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SATuRN & BioAfrica Newsletter

Southern Africa Treatment and Resistance Network

Introduction:

The concept behind this newsletter is that anyone with 15 minutes to spare can learn about the work of SATuRN and our Biofrica research group

The newsletter is presented as a PDF document with links to complete articles at bioafrica.net. In our third issue of 2064, we would like to bring attention to our participation in the AIDS 2016 conference and our AWACC and CAPRISA clinical care training program in KwaZulu-Natal.

We have also included interesting news, blogs, reports, tweets, publications and training information produced by our network

Produced by: Tulio de Oliveira, Henry Sunpath, Yunus Moosa, Justen Manasa, Gillian Hunt, Jennifer Giandhari.

Highlights:

Workshop: Annual Workshop on Advanced Clinical Care (AWACC), Durban, 9-10 October 2016.

PhD position x2 : DST Professional development program (PDP) PhD Fellowship at SATuRN & CAPRISA in HIV-1 Drug Resistance and HIV-1 Phylogenetic analysis

Publication: Contribution of Gag and Protease to HIV-1 Phenotypic Drug Resistance in Pediatric Patients Failing Protease Inhibitor-Based Therapy

Publication: HIV drug resistance levels in adults failing first-line antiretroviral therapy in an urban and a rural setting in South Africa

News: South Africa's bid to end AIDS & Social cycle aids HIV spread

Brief: News & Publications on Rural vs Urban HIV Drug Resistance

First two South African MSc students graduate from the MRC Flagship Program: Inspiring blogs about their experiences and achievements

"Megan Druce and Sthembiso Msweli are two very bright South Africans who have successfully completed their MSc as part of the UKZN Flagship program at the MRC. They both wrote inspiring blogs, the first is about a Cum Laude degree which allowed the award of a scholarship for a PhD in Germany, the second is about the history of a laboratory technologist from rural KZN, who after graduating was promoted to laboratory manager."

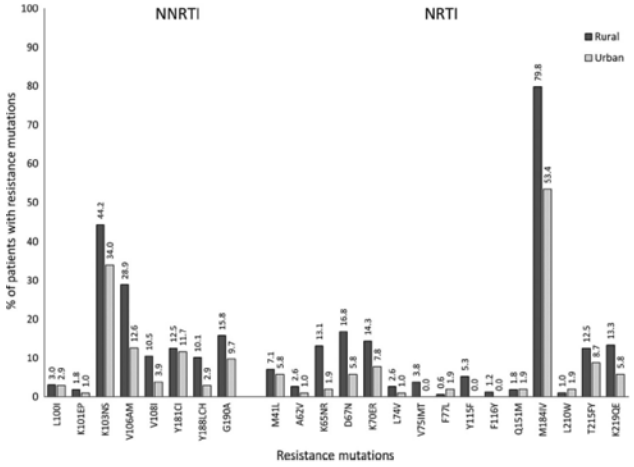
Link: http://bioafrica.net/news.php?id=151

Prof. Tulio de Oliveira is elected president of the South African Society for Bioinformatics (SASBi)

"Professor Tulio de Oliveira, Nelson R Mandela School of Medicine, University of KwaZulu-Natal, was elected the president of SASBi from 2016-2018"

Link: http://bioafrica.net/peoplephp?peopleid=1

Publication: HIV drug resistance levels in adults failing first-line antiretroviral therapy in an urban and a rural setting in South Africa



Objectives: Urban and rural HIV treatment programmes face different challenges in the long-term management of patients. There are few studies comparing drug resistance profiles in patients accessing treatment through these programmes.

Link: bioafrica.net/publications.php?pubid=126

Results: Data for 595 patients were analysed: 492 patients from a rural setting and 103 patients from an urban setting. The urban group had lower CD4 counts at treatment initiation than the rural group (98 vs. 126 cells/lL, respectively; P = 0.05), had more viral load measurements performed per year (median 3 vs. 1.4, respectively; P < 0.01) and were more likely to have no drug resistance mutations detected (35.9% vs. 11.2%, respectively; P < 0.01). Patients in the rural group were more likely to have been on first-line treatment for a longer period, to have failed for longer, and to have thymidine analogue mutations.

Conclusions: The frequency and patterns of drug resistance differed between the urban and rural sites. Despite these differences, based on the genotypic susceptibility scores, the majority of patients across the two sites would be expected to respond well to the standard second-line regimen.

