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BRISBANE, QLD
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the art of ART

2019 CONFERENCE KEY FINDINGS REPORT

The Art of ART 2019, held in Brisbane, Australia, was a series of plenary sessions and interactive workshops for S100 prescribers, nurses and pharmacists with a focus on the nuances of ART prescribing and contemporary HIV management in Australasia. This report provides a summary of key learnings. The meeting is a complimentary event organised by ASHM through an unconditional educational grant from ViiV Healthcare.

Videos and slides of the presentations and workshops are available on the Art of ART 2019 program page.

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About ASHM Conference and Events

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The Future of HIV Treatment - New Drugs and New Strategies

Dr Janine Trevillyan

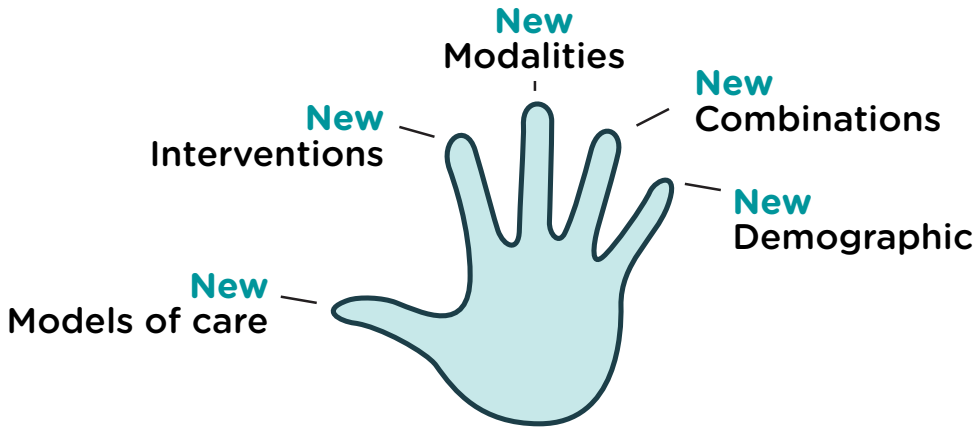
Infectious Diseases Physician and Senior Research Fellow

Read the speaker slides | Watch the video presentation

Take Home Messages

1. New agents are promising, particularly for heavily treatment experienced individuals.
2. Dual therapy regimens are an option but suitable patients need to be carefully selected.
3. Injectable regimens seem efficacious but the question of who should use them remains to be answered.
4. The demographic is changing and so how we provide care needs to as well.

In 2019, HIV treatment is highly effective, has modest side effects and viral suppression is achievable in most PLHIV. Peering into the future for those living with well controlled HIV, the following are factors to consider:



New Interventions

Doravirine (DOR)	A novel next generation NNRTI with in vitro activity against most prevalent NNRTI resistance mutations. Dosed once daily without food restrictions, it is being developed as a single entity (Pifeltro) and as a fixed dose combination with Emtricitabine (3TC) and Tenofovir Disoproxil Fumarate (TDF) (Delstrigo). DRIVE-Ahead and DRIVE-Forward shows non-inferiority when compared to Efavirenz (EFV) or boosted Darunavir(DRV/r).
Fostemsavir	A gp20 attachment inhibitor and pro-drug for the active metabolite, Temsavir. By binding to the viral envelope glycoprotein (gp20), the virus is prevented from attaching to CD4+ cells. This is the first drug in a new class with no in vitro cross resistance with any other antiretroviral drug, hence anticipated use in those with drug resistance. BRIGHTE showed HIV suppression in a significant proportion of participants and modest but significant rises in CD4 cell count.
Ibalizumab	A monoclonal antibody, this drug is a gp20 attachment inhibitor. For parenteral use, it requires a loading dose followed by fortnightly IV infusions and must be used in combination with other ART. It is very expensive (USD$118,000/annum) and currently FDA approved for PLHIV with triple class resistance. Diarrhoea was the most commonly reported adverse event (AE) however most serious AEs were secondary to underlying advanced HIV.

New Combinations

Note: ARV monotherapy is NOT the answer.

