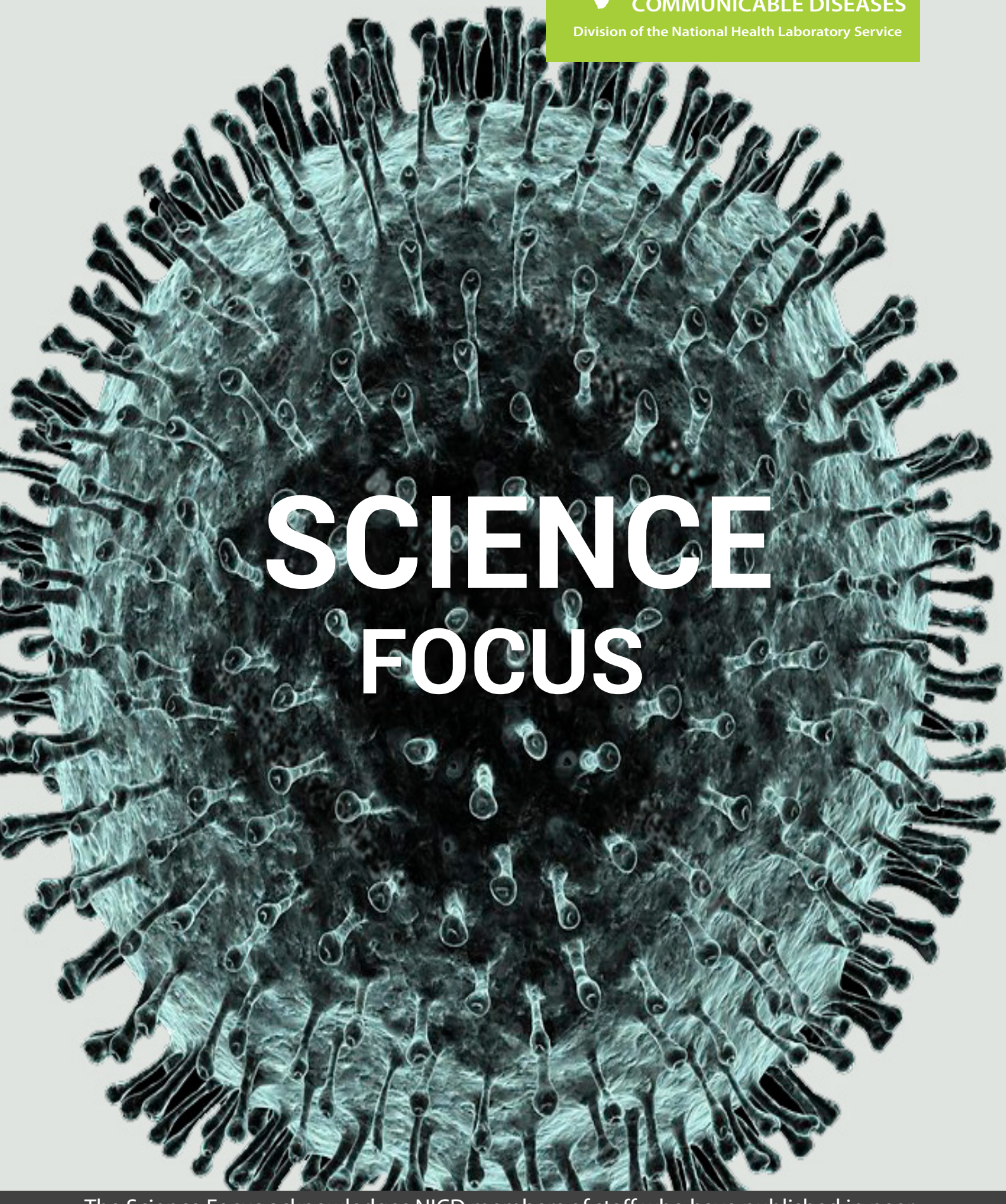
Issue 14- July 2020

NATIONAL INSTITUTE FOR COMMUNICABLE DISEASES
Division of the National Health Laboratory Service



SCIENCE FOCUS

The Science Focus acknowledges NICD members of staff who have published in peer-reviewed journals. This publication is a compilation of scientific publications where an NICD staff member is either the first or last author.

Editor's Note

The Science Focus Issue 14-July 2020, presents some highlights of the National Institute for Communicable Diseases' (NICD) latest major research achievements starting with a seminal report on the outbreak of listeriosis in South Africa by Dr Juno Thomas and colleagues. The study generated significant attention for the research team globally.

As can be seen in this issue, NICD researchers continue to lead the nation in publishing important public health articles, and in high-impact journals such as the New England Journal of Medicine and The Lancet Infectious Diseases.

We once again feature outstanding statistical findings pertaining to the research output of the financial year 2019/2020. In this issue, we feature the number of peer-reviewed articles produced and the top 10 most published authors and the top seven high impact factor score articles. Lastly, we feature the first and last NICD authors who have published articles within the review period – quarter three and four of 2019/2020.

Once again, we encourage members of staff to continue to send their contributions to the Communications Unit in order to be featured in the next quarter.

On behalf of the team.

Sinenhlanhla Jimoh
Senior Communications Manager

EXCEPTIONAL RESEARCH STATISTICS

NUMBER OF PEER REVIEWED ARTICLES PRODUCED

180

FINANCIAL YEAR
2019/2020

TARGET: 140

TOP 10

MOST PUBLISHED AUTHORS IN 2019/2020

1

PROF ANNE VON GOTTBERG

2

PROF CHERYL COHEN

3

PROF LYNN MORRIS

4

PROF NELESH GOVENDER

5

PROF CAROLINE TIEMESSEN

6

DR SIBONGILE WALAZA

7

PROF GAYLE SHERMAN

7

PROF ADRIAN PUREN

7

PROF PENNY MOORE

8

PROF NAZIR ISMAIL

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DR MELINDA SUCHARD

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PROF JOHN FREAN

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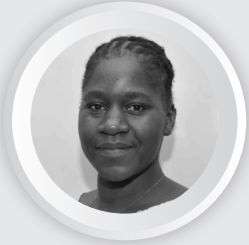


DR TENDESAYI KUFA

10

DR KERRIGAN McCARTHY

TOP 7

HIGH IMPACT FACTOR SCORE ARTICLES IN 2019/2020

Journal Name	Title	NICD Authors	Score
The New England Journal of Medicine	Prediction of susceptibility to first-line tuberculosis drugs by DNA sequencing	Nazir Ismail and Shaheed Vally Omar	79.260
New England Journal of Medicine	Outbreak of listeriosis in South Africa associated with processed meat	Juno Thomas, Nevashan Govender, Kerrigan McCarthy, Linda Erasmus, et al	70.67
The Lancet	The complex challenges of HIV vaccine development require renewed and expanded global commitment	Lynn Morris	59.102
Cell	High-throughput mapping of B-cell receptor sequences to antigen specificity	Rutendo Mapengo, SimoneRichardson, Charissa Oosthuysen, Lynn Morris	36.216
The Lancet Infectious Diseases	Meningitis: A frequently fatal diagnosis in Africa	Anne von Gottberg	27.516
The Lancet Infectious Diseases	Improving human rabies post-exposure prophylaxis: Comment	Lucille Blumberg	27.516
The Lancet Infectious Diseases	Leave no one behind: Response to new evidence and guidelines for the management of cryptococcal meningitis in low-income and middle income countries	Nelesh Govender	25.148
The Lancet Infectious Diseases	Multidrug-resistant tuberculosis outbreak in South Africa	Nazir Ismail and Kerrigan McCarthy	25.148
The Lancet Infectious Diseases	Tenofovir 1% vaginal gel for prevention of HIV-1 infection: A phase 3, randomised, double-blind, placebo-controlled trial	Lynn Morris	25.148
The Lancet Infectious Diseases	Prevalence of drug-resistant tuberculosis in South Africa – Authors' reply	Nazir Ismail	25.148
The Lancet Infectious Diseases	Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: A national and sub-national cross-sectional survey	Nazir Ismail	25.148
Lancet Respiratory Medicine	Live attenuated influenza vaccines for African children	Cheryl Cohen	22.992

FEATURED RESEARCH ABSTRACTS FOR THE SECOND AND THIRD QUARTER OF 2019/20

Dr Juno Thomas

Prof Lucille Blumberg

Outbreak of listeriosis in South Africa associated with processed meat

Thomas J, *Govender N, McCarthy KM, Erasmus LK, Doyle TJ, Allam M, Ismail A, Ramalwa N, Sekwadi P, Ntshoe G, Shonhiwa A, Essel V, Tau N, Smouse S, Ngomane HM, Disenyeng B, Page NA, Govender NP, Duse AG, Stewart R, Thomas T, Mahoney D, Tourdjman M, Disson O, Thouvenot P, Maury MM, Leclercq A, Lecuit M, Smith AM,* ***Blumberg LH.***

New England Journal of Medicine
Impact Factor: 70.67

Background: An outbreak of listeriosis was identified in South Africa in 2017. The source was unknown.

Methods: We conducted epidemiologic, trace-back, and environmental investigations and used whole-genome sequencing to type *Listeria monocytogenes* isolates. A case was defined as laboratory-confirmed *L. monocytogenes* infection during the period from June 11, 2017, to April 7, 2018.

Results: A total of 937 cases were identified, of which 465 (50%) were associated with pregnancy; 406 of the pregnancy-associated cases (87%) occurred in neonates. Of the 937 cases, 229 (24%) occurred in patients 15 to 49 years of age (excluding those who were pregnant). Among the patients in whom human immunodeficiency virus (HIV) status was known, 38% of those with pregnancy-associated cases (77 of 204) and 46% of the remaining patients (97 of 211) were infected with HIV. Among 728 patients with a known outcome, 193 (27%) died. Clinical isolates from 609 patients were sequenced, and 567 (93%) were identified as sequence type 6 (ST6). In a case–control analysis, patients with ST6 infections were more likely to have eaten polony (a ready-to-eat processed meat) than those with non-ST6 infections (odds ratio, 8.55; 95% confidence interval, 1.66 to 43.35). Polony and environmental samples also yielded ST6 isolates, which, together with the isolates from the patients, belonged to the same core-genome multilocus sequence typing cluster with no more than 4 allelic differences; these findings showed that polony produced at a single facility was the outbreak source. A recall of ready-to-eat processed meat products from this facility was associated with a rapid decline in the incidence of *L. monocytogenes* ST6 infections.

Conclusions: This investigation showed that in a middle-income country with a high prevalence of HIV infection, *L. monocytogenes* caused disproportionate illness among pregnant girls and women and HIV-infected persons. Whole-genome sequencing facilitated the detection of the outbreak and guided the trace-back investigations that led to the identification of the source.

Prof Lucille Blumberg

Improving human rabies post-exposure prophylaxis: *Comment*

Blumberg L, *Rupprecht CE.*

The Lancet Infectious Diseases
Impact Factor: 27.516

In The Lancet Infectious Diseases, Tineke Cantaert and colleague illustrate a strong commitment in Cambodia to preventing human rabies by rapid intradermal delivery of post-exposure prophylaxis. The investigators included 116 people bitten by rabies virus-positive dogs and 20 people bitten by rabies virus-negative dogs who attended Institut Pasteur du Cambodge, Phnom Penh, Cambodia, between April 20, 2016, and Feb 9, 2018. Patients received intradermal vaccination on days 0, 3, 7, and 28, and serum samples were obtained for detection of rabies virus neutralising antibodies on days 0, 7, 28, and 42. This well designed cohort study showed that exposed people had rabies virus neutralising antibody titres after three rabies vaccine sessions (of two intradermal doses each) that were similar to titres observed immediately before a fourth vaccine session on day 28. The authors concluded that rabies post-exposure prophylaxis could be abridged to a 1-week (three sessions of two doses on days 0, 3, and 7) intradermal regimen. Recognising the possibility of long incubation periods, the investigators contacted all patients after 1 year and found that all were still alive. These compelling data help identify the best use of human rabies post-exposure prophylaxis in developing countries, which should be used in combination with mass vaccination of dogs.

