

Research Activities

The Alfred Infectious Diseases Unit (IDU) incorporates a large clinical service with active research programs in the fields of HIV, viral hepatitis, infections in the immunosuppressed (such as those with malignancy, in intensive care and post-splenectomy), influenza, drug resistant organisms, antibiotic use and infection prevention and hospital epidemiology.

HIV

Our research in HIV ranges from basic laboratory studies through to clinical research and public health. We have significantly expanded our basic and clinical research programs aimed at understanding where HIV 'hides' in patients on treatment and how HIV can be eliminated in these long-lived cells. This work has recently attracted the award of three NHMRC Project Grants and a fellowship from the American Foundation for AIDS Research (AmFAR) to Dr Suha Saleh and an investigator-initiated Merck sponsored clinical trial on the role of vorinostat in eliminating latent HIV infection (awarded to Dr Lewin, Dr Elliott and Dr Hoy). In recognition of some of this work, Professor Lewin gave the plenary lecture at the opening ceremony of the World AIDS Conference in Vienna in July 2010 on 'Strategies for HIV Cure'. This conference attracts over 25,000 delegates and 2,000 journalists and is the most widely covered health related conference globally.

We also investigate the genetic factors that play a role in recovery of the immune system following treatment of patients with HIV infection. PhD student Reena Rajasuriar has initiated two new international collaborations in Uganda (in collaboration with UCSF) and in Malaysia (in collaboration with the University of Malaya) to further understand a particular genetic mutation that controls cell division.

The Clinical Research Unit is actively involved in multiple international studies to evaluate new treatment strategies and antiretroviral agents. Dr Julian Elliott, head of the Clinical Research Unit, is currently establishing a Melbourne-wide prospective cohort of patients with HIV infection in collaboration with the Burnet Institute, the Victorian Infectious Diseases Reference Laboratory, several high case load GPs and other tertiary hospitals. We hope to better understand complications of anti-HIV treatment in this cohort. Dr Elliott, together with Professor Lewin, was also awarded an NHMRC Partnership Grant for \$1.5 million to perform a randomised clinical trial of a new model of care for patients with HIV infection. The Alfred hospital, Australasian Society for HIV Medicine (ASHM) and the National Association for People Living with HIV are all financial partners in the project providing an additional \$1.5 million over five years.

Our expertise in understanding the clinical impact and pathogenesis of HIV-related complications such as dementia, cardiovascular disease and bone disease was recognised with Dr Edwina Wright giving the plenary lecture at the 2010 national ASHM meeting and her receipt of an NHMRC Postdoctoral Clinical Training Fellowship. Kate Cherry was an invited speaker at the 3rd International Congress on Neuropathic Pain (Athens) and the 13th World Congress on Pain (Montreal) on the topic of 'HIV associated neuropathy'.

Professor Jennifer Hoy, Director of HIV Medicine, chaired the 'HAART at 15' symposium at the 18th Conference on Retroviruses and Opportunistic Infections. Edwina Wright and Jennifer Hoy are co-chairs of two substudies of the START Study, examining the effects of early versus deferred antiretroviral treatment on neurological disease and bone disease in patients with HIV infection. Professor Hoy and Kerrie Watson are members of the Steering Committee of the Australian HIV Observational Cohort study, which collects data from over 2,000 HIV patients and provides information on the trends of treatment, survival and disease progression.

Viral Hepatitis

Research in viral hepatitis combines basic laboratory and clinical work. We are determining how HIV and hepatitis B virus (HBV) may potentially interact in the same liver cell and how the immune system responds to HBV when a person also has HIV. Dr Megan Crane was awarded the highly competitive Mathilde Krim Biomedical Fellowship from AmFAR. We are continuing to collaborate on a multicentre international study investigating the natural history of HIV-HBV infection and have an active program to identify and characterise drug resistance to anti-HBV medication in Australia and Thailand under the supervision of Dr Jennifer Audsley.

