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Brazilian biomedical and epidemiological research vis-à-vis the UNGASS targets

ABSTRACT

The focus of the present study is the Brazilian response within science, technology and innovation to the targets formulated in the UNGASS document. An analysis was made of items 70-73 of the UNGASS Draft Declaration of Commitment on HIV/AIDS (2001), which defined science, technology and innovation targets relating to HIV/AIDS. The main topics listed in these items were put into operation in the form of keywords, in order to guide systematic searches within the standard biomedicine databases, also including the subdivisions of the Web of Science relating to natural and social sciences. The success of Brazilian research within the field of characterization and isolation of HIV-1 is undeniable. Phase II/III vaccine studies have been developed in Rio de Janeiro, Belo Horizonte and São Paulo. Empirical studies on the monitoring of primary resistance have been developed in specific populations, through the Brazilian HIV Resistance Monitoring Network. Within the field of monitoring secondary resistance, initiatives such as the National Genotyping Network have been highlighted. Two national systems – the Mortality Information System and the Notifiable Diseases Information System-AIDS – and some studies with wider coverage have given rise to work on trends within the epidemic. The production of high-quality generic medications and their free distribution to patients have been highlighted. Brazil has implemented a consistent and diversified response within the field of HIV/AIDS, with studies relating to the development of vaccines, new medications and monitoring of the epidemic.

KEYWORDS: Acquired immunodeficiency syndrome, prevention & control. Acquired immunodeficiency syndrome, epidemiology. AIDS vaccines. Technological development, trends. Biomedical technology, trends. Drug resistance, viral.

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INTRODUCTION

The base document of the United Nations General Assembly Special Session on HIV/AIDS (UNGASS) defines targets for Science, Technology and Innovation relating to HIV/AIDS in its items 70-73. The present text analyses some of the main items in this section, giving emphasis to core questions in public health, rather than to its interfaces with broader markers for action within civil society, for formulation and implementation of public policies and for industrial policy strategies.

Some matters that have not been dealt with cannot be retrieved from the databases that guided the search for references. Such information often cannot be retrieved through investigations of any public database. This is because it comes from official documents that are sometimes confidential in nature; sometimes they are indeed industrial secrets (regarding the development of new drugs). Therefore, the present review must not be seen as exhaustive.

This review included standard databases in biomedicine, as well as their interfaces with the fields of Science, Technology and Innovation ("STI"). However, since this is a pandemic taking place in a world where several global STI networks are in operation, the analysis of the Brazilian response within STI must incorporate in its discussion the key texts that are produced worldwide. Because of the extent of the present review, the results are presented in the form of two papers, of which the present article is the first part.

METHODOLOGICAL PROCEDURES

The main subjects listed in items 70-73 of the UNGASS document were worked on as key words ("uniterms") to guide systematic searches in the main databases within biomedicine, such as MEDLINE and SciELO. *A priori*, no specific time period or geographical delimitation was defined for the searches, despite the obvious emphasis on publications that gave Brazilian responses, written by Brazilian and/or foreign authors who are continuously active in Brazil.

The topic of "STI in HIV/AIDS" goes beyond the field of biomedicine and has interfaces with social life, as well as scientific and technological policies, and it is related to questions within the sociology of science (which were dealt with circumstantially here). Thus, the searches in the bibliographic databases also included the Institute for Scientific Information (ISI), through its Web of Science, in its subdivisions relating to Natural Sciences (SCI-Expanded) and Social Sciences (SSCI).

There was no historical aim, such as retrieval of the recollections of social movements or critical analysis of the interface between activism, public policies and decision-making, in relation to essential questions like access to antiretroviral drugs. Within this, a mixture of initiatives from civil society and judicial decisions exist, which go beyond the field of STI but may have a central role regarding scientific and technological developments that were translated into practical measures.³⁵

Items 70-73 of the document contain a broad and heterogeneous HIV/AIDS research agenda. For this reason, we chose to emphasize certain items, in particular the fields in which the Brazilian and international indexed literature are shown to be more consistent. Some topics such as international cooperation in STI cannot be retrieved from indexed scientific papers, and these are carried in government and agency reports, in the so-called "gray literature". Such articles are of vital importance for the formulation of policies, but access to them is restricted to policy formulators and their closest interlocutors.

Likewise, it was not possible to review the whole collection of Brazilian research accumulated over more than two decades of conferences on HIV/AIDS. In particular, the large international conferences that initially took place annually and are now biannual can be mentioned. Submissions of papers by Brazilian authors form the second or third largest body of work in the world, after the United States, the world leader in research. The collection of Brazilian abstracts presented at the largest international congresses in the field is of the order of thousands of studies (International AIDS Conference, Retrovirus and Opportunistic Infections Conference, and the International AIDS Society Conference on Pathogenesis and Treatment). They include papers ranging from basic science to the evaluation of actions by local services and by non-governmental organizations.