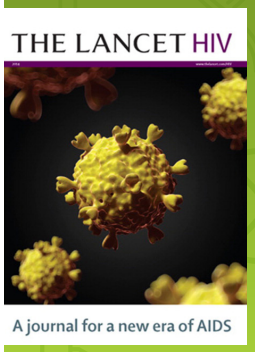
Prof Lynn Morris

Engineered HIV antibody passes muster

Morris L.

The Lancet HIV
Impact Factor: 14.753

In The Lancet HIV, Gaudinski and colleagues report promising results of a small first-in-human clinical trial involving VRC07-523LS, an artificial antibody that has been extensively modified to improve its activity against HIV. VRC07-523LS was safe and well tolerated, and no serious adverse events or dose-limiting toxic effects were observed. This is an important milestone for HIV antibody immunoprophylaxis as it opens up opportunities for designing ideal antibodies that could be used to halt the unrelenting spread of HIV infection.



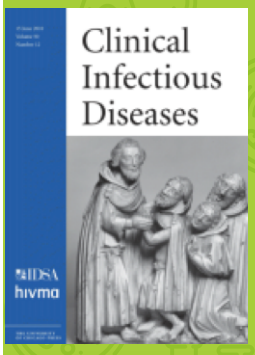
Prof Cheryl Cohen

The impact of human immunodeficiency virus exposure on respiratory syncytial virus–associated severe respiratory illness in South African infants, 2011–2016

McMorrow ML, Tempia S, Walaza S, Treurnicht FK, Moyes J, Cohen AL, Pretorius M, Hellferscee O, Wolter N, von Gottberg A, Nguweneza A, McAnerney JM, Naby F, Mekgoe O, Venter M, Madhi SA, ***Cohen C.***

Clinical Infectious Diseases
Impact Factor: 9.005

From 2011 through 2016, we conducted surveillance for severe respiratory illness in infants. Human immunodeficiency virus exposure significantly increased the risk of respiratory syncytial virus (RSV)–associated hospitalisation in infants aged <5 months. More than 60% of RSV-associated hospitalisations occurred in the first 4 months of life and may be preventable through maternal vaccination or birth-dose monoclonal antibody.



Dr Simone Richardson

Prof Lynn Morris

IgG3 hinge length enhances neutralisation potency and Fc effector function of an HIV V2-specific broadly neutralising antibody

Richardson SI, *Lambson BE, Crowley AR, Bashirova A, Scheepers C, Garrett N, Abdool Karim S, Mkhize NN, Carrington M, Ackerman ME, Moore PL,* ***Morris L.***

PLOS Pathogens
Impact Factor: 6.436

Broadly neutralising antibodies (bNAbs) protect against HIV infection in non-human primates and their efficacy may be enhanced through interaction with Fc receptors on immune cells. Antibody isotype is a modulator of this binding with the IgG3 subclass mediating potent Fc effector function and is associated with HIV vaccine efficacy and HIV control. BNAb functions are typically assessed independently of the constant region with which they are naturally expressed. To examine the role of natural isotype in the context of a bNAb lineage we studied CAP256, an HIV-infected individual that mounted a potent V2-specific bNAb response. CAP256 expressed persistently high levels of plasma IgG3 which we found mediated both broad neutralising activity and potent Fc function. Sequencing of germline DNA and the constant regions of V2-directed bNAbs from this donor revealed the expression of a novel IGHG3 allele as well as IGHG3*17, an allele that produces IgG3 antibodies with increased plasma half-life. Both allelic variants were used to generate CAP256-VRC26.25 and CAP256-VRC26.29 IgG3 bNAbs and these were compared to IgG1 versions. IgG3 variants were shown to have significantly higher phagocytosis and trogocytosis compared to IgG1 versions, which corresponded to increased affinity for FcγRIIa. Neutralisation potency was also significantly higher for IgG3 bNAbs, particularly against viruses lacking the N160 glycan. By exchanging hinge regions between subclass variants, we showed that hinge length modulated both neutralisation potency and Fc function. This study showed that co-operation between the variable and natural IgG3 constant regions enhanced the polyfunctionality of antibodies, indicating the value of leveraging genetic variation which could be exploited for passive immunity.

Prof Cheryl Cohen

Vaccinating mothers to protect their babies against influenza

Cohen C, *Nunes MC.*

The Journal of Infectious Diseases
Impact Factor: 5.045

Influenza virus infection is responsible for significant morbidity and mortality in children, particularly among those younger than 6 months. Preventing influenza in these young infants is, therefore, an important health priority. Efforts to prevent influenza in infants aged <6 months through direct vaccination have not been successful, because of inadequate infant immune responses. Providing passive protection to the infant through vaccinating pregnant women may be an attractive alternative to direct immunisation.

The efficacy of seasonal influenza vaccination during pregnancy in preventing laboratory-confirmed influenza in infants younger than 6 months has been demonstrated by 4 randomised, controlled trials from Bangladesh, South Africa, Mali, and Nepal. It is also critical to evaluate the effectiveness of this strategy when implemented through routine public health programmes outside of controlled clinical trials; equally important is documentation of results from different geographical areas and use of different clinical endpoints.

Dr Melinda Suchard

Prof Lucille Blumberg

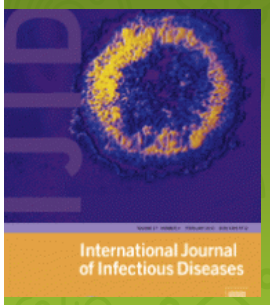
Extra time and penalties in the polio end game

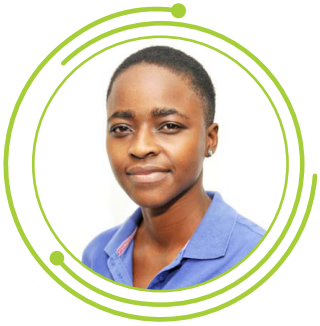
Suchard MS, *Tomori O,* ***Blumberg L.***

International Journal of Infectious Diseases
Impact Factor: 5.045

As public health fans celebrate 3 years since the last child was paralysed by wild poliovirus in Nigeria, global media is announcing that Africa is now polio-free. Confusingly, the number of African countries concurrently battling with circulating vaccine derived poliovirus (cVDPV) is alarmingly high. Eleven African countries suffering cVDPV outbreaks are currently listed on the website of the Global Polio Eradication Initiative (GPEI) (World Health Organization, 2019), while wild poliovirus type 1 continues to circulate in Pakistan and Afghanistan. In Geneva, sponsors are laboring to contain unrelentingly escalating costs of the world's largest ever public health programme. Funders are desperate to transfer human and infrastructural resources to more pressing health priorities. Spectators are left bewildered at the mixed messages bombarding the unsuspecting public.

When, exactly, will Africa be "polio-free"? Is it wise to use such terminology while circulating vaccine derived polio virus (cVDPV) rages on simultaneously in several African countries? Similarly, will referees (the Global Certification Commission) declare the world "polio-free" following wildtype poliovirus interruption globally, or only after disappearance of cVDPV? Who is going to bankroll the decade of fire-fighting cVDPV likely to follow withdrawal of oral polio vaccine? Are we going to sit back and relax after wildtype polio interruption and sweep cVDPV under the carpet, hoping it will disappear on its own?





Dr Tsidiso Maphanga

Prof Nelesh Govender

Human Blastomycosis in South Africa caused by *Blastomyces percursus* and *Blastomyces emzantsi* sp. nov., 1967 to 2014

Maphanga TG, *Birkhead M, Muñoz JF, Allam M, Zulu TG, Cuomo CA, Schwartz IS, Ismail A, Naicker SD, Mpembe RS, Corcoran C, de Hoog S, Kenyon C, Borman AM, Frean JA,* ***Govender NP.***

Journal of Clinical Microbiology
Impact Factor: 4.959

We re-evaluated 20 cases of blastomycosis diagnosed in South Africa between 1967 and 2014, with *Blastomyces dermatitidis* considered to be the etiological agent, in light of newly described species and the use of more advanced technologies. In addition to histopathological and/or culture-based methods, all 20 isolates were phenotypically and genotypically characterised, including multilocus typing of five genes and whole-genome sequencing. Antifungal susceptibility testing was performed as outlined by Clinical and Laboratory Standards Institute documents M27-A3 and M38-A2. We merged laboratory and corresponding clinical case data, where available. Morphological characteristics and phylogenetic analyses of five-gene and whole-genome sequences revealed two groups, both of which were closely related to but distinct from *B. dermatitidis*, *Blastomyces gilchristii*, and *Blastomyces parvus*. The first group (n = 12) corresponded to the recently described species *Blastomyces percursus*, and the other (n = 8) is described here as *Blastomyces emzantsi* sp. nov. Both species exhibited incomplete conversion to the yeast phase at 37°C and were heterothallic for mating types. All eight *B. emzantsi* isolates belonged to the α mating type. Whole-genome sequencing confirmed distinct species identities as well as the absence of a full orthologue of the BAD-1 gene. Extrapulmonary (skin or bone) disease, probably resulting from hematogenous spread from a primary lung infection, was more common than pulmonary disease alone. Voriconazole, posaconazole, itraconazole, amphotericin B, and micafungin had the most potent in vitro activity. Over the 5 decades, South African cases of blastomycosis were caused by species that are distinct from *B. dermatitidis*. Increasing clinical awareness and access to simple rapid diagnostics may improve the diagnosis of blastomycosis in resource-limited countries.

Dr Shaheed Vally Omar

Validation of bedaquiline phenotypic drug susceptibility testing methods and breakpoints: A multi-laboratory, multi-country study

Kaniga K, Aono A, Borroni E, Cirillo ED, Desmaretz C, Hasan R, Joseph L, Mitarai S, Shakoor S, Torrea G, Ismail NA, ***Omar SV.***

Journal of Clinical Microbiology
Impact Factor: 4.959

Drug-resistant tuberculosis persists as a major public health concern. Alongside efficacious treatments, validated and standardised drug susceptibility testing (DST) is required to improve patient care. This multi-country, multi-laboratory external quality assessment (EQA) study aimed to validate the sensitivity, specificity, and reproducibility of provisional bedaquiline MIC breakpoints and World Health Organization interim critical concentrations (CCs) for categorizing clinical *Mycobacterium tuberculosis* isolates as susceptible/resistant to the drug. Three methods were used: Middlebrook 7H11 agar proportion (AP) assay, broth microdilution (BMD) assay, and mycobacterial growth indicator tube (MGIT) assay. Each of the five laboratories tested the 40-isolate (20 unique isolates, duplicated) EQA panel at three time points. The study validated the sensitivity and specificity of a bedaquiline MIC susceptibility breakpoint of 0.12 µg/ml for the BMD method and WHO interim CCs of 1 µg/ml for MGIT and 0.25 µg/ml for the 7H11 AP methods. Categorical agreements between observed and expected results and sensitivities/specificities for correctly identifying an isolate as susceptible/resistant were highest at the 0.25, 0.12, and 1 µg/ml bedaquiline concentrations for the AP method, BMD (frozen or dry plates), and MGIT960, respectively. At these concentrations, the very major error rates for erroneously categorising an isolate as susceptible when it was resistant were the lowest and within CLSI guidelines. The most highly reproducible bedaquiline DST methods were MGIT960 and BMD using dry plates. These findings validate the use of standardised DST methodologies and interpretative criteria to facilitate routine phenotypic bedaquiline DST and to monitor the emergence of bedaquiline resistance.