2DRs aim to minimise toxicities, reduce pill burden (size) and reduce cost to governments. Ultimately, the selection of a regimen should be individualised and guided by:

- Virologic efficacy
- Toxicity
- Pill burden
- Dosing frequency
- Drug-drug interaction potential
- Resistance testing results
- Comorbid conditions
- Cost

SWORD I & II (Dolutegravir/Rilpivirine) and GEMINI I & II (DTG/3TC vs DTG/TDF/3TC) have shown non-inferiority in those 2DR combinations with specific caveats:

- SWORD - Rilpivirine needs to be taken with food;
- ACTG5353/Gemini – Viral Load < 500,000, only mild hepatic impairment, no Hepatitis B infection, no known resistance mutations.

There are some as yet unanswered questions regarding 2DR:

- Are they enough to control viral reservoir?
- Is there going to be a side effect benefit when compared with 3-drug TAF regimens?
- Is there an association with higher levels of immune activation?
- Is it applicable in special populations?
  - African and Asian settings?
  - Breast feeding women?
- How effective is it when there is prior resistance or high viral loads?
- What about its use in advanced HIV at presentation?

New Modalities

ATLAS and FLAIR (**Cabotegravir** and **Rilpivirine**: 2DR monthly injections) were similar trials that were reported at CROI 2019 with similar outcomes.

FLAIR showed similar efficacy and non-inferiority when compared to standard of care.

Reported AEs were minor with headache being most common, however this didn't lead to discontinuation of therapy. Injection site reactions were mild (99%) and resolved within 7 days (88%), most frequently reported at initiation.

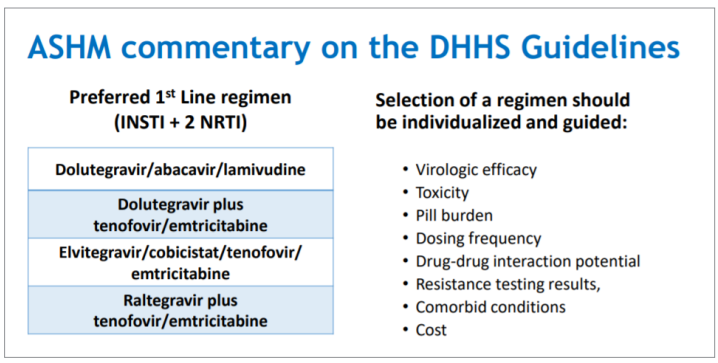
Participant satisfaction was high with injectables despite adverse events.

New Demographics

- PLHIV are aging with multimorbidity increasingly common. The burden of medical co-morbidities is much higher in PLHIV than the general population.
- Serious non-AIDS diseases are now the leading cause of death with cardiovascular disease leading the charge.
- Weight gain is an emerging issue with the use of integrase inhibitors; the effect seems to be most pronounced with Dolutegravir but also seen with Elvitegravir and Raltegravir. There may also be a signal with Tenofovir Alafenimide.

New Models of Care

- Current models of care may be outdated. We need to look at individualised patient focused models of care that are appropriate for the individual. Peer mentoring is one such model of care.
- The use of technology to link individuals to networks or as reminders for appointments or taking medication is another model.
- Going into the future, a multidisciplinary approach is increasingly needed.



Read the Australian commentary on the DHHS Guidelines, administered by ASHM.

Drug-Drug Interactions (DDIs): New ART and New Co-medications

Professor Saye Khoo

University of Liverpool, UK

Read the speaker slides | Watch the video presentation

Take Home Messages

1. DDIs are inevitable, unavoidable, and (usually) manageable.
2. Polypharmacy and comorbidities increase the complexity and risk of clinically important DDIs.
3. We need to treat comorbidities.
4. There is increased polypharmacy in PLHIV across all age groups.

Key to successful DDI management is:

5. Understanding pharmacokinetic (PK) and pharmacodynamic (PD) effects;
6. Targeted interventions and guidelines for PLHIV with multiple comorbidities;
7. Avoiding fragmented care;
8. Full reconciliation of medicines.

In 2019, particular DDIs between ART and medications to be aware of include:

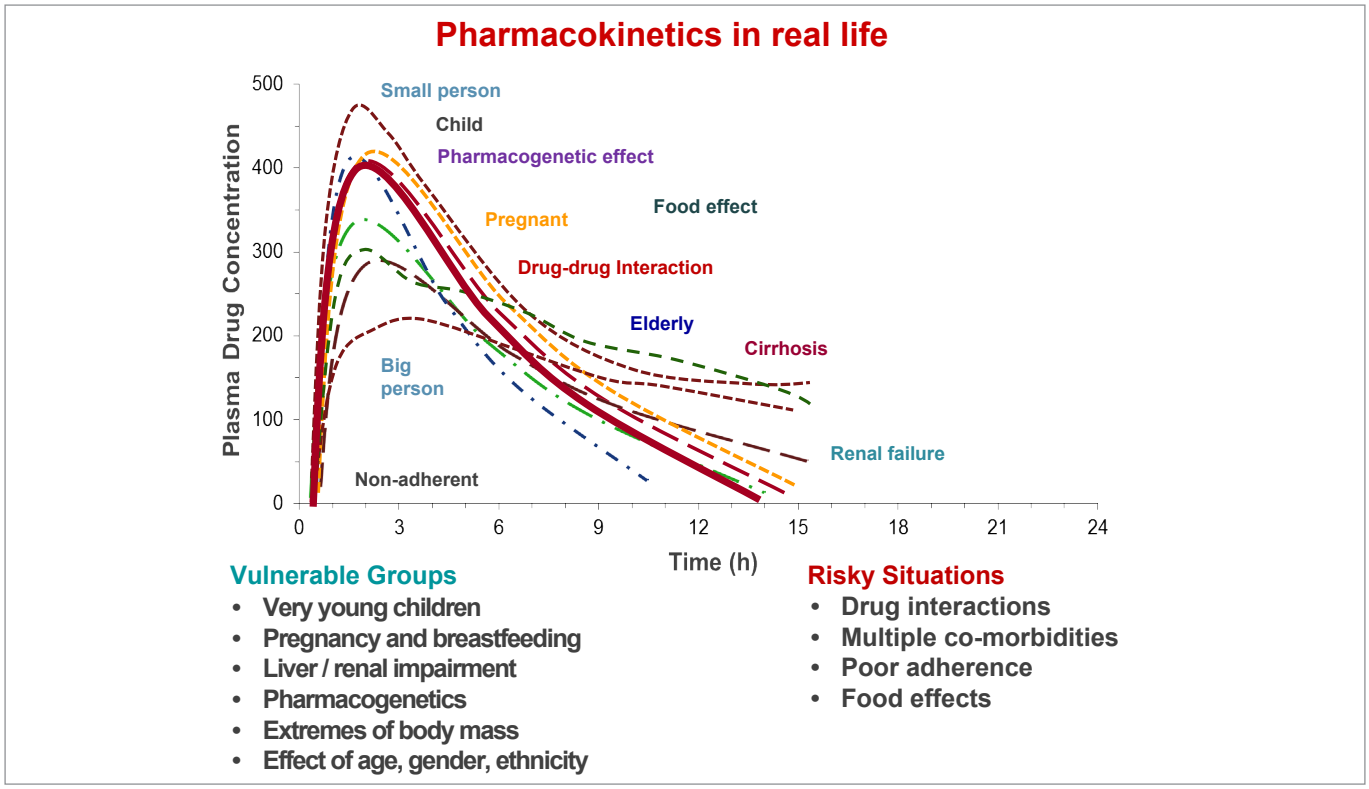
9. TB medications;
10. Antiplatelet agents and novel oral anticoagulants (NOACS);
11. Lipid lowering medications (statins) and
12. Antacids and proton inhibitors (PPIs).

What can you do?

13. Screen for and manage DDIs;
14. Assess burden of therapy;
15. Adopt a tailored approach to prescribing.

Overview

- The association of polypharmacy with increased risk of DDIs, hospitalisations and mortality is well documented.
- We need to treat all comorbidities, taking into consideration individual benefits vs aggregated risk and burden of co-morbidities.
- When prescribing, it is important to consider and calculate risks using data bases such as QRISK3, FRAX score, DDI tools (such as Liverpool HIV iChart), Charlson Comorbidity Index, etc. to avoid further burden to patients' health outcomes.
- Guidelines and DDIs databases do not cater for the complexity of multiple medications on each organ. However, knowledge of physiological factors e.g. organ dysfunctions, comorbidities clusters and pharmacogenetics profile may help predict the direction and magnitude of DDIs.



PK & PD and Ageing

- In general, common culprits causing adverse effects and DDIs in the elderly involve anticholinergic and antipsychotic medications which are associated with increased risk of confusion and falls.
- Adverse effects of SSRIs in people over 50 years of age may be associated with SIADH (Syndrome of Inappropriate Antidiuretic Hormone Secretion), hyponatremia, loss of bone density, double risk of falls and fractures.
- De-prescribing of antacids and proton pump inhibitors (PPIs) and benzodiazepines may reduce adverse effects and potential DDIs.

