

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 cryptococcal 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 (Ndemi *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; Ndemi *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 sub-Saharan 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



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

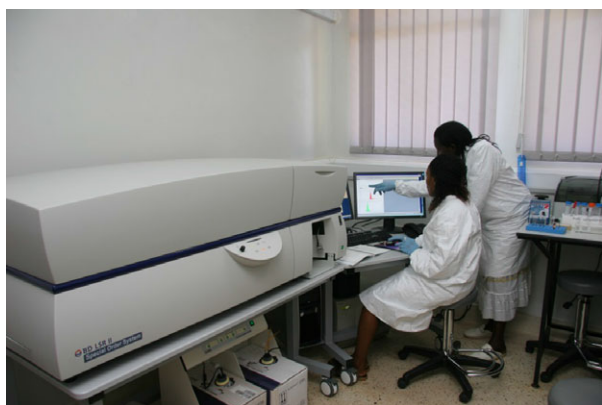


Figure 5 Immunology staff working on the BD LSR II flow cytometer.

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.

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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References

- ARROW Trial team (2013) Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomised factorial trial. *Lancet* **381**, 1391–1403.
- Asiki G, Mpendo J, Abaasa A *et al.* (2011) HIV and syphilis prevalence and associated risk factors among fishing communities of Lake Victoria, Uganda. *Sexually Transmitted Infections* **87**, 511–515.
- Asiki G, Murphy G, Nakyingi-Miiri J *et al.* (2013) The general population cohort in rural south-western Uganda: a platform for communicable and non-communicable disease studies. *International Journal of Epidemiology* **42**, 129–141.
- Babiker AG, Emery S, Fätkenheuer G *et al.* (2013) Considerations in the rationale, design and methods of the Strategic Timing of AntiRetroviral Treatment (START) study. *Clinical Trials* **10**, S5–S36.
- Bernays S, Seeley J, Rhodes T & Mupambireyi Z (2014) What am I 'living' with? Growing up with HIV in Uganda and Zimbabwe. *Sociology of Health and Illness* in press.
- Biraro S, Shafer L, Kleinschmidt I *et al.* (2009) Is sexual risk taking behaviour changing in rural south-west Uganda? Behaviour trends in a rural population cohort 1993–2006. *Sexually Transmitted Infections* **85**, i3–i11.
- Brown M, Kizza M, Watera C *et al.* (2004) Helminth infection is not associated with faster progression of HIV disease in coinfecting adults in Uganda. *Journal of Infectious Diseases* **190**, 1869–1879.
- Bwakura-Dangarembizi M, Kendall L, Bakeera-Kitaka S *et al.* (2014) A randomized trial of prolonged co-trimoxazole in HIV-Infected children in Africa. *New England Journal of Medicine* **370**, 41–53.
- Darrow WW, Echenberg DF, Jaffe HW *et al.* (1987) Risk factors for human immunodeficiency virus (HIV) infections in homosexual men. *American Journal of Public Health* **77**, 479–483.
- DART Trial Team (2008) Fixed duration interruptions are inferior to continuous treatment in African adults starting therapy with CD4 cell counts < 200 cells/ μ l. *AIDS* **22**, 237–247.
- Elliott AM, Luzze H, Quigley MA *et al.* (2004) A Randomized, Double-Blind, Placebo-Controlled Trial of the Use of Prednisolone as an Adjunct to Treatment in HIV-1 – Associated Pleural Tuberculosis. *Journal of Infectious Diseases* **190**, 869–878.
- Elliott AM, Mpairwe H, Quigley MA *et al.* (2005) Helminth infection during pregnancy and development of infantile eczema. *JAMA* **294**, 2028–2034.
- Fidler S, Porter K, Ewings F *et al.* (2013) Short-course antiretroviral therapy in primary HIV infection. *The New England Journal of Medicine* **368**, 207–217.
- French N, Nakyingi J, Carpenter L *et al.* (2000) 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *The Lancet* **355**, 2106–2111.
- French N, Nakyingi J, Lugada E, Watera C, Whitworth JA & Gilks CF (2001) Increasing rates of malarial fever with deteriorating immune status in HIV-1-infected Ugandan adults. *AIDS* **15**, 899–906.
- Gryseels M, Pool R & Nnalusiba B (2002) Women who sell sex in a Ugandan trading town: life histories, survival strategies and risk. *Social Science and Medicine* **54**, 179–192.
- Jaffar S, Amuron B, Foster S *et al.* (2010) Rates of virological failure in patients treated in a home-based versus a facility-based HIV-care model in Jinja, southeast Uganda: a cluster-randomised equivalence trial. *The Lancet* **374**, 2080–2089.
- Kaleebu P, Orth JW, Hamilton L *et al.* (2000) Molecular epidemiology of HIV type 1 in a rural community in southwest Uganda. *AIDS Research and Human Retroviruses* **16**, 393–401.
- Kaleebu P, Ross A, Morgan D *et al.* (2001) Relationship between HIV-1 Env subtypes A and D and disease progression in a rural Ugandan cohort. *AIDS* **15**, 293–299.
- Kaleebu P, French N, Mahe C *et al.* (2002) Effect of human immunodeficiency virus (HIV) type 1 envelope subtypes A and D on disease progression in a large cohort of HIV-1—positive persons in Uganda. *Journal of Infectious Diseases* **185**, 1244–1250.
- Kamali A, Seeley JA, Nunn AJ, Kengeya-Kayondo JF, Ruberantwari A & Mulder DW (1996) The orphan problem: experience of a sub-Saharan Africa rural population in the AIDS epidemic. *AIDS Care* **8**, 509–516.
- Kamali A, Carpenter LM, Whitworth JAG, Pool R, Ruberantwari A & Ojwiya A (2000) Seven-year trends in HIV-1 infection rates, and changes in sexual behaviour, among adults in rural Uganda. *AIDS* **14**, 427–434.
- Kamali A, Quigley M, Nakyingi J *et al.* (2003) Syndromic management of sexually-transmitted infections and behaviour change interventions on transmission of HIV-1 in rural Uganda: a community randomised trial. *The Lancet* **361**, 645–652.
- Kawuma R, Bernays S, Siu GE, Rhodes T & Seeley J (2014) 'Children will always be children': exploring perceptions and experiences of children living with HIV who may not take their treatment and why they may not tell. *African Journal of AIDS Research* **13**, 189–195.
- Kengeya-Kayondo J-F, Kamali A, Nunn AJ, Ruberantwari A, Wagner H-UH & Mulder DW (1996) Incidence of HIV-1

