

Chapter 2

CAPRISA: Establishing a Research Centre to Undertake HIV Clinical Trials

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1 Background

The HIV/AIDS epidemic in South Africa is amongst the worst in the world. There are several unique features of the sub-Saharan HIV epidemic; it has been characterised as an explosive [1] epidemic, it is predominantly clade C [2], core groups are difficult to identify since the general heterosexual population is severely affected, the peak HIV prevalence rates demonstrate a marked gender difference (15–25 year women and 25–35 year men), and there is a preponderance of women amongst the HIV infected [3]. Denial and stigma were commonplace and discrimination against those infected abounded. Unfortunately, the scale of the response had simply not been able to keep pace with the rapid progression of the epidemic.

The early research response to AIDS in South Africa focused on defining the epidemic, measuring it and trying to predict its future course. Research during the first 10 years of the epidemic, until the mid-1990s, was comprised predominantly of knowledge, attitude and practice studies and HIV seroprevalence surveys. The mid-1990s saw the emergence of three new streams of AIDS research; firstly a re-emergence of molecular research characterising viral subtypes, viral receptor usage and immune responses; secondly the emergence of a clinical research effort, which included pharmaceutical industry sponsored therapeutic trials, and thirdly, the development of a new prevention research effort, comprising mainly phase III

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prevention trials, some of which occurred through the US National Institutes for Health (NIH)-funded HIV network known as HIVNET. The clinical research effort in South Africa comprised two components; the first led to several important studies of clinical presentation, diagnosis and management of AIDS and the second led to a multitude of therapeutic trials. In the mid-1990s, the number of prevention and therapeutic trials had increased exponentially. However, a distinct difference in the two types of trials emerged. The prevention trials, like the nonoxynol-9 microbicide trial, Petra Trial, Hlabisa STD trial and the vitamin A/exclusive breastfeeding trial, were being devised by South Africans in response to the pressing local problems of the AIDS epidemic. On the other hand, South Africa served as a convenient site for drug company therapeutic trials in which South African scientists had little contribution or ownership.

In the late 1990s, a new stream of research on HIV vaccines emerged, galvanised by support from the International AIDS vaccine Initiative (IAVI), South African AIDS Vaccine Initiative (SAAVI), the Joint United Program on HIV/AIDS (UNAIDS) and the HIV Vaccine Trial Network (HVTN). The transition from a preponderance of descriptive AIDS research to the dominance of intervention AIDS research occurred through a combination of a growing and maturing AIDS research community, newly established post-apartheid international collaboration and availability of funds from international agencies like UNAIDS, World Health Organisation and NIH.

2 Establishing a Research Centre to Undertake HIV Clinical Trials

As South Africa grappled with the epidemic in the 1990s, local AIDS researchers faced growing pressure to find public health solutions. The NIH's Comprehensive International Program of Research on AIDS (CIPRA) funding opportunity announcement presented a unique opportunity for South African scientists, in collaboration with leading US scientists, to make a new significant contribution to AIDS research.

A network of leading South African AIDS scientists had developed in the 1990s through the Fogarty AIDS training program, the NIH-sponsored HIV Prevention Trials Unit and HIV Vaccine Trials Unit, and the IAVI sponsored Alphavax HIV vaccine project. In 2001, senior AIDS researchers from some of South Africa's major research groups at the University of KwaZulu-Natal (formerly University of Natal), National Institute for Communicable Diseases (formerly National Institute for Virology), University of Cape Town, University of the Western Cape, University of Durban-Westville, Anglo-American's Aurum Health Research Unit and Columbia University in New York decided to combine their efforts to establish a multi-disciplinary collaborative program known as the Centre for the AIDS

Programme of Research in South Africa (CAPRISA). These AIDS researchers had experience with high-risk cohorts of sex workers, migrant workers and adolescents, had a track record of collaboration, well-established sound local leadership and collaborative research and training links with several US institutions. The creation of CAPRISA resulted in a consolidation of this group’s previous and existing collaborations and elevated it to the level of a vibrant, well co-ordinated and integrated team.

