

MRC/UVRI PUBLICATIONS DIGEST – JULY 2016

Kasirye RP, Baisley K, Munderi P, Levin J, Anywaine Z, Nunn A, Kamali A, Grosskurth H. Incidence of malaria by cotrimoxazole use in HIV-infected Ugandan adults on antiretroviral therapy: a randomized, placebo-controlled study. *AIDS*. 2016 Feb 20;30(4):635-44. doi: 10.1097/QAD.0000000000000956.

INTRODUCTION:

Previous un-blinded trials have shown increased malaria among HIV-infected adults on antiretroviral therapy (ART) who stop cotrimoxazole (CTX) prophylaxis. We investigated the effect of stopping CTX on malaria in HIV-infected adults on ART in a double-blind, placebo-controlled trial.

METHODS:

HIV-infected Ugandan adults stable on ART and CTX with CD4 cell count at least 250 cells/ μ l were randomized (1 : 1) to continue CTX or stop CTX and receive matching placebo (COSTOP trial; ISRCTN44723643). Clinical malaria was defined as fever and a positive blood slide, and considered severe if a participant had at least one clinical or laboratory feature of severity or was admitted to hospital. Malaria incidence and rate ratios were estimated using random effects Poisson regression, accounting for multiple episodes.

RESULTS:

A total of 2180 participants were enrolled and followed for a median of 2.5 years; 453 malaria episodes were recorded. Malaria incidence was 9.1/100 person-years (pyrs) [95% confidence interval (CI) = 8.2-10.1] and was higher on placebo (rate ratio 3.47; CI = 2.74-4.39). Malaria in the placebo arm decreased over time; although incidence remained higher than in the CTX arm, the difference between arms reduced slightly (interaction P value = 0.10). Fifteen participants experienced severe malaria (<1%); overall incidence was 0.30/100 pyrs (CI = 0.18-0.49). There was one malaria-related death (CTX arm).

CONCLUSION:

HIV-infected adults - who are stable on ART and stop prophylactic CTX - experience more malaria than those that continue, but this difference is less than has been reported in previous trials. Few participants had severe malaria. Further research might be useful in identifying groups that can safely stop CTX prophylaxis.

Asiki G, Stockdale L, Kasamba J, Vudriko T, Tumwekwase G, Johnston T, Kaleebu P, Kamali A, Seeley J, Newton R. Pilot study of antibodies against varicella zoster virus and human immunodeficiency virus in relation to the risk of developing stroke, nested within a rural cohort in Uganda. *Trop Med Int Health*. 2015 Oct;20(10):1306-10. doi: 10.1111/tmi.12556. Epub 2015 Jul 23.

OBJECTIVE:

The risk of stroke rises after episodes of herpes zoster and chickenpox, which are caused by varicella zoster virus (VZV). We conducted a pilot case-

control study of stroke, nested within a long-standing cohort in Uganda (the General Population Cohort), to examine antibodies against VZV prior to diagnosis.

METHODS:

We used stored sera to examine the evolution of IgG and IgM antibodies against VZV among 31 clinically confirmed cases of stroke and 132 matched controls. For each participant, three samples of sera were identified: one each, taken at or near the time of (pseudo)diagnosis, between 5 and 10 years prior to diagnosis and at 15 years prior to diagnosis.

RESULTS:

All participants had detectable antibodies against VZV, but there were no significant differences between cases and controls in the 15 years prior to diagnosis. As a secondary finding, 16% (5/31) of cases and 6% (8/132) of controls had HIV (OR 3.0; 95% CI 0.8-10.1; P = 0.06).

CONCLUSIONS:

This is the first prospective study to examine a biological measure of exposure to VZV prior to diagnosis of stroke and although we identified no significant association, in this small pilot, with limited characterisation of cases, we cannot exclude the possibility that the virus is causal for a subset. The impact of HIV on risk of stroke has not been well characterised and warrants further study.

Asiki G, Baisley K, Newton R, Marions L, Seeley J, Kamali A, Smedman L. Adverse pregnancy outcomes in rural Uganda (1996-2013): trends and associated factors from serial cross-sectional surveys. *BMC Pregnancy Childbirth*. 2015 Oct 29:279. Doi: 10.1186/s12884-015-0708-8.

