Mbeya Medical Research Programme

THE MISSION

For more than ten years, the Mbeya Medical Research Program (MMRP) has conducted research on the three major infectious diseases: HIV/AIDS, malaria and tuberculosis, with the ultimate goal of evaluating the safety and efficacy of vaccines and new drugs. Relevant new findings can be put to effect immediately through close involvement of the Tanzanian health authorities.

In order to accomplish our mission, we conduct in a comprehensive research program that takes into account all aspects of the diseases a rural region of Southwest Tanzania:

- Epidemiology to establish the dimensions and characteristics of the problems.
- Social science to identify behaviours enhancing the spread of the disease, but also to understand the effect of the disease on the social network and the life of the population.
- Operational research to help solve current practical health problems.
- Clinical trials to introduce new and alternative therapeutic options and vaccines.
- Basic science, with emphasis on microbiological, immunologic and genetic research on the pathogens and the host to contribute to the development of more effective vaccines and drugs.

To ensure an immediate, practical benefit to the host region and the participating individuals this research program:

- is fully embedded into the Tanzanian health care system and provides improved and comprehensive health services to its participants;
- is an integral part of ongoing health interventions that provide education and technical assistance to medical institutions and specialised medical care to patients;
- fully integrates the populations under study into the planning, conduct and discussion of findings of the research;
- conducts an extensive capacity building program for Tanzanian scientists, physicians and technical personnel to empower them to fully participate in planning and conduct of health research.

WHY MBEYA?

RESEARCH EMBEDDED INTO A BROAD BASED HIV/AIDS PREVENTION PROGRAM:
Under the auspices of the regional Tanzanian Ministry of Health, MMRP works together with the Mbeya Regional AIDS Control Program that offers the complete set of approaches to HIV prevention. These include education (IEC), voluntary testing and counselling (VCT), promotion of behaviour change and condom provision, prevention of mother to child transmission (PMTCT), and, most importantly, the control of cofactors that increase HIV transmission such as sexually transmitted infections (STI). This prevention makes our research not only ethically sound, but also sets an environment of trust and hope that facilitates any research activity and is key to sustainability.

SYMBIOSIS BETWEEN INNOVATIVE BASIC RESEARCH AND RESEARCH THAT ADDRESSES CURRENT PRACTICAL HEALTH PROBLEMS:
The close interaction between health prevention and health research is also reflected in the unique breadth of research lines that the MMRP conducts.
Studies address basic research questions such as the frequency of HIV superinfection (*HISIS**) and its relevance for correlates of protection against HIV (*HISIS & CTL**), to practical studies that address issues on pathogenesis of sexually transmitted diseases and their role in HIV transmission as well as the effectiveness of syndromic treatment of STD's as proposed in the national guidelines (*HISIS & STI**), to clinical trials on new interventions in this domain (*HISIS & STI**) and epidemiological and social behaviour studies (*HISIS, CODE**) that characterize vulnerable groups, develop specific education packages to reduce high risk behaviour. New findings can be put immediately into effect through the close collaboration with the Tanzanian health authorities. The integration of the different research activities create a situation rather unique in Africa where people at risk are not only observed, but where a maximal level of preventative intervention is implemented so to obey to the fundamental ethical rule of "first, do not harm".

MORE THAN A DECADE OF EXPERIENCE & COOPERATION:
The long history of AIDS intervention and research provides a profound knowledge on the epidemiology of HIV, TB and Malaria, a comprehensive understanding of social behaviour patterns related to these epidemics. The research activities can rely on a functional administrative structure that has been dedicated to fight HIV/AIDS for more than a decade. Mbeya has very transparent and accountable administrative structures; this allows MMRP to maintain a close and confident working relation with the projects key stake holders, the Regional Medical Officer and the Director of the Mbeya Referral Hospital. Through this partnership MMRP is directly linked with the Tanzanian Ministry of Health in Dar-es-Salaam.

UNIQUE SCIENTIFIC PARTNERSHIPS BETWEEN INSTITUTIONS IN AFRICA, EUROPE AND THE US:
The core members of the MMRP are the Tanzanian Ministry of Health (represented through the Mbeya Medical Office and the Mbeya Referral Hospital) and the Department of Infectious Diseases & Tropical Medicine at the University of Munich. MMRP received vital scientific and financial support through the European Commissions International Cooperation (INCO) Research Program, the Walter Reed Program, the Muhimbili University College of Health Sciences, Dar-es-Salaam, the University of Cape Town, the National Institute of Communicable Diseases, Johannesburg, the London School of Hygiene & Tropical Medicine and the National Public Health Institute, Helsinki. The programme has indeed been evolving in the past not only against a background of strong North – South partnership but in bringing in S&T competence where needed through consortium with other EU based researchers, other countries of the region and the US.

UNIQUE EPIDEMIOLGICAL FEATURES:
The geographic location of Mbeya in South-western Tanzania on two cross roads of the Trans-African highway causes several epidemiological features that are unique. Mbeya region is at the transition of the East and South African HIV epidemic. Three of the most globally important HIV-1 subtypes contribute in substantial percentages to the epidemic in Mbeya, and enfranchising Mbeya as an ideal place to evaluate vaccines composed of multiple clades.

MBEYA REGION:

CATION:

nzania is situated in Eastern Africa
l has 21 regions and 116 districts. Its
pulation is estimated to be around 30
ion and about one-fifth live in urban
as

eya is situated in the Southwestern
hlands of Tanzania, bordering Zambia
l Malawi. The region covers about
00 square kilometres and most
lements are situated in the
thwestern part of the region at an
ude between 400 and 1,700 metres.
e total population in the region is,
ording to 2002 census, 2.07 million.
e region has 8 administrative districts.
jor roads from Dar es Salaam to
nbia and Malawi, continuing to
babwe, Botswana and South Africa
ss through the region.