One of the major strengths of this team was its multi-disciplinary nature; CAPRISA brought together a team of South African researchers who had expertise in the areas of basic and molecular epidemiology, virology, immunology, infectious disease medicine, HIV primary care and service delivery, bioinformatics, social and behavioural science, statistics, ethics and health policy. Several international investigators contributed to the establishment of CAPRISA through their knowledge and experience by providing advice, training and support in HIV therapy, assay development, training and external quality assurance of complex laboratory assays. CAPRISA synergistically combined the complementary contribution of each discipline and each team member to make fundamental contributions to understanding clade C, heterosexually acquired HIV infection, elaborating the mechanisms by which prevention and therapy may impact on HIV natural history, and devising affordable programmatic approaches for making antiretroviral therapy a reality in resource-limited settings (Table 1).

Table 1 Extract of the summary statement and list of participating institutions and key personnel involved in the original CIPRA application
DESCRIPTION. State the application is broad, long-term objectives and specific aims, making reference to the health relatedness of the project. Describe concisely the research design and methods for achieving these goals. Avoid summaries of past accomplishments and the use of the first person. This description is meant to serve as a succinct and accurate description of the proposed work when separated from the application. If the application is funded, this description, as is, will become public information. Therefore, do not include proprietary/confidential information
The Collaborative AIDS Program of Research in South Africa (CAPRISA) is a multi-institutional team with well-established local leadership and expertise in the areas of basic and molecular epidemiology, virology, immunology, infectious disease medicine, HIV primary care and service delivery, bioinformatics, social and behavioural science, statistics, ethics and health policy. CAPRISA has three goals; (i) to undertake globally relevant and locally responsive research that contributes to understanding HIV pathogenesis and epidemiology as well as the nexus between tuberculosis and AIDS care, (ii) to build local research infrastructure though cores of expertise and (iii) to provide training through research fellowships tenable both in South Africa and the USA. CAPRISA comprises four research projects. The epidemiological studies on monitoring and deciphering the nuances of the evolving HIV/AIDS epidemic in a rural South African community lay the foundation for assessing the impact of therapeutic and prevention programs at community level. The clinical, immunological and virological studies on acute HIV infection elucidate the host and viral factors influencing the viral set (continued)

Table 1 (continued)

point and immune escape. Since the set point is currently the best prognostic marker of progression to AIDS, these data could have a substantial impact on future therapeutic and prevention research. Linked to this, is the study on highly exposed persistently seronegative individuals, which will provide clues to the genetic and immunological mechanisms of protection from HIV infection. The innovative clinical study integrating antiretroviral therapy into the tuberculosis directly observed therapy strategy could provide a mechanism for facilitating the implementation of antiretroviral therapy, with high levels of adherence, in developing countries.

An Executive Committee comprising the Project and Core Leaders governs CAPRISA. Besides managing the day-to-day CAPRISA operations, this committee also develops plans for future studies for review by the CAPRISA Scientific Advisory Board. Local research infrastructure is built through Cores for administration, epidemiology/biostatistics, viral diversity/bioinformatics and immunology. South African laboratories will be equipped to conduct assays locally and international collaborators will assist with training, advice, support, assay development and quality control. The training program includes several long- and short-term fellowships each year in laboratory science, clinical and epidemiological research and ethics.

If successful, CAPRISA could make seminal contributions to understanding the epidemiology of the subtype C, heterosexually acquired HIV infection, elaborating early immune responses in HIV infection, developing an understanding of the phenomenon of resistance to HIV infection, and making a contribution to AIDS care relevant to the developing world.

PERFORMANCE SITE (S) (organisation, city, state)

University of Natal, Durban, South Africa

University of Cape Town, South Africa

National Institute of Virology, Johannesburg, South Africa

University of the Western Cape, Bellville, South Africa

University of Durban-Westville, Durban, South Africa

Aurum Health Research (Pty) Ltd, Welkom, South Africa

Columbia University, New York, USA

Harvard University, Boston, USA

Duke University, Durham, USA

University of Washington, Seattle, USA

Yale University, New Haven, USA

University of North Carolina, Chapel Hill, USA

Henry Jackson Foundation, Rockville, Maryland, USA

Key personnel

Salim Abdool Karim , MBChB, MMED Ph.D.	Principal Investigator
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	Core Leader: A
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	Project Leader: 4
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Clive Gray , Ph.D.	Project Leader: 3
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Quarraisha Abdool Karim , Ph.D.	Project Leader: 1
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Brian Gerard Williamson , Ph.D.	Core Leader: B
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Carolyn Williamson , Ph.D.	Core Leader: C
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(continued)

