UZ-UCSF Collaborative Research Programme: 1994–2014

Twenty years of innovative research on HIV and AIDS prevention, care and treatment in Zimbabwe and globally

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UZ UCSF

Saving lives through innovative research strategies

We dedicate this Twentieth Anniversary Report, with profound gratitude, to the men, women, and children of Zimbabwe who have participated in our HIV/AIDS research studies.

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Cover photo of Dombashawa, Harare, Zimbabwe:
Amy J. Markowitz
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Emily Patrick, and Amy J. Markowitz

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Zimbabwe National Family Planning Council

Acronyms and abbreviations

ACTG	AIDS Clinical Trials Group
AIDS	Acquired Immunodeficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral Drug
BSc	Bachelor of Science
CAB	Community Advisory Board
CAP	College of American Pathologists
CBO	Community-based Organisation
CDC	U.S. Centers for Disease Control and Prevention
CFAR	Centers for AIDS Research
COC	Combined Oral Contraceptives
CRS	Clinical Research Site
CTU	Clinical Trials Unit
DAIDS	National Institute of Allergy and Infectious Diseases-Division of AIDS
DART	Development of Antiretroviral Therapy in Africa Trial
DfID	Department for International Development
DMPA	Depot-medroxyprogesterone Acetate
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked Immunosorbent Assay
ESTP	Emergency Short Term Plan
FBO	Faith-based Organisation
FRCOG	Fellow of the Royal College of Obstetricians and Gynaecologists
FRCP	Fellow of the Royal College of Physicians
GCLP	Good Clinical Laboratory Practice
GSK	GlaxoSmithKline
HIV	Human Immunodeficiency Virus
HIVNET	HIV Network for Prevention Trials
HPTN	HIV Prevention Trials Network
HPTU	HIV Prevention Trials Unit
HPV	Human Papillomavirus
HVTN	HIV Vaccine Trials Network
IMPAACT	International Maternal, Pediatric, Adolescent AIDS Clinical Trials Network
IRB	Institutional Review Board
IRIS	Immune Reconstitution Inflammatory Syndrome
ISO	Independent Service Organisation
KAP	Knowledge, Attitudes, and Practices
MBChB	Bachelor of Medicine and Bachelor of Surgery
MIRA	Methods for Improving Reproductive Health In Africa
MMed	Master of Medicine
MoHCC	Zimbabwe Ministry of Health and Child Care
MPHE	Master's in Public Health Education
MSM	Men Who Have Sex with Men
MTN	Microbicides Trial Network
MTP1	Mid Term Plan 1
MTP2	Mid Term Plan 2
NGO	Non-governmental Organisation
NIAID	U.S. National Institute of Allergy and Infectious Diseases

NICHD	U.S. Eunice Kennedy Shriver National Institute of Child Health and Human Development
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTI	Nucleoside (Nucleotide) Reverse Transcriptase Inhibitors
NVP	Nevirapine
PACTG	Pediatric AIDS Clinical Trials Group
PACTU	Pediatric AIDS Clinical Trials Unit
PCR	Polymerase Chain Reaction
PEPFAR	U.S. President's Emergency Plan For AIDS Relief
PharmD	Doctor of Pharmacy
PMTCT	Prevention of Mother-to-Child Transmission
PrEP	Pre-exposure Prophylaxis
SANAS	South African National Accreditation System
SRH	Sexual and Reproductive Health
STI	Sexually Transmitted Infection
TB	Tuberculosis
UCHSC	University of Colorado Health Science Center
UCSF	University of California, San Francisco
UKNEQAS	United Kingdom National External Quality Assessment Service
UNAIDS	Joint United Nations Programme on HIV and AIDS
USAID	U.S. Agency for International Development
UZ	University of Zimbabwe
UZCHS	University of Zimbabwe College of Health Sciences
UZ-CRC	University of Zimbabwe-Clinical Research Centre
VQA	Virology Quality Assurance
WHO	World Health Organization
ZAPP	Zimbabwe AIDS Prevention Programme
ZNASP	Zimbabwe National HIV and AIDS Strategic Plan
ZNFPC	Zimbabwe National Family Planning Council

Message from the Leadership

The story of the UZ-UCSF Collaborative Research Programme and Clinical Trials Unit is unique. It is a truly collaborative, global research enterprise—both a place and an ethos in which the enigmas of the pandemic, in the face of socio-economic difficulties, inspire a sustained collective effort to rise and meet the next challenge. Our study participants, the dedicated staff, and our esteemed sponsors have supported the UZ-UCSF Programme's rise from a single research project about local HIV risk factors to become what the Dean of the University of Zimbabwe College of Health Sciences, Professor Midion Mapfumo Chidzonga, hailed as "our flagship HIV and AIDS research programme at the University of Zimbabwe." We are humbled, thankful, and motivated to do what is required to stem the tide of HIV and AIDS. While this report provides only a glimpse of our work to date, we hope it inspires you to become a collaborator in our efforts toward elimination of HIV infection for future generations.

Programme Leadership

Z. M. Chirenje, MD, FRCOG, with over two decades of experience in research administration and scientific leadership, is a founding Principal Investigator and Executive Director of the Programme. He is a Professor of Obstetrics and Gynaecology at the University of Zimbabwe College of Health Sciences and also holds an appointment in the Department of Obstetrics, Gynecology, and Reproductive Sciences at the UCSF School of Medicine. Dr. Chirenje is a member of the scientific advisory committee of the International Partnership for Microbicides, as well as a member of the World Health Organization (WHO) HPV expert committee.

Tsungai Chipato, MBChB, FRCOG, is a Professor of Obstetrics and Gynaecology at the University of Zimbabwe College of Health Sciences with more than 16 years of experience leading clinical trials, including pharmacokinetic studies and Phase III placebo controlled trials. He is a Co-Director of the UZ-UCSF Programme, sits on the Executive Committee, and serves as Leader of the St. Mary's Clinical Research Site. Dr. Chipato is a member of the Medical Research Council of Zimbabwe Technical Committee and is the current Chair of the Board of the Zimbabwe National Family Council.

James G. Hakim, MBChB, FRCP, is a Professor of Medicine at the University of Zimbabwe College of Health Sciences and a cardiologist with 20 years of experience conducting clinical trials. He holds a position as an adjunct Professor of Medicine at the University of Colorado, Denver. Dr. Hakim has served as Co-Director of the UZ-UCSF Programme since 2000, sits on its Executive Committee, and is the Leader of the Parirenyatwa Clinical Research Site. He is an active member of national and global research networks setting priorities for AIDS and HIV clinical trials.

Mike Mbizvo, D.Phil, M.Phil, MSc, with more than 25 years of global and national research leadership experience, is a Professor at the University of Zimbabwe College of Health Sciences and a founding Principal Investigator of the UZ-UCSF Programme. Until March 2013 he served as Director of Reproductive Health and Research at the World Health Organization (WHO), Geneva, setting policy development and strategic research direction, including global standards for improving HIV prevention and care. Upon retirement from WHO in 2013, Dr. Mbizvo returned to the University of Zimbabwe and serves on the Executive Committee of the UZ-UCSF Programme.

Executive summary

This Twentieth Anniversary Report presents the history and achievements of the **UZ-UCSF Collaborative Research Programme and Clinical Trials Unit** (the Programme), a research collaboration between the University of Zimbabwe (UZ) and the University of California, San Francisco (UCSF). We are committed to conducting innovative, rigorous research on HIV and AIDS, including studies on the prevention and treatment of the disease and its comorbidities. In turn, this effort will help achieve the goal of HIV elimination in Zimbabwe through the implementation of a broad program of evidence-based prevention interventions.

The HIV/AIDS pandemic in Zimbabwe

Currently HIV prevalence in Zimbabwe is 15% in people aged 15–49 years, and the incidence rate is approximately 1%. As of 2012, an estimated 1.3 million adults and children are living with HIV/AIDS. The main route of HIV transmission is overwhelmingly heterosexual (>90%). The face of AIDS in Zimbabwe today is predominately female, but with co-morbidities such as TB and HIV-associated cancers increasing among all populations.

Aligning global AIDS research with national priorities

Zimbabwe's most recent strategic plan, ZNASP 2011–2015, sets out four goals: Reduce overall HIV incidence by 50%, reduce child HIV incidence to <5%, reduce overall HIV/AIDS mortality by 38%, improve efficiency and effectiveness of the national multi-sectorial response. Research conducted by the UZ-UCSF Programme is closely aligned with Zimbabwe's national goals and global research priorities.

History of the Programme

The Programme represents the 20-year integration and evolution of three existing pillars of research and clinical care sites at UZ: the UZ-UCSF HIV Prevention Trials Unit, the UZ-Clinical Research Centre, and the UZ Paediatric AIDS Clinical Trials Unit. Together with collaborating UCSF research scientists and clinicians, we have grown from a modest beginning of three visionary leaders, a graduate student, a social scientist and two skilled research nurses to an internationally recognised Centre of Excellence for global HIV/AIDS research. The Programme is a vital collaborative effort of the UZ College of Health Sciences (UZCHS) and UCSF's Bixby Center for Reproductive Health, Department of Obstetrics, Gynecology and Reproductive Sciences. With principal funding through the U.S. National Institute of Allergy and Infectious Diseases-Division of AIDS (NIAID-DAIDS), our sustained growth and scientific contributions would not be possible without the ongoing support of the Zimbabwe Ministry of Health and Child Care (MoHCC), City of Chitungwiza Department of Health, City of Harare Health Department, and global health research foundations and collaborating universities around the world. With these partners' generous contributions of human resources, physical space, and material support we have an uninterrupted 20-year history of conducting innovative, groundbreaking research. Since the inception of the Programme we have conducted 63 research studies, and have enrolled 15,390 participants; 22 of these studies are ongoing, and we continue to develop capacity to identify and respond to emerging scientific priorities.

Programme leadership and infrastructure

The Programme is led by Principal Investigator (PI), Dr. Z. Mike Chirenje with senior leaders Dr. James Hakim (Parirenyatwa CRS leader), Dr. Tsungai Chipato (St. Mary's CRS Leader), and Dr. Mike Mbizvo who are advised by an Executive Committee and a Community Advisory Board. Professional administrative managers at both universities have worked together for over 15 years with a governance structure built on principles of inclusiveness of scientific, community, and administrative functions.

Six Clinical Research Sites (CRSs) form the core of our research programme: two are in Harare (Parirenyatwa, Spilhaus) and four are in Chitungwiza (Seke South, Zengeza, Seke North, St. Mary's). We employ over 300 full-time, qualified employees including 13 Medical Officers, 11 Pharmacists, 45 Research Nurses, and 12 Laboratory Scientists working on high priority prevention and treatment trials. Research conducted at the CRSs are supported by **both site-specific and Central Pharmacies and Laboratories**. These departments have proactively prepared to support future research priorities, including tuberculosis co-infection and vaccine research, with infrastructure investment and advanced personnel training.

The Community Department and a Community Advisory Board (CAB) serve as ambassadors between the local communities and the Programme. CAB activities in community sensitisation have resulted in rapid research study enrollment, a greater than 95% participant retention rate, and the timely dissemination of study findings to those whose lives are profoundly affected by the research and without whose participation the studies could not take place.

Key Programme achievements

Research/mentoring/dissemination

Our studies have helped to shape national and global responses to the pandemic, and have defined policies and standards regarding the course of HIV acquisition, prevention, treatment, and care. Some examples include groundbreaking research in antiretroviral therapy (ART) for HIV prevention, including ART in TB co-infected patients, ART for prevention in serodiscordant couples, and initiation and monitoring of paediatric ART. Other areas of research expertise include: microbicides for HIV prevention, community HIV testing strategies, and prevention of mother-to-child transmission. Additionally, we contribute to the national and global HIV/AIDS challenge by mentoring the next generation of Zimbabwean and global researchers. To date we have supported over 200 upper-level students and postgraduates with didactic and field training in clinical research. The extent of the Programme's contributions is reflected in more than 100 high quality scientific manuscripts published in major international journals.

