HIV/Sexual Health Clinical Education Session

http://courses.ashm.org.au/HIV/hiv-sexual-health-clinical-education-session/

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Journal Club - SSHC-ASHM

Dr Rick Varma
Sexual Health Physician
Staff Specialist
Clinical Services Manager Sydney Sexual Health Centre

Current Opinion HIV and AIDS

- X 6 issues / year
- 41/ 150 immunology
- 18/84 infectious diseases
- IF 4.05

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Current Opinion HIV and AIDS

- Review articles
- launched in 2006. series of review journals designed to provide a systematic and critical assessment of the literature as presented in the many primary journals.
- HIV and AIDS are divided into nine sections that are reviewed once a year. Each section is assigned a Section Editor, a leading authority in the area, who identifies the most important topics at that time.
- First time @SSHC journal club

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Current Opinion HIV and AIDS

- specific themed issues : past 12 months -June 2018-2017
- cardiovascular disease
- malignancy
- IT
- ~~HIV cure~~
- new medications
- ~~microbiome~~

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Are we successfully managing cardiovascular disease in people living with HIV?

Hatleberg CI, Lundgren JD, Ryom L.

- screening and prevention of CVD in PLWHIV is suboptimal, reasons for not clear
  - data are still scarce both in the primary and secondary preventive setting.
  - need for further studies investigating barriers to optimal CVD risk factor management in PLWHIV.
- no optimal routine risk screening tools available to accurately detect early and subclinical disease in PLWHIV
- PLWHIV are undertreated with preventive drugs such as stains and aspirin and anti-hypertensives.

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Are we successfully managing cardiovascular disease in people living with HIV?

- Smoking cessation programmes that have evidence of being effective over long term still need to be developed, need for further data on exercise and appropriate diets in PLWHIV.
- HIV + women is a particular subgroup who are at risk of being under-diagnosed and undertreated, and need for increased focus on this subgroup.

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Are we successfully managing cardiovascular disease in people living with HIV?

- PLWHIV have a high prevalence of noncalcified plaques, which are more strongly associated with acute coronary syndrome
- D:A:D risk score model is the only model developed for PLWHIV and performs better than the FHS and SCORE models, although a significant proportion of PLWHIV categorized as low CVD risk still has evidence of subclinical atherosclerosis

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Are we successfully managing cardiovascular disease in people living with HIV? Research questions

- screening for CVD -
  - imaging > biomarkers for subclinical disease
  - https://www.youtube.com/watch?v=QtvGVkTpCZI
  - risk scores ? DAD and ACVD but underperform in some with low risk
  - how to combine the above?
- primary prevention
  - optimal smoking cessation models still to be defined
  - physical activity : PLWHIV less active ? optimal interventions

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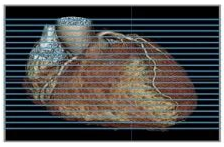
Are we successfully managing cardiovascular disease in people living with HIV? Research questions

[redacted]

The CAC scan



[redacted]

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Are we successfully managing cardiovascular disease in people living with HIV? Research questions

- medical primary prevention suboptimal
  - underprescribing Anti- HT, statins, oral hypoglycaemics - why?
  - increased risk of newer PI and CVD? impact of new regimens?
- secondary prevention
  - as above
  - additionally PLWHIV less invasive cariac interventions - why?

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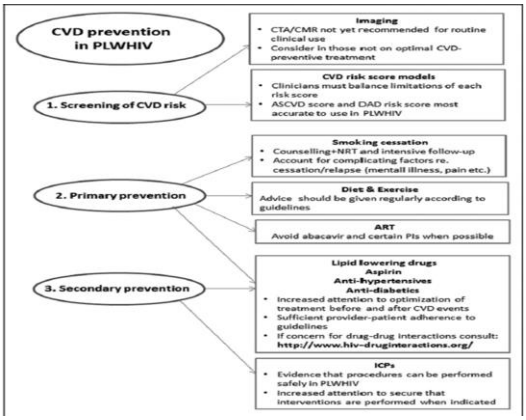
Current Opinion HIV and AIDS



