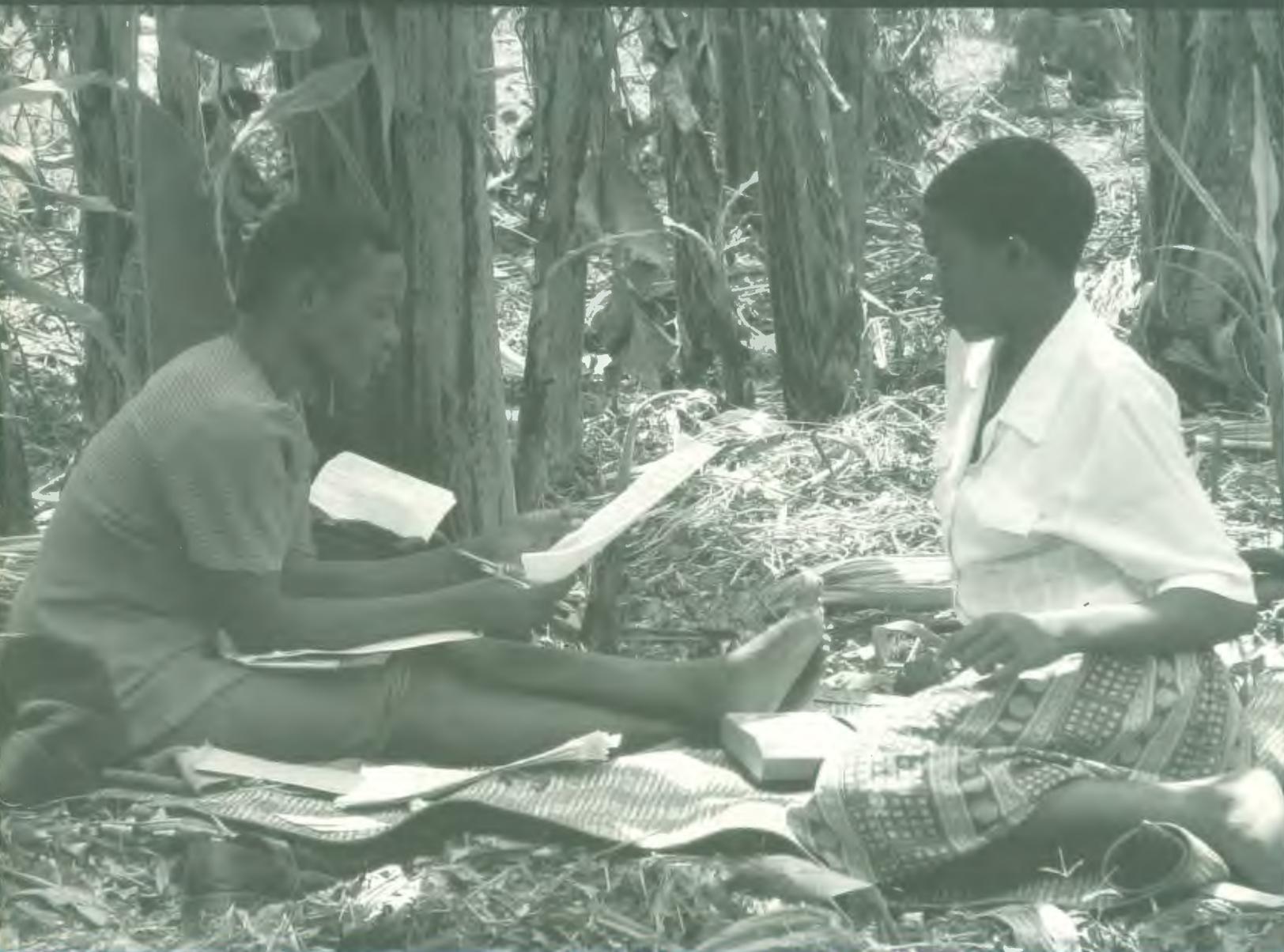


RAKAI HEALTH SCIENCES PROGRAM



A N N U A L R E P O R T 2 0 0 3 - 2 0 0 4

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Foreword by: David Serwadda, Nelson Sewankambo,
Fred Wabwire-Mangen, Tom Lutalo, Maria Wawer and Ron Gray

For us, the “ancient” principal investigators on the Rakai Health Sciences Program, the year 2004 represents a culmination of many hopes. When David Serwadda, Nelson Sewankambo and Maria Wawer first met in 1987, and initiated a small community cohort study (sera were spun at night with a manual centrifuge in a tiny rented room at the Mulano bar-hotel in Kyotera), we could not have imagined what Rakai would become. As Ron Gray, Tom Lutalo and Fred Wabwire Mangen, joined the “ancients”, the Program moved into a few rented rooms in a local tin-roofed shop in Kalisizo and initiated a number of much larger community prevention trials and studies. Even then, we would not have imagined that the Program would expand to encompass its current team of over 400 highly dedicated and energetic young principal investigators, multidisciplinary professionals and support staff, conducting a wide range of reproductive health research and service activities.

Most of all, the possibility that we would be completing and opening the Rakai Health Sciences Center, with its state-of-the-art laboratory, data and clinical resources, would have seemed completely improbable. For this, we owe a deep debt of gratitude to a number of key supporters, including the Uganda Virus Research Institute, the Rakai Town Council, the Doris Duke Charitable Foundation, the US National Institutes of Health International Center for Excellence in Research collaboration, and the Bill and Melinda Gates Foundation.

The Rakai Program is now at a major inflection point. Although our commitment to community-based research and services remains as solid as ever, the Program will be able to dramatically expand clinical and basic sciences, with the aim of better understanding HIV and related reproductive health problems and infections in Rakai. The advent of antiretroviral therapy, initiated (among others) by the Rakai Program (with support from the Uganda CDC PEPFAR), also changes the HIV paradigm, and it will be crucial to track the health, epidemiological and social impacts of this service. We thus owe a great debt to the population and leadership of Rakai District, without whose support there would be no Rakai Health Sciences Program, and who, with their unflinching commitment to research participation, have provided invaluable information for Uganda, other African countries, and the world. Through the Community Advisory Board, town meetings and other intensive contacts, the residents of Rakai also ensure the Rakai Program remains respectful and ethical in its collaboration with study participants, and provides appropriate services.

As we look back on the past 17 years, and look forward to the future, we would like to acknowledge the commitment and support offered to the Program by the US National Institutes of Health including NIAID, NICHD, NIMH, NCI, the Office of AIDS Research and Fogarty International. We also acknowledge the invaluable support from The Bill and Melinda Gates Foundation and the Gates Institute for Population and Reproductive Health at Johns Hopkins, the Doris Duke Charitable Foundation, Walter Reed Army Institute of Research, the Rockefeller Foundation, and many other generous donors.

Colleagues and friends at these institutions, as well as at Makerere, Johns Hopkins and Columbia Universities, have contributed extensively to the scientific integrity and productivity of the Program, and helped smooth the hurdles of the many challenges of present-day research.

Thank you, All

With your support, we look forward to the next 17+ years.

Rakai Project becomes the Rakai Health Sciences Program



Change of names reflected everywhere

As a result of increased and diversified activities, the Rakai Project has changed its name into the **Rakai Health Sciences Program**.

The program is still a collaboration between the Ministry of Health through the Uganda Virus Research Institute, Makerere University, Columbia University, Johns Hopkins University and Rakai District.

In its initial years, the program focused on HIV/AIDS research in the community, including evaluation of health education and condom promotion. Over the years, activities have increased both in nature and volume. While not losing sight of the community-based approach to HIV epidemiology and prevention, major areas of activity have expanded to include:

- laboratory and clinical research,
- randomized trials of new prevention strategies
- health professional training,
- expanded community services including HIV voluntary testing and counseling, provision of HIV anti-retroviral therapy (ART), general and HIV-related medical care, prevention of mother-to-child transmission of HIV, family planning services, prevention of cervical cancer and specialized services for adolescents.

The new name signals our long term commitment to contribute to the understanding of HIV/AIDS, develop evidence-based programs to improve the health of the population of Rakai and of Uganda, and to the share of information and experience with colleagues and health professionals throughout Uganda and globally.

“The Program is a blessing to the Rakai District”

-LCV Chairman

Mr. Vincent Ssemakula,
Head of the Rakai
District Administration



Rakai District has suffered seriously from the effects of AIDS since it first surfaced around 1982. We all know that AIDS has claimed the lives of Rakai professionals, farmers, traders, and others, and has seriously undermined economic productive capacity. Furthermore, the death of so many parents has left behind large numbers of orphans, estimated at 38,000. Some of these head families and have to fend for their siblings. Other related problems have been an increase in the demand for medical care for opportunistic infections, and the stigma, isolation and discrimination of persons living with HIV.

Thanks to the Rakai Health Sciences Program, much has now changed. First of all, the people of Rakai now know that AIDS is a disease caused by a virus passed on from one person to another, and not by witchcraft. It is also common knowledge now that most people in Rakai get infected through heterosexual contact with an infected person. This awareness has now reached an estimated 90%. Equally encouraging, is the increasing number of people who are now willing to come out openly and declare publicly that they have HIV/AIDS. It is also interesting to note that large numbers of people now come freely to the clinic to take an HIV test, undergo counseling and live positively with HIV/AIDS.

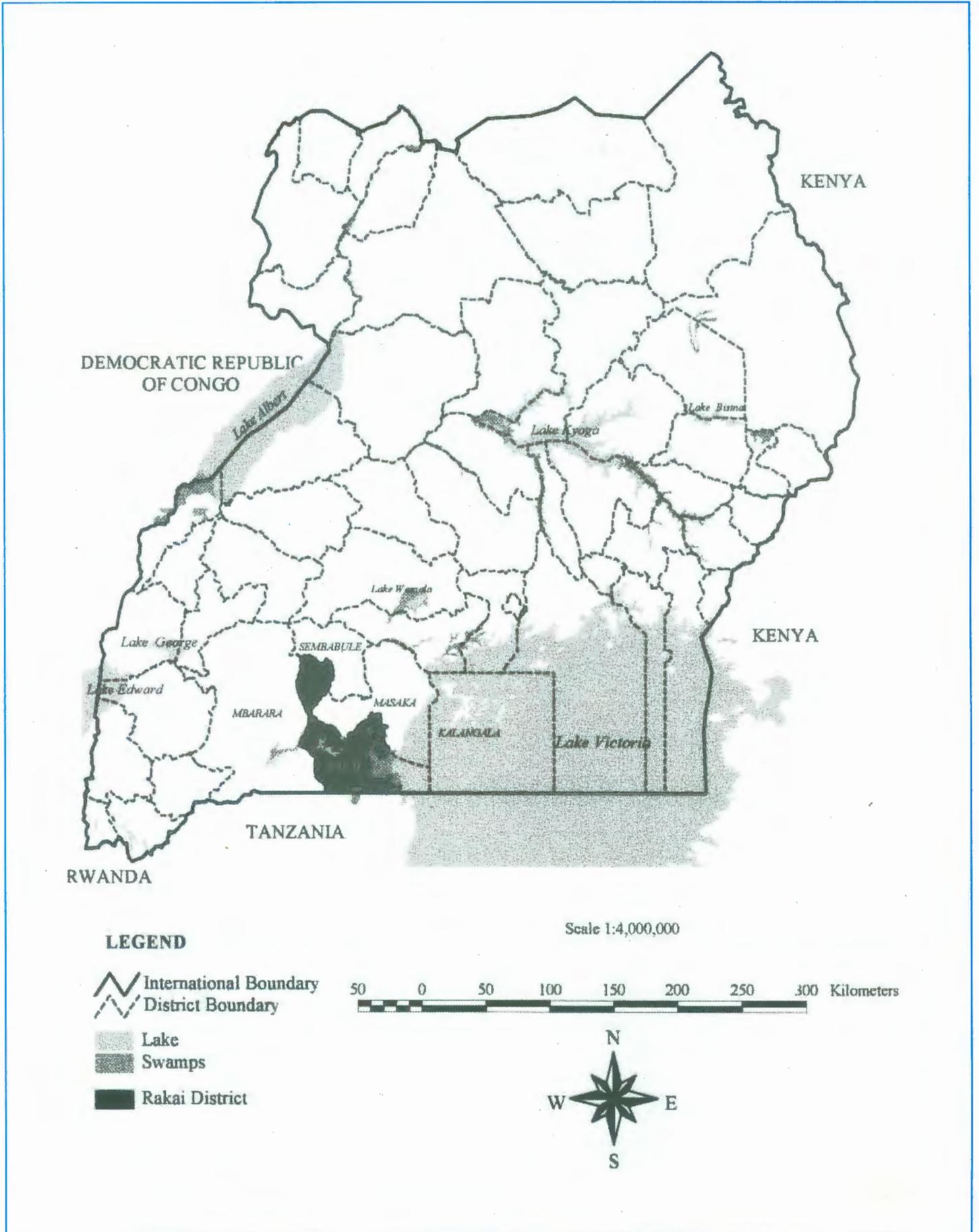
All the above efforts by Rakai Health Sciences Program have produced one major outcome: the rate of HIV prevalence has now declined significantly. Without the timely intervention of Rakai Program the district would have found it extremely difficult to tackle the AIDS threat. At the beginning there was nothing being done. There was widespread panic. We are, therefore, very grateful to all the staff of the Rakai Program, for a wonderful job done.

A handwritten signature in black ink, appearing to read "Vincent Ssemakula".