OBJECTIVE:

Community based evidence on pregnancy outcomes in rural Africa is lacking yet it is needed to guide maternal and child health interventions. We estimated and compared adverse pregnancy outcomes and associated factors in rural south-western Uganda using two survey methods.

METHODS:

Within a general population cohort, between 1996 and 2013, women aged 15-49 years were interviewed on their pregnancy outcome in the past 12 months (method 1). During 2012-13, women in the same cohort were interviewed on their lifetime experience of pregnancy outcomes (method 2). Adverse pregnancy outcome was defined as abortions or stillbirths. We used random effects logistic regression for method 1 and negative binomial regression with robust clustered standard errors for method 2 to explore factors associated with adverse outcome.

RESULTS:

One third of women reported an adverse pregnancy outcome; 10.8% (abortion = 8.4%, stillbirth = 2.4%) by method 1 and 8.5% (abortion = 7.2%, stillbirth = 1.3%) by method 2. Abortion rates were similar (10.8 vs 10.5) per 1000 women and stillbirth rates differed (26.2 vs 13.8) per 1000 births by methods 1 and 2 respectively. Abortion risk increased with age of mother, non-attendance of antenatal care and proximity to the road. Lifetime stillbirth risk increased with age. Abortion and stillbirth risk reduced with increasing parity.

DISCUSSION:

Both methods had a high level of agreement in estimating abortion rate but were markedly below national estimates. Stillbirth rate estimated by method 1 was double that estimated by method 2 but method 1 estimate was more consistent with the national estimates.

CONCLUSION:

Strategies to improve prospective community level data collection to reduce reporting biases are needed to guide maternal health interventions.

Hargreaves JR, Stangl A, Bond V, Hoddinott G, Krishnaratne S, Mathema H, Moyo M, Viljoen L, Brady L, Sievwright K, Horn L, Sabapathy K, Ayles H, Beyers N, Bock P, Fidler S, Griffith S, [Seeley J](#), Hayes R; HPTN 071 (PopART) study team. HIV related stigma and universal testing and treatment for HIV prevention and care; design of an implementation science evaluation nested in the HPTN 071 (PopART) cluster-randomized trial in Zambia

BACKGROUND:

Stigma and discrimination related to HIV and key populations at high risk of HIV have the potential to impede the implementation of effective HIV prevention and treatment programmes at scale. Studies measuring the impact of stigma on these programmes are rare. We are conducting an implementation science study of HIV-related stigma in communities and health settings within a large, pragmatic cluster-randomized trial of a universal testing and treatment intervention for HIV prevention in Zambia and South Africa and will assess how stigma affects, and is affected by, implementation of this intervention.

METHODS/DESIGN:

A mixed-method evaluation will be nested within HIV prevention trials network (HPTN) 071/PopART (Clinical Trials registration number [NCT01900977](#)), a three-arm trial comparing universal door-to-door delivery of HIV testing and referral to prevention and treatment services, accompanied by either an immediate offer of anti-retroviral treatment to people living with HIV regardless of clinical status, or an offer of treatment in-line with national guidelines, with a standard-of-care control arm. The primary outcome of HPTN 071/PopART is HIV incidence measured among a cohort of 52 500 individuals in 21 study clusters. Our evaluation will include integrated quantitative and qualitative data collection and analysis in all trial sites. We will collect quantitative data on indicators of HIV-related stigma over 3 years from large probability samples of community members, health workers and people living with HIV. We will collect qualitative data, including in-depth interviews and observations from members of these same groups sampled purposively. In analysis, we will: (1) compare HIV-related stigma measures between study arms, (2) link data on stigma to measures of the success of implementation of the PopART intervention and (3) explore changes in the dominant drivers and manifestations of stigma in study communities and the health system.

DISCUSSION:

HIV-related stigma may impede the successful implementation of HIV prevention and treatment programmes. Using a novel study-design nested within a large, community randomized trial we will evaluate the extent

to which HIV-related stigma affects and is affected by the implementation of a comprehensive combination HIV prevention intervention including a universal test and treatment approach.

Kasirye R , Grosskurth H , Munderi P, Levin J, Anywaine Z, Nunn A, Kamali A, Baisley K. Longitudinal effect of CD4 by cotrimoxazole use on malaria incidence among HIV-infected Ugandan adults on antiretroviral therapy: a randomized controlled study. *Malar J.* 2016 Jul 15;15:361. doi: 10.1186/s12936-016-1426-z.