News: Social cycle aids HIV spread

Nature (Vol. 535, pp. 335, 2016) report our recent results on the use of genetic sequences to uncover HIV-1 transmission patterns in young woman in South Africa (de Oliveira et al. Lancet HIV 2016). The paper was presented as a Keynote at AIDS 2016 conference.

Sex between young women and older men is no secret in South Africa. The name 'blesser' is commonly used to describe a man who may at first pay for a teenager's bus fare to high school, then buy school supplies she cannot afford, and perhaps lunch at a decent cafe. Over time, the adolescent sleeps with her provider.

A genetic analysis, lead by Prof. Tulio de Oliveira, now suggests how this social phenomenon plays into the cycle of HIV transmission in the country, which has the world's largest HIV epidemic. By analysing the similarity of viral genetic sequences from nearly 1,600 people with HIV in one community in KwaZulu-Natal, the study shows that adolescent girls and women in their early 20s tend to pick up the virus from men aged around 30. When the women grow older, they go on to infect their long-term partners, who in turn may pass the virus on through affairs with younger women.

This is the engine driving high rates of HIV, says epidemiologist Salim Abdool Karim, senior author of the study and director of the Centre for the AIDS

Researchers have long known of the high burden of HIV infections in young South African women, and that they get infected by older men, says ***Thomas Quinn, an epidemiologist at Johns Hopkins Bloomberg School of Public Health*** in Baltimore, Maryland, who was not involved in the study. But, he says, ***'it is very exciting to use molecular genetic information to actually show how the virus spreads among people'*** ' and to pinpoint the ages of women and men at key points in the cycle of HIV transmission.

Link: http://www.bioafrica.net/news.php?id=156

CAPRISA

CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

DST-NRF PROFESSIONAL DEVELOPMENT PROGRAM (PDP) PHD FELLOWSHIP IN

Genomics, Bioinformatics & Drug Resistance

Mentors:

Prof. Tulio de Oliveira: Research Associate CAPRISA, Professor UKZN

Dr Kogie Naidoo: Head Treatment Research Programme, CAPRISA

The PDP Programme at CAPRISA aims to develop and retain South African scientists and professionals of the highest calibre. The genomics and bioinformatics project is inter-disciplinary and involves collaboration between the CAPRISA – MRC HIV-TB Pathogenesis and Treatment Research Unit and the Flagship Program of the MRC, which are two of the most prestigious research programs in South Africa.

This PhD programme optimally exemplifies how genomics, clinical and bioinformatics information can directly and immediately impact human health in Africa. The project aims to identify factors associated with HIV-1 drug resistance in patients failing antiretroviral therapy (ART). By focusing on the application of Next Generation Sequencing (NGS) to produce whole genomes of the virus, researchers aim to identify new viral mutations associated with drug resistance. This could guide future drug regimens and provide further insight into patients failing ART-based therapy.

The programme aims to:

- Characterise the clinical and genetic causes of acquired drug resistance using a multi-disciplinary analysis approach.
- Determine the frequency of drug resistance–associated mutations in the whole genome, including minority population level.
- Use genome wide association studies (GWAS) to identify novel mutations which are associated with ART failure.
- Formulate strategies to prevent and manage drug resistance.

As part of the PhD the student will receive hands-on laboratory experience in NGS and Bioinformatics.

The PhD fellow will be awarded a fellowship stipend of ZAR 180,000 per annum. Applications are invited from South African or permanent resident students. Please submit a CV and a letter of motivation (max. 500 words) by 20 October 2016 to sma.mzobe@caprisa.org