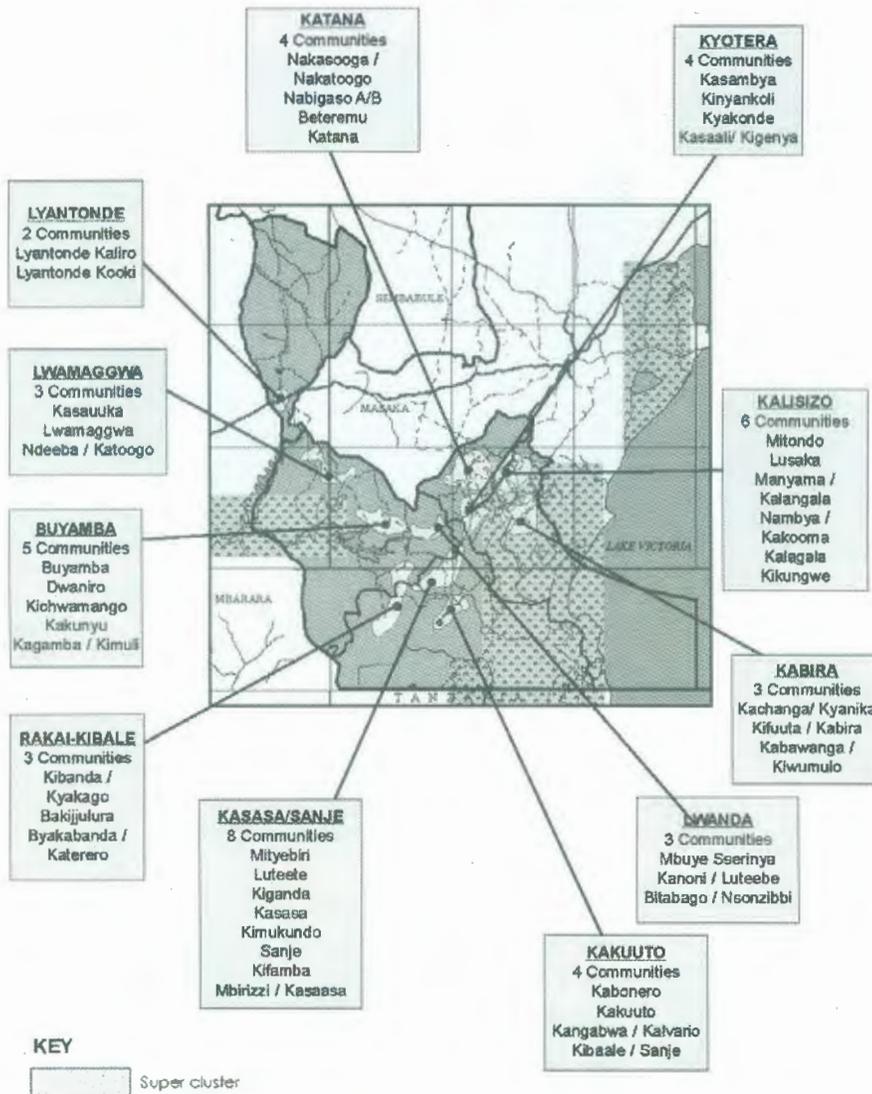


Vincent Ssemakula, LC 5 Chairman

Map of Uganda showing location of Rakai District



Map of the Rakai District showing Current Program Operational Areas



Rakai District Profile

General Information

Total area: 4,973Km²
 Total Population 471,806 (323,262 males, 239,544 females)
 Urban Population: 0.7%
 Mean Household size: 4.4
 Main urban centers: Lyantonde town-7,477
 Kyotera town-7,678
 Rakai town - 6,148
 Population growth rate: 2.8%
 Languages: Luganda, Lunyankore, Lunyarwanda

Social Indicators

Total fertility rate (women 15-49) 7.2
 Maternal mortality rate: 505 deaths per 100,000 live births

infant mortality: 71.9/1000 births
 Adult literacy rate: 69% (women, 76.4 (men)

Politics

Head of Local Government: Mr. Vincent Semakula
 Central Government Representative: Mr. Yasin Kasibante

Economy

Main activity: 76.7% of the population depend on subsistence agriculture.
 Main crops: Plantains, Cassava, Maize, Beans, Millet, Sorghum, Sweet potatoes, Groundnuts, Coffee.
 Animal rearing: Mainly Cattle

Source: Uganda Bureau of Statistics - Entebbe



Uganda Virus Research Institute (UVRI) of Uganda's Ministry of Health, host institution of the Rakai Health Sciences Program. View of main campus.

The Uganda Virus Research Institute (UVRI)

THE RAKAI PROGRAM'S IMPLEMENTING INSTITUTION OF UGANDA'S MINISTRY OF HEALTH

A word form Dr. Miph Musoke, Acting Director, 2002

2003 marks the Uganda Virus Research Institute's 68th year of involvement in infectious diseases research. In 1984 the first blood samples from patients with 'Slim' disease were tested in the UK and found to be positive for HIV antibodies. I am glad to mention that one of the first Programs to work with UVRI in conducting large scale seroepidemiological studies on HIV/AIDS was the Rakai Project, now renamed the Rakai Health Sciences Program. From 1988 up to the present, the Institute has worked with researchers from Makerere, Columbia University, and Johns Hopkins University and Rakai District authorities to implement various studies related to HIV/AIDS and to execute community interventions. This collaboration has brought scientific achievements to UVRI and has assisted the Institute regain its international image. UVRI recently acquired land in Kalisizo town, to enable the Rakai Program establish a permanent base within Rakai District. Construction of a new research complex on this piece of land is commendable. At the UVRI main campus, Entebbe, the Institute has secured and permanently allocated additional land specifically for the Rakai Program. There is no doubt many people in Uganda stand to benefit as the Program's scope of activities expands.

*Dr. Miph Musoke,
Ag. Director UVRI*





*Part of the Rakai Laboratory at
UVRI, Entebbe.*

Overseeing data and analyses at UVRI since 1991

Thomas Lutalo. BStat, MSc, Mr. Tom Lutalo is a UVRI senior member of staff as well as a Principal Investigator with the Rakai Program. He is an expert in medical statistics and data analysis. He has directed the Rakai Project data management center for the past 9 years and is also a Principal Investigator on the Rakai Study of contraception and fertility funded by the Bill and Melinda Gates Institute for Reproductive Health at JHU. He is a member of the UVRI Scientific and Ethics Committee.



Tom Lutalo at his UVRI Office



Founded in 1922, Makerere is one of the oldest leading Universities in Africa. All senior principal co-investigators have academic appointments at Makerere in the **Makerere Medical School** and the **Institute of Public Health** both located in Kampala.

David Serwadda, MBChB, MSc, MMed, MPH. Associate Professor and Director of Makerere University's Institute of Public Health, Dr. Serwadda is an infectious disease epidemiologist who was one of the first researchers to identify AIDS in Uganda. He is one of the founders of the Rakai Project and has been a Rakai Program Ugandan Principal Investigator since 1988.



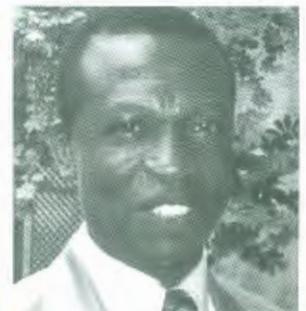
Prof. Nelson Sewankambo, MBChB, MMed, MSc, Professor and Dean of the Makerere Faculty of Medicine, Dr. Sewankambo is one of the three founders of the Rakai Health Sciences Program. He has been a Ugandan Principal Investigator since 1988.



Prof. Fred Wabwire-Mangen, MBChB, MPH, PhD, Associate Professor and former Director of the Institute of Public Health, Dr. Wabwire-Mangen has been a Ugandan Principal Investigator on the Rakai Program since 1995.



Dr Stephen Watya, MBChB, M.Med, Dip. Pub. Health. Dr Watya is a Professor of Urology and is the Consultant Urologist for the Rakai circumcision trials.



Columbia University



Maria Wawer, MD, MHSc, FRCP (C), Professor of Clinical Public Health Heilbrun Department of Population and Family Health. She was one of the three pioneers who established the Rakai Health Sciences Program in 1987 and is a Rakai Program Principal Investigator.

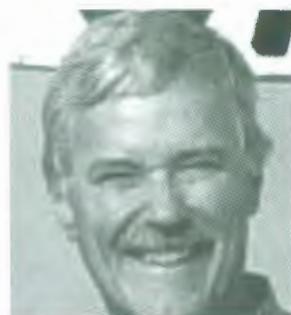


Jennifer Wagman, BA, MHS. A behavioural scientist stationed in Rakai, Uganda. Ms Wagman supervises field-based ethnographic and qualitative research.

Johns Hopkins University



Ronald H. Gray, MD, MSc, is the Robertson Professor of Reproductive Epidemiology in the Department of Population and Family Health Sciences with joint appointments in Epidemiology and International Health. Dr. Gray is a Principal Investigator with the Rakai Health Sciences Program.



Thomas S. Quinn MD is a Professor in the Division of Infectious Diseases at Johns Hopkins Medical School, with a joint appointment in the Departments of International Health, and Molecular Microbiology and Immunology at the Johns Hopkins Bloomberg School of Public Health. Dr. Quinn is also a Senior Investigator, Laboratory of Immunoregulation, NIAID/NIH. He is the Principal Investigator on the NIAID/Rakai Program International Center for Excellence in Research (ICER) collaboration.



Heena Brahmabhatt, PhD is a Research Scientist in the Department of Population and Family Health Sciences at the Johns Hopkins, and a Rakai Program Co-Investigator.

Rakai Program Becomes an NIAID/NIH Collaborating “International Center for Excellence in Research” (ICER)

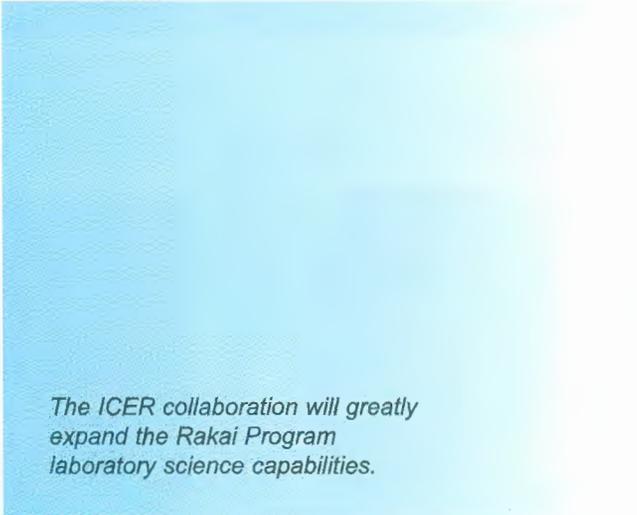
In 2002 the Rakai Health Services Program was selected by the Division of Intramural Research of the National Institute of Allergy and Infectious Diseases (NIAID), NIH, to be a collaborating International Center for Excellence in Research (ICER). Dr. Thomas Quinn, a Senior Investigator at NIAID and Professor of Medicine at Johns Hopkins University is the U.S.-based Principal Investigator and Dr. Nelson Sewankambo, Dean of the Makerere University Faculty of Medicine, is the Ugandan PI. Dr. Steven Reynolds is the NIH Scientist in Uganda. The Rakai Project was selected based on its long term expertise in HIV research, contributions to public health within a community-based setting, and its long-term affiliations with NIAID. The primary goal of the ICER program is to develop a sustained research program of excellence in areas of high infectious disease burden, through partnerships with scientists and research managers at NIH and foreign institutions. The NIAID ICER program has supported the equipping of laboratory and data facilities in the new Rakai Health Sciences Center described on page 35 of this report and will support research on infectious diseases of public health importance. With the award of the ICER to the Rakai Health Sciences Program, NIAID/NIH has made a long-term commitment to help foster the development of laboratory and clinic-based research, including the training of Ugandan scientists.



Steven J. Reynolds, MD, MPH



Steven J. Reynolds, MD, MPH is a staff clinician at NIAID and an Assistant Professor of Medicine at Johns Hopkins University. Dr. Reynolds is an Infectious Disease physician posted full time in Uganda as the Scientific Director of the International Center of Excellence in Research. Before joining the Rakai team, he worked in India on a number of HIV epidemiological studies and clinical trials of vaginal microbicides.



The ICER collaboration will greatly expand the Rakai Program laboratory science capabilities.

The New Generation of Rakai Principal Investigators



Dr. Kigozi Godfrey MBChB, MPH. Dr. Kigozi obtained his MPH from Johns Hopkins and is a Rakai Program co-Principal Investigator. He has overseen a number of complex Rakai Program studies including the STD Control for Maternal and Infant Health Study, and the HIV Molecular Epidemiologic Study (MER). Currently, he is the Medical Director of Field activities and oversees the Male Circumcision trials. - He is a member of the Science and Ethics committee of UVRI and is based at the Kalisizo Field Station.



Mr. Fred Nalugoda B.Stat, MHS. Co-Principal Investigator completed his MHS degree at Johns Hopkins. Mr. Nalugoda is one of the Rakai Program's most senior scientific staff and has detailed knowledge of the Program, especially the Rakai Community Cohort Study (RCCS). He coordinated the Community Opinion Leader (OL) Intervention study, and currently oversees fieldwork for the Socio Ethnographic Research on Networks (SOCERNET)- He is Director of the Kalisizo Field Research Station.



Dr. Noah Kiwanuka MBChB, MPH. Co- Principal Investigator completed his MPH at Johns Hopkins and is currently doing a PhD at Case Western University. He supervised field work for the STD control for AIDS prevention trial, CHER, Bacterial vaginosis studies and the Male Circumcision trial. He was previously a member of the Science and Ethics committee of UVRI and the Law and Human rights committee of the African AIDS Vaccine Program (AAVP) He is currently on leave at case Western Reserve University, USA.



Dr. Mohammed Kiddugavu MBChB, MPH Co-Principal Investigator and Johns Hopkins MPH graduate.. Dr. Kiddugavu is an investigator on the Natural History of HPV infection, and the Benefits and Risks Ethics study, and, he currently directs the Rakai Community Cohort Study. He is based at Kalisizo Station.

