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The Medical Research Council (UK)/Uganda Virus Research Institute Uganda Research Unit on AIDS – '25 years of research through partnerships'

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Abstract For the past 25 years, the Medical Research Council/Uganda Virus Research Institute Uganda Research Unit on AIDS has conducted research on HIV-1, coinfections and, more recently, on non-communicable diseases. Working with various partners, the research findings of the Unit have contributed to the understanding and control of the HIV epidemic both in Uganda and globally, and informed the future development of biomedical HIV interventions, health policy and practice. In this report, as we celebrate our silver jubilee, we describe some of these achievements and the Unit's multidisciplinary approach to research. We also discuss the future direction of the Unit; an exemplar of a partnership that has been largely funded from the north but led in the south.

keywords HIV, AIDS, Uganda, Medical Research Council/Uganda Virus Research Institute, coinfections, research, multidisciplinary

Introduction

This year 2014, we celebrate 25 years of the Medical Research Council/Uganda Virus Research Institute (MRC/UVRI) Uganda Research Unit on AIDS. On 12th December 1988, the initial memorandum of understanding (MoU) between the Uganda and British governments was signed, leading to the establishment of MRC/UVRI. The MRC/UVRI research programme activities were initiated in 1989 in Kyamulibwa, in Masaka district (Figures 1 and 2). The unique feature of the programme has been its multidisciplinary nature encompassing epidemiology, clinical medicine, basic science and social science, with strong community development, statistical and laboratory support. Capacity building has also been an important component of the Unit's work. The theme of our celebrations is '25 Years of Research Excellence through Partnerships' in recognition of the fact that the achievements and successes we have registered have only been possible through partnerships.

In 1986, the new Uganda Government recognised the danger of the HIV epidemic and acted quickly to make the problem public, including an appeal for international support to combat the disease. An invitation was extended to the United Kingdom MRC through the Uganda Ministry of Health to support the AIDS Control and Prevention Programme with both human and material resources. MRC sought support to fund the proposed HIV/AIDS research in Uganda and the Overseas Development Administration (ODA) – the predecessor of the UK Department for International Development (DFID) – agreed to fund the research. The MoU establishing the collaboration and the creation of the MRC/ODA/UVRI Programme on AIDS was signed, and the MRC was established at UVRI in Entebbe (Figure 3).

At that time, knowledge of the epidemiology of HIV-1 in Africa was based largely on studies of patients attending urban hospitals and of selected urban populations such as antenatal care attendants; there were limited data on the extent of the epidemic among rural populations. Though it was known that HIV is heterosexually transmitted, there were no available data on risk factors for transmission or of rates of disease progression. It was therefore urgent that research be initiated in a rural setting to help fill these knowledge gaps and inform policies on prevention. The research area was selected because of proximity to Rakai district, where the first cases were reported in 1983 and from where the disease was presumed to have spread to neighbouring districts.

The programme grew considerably over the years. New research sites were opened in Masaka, then Entebbe, Kampala and Jinja. Working with various partners, the research findings of the Unit have contributed to the understanding and control of the HIV epidemic in

Figure 1 The laboratory at Kyamulibwa field station in 1990.

Figure 2 Community meeting in Kyamulibwa, Masaka District, 2009.

Figure 3 Uganda Virus Research Institute.

Uganda and globally and informed the future development of biomedical HIV interventions and health policy and practice. We have tackled all aspects of the epidemic from basic science through to public health policy. The achievements have been possible through partnerships established with many different individuals and organisations. We summarise some of these achievements in three periods.

1989–1999

The original research investigated the epidemiology of HIV infection through annual surveys of a General Population Cohort (Nunn *et al.* 1994) with associated in-depth qualitative research on the impact of the epidemic in the rural setting (Seeley *et al.* 1993). Both a counselling and a community development section were set-up to support research activities and to promote the well-being of community members (Seeley *et al.* 1991; Nakibinge *et al.* 2009). Activities of this section included the establishment of various programmes such as school health education and community-based health care (Seeley *et al.* 1992). The first ten years provided important data on HIV prevalence and incidence including age-specific population attributable risks for HIV-1 infection (Mulder *et al.* 1994; Kengeya-Kayondo *et al.* 1996). The role of sexual behaviour in the HIV-1 epidemic was confirmed. The factor most strongly associated with increased risk of HIV infection was a greater number of lifetime sexual partners (Malamba *et al.* 1994). In addition, early studies showed that young women were at a higher risk of infection than men (Nunn *et al.* 1994). On the other hand, HIV infection among children aged 0–12 years was almost exclusively the result of mother-to-child transmission. No infections were attributed to parenteral exposure, non-sexual casual or household contact or insects (Mulder *et al.* 1996). Valuable information was generated on the biological and behavioural risk factors influencing transmission (Seeley *et al.* 1994) and the impact of the epidemic on children (Kamali *et al.* 1996).