ANTI-HIV/AIDS VACCINES AND MOLECULAR EPIDEMIOLOGY OF HIV

At present, the development of vaccines for HIV/AIDS is going through a crisis. Despite the progress in the fields of molecular biology, virology and immunology, as yet there are no consensual definitions for optimal combinations of specific immune responses that would indeed be protective against HIV.⁴⁴ Likewise, although the worldwide efforts within the field of HIV-1 molecular epidemiology are praiseworthy, there are no clear parameters that allow for correlation between the viral diversity and

specific patterns of transmissibility,⁶⁴ immune response²⁸ and “natural” history of the infection.²⁵ “Natural” is here in quotation marks because in Brazil there are no “natural histories” of infection by HIV, since there is widespread availability of antiretroviral medications that totally alter the natural course of the infection.

The paradigm of sterile immunity seems to have been definitively supplanted. In its place, some other alternatives have emerged: these include vaccines that would allow partial protection and/or slower evolution of the HIV infection towards the clinical syndrome (AIDS), and would stop its progression, if possible.

The complex interrelations between the action of vaccines that induce partial protection (so called “imperfect” vaccines) and initiatives within the field of prevention have been investigated by British² and American⁸ research teams at broad population level. Although in the form of isolated initiatives, such questions are not strange to Brazilian science.⁵⁴ There is, however, no single line of research in Brazil that considers not only the mathematical modeling, but also the collection of empirical data and parameter determinations from these data, in the form of models bearing specific Brazilian characteristics. Efforts along the lines of modeling the impact of imperfect vaccines should be encouraged within the context of the co-circulation of different viral strains. As examples, the paper from Blower et al⁹ (2005) in South Africa and the recently developed theoretical perspective developed by Massad et al⁵⁵ (2006) can be cited.

The success of Brazilian research in the field of characterizing and isolating HIV-1 is undeniable. Brazil has set up a wide network of laboratories and stimulated academic cooperation, with notable results from mapping the molecular epidemiology of HIV, despite the size and regional diversity of the country. With the exception of Salvador, Bahia, which has a national reference laboratory and has produced some papers, the research groups have undeniably been concentrated in the Southeast region.^{26,32} These groups have shown an ability to establish partnerships with research teams in the Northeast³⁶ and in other Latin American countries.^{23,90} Furthermore, teams with independent production relating to coinfection between HIV and human T-lymphotropic virus (HIV/HTLV) have emerged outside of the science and technology axis in the Southeast, like in Pará.⁴⁵

The monitoring on the progressive dissemination of HIV-1 subtype C in the Southern region of the country is impressive and comparable with the most refined molecular epidemiological studies worldwide.^{65,71,73}

Within the national effort to acquire skills for developing phase II/III vaccine studies, important findings have been obtained from studies conducted in Rio de Janeiro, RJ, and Belo Horizonte, MG, and from preliminary studies in São Paulo.

In a general manner, these Brazilian studies can be divided into two categories. Firstly, there are studies developed from primarily national initiatives with support from WHO and, more recently, the Joint United Nations Programme on HIV/AIDS (UNAIDS), for example, recruiting men who have sex with men (MSM) in Rio de Janeiro^{74-76,79} and Belo Horizonte.^{21,47} Secondly, there are studies that form part of an international network, initially in Rio de Janeiro, and more recently in São Paulo, sponsored by the National Institutes of Health (NIH) of the United States.

The projects sponsored by NIH basically consist of the Praça XI Project, which recruited MSM,^{41,60} and more recent projects that have been recruiting heterosexual men and women who are at particular risk of HIV infection and other sexually transmitted infections,⁶ with some degree of overlap between them.⁶⁸

From the analysis of the Brazilian findings, there would not be any way, at present, to test the vaccines of partial efficacy in the field because, hypothetically, there would be little difference in the rates of AIDS incidence and progression to AIDS between those who were vaccinated and those who were not. This is because, invariably, the populations recruited have low rates of seroconversion to HIV (in addition to the generally slow progression to the clinical syndrome).