The New Generation of Rakai Principal Investigators

Dr. Zikulah Namukwaya MBChB, MPH. She joined the Rakai Health Sciences Program in July 2000 and completed a MPH at Johns Hopkins in 2002. She coordinated the BV study and currently she coordinates the Reproductive Health project. She is based at Kallsizo Station.



Dr. Fred Makumbi BSc. MHS, PhD Fred Makumbi joined the Rakai Program in 1992 as a Census Team Leader. From 1995 to 1999 he worked as a Data Coordinator. Through the Rakai Program he was awarded a Gates and Fogarty AITRP scholarship in August 1999 and completed the MHS degree at Johns Hopkins University. He subsequently received support from the Gates Institute for Reproductive Health and completed his PhD in demography, and epidemiology in 2004. He now directs the Statistical Analysis Unit in Rakai.



Catherine Kibirige BSc. MSc. Ms Kibirige is pursuing PhD studies in the Department of Microbiology and Molecular Immunology at Johns Hopkins University. She will rejoin the Rakai Program in 2006.



Dr. Josep Kagayi MBChB, MPH. Dr Kagayi joined the Program as a medical doctor in 2000. He has previously coordinated the CHER and the PMTC program until mid-2003 when the Program sponsored him for a Master of Public Health program at Johns Hopkins University. He currently directs the Program's antiretroviral services.



Rakai Program Management structure

The Rakai Health Sciences Program is headed by an Executive Committee composed of 10 senior and junior principal investigators. In Uganda these are Dr. David Serwadda, Dr. Fred Wabwire-Mangen, Dr. Nelson Sewankambo, Mr. Tom Lutalo, Dr. Godfrey Kigozi, Dr. Noah Kiwanuka, Mr. Fred Nalugoda, and Dr. Mohammed Kldugavu. In the U.S. the PIs are Dr. Maria Wawer, and Dr. Ron Gray. Decision making is collective, and all research or clinical projects are jointly directed by Ugandan and U.S. investigators.

In addition to the PIs, there are ten Ugandan physicians of whom eight are full time Rakai employees. The part-time physicians include Dr. Stephen Watya a Consultant Urologist at Mulago Hospital who supervises surgery for the ongoing male circumcision trial, and Dr. Dan Murokora, an obstetrician gynecologist who supervises cervical cancer screening. Each medical field protocol is directly supervised by a physician.

The Project organization is structured around functional departments, research activities and services. The departments are Data Management (Tom Lutalo), Laboratory (Pius Opendi), Cohort Survey (Meddie Kiddugavu, Fred Nalugoda and Noah Nyende), Statistical analysis (Fred Makumbi), Qualitative research/Ethnography (Jennifer Wagman and Neema Nakyango), VCT (John Semanda), Community Mobilization (James Ludigo), Health Education (Joseph Matovu), Quality Control (Grace Kigozi), and Logistics (Abby Mussisi and Prossy Namayanja).

The financial and grants management is directed by Mrs. Alice Nabasumba Gumira. Roy Fred Kiggundu is the Kalisizo Station Manager. External financial management and oversight is provided by Acclaim Africa Inc., an independent accounting and auditing firm. Financial oversight is also provided by Columbia and Johns Hopkins Universities. This system of in-country independent accounting and monitoring by Acclaim, backstopped by the U.S. universities, ensures fiscal integrity. The Program also retains Ugandan lawyers from the firm of Katende Ssempebwa and Associates. Two of the firm's partners received law degrees in the US [Harvard and Columbia University] and are licensed both in New York and Uganda. The lawyers assist with matters such as land titles, worker's compensation, and advice on Ugandan tax statutes.

The location of the Project within the Uganda Virus Research Institute (UVRI) has numerous advantages. The UVRI has its own ethical Institutional Review board (IRB), the Scientific and Ethics Committee (SEC) which is the in-country IRB of record responsible for approval and renewal of all research projects. The SEC has a US Federal Wide Assurance, indicating it is in compliance with all pertinent US Federal Regulations. In addition, the UVRI provides laboratory, data management and administrative space in Entebbe, as well as support services. Mr. Tom Lutalo, a Rakai Project PI, is also a senior UVRI staff member who ensures efficient liaison with the UVRI Director.

Mrs. Alice Nabasumba Gumira - B.com. Dip.(Bus. Studies);

She holds a Bachelor of Commerce degree with specialisation in accounting from Makerere University plus an Advanced Financial Accounting Course with ESAMI (Durban, South Africa) in 2001. Ms Nabasumba worked with the Rakai Program from 1994 up to 1996 after which she joined the Institute of Public Health as an Accountant in charge of the multi-donor funded Master of Public Health Program. Since September 2001, she is working as Rakai Program's Grants and Financial Administrator

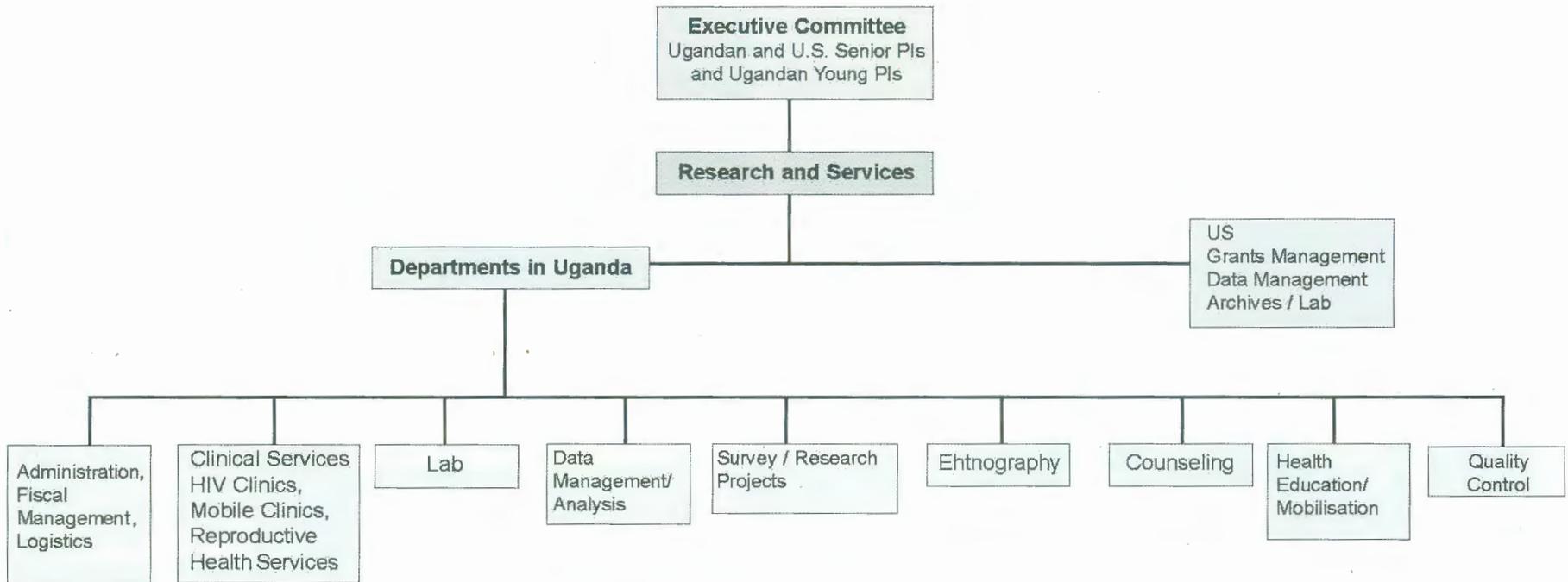


Mr. Royfred Kiggundu, B.ED, Dip. Educ.,Dip. (Banking),

He holds a Bachelor of Education degree with specialisation in Administration and evaluation from Makerere University. Mr. Kiggundu has held various administrative posts in the Education, Banking and NGO sectors. He joined the Rakai program in 1992 and has since been in charge of Administration at Kalisizo field Station as the Station Manager



MANAGEMENT



OVERSIGHT AND DUE DILIGENCE



Rakai Program Community Liaison



*Rakai
Community
Advisory Board
with some
Program staff.*

THE COMMUNITY ADVISORY BOARD

The program's Community Advisory Board (CAB) consists of community civil and religious leaders, as well as community representatives and provides advice to the Project on the conduct of research. The CAB also provides a mechanism for the Project to feed back research findings to participating communities.



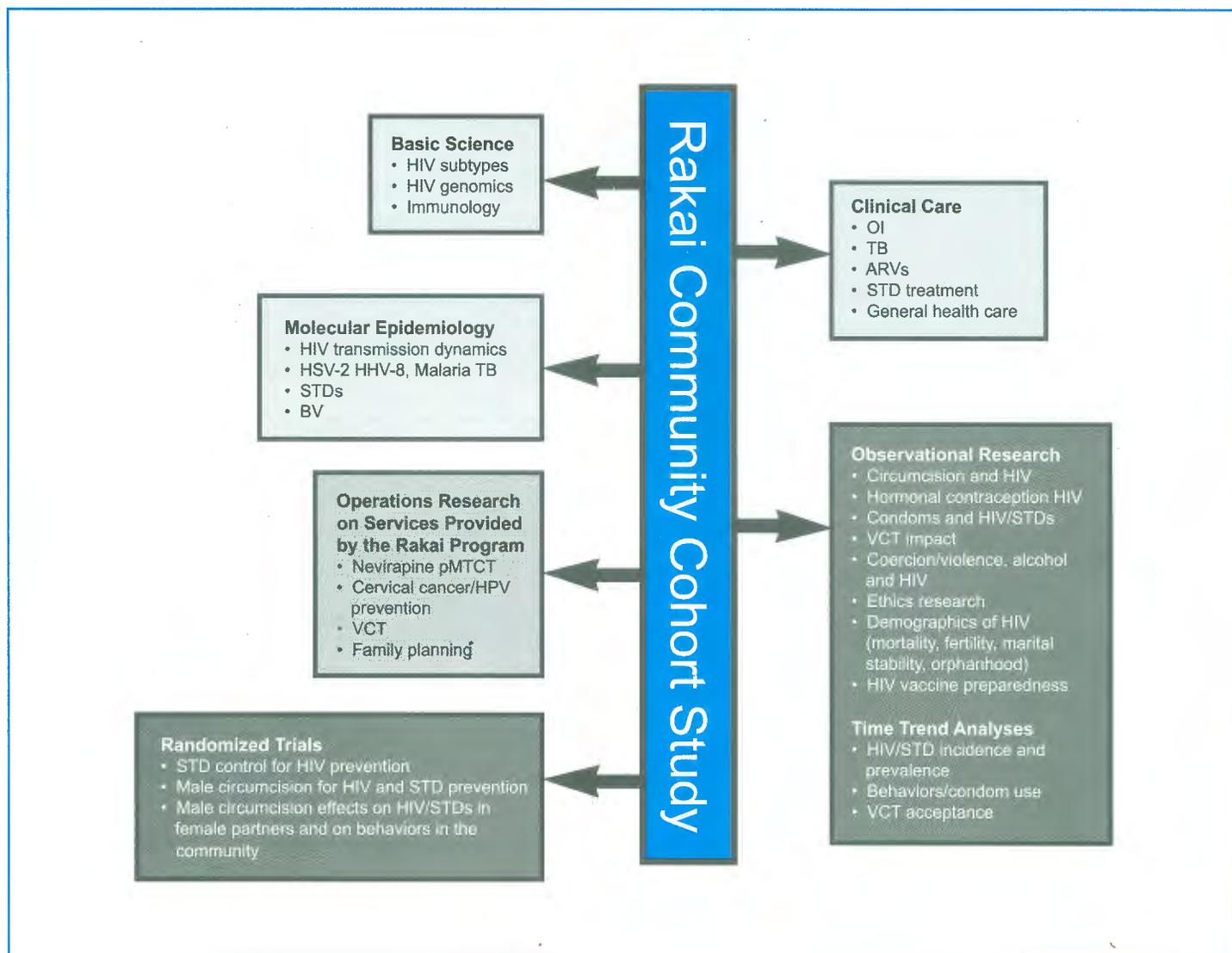
*The UVRI Science and Ethics Committee
(above) chaired by Dr. Jonathan Mermin
(2nd left) reviews and approves all Rakai
program research.*

ETHICAL CONDUCT OF RESEARCH

All Rakai Program research projects are reviewed and approved by IRBs in Uganda (the Science and Ethics Committee of the UVRI, and the Uganda National Council of Science and Technology), and at Johns Hopkins and Columbia Universities. All project personnel have received training and certification in the ethical conduct of research.

Research Activities in 2003-4

STRUCTURE OF RESEARCH IN RAKAI



Dr. Kiddugavu discussing data collecting forms with part of the survey team at Kalisizo Station, November 2003.

Rakai Community Cohort Study (RCCS)



Participants are interviewed in private to ascertain sociodemographic, health and behavioral information.

Since its inception in 1988, the core of the Rakai Program has been the Rakai Community Cohort Study (RCCS). The current 50 village cohort was established in 1994/5, based in part on an earlier smaller cohort study initiated in 1989. The cohort enrolls all resident, consenting adults aged 15-49. All participants are followed annually in the home, at which time they provide survey information, and biological samples for detection of HIV, STDs, and other infections. This is an open cohort which enrolls new in-migrants and newly age eligible residents at each annual survey visit. The open cohort structure maintains the number of participants under surveillance at around 12,000 annually, and prevents the cohort population becoming atypical due to attrition.