Studies showed that the proportions of deaths that would have been avoided in the absence of HIV were 44% for adult men, 50% for adult women and 89% for all adults aged 25–34 years (Mulder *et al.* 1994). This work indicated the devastating effects of the epidemic on families and communities in rural areas, where the majority of Ugandans lived. In the mid-1990s, our work showed declining HIV prevalence, especially among young adults in the general population (Mulder *et al.* 1995) and later provided the first data on the declining HIV incidence in some age groups (Mbulaiteye *et al.* 2002). This may have been because of interventions in

the population and suggested that some measures could lead to epidemic control.

In 1990, a clinical cohort of HIV-infected people called the 'Natural History Cohort' in the era before antiretroviral treatment (ART) became available was set-up to investigate clinical manifestations and progression of the disease (Morgan *et al.* 1997). Participants were seen routinely every three months for investigation and treatment if they were sick. This cohort provided important information including the survival times of HIV-infected individuals in subSaharan Africa which, unexpectedly, were not dissimilar to those described in high-income countries.

In the late 1990s, the Unit contributed significantly to the understanding of the molecular epidemiology of HIV-1, showing that the prevalent HIV-1 subtypes circulating were A and D (Yirrell *et al.* 1998; Kaleebu *et al.* 2000). In late 1999, when MRC participated in the first HIV vaccine trial in Africa, there was intense debate as to whether using a subtype B-based vaccine in a region with diverse subtypes was ethical and scientifically justifiable (Mugerwa *et al.* 2002).

At the same time, a cohort of HIV-1-infected adults was established in Entebbe (Entebbe Cohort) to undertake a randomized trial of a polyvalent pneumococcal vaccine, in an effort to counter the impact of an important opportunistic infection (French *et al.* 2000). The cohort was to provide valuable information on the management of HIV and associated opportunistic infections in the pre-ART era (French *et al.* 2001; Watera *et al.* 2006). Investigations on tuberculosis–HIV interactions were initiated, such as a trial of prednisolone on HIV-associated tuberculosis, which revealed that prednisolone resulted in increased incidence of HIV-associated Kaposi's sarcoma (Elliott *et al.* 2004).

The rise of non-communicable disease is a major challenge in subSaharan Africa. The Unit began collaborations with various partners in the mid-1990s. This work provided some key insights into the impact of HIV and other factors on the risk of cancer in Uganda (Newton *et al.* 2001). Research in this area has been expanded and diversified over the last half decade, as non-communicable diseases have grown in relative importance as a cause of morbidity and mortality in low-income countries.

1999–2009

We continued to observe changes in reported sexual behaviour, especially among young people, who were adopting safer sex practices, but risky sexual behaviours increased in the middle-aged and older adults (Kamali *et al.* 2000; Biraro *et al.* 2009; Shafer *et al.* 2011).

While evidence for an association between HIV infection and the presence of other sexually transmitted diseases (STDs) was consistent in many studies (Darrow *et al.* 1987; Kreiss *et al.* 1988; Plummer *et al.* 1991), it was recognised that those STDs could just be a marker for sexual behaviour. A landmark study – the Masaka Intervention Trial – was a community randomized trial which aimed at determining the effectiveness of a behavioural change intervention through information, education and communication (IEC) alone or in combination with improved STD management on HIV transmission. There was no difference between intervention arms in the incidence of HIV (Kamali *et al.* 2003), but the experience gained from this trial was a stepping stone for future clinical and prevention trials.

During this period, the natural history cohort generated the first data on survival time in rural African populations, showing that survival with HIV in Africa was broadly similar to that in industrialised countries (Morgan *et al.* 2002). These data contributed to global estimates and projections of HIV infections. Natural history cohort data also showed that in women who became pregnant, CD4 cell count decline was significantly faster after pregnancy than before (Paal *et al.* 2007); that malaria had little detrimental effect on risk of death among HIV-infected people (Quigley *et al.* 2005); and that fertility is reduced from the earliest asymptomatic stage of HIV infection as a result of both a reduced incidence of recognised pregnancy and a increased fetal loss (Ross *et al.* 2004).