HEALTH FACILITIES:

The health facilities of Mbeya region consist of 15 hospitals (1 referral hospital, 1 regional hospital, 5 district hospitals, 5 mission hospitals and 3 private hospitals), 29 health centres and 271 dispensaries. The main hospital, Mbeya Referral Hospita,l is located in Mbeya urban and serves as a consultant hospital for 6 million people in four regions of the southern zone, namely Mbeya, Iringa, Rukwa and Ruvuma. By the end of 2001, the hospital had 640 workers including 46 doctors, 211 nurses, 230 attendants, 25 technicians and 108 others. The hospital offers both in-patient and outpatient services and has 477 beds. MMRP is fully integrated into the Mbeya Referral Hospital; our program has taken over the quality control of the Regional HIV Reference laboratory and presently promotes the implementation of region-wide provision of antiretroviral treatment and care through a number of applications to various funding bodies.

PREVENTION PROGRAMS:

The **Mbeya Regional AIDS Control Program** began in September 1988 as a collaborative effort of the Tanzanian Ministry of Health, the German Technical cooperation (GTZ) and the University of Munich. It started as a regional blood safety initiative and an HIV/STD reference laboratory at Mbeya Referral Hospital. Progressive development towards a comprehensive HIV/AIDS/STD control program was undertaken in 1991. The main components are education to encourage safe sexual behaviour (IEC), voluntary testing and counselling (VCT), promotion of behaviour change and condom provision, prevention of mother to child transmission (PMTCT), and most importantly the control of cofactors that increase HIV transmission such as sexually transmitted infections (STI). Other supporting organizations are/were DFID, E.C., JICA, PSI and AXIOS.

PMTCT Program (**P**revention of **M**other **t**o **C**hild **T**ransmission) began in 2001 with sponsorship through UNICEF at the Mbeya Referral Hospital and was expanded through GTZ to all of Mbeya municipality.

The **STI Control program** began in 1989 with the screening of pregnant women for syphilis using the RPR assay in 40 selected health facilities and treating the positives and their partners. In 1990 the program started treatment of all common STIs, the first STI clinic was established at the Mbeya Referral Hospital. STI services extended to district and mission hospitals in 1992 and eventually to all health centres and some dispensaries by 1995. Currently, these services are available in all 295 health facilities.

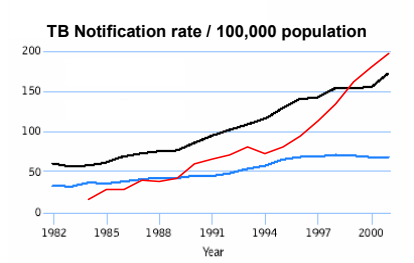
KIHUMBE is a small community-based NGO launched in 1991 supported by the Mbeya Regional AIDS Control Program and by the MMRP which provides Home Based Care Services. Their analysis of community needs has identified several key issues, such as an increased number of HIV/AIDS patients, an increase in the number of orphans and vulnerable children, and an increasingly poor economic status of HIV infected individuals over the past years. This analysis has led them to develop a broad objective to care for patients in their homes, support families affected by the epidemic and mobilize and educate the community on VCT and how to reduce the spread of HIV.

DISEASE BURDEN: (typical for Africa with HIV as the fastest growing cause of death)

Top-five diseases Morbidity & Mortality year 2001 Mbeya – Region (Source: Ministry of Health)

Rank	Morbidity			Prevalence rate /1000 Pop.	Mortality		
	Disease	Cases	%		Disease	Deaths	%
1	Malaria	607,393	34	277	Malaria	915	35
2	Acute respir. Infect	262,330	15	119	Anaemia	426	16
3	Diarrhoea	187,704	11	86	AIDS	404	15
4	Pneumonia	120,318	7	55	Pneumonia	289	11
5	Intestinal Worm	73,140	4	33	Tuberculosis	213	8
Total Cases		1,250,885		Total Deaths		2,247	

Malaria is endemic in Mbeya region with different intensities correlating with the altitude above sea level. Mbeya has areas that have hyperendemic malaria, seasonal malaria and sporadic malaria. Since large parts of the population live in areas above 1700m, Mbeya is not as badly affected as the rest of Tanzania. In 2001, 607.693 malaria cases were reported and 915 deaths. Malaria is still the number one disease for hospital admissions and deaths in Mbeya region. Compared to other African countries, malaria mortality is relatively low, documenting the level and quality of treatment available, but prevention has not yet reached the level targeted by the Tanzania government control efforts. Most of the research capacity on malaria in Tanzania is related to the local (ENHR) Essential National Health Research efforts movement set up in the 80's which allowed training of a large number of local research specialists and has achieved an excellent international reputation.



Year 2001

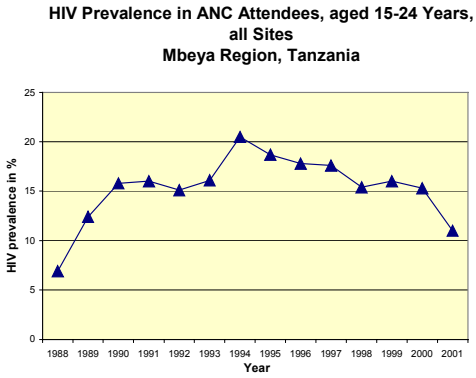
all cases in Tanzania:	61,603 =	notification rate 171
all cases in Mbeya:	4,053 =	notification rate 196
smear positive cases		notification rate 69

Adapted from the WHO report on TB, 2002

osis was very much under control when Tanzania lly implemented DOTS (direct observed treatment, se) in the 70's. With the onset of the HIV epidemic, sis again became a major health problem. Today the annual TB incidence rate is 0,3%. In the TB ward in)-60% of all newly diagnosed TB cases are HIV

nvinced that mortality due to AIDS is heavily rted and many patients that died due to pneumonia, piratory infection, TB or diarrhoea were in fact ith HIV.

HIV/AIDS data from Mbeya are among the most complete available in Africa. Trends in women attending antenatal clinics have been monitored for the past 15 years. These data have been recently complemented by the MMRP with in-depth analysis of specific study populations.
When sentinel surveillance started in 6 urban, rural and roadside ante natal care centres, the HIV prevalence varied between 4 – 8%. By 1995 the prevalence had increased substantially in all centres, to about 20%, but is declining (rural and roadside) or stabilising (urban) since then (Fig1, Tab.1).