The Rakai Community Cohort Study (RCCS) provides a framework within which multiple sub-studies can be conducted at modest incremental cost. Building on the prospective cohort design, Rakai investigators have conducted large scale randomized trials, operations research, studies of molecular epidemiology, including the effects of HIV viral load and subtypes on dynamics of transmission, observational studies on the links between male circumcision and HIV acquisition/transmission, and on the socio-behavioral determinants of HIV risk. Other studies have examined the impact of HIV on demographic parameters, household composition, orphanhood and marital stability. The cohort has also facilitated provision and evaluation of voluntary HIV counseling and testing (VCT), prevention of mother-to-child HIV transmission (PMTCT), promotion of family planning and screening for cervical cancer. More recently we have introduced antiretroviral (ARV) therapy, and the cohort will provide a mechanism for evaluating the impact of ARVs on HIV epidemiology and risk behaviors at a population-level. All research projects described in the remaining part of this chapter are nested in RCCS.

Male circumcision for HIV and STD Prevention Trial



Studies by the Rakai Health Sciences Program (RHSP) (Kelly et al AIDS 1999, Gray et al AIDS 2000), and other researchers found that male circumcision is associated with reduced rates of HIV acquisition in men, and reduced rates of HIV transmission from circumcised men to their female partners. However, these observational studies are not conclusive because risk behaviors and other characteristics differ between circumcised and uncircumcised men. For example, most circumcised men in Rakai are Muslims, and their lower rates of HIV acquisition may be due to cultural practices such as abstinence from alcohol and post-coital genital cleansing. Therefore, clinical trials are needed to assess the potential for male circumcision as a means of HIV prevention before policies or programs can be implemented.

With NIH funding, RHSP is conducting a randomized trial to assess the efficacy of male circumcision to prevent HIV and STD acquisition in 5000 HIV-negative males who accept voluntary counseling and testing (VCT). With Gates Foundation support, the RHSP is conducting a complementary trial of circumcision in approximately 800 HIV-positive men to evaluate circumcision safety and potential reductions in male STD acquisition, as well as the potential of male circumcision to reduce HIV and STD transmission to sexual partners. The Gates trial will also assess the effects of male circumcision on sexual risk behaviors in both men and women in the entire community.

If the trials demonstrate efficacy, the finding would have profound implications for HIV prevention because a single surgical procedure may afford life-long HIV risk reduction for the man and his sexual partner. This could be an extremely cost-effective intervention because the initial cost of surgery would be offset by the long-term prevention of disease, with no recurrent costs.

The RHSP completed a Stage 1 (pilot phase), to establish circumcision safety, acceptability and feasibility. Enrollment, randomization and follow up is now being conducted for the main Stage 2 of the trials. Completion is planned for 2007.



Dr. Stephen Watya (second left) preparing the circumcision team for the next client.

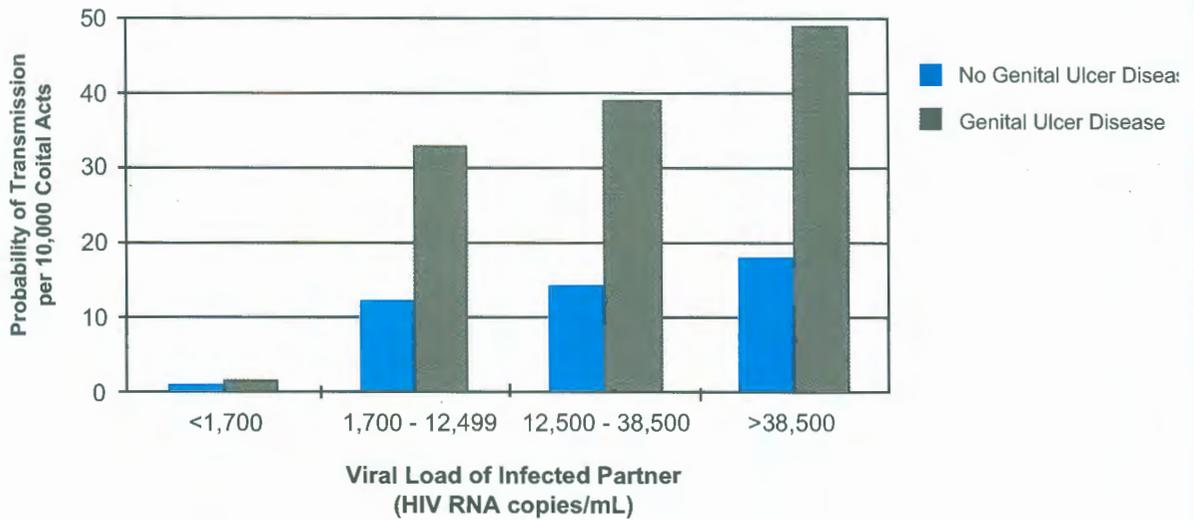


The Program has set up a modern operating theatre at the field headquarters in Kalisizo, Rakai District.

Studies of HIV Transmission Dynamics and the Role of HSV-2

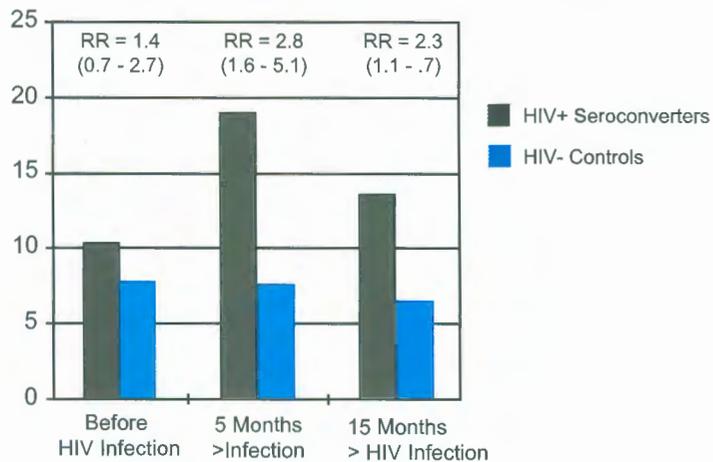
We have estimated the risk of HIV transmission and acquisition using data from HIV-discordant couples retrospectively identified in the RCCS (Quinn *et al NEJM*, 2000, Gray *et al Lancet* 2001, Wawer *et al JID*, 2005). These studies showed that the HIV viral load in the HIV+ partner was the major determinant of transmission risk (each log increase in viral load was associated with a 2.5-fold increased incidence of HIV). The overall transmission probability per coital act was 0.0011 or ~ 1/1000 acts, increased with genital ulcer disease (GUD), and was higher in younger persons.

Probability of HIV Transmission per Coital Act in Monogamous, Heterosexual, HIV-Discordant Couples in Rakai, Uganda



Source: Gray *et al., Lancet* 2001;257:1149

HIV Infection increases genital ulcer disease (GUD)

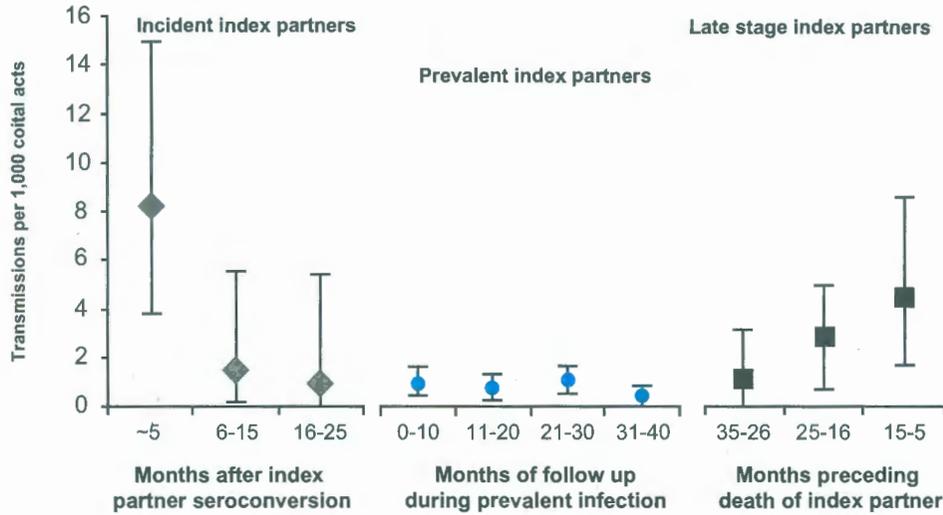


Source: Serwadda *et al., JID* 2003

Proportion of participants reporting GUD (past year) by HIV status

More recently we assessed the rate of HIV transmission per coital act by stage of HIV infection in the index positive partner (Wawer *et al JID*, 2004 in press). The transmission rate was 0.008 per act within ~2.5 months of index partner seroconversion, declined to 0.0008 during latency, and increased again with the onset of AIDS. These transmission risks by stage of disease reflect the level of viremia. In separate studies of HIV seroincident cases, we found that HSV-2 seropositivity was associated with HIV acquisition (Serwadda *et al JID*, 2003). Also, there were high rates of GUD (19%) following HIV seroconversion, particularly in HSV-2 seropositive subjects. The high rate of GUD is likely to partly explain the high per coital transmission rates observed following HIV seroconversion.

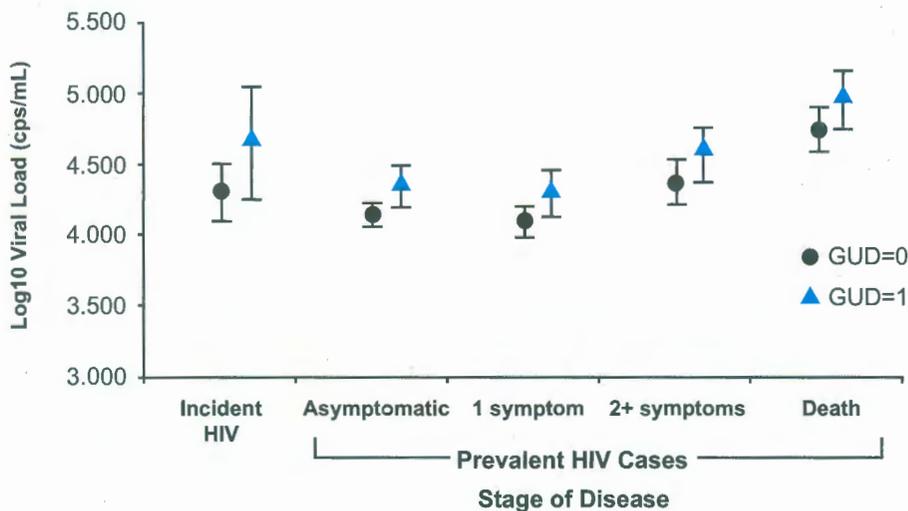
Figure 1. HIV transmission per coital act, and 95% confidence intervals, by follow-interval.



Source: Wawer *et al.*, *JID* in press

The RHSP also assessed the determinants of HIV viral load, and found that HIV-incident cases with GUD and HSV-2 coinfections had significantly higher HIV-1 viremia than persons without GUD (Gray *et al JID*, 2003). Similarly, GUD (which is largely due to HSV-2), is associated with higher viremia, both among incident and prevalent HIV cases. These findings suggest that HSV-2 may upregulate HIV viral load, and that HSV-2 suppressive therapy in HIV-infected persons may improve prognosis and diminish HIV infectivity.

Adjusted HIV Viral Load by Stage of HIV Infection and GUD in Persons Aged 15-29



Source: Gray *et al.*, *JID* 2003

HIV Molecular epidemiology

In collaboration with the Walter Reed Army Institute of Research (WRAIR) and scientists at Johns Hopkins, we have followed persons with incident HIV infections to determine the trajectory of the post-seroconversion peak viremia and achievement of set point. This study collected viable cells for viral culture and full length sequencing in Dr. Francine McCutchen's lab at WRAIR. Full length sequencing has been completed on 47 samples, and Multiregion Hybridization Assay (MHA) has been run on 409 samples. The distribution of subtypes is A 14.4%, D 57.2%, C 0.5%, and recombinants AD 22.6%, CD 3.9%, ACD 0.5%. The MHA provides a rapid screening method as an alternative to full length sequencing. MHA subtyping will be conducted on all HIV-prevalent samples from 1994-5 and 2002-03 to assess changes in subtypes over time.

Viral genotyping has also been used to assess the accuracy of self-reported sexual behaviors. In initially HIV discordant couples among whom the negative partner became infected, molecular linkage was performed using sequence data from the *gag* and *gp41* regions. Among couples in which the HIV-negative partners reported they were monogamous, the transmitted virus was identical to that of the HIV-positive partner in 91.3% of transmission events. In couples where the HIV-negative partner indicated they were not monogamous, the virus was identical in both members in only 65% of transmission events.

Among 372 HIV-discordant couples, transmission was lower with subtype D infections (7.6%), than with subtype A (17.2%) or AD recombinants (13.9%). Multivariate analyses, adjusted for age, stage of index partner's disease, GUD and viral load, showed that relative to subtype D, the transmission rates was significantly increased with subtype A (RR = 4.4, CI 1.7-11.9), and recombinant infections (RR = 1.7, CI 0.8-3.7). Also, with Dr. Lau at CDC, we determined that mother-to-child HIV transmission rates were 16.7% with subtype A, 22.6% with subtype D, and 5.9% with AD recombinant maternal infections. However, because of small numbers, these differences were not statistically significant.



Reformulating Nevirapine syrup as 0.6 mL single pediatric dose for maternal provision to infants born at home.

Studies of Mother-to-Child HIV Transmission (MTCT)

PROVISION OF NEVIRAPINE (NVP) FOR MTCT PREVENTION IN RURAL POPULATIONS

The RHSP conducted operations research to determine how best to deliver nevirapine (NVP) for prevention of mother-to-child HIV transmission (pMTCT) in a rural setting where the majority of women deliver at home. To accomplish this, HIV positive pregnant women were provided with NVP tablets, and with the pediatric NVP syrup, reformulated as a single 0.6 ml dose. Mothers were taught how to take the NVP tablets at onset of labor and how to provide the syrup to their baby within 72 hours of birth (Kagaayi *et al* *JAIDS* in press, 2005). The reformulated syrup was stable and sterile for 6 months (Rexroad *et al* *JAIDS* submitted).