Results from a double-blind, randomized, placebo-controlled trial of the 23-valent pneumococcal vaccine in HIV-1-infected people in the Entebbe cohort showed no benefit in preventing pneumococcal disease in this population (French *et al.* 2000). In contrast, studies in the Entebbe cohort showed that co-trimoxazole prophylaxis reduced HIV mortality by 23% and reduced rates of malaria by 68% (Watera *et al.* 2006). The Entebbe cohort provided opportunities to confirm the existence of cross-clade cellular immune responses (McAdam *et al.* 1998; Rutebemberwa *et al.* 2004). We demonstrated that cellular immune responses to the core parts of the virus correlated with slower disease progression (Serwanga *et al.* 2009) and that disease progression differed between HIV-1 subtypes A and D (Kaleebu *et al.* 2001, 2002). There was no evidence that helminth infection was associated with faster HIV progression (Brown *et al.* 2004), contrary to widely advocated hypothesis on the potential effects of helminth-induced T-helper (Th)2-induced immunological bias.

A major development during this decade was the introduction of antiretroviral drugs (ARVs) in Uganda in 2004, to treat people with HIV. Our focus changed to

studying HIV-1-infected patients on treatment and to design studies that could lead to simpler approaches to deliver ART. Using data from our cohorts, we provided feedback on the effectiveness of the ARV roll-out in Uganda. We also contributed to social and behavioural studies in the ART era, including adherence studies and cost effectiveness analyses of ART delivery strategies (Seeley *et al.* 2009; Russell & Seeley 2010; Lara *et al.* 2012; Mbonye *et al.* 2013).

The contribution of high-risk populations such as truck drivers, fishing communities and commercial sex workers to the epidemic was already recognised, especially along the trans-African highway. The programme contributed studies on sexual networks and behaviours (Pickering *et al.* 1997a,b; Gryseels *et al.* 2002).

The Unit took part in other important clinical trials that included the DART (multicentre trial) and the Jinja trials, looking at simple ways of delivering ART; these showed that ART could be delivered safely using minimal laboratory monitoring and that structured treatment interruption regimens were not appropriate (DART Trial Team 2008). The Jinja trial showed that home-based ART delivery using trained lay workers was effective (Jaffar *et al.* 2010; Woodd *et al.* 2014). These two studies had a significant impact on the roll-out of ART in resource limited settings. Another was the cryptococcal disease prophylactic trial, which showed that systemic cryotococcal disease can be prevented reliably and cost-effectively through oral medication with fluconazole (Parkes-Ratanshi *et al.* 2011). The ARROW trial, completed in 2009, revealed that ART can be delivered to children with minimal laboratory monitoring (ARROW Trial team 2013).

The Unit was part of the UK Microbicide Development Programme that conducted a number of microbicide trials including the large phase III trial of PRO2000 which, however, did not show benefit in prevention of HIV transmission (McCormack *et al.* 2010). This decade also saw the initiation of long-term collaboration with the International AIDS Vaccine Initiative (IAVI). This partnership has helped build our capacity to conduct HIV vaccine trials including the conduct of two phase I vaccine trials in Masaka, but also to prepare cohorts for phase III efficacy trials (Ruzagira *et al.* 2011).

Our work gradually became a major source of data on ART drug resistance, including provision of data on HIV-transmitted drug resistance, with low to moderate resistance, as defined by WHO, reported in different populations (Ndembi *et al.* 2008, 2011). Further capacity was built to study drug resistance, with the basic sciences laboratories becoming the national and regional HIV drug resistance reference laboratories. These activities have allowed us to make a contribution to understanding of the development of resistance among those infected with HIV subtypes A and D (Lyagoba *et al.* 2010; Ndembi *et al.* 2010).

In 2001, work on the Entebbe Mother and Baby Study began. Addressing the hypothesis that maternal helminth infection might influence the infant response to BCG, the study was designed as a trial of anthelmintic treatment during pregnancy. In fact, at age one year, no effect of the intervention on responses to mycobacterial antigens was observed, but treatment of maternal hookworm resulted in reduced Th2 responses to tetanus antigens (Webb *et al.* 2011). In addition, there was striking evidence that maternal worm infections protect against eczema in childhood and that treatment of maternal worms results in increased incidence of eczema (Elliott *et al.* 2005; Mpairwe *et al.* 2011, 2014). These results led to a broadening of the remit of the coinfection work, to explore the wider effects of chronic immunomodulating infections on human immunity and disease patterns and of maternal infections on infant immune responses.

