43rd Annual Medicine Research Day - Mentorship

Wednesday 4th October 2-6pm
Thursday 5th October 8am-6pm

University of Cape Town & Groote Schuur Hospital Department of Medicine
Nico Malan Conference Centre Groote Schuur Hospital
DEPARTMENT OF MEDICINE
43rd ANNUAL RESEARCH MEETING

DATE: 4-5 OCTOBER 2017
VENUE: NICO MALAN CONFERENCE CENTRE,
GROOTE SCHUUR HOSPITAL

Programme

Wednesday 4th October 2017

Session I
Chair
Prof Marc Blockman

14:00 – 14:05  Prof Ntobeko Ntusi
OPENING SESSION WITH WELCOME

14:05 – 14:25  Prof Alta Schutte
The importance of Mentorship in Research

14:25 – 14:45  Prof Valerie Mizrahi
How to write a grant

14:45 – 15:05  Prof Keertan Dheda
How to write a research paper

15:05 – 15:25  A/Prof. Liesel Zuhlke
Parenting and research: joys and challenges

15:25 – 15:45  A/Prof. Joel Dave (Con) vs A/Prof. Bridget Hodkinson (Pro)
"Is a PhD necessary to become a successful clinician scientist in South
Africa?"

15:45 – 16:15  Tea/Coffee

Session II
16:15 – 18:00  POSTER PRESENTATIONS AND ADJUDICATION
Posters will remain on display in Nico Malan Conference Centre on
the 5th October
Poster Abstracts

Cape Town: How age friendly is the city? An exploratory study.

Tarryn Blouws*, Sebastiana Kalula, Monica Ferreira

Introduction: Worldwide population ageing calls for a growing need to integrate older people in social life and enable them to live active healthy lives. The living environment of the majority of older citizens of Cape Town remains characterised by infrastructural and developmental deficits. This study investigated older citizens’ experience and perceptions of the “age friendliness” of their communities in the City of Cape Town.

Subjects and Methods: The study employed research methodology advocated by the WHO’s project on “Age friendly Cities,” based on the Vancouver Protocol 2006. Low-income suburbs of Cape Town were selected and qualitative research methods (focus groups with members and interviews with managers of service centres) were used to collect and analyse the data.

Results: A sample 97 participants, mean age 70 years (range 54-83) were recruited. Eight domains constructed for the assessment of age friendliness were: physical environment, transport, housing, social participation, respect and social inclusion, civic participation, community support and health services, and communication and information.

Interpretation: Barriers to social inclusion and participation were: Government restriction in income generating activities for social pensioners; features of the physical environment particularly uneven, poorly lit and unsafe sidewalks; short timing at traffic light for pedestrian-crossings; public transport services that was inaccessible to commuters with disability and younger commuters not offering their seats to them. Ageistic attitudes of personnel and the unfriendly services at public healthcare facilities were widely reported. Services and support from religious and other community agencies and travel concessions from government were greatly valued. Lack of exposure and inability to access pertinent electronic information was a concern for a large number.

A productive and inclusive society calls for stakeholders to address the concerns
HIV-associated neuropathy and autonomic dysfunction in South Africans on established ART impacts daily living

Meagan T. Dudley*, Megan Borkum, Jeannine M. Heckmann

Introduction: A common complication of HIV and anti-retroviral therapy (ART) is distal sensory polyneuropathy (DSP). Older age and previous TB are risk factors for DSP among HIV-infected Africans before and after ART initiation. Little is known about autonomic dysfunction in Africans on established ART and the impact of DSP and autonomic impairment on their quality of life. Our aim was to describe the frequency, characteristics and functional consequences of DSP and autonomic dysfunction in an HIV-infected community-based cohort after at least 5 years of ART.

Subjects and Methods: HIV-infected South Africans on the government-sponsored ART programme for at least 5 years were invited to participate in this cross-sectional analysis. Each consenting participant underwent a focussed neurological assessment using the Brief Peripheral Neuropathy Screen (BPNS) and a reduced version of the Total Neuropathy Score (rTNS). DSP was defined as the presence of at least 2 neuropathic signs in a distal and symmetrical distribution, and symptomatic DSP (SDSP) when accompanied by neuropathic symptoms. We used a modified version of the Lower Extremity Functional Scale (LEFS) to assess lower limb physical ability, and the Survey of Autonomic Symptoms (SAS) questionnaire to assess the presence and severity of autonomic symptoms.

Results: The 67 participants were Black with a median age of 41 years (interquartile range (IQR) 46-36) and 61 (91 %) were women. The median duration of ART was 7 years (IQR 6-10). DSP criteria were met in 54 (80.6%) and 24 (44.4%) had symptomatic DSP. Comparing participants with DSP to those without DSP, there was no difference in gender (P=0.41), age (P=0.79), current CD4 (P=0.59), viral suppression (P=0.39), ART duration (P=0.23) or previous TB (P=0.72) in those with DSP. Similar outcomes were obtained for SDSP. Autonomic symptoms were present in 40 (60%) participants and were more likely to occur in those with SDSP than those without SDSP (P=0.011). We found that those with DSP and SDSP had significantly lower LEFS percentage scores than those without (P=0.039 and P=0.013 respectively).

Interpretation: DSP remains a common complication of HIV in the modern era of ART and can lead to significant functional impairment. Autonomic dysfunction is prevalent in SDSP.
The role of excitatory GABAergic signalling on benzodiazepine efficacy during prolonged seizures

RJ Burman*, AA Katz, AJ Trevelyan, CJ Akerman, JV Raimondo

Introduction: The preferred first-line treatment of status epilepticus (SE) includes benzodiazepines (BZP), a class of GABAA receptor (GABAAR) agonists. In a subset of patients however, BZP prove to be ineffective in terminating SE. Previous data from in vitro models has demonstrated that during single seizures, instead of being inhibitory, GABA can in fact become excitatory. This is due to a disruption in the transmembrane chloride (Cl-) gradient that follows periods of neuronal hyperexcitability. The aim of this study is investigate the role of this excitatory GABAergic signalling during an in vitro replica of SE, termed the late recurrent discharge (LRD) phase. Furthermore, we aim to investigate how this transient shift in GABAergic function may affect the efficacy of the commonly used BZP, diazepam (DZP).

Subject and Methods: Experimental study on organotypic cultured brain slicing using advanced cellular electrophysiology and imaging techniques.

Results: We show that when using the 0 Mg2+ proconvulsant model, if DZP is washed in before the onset of seizure-like events (SLEs), DZP significantly reduced the duration of SLEs while causing a decline in SLE frequency. However, when applied during the LRD phase, DZP appears to significantly increase discharge duration without changing the inter-discharge interval. Using optogenetics, we then demonstrate that activation of interneurons during LRD drives depolarising GABAAR currents. Lastly, we show that activation of interneurons during LRD can entrain the network. Furthermore, this entrainment can be blocked by washing in the GABAAR blocker, picrotoxin.

Interpretation: We show that DZP has differential anticonvulsant effect. Furthermore, it appears that interneurons drive the propagation of the LRD through a strongly depolarising GABAAR activation. We postulate that this shift in GABAergic function and resultant change in DZP efficacy may the result of activity-driven changes in the transmembrane Cl- gradient.
CD73 expression in tissue granulomas is significantly increased in Intestinal tuberculosis (ITB) when compared to Crohn’s disease (CD) in a South African cohort

Gillian Watermeyer* Michael Locketz

Introduction: Overlap of clinical, endoscopic, and radiographic features, coupled with a poor microbiological yield makes differentiating Crohn’s disease (CD) from Intestinal tuberculosis (ITB) challenging. A potential histological differentiating mechanism is the use of immunohistochemical staining for the mesenchymal stem cell marker CD73, as a pilot study showed ITB but not CD granulomas stained positive for this marker. The aim of this study was to assess the value of CD73 in differentiating ITB from CD granulomas in a South African cohort.

Methods: Patients with confirmed CD or ITB were identified from a pathology database. Tissue sections were reviewed by a pathologist to confirm the presence of granulomas. These were then stained with a mouse monoclonal anti-CD73 antibody. The slides were examined together by a pathologist and gastroenterologist in a blinded manner for anti-CD73 staining around granulomas.

Results: 96 cases were available for analysis; 50 cases of ITB and 46 cases of CD. Thirty percent of CD granulomas (14/46) stained positive for CD73, while CD73 positivity was seen in 52% (26/50) of cases of ITB. This was statistically significant (OR 2.48, 95% CI 1.1-5.72, p=0.03). The AUC was 0.61. Sensitivity of CD73 in predicting ITB was 52% and specificity 70%. Overall CD73 staining of granulomas correctly classified only 60% of cases.

Conclusion: In our study we have shown that significantly more patients with ITB express CD73 in their granulomas than those with CD. However the relatively poor sensitivity, specificity and AUC make this test unlikely to be of value in our clinical practice.
Establishment and evaluation of a smoking cessation clinic in South Africa

G Tadzimirwa*, C Day, C Cooper, A Esmail, M Kamkuemah, K Dheda, R van Zyl-Smit,

Introduction: There are an estimated 7 million smokers in South Africa (SA), with high smoking-related mortality. SA is ranked as the second most stressful country to live in globally. A dedicated smoking cessation clinic was established at Groote Schuur Hospital in 2014. This facility was the first in SA to provide a clinical service and training centre. Objectives are to motivate the health authorities to fund psychological support services, counselling, and access to nicotine replacement therapy.

Subjects and Methods: Data on all patients who visited the clinic between 2014 and 2016 were captured. These included demographics, smoking history, nicotine dependence, CO levels and depression scores. All patients provided consent for data collection and audit. The UCT Faculty of Health Sciences Research Ethics committee and Hospital administration approved the review.

Results: Over a 2.5-year-period, 97 patients were seen. The mean (SD) age of patients was 51.1 (10.9) years, with 59.8% male patients. The median (IQR) age of smoking onset was 16 (8 - 28) with a median (IQR) cigarette consumption of 18 (2 - 80) per day. Men smoked more than women at 21 v. 14 cigarettes per day (p=0.002), resulting in a higher number of total cigarette packs year: 34 v. 22 (p=0.001). The level of nicotine dependence was moderate: the mean Fagerström test score was 5.3: men 6 v. women 5 (p=0.06). Half of the patients had a Fagerström score ≥6, and 22% ≥8. The median (IQR) PHQ-9 depression score was 8 (4-11) with 49% of patients displaying symptoms of at least minor depression (score ≥10), similar in both men and women. At baseline, >60% had high (≥2/4) Wisconsin Smoking Withdrawal Scale anxiety and anger scores.

Interpretation: In this group seeking help to quit smoking, moderate levels of nicotine addiction existed. Additionally, moderate depression and anxiety symptoms co-existed. These data support the need for pharmacotherapy in some patients, but additional intensive psychological support is urgently required.
The 5-year outcomes of patients receiving haemodialysis versus peritoneal dialysis at Groote Schuur Hospital, Cape Town, South Africa.

Kenneth D. Crombie*, Bianca J. Davidson, Kathryn Manning, Brian L. Rayner, Nicola Wearne

Introduction: Despite the rising global prevalence of chronic kidney disease, dialysis remains restricted in South Africa and acceptance onto many renal replacement programs is limited to those suitable for transplantation. Few studies exist comparing survival outcomes of peritoneal dialysis [PD] and haemodialysis [HD] patients from developing countries. In addition, data of those switching to HD are conflicting.

Subjects and Methods: This retrospective cohort study compares survival outcomes of patients receiving HD or PD at Groote Schuur Hospital, South Africa, from 2010-2015.

Results: A total of 174 patients were assigned to HD and 189 to PD, of which 42 switched to HD. The majority (68.31%) of patients were under 45 years. More black Africans received HD. The most common causes of death were infection (26%) and fluid overload (19%). Having removed those PD patients whom modality switch was denied due to contraindications to transplantation, survival probability at 1-, 2- and 5- years for HD versus PD was 98.68% (CI: 94.84-99.67), 96.95 (CI: 91.98-98.86) and 83.52% (CI: 71.75-90.70) versus 96.73% (95% CI: 92.32-98.63), 89.95 (95% CI: 83.17-94.1) and 76.69 (95% CI: 60.97-86.73) respectively. (p=0.107) The survival probability of those patients who switched from PD to HD, for the same intervals was 100%, 97.37% (95% CI: 82.75-99.63) and 97.37% (95% CI: 82.75-99.63). (p=0.001)

Interpretation: In this setting, PD is not inferior to HD and those patients switching from PD to HD have the best survival outcomes. Therefore, the current local PD first policy is justified, although interventions should be aimed at improving outcomes.
A protocol for a systematic review of the diagnostic accuracy of hand-held echocardiography for the detection of rheumatic heart disease in school-aged children and adolescents

Lisa H Telford*, Liesl J Zühlke, Eleanor A Ochodo, Mark E Engel

Introduction: Hand-held echocardiography presents an opportunity to address the need for cost-effective methods of diagnosing rheumatic heart disease (RHD) in developing countries where the disease carries high morbidity and mortality. Studies have demonstrated moderate sensitivity as well as high specificity and diagnostic odds for detecting latent RHD. We describe a protocol for systematic review of published primary diagnostic test accuracy studies to evaluate the evidence for this portable technology in diagnosing suspected RHD.

Subjects and Methods: Electronic search strategies will be conducted among various data sources including PubMed, Scopus, ISI Web of Science and EbscoHost. Primary observational studies of diagnostic accuracy of hand-held echocardiography versus standard echocardiography will be selected. Data extraction will be undertaken by two reviewers independently, to assess the methodological validity and quality of each study against QUADAS-2 criteria. In addition, information relating to metrics of diagnostic accuracy and demographics will be extracted. Forest plots of sensitivity and specificity as well as a scatter plot in Receiver Operating Characteristic (ROC) space will be used to investigate heterogeneity of studies. If possible, a meta-analysis will be conducted to produce summary results of sensitivity and specificity using the Hierarchical Summary Receiver Operating Characteristic (HSROC) method. Subgroup analyses will include age, gender, geographical location and expertise of echocardiographic interpreter. Finally, a sensitivity analysis to investigate the effect of studies with a high risk of bias will be undertaken.

Interpretation: This systematic review will provide a summary of the diagnostic accuracy of hand-held echocardiography. Results may feed into evidence-based guidelines and should the findings of this review warrant a change in clinical practice, a one-page summary report will be disseminated among leading healthcare professionals in the field. It is anticipated that further studies will be needed in order to develop a standardized diagnostic protocol for hand-held echocardiographic screening by non-experts.
Establishing the normal values for High - Resolution Anorectal Manometry and Ultrasound anatomical sphincter assessment in asymptomatic woman.