The NVP study showed that maternal self-medication and maternal provision of infant syrup was feasible and effective. One hundred and five HIV+ women were provided with a "pregnancy package" containing maternal NVP and infant NVP syrup, and multivitamins. HIV-negative women also received identically packaged multivitamins, to prevent stigmatization of the HIV-infected mothers. Among the HIV+ women, over 90% took the maternal dose and provided the infant dose, and MTCT was 7.5% (95%CI 1.2-13.8%), which is significantly lower than the rate of 19.4% observed prior to this program.



Pediatric nevirapine syrup was reformulated as a 0.6 mL single infant dose in a 3 mL light-opaque capped syringe to facilitate oral administration, compared with the 240 mL multidose container provided by the manufacturer.

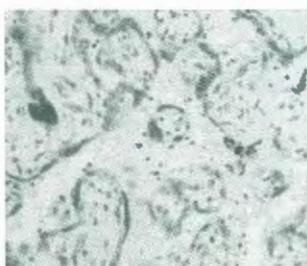
A Rakai Program physician exams a baby during home-based care provided to both HIV+ and HIV- mothers.



MTCT AND MALARIA CO-INFECTION

In secondary data analysis of placentas collected during the prior STD Control for Maternal and Infant Health Trial, we found that placental malaria (as identified by H & E stain) was more common in HIV+ than HIV- mothers (13.6% versus 8.6%, $p = 0.04$). Among HIV+ women, MTCT rates were significantly increased with placental malaria after multivariate adjustment for HIV-1 viral load, $RR=2.89$, $CI: 1.12-7.52$. (Brahmbhatt *et al AIDS* 2003).

However, H&E is not the optimal stain for malaria diagnosis, so placental tissues were re-stained with Giemsa and assessed by immunohistochemistry using Histidine Rich Protein II (HRPII) antibody which is specific for *P. falciparum*. The rate of detected malaria increased to 37.6% in HIV+ women, and the rates of MTCT were 29.3% with malaria coinfection versus 10.3% in the absence of coinfection ($adj\ RR = 7.9$, $CI 1.3-48.5$). This suggests that improved staining improved diagnosis and reduced misclassification (Brahmbhatt *et al. Bangkok Conference 2004, LbOrC20, Late breaker*). If these findings are supported by randomized trials, intensive malaria control may provide an important adjunct therapy for prevention of MTCT.

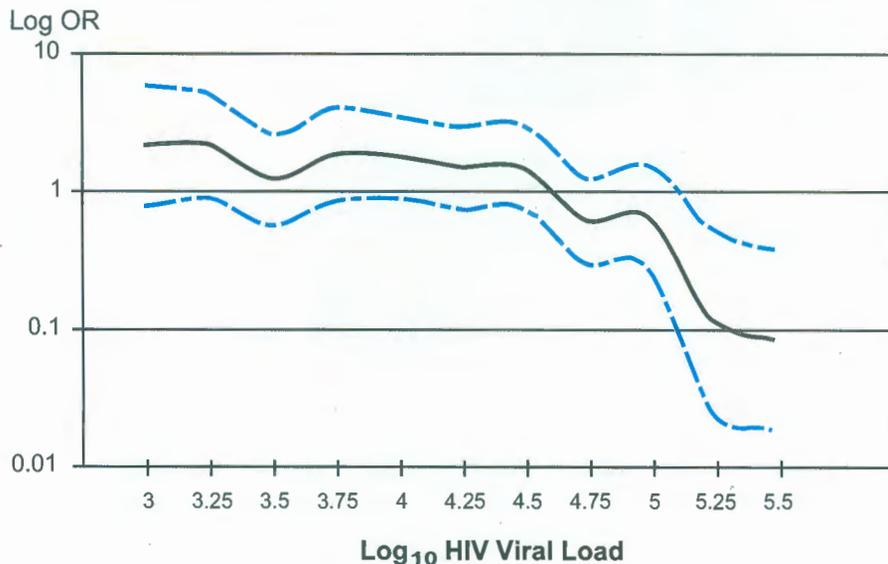


*HRPII staining of *P falciparum* in placental tissues*

HIV and fertility

The Rakai Project first reported that HIV-infected women have reduced rates of pregnancy and that the suppression of fertility was due to HIV infection of the female partner, but not the male, particularly if the infected woman was symptomatic (Gray *et al Lancet* 1998). These findings have implications for HIV surveillance via antenatal clinics (ANC). Under a grant from NICHD, we have extended this work to show that the reduction in fertility is associated with HIV viral loads >4.99 log copies/mL (Nguyen *et al STDs and AIDS*, 2004, submitted).

Relative Odds of Live Birth Associated with HIV Viral Load



Source: Nguyen *et al STDs and AIDS*, 2004, submitted



Screening HIV+ pregnant women for HAART eligibility

We evaluated whether symptomatology can be used to screen HIV+ mothers for HAART treatment eligibility. If women were asymptomatic, none met the DHHS criteria for initiating HAART ($CD4 < 350$, viral load $> 55,000$). However, the presence of symptoms had poor specificity. Thus, screening using symptoms should not be used in place of CD4 counts as a method to identify HAART eligible women (Nguyen *et al. Int J STD & AIDS*, 2005 forthcoming).

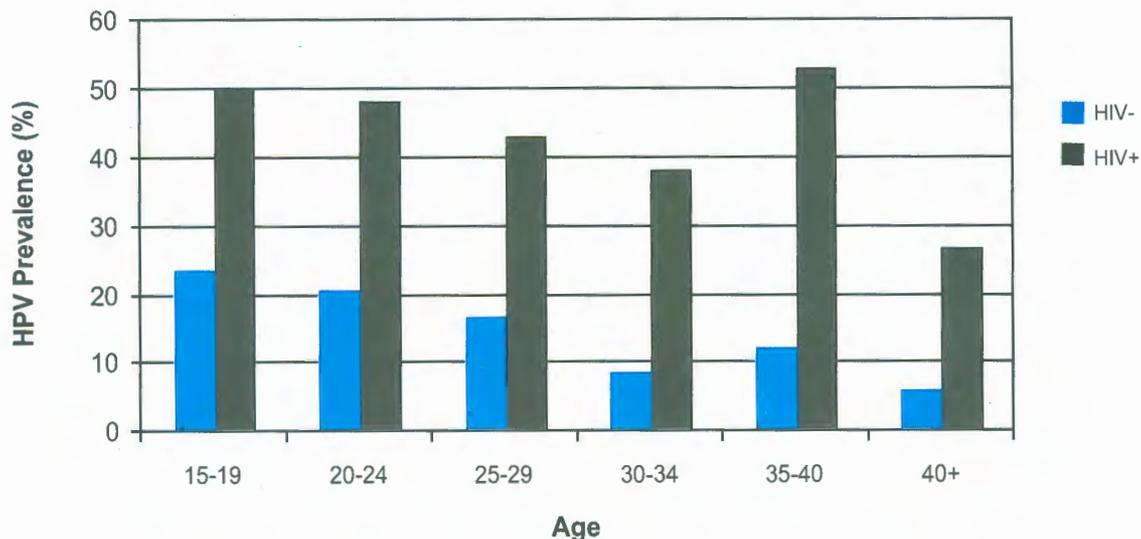
NATURAL HISTORY OF HPV INFECTION AND CERVICAL NEOPLASIA

Cervical cancer is a major health problem in Uganda, and because women are often reticent to accept pelvic exams for cancer screening, many present with advanced, invasive disease. The RHSP assessed the utility of self-collected vaginal swabs for diagnosis of high risk HPV using Hybrid Capture 2 assays and strip PCR. Women who provided three sequential swabs at annual intervals were invited for colposcopy, visual inspection under acetic acid (VIA), and biopsy of visible lesions. Cryotherapy or referral was provided for treatment. HPV detection from self-collected vaginal swabs was as sensitive as physician collected cervical swabs, showing that this methodology can be used for HPV screening. Preliminary results show a higher prevalence of HPV infection in HIV+ women (42%) versus HIV-negative women (15%). High HPV prevalence was observed at all ages in the HIV+ women, but prevalence decreased with age in HIV- women. HPV infection persisted over 36 months in 78.1% in HIV+/HPV+ women, compared with 55.6% in HIV-/HPV+ women, suggesting delayed clearance of the virus (HR = 1.75, CI 1.03-2.94). The incidence of new HPV infections was 14.1% in HIV+ and 8.5% in HIV-negative women, (RR 2.03, CI 1.24-3.33). Strip PCR showed that HIV+ women had more concurrent infections with multiple HPV types. Pathology is still being processed. (Safaeian *et al.* in preparation).



Dr. Dennis Buwembo inspecting the computerized images from coloposcopic examination of cervical neoplasia.

HPV prevalence by age



HIV epidemic modeling

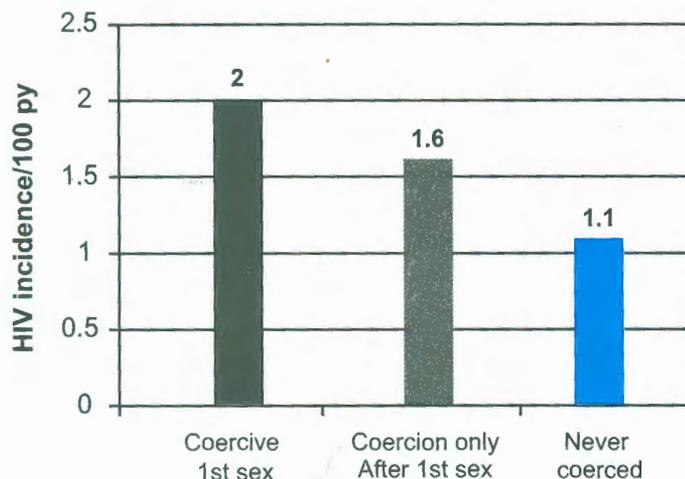
Using the empirical data on HIV transmission rates per coital act, viral load distributions and sexual networks from Rakai, we constructed a stochastic simulation model of the HIV epidemic. The model parameters fit observed HIV incidence (1.5 per 100 py) and estimates of the current reproductive number ($R_0 = 1.4$). Using empirical data on the effectiveness of HAART derived from two US clinics, we simulated the effects of HAART on the HIV epidemic in Rakai and found that ARVs initiated according to DHHS guidelines cannot contain the HIV epidemic. Moreover, even modest behavioral disinhibition can rapidly offset any public health benefits of HAART on HIV transmission in the community. We also applied this model to theoretical vaccines and showed that even a low efficacy vaccine (~25%) in conjunction with HAART, can interrupt the epidemic. (Gray *et al AIDS* 2004).

We and the MRC (UK) collaborated in Uganda conducted community-randomized trials of STD control for HIV Prevention, and found that, despite reductions in treatable STDs, there was no impact on HIV incidence. This was in contrast to an earlier trial in Mwanza, Tanzania, which reported reduced HIV incidence following syndromic STD management. In collaboration with Erasmus University in Rotterdam and investigators at the London School of Hygiene, we have pooled data from three trials of STD control for HIV prevention (Mwanza, Tanzania; Rakai and Masaka, Uganda). The modeling was designed to assess the divergent findings from these trials. The nature of the STD intervention cannot explain the lack of impact in Uganda, because Masaka used syndromic management similar to Mwanza. Models suggest that in the mature, generalized HIV epidemic setting of the two Ugandan trials, treatable STD cofactors only play a modest role, and that most transmission occurs independently of STD infections or symptoms. This suggests that STD control is not a viable method for HIV prevention in mature HIV epidemics.

Research on risk factors for HIV infection

Using data from the RCCS, Rakai investigators have assessed risk factors for HIV acquisition. HSV-2 was associated with increased risk of HIV acquisition (OR = 1.7, CI 1.2-2.4), and with increased HIV-1 viremia following seroconversion (Serwadda *et al JID*, 2003). Hormonal contraception (pill and depo provera) were not found to be associated with incident HIV in adjusted analyses (Kiddugavu *et al AIDS* 2004). Young women aged 15-19 were at increased risk of HIV acquisition if their sexual partner was ten or more years older than themselves (Kelly *et al JAIDS* 2003). Coercive sexual debut was associated with subsequent risk behaviors and elevated risk of HIV acquisition (RR = 2.0, CI 1.3-3.1), but coercion subsequent to sexual debut was not associated with elevated risk (Koenig *et al AIDS*, submitted).

HIV incidence and sexual coercion in Women <25



HIV incidence associated with sexual coercion in young women

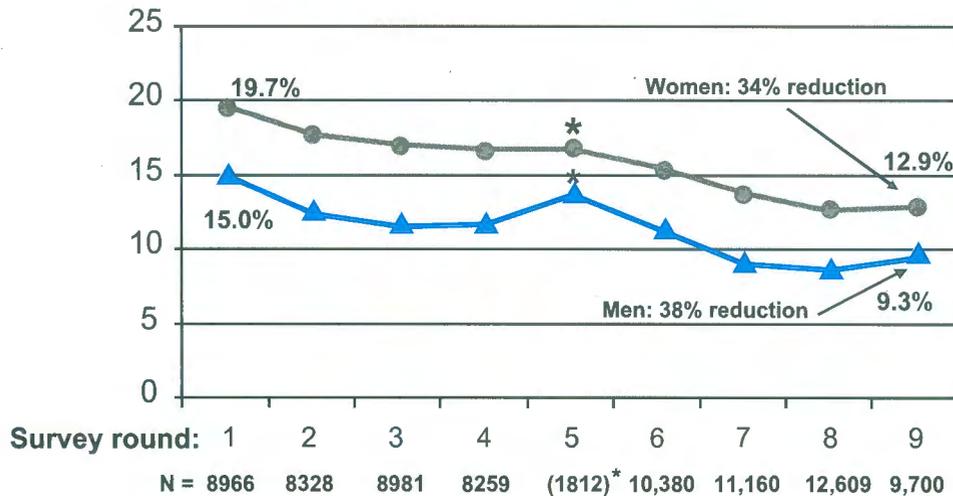
Alcohol consumption before sex was found to increase the risk of HIV infection (RR = 1.66, CI 1.16-2.38 among men, and RR = 1.40, CI 1.02-1.92 among women). Risks were further enhanced if both partners consumed alcohol before sex (Zablotska, PhD thesis 2004).