Mr Thabo Mohale

Prof Anne von Gottberg

Genomic differences among carriage and invasive nontypeable pneumococci circulating in South Africa

Mohale T, *Wolter N, Allam M, Nzenze SA, Madhi SA, du Plessis M,* ***von Gottberg A.***

Microbial Genomes
Impact Factor: 4.853

Most pneumococci express a polysaccharide capsule, a key virulence factor and target for pneumococcal vaccines. However, pneumococci showing no serological evidence of capsule expression [nontypeable pneumococci (NTPn)] are more frequently isolated from carriage studies than in invasive disease. Limited data exist about the population structure of carriage NTPn from the African continent. We aimed to characterise carriage NTPn and compare them to previously described invasive NTPn. Carriage and invasive NTPn isolates were obtained from South African cross-sectional studies (2009 and 2012) and laboratory-based surveillance for invasive pneumococcal disease (2003-2013), respectively. Isolates were characterised by capsular locus sequence analysis, multilocus sequence typing, antimicrobial non-susceptibility patterns and phylogenetic analysis. NTPn represented 3.7% (137/3 721) of carriage isolates compared to 0.1% (39/32 824) of invasive isolates (P<0.001), and 24% (33/137) of individuals were co-colonized with encapsulated pneumococci. Non-susceptibility to cotrimoxazole [84% (112/133) vs. 44% (17/39)], penicillin [77% (102/133) vs. 36% (14/39)], erythromycin [53% (70/133) vs 31% (12/39)] and clindamycin [36% (48/133) vs. 18% (7/39)] was higher (P=0.03) among carriage than invasive NTPn. Ninety-one per cent (124/137) of carriage NTPn had complete deletion of the capsular locus and 9% (13/137) had capsule genes, compared to 44% (17/39) and 56% (22/39) of invasive NTPn, respectively. Carriage NTPn were slightly less diverse [Simpson's diversity index (D)=0.92] compared to invasive NTPn [D=0.97]. Sixty-seven per cent (92/137) of carriage NTPn belonged to a lineage exclusive to NTPn strains compared to 23% (9/39) of invasive NTPn. We identified 293 and 275 genes that were significantly associated with carriage and invasive NTPn, respectively. NTPn isolates detected in carriage differed from those causing invasive disease, which may explain their success in colonisation or in causing invasive disease.

Dr Selamawit Woldesenbet

Prof Adrian Puren

Viral suppression and factors associated with failure to achieve viral suppression among pregnant women in South Africa: A national cross-sectional survey

Woldesenbet S, *Kufa T, Barron P, Chirombo BC, Cheyip M, Ayalew K, Lombard C, Manda S, Diallo K, Pillay Y,* ***Puren A.***

AIDS
Impact Factor: 4.499

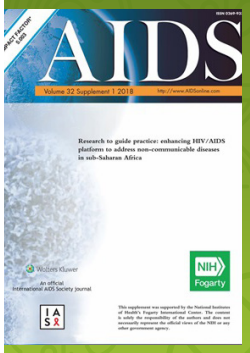
Objective: To describe viral load levels among pregnant women and factors associated with failure to achieve viral suppression (viral load ≤50 copies/ml) during pregnancy.

Design: Between 1 October and 15 November 2017, a cross-sectional survey was conducted among 15-49-year-old pregnant women attending antenatal care (ANC) at 1 595 nationally representative public facilities.

Methods: Blood specimens were taken from each pregnant woman and tested for HIV. Viral load testing was done on all HIV-positive specimens. Demographic and clinical data were extracted from medical records or self-reported. Survey logistic regression examined factors associated with failure to achieve viral suppression.

Result: Of 10 052 HIV-positive participants with viral load data, 56.2% were virally suppressed. Participants initiating antiretroviral therapy (ART) prior to pregnancy had higher viral suppression (71.0%) by their third trimester compared with participants initiating ART during pregnancy (59.3%). Booking for ANC during the third trimester vs. earlier: [adjusted odds ratio (AOR) 1.8, 95% confidence interval (CI):1.4-2.3], low frequency of ANC visits (AOR for 2 ANC visits vs. ≥4 ANC visits: 2.0, 95% CI:1.7-2.4), delayed initiation of ART (AOR for ART initiated at the second trimester vs. before pregnancy:2.2, 95% CI:1.8-2.7), and younger age (AOR for 15-24 vs. 35-49 years: 1.4, 95% CI:1.2-1.8) were associated with failure to achieve viral suppression during the third trimester.

Conclusion: Failure to achieve viral suppression was primarily associated with late ANC booking and late initiation of ART. Efforts to improve early ANC booking and early ART initiation in the general population would help improve viral suppression rates among pregnant women. In addition, the study found, despite initiating ART prior to pregnancy, more than one quarter of participants did not achieve viral suppression in their third trimester. This highlights the need to closely monitor viral load and strengthen counselling and support services for ART adherence.



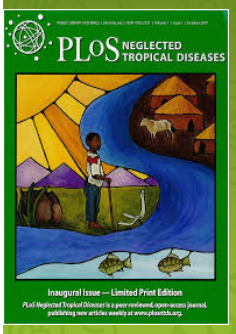
Ms Serisha Naicker

Prof Nelesh Govender

Decreasing fluconazole susceptibility of clinical South African *Cryptococcus neoformans* isolates over a decade

Naicker SD, *Mpembe RS, Maphanga TG, Zulu TG, Desanto D, Wadula J, Mvelase N, Maluleka C, Reddy K, Dawood H, Maloba M,* ***Govender NP.***

Plos Neglected Tropical Diseases
Impact Factor: 4.487



Cryptococcus neoformans, a pathogenic fungal species-complex with an environmental niche, is the most common cause of meningitis among HIV-seropositive adults in sub-Saharan Africa. Fluconazole is recommended in combination with amphotericin B for induction treatment of cryptococcal meningitis and as monotherapy for consolidation and maintenance treatment. Fluconazole is also commonly prescribed to HIV-seropositive individuals for other indications; fluconazole exposure may result in secondary resistance if patients have concurrent active cryptococcal disease. Azole fungicides used in agriculture may potentially drive primary cryptococcal resistance when the fungus is exposed to these fungicides in the environment. We aimed to determine fluconazole MICs in 2017 and compare these values to those obtained in a 2007–2008 South African survey to assess whether fluconazole resistance had emerged in *C. neoformans* over a decade. We found that the proportion of isolates with an MIC of ≥16 μg/ml increased from 0% in 2007–2008 to 7% in 2017. MIC50 and MIC90 values were also two-fold higher in 2017 compared to 2007–2008. These study findings provided evidence for higher fluconazole dose recommendations (in combination with amphotericin B for the induction phase and as monotherapy for consolidation and maintenance phases) in the 2019 Southern African guideline for HIV-associated cryptococcosis.

Dr Zanele Ditse

Prof Lynn Morris

Effect of HIV envelope vaccination on the subsequent antibody response to HIV infection

Ditse Z, *Mkhize NN, Yin M, Keefer M, Montefiori DC, Tomaras GD, Churchyard G, Mayer KH, Karuna S, Morgan C, Bekker L, Mlisana K, Gray G. Moodie Z, Gilbert P, Moore PL, Williamson C,* ***Morris L.***

American Society for Microbiology
Impact Factor: 4.447

Analysis of breakthrough HIV-1 infections could elucidate whether prior vaccination primes are relevant immune responses. Here, we measured HIV-specific antibody responses in 14 South African volunteers who acquired HIV infection after participating in phase 1/2 trials of envelope-containing immunogens. Serum samples were collected annually following HIV-1 infection from participants in trials HVTN 073 (subtype C, DNA/MVA, phase 1 trial, n = 1), HVTN 086 (subtype C, DNA/MVA/gp140 protein, phase 1 trial, n = 2), and HVTN 204 (multisubtype, DNA/adenovirus serotype 5 [Ad5], phase 2 trial, n = 7) and 4 placebo recipients. Binding and neutralising antibody responses to Env proteins and peptides were determined pre- and post-HIV infection using an enzyme-linked immunosorbent assay and the TZM-bl cell neutralisation assay, respectively. HIV-infected South African individuals served as unvaccinated controls. Binding antibodies to gp41, V3, V2, the membrane-proximal external region (MPER), and the CD4 binding site were detected from the first year of HIV-1 subtype C infection, and the levels were similar in vaccinated and placebo recipients. Neutralising antibody responses against tier 1A viruses were detected in all participants, with the highest titers being to a subtype C virus, MW965.26. No responses were observed just prior to infection, indicating that vaccine-primed HIV-specific antibodies had waned. Sporadic neutralisation activity against tier 2 isolates was observed after 2 to 3 years of HIV infection, but these responses were similar in the vaccinated and placebo groups as well as the unvaccinated controls. Our data suggest that prior vaccination with these immunogens did not alter the antibody responses to HIV-1 infection, nor did it accelerate the development of HIV neutralisation breadth.

Importance: There is a wealth of information on HIV-specific vaccine-induced immune responses among HIV-uninfected participants, however, data on immune responses among participants who acquire HIV after vaccination are limited. Here we show that HIV-specific binding antibody responses in individuals with breakthrough HIV infections were not affected by prior vaccination with HIV envelope-containing immunogens. We also found that these vectored vaccines did not prime tier 2 virus-neutralising antibody responses, which are thought to be required for prevention against HIV acquisition, or accelerate the development of neutralisation breadth. Although this study is limited, such studies can provide insights into whether vaccine-elicited antibody responses are boosted by HIV infection to acquire broader neutralising activity, which may help to identify antigens relevant to the design of more effective vaccines.

Prof Caroline Tiemessen

HIV and solid organ transplantation: Where are we now?

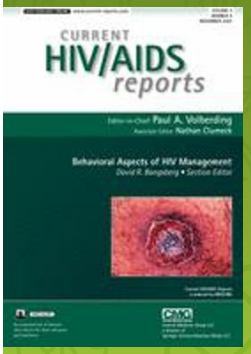
Botha J, Fabian J, Etheredge H, Conradie F, ***Tiemessen CT.***

Current HIV/AIDS Reports
Impact Factor: 4.382

Purpose of review: We review the international evolution of HIV and solid organ transplantation over 30 years. We emphasise recent developments in solid organ transplantation from HIV-infected to HIV-uninfected individuals, and their implications.

Recent findings: In 2017, Johannesburg, South Africa, a life-saving partial liver transplant from an HIV-infected mother to her HIV-uninfected child was performed. This procedure laid the foundation not only for consideration of HIV-infected individuals as living donors, but also for the possibility that HIV-uninfected individuals could receive organs from HIV-infected donors.

Summary: Recent advances in this field are inclusion of HIV-infected individuals as living organ donors and the possibility of offering HIV-uninfected individuals organs from HIV-infected donors who are well-controlled on combination antiretroviral therapy (cART). The large number of HIV-infected individuals on cART is an unutilised source of otherwise eligible living organ donors. HIV-positive-to-HIV-negative organ transplantation has become a reality, providing possible new therapeutic options to address extreme organ shortages.



Mrs Rebecca van Dorsten

Prof Lynn Morris

Neutralisation breadth and potency of single-chain variable fragments derived from broadly neutralising antibodies targeting multiple epitopes on the HIV1 envelope

van Dorsten T, *Lambson BE, Wibmer CK, Weinberg MS, Moore PL,* ***Morris L.***

Journal of Virology
Impact Factor: 4.324

Passive administration of HIV-directed broadly neutralising antibodies (bNAbs) can prevent infection in animal models, and human efficacy trials are underway. Single-chain variable fragments (scFv), comprised of only the variable regions of antibody heavy and light chains, are smaller molecules that may offer advantages over full-length IgG. We designed and expressed scFv of HIV bNAbs prioritised for clinical testing that target the V2-apex (CAP256-VRC26.25), V3-glycan supersite (PGT121), CD4 binding site (3BNC117), and MPER (10E8v4). The use of either a 15 - or 18 -amino-acid glycine-serine linker between the heavy - and light-chain fragments provided adequate levels of scFv expression. When tested against a 45-multisubtype virus panel, all four scFv retained good neutralising activity, although there was variable loss of function compared to the parental IgG antibodies. For CAP256-VRC26.25, there was a significant 138-fold loss of potency that was in part related to differential interaction with charged amino acids at positions 169 and 170 in the V2 epitope. Potency was reduced for the 3BNC117 (13-fold) and PGT121 (4-fold) scFv among viruses lacking the N276 and N332 glycans, respectively, and in viruses with a longer V1 loop for PGT121. This suggested that scFv interacted with their epitopes in subtly different ways, with variation at key residues affecting scFv neutralisation more than the matched IgGs. Remarkably, the scFv of 10E8v4 maintained breadth of 100% with only a minor reduction in potency. Overall, scFv of clinically relevant bNAbs had significant neutralising activity, indicating that they are suitable for passive immunisation to prevent HIV-1 infection.

