SATuRN: Newsletter

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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

The newsletter is presented as a PDF document with links to complete articles at the bioafricanet website. In our first issue of 2014 our newsletter we focus on our **new seminar series and publications & results from SATURN partners.**

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

Produced by: Tulio de Oliveira, Tobias Rinke de Wit, Justen Manasa, Siva Danaviah, Gillian Hunt, Lynn Morris, Jose Ijedema & Chris Seebregts

bioafrica.net/saturn

Highlights:

Seminar: Prof. Peter Piot (LSHTM) - Old and new challenges for HIV control

Seminar: Dr. Like Daum (Texas) - Next-generation sequencing for identifying drug resistance in Mycobacterium Tuberculosis

Publication: Sensitive TDF Resistance Screening of HIV-1 From the Genital and Blood Compartments of Women With Breakthrough Infections in the CAPRISA 004 TDF Gel Trial

CROI: Favorable Long-term Outcomes of 2nd-line ART Despite Drug-Resistant HIV-1 in Sub-Saharan Africa: PASER-M cohort

Video: HIV-1 Drug Resistance in Children in rural South Africa

Workshop: Bioinformatics in the Tropics IV, 29 May to 1 June 2014, Fiocruz, Salvador, Brazil

Brief: News, Blogs & Videos on our work and collaborators

News: Bioinformatics in the Tropics Brazil 2014, FioCruz, Salvador, Brazil, 29 May to 1 June 2014

FioCruz - 2014-03-19

"This is a series of four workshops, which will be presented in Brazil (2013 & 2014), South Africa (2013) and Uganda (2014) as part of a south to south capacity building programme in Africa and Latin America. The objective is to train post-doctoral researchers to become trainers and post-graduate students to use bioinformatics software applications.."

Link: http://www.bioafrica.net/bioinformaticsworkshop.html

Video: HIV-1 Drug Resistance in Children in rural South Africa

Siva Danaviah - 2014-03-01

"In a short interview, Dr. Siva Danaviah describes drug resistance patterns in HIV-infected children on antiretroviral therapy (ART) and its impact to inform public health policies in high prevalence settings. The aim of this study was to characterise the acquired drug resistance in HIV-infected children failing first-line ART in a decentralised rural HIV program in South Africa."

Link: http://www.bioafrica.net/videos.php?id=20

News: Interactive Biostatistics Course, Durban, 26-30 may 2014

K-RITH- 2013-03-03

"K-RITH is offering an innovative course in the biostatistical methods used in medical research. This hands-on course is taught by Harvard biostatistician, Dr. Lori Chibnik. Participants will apply these techniques to their own research. Better understand results presented in medical literature."

Link: http://bioafrica.net/news.php?id=110

Video: HIV-1 Drug Resistance a PhD thesis summary

Justen Manasa – 2014-01-29

"This is a 8 minutes video that summarizes the PhD thesis of Justen Manasa. This video cover the affordable and open accessible SATuRN/Life Tech genotyping method, SATuRN data curation process using RegaDB and a number of manuscripts on transmitted and acquired resistance in rural South Africa"

Link: http://www.bioafrica.net/videos.php?id=18

Blog: Twitter Q&A on HIV drug resistance in Africa

Tulio de Oliveira - 2014-01-15

"For the sake of interaction with the greater community, we decided to circulate the paper on twitter and ask for questions. We asked for Internet users to identify their questions with the HashTag: #HIVDRAfrica. We had received and answered many interesting questions. We had fun answering the questions and interacting with our audience!"

Link: http://www.bioafrica.net/blogs.php?id=32

Seminars: Five monthly seminars in KZN!

Our seminars are presented in Durban at the Nelson R Mandela School of Medicine and at Africa Centre headquarters in Mtubatuba. These seminars are open to the public. Please attend our seminars, they are really interesting, fun and interactive.

Link:
http://www.bioafrica.net/seminars.php

Latest seminars:

Prof. Peter Piot (Director of London School of Hygiene and Tropical Medicine) -- Old and new challenges for HIV control – 1st Apr 2014, Mtubatuba.