Table 1 (continued)

	Project Leader: 2
Lynn Morris, DPhil	Core Leader: D
Other key personnel	
South Africa	U.S.A.
Farida Amod, MBChB, FCPATH	Ronald Bayer, Ph.D.
Sharon Cassol, Ph.D.	Wafaa El-Sadr, MD, MPH
Gavin Churchyard, Ph.D.	Guido Ferrari, MD
Mahomed Dada, MBChB, MMed	Gerald Friedland, MD
Robert Dorrington, Ph.D.	Phillip Goulder, MD, MRCP, DPhil
Eleanor Gouws, MS, MPH	Scott Hammer, MD
Winston Hide, Ph.D.	Christine Hogan, MD, MPH
Champaklal Jinabhai, MBChB, MMed	David Hoos, MD, MPH
Honest Kagoro, MSc	Bruce Levin, Ph.D.
Ayesha Kharsany, Ph.D.	Francine McCutchan, Ph.D.
Umesh Laloo, MBChB, FCP, MD	Juliana McElrath, MD
Gethwana Makhaye, B Soc Sci (Hons)	David Montefiori, Ph.D.
Maila Matjila, MBChB, MMed	James Mullins, MD, Ph.D.
Jagidesa Moodley, MBChB, MD	Marita Murrman, EdD
Landon Myer, MA	Paul Sharp, Ph.D.
Maria Papathanasopoulos, Ph.D.	Zena Stein, MD
Adrian Puren, Ph.D.	Ezra Susser, MD, Dr. PH
Linda Richter, Ph.D.	Mervyn Susser, MBChB, MRCP
Cathal Seoighe, Ph.D.	Ronald Swanstrom, Ph.D.
Mpilenhle Sithole, Ph.D.	Bruce Walker, MD
Willem Stürm, Ph.D.	
Jo van Harmelen, Ph.D.	

Through CAPRISA, the various existing, and in some cases long-standing, South African-United States collaborations were consolidated and expanded. CAPRISA drew upon the unique strengths of each local and international member of the team to benefit from the synergy of working together.

Through CAPRISA:

- the team moved beyond the conduct of prevention trials by combining this strength with fundamental research that enabled a deeper understanding at the molecular level. This provided an opportunity for South Africa to also contribute to the design of interventions, to an understanding of how interventions work and to better measurement of the impact of interventions,
- the team moved beyond being a site for research to becoming a model of local leadership in excellence in AIDS research embracing innovation, responsiveness to South Africa's needs and training to continue to build local research capacity,

- a strong new foundation and research infrastructure was created for existing and future research, not only for CAPRISA but also for research funded by other sources and being conducted outside the ambit of CAPRISA,
- a longer term vision was created leading to a stable long-term collaboration thereby creating an impetus for neglected areas of AIDS research, such as operational research for the implementation of antiretroviral therapy, and
- South African AIDS research was able to make a significant contribution to global research on AIDS prevention and therapy.

3 The CAPRISA Projects and Cores

The HIV/AIDS epidemic in South Africa had created many new challenges, particularly those related to the distinctive characteristics of the epidemic in this region. Fundamental to understanding these characteristics, was the need for a comprehensive understanding of the epidemiology of HIV in South Africa. The gender differences in HIV prevalence coupled with age-related behavioural and biological factors needed to be elucidated. Factors influencing progression to AIDS and mechanisms of protection from HIV infection were largely unexplored in southern Africa. The issue of whether subtype C viruses were different from others in its natural history, pathogenesis and prognosis was yet another interaction that needed to be further understood.

CAPRISA proposed to establish four inter-related projects that address the need to understand HIV infection at the levels of the community, health service provision, individual host, virus and immune responses. The projects proposed (described below) were supported by four cores dealing with administration, epidemiology/biostatistics, viral diversity/bioinformatics and immunology. The overall goal was to produce a locally appropriate but globally relevant research response to the explosive HIV/AIDS epidemic in South Africa.