Importance: Monoclonal antibodies have been isolated against conserved epitopes on the HIV trimer and are being investigated for passive immunisation. Some of the challenges associated with full-sized antibody proteins may be overcome by using single-chain variable fragments (scFv). These smaller forms of antibodies can be produced more efficiently, may show fewer off-target effects with increased tissue penetration, and are more adaptable to vectored-mediated expression than IgG. Here, we demonstrate that scFv of four HIV-directed bNAbs (CAP256-VRC26.25, PGT121, 3BNC117, and 10E8v4) had significant neutralising activity against diverse global strains of HIV. Loss of potency and/or breadth was shown to be due to increased dependence of the scFv on key residues within the epitope. These smaller antibody molecules with functional activity in the therapeutic range may be suitable for further development as passive immunity for HIV prevention.

Prof Nazir Ismail

Dr Shaheed Vally Omar

Epidemiological cut-offs for Sensititre susceptibility testing of *Mycobacterium tuberculosis*: Interpretive criteria cross validated with whole genome sequencing

Ismail NA, *Ismail F, Joseph L, Govender NP, Blows L, Kaniga K,* ***Omar SV.***

Scientific Reports
Impact Factor: 4.011

Universal drug susceptibility testing (DST) is an important requirement of the End TB Strategy. The Sensititre broth micro-dilution assay (BMD) tests multiple drugs quantitatively. We defined interpretive criteria for this assay and analysed genotypic-phenotypic relationships. Three hundred and eighty five *Mycobacterium tuberculosis* clinical isolates were processed for BMD and whole genome sequencing. The epidemiological cut-off value 99% (ECV99) amongst genotypically wild type (gWT) strains defined susceptibility. Minimum inhibitory concentration distributions of the resistance-associated variants (RAVs) for each drug were analysed. Susceptibility (µg/mL) criteria were determined as follows: rifampicin (≤0.125), isoniazid (≤0.25), ethambutol (≤2.0), moxifloxacin (≤0.5), levofloxacin (≤1.0), amikacin (≤2.0), kanamycin (≤8.0), capreomycin (≤4.0), clofazimine (≤0.25) and linezolid (≤2.0). Most drugs showed clear separation between gWT and RAV. Isoniazid showed a tri-modal pattern with 14/17 strains at ECV99 harbouring a fabG1 c. -15C>T RAV. Ethambutol RAVs at embB codons 306, 405 and 497 were responsible for resistance and showed differential distributions. Moxifloxacin RAVs (gyrA codon 90) were a dilution or two higher than the ECV99 while gyrB RAVs were uncommon and showed drug specific resistance propensity. Interpretive criteria established were robust facilitating progress towards universal DST and individualised precision medicine. This study demonstrates the value of quantitative DST to accurately interpret mutation data.

Dr Selamawit Woldesenbet

Prof Adrian Puren

Assessment of readiness to transition from antenatal HIV surveillance surveys to PMTCT programme data-based HIV surveillance in South Africa: The 2017 Antenatal Sentinel HIV Survey

Woldesenbet SA, *Kufa T, Barron P, Ayalew K, Cheyip M, Chirombo BC, Lombard C, Manda S, Pillay Y,* ***Puren AJ.***

International Journal of Infectious Diseases
Impact Factor: 3.538

Objective: South Africa has used antenatal HIV surveys for HIV surveillance in pregnant women since 1990. We assessed South Africa's readiness to transition to programme data based antenatal HIV surveillance with respect to PMTCT uptake, accuracy of point-of-care rapid testing (RT) and selection bias with using programme data in the context of the 2017 antenatal HIV survey.

Methods: Between 1 October and 15 November 2017, the national survey was conducted in 1 595 public antenatal facilities selected using stratified multistage cluster sampling method. Results of point-of-care RT were obtained from medical records. Blood samples were taken from eligible pregnant women and tested for HIV using immunoassays (IA) in the laboratory. Descriptive statistics were used to report on: PMTCT uptake; agreement between 0HIV point-of-care RT and laboratory-based HIV-1 IA; and selection bias associated with using programme data for surveillance.

Results: PMTCT HIV testing uptake was high (99.8%). The positive percent agreement (PPA) between RT and IA was lower than the World Health Organization (WHO) benchmark (97.6%) at 96.3% (95% confidence interval (CI): 95.9%-96.6%). The negative percent agreement was above the WHO benchmark (99.5%), at 99.7% (95% CI: 99.6%-99.7%) nationally. PPA markedly varied by province (92.9%-98.3%). Selection bias due to exclusion of participants with no RT results was within the recommended threshold at 0.3%.

Conclusion: For the three components assessed, South Africa was close to meeting the WHO standard for transitioning to routine RT data for antenatal HIV surveillance. The wide variations in PPA across provinces should be addressed.

Dr Etienne Muller

Dr Ranmini Kularatne

The changing epidemiology of genital ulcer disease in South Africa: Has donovanosis been eliminated?

Muller, EE, Kularatne, R.

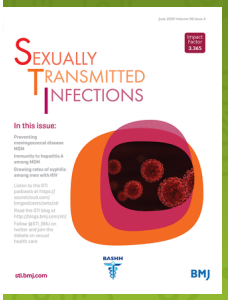
Sexually Transmitted Infections
Impact Factor: 3.365

Objectives: We used an in-house molecular assay for the detection of *Klebsiella granulomatis* in ulcer specimens collected over a 12-year surveillance period in order to determine whether a diagnosis of donovanosis could be ascribed to genital ulcer disease (GUD) of unknown aetiology in our setting.

Methods: Between 2007 and 2018, a total of 974 genital ulcer specimens with no previously identified sexually transmitted (STI) pathogens were selected from STI aetiological surveys conducted in all nine provinces of South Africa. Giemsa-stained ulcer smears from the same participants had previously been routinely analysed for the presence of typical Donovan bodies within large mononuclear cells. A *Klebsiella* screening assay targeting the phoE (phosphate porin) gene was used in combination with restriction digest analysis and sequencing to confirm the presence of *K. granulomatis*.

Results: The *Klebsiella* screening assay tested positive in 19/974 (2.0%) genital ulcer specimens. Restriction digest analysis and nucleotide sequencing of the phoE gene confirmed that none of these specimens was positive for *K. granulomatis* DNA. Similarly, Donovan bodies were not identified in the Giemsa stained ulcer smears of these specimens.

Conclusion: This is the first study to assess *K. granulomatis* as a cause of genital ulceration in South Africa over a 12-year surveillance period using molecular methods. The results demonstrate that *K. granulomatis* is no longer a prevalent cause of GUD in our population.

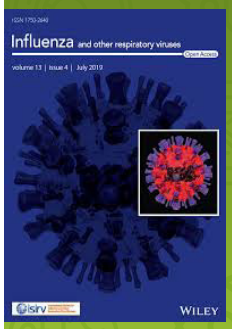


Dr Sibongile Walaza

Influenza and tuberculosis co-infection: A systematic review

Walaza S, *Cohen C, Tempia S, Moyes J, Nguweneza A, Madhi SA, McMorrow M, Cohen AL.*

Influenza and Other Respiratory Viruses
Impact Factor: 3.094



Introduction: There are limited data on risk of severe disease or outcomes in patients with influenza and pulmonary tuberculosis (PTB) co-infection compared to those with single infection.

Methods: We conducted a systematic review of published literature on the interaction of influenza viruses and PTB. Studies were eligible for inclusion if they presented data on prevalence, disease association, presentation or severity of laboratory-confirmed influenza among clinically diagnosed or laboratory-confirmed PTB cases. We searched eight databases from inception until December 2018. Summary characteristics of each study were extracted, and a narrative summary was presented. Cohort or case-control studies were assessed for potential bias using the Newcastle-Ottawa scale.

Results: We assessed 5 154 abstracts, reviewed 146 manuscripts and included 19 studies fulfilling selection criteria (13 human and six animal). Of the seven studies reporting on the possible effect of the underlying PTB disease in patients with influenza, three of four analytical studies reported no association with disease severity of influenza infection in those with PTB, whilst one study reported PTB as a risk factor for influenza-associated hospitalisation. An association between influenza infection and PTB disease was found in three of five analytical studies; whereas the two other studies reported a high frequency of PTB disease progression and complications among patients with seasonal influenza co-infection.

Conclusion: Human analytical studies of an association between co-infection and severe influenza- or PTB-associated disease or increased prevalence of influenza co-infection in individuals' hospitalised for PTB were not conclusive. Data are limited from large, high-quality, analytical epidemiological studies with laboratory-confirmed endpoints.

Dr Erika van Schalkwyk

Prof Nelesh Govender

Screening for invasive fungal disease using non-culture-based assays among inpatients with advanced HIV disease at a large academic hospital in South Africa

van Schalkwyk E, *Mhlanga M, Maphanga TG, Mpembe RS, Shillubane A, Iyaloo S, Tsotetsi E, Pieton K, Karstaedt AS, Sahid F, Menezes CN, Tsitsi M, Motau A, Wadula J, Seetharam S, van den Berg E, Sriruttan C,* ***Govender NP.***

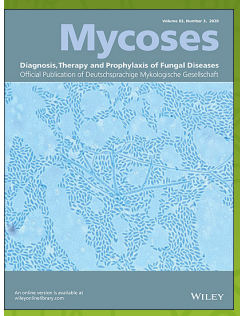
Mycoses
Impact Factor: 3.065

Introduction: Despite widespread access to antiretroviral therapy (ART), the burden of advanced HIV disease in South Africa is high. This translates into an increased risk of AIDS-related opportunistic infections, including invasive mycoses.

Methods: Using a limited number of non-culture-based diagnostic assays, we aimed to determine the prevalence of invasive mycoses and tuberculosis among hospitalised adults with very advanced HIV (CD4 counts <100 cells/μL) at a large academic hospital. We conducted interviews and prospective medical chart reviews. We performed point-of-care finger stick and serum cryptococcal antigen lateral flow assays; serum (1→3) ß-D-glucan assays; urine *Histoplasma* galactomannan antigen enzyme immunoassays and TB lipoarabinomannan assays.

Results: We enrolled 189 participants from 5 280 screened inpatients. Fifty-eight per cent were female, with median age 37 years (IQR: 30-43) and median CD4 count 32 cells/μL (IQR: 13-63). At enrolment, 60% (109/181) were receiving ART. Twenty-one participants (11%) had a diagnosis of an invasive mycosis, of whom 53% (11/21) had cryptococcal disease. Thirteen participants (7%) had tuberculosis and a concurrent invasive mycosis. ART-experienced participants were 60% less likely to have an invasive mycosis than those ART-naïve (adjusted OR: 0.4; 95% CI 0.15-1.0; P = .03). Overall in-hospital mortality was 13% (invasive mycosis: 10% [95% CI 1.2-30.7] versus other diagnoses: 13% (95% CI 8.4-19.3).

Conclusions: One in ten participants had evidence of an invasive mycosis. Diagnosis of proven invasive fungal disease and differentiation from other opportunistic infections was challenging. More fungal-specific screening and diagnostic tests should be applied to inpatients with advanced HIV disease.