Link: http://www.bioafrica.net/news.php?id=112

Dr Luke Daum, (University of Texas / LongHorn Vaccines & Diagnostics) - Next-generation sequencing for identifying drug resistance in Mycobacterium Tuberculosis - 28 March 2014, Durban

Link: http://www.bioafrica.net/news.php?id=104

Dr. Eduan Wilkinson, (Africa Centre / UKZN) - HIV-1 Transmission during Early Infection in Men Who Have Sex with Men: A Phylodynamic Analysis - 19 February 2014, Mtubatuba

Link: http://www.bioafrica.net/news.php?id=106

Prof. Susan Engelbrecht, (Stellenbosch University / Tygerberg NHLS) - 30 years of HIV diversity research: a personal perspective - 31 January 2014, Durban

Link: http://www.bioafrica.net/news.php?id=105

Database, Vol. 2014, Article ID bat082, doi:10.1093/database/bat082

Original article

Southern African Treatment Resistance Network (SATuRN) RegaDB HIV drug resistance and clinical management database: supporting patient management, surveillance and research in southern Africa

Justen Manasa[1], Richard Lessells[1,2], Theresa Rossouw[3], Kevindra Naidu[1], Cloete Van Vuuren[4], Dominique Goedhals[4], Gert van Zyl[5,6], Armand Bester[4], Andrew Skingsley[1], Katharine Stott[1], Siva Danaviah[1], Terusha Chetty[1], Lavanya Singh[7], Pravi Moodley[7], Collins Iwuji[1,8], Nuala McGrath[1,9], Christopher J. Seebregts[10,11] and Tulio de Oliveira[1,12,*]

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Substantial amounts of data have been generated from patient management and academic exercises designed to better understand the human immunodeficiency virus (HIV) epidemic and design interventions to control it. A number of specialized databases have been designed to manage huge data sets from HIV cohort, vaccine, host genomic and drug resistance studies. Besides databases from cohort studies, most of the online databases contain limited curated data and are thus sequence repositories. HIV drug resistance has been shown to have a great potential to derail the progress made thus far through antiretroviral therapy. Thus, a lot of resources have been invested in generating drug resistance data for patient management and surveillance purposes. Unfortunately, most of the data currently available relate to subtype B even though >60% of the epidemic is caused by HIV-1 subtype C. A consortium of clinicians, scientists, public health experts and policy markers working in southern Africa came together and formed a network, the Southern African Treatment and Resistance Network (SATuRN), with the aim of increasing curated HIV-1 subtype C and tuberculosis drug resistance data. This article describes the HIV-1 data curation process using the SATuRN Rega database. The data curation is a manual and time-consuming process done by clinical, laboratory and data curation specialists. Access to the highly curated data sets is through applications that are reviewed by the SATuRN executive committee. Examples of research outputs from the analysis of the curated data include trends in the level of transmitted drug resistance in South Africa, analysis of the levels of acquired resistance among patients failing therapy and factors associated with the absence of genotypic evidence of drug resistance among patients failing therapy. All these studies have been important for informing first- and second-line therapy. This database is a free password-protected open source database available on www.bioafrica.net.

Database URL: http://www.bioafrica.net/regadb/

BRIEF REPORT

Sensitive Tenofovir Resistance Screening of HIV-1 From the Genital and Blood Compartments of Women With Breakthrough Infections in the CAPRISA 004 Tenofovir Gel Trial

Xierong Wei,[1] Gillian Hunt,[4] Salim S. Abdool Karim,[2,6] Vivek Naranbhai,[6] Sengeziwe Sibeko,[6] Quarraisha Abdool Karim,[2,6] Jin-fen Li,[1] Angela D. M. Kashuba,[3] Lise Werner,[6] Jo-Ann S. Passmore,[5,6] Lynn Morris,[4] Walid Heneine,[1] and Jeffrey A. Johnson[1]

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The Centre for the AIDS Programme of Research in South Africa 004 (CAPRISA 004) study demonstrated that vaginally applied tenofovir gel is a promising intervention for protecting women from sexually acquiring human immunodeficiency virus (HIV). However, the potential for emergence of tenofovir resistance remains a concern in women who seroconvert while using the gel despite the lack of plasma virus resistance as assessed by population sequencing during the trial. We applied highly sensitive polymerase chain reaction–based assays to screen for tenofovir resistance in plasma and vaginal swab specimens. The absence of mutation detection suggested little immediate risk of tenofovir-resistant HIV-1 emergence and forward transmission in settings in which gel users are closely monitored for HIV seroconversion.

Keywords. Vaginal microbicide; HIV prevention; preexposure prophylaxis; tenofovir gel; topical PrEP.