BACKGROUND:

The effect of CD4 count on malaria incidence in HIV infected adults on antiretroviral therapy (ART) was assessed in the context of a randomized controlled trial on the effect of stopping cotrimoxazole (CTX).

METHODS:

This study presents a sub-analysis of the COSTOP trial (ISRCTN44723643) which was carried out among HIV-infected Ugandan adults stable on ART with CD4 counts ≥ 250 cells/ μ l. Participants were randomized (1:1) to continue CTX or stop CTX and receive matching placebo, and were followed up for a minimum of 1 year (median 2.5 years). CD4 counts were measured at baseline, 3 months and then every 6 months. Clinical malaria was defined as fever and a positive blood slide. First, the relationship between current CD4 count during follow-up and malaria among participants on placebo was examined; using random effects Poisson regression to account for repeated episodes. Second, the effect of CD4 count at enrolment, CD4 count at ART initiation, and CD4 count during follow-up on malaria, was assessed within each trial arm; to examine whether the effect of CD4 count differed by CTX use.

RESULTS:

2180 participants were enrolled into the COSTOP trial. The incidence of clinical malaria was approximately four episodes/100 person years in the CTX arm and 14 episodes/100 person years in the placebo arm. There was no evidence of an association of current CD4 and clinical malaria incidence ($P = 0.56$), or parasitaemia levels ($P = 0.24$), in the placebo arm. Malaria incidence did not differ by CD4 count at ART initiation, enrolment or during follow up, irrespective of CTX use. When compared with participants in the lowest CD4 stratum, rate ratios within each trial arm were all close to 1, and P values were all above $P = 0.30$.

CONCLUSIONS:

The immune status of HIV infected participants who are stable on ART as measured by CD4 count was not associated with malaria incidence and did not modify the effect of stopping CTX on malaria. The decision of whether to stop or continue CTX prophylaxis for malaria in HIV infected individuals who are stable on ART should not be based on CD4 counts alone. COSTOP trial registration number ISRCTN44723643.

Mbonye M, Seeley J, Nalugya R, Kiwanuka T, Bagiire D, Mugenyi M, Namale G, Mayanja Y, Kamali A. Test and treat: the early experiences in a clinic serving women at high risk of HIV infection in Kampala. *AIDS Care*. 2016;28 Suppl 3:33-8. doi: 10.1080/09540121.2016.1164804.

At the end of 2013, the Government of Uganda issued guidance recommending provision of Anti-Retroviral Treatment (ART) to HIV-positive people in key populations, including female sex workers, regardless of CD4 cell count. We describe the implementation of this new guidance in a clinic serving women at high risk of HIV infection in Kampala. Between July and December 2015, we conducted repeat in-depth interviews with 15 women attending the clinic after the change in guidelines, to explore their perceptions regarding prompt ART initiation. The sample included some women who were HIV-negative and women who had both started and deferred ART. We conducted a data-led thematic analysis of the material from the interviews. A total of 257 of 445 eligible women had started ART; others were undecided or had not returned to the clinic after receiving the new information. Participants recounted varying experiences with the provision of prompt treatment. At an individual level, a history of treatment for opportunistic infections and other illnesses, coupled with relatively poor health, encouraged some to initiate ART promptly. However, knowledge of friends/relatives already on ART who had experienced side effects caused others to delay starting, fearing the same experience for themselves. A number of women questioned why they should start treatment when they were not sick. Situational factors such as work and residence (with many sharing single rooms) caused discomfort among newly diagnosed women who feared disclosure and stigma that would result from taking ART when they were not ill. Alcohol consumption and irregular working hours affected perceptions of future adherence, making prompt ART harder to embrace for some. Our findings show the challenges that influence the delay of treatment initiation, and/or the decision to defer receiving information on ART, with implications for the success of the test and treat programmes and guidelines.