Meeting the challenges ahead

As we move into our next decade, we are prepared to meet the pandemic's future challenges. We will continue to implement high impact research in HIV prevention, that will ultimately identify effective biomedical interventions (ARV-based gel formulations, the vaginal ring, or long-acting intramuscular injection) that women will find acceptable, are willing to use, and can choose among.

We will evaluate best strategies to improve ART adherence by testing objective, real-time measures that can assist in adherence messaging for HIV-infected populations, and continue research into treatment and management of co-morbidities. We will conduct combined prevention trials that include voluntary medical male circumcision, antiretroviral pre-exposure prohylaxis (PrEP), and HIV risk reduction packages. We will evaluate the best therapeutic interventions to reduce co-morbid infections and HIV-related cancers. The Programme will continue to conduct research to optimise reduction of mother-to-child transmission and treatment of HIV-infected mothers and children. Finally, we will initiate research toward the discovery of a vaccine for HIV, as part of the global effort to control the pandemic. As always, for the men, women, and children in our trials we will provide the highest quality of ethical care, including cutting-edge diagnostics, therapies, and specialist referrals aimed at supporting their health, safety, and well being.

The UZ-UCSF Programme remains dedicated to conducting front line research. It is only through this continued commitment that we will be able to conquer the HIV pandemic and declare it a thing of the past.

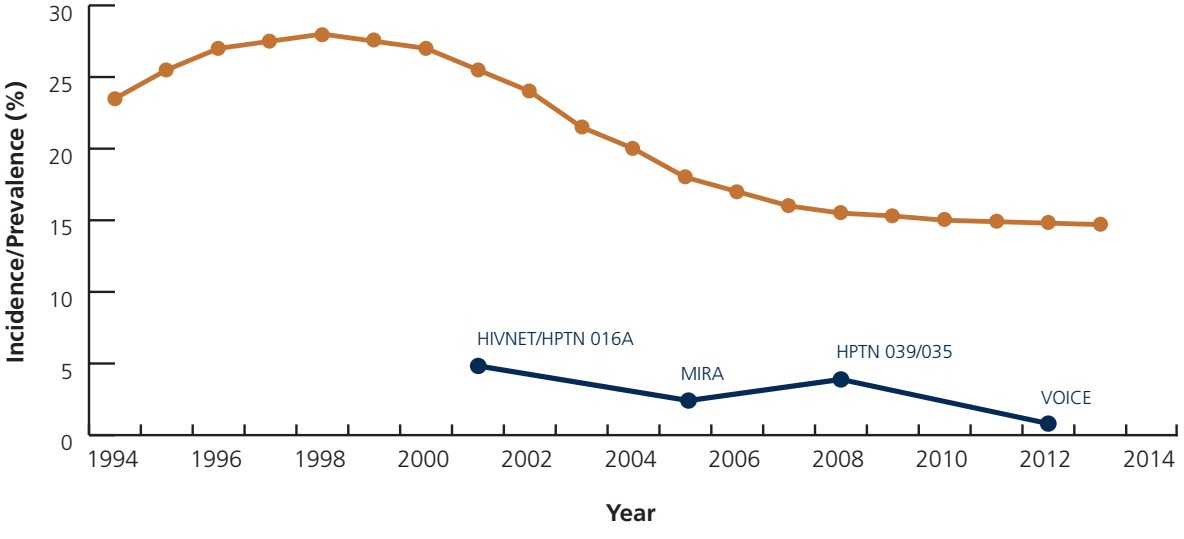
Figure 1. Map of Zimbabwe

Status at a glance: The HIV/AIDS pandemic in Zimbabwe

The University of Zimbabwe-University of California San Francisco Collaborative Research Programme and Clinical Trials Unit (UZ-UCSF Programme) sits in Harare, Zimbabwe (Figure 1), an epicentre of the global HIV pandemic. Zimbabwe continues to be extraordinarily burdened by HIV/AIDS. Among its population of 13 million people (52% female), the prevalence of HIV is 15% among adults age 15–49 years, including pregnant women.[1] The HIV incidence rate is approximately 1%[2] (see Figure 2).

As of 2012,[3] an estimated 1.3 million adults and children in Zimbabwe were living with HIV/AIDS. There were 186,745 HIV-infected children age <15 years; the number of orphans attributed to AIDS was 947,010. Data from the 2012 Zimbabwe Census report 161,000 adolescents living with HIV/AIDS. AIDS-related deaths have decreased from 75,130 in 2011 to 63,736 in 2012. The route of HIV transmission in Zimbabwe is mainly heterosexual (90%). High fertility rates (3.8 per woman) are associated with a vertical transmission rate (from mother to child during pregnancy) of 14%.

Figure 2. National HIV prevalence and HIV incidence from UZ-UCSF studies



The figure demonstrates a decline in Zimbabwe's National HIV prevalence that is mirrored by the decline in incidence evidenced by studies conducted by the UZ-UCSF Programme.

Progress has been steady, but is fragile. A snapshot comparison of data from even a decade ago makes this abundantly clear: in 2004, adult (age 15–49 years) HIV prevalence was estimated at 24.6%,[4] and it was estimated that 564 adults and children became infected with HIV daily.[5] Life expectancy had dropped from 66 years in 1997 to 38 years in 2002,[5, 6] it has gradually risen to 48 years for women and 50 years for men as of the 2012 census.[3] Women in Zimbabwe continue to be disproportionately affected by HIV/AIDS: although constituting 52% of the population, 58% of those living with HIV/AIDS in 2012 were women.

Today, Zimbabwe is still ranked among the highest burden countries for both TB and HIV. The incidence of TB cases was 433/100,000 in 2012, compared with 97/100,000 in 1990.[7] Among AIDS-related malignancies, 2010 data report 795 women had cervical cancer (32.2% of cancers among women), 528 persons (323 males and 205 females) had Kaposi sarcoma, and 248 (107 female and 141 male) had non-Hodgkin lymphoma. The Zimbabwe MoHCC introduced a National Antiretroviral Treatment (ART) programme in 2004 that currently treats 550,000 adults and 40,000 children. Using existing Zimbabwean guidelines, these figures represent 72% and 42% of treatment eligible adults and children, respectively.

Collaboration to address the pandemic: Aligning global AIDS research with national priorities

The widespread burden of disease on a demographically heterogeneous population, and the excellent training of the UZ-UCSF Programme research scientists, have made Harare a magnet for global HIV/AIDS research. The Programme's wide-reaching HIV/AIDS research workstreams are determined according to priorities developed through international collaborations, and focus on national and global strategic areas, including: Adult HIV Therapeutics, HIV-associated Infections in Paediatric and Maternal Populations, and Integrated HIV Prevention.

Our major sponsor, the U.S. National Institute of Allergy and Infectious Diseases Division of AIDS (NIAID-DAIDS) an institute of the U.S. National Institutes of Health, has established global Clinical Trials Units (http://www.niaid.nih.gov/about/organization/daids/networks/pages/daidsnetworks.aspx) to serve as centres of excellence at which to conduct rigorously designed HIV/AIDS studies. As one of 37 such global centres, and one of the largest, with six Clinical Research Sites (CRSs) in and near Zimbabwe's capital, Harare, we conduct studies across four DAIDS Research Networks: Microbicides Trial Network (MTN), International Maternal, Pediatric, Adolescent AIDS Clinical Trials (IMPAACT), AIDS Clinical Trials Group (ACTG), and HIV Prevention Trials Network (HPTN). We are preparing for a fifth network, the HIV Vaccine Trials Network (HVTN).

Global research priorities have evolved alongside the Zimbabwe national response to the HIV epidemic. Following the first reported case of HIV/AIDS in 1985 (see timeline below), a series of proactive policies and strategic plans have guided the national response.[8] The Programme is one of the multi-sectorial agencies responding directly or indirectly to the Government of Zimbabwe's national strategy.

Historical timeline of Zimbabwe's national response to the HIV/AIDS pandemic

1985	First case of AIDS in Zimbabwe reported
1987	Government establishes National AIDS Coordination Programme to lead national response, creates Emergency Short Term Plan (ESTP)
1989	HIV prevalence estimated to be 10% of the adult population
1989	Auxillia Chimusoro becomes first Zimbabwean to reveal her HIV-positive status on national television
1990–1997	HIV prevalence rises dramatically, peaking at 26.5% in 1997
1993	Mid Term Plan launched (MTP1)
1994–1999	Mid Term Plan 2 launched (MTP2)
1999	President launches National AIDS Policy and National Strategic Framework
1999	National AIDS Council formed through Act of Parliament to coordinate and facilitate the national multi-sectorial response to HIV/AIDS
1999	Nevirapine antiretroviral drug made available for PMTCT
1999	National PMTCT Programme launched in four districts
2000–2004	National HIV and AIDS Strategic Framework implemented
2002	President declares HIV a Zimbabwe National Health Emergency, introduces AIDS levy
2004	National ART Programme launched with 5 treatment centres; HIV prevalence estimated at 24.6% of adult population
2006–2010	Zimbabwe National HIV and AIDS Strategic Plan 1 (ZNASP 1)
2011–2015	Zimbabwe National HIV and AIDS Strategic Plan 2 (ZNASP 2)
2014	HIV prevalence estimated at 15% of adult population

Zimbabwe has adopted Resolution 65/277 of the UN General Assembly of 2011, The Political Declaration on HIV and AIDS: Intensifying our Efforts to Eliminate HIV and AIDS. This document was the foundation for Zimbabwe's National HIV and AIDS Strategic Plan (ZNASP 2011–2015), which sets out four goals (impact areas):

- **Reduce overall HIV incidence by 50%**
- **Reduce child HIV incidence to <5%**
- **Reduce overall HIV/AIDS mortality by 38%**
- **Improve efficiency and effectiveness of the national multi-sectorial response**

Research conducted by the UZ-UCSF Programme is closely aligned with Zimbabwe's national goals as well as global research priorities. In the sections that follow, we present our history and achievements over the past two decades, identifying the interventions that will help reduce incidence in both children and adults, and establishing best practices to care for those who have HIV coupled with co-morbidities such as tuberculosis, and AIDS-related malignancies.

The creation of today's UZ-UCSF Collaborative Research Programme and Clinical Trials Unit: Three pillars supporting a unity of purpose

The UZ-UCSF Collaborative Research Programme and Clinical Trials Unit represents the 20-year integration and evolution of three existing pillars of research and clinical care sited at the University of Zimbabwe: 1) the UZ-UCSF HIV Prevention Trials Unit; 2) the UZ-Clinical Research Centre; and 3) the UZ Paediatric AIDS Clinical Trials Unit. Their shared commitment was to the evidence-based investigation of the HIV/AIDS pandemic, coupled with tireless efforts to prevent and treat the disease and its comorbidities for the men, women, and children of Zimbabwe.

The first pillar: UZ-UCSF HIV Prevention Trials Unit (UZ-UCSF HPTU)

In 1994, Dr. Chirenje opened Zimbabwe's first colposcopy unit, pioneering the country's cervical cancer screening programme, sited at the Zimbabwe National Family Planning Council's (ZNFPC) Spilhaus Clinic. Dr. Mbizvo and Dr. Chirenje received a request from colleagues in the U.S., Dr. Nancy Padian (UCSF), and Dr. David Katzenstein (Stanford University), to serve as mentors for a postdoctoral graduate student, Janneke van de Wijgert. With funding support from CONRAD, a Fogarty International AIDS Training Grant, and UCSF, this newly formed international team launched a study to determine if intravaginal practices, such as cleaning the vagina with the fingers, wiping the vagina, or inserting traditional substances, were associated with disturbances of vaginal flora and acquisition of HIV and STDs among Zimbabwean women (see box on right).