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- infection in adults and socio-demographic characteristics of seroconverters in a rural population in Uganda: 1990–1994. *International Journal of Epidemiology* 25, 1077–1082.
- Kinyanda E, Hoskins S, Nakku J, Nawaz S & Patel V (2011) Prevalence and risk factors of major depressive disorder in HIV/AIDS as seen in semi-urban Entebbe district, Uganda. *BMC Psychiatry* 11, 205.
- Kreiss J, Carael M & Meheus A (1988) Role of sexually transmitted diseases in transmitting human immunodeficiency virus. *Genitourinary Medicine* 64, 1–2.
- Kuteesa MO, Seeley J, Cumming RG & Negin J (2012) Older people living with HIV in Uganda: understanding their experience and needs. *African Journal of AIDS Research* 11, 295–305.
- Lara AM, Kigozi J, Amurwon J *et al.* (2012) Cost effectiveness analysis of clinically driven versus routine laboratory monitoring of antiretroviral therapy in Uganda and Zimbabwe. *PLoS One* 7, e33672.
- Lyagoba F, Dunn DT, Pillay D *et al.* (2010) Evolution of drug resistance during 48 weeks of zidovudine/lamivudine/tenofovir in the absence of real-time viral load monitoring. *JAIDS: Journal of Acquired Immune Deficiency Syndromes* 55, 277–283.
- Maher D, Waswa L, Baisley K, Karabarinde A, Unwin N & Grosskurth H (2011) Distribution of hyperglycaemia and related cardiovascular disease risk factors in low-income countries: a cross-sectional population-based survey in rural Uganda. *International Journal of Epidemiology* 40, 160–171.
- Malamba SS, Wagner H-U, Maude G *et al.* (1994) Risk factors for HIV-1 infection in adults in a rural Ugandan community: a case-control study. *AIDS* 8, 253–258.
- Mbonye M, Seeley J, Ssembajja F, Birungi J & Jaffar S (2013) Adherence to antiretroviral therapy in Jinja, Uganda: a six-year follow-up study. *PLoS One* 8, e78243.
- Mbulaitaye S, Mahe C, Whitworth J *et al.* (2002) Declining HIV-1 incidence and associated prevalence over 10 years in a rural population in south-west Uganda: a cohort study. *The Lancet* 360, 41–46.
- McAdam S, Kaleebu P, Krausa P *et al.* (1998) Cross-clade recognition of p55 by cytotoxic T lymphocytes in HIV-1 infection. *AIDS* 12, 571–579.
- McArthur M, Birdthistle I, Seeley J, Mpendo J & Asiki G (2013) How HIV diagnosis and disclosure affect sexual behavior and relationships in Ugandan fishing communities. *Qualitative Health Research* 23, 1125–1137.
- McCormack S, Ramjee G, Kamali A *et al.* (2010) PRO2000 vaginal gel for prevention of HIV-1 infection (Microbicides Development Programme 301): a phase 3, randomised, double-blind, parallel-group trial. *The Lancet* 376, 1329–1337.
- Morgan D, Malamba SS, Maude GH *et al.* (1997) An HIV-1 natural history cohort and survival times in rural Uganda. *AIDS* 11, 633–640.
- Morgan D, Mahe C, Mayanja B, Okongo JM, Lubega R & Whitworth JA (2002) HIV-1 infection in rural Africa: is there a difference in median time to AIDS and survival compared with that in industrialized countries? *AIDS* 16, 597–603.
