CAPRISA
CENTRE FOR THE AIDS PROGRAMME OF RESEARCH IN SOUTH AFRICA

Newsletter

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Genetics affects moxifloxacin PK in South African tuberculosis patients

Results from the CAPRISA 011 study known as IMPRESS (**Impr**oving Retreatment Suc**cess**) trial, showing that genetic variability affects the way that moxifloxacin is metabolised, were recently published in the journal *Pharmacogenomics*.

Moxifloxacin is recommended by the World Health Organisation for the treatment of multi-drug resistant (MDR) TB and is emerging as a key drug in the development of novel shorter rifampicin-sparing drug regimens for the treatment of both drug susceptible and MDR-TB. Moxifloxacin is metabolized by uridine-diphosphate glucuronosyltransferases enzymes and is a substrate of the multi-drug transporter P-glycoprotein, coded for by the UGT1A and ABCB1 genes.

This study set out to assess the effect of genetic variation in drug metabolising and transporter enzymes on TB drug concentrations and pharmacokinetics (PK). Specifically, the prevalence and effect of genetic variability in UGT1A and ABCB1 genes on moxifloxacin PK was assessed.

This study showed that there was extensive genetic variability in UGT1A and ABCB1 in this population and the data adds to the current evidence of genetic variants having PK relevance among Africans.

Genotypes of UGT1A single nucleotide polymorphisms (SNP's), (rs8175347 and rs3755319) and ABCB1 SNP rs2032582 were significantly associated with changes in moxifloxacin PK parameters. Participants with TA 5/6 repeats for rs8175347 SNP had ~21% reduced clearance and 26% higher area under the concentration-time curve (AUC) when compared to TA 6/6, 6/7 and 7/8 repeats (p=0.001). Individuals with AC or AA genotype for rs3755319 had ~12% higher moxifloxacin clearance, and thus lower AUC levels compared to individuals with the CC genotype (Figure).

Participants with the CA genotype of the ABCB1 SNP rs2032582 were found to associate with 40% reduced pre-hepatic bioavailability and thus lower AUC (p= 0.01)

Clinical relevance of the effects of genetic variation on moxifloxacin PK and exposure requires further investigation. However, given that moxifloxacin exhibits concentration-dependant bactericidal activity, changes in drug concentrations are likely to impact TB treatment efficacy and outcomes.

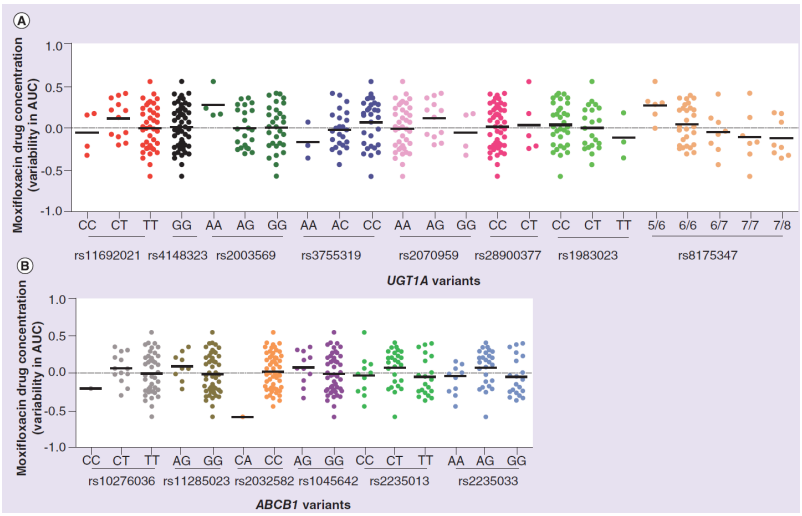

Figure: *Distributions of (A) UGT1A and (B) ABCB1 genotypes using variability in mean moxifloxacin concentration (AUC)* *μg · h/ml from the base nonlinear mixed-effects model*

For further reading see: Naidoo A, et al. Effect of genetic variation in UGT1A and ABCB1 on moxifloxacin pharmacokinetics in South African patients with tuberculosis. Pharmacogenomics 2018; 19(1):17-29.

In this Issue

Our feature story this month focuses on the pharmacogenetic study to determine the effect of genetic variation in drug metabolising and transporter enzymes on TB drug concentrations and pharmacokinetics.

On page 2 we report on the scaling up of TB HIV integration in Primary Health Care clinics in two rural districts in KwaZulu-Natal and, the Grant and manuscript writing workshop funded by the NIH.