HIV prevalence by site	All ages:		15-24 years:	
	1994/95	2001	1994/5	2001
All sites	20.3%	11.9%	20.6%	11.7%
Urban	20.7%	17.0%	20.6%	17.6%
Rural	16.5%	6.3%	15.6%	4.7%
Roadside	25.6%	9.8%	26.7%	7.5%

(Source graph & table: MOH/GTZ regional sentinel surveillance report)

Cohort prevalences	All participants	Women	Men
CODE Mbeya urban (age 18-45)	19,6%	21.8%	15.5%
CODE Mbeya rural (age18-45)	14,4%	14.9%	12.0%
HISIS High risk Mbeya Region (age 18-35)		67,8%	

(Source MMRP)

In addition to data in pregnant women, MMRP collected population-based HIV prevalence data during the recruitment of its study populations (cohorts). These data correlate very well with the data in pregnant women. The prevalence in the high risk population of women working in bars (HISIS) is as high as 68%, in the urban general population 19,6% and in the rural population (CODE) 14,4%.

EXAMPLES OF MMRP RESEARCH

EPIDEMIOLOGY

Studying the epidemiology of HIV is more complex then that of malaria and tuberculosis. To establish exact numbers of incidence, defined groups of individuals need to be enrolled into a study population (cohort) and followed over several years. Such research is labour and cost intensive.
Two cohorts of 3000 individuals recruited from a general population (*CODE**) and 600 women working in the high risk environment of bars (*HISIS**) have been established. Both cohorts are followed up closely in 3-6 monthly intervals for 3-4 years. Besides data for prevalence and incidence of HIV, the morbidity due to other infectious diseases is recorded, the natural course of HIV infection is monitored, and set-points for viral load and CD4/CD8 are established.

SOCIAL SCIENCE

To describe the risk behaviour for HIV and STI in different study populations, our data collection instruments have been designed so that data from different cohorts can be compared directly. In addition, social science is monitoring study compliance and the willingness of study participants to take part in future studies, including vaccine trials.
Before the start of every cohort a censuses is conducted. This demographic monitoring describes the population from which the cohort is recruited, permits standardisation of the results, and provides the opportunity to translate them directly into policies that improve the living situation of the initial population. These studies are complemented with KABP (Knowledge, Attitude, Behaviour, Practices) studies in other populations including adolescents, truck drivers and other risk groups

OPERATIONAL & CLINICAL RESEARCH

A whole battery of operational research studies is conducted within the HISIS and the additional STI/RTI research project (*STI** studies). Since it is known that the presence of sexually transmitted diseases is a major factor contributing to susceptibility to HIV infection and disease progression, all of our HIV research activities include STI components. The additional set of studies on STI/RTI evaluates the validity of the syndromic diagnosis and assesses the effect of regular STI/RTI screening and treatment on prevalence in a high risk population. A further study is underway to determine the aetiology of ulcerative STI among female bar workers and STI patients of both sexes attending public health facilities in Mbeya town. Data show that HSV is causing the vast majority of genital ulcerations in Mbeya (*STI**) currently.
In the field of tuberculosis, we evaluate improved rapid direct antigen assays to diagnose tuberculosis. The current method of smear microscopy is insuffiently accurate in HIV/TB co-infection and so labour intensive that t is impossible to cope with the rising demand. A simpler detection of active tuberculosis would dramatically facilitate the diagnosis and subsequent therapeutical monitoring of TB patients.

CLINCIAL TRIALS

Currently, we are conducting a phase III clinical trial to compare the efficacy of the standard treatment (penicillin-injection based) of syphilis with a single oral dose of Azithromycin (*STI**), a new powerful antibiotic active against many sexually transmitted pathogens which obviates the need to treat with a list of several drugs for weeks. Another phase III / IV trial will compare the efficiency of branded versus generic HIV drugs (*MARVIN**). In addition, trials to establish new drugs for therapy of malaria and TB and compare them to standard treatment have been initiated.
The first clinical trials for HIV vaccines are anticipated for late 2004 with vaccine candidates provided either by partners from the EU and/or the US.

BASIC SCIENCE

The two major aspects of the basic science component are the characterisation of circulating HIV strains and the description of immune responses to those strains.
Continuously supported through funds from the E.C., Mbeya region, in regard to HIV subtypes, is one of the best described regions of the world. In concordance with the majority of researchers, we believe that an HIV vaccine should match as much as possible the circulating subtypes in the region where it is evaluated. In Mbeya region, three major subtypes are circulating (A, B/D and C) (*Molecular epidemiology**). This makes Mbeya highly attractive for vaccine evaluations.
A major obstacle to the development of a successful HIV vaccine is the dearth of information on correlates of protective immunity and the breadth of cross protection among multiple HIV-1 subtypes. The HIV-1 Superinfection Study (*HISIS**) will be the first study to systematically investigate infection of HIV-1 positive individuals with a second HIV-1 subtype. We maintain that a superinfection represents the failure of an HIV infection to induce immunity capable of preventing a second HIV infection. Therefore understanding the biology of superinfection is essential for the understanding of correlates that are protective for HIV-infection and are therefore essential for the development of HIV-vaccines (*HISIS & CTL**).

THE FUTURE & EXAMPLES OF PARTICIPATING IN EDCTP

VACCINE EVALUATIONS

We anticipate starting with the first HIV vaccine evaluations in 2004/05. We are in negotiations with vaccine developers in Europe and in North America. We plan to move rapidly from phase I/II trials into phase III trials within a few years. This means preparing in parallel for these trials which might encompass a dozen volunteers in a Phase I to several thousands with long term follow up in a Phase III.

NETWORKING AND ASSISTING OTHER HIV TRIAL SITES

We anticipate that promising vaccine candidates will be evaluated in more than one country, and we are currently initiating a network of trial sites that could, prepare for joint studies under common standards and assist trial sites under development with practical technical help (see *Adavance-HIV**). Such a network for technical assistance and development of trial sites will dramatically reduce the time needed (normally 5-7 years) to develop an HIV trial site. We hope that such a network could be supported in the framework of a South-South-cooperation within the EDCTP. A network of trial sites is only useful if a minimum of common standard procedures and reference methods are used. Otherwise data from different locations can be not compared.