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Online to offline

- Online-to-offline (O2O) models, integrating emerging technologies in HIV service delivery. opportunities to tailor online outreach, identify and engage key populations, and enable seamless transition to HIV clinical services.
- Understanding how O2O models integrate and harness technologies could help enable rapid and massive scale-up of clinical services globally.
- plethora of online studies targeting populations vulnerable to HIV, compelling studies with the central theme and goal of reaching, identifying and engaging online key populations, optimizing O2O linkages and demonstrating offline service uptake remain limited

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Online to offline

- HIV services throughout the wall remain essentially traditional
- 4 model
  - information O2O
    - challenges in ascertaining success - who linked in for testing?
  - promotion O2O
    - pre and post promotion assessment
  - ecounselling 020
    - realtime video conferencing to link clients into services eg whatsapp
  - integrated 020
    - fully integrated systems eg online risk assessment, barcodes for pathology ordering

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Technological methods to measure adherence to ART and PrEP

Lindsey Garrison Jessica Haberer

- Real time Electronic Adherence Monitors (EAM)
  - https://youtu.be/XtvMClIqzhQ
  - https://youtu.be/6vh3V6Y58Tk
- SMS
- Digital medicine Systems
- PK (blood > hair)

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Realtime EAM

Digital medicine systems

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The FDA has approved the first digital pill

Abilify MyCite raises new privacy concerns

By Thuy Ong | @ThuyOng | Nov 14, 2017, 7:06am EST

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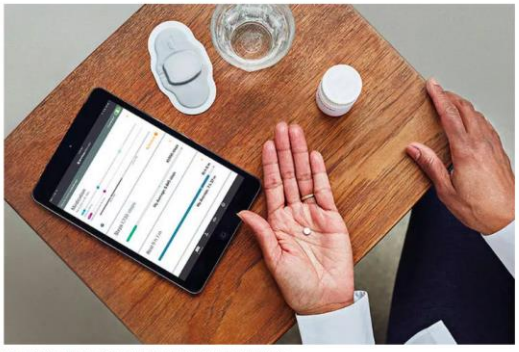

Example of a digital medicine system | Photo: Proteus Digital Health

Technological methods to measure adherence to ART and PrEP

adhere tech

vitality glow caps

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Technological methods to measure adherence to ART and PrEP

Table 1. Summary of studies involving real-time electronic adherence monitors from 2010 to 2017

Device	Published studies	Website	Location	Registered, ongoing studies
AdhereTech	–	http://www.adheretech.com/	USA	NCT02740556, NCT02690649, NCT03052257
GlowCaps	[9,10]	http://www.vitality.net/	USA	NCT01756001, NCT01890018, NCT02472925, NCT01800201, NCT02139202
MedMinder	[11–16]	http://www.medminder.com	USA	–
MedSignals	[17–22]	http://www.medsignal.com	USA	–
Sensemedic Smart	[23•,24–26]	http://sensemedic.com/site/index	Netherlands	NCT03011580
Tel-Me-Box[b]	–	–	USA	NCT03086655[a]
Wisepill Wisebag RM-1000	[6,7,27–47] [8,48,49] –	http://www.wisepill.com/	South Africa	NCT02915367[a], NCT02611362[a], NCT02573376, NCT01817621[a], NCT01790373[a]

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Technological methods to measure adherence to ART and PrEP

Table 2. Pharmacokinetic adherence measure specifications from 2010 to 2017

Pharmacokinetic measure	Published studies	Typical duration of drug exposure measured*	Collection method	Storage	Registered ongoing studies
Plasma	[44,72–76]	Days	Whole blood is collected and centrifuged	−20°C or lower	ART: NCT02833441 PrEP: NCT03012607, NCT02237027
Hair	[77–81,82**,83]	Weeks to months	Approximately 50–100 strands of hair are cut close to scalp; drug levels measured from distal portion	Ambient temperatures without biohazard precautions [79,84]	ART: NCT02833441, NCT03086655, NCT02761746, NCT01786148, NCT02846350 PrEP: NCT02710032, NCT02962739
DBS	[80,85–89,90*, 91*,92,93]	Days to months	Spot whole blood onto filter paper by finger prick or venipuncture	Ambient temperatures for up to 7 days, −20°C or lower for long-term storage [92]	ART: NCT02797093, NCT02012621, NCT02833441 PrEP: NCT02371525, NCT02022657, NCT02213328, NCT02891720, NCT02962739
PBMCs	[94,95]	Days to weeks	Whole blood is collected and then centrifuged for extraction of PBMCs	−20°C or lower	ART: NCT02797093 PrEP: NCT02401230