Mr Alex Jeanrenraud

Dr Shune Oliver

Second generation effects of larval metal pollutant exposure on reproduction, longevity and insecticide tolerance in the major malaria vector *Anopheles arabiensis* (Diptera: Culicidae)

Jeanrenaud ACSN, *Brooke BD,* ***Oliver O.***

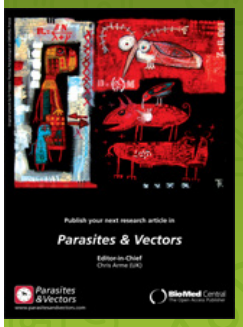
Parasites and Vectors
Impact Factor: 3.031

Background: Members of the *Anopheles gambiae* complex breed in clean, sunlit temporary bodies of water. Anthropogenic pollution is, however, altering the breeding sites of the vectors with numerous biological effects. Although the effects of larval metal pollution have previously been examined, this study aims to assess the transgenerational effects of larval metal pollution on the major malaria vector *An. arabiensis.*

Methods: Two laboratory strains of *An. arabiensis,* SENN (insecticide-susceptible) and SENN-DDT (insecticide-resistant), were used in this study. After being bred in water polluted with either cadmium chloride, copper nitrate or lead nitrate, several life history characteristics that can have epidemiological implications (fertility, apoptotic damage to reproductive structures, adult longevity and insecticide tolerance) were examined in the adults and compared to those of adults bred in clean water.

Results: All metal treatments reduced fecundity in SENN, but only lead treatment reduced fertility in SENN-DDT. Cadmium chloride exposure resulted in apoptosis and deformation of the testes in both strains. After breeding generation F0 in polluted water, F1 larvae bred in clean water showed an increase in longevity in SENN-DDT adult females. In contrast, after breeding the F0 generation in polluted water, longevity was reduced after cadmium and copper exposure in the F1 generation. Larval metal exposure resulted in an increase in insecticide tolerance in adults of the SENN strain, with SENN-DDT adults gaining the greatest fold increase in insecticide tolerance.

Conclusions: This study demonstrates that a single exposure to metal pollution can have transgenerational effects that are not negated by subsequent breeding in clean water.



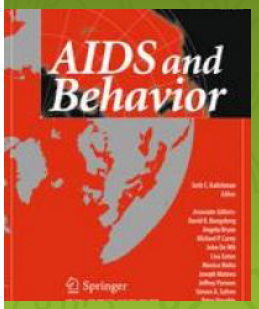
Dr Tendesayi Kufa

Dr Ranmini Kularatne

Medical male circumcision and associations among sexually transmitted infections service attendees

Kufa T, Radebe F, Maseko V, Puren A, ***Kularatne R.***

AIDS and Behavior
Impact Factor: 2.906



Medical male circumcision (MMC) is a proven intervention for preventing HIV acquisition among males. We describe the circumcision status, eligibility for MMC referral and associations with HIV positivity among symptomatic males attending sexually transmitted infections (STI) services. This study was a secondary analysis of cross-sectional data collected during sentinel surveillance for STI aetiologies. In the sentinel surveillance conducted at primary care facilities located in six South African provinces, an anonymous questionnaire was administered followed by collection of appropriate genital and blood specimens for laboratory testing including HIV, rapid plasma reagin (RPR) and HSV-2 serological testing. During analysis, multivariable logistic regression was used to determine association between prevalent HIV infection and male circumcision among males who were HSV-2 AND/OR RPR serology positive and among those who were negative. A total of 847 males were included in the analysis, among whom the median age was 28 years (IQR 24-32 years) with 26.3% aged < 25 years. Of these, 166 (19.6%) were medically circumcised, 350 (41.4%) traditionally circumcised while 324 (39%) were not circumcised. The yield of assessment for MMC referral was 27.7%. Overall HIV positivity was 23.1%. Compared to no circumcision, MMC had a statistically insignificant 62% lower odds of being HIV positive -among males who were HSV-2 and RPR negative- adjusted odds ratio [aOR] 0.38 [95% confidence interval (CI) 0.12-1.18], p = 0.094. Among those HSV-2 AND/OR RPR positive, MMC had a statistically insignificant 26% lower odds of being HIV positive- aOR 0.74 (95% CI 0.41-1.36), p = 0.334. In both groups HIV positivity increased with age but was positively associated with condom use at last sexual encounter [aOR 3.41 (95% CI 1.43-8.15)] and previous treatment for an STI syndrome [aOR 3.81 (95% CI 1.60-9.05)] among those HSV-2 and RPR negative. High HIV positivity and high yield of eligibility for VMMC referral among males attending STI services points to the need for better integration of HIV prevention and treatment with STI care.

Ms Ashley Burke

Metabolic rate does not vary with seasonal change in *Anopheles arabiensis* adults in South Africa

Burke AM, *Brooke BD, Duncan FD.*

Journal of Insect Physiology
Impact Factor: 2.862

An important component of South Africa's malaria elimination agenda is identifying the entomological drivers of residual transmission, especially those that present opportunities for enhanced vector control. Seasonal mosquito density correlates directly with malaria transmission in South Africa. Transmission is highest during the warm rainy season and lowest, but not entirely absent, during the cooler dry season. The factors that sustain dry-season mosquito survival remain unknown. The aim of this project was, therefore, to investigate seasonal change in metabolic rate to determine the presence or absence of winter dormancy in malaria vector mosquitoes. Metabolic rate, determined by CO2 production during closed-system respirometry, was measured from wild anophelines collected from KwaZulu-Natal Province, South Africa. Monthly sampling spanned all four seasons (summer, autumn, winter, and spring) in 2017. *Anopheles arabiensis* and *An. parensis* specimens formed the majority of the total 437 identified specimens (n = 216 and n = 162, respectively). Metabolic rate data from wild-caught mosquitoes showed no significant seasonal disparities for *An. arabiensis* and *An. parensis* males and females. Further laboratory experiments assessed the effect of manipulated photoperiod, representing seasonal day-length changes, on the metabolic rate of colonized *An. arabiensis* mosquitoes. Simulations of midwinter (10 h:14 h light dark) and midsummer (14 h:10 h) day-length showed no significant effect on the metabolic rate of these mosquitoes. Age (in days) had a significant effect on the metabolic rate of both male and female colonized adult *An. arabiensis* mosquitoes, which may be linked to developmental factors during maturation of adults. These data suggest that the South African populations of the malaria vector species *An. arabiensis* and *An. parensis* do not curtail their breeding and foraging activities during the colder and drier winter months. Overwintering by diapause does not appear to be triggered in the adult mosquito stage in *An. arabiensis*. However, their respective population densities do decrease considerably during winter leading to reduced malaria transmission and the opportunity for control by winter larviciding of known breeding sites.

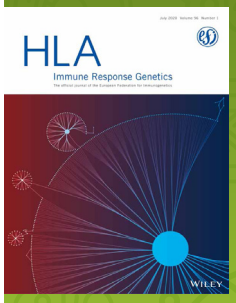
Dr Shayne Loubser

Prof Caroline Tiemessen

Identification of a novel allele, HLA-DPB1*34:01:01:03, in Black South African individuals

Loubser S, Kwenda S, Sengupta D, ***Tiemessen CT.***

HLA: Immune Response Genetics
Impact Factor: 2.785



Genetic characterisation of a non-coding region allelic variant, HLA-DPB1*34:01:01:03, in Black South African individuals. The Major Histocompatibility Complex (MHC) located on the short arm of chromosome 6, encodes many immunerelated proteins, including HLA class I and II molecules, important for the development of immunity to pathogens. The MHC region also shows the highest degree of genetic polymorphism in the human genome as exemplified by the rich diversity of allelic variants documented for HLA loci in global populations. In terms of HLA nomenclature, subsets of allelic variants can differ by single nucleotide polymorphisms (SNPs) or insertion/deletions (indels) that map to non-coding regions, such as introns or to the 30/50 untranslated regions, in which case the designated allele name changes at the fourth field of resolution.

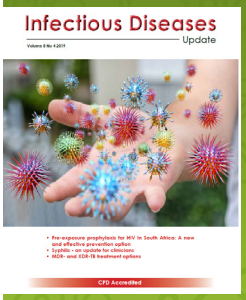
Dr Ranmini Kularatne

Syphilis – an update for clinicians

Kularatne R.

Infectious Diseases Update
Impact Factor: 2.785

Syphilis is a venereal disease caused by the spiral-shaped bacterium *Treponema pallidum* subspecies *pallidum*. The disease is endemic worldwide, with a 2016 global prevalence estimate of 0.5% (95% uncertainty interval (UI): 0.4-0.6) and an incidence estimate of 6.3 million cases (95% UI: 5.5 – 7.1 million) among persons aged 15-49 years. Prevalence was highest in the World Health Organization (WHO) Africa region. In South Africa, 2017 estimates for syphilis prevalence and incidence were 0.5% (95% CI: 0.32 – 0.8%) and 70 675 cases, respectively, in the general adult (15-49 year-old) population. A general decline in syphilis prevalence between 1990 and 2017 in the country was attributed to the implementation of various public health interventions such as the roll out of syndromic management for genital ulcer disease, ante-natal syphilis screening and treatment, syphilis screening as a component of the comprehensive case management of HIV, and voluntary male medical circumcision. In recent years there has been a resurgence of syphilis in the United States of America and Western Europe, especially among men-who-have-sex-with-men (MSM). This epidemic has been linked to HIV infection and substance abuse, and is attributed to challenges in control efforts as well as risk.



Dr Ashika Singh-Moodley

Prof Olga Perovic

Unconventional SCCmec types and low prevalence of the Panton-Valentine Leukocidin exotoxin in South African blood culture *Staphylococcus aureus* surveillance isolates, 2013-2016

Singh-Moodley A, *Strasheim W, Mogokotleng R, Ismail H,* ***Perovic O.***

PLOS One
Impact Factor: 2.776

Staphylococcus aureus is a healthcare-associated pathogen that can harbour multiple antimicrobial resistance determinants and express multiple virulence factors, e.g. Panton-Valentine Leukocidin (PVL). Unknown staphylococcal cassette chromosome mec (SCCmec) typing patterns were previously observed among 11% (n = 52) of methicillin-resistant *S. aureus* (MRSA) isolates; we further investigated these as well as the proportion of PVL, encoded by lukS/F-PV, in 761 *S. aureus* isolates from patients with a diagnosis of pneumonia/lower respiratory tract, skin/soft tissue, bone and joint infection. *S. aureus* isolates from blood culture were identified and antimicrobial susceptibility testing was performed using automated systems. Conventional PCR assays were used to identify the ccr and mec gene complexes in mecA-positive isolates with an unknown SCCmec type and screen for lukS/F-PV. Epidemiological data was used to classify isolates as healthcare - or community -associated infections. Antimicrobial susceptibility profiles according to SCCmec type and PVL were reported. Of the unknown SCCmec types, isolates were interpreted as type I-like (86%, 38/44), type II-like (9%, 4/44) and type III-like (5%, 2/44). Eight isolates did not produce definitive results. Of all MRSA isolates, majority were multidrug-resistant as indicated by their non-susceptibility to most antimicrobial agents; 92% were healthcare-associated. PVL was seen in 14% of the isolates (MRSA: 25%, MSSA: 75%); 56% were classified as healthcare-associated infection. The SCCmec typing method did not definitively classify all unknown isolates into clearly defined types. It showed that majority of these isolates were not the conventional types; untypeable elements appeared to be composite SCCmec elements, consisting of multiple ccr gene complexes. Majority of the MRSA isolates were non-susceptible to most antibiotics indicating that multiple resistance genes are present in our population. Furthermore, the proportion of PVL was low and more prevalent in MSSA.

Dr Vanessa Quan

Prof Nelesh Govender

Pathways to care and outcomes among hospitalised HIV-seropositive persons with cryptococcal meningitis in South Africa

Quan V, *Toro-Silva S, Sriruttan C, Chetty V, Chihota V, Candfield S, Vassall A, Grant AD,* ***Govender NP.***

PloS One
Impact Factor: 2.776

Introduction: Cryptococcus causes 15% of AIDS-related deaths and in South Africa, with its high HIV burden, is the dominant cause of adult meningitis. Cryptococcal meningitis (CM) mortality is high, partly because patients enter care with advanced HIV disease and because of failure of integrated care following CM diagnosis. We evaluated pathways to hospital care, missed opportunities for HIV testing and initiation of care.