Rifampicin and TAF

PK studies indicated that there is no interaction between Rifampicin and TDF (Tenofovir Disoproxil Fumarate). Tenofovir Alafenamide (TAF) is a substrate of a number of transporters; P-gp and BCRP in GIT and its hepatic uptake is facilitated by organic anion- transporting polypeptide 1B1 & 1B3 (OATP1B1 & OATP1B3).

However, TAF is a prodrug of tenofovir and TAF is hydrolysed to a pharmacologically active form, TVF-DP.

Co-administration of TAF with P-gp/BCRP inhibitors such as cobistat, or ART protease inhibitors (PIs) has resulted in increased TAF exposure.

Co-administration of TAF with Rifampicin results in decreased absorption of TAF from GI tract.

To ensure efficacy in treatment of TB twice daily dose of TAF may be considered with Rifampicin, but not with TDF.

	TAF Once /day	TAF Twice /day
	AUC	AUC
Plasma Conc. TAF	▼ 55%	▼ 20%
Plasma Conc. TFV-DP	▼ 36%	▼ 24%

Rifampicin and Bictegravir (BIC)

BIC is a potent integrase strand transfer inhibitor (INSTIs) with a high barrier to resistance. In Australia, BIC is co-formulated with NRTI backbone of emtricitabine/tenofovir alafenamide (FTC/TAF). BIC is metabolised by CYP3A4 and UGT1A1 in the liver.

Co-administration of a once daily dose of BIC with Rifampicin (a potent inducer of CYP3A4 and UGT1A1) has showed a marked reduction in plasma concentration of BIC for twice daily dose with FTC/TAF combination. As a result, co-administration of Rifampicin with BIC/TAF results in decreased concentrations of both BIC and TAF and is therefore not recommended.

	Once /day	Twice /day
	AUC	AUC
Plasma Conc. BIC (75mg)	▼ 75%	▼ -
Plasma Conc. BIC/FTC/TAF	▼▼ -	▼ 61%

Rifampicin co-administration with Raltegravir (RAL) or Dolutegravir (DTG)

RAL is metabolised by UGT1A1 and DTG is metabolised primarily by UGT1A1 and to a lesser extent by CYP3A4.

Co-administration of Rifampicin with RAL with either 400mg twice/day or 800mg twice/day is recommended however, 1200mg RAL once/day with Rifampicin is not recommended.

Similarly, twice/day dose of DTG is recommended with Rifampicin.

Effects of Boosting: Cobicistat (COBI) vs Ritonavir (RTV): PK vs PD effects

Ritonavir (RTV) is an inhibitor of CYP3A and CYP2D6 and inducer of CYP3A, CYP1A2, CYP2B6, CYP2C9, and CYP2C19 and UGT enzymes. It also exhibits a biphasic, time-dependent effect on P-glycoprotein of inhibition followed by induction. Cobicistat is only an inhibitor of CYP3A4, CYP2D6 (week) enzymes, P-gp and BCRP transporters.

Darunavir/Ritonavir (DRVr) or Darunavir/ Cobicistat (DRVc)	Pharmacokinetics studies indicated that DRVr or DRVc had no clinically significant effect on the PK of DTG or vice versa and no dose adjustment is recommended.
Clopidogrel vs Prasugrel	Clopidogrel is a prodrug and metabolised by CYP3A4, CYP2B6, CYP2C19 and CYP1A2 to active metabolites. Prasugrel is also a prodrug and metabolised by CYP3A4 and CYP2B6 to its active metabolite. Although PK levels of both clopidogrel and prasugrel were reduced by RTV or COBI, this decrease did not impair the antiplatelet effect of prasugrel. Prasugrel recommended to be used with ARV boosted COBI or RTV but not clopidogrel.
NOACs & COBI vs RTA	Rivaroxaban is transported by P-gp and BCRP and metabolised by CYP3A4, CYP3A5 and CYP2J2. Similarly, apixaban is transported by P-gp and metabolised by CYP3A4. Inhibition of the enzymes and transporters by RTV or COBI result in increased risk of bleeding and is therefore not recommended. There is a PK interaction between COBI and dabigatran due to P-gp inhibition. Caution is recommended with RTV in renal impairment when doing once/day (no data available in twice /day dosing of RTV).
Magnitude of DDIs with Statins: Atorvastatin vs Rosuvastatin	The differences in magnitude of DDIs with statins is explained by different metabolic pathways and an affinity for binding to transporter. Rosuvastatin is transported by OATP1B1 and BCRP whereas atorvastatin is transported by OATP (1B1, 1B3 and 2B1) and metabolised by CYP3A4. There is differential inhibition by COBI or RTV influencing DDI. Careful monitoring is therefore recommended.