ASSURING THE HIGHEST LOCALLY OBTAINABLE STANDARDS OF CARE

MMRP regards its close cooperation with intervention and clinical care programs as one of the keys to its success. We therefore will invest in all new intervention strategies. In the field of HIV we are currently applying for financial support to provide the complete region with antiretroviral (ARV) treatment. In the preparation of such a large scale therapeutic intervention, we will conduct clinical trials to explore the feasibility of different drug regimens, patient management schemes and distribution systems (*MARVIN**). We believe that only an organized and controlled introduction of ARVs into rural Africa can be successful.

RESEARCH INFRASTRUCTURE

The MMRP aims to be fully prepared for the evaluation of HIV vaccines and drugs by the end of 2003. Currently the project has established the following infrastructure:

HUMAN RESOURCES & CAPACITY BUILDING:
48 Tanzanian, 9 German and one staff from the London School (LSHTM) are currently working with the MMRP.
MMRP considers training as a key investment in the future. MMRP currently supports several PhD students. It supports the education of upgrading clinician, laboratory technicians and counsellors. The key staff have attended workshops related to Good Clinical Practice (GCP) and Good Laboratory Practice (GLP). Whenever needed consultants are visiting MMRP e.g. to implement QA/QC in the laboratory, to maintain technical equipment or to train interviewers in quantitative and qualitative research techniques.

TECHNICAL INFRASTRUCTURE:
The main infrastructure has been established on the compound of the Mbeya Referral Hospital. This setup enables a close interaction between clinical services and research:

- Study participants can be recruited from the patient pool.
- Trial participants can be referred for further investigations to the hospital.
- Doctors and nurses can share knowledge and experiences with other hospital staff.
- Trial participants can use the anonymity of a large hospital to avoid stigmatisation.

CLINICAL FACILITIES
MMRP operates one research clinic on the compound of the Referral Hospital, one clinic in the village of Itende, and 15 outreach/mobile clinics that are visited once every 3 months.
The main clinic (below) can handle up to 50 patients daily. In the morning, study participants are seen for scheduled follow-up visits. In the afternoon, the clinic provides, free of charge, treatment for acute diseases of the study participants.
At a reception the participants are identified by a photo ID, they then see a study nurse, clinician, HIV counsellor, interviewer and donate blood within the clinic in its own “acute” laboratory that can perform, rapid ELISAs for STI’s, and does all parasitological analysis.

MOBILE CLINICS:
The follow up of our high risk cohort of women working in bars is conducted in 20 High Transmission Areas (HTA); these are villages that are situated along the Trans-African Highway. Since it is impossible to establish in each village a fully functional clinic, MMRP brings all equipment needed to the Centres and transforms them for one day into a fully operational research clinic.

CENTRAL LABORATORY:
Over the last 8 years MMRP has developed a state of the art laboratory that can process up to 60 blood samples a day. The staff of one biologist, 10 laboratory technicians, 5 laboratory assistants perform all procedures under GLP conditions.
The cell isolation and processing unit (see below) has 5 laminar flow hoods and 4 large volume centrifuges. Before samples arrive from the clinics all materials for cell processing have been prepared to ensure a smooth workflow.



Assays performed at the laboratory include haematology, serology for HIV, Syphilis, Hepatitis B+C, HSV, Flowcytometry for CD4/CD8 count, Immunologic techniques such as ELISPOT and intracellular cytokine staining (ICC), Parasitology, Viral load determination and clinical chemistry
As the most sophisticated unit, the laboratory is equipped to resist all unfavourable conditions. The laboratory is kept behind an airlock under constant positive pressure to keep dust outside. All important machines are protected against power interruptions and surge. An automatic backup generator ensures continuous power supply. The laboratory has its own 5.000 litre water tank and is therefore independent of the public water supply for least a week. All refrigerators and incubators are monitored electronically for constant temperature.

ADMINISTRATIVE BUILDING:
The administrative unit has 20 workplaces equipped with computers to enter data and do data analysis. All data are entered in real time. At the end of each week the full set of data is complete. All three buildings (clinic, laboratory and office) are connected with a computer network and all data are independently secured on two servers.
MMRP is connected to the rest of the world through a satellite connection. It also will offer its internet services to the Referral Hospital (starting December 03).



LOGISTICS:
Most of the technical laboratory equipment and supply is shipped from Europe. MMRP has established the infrastructure to receive perishable goods within 3 days from Europe. Other consumables are ordered in bulk and are sent 1-2 times a year in a large container. Four times a year we are sending a subset of the collected samples, cryopreserved in liquid nitrogen, to Europe and from there to our partners around the world for various analyses.

ETHICAL REVIEW:
All research projects are first seen by the Institutional Review Board (IRB) registered with the funding bodies. The proposals are then also forwarded to the National Ethical Review at the National Institute of Medical Research (NIMRI) in Dar es Salaam.

MMRP AT A GLANCE:

CORE SCIENTIFIC STAFF:

1. Catharina Boehme, MD, Research clinician TB
2. Steffen Geis, MD, Deputy MMRP Coordinator
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5. Michael Hoelscher, MD, Scientific Director
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11. Itrosi Sanga, MD, Research Clinician
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CORE ADMINISTRATIVE & TECHNICAL STAFF:

1. Amon Mwakamele, Watchman
2. Asia Burchard, Clinician
3. Azania Ntakije, Study Nurse
4. Caroline Edward Masoli, Lab Ass, Cell processing
5. Charles Mwasegile, Driver/Field Coordinator
6. Christina Kasambala, Data Entry
7. Clara Mwaisaka, Clinician
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10. Dauson Mwamende, Watchman
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42. Stella Kapungu, Study Nurse Assistant
43. Triphonia Mbena, Lab Ass, STI & Haematology
44. Tumpe Muhondwa, Interviewer
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ANNEX – DESCRIPTION OF ONGOING RESEARCH ACTIVITIES:

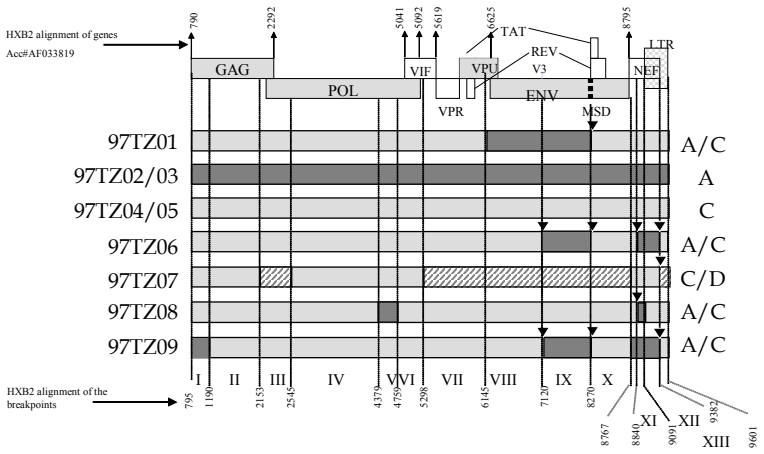
HIV MOLECULAR EPIDEMIOLOGY OF MBEYA REGION

Purpose:

The role of HIV molecular virology work is to acquire, develop, and maintain a detailed description of the HIV strains circulating in Mbeya region. This information is the basis for vaccine development and evaluation. The MMRP aims to comprehensively describe the HIV epidemic in Mbeya region, by the use of a newly developed genetic sub-typing tool.

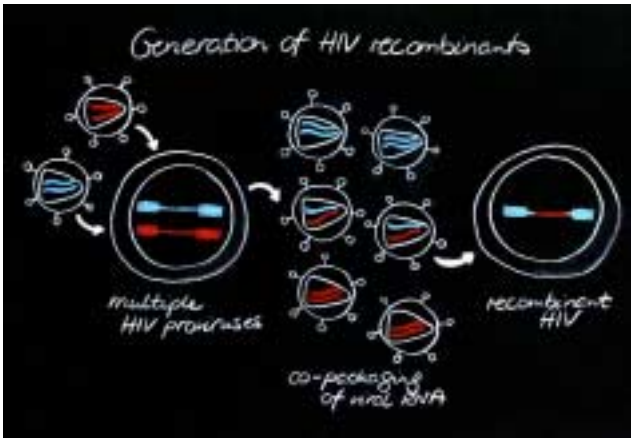
Results:

HIV Subtyping was the start off all research studies conducted within MMRP. In 1995 we used V3 serotyping to establish the large proportions of circulating subtypes in Mbeya. We were able to show in a retrospective study among women attending antenatal care that the proportions of subtypes [illegible] D 13%, non-typable 7%) [1].



The introduction of full genome sequencing through our new partner, the Walter Reed Program, revealed that various recombinations between the three subtypes A, C and D contributed with 55% the largest share of all subtypes. Most interestingly was the fact that none of the recombinant strains had the same structure. So far Mbeya has the highest reported rate for unique recombinant strains in the world [2].

[illegible] ion hybridisation assay (MHA) [3], [illegible] ll HIV+ participants in all the [illegible] ss the results conquer with [illegible] he population studied (A 12%, C 28%, D 5%, recombinants 55%).



Recombinant strains are newly generated when one individual is infected with more than one HIV strain (dual infection). The high percentage of unique recombinant strains led us to the assumption that dual infection should be a common event in a setting where more than one HIV subtype co-circulate. We therefore initiated the HIV superinfection study (HISIS).

Picture left (Andreas Meyerhans)

Partners:

The partners in this research are the Walter Reed Program, the Department of Infectious Diseases and Tropical Medicine at the LMU and the local Tanzanian Ministry of Health, the HIV lab in KTL Finland, the Cape Town Dept of Virology, the Muhumbili University College of Health in Dar.

Publications:

1. **Hoelscher** et al.: HIV type 1 V3 serotyping of Tanzanian samples: Probable reasons for mismatching with genetic subtyping. AIDS-RES-HUM-RETROVIRUSES 1998; 14/2 (139-149)
2. **Hoelscher** et al.: High proportion of unrelated HIV-1 intersubtype recombinants in the Mbeya region of southwest Tanzania. AIDS. 2001 Aug 17;15(12):1461-1470
3. **Hoelscher** et al.: Detection of HIV-1 subtypes, recombinants, and dual infections in east Africa by a multi-region hybridization assay. AIDS. 2002 Oct 18;16(15):2055-64.

HISIS (HIV-**S**uper**i**nfection **S**tudy)

Purpose:

The **HISIS** started in September 2000 to establish a rational understanding of the behavioural, immunologic and virologic factors that lead to HIV dual and superinfections. Dual infection refers to the presence of two or more HIV-1 subtypes or recombinant forms in a single individual. The serial acquisition of subtypes or recombinants is called superinfection. Dual and superinfection have been observed occasionally but not studied systematically in any population. We maintain that superinfection represents the failure of an HIV infection to induce immunity capable of preventing a second HIV infection. Understanding the biology of superinfection is essential for the understanding of correlates that are protective for HIV-infection and are therefore essential for the development of HIV-vaccines.

Approach:

The study design is based on the longitudinal follow-up of a cohort of 600 bar workers in High Transmission Areas along the Trans-African highway in Mbeya Region, Southwest Tanzania, where three HIV-1 subtypes (A, C, D) co-circulate. We are first establishing the frequency of HIV dual and superinfection, observe determine the timing of superinfection with respect to clinical stage, determine the rate of protection against superinfection and if substantial protection is verified in individuals, we will determine these correlates for protection. In addition to the epidemiological, virologic and immunologic factors we also describe social aspects of the study population, in particular the reasons for their risk behaviour, and will develop methods to assess and compare risk behaviour and propose adapted interventional measures. With special focus on sexual transmitted infections (STI) we monitor the prevalence and incidence of sexually transmitted infections and evaluate factors that could be related to higher HIV-susceptibility or infectivity.

Practical aspects:

Enrolment and maintenance of contact is carried out through an established network of contact persons. Every 3 months for 4 years participants are visited in their village (30 women in each of 20 villages). For the visits MMRP erects a mobile clinic to augment the poor infrastructure of the local health facility. The evening before the examination, all women convene and receive a health education session. The following morning, they are interviewed, clinically examined and undergo a blood draw. Each visit we collect a complete set of specimens (blood, vaginal swab and lavage). Regular interviews provide a description of the domain of sex work and bar workers in their communities. In-depth interviews determine the social profile of sex work, risk perception, prevention strategies. Through an information (IEC) campaign we promote condom use and regular health care and STI treatment, which is provided as part of the study.