Jane Elizabeth Christie Botha*, Sandie Thomson, Radu Tutuian

Introduction: Anorectal function testing and morphological sphincter assessment are investigations used to guide management, both surgical and non-surgical, in patients with benign anorectal disorders. High Resolution Anorectal Manometry (HRAM) is an evolving technique requiring individual laboratory standardization.

Aims: (i) To determine normal values for anal sphincter function metrics using a water perfused HRAM system in healthy women with no anorectal symptoms, from the Cape Metropole. (ii) To establish the effects of age, parity, body mass index and ethnicity on these values. (iii) To compare these metrics to those using HRAM systems in other laboratories.

Subject and Methods: Forty-five healthy female adult subjects, 15 from each of the 3 major ethnic groups, underwent HRAM using a 20-channel water perfused system. Participants with anal sphincter disruption on 3D anorectal ultrasound were excluded. Age, parity, ethnicity and BMI were documented. Traditional anal sphincter function tests were measured at rest, squeeze, endurance squeeze, bearing down and coughing. Recto Anal Inhibitory Reflex and rectal sensation volumes were also assessed.

Results: The mean age in this cohort was 36 years (Range 18 to 71 years). Eighteen were nulliparous and twenty seven had 1 to 4 children. The anal sphincter function measurements were not significantly affected by age, parity, ethnicity, or BMI. Current study had 45 subjects compared to Carrington study who had 96 female subjects. The average mean resting anal pressures were 66 and 65mmHg. The average absolute squeeze pressures were 70 and 173 mmHg.

Conclusions: This study provides normal ranges of anal function metrics which will be useful in interpreting data from our patient population. Of the demographic parameters the effect of parity requires further investigation. Resting metrics correlate well, but dynamic metrics are significantly lower than the comparator study.
Predictors of emergency colectomy in patients admitted with acute severe ulcerative colitis

N N Mokhele*, S R Thomson, G A Watermeyer

Introduction: Acute Severe Ulcerative Colitis (ASUC) is a life-threatening condition which requires urgent and aggressive medical therapy to reduce mortality, morbidity and avoid surgery. To facilitate this process, it is essential to identify patients at high risk of poor outcomes and emergency colectomy. Numerous such risk factors have been described in Western literature, however there is no local data addressing this issue. As such it is unclear if these predictors are applicable in our setting. The aim of this study is thus to identify risk factors for emergency colectomy in patients admitted to Groote Schuur Hospital with ASUC.

Subjects and Methods: A retrospective cohort study of 98 patients admitted with ASUC between January 2003 and January 2013 was performed. Clinical, demographic, laboratory and endoscopic factors on admission and 3 days thereafter were analysed as predictors of colectomy by univariate and multivariate analysis.

Results: Twenty-five percent of the cohort underwent emergency colectomy. On univariate analysis, factors predicting colectomy on admission were exposure to oral corticosteroids (p=0.01), megacolon (p=0.049) or mucosal islands (p=0.04) on abdominal X-ray, and a short duration from UC diagnosis until presentation with ASUC (p=0.04). The only variable that was significantly associated with colectomy on day 3 was serum albumin (p=0.01). This was also the only variable to remain significant on multivariate analysis (OR 0.79, 95% CI 0.65–0.97, p=0.01).

Interpretation: ASUC is a medical emergency and predicting colectomy risk aids in therapeutic management. The only variable significantly associated with the need for surgery in our study was hypoalbuminaemia on day 3. Given the small study numbers a larger prospective study would be of value.
The impact of vascular calcification among dialysis dependent South African CKD patients. A five year follow up study. Cardiovascular mortality and morbidity, ethnic variation and hemodynamic correlates

K. Simba*, M. Borkum, N. Erasmus, W. Bhasera, C. Swanepoel, R. Freercks and B. Rayner

Background: Cardiovascular (CV) complications are the leading cause of death in patients with chronic kidney disease (CKD) where vascular calcification is a strong prognostic marker of CV disease mortality. Studies in Western countries suggest ethnic differences in vascular calcification. While there is an apparent survival advantage among Blacks on dialysis, there is little published data on this in Sub-Saharan Africa.

Methods: A five-year longitudinal study of dialysis patients previously recruited for a cross-sectional assessment of vascular calcification. Participants were recalled for: anthropometry, vascular stiffness measurement using a Sphygmocor device and a 12-lead electrocardiogram (ECG). Medical records were reviewed for clinical history.

Results: Of the 74 initial participants, 66 were located; 42 participants were still alive and 24 (36.9%) had died. Of those that died, 1/24, had an unknown current status of dialysis modality. Blacks constituted 23 of 42 (54.8 %) participants that were alive at follow up. 13/24 (54.2%) of the patients with coronary artery calcium (CAC) score ≥1 died versus 11/24 (45.8%) with CAC score of 0 (p=0.564). Participants with a higher initial Fibroblast Growth Factor 23 (FGF-23) at baseline also had a greater probability of dying (p=0.075). There was lack of progression in vascular calcification among Blacks compared to non-Blacks, (p=0.066) and blacks had lower parathyroidectomy rates compared to non-Blacks at follow-up (p=0.036). Those alive at follow-up had a higher mean BMI (27.1±7.1kg/m² versus baseline 24.4±4.2kg/m² (p<0.015). 6 of 33 (18.2%) transplanted developed diabetes compared to 1/28 and 1/4 for IHD and PD respectively (p=0.144). There was a significant regression in left ventricular hypertrophy (LVH) criteria adjusted for weight in both Sokolow-Lyon (p=<0.001 and Cornell Voltage Criteria (p=0.027). Central aortic systolic pressures (CASP) and pulse wave velocities (PWV) were higher in the study population than age matched normative values.

Conclusion: Non-blacks showed a significant increase in vascular calcification and had higher parathyroidectomy rates than Blacks. This suggests a possible unique genetic difference in calcium phosphate metabolism. Higher baseline CAC scores and FGF-23 levels were associated with greater mortality but this was not statistically significant. A significant regression in LVH criteria on ECG on 5-year follow up was observed.
Predictors of pre-treatment loss to follow-up of microbiologically proven TB cases: a multicentre study

Philippa Randall*, Grant Theron, Jaisubash Jayakumar, Malika Davids, Anil Pooran, Ali Esmail, Jonny Peter, Lynn Zijenah, Petra Clowes, Dan Stein and Keertan Dheda

Introduction: GeneXpert has positively transformed the diagnosis of tuberculosis (TB). However, there are still several hurdles to achieving treatment initiation. Individuals who are diagnosed with TB, but fail to initiate treatment, are termed ‘pre-treatment loss to follow up’ (PLF). PLFs represent 10% to 40% of diagnosed cases and failure to initiate treatment increases transmission and TB-related mortality. To inform clinical practice and public health policy we investigated the frequency of PLF, and patient-specific and microbiological factors associated with it.

Subjects and Methods: The parent study was a pragmatic randomised controlled multicentre study, which recruited adults with suspected TB from periurban primary healthcare TB clinics in South Africa, Zimbabwe, Zambia and Tanzania. Eligible participants were randomly assigned to one of two arms: GeneXpert MTB/RIF assay performed at the clinic or sputum smear microscopy. We analysed data to determine the frequency of PLF, and the socio-demographic and clinical predictors of PLF compared to those who initiated TB treatment.

Results: Of the 1502 individuals screened, 367 culture positive TB cases were identified, 88% (324/367) of which were initiated on treatment and 12% (43/367) were classified as PLF. The time to culture positivity was significantly longer (p-value = 0.011; OR = 0.956), clinic and laboratory-based GeneXpert CT values significantly higher (p-value = 0.002; OR 4.341) and the 10-item Kessler Psychological Distress Scale (K-10) score (p-value = 0.011; OR 1.057) was significantly lower in the PLF group when compared to those who were initiated on anti-TB treatment.

Interpretation: Patients who were minimally psychologically distressed about their symptoms, and with a low microbiological burden, were more likely to default after diagnostic confirmation. These data inform public health containment strategies and suggest that patient education about the implications of their TB diagnosis, despite having minimal disease, is likely important to reduce PLF.
Title: Audit of Tertiary level sleep clinic in Sub-Saharan Africa

H A. Tariq*, C. Daniels, G. Calligaro, R. Raine, C. Koegenberg, K. Dheda, G. Symons

Introduction: Obstructive sleep apnoea (OSA) is a common condition. Affected individuals develop multisystem complications having a significant impact on their health, psychological state as well as socioeconomic standing. There is limited literature describing sleep disordered breathing amongst Sub-Saharan patients.

Subjects and Methods: Retrospective audit of the Sleep Registry of patients referred to the Sleep clinic at E16 Respiratory Clinic at Groote Schuur Hospital from 2014-2016. The aims of this study are to describe the demographics and anthropometrics of all patients attending the Sleep clinic at Groote Schuur Hospital; to quantify and describe the patient profile, risk factors and severity of the patients diagnosed with OSA.

Results: In terms of gender of patients attending the clinic 62% were Male and 38% female. The 3 most common indications for sleep studies were snoring, poor quality of sleep and excessive somnolence. There were 164 polysomnography studies performed with 140 patients with Apnoea–Hypopnea Index of >5. In terms of severity of disease, it was found that there were a greater proportion of men with a severe AHI relative to women.

Interpretation: Majority of the patients referred to the clinic were male with a greater number of male patients with severe AHI relative to female. A large proportion of patients have similar demographic and anthropometric findings to the global description of OSA patients. This research serves as the first step to describe a Sub-Saharan sleep disorder patient profile. Further research needs to be done to define any specific correlations between the co-morbidities and diagnosis of OSA.
linkTB: A web-based application for the identification and interactive visualization of infectious disease transmission routes.

Jason D. Limberis, Grant Theron, Keertan Dheda

Introduction: Molecular epidemiological investigations and the inference of patient-to-patient transmission are commonly utilized in infectious disease tracking. More researchers are becoming exposed to this kind of data following the recent decrease in gene sequencing costs. However, simple and clinician-friendly tools to visually and interactively explore phylogenies (strain types), infer patient-to-patient disease transmission, and interrogate these with drug resistance readouts, are scarce.

Subjects and Methods: We developed a web-based application using R (v3.4.0) to examine the relatedness of gene sequence data. The application is hosted on an online server and utilizes user uploaded data. The user interface was created using the packages shiny (v1.0.3.9000). Plots were created using ggplot2 (v2.2.1.9000), phylocanvas (v0.1.1), heatmaply (v0.10.1), visNetwork (v1.0.3), plotly (v4.7.0.9000), leaflet (v1.1.0), and timevis (v0.4) packages. Statistical analyses and calculations are performed using base R and ape (v4.1). Drug resistance mutations were used as described by ReSeq-TB and Walker TB-panel.

Results: We created a user-friendly web-based application (https://sciencebuff.shinyapps.io/linkTB) allowing users to explore the relatedness of isolates gene sequence data. Users upload a variant matrix (which can be created using a pre-constructed pipeline: https://github.com/sciencebuff/WGS_pipeline_IlluminaPE) and associated metadata. The metadata may include any information linked to the uploaded sequences such as patient HIV-status, isolate phenotypic resistance patters etc. The user can then visually and interactively explore different phylogenetic distances and interaction networks based on these. The geospatial layout of these networks can be explored and principal component analysis can be done. In the case of M. tuberculosis, drug resistance encoding mutations can be identified, and strain SNP lineage typing done. Several examples will be outlined.

Interpretation: Phylogenetic inference of patient-to-patient-transmission, and hence tracking of infectious diseases, is an underutilized public health intervention. We have developed user-friendly tool that will afford researchers the ability to determine drug resistance, identify and explore transmission networks, and geospatially identify hotspots of transmission.
The utility of endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) for the diagnosis of mediastinal lesions in a resource-limited TB and HIV endemic setting.

S. Mothilal*, A. Esmail, L. Mottay, S. Oelofse, G. Calligaro, K. Dheda

Introduction: Diagnostic evaluation by mediastinoscopy is associated with increased risk, cost, and hospitalisation. Although EBUS-TBNA may be a useful alternative there are hardly any data from TB and HIV endemic settings that have limited access to surgical facilities.

Methods: We prospectively evaluated 154 patients who underwent EBUS-TBNA between March 2013 and July 2017 at Groote Schuur Hospital. The indications for EBUS-TBNA were undiagnosed mediastinal lesions and staging assessment of lung cancer. Patients without diagnostic clarity after EBUS underwent mediastinoscopy or appropriate surgical biopsy.

Results: The diagnostic accuracy of EBUS-TBNA regardless of the indication was 68.7% (95% CI 57.7-75.7) with a PPV of 100% (95% CI 94.7-100), and NPV of 63.9% (95% CI 52.1-71.9). Overall, EBUS-TBNA diagnosed TB in 19/24 patients (79.2%). Sarcoidosis was diagnosed in 6/16 (37.5%) patients with EBUS-TBNA alone and 11/16 (68.8%) patients when combined with transbronchial biopsy. Malignant disease was diagnosed in 39/54 (72.2%) patients. False negative results (EBUS –ve but mediastinoscopy +ve) were obtained in 31 patients (20%) of whom 15 had malignancy, 5 had TB, and 5 had sarcoidosis. 14/154 (9.1%) patients referred were HIV-infected of whom EBUS-TBNA diagnosed TB in 5 patients, sarcoidosis in 1 patient, and benign disease in 7 patients, with 1 false negative diagnosis in a patient with lymphoma (overall sensitivity of EBUS-TBNA in HIV-infected persons was 92.9%).

The procedure was well tolerated in 149/154 (96.7%) patients with reversible complications occurring in 5/154 (3.2%) patients including minor bleeding (less than 50ml) and transient arterial desaturation (pulse oximetry less than 90%).

Conclusions: EBUS-TBNA is a safe and useful diagnostic tool in HIV-infected and uninfected patients with mediastinal pathology and avoided surgical intervention in ~70% of patients. These data inform clinical practice in resource-limited TB and HIV endemic settings.
Diagnosing Tuberculosis in Hospitalized HIV-Infected, sputum-expectorating, and sputum-scarce patients: The role of urinary Lipoarabinomannnan and GeneXpert-MTB/RIF.

Aliasgar Esmail*, Natasha F Sabur, Mantaj S Brar, Mohammed Fadul, Suzette Oelofse, Lynelle Mottay, Keertan Dheda

Introduction: GeneXpert-MTB/RIF and urinary lipoarabinomannnan are tests that are effective for diagnosis of tuberculosis in the setting of advanced HIV co-infection. Guidelines are unclear on the role LAM testing in the context of specific patient sub-groups and day-to-day clinical practice.