Risk of major depressive disorder among older persons living in HIV-endemic central and southwestern Uganda. Kinyanda E, Kuteesa M, Scholten F, Mugisha J, Baisley K, Seeley J. *AIDS Care*. 2016 Jun 5:1-6. [Epub ahead of print]

Major depressive disorder (MDD) is projected to become the second most common cause of disability by 2020 calling for a better understanding its antecedents across the lifespan and in diverse socio-cultural settings. In this paper we describe the risk factors of MDD among older people (50 years +) living in HIV-endemic central and southwestern Uganda. A cross-sectional study was undertaken among 471 respondents (50 years +) participating in the Wellbeing of Older People's Study cohort of the MRC/UVRI Uganda research Unit on AIDS in Uganda. Participants were from five strata: HIV negative, HIV positive on ART, HIV positive not on ART, having an adult child on ART, and having an adult child who died of HIV. Overall MDD prevalence was 9.2% (95% CI 6.7-12.2%) with a prevalence among males of 7.4% (95% CI 4.0-12.3%) and females of 10.3% (95% CI 7.0-14.3%). Factors significantly associated with MDD included: declining socio-economic status, increasing disability scores, decreasing mean grip strength, reported back pain, and not having hypertension. Marginally associated with MDD was being HIV infected and not on ART.

Wekesa C, Asiki G, Kasamba I, Waswa L, Reynolds SJ, Nsubuga RN, Newton R, Kamali A.
Atherogenic Risk Assessment among Persons Living in Rural Uganda. *J Trop Med.* 2016;2016:7073894. doi: 10.1155/2016/7073894. Epub 2016 Jun 22.

Hypertension and dyslipidemia are independent risk factors for coronary heart disease and commonly coexist. Cardiovascular risk can be reliably predicted using lipid ratios such as the atherogenic index, a useful prognostic parameter for guiding timely interventions. Objective. We assessed the cardiovascular risk profile based on the atherogenic index of residents within a rural Ugandan cohort. Methods. In 2011, a population based survey was conducted among 7507 participants. Sociodemographic characteristics, physical measurements (blood pressure, weight, height, and waist and hip circumference), and blood sampling for non fasting lipid profile were collected for each participant. Atherogenic risk profile, defined as logarithm base ten of (triglyceride divided by high density lipoprotein cholesterol), was categorised as low risk (<0.1), intermediate risk (0.1-0.24), and high risk (>0.24). Results. Fifty-five percent of participants were female and the mean age was 49.9 years (SD ± 20.2). Forty-two percent of participants had high and intermediate atherogenic risk. Persons with hypertension, untreated HIV infection, abnormal glycaemia, and obesity and living in less urbanised villages were more at risk. Conclusion. A significant proportion of persons in this rural population are at risk of atherosclerosis. Key identified populations at risk should be considered for future intervention against cardiovascular related morbidity and mortality. The study however used parameters from unfasted samples that may have a bearing on observed results.

Asiki G, Reniers G, Newton R, Baisley K, Nakiyingi-Miiri J, Slaymaker E, Kasamba I, Seeley J, Todd J, Kaleebu P, Kamali A.
Adult life expectancy trends in the era of antiretroviral treatment in rural Uganda (1991-2012). *AIDS.* 2016 Jan 28;30(3):487-93. doi: 10.1097/QAD.0000000000000930.

OBJECTIVE:

To estimate the impact of antiretroviral therapy (ART) on population-wide adult life expectancy.

STUDY DESIGN:

A population-based open cohort study with repeated HIV status measurements and registration of vital events in Southwestern Uganda (1991-2012).

METHODS:

Nonparametric survival analysis techniques are used for estimating trends in the adult life expectancy of the general population (aged 15 and above), the adult life expectancy by HIV status, and the adult life expectancy deficit. The life expectancy deficit is estimated as the difference between overall life expectancy and life expectancy of the HIV-negative population. All estimates are disaggregated by sex.

RESULTS:

Between 1991-1993 and 2009-2012, population-wide adult life expectancy increased from 39.3 [95% confidence interval (CI): 35.9-42.8] to 56.1 years (95% CI: 54.0-58.5) in women, and

from 38.6 (95% CI: 35.4-42.1) to 51.4 years (95% CI: 49.2-53.7) in men. Most of the adult life expectancy gains coincide with the introduction of ART in 2004; as evidenced by an increase in the adult life expectancy of people living with HIV between 2000-2002 and 2009-2012 of 22.9 and 20.0 years for women and men, respectively. Over the whole period of observation, the adult life expectancy deficit associated with HIV decreased from 16.1 (95% CI: 12.7-19.8) to 6.0 years (95% CI: 4.1-7.8) among women, and from 16.0 (95% CI: 12.1-19.9) to 2.8 years (95% CI: 1.2-4.6) among men.