Blood transfusion and sexual risk behaviors were found to be risk factors for incident HIV infection, but receipt of medical injections was not associated with HIV risk (Kiwauka *et al AIDS* 2004, Thoma *et al Lancet* 2004).

Time trends in risk behaviors and HIV in Rakai (preliminary data)

The RCCS provides annual interview and HIV data on all adults 15-49. This provides a continuous data series with which to monitor trends in the Rakai population. Zikulah Namukwaya evaluated trends among adolescents 15-19, and showed that between 1994 to 2002, there was a gradual but significant decline in the age of first intercourse among boys from 17.1 to 16.2 years, gradual reductions in sexual abstinence among teenagers, and increases in non-marital sexual partners. These trends were offset by substantial increases in condom use by adolescents, and there were no significant changes in HIV prevalence or incidence in adolescents over time.

HIV Prevalence % (age standardized), males and females aged 15-49, 1994/5-2002/3



* Because of financial constraints, the RHSP could not conduct a full survey in round 5, and data from that year do not accurately represent trend 5.

As has been reported elsewhere in Uganda, HIV prevalence in Rakai cohort communities declined significantly in the decade 1994-2003.

Research on the social impact of HIV

HIV infection was shown to be a major cause of marital disruption due to divorce/separation (OR = 1.94, CI 1.42-2.68) and widowhood (OR = 7.56, CI 5.64-10.10). Among couples, female HIV infection, but not male infection, was associated with increased risks of divorce/separation (Porter *et al Demography*, 2004). Sexual coercion was found to be prevalent, with 24.2% of women reporting having been coerced into a sexual relationship, and in 78.6% of cases, coercion entailed physical violence. Coercion was more common if the woman perceived her male partner to be at risk of HIV (Koenig *et al Soc Sci Med* 2004)

Dr. Fred Makumbi assessed orphanhood in Rakai for his PhD dissertation. The prevalence of orphanhood was 22.7% if one or both parents had been HIV+, compared to 7.9% if both had been HIV-negative. Incident orphanhood was 8.2% per year if one or both parents were infected, compared to 0.5% per year if both parents were negative (IRR = 18.93, CI 8.34-42.99). The population attributable fraction of orphanhood associated with parental HIV was 37.3%. (Makumbi *et al AIDS*, submitted). AIDS is having a profound effect on household structure. Heads of households are more likely to be HIV infected than other adult members (Males OR = 2.13, CI 1.65-2.52, and females OR = 1.42, CI 1.15-1.63). Mortality among HIV-infected household heads was high, particularly among females (Nalugoda *et al AIDS Care* 2004).

Research on voluntary HIV counseling and testing (VCT) and family planning

The RHSP provides HIV risk reduction education to all community cohort participants in 50 villages and offers free VCT via community-based resident counselors. The acceptance of VCT has increased from 10% in 1994-95 up to 80% in 2003. However, use of VCT is selective, with lower acceptance among HIV+ positive persons (RR = 0.72, CI 0.68-0.76). Acceptance of VCT was increased among persons who previously received their HIV results and among married individuals. Couples counseling is accepted by about 30% of married persons, and a further 25% said they received results as individuals but shared results with their partners. However, acceptance of VCT was not associated with a reduction in risk behaviors in HIV-negative individuals or in or reduced HIV incidence. (Mattovu et al AIDS accepted 2004).

In separate analyses, we assessed the effects of VCT acceptance on use of family planning (Kagayi 2004, MPH thesis). Among HIV+ women, use of contraception was increased among VCT recipients (48.5%) compared with women who declined VCT (34.3%). The adjusted rate ratio for female controlled methods was RR=1.93 (CI 1.20-3.15), for condom use RR = 1.7 (CI 1.02-2.84), and for dual method use RR=4.56 (CI 1.36-15.32). However, among HIV negative women, receipt of VCT did not significantly increase uptake of family planning (40.1% in acceptors and 38.2% in non-acceptors, p=0.4). Thus, VCT appears to increase uptake of family planning among infected women.

We conducted a community randomized trial to determine whether promotion of family planning through community VCT counselors and outreach could improve uptake of contraceptive use. The family planning promotion effort significantly increased use of hormonal contraceptive methods (pill and injectables).



Acceptance of VCT in rural Rakai has increased.

Qualitative research

To support the biomedical research efforts, we have established a full-time Ethnographic Team which conducts qualitative research via focus groups and in depth interviews, in order to facilitate the planning, conduct and interpretation of RHSP studies.

In the Rakai Social and Ethnographic Research on Networks and Community Opinion Leaders (SOCERNET) we conducted qualitative research social networks, with the objective of identifying popular opinion leaders who could become agents of behavioral change.

Other qualitative studies assessed the acceptability of circumcision, and the cultural and religious attitudes towards the procedure. No obstacles to the acceptability of male circumcision were identified. We have also assessed why there is a high rate of repeat VCT receipt in the Rakai population, and through focus groups we found that HIV-uninfected persons who received negative results on several occasions mistakenly believed themselves to be immune to HIV or to have been fortunate in their choice of partner. Health education messages to overcome these incorrect perceptions were intensified as a result of the focus group research.



*Ethnographic Research:
A Rakai Program worker
conducting an in-depth
interview in Kabira region*

Studies on research ethics

In collaboration with Dr. Ezekiel Emanuel, Chief of Clinical Bioethics at NIH, we have conducted research on coercive inducement to participate in research, and shown that subjects feel free to decline participation in part or in whole.

The RHSP has always endeavored to maintain confidentiality of HIV status information in order to avoid stigmatization and social harms. This has included enrollment of HIV+ and HIV- participants into studies, and non-disclosure of HIV status on consent forms. This issue led to a paper on the ethics of disclosing HIV results on copies of consent forms provided to research participants (Gray *et al* *JAIDS*, 2004).

Research on genital tract infections

Male circumcision has been shown to decrease the risk of HIV infection, but data from Rakai suggest that circumcision is not protective against other STIs (Gray *et al* *AIDS* 2004).

A reanalysis of data from the trial of STD Control for Maternal Infant Health, showed that treatment of trichomonas during pregnancy was associated with increased risk of low birth weight (RR 2.49, CI 1.12-5.50), preterm birth (RR = 1.28, CI 0.81-2.02), and child mortality (RR = 1.58, CI 0.99-2.52). (Kigozi *et al* *Amer J Obstet Gynecol*, 2003). Also, secondary data analysis of the STD Control Trial showed that treatment of syphilis with azithromycin was as effective as treatment with benzathine penicillin (Kiddugavu *et al*, *STDs*, 2004)

A NIH supported study of the natural history and etiology of BV followed 300 women with weekly self-collected vaginal swabs for Gram stain morphology to study the natural history of BV. BV was common: 44.7% of women had BV at enrollment, and 28.3% of women had persistent BV for 12 months. In contrast, among women with normal vaginal flora at enrollment, 71.0% had normal flora over 12 months, and only 12.9% progressed to BV. Among women with intermediate flora at enrollment, 65.5% reverted to normal and 10.9% progressed to BV over twelve months. The risk factors for developing BV included having BV at enrollment, being sexually active, menstruation, and insertion of substances into the vagina. Factors associated with reduced BV risk included normal flora at baseline, pregnancy and metronidazole treatment.

Provision of Antiretroviral Therapy and Evaluation of ARV Programs

In 2004, the Rakai Health Sciences Program received support from the Presidential Emergency Fund for AIDS Relief, via CDC – Uganda to provide antiretroviral (ARV) therapy. Under this award, HIV-positive persons enrolled in the Rakai cohort or resident in adjacent communities will be offered screening for ARVs, and those with symptoms of AIDS or CD4 counts below 250 will be provided with home-based treatment. Treatment monitoring and re-supply will be provided through the RHSP Suubi (“Hope”) clinics which visit each community at two weekly intervals. The program is modeling on a successful CDC service in Tororo, in which VCT and health education are offered to all household members of the index ARV recipient, and ARVs are provided for all other family members found to be eligible, including infants and children. The goal is to increase support for the index infected person and to reduce the risks that drugs will be shared with others. Families are also counseled on ways to support relatives using ARVs, in order to encourage adherence. In keeping with the CDC Tororo strategy, Rakai ARV users are also offered clean water vessels for family use (large jerry cans and sodium hypochlorite for water disinfection) and insecticide-impregnated mosquito nets.

In 2004 we received bridging support from the NIH Office of AIDS Research (OAR) to initiate evaluation of the ARV program in 2004-05, and we subsequently received an RO1 award to evaluate this program from 2005-2010. This study will address the effects of ARVs on HIV incidence and prevalence, and on sexual risk behaviors in the Rakai population. We will monitor the emergence of known ARV resistant mutations and the transmission of resistant strains, as well as identify novel mutations that may emerge. The study will also evaluate treatment response and the presence of resistant mutations in women who previously received nevirapine for pMTCT, and assess MTCT rates in women using ARVs. The utilization of HIV-related services (VCT, ARV screening, ARV initiation and adherence) will be measured in the population as a whole and in subgroups whose acceptance may be affected by stigma and social vulnerability, such as young unmarried persons, women who report marital violence, and children. The impact of ARVs on pregnancy intention and fertility will also be examined. Finally the study will assess the demographic impact of ARVs on mortality, orphanhood marital and household stability.



*Combining services,
research and training:
an example from the
Rakai program*

Joseph Matovu joined the Rakai Project in 1997. Since 1999, he has been the VCT Supervisor for the Project's community-based VCT program. The Program sponsored Mr Matovu for a Master of Health Sciences (MHS) Program at the Johns Hopkins Bloomberg School of Public Health in the department of International Health. As part of his Masters program, he took courses in health communication, qualitative research, and family planning policies and programs, among others. During his stay in USA, Mr. Matovu briefly worked with the Johns Hopkins University Center for Communications Programs (JHU-CCP) as an intern on a “Sports for Life” program that uses sports in the social marketing of HIV/AIDS prevention interventions to health education sports fans and players. He plans to use this experience to further improve and evaluate the Rakai program's outreach via community soccer and netball leagues. Mr. Matovu's recent publication, “The Rakai project counseling program experience” appeared in the Journal of Tropical Medicine and International Health. Currently, he is examining the effect of VCT on prospective risk behavior and HIV-incidence in Rakai, Uganda.

Rakai Program appoints Document Specialists

To ensure that the Rakai Health Sciences Program complies with GCP standards and all applicable regulatory requirements, several secure offices at Kalisizo and Entebbe Stations are devoted to managing essential documents. All documents are tracked, readily accessible, and retained in secure locked offices.



Mark Sennono, a Data Management Supervisor, organizing files at Kalisizo station.

The Program establishes the Quality Control department

The Quality Control Department was established as an independent department to ensure that all studies are conducted in compliance with approved protocols, standard operating procedures; and Good Clinical Practice. A major task is to ensure that personnel are trained, both at the start of a study and at intervals during the study. The Quality Control Department also examines data collection procedures, routinely checks for data quality and errors and tracks any missing or delayed data.



Grace Kigozi, BA, MPH, Head of the newly established quality control department.

Rakai Program is working with INDEPTH

INDEPTH is an International network of 29 Demographic Surveillance System (DSS) field sites in 17 countries, located in Africa and Asia. INDEPTH facilitates data analysis, capacity strengthening, comparative analyses and applications to policy and practice. A number of project staff have participated in workshops and meetings organized by INDEPTH. The INDEPTH Executive Director, Prof Fred Binka together with other INDEPTH officials visited the Rakai Site on 27th February 2003.

Training Programs

The Rakai Health Sciences Program is committed to degree and non-degree professional training in Uganda and the U.S., and is actively working to establish the Rakai Training Center as a national and international field training resource. Our vision is that the Rakai Training Center will be designated as an extramural Tertiary Education Institution of Makerere University, and that the Rakai scientists will be granted faculty appointments in the Institute of Public Health. This will enhance career development for junior scientists and provide a formal mechanism for Rakai to become an accredited training institution.

TRAINING IN THE UNITED STATES

With funds from the Fogarty International Center at NIH, the Gates Institute for Population and Reproductive Health at Johns Hopkins University, and the Doris Duke Charitable Foundation, the Rakai Program is providing both degree and short-term training for project professional staff and other Ugandan candidates.

PhD TRAINING 2003-4; JOHNS HOPKINS

Ms. Catherine Kibirige -PhD in HIV Virology and Molecular Immunology (2002-2006)
Dr. Fredrick Makumbi -PhD program in Demography completed 2003

MASTERS DEGREE TRAINING 2003-04; JOHNS HOPKINS

Dr. Hannah Kibuuka -Masters of Public Health (2002-3)
Mrs. Grace Kigozi -Masters of Public Health (2002-3)
Dr. Zikulah Namukwaya -Masters of Public Health (2002-3)
Dr. Jim Aizire -Masters of Science in Epidemiology (2002-3)
Mr. Joseph Matovu -Masters of Health Sciences (2003)
Dr. Joseph Kaagayi -Masters of Public Health 2004

SHORT TERM TRAINING; JOHNS HOPKINS

Anthony Ndyanabo -Special student in biostatistics 2003-04
Mr. Robert Kakaire -Summer Epidemiology and Statistics Course
Mrs. Noelyn Aliddeki -Summer Epidemiology and Statistics Course
Mr. Robert Ssekubugu -Summer Research and Ethics Course.