You can check further drug interactions on the HIV Drug Interactions website. The site also provides prescribing resources, latest news and videos.

Read about drug-drug interactions on the Antiretroviral Guidelines website managed by ASHM.

HIV Cure 101: Progress and Challenges

Dr James McMahon

ID Physician, Infectious Disease Unit, Alfred Hospital, Australia

Read the speaker slides

Watch the video presentation

Read 'Barriers and strategies to achieve a cure for HIV'

Take Home Messages

1. Numerous challenges need to be overcome in order to achieve HIV cure.
2. It is likely that a combination strategy will provide the greatest chance of success to achieve this goal.

In 2019, HIV treatment is highly effective, has modest side effects and viral suppression is achievable in most PLHIV. Peering into the future for those living with well controlled HIV, the following are factors to consider:

Barriers to HIV Cure

- **Latent HIV infection:** This refers to integration of HIV DNA into CD4 T cells that are not actively producing HIV. Antiretroviral therapy does not impact this latent reservoir. Tissue reservoirs such as lymph nodes, gut associated lymphoid tissue and the central nervous system are the main sites of latent infection. These sites are relative sanctuaries from the immune system and ART.
- **Intact versus defective virus:** The majority (estimated > 80%) of HIV is defective/replication incompetent, so the challenge is finding and targeting virus capable of replication that would lead to viral rebound if ART was ceased.
- **Clonal expansion versus residual replication:** It's now thought that the latently infected cell population is maintained by the proliferation of latently infected cells rather than residual viral replication with infection of new CD4 cells. Proliferation of infected cells will not be affected by ART.

Framework for HIV Cure/Remission Strategies

- Key interventions currently being studied in this area include:
- Increasing the host immune response towards HIV:
  - Therapeutic vaccines
  - Antibodies that can identify HIV and HIV infected cells
  - Immune checkpoint inhibitors
- Methods to tackle the virus directly:
  - Latency reversal to enhance the production of HIV from infected cells
  - Block and lock to push HIV infected cells into a prolonged deep latency
- Making cells resistant to HIV infection:
  - In cases of long term remission and HIV cure after stem cell transplants for lymphoma or leukemia in people with HIV, the donor CD4 cells did not express CCR5 receptors and therefore couldn't be infected by any residual HIV that can only infect T-cells that express CCR5.

Table: Comparison of 3 cases of HIV Remission

Compare the 3 cases

	London patient	Dusseldorf patient	Berlin patient
Underlying condition	Hodgkin's Lymphoma	AML	AML
HSCT, donor CCR5 Δ32/Δ32	Once	Once	Twice
Conditioning	reduced intensity: anti–CD52 (alemtuzumab)	reduced intensity: fludarabine/ treosulfan	Total body irradiation (twice)
GvH disease	Grade 1	Grade 1	Grade 1
Chimerism post HSCT	100%	100%	100%
ART post-transplant	16 months	66 months	None
Time with HIV remission	18 months	3 months	12 years

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Broadly Neutralising antibodies (bNAbs)

- These are being studied in prevention, treatment and cure.
- People living with HIV generate antibodies to HIV but this is usually an ineffective immune response. A small number of individuals have generated antibodies which can bind to HIV and prevent HIV viruses from infecting new cells. These specific antibodies have been identified and subsequently cloned as a potential HIV treatment.
- Numerous bNAbs have been isolated and have progressed to clinical trials using both single and combination bNAb approaches.
- Studies where these bNAbs have been given and ART ceased have shown delays in viral rebound off ART with small numbers of people having ongoing control of viral replication even when the bNAbs have been eliminated from their system.
- It is possible that these bNAbs are increasing immune responses to HIV separate to their ability to bind the virus. Whether these bNAbs can increase these immune responses against HIV is an active area of research.