The CAPRISA project on the evolving epidemiology of HIV/AIDS (Project 1) aimed to collect the essential epidemiological data to understand trends in HIV prevalence and incidence, AIDS incidence and AIDS mortality. The CAPRISA epidemiological studies on tracking and deciphering the nuances of the evolving South African HIV/AIDS epidemic were the foundation of this program. Not only would these studies provide the essential baseline data for assessing the community level impact of future antiretroviral therapy and HIV prevention interventions, but the process of undertaking these studies would strengthen current efforts to develop and test community-based interventions such as microbicides, vaccines, adolescent behavioural change, voluntary counselling and testing and any other intervention aimed at preventing or treating HIV/AIDS. The studies would also lay the foundation for the assessment of the impact of therapeutic and prevention programs at community level.

The CAPRISA project on acute seroconvertors (Project 2), took the bold step of trying to identify infected individuals even before they acquired HIV. The project proposed to study the viral diversity in the acute seroconvertors in Project 2 and the recently infected individuals from Project 1. The acute seroconvertors in Project 2 were followed-up more intensely to study the host and viral factors that affect the set point. Since the set point was the best prognostic indicator of progression to AIDS, it was one of the most common endpoints used in clinical trials for therapy and, in some instances, prevention. Since little was known about the set point in the southern African setting, this project was an essential prelude to future therapeutic and prevention efficacy trials. The clinical spectrum of acute retroviral disease was also studied to identify any distinguishing symptoms and/or signs that mark a difference from that seen in the developed world. Some of the host factors that may result in differences are HLA distribution, younger age of infection and predominant heterosexual mode of transmission while the viral subtype differences (subtype C in southern Africa versus subtype B in developed countries) were also assessed as they may also impact on the set point.

In the Project 2 acute seroconvertors, the assessment of early CTL responses to Tat, Nef, Gag and other peptides, together with genetic characterization of the earliest viral swarms, provided valuable baseline data to investigate viral escape. The selective pressure of both cellular and later humoral responses were investigated to understand viral escape.

The role of HLA, coreceptor use and humoral responses, was investigated to determine whether they influence the set point. The early evolution of the virus in the presence of initial CTL and neutralising antibody responses provided clues to understanding the mechanisms of viral escape. Project 2 provided important data for future secondary prevention interventions, i.e. interventions aimed at preventing AIDS after HIV has occurred. Such interventions, which aim to reduce the set point, have potential benefits for the patient by reducing the risk of progression to AIDS and, importantly, have potential public health benefits by reducing the risk of transmission of the virus.

Within the cohorts of high risk individuals in Project 2, there are small numbers of individuals who are at high risk but do not become infected with HIV. These highly exposed persistently seronegative individuals were investigated in Project 3 to discover clues to protection from HIV infection. A cohort of HIV negative female sex workers was established. During the follow-up of these Project 3 participants, T cell and macrophage function were examined to determine what role, if any, they play role in protection from HIV infection. In Project 3, the possibility of latent HIV infection in CD4+ T cells was investigated to determine if low-level infection was intermittently stimulating T cell immunity in these individuals. Project 3 also aimed to assess whether stimulation by other sexually transmitted infections induces cytokine/chemokine expression which can render cells of the monocyte/macrophage lineage resistant to HIV infection.

The CAPRISA clinical, immunological and virological studies on acute HIV infection and mechanisms of resistance amongst highly exposed persistently seronegative individuals complemented and strengthened the team's existing research on HIV immunology and natural history.

Highly exposed persistently seronegative individuals are only a small group; the majority of those at high risk of HIV were becoming infected and were progressing to AIDS. The most common AIDS-defining illness in these patients is tuberculosis. As the cost of the antiretroviral drugs was falling and their affordability in middle-income countries was imminent in 2002, the key question in the original CIPRA grant was not *whether* to introduce antiretroviral therapy but *how* to do so.