Results:

First results show a very high HIV prevalence of 68%, and an average annual incidence of 6%. Through our accompanying intervention activities we could reduce the initial incidence from 12 % to 4%. After 3 years of study duration, we maintain a follow-up rate of more than 85%. The technically much more challenging analysis of multiple infections is still ongoing. Very preliminary results indicate that we can identify many multiply infected individuals.

Sponsors:

The HISIS research is funded by multiple sponsors. Cohort development and follow up as well as all social behaviour research and a share of the STI research is funded by the INCO program of the European Commission. Additional studies on the aetiology of ulcerative STI and a clinical trial on the treatment of Syphilis are funded by the Wellcome Trust. The Walter Reed Program provides the majority of means for the molecular analysis of HIV strains.

Partners:

Partners in this project are the local Tanzanian Ministry of Health, the Department of Infectious Diseases and Tropical Medicine at the LMU, Munich, the Walter Reed Program, Rockville.; the Centre for Population Studies, London School of Hygiene and Tropical Medicine; the KTL, National Public Health Institute, Helsinki; the Department of Medical Microbiology, University of Cape Town; the Muhimbili University College of Health Sciences, Dar es Salaam.

STI

Studies on the epidemiology and control of STI and their interaction with HIV

Purpose:

The overall purpose of the studies on STI is to fill current knowledge gaps regarding the effective control of STI/RTI. The objectives of the five main studies are:

- to evaluate the effectiveness of a single dose 2 g Azithromycin orally compared to the standard treatment with injections of 2.4 MU Benzathine Penicillin i.m. in a randomised clinical trial
- to assess the effect of regular 3-monthly screening and treatment for STI/RTI in a high-risk population (female bar workers) in a longitudinal study
- to determine aetiologies of genital ulcerations in Mbeya Region and to assess the appropriateness of syndromic management guidelines in view of the findings in a cross-sectional study
- to assess the effect of genital herpes on genital HIV shedding in cross-sectional and longitudinal studies
- to determine the extent of immunity against re-infection with *T.pallidum* after syphilis treatment in a longitudinal study

Approach:

The studies are integrated in (a) STI/RTI prevention and care activities among bar workers in Mbeya Region, and (b) routine health care at public health facilities in Mbeya town. Through the direct involvement of regional and national public health decision makers and health care personnel in the planning and monitoring of the studies and through training and supervision of health care providers, the conduct and the results of the studies will serve to further improve the current practice of STI/RTI control in Mbeya Region and similar settings.

Female bar workers participating in the barworker cohort are examined clinically and treated on the spot according to STI syndromic management guidelines of the MoH of Tanzania every three months. Genital specimens are taken for laboratory investigations and women found to be infected with STI pathogens are treated at the next encounter (after 2 weeks to 3 months). Trends in STI/RTI prevalence and incidence are observed.

For the clinical trail of Azithromycin for syphilis treatment, (a) patients with syphilis attending public health facilities in Mbeya town and (b) participants of the bar worker cohort, are randomised to either Azithromycin or Benzathine Penicillin. The clinical and serological response to treatment is observed for one year and cure rates are compared. Final results will be available by September 2003.

For the study on genital HIV shedding in HIV infected women (female bar workers) in relation to genital herpes, the HIV viral load in vaginal lavage specimens of women with herpetic lesions is compared with that of women without such lesions.

To determine whether immunity against re-infection with *T.pallidum* persists after treatment of latent syphilis, we compare the incidence of first infections with *T.pallidum* with the incidence of re-infections among participants of the bar worker cohort.

Results:

- Preliminary results show that The prevalence of STI/RTI among female barworkers was high at baseline: active Syphilis (18%), TPPA+ve (45%), Gonorrhoea (22%), Chlamydia infection (12%), HSV-2 +ve (90%), Trichomoniasis (24%), bacterial vaginosis (40%)
- 3-monthly screening of barworkers for STI/RTI and treatment reduces the prevalence of syphilis and trichomoniasis, but not of bacterial vaginosis (results on other STI not yet available)
- HSV is the main causative agent of genital ulcerations

Sponsors:

This work is supported by The Wellcome Trust, the European Commission, INCO programme and the Department for International Development, DFID, UK

Partners:

The STI studies are conducted by the LSHTM in collaboration with Tanzanian and international institutions: The Muhimbili University College of Health Sciences; Ministry of Health of the United Republic of Tanzania; National Institute of Medical Research; The Department of Infectious and Tropical Diseases of the University of Munich; The Institute for Tropical Medicine-Prince Leopold, Antwerp; The Dept.of Medical Microbiology, University of Manitoba; The Dept. of Genito-Urinary Medicine, St George's Hospital, London;, Virology Laboratory, INSERM U430, Paris.

HISIS & CTL

Purpose:

The broad objective of this study is to investigate the hypothesis that the quality, breadth, and specificity of the CTL response against HIV-1 is a key determinant in protection, both from an initial HIV-1 infection, and from superinfection with a second HIV-1 subtype. Definition of protective CTL responses, and a direct evaluation of cross-subtype immunity, will guide the design and evaluation of candidate vaccines in the region. Infrastructure and personnel development in Tanzania during this project will also materially support preparation for candidate vaccine evaluation.

Approach:

This study started in April 2003 and is the immunological work up of selected individuals from the HISIS study. We selected 30 individuals that remained HIV negative over the last 3-4 years despite continuous exposure to HIV (HEPS), 30 individuals that were HIV infected but remained infected with a single strain and individuals that are infected with more then one HIV strain. In those individuals we are assessing the quality of the CTL response, together with related parameters such as viral load and diversity, HLA type, and, in the case of superinfection, the recognised CTL epitopes in the strains causing the initial infection and superinfection, respectively.

Practical aspects:

This project is of strategic importance for the capacity building of the research site in Mbeya. Since the cellular immune responses are best analysed on fresh samples, all of the laboratory methods have been established at the research centre in Mbeya. These methods are exactly the same that are needed for a vaccine evaluation in the future. The HISIS & CTL project gives us therefore the unique chance to first describe the natural cellular immune response as baseline for future vaccine trials, but also to have established all methods compliant with CLP standards.