Once the logistic problems have been overcome, with the creation of an adequate clinical and laboratory infrastructure in centers of excellence, and counting on patient retention rates and availability of psychosocial support that do not differ from international standards, there remains the challenge of establishing and capacitating an expanded network of research centers. This seems to be the only viable strategy within the context of a stable epidemic (or even a declining one): to form a “pool” of centers, recruiting volunteers in their thousands, along the lines of recent initiatives in the United States that have aimed to assess the role of HIV coreceptors in relation to the acquisition and progression of HIV infection.⁵⁶ Obviously, the immense size of such initiatives requires massive investments and capacitation of significant numbers of professionals, and also dialogue with civil society and observance of standards of excellence regarding research ethics.

MONITORING VIRAL RESISTANCE: PRIMARY AND SECONDARY RESISTANCE

When Brazil started to implement its policy of universal access to antiretroviral drugs, there were many who predicted that resistant strains would emerge in an “uncontrolled” manner, using an erroneous metaphor that described developing countries as “Petri dishes”.⁶³

Ten years have now passed since powerful antiretroviral therapy (Highly Active Antiretroviral Therapy, HAART) was introduced into Brazil. It must be emphasized that the country has been capable of implementing the means for monitoring and quality assessment, and it presents resistance rates that are comparable to those observed in developed countries. On the other hand, it is known that the emergence and possible transmission of resistant strains is an undesirable but inevitable consequence of large-scale introduction of antiretrovirals. It is, therefore, an immense challenge.

Viral resistance has two dimensions. From an individual focus, its emergence is translated as therapeutic failure requiring progressive substitution of the therapeutic methods in use at any given time. Collectively, resistance means dealing with patients presenting primoinfection with viruses that are resistant to first-line medication,¹⁰ and an ever-growing proportion of newer, more complex and usually more expensive medications that are protected by patent laws, participation in the “portfolio” of therapeutic alternatives.

Therefore, due to the immediate challenges placed upon the clinical management of people living with HIV/AIDS and undergoing treatment, it is necessary to continuously monitor the emergence of secondary resistance at its outset and, in parallel, to implement systematic surveillance of primary resistance.

Within the field of monitoring secondary resistance, the initiatives of the National Genotyping Network (RENAGENO) and the monitoring network for the emergence of secondary resistance in patients presenting therapeutic failure can be highlighted. These studies are nationwide⁸⁴ and regional,²⁷ and also include studies on specific populations, such as children living with HIV/AIDS who are using HAART^{14,48,49} and patients who are potential transmitters of resistant viruses in the context of occupational accidents.³¹

Within the field of monitoring primary resistance, there are prominent review papers⁷² and empirical studies developed among specific populations, such

as the soldiers,⁶² blood donors³⁰ and a pool of recently diagnosed patients in testing and counseling centers, by the “Brazilian Network for Monitoring HIV Resistance” (HIV-BResNet).¹⁵

It has also been observed that there is a concentration of publications in indexed journals from some research groups located in centers of excellence in the Southeast region, albeit in partnership with emerging groups in locations with less infrastructure and experience (sometimes through networks with national coverage). However, it must be mentioned that papers published in indexed journals reflect more the scientific “expertise” than the operational capacity of a given laboratory. It is possible that there are laboratories with operational capacity in terms of optimal interaction with the clinical demands that are incapable of translating their findings into scientific papers.

NEW DRUGS AND MEDICATIONS AND THEIR IMPACT ON PEOPLE LIVING WITH HIV/AIDS

The question of the development of and access to new drugs and medications for HIV/AIDS is central to controlling the epidemic. Brazil has advanced considerably in the field of public policies regarding treatment for people living with HIV/AIDS, having implemented a pioneering program and wide-ranging access to antiretroviral medications and monitoring. However, the presence of adverse events from the different medications that make up the therapeutic arsenal in use today and the emergence (and possible transmission) of resistant strains are a continual challenge.

Brazil has advanced in four main ways: 1) operationally, through the implementation of a network for acquisition, storage, distribution and monitoring of antiretroviral drugs; 2) in assessing the bioequivalence of generic drugs and producing them domestically, even though *stricto sensu* scientific publications in this field are still rare; 3) through introducing Brazilian research centers into phase III/IV international clinical trials; 4) through research on candidate products (future drugs).