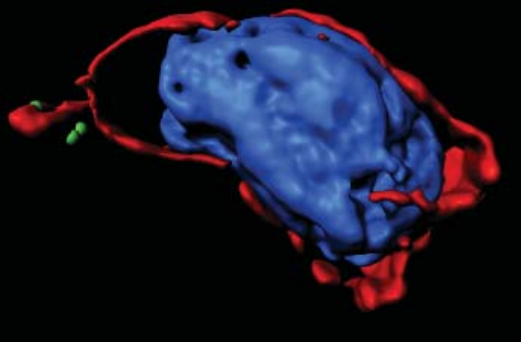
Fungal Infections

Fungal infections are a major cause of death in patients with leukaemia and after transplantation. We completed a randomised controlled trial examining the impact of new diagnostic tests for deep tissue infection with *Aspergillus* on the earlier diagnosis of infection and patient outcomes. We started a project measuring levels of azole antifungal agents in lung tissue of lung transplant recipients to determine activity specifically at the site where infection usually occurs.

The fungus *Cryptococcus* is rarely seen in Australia but is the second commonest cause of death in HIV-infected patients in Africa. Dr Christina Chang is undertaking her PhD under Professor Lewin, Dr Elliott and Professor Martyn French (Royal Perth Hospital). Christina is based at the King Edward Hospital, Durban, and has established one of the largest prospective cohorts of HIV-infected patients with cryptococcal meningitis who are initiating anti-HIV therapy. She was awarded a Pfizer Neurosciences Grant and a grant from ANZ Trustees (with Dr Orla Morrissey) to fully characterise the cryptococci isolated from these patients.

Dr Suha Saleh works in the HIV and Hepatitis Immunopathogenesis Laboratory.





3D fluorescent imaging of the HIV virus (green) entering a resting CD4+ T-cell showing the nucleus (blue) and cytoskeleton (red). Courtesy of Candida da Fonseca Pereira, postdoctoral researcher.

General Infectious Diseases

Dr Anton Peleg was recruited to The Alfred as part of a joint appointment between the Departments of Medicine and Microbiology, Monash University, following a very successful postdoctoral fellowship at Harvard Medical School. As a result, several new research programs have been initiated in general infectious diseases.

Influenza

The Alfred, in conjunction with Australian National University, has led a national hospital-based surveillance system to provide real-time reporting of influenza hospitalisations, clinical data on influenza and pneumonia, and estimates of influenza vaccine effectiveness. Associate Professor Allen Cheng was a chief investigator on a study to monitor for serious complications of influenza vaccination.

Drug Resistant Organisms

PhD student Ching Jou Lim initiated studies to look at rates of bacterial resistance and antibiotic use in long-term care facilities and in patients presenting from the community to The Alfred Emergency Department. Such studies will assist in characterising reservoirs of antibiotic resistance and help guide initial antibiotic prescribing. Dr Peleg has also initiated studies to assess the long-term trends in antibiotic resistance in high-risk units at the Alfred, including the Burns, Respiratory and Haematology Units. Dr Peleg was invited to give a keynote address at the International Acinetobacter Meeting in Rome and a plenary lecture at the International Conference on Antimicrobial Agents and Chemotherapy in Boston. He was also chosen for the Monash Research Accelerator Program.

Dr Cheng led the development of national treatment guidelines for *Clostridium difficile* infection and designed a national period prevalence survey for this infection with colleagues at the University of Western Australia and the University of Queensland. A case control study was performed to examine risk factors for colonisation with vancomycin resistant enterococci, and the use of antiseptic washcloths to prevent transmission with this organism was evaluated.

Improving Antibiotic Use

Guidance, an electronic decision support system to improve antibiotic usage within the hospital, was rolled out over 2010 with considerable input from IDU staff. Multiple research projects related to appropriate use and appropriate dosing of antibiotics in collaboration with the Pharmacy Department are under way. Dr Cheng was an organiser of the Antibiotic Resistance Summit held in Sydney in February 2011 and performs studies on the toxicity of aminoglycoside antibiotics and the pharmacokinetics of vancomycin.

Spleen Registry

The Spleen Registry was involved in a number of studies to define risk in certain patient groups who have had their spleen removed. We have developed and evaluated a new test to measure the immune system after the spleen is removed. We are also evaluating optimal vaccine use in these patients as part of an NHMRC-funded study.