Results:

All methods are set up and a quality control system has been established. With our partners in South Africa we are analysing the current visit (follow up 11) of the HISIS study.

Sponsors:

This work is supported by an European Commission Framework 5 INCO grant and receives reagents and technical support through the Walter Reed Program.

Partners:

Partners are the local Tanzanian Ministry of Health, the Department of Infectious Diseases and Tropical Medicine at the LMU, Munich; the National Institute for Communicable Diseases, Johannesburg; the Walter Reed Program, Rockville; the Department of Medical Microbiology, University of Cape Town and the KTL, National Public Health Institute, Helsinki.

CODE (Cohort **de**velopment study in Mbeya Municipality)

Purpose:

The purpose of the study is to assess the suitability of different population groups for vaccine evaluation. Three subgroups are compared in regard to recruitment efficiency, rate of follow-up, costs and good understanding of medical research. This effort is in preparation for the evaluation of candidate vaccines with the aim to develop the vaccine reagents, infrastructure and databases required to plan and execute trials in the future. The project is complementing other cohort development projects of partners in East Africa (Uganda and Kenya).

Approach:

Objectives are to study the prevalence, incidence and risk factors for HIV in the region. The cohort is subdivided into 3 different subgroups, depending on the recruitment method (household-based village, household-based urban, public advertising urban). This division allows the identification of the optimal cohort development. A questionnaire is administered, a physical examination performed and a small blood sample (20 cc) is collected for STI and HIV testing. The information collected will estimate the risk factors for HIV transmission and assess the incidence and prevalence of HIV in the adult population, determine the genotype of circulating HIV strains and provide observations of viral load and CD4/CD8 after seroconversion. Individual strains will be used as sources for reagents for vaccine development and evaluation. The description of risk behaviour and attitude towards vaccination will give important information for education campaigns for future vaccine evaluation programs. The data generated by this study will be critical for the development of effective prevention programs in this population including vaccine trials. In addition, malaria, TB and other diseases of relevance to HIV pathogenesis will be documented and monitored.

Practical aspects:

The recruitment of 3096 adults at two locations, in Itende village and in Mbeya town within 6 months (Oct 03/ March 04) has been a major logistic undertaking. This has been only possible through the erection of two independent research clinics (one at the Mbeya Referral Hospital and one at the Health Centre in Itende). In these clinics patients are seen in the mornings for scheduled visists of the study. In the afternoon the study provides medical services for acute diseases for all study participants free of charge. Participants value this service very much. As a additional benefit this set up gives us the chance to monitor and described the disease burden of our study population in detail.

Sponsors:

The work is funded through the Walter Reed Program.

Partners:

Scientific partners are the Regional Tanzanian Ministry of Health, the Dept. of Infectious Diseases & Tropical Medicine, LMU and the Walter Reed Program.

SOCIAL SCIENCES:

Purpose:
Measuring human behaviour is a difficult task under many aspects. In MMRP we are mainly concerned with high risk behaviour for HIV and with adherence for drugs in clinical trials. Researchers have to rely mainly on self-reports which need to be reliable and valid but also replicable over time and in different contexts. So far, many approaches have been developed and tested and none has proved to be a "gold standard". Errors and biases hamper the monitoring of risk behaviour for HIV. And HIV vaccine trials in particular require not only one time-point surveys in changing populations but repeat monitoring of the same individuals.

Approach:
Face-to-face questionnaires are most commonly used to establish quantitative information. However they are prone to social desirability bias. Therefore MMRP has established self-administered questionnaire formats which can also be used by illiterate populations. They reduce the temptation for the respondent not to tell the truth especially in sensitive questions but they don't get rid of the recall effect (behaviours taken place some time ago are remembered worse than recent activities). MMRP has developed so-called diary formats filled by the respondent on a daily basis used in the high risk population to establish objective information on sexual risk behaviour. An external validation using biomarkers is ongoing looking at the feasibility of using laboratory findings to validate sexual high risk behaviour.

The same strategy will be used to establish reliable and valid clinical data on the adherence to drugs (e.g. ARVs in MARVIN) and their side effects. The medical history forms will be compared with a diary developed to collect data on drug intake and its side effects.

All methods mentioned above are employed to obtain self-reported quantitative data and comparisons will establish the most reliable and valid method to be used in research cohorts or clinical trials in settings like Mbeya.

Practical aspects:
All new methods were established in close collaboration with the Tanzanian staff and extensive training of MMRP interviewers has been organized. All methods have been introduced carefully to the study participants and especially the diary studies have been monitored closely. The existing cohorts in a high risk population and the general population enable the researchers to test the methods in different population groups and also to compare results between them. The nature of follow up visits enables to test different strategies at different time points.

Sponsors:
The main funds are coming from the HISIS study funded by the European Commission - INCO. A special fund for the diary studies has been obtained from the DFID Reproductive and Sexual Health Grant.

Partners:
Partners in these studies are Regional Tanzanian Ministry of Health, the Dept. of Infectious Diseases & Tropical Medicine, LMU, and the Centre for Population Studies at the London School of Hygiene and Tropical Medicine.

Evaluation of a rapid direct antigen test for tuberculosis

Purpose:

Main purpose of the proposed project is the development and clinical evaluation of a rapid direct antigen test for diagnosis of pulmonary tuberculosis using an immunochromatographic test format. One major obstacle in the fight against tuberculosis is the lack of an inexpensive, easy to use and sensitive method to detect TB infected patients. The only method that is affordable in many parts of the developing world is the microscopy smear test. It is used to detect TB-patients and monitor their treatment success. Unfortunately this test is labour intensive and is mainly used to detect "productive, open", pulmonary TB. In addition the sensitivity depends dramatically on the quality of the test performers. More advanced methodologies such as culture and PCR are technically difficult, not that reliable and therefore not widespread in rural Africa.