Harnessing the infrastructure of the colposcopy unit, and enlisting the assistance of research nurses Magda Mwale and Prisca Nyamapfeni, and Social Scientist Gertrude Sakutukwa, Dr. Chirenje and the study team enrolled 169 Zimbabwean women, recruited from the family planning clinics of the Zimbabwe National Family Planning Council, primary care clinics of the City of Harare Health Department, and the postnatal clinic at Harare Central Hospital. This study established goodwill for research in the community by implementing best practices continued today:

- cervical cancer screening and treatment for all research participants
- Community Advisory Board participation
- free HIV testing, and treatment of curable STIs for participants and their partners

By the study's completion the research unit had not only collected useful scientific data, but as importantly, had built goodwill and trust in the community. The site was the first to implement cervical cancer screening and treatment for all research participants, at no cost, a practice since adopted by most research sites in HIV endemic countries. From the beginning, all research participants received respectful attention, free HIV testing, and treatment of curable STIs for themselves and their partners. Importantly, a Community Advisory Board was established to initiate and maintain ties between the researchers and the community (1995), the first site in an HIV endemic region to do so.

On the strength of its success,[9] the UZ-UCSF collaboration received its first international recognition as a sophisticated, research-ready site at which to conduct HIV-related trials.

From this productive start, the UZ-UCSF Collaborative Research Programme was founded, recruiting faculty from the Departments of Obstetrics and Gynaecology at UZ and from the Department of Obstetrics, Gynecology and Reproductive Sciences at UCSF. Under the direction of Drs. Chirenje, Mbizvo, and Padian, this collaboration became the UZ-UCSF HIV Prevention Trials Unit (UZ-UCSF HPTU). In the first years, the UZ-UCSF HPTU mainly conducted observational studies, researching questions including the acceptability of vaginal microbicides and condom promotion for HIV prevention.

In 1998, the site was awarded a grant from the NIAID-DAIDS HIV Prevention Trials Network (HIVNET), through the Zimbabwe AIDS Prevention Programme (ZAPP). The unit was the first and only site in the world to conduct the HIVNET 023 study, which established the safety and dosages of single dose nevirapine to prevent mother-to-child transmission of HIV to newborns. Shortly thereafter, HIVNET recruited the Programme to participate in four multi-site HIV prevention clinical trials, led by Principal Investigator Dr. Tsungai Chipato from the University of Zimbabwe.

In 2000, NIAID-DAIDS announced formation of its international HIV Prevention Trials Network (HPTN), to develop and test promising non-vaccine strategies to prevent the spread of HIV/AIDS. The UZ-UCSF HPTU was among the first sites selected for participation, aided by the reputation built after its high level conduct of the Development of Antiretroviral Therapy in Africa (DART) study, one of the first large ART studies in the region. This ability to conduct ART studies was instrumental in its being chosen in 2001 as a site for the landmark HPTN 052 study, which confirmed the effectiveness of ART use in preventing HIV transmission in HIV-serodiscordant couples. Under the local leadership of Dr. James Hakim of the UZ Department of Medicine, this seminal study proved that treating the HIV-positive partner with ART could prevent infection of the HIV-negative partner.

The second pillar: UZ-Clinical Research Centre (UZ-CRC)

The UZ-CRC was established in 2002 under the DAIDS Network AIDS Clinical Trials Group (ACTG) as one of the initial twelve non-US Clinical Trials Units (CTUs). Under this initiative, the UZ-CRC was paired with an ACTG Clinical Trials Unit at the University of Colorado Health Science Center (UCHSC) for training and mentoring. The UZ-CRC and UCHSC collaboration grew to include research activities in Kaposi sarcoma, and acute/early HIV infections.

The third pillar: UZ-Paediatric AIDS Clinical Trials Unit (UZ-PACTU)

The UZ-PACTU was established in 2003 under the leadership of Dr. Mutsa Bwakura-Dangarembizi, with the objective of developing research infrastructure, capacity, and clinical expertise to participate in perinatal and paediatric research studies that form the NIAID-DAIDS Pediatric AIDS Clinical Trial Group (PACTG). Its initial study involved observation and follow-up of children born to women enrolled in ACTG and HPTN studies who were exposed to a range of antiretroviral (ARV) drugs during pregnancy.

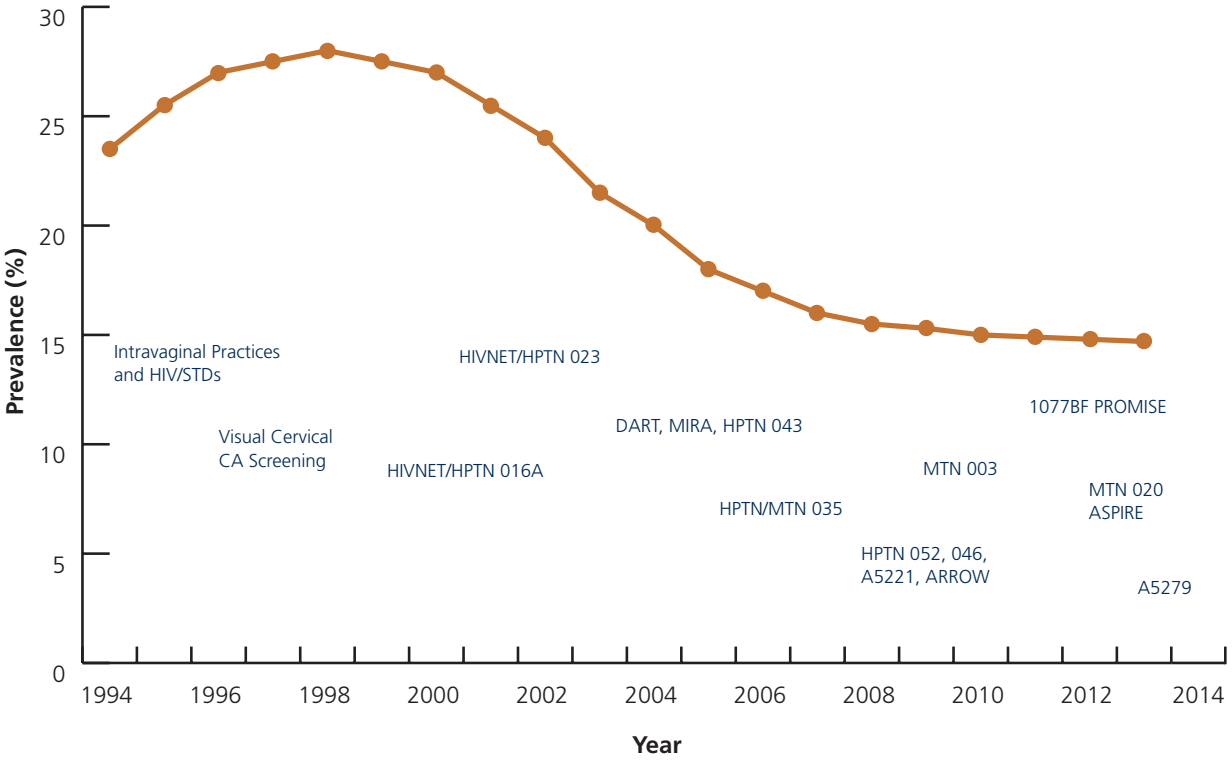
The launch of the UZ-UCSF Collaborative Research Programme and Clinical Trials Unit

From these years of individual efforts and with unity of purpose, in 2004 the three programmes combined to form the University of Zimbabwe-University of California San Francisco (UZ-UCSF) Collaborative Research Programme, with its Clinical Trials Unit. Our growth over the past 20 years has been exponential but our mission has never changed: to implement high quality science addressing HIV prevention and therapy. The fundamental aim, shared by our partners in the Zimbabwe MoHCC, is the control and elimination of Zimbabwe's HIV/AIDS epidemic. We contribute to national and global policy as a centre of excellence at the UZ College of Health Sciences (UZCHS).

From a modest beginning of three visionary leaders, a graduate student, a social scientist and two skilled research nurses operating in a single room, and through the unwavering support of our sponsors, our collaborating universities, MoHCC, Chitungwiza City Department of Health, and Harare City Health Department, we have matured into a well-respected, robust research centre. The Programme now employs over 300 staff at six clinical research sites (CRSs) within and surrounding Harare. Over the past 20 years we have collaborated on 63 research studies, enrolling 15,390 participants, including 512 mother-infant pairs.

At the time of this report, we are collaborating on 22 multi-site research studies, enrolling 1,286 participants (918 female, 262 male, 106 children), and 879 mother-infant pairs. This capacity, coupled with our state-of-the-art laboratory and pharmacy facilities, positions us to engage in sophisticated, groundbreaking research on HIV prevention, treatment of HIV infectious and non-infectious comorbidities, as well as vaccine trials. We are poised to take on the future challenges of the HIV/AIDS pandemic, with the energy and commitment borne of two decades of challenges and hard-won successes.

Figure 3. Timeline of representative Programme studies



Zimbabwe in recent years, has recorded significant decline in HIV prevalence. This decline is a result of collective efforts and the participation of key stakeholders, who include local and international scientists, who provided cutting-edge research and evidence that informed and guided our national response and programme implementation.

We are proud of our association with the UZ-UCSF Programme, a local and international university collaborative programme that has generated important research evidence that helped strengthen our programmes.

– Dr. Owen Mugurungi MD, MSc STI/HIV&AIDS
Director, AIDS & TB Programme
Zimbabwe Ministry of Health and Child Care

Summary of key achievements of the UZ-UCSF Programme

In pursuit of the objective to contribute to the national and global HIV/AIDS challenge, we are engaged in mentoring the next generation of Zimbabwean and global researchers. We have continuously committed to strengthening human resources as well as infrastructure to conduct and coordinate multidisciplinary research in HIV and sexual and reproductive health (SRH). The Programme's study findings have helped to shape national and global responses to the pandemic, and have defined policies and standards regarding the course of HIV acquisition, prevention, treatment, and care.

Mentoring

Our development of scientific human resources is evidenced by the over 200 local and international Master's Degree, doctoral, and other postgraduate students that have been supported by the Programme (see table on right). The Programme provides financial support as well as fieldwork opportunities and mentoring in clinical research design, scientific writing, and publication. Further support is provided by The Fogarty Foundation with didactic coursework to build capacity with independent researchers. Our mentored postgraduates have gone on to positions of leadership in NGOs and academic centres around the world.