2009–present

While our studies in the rural population continued to provide encouraging evidence that HIV incidence is in decline, particularly since early 2000, a reversal was seen in some age groups. The epidemic was shifting demographically to encompass married couples and older age groups. The infection rates in some high-risk populations, such as those living in fishing communities around Lake Victoria and commercial sex workers, had reached alarming proportions (Asiki *et al.* 2011; Seeley *et al.* 2012; Vandepitte *et al.* 2013). However, with the introduction of ART, survival of HIV-1-positive persons has also improved dramatically, and HIV has become a chronic condition with both individual and societal consequences. This has reduced mortality in our cohorts and resulted in a rising HIV prevalence as infected people survive longer. Hence, our focus during this period is changing the face of the epidemic with an emphasis on HIV prevention research, especially in key populations, and on managing HIV as a chronic disease. Interestingly, we showed that contrary to common belief and despite the fact that many people in high-risk populations are highly mobile, they still had high retention rates and could be suitable for intervention studies (Asiki *et al.* 2011; McArthur *et al.* 2013).

To understand the main sources of HIV infections, we took a multidisciplinary approach that involved identifying HIV transmission networks and linkages using molecular virology combined with epidemiology and social science. Similar approaches within the high-risk groups have shown transmission networks and linkages

(Ssemwanga *et al.* 2012; Nazziwa *et al.* 2013) and observed that most of the transmissions occurring in the fishing communities come from individuals who have been infected for some time rather than incident cases.

We have therefore initiated studies to investigate factors limiting access to HIV prevention interventions and to assess the feasibility of conducting HIV combination interventions in fishing communities in Uganda. These pilot studies will inform the design of effectiveness trials of combination prevention in key populations and hard-to-reach communities.

In an effort to tackle the needs of the fishing communities, we are working regionally with other partners and have initiated the Lake Victoria Fishing Consortium, allowing a broader approach to intervention and health system research. Research in high-risk populations has allowed us to make contributions in other areas such as STDs, where we reported *Neisseria gonorrhoea* resistance to ciprofloxacin (Vandepitte *et al.* 2014); host immunological factors associated with resistance to HIV infection in highly exposed seronegative individuals (Pala *et al.* 2013); and rates of HIV-1 superinfection (Redd *et al.* 2014).

Studies of HIV across the life course are generating important data on the impact of HIV in people over 50 years living with HIV, who face particular challenges and face stigma because the infection is seen as a young persons' disease (Kuteesa *et al.* 2012; Nyirenda *et al.* 2013). Children/young people living with HIV have different problems, such as adherence and disclosure (Bernays *et al.* 2014; Kawuma *et al.* 2014).

In 2012, we became part of the International Partnership on Microbicides (IPM) by participating in a microbicide phase III programme evaluating the safety and efficacy of dapivirine (NNRTI) vaginal ring in preventing HIV-1 among sexually active HIV-negative women. We also successfully completed a phase I HIV vaccine trial in Masaka using Ad35-GRIN and F4co adjuvanted with AS01B/AS01E.

We follow one of the longest treatment cohorts in Africa where many participants have been on ART for more than 10 years and were initiated on different first-line regimens. This provides an opportunity to describe the long-term safety and toxicity of ART and factors associated with the development of drug resistance. We have been part of a number of other multicentre clinical studies such as START (Babiker *et al.* 2013), SPARTAC (Fidler *et al.* 2013) and SALIF; the latter is a phase 3b trial which will give data on a novel fixed dose (TDF/3TC/ Rilpivirine) combination, which could provide a much needed alternative to non-nucleoside reverse transcriptase inhibitors (NNRTI) based first-line regimen for Africa. Soon to be completed is the COSTOP, a study looking at the safety of discontinuing co-trimoxazole prophylaxis among HIV-infected adults on ART in Uganda; the results will have important policy implications. Among children, continuing co-trimoxazole prophylaxis after 96 weeks of ART was beneficial compared to stopping prophylaxis, with fewer hospitalizations for both malaria and infection not related to malaria (Bwakura-Dangarembizi *et al.* 2014).

The partnerships, infrastructure and multidisciplinary approach to research developed over the 25 years in the Unit are now being used to expand activities in order to address important research questions related to non-communicable diseases. These research questions include the epidemiology and genetics of communicable and non-communicable diseases, whose understanding is important to address the limited data on the burden and risk factors for non-communicable diseases in subSaharan Africa. This work is beginning to generate important information (Maher *et al.* 2011; Asiki *et al.* 2013; Murphy *et al.* 2013a,b, 2014; Riha *et al.* 2014).