MASTERS DEGREE TRAINING, UNIVERSITY OF ALABAMA

Mr. Boaz Iga, Masters training in Laboratory management, University of Alabama 2004-06

UGANDA-BASED TRAINING FOR PROGRAM STAFF

TRAINING AT MAKERERE UNIVERSITY 2003-2004

Mr. Boaz Iga -Bachelor of Biomedical Laboratory Technology at Makerere University. (2001-2003)
Ms. Sarah Kalibbala -Bachelor of Biomedical Laboratory Technology at Makerere University. (2001-2003)
Mr. Roy Fred Kiggundu -Bachelor of Arts in Education (2001-2003)
Mr. Charles Kagulire -Bachelor of Biomedical Laboratory Technology at Makerere University. (2003-2005)
Mr. Simon Aluma -Bachelor of Biomedical Laboratory Technology at Makerere University. (2003-2005)
Mr. William Ddaki -Bachelor of Social Sciences (2001 - 2004)

OTHER TRAINING:

Mr. Joseph Sembatya -Diploma in Health Administration - Uganda, Christian University, Mukono.
Ms. Sophie Kyomuhendo -ACCA Course
Mr. Kimera Edward -BA (SWASA) Kampala University.
Mr. Robert Kairania -counselor training course in Nairobi Kenya
Dr. Pius Opendi, South African training in GLP and US training in laboratory management

Ms. Sarah Kalibala, South African IATA training in dangerous goods shipment
Mr. Iga Boaz -Good Clinical Practice and Good Laboratory Practice, South Africa.
Dr. Zikulah Namakwya and Dr. Gertrude Nakigozi, training in HIV management and ARVs, Institute of Infectious Diseases, Mulago Hospital
Dr. Meddie Kiddugavu and Dr. Joseph Kagayi, clinical training in HIV management at Johns Hopkins Hospital and at Harlem Hospital, New York
Thirty Heads of Departments and Supervisors attended a week long Supervision and Management Course conducted by Uganda Matyrs University Nkozi at Kalisizo Program Offices in July 2003.
Twenty two project counselors received training in counseling and mitigation of domestic violence, provided by the AIDS Information Center (AIC), TASO (The AIDS Support Organization) and the Federation of Ugandan Women.
HIV/AIDS counselors, attended a one week course in palliative care conducted by the Hospice Uganda at Kalisizo, April 2003.

PHD PROGRAMS AT MAKERERE:

Professional staff who have completed Master's degrees at Johns Hopkins are encouraged to enroll in PhD programs at Makerere, using a "sandwich" PhD program whereby Makerere University will award the degree, but under a Memorandum of Understanding with the Johns Hopkins University, Bloomberg School of Public Health (BSPH), candidates can take advanced courses and receive mentoring at BSPH. The "sandwich" PhD avoids the high cost of tuition associated with US-based programs (thus enabling the Program to support more doctoral candidates), and helps build the Makerere Ph.D. program. Three Rakai Program professionals are currently applying for the Makerere "sandwich" PhD.

GOOD CLINICAL PRACTICES, GOOD LABORATORY PRACTICES AND ETHICS TRAINING

Over 60 Rakai Program professionals have completed such training and certification, provided to the project by NIH, WRAIR and Westat. The Program plans to have all staff attend GCP courses. All Rakai Program personnel who have contact with study participants or participant data have received ethics training based on Johns Hopkins University and Columbia University materials.

SUPPORT TO THE RAKAI DISTRICT HEALTH SERVICES

The Program sponsored two Rakai District Health Team members for studies at Johns Hopkins University. Dr. Robert Mayanja, the Rakai District Director of Health Services, and Haji Abdu Mugerwa, the Rakai District Leprosy/TB Coordinator, attended the 2003 Summer training course in Epidemiology and Statistics at Johns Hopkins.

"The Rakai Program has built the capacity of Rakai District health workers through training, imparting counselling skills and facilitating health educators. Through this support I was able to attend the 2002-2003 Summer HIV/AIDS epidemiology course at Johns Hopkins University, USA".
Dr. Mayanja Robert, Rakai District Director of Health Services.



Programs clinical officers and laboratory technicians at a joint graduation party, July 2003. They are joined by Dr. Joseph Kagayi (sitting 4th left) and Roy Fred Kiggundu (sitting 5th left).

TRAINING FOR NON-PROGRAM UGANDAN PROFESSIONALS

Rakai is a designated field training site for Makerere University and provides rotations for MPH, medical and social science students each year. Training under Rakai Program is both practical and didactic, providing rotations through all cohort activities, including lab and data management, as well as rotations through the District Health Services.

US STUDENTS

Although Rakai Program does not provide scholarships for American students, Rakai data are available for Master's and PhD dissertations, contingent on the agreement of senior investigators in Uganda and on collaboration between the student and Ugandan project counterparts. To date, 7 US-based PhD students and 4 Master's students have based their dissertations on Rakai data. US students and Fellows have also been given the opportunity for work-study in Rakai.

Community Services



Changing lives in rural communities: The Program's Resident Counselor, Mr. Ssebugenyi Muhamad conducting an HIV / AIDS education session



Buyamba Trading Center has become a meeting place where rural health workers meet Rakai Program workers for education about general health matters.

VOLUNTARY HIV TESTING AND COUNSELING SERVICES

The Rakai Program has established a unique community-based voluntary HIV counseling and testing (VCT) program. To date, 80% of the population in the study communities have received VCT, and ~33% have accepted couples counseling. We have integrated family planning into VCT, and shown increased uptake of hormonal contraception by HIV+ women. Counselors have received training in the prevention or mitigation of domestic violence, and provide outreach and long-term support services. This VCT model has been adopted by other programs in Uganda and elsewhere.

PREVENTION OF MOTHER-TO-CHILD HIV TRANSMISSION (MTCT)

With support from the Elizabeth Glaser Pediatric AIDS Foundation (EGPAF) and the Johns Hopkins Gates Institute, the Rakai Program screened more than 4000 pregnant women and provided nevirapine to over 400 HIV-infected mothers, using maternal self-medication and maternal provision of infant nevirapine syrup for home deliveries. This maternal self-medication approach has now been adopted by other groups in Uganda and elsewhere in sub-Saharan Africa.

GENERAL MEDICAL CARE AND STD TREATMENT

The Program provides syndromic STD management, treatment of current illnesses and antenatal care through mobile and static clinics, as well as specialized care for adolescents via the adolescent health clinics.

PROMOTION OF ABSTINENCE, MONOGAMY AND CONDOM (ABC) AND FAMILY PLANNING

HIV prevention using the ABC strategy is promoted via community-wide health education, including a mobile video van, drama groups, and outreach programs using Community Based Reproductive Health Agents, and VCT counselors. Condoms are provided by social marketing and free supplies are available through community condom depots. Condom use has increased dramatically; current condom use is ~33%, and 47% report condom use with non-permanent partners. We have shown that consistent condom use reduces the risk of HIV and STDs.



Program workers educating rural women of Katana Community about family planning. The HPV screening team counselling a client at Kalisizo Hospital.

US AMBASSADOR INAUGURATES RAKAI PROGRAM'S ADOLESCENT CENTER



Ambassador Jimmy Kolker, inaugurates the Rakai Program Adolescent Center in Kalisizo Town, January 2003. The Center has become popular for teens, especially students from neighbouring schools.

PARTNERSHIP WITH KALISIZO HOSPITAL



Pediatric Ward - Kalisizo Hospital.

During 2003 the Rakai Program assisted Kalisizo Hospital to renovate the Pediatric Ward. This is in line with our mission of developing health infrastructure in non-program areas of the Rakai District.

RAKAI PROGRAM REFURBISHES BUYAMBA HEALTH CENTER

During 2003, one of the Program's achievements was the contribution of building materials towards the renovation of Buyamba Health Center. Completion of this unit will greatly reduce the distance to nearest health unit for many people in Buyamba communities.

EVOLUTION OF THE RAKAI PROGRAM PHYSICAL INFRASTRUCTURE IN KALISIZO, RAKAI

Since 1988, with funding provided by NIH, World Bank, Rockefeller Foundation, Gates Foundation, WRAIR and other sponsors, the Rakai Program has established a research, data and administrative infrastructure at the Uganda Virus Research Institute in Entebbe and in Kalisizo, Rakai. In Kalisizo, the Project rents more than 10 buildings, most of which have been renovated to accommodate expanding activities. Infrastructure development in Kalisizo has included the installation of water tanks, electrical generators, a large incinerator for biohazardous waste, a fuel(gas) pump station, parking services, and a maintenance garage for the fleet of 17 vehicles.

Space constraints in the existing Rakai rented buildings in Kalisizo severely limited the Program's ability to take on new research, clinical care of HIV+ persons, and training. In 2001, the Kalisizo Town Council donated land to enable the construction of a permanent research and clinical facility in the District.

The RHSC was designed by Mr. Bharat Gupta of Landplan, Kampala, with assistance from experts in the USA. The structure was designed to meet U.S. standards for laboratory and clinical facilities. The contractor Mr. Senyani was selected by competitive bidding.

THE NEW RAKAI HEALTH SCIENCES CENTER

This complex will provide a state of the art research center with extensive space for laboratories, data management and data storage; clinical facilities (including outpatient clinics, operating theaters and X-ray room); training facilities including a conference room, and student work space), and offices for scientists. This long-term will provide the infrastructure for future research, training, services, and technology transfer.

Funding for the building was received from the Doris Duke Charitable Foundation, The Bill & Melinda Gates Foundation, The Gates Institute for Population and Reproductive Health at Johns Hopkins, and University Loans. The NIH/NIAID International Center for Excellence in Research Contract is equipping the laboratory.

The laboratory is an air conditioned 3600 ft² state-of-the-art facility. It includes rooms designated for lab accession, clinical microbiology, tissue culture, serology, nucleic acid amplification and laboratory support. The laboratory is outfitted with Maxlab electroplated steel casework with 1" thick epoxy resin benchtops. State-of-the art equipment include two fume hoods, multiple Hereaus biological safety cabinets, FACscount flow cytometers, a Selectra E Blood Chemistry Analyzer, multiple Revco -80oC, -20oC and 4oC freezer and refrigerators for sample and reagent storage, a Coulter AcT Diff 5 cell counter, five Hereaus Megafuge refrigerated centrifuges, automated Bio-Tec plate washers and plate readers, several Zeiss microscopes including units with phase contrast and fluorescent capacities, dead air box nucleic acid isolation workstations, Perkin Elmer 9700 thermocyclers, and a Gel Logic digital imaging system. In addition, a P3 lab, mainly for TB culture, will be completed in the near future.

The clinical facility includes a patient waiting and reception area, pharmacy, Xray, four examination rooms, two operating theaters, sluice, autoclave and storage, as well as patient changing rooms and offices for surgical staff. The two theaters, designed for outpatient surgery, are mainly used for male circumcision at this time, but will provide facilities for colposcopy and other procedures.

Guest house accommodation is available for visiting scientists and students.



The main entrance to the Rakai Health Sciences clinical and research facility

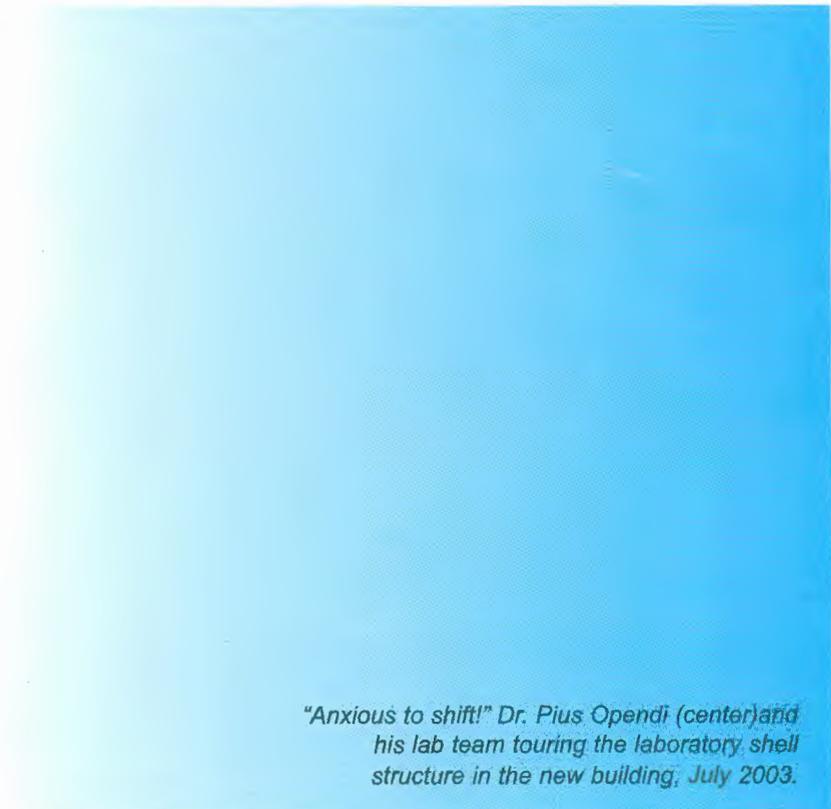
Construction of the new Rakai Health Sciences Center (RHSC)



The courtyard of the new Rakai Health Sciences Center



A laboratory room in the new RHSC.



"Anxious to shift!" Dr. Pius Opendi (center) and his lab team touring the laboratory shell structure in the new building, July 2003.





Program IT experts Edward Kabayi and Mark Mugaga working in the Entebbe Server Room.