UZ-UCSF Programme support of postgraduate and other training

Level of Study	Area of Research	Post-graduates
MPH	Public Health	5
Other Master's Degrees	Biostatistics, Medical Microbiology, Clinical Epidemiology, Clinical Chemistry, Clinical Trials, Developmental Studies, Social Sciences, Business Administration	30
PhD	International Community Health	1
Other Staff Development Fellowships	Advanced TB Lab Diagnostics, NIAID Grants Policy and Management, Laboratory Information Systems, Laboratory Data Management Systems, ISO15189, Cytology Training, HIV Management, Business Administration and Management, Clinical Quality Management Systems	198

Key scientific contributions

The Programme's key contributions to the global HIV/AIDS knowledge base span domains of ART for prevention of HIV, ART in TB co-infected patients, prevention of mother-to-child transmission, community HIV testing strategies, and initiation of paediatric ART, among other topics. A complete presentation of the Programme's 63 research studies over two decades is presented in the Appendix (and see Figure 3 on facing page). The extent of the Programme's contributions is reflected in more than 100 high quality scientific manuscripts published in the past two decades. Scientific findings and policy contributions from representative studies in which the Programme has participated include:

ART for Prevention in Serodiscordant Couples (Study HPTN 052)

The landmark 2011 HPTN 052 study was the first clinical trial to show that treating HIV-infected individuals with ART could reduce the risk of sexual transmission of HIV to their uninfected partners by 96%.[10] This study enrolled 1,763 HIV-serodiscordant couples at sites in Africa, Asia, and the Americas, with Zimbabwe contributing 240 couples. The study was nominated as the *Science* study of the year in 2011. Findings have informed global and national policies and programmes on HIV treatment, care, and prevention. The study forms the backbone of the 2012 recommendation by WHO to offer ART to all HIV-positive partners in a serodiscordant relationship, irrespective of CD4 count.[11]

The Development of Antiretroviral Therapy in Africa (DART Trial)

DART was one of the first large clinical trials of ART conducted in Zimbabwe and Uganda, enrolling 3,321 symptomatic, HIV-infected adults who had not been treated with ART (ART-naïve). The DART results, published 2010 in *The Lancet*, demonstrated that ART could be safely given with good clinical monitoring (and without expensive, routine biochemistry and haematology monitoring) in an African setting.[12]

ART in TB/HIV Co-infected Patients (Study ACTG A5221)

The A5221 trial was one of three major studies that put to rest debate as to when ART should be initiated in HIV-positive patents co-infected with TB. The aim of the study was to determine the efficacy and safety of initiating ART in HIV/TB co-infected patients early (within 2 weeks) compared with delayed initiation (8–10 weeks) after diagnosis of tuberculosis. The findings, published in the *New England Journal of Medicine* in 2011, demonstrated that for patients with CD4 counts >50 cmm there was no difference in efficacy whether ART was started earlier or later. However, starting ART early was associated with greater risk of IRIS (Immune Reconstitution Inflammatory Syndrome). For patients with CD4 count < 50 cells/cmm, starting ART early was more efficacious than delaying treatment.[13]

Prevention of Mother-to-Child Transmission (Study HPTN 046)

The milestone HPTN O46 study was sponsored by NIAID, NICHD, and later by the IMPAACT Network. The Programme demonstrated the benefits and safety of an extended infant nevirapine (NVP) regimen to prevent breast milk transmission of HIV, particularly in infants of HIV-infected mothers who did not require ART for their own health. Published first in *The Lancet*[14] in 2012 with further confirmatory results published in JAIDS in 2014,[15] HPTN 046 findings supported policy decisions to disseminate guidelines about the use of extended NVP in breastfeeding infants born to HIV-infected women. Study results from the HPTN 046 trial supported the Zimbabwe MoHCC's policy decision to adopt PMTCT Option A from the WHO 2010 guidelines.

Monitoring ART in African Children (ARROW Trial)

In this trial funded by the Department for International Development (DfID, UK) and the Medical Research Council (UK), Ugandan and Zimbabwean HIV-infected children or adolescents aged 3 months to 17 years and eligible for ART, were evaluated to determine whether ART monitoring could be safely conducted with careful clinical care and follow-up, rather than with expensive routine lab tests. As well, we investigated whether the combination therapy of NNRTI plus NRTI-based three-drug or four-drug ART could be given across childhood without expensive, routine toxicity monitoring. Our results,[16] published in 2013 in *The Lancet*, suggested that ART rollout should take priority, and that careful clinical monitoring could be safely used in place of routine lab tests. Data from the P1060 study are also noteworthy, as they supported the guideline change to treat all HIV-infected infants with a protease inhibitor-based regimen, especially those exposed to NVP.[17, 18]

Community HIV Testing Strategies (Study HPTN 043)

The Programme's HPTN 043 multi-centre study,[19] published in *The Lancet Infectious Diseases*, demonstrated that community mobilization boosts HIV testing rates in developing country settings. This study, in which the

Programme enrolled 33,958 participants (of 192,823 across the five global sites) was the first international randomized controlled Phase III trial to determine the efficacy of a community-level intervention with an HIV incidence endpoint. Importantly, 12,435 of our participants then entered the intervention phase (of 71,842 participants globally). Based on these results, the MoHCC scaled up HIV screening across Zimbabwe, including in rural communities.

Microbicides for HIV Prevention (HPTN 035 and MTN 003)

Programme results from the HPTN 035 study demonstrated that non-ARV based microbicides do not prevent HIV acquisition among women at risk.[20] The VOICE trial (MTN 003) found that daily tenofovir gel, oral tenofovir, and oral Truvada® did not reduce the risk of HIV acquisition in young women at risk for HIV.[21] Notably, most participants in VOICE failed to use the study products daily, particularly young, unmarried women. This highlights the urgent need for safe, effective and practical HIV prevention methods that young, unmarried women will actually use. Results of two on-going qualitative behavioral studies should help to better understand the reasons why so many women did not use the study products in VOICE.

Hormonal Contraception (HC) and the Risk of HIV-1 Acquisition

The Programme was among the first centres to study and publish[22] on the relationship between hormonal contraception and risk of HIV acquisition (HIVNET 021). In this NIH-funded multi-centre observational study, we evaluated the risk of HIV acquisition among women using combined oral contraceptives (COC) and depot-medroxyprogesterone acetate (DMPA). This study was among the first to have informed WHO's recommendations on hormonal contraception and HIV risk, promulgated by an expert panel convened by UZ-UCSF leader Dr. Mbizvo, and which included UZ-UCSF PI Dr. Chipato.

Hormonal Contraception and the Risk of HIV-1 Genital Shedding among Women with Primary HIV infection

In another of our studies,[23] among women who sero-converted during an HC and HIV acquisition study, plasma and cervical viral loads during acute and early HIV infection were assessed in a prospective cohort. The HIV viral loads were highest during acute infection and then declined up to six months following infection, when a "setpoint" was attained.

Methods for Improving Reproductive Health in Africa (MIRA) Trial

With funding from the Bill and Melinda Gates Foundation, the Programme conducted a multi-centre randomized controlled trial in HIV-negative women to determine the potential for diaphragm and lubricant gel insertion to prevent HIV acquisition. The study demonstrated that there was no added protective benefit against HIV infection when the diaphragm and lubricant gel were provided in addition to condoms and a comprehensive HIV prevention package.

Capacity development in response to emerging scientific priorities

The Programme has demonstrated rapid and flexible responses to emerging scientific priorities with a highly attuned and scientifically sophisticated leadership, centralized management, and a Programme-wide policy of continuous human resource training and infrastructure updates, combined with deeply rooted Community Advisory Boards.

The Programme's infrastructure and capacity for growth are presented in a later section of this report, however, several achievements are notable. Upon recognising the increasing prevalence of HIV-associated malignancies, and following a visit from the AIDS Malignancy Consortium in 2009, the Programme constructed an aseptic room for handling cytotoxic drugs to accommodate oncology studies. We have established a bio-safety level 3 containment TB laboratory and a pharmacology specialty lab to support pharmacokinetic and bioequivalence studies. We will recruit participants from the greater Harare area to address non-infectious co-morbidities

such as metabolic syndromes, neuropsychological complications, and premature aging that result from chronic HIV infection. The same population will also provide participants for studies on infectious co-morbidities, such as TB.

Additionally, we are developing HIV Vaccine Clinical Trials capacity. We have sensitised our Internal Review Boards (IRBs), regulatory bodies, the CAB, and the community at large, to our intention to participate in future HIV vaccine trials. The DAIDS Vaccine Network leadership conducted a site visit in January 2013 and expressed high interest in collaborating with the Programme as vaccine trials are funded.

Collaboration and harmonisation with research regulatory authorities

The UZ-UCSF Programme conducts clinical research pursuant to national, regional, municipal, and institutional regulations. We work closely with Zimbabwe's regulatory framework to ensure ethical and scientifically sound research that informs health policy and practice in the country. Our Programme has benefitted from the guidance and support of IRB leadership at all levels to ensure compliance and the timely approval of new studies, annual renewals, and permits. In particular we would like to recognise the tireless efforts of the University of Zimbabwe Joint Parirenyatwa Hospital and College of Health Sciences Research Ethics Committee, Medical Research Council of Zimbabwe, Research Council of Zimbabwe, Medicines Control Authority of Zimbabwe, and the UCSF Committee on Human Research in working toward our common goal of research conduct that meets the highest human research protection standards. The following is a summary of the regulatory institutions that mandate regulatory compliance, illustrating ways that we have worked together to ensure the highest standards of practice:

University of Zimbabwe, Joint Parirenyatwa Hospital and College of Health Sciences Research Ethics Committee (JREC)

UZ-UCSF Collaborative Research Programme is affiliated with the University of Zimbabwe College of Health Sciences (UZCHS). Investigators of Record conducting research in the Programme are faculty members at the UZCHS, thus their research studies are reviewed by JREC. JREC offers initial as well as continuing review of applications.

Medical Research Council of Zimbabwe (MRCZ)

The MRCZ is the National Ethics Committee (NEC), established by the Government of Zimbabwe to provide health researchers and institutions with independent ethics oversight. The MRCZ has established a Technical Committee (TC) that serves as the National Research Ethics Committee. The TC provides ethical review of new and continuing applications.

Research Council of Zimbabwe (RCZ)

RCZ advises government on issues of research for sustainable development. RCZ requires that all foreign researchers/investigators and any person wishing to conduct research in Zimbabwe on behalf of a foreign institution, foreign organization, or other foreign person obtain a Foreign Researcher Permit prior to initiation of research activity. RCZ also approves shipment of research-related biological specimens outside the country.

Medicines Control Authority of Zimbabwe (MCAZ)

The MCAZ requires that all clinical trials involving new drugs, new applications of a drug, new dosage levels, or new medical devices be approved before trial implementation. MCAZ, through its regulatory unit, inspects and monitors clinical trials periodically; this inspection includes review of trial documents, facilities, and any other resources that are deemed related to the clinical trial. All seven pharmacies under UZ-UCSF are MCAZ approved.

University of California, San Francisco Committee on Human Research (CHR)

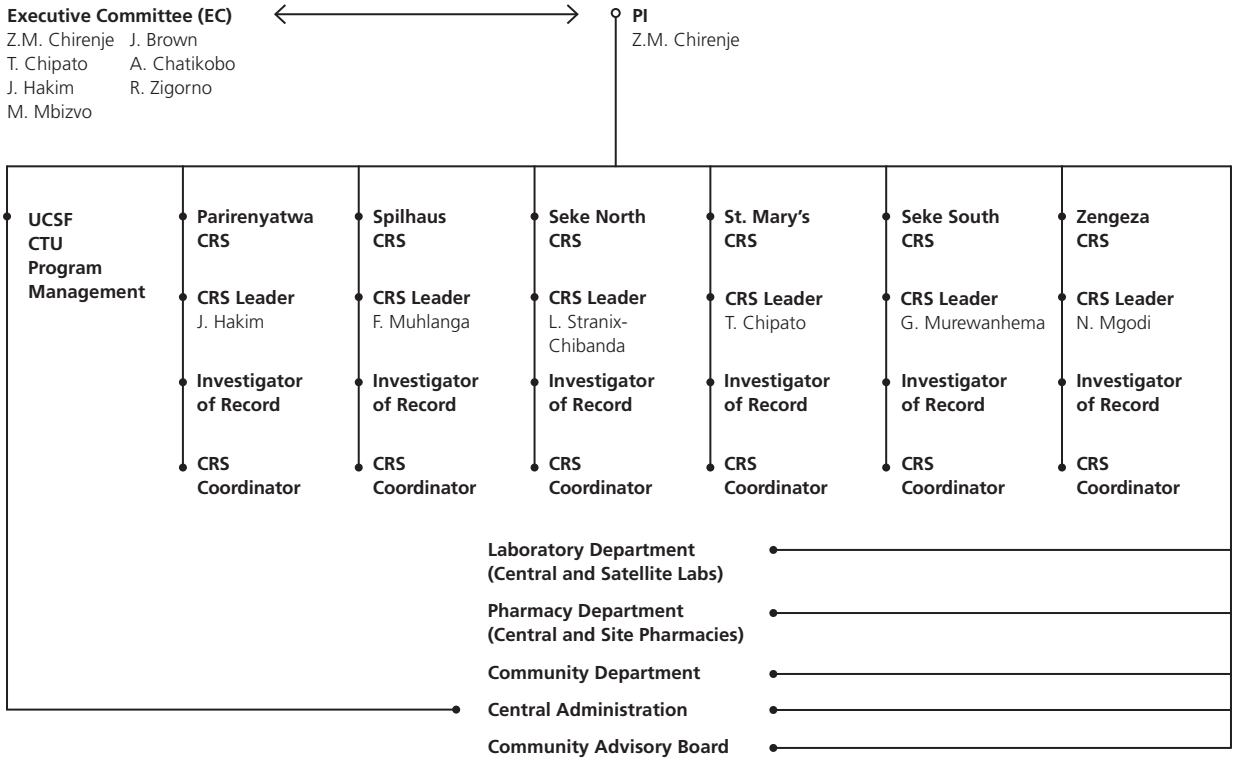
Investigators with an appointment at UCSF must also seek approval from UCSF's CHR. Applications to the UCSF CHR are generally submitted in conjunction with submissions to MRCZ and the approval takes place in a parallel timeline.