CAPRISA hosts a DST-NRF Centre of Excellence in HIV Prevention

CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy

CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit

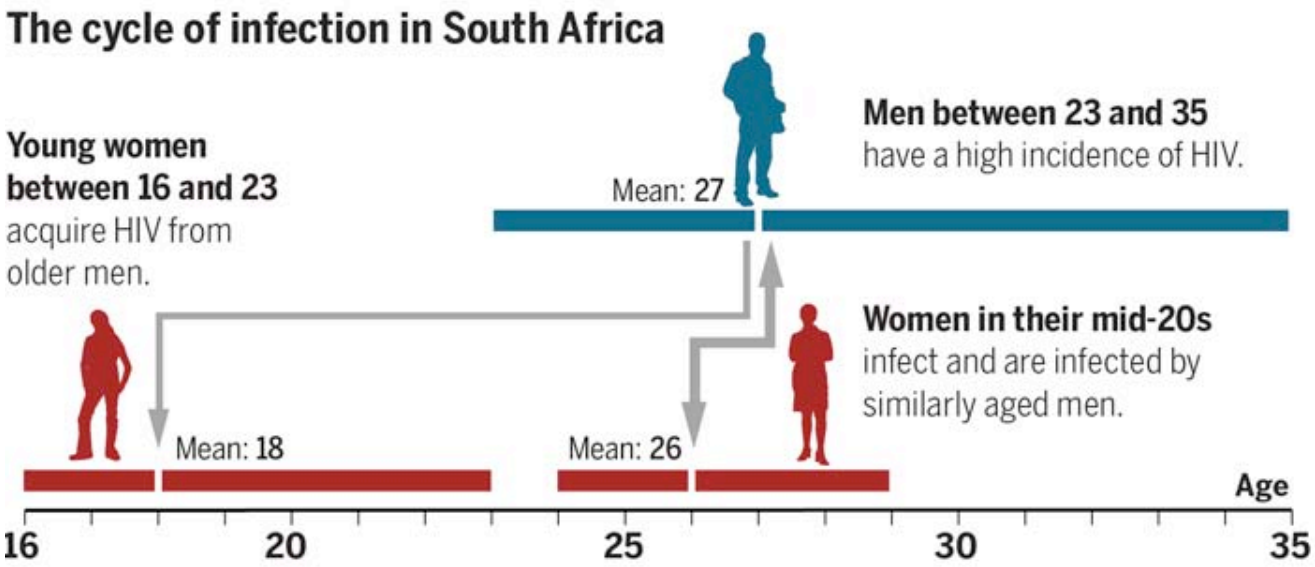
Partner Institutions: University of KwaZulu-Natal, Inyuvesi YaKwaZulu-Natali; Columbia University Mailman School of Public Health; National Institute for Communicable Diseases; University of Cape Town

www.caprisa.org & www.bioafrica.net

Dates: 6 and 7 October 2016

Venue: Durban International Conference Centre (ICC)

News: South Africa's bid to end AIDS & The cycle of infection in South Africa



Science magazine (Vol. 353, Issue 6294, pp. 18-21, 2016). This issue was published before the AIDS conference in Durban 2016 and highlights some of our research, including our treatment as prevention trial (TasP) as well our phylogenetic analysis.

To understand the pattern of viral spread, CAPRISA and Prof. Tulio de Oliveira team at Africa Centre mapped out the infection cycle between men and women of different ages in KwaZulu-Natal. The study analyzed the genetic sequences of HIV isolated from 858 men and women, all between 16 and 35 years old, who belonged to the same sexual networks. The viral genetics linked different isolates and indicated which ones were older, allowing the researchers to infer who infected whom. Teenage girls were infected by men who were, on average, 8 years older. After the age of 24, people typically became infected by partners their own age, with transmission more frequently moving from woman to man. 'They are trying to find lifetime partners at this age,' Karim says. These older men are the same group having sex with the youngest women. 'We have to break the chain between men in their late 20s and teen girls,' he says.

In the infection-cycle study, men who infected younger women had extremely high HIV levels, indicating they recently acquired the virus and thus would not appear infected on standard antibody-based tests.

'If your strategy is to test and treat these people, you're not going to catch them,' Karim says. Men are also less connected to the health care system and often migrate for work, he adds, making it more difficult to help those who know they are infected fully suppress the virus. Giving PrEP to young women sidesteps the male dilemma. 'We just have to protect girls for 5 years in that critical risk period until they find their partners,' he says.

Link: http://www.bioafrica.net/news.php?id=155

News: Open Access Publication

Contribution of Gag and Protease to HIV-1 Phenotypic Drug Resistance in Pediatric Patients Failing Protease Inhibitor-Based Therapy