CAPRISA Project 4 addressed the central issue of therapeutic adherence in the implementation of antiretroviral therapy in resource-constrained settings. A randomised control trial was conducted to assess the effectiveness of integrated tuberculosis and HIV care, including antiretroviral drugs provided through the tuberculosis directly observed therapy program with an enhanced adherence intervention.

Since tuberculosis is the commonest presenting illness in AIDS patients in much of the developing world, the integration of HIV and tuberculosis care was an efficient method of identifying those in greatest need of antiretroviral therapy. Project 4 studied the strategy of linking antiretroviral therapy to the widely available, affordable and sustainable tuberculosis directly observed therapy strategy. It tested whether, by addressing issues of therapeutic potency and adherence, therapeutic outcome for both diseases could be enhanced. This study was innovative and both complemented and strengthened the current efforts by the private sector, in particular, the Anglo-American mining conglomerate to introduce antiretroviral therapy.

3.1 Overall Specific Aims of CAPRISA at Inception

1. To describe the evolving epidemiology of HIV infection, impact of AIDS on the social conditions of a community, impact of AIDS-related clinical illness on healthcare provision, and trends in mortality rates as a prelude to future HIV prevention and therapeutic interventions.
2. To describe the course of acute HIV infection and determine the host and viral factors influencing the level of the set point in anticipation of future intervention studies where it is the primary outcome.
3. To characterise cell-mediated and mucosal immune responses in highly exposed persistently seronegative individuals to decipher clues to the nature of HIV resistance and thereby contribute to devising HIV prevention strategies.
4. To assess the feasibility and effectiveness of the tuberculosis directly observed therapy strategy in maintaining high levels of adherence to antiretroviral therapy in patients co-infected with tuberculosis, the most common presenting AIDS illness in South Africa.

5. To complement and extend the current South African Fogarty AIDS Training Program to build in-country AIDS research capacity.
6. To establish the research infrastructure required for the conduct of current and future basic, clinical, epidemiological and operational research in HIV prevention and care.

4 CAPRISA Is Born!

CAPRISA was established as an independent not-for-profit legal entity to undertake AIDS research in 2002. It was one of five Research Centres established with CIPRA funding throughout the world and has become a well-established, world-renowned AIDS Research Centre conducting innovative research on HIV pathogenesis, TB-HIV treatment and HIV prevention. CAPRISA's research aims to contribute new knowledge on HIV and TB prevention and treatment. The main goals of CAPRISA are to conduct locally responsive and globally relevant research on HIV/AIDS and TB, with a strong focus on HIV prevention, while building research infrastructure and providing research training opportunities for the next generation of scientists. Although CAPRISA was initially funded to only undertake Project 2 and Project 4, the CIPRA grant served as a strong foundation to diversify its funding base and support cutting edge research. CAPRISA has continued to build on the foundation studies funded by CIPRA and has moved on to answering the next set of questions emanating from the completion of the CIPRA-funded research. Research at CAPRISA is currently conducted in four main Scientific Programs namely: HIV Pathogenesis and Vaccines, HIV and TB treatment, Microbicides, and Prevention/Epidemiology with several concurrent studies ongoing in each of the research areas. CAPRISA has a proven track record for conducting high-impact studies which have influenced the microbicide and vaccine fields as well as international TB-HIV treatment guidelines.

Research activities at CAPRISA are currently supported by nine research support cores including Administration, Statistics and Data Management, Information Systems, Laboratory, Quality assurance, Community, Pharmacy, Bioethics, Media and Communications and Training. Many of these cores were not part of the original CIPRA application but once the centre was established, it soon became apparent that other cores would be required. The data management, pharmacy and laboratory cores in particular have proved to be invaluable.

Significant investments were made to establish a state-of-the-art data management system at CAPRISA to cope with the large volume of data being generated by studies. Although both paper-based and electronic data management systems are used, CAPRISA chose to invest in the DataFax system as its primary electronic data management system. CAPRISA has a high-level computing capability including broadband access, made possible by their links, mostly with microwave technology,

with the University of KwaZulu-Natal IT systems. Faxing is seldom, if ever, done through analogue telephone lines.