Infrastructure and capacity of the UZ-UCSF Programme

Scientific leadership

The UZ-UCSF Leadership has fostered two decades of successful, uninterrupted scientific governance, collaboration, implementation, and management of multi-centre HIV / AIDS prevention and treatment trials. Principal Investigator (PI), Dr. Chirenje, and senior leaders Dr. Hakim (Parirenyatwa CRS leader), Dr. Chipato (St. Mary's CRS Leader), and Dr. Mbizvo are advised by an Executive Committee (EC) and a Community Advisory Board. Our successes have been cultivated by robust collaborations at the highest scientific levels with internationally respected investigators, including Dr. Joelle Brown transitioning in 2014 into the role occupied by Dr. Suellen Miller from 2008–2014 (UCSF), Dr. Thomas Campbell (University of Colorado, Denver), Dr. Yvonne Maldonado (Stanford University), Dr. Philip Hopewell (UCSF), Dr. Joel Palefsky UCSF), and Dr. Arthur Reingold (UC Berkeley) (see Figure 4).

Figure 4. UZ-UCSF Programme organogram



Collaboration and support: UZ and UCSF

The UZ-UCSF Programme is a collaborative effort between the UZCHS and UCSF's Bixby Center for Reproductive Health, housed within the UCSF Department of Obstetrics, Gynecology and Reproductive Sciences. Professional managers at both universities have worked together for over 15 years with a governance structure built on principles of inclusiveness of scientific, community, and administrative functions. UCSF maintains financial oversight, while centralised administrative functions at both UZ and UCSF oversee daily operational activities that support uninterrupted study execution and compliance matters. Close coordination ensures procurement of adequate supplies, recruitment and retention of qualified and experienced staff, an organised transportation fleet, as well as updated communication channels and information technology facilities.

The University of Zimbabwe College of Health Sciences is proud to host the UZ-UCSF Collaborative Research Programme, a global centre of excellence in HIV prevention, treatment, and care research. As it celebrates 20 years of research innovation, I wish to reaffirm the College's commitment to research excellence, as demonstrated by the Programme. The Programme, our flagship centre for collaborative research on HIV, has a record of achievement that provides clear testimony of the dedication of its staff and its Principal Investigators to ensuring that Zimbabwe remains at the cutting edge of HIV research. On behalf of the College, I thank and commend the Programme, the study participants, and the donors who have made it possible to attain these milestones.

– Professor Midion M. Chidzonga, Dean
University of Zimbabwe College of Health Sciences

We receive strong and ongoing support from the UZCHS and its Dean. The UZCHS provides 15 consultants from the Departments of Internal Medicine, Paediatrics, Infectious Disease, Obstetrics and Gynaecology, Laboratory Science, and Clinical Pharmacology, who dedicate up to 40% of their effort as Investigators of Record for our research studies.

Collaboration and support: National and municipal health departments

The Municipal Health Departments of Harare and Chitungwiza, as well as the Government of Zimbabwe, through the MoHCC, have been full partners with their contributions of physical space, material goods, and administrative backing to support the conduct of trials and care for patients and participants.

Programme administative and research infrastructure

Administrative Department

The Programme's Research Office at 10 Routledge, Milton Park, Harare brings all research administration staff under one roof. Our Administration Office at 15 Phillips Avenue, Belgravia, Harare centrally coordinates and supports CRS activities, Central Pharmacy, and Central Laboratory, as well as procurement and our transportation fleet. The Administrative Core's professional managerial experience and adherence to international auditing standards have increased our capacity to competently manage a diversity of complex grants.

The Clinical Research Sites (CRSs)

The six Clinical Research Sites (CRSs) sit within close proximity: two sites are in the city of Harare (Parirenyatwa, Spilhaus), and four sites are in the neighbouring city of Chitungwiza (Seke South, Zengeza, Seke North, St Mary's) (see Figure 5). Two additional sites located in nearby Mutoko and Epworth provide extended capacity to support ongoing and planned research.

Figure 5. Location of UZ-UCSF Programme and CRSs

1. Administrative Site (Phillips Ave)
2. Central Laboratory
3. Parirenyatwa CRS
4. Central Pharmacy and Research Offices (Routledge Ave)
5. TB Laboratory
6. Spilhaus CRS
7. Seke North Clinic
8. St. Mary's Clinic
9. Seke South Clinic
10. Zengeza Clinic

CRS staffing and infrastructure

The Programme's staffing plan is an organic model that expands or contracts to meet real-time research activity. It is currently well-supported by over 300 full-time, qualified employees at UZ-UCSF, including 13 Medical Officers, 11 Pharmacists, 45 Research Nurses, and 12 Laboratory Scientists. Cross-training ensures that staff can be deployed to an area of scientific need without extensive re-training or loss of time.

All CRSs are appointed with consultation and examination rooms, counseling rooms, and air-conditioned participant reception areas featuring televisions and water dispensers. Receptionists, each with a desktop computer, register participants, schedule clinic visits, and provide reimbursement for study participation. Caretakers prepare refreshments for participants. Private consultation and examination rooms are well-equipped with diagnostic sets, blood pressure machines, and X-ray viewing boxes. Data management areas have secure data capture and transmission rooms, as well as secure storage of study binders. DAIDS-approved, MCAZ-certified on-site pharmacies dispense study products and primary care medications and counsel participants; DAIDS-certified on-site laboratories perform HIV rapid tests, pregnancy tests, gram stains, urinalysis, testing for Trichomonas vaginalis, and wet mounts, depending on the study, with capacity to process up to 60 participant samples daily. Data transmission and communication have evolved from data-faxing in 2004 to eDATA in 2011, following an expansion in Information Communication Technology capacity to include reliable fibre-optic internet connection and e-mail access. Each CRS has a back-up generator to ensure continuous electrical service as well as a bore hole ground well for uninterrupted water supply.

CRS scope of research and study populations

The continued burden of the disease and its co-infections make HIV prevention and treatment trials clear priorities. Prevalence and incidence rates in our catchment area, and the characteristics of the population with HIV co-morbidities, uniquely meet the thematic areas of the DAIDS Research Networks and that of other funders.

The CRSs enroll seronegative at-risk populations, ART-naïve and treatment-experienced adults and children, HIV-infected pregnant women and their children, and HIV-infected adolescents from the urban Harare centre and outlying semi-urban catchment areas of Chitungwiza. We have created a centralized participant database to eliminate the possibility of co-enrollment in more than one trial involving investigational products, medical devices, or other study products that would compromise safety.

We have direct access to a population of 8,000 **ART-experienced patients** registered in a database of the Parirenyatwa Hospital and Care and Treatment Centre. These patients are a valuable resource to screen and enroll for studies on virologic control/cure, inflammation and long-term complications (TB, Kaposi sarcoma, cervical cancer, Hodgkin Lymphoma, cardiovascular, renal, hepatic, neuropsychological conditions, premature aging). The **2,600 HIV-infected infants, children, and adolescents** at Parirenyatwa Care and Treatment Centre are available for potential recruitment into paediatric and adolescent clinical trials.

In Chitungwiza, we have annual access to **8,075 HIV infected pregnant women, their children, and male partners** for strategies to address HIV and HIV-associated infections in paediatric and maternal populations. The Spilhaus and Chitungwiza CRSs have access to a pool of HIV-negative **women of reproductive age** seeking family planning, childhood immunization, post-natal care, cervical cancer screening and other reproductive health care, including diagnosis and treatment of STIs; these will be tapped for recruitment to safety and efficacy studies on microbicides and ART pre-exposure prophylaxis (PrEP) with the drug Truvada® among these sub-specialized populations. Our research catchment community has begun to be sensitised to men who have sex with men (MSM), as evidenced by enrollment of the first MSM couple in HPTN 052 at the Parirenyatwa CRS. We actively engage the local IRBs, CAB, MoHCC, and community leaders on the need to collect data on the HIV burden among MSM and potential strategies to conduct rectal microbicides trials.

The six Clinical Research Sites

Parirenyatwa Clinical Research Site (Pari CRS)

In 2002, local scientists established what is now known as the Parirenyatwa Clinical Research Site (Pari CRS), recognising the potential to conduct wide-ranging clinical studies with a diverse populace burdened with a high prevalence of infectious diseases, including HIV/AIDS, TB, and malaria. Pari CRS is located within the city of Harare on the campus of the Parirenyatwa Group of Hospitals, and has successfully conducted clinical trials enrolling men, women, and children. James Hakim, MBChB, FRCP, with a 20-year track record of conducting global and national HIV research, is the CRS Leader. Dr. Hakim manages a team of experienced researchers that includes 7 Medical Officers, 4 Pharmacists, 2 Laboratory Scientists, 15 Research Nurses and 4 Counselors, 3 Data Managers, and 25 support staff.

Pari CRS occupies and conducts studies in three clinic locations at Parirenyatwa Hospital: the University of Zimbabwe Clinical Research Centre (UZ-CRC), the Family Care Centre Research Clinic, and the Parirenyatwa Kaposi Sarcoma Outpatient Clinic. In addition to the infrastructure present at all CRSs, Pari CRS is uniquely supported by a new Level 3 TB laboratory for diagnostic studies and a pharmacology laboratory, which will allow the site to participate in clinical trials on emerging TB therapies for adults and children with HIV (see box on right and Appendix).

Parirenyatwa CRS major achievements

- Zimbabwe site for international DART study, demonstrating the safety and efficacy of clinical monitoring alone in adults after ART initiation
- Use of nevirapine-based first-line ART in women with previous exposure for PMTCT associated with poorer outcomes compared with PI-based first-line regimens if used within the first 24 months post-exposure (Study A5208)
- Zimbabwe site for international study finding 96% reduction in risk of HIV transmission in discordant couples when positive partner is on ART (HPTN 052)
- First-line use of nevirapine in children exposed to nevirapine for PMTCT associated with poorer outcomes than using a PI-based regimen (Study 1060)
- ART within 2 weeks of commencing TB treatment beneficial to patients with CD4 counts <50 vs delaying ART until end of TB treatment (Study A5221)
- Zimbabwe site for the international ARROW study, demonstrating the safety and efficacy of clinical monitoring alone in children after ART initiation

Future objectives: The Pari CRS will continue implementation of research to improve standards of care for the prevention and treatment of HIV/AIDS, and to ensure uninterrupted and sustained advances in biomedical prevention and clinical care for people living with, or who are at-risk for, HIV/AIDS. Anticipated basic science research will identify HIV reservoirs and test interventions that will potentially eradicate them. Achieving a

functional cure for ART-experienced patients, as well as evaluating new drugs and formulations for HIV and TB treatment and prevention, will be research priorities. Finally, we have prioritized preparation to allow us to conduct future HIV vaccine research at this CRS.