A health systems research project was set-up in rural, semi-rural and urban settings in both Uganda and Tanzania (Peck *et al.* 2014) which plans to move into interventions research. Our research into mental health problems has expanded to include studies of psychiatric complications associated with HIV/AIDS where we see high rates of major depressive disorders (Kinyanda *et al.* 2011).

The results of the Entebbe Mother and Baby Study regarding helminths and allergy-related diseases have led directly to the development of a new intervention trial, the Lake Victoria Island Intervention Study on Worms and Allergy-related diseases (LaVIISWA). This is a cluster-randomised trial of intensive versus standard intervention against helminth infection, undertaken in island communities where the prevalence and intensity of schistosomiasis are particularly high.

As summarised above, MRC/UVRI has made significant contributions to HIV research over the 25 years. The initial years were aimed at understanding the new epidemic in a rural African setting and later in other high-risk groups. The later years allowed us to contribute knowledge to newer interventions and disease interactions. Our comparative advantage has been the multidisciplinary approach to our research and the longitudinal data and specimens. In response to the changing epidemic, we have also broadened our activities to non-communicable diseases and other areas.

Capacity building

Capacity building – both in terms of people and infrastructure – has been an important part of our mission

right from the start. This has helped establish us as an internationally recognised centre for research on HIV and other communicable diseases. The outcome of this process is a highly productive research Unit, influencing local and international policy and scientific thinking. The Unit has also played an important role in the capacity building for UVRI that includes training of staff, creating an academic environment including opportunities for short and long courses, seminars, supervision of staff and provision of laboratory space, among others (Figures 4 and 5). We have also supported the construction of a new clinic, training building, laboratories and other infrastructure. Over the years, we have created strong collaborations with various universities including Makerere University. More recently, the Makerere University UVRI (MUII) programme, of which we are a partner, has further strengthened our links to the University sector in Uganda. In the past 25 years, we supported 44 PhD students and 74 MSc students. Some of these have gone on to become leaders in their field within the Unit and at other places in Uganda and elsewhere.

Figure 4 Bioinformatics training being conducted at the main site in Entebbe, 2013.

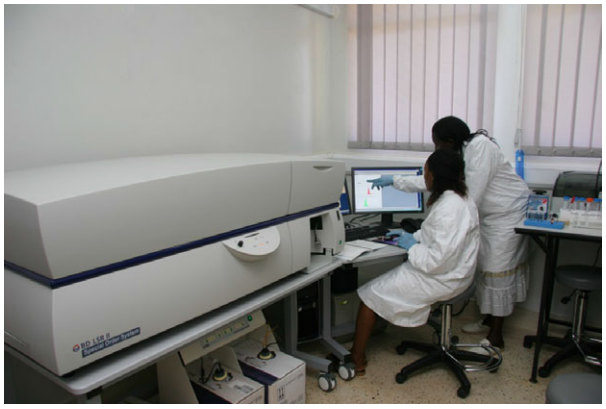

Figure 5 Immunology staff working on the BD LSR II flow cytometer.

The future

HIV will remain a health challenge for some years to come; this epidemic remains our major focus, and we will continue with cutting edge research, taking advantage of our multidisciplinary approach and the exceptional international collaborations.

We are in a strong position to contribute to vaccine development and trials by virtue of our excellent laboratory facilities, our collaborations and our work on other factors that may influence and impair the immune response to vaccines in tropical or resource-poor settings.

We have ongoing non-communicable disease research including mental health, especially as it relates to infectious diseases, and working in partnerships, this will be an area of continued interest. New opportunities in genotyping and bioinformatics provide new avenues to understand the relationship between genetics and infections, non-communicable diseases and responses to vaccines. Indeed, two of our major cohorts have available data from genome-wide association studies (GWAS).

We have initiated health systems and implementation research and have important regional collaborations in this field. We consider this as a key cross-cutting area in which to build capacity. There are other areas the MRC may contribute, such as maternal and child health and neglected diseases.

In all areas, we will make it a priority to build more human capacity to have more senior researchers as future leaders. To remain competitive, we will continue to value and strengthen partnerships and collaborations, including strengthening our links with UVRI and regional universities. This has, indeed, been 25 Years of Research Excellence through Partnerships.

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