Subjects and Methods: This study represents a post hoc sub-group analysis of data from a randomized multi-centre parent study. For this analysis, the study population were divided into two groups: (i) sputum-scarce patients (unable to produce sputum); (ii) sputum-expectorating patients. Diagnostic utility of urine LAM in sputum-scarce patients was compared to those who expectorated sputum. In addition, we compared LAM to GeneXpert-MTB/RIF in sputum-expectorating patients.

Results: 2528 HIV-infected patients from the parent study were included in this analysis. Patients were randomized (1:1) to either LAM plus routine diagnostic tests for tuberculosis (smear microscopy, Xpert-MTB/RIF, and culture; LAM group n=1257) or routine diagnostic tests alone (no LAM group n= 1271). 187/2528 (7%) patients were sputum-scarce. These patients were more likely to test urine LAM positive (31% vs. 21%, p=0.04). The diagnosis of TB was made in an additional 19% of sputum-scarce patients using LAM (PPV 63% (95% CI 43-82)).

561/1257 (45%) of patients in the LAM arm of the study also had sputum GeneXpert-MTB/RIF and sputum culture results. In this population, urine LAM had a sensitivity and specificity of 38.1% (30.9-45.7%) and 88.1% (84.3–91.1%), respectively, whilst performance for Xpert-MTB/RIF on sputum samples was 75.0% (67.9–81.2%) and 95.1% (92.4–97.0), respectively. The incremental yield of adding urine LAM to Xpert MTB/RIF was 18%.

Interpretation: Our findings support the use of urine LAM testing in sputum-scarce hospitalized HIV-infected patients however, in sputum-expectorating patients, where both molecular and antigen testing is available, urine LAM has modest incremental yield over Gene Xpert-MTB/RIF.
Clinico-Pathological features of repeat renal biopsies in patients with lupus nephritis at Groote Schuur Hospital, Cape Town

Shepherd Kajawo*, Francois CJ Botha and Ikechi G Okpechi

**Background:** Repeat renal biopsies in patients with lupus nephritis (LN) are usually performed to guide treatment or to establish disease chronicity. Their value is not clear from available literature. There is also no available data in Africa to guide clinicians.

**Subjects and Methods:** This was a retrospective study of patients undergoing a repeat renal biopsy between January 2003 and December 2014 from a single centre in Cape Town, South Africa. Relevant demographic, clinical and histological records of patients with repeat renal biopsies were documented. Comparison of data from 1st and 2nd renal biopsy was performed.

**Results:** 44 patients had at least 2 biopsies performed during the study period. Most patients were females (81.8%). The mean biopsy interval was 2.8±1.8 years. Proteinuria was the main indication for repeat biopsy (36.1%). The glomerular filtration rate and proteinuria worsened between the two biopsies (p=0.001 and 0.019) respectively suggesting disease progression. Most patients (65.4%) with a non-proliferative class of LN at first biopsy progressed into a proliferative class whereas patients with initial proliferative LN at first biopsy (77.8%) remained as proliferative at repeat biopsy. Treatment was changed in 85% of patients at second biopsy.

**Interpretation:** Repeat renal biopsies in patients with LN presents a useful means of assessing disease progression and provides guidance regarding modification of treatment. More studies are however required to evaluate the value of repeat biopsies and perhaps the need for protocol renal biopsies in patients with LN.
**Bronchial thermoplasty for severe persistent asthma: experience from Cape Town, South Africa.**

**Ayanda Trevor Mnguni**, Aliasgar Esmail, Anil Pooran, Malika Davids, Lynelle Mottay Suzette Oelofse, Louis De Jager, Jurgen Geitner, Helen Wainwright, Gregory Calligaro, Keertan Dheda

**Introduction:** Bronchial thermoplasty (BT) is a Global Initiative for Asthma-recommended step-5 therapy for severe persistent asthma in uncontrolled patients despite optimal medical therapy. However, there are no outcome data for severe asthma in resource-limited settings.

**Methods:** Patients whose asthma symptoms remain uncontrolled despite receiving moderate dose ICS/LABA, and who have frequent exacerbations (≥2), hospitalization or chronic OCS (>50%) use in the previous year were prospectively enrolled. The BT procedures were performed at Groote Schuur Hospital and the University of Cape Town Academic Hospital. The primary outcome was a decrease in number of exacerbations (defined as the need for adjunct oral corticosteroids or antibiotics) recorded in the 12 months before the procedure, compared to 12 months after completion of the final BT treatment. Secondary outcomes included differences in Asthma Control Test (ACT) scores, overall chronic oral corticosteroid dose (in milligrams per month), the number of asthma classes of medications used pre- and post-BT, and the need for admission post-procedure.

**Results:** 12 patients [50% male; median age (inter-quartile range; IQR) of 59 (46-64); 10/12(83%) on OCS and 8/12(66%) with previous ICU admission] underwent BT (36 procedures) and completed the 12-month post-procedure follow-up period. The number of exacerbations (median; IQR) decreased significantly post-BT [12 (6-12) vs. 2 (0.3-3), p=0.0002). ACT scores post-BT were also significantly higher [7.5 (6.0-11.8) vs. 14.5 (11.25-17.75); p=0.012). There was a reduction in the median monthly oral corticosteroid dose before and after treatment BT [300mg (200-450) vs. 240mg (40-450)]. Number of classes of asthma medications was unchanged. BT was well tolerated but 3/36 (8%) patients developed post-procedural bronchospasm requiring overnight admission, one of whom developed a pneumothorax which was managed conservatively.

**Conclusions:** In this small single-centre study, in a resource-poor setting that enrolled patients with disease more severe than in published clinical trials, BT reduced exacerbations and improved asthma control.
Prevalence of peritonitis and mortality amongst patients on peritoneal dialysis in Africa: A protocol for a systematic review

Mothusi W. Moloi*, Shepherd Kajawo, Jean Jacques Noubiap, Udeme Ekrikpo, Andre P. Kengne, Ikechi Okpechi

Introduction: Chronic kidney disease (CKD) remains a significant contributor to morbidity and mortality worldwide with a global prevalence of 13.4% relative to 13.9% in Africa. Peritoneal dialysis (PD) is the most suitable modality of renal replacement in Africa, however, due to several socio-economic factors it is often complicated by PD-related peritonitis, the main contributor to morbidity and mortality amongst patients on PD.

Subjects and Methods: We conducted a systematic review of studies done in Africa on African patients with CKD treated with PD to estimate the prevalence of PD-related peritonitis, causative organisms, rates of dialysis modality switch and mortality. Relevant studies published from the 1st of January 1980 to the 31st of December 2016 were identified by searching through PubMed, Africa Journal Online and Google Scholar. Key search terms were: ‘peritoneal dialysis’, ‘peritonitis’ and ‘Africa’.

Results: A total of 11 studies were included for analysis from 41 identified studies; most were conducted in South Africa (63.6%) and all had a retrospective design. The number of patients per study ranged from 26 to 263 (Min-Max) with a total of 1219 patients included. The mean ages of participants were 9.3 ± 5.7 to 56 ± 25 years (Min-Max) and the median time on PD 7.0 (0.4–36.8) to 27 (1–51) months. Chronic glomerulonephritis and hypertension were the commonest causes of CKD. PD-related peritonitis ranged from 0.60 to 2.7 episodes per patient year, with earlier studies reporting the highest rates. Staphylococci were the commonest cause of peritonitis followed by pseudomonas. Most studies reported high rates of culture negative peritonitis. Temporary and permanent modality switch to HD were warranted in 10% and 16.4% of patients respectively. PD-related mortality accounted for 12% of all deaths while sepsis was the main contributor to death.

Interpretation: High rates of PD-related peritonitis are seen in African patients receiving PD and significantly contributes to modality switch to HD and morbidity in this patient population.
Exome sequencing in South Africa: stakeholder views on feedback of individual research results and incidental findings

Nicole van der Merwe*, Raj Ramesar, Jantina De Vries

Introduction: Whole exome sequencing (WES) forms part of the growing arsenal of tools available to clinicians/healthcare workers for identification of causative gene variants to aid diagnosis or treatment. An important challenge currently under debate is the return of incidental findings (IFs). Internationally, various recommendations on how to deal with IFs have been developed, however, no published data has been generated on this topic in South Africa. Our aims were to explore the views and experiences of stakeholders regarding the feedback of IFs in the context of WES, and to explore the potential role of genetics counsellors (GCs) in the feedback process.

Subjects and Methods: Seventeen participants including clinicians, genomics researchers, and GCs were recruited from the University of Cape Town, Stellenbosch University, as well as two private hospitals in Cape Town. Semi-structured interviews were conducted, and the transcripts analysed using the framework approach for data analysis.

Results: Through this approach, four themes (and sub-themes) were identified namely, WES practice, IFs in WES, ethical considerations and implications, and feedback of findings.

Interpretation: Participants have avoided the possibility of obtaining IFs by using targeted WES analysis. Current roadblocks for the clinical adoption of WES include a lack of local guidelines, complexities relating to variant interpretation, the underrepresentation of people of African ancestry in reference genomes, the lack of resources and current knowledge. Suggestions to overcome these have been provided. A range of views were expressed regarding the requirements for informed consent, from comprehensive, detailed consent to broad coverage of risks and benefits. The importance upscaling GC training with curriculums including WES data interpretation, as well as upskilling of clinicians and genetic nurses were emphasised by participants. Future research should focus on exploring community understanding and views of what results should be fed back, prior to the development of guidelines for disclosure.
Exercise intervention alters HDL subclass distribution and function in obese women

Nicholas J. Woudberg*, Amy E. Mendham, Julia H. Goedecke and Sandrine Lecour

Introduction: Obesity is a major risk factor for cardiovascular disease and alters HDL function and subclass distribution. Exercise benefits obese patients by reducing cardiovascular risk. However, the effect of exercise on HDL function and subclass is unknown. We therefore aimed to investigate how an exercise intervention may improve HDL function and alter HDL subclass in obese women.

Subjects and Methods: Thirty-two obese black South African women were recruited and randomly assigned to exercise (40-60 min of aerobic and resistance exercise 4 times/week, n=20) or control (no exercise, n=12) conditions for 12-weeks. HDL functionality was assessed by measuring reverse cholesterol efflux capacity, anti-inflammatory function, paraoxonase (PON) activity and platelet activating factor acetylhydrolase (PAF-AH) activity. PON-1 and PAF-AH expression were determined in serum using Western blotting. Levels of large, intermediate and small HDL subclasses were measured using Lipoprint®.

Results: Independent of effects on body composition, exercise lowered PON activity (-0.08±0.02 vs +0.01±0.02 U/L, p<0.05 for interaction) and PAF-AH serum expression compared to the control (-0.27±0.08 vs 0.13±0.10 Arbitrary Units (AU), p<0.05 for interaction). Exercise decreased the distribution of small HDL subclasses compared to the control (-2.0±0.7% vs +1.7±0.9%, p<0.05 for interaction). Exercise did not alter HDL reverse cholesterol efflux capacity and anti-inflammatory function

Interpretation: A 12-week aerobic intervention was associated with improvements in HDL functionality and decreases in small HDL subclasses. The beneficial effect of exercise on HDL function and composition is a possible mechanism by which exercise reduces cardiovascular risk in obese women.
Assessing the utility of a heritable connective tissue panel in a resource constrained setting.

Rizqa Sulaiman-Baradien*, Nakita Laing, Ambroise Wonkam, Karen Fieggen, Nico De Villiers

Introduction: Suspicion of an inherited connective tissue disorder is a common indication for referral to medical genetic services. Phenotypic overlap is well described and a clinical diagnosis may not always be possible. The implications of a positive diagnosis are far reaching and allow for better management for the index patient and family. Molecular genetic panel tests using next generation sequencing technologies have been proven to be of particular value in disorders where there is both genetic and phenotypic heterogeneity and may prove to be a cost-effective way reduce unnecessary investigation and screening in resource constrained areas. We aimed to establish a proof of principle of clinical utility using panel testing for inherited connective tissue disorders in adult and paediatric cardio-genetic clinics in Cape Town.

Subjects and Methods: Patients with features of an inherited connective tissue disorder (n=1) or Marfan syndrome (n=4) were carefully selected. In collaboration with Ampath Laboratories, DNA samples were tested with a connective tissue panel test of 15 genes. In silico prediction, clinical correlation and literature review were used to determine the pathogenicity of variants.

Results: Three of five patients had causative mutations identified, one in FBN1, one in TGFBR1 and one in TGFBR2. A case study of one of these patients, a 36-year-old woman with severe aortic root dilatation and a strong family history of sudden cardiovascular death is presented as an illustrative case whereby a pathogenic mutation in TGFBR1 in keeping with Familial Thoracic Aortic Aneurysm and Dissection Syndrome / Loeys Dietz 1 Syndrome was identified, facilitating cascade testing within the family.

Interpretation: This preliminary study illustrates how a molecular diagnosis has allowed for more targeted genetic counselling and management of patients allowing retrospective cascade counselling and testing in their families. Further analysis with the inclusion of more families and other inherited cardiovascular conditions could allow additional evaluation of the economic and psycho-social impact of the wider use of targeted panel testing in Cardio-genetic practice.
Genetic counselling in Cardio-genetic research: A case report of CDH2

Nakita Laing*, Sarah Kraus, Gasna Shaboodien, Maryam Fish and Bongani Mayosi

**Introduction:** Genetic mutations in cadherin-2 (CDH2) have recently been described as a novel cause of Arrhythmogenic right ventricular cardiomyopathy (ARVC). ARVC is a heterogenous autosomal dominant condition increasing the risk for sudden cardiac death (SCD) in young individuals. We report on a large family key to the identification of this novel cause of ARVC. The case report focuses mainly on the role of, and challenges faced, by genetic counsellors in the research setting of cardiovascular genetics.

**Case description:** The family was initially referred in 1996 when several family members were diagnosed as being clinically affected with ARVC based on the 1994 Task force criteria. A genetic counsellor became involved with the family in 2012 after a possible molecular cause was identified. The process of genetic counselling in this research setting included: telephonic discussions and arrangement of a family meeting to discuss the condition, the research progress, re-sampling and extension of the family history; Facilitation of phenotyping of key family members; and cascade screening of distant relatives at risk for the condition for early identification of disease. Following review of the molecular results and reclassification of individuals according to the updated 2010 Task force criteria, the phenotypic and genotypic information was integrated, allowing the identification of the novel CDH2 gene mutation. Translation of these research findings via telephonic result delivery has been performed which has also allowed presymptomatic testing in at risk individuals.

**Discussion:** This case highlights the role of the genetic counsellor specifically in the maintenance of open communication and relationships with the research team allowing feedback of research progress, ethical consideration of cascade screening and result delivery. Ongoing facilitation of presymptomatic testing and genetic counselling in this family allows the possibility to prevent SCD in newly identified at risk individuals.
DAA therapy for hepatitis C – the Liver Clinic experience to date

Mark Sonderup, Neliswa Gogela, * Wendy Spearman

**Introduction:** Direct Acting Antivirals (DAA) have revolutionized hepatitis C management. Historically, sustained virological response (SVR) rates ranged between 40-60%. Through access programs and generics, DAAs are affordable and accessible. We review our experience with DAAs to date.