Globally, women are disproportionately affected by human immunodeficiency virus (HIV) infection and the availability of efficacious female-controlled products for preventing virus acquisition is essential to alleviating this burden. In the wake of several trials of barrier microbicides that demonstrated no protection against HIV, vaginal microbicides containing antiretroviral drugs have become leading candidates for the prevention of HIV sexual transmission in women. The Centre for the AIDS Programme of Research in South Africa 004 trial (CAPRISA 004) assessed the efficacy of 1% tenofovir gel in sexually active women and identified a 39% lower HIV incidence in the tenofovir gel arm compared with the placebo arm, an effective incidence rate ratio of 0.61 (confidence interval, .4–.94; $P = .02$) [1]. Subsequent examination of vaginal aspirates with quantifiable tenofovir concentrations found that seroconversion in the tenofovir gel arm was associated with a lower tenofovir concentration geometric mean (634.85 ng/mL) than in women who remained protected (7582.76 ng/mL; $P = .09$ [t test]).

As with any intervention involving antiretroviral drugs, emergence of drug resistance is a concern. Trace concentrations of tenofovir can be detected in vaginal aspirates up to 30 days after gel application; thus, the long suboptimal tenofovir tail may provide an environment for transmitted virus to develop drug resistance. In the primary CAPRISA 004 data analysis [1], bulk sequence genotyping of tenofovir gel breakthrough infections identified no drug resistance in plasma virus several months after seroconversion. However, there were limitations to this resistance analysis. Foremost, the time since seroconversion and, hence, drug exposure was approximately 5 months, which may have been sufficiently long to allow for resistance to decay below detection by population genotyping. Moreover, topically applied drug remains concentrated in the vaginal compartment with little systemic exposure. Therefore, drug pressure may not have been sufficient for resistance mutations to emerge or become detectable in the peripheral circulation when examined by bulk sequencing.

In this study, we applied polymerase chain reaction (PCR)–based mutation screening assays with improved sensitivity to reexamine HIV seroconverters in the CAPRISA 004 trial for evidence of tenofovir drug resistance in plasma virus that might have emerged at levels below what could be detected by bulk sequence analysis. Moreover, we evaluated whether virus colocalized with tenofovir gel in the vaginal compartment might result in higher levels of the K65R resistance mutation than what was observed for plasma. The combination of assays with improved sensitivity for mutation detection, analysis of samples collected closer to the time of gel use and seroconversion, and examination of HIV in the vaginal compartment afforded a more rigorous assessment of both drug resistance transmission and emergence in this tenofovir vaginal gel trial.

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Favorable Long-term Outcomes of 2nd-line ART Despite Drug-Resistant HIV-1 in Sub-Saharan Africa

PASER-M cohort

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keywords
Drug Resistance
Second-line Antiretroviral Treatment
sub-Saharan Africa

background

- With the expansion of antiretroviral therapy (ART) in resource-limited settings, the number of people with treatment failure and need for 2nd-line regimens will increase.
- We assessed the long-term effectiveness of boosted protease inhibitor (bPI)-based 2nd-line ART in 13 African settings, in patients with and without extensive nucleoside reverse transcriptase inhibitor (NRTI) resistance mutations at the time of regimen switch.
- Additionally, we explored the accumulation of protease resistance mutations.

methodology

- In a prospective observational cohort, HIV-RNA and genotypic resistance testing was performed in adults who switched to bPI-based 2nd-line regimens at 13 clinical sites in Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe.
- Genotypic sensitivity score (GSS) was calculated using the Stanford algorithm.
- Associations between mutations present at the time of switch and virological failure (VF) after 12 or 24 months of ART were assessed using chi-square and Fisher's exact tests using Stata 12.

results

Figure 1 & Table 1

- Of 243 patients who started 2nd-line ART, 54% harbored drug resistant HIV with a GSS < 3, leading to a partially active 2nd-line regimen. After 12 and 24 months, 88% and 79% of patients were retained in care, respectively
- After 12 months, 29 out of 206 (14%) patients with available viral load (VL) had VF, compared to 27 out of 177 (15%) after 24 months (p=0.745).
- Of 29 patients with VF at 12 months, 10 (35%) also had VF at 24 months, 10 (35%) were re-suppressed, and the remainder was lost to follow-up, died or switched to 3rd-line ART.
- A partially active 2nd-line regimen at the time of switch was not significantly associated with VF at 12 or 24 months of follow-up (p=0.586 and p=0.897, respectively).
- At 12 and 24 months, 53% and 75% of patients with genotypic test results harbored drug resistant HIV, respectively.