We congratulate Kate Simeon as the recipient of the Lancet-CUGH Best Student poster award; we report on Nonhlanhla Yende-Zuma's poster presentation at CROI and congratulate the head of CAPRISA Laboratories on her appointment to the Executive committee of SACRA on page 3.

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Scaling up TB HIV integration in primary health care clinics

(L-R) Regina Mlobeli (Study Coordinator, CAPRISA) Taruna Chetty (Research Fellow, CAPRISA), Maureen Tshabalala (QI Advisor, IHI) Kogie Naidoo (SUTHI Principal Investigator, CAPRISA) Santhana Gengiah (Study Coordinator, CAPRISA)

The CAPRISA 013 study is testing the effectiveness of a Quality Improvement model to integrate TB and HIV services in Primary Health Care (PHC) Clinics in the two rural districts of King Cetshwayo and Ugu in KwaZulu-Natal. On the 15 – 16 March, CAPRISA and the Institute for Healthcare Improvement (IHI) conducted a Quality Improvement workshop with healthcare workers from 20 PHC clinics at the Pumula Beach Hotel in Port Shepstone. The purpose of the workshop was to create a community of health care workers dedicated to improving TB and HIV outcomes using Quality Improvement methodology. The two-day workshop focused on sharing ideas and best practices to enhance TB and HIV service integration. It also provided the opportunity to receive feedback from healthcare workers on the challenges and successes of implementing the QI model.

Grant & manuscript writing workshop

CAPRISA recently hosted a week-long Grant and Manuscript writing workshop for young investigators, new Principal Investigators and post-graduate students as part of its NIH-funded CAPRISA Research Administration and Management Training Program. Delegates at the workshop were from UKZN, the Centre for Infectious Disease Research in Zambia (CIDRZ), the Durban University of Technology (DUT), the Department of Health and CAPRISA.

"This workshop covered all aspects of grants writing, including setting goals and specific aims, completing an NIH grant application, preparation of supporting documentation with a special emphasis on human subjects research and clinical trials, grant and financial reporting, compliance with funder's requirements, and financial accountability," said Principal Investigator of the Program, Dr Cheryl Baxter. The workshop also included a manuscript writing component and all delegates left the workshop with a completed first draft of their manuscript.

CAPRISA fellow receives a Lancet-CUGH Best Student poster award

CAPRISA fellow Kate Simeon received a Lancet-CUGH Best Student poster award at the 9th Annual Consortium of Universities in Global Health (CUGH) Conference in New York. Simeon's poster assessing the "Cost of Point-of-Care Test Monitoring for HIV-Positive Patients on Antiretroviral Therapy" was the overall winner in the Implementation Science Track. Simeon, who is studying Medicine at the University of Washington, undertook a 12-week fellowship placement with CAPRISA's STREAM point-of-care (POC) Viral Load study, a randomized implementation trial assessing POC monitoring for patients receiving ART. Using micro-costing data and time and motion studies, Simeon found that POC monitoring is potentially cost saving compared to standard laboratory monitoring. A full cost-effectiveness analysis is planned when STREAM finishes in late 2018. The prize was presented by Zoe Mullan, editor of the Lancet Global Health, at the Annual CUGH Awards Ceremony. The CUGH, held from 16-18th March, is the world's leading academic global health conference, and this year was co-hosted by Columbia and Stellenbosch Universities.

An age-stratified risk score to predict HIV acquisition in young South African women

Nonhlanhla Yende-Zuma, CAPRISA's head of Statistics, attended the Conference on Retroviruses and Opportunistic Infections (CROI) from 4 - 7 March in Boston, Massachusetts and presented a poster entitled, "An age-stratified risk score to predict HIV acquisition in young South African women". The presentation was made on behalf of Emma Burgess who is under the mentorship of Professor Quarraisha Abdool Karim, associate Scientific Director CAPRISA and Dr Delivette Castor from USAID. Yende-Zuma said that the CAPRISA 004 dataset was used to assess the performance of a risk score that was derived from the Vaginal and Oral Interventions to Control the Epidemic (VOICE) study. "We modified the score for age-specific prediction with the aim of identifying few modifiable behavioural and partner risk factors that may further predict HIV acquisition among young women," said Yende-Zuma. She explained that "prioritizing highest risk women in HIV hyperepidemic settings remains important for optimized introduction and scale of new prevention methods like oral PrEP."