With Dr Mark Polizzotto in the Haematology Unit, we measured the added risk of splenectomy on infection risk in the HIV population. We measured changes in IgM memory B cells in patients with asplenia and in those patients with medical conditions that may result in asplenia.

Major Findings

- Fully characterised a novel *in vitro* model of latent HIV infection which is now being used to screen compounds that may reverse or eliminate latency
- Showed that dendritic cells assist HIV in establishing latent infection
- Showed that genetic markers that predict immune recovery following anti-HIV treatment are significantly different in Caucasians and Africans
- Showed that in HIV-HBV co-infection, there are high levels of gut-derived bacteria in the general circulation and this may contribute to worse liver disease in these patients
- In collaboration with the INSIGHT Network, we showed that the only adverse effect of continuous antiretroviral therapy in HIV infection is greater loss of bone compared to those treated to keep their immune function above the level at which opportunistic infections and malignancies occur
- Showed that interruption of antiretroviral therapy causes changes in lipids and lipoprotein subclasses associated with cardiovascular disease
- Characterised the risk factors for candidaemia-related mortality in cancer patients
- Characterised the current cost of a deep tissue fungal infection in Australia using novel economic modelling

Research Achievements

Researchers in IDU were awarded various NHMRC grants: six Project Grants, a Partnership Grant, two Early Career (Postdoctoral) Fellowships and a Career Development Fellowship. Other major grants included an AmFAR Mathilde Krim Postdoctoral Fellowship (Crane/Lewin), AmFAR Postdoctoral Fellowship (Saleh/Lewin) and a National Institutes of Health RO1 grant (Hoy) on the effect of untreated HIV versus early antiretroviral therapy on bone mineral density.

Awards

- Fiona Wightman (PhD student with Professor Sharon Lewin) received a Young Investigators Award to attend the Conference of Retroviruses and Opportunistic Infections (CROI) in San Francisco
- Dr Michelle Anada Rajah (PhD student with Associate Professor Monica Slavin) received an antifungal award from the Australasian Society for Infectious Diseases (ASID)
- Dr Anton Peleg received the Frank Fenner Award for Excellence in Infectious Diseases from ASID
- Associate Professor Margaret Hellard received the Fenner Award from the Burnet Institute
- Dr Edwina Wright received the Victorian AIDS Council/ Gay Mens' Health Clinic Research Excellence Award

Current Projects

A complete list of current projects is available from <http://www.alfredresearch.org/research/researchrep10.htm>

Postgraduate Students

13 PhD Students
1 Masters Student

Publications

59 Journal Articles
3 Books
28 Book Chapters

AMREP Research Report 2010

Infectious Diseases – Current Projects

Basic HIV Research

- The role of naïve T-cells in HIV viral persistence (Lewin)
- The role of chemokines in establishing latent infection in resting T-cells (Lewin, Cameron)
- Interactions between dendritic cells and T-cells to establish latent infection (Lewin, Cameron)
- Role of histone deacetylase inhibitors in the elimination of HIV from the latent reservoir (Lewin)
- Identification of the cellular defect that leads to long term hepatitis B virus (HBV) infection and how this is altered in the setting of HIV–HBV co-infection (Lewin)
- Relationship between genetic polymorphisms and immune restoration in individuals receiving HAART (Lewin, Cameron)
- Development of a rapid high throughput test to assess HIV co-receptor usage and fitness (Lewin)
- Lineage and functional relationship of dendritic cells and monocytes (Cameron)
- The effect of anti-HIV drugs on telomere length (Lewin)

HIV–Hepatitis B Co-infection

- The interaction of HIV and HBV in the cells of the liver, specifically the hepatocyte (Lewin)
- The natural history of HIV and HBV infection and the role of HBV drug resistance in liver disease progression (Lewin)
- Identification and characterisation of HBV mutations that lead to resistance to tenofovir in Australia and Thailand (Sasadeusz)
- The change in the immune system in HIV–HBV co-infected patients who develop hepatitis after starting HIV and HBV treatment (Lewin)
- A surveillance program for the detection of HBV resistance to tenofovir in HIV–HBV co-infected patients (Lewin, Sasadeusz, Audsley)
- A study of non-invasive evaluation of liver fibrosis in HIV–HBV co-infection using the Fibroscan (Lewin, Sasadeusz, Audsley, Iser)