Combination interventions

- TLR7 (Toll-like receptor 7) agonists stimulate an innate immune system response and have the potential to promote CD8 T-cells (also called cytotoxic T-cells) to target HIV infected cells.
- Interventions using both TLR7 agonists and bNAbs are being combined in clinical trials.
- Non-human primate studies presented at CROI 2019 have proved promising in achieving sustained virological suppression after these interventions are given and then ART is ceased.
- Importantly, the monkeys that were 'cured' in this study, had very low pre-ART viral loads (treated shortly after they were infected) and had small viral reservoirs, so it is difficult to establish what impact these interventions may have in the real world setting.
- "Kick and kill" involves switching on latently infected cells which can then be killed by a second agent. Although the agents studied were well tolerated, they have not lead to a reduction in the HIV reservoir.

Post Treatment Control

- Some individuals treated with ART will not have virological rebound if ART is ceased. This was first observed in the French Visconti cohort, and later in the CHAMP study of individuals who started ART soon after HIV infection.
- Approximately 15% of individuals who commence ART early after HIV acquisition (within 6 months) will continue to maintain virological suppression if they subsequently interrupt ART.

HIV Cure Trials: The Community Perspective

Mr Cipriano Martinez

President, National Association of People Living with HIV Australia

Read the speaker slides	Watch the video presentation

Take Home Messages

1. With around 10 million people globally still not receiving treatment, a cure for HIV remains critical.
2. To find a cure we need altruistic PLHA willing to participate in trials and suspend ART.
3. There is a disconnect between researchers understanding of personal benefit of trials and the participants hope and desire for a cure. Sometimes people's desire for a cure may mean they are not approaching a trial in a rational way.
4. Cure trials can result in other breakthroughs, even if they don't succeed in finding a cure.
5. PLHIV need clinicians to offer balanced hope: a belief that real and ongoing efforts and advances, even if only small and incremental, will eventually lead to worthwhile progress.

A study of community and provider attitudes towards ATI found:

- PLHIV preferred monthly monitoring - see Jillian Lau study.
- PLHIV are less accepting of sustained viremia during ATI, but around 20% would accept it for a period of time.
- U=U is incredibly important for many people with HIV. Cure interventions must not jeopardise a return to UVL.

Visit www.HIVcure.com.au

Peer Navigators: Learnings from Queensland Positive People

Satrio Nindyo Isitko

Peer Navigation Team Leader, Queensland Positive People

Read the speaker slides	Watch the video presentation

Take Home Messages

1. Peer navigation gets better health outcomes through improved local responses, tailored programs and increased self-determination and self-development.
2. Specifically, it helps PLHIV with practical support: HIV health education, navigation of the health system, connection to services, support to overcome stigma and discrimination and peer connectedness.
3. The practice is evolving. What began many years ago as informal conversations has become a quality, structured service with reporting, evaluation, training and guidelines.
4. The increased focus on structure and professionalism needs to continue. A move from of casual employment to full time and part time employment models along with appropriate renumeration should be considered.
5. There is work to be done to improve the relationship between peer navigators and clinicians.
6. The ultimate vision is to have peer navigation fully integrated into the health system, not just in HIV but other sectors as well.

Watch the Peer Navigation Animation Video released by ASHM

ADDRESSING INTERNALISED STIGMA

Nathan Butler

Peer Project Officer, Queensland Positive People

Read the speaker slides | Watch the video presentation

Take Home Messages/Key Learnings from the Workshop and Module

1. Internalised stigma can be a challenging subject for participants to identify and wish to challenge.
2. Quantitative data was less than optimal and some of these challenges around data collection were identified. However the qualitative data collected demonstrated the positive impacts of the intervention.
3. The uptake and engagement with the PN module has been high and well received by clients.

Stigma impacts people in different ways, all of which lead to poorer health outcomes. Common experiences include:

- Fear of being tested for HIV;
- Disengagement from health care;
- Hiding status from friends and family;
- Poorer mental health;
- Isolation;
- Feelings of helplessness.

To address this QPP developed a workshop and a peer navigation module to build resilience and reduce the impact of stigma.

About ASHM

ashm

ASHM is a peak organisation of health professionals in Australasia and New Zealand who work in HIV, viral hepatitis, other BBVs and sexually transmissible infections. ASHM draws on its experience and expertise to support the health workforce and to contribute to the sector, domestically and internationally.

ASHM provides clinical guidance on the management of HIV including texts, guidelines, training, accreditation and continuing professional development activities to ensure that people treating HIV have access to contemporary evidence-based research and best practice. For more information visit the ASHM website.