Spilhaus Clinical Research Site (Spilhaus CRS)

The Spilhaus CRS is located at the Zimbabwe National Family Planning Council Clinic (ZNFPC), within the grounds of Harare Central Hospital, one of the four largest referral hospitals in Zimbabwe. Since its establishment in 1994, 13 studies have been completed at the site. Dr. Felix Muhlanga, MBChB, MMed, oversees site administrative and scientific operations, managing a team of experienced investigators. In addition to the infrastructure common at all CRSs, Spilhaus CRS has established a cervical cancer screening and treatment programme as part of standard of care for all participants (see box on right and Appendix).

Future objectives: Our future research agenda will include studies on microbicides to prevent HIV infection and integrated strategies to prevent HIV. Novel questions that Spilhaus CRS seeks to answer concern the possible effects of Depo-Provera on HIV acquisition, and the impact of mixed contraceptive methods on target immunological cells in the female genital tract. With the FDA's 2012 approval of Truvada® for use as PrEP, we will also contribute evidence on pregnancy outcomes while taking Truvada® for PrEP, as well as evaluating viral isolates for resistance. Additionally, we will recruit from the population of at-risk adult men who present to the ZNFPC annually for medical male circumcision (MMC).

Spilhaus CRS major achievements

- In 1998, first site to establish a formal Community Advisory Board
- Significant contribution to Zimbabwe national policy on cervical cancer screening; cervical cancer is the most common cancer among women in Zimbabwe
- Zimbabwe site for the international Hormonal Contraception Study, which was among the first to study and publish on the relationship between hormonal contraception and risk of HIV acquisition
- Zimbabwe sites for the international HPTN035 study, which demonstrated that first and second generation (non-antiretroviral based) microbicides do not prevent HIV in women at risk for HIV. These results, as well as those from the MDP Trial, N9, Carraguard, Cellulose Sulphate, and SAVVY trials, provided much needed data to help push the agenda for third and fourth generation microbicides
- Zimbabwe sites for the international VOICE Study (MTN-003), which clearly demonstrated that daily use of tenofovir vaginal gel, oral tenofovir, and oral Truvada® do not reduce the risk of HIV acquisition in young, unmarried women
- High level of participant retention achieved via thorough education of participants and collection of accurate locator information at study entry
- Improved retention of and adherence by women participating in clinical trials due to innovative Male Partner Involvement effort

Seke North and St. Mary's Clinical Research Sites

Seke North and St. Mary's are two separate Clinical Research Sites with closely matched scientific objectives, located in Chitungwiza, a satellite city of Harare. The Seke North CRS is located on the grounds of the Makoni Primary Care Clinic and is led by Lynda Stranix-Chibanda, MBChB, MMED; the St. Mary's CRS is located on the grounds of the St. Mary's Primary Care Clinic and is led by Dr. Tsungai Chipato, MBChB, FRCOG, also a UZ-UCSF Programme Executive Committee member.

Both CRSs began conducting NIH-funded research in 1998, with the recruitment of a cohort of HIV-infected pregnant women to participate in a pilot prevention of mother-to-child-transmission trial in Zimbabwe. Since 2002, over 1,000 participants have been enrolled across four large clinical trials conducted at the sites. Each CRS has capacity to manage up to 750 participants at a time, across multiple research studies (see box on right and Appendix).

Future objectives: The future research agenda at St. Mary's and Seke North CRSs includes research that investigates integrated HIV prevention strategies, as well as strategies to address HIV and HIV-associated infections in paediatric and maternal populations. The CRSs also have plans to expand the scope of work beyond the prevention of mother-to-child-transmission of HIV. We have ready access to women attending maternity services, their male partners, and their offspring in a community with high prevalence and incidence of HIV, and co-infection with TB, hepatitis, and Human Papilloma Virus (HPV). Recent service programs have led to rising community awareness and acceptance of medical male circumcision. Evolving diagnostic services permit study of the complications of longstanding HIV infection and treatment. Links with the local TB programme and TB diagnostic testing are expected to strengthen, permitting ready implementation of further TB treatment and prevention studies.

Seke North and St. Mary's CRSs major achievements

- During the cholera epidemic in September 2008, CRS leadership engaged local authorities to allow research activity to continue operations despite the Seke North municipal clinic being closed and designated a cholera treatment facility by MoHCC; study staff were trained in cholera prevention strategies, with no cases recorded among participants or staff
- Zimbabwean data alone used to establish the safety and trough concentrations of nevirapine for infants born to HIV-infected mothers (HIVNET 023 through ZAPP-UZ), laying the foundation for subsequent multi-site trials of extended nevirapine prophylaxis to prevent vertical transmission of HIV through breast milk in the HPTN 046 study conducted at our sites and elsewhere (e.g., HIVNET 012, PEPI, SWEN, BAN, Kesho Bora, MamaBana)
- The HPTN 046 study examined the safety and efficacy of a 6-month regimen of infant nevirapine prophylaxis. Results demonstrated to be superior to a 6-week regimen; effect was lost once the drug was stopped underscoring the need to continue prophylaxis throughout the period of exposure to HIV in breast milk
- High levels of retention were achieved among trial participants due to comprehensive participant education sessions and collecting detailed locator information at study entry

Seke South and Zengeza Clinical Research Sites
The Seke South and Zengeza CRSs are two separate Clinical Research Sites with closely matched scientific objectives, located in Chitungwiza, approximately 30km south of Harare. Each CRS is located within its respective Municipal Clinic. These CRSs conduct high quality research in female-controlled HIV/STI prevention strategies, including microbicides and cervical barriers, as well as integrated strategies to prevent HIV infection. Zengeza CRS is headed by Nyaradzo Mavis Mgodi, MBChB, MMED; Grant Murewanhema, MBChB is the CRS Leader for Seke South. The CRSs have grown in capacity from screening, enrollment, and retention of 500 participants/year with current capacity to manage 900 study participants per year across multiple studies (see box on right and Appendix).

Even when a trial provides an answer that's not what we hoped for, it still brings us closer to our ultimate goal of finding HIV prevention methods for women that will be effective and safe. Women remain most vulnerable to HIV and there is an urgent need for effective, female-controlled HIV prevention methods that women will actually use. It is my hope that this will happen in my lifetime, but if it is delayed, I will be content in the knowledge that we have left a legacy for women over the whole world.

– Dr. Nyaradzo Mavis Mgodi, Zengeza Clinical Research Site Leader

Future objectives: The future research agenda will include studies on microbicides to prevent HIV infection and integrated strategies to prevent HIV infection. We will also contribute significantly to answering questions on pregnancy outcomes for women taking Truvada,® as well as evaluating viral isolates for resistance in individuals taking PrEP.

Seke South and Zengeza CRSs major achievements

- Zimbabwe sites for the international HPTN039 study; this study found no evidence that twice-daily acyclovir prevents HIV infection among HSV-2 infected women and men who have sex with men. Further, the study provided additional evidence that acyclovir reduces the occurrence of genital ulcers in HSV-2-infected individuals
- Zimbabwe sites for the international HPTN035 study; this study demonstrated that first and second generation (non-antiretroviral based) microbicides do not prevent HIV in women at risk for HIV. These results, as well as those from the MDP Trial, N9, Carraguard, Cellulose Sulphate, and SAVVY trials, provided much needed data to help push the agenda for third and fourth generation microbicides
- Zimbabwe sites for the international VOICE Study (MTN-003), which clearly demonstrated that daily use of tenofovir vaginal gel, oral tenofovir, and oral Truvada® do not reduce the risk of HIV acquisition in young, unmarried women
- High level of participant retention achieved via thorough education of participants and collection of detailed locator information at study entry
- Improved retention of and adherence by women participating in clinical trials due to innovative Male Partner Involvement effort
- During nationwide cholera and dysentery epidemics research activities continued uninterrupted despite the closure of the municipal primary care clinic at Seke South

Community Department and Community Advisory Boards

The UZ-UCSF Programme's Community Department, Outreach Workers, and Community Advisory Board (CAB) members are the ambassadors to community engagement for participation in research. Their immense efforts in community sensitisation and education have resulted in our achieving rapid study enrollment, maintaining a greater than 95% participant retention rate, and timely disseminating results from our studies. The UZ-UCSF CAB was first established in 1995, and has evolved into four dedicated subgroups, specialised according to research priority areas. This focused approach achieves effective community involvement and engagement, while still retaining geographical and direct-stakeholder representation.

The Community Department is led by Charles Chasakara, BsC, the Programme's Community Liaison Coordinator, who brings 10 years of experience in public health research and who has been involved in the Community Department since 2008. CAB members include political and community leaders, health service providers, religious and traditional leaders, government institutions, NGOs, CBOs, FBOs, and direct stakeholders of highly affected populations, including people living with HIV/AIDS, women, and adolescents.

Our community outreach and research dissemination efforts take many forms. We hold regularly scheduled events, using didactic, dramatic, and culturally tailored modes to present findings, promote the Programme's research efforts, and educate our stakeholders about research activities. We have collectively reached many thousands of community members and potential participants over the course of the years. The Programme organizes an annual Research Day, where information on completed, ongoing, and planned research studies are presented, including discussion of their implication for health policy in Zimbabwe. Speakers and guests include local stakeholders, personnel from the MoHCC (including the Minister and his Permanent Secretary), municipal health authorities, local Institutional Review Boards and regulatory authorities, U.S. government institutions in Zimbabwe (including staff from the U.S. Embassy, USAID, and CDC), the CAB, and local and international academic leaders. Our CAB members have also made seminal contributions to international CABs, Community Working Groups, and the DAIDS Research Networks (see box below).

UZ-UCSF Community Advisory Board addresses women

Community Advisory Boards and Community Department major achievements

- CAB outreach and activity has contributed to study subject retention rates of >95%
- Our participant "Red Carpet Treatment" referral systems, in concert with the municipal health departments, triages patients to medical facilities for services we do not provide, where, upon presentation of referral letters, participants are attended to without delay
- Outreach to leaders of a Chitungwiza religious sect opposed to all medical intervention and research resulted in the screening and enrolling of participants from this previously inaccessible community
- CABs have been instrumental in correcting multiple inaccurate impressions of UZ-UCSF Programme activities, where misinformation threatened continued clinic and research operations

We were very excited to hear that if a positive partner in an HIV discordant couple takes ART consistently they will protect their negative partner from getting HIV. We now know of an HIV prevention method that has been tested by us here in Zimbabwe. The use of ART will go a long way in reducing the number of new cases of HIV. We look forward to the UZ-UCSF leadership to bring us more studies like this, which have very high impact in our communities.

– Mrs. Rosemary Chitagu (CAB Member and former participant HPTN 052 Trial)

Future objectives: We will continue to leverage our strong community ties, intensify community involvement and promote active CAB participation through all stages of research. A unique periodic community re-mapping exercise will capture the shifting characteristics of HIV acquisition in the Programme's catchment areas by targeting suspected new "hot spots"—areas associated with high HIV risk behaviors—such as nightclubs, beer halls, ex-urban farms, shanty settlements, overcrowded resettlement areas, and other locations where marginalised populations reside. The Community Department and CAB will develop and administer a Knowledge, Attitudes, and Practices (KAP) survey to communities to assess the effects of our outreach activities on the communities' research literacy.