Hepatitis B Virus Research

- Define the relationship between HLA type and HBV evolution (Lewin)
- Effects of pregnancy on the natural history of HBV infection (Sasadeusz, Giles)

NeuroAIDS Research

- SMART neurological substudy (Wright)
- The Australian National NeuroAIDS Brain and Tissue Bank Project (Wright, Wesselingh)
- Genetic risk factors for antiretroviral toxic neuropathy (Cherry)
- Establishing the use and interpretation of an LM-PCR-based phenotypic assay for antiretroviral toxicity (Cherry)
- Depression, neuropsychiatry and HIV (Mijch)

HIV Clinical Research

- Exercise and HIV (Fillipas, Cherry)
- Studies investigating the effectiveness of flupirtine (a novel analgesic) for treating pain from HIV-neuropathy that is not adequately controlled by opioids (Cherry)
- The prevalence of metabolic syndrome, lipodystrophy and cardiovascular risk in an ambulant aging male HIV-infected cohort (Woolley, Hoy)
- Vitamin D supplementation in HIV infection (Woolley, Hoy)
- The immunopathogenesis of antiretroviral associated Grave's disease in HIV infection (Majumdar, Hoy)
- A cross-sectional study of the relationship between carotid artery atherosclerosis and immune cell function (Crowe, Jawarowski)

- The relationship between HIV infection and hepatitis B infection in a Melbourne HIV cohort, and an evaluation of current hepatitis B prevention practices (Giles, Hoy)
- To evaluate the role of lipid profiling for prediction of coronary heart disease in the HIV positive population (Hoy, Meikle)
- Correlation of ankle brachial index (ABI) to Framingham risk score in HIV infected versus non-HIV infected patients (Hoy, Hewagama)
- Framingham risk and cardiovascular disease (Hoy, Crowe, Madigan)
- STEAL bone mineral density and bone turnover markers substudy (Hoy)
- SMART bone mineral density substudy (Hoy)
- Switch from tenofovir to raltegravir for low bone mineral density (Hoy)
- Audit of adherence to Australian HIV treatment guidelines (Hoy)
- START bone mineral density substudy (Hoy)
- HIV seroconversion in NPEP users: a data linkage study (Pierce)
- A cross-sectional study of the relationship between carotid artery atherosclerosis and immune cell function (Crowe, Jawarowski)
- Source tracing in the setting of HIV NPEP (Pierce, Armishaw)
- Switch from tenofovir to raltegravir for low bone mineral density (Hoy)
- SECOND-LINE: a randomised open-label study comparing the safety and efficacy of ritonavir boosted lopinavir and 2-3 N(t)RTI backbone versus ritonavir boosted lopinavir and raltegravir in participants virologically failing first-line NNRTI/2N(t)RTI therapy (Elliott, Hoy)
- CORAL: randomised double-blind placebo controlled study to measure the effect of antiretroviral therapy (ART) intensification with raltegravir and/or hyper-immune bovine colostrum on CD4+ T cell count in ART treated, HIV infected individuals with suboptimal CD4+ T cell responses despite prolonged virologic suppression (Lewin, Hoy, Elliott)
- START: Strategic Timing of AntiRetroviral Treatment (Hoy, Wright)
- DAD: the Australian HIV observational database and data on adverse events of anti-HIV drugs (Hoy)
- PHAEDRA: a prospective cohort study of individuals recently infected with HIV, to determine immunological, virological and therapeutic factors related to disease progression (Hoy)
- Impact of HIV infection and treatment with highly active antiretroviral therapy on reverse cholesterol transport (Hoy)
- Framingham – ankle brachial index (ABI) and pulse wave velocity (PWV) study (Hagawama, Hoy)
- Concept mapping contemporary issues facing people living with HIV (Elliott, Roney)

Influenza

- The FluCAN surveillance system: establishing a rapid alert system for severe respiratory illness in adults (Cheng)
- Antibody seroconversion in patients with PCR proven 2009 H1N1 influenza (Cheng)
- Targeted active surveillance for Guillain-Barré Syndrome following the introduction of H1N1 vaccine (Cheng)
- FLU003: an international observational study to characterize adults who are hospitalized with complications of influenza A pandemic H1N1 (Elliott, Cheng, Hoy)