The Data management systems used in CAPRISA are CFR Part 11 compliant and Data Management standard processes are aligned with the Good Clinical Data Management Processes (GCDMP). The Data Management Department is capable of high-throughput capacity due to experienced staff and a robust information technology infrastructure, with about 150,000 case report forms (CRFs) being successfully processed each year. Some examples of the Core's capacity for high throughput and coordination and management of data for large studies comes from the CAPRISA 004 tenofovir gel trial with 181,000 records successfully faxed and validated in 3 years, and the CAPRISA 007 RHIVA trial with 250,000 records being processed in 2 years.

The CAPRISA Laboratory was established in 2003 with a small, well-defined portfolio that has grown to include the following specialised assays including: Immunophenotyping CD3/CD4/CD8, HIV RNA PCR by Roche TaqMan v 2.0 and Abbott M2000, HIV DNA PCR using the Roche TaqMan v2.0, HIV ELISA manual and using the BEP 2000, HIV Western Blot, rapid *Trichomonas* and BV testing, wet mount and microscopy, HSV and HPV ELISA, and HPV genotyping. Specimen processing includes: peripheral blood mononuclear cell (PBMC) preparations, cytobrush washing and processing, cervical vaginal lavage processing, and routine serum and plasma processing and storage.

The Laboratory Core (see Chap. 12) supports all research underway at CAPRISA, including providing input during protocol design on the use of suitable assays, development of Laboratory Request Forms (LRF) for documenting laboratory requests and findings, and setting up systems required for ensuring high quality on-site testing, specimen shipment, processing and capturing of all specimens received and following up on outstanding laboratory results. The Laboratory Core also maintains a specimen repository, which has 14 ultrafreezers and five liquid nitrogen freezers, currently holding close to a million barcoded vials such that an individual vial can be retrieved on request within an hour. This bio-bank is an important resource and has generated numerous new research ideas.

The CIPRA funding was also essential for the establishment of the necessary clinical research infrastructure to conduct clinical trials. CAPRISA currently conducts its clinical trials at two CAPRISA Research Clinics in KwaZulu-Natal; one located in Durban (urban site) and the other in Vulindlela (rural site). These sites have well-developed clinical trial infrastructure and trained staff with experience in conducting clinical trials.

The CAPRISA Vulindlela Research Clinic is situated in a rural community with approximately 90,000 residents in the KwaZulu-Natal midlands, about 150 km north-west of Durban. CAPRISA has conducted several clinical trials at this rural research clinic. The Vulindlela Research Clinic is conveniently located adjacent to a provincial department of health run clinic called the Mafakatini Primary Health Care Clinic.

The CAPRISA eThekweni Research Clinic is located adjacent to the Prince Cyril Zulu Communicable Disease Centre, which provides services specifically for the

diagnosis and treatment of STIs and tuberculosis. The clinic is conveniently situated in the Warwick triangle in the transport hub of Durban, making it readily accessible in terms of the transport infrastructure. Annually, approximately 40,000 cases of STIs are treated at this clinic, approximately 36,000 of which are new cases. The majority of the STI patients accessing these facilities are self-referred, either symptomatic with genital ulceration and/or vaginal discharge syndrome or as contacts of patients with a diagnosis of a STI and include both males and females.

5 Progress to a Well-Established AIDS Research Organisation

Since those early days when CAPRISA was created, the organisation is today a well-established and world-renowned research institute. It has undertaken several pivotal studies, breaking new ground on the use of antiretrovirals for HIV prevention and on TB-HIV treatment, amongst others. CAPRISA is recognised as a global Centre of Excellence, producing high-impact research on HIV prevention and treatment. On 13 December 2013, CAPRISA was formally recognised as an independent research organisation eligible for funding from the government's National Research Foundation (NRF). The Department of Science and Technology (DST) declared CAPRISA as one of eight organisations with this official status, as published in Government Gazette (No. 37123) of 2013. This status enables CAPRISA to become part of the research activities, funding streams and fora that constitute the official South African research landscape. CAPRISA is a UNAIDS Collaborating Centre on HIV Research and Policy, a SA MRC Collaborating Centre for HIV and TB Research, a SA MRC-CAPRISA HIV-TB Pathogenesis and Treatment Research Unit and a NRF-DST Centre of Excellence in HIV Prevention.

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