Chitungwiza Community Awareness and Social Responsibility Day event banner

Laboratory Department

UZ-UCSF laboratory activities started in 1994 with one satellite laboratory at Spilhaus Family Planning Clinic. It offered a limited number of rapid assays; the remaining tests were outsourced. Today, the Laboratory Department, under the direction of Marshall Munjoma, PhD, is composed of a multidisciplinary Central Laboratory at UZCHS, a biosafety level 3 Tuberculosis (TB) laboratory at the nearby Wilkins Infectious Disease Hospital, a cytology laboratory in the UZ Department of Obstetrics and Gynaecology, and satellite labs at each of the six CRSs. The Central Laboratory is certified by the NIAID-DAIDS as a full reference laboratory, certified according to Good Clinical Laboratory Practice (GCLP), and is also ISO 15189 accredited. Compliance to GCLP and ISO 15189 is monitored annually by a DAIDS-appointed auditor and the South African National Accreditation System (SANAS). Proficiency testing is provided by the College of American Pathologists (CAP), Virology Quality Assurance (VQA) and United Kingdom National External Quality Assessment System (UKNEQAS).

The Central Laboratory receives a daily average of 350 samples (blood, urine, breast milk, and swabs) from 120 participants at the CRSs and provides testing in clinical chemistry, serology, immunology, haematology, and molecular diagnostics. Our specimen repository contains a liquid nitrogen plant and is capable of storing up to twenty -80°C and five -20°C freezers. The assays performed include liver function tests, kidney function tests, cardiac function tests, metabolic tests, full blood count, multi-parameter flow cytometry, DNA PCR, viral load test, western blot, and ELISAs. A dot-blot assay capable of genotyping up to 40 HPV types is being introduced into the system. The satellite labs perform a variety of rapid tests for the diagnosis of HIV, BV, and urine chemistry. Plans are under way to equip each of the satellite clinics with a GeneXpert machine for on-site diagnosis of Chlamydia trachomatis and Neisseria gonorrhoea infections (see box below).

Laboratory Department major achievements

- We have expanded our capacity in cytology, histology, and advanced TB testing, allowing us to conduct research in emerging research priority areas
- Consistentency of results has resulted in the Central Laboratory receiving regional responsibilities from the Primary Network Laboratory

Future objectives: To respond adequately to both the local and international research agendas, laboratory personnel train continuously to acquire the skills that will enable the Programme to participate in future HIV vaccine trials, characterize vaginal immune cells using multi-parameter flow cytometry, and perform HIV genotype resistance testing.

Pharmacy Department

The UZ-UCSF Pharmacy Department includes a Central Pharmacy and seven pharmacies located at the CRSs. The pharmacies follow sponsor guidelines, Good Clinical Practice (GCP), and the Medicines Control Authority of Zimbabwe (MCAZ) clinical trials regulations. The centralised structure enables CRS pharmacy staff to focus primarily on study-specific activities. Our cross-trained staff dispenses investigational study products and

primary care drugs to an average of 20–25 participants per day at each CRS. A Chemotherapy Aseptic Room is housed within the Main Pharmacy of the Parirenyatwa Main Hospital. A class II Biosafety Cabinet has been installed in the preparation area. Pharmacy Director, Dr. Chiedza Maponga, PharmD, MPHE, provides advice on Central and CRS pharmacies' establishment plans, drug regulatory matters, and drug supply chain management, and provides expert guidance on pharmacokinetic studies executed in the Programme.

Since the Programme's founding, we have conducted increasingly sophisticated studies; pharmacists are trained in the handling of complex Phase I/II pharmacokinetic studies; they receive hands-on experience in advanced pharmacotherapy research through the Harare International Specialty Pharmacology Lab. The laboratory is used to conduct drug interaction tests for ARVs and anti-tuberculosis drugs and for ARVs and complementary (herbal) medicines, as well as bioequivalence tests for different brands of ARVs, adverse event monitoring, and nutrition pharmacology (see box below).

Pharmacy Department major achievements

- Establishment of Chemotherapy Aseptic Room
- Fine-tuning of processes to ensure timely and accurate deliveries of study products, including improved study product use projections, engagement of local regulatory bodies to facilitate the clearance of study products, training of clearing agents in handling shipments containing drugs for investigational use, and expedited study product importation approvals
- Centralised study product destruction for all CRS pharmacies, improving efficiency of compliance with DAIDS requirements. We estimate that we have saved more than 30 hours in personnel time and US$1,200 annually with this centralised destruction protocol

Future objectives: The Pharmacy Department has capacity to participate in pharmacokinetic, vaccine, and oncology studies, and is working on building capacity for post-trial care of participants who exit from HIV treatment studies and those who seroconvert in HIV prevention studies.

Meeting the challenges ahead

We are proud of the accomplishments and collaborations developed in the first 20 years of the UZ-UCSF Collaborative Research Programme and Clinical Trials Unit. Yet, some questions remain unanswered and inform the challenging research priorities of the DAIDS Research Networks and the Programme. For example:

- Which behavioral, biomedical, and structural interventions are most effective alone and in combination for preventing HIV infection *differentially* for women, for men, and for children?
- With the current state of the evidence, which existing and candidate treatments are most efficacious and least harmful for AIDS and AIDS-related illnesses and co-morbidities, such as TB and hepatitis? How might these change as the virus and etiologies of the co-morbidities mutate?
- Given the current evidence base, which ARV-based microbicides delivery formulations, such as vaginal rings or other delivery systems, do women find acceptable (and are willing to use) for HIV prevention, and in the future, as a multi-purpose intervention for prevention of pregnancy and HIV?
- What are the optimal strategies for preventing transmission of HIV from mother to child during pregnancy, labor and delivery, and breastfeeding?
- What must an HIV vaccine do to induce protective and long lasting immunity? How can a safe, effective, and durable vaccine be developed and tested?
- What strategies can be implemented to maximize adherence to ART in different populations, such as children, adolescents, and adults chronically infected with HIV?

The Programme will continue to work in partnership with research collaborators, sponsors, and donors at the international, national, and local levels to address these unanswered questions, which align with the goals of the Zimbabwe Ministry of Health and Child Care to: reduce overall HIV incidence by 50%, reduce child HIV incidence to <5%, reduce overall HIV/AIDS mortality by 38%, and reduce the incidence of TB and cervical cancer.

Ongoing and planned research studies at UZ-UCSF will address four strategic areas, including: optimal HIV treatments and prevention and treatment of HIV co-morbidities such as TB and cervical cancer, best strategies to prevent HIV in paediatric and maternal populations, integration of biomedical and behavioral HIV prevention strategies such as topical microbicides and PrEP, and discovery of vaccines. As always during execution of these groundbreaking studies, close attention will be paid to ensuring delivery of the highest standard of ethical and clinical care for our participants, including diagnostics, drug therapy, and referral to specialised care when required.

Strategic areas addressed by ongoing and future research at UZ-UCSF

HIV treatment and prevention of AIDS-related illnesses and co-morbidities

We will continue to work closely with the ACTG to contribute to the knowledge base for both prevention and treatment best practices for a wide range of AIDS-related illnesses and co-morbid diseases, including: hepatitis, cervical cancer, and TB particularly, multidrug-resistant TB. Priorities for ACTG include: HIV cure and eradication of reservoirs; investigation of tuberculosis B and C, including newer drugs, shorter regimens, and more effective drugs for multidrug-resistant TB and management of

inflammation and long-term complications. We will also research optimal strategies for preventing cancer of the cervix in women with HIV.

Paediatric and maternal populations

The Programme will continue to partner with IMPAACT to research the most effective ways to prevent mother-to-child transmision of HIV, addressing the main mode of HIV infection in children. We also look forward to investigating the use of vaccines in children to prevent rotavirus and other infections.

Integrated HIV prevention

We are enthused about continuing our HIV prevention research with the MTN and HPTN. We will undertake research to investigate the effectiveness of combining multiple strategies for HIV preventions, such as voluntary medical male circumcision, PrEP, and HIV risk reduction. Additionally, we will evaluate the optimal delivery route for antiretroviral-based microbicides (e.g., intravaginal rings) for HIV prevention in women.

HIV vaccines

In 2013 the Programme was invited to join the consortium of international research sites working toward the discovery of a safe and globally effective vaccine for HIV. The initiative is led by the HVTN, an international collaboration of scientists and educators with funding from NIAID. The HVTN is the largest clinical trials program devoted to the development and testing of preventive HIV vaccines worldwide. The HVTN investigators, who are leaders in HIV and vaccine research in their countries, work collectively and enjoy strong relationships with inventors of vaccines and a wide variety of scientists working in the areas of HIV virology, immunology, and pathogenesis. The UZ-UCSF Programme, with its scientific expertise and sophisticated infrastructure, looks forward to participating in this global effort to move us toward a safe, effective, and durable HIV vaccine that will save lives and reduce the burden of this disease worldwide.

Four examples of ongoing, goundbreaking research at UZ-UCSF

Prevention of mother-to-child transmission of HIV
The IMPAACT PROMISE/1077BF study, 'Promoting Maternal and Infant Survival Everywhere' seeks to optimise maternal treatment while reducing vertical transmission during pregnancy, labor and delivery, and breastfeeding. Study results expected in 2016.

A vaginal ring to prevent HIV acquisition
ASPIRE/MTN 020 is a Phase III study to determine whether a woman's use of a vaginal ring containing the ARV drug dapivirine is a safe and effective HIV prevention method. ASPIRE represents a major step forward in the evaluation of a promising female-controlled method of long-acting protection. Study results expected in early 2015.

Effectiveness of short-course treatment to prevent active TB
HIV-infected people are at increased risk of developing active TB. The standard course of treatment for TB is 6 to 9 months of isoniazid. A shorter course may be as effective and potentially increase treatment adherence. The primary goal of ACTG Trial A5279 is to determine whether a 4-week rifapentine plus isoniazid treatment regimen or the standard 9-month isoniazid regimen is most effective in preventing active TB in HIV-infected patients. The study will also compare safety, tolerability, and adherence to treatment. Study results expected in 2018.

Prevention of cervical cancer in women with HIV
Cervical cancer is the leading cause of cancer death among Zimbabwean women. The ACTG A5282 trial will look for the best way to prevent cervical cancer in women with HIV and high-risk human papilloma virus (HPV). This study will investigate a novel HPV test-and-treat strategy using cryotherapy compared with the standard of care, which is based on the Pap test. Study results expected in 2016.

Conclusion

The UZ-UCSF Programme remains dedicated to conducting front line research on strategies to prevent HIV and provide AIDS care and treatment. This effort, in turn, will help achieve the goal of HIV elimination in Zimbabwe through the eventual implementation of a broad program of evidence-based prevention interventions. It is only through this continued commitment to HIV prevention and treatment research, and to the well being of those living with HIV, that we will be able to conquer the HIV pandemic and declare it a thing of the past.