Two weaknesses stand out. One of them, of a purely scientific nature, is the almost complete lack of Brazilian studies on the adverse events that are associated with antiretroviral drugs, except for papers relating to secondary dyslipidemia through the use of antiretroviral medications.^{50,66} The second weak point has its roots in the lack of capacity for transforming innovations into finished industrial products, as has

occurred in the field of developing vaccines against different infectious diseases and medications that are based on products coming from Brazilian fauna and flora. In this latter case, the classic example of Brazilian industry's inability to develop an antihypertensive medication can be cited: the peptide isolated by Brazilian researchers was subsequently patented by multinational industrial companies. Isolated from jararaca snake venom, this peptide is capable of inhibiting the conversion of angiotensin I into II, which is central to the dynamics of arterial hypertension.⁷⁸

Such questions relate to Brazilian technological capacity, economic policy and, in particular, industrial policy, especially in the fields of fine chemistry and drug development. Brazil has not been able to fill the gap hiatus between innovation and product development (except through joint ventures). In the field of vaccine development (other than for HIV/AIDS), this challenge has been met by technology transfers and cooperation agreements between Brazilian institutions (such as the Fundação Oswaldo Cruz and the Instituto Butantan), and between these and international companies through multilateral cooperation initiatives.¹⁷

Brazil has been using reverse engineering procedures with the aim of understanding the processes involved in the synthesis of essential drugs that are protected by patents. However, the reverse engineering tool is only a short-term instrument for obtaining reductions in the cost of acquiring medications, insofar as it provides backing for the government's price negotiations with the pharmaceutical industries and enables national production of the drug in the event of patent loss.

Over the medium to long term, however, nothing replaces national skills acquisition for developing all the phases in the synthesis and production of new drugs that can subsequently be transformed into commercial products. It is only in this way that the country will cease to be led along by the multinational companies, with its own logic for research and development and its own strategies for putting products on the market and establishing prices.

Brazil has been advancing in the search for original products with antiretroviral activity, through a few research groups working in this field. For example, products that act such that they have the potential to inhibit the viral enzyme protease,⁵⁸ or other phases of the viral replication cycle, can be synthesized or extracted from compounds present in algae^{4,59} and in the African plant *Tabernanthe iboga*.⁶⁹

Progress has also been seen in the development and application of modern techniques for analyzing the bioequivalence of antiretroviral drugs.^{43,46} Likewise, studies on the pharmacokinetics of antiretroviral medications under "real" treatment conditions (i.e. beyond the usual evaluations under "optimal" conditions) have considered the presence and effect of intestinal parasitosis and malnutrition on the absorption of the drugs.¹² Such studies are essential for the production of high-quality generic drugs that are equivalent to the original ones produced by the multinationals, and also for evaluating generic and non-generic medications under "real" conditions of use, as well as for their utilization under the controlled conditions of phase III clinical trials.

More recently, Brazilian researchers have started studies in the field of antiretroviral pharmacogenetics. Such studies are essential over the long term, for defining medications and therapeutic schemes that are appropriate for the genetic profile of the Brazilian population.⁹¹

Within the field of studies on new medications that are being developed by the multinational pharmaceutical industry, Brazil has actively participated in phase III multicenter protocols, through some of its clinical research groups. Clinical assessments of new medications and/or therapeutic schemes have been performed on large groups of patients.^{29,42,88,89,92}

In a developing country with a program that makes antiretroviral drugs available at zero cost to approximately 180,000 patients, it is essential to adequately implement the different stages involved in the acquisition, storage, prescription and distribution of these drugs. Furthermore, it is also necessary to adequately monitor the different components of the treatment, including compliance to therapeutic schemes, management of complex cases⁵¹ and evaluation of the impact of the treatment on the survival and quality of life of people living with HIV/AIDS.

Studies using different methodologies, assessing data that sometimes relate to individual patients and at other times relate to compiled databases, have demonstrated that HAART has had a dramatic impact regarding increased survival of patients living with HIV/AIDS.^{1,3,19,40,53,67} On the other hand, there is still much to be done regarding systematic assessment of the quality of life of people living with HIV/AIDS who are undergoing antiretroviral treatment. So far, there are only a few multicenter trials, which are still at a preliminary stage (validation of a standard tool) and are being developed by specialists from the World Health Organization.⁹⁴ There are also some studies

on specific populations, such as women living with HIV/AIDS who have relevant psychiatric comorbidity.⁸⁶ This gap must be filled by Brazilian research, coming from studies exclusively relating to survival (which are undoubtedly essential) and going towards studies that simultaneously incorporate the questions of the survival and quality of life of patients living substantially longer.