Nonhlanhla Yende-Zuma, head of Statistics, CAPRISA at the CROI meeting in Boston

Appointment to SACRA executive committee

Natasha Samsunder Director of CAPRISA Laboratories, will serve on the executive committee of the South African Clinical Research Association (SACRA) for a two year term (2018 – 2020). SACRA is the 'only professional body that represents all Research Clinical Trials-related professionals'. Nicolette Stott, Chair of SACRA said that all 'executive members are voted in'. She said that SACRA has through the past years helped to support the ongoing "learning and development of knowledge and research in the Clinical Trials Industry." Commenting on her appointment, Samsunder said: "I am honoured to serve on SACRA's executive committee and will use the opportunity advance the scientific agenda of clinical trials in South Africa."

Scientific papers published in 2018

10*	Govender K, George G, Beckett S, **Montague C, Frohlich J**. Risk Compensation Following Medical Male Circumcision: Results from a 1-Year Prospective Cohort Study of Young School-Going Men in KwaZulu-Natal, South Africa. *International Journal of Behavioural Medicine* 2018;25(1):123-130. doi: 10.1007/s12529-017-9673-0.
11	**Moosa Y,** Tanko RF, **Ramsuran V**, Singh R, Madzivhandila M, **Yende-Zuma N**, Abrahams MR, Selhorst P, Gounder K, Moore PL, **Williamson C, Abdool Karim SS, Garrett NJ,** Burgers WA. Case report: mechanisms of HIV elite control in two African women. *BMC Infectious Diseases*. 2018;18 (1):54.
12	Naidoo N, Pillay B, Bubb M, Pym A, Chiliza T, **Naidoo K**, Ndungù T, Kasprowicz V, Pillay M. Evaluation of a synthetic peptide for the detection of anti-Mycobacterium tuberculosis curli pili IgG antibodies in patients with pulmonary tuberculosis. *Tuberculosis*. 2018; 109:80-84. https://doi.org/10.1016/j.tube.2018.01.007
13	Chikata T, Van Tran G, Murakoshi H, Akahoshi T, Qi Y, **Naranbhai V**, Kuse N, Tamura Y, Koyanagi M, Sakai S, Nguyen DH, Nguyen DT, Nguyen HT, Nguyen TV, Oka S, Martin MP, Carrington M, Sakai K, Van Nguyen K, Takiguchi M. HLA class I-mediated HIV-1 control in Vietnamese infected with HIV-1 subtype A/E. *Journal of Viroloy* 2018; 92(5). pii: e01749-17. doi: 10.1128/JVI.01749-17.
14	Reh L, Magnus C, Kadelka C, Kühnert D, Uhr T, Weber J, **Morris L, Moore PL**, Trkola A. Phenotypic deficits in the HIV-1 envelope are associated with the maturation of a V2-directed broadly neutralizing antibody lineage. *PLoS pathogens 2018*; 14(1):e1006825. doi: 10.1371/journal.ppat.1006825.
15	Serwanga J, Ssemwanga D, Muganga M, Nakiboneka R, Nakubulwa S, Kiwuwa-Muyingo S, **Morris L**, Redd AD, Quinn TC, Kaleebu P, HIV Superinfection Study Group. HIV-1 superinfection can occur in the presence of broadly neutralizing antibodies. *Vaccine* 2018; 36(4):578-586. doi: 10.1016/j.vaccine.2017.11.075.
16	Montefiori DC, Roederer M, **Morris L**, Seaman MS. Neutralization tiers of HIV-1. *Current Opinion in HIV and AIDS*. 2018; 13(2):128-36. doi: 10.1097/COH.0000000000000442.
17	**Harichund C**, Moshabela M. Acceptability of HIV Self-Testing in Sub-Saharan Africa: Scoping Study. *AIDS and Behavior* 2018; 22(2):560-568. doi: 10.1007/s10461-017-1848-9
18	**Dorward J, Yende-Zuma N, Samsunder N, Abdool Karim Q,** Drain PK, **Garrett N.** Clinic-Based Evaluation of A Point-Of-Care Creatinine Assay to Screen for Renal Impairment Amongst Hiv-Positive Patients Receiving Tenofovir Disoproxil Fumarate. *JAIDS* 2018; 77(4):e36-e39. doi: 10.1097/QAI.0000000000001613.

**continuation from previous newsletter*

Scientific Reviews

Abstracts submitted for review		Manuscripts submitted for review		Ancillary studies submitted for review	
Total#	Cumulative^	Total#	Cumulative^	Total#	Cumulative^
5	395	1	231	1	85

 # for month, ^ since committee initiation