**Subjects and Methods:** Patients sequentially treated with DAAs are included in a registry with virological data confirmed via standard lab techniques. A variety of DAA combinations were used as per standard guidelines and protocol, availability, cost and genotype (GT). Treatment outcomes are documented.

**Results:** 120 patients are included in the analysis, 84 men; median age 54 years with men significantly younger than women; median age 51 [IQR 46-59], 61 [IQR 49-68]; p=0.0083, respectively; 18% were HIV co-infected, 18% were treatment experienced. Genotype distribution included 28% (n=33) GT 1a, 14 % (n=17) GT 1b, 8% (n=10) GT 2, 14% (n=17) GT 3, 16% (n=19) GT 4 and 20% (n=24) GT 5a. Fibrosis score distribution was 2.5% F0; 26.6% F1; 26.6% F2; 14.3% F3 and 30% F4. Baseline median HCV viral load was log 5.9 [IQR 5.5-6.5]. On treatment, week 4 HCV RNA was undetectable in 76%, below the LLOQ in 13% and detectable in 11%, respectively. Baseline, week 4 and end of treatment median ALT was 79 [43-118]; 23 [16-31] and 22 [16-28], respectively, p<0.0001. To date, per protocol SVR 12 is 94% while for individual regimens, SVR 12 is - 98% for Sofosbuvir(SOF)/Ledipasvir(LDV); 94% for SOF/Daclatasvir (DCL), 100% SOF/Simeprevir(SIM); 100% Paritaprevir(PTV)/Ombitasvir(OMB)/Dasabuvir(DSV); 90% for PTV/OMB and 80% for SOF/Ribavirin. For SOF/DCL, SVR12 was 100% in GT-5 patients with 2 patients – a GT1a and 3a respectively failing SOF/DCL; for SOF/Ribavirin SVR12 was 100% in GT-2 with 2 patients – a GT-3a and 4b – failing therapy. HIV status did not influence SVR.

**Interpretation:** To date, our experience with DAA therapy in a pan-genotypic population, with many difficult to treat patients, confirms its markedly superior efficacy in achieving a SVR. Treatment availability and access should be expanded and up scaled.
Snowball sampling as a recruitment strategy in a hard to reach population

Ingrid Courtney*, Regina Panda, Nobukhosi Gwele, Bongani Cweya, Ingrid Katz, Catherine Orrell

Issues: The UNAIDS 90-90-90 treatment targets aim to dramatically increase the number of the people who receive HIV testing, link to antiretroviral therapy (ART) and achieve viral suppression by 2020. In South Africa less than half of those people known to be infected with HIV are on treatment, despite current WHO and South African recommendations that all HIV-positive individuals should take antiretroviral therapy (ART). In our previous study more than a third of newly diagnosed individuals did not return for their CD4 count results and a further 25% eligible for ART, did not access treatment within 3 months.

Our current study focusses on these individuals who have “refused” treatment. It is a multi-component, socio behavioural intervention aimed at promoting early and enduring uptake of treatment among PLWH in SA who otherwise would not access the benefits of freely available treatment. Our population is hard to reach as they have refused to initiate ARV’s despite being eligible to initiate.

This abstract addresses the challenge of seeking out and recruiting individuals who otherwise would not access care.

Project: We required 90 participants to be enrolled and followed for a total of 6 months (3 months of intervention and 3 months follow up). We used community-based treatment ambassadors to approach people they knew in the local community who were refusing to access ART and we intended to access further potential participants at local clinics or HIV testing sites. In reality, we have found that snowball sampling has becomes our most important recruitment strategy.

Snowball sampling is a nonprobability sampling technique where existing study participants recruit further participants from among their acquaintances. This sampling technique is often used in hidden populations which are difficult to reach or researchers to access.

The personal nature of snowball sampling builds trust between the researcher and the participants. It leverages the social networks of the participants. It makes them an active part of the research study which is community based. It builds and reinforces community cohesion.

Lessons learnt: This hard to reach population feels stigmatized and at large have not disclosed their HIV status. Thus, the impact that snowballing sampling can have on a community is exponential. Making a success of this technique largely depends on the initial contact and connections made during the early part of the participants enrolment and randomized process.

We hypothesise that due to the interpersonal nature of snowball sampling as a recruitment technique in a hard to reach population it will have a greater impact on mobilising the community, promoting agency and actively empowering them to make healthy life choices.
Heart rate as a novel target for peripartum cardiomyopathy?

Aqeela Imamdin*, Feriel Azibani, Lionel Opie, Karen Sliwa, Sandrine Lecour

Introduction: Peripartum cardiomyopathy (PPCM) is a cause of acute heart failure manifesting late during pregnancy, or within 6 months of delivery. One of its main symptoms is elevated heart rate (HR). During normal pregnancy, the HR is elevated but recovers approximately 4 weeks after delivery in humans. Experimental studies suggest that reducing HR with an inhibitor of the sino-atrial node may be of benefit in the setting of acute heart failure.

Aim: We explored whether long-term administration of Ivabradine would improve the outcome of heart failure in a mouse model of PPCM.

Subjects and Methods: Retrospective data analysis was conducted on clinical records of 27 PPCM patients. HR results were obtained at baseline and at 6 months follow-up from PPCM patients enrolled at the Cardiac Maternity Clinic at Groote Schuur hospital from 2012 – 2015. Poor outcome was defined as HR above 75 beats per minute (BPM) after 6 months of standard heart failure therapy.

Results: Poor outcome was observed in 19 out of 24 patients (74%) at 6 months on standard therapy with diuretics (78±8mg/day), ACE inhibitors (12±2mg/day) and beta-blockers (22±3mg/day). Average HR values were 95±3 BPM at baseline (n=27), and 83±12 BPM at 6 months (n=24, 1 deceased).

Interpretation: Standard therapy for PPCM did not satisfactorily improve HR in patients. This result supports that modifying HR without targeting the sympathetic nervous system or blood pressure in PPCM may be beneficial. Further exploration of this hypothesis in a mouse model of PPCM is required to test this novel concept.
Adolescent girls' PrEP uptake from a community-based mobile clinic: early results from the POWER cohort study

E Rousseau-Jemwa*, Linda-Gail Bekker

**Introduction:** PrEP (pre-exposure prophylaxis) is one of the most effective ways to prevent HIV acquisition in the world today. WHO recommends that PrEP should be offered to all population groups at 'substantial risk of HIV infection'. Adolescent girls and young women are considered one such population, also defined as key populations, in Southern and Eastern Africa. Optimal PrEP delivery models to key populations may vary.

**Subjects and methods:** The POWER study is a prospective cohort study enrolling up to 1000 sexually active HIV negative women aged 16-25 from a tailored, adolescent friendly mobile clinic providing sexual and reproductive health services (SRH). The primary objective of the study is rate of uptake of and adherence to PrEP. All young women visiting the mobile clinic were invited to view a promotional video, educating women about HIV prevalence and risks in their community, and the effectiveness of PrEP for HIV prevention. Thereafter, during individual SRH consultations, all eligible young women were offered PrEP with the option to accept, delay or refuse uptake.

**Results:** PrEP uptake was 22.4% (39 among 174 eligible so far), with majority (61.5%) falling in the 16-19 year age group. 35.9% of the group had a positive STI (gonorrhea and/or chlamydia) GeneXpert result. Only 7.7% had multiple partners, while 80% reported not able to use condoms on most occasions with their regular partner, contributing to the high concern (76.9%) of contracting HIV in the next year. At the month 1 follow-up visit 37% came for PrEP refills within the allowable window. From the group of potentially eligible girls who declined PrEP, 60% sited that they needed more time to decide.

**Interpretation:** PrEP uptake seems to be associated with younger age and high HIV risk perception related to inconsistent male condom usage. While a large number of potentially eligible adolescent girls chose to delay the decision regarding PrEP uptake, those who did initiate self-selected appropriately as indicated by high STI prevalence. Early data suggests ongoing work in ensuring persistence post uptake is required. PrEP delivery from a mobile clinic is feasible but requires optimization.
Ivermectin versus permethrin in the treatment of scabies: a systematic review and meta-analysis of randomized controlled trials

Ashar Dhana*, Hsi Yen, Jean-Phillip Okhovat, Eunyoung Cho, NaNa Keum, Nonhlanhla P. Khumalo

Introduction: Scabies affects over 130 million people. Permethrin is considered the most effective topical treatment for scabies. Ivermectin is the only oral alternative and can also be applied topically. Since trials comparing oral or topical ivermectin with topical permethrin have been inconclusive, we performed a meta-analysis.

Subjects and Methods: We searched PubMed, EMBASE, Cochrane Library, and references of articles for randomized controlled trials. The primary outcome was treatment failure. Secondary outcomes were persistence of itch and adverse effects. Two independent authors reviewed titles and abstracts, extracted data, and assessed study quality. We calculated pooled risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model.

Results: We included 15 trials involving 2,172 patients. Oral ivermectin was associated with increased risk of treatment failure compared with topical permethrin (RR 1.33, 95% CI 1.04-1.72, treatment failure rate: 14% [122/860] vs 10% [85/831], I²=0%, n=1,691). Meta-regression revealed no heterogeneity by study characteristics. Visual inspection of the funnel plot revealed no evidence of publication bias. Oral ivermectin was associated with a non-significant increased risk of persistent itch (RR 1.32, 95% CI 0.91-1.93, persistent itch rate: 13% [57/432] vs 10% [39/389], I²=0%, n=821). Topical ivermectin was associated with a non-significant increased risk of treatment failure compared with topical permethrin (RR 1.49, 95% CI 0.88-2.51, treatment failure rate: 10% [30/291] vs 7% [20/289], I²=0%, n=580). One trial found no significant difference in itch persistence between both agents. Number of adverse effects were few: 4.3% for oral ivermectin, 4.6% for topical permethrin, and 6.9% for topical ivermectin. There were no serious adverse effects. Limitations include potential performance bias and trial exclusion of pregnant women and children.

Interpretation: Oral ivermectin is less effective than topical permethrin. Topical ivermectin may have similar efficacy to topical permethrin, but further trials are warranted given the smaller sample size of this comparison. All three agents have low treatment failure rates and are well tolerated.
Skin manifestations are common and associated with a higher prevalence of congenital abnormalities in Zika virus infection

Lerinza van den Worm*, Nonhlanhla P. Khumalo

Introduction: The Zika virus was discovered in the rhesus monkeys of the Zika forest in Uganda and first reported in humans in 1952. Only 70 years later, in December 2015, the Zika virus outbreak occurred, and in February 2016 the World Health Organization declared a public health emergency because of associated congenital deformities. As of March 10, 2017, the Pan American Health Organization (PAHO) had cumulative reported 2,767 cases of confirmed congenital syndrome associated with Zika virus infection. However, details on individual cases are not published, making it impossible to analyze the proportion with skin involvement. Studies reviewing mothers of infants born with Zika-associated microcephaly also suggest that skin involvement is common (74%, 46% and 72%). What is still unclear is whether there is a correlation between skin involvement and adverse neurological outcomes.

Subjects and Methods: We incidentally recently conducted a Pubmed search for “Zika and Cases,” limited to “5 years” and “English.” The search yielded 346 results; 57 of these studies reported on the symptoms experienced by Zika patients, and 17 studies included pregnant patients infected with Zika virus who reported on a congenital outcome. We performed a Chi-Square test to determine if the difference between the congenital outcomes in those patients with and without skin involvement is significant. The magnitude of this difference can be estimated using the odds ratio with a 95% confidence interval.

Results: The identified 57 studies reported on 841 patients infected with Zika virus; a symptomatic rash was reported in 698 (83%) of these patients. Pregnant patients were included in 17 studies, and there were 283 pregnant patients; a rash occurred in 256 (91%) patients (mostly during the 1st and 2nd trimester). The remaining 27 patients did not report skin manifestations during pregnancy. The skin manifestations were described as a “maculopapular rash” (or exanthema) in six cases, a “pruritic rash” in two cases, and in the majority (248) merely as “rash.” In patients with skin manifestations, seven (3%) had no abnormalities and 249 (97%) adverse congenital outcomes. These adverse outcomes included microcephaly, fetal demise, macular atrophy, and craniofacial disproportion. Of the patients who did not experience a rash during pregnancy, 3 (11%) had no abnormalities, and 24 (89%) had adverse congenital outcomes including fetal demise, craniofacial disproportion, microcephaly, macular atrophy, and hip dysplasia. Using the values, we found the patients with skin involvement had a significantly higher probability of having adverse congenital outcomes (P-value 0.025). Patients with adverse congenital outcomes were also four times more likely to have skin involvement (OR 4.446). This was established with a 95% confidence interval (1.079, 18.32).

Interpretation: Considering the common embryologic development of the skin and the brain from the ectoderm, an association between the two organs from a congenital infection would not be surprising. In this report, skin involvement predicted a significantly higher probability of adverse congenital outcomes (P-value 0.025). The patients who had adverse congenital outcomes were four times more likely to have a history of a rash during pregnancy (OR 4.446).
95% CI 1.079, 18.321). Many more studies are needed to determine whether there is a positive correlation between skin manifestations and congenital outcome in Zika virus infection during pregnancy. Potential ascertainment bias may have occurred because only published cases were included in this review. However, considering that previous reports suggest that only 20% of individuals experience symptoms during Zika virus infection (maculopapular rash, arthralgia, malaise, headache, fever, conjunctivitis) the report by Andersen et al. of 91.3% in 264 patients and this report of 83% in 841 patients suggest that skin involvement might be more common in Zika patients presenting for healthcare than previously reported. The morphology and distribution of the “rash” experienced in Zika virus requires elucidation to aid early clinical diagnosis and appropriate patient management. This report also found a high prevalence of congenital abnormalities (89% and 97%), both much higher than the 46% of affected babies previously reported in pregnant women infected with Zika virus.
Thursday, 5th October

Oral presentations
Thursday, 5th October 2017

08:00 – 08:05  Opening remarks
Prof Ntobeko Ntusi

SESSION I

Chairperson: Prof Sandie Thomson & Prof Asgar Kalla

08:05 – 08:17  Melissa Nel (Neurology)
Gene expression profiling of myocyte cultures identifies perturbed
genome networks in ophthalmoplegic Myasthenia Gravis

08:17 – 08:29  Malika Davids (Pulmonology)
Anatomically distinct pathophysiological map of a pulmonary
tuberculosis cavity

08:29 – 08:41  Michele Tomasicchio (Pulmonology)
An autologous dendritic cell vaccine polarizes a Th-1 response which is
tumoricidal to patient-derived breast cancer cells.