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Protease inhibitors (PIs) are used as a first-line regimen in HIV-1-infected children. Here we investigated the phenotypic consequences of amino acid changes in Gag and protease on lopinavir (LPV) and ritonavir (RTV) susceptibility among pediatric patients failing PI therapy. The Gag-protease from isolates from 20 HIV-1 subtype C-infected pediatric patients failing an LPV and/or RTV-based regimen was phenotyped using a nonreplicative *in vitro* assay. Changes in sensitivity to LPV and RTV relative to that of the matched baseline (pretherapy) sample were calculated. Gag and protease amino acid substitutions associated with PI failure were created in a reference clone by site-directed mutagenesis and assessed. Predicted phenotypes were determined using the Stanford drug resistance algorithm. Phenotypic resistance or reduced susceptibility to RTV and/or LPV was observed in isolates from 10 (50%) patients, all of whom had been treated with RTV. In most cases, this was associated with protease resistance mutations, but substitutions at Gag cleavage and noncleavage sites were also detected. Gag amino acid substitutions were also found in isolates from three patients with reduced drug susceptibilities who had wild-type protease. Site-directed mutagenesis confirmed that some amino acid changes in Gag contributed to PI resistance but only in the presence of major protease resistance-associated substitutions. The isolates from all patients who received LPV exclusively were phenotypically susceptible. Baseline isolates from the 20 patients showed a large (47-fold) range in the 50% effective concentration of LPV, which accounted for most of the discordance seen between the experimentally determined and the predicted phenotypes. Overall, the inclusion of the *gag* gene and the use of matched baseline samples provided a more comprehensive assessment of the effect of PI-induced amino acid changes on PI resistance. The lack of phenotypic resistance to LPV supports the continued use of this drug in pediatric patients.

Protease inhibitors (PIs) are potent antiretroviral drugs which inhibit the function of the HIV-1 protease enzyme, thereby preventing viral maturation (1). In South Africa, the use of ritonavir (RTV)-boosted lopinavir (LPV/r) is recommended as a first-line regimen for pediatric patients <3 years of age and as a second-line regimen for adults and older children (2). Prior to 2008, RTV was used as a single PI in infants <6 months of age and also for those receiving rifampin for the cotreatment of tuberculosis (3, 4). It is estimated that over half a million HIV-1-infected infants are being treated with PIs, and 140,000 of these infants reside in South Africa (5). Current guidelines recommend treatment of infants immediately upon a diagnosis of HIV infection, and treatment according to these guidelines has been associated with good clinical outcomes (6, 7). Nevertheless, an analysis of children treated in South Africa showed that the probability of virological suppression at age 12 months was only 56% (8). This may be due to the higher viral loads and challenges associated with accurate dosing in infants, placing them at a potentially greater risk for developing PI drug resistance than adult patients (9).

Resistance to PIs is characterized by the gradual accumulation of major mutations in the protease gene, including M46I, I54V, and V82A, as well as accessory mutations that can enhance resistance but appear to have no effect individually (10). However, many adults and children fail PI-based therapies in the absence of any protease resistance-associated amino acid substitutions (11–13). While such cases are often attributed to poor adherence, it has been suggested that regions outside protease may contribute to PI resistance (1, 9, 14–16). HIV-1 protease recognizes and cleaves the Gag and Gag-Pol polyproteins at specific cleavage sites (CSs) to produce infectious virions. Since PIs inhibit the cleavage of viral proteins, this prevents the formation of mature infectious particles (17). PI resistance mutations on their own reduce viral fitness; however, amino acid substitutions at the Gag CS and non-CS that restore viral fitness in the presence of protease sub-

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Supplemental material for this article may be found at http://dx.doi.org/10.1128/AAC.02682-15.

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SATuRN's partners featured publications!

Contribution of Gag and Protease to HIV-1 Phenotypic Drug Resistance in Pediatric Patients Failing Protease Inhibitor-Based Therapy.
Giandhari J, Basson AE, Sutherland K, Parry CM, Cane PA, Coovadia A, Kuhn L, Hunt G, Morris L, Antimicrob Agents Chemother. (2016), 60(4):2248-56.

HIV drug resistance levels in adults failing first-line antiretroviral therapy in an urban and a rural setting in South Africa.
Rossouw TM, Nieuwoudt M, Manasa J, Malherbe G, Lessells RJ, Pillay S, Danaviah S, Mahasha P, van Dyk G, de Oliveira T, HIV Med. (2016), 2016 :doi: 10.1111/hiv.12400.

Origin, imports and exports of HIV-1 subtype C in South Africa: A historical perspective.
Wilkinson E, Rasmussen D, Ratmann O, Stadler T, Engelbrecht S, de Oliveira T, Infection, Genetics and Evolution (2016), S1567-1348(16)30298-2:doi: 10.1016/j.meegid.2016.07.008.

Training course title, location and date

Oct 2016 **Annual Workshop on Advanced Clinical Care - AIDS (AWACC) & SATuRN workshop 2016,** International Convention Centre (ICC), Durban, South Africa, 6 and 7 October 2016.

For more information on how to participate in SATuRN activities please contact:

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