Methods: We performed a cross-sectional study at five public-sector urban hospitals. We enrolled adults admitted with a first or recurrent episode of cryptococcal meningitis. Study nurses conducted interviews, supplemented by a prospective review of medical charts and laboratory records.

Results: From May to October 2015, 102 participants were enrolled; median age was 40 years (interquartile range [IQR] 33.9-46.7) and 56 (55%) were male. In the six weeks prior to admission, 2/102 participants were asymptomatic, 72/100 participants sought care at a public-sector facility, 16/100 paid for private health care. The median time from seeking care to admission was 4 days (IQR, 0-27 days). Of the 94 HIV-seropositive participants, only 62 (66%) knew their status and 41/62 (66%) had ever taken antiretroviral treatment. Among 13 participants with a known previous CM episode, none were taking fluconazole maintenance therapy. In-hospital management was mostly amphotericin B; in-hospital mortality was high (28/92, 30%). Sixty-four participants were discharged, 92% (59/64) on maintenance fluconazole, 4% (3/64) not on fluconazole and 3% (2/64) unknown. Twelve weeks post-discharge, 31/64 (48%) participants were lost to follow up. By 12 weeks post-discharge 7/33 (21%) had died. Interviewed patients were asked if they were still on fluconazole, 11% (2/18) were not.

Conclusions: Among hospitalised participants with CM, there were many missed opportunities for HIV care and linkage to ART prior to admission. Universal reflex CrAg screening may prompt earlier diagnosis of cryptococcal meningitis but there is a wider problem of timely linkage to care for HIV-seropositive people.

Dr Selamawit Woldesenbet

Prof Adrian Puren

Awareness of HIV-positive status and linkage to treatment prior to pregnancy in the 'test and treat' era: A national antenatal sentinel survey, 2017, South Africa

Woldesenbet S, *Kufa T, Cheyip M, Ayalew M, Lombard C, Manda S, Nadol P, Barron P, Chirombo B, Igumbor E, Pillay Y,* ***Puren AJ.***

PloS One
Impact Factor: 2.776

Introduction: Knowledge of HIV status in South Africa (SA) is reported to be 90% among people living with HIV. National level estimates could mask population-specific levels, which are critical to monitor programme coverage and potential impact. Using data from the 2017 national antenatal sentinel survey, we assessed knowledge of HIV-positive status, initiation of antiretroviral therapy (ART), and socio-demographic characteristics associated with knowledge of HIV-positive status prior to the current pregnancy among women attending antenatal care.

Methods: Between 1 October and 15 November 2017, a nationally representative sample of 32 716 pregnant women were enrolled from 1 595 public health facilities selected from all districts of SA. Data on age, gravidity, knowledge of HIV-positive status and ART initiation prior to pregnancy were extracted from medical records. A blood sample was collected from each woman regardless of prior knowledge of HIV status or ART history, and tested for HIV in the laboratory. All HIV-positive pregnant women enrolled in the survey were eligible for inclusion in the analysis. Multivariable survey logistic regression was used to examine factors associated with knowledge of HIV-positive status prior to the current pregnancy.

Results: Of 10 065 eligible HIV-positive women, 60.8% (95% confidence interval (CI): 59.9%-61.7%) knew their HIV status prior to the current pregnancy, of whom 91.1% (95% CI: 90.4%-91.7%) initiated ART prior to the current pregnancy. Knowledge of HIV-positive status was lower among adolescent girls and young women (15-24 years) (38.9%) and primigravid women (40.5%) compared with older women (35-49 years) (75.5%) and multigravid women (64.7%). In a multivariable analysis, significant effect modification was found between gravidity and age (P value = 0.047). Being in the age group 15-24 years compared to the age group 35-49 years decreased the odds of knowing HIV-positive status by 80% (adjusted odds ratio (AOR): 0.2, 95% CI: 0.1-0.4) among primigravid women and by 60%(AOR: 0.4, 95% CI: 0.3-0.4) among multigravid women.

Conclusion: Knowledge of HIV-positive status prior to the current pregnancy fell short of the target of 90% among pregnant women living with HIV. This was especially low among adolescent girls and young women, highlighting the gap in youth-friendly reproductive health and HIV testing services.

Prof Gayle Sherman

Time of HIV diagnosis, CD4 count and viral load at antenatal care start and delivery in South Africa

Onoya D, Nattey C, Jinga N, Mongwenyana C, ***Sherman G.***

PloS One
Impact Factor: 2.776

Background: Despite the success of prevention of mother to child transmission (PMTCT) programme in South Africa, the 30% HIV prevalence among women of childbearing age requires the PMTCT programme to be maximally efficient to sustain gains in the prevention of vertical HIV transmission. We aimed to determine the immunologic and virologic status at entry into antenatal care (ANC) and at childbirth among HIV positive women who conceived under the CD4<500 cells/μl antiretroviral therapy (ART) eligibility threshold and universal test, and treat (UTT) policies in the Gauteng Province of South Africa.

Method: We conducted a retrospective cohort study of 692 HIV positive adult (>18 years) postpartum women who gave birth between September 2016 and December 2017. Demographic, viral load (VL) and CD4 data at ANC start (3–9 months before delivery) and delivery (3 months before/after) were obtained from medical records of consenting women. We compared CD4≥500 cell/μl and viral load (VL) suppression (<400 copies/ml) rates at ANC start and delivery among women with a pre-pregnancy ART, women known HIV positive but with in-pregnancy ART and newly diagnosed women with in-pregnancy ART. Predictors of having a high CD4 and suppressed VL were assessed by log-binomial regression.

Results: Of the 692 participants, 394 (57.0%) had CD4 data and 326 (47.1%) had VL data. Overall women with a pre-pregnancy ART were more likely to start ANC with CD4 count ≥500 cell/μl (46.3% vs. 24.8%, adjusted risk ratio (aRR) = 1.9; 95% confidence interval (95% CI): 1.4–2.5), compared to newly diagnosed women. This difference was no longer apparent at the time of delivery (aRR 1.2 95% CI: 0.4–3.7). Similarly, viral suppression at delivery was higher among women with pre-pregnancy ART (87.2% vs. 69.3%, aRR 1.3, 95% CI: 1.1–1.6) as compared to the newly diagnosed women. Viral suppression rate among newly diagnosed women increased substantially by the time of delivery from 43.5% to 69.3% (p = 0.001).

Conclusion: These results show that pre-pregnancy ART improves immunologic and virologic control during pregnancy and call for renewed efforts in HIV testing, linkage to ART and viral monitoring.

Prof Caroline Tiemessen

The FCGR2C allele that modulated risk of HIV-1 infection in the Thai RV144 vaccine trial is implicated in HIV-1 disease progression

Lassauniere R, Paximadis M, Ebrahim O, Chaisson R, Martinson N, ***Tiemessen CT.***

Genes and Immunity
Impact Factor: 2.631

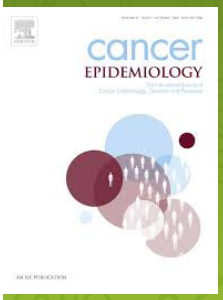
In the HIV-1 Thai RV144 vaccine trial — the only trial to demonstrate any vaccine efficacy to date — a three-variant haplotype within the Fc gamma receptor 2C gene (FCGR2C) modified the risk of HIV-1 acquisition. A similar vaccine regimen is currently being evaluated in South Africa in the HVTN702 trial, where the predominant population is polymorphic for only a single variant in the haplotype, c.134-96C>T. To investigate the significance of c.134-96C>T in HIV-specific immunity in South Africans, this study assessed its role in HIV-1 disease progression. In a cohort of HIV-1-infected South African controllers (n = 71) and progressors (n = 73), the c.134-96C>T minor allele significantly associated with increased odds of HIV-1 disease progression (odds ratio 3.80, 95% confidence interval 1.90–7.62; P = 2.0 × 10–4, PBonf = 2.4 × 10–3). It is unlikely that the underlying mechanism involves wild-type FcγRIIc function, since only a single study participant was predicted to express wild-type FcγRIIc as determined by the FCGR2C c.798+1A>G splice-site variant. Conversely, in silico analysis revealed a potential role for c.134-96C>T in modulating mRNA transcription. In conclusion, these data provide additional evidence towards a role for FCGR2C c.134-96C>T in the context of HIV-1 and underscore the need to investigate its significance in the HVTN702 efficacy trial in South Africa.

Mr Wenlong Chen

Johannesburg Cancer Study (JCS): Contribution to knowledge and opportunities arising from 20 years of data collection in an African setting

Chen WC, *Singh E, Muchengeti M, Bradshaw D, Mathew CG, Babb de Villiers C, Lewis CM, Waterboer T, Newton R, Sitas F.*

Cancer Epidemiology
Impact Factor: 2.619



The Johannesburg Cancer Study (JCS) aims were to examine whether cancer risk factors identified in Western countries applied to black patients in Johannesburg, South Africa and to understand the impact of HIV on cancer risk, with a view to identifying previously unrecognised HIV associated cancers. A total of 24 971 black patients with an incident histologically proven (>95%) cancer of any type were enrolled between 1995-2016. Response rates were >90%. Patients provided informed consent, lifestyle and demographic information using a structured questionnaire; 19 351 provided a serum sample and 18 972 a whole blood sample for genomic analyses. This is currently the largest cancer epidemiological biobank in Africa. JCS uses a cancer case-control method; controls being cancer types unrelated to exposures of interest. Published results show the importance of HIV in several cancers known to be infection associated e.g. Kaposi sarcoma (OR = 1 683; CI = 595-5194) in those with high Kaposi-sarcoma-associated-herpesvirus titres; no effect of HIV on lung or liver cancer-in the latter showing a strong association with HBVDNA, sAg and c positivity (OR = 47; CI = 21-104). Comparable data to higher-income country studies include lung cancer ORs in relation to smoking (15+g tobacco/day) (ORMales = 37; CI = 21-67, ORFemales = 18.5; CI = 8-45) and associations between alcohol and oesophageal cancer in smokers (ORM&F = 4.4; CI = 3-6). Relationship between hormonal contraception declined to null 10 or more years after stopping for breast (OR = 1.1; CI = 0.9-1.4) and cervical cancer (OR = 1.0;CI = 0.8-1.2), and protective effects shown, five or more years after stopping for ovarian (OR = 0.6; CI = 0.4-1) and endometrial cancer (OR = 0.4; CI = 0.2-0.9). Preferential access is based on data requests promoting data pooling, equal collaborative opportunities and enhancement of research capacity in South Africa. The JCS is a practical and valid design in otherwise logistically difficult settings.

Dr Ashika Singh-Moodley

Prof Olga Perovic

Carbapenem-resistant Enterobacteriaceae in patients with bacteraemia at tertiary hospitals in South Africa, 2015 to 2018

Perovic O, *Ismail H, Quan V, Bamford C, Nana T, Chibabhai V, Bhola P, Ramjathan P, Swe Swe-Han K, Wadula J, Whitelaw A, Smith M, Mbelle N,* ***Singh-Moodley A.***

European Journal of Clinical Microbiology & Infectious Diseases
Impact Factor: 2.906

Enhanced surveillance for carbapenem-resistant Enterobacteriaceae (CREs) was established at national sentinel sites in South Africa. We aimed to apply an epidemiological and microbiological approach to characterise CREs and to assess trends in antimicrobial resistance from patients admitted to tertiary academic hospitals. A retrospective analysis was conducted on patients of all ages with CRE bacteraemia admitted at any one of 12 tertiary academic hospitals in four provinces (Gauteng, KwaZulu-Natal, Western Cape and Free State) in South Africa. The study period was from July 2015 to December 2018. A case of CRE bacteraemia was defined as a patient admitted to one of the selected tertiary hospitals where any of the Enterobacteriaceae was isolated from a blood culture, and was resistant to the carbapenems (ertapenem, meropenem, imipenem and/or doripenem) or had a positive result for the Modified Hodge Test (MHT) according to the Clinical and Laboratory Standards Institute (CLSI) guidelines. A positive blood culture result obtained after 21 days of the last blood culture result was regarded as a new case. To distinguish hospital-acquired (HA) from the community-acquired (CA) bacteraemia, the following definitions were applied: the HA CRE bacteraemia was defined as a patient with CRE isolated from blood culture ≥72 h of hospital admission or with any prior healthcare contact, within 1 year prior to the current episode or referral from a healthcare facility where the patient was admitted before the current hospital. A case of the CA CRE bacteraemia was defined as a patient with CRE isolated from blood culture <72 h of hospital admission and with no prior healthcare contact. The majority of carbapenem-resistant Enterobacteriaceae (CRE) (70%) were hospital-acquired (HA) with *Klebsiella pneumoniae* being the predominant species (78%). In-hospital mortality rate was 38%. The commonest carbapenemase genes were bla-OXA-48 (52%) and bla-NDM (34%). The high mortality rate related to bacteraemia with CRE and the fact that most were hospital-acquired infections highlights the need to control the spread of these drug-resistant bacteria. Replacement with OXA-48 is the striking finding from this surveillance analysis. Infection control and antibiotic stewardship play important roles in decreasing the spread of resistance.