- Mpairwe H, Webb EL, Muhangi L *et al.* (2011) Anthelmintic treatment during pregnancy is associated with increased risk of infantile eczema: randomised-controlled trial results. *Pediatric Allergy and Immunology* 22, 305–312.
- Mpairwe H, Ndiranza J, Webb EL *et al.* (2014) Maternal hookworm modifies risk factors for childhood eczema: results from a birth cohort in Uganda. *Pediatric Allergy and Immunology* 25, 481–488.
- Mugerwa RD, Kaleebu P, Mugenyi P *et al.* (2002) First trial of the HIV-1 vaccine in Africa: Ugandan experience. *British Medical Journal* 324, 226–229.
- Mulder DW, Nunn AJ, Wagner H-U, Kamali A & Kengeya-Kayondo JF (1994) HIV-1 incidence and HIV-1-associated mortality in a rural Ugandan population cohort. *AIDS* 8, 87–92.
- Mulder D, Nunn A, Kamali A & Kengeya-Kayondo J (1995) Decreasing HIV-1 seroprevalence in young adults in a rural Ugandan cohort. *British Medical Journal* 311, 833–836.
- Mulder DW, Nunn A, Kamali A & Kengeya-Kayondo JF (1996) Post-natal incidence of HIV-1 infection among children in a rural Ugandan population: no evidence for transmission other than mother to child. *Tropical Medicine and International Health* 1, 81–85.
- Murphy GA, Asiki G, Ekoru K *et al.* (2013a) Sociodemographic distribution of non-communicable disease risk factors in rural Uganda: a cross-sectional study. *International Journal of Epidemiology* 42, 1740–1753.
- Murphy GA, Asiki G, Young EH *et al.* (2013b) Cardiometabolic Risk in a Rural Ugandan Population. *Diabetes Care* 36, e143.
- Murphy GA, Asiki G, Nsubuga RN *et al.* (2014) The use of anthropometric measures for cardiometabolic risk identification in a rural African population. *Diabetes Care* 37, e64–e65.
- Nakibinge S, Maher D, Katende J, Kamali A, Grosskurth H & Seeley J (2009) Community engagement in health research: two decades of experience from a research project on HIV in rural Uganda. *Tropical Medicine and International Health* 14, 190–195.
- Nazziwa J, Njai H, Ndembi N *et al.* (2013) HIV-1 transmitted drug resistance and evidence of transmission clusters among recently infected antiretroviral naïve individuals from Ugandan fishing communities of Lake Victoria. *AIDS Research and Human Retroviruses* 29, 788–795.
- Ndembi N, Lyagoba F, Nanteza B *et al.* (2008) Transmitted antiretroviral drug resistance surveillance among newly HIV type 1-diagnosed women attending an antenatal clinic in Entebbe, Uganda. *AIDS Research and Human Retroviruses* 24, 889–895.
- Ndembi N, Goodall RL, Dunn DT *et al.* (2010) Viral rebound and emergence of drug resistance in the absence of viral load testing: a randomized comparison between zidovudine-lamivudine plus nevirapine and zidovudine-lamivudine plus abacavir. *Journal of Infectious Diseases* 201, 106–113.
- Ndembi N, Hamers RL, Sigaloff KC *et al.* (2011) Transmitted antiretroviral drug resistance among newly HIV-1 diagnosed young individuals in Kampala. *AIDS* 25, 905–910.
- Newton R, Ziegler J, Beral V *et al.* (2001) A case-control study of human immunodeficiency virus infection and cancer in