The quality and broad coverage of Brazilian studies must also be highlighted, in relation to compliance with antiretroviral drugs, patients' characteristics,^{11,22,61} health professionals' characteristics,⁵¹ and the context and types of service within which the relationship between the health professional and patient occurs,³⁹ and even with regard to a set of factors relating to all these dimensions analyzed together.⁵⁷

Other papers have been exploring the relationship between high levels of compliance with therapy (or, alternatively, noncompliance) and the central clinical-laboratory parameters, such as viral suppression or its diametric opposite, virological failure.^{13,70,87} Although much is being achieved in Brazilian research, there is still much to be done in comparison to the refinement that international research has reached in this field. For example, there is room for careful monitoring of the emergence of mutations and viral resistance caused by equally subtle variations in the patterns of use of these medications. Such variations in use may even lead to the creation of new problems regarding the association between optimal compliance and viral suppression, which are intuitively or empirically verifiable under different circumstances.⁹³

Even though specific deficiencies in Brazilian scientific production must be recognized, and despite the gaps in the fields of fine chemistry or basic research for new drugs, there is no doubt that Brazil has a leading role in the developing world, and it has been acting as a vital partner in the South-South cooperation networks relating to HIV/AIDS.^{7,37,38,85}

MONITORING THE EPIDEMIC (EPIDEMIOLOGICAL SURVEILLANCE AND MODELING)

Judicious implementation of public policies must take into account the fact that the policies implemented represent an investment of public money. Therefore, these policies must be carefully assessed according to parameters that aim towards equality and the maximization of results, with minimization of non-justifiable spending. In order to achieve such an aim, it is necessary to develop national monitoring systems to evaluate the impact of effectively im-

plemented measures and to correct the courses of all the programs that are shown to have little or no effect.

The present segment leaves aside the ethical questions that belong to each specific intervention. It documents the role of analysis of the national database and specific surveillance and monitoring studies in the formulation and monitoring of public policies in the fields of prevention and treatment.

A vast number of studies have been developed from the data in the Notifiable Diseases Information System-AIDS (SINAN-AIDS) and the Mortality Information System (SIM). Studies registered here are solely those that, in effect, were population-based and had national coverage.

With regard to the impact of antiretroviral therapy, the pioneering study by Chequer et al²⁴ (1992) relating to the pre-HAART period, and the studies by Marins et al^{52,53} (2003; 2005) relating to the period following the introduction of HAART, deserve special attention. These studies were developed from representative sample data from AIDS cases registered in Brazil. There is also the study by Hacker et al⁴⁰ (2004), which is of ecological nature. The recent paper by Brito et al¹⁶ (2005) explores the trends within the epidemic in the post-HAART era, giving emphasis to regional aspects. The question is also dealt with by Barbosa & Struchiner⁵ (2003), by means of mathematical modeling.

Brazil has studies that are representative of the population and continuous in time, and this has made it possible to establish trends within the epidemic, from analysis of serial sectional study panels. The successive assessment rounds on data from Brazilian army conscripts^{81,83}, the sentinel studies on pregnant women,⁷⁷ and also the use of the latter for estimating the number of people infected with HIV in this country can be highlighted.⁸⁰

Among the studies that are nationally representative, albeit without periodicity (as yet), the recent papers by Szwarcwald et al⁸² (2005) and Calazans et al¹⁸ (2005), assessing sexual practices, risky behavior and protection for young Brazilians, can be highlighted.

The use of other information systems for evaluating public policies has not been so successful, with few publications. This indicates the deficient and even discrepant integration between different systems. The work by Ferreira et al^{33,34} documents and evaluates the discrepancies between SINAN-AIDS and the Hospital Information System.

The use of other information systems is still halting,

probably due to their incompleteness and/or inconsistency. This is mentioned in the only paper on this subject that was found, which indirectly used data relating to the dispensing of antiretroviral drugs.²⁰

In summary, it can be seen that the two national systems (SIM and SINAN-AIDS) and some studies of broader coverage have given rise to papers published in indexed journals. The same needs to be achieved by other studies with national coverage and databases that present deficiencies that have made it difficult to analyze their results. There is a need to improve, update and integrate the databases that already exist, so that they can be fully utilized for formulating, monitoring and assessing public policies.

CONCLUSIONS

Brazil has implemented a consistent and diversified response within the field of HIV/AIDS, consisting of

studies relating to the development of anti-HIV/AIDS vaccines, including studies on HIV molecular epidemiology, viral resistance monitoring, new medications and epidemic monitoring.

Regarding the development of vaccines and their evaluation in representative samples, Brazil today faces complex questions relating to the dynamics of the epidemic itself (low prevalence and incidence) and materials (infrastructure). On the other hand, the country has been showing its competence in mapping out HIV molecular epidemiology.

Brazil is distinguished by high-quality domestic production of generic drugs, even though the expansion of the offer of these drugs at zero cost to patients is accompanied by significant adverse effects, relating to different medications and therapeutic schemes, and the emergence of resistant viral strains, all of which are central questions for research on HIV/AIDS today.

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