Dr Shayne Loubser

Prof Caroline Tiemessen

Human leukocyte antigen class I (A, B, C) and class II (DPB1, DQB1, DRB1) allele and haplotype variation in Black South African individuals

Loubser S, *Paximadis M, Gentle NL, Puren A,* ***Tiemessen CT.***

Human Immunology
Impact Factor: 2.202

South Africa has a population of 58.78 million, of which 80.7% are Black African individuals, representing 9 predominant ethnic/linguistic groups (Zulu, Xhosa, Pedi, Tswana, South Sotho, Tsonga, Swati, Venda and Ndebele). HIV-1 and *Mycobacterium tuberculosis* infection are the leading causes of death (7.8% and 5.9%, respectively) in this population group. To provide reference HLA allele and haplotype data for studies of gene-associations with infectious/ non-infectious diseases or vaccine development, we have updated previously published HLA class I (A, B, C) and class II DRB1 genotypes and determined high-resolution class II (DPB1, DQB1) genotypes for n = 142 healthy, unrelated Black South African individuals.

Mrs Leanne Nicole Lobb

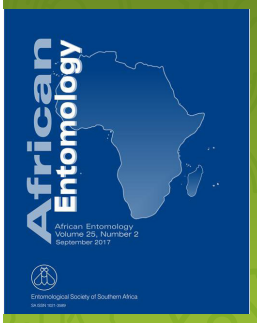
Prof Lizette Koekemoer

The effect of egg storage of laboratory reared *Anopheles arabiensis* on egg hatch synchronisation, pupation success and pupal production time

Lobb LN, *Munhenga G, Yamada H,* ***Koekemoer LL.***

African Entomology
Impact Factor: 0.536

Use of the sterile insect technique (SIT) targeting the malaria vector *Anopheles arabiensis* has been proposed and is currently under investigation. The SIT requires production of large numbers of sterile males and therefore mass-rearing of the target species is required. One critical factor during mass-rearing for sterile releases is the need to synchronise developmental life stages to assist in pupae and adult harvesting during production. However, by nature *An. arabiensis* egg hatching, and subsequent development is staggered as a survival strategy resulting in unsynchronised production. This causes a loss in efficiency during mass-rearing. This study aimed to investigate the effect of egg storage on egg hatch synchronisation, survival rate of aquatic life stages and the subsequent effect on production lead-time of a laboratory-reared *An. arabiensis* strain. Eggs from colonised *An. arabiensis* were collected, drained onto a filter paper to remove excess water, and stored for an increasing number of days, up to four days. After the storage time, proportion hatching and pupating as well as the time to hatch and pupation were measured and analysed using a one-way ANOVA and a Kaplan-Meier Survival analysis, respectively. No significant difference was observed in the proportion hatching or pupating between the different storage durations. However, there was a significant reduction in time to hatch and pupate. In conclusion, egg storage is a viable method to synchronise hatching, which could, in combination with other factors, assist in synchronous production of pupae for this strain without having adverse effects on survival.



Prof Nelesh Govender

Southern African HIV Clinicians Society guideline for the prevention, diagnosis and management of cryptococcal disease among HIV-infected persons: 2019 update

Govender NP, *Meintjes G, Mangena P, Nel J, Potgieter S, Reddy D, Rabie H, Wilson D, Black J, Boulware D, Boyles T, Chiller T, Dawood H, Dlamini S, Harrison T, Ive P, Jarvis J, Karstaedt A, Madua M, Menezes C, Moosa M, Motlekar Z, Shroufi A, Stacey S, Tsitsi M, van Cutsem G, Variava E, Venter M, Wake R.*

Southern African Journal of HIV Medicine
Impact Factor: Score unavailable

Six years after the Southern African HIV Clinicians Society cryptococcal disease guideline was published in 2013, cryptococcal meningitis (CM) remains an important cause of mortality among antiretroviral treatment (ART)-naïve and ART-experienced HIV-seropositive adults in South Africa. Several important practice-changing developments led us to update the guideline to diagnose, prevent and manage this common fungal opportunistic infection. The World Health Organization (WHO) published a guideline for advanced HIV disease in 2017 and a guideline relevant to resource-limited settings for HIV-associated CM in 2018. Cryptococcal antigen (CrAg) screening and pre-emptive treatment reduced all-cause mortality among ambulatory participants in a randomised clinical trial in Zambia and Uganda. Following an evaluation of reflex versus provider-initiated screening, national reflex laboratory CrAg screening was implemented in South Africa in 2016. Recently, completed clinical trials conducted in resource-limited settings have provided evidence for the best first-line antifungal regimens for CM and the role of corticosteroids in CM. Finally, international and local advocacy efforts have resulted in increasing, yet still limited, access to flucytosine and a reduced cost of liposomal amphotericin B for the treatment of CM.

Dr Ashika Singh-Moodley

Dr Arshad Ismail

Complete genome sequence of a *Staphylococcus aureus* isolate from a nasopharyngeal swab from a mine worker in South Africa

Singh-Moodley A, *Allam M, Ismail H, Perovic O, Strasheim W, Mtshali S,* ***Ismail A.***

Microbiology Resource Announcements
Impact Factor: Score unavailable

Staphylococcus aureus is a gram-positive, facultative anaerobic bacterium and a major pathogen causing both nosocomial and community-acquired infections. *S. aureus* has a wide spectrum of clinical manifestations, including wound infections, pneumonia, septicemia, and endocarditis. Here, we report the full genome sequence of *S. aureus* NP66 recovered from a nasopharyngeal swab collected from a male mine worker during an outbreak of Panton-Valentine leukocidin-producing methicillin-susceptible *S. aureus* infection in a gold mine in South Africa. Ethical clearance was obtained from the University of the Witwatersrand Human Research Committee (protocol number M10464). The nasopharyngeal swab obtained from the mine worker was cultured as per standard microbiological procedures. For the recovery of bacterial colonies, the swab was subcultured onto 5% horse blood, MacConkey and/or Chapman's salt agar plates (Diagnostic Media Products [DMP], National Health Laboratory Service [NHLS], South Africa) and incubated overnight at 37°C. Bacterial colonies were subcultured onto fresh 5% horse blood agar plates (DMP, NHLS) and identified to the species level using matrix-assisted laser desorption/ionization – time of flight (MALDI-TOF) mass spectrometry (Bruker Daltonik, Bremen, Germany). Overnight, bacterial cultures were started from single colonies and grown at 37°C. The genomic DNA was extracted using the QIAamp DNA minikit (Qiagen, Germany). The PacBio library was produced using a SMRTbell template prep kit 1.0, and a single SMRTbell 10-kb library was prepared according to the protocol 'Preparing SMRTbell Libraries Using PacBio Barcoded Adapters for Multiplex SMRT Sequencing' (Pacific Biosciences, Menlo Park, CA, USA). The genome was sequenced using a single-molecule real-time (SMRT) cell with the PacBio Sequel sequencing platform, following the manufacturer's specifications, with on-plate concentration of 4 pM using Sequel chemistry V2 and a 10-hour movie time. Sequencing yielded 765 268 787 bases from 316 295 reads, with an average length of 2 419 bp. The quality of the reads was determined and analysis of the data was performed using PacBio SMRT link version 5.1. The generated subreads were assembled using Hierarchical Genome Assembly Process version 4 (HGAP4) followed by circularisation using Berokka (https://github.com/tseemann/berokka) and annotation using the NCBI Prokaryotic Genome Annotation Pipeline (PGAP). The Comprehensive Antibiotic Resistance Database (CARD), PlasmidFinder, the Virulence Factor Database (VFDB), and spaTyper version 1 were used to predict the resistance genes, plasmids, virulence genes, and spa type, respectively. Multilocus sequence typing (MLST) was

determined using mlst (https://github.com/tseemann/mlst). Default settings were used in all software unless otherwise noted. A total of 295 201 filtered subreads were generated after sequencing (average subread length, 2 400 bp; subread N50, 2 898 bp; 249-fold coverage). The reads were assembled, and we found that the complete genome sequence of *S. aureus* NP66 consists of 2 752 396 bp with a G+C content of 32.9%, including 2 703 protein-coding genes, 78 pseudogenes, and 82 RNA genes (19 rRNAs, 59 tRNAs, and 4 noncoding RNAs). Using the CARD database, we found 11 antibiotic resistance genes in this genome, including the beta-lactamase resistance gene (blaZ, 94.66% identity), the fosfomycin resistance gene (fosB3, 99.28% identity), and others, such as genes encoding the two-component system ArlS-ArlR, which plays a role in capsule production (arlR, 100% identity; arlS, 100% identity), and genes encoding efflux pumps (LmrS, 99.38% identity; mepR, 100% identity; mgrA, 100% identity; norA, 100% identity). The isolate was negative for the Panton-Valentine leukocidin exotoxin but did harbour 75 potential genes associated with virulence factors. Furthermore, no plasmids were present. The spa type was t909, and MLST analysis revealed that the isolate belonged to sequence type 12 (ST12).

Prof John Frean

Gnathostomiasis acquired by visitors to the Okavango delta, Botswana

Frean J.

Tropical Medicine and Infectious Diseases
Impact Factor: Score unavailable

Gnathostomiasis is a zoonotic nematode parasite disease, most commonly acquired by eating raw or undercooked fish. Although the disease is well known in parts of Asia and Central and South America, relatively few cases have been reported from Africa. Raw fish consumed in the Okavango River delta area of Botswana, and in nearby western Zambia, has previously produced laboratory-proven gnathostomiasis in tourists. The purpose of this communication is to record additional cases of the infection acquired in the Okavango delta, and to alert visitors to the inadvisability of eating raw freshwater fish in the southern African region.

Dr Batsirai Mabvakure

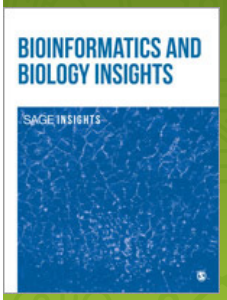
Prof Penny Moore

Advancing HIV vaccine research with low-cost high-performance computing infrastructure: An alternative approach for resource-limited settings

Mabvakure BM, *Rott R, Dobrowsky L, van Heusden P, Morris L, Scheepers C,* ***Moore PL.***

Bioinformatics and Biology Insights
Impact Factor: Score unavailable

Next-generation sequencing (NGS) technologies have revolutionised biological research by generating genomic data that were once unaffordable by traditional first-generation sequencing technologies. These sequencing methodologies provide an opportunity for in-depth analyses of host and pathogen genomes as they are able to sequence millions of templates at a time. However, these large datasets can only be efficiently explored using bioinformatics analyses requiring huge data storage and computational resources adapted for high-performance processing. High-performance computing allows for efficient handling of large data and tasks that may require multi-threading and prolonged computational times, which is not feasible with ordinary computers. However, high-performance computing resources are costly and therefore not always readily available in low-income settings. We describe the establishment of an affordable high-performance computing bioinformatics cluster consisting of 3 nodes, constructed using ordinary desktop computers and open-source software including Linux Fedora, SLURM Workload Manager, and the Conda package manager. For the analysis of large antibody sequence datasets and for complex viral phylodynamic analyses, the cluster out-performed desktop computers. This has demonstrated that it is possible to construct high-performance computing capacity capable of analysing large NGS data from relatively low-cost hardware and entirely free (open-source) software, even in resource-limited settings. Such a cluster design has broad utility beyond bioinformatics to other studies that require high-performance computing.