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- adults and children residing in Kampala, Uganda. *International Journal of Cancer* **92**, 622–627.
- Nunn AJ, Kengeya-Kayondo JF, Malamba SS, Seeley JA & Mulder DW (1994) Risk factors for HIV-1 infection in adults in a rural Ugandan community: a population study. *AIDS* **8**, 81–86.
- Nyirenda M, Newell ML, Mugisha J *et al.* (2013) Health, well-being, and disability among older people infected or affected by HIV in Uganda and South Africa. *Global Health Action* **6**, 19201.
- Paal LVd, Shafer LA, Mayanja BN, Whitworth JA & Grosskurth H (2007) Effect of pregnancy on HIV disease progression and survival among women in rural Uganda. *Tropical Medicine and International Health* **12**, 920–928.
- Pala P, Serwanga J, Watera C *et al.* (2013) Quantitative and qualitative differences in the T cell response to HIV in uninfected Ugandans exposed or unexposed to HIV infected partners. *Journal of Virology* **87**, 9053–9063.
- Parkes-Ratanshi R, Wakeham K, Levin J *et al.* (2011) Primary prophylaxis of cryptococcal disease with fluconazole in HIV-positive Ugandan adults: a double-blind, randomised, placebo-controlled trial. *The Lancet infectious diseases* **11**, 933–941.
- Peck R, Mghamba J, Vanobberghen F *et al.* (2014) Preparedness of Tanzanian health facilities for outpatient primary care of hypertension and diabetes: a cross-sectional survey. *The Lancet Global Health* **2**, e285–e292.
- Pickering H, Okongo M, Bwanika K, Nnalusiba B & Whitworth J (1997a) Sexual behaviour in a fishing community on Lake Victoria, Uganda. *Health Transition Review* **7**, 13–20.
- Pickering H, Okongo M, Ojwiya A, Yirrell D & Whitworth J (1997b) Sexual networks in Uganda: mixing patterns between a trading town, its rural hinterland and a nearby fishing village. *International Journal of STD and AIDS* **8**, 495–500.
- Plummer FA, Simonsen JN, Cameron DW *et al.* (1991) Cofactors in male-female sexual transmission of human immunodeficiency virus type 1. *Journal of Infectious Diseases* **163**, 233–239.
- Quigley MA, Hewitt K, Mayanja B *et al.* (2005) The effect of malaria on mortality in a cohort of HIV-infected Ugandan adults. *Tropical Medicine and International Health* **10**, 894–900.
- Redd AD, Ssemwanga D, Vandepitte J *et al.* (2014) Rates of HIV-1 superinfection and primary HIV-1 infection are similar in female sex workers in Uganda. *AIDS* **500**, 14–00349.
- Riha J, Karabarinde A, Ssenyomo G *et al.* (2014) Urbanicity and Lifestyle Risk Factors for Cardiometabolic Diseases in Rural Uganda: a Cross-Sectional Study. *PLoS Medicine* **11**, e1001683.
- Ross A, Van der Paal L, Lubega R, Mayanja BN, Shafer LA & Whitworth J (2004) HIV-1 disease progression and fertility: the incidence of recognized pregnancy and pregnancy outcome in Uganda. *AIDS* **18**, 799–804.
- Russell S & Seeley J (2010) The transition to living with HIV as a chronic condition in rural Uganda: working to create order and control when on antiretroviral therapy. *Social Science and Medicine* **70**, 375–382.
- Rutebemberwa A, Auma B, Gilmour J *et al.* (2004) HIV type 1-specific inter- and intrasubtype cellular immune responses in HIV type 1-infected Ugandans. *AIDS Research and Human Retroviruses* **20**, 763–771.
- Ruzagira E, Wandiembe S, Abaasa A *et al.* (2011) Prevalence and incidence of HIV in a rural community-based HIV vaccine preparedness cohort in Masaka, Uganda. *PLoS One* **6**, e20684.