08:41 – 08:53  Anil Pooran (Pulmonology)
A human lung orientated approach to correlates of risk in tuberculosis

08:53 – 09:13  Division research highlights from Division of Infectious Diseases
Prof Graeme Meintjes (20 mins)

09:13 – 09:25  Mothusi W. Moloi (Nephrology)
Association between Carotid Intimal Thickness, Monocyte Activation
and Renal Function Amongst HIV infected Patients in Botswana

09:25 – 09:37  Gill Watermeyer (Gastroenterology)
Differentiating Crohn’s disease (CD) and Intestinal Tuberculosis (ITB) at
presentation in patients with tissue granulomas

09:37 – 09:49  Nicholas J. Woudberg (Hatter)
Alteration in the composition and function of high-density lipoproteins
in hypertensive patients with heart failure

09:49 – 10:01  Nevadna Singh (Pulmonology)
Outcomes of patients undergoing resectional surgery for extensively
drug-resistant (XDR) pulmonary tuberculosis

10:01 – 10:20  Tea/Coffee
## SESSION II

**Chairperson: Prof Naomi Levitt & Prof Nicolas Novitzky**

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<td>Characteristics of Hepatitis B and C prevalence in key populations in South Africa</td>
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<td>10:32 – 10:44</td>
<td>Charlotte Schutz (CIDRI, IIDM)</td>
<td>Biomarkers associated with high early mortality in hospitalised patients with HIV-associated tuberculosis</td>
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<td>Charle Viljoen (Cardiology)</td>
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<td>Prof Jeanine Heckmann (20 mins)</td>
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<td>Emily Krogstad (Desmond Tutu)</td>
<td>Listening to at-risk youth: perspectives of young women and men in South Africa on the design of an implant for HIV prevention</td>
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<td>12:04 – 12:16</td>
<td>Rannakoe Lehloeny (Dermatology)</td>
<td>Randomized controlled single blinded trial comparing escalating versus full dose rechallenge in patients with tuberculosis-associated severe cutaneous adverse drug reactions.</td>
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SESSION III
Jack Bock Lecture 2017

Introduction of Speaker: A/Prof Sandrine Lecour

13:00 – 13:30 Speaker: Prof Vicki Lambert

The nexus between physical activity, obesity and food insecurity in LMICs: tackling “wicked problems” for public health

Professor Estelle Lambert is head of the Division of Exercise Science and Sports Medicine (ESSM), in the Department of Human Biology, Faculty of Health Sciences, and has been a fellow of the University of Cape Town since 2009. NIH, at the University of Cape Town. She is a National Research Foundation, B2-rated scientist, and is the author or co-author on over 205 peer-reviewed scientific publications. She is actively involved in research on physical activity and obesity and health, particularly in the Global South, and more underserved communities. She has acted as a consultant to the United States Centers for Disease Control and World Health Organization (WHO) on issues related to the Role of Diet and Activity in the Prevention of Non-Communicable Diseases, and Developing a Global Policy for Promoting Physical Activity for Health. She currently serves on the executive council of the International Society for Physical Activity and Health, and was a member of the Scientific Advisory Council for the International Obesity Task Force (2009-2014).

At present, she is the chairperson of the global advocacy movement for physical activity, Agita Mundo, and the first chair-person of the African Physical Activity Network (2007-2013), with more than 200 members representing more than 10 countries. She is the in-country principal investigator for South Africa for the NIH-funded, Modelling the Epidemiological Transition study (METS), was the co-principal investigator for WDF-funded, school-based intervention, Health Kick, as well as the South African principal investigator for the ISCOLE study (International Study on Childhood Obesity, Lifestyle and Environment). She is presently the principal investigator of the STOP-SA Study (Slow, Stop or Stem the Tide of Obesity in the People of South Africa). She has been a co-author of 2 Lancet series concerning physical activity and health, and one on obesity and health. She recently served on the South African Department of Health National Obesity Task Force, the end result of which was the Strategy for the Prevention and Control of Obesity in South Africa, 2015-2020. She is also the lead researcher for the Healthy Active Kids South Africa Report Card consensus and advocacy initiative, having produced a report card in 2007, 2010, 2014 and now 2016. Her current area of research focus is the nexus between obesity and food insecurity, and factors that shape health decisions in choice-constrained settings.
Session IV: Chairperson: Prof Nonhlanhla Khumalo & Prof Gillian Ainslie

13:30 – 14:05
Research Dragon’s Den:
Facilitators: Prof Liesl Zuhlke & Dr Blanche Cupido
Dragons: Prof Ntobeko Ntusi & Prof Graeme Meintjes
Participants: Dr Phumla Sinxadi, Dr Sean Wasserman, Dr Phindile Gina, & Dr Charle Viljoen

14:05 – 14:17
Chimota Phiri (Nephrology)

14:17 – 14:29
Helen Cross (Neurology)
Flail arm variant of motor neuron disease in the Western Cape with case-unaffected parents trio exome study

14:29 – 14:41
Wynand Goosen (Pulmonology)
Drug penetration gradients in pulmonary cavities generate heterogeneity and extensively drug-resistant tuberculosis.

14:41 – 14:53
Shepherd Kajawo (Nephrology)
Incidence of complications in adults after percutaneous native renal biopsy in low to middle income countries: A systematic review

14:53 – 15:05
Philippa Randall (Pulmonology)
Concentration of urine lipoarabinomannan improves the sensitivity of the Determine LAM TB lateral flow assay

15:05 – 15:17
Jason D. Limberis (Pulmonology)
Infectiousness of patients with drug sensitive and drug resistant tuberculosis.

15:17 – 15:29
Richard Court (Clinical Pharmacology)
The bioavailability of rifampicin in fixed dose combinations widely used in South Africa to treat drug-susceptible tuberculosis

15:29 – 15:41
Luhan Swart (Haematology)
HIV-associated Hodgkin lymphoma at Groote Schuur Hospital, Western Cape, South Africa

15:41 - 15:53
S da Silva (Dermatology)
The use of hair to detect (and monitor) chronic hyperglycemia - a pilot study

15:53 – 16:10
Tea
38th Annual Bernard Pimstone Memorial Lecture

Introduction of Speaker: Prof Ike Okpechi

Speaker: Prof Alta Schuute

Putting the Hype back into Hypertension: Perspectives on the Progression and Prevention of Hypertension in South Africa

Alta Schutte is Professor of Physiology and the DST/NRF SARChI Chair in the Early Detection and Prevention of Cardiovascular Disease in South Africa – hosted by the Hypertension in Africa Research Team (HART) at the North-West University. She is also the Director of MRC Extramural Unit for Hypertension and Cardiovascular Disease.

Her research focus on the identification of early markers for the development of hypertension, and ultimately the prevention of cardiovascular disease in the black South African population. She has published nearly 200 papers on the topic of hypertension, is regularly invited as keynote speaker to international hypertension meetings, and supervised over 60 honours and postgraduate students. She has been acknowledged for her work as the winner of the Distinguished Young Women Scientist in the Life Sciences award; and NSTF South 32 TW Kambule Award (2016/2017); the British Association Medal from the Southern Africa Association for the Advancement of Science (S2A3). She was also the recipient of the Meiring Naude Medal from the Royal Society of South Africa, and the AU-TWAS (African Union & The World Academy of Sciences) Award.

She serves on the Editorial Board of established cardiovascular journals, such as the European Journal of Preventive Cardiology, Journal of Human Hypertension, Current Hypertension Reports, Current Obesity Reports, and Clinical Science. She is one of 20 founding members of the South African Young Academy of Science (SAYAS); the immediate Past President of the Southern African Hypertension Society (SAHS); and the Vice President of the International Society of Hypertension (ISH).
Chairperson: Prof Ntobeko Ntusi

17:00 – 18:30 Department of Medicine Cocktail Party and Awards ceremony

- Best poster presentation Prize
- Department of Medicine Best Publication Award
- Bernard Pimstone Prize
- Department of Medicine Prize for Clinical Research
SESSION 1

Chairperson:

Prof Sandie Thomson
&
Prof Asgar Kalla

08:05am – 10:01am
Gene expression profiling of myocyte cultures identifies perturbed gene networks in ophthalmoplegic Myasthenia Gravis

M Nel*, S Prince, J M Heckmann.

Introduction: While extraocular muscles are affected early in Myasthenia Gravis (MG), we have identified a distinct sub-phenotype of treatment-resistant ophthalmoplegia (OP-MG) frequently observed in patients with African-genetic ancestry. We speculate that OP-MG may result from aberrant responses in muscle damage/repair pathways, although the exact cause is unknown. Using both a candidate gene and an extended whole exome sequencing (WES) approach in an extreme sample of OP-MG vs control MG individuals we have previously identified OP-MG associated gene variants in a number of genes which share common biological roles related to the immune response, myogenesis and gangliosphingolipid biosynthesis.

Subjects and Methods: 16 individuals with MG and African-genetic ancestry were recruited, 10 with OP-MG and 6 with no ophthalmoplegia (control MG). We performed skin biopsies and developed a ‘muscle’ model for each individual by transdifferentiating dermal fibroblasts into myocytes through transduction with an adenovirus expressing MyoD. To mimic patient-specific MG-induced muscle pathway responses, we stimulated the myocytes with homologous AChR-antibody positive MG sera (MGS) and profiled the expression of 83 relevant genes using a quantitative PCR array.

Results: Differential gene expression analysis identified genes which were differentially expressed between OP-MG and control MG myocytes (fold change <1.5 or >1.5, p<0.05). For example, control MG myocytes exposed to MGS upregulated the expression of ST3GAL6 and SPHK1, two enzymes involved in gangliosphingolipid biosynthesis. In addition, the expression levels of numerous gene pairs involved in myogenesis pathways were negatively correlated in control MG, but positively correlated in OP-MG.

Interpretation: The observation of differential gene expression and correlation between the two sub-phenotypes suggests that OP-MG is characterised by perturbations in novel regulatory gene networks. The dysregulated expression of genes involved in the myogenesis and gangliosphingolipid pathways provides support for the hypothesis that the EOM synaptopathy in OP-MG may be attributed to altered muscle regeneration.
Anatomically distinct pathophysiological map of a pulmonary tuberculosis cavity


Introduction: There is poor understanding of protective immunity and the pathogenesis of cavitation in tuberculosis patients. There has, hitherto, not been a detailed transcriptomic spatial map of tuberculosis lung cavities.

Subjects and Methods: We systematically biopsied anatomically discrete locations in tuberculosis cavities from lungs of patients undergoing surgical resection (n=14), and controls without tuberculosis (n= 10), to construct a cavity-specific spatially compartmentalized map using RNA sequencing and histology. Biopsies were obtained from eight specific positions within and around the cavity immediately post resection. Differentially expressed genes compared to controls were mapped to physiological pathways.

Results: The median lung cavity volume was 50cm³ (range: 15-389cm³). RNA sequence reads, of which 31% were splice variants, mapped to 19,049 annotated human genes. In peri-cavitary normal appearing lung tissue only 33% of pathways showed significant expression change despite having a similar bacillary burden to diseased tissue. However, in the cavity wall 72% of pathways showed high intensity increased expression. By contrast, in the cavity center with a high bacillary burden, 53% of pathways were massively downregulated, which differed from airways and sputum. In particular, several neuroendocrine pathways (dopamine, glutamate, synaptic long-term signaling) were significantly downregulated together with those encoding for calcium, RIG1, and other pathogen-recognition receptors. Genes encoding for EIF2, TREM-1 and PPAR-ϒ signaling, amongst others, were upregulated.

Interpretation: These data may have important implications for understanding the pathogenesis of failed host immunity and have uncovered several, hitherto, unrecognized pathways and targets that may be useful for the design of vaccines, host-directed therapies, and transmission prevention.
An autologous dendritic cell vaccine polarizes a Th-1 response which is tumoricidal to patient-derived breast cancer cells.


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**Introduction**: Breast cancer remains one of the leading causes of cancer-associated death worldwide. Conventional treatment is associated with substantial toxicity and suboptimal efficacy. We therefore developed and evaluated the *in vitro* efficacy of an autologous dendritic cell (DC) vaccine to treat breast cancer.

**Subjects and Methods**: We recruited 12 female patients with stage 1, 2, or 3 breast cancer and matured their DCs with autologous tumour-specific lysate, a toll-like receptor (TLR)-3 and 7/8 agonist, and an interferon-containing cocktail. The efficacy of the vaccine was evaluated by its ability to elicit a cytotoxic T-lymphocyte response to autologous breast cancer cells *in vitro*.

**Results**: Matured DCs (> 60% upregulation of CD80, CD86, CD83, and CCR7) produced high levels of the Th1 effector cytokine, IL12-p70 (1.2ng/ml; p<0.0001), compared to DCs primed with tumour lysate, or matured with an interferon-containing cocktail alone. We further showed that matured DCs enhance antigen-specific CD8+ T-cell responses to HER-2 (4.5%; p<0.005) and MUC-1 (19%; p<0.05) tetramers. The mature DCs could elicit a robust and dose-dependent antigen-specific cytotoxic T-lymphocyte response (65%) which was tumoricidal to autologous breast cancer cells *in vitro* compared to T-lymphocytes that were primed with autologous lysate loaded-DCs (p<0.005). Lastly, we showed that the mature DCs post-cryopreservation maintained high viability, maintained their mature phenotype, and remained free of endotoxins or mycoplasma.

**Interpretation**: We have developed a DC vaccine that is cytotoxic to autologous breast cancer cells *in vitro*. The tools and technology generated here could now be applied to a phase I/IIa clinical trial.
A human lung orientated approach to correlates of risk in tuberculosis

Anil Pooran*, Malika Davids, Richard Meldau, Fawziyah Thompson, Phindile Gina, Philippa Randall, Lynelle Mottay, Ali Esmail, Keertan Dheda

Introduction: Currently tested vaccines against tuberculosis have been ineffective. Evidence suggests that a robust Th1 immune response is insufficient to prevent disease progression. Immunological correlates of risk are poorly understood within the human lung, the organ of initial contact with *M. tuberculosis*. We evaluated a comparative, first in man, lung antigenic challenge model (PPD and live BCG) to investigate local *in vivo* pulmonary immune responses in HIV-uninfected individuals with different risk susceptibility profiles based on clinical, radiological and immunodiagnostic profiles (immunodiagnostic test negative despite exposure; presumed LTBI; previous active TB; recurrent TB; self-cured TB).