Prof Gayle Sherman

The impact of health programmes to prevent vertical transmission of HIV. Advances, emerging health challenges and research priorities for children exposed to or living with HIV: Perspectives from South Africa

Goga A, Slogrove A, Wedderburn CJ, Feucht U, Wessels J, Ramokolo V, Bhana A, du Plessis N, Green RJ, Pillay Y, ***Sherman G.***

South African Medical Journal
Impact Factor: Score unavailable

Over the past three decades, tremendous global progress in preventing and treating paediatric HIV infection has been achieved. This paper highlights the emerging health challenges of HIV-exposed uninfected (HEU) children and the ageing population of children living with HIV (CLHIV), summarises programmatic opportunities for care, and highlights currently conducted research and remaining research priorities in high HIV-prevalence settings such as South Africa. Emerging health challenges amongst HEU children and CLHIV include preterm delivery, suboptimal growth, neurodevelopmental delay, mental health challenges, infectious disease morbidity and mortality, and acute and chronic respiratory illnesses including tuberculosis, pneumonia, bronchiectasis and lymphocytic interstitial pneumonitis. CLHIV and HEU children require three different categories of care: (i) optimal routine child health services applicable to all children; (ii) routine care currently provided to all HEU children and CLHIV, such as HIV testing or viral load monitoring, respectively, and (iii) additional care for CLHIV and HEU children who may have growth, neurodevelopmental, behavioural, cognitive or other deficits such as chronic lung disease, and require varying degrees of specialised care. However, the translation thereof into practice has been hampered by various systemic challenges, including shortages of trained healthcare staff, suboptimal use of the patient-held child's Road to Health book for screening and referral purposes, inadequate numbers and distribution of therapeutic staff, and shortages of assistive/diagnostic devices, where required. Additionally, in low-middle-income high HIV-prevalence settings, there is a lack of evidence-based solutions/models of care to optimise health amongst HEU and CLHIV. Current research priorities include understanding the mechanisms of preterm birth in women living with HIV to optimise preventive interventions; establishing pregnancy pharmacovigilance systems to understand the short-, medium- and long-term impact of in utero ART and HIV exposure; understanding the role of preconception maternal ART on HEU child infectious morbidity and long-term growth and neurodevelopmental trajectories in HEU children and CLHIV, understanding mental health outcomes and support required in HEU children and CLHIV through childhood and adolescence; monitoring HEU child morbidity and mortality compared with HIV-unexposed children; monitoring outcomes of CLHIV who initiated ART very early in life, sometimes with suboptimal ART regimens owing to medication formulation and registration issues; and testing sustainable models of care for HEU children and CLHIV including later reproductive care and support.

Dr Melinda Suchard

Mr Clement Adu-Gyamfi

Indoleamine 2, 3-dioxygenase (IDO)-mediated tryptophan catabolism: A leading star or supporting act in the tuberculosis and HIV pas-de-deux?

Adu-Gyamfi CG, *Savulescu DM, George JA,* ***Suchard MS.***

Frontiers Cellular and Infection Microbiology
Impact Factor: Score unavailable

Progression from latency to active tuberculosis (TB) disease is mediated by incompletely understood host immune factors. The definitive characteristic of progressive human immunodeficiency virus (HIV) disease is a severe loss in number and function of T lymphocytes. Among the many possible mediators of T lymphocyte loss and ineffective function is the activity of the immune-modulatory enzyme indoleamine 2, 3-dioxygenase (IDO). IDO is the rate-limiting enzyme converting tryptophan to kynurenine. IDO activity was initially recognised to mediate tolerance at the foeto-maternal interface. Recently, IDO activity has also been noted to play a critical role in immune tolerance to pathogens. Studies of host immune and metabolic mediators have found IDO activity significantly elevated in HIV and TB disease. In this review, we explore the link between IDO-mediated tryptophan catabolism and the presence of active TB disease in HIV-infected patients. We draw attention to increased IDO activity as a key factor marking the progression from latent to active TB disease in HIV-infected patients.

Dr Mpho Sikhosana

Dr Kerrigan McCarthy

Atypical presentation of herpes simplex virus type 1 infection in paediatric burns patients in a large tertiary hospital, South Africa

Sikhosana ML, *Salloo A, Birkhead M,* ***McCarthy K.***

African Journal of Laboratory Medicine
Impact Factor: 2.906

Introduction: Herpes simplex virus has been reported in the literature to commonly complicate burn wounds. However, there is paucity of such data in the South African setting.

Case presentation: Eight paediatric burns patients with ages ranging between 10 months and 5 years, presented with a febrile maculopapular rash illness in a paediatric ward of a large South African tertiary hospital. The rash became vesicular in three cases, involving the limbs and face. Varicella was suspected.

Management and outcome: Medical records of suspected cases were reviewed. Blood, vesicular fluid and scab samples were collected. Electron microscopy of vesicular fluid revealed herpes virus particles. Laboratory testing confirmed herpes simplex virus type 1.

Conclusion: Herpes simplex virus type 1 infection can present atypically in burns patients.

Ms Rindizani Magobo

Prof Nelesh Govender

Multilocus sequence typing of azole-resistant *Candida auris* strains, South Africa

Magobo R, *Mhlanga M, Corcoran C,* ***Govender NP.***

Southern African Journal of Infectious Diseases
Impact Factor: Score Unavailable

Background: *Candida auris* is an emerging multidrug-resistant fungal pathogen associated with high mortality.

Methods: We investigated the genetic relatedness of clinical *C. auris* isolates from patients admitted to either public- or private-sector hospitals, which were submitted to a reference laboratory from 2012 to 2015. Patient demographics and clinical details were recorded. We performed antifungal susceptibility testing, sequencing of the hotspot 1 and 2 regions of the FKS1 and FKS2 genes for all isolates with an echinocandin minimum inhibitory concentration (MIC) of ≥1 µg/mL and cluster analysis using multilocus sequence typing.

Results: Eighty-five isolates were confirmed as *C. auris*. The median patient age was 59 years [inter-quartile range (IQR): 48–68 years], with male patients accounting for 68% of cases. Specimen types included urine (29%), blood (27%), central venous catheter tips (25%), irrigation fluid (7%), tissue (5%), respiratory tract specimens (4%) and other (3%). Ninety-seven per cent of isolates were resistant to fluconazole, 7% were resistant to both fluconazole and voriconazole, 8% were resistant to both fluconazole and echinocandins (considered multidrug resistant) and all were susceptible to amphotericin B. Of the 15 randomly selected fluconazole-resistant isolates, 14 isolates had an isavuconazole MIC ≤1 µg/mL. No FKS mutations were detected. Multilocus sequence typing (MLST) analysis grouped isolates into two clusters: cluster 1 and cluster 2 comprising 83 and 2 isolates, respectively.

Conclusions: Azole-resistant *C. auris* strains circulating in South African hospitals were related by MLST, but the possibility of nosocomial transmission should be explored using a more discriminatory technique, for example, whole genome sequencing.

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Prof Olga Perovic

Prof John Frean

External quality assessment of bacterial identification and antimicrobial susceptibility testing in African national public health laboratories, 2011–2016

Perovic O, *Yahaya AA, Viljoen C, Ndihokubwayo JB, Smith M, Coulibaly SO, De Gouveia L, Oxenford CJ, Cognat S, Ismail H,* ***Frean J.***

Tropical Medicine and Infectious Disease
Impact Factor: Score unavailable

Background: In 2002, the World Health Organization (WHO) launched a regional microbiology external quality assessment (EQA) programme for national public health laboratories in the African region, initially targeting priority epidemic-prone bacterial diseases, and later including other common bacterial pathogens.

Objectives: The aim of this study was to analyse the efficacy of an EQA programme as a laboratory quality system evaluation tool.

Methods: We analysed the proficiency of laboratories' performance of bacterial identification and antimicrobial susceptibility testing (AST) for the period 2011-2016. The National Institute for Communicable Diseases of South Africa provided technical coordination following an agreement with WHO, and supplied EQA samples of selected bacterial organisms for microscopy (Gram stain), identification, and antimicrobial susceptibility testing (AST). National public health laboratories, as well as laboratories involved in the Invasive Bacterial Diseases Surveillance Network, were enrolled by the WHO Regional Office for Africa to participate in the EQA programme. We analysed participants' results of 41 surveys, which included the following organisms sent as challenges: *Streptococcus pneumonia, Haemophilus influenzae, Neisseria meningitidis, Salmonella* Typhi, *Salmonella* Enteritidis, *Shigella flexneri, Staphylococcus aureus, Streptococcus agalactiae, Streptococcus anginosus, Enterococcus faecium, Serratia marcescens, Acinetobacter baumannii, and Enterobacter cloacae.*

Results: Eighty-one laboratories from 45 countries participated. Overall, 76% of participants obtained acceptable scores for identification, but a substantial proportion of AST scores were not in the acceptable range. Of the 663 assessed AST responses, only 42% had acceptable scores.

Conclusion: In the African Region, implementation of diagnostic stewardship in clinical bacteriology is generally suboptimal. This report illustrates that AST is poorly done compared to microscopy and identification. It is critically important to make the case for implementation of quality assurance in AST, as it is the cornerstone of antimicrobial resistance surveillance reporting and implementation of the Global Antimicrobial Resistance Surveillance System.

Dr Bianca Da Costa Dias

Prof Caroline Tiemessen

The impact of bone marrow stromal antigen-2 (BST2) gene variants on HIV-1 control in black South African individuals

Da Costa Dias B, *Paximadis M, Martinson N, Chaisson RE, Ebrahim O,* ***Tiemessen CT.***

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Bone marrow stromal cell antigen 2 (BST2 or tetherin) is a host-encoded, interferon-inducible antiviral restriction factor which blocks the release of enveloped viruses. Few studies have assessed the role of BST2 polymorphisms on HIV-1 acquisition or disease progression in sub-Saharan Africa. This study investigated the frequency of four HIV-1-associated BST2 variants rs3217318, rs12609479, rs10415893 and rs113189798 in uninfected and HIV-1 infected black South Africans. Homozygosity for the rs12609479-A minor allele, previously associated with decreased HIV-1 acquisition risk, was underrepresented in HIV-1 uninfected black South Africans (2%) compared to reference African (9%) and in particular European populations (61%) (p =. 047 and p <. 0001, respectively). To determine if any of these gene variants influenced HIV-1 control in the absence of antiretroviral treatment (ART), we compared HIV-1 infected ART-naïve progressors [n = 72] and controllers [n = 71], the latter includes elite controllers [EC: n = 23; VL <50 RNA copies/ml]. Heterozygosity for the rs12609479 SNP (G/A) was enriched in progressors compared to ECs (47.2% vs 21.7%, OR = 3.50 [1.16–10.59], p =. 03), while rs113189798 heterozygosity (A/G) showed a strong trend of overrepresentation in ECs compared to progressors (47.8% vs 26.4%, OR = 0.39 [0.14–1.04], p =. 07). Heterozygosity for the promoter indel rs3217318 (i19/Δ19) was associated with a faster rate of CD4+ T-cell decline in progressors (p =. 0134). Carriage of the rs3217318 (i19/Δ19), rs12609479 (G/G), rs10415893(G/A) and rs113189798 (A/G) combined genotype, denoted as i19Δ19 GG GA AG, was associated with significantly higher CD4+ T-cell counts in progressors (p =. 03), a finding predominantly driven by the _GG_AG combination. Our data suggest that the possession of select BST2 genotype combinations may be implicated in HIV-1 disease progression and natural spontaneous control.

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