- Seeley J, Wagner U, Mulemwa J, Kengeya-Kayondo J & Mulder D (1991) The development of a community-based HIV/AIDS counselling service in a rural area in Uganda. *AIDS Care* **3**, 207–217.
- Seeley JA, Kengeya-Kayondo JF & Mulder DW (1992) Community-based HIV/AIDS research—Whither community participation? Unsolved problems in a research programme in rural Uganda. *Social Science and Medicine* **34**, 1089–1095.
- Seeley J, Kajura E, Bachengana C, Okongo M, Wagner U & Mulder D (1993) The extended family and support for people with AIDS in a rural population in south west Uganda: a safety net with holes? *AIDS Care* **5**, 117–122.
- Seeley JA, Malamba SS, Nunn AJ, Mulder DW, Kengeya-Kayondo JF & Barton TG (1994) Socioeconomic status, gender, and risk of HIV-1 infection in a rural community in South West Uganda. *Medical Anthropology Quarterly* **8**, 78–89.
- Seeley J, Russell S, Khana K, Ezati E, King R & Bunnell R (2009) Sex after ART: sexual partnerships established by HIV-infected persons taking anti-retroviral therapy in Eastern Uganda. *Culture, Health and Sexuality* **11**, 703–716.
- Seeley J, Nakiyingi-Miiri J, Kamali A *et al.* (2012) High HIV incidence and socio-behavioral risk patterns in fishing communities on the shores of Lake Victoria, Uganda. *Sexually Transmitted Diseases* **39**, 433–439.
- Serwanga J, Shafer LA, Pimego E *et al.* (2009) Host HLA B* allele-associated multi-clade Gag T-cell recognition correlates with slow HIV-1 disease progression in antiretroviral therapy-naive Ugandans. *PLoS One* **4**, e4188.
- Shafer LA, Nsubuga RN, Seeley J, Levin J & Grosskurth H (2011) Examining the components of population-level sexual behavior trends from 1993 to 2007 in an open Ugandan cohort. *Sexually Transmitted Diseases* **38**, 697–704.
- Ssemwanga D, Kapaata A, Lyagoba F *et al.* (2012) Low drug resistance levels among drug-naive individuals with recent HIV type 1 infection in a rural clinical cohort in southwestern Uganda. *AIDS Research and Human Retroviruses* **28**, 1784–1787.
- Vandepitte J, Weiss HA, Bukkenya J *et al.* (2013) Alcohol use, mycoplasma genitalium, and other STIs associated with HIV incidence among women at high risk in Kampala, Uganda. *Journal of Acquired Immune Deficiency Syndromes* **62**, 119–126.
- Vandepitte J, Hughes P, Matovu G, Bukkenya J, Grosskurth H & Lewis DA (2014) High prevalence of ciprofloxacin-resistant gonorrhoea among female sex workers in Kampala, Uganda (2008–2009). *Sexually Transmitted Diseases* **41**, 233–237.
- Watera C, Todd J, Muwonge R *et al.* (2006) Feasibility and effectiveness of cotrimoxazole prophylaxis for HIV-1-infected

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- adults attending an HIV/AIDS clinic in Uganda. *JAIDS: Journal of Acquired Immune Deficiency Syndromes* 42, 373–378.
- Webb EL, Mawa PA, Ndibazza J *et al.* (2011) Effect of single-dose anthelmintic treatment during pregnancy on an infant's response to immunisation and on susceptibility to infectious diseases in infancy: a randomised, double-blind, placebo-controlled trial. *The Lancet* 377, 52–62.
- Woodd SL, Grosskurth H, Levin J *et al.* (2014) Home-based versus clinic-based care for patients starting antiretroviral therapy with low CD4+ cell counts: findings from a cluster-randomized trial. *AIDS* 28, 569–576.
- Yirrell DL, Pickering H, Palmarini G *et al.* (1998) Molecular epidemiological analysis of HIV in sexual networks in Uganda. *AIDS* 12, 285–290.

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