Table 2

- Protease mutations increased over time and were present in 1 (6%) and 6 (30%; p=0.097) sequences after 12 and 24 months of bPI-based 2nd-line ART.
- There was no accumulation of thymidine analogue mutations (TAMs).
- Protease mutations were M46I (n=5), V82A (n=4), L76V (n=2) and I84V (n=1), and occurred in combination with NRTI mutations in all occasions (p=0.042).
- A partially active regimen at the time of switch was not significantly associated with protease resistance development (p=0.354).

conclusions

- **Favorable virological response to 2nd-line bPI-based ART was maintained over 2 years, despite extensive NRTI resistance at the time of switch.**
- **While still infrequent by month 24, increasing protease resistance over time may become a barrier to successful long-term bPI-based ART in resource-limited settings.**

Twitter: SATuRN has a very active YouTube Channel and Twitter

SATuRN YouTube channel:

In these new sections of the bioafrica.net and YouTube websites, we disseminate videos of our work and its application in everyday life

Links:

http://www.youtube.com/bioafricaSATURN

http://www.bioafrica.net/videos.php

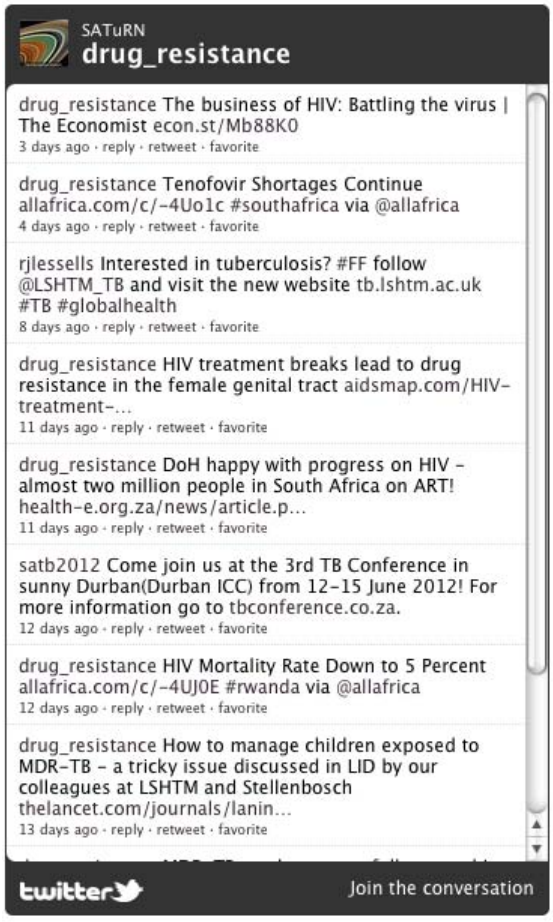
SATuRN Twitter Account:

SATuRN has a very active twitter account. In addition, collaborators have tweeted at HIV & TB drug resistance events and conferences around the globe…

Links:

http://www.twitter.com/drug_resistance

http://www.bioafrica.net/



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OPEN ACCESS

SATuRN's partners featured publications!

Sensitive Tenofovir Resistance Screening of HIV-1 From the Genital and Blood Compartments of Women With Breakthrough Infections in the CAPRISA 004 Tenofovir Gel Trial.
Wei X, Hunt G, Abdool Karim SS, Naranbhai V, Sibeko S, Abdool Karim Q, Li JF, Kashuba AD, Werner L, Passmore JA, Morris L, Heneine W, Johnson JA. J Infect Dis. 2014 Feb 11. [Epub ahead of print]

Implementing antiretroviral resistance testing in a primary health care HIV treatment programme in rural KwaZulu-Natal, South Africa: early experiences, achievements and challenges
Lessells RJ, Stott KE, Manasa J, Naidu KK, Skingsley A, Rossouw T, de Oliveira T, BMC Health Services Research (2014), 14:116:doi:10.1186/1472-6963-14-116.

Drug resistance in children at virological failure in a rural KwaZulu-Natal, South Africa, cohort
Pillay S, Bland RM, Lessells RJ, Manasa J, de Oliveira T, Danaviah S., AIDS Res Ther. (2014), 11(1):3. doi: 10.1186/1742-6405-11-3

Training course title, location and date

Apr 2014	**Bioinformatics in the Tropics - Uganda 2014,** Uganda Virus Research Institute, Entebbe, Uganda, 7th to 10th April 2014
May 2014	**Bioinformatics in the Tropics – Brazil 2014,** FioCruz, Salvador, Brazil, 29 May to 1at June 2014
Sep 2014	**19th International Bioinformatics Workshop on Virus Evolution and Molecular Epidemiology** National Institute for Infectious Diseases "L Spallanzani", Rome, Italy, September 7-12, 2014

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

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