Approach:

Together with a company that developed a prototype rapid direct antigen immunoassay detecting the presence of *Mycobacterium tuberculosis* in clinical specimens such as urine, blood and sputum, we want to explore the sensitivity and specificity in an African clinical setting. Immunological assays detecting directly TB antigens or antibodies against TB have been identified as most promising candidates to substitute and complement smear testing. After the new assay has proven its feasibility under field conditions, we will explore the clinical relevance of the direct detection TB antigen. We anticipate that such an assay has the potential to dramatically enhance the detection of individuals with active TB disease and will in combination with new short course treatments help to reduce the burden of TB.

Sponsors:

This research is funded by Chemogen Inc. We have applied for a follow up grant with WHO-TDR TDR/diagnositics initiative.

Partners:

Partners involved in the project are the Mbeya Regional TB & Leprosy Program, the Department of Infectious Diseases and Tropical Medicine at the LMU, Munich and Chemogen Inc, Portland, ME, US.

MARVIN (Mbeya **a**nti**r**etro**v**iral **in**itiation study)

Purpose:

Despite the proven success of antiretroviral therapy (ARV), in Africa, where 70% of HIV infected individuals live, ARV is still not an option. This is not due to the absence of potent drug regimens, but due to missing infrastructure to apply Western concepts of care and support. It will be highly unrealistic to install Western infrastructure in rural Africa, and therefore simplified regimens and drug supply concepts need to be evaluated for their feasibility for Africa. The evaluation of such concepts ideally is evaluated in controlled clinical trials. Not only can the results scientifically be analysed, such trials can be also used to train health personnel and built up the necessary infrastructure for a later hand over of ARV into the general health care system. If ARVs will be introduced in an uncoordinated manner outside controlled clinical trials, the failure of such action is guaranteed. This means that in many parts of Africa only a short window of opportunity remains to lead a movement into the right direction.

On the other hand we are convinced that especially such regions that are preparing for HIV vaccine trials in the next months, should be favoured with the support for antiretroviral therapy. With increasing ethical requirements an established ARV program is precondition for any HIV vaccine trial.

Research questions:

- Do single pill treatments, compared with original drug combinations, increase therapeutic efficacy in resource poor settings?
- What is a feasible and sustainable care and drug supply system?
- Can lower health care facilities (such as Health Care Centres, dispensaries and private pharmacies) serve as drug supply and therapy supervision centres?
- How important for therapeutic success is a parallel support though the community (family, self help groups, etc)?

Approach:

The proposed research would use a two step approach. In part one a randomized controlled clinical trial with three arms (standard branded regimen incl. Nevirapine versus same combination as a generic single pill versus only available branded single pill combination) would compare the biological outcomes (CD4 / viral load), intolerance/drug toxicity and adherence. The study evaluates effectiveness by measuring viral load below 50 RNA copies/ml of plasma. We assume that the standard treatment would be in 75% of the cases effective.

Part two would then carry forward the most feasible drug regimen into a more operational research. Different modes of drug supply and support to the patient would be evaluated on their effect on efficacy and adherence. The spectrum of supervision and support will range from direct observed treatment (DOT) to more realistic supply/support systems like delivery of drugs though Health Care Centres or private pharmacies.

Leveraged infrastructure:

The Mbeya Medical Research Project has a longstanding history of conduction of research and has the main infrastructure already in place. With assistance of external funds a Centre of Excellence (CoE) will be constructed. This CoE will be handed over during the course of the study into the normal hospital services including all the staff that has been trained during the research study.

Added value:

The proposed study will establish guidelines for the use of ARV in resource poor settings. It will evaluate what minimal support has to be given to the patients. In a side study therapy efficacy of patients that are treated outside this controlled trial by regional doctors would be compared to study participants. In addition to the scientific objectives, the study will build up the complete infrastructure for the Mbeya region to manage HIV patients after the end of the study. This will facilitate the conduct of the vaccine trails that are planned for the near future.

Negotiations for funding of this project are ongoing, but shall be assured by end of 2003.

ADVANCE-HIV *(working title)*
NETWORK TO TECHNICALLY SUPPORT THE DEVELOPMENT OF HIV CLINICAL TRIAL SITES

At a glance:
A network of experts:

- To develop a handbook and checklist for clinical HIV trial site development.
- To offer technical advice and tailored practical solutions for all components necessary for development of a clinical vaccine trial site
- To organize a quality assurance and quality control network of clinical and laboratory investigators.
- To facilitate the conduct of concerted clinical and laboratory studies in coordination with the EDCTP director and partnership board.

Background:
Purpose of the EDCTP is to promote the development of clinical trial sites for HIV/AIDS, malaria and TB. The existing trial sites are at various stages of development and have very different capacities. Some trial sites will be newly developed, with very little pre-existing infrastructure and knowledge. To develop such an "inexperienced" site to be fully prepared will take a concerted, ambitious team at least 6 years. We want to reduce this time and the mistakes done through help from experts that have already gone through the same process.
Since the major aim of the EDCTP is to sponsor capacity development in a certain number of locations to increase the capability to conduct trials under a minimum of common standard, a network we propose is of essential importance.

The idea
A consortium of African and European clinical trialists and researchers will form a network that first develops a handbook for clinical trial sites to be followed by tailored technical solutions to all aspects of cohort development spanning from epidemiology, social science, cohort development, routine safety blood testing, immunology, virology, medical care, data management, communication and shipping.
Trial sites, including those used by industrial partners can use this practical assistance to reduce the time to develop in-country systems and focus more on the scientific and political aspects. In our experience, research projects in developing countries do not fail because of wrong scientific ideas, but due to a failure to solve "simple" technical problems.
This network would offer training courses and have experienced staff to serve as consultants to the developing trial site for periods of time. This would be available until the specific method can be implemented independently at each site. This network would also offer a stringent quality control and quality assurance program within the context of joint studies that would be used to answer common questions as well as establishing the different methodologies.

Implementation:
The network of excellence would initially consist of 4-6 institutions having longstanding experience in clinical trial site development. However the consortium would be open to new partners with complementary expertise and would offer services to all trial sites under development.

Possible partners & expertise:
This would be a predominantly South-South driven initiative.

Mbeya Medical Research Programme, TZ	Cohort development, Social Science, Medical services
Nat. Inst. Communicable diseases, RSA	Immunology Laboratory expertise and vaccine endpoints
London School of Hygiene & Trop Medicine	Epidemiology, Social Science
Uganda, Senegal etc	to be defined

And more