Infections in the Immunosuppressed

- Strategies to improve adherence to current best practice guidelines for the prevention of overwhelming post splenectomy sepsis (OPSI) (Spelman)
- Quantification of the risk of OPSI by using outcome data in specific patient sub-groups (patients who have undergone removal of their spleen or have damaged their spleen following trauma) (Spelman)
- The role of quantification of IgM specific immune memory B-cells as a marker of immune function in patients post-splenectomy (Cameron)
- The ASPID Study: a multicentre randomised controlled trial comparing two strategies for the diagnosis of invasive aspergillosis in high-risk haematology patients (Slavin, Morrissey)

- A randomised, stratified, open label, Phase 2 pilot study on the safety of a daily, intermittent, or weekly administration of 1, 3 or 10mg/kg of AmBisome® in antifungal primary prophylaxis of high-risk patients with acute myeloid leukaemia (Morrissey)
- An economic evaluation of invasive fungal infections among patients undergoing stem cell transplantation or chemotherapy for acute leukaemia (Morrissey, Ananda-Rajah, Slavin, Cheng)
- Prospective use of genes containing coding tandem repeats as markers for genotyping *Aspergillus fumigatus* clinical isolates and investigation of the relationship of genotype with the spectrum of clinical infection (Morrissey, Kidd)
- SCARE: global surveillance of emerging antifungal resistant *Aspergillus* (Morrissey, Kidd)
- Prospective cohort study examining use of therapeutic drug monitoring in patients on voriconazole prophylaxis for the prevention of invasive fungal infections (Morrissey, Cheng)
- Microbiological trends and outcomes in lung transplant recipients; an 8-year perspective (Peleg, Cheng)
- Microbiological trends in stem cell transplant recipients (Peleg, Morrissey, Cheng)
- Microbiological trends in patients with burns: a 10-year perspective (Peleg, Padiglione, Cheng)

Antibiotic and Antibiotic Resistance Studies

- Development of *in vitro* and *in vivo* pharmacodynamic models to better understand dosing and toxicity of a new antibiotic linezolid (Spelman)
- Study of the usefulness of antimicrobial susceptibility testing in patients with cystic fibrosis (Spelman)
- Case control study to identify risk factors for vancomycin resistant enterococci (VRE) bacteremia (Spelman)
- Case case control study to identify risk factors for the development of metallo-beta-lactamases (Spelman)
- Investigation into optimal methods of typing VRE (Spelman)
- Multi-national study of acinetobacter bloodstream infection: clinical outcomes and global epidemiology (Spelman)
- Participation in national reporting of antimicrobial usage patterns (National Antimicrobial Utilisation Surveillance Program) and ongoing audits of antimicrobial use (Cheng, Morrissey)
- Development of pharmacokinetic models for antibiotics, including cefepime (Padiglione)
- A multicenter, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of aerosolized ALN-RSV01 plus standard of care in lung transplant patients infected with respiratory syncytial virus (Peleg)

General Infectious Diseases

- International Collaboration on Endocarditis (ICE) (Spelman)
- The Australian Group for Antimicrobial Resistance (AGAR) annual and bi-annual studies on resistance patterns for *Staphylococcus aureus*, both community and hospital acquired, gram negative bacilli, and streptococcus pneumoniae. (Spelman)
- Australia New Zealand Cooperative on Outcomes in Staphylococcal Sepsis (Spelman)
- Study of infections in ventricular assist devices (Spelman)
- Study of the changing clinical patterns and microbiology of necrotising fasciitis and myonecrosis (Spelman)
- Usefulness of antimicrobial susceptibility testing of *Pseudomonas aeruginosa* in cystic fibrosis (Spelman)
- Effective response to H1N1/09 pandemic influenza, including NHMRC-funded studies of influenza in health care workers, hospital-based surveillance, community transmission and immunology (Cheng)
- Victorian Nosocomial Infection Surveillance System: participation in statewide programs for hospital-acquired infections and hand hygiene (Spelman, Cheng)
- Collaborative work in viral infection, bacterial carriage and otitis media in Indigenous children (Cheng)