City of Harare

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Appendix

Research studies conducted at the UZ-UCSF Programme (1994–2014)

Year	Title	Sponsor	Location(s)
1994–1996	Intravaginal Practices and Association with HIV and STDs9	CONRAD	Spilhaus
1994–1997	Visual Inspection of the Cervix as a Primary Means of Cervical Cancer Screening	USAID	Spilhaus
1999–2000	HIV Risk Reduction Through HSV-2 Prevention (Ancillary to HIVNET/HPTN 016A)	Fogarty	Spilhaus Seke South
1999	Phase I Trial of the Topical Microbicide BufferGel	NIH	Spilhaus
1999–2000	Clinical Trial to Evaluate the Safety and Acceptability of Nonoxynol-9 Gel	NIH	Spilhaus
1999–2003	HIVNET/HPTN 016A: Condom Promotion and Counseling for HIV Prevention	HIVNET/HPTN	Spilhaus Seke South
1999–2003	Acceptability of Diaphragm Use to Prevent HIV and STIs	CONRAD	Spilhaus
2000–2001	HIVNET/HPTN 016A Substudy: Association of Sexually Transmitted Infections and HIV Among Women Attending the Condom Promotion and Counseling Study in Harare	HIVNET/HPTN	Spilhaus Seke South
2000–2001	HIVNET/HPTN 023: Safety and Trough Concentrations of Nevirapine Prophylaxis Given Daily, Twice Weekly, or Weekly in Breast-Feeding Infants from Birth to 6 Months	HIVNET/HPTN	Seke North St. Mary's
2000–2003	The Reliability of ACASI Data Collection in Zimbabwe	NIH	Spilhaus
2000–2005	Hormonal Contraception and the Risk of HIV-1 Acquisition Among Young Women in Uganda and Zimbabwe22	NIH	Spilhaus Seke South
2001–2005	Oral Candidiasis Marker of HIV-Disease Progression Among Zimbabwean Women	NIH	Harare Central Hospital
2001–2007	Differences in CD4 Counts in Ugandan and Zimbabwean Women Participating in the Hormonal Contraception and Risk for HIV-1 Acquisition Study	NIH	Spilhaus Seke South
2003–2008	Routine Versus Clinically Driven Laboratory Monitoring of HIV Antiretroviral Therapy in Africa (DART): A Randomized Non-Inferiority Trial12	Rockefeller Foundation	Parirenyatwa
2003–2012	HPTN 043: A Phase III, Randomized, Controlled Trial of Community Mobilization, Mobile Testing, Same-Day Results, and Post-Testing Support for HIV in Sub-Saharan Africa and Thailand (Project Accept)19	HPTN	Mutoko
2003–2007	Diaphragm and Lubricant Gel for Prevention of HIV Acquisition in Southern African Women: A Randomized, Controlled Trial (MIRA)	Gates	Epworth Makoni
2004–2008	HPTN 039: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial of Acyclovir for the Reduction of HIV Acquisition Among High Risk HSV-2 Seropositive, HIV Seronegative Individuals	HPTN	Zengeza

2004–2008	HPTN 039-01: Prospective Cohort Study of HPTN 039 Seroconverters: The Effect of HSV-2 Suppression on HIV-1 Viral Set Point	HPTN	Zengeza
2004–2008	HPTN 039-02: A Sub-Study to Investigate the Factors Associated with Medication Adherence and its Measurement in HPTN 039	HPTN	Zengeza
2005–2008	HPTN/MTN 035: Phase II/IIb Safety and Effectiveness Study of the Vaginal Microbicides BufferGel and 0.5% PRO2000/5 Gel (P) for the Prevention of HIV Infection in Women20	HPTN/MTN	Spilhaus Seke South
2005–2008	MTN/HPTN 035A: Preventative Misconception as a Motivation for Participation and Adherence in Microbicide Trials	HPTN	Spilhaus
2005–2009	A5175: A Phase IV, Prospective, Randomized, Open-Label Evaluation of the Efficacy of Once-Daily PI & Once-Daily Non-NRTI - Containing Therapy Combinations for Initial Treatment of HIV-1 Infected individuals from Resource - Limited Settings (PEARLS) Trial	ACTG	Parirenyatwa
2005–2009	A5199: International Neuropsychological Assessment of Patients Initiating Antiretroviral Therapy in Resource-Limited Settings	ACTG	Parirenyatwa
2006–2008	Economic Opportunities for Zimbabwean Adolescent Orphans	NIH	Chitungwiza
2006–2008	A5190/P1054: Assessment of Safety and Toxicity among Infants Born To HIV-1-Infected Women Enrolled in Antiretroviral Treatment Protocols in Diverse Areas of the World	ACTG IMPAACT	Parirenyatwa
2007–2012	Routine Versus Clinically Driven Laboratory Monitoring and First-Line Antiretroviral Therapy Strategies in African Children with HIV (ARROW): A 5-year, Open-Label, Randomized Factorial Trial16	UK Medical Research Council	Parirenyatwa
2007–present	HPTN 052: A Randomized Trial to Evaluate the Effectiveness of Antiretroviral Therapy Plus HIV Primary Care Versus HIV Primary Care Alone to Prevent the Sexual Transmission of HIV-1 in Serodiscordant Couples10	HPTN	Parirenyatwa
2007–present	MTN 015: An Observational Cohort Study of Women Following HIV-1 Seroconversion in Microbicide Trials	MTN	Spilhaus Seke South Zengeza
2007–2010	A5185s: A Substudy of A5175: Effect of Initial Antiretroviral Treatment on Genital Compartment Virus in Individuals from Diverse Areas of the World	ACTG	Parirenyatwa
2007–2010	A5221: A Strategy Study of Immediate Versus Deferred initiation of Antiretroviral Therapy for AIDS Disease-Free Survival in HIV-Infected Persons Treated for Tuberculosis with CD4 <250 Cells/mm3 (STRIDE)13	ACTG	Parirenyatwa
2007–2011	A5208: Optimal Combination Therapy After Nevirapine Exposure (OCTANE)	ACTG	Parirenyatwa
2007–2011	HPTN/IMPAACT 046: Phase III Trial to Determine Efficacy and Safety of an Extended Regimen of Nevirapine in Infants Born to HIV Infected Women to Prevent Vertical HIV Transmission During Breastfeeding14, 15	HPTN IMPAACT	Seke North St. Mary's
2007–2008	Linking Alcohol Use with HIV Risk Behavior and HIV Prevalence Among Beer Hall Patrons in Harare, Zimbabwe	NIH	City of Harare Beer Hall Outlets
2007–present	P1060: Phase II, Parallel, Randomized, Clinical Trials Comparing the Responses to Initiation of NNRTI-Based Versus PI-Based Antiretroviral Therapy in HIV-Infected Infants Who Have and Have Not Previously Received Single Dose Nevirapine for Prevention of Mother-to-Child HIV Transmission17, 18	IMPAACT	Parirenyatwa

2007–2012	Non-Pneumatic Anti-Shock Garment (NASG), A First-Aid Device to Decrease Maternal Mortality from Obstetric Hemorrhage: A Cluster Randomized Trial	NIH Gates	City of Harare Polyclinics Parirenyatwa and Harare Central Hospitals
2008–2009	An Acceptability and Safety Study of the Duet Cervical Barrier and Gel Delivery System in Zimbabwe	NIH Gates	Epworth
2009–2010	Willingness of Clinicians to Integrate Microbicides into HIV Prevention Practices in Southern Africa	NIH	Spilhaus
2009–present	P1070: Dose-Finding and Pharmacogenetic Study of Efaviranz in HIV-Infected and HIV/TB Co-Infected Infants and Children ≥ 3 Months to < 36 Months of Age	IMPAACT	Parirenyatwa
2009–2012	MTN 003 (VOICE): Safety and Effectiveness of Tenofovir 1% Gel, Tenofovir Disoproxil Fumerate Tablet, and Emtricitabine/Tenofovir Disoproxil Fumerate Tablet for the Prevention of HIV Infection in Women21	MTN	Spilhaus Seke South Zengeza
2009–2013	MTN 003B: Bone Mineral Density Substudy of VOICE	MTN	Spilhaus Seke South Zengeza
2010–present	MTN 016 (EMBRACE): HIV Prevention Agent Pregnancy Exposure Study	MTN	Spilhaus Seke South Zengeza
2010–present	P1072: Safety and Immunogenicity of a Live, Attenuated, Rotavirus Vaccine (ROTATEQ) In HIV-Infected and Uninfected Children Born To HIV-Infected Mothers	IMPAACT	Parirenyatwa
2010–2012	Establishment of Laboratory Reference Values for Harare, Chitungwiza, and Mutoko	NIH	Various clinics in Harare, Chitungwiza, and Mutoko
2010–2012	A5225: A Phase I/II Dose-Finding Study of High-Dose Fluconazole Treatment in AIDS-Associated Cryptococcal Meningitis	ACTG	Parirenyatwa
2010–2012	A5234: International Trial of Modified Directly Observed Therapy versus Self-Administered Therapy for Participants with First Virologic Failure on a Non-Nucleoside Reverse Transcriptase Inhibitor-Containing Antiretroviral Regimen	ACTG	Parirenyatwa
2011–present	P1073: Study of Immune Reconstitution Inflammatory Syndrome (IRIS) for International Sites Initiating Highly Active Antiretroviral Therapy (HAART) in Infants and Children < 72 months of Age	IMPAACT	Parirenyatwa
2011–present	1077BF (PROMISE): Promoting Maternal and Infant Survival Everywhere	IMPAACT	Parirenyatwa Seke North St. Mary's
2011–present	P1084s: Maternal and Infant Monitoring for Evidence of Toxicity Related to Tenofovir Exposure: The Bone and Kidney Health Substudy of the IMPAACT 1077 PROMISE Protocol	IMPAACT	Parirenyatwa Seke North St. Mary's

2011–2012	A5265: A Phase III, Open-Label, Randomized, Assessment-Blinded Clinical Trial to Compare Safety and Efficacy of Topical Gentian Violet to that of Nystatin Oral Suspension for the Treatment of OC in HIV-1 Infected Participants in Non-US Settings	ACTG	Parirenyatwa
2011–2012	PEPFAR 046: Integrating Family Planning into PMTCT: A Novel Approach in Zimbabwe (A Substudy of HPTN/IMPAACT 046)	PEPFAR	Seke North
2012–present	Disclosure Intervention for Zimbabwean Parents	NIH	Mutoko
2012–present	MTN 020 (ASPIRE): A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Phase III Safety and Effectiveness Trial of a Vaginal Matrix Ring Containing Dapivirine for the Prevention of HIV-1 Infection in Women	MTN	Spilhaus Seke South Zengeza
2012–present	A5264: A Randomized Evaluation of Antiretroviral Therapy Alone or with Delayed Chemotherapy Versus Antiretroviral Therapy with Immediate Adjunctive Chemotherapy for Treatment of Limited Stage AIDS-KS in Resource Limited Settings	ACTG	Parirenyatwa
2012–present	MTN 003D: An Exploratory Study of Potential Sources of Efficacy Dilution in the VOICE Trial	MTN	Seke South Zengeza
2013–present	A5263: A Randomized Comparison of Three Regimens of Chemotherapy with Compatible Antiretroviral Therapy for Treatment of Advanced AIDS-KS in Resource Limited Settings	ACTG	Parirenyatwa
2013–present	A5273: A Multicenter Study of Options for SEcond-Line Effective Combination Therapy (SELECT)	ACTG	Parirenyatwa
2013–present	A5274: Reducing Early Mortality and Early Morbidity by Empiric Tuberculosis Treatment Regimens	ACTG	Parirenyatwa
2013–present	A5278: Pharmacology Substudies of A5263 and A5264	ACTG	Parirenyatwa
2013–present	A5279: Phase III Clinical Trial of Short-Course Rifapentine/Isoniazid for the Prevention of Active Tuberculosis in HIV-Infected Adults with Latent Tuberculosis Infection	ACTG	Parirenyatwa
2013–present	A5282: A Randomized, Phase II Trial to Compare an HPV Test-and-Treat Strategy to a Cytology-based Strategy for Prevention of CIN 2+ in HIV-Infected Women	ACTG	Parirenyatwa
2013–present	A5288: Management Using the Latest Technologies in Resource-Limited Settings to Optimize Combination Therapy After Viral Failure (MULTI-OCTAVE)	ACTG	Parirenyatwa
2013–present	P1104s: Longitudinal Developmental and Neuropsychological Assessments of HIV-Infected Participants and HIV-Uninfected	IMPAACT	Parirenyatwa
2013–present	HIV-Target Cell Response in Women Initiating Various Contraceptive Methods in High HIV-Incidence Areas: CHIC 02A	Gates	Spilhaus

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