CONCLUSION:

Population-wide life expectancy increased substantially, largely driven by reductions in HIV-related mortality. Women have gained more adult life years than men since the introduction of ART, but the burden of HIV in terms of the life years lost is still larger for women than it is for men.

Heckerman D, Gurdasani D, Kadie C, Pomilla C, Carstensen T, Martin H, Ekoru K, Nsubuga RN, Ssenyomo G, Kamali A, Kaleebu P, Widmer C, Sandhu MS.

Linear mixed model for heritability estimation that explicitly addresses environmental variation. Proc Natl Acad Sci U S A. 2016 Jul 5;113(27):7377-82. doi: 10.1073/pnas.1510497113.

The linear mixed model (LMM) is now routinely used to estimate heritability. Unfortunately, as we demonstrate, LMM estimates of heritability can be inflated when using a standard model. To help reduce this inflation, we used a more general LMM with two random effects—one based on genomic variants and one based on easily measured spatial location as a proxy for environmental effects. We investigated this approach with simulated data and with data from a Uganda cohort of 4,778 individuals for 34 phenotypes including anthropometric indices, blood factors, glycemic control, blood pressure, lipid tests, and liver function tests. For the genomic random effect, we used identity-by-descent estimates from accurately phased genome-wide data. For the environmental random effect, we constructed a covariance matrix based on a Gaussian radial basis function. Across the simulated and Ugandan data, narrow-sense heritability estimates were lower using the more general model. Thus, our approach addresses, in part, the issue of "missing heritability" in the sense that much of the heritability previously thought to be missing was fictional. Software is available at <https://github.com/MicrosoftGenomics/FaST-LMM>.

Mbonye M, Siu GE, Kiwanuka T, Seeley J.

Relationship dynamics and sexual risk behaviour of male partners of female sex workers in Kampala, Uganda. Afr J AIDS Res. 2016 Jul;15(2):149-55. doi: 10.2989/16085906.2016.1197134.

Regular male partners of female sex workers (FSWs) represent an important population to reach with HIV-prevention interventions. This paper discusses the relationship dynamics and HIV/sexually transmitted infection risk behaviour of men involved with self-identified FSWs in Kampala. Between 2011 and 2014 we conducted repeat in-depth interviews with 42 male partners of FSWs attending a clinic for women at high risk of HIV-infection in Kampala. Men publicly struggled with the stigma of dating women who are considered to be engaged in a shamed profession, but privately saw meaning in these relationships. In coping with the stigma, some described the work of their partners in terms that distanced them from sex work, while others struggled to have the control that "being a man"

demanded since they could not monitor all movements of their partners. Dealing with HIV disclosure was hard and seeking support was difficult for some of the men, leading to missed opportunities and guilt. Despite challenges, relationships with sex workers offered men some benefits such as access to much needed care and treatment. A few men also admitted to being motivated by material and financial benefits from sex workers who they perceived as being rich and this was one factor that helped them sustain the relationships. These findings offer insights into the complex relationship dynamics within high risk sexual partnerships. However, the findings suggest that effective interventions that are couple centered can be established to promote better health.

Mbonye M, Kuteesa M, Seeley J, Levin J, Weiss H, Kamali A.

Voluntary medical male circumcision for HIV prevention in fishing communities in Uganda: the influence of local beliefs and practice. *Afr J AIDS Res.* 2016 Jul 22:1-8. [Epub ahead of print]

Local beliefs and practices about voluntary medical male circumcision (VMMC) may influence uptake and effectiveness. Data were gathered through interviews with 40 people from four ethnically mixed fishing communities in Uganda. Some men believed that wound healing could be promoted by contact with vaginal fluids while sex with non-regular partners could chase away spirits - practices which encouraged unsafe sexual practices. Information given by providers stressed that VMMC did not afford complete protection from sexually-transmitted infections, however, a number of male community members held the view that they were fully protected once circumcised. Both men and women said that VMMC was good not just for HIV prevention but also as a way of maintaining hygiene among the men. The implementation of VMMC in high-HIV prevalence settings needs to take account of local beliefs about circumcision, working with local religious/social group leaders, women and peers in the roll-out of the intervention.