IMPROVEMENT OF THE RAKAI PROGRAM INFORMATION TECHNOLOGY (IT) NETWORK IN 2003

Over 40 desktop computers and 10 laptops have been connected to a broadband Internet connection and the entire Kalisizo Station has been cabled for a local area network. With NIH/ICER funds, a satellite dish allows broadband internet connectivity. This provides access to the Library of Medicine for journals as well as the prospect of telemedicine to assist in patient care.

THE PROGRAM ACQUIRES A MODERN INCINERATOR



Ivan Sebugenyi, a lab technician with the Rakai Program has been trained to operate and supervise the new incinerator

For proper disposal of biological waste, the Rakai Health Sciences Program purchased a modern Maximaster MKII incinerator capable of burning waste at 45 kg per hour. The unit was installed at Kalisizo Station in 2004. Some of its design features include a twin combustion chamber, a high grade composite lining, double doors for continuous loading, integral 'venturi' panel emission arrestment compatible to the U.K. Clean Air Act, and a manometer drought indicator. With this type of incinerator, environmental pollution is minimal.

Study visit by the Ugandan Members of Parliament

On August 16 2002, the Standing Committee on HIV/AIDS of the Parliament of Uganda visited the Rakai Program. The Committee reports to the Ugandan parliament twice a year. In preparation for the first report, the Committee visited the Rakai Health Sciences Program. The MP's noted with satisfaction the various studies and health interventions being carried out by the program. "We are happy to note that results from these studies have proven pivotal in the implementation of various national response initiatives" said Hon Dr. Elioda Tumwesigye, MP Sheema.



Great job! Members of the Ugandan Parliament appreciated work being by the Rakai Program. L - R: Hon H. Katuramu, Hon. Dr. Elioda Tumwesigye, Chairperson of the Committee, Hon J.B. Kagoro and Hon. Annette Mukabeba addressing Rakai Project Committee. Other members include-Scientists at Kalisizo Station, February 2003.

United Nations (UN) Ambassador of Hope visits Rakai Program area



In July 2003 the UNICEF Ambassador of Hope, also wife of former South African President Nelson Mandela, Graca Machel (Second left), visited the Rakai District of Uganda. "When you look in the eyes of these children (orphans), you see people with dreams and expectation that you are forced to think of answers," said Machel. "This has drained me emotionally," she added.

Funding Institutions in 2003-4

(in alphabetical order)

Bill and Melinda Gates Foundation, Seattle, USA

Center for AIDS Research, Johns Hopkins University-National Institutes of Health, USA

Doris Duke Charitable Foundation, New York

Fogarty International Center, National Institutes of Health, USA

Gates Institute for Population and Reproductive Health, Johns Hopkins University

International Center for Excellence in Research, (ICER) NIAID, National Institutes of Health, USA

Malaria Institute, Johns Hopkins University, USA

National Institute of Allergy and Infectious Diseases, National Institutes of Health, USA

National Institutes of Child Health and Development, National Institutes of Health, USA

National Institutes of Mental Health, National Institutes of Health, USA

Office of AIDS Research, National Institutes of Health, USA

Presidential Emergency Program for AIDS Response, CDC, Uganda

Walter Reed Army Institute of Research/Henry M. Jackson Foundation, USA

THANK YOU TO DEPARTING FRIENDS AND COLLEAGUES OF THE RAKAI HEALTH SCIENCES PROGRAM

Although it is not possible to acknowledge and thank all the old friends and colleagues who have contributed to the Rakai Program over the years, we would like to mention a few key persons who left in 2003-04

Dr. Sylvester D. K. Sempala

Dr. Sempala, Director of the Uganda Virus Research Institute since the inception of the Rakai Program/UVRI collaboration, retired in 2003. His supportive leadership and wise guidance are missed by all RHSP personnel.

Mr. Maako Musagara

Maako Musagara, who joined the Program in 1989, was the Senior Administrator of the Rakai Program for the past decade. In 2004, he retired from Rakai to pursue other professional pursuits. His loyalty and hard work helped make the Program what it is today and we are very grateful for his efforts.

Ms. Mary Meehan.

Mary, a Columbia University/Johns Hopkins staff member, was resident in Uganda and directed the Rakai Program laboratory in Uganda for 7 years. During this time, she trained many Ugandan counterparts and provided invaluable technical assistance. In 2003, Mary (reluctantly) left the Program, feeling it was time to return to the US with her family. She and her three great daughters will be missed!

IN MEMORIAM

It is with deep regret that the Rakai Program saw the passing of valued friends and colleagues in 2003/04.

Mr. Swaibu Ssemiyaga.

Mr. Ssemiyaga was the first full-time Rakai Program staff member, joining the Program as a driver in 1988. He became the Senior Vehicle Supervisor and oversaw the carpool and transport staff for over a decade, seeing the fleet grow to almost 20 vehicles. In his time, not a single Rakai Program vehicle needed to be decommissioned, a tribute to his dedication and hard efforts. Mr. Ssemiyaga, who retired in 2003, died in 2004.

Ms. Connie Wandagha, Family Planning Team member.

Mr. Luke Kabali Kalanzi, Ethnography Team member.

Ms. Florence Nabaseruka, Data Team member.

Appendices

RAKAI PROGRAM GRANT SUPPORT, 2003-04

Awarded, funding will start in 2005:

NIH (NICHD) R01 HD 050180.

ARV Effects on HIV Epidemiology and Behaviors, Rakai, Uganda.

Period of Support: 4/05-3/10

Grant objectives: To assess the behavioral, epidemiological and virological effects of ARV introduction in rural Rakai, Uganda, including community perceptions and behaviors (in both HIV+ and HIV-uninfected persons), HIV and STD incidence and prevalence, mother-to-child HIV transmission, emergence of drug resistant quasi-species (including novel mutations in HIV subtypes A and D) and transmission of resistant mutations in the community. The study is nested within the Rakai Community Cohort Study.

ACTIVE

NIH (NIAID) R01 /U01 AI 61171

Randomized Trial of Male Circumcision for HIV prevention, Rakai-Uganda.

Period of support: 09/2002-08/2007

Objectives to determine whether post-pubertal male circumcision reduces HIV and STD acquisition.

Bill and Melinda Gates Foundation.

Trial of Male Circumcision: Effects: HIV, STD and Behavioral Effects in Men, Women and the Community, Rakai, Uganda.

Period of support: 10/02 - 09/07.

Grant objective: to assess the safety and STD effects of male circumcision in HIV+ men; to assess effects of male circumcision on HIV and STD risk in female partners; and to assess behavioral effects of male circumcision in men, women and the community.

NIH NIAID Intramural Program International Center for Excellence in Research (ICER).

Laboratory support for Rakai Program research activities.

Period of support: 2003 - ongoing.

The Rakai Program has been designated as one of only three current ICERs world-wide. The award provides ongoing laboratory support (equipment, technical assistance, supplies) and fosters collaboration between NIAID intramural scientists and Rakai Program researchers. Ongoing studies include assessment of the effects of HIV viral load on the dynamics of the HIV epidemic, full length HIV sequencing and transmission linkages, sequestration of resistant HIV quasispecies, HIV interactions with selected other pathogens.

NIH Office of AIDS Research (OAR) Grant to Assess ARV effects on HIV Epidemiology and Community Behaviors.

Period of support: 9/04-8/05.

Grant objective is to provide bridging support for the evaluation of the effects of introducing ARVs within the Rakai Community Cohort Study.

PEPFAR (subgrant from the Uganda-CDC President's Emergency Preparedness Fund for AIDS Response (PEPFAR)).

Period of support: 2004 – ongoing.

Objective: Provision of antiretroviral medication and HIV prevention services within the 50 villages in the Rakai Community Cohort Study, and in surrounding communities.

Doris Duke Charitable Foundation

Infrastructure, Research and Training Support for the Rakai Research Collaboration

Period of support: 2003-2005.

Grant goals: To develop the Rakai Program laboratory infrastructure in Kalisizo, Rakai District; and to provide training in lab and clinical research and activities.

NIH (NIAID) R01 AI47608-01

Bacterial Vaginosis Natural History, Etiology and Sexual Transmission Study

Period of support: 08/00-07/05

Grant objective: to assess the natural history of BV and to explore etiologies, including the potential role of *Lactobacillus* bacteriophages. Study conducted in rural Rakai District, Uganda.

Fogarty International Training Grant, National Institutes of Health

AIDS International Training and Research Program (AITRP)/Johns Hopkins

Fogarty International Training Grant, National Institutes of Health

International Training and Research on Population and Health,

Period of support 2/29/00-06

Completed during 2003-04

Center for AIDS Research, Johns Hopkins University

Case control study of vitamin A and retinol prior to HIV seroconversion

Type-specific HPV PCR assays in HIV+ and HIV- women

Effects of malaria on MTCT

Johns Hopkins Malaria Institute

HIV and malaria co-infection during pregnancy and MTCT. PI Heena Brahmhatt

Gustav Marin Innovative research Award

Self-collected vaginal swabs for HPV detection for cervical cancer screening,

NICHD, National Institutes of Health

STDs, fertility, marriage and demographic projections,

Fogarty International Training Grants, National Institutes of Health

HIV and Related Malignancies, Rakai: \$200,000

HIV behavioral intervention research, Rakai:

Gates Institute for Population and Reproductive Health, Johns Hopkins University

Operations research on family planning and training award,

Gates Foundation-CREATE Collaboration

Community-based TB treatment and prevention in the context of HIV.

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LIST OF CONTACT E-MAIL ADDRESSES

| | |
|----------------------------|---------------------------------------|
| Dr. Joseph Kagaayi | jokagai@yahoo.com |
| Dr. Meddie Kiddugavu | mkidduga@infocom.co.ug |
| Dr. Godfrey Kigozi | gkigozi@infocom.co.ug |
| Mr. Tom Lutalo | tlutalo@rakaiproject.or.ug |
| Dr Fred Makumbi | fmakumbi@rakaiproject.or.ug |
| Ms. Alice Nabasumba | anabasumba@rakaiproject.or.ug |
| Mr. Fred Nalugoda | fnalugoda@infocom.co.ug |
| Dr. Steven J Reynolds | sreynol1@jhmi.edu |
| Dr. David Serwadda | dserwada@imul.com |
| Dr. Nelson N. K Sewankambo | sewankam@infocom.co.ug |
| Dr. Fred Wabwire-Mangen | fwabwire@imul.com, fwabwire@iph.ac.ug |
| Ms. Jennifer Wagman | jwagman@rakaiproject.or.ug |

Dr. Maria Wawer mwawer@jhsph.edu

Dr. Ron Gray rgray@jhsph.edu
Dr. Tom Quinn tqinn2@jhmi.edu

KEY ACRONYMS

ARV: Antiretroviral therapy
BV: Bacterial vaginosis
CAB: Community Advisory Board
CDC: Centers for Disease Control and Prevention, USA
GCP: Good Clinical Practice
GLP: Good Laboratory Practice
GUD: Genital ulcer disease
HPV: Human papilloma virus
HSV-2: Herpes simplex virus type 2
ICER: International Center for Excellence in Research
MTCT: Mother-to-child transmission of HIV
NIAID: US National Institute of Allergies and Infectious Diseases
NICHD: US National Institute of Child Health and Development
NIH: US National Institutes of Health
NIMH: US National Institute of Mental Health
NVP: Niverapine
OAR: Office of AIDS Research
OI: Opportunistic infection
p-MTCT: Prevention of mother-to-child transmission of HIV
RHSC: Rakai Health Sciences Center
RHSP: Rakai Health Sciences Program
RCCS: Rakai Community Cohort Study
STD: Sexually transmitted disease
UNCST: Uganda National Council on Science and Technology
UVRI: Uganda Virus Research Institute
VCT: Voluntary HIV counseling and testing
WRAIR: Walter Reed Army Institute of Research

PROVIDERS OF SERVICES TO THE RAKAI PROGRAM

Lawyers

Katende Ssempebwa & Company Advocates Radiant House Plot 20 Kampala Rd. P.O.Box 2344 Kampala, Uganda.
Tel: 041-233770, 233908 Fax: 041-257544
Contact persons: 1. Mr. Sim Katende 2. Mr. Sam Omongole

Accounts Operators

ACLAIM Africa Ltd Kisozi House Ground Floor 8 Kyaggwe Rd. P.O.Box 7202 Kampala, Uganda.
Tel: 041-231040, 077-731040
Contact person: Mr. Andrew Kingston

Motor vehicle Insurance

American Insurance Group (Uganda)
Worldwide Insurance Specialists
60 Bombo Rd. P.O. Box 7077, Kampala, Uganda.
Tel. 041-533781/541556
Contact person: Mr. Daniel Kayiwa

Staff Insurance

United Assurance Company Ltd 1 Kimathi Avenue P.O.Box 7185 Kampala, Uganda.
Tel: 041-234190/1/2; Fax: 041-256388
Contact person: Mr. Kanyike Moses

Clearing & Forwarding Agents

SDV-Transami Entebbe Airport Tel: 041-320065 Fax: 041-320383
Contact person: Mr. Benon Kyeza

Travel

Lets Go Travel 1st Floor Yusuf Lule Rd. Tel: 041-346667/8/9
Contact person: Alice 077 -731525

Data/Internet Communications

1. Afsat Communications Uganda Ltd. Plot 1 Colville St. - Plot 5 Portal Av.
P.O. Box 25745 Kampala, Uganda. Tel: 041-343780 Fax: 041-343334
Contact person: Mr. David Kyobe
2. NIH/NIAID (USA)

Architects & Engineers

Landplan Group Uganda. 4th Floor Diamond Trust Bldg.
P.O. Box 9153 Kampala, Uganda. Tel: 041-345576 Fax: 041-345546
Contact person: Mr. Bharat Gupta

Bankers

Centenary Rural Development Bank
Barclays Bank
Stanbic Bank



RAKAI

Health Sciences Program Profile