Subjects and Methods: PPD, live BCG, and saline (control) were instilled into different lung segments via bronchoscopy under conscious sedation. Initial experiments were performed to optimise BCG and PPD concentrations. Bronchoalveolar lavage (BAL) was performed prior to antigenic challenge (baseline) and 72 hours post-challenge. Peripheral blood samples and BCG challenged skin biopsy samples were concurrently collected. Flow cytometry was used to analyse BAL and peripheral blood cells for cell surface markers and cytokine/chemokine expression profiles associated with innate and cell-mediated immune pathways.

Results: Antigenic challenge using BCG ($10^4$ CFU) and PPD (0.5TU) was optimal in generating measurable alveolar immune responses [increase in total cell numbers from baseline: (BCG-driven, $p=0.03$; PPD-driven, $p=0.004$)]. Immune responses were highly compartmentalized in the lung compared to the peripheral blood. PPD challenge in those with previous TB showed significantly increased TLR2+IL6+ co-expression in macrophages ($p=0.01$) but decreased biomarker-specific T cell expression [CD4+TNFα ($p=0.05$), CD8+TNFα ($p=0.02$), and Th17 homing cells i.e. CD4+IL17+CCR6+; $p=0.004$]. However, a high degree of inter-patient variability was observed.

Interpretation: These preliminary findings demonstrate the feasibility of using an *in vivo* mycobacterial-specific human lung antigenic challenge model. The emerging data will likely have implications for the design of vaccines and immunotherapeutic interventions.
Association between Carotid Intimal Thickness, Monocyte Activation and Renal Function Amongst HIV infected Patients in Botswana

M.W Moloi*, L. Mokgatlhe, I.G. Okpechi, M. Mosepele

Introduction: HIV infection is associated with immune dysregulation, inflammation and increased monocyte activation. These changes lead to premature atherosclerosis. The relationship between HIV-associated sub-clinical atherosclerosis, monocyte activation and renal function has not been well elicited.

Subjects and Methods: We studied virally suppressed HIV positive patients on ART, aged between 30 and 50 years old in Botswana to assess the role played by carotid intima media thickness (CIMT), soluble CD163 on estimated glomerular filtration rate (eGFR). CIMT was measured using sonocal® edge detection software using stored still images. Unadjusted analysis was performed to assess association between cardiovascular (CVD) risk factors / CIMT / log sCD163 and statistically significant variables included in a multiple variable linear regression model to assess the same associations.

Results: 197 participants were included in the analysis. The mean age of patients was 39.08±5.03 years, females (56.4%) were significantly younger (p=0.021). Serum creatinine was significantly higher in men (72.50 (IQR 64.00-83.25) vs 57.00 (IQR 50.00-65.00) mmol/L, p<0.001) but there was no gender difference in eGFR (p=0.122) and mean CIMT was relatively higher in men (p=0.038) while there was no gender difference in log sCD163 levels (p=0.473). Hypertension was present in 33% of participants while (3%) had CKD. The median duration of ART was 9.0 (IQR 10.0-7.0) years while the median CD4 T lymphocyte count at baseline and enrolment were 128.0 (IQR 182.0-53.5) and 542.0 (IQR 696.5-412.5) cells/mm3 respectively. There was no statistically significant relationship between mean CIMT nor log sCD163 (β -0.209, 95% CI -0.544, 0.125, p = 0.218 and β -0.013, 95% CI -0.044, 0.018, p = 0.422) and log eGFR.

Interpretation: There was no significant relationship between eGFR and CIMT or eGFR and sCD163 amongst younger HIV patients on fully suppressive ART. Hypertension remains the prevalent in this population.
Incidence of complications in adults after percutaneous native renal biopsy in low to middle income countries: A systematic review

Shepherd Kajawo*, Jean Jacques Nobiap, Udeme Ekrikpo, Andre Pascal Kegne, Ikechi Okpechi

Background: Kidney biopsy is essential in guiding clinicians to diagnose, treat and prognosticate renal disease. However, the procedure can be marred by various complications. The reported occurrence varies among countries or regions and is also affected by several clinical and technical factors. This systematic review aims to evaluate the incidence of major complications after percutaneous renal biopsy in low to middle income countries (LMIC).

Subject and Methods: We included studies of populations from LMIC as per the published World Bank 2017 country list. Relevant abstracts published from 1 January 1980 to 30 June 2017 were searched in PubMed. Two review authors independently screened, selected studies, extracted data and assessed the risk of bias in each study. A third reviewer arbitrated in cases of disagreements. The data was entered on Excel spreadsheet and analysed according to geographical region and Income group.

Results: 18 studies with total biopsies of 7,474 biopsies met inclusion criteria. The ages ranged 19 to 68. Most of the studies 67% were from Asia and very few studies from Africa region 5%. The rate of macroscopic haematuria was min 0.9% to max 9.7%. The highest bleeding rates were in lower income countries. Red cell transfusion rates ranged from 0.3% to 11%. Higher rates of transfusion were seen with 14-gauge needles compared with smaller needles. There were also higher bleeding complications reported from studies coming from lower income group countries compared to those from middle income groups. Nephrectomy rates were very low 0.5% to 1 %. There was also a higher trend of complications from African region compared to other continents. There was no death reported from renal biopsies.

Interpretation: There are few studies of renal biopsies reported from low income countries with the bulk of studies coming from Asia. There also appears to be a higher trend in bleeding complications in this region. There is therefore need for intervention to increase biopsy rates in low income countries and strategies to reduce complications. A Metanalysis is recommended and a comprehensive search of other databases and grey literature to try to identify more studies from low income countries not published in PubMed.
Alteration in the composition and function of high-density lipoproteins in hypertensive patients with heart failure

Nicholas J. Woudberg*, Richard James, Olusoji Billyrose, Dike Ojji, Miguel Frias, Sandrine Lecour

Introduction: Hypertension related complications account for 9.4 million worldwide deaths and is a major contributor to cardiovascular disease (CVD), including heart failure. The pathophysiology of the disease involves endothelial dysfunction, an effect that may be enhanced with high-density lipoprotein (HDL) dysfunction. We aim to compare HDL composition and function in healthy and hypertensive patients with/without heart failure.

Subjects and Methods: Nigerian patients (n=90) were divided into healthy controls, hypertensive patients and hypertensive patients with heart failure (HFF) (inclusion criteria measured by echocardiography and blood pressure). HDL function was assessed by measuring paraoxonase activity, HDL anti-inflammatory function and HDL-mediated activation of endothelial nitric oxide synthase (eNOS). ApoA1 and ApoM in HDL were measured using Western blot techniques whilst sphingosine-1-phosphate (S1P) was assessed using mass spectroscopy. HDL subclass distribution was measured using Lipoprint® system.

Results: S1P content in HDL was lower in HFF patients compared to controls (165 ± 55 vs 201 ± 73 pmol/mg, p<0.05). ApoA1 was unchanged. HDL subclass distribution shifted in HFF patients from large (48 ± 15 vs 63 ± 7%, p<0.005) to small HDL (7 ± 9 vs 2 ± 4%, p<0.05) compared to controls. Paraoxonase activity and anti-inflammatory function did not differ between groups. In contrast to HDL from control patients, HDL from all hypertensive patients failed to activate eNOS.

Interpretation: HDL composition, subclass and function are modified in patients with hypertension and heart failure. Our data suggest that these changes in HDL may contribute to the pathophysiology of heart failure associated with hypertension.
Outcomes of patients undergoing resectional surgery for extensively drug-resistant (XDR) pulmonary tuberculosis


Introduction: The overall treatment outcomes of XDR-TB with the available chemotherapeutic regimens in South Africa are poor. In appropriate patients with localized disease and adequate pulmonary reserve, surgery is an important adjunctive part of management. However, outcomes of surgery in these patients are unknown.

Objectives: To evaluate outcomes (culture-conversion, and treatment-related failure, completion or cure) and all-cause mortality in patients who have undergone resectional lung surgery for XDR-TB.

Methods: All consenting XDR-TB patients undergoing surgery at GSH between July 2010 and December 2016 were prospectively enrolled. Patients were offered lung resection based on conventional physiological and radiological assessments of operability and resectability, as determined by a multidisciplinary team at Groote Schuur Hospital. Patients were followed up to determine mortality status and treatment outcomes at 24 months after surgery.

Results: A total of 35 patients underwent surgery. The mean age was 36; 17/35 (49%) were male, and 26% were HIV-positive. Pneumonectomy was the most common procedure performed (57%). In total, 4 patients (11%) were lost to follow up by the end of the 2-year follow up period. There were 6/35 (17%) deaths within the first 6 months after surgery, and a further 6 deaths by 2 years. Total all-cause mortality was 34% at 2 years. In patients who were sputum positive at the time of surgery 11/29 (15%) culture converted by 6 months. Only 6/26 (23%) of sputum positive patients maintained culture conversion to 2 years and are considered programmatically cured. In those who were culture negative at surgery 3/5 (60%) remained culture negative at 2 years.

Interpretation: Resectional surgery for XDR-TB in combination with chemotherapy resulted in a cure in a minority of patients. These data inform clinical practice and underscores the need for adjunctive therapy with effective drugs if surgical outcomes are to be improved.
SESSION 2

Chairperson:

Prof Naomi Levitt

&

Prof Nicolas Novitzky

10:20am – 10:40am
Characteristics of Hepatitis B and C prevalence in key populations in South Africa

Mark Sonderup*, Nishi Prabdial-Singh, Jack Manamela, Adrian Puren, Andrew Scheibe, Katherine Young, Lorraine Moses, Anna Versfeld, Kevin Rebe, Nelson Madeiros, Dawie Nel, Harry Hausler, C. W. Spearman

Introduction: Few data exist on the prevalence of hepatitis B and C (HBV, HCV) in vulnerable and key populations in South Africa, knowledge which is key to achieving elimination. We elected to characterize prevalence in 3 key populations – men who have sex with men (MSM), sex workers (SW) and people who use/inject drugs (PWUD/ID).

Subjects and Methods: Prospectively, participants from self-identified key population groups were recruited from 7 urban centres. Relevant demographic data was captured. For HBV, HBsAg was screened using the point of care (POC) Determine® test and for hepatitis C, the HCV Oraquick POC test. Laboratory based ELISA was performed to validate HCV POC screening tests. In HCV positive screens, viremia was confirmed with RNA quantification using the COBAS® AmpliPrep/ TaqMan® HCV test (Roche diagnostics) and genotype (GT) with the VERSANT® HCV Genotype assay.

Results: To date, n=2229 participants have been screened including 541 MSM, 1159 SW and 529 PWUD/ID. Median age (years) in each group was 34 [IQR 25-40]; 30 [IQR 24-33] and 32 [26-36], respectively; males, 85%, predominating in the PWUD/ID and females, 87%, in the SW group. Ethnic/race distribution of participants was 42.6% Black, 38% White, 17.4% Mixed Ancestry and 2.1% Asian. Overall, 14% (n=323) were HCV POC test positive and 4% (n=96) HBsAg positive. Positive HCV and HBsAg POC tests, respectively, were distributed as follows between groups: HCV - 57% (n=304) PWUD/ID; 3% (n=16) MSM and 0.003% (n=3) in SW; HBsAg - 5% (n=28) PWUD/ID; 4% (n=19) MSM and 4% (n=49) in SW. In the HCV POC test positive group, 28.8% were HIV co-infected, with most, 92%, in the PWUD/ID group. Of those who screened HCV POC positive, 75.8% were viremic. Overall, median HCV viral load (log IU/ml) was 5.5 [IQR 4.9-6.0] with no difference observed between groups - 5.7 [IQR 5.0-6.1] MSM; 5.5 [IQR 4.9-6.0] PWUD/ID and 4.3 [range 2.9-5.6] SW, respectively; p=0.55. Genotype distribution included 67.5% GT1a, 1.7% GT1b, 3% GT1 (no subtype); 0.9% mixed GT 1a and 3; 25.2% GT3 and 1.7% GT4. Notably, GT1a correlated significantly with Black compared to White ethnicity/race, r = 0.87, p = 0.0021 and with male gender, r = 0.97, p < 0.0001.

Interpretation: In this unique study of key populations in South Africa, hepatitis B mirrors known general population HBV seroprevalence rates, however, hepatitis C prevalence is significant with GT 1a and 3 predominating. These data have implications for viral hepatitis elimination strategies being developed in South Africa.
Biomarkers associated with high early mortality in hospitalised patients with HIV-associated tuberculosis


Introduction: Despite the availability of antiretroviral and TB treatment, there is high early mortality among inpatients diagnosed with HIV-associated TB. HIV infection impairs gastrointestinal (GI) mucosal immunity and barrier function allowing translocation of bacterial products. We hypothesised that impaired GI barrier function in patients hospitalised with HIV-associated TB contributes to systemic immune activation and mortality. We measured biomarkers related to bacterial product translocation and immune activation, and their association with mortality, in hospitalised HIV-infected TB patients.

Subjects and Methods: A prospective cohort study was conducted at Khayelitsha Hospital. HIV-infected patients with CD4 T-cell count <350 cells/µl and suspected TB were enrolled. Clinical samples were obtained at TB treatment initiation and 12-week mortality ascertained. Inflammation and translocation biomarkers were measured using ELISA and 27-plex Luminex.

Results: Of 659 patients, 570 (86.5%) were diagnosed with TB (85% of cases were microbiologically-proven). Twelve-week mortality was 21% (121/570). Median time to death was 13 days [IQR = 4-35 days]. Patients who died were older (39 vs. 35 years, p<0.001) with lower CD4 counts (39 vs. 62.5 cells/µl, p=0.001) and more frequently grew MTB on blood culture (55% (64/121) vs. 35% (153/440), p=0.001). Fatal cases had significantly higher CRP, procalcitonin, d-dimer, interleukin(IL)-6, IL-1 receptor antagonist, IL-8, interferon-gamma induced protein 10, monocyte chemotactractant protein (MCP)-1, macrophage inflammatory proteins (MIP)-1alpha, MIP-1beta, soluble CD14, venous lactate (2.3 vs. 1.7 mmol/l, p<0.001) and trefoil factor 3 (indicative of GI-mucosal damage). Patients who died had significantly lower haemoglobin (7.9 vs 8.8 g/dL, p=0.002), TNF-alpha, interferon-gamma, eotaxin, basic fibroblast growth factor (FGF), IL-12p70, IL-4, IL-5, IL-7, IL-13, IL-17, RANTES protein, platelet-derived growth factor (PDGF)-BB and endotoxin core-IgM antibody (potentially indicating higher endotoxin blood levels).

