as metabolic syndrome and different cardiovascular complications, have been increasingly diagnosed among people living with HIV/AIDS. Data on cardiovascular complications of AIDS patients under HAART are currently scarce in Brazil. A small study carried out in a referral center in São Paulo in the early 2000s measured antibodies to modified low-density lipoprotein (mLDL) and clinical manifestations of lipodystrophy. The authors observed a significant reduction in anti-mLDL antibody levels, related both to lipodystrophy and to advanced immunodeficiency, which may help explain the rapid development of ischemic coronary artery disease in some of these patients [81].

Discussion

The dramatic increase in survival of AIDS patients after the introduction of HAART in Brazil is undeniable. The introduction of HAART at no cost at the point of delivery, in the context of universal access, has lead to major improvements in survival and quality of life for the vast majority of people living with HIV/AIDS across different regions and contexts of Brazil, a country facing one of the most unequal distributions of income in the world. However, despite the undeniable success of the Brazilian program, the adverse social and economic conditions faced by many Brazilians remain a key challenge for any initiative aspiring to equality and fair allocation of resources.

Brazilian scientific capacity has been growing quickly in recent years, but is still timid and limited in terms of its broad scientific output in the field of HIV/AIDS [3,82], as well in many other areas. Most studies and researchers (in the field of HIV/AIDS, as in any other field) are concentrated in a few research centers which are located in the major metropolitan areas of the industrialized southeastern and southern regions. This situation partially compromised this study's attempt to assess the Brazilian response to the AIDS epidemic beyond the usual aggregated analyses. There is no shortcut to the comprehensive evaluation of a large program targeting over 160,000 individuals living with AIDS and receiving HAART from a network of more than 500 dispensing units, scattered over a continent-sized country.

Despite such limitations, available evidence points to the relevant role that low education plays as a deterrent to optimal adherence to HAART, especially in the context of smaller health units and/or middle-sized cities and/or cities located far from the southeastern metropolitan centers. There is a pressing need to carry out studies with a nationwide coverage, as well as specific studies targeting smaller units and/or local health networks operating in small and faraway municipalities.

A recent paper [83] advanced the hypothesis that universal access to HAART in a context of social and economic inequalities could reinforce, instead of alleviate, the underlying inequalities. The authors, however, did not find ecological evidence to corroborate their hypothesis, at least for the city of São Paulo, the largest and richest Brazilian city, where deep social inequalities prevail. Further studies are necessary to explore this hypothesis in different local and regional contexts.

Overall, adherence rates in Brazil are comparable to those found in developed countries. A recent review and meta-analysis [39] showed that adherence to HAART in various sub-Saharan African countries is comparable to, or, in some cases, better than, North American and European standards. These findings, in addition to the Brazilian ones, reinforce the message that properly implemented programs to increase access to HAART in developing countries can achieve excellent outcomes.

Similarly, the review by Petersen et al. [5], as well as the most recent data on viral resistance

from Brazil, documented that the somber predictions of an uncontrollable spread of resistant viral strains associated with Brazil's launch of its program of universal access, did not materialize. This review has many limitations, due to the fact that it retrieved only peer-reviewed papers indexed by two major databases, MEDLINE and SciELO (with an international and regional scope, respectively). From one point of view, such strict criteria represent a deliberate effort toward higher scientific quality. On the other hand, such criteria likely excluded the smaller/emergent research groups working in Brazil, facing serious infra-structural and/or manpower deficits, such as inadequate training in the use of modern statistical methods and/or poor command of English, and consequent inability to publish their findings in major international journals [84]. In this sense, the very information about those populations and settings which are most in need may have been excluded.

Another aspect of the same problem refers to the progressive spread of the epidemic to smaller municipalities and faraway localities [85]. In this sense, despite the growing number of HIV/AIDS publications in Brazil in recent years, the gap between the available literature, vis-à-vis the actual characteristics of the epidemic, may be widening, instead of being properly addressed.

A specific limitation, made evident by this review, refers to the measurement of adherence. Future research must assess as many services and populations as possible, but such a concerted effort should incorporate strict methodological rules toward the progressive standardization of methodological strategies, instruments, and definitions. At the least, a future study should evaluate the validity of self-reports in Brazil (using electronic devices as a gold standard), as has been done in developed countries [86].

Recently, calls have been made to evaluate the future sustainability of the Brazilian program [87]. The Brazilian program seems to be a victim of its own success, in the sense that current achievements have fostered new and complex demands. A warning alert comes from recent data on ARV costs. After years of sustained decline, the Brazilian program of universal access is currently facing rising aggregate costs [87] as a growing contingent of people enter and remain in treatment for a longer time, and their physicians demand an increasingly diverse and sophisticated arsenal of new medicines. These new medicines are protected by patents and tend to be much more expensive than the current "basic basket of ARVs", whose price is kept low via domestic production of generic ARVs.

As untoward effects and adverse reactions accumulate, resistance increases (slowly, but continuously) and patients switch from first to second-line therapies (sometimes to salvage therapies). As this occurs, the delivery of ARVs and the continuous monitoring of patients under HAART becomes more complex and costly. Close monitoring of the emergence and eventual transmission of resistant strains has been one of the major achievements of the Brazilian initiative [3,5]. On the other hand, the paucity of references and studies on major causes of morbidity and mortality in the post-HAART era constitutes a major deficiency of Brazil's scientific effort in the field of HIV/AIDS.

Whatever the challenges ahead and the current limitations in terms of a better and broader evaluation of the Brazilian universal access program, the overall balance is positive and may pave the way for other developing countries to increase access to ARVs. The challenges to be faced by other developing countries, with fewer resources and much larger epidemics, compared to Brazil, may seem formidable. However, improved access to ARVs, fully integrated with initiatives aiming to avert new infections and prevent further spread of HIV from already infected individuals, constitutes an essential step of any serious attempt to effectively curb the AIDS epidemic worldwide [88].

Resumo

Procedeu-se a uma revisão abrangente de artigos publicados entre 1996-2006, período posterior à introdução da terapia anti-retroviral de alta potência (HAART) no Brasil. Foram revisados artigos disponíveis nas bases de dados MEDLINE e SciELO, a partir de combinações de palavras-chave que contemplam os principais temas na área do tratamento e manejo da AIDS na era pós-HAART: doenças oportunistas e co-infecções, aderência à terapia, sobrevida pré e pós-HAART, eventos adversos e efeitos colaterais, emergência e eventual transmissão de cepas virais resistentes e complicações cardiovasculares e metabólicas, além de questões relativas ao acesso e à eqüidade. Em suma, observa-se uma transformação profunda no campo da AIDS no período pós-HAART, com aumento dramático da sobrevida e da qualidade de vida, e redução expressiva dos episódios de doenças oportunistas. Por outro lado, novas questões se colocam, como a relevância das co-infecções de evolução lenta, como a hepatite C, os distúrbios metabólicos e cardiovasculares, e o desafio posto pela emergência de cepas resistentes, com repercussões individuais (falha virológica) e coletivas (resistência primária e secundária em nível da comunidade) e, conseqüente, aumento de custos da terapia.

Síndrome de Imunodeficiência Adquirida; Terapia Anti-Retroviral de Alta Atividade; Sobrevida

Contributors

M. A. Hacker abstracted and summarized the papers and wrote, in cooperation with the other co-authors, the paper. A. Kaida and R. S. Hogg discussed the findings in the context of international literature and wrote the paper in cooperation with the other co-authors. F. I. Bastos conceived the review protocol, retrieved national and international papers, and wrote the paper in cooperation with the other co-authors.

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