Interpretation: Approximately one-fifth of hospitalised patients diagnosed with HIV-associated TB died within 12 weeks. Mortality associated with higher levels of markers of systemic immune activation and GI-mucosal damage.
Outcomes of a PD-First Programme in Cape Town, South Africa

Bianca, Davidson*, Kathryn Manning, Brian Rayner, Nicola Wearne

Background: South Africa [SA] currently performs the most peritoneal dialysis in Africa. Yet, outcome data is limited. With the collision of epidemics of communicable and non-communicable diseases in Africa the need for chronic dialysis is escalating. Peritoneal dialysis [PD] remains a life-saving modality especially as haemodialysis is limited in the state sector.

Methods: We retrospectively analysed all patients undergoing PD at Groote Schuur Hospital from January 2008 until June 2014 and thereafter prospectively until June 2015. Variables included demographics, adequacy, modality, fluid, cardiovascular risk and diabetes. The influence of these variables on peritonitis rate, technique and patient survival were assessed.

Results: 230 patients were initiated on PD, 31 were excluded as they were on PD for < 90 days. The mean age was 39.7 +/- 10.4 years [SD], 49.8% were male and 63.8% were mixed ancestry. 9.8% were diabetic at dialysis initiation. The average length of time on PD was 17 months (IQR 8 – 32). The peritonitis rate was 0.87 events per patient years. One, 2 and 5-year patient and technique survival was 91.3%, 79.6% and 50.2% and 79.3%, 64.8% and 30.5% respectively. Fluid overload (p=0.002) and low haemoglobin (p=0.001) were independent risk factors for poor survival. African race (HR 1.95, 95% CI (1.20 – 3.17) and fluid overload (p=0.001) were both predictors of technique failure.

Conclusions: In our PD-First programme the results are encouraging, despite lack of home visits due to safety, resource limitations and a high disease burden. Technique failure in African race needs further evaluation. Peritoneal dialysis remains a viable, life-saving alternative in an African setting.
Online ECG training improves ECG interpretation skills of medical interns

Charle Viljoen*, Rachel Weiss, Vanessa Burch, Kathryn Manning, Ashley Chin, Mpiko Ntsekhe, Rob Scott Millar

Introduction: Junior doctors often struggle with electrocardiography. Incorrect ECG interpretation could result in inappropriate decisions with adverse outcomes. We assessed the impact of a web-based learning package, ECG ONLINE (http://ecgonline.uct.ac.za), on the ECG training of interns.

Subjects and Methods: Interns at Groote Schuur Hospital were studied prospectively between July and October 2015. Participants voluntarily completed multiple-choice tests eight weeks apart, before and after they received access to ECG ONLINE. Each test comprised of the same 35 topics, but different ECGs. Test scores were correlated with the number of ECGs that participants analysed online.

Results: Of the 63 interns invited to participate, 37 were enrolled. Mean test scores improved from 45% (SD 15.2) to 54% (SD 16.5) between the pre-intervention and post-intervention tests (p < 0.001). The proportion of participants who correctly diagnosed atrial fibrillation and ventricular tachycardia improved from 26% to 69% (p < 0.001) and 39% to 62% (p = 0.049) respectively. In the fourteen participants who completed more than half the online modules, mean scores improved from 49% to 61% (p = 0.013) between the pre-intervention and post-intervention tests, versus 43% to 55% (p = 0.002) in the seventeen who completed less than half the online modules. Participants who did not access the website showed no improvement, (39% to 40%, p = 0.756).

Interpretation: Interns lack ECG interpretation skills, which can be significantly improved by a self-directed online programme. Web-based learning is an inexpensive, accessible and flexible learning option. Wider use in undergraduate and postgraduate education needs to be determined.
Effect of new teaching methods on medical students’ self-efficacy

Fiona Drummond*, Harold Amaler, Sean Wasserman, Tasnim Bana, Stella Botha, Vanessa Burch

Introduction: Students’ self-efficacy beliefs influence their learning and the likelihood of engaging with, and completing, complex tasks such as making a diagnosis. Strategies for organizing, prioritising and visualising information to facilitate clinical reasoning during patient consultations are not routinely used, and their impact on students' self-efficacy beliefs are not known. This study compared the impact of traditional bedside teaching (BT), diagnostic maps (DM), structured reflection charts (SRC) and algorithm-based treatment guidelines (PACK) on students' self-efficacy beliefs regarding their diagnostic reasoning ability during patient encounters.

Subjects and Methods: 4th year medical students completing a medical clerkship (January - June 2016) were invited to participate in the study. They spent 2 weeks in OPD using DM, SRC and PACK during patient encounters. A 9-item diagnostic reasoning self-efficacy scale was used to determine the self-efficacy effect of these methods, as compared to traditional bedside teaching (BT). The Study was approved by UCT.

Results: All 88 students completed and participated in the study. Global ratings of clinical reasoning self-efficacy beliefs were significantly improved after completing the clerkship (p<0.0001). BT had a greater positive effect on self-efficacy beliefs for data gathering and analysis as compared to DM (p<0.0001), SR (p<0.0001) and PACK (p<0.0001). DM and SRC, as compared to BT, had an equivalent (p>0.05) or greater positive effect (p<0.001) on student’ self-efficacy beliefs regarding data synthesis ability. PACK had a significantly greater positive effect on students’ beliefs about their ability to develop basic management plans, as compared to DM, SR and BT (p<0.001 for all comparisons).

Interpretation: Novel cognitive strategies for organizing, prioritizing and visualizing clinical information had a positive effect on the self-efficacy beliefs of students’ regarding their clinical reasoning ability during patient consultations.


**Introduction:** South African adolescents are at risk for HIV acquisition. PrEP is licensed and being offered to key populations, but not yet to adolescents. This open-label 12-month PrEP study examined uptake, safety and adherence to PrEP and assessed sexual risk behaviour among adolescents in Soweto and Cape Town, South Africa.

**Subjects and Methods:** Sexually active, healthy, HIV negative, adolescents (15-19 years) participated in a study of Tenofovir/Emtricitabine PrEP. Participants were asked to take daily PrEP for at least 3 months, were seen monthly, after which they could opt-out of PrEP if preferred. At subsequent 3-monthly follow-up visits, participants could decide to stay on or off PrEP per preference. Laboratory and clinical safety monitoring occurred at each visit, including HIV and pregnancy testing. Plasma and dried blood spots (DBS) were serially collected for tenofovir (TFV) and tenofovir diphosphate (TFV-DP) levels at every PrEP refill visit. Plasma TFV levels were offered at each visit as part of adherence counselling.

**Results:** 244 individuals were screened, 148 were enrolled (median age 18, 67% F). 3 (1%) had undiagnosed HIV and 9 (6%) were pregnant at screening. STI diagnosis at baseline was high (40%) and remained high throughout. 26 (18%) participants opted out of PrEP at 12 weeks. Thereafter PrEP opt-out (and opt-in) at months 6 and 9 included 41% and 43% (5% and 7%) of the cohort respectively. PrEP was safe and reasonably well tolerated. Plasma TFV levels were detectable in 57% of participants at week 12, 38% at week 24 and 38% at study end. One HIV seroconversion occurred on study (0.76/100 person-years) in a 19 year old woman who had stopped PrEP 24 weeks prior to diagnosis.

**Interpretation:** Pluspills enrolled a cohort of self-selected adolescents at high risk of HIV acquisition and offered an opportunity to engage on ethical norms for adolescent research. PrEP was safe and tolerable in those who persisted. However PrEP usage decreased and adherence diminished over time, when visits became less frequent. STI diagnoses remained constant and HIV incidence was low. SA adolescents need access to PrEP with tailored adherence support and potentially augmented visit schedules.
Listening to at-risk youth: perspectives of young women and men in South Africa on the design of an implant for HIV prevention


Introduction: Poor user adherence has been a major challenge for many pre-exposure prophylaxis (PrEP) products upon reaching clinical trials. For PrEP products still in development, integrating end-user preferences into early-stage design could help to overcome this challenge. In this qualitative study, we sought to learn from young men and women in South Africa about their preferences for the design of an implant for HIV prevention.

Subject and Method: We conducted a series of 14 focus group discussions (FGDs) with young men and women ages 18-24 in Cape Town and Soshanguve, South Africa (n=105 participants total). FGDs followed a semi-structured guide with questions on previous experience with contraceptive implants, preferences for physical characteristics of an implant, participant-driven ideas for implant design, and social adoption considerations. FGDs were facilitated in English and Xhosa, Tswana, or Sotho by a biomedical engineer and a social scientist, and were audio-recorded and transcribed. Rapid analysis of qualitative data was done through comprehensive summary reports of FGD audio files.

Results: Although there were some concerns raised about potential side effects of the implant prototypes and their “plastic”-like appearance, most participants were excited about an implant for HIV prevention and preferred it over other dosage forms like pills or injections due to its longer duration. Participants expressed preferences for several design features: longer duration (3 months to >1 year) was more important to most participants than the size or number of implants. The majority of participants preferred a more flexible vs. stiff implant, as they perceived it to be more discreet (less palpable) and more comfortable. Nearly all participants favored a biodegradable implant to avoid removal and to reduce clinic visits.

Interpretation: This study offers preliminary evidence to suggest that an implant for HIV prevention that provides long-lasting protection (>3 months), is flexible and discreet, and biodegrades would be acceptable to young South Africans. Integrating such end-user research into design is critical in creating a PrEP product that will not only be effective in the lab, but also more likely to achieve high adherence in target populations.
**Introduction:** Cutaneous adverse drug reactions (CADR) to first-line anti-tuberculosis (TB) drugs pose a management challenge considering the limited number of effective, safe and affordable alternatives. Rechallenge with first-line drugs to identify the offending drug is feasible. However, there are limited data on the safest and most efficient protocols. It is not clear if incremental escalating dose protocols are safer than full dosing when rechallenging.

**Subjects and Methods:** Adults with definite or probable TB who developed severe CADR whilst on at least one first-line anti-TB drug were randomized to a sequential full dose rechallenge or sequential escalating doses of first-line drugs (rechallenge sequence = isoniazid, rifampicin, pyrazinamide and ethambutol). Before initiating oral rechallenge, a patch test was performed and if it was positive, the drug was eliminated from the regimen. If the patch test was negative, a skin prick test was done. If both were negative, an oral rechallenge was performed as per randomization. Rechallenge reactions were graded using Common Terminology Criteria for Adverse Events (CTCAE) criteria. The primary outcomes were the frequency and severity of rechallenge reactions in each arm.

**Results:** 98 patients were randomized, 49 to each arm. 90/98 were HIV-infected, 71% presented with DRESS syndrome, and 23% Stevens Johnson syndrome. 19/98 (19.4%) patients experienced rechallenge reactions to skin tests (12 to patch tests and 7 to skin prick tests). 149 and 147 oral rechallenges to individual drugs were performed in the escalating and full dose arms, respectively. Escalating dose protocols resulted in 17/149 (11.4%) rechallenge reactions, significantly lower than full dose protocols that resulted in 31/147 (21.1%) reactions, (p=.024).

20 reactions were mild, 22 moderate, 3 severe and life-threatening, respectively. There was no significant difference in the severity of rechallenge reactions in the two arms. There was no difference in the proportion of patients or drugs successfully re-started in each arm. The duration of hospitalization was also not different between the two arms.

**Interpretation:** Full dose rechallenge is likely clinically acceptable as it was not associated with an increased frequency of severe rechallenge reactions or a reduction in the proportion of successful drug restarts. These data inform the management of patients with CADR in HIV endemic settings. A cost analysis study is underway.
SESSION 3

Chairperson:
Prof Nonhlanhla Khumalo
&
Prof Gillian Ainslie

13:35 – 16:10 pm

Chimota Phiri*, Martha Amwaama, Udemo Ekrikpo, Ikechi Okpechi

Introduction: Human immunodeficiency virus (HIV) infection is a common cause of chronic kidney disease (CKD) in Sub-Saharan Africa. By 2016, an estimated 19.1 million people in Sub-Saharan Africa were living with HIV and with the introduction of antiretroviral therapy (ART) the burden of chronic kidney disease due to HIV is expected to increase as people are living longer.

Subjects and Methods: We searched PubMed and Arican Journal On-Line (AJOL) for articles published between January 1990 and December 2016. CKD was defined as estimated glomerular filtration rate (eGFR) <60ml/min using the MDRD, Cockcroft-Gault or CKD-EPI equations or the presence of albuminuria quantified by UPCR, ACR or urine dipsticks.

Results: Eighteen full articles were selected from 176 identified studies from our search. The selected papers were from eight countries (Burundi, Ghana, Nigeria, Kenya, South Africa, Congo, Uganda and Tanzania) representing a sample size of 9167 of which 60.7% were female and the mean age was 37.6+/- 8.9. Nine studies (50%) used both Cockroft-Gault equation and MDRD methods of reporting CKD in HIV population. One study (5%) used MDRD, Cockcroft-Gault equation and CKD-Epi to report on CKD. Overall, MDRD was the most used method in 13 (72.2%) of the studies. Urine dipsticks was the most prevalent method of assessing proteinuria in 12 (66.6%) of the studies. Only 7 studies (38.8%) quantified proteinuria using UPCR or ACR. One study (5%) reported CKD using CKD-Epi equation which is the recommended method as per KDIGO guidelines reflecting limitation of availability of ideal reporting methods across Sub-Saharan region.

Interpretation: CKD is common in HIV-infected people in Africa. There is need to improve CKD reporting using CKD-Epi as per KDIGO guidelines inorder to standardize results in HIV population. HIV treatment programs need to intensify screening for CKD to identify patients for early treatment initiation and institute other measures to retard CKD progression.
Flail arm variant of motor neuron disease in the Western Cape with case-unaffected-parents trio exome study

Helen Cross*, Mahjoubeh Jalali, Sefid Dashti, Junaid Gamieldien, Jeannine M Heckmann

Introduction: Despite worldwide prevalence of motor neuron disease (MND), clinical and genetic data in African populations are sparse. Flail arm (FA) variant, a subtype MND, is defined as lower motor neuron involvement restricted to the proximal arms, for > 12 months. This study described the clinical phenotype of the FA variant seen at the MND clinic. In collaboration with SANBI, whole exome sequencing (WES) was performed on a case-unaffected-parents trio to discover functional gene variants.

Subjects and Methods: Patients presenting March 2014 to September 2016 were included. A clinical description of each FA-MND case was conducted. WES was performed on a family-trio with mixed African genetic-ancestry. Rare/novel variants predicted to potentially impact gene function were prioritized. Clinical MND and related gene ontology terms were used in a knowledge-driven bioinformatics approach to further prioritize variants.

Results: Six FA cases, all with African genetic-ancestry, comprised 13% of the MND cohort. Main phenotypic features were male predominance (100% FA vs 66% MND) and a protracted disease course (survival 4 to >12 years). Asymmetrical onset was common, with contralateral upper limb involvement 2 months - 10 years later. Most patients developed spasticity, but ≥3 years after symptom onset. Almost all showed signs of spread to other body regions, but with marked variability in time span (1-11 years). The case with earliest spread had shortest survival. The WES trio study found three rare, potentially function-impacting recessive variants in the FA patient: KCNA1, NRIP1 and RHOXF2B.

Interpretation: This series showed similar frequencies of FA variant to Caucasian cohorts. Spread to other body regions does eventually occur, although predominant proximal arm involvement remains. Rate of spread impacts overall prognosis. Based on the WES findings, we postulate that the gene risk variants may have a collective effect, resulting in motor neurons which are vulnerable to hyperexcitability and neurotoxicity.
Drug penetration gradients in pulmonary cavities generate heterogeneity and extensively drug-resistant tuberculosis.


Introduction: Multidrug and extensively drug-resistant tuberculosis result from acquired drug resistance (ADR) and may occur despite effective treatment adherence. ADR often arises within the lung cavity but how it develops and what drives it remains poorly understood.

Subjects and Methods: We recruited multidrug-resistant tuberculosis patients who underwent therapeutic lung resection following treatment failure on an eight-drug regimen. Antibiotic concentrations were measured in the blood at seven different biopsy sites across each cavity wall. Mycobacterium tuberculosis was grown from each biopsy site and MICs of each drug identified. Whole genome sequencing was performed for each biopsy site and pre-treatment serial sputum isolates. Correlation coefficients between drug concentration and MIC were calculated.

Results: Fourteen patients who had been on treatment for a median of 13 (range: 5-31) months were recruited. MICs and drug-resistance associated mutations differed between geospatial locations within each cavity, and differed from pre-treatment sputum isolates, consistent with ongoing ADR. There were large concentration-distance gradients into the cavity for each antibiotic, which inversely correlated with MICs, and therefore ADR. The number of drugs detected at each location was also inversely correlated with MIC. Concentration exposures known to amplify drug-resistant subpopulations were encountered in all cavities. Sputum MIC had an accuracy of only 49-48% (95% CI: 52-51-79-71%) in predicting cavitary MICs.

Interpretation: Variable drug penetration gradients across the TB cavity create foci of low antibiotic concentrations associated with drug-resistance acquisition. These data inform interventional strategies relevant to diagnostics, clinical trials, drug delivery, and dosing, to prevent development of ADR.
Differentiating Crohn’s disease (CD) and Intestinal Tuberculosis (ITB) at presentation in patients with tissue granulomas

Watermeyer G* Thomson S

Introduction: Overlap of clinical, endoscopic, radiographic and histological features, coupled with a poor microbiological yield makes differentiating CD from ITB challenging. Granulomas are present in both diseases; in CD they predict the need for immunosuppressive therapy which before initiation requires ITB to be excluded. The aim of this study is thus to compare patients with granuloma-positive CD or ITB, in order to identify factors that may aid in differentiating them.

Methods: a retrospective cohort study evaluating patients with granuloma-positive CD or ITB. Subjects were identified from a pathology database and information extracted from patient folders, laboratory and radiology records.

Results: Sixty eight ITB and 48 CD cases were identified. Patients with ITB were more likely to be male, have HIV infection, isolated colonic involvement, night sweats, and tachycardia at presentation. ITB was also associated with lower serum albumin and haemoglobin concentrations, higher CRP values, X-ray features suggesting active TB and lymphnodes >1cm on cross-sectional imaging. Extra-intestinal manifestations were predictive of CD. There were no significant differences in age at diagnosis, smoking status, symptom duration, or perianal disease. On multivariate analysis HIV positivity (OR 29.72, 95% CI 2.15-410.96, p=0.01), isolated colonic disease (OR 6.17, 95% CI 1.17-32.52, p=0.03) and the absence of EIMs (OR 0.10, 95% CI 0.01-0.65, p=0.02) remained as significant risk factors for ITB.

Conclusion: excluding ITB is essential when considering potent immunosuppressive therapies for CD. This study focused on subjects with tissue granulomas at diagnosis as this predicts a severe course of CD. Several clinical and biochemical factors were identified which will aid in making the correct diagnosis, notably HIV infection which is the strongest risk factor for ITB in this study. This is the 1st study to our knowledge to focus solely on granuloma positive ITB and CD
Concentration of urine lipoarabinomannan improves the sensitivity of the Determine LAM TB lateral flow assay

Philippa Randall*, Gabriel Wisenfeld Paine, Richard Meldau, Malika Davids, Anil Pooran and Keertan Dheda

Introduction: The commercially available Alere TB Determine LAM lateral flow assay (LF-LAM) is a urine-based test that detects lipoarabinomannan (LAM), a cell wall component of *Mycobacterium tuberculosis*. In a randomised controlled trial, urine LAM was shown to significantly decrease mortality in hospitalised patients with severe immunosuppression, which lead to WHO endorsement. However, sensitivity remains suboptimal. We examined whether concentrating LAM in the urine through heating, centrifugation and molecular weight cut-off filtration could improve the sensitivity of the existing assay.

Subjects and Methods: The urine samples of 101 individuals was subjected to heating (100°C water bath), centrifugation (3500 rpm for 15 minutes) and the resulting supernatant was molecular weight cut-off filtered (100kDa and 3kDa). The urine was applied to LF-LAM and the LAM grade documented prior to and following each process. Single sputum Xpert MTB/RIF and/or TB culture positivity or negativity served as the reference standard for confirmed TB (n = 70) and unlikely TB (n = 31), respectively.

Results: Overall, there was incremental increase in mean urine LAM grade following each concentration procedure. (p<0.001). A significant increase in urine LAM sensitivity from 14.20% (95% CI; 6.09 – 22.49) to 47.14% (95% CI; 35.45 – 58.83) was observed following urine processing. (p<0.0001). When stratified for CD4 count (≤50, ≤100, >100), the sensitivity increase was CD4 dependent and was 65.79% (95% CI; 50.71 – 80.87), 31.58 (95% CI; 10.68 – 52.48) and 15.38 (95% CI; 0.00 – 34.99) in the 3 groups, respectively. (p<0.0001). The concentration methodology had no effect on specificity [100% throughout the study (n=31)].

Interpretation: The stepwise process of heating, centrifugation, and molecular weight cut-off filtration significantly enhances the sensitivity of the LF-LAM assay without compromising specificity.
**Infectiousness of patients with drug sensitive and drug resistant tuberculosis.**

**Jason D. Limberis*, Liezel Smith, Rouxjeane Venter, Ruth Wilson, Mariana De Kock, Elize Pietersen, Kevin P. Fenelly, Rob Warren, Grant Theron, Keertan Dheda**

**Introduction:** Patient infectiousness underpins tuberculosis (TB) transmission and hence disease burden. However, studies about the infectiousness of patients with drug-resistant versus drug-sensitive TB (including heterogeneity in infectious aerosol production) have, hitherto, not been conducted. The ability to identify highly infectious patients would allow for the rational allocation of scarce resources.

**Subjects and Methods:** Patients recently diagnosed with active-TB were recruited in Cape Town. A cough aerosol sampling system (CASS) was employed to determine the presence of, and enumerate, culturable *M. tuberculosis* bacilli in the cough aerosols of patients. The CASS consisted of a cubicle housing an Anderson cascade impactor enabling the collection of particles of known size distribution onto plates holding selective growth media. Patients entered the cubicle and cough as frequently as was comfortable for two, 5-minute sessions. The plates were incubated at 37°C and *M. tuberculosis* CFU enumerated. A threshold of ≥10CFU is associated with proxies of human transmission. Clinical characteristics were collected. Mycobacterial burden tests (MGIT culture, Ziehl-Neelsen smear microscopy), drug susceptibility for 12 drugs, and next generation whole genome sequencing (WGS) were performed.

**Results:** 186/453 (41%) patients who underwent CASS were HIV-coinfected (50% on ARVs). 393/453 (87%) patients were MGIT culture positive and 300/453 (66%) were Ziehl-Neelsen smear positive. 316/453 (70%), 95/453 (21%) and 42/453 (9%) had 0, 1-9 or ≥10 *M. tuberculosis* CFU in their cough aerosols respectively. Overall, 123/203 (61%), 132/173 (76%) and 57/73 (78%) patients had no *M. tuberculosis* CFU in those with DS-, MDR-, and XDR-TB.

Multivariate analysis revealed that MGIT culture time to positivity, HIV-coinfection, age, Ziehl-Neelsen smear grade, TBscore and treatment with moxifloxacin are associated with *M. tuberculosis* CFU in patients cough aerosol. WGS did not identify any *M. tuberculosis* genetic correlates of infectiousness.

**Interpretation:**

This is the first study describing the infectiousness of patients with MDR- and XDR-TB. We demonstrate heterogeneity in *M. tuberculosis* cough aerosol culture positivity, and that only a minority of patients ~10% are “extremely infectious” having ≥10CFU. We identified several clinical markers of this infectiousness. There is a need for a scalable, cheap and logistically simple method to assess patient infectiousness.
The bioavailability of rifampicin in fixed dose combinations widely used in South Africa to treat drug-susceptible tuberculosis

Court R*, Chirehwa MT, Wiesner L, Wright B, Smythe W, Kramer N, Roscigno G, McIleron H

Introduction: Tuberculosis treatment success rates for South Africa remain below the global average. Rifampicin drives treatment response in patients with drug-susceptible tuberculosis and low rifampicin concentrations are associated with worse treatment outcomes. It is important to exclude poor drug quality as a contributor to low rifampicin exposures.

Subjects and Methods: We performed an open-label 3-way cross-over bioavailability study of 3 rifampicin-containing formulations widely used in the South African National Tuberculosis Control programme. The 2-drug fixed dose combination tablet (FDC), Rimactazid® and the 4-drug FDC, Rifafour® were compared against a single drug reference product, Rimactane®. Single doses (600 mg rifampicin) were administered 2 weeks apart in random sequence. Blood samples were collected predose and 1, 2, 3, 4, 6, 8 and 12 hours postdose. Plasma rifampicin concentrations were measured using liquid chromatography mass spectrometry. The 90% CI of the geometric mean ratio (GMR) for the area under the concentration-time curve (AUC₁₂) was used to compare bioavailability of the respective FDCs to the single drug reference. Simulations were used to predict the impact of the findings on rifampicin exposures in patients.

Results: 20 healthy volunteers completed the study with median age and BMI of 22.8 years and 24.2 kg/m² respectively. The GMR (90%CI) of Rifafour®/Rimactane® for AUC₁₂ (78% [69%-89%]) showed an average reduction of 20% in the bioavailability of rifampicin in Rifafour®. The GMR of Rimactazid®/Rimactane® (104% [97%-111%]) suggested bioequivalence. No significant period or sequence effects were observed. Simulations suggest that rifampicin doses should be adjusted to compensate for poor bioavailability of rifampicin in Rifafour® and that weight band doses should be revised to prevent systematic underdosing of low weight patients.

Interpretation: It is critical that substandard drug products do not compromise tuberculosis treatment outcomes in South Africa. Ongoing surveillance of the in vivo bioavailability of rifampicin combined with improved weight band-based dosing are recommended.
HIV-associated Hodgkin lymphoma at Groote Schuur Hospital, Western Cape, South Africa

Luhan Swart*, Nicolas Novitzky, Jessica Opie

Introduction: Infection with human immunodeficiency virus (HIV) is associated with an increased risk of developing Hodgkin lymphoma (HL). While South Africa (SA) has a high HIV prevalence rate there is no outcome-based data for HIV-associated HL.

Subjects and Methods: We studied the clinical and laboratory data of 219 adults with HL of whom 29% were HIV positive (HIV+). Primary outcome measures included demographic parameters, histology, bone marrow infiltration (BMI), presentation CD4 count, HIV-viral loads (HIV-VL), infection with tuberculosis (TB) and 5-year overall survival (OS).

Results: The median age at presentation (32 years) was similar in the HIV+ and HIV negative (HIV-) populations. Females predominated in the HIV+ group, (Male: Female ratio of 0.7:1). The diagnosis of HL was made on bone marrow biopsy (BMB) in 17% of cases. The 5-year OS was 56%. More HIV+ patients did not receive chemotherapy than HIV- patients (31% vs 3%). The HL histological subtype varied according to HIV status. 39% were anti-retroviral therapy (cART) naive at HL diagnosis. The median presentation CD4 count of HIV+ patients was 149 x106/L and they had received anti-TB therapy more frequently than HIV- patients (72% vs 17%; p= 0.007). HIV positivity, BMI, CD4 count, histological subtype and recent treatment for TB had a significant impact on 5-year OS (p < 0.01). BMI was more common in HIV+ patients (61% vs 28%; p= 0.006) who had a 5-year OS of 18%.

Interpretation: BMB provided the diagnosis in 17%, confirming its diagnostic utility in our setting. BMI by HL was more common in HIV+ and was associated with significantly worse survival.
The use of hair to detect (and monitor) chronic hyperglycemia - a pilot study


Introduction: Diabetes Mellitus is a metabolic disorder characterized by hyperglycaemia, which is associated with debilitating and life threatening complications. It is, therefore, vital for diabetics to monitor their blood sugar levels and keep them controlled (<8mmol/L). Chronic estimates of glucose control are obtained using glycated haemoglobin A1 (HbA1c) valid for 8-12 weeks. Non-invasive methods of monitoring long term glycaemic control may be useful. Since scalp hair consists of 65-95% protein which is subject to glycation, we wished to test the hypothesis that measurement of glycated hair protein could be used as an alternative surrogate marker to HbA1c for long-term glycaemic control beyond 12 weeks depending on hair length.

Subjects and methods: Scalp hair and blood samples (for HbA1c) were collected from 46 diabetic and 46 healthy control subjects. There were 26 diabetic adults (30-70 years), recruited from the outpatient clinic at Groote Schuur hospital and 20 children (7-18 years), recruited from the diabetic clinic at the Red Cross children’s hospital. There were 29 healthy control adults (26-65 years) and 17 children (7-17 years). Hair samples were washed using 1% sodium dodecyl sulphate and analysed using Fourier transform infrared-attenuated total reflection (ATR-FTIR) spectroscopy. Spectra were analysed using statistical software (SIMCA, Umetrics).

Results: Orthogonal Projections to Latent Structures Discriminant Analysis OPLS-DA models between spectra obtained from hair of diabetic participants and those from control hair show good separation and predictive ability. OPLS-DA models showed the best separation when including only spectra obtained from hair of participants with the highest HbA1c when compared to matched controls indicating correlation between HbA1c and spectra.

Interpretation: The model is able to distinguish between spectra obtained from hair of diabetics and that from healthy patients, demonstrating the ability to detect and possibly monitor chronic hyperglycemia in hair. Our findings suggest that this technology may potentially be adapted to a handheld device for screening and monitoring long-term hyperglycaemia.