Ongoing studies were identified through a search of Clinicaltrials.gov; publications were identified through a search of PubMed and Google Scholar.
ART, antiretroviral therapy; DBS, dried blood spots; PBMC, peripheral blood mononuclear cells; PrEP, preexposure prophylaxis.
*Variation reflects differences in drug half-life and assay used.

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Lung Cancer in persons with HIV

- Increased risk of lung cancer in HIV-infected persons is primarily due to higher smoking rates, but emerging evidence also implicates immunosuppression and inflammatory processes.
- Lung cancer outcomes may be worse in HIV-infected persons in the antiretroviral era, but this may stem, in part, from treatment disparities.
- Early detection of lung cancer using chest computed tomography (CT) is being increasingly adopted for smokers in the general population, and recent studies suggest that it may be safe and efficacious in HIV infected smokers

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Lung Cancer disparities in USA treatment in PLWHIV

Table 1. Recent studies of lung cancer treatment disparities in United States HIV-infected persons

Study	Lung cancer diagnosis years	HIV+ lung cancers (*N*)	HIV− lung cancers (*N*)	% HIV + treated	% HIV − treated	Other/notes
Marcus *et al.* 2015 [43▪]	1996–2011	80	507	64%	76%	Lung cancer only NADC with treatment disparities: lung surgery 16% (HIV+) vs. 28% (HIV−)
Suneja *et al.* 2016 [51]	2003–2011	1420	353156	67.3%	86.4%	Adjusted OR* = 2.46 (95% CI 2.19–2.76)
Suneja *et al.* 2014 [52]	1996–2010	581	260652	65.1%	75.9%	Adjusted OR* = 2.18 (95% CI 1.80–2.64)
Lee *et al.* 2013 [53]	1998–2007	174	3480	58.0%	59.6%	HIV not independently associated with receipt of guidance concordant treatment
Suneja *et al.* 2013 [54]	1995–2009	337	156593	60.3% (lung)	77.5%	Adjusted OR** = 0.39 (95% CI 0.30–0.52)

CI, confidence interval; NADC, non-AIDS-defining cancer; OR, odds ratio.
*Odds ratio for lung cancer treatment associated with lack of HIV infection.
**Odds ratio for lung cancer treatment associated with HIV infection.

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Table 2. Recent studies of lung cancer outcomes in HIV infected persons

Study	Study period	HIV+ lung cancers (*N*)	HIV− lung cancers (*N*)	Overall survival	Other outcome measures associated with HIV
Crequit *et al.* 2016 [44]	1996–2013	73	N/A	13.2 months	*EGFR* mutations associated with better survival
Coghill *et al.* 2015 [55▪]	1996–2010	1058	327866	–	HR for lung cancer-specific mortality = 1.28 (95% CI 1.17–1.39)
Hleyhel *et al.* 2015 [56]	1992–2009	446	N/A	–	5-year OS for lung cancer = 16%
Marcus *et al.* 2015 [43▪]	1996–2011	80	507	–	5-year OS for lung cancer = 9.5% Adjusted HR for lung cancer-specific mortality = 1.3 (95% CI 1.0–1.7)
Bearz *et al.* 2014 [50]	1986–2003	68	N/A	–	N/A
Gotti *et al.* 2014 [57]	1998–2012	35	N/A	3.7 months	1-year OS for lung cancer = 28%
Worm *et al.* 2013 [58]	2004–2010	140	N/A	–	1-year OS for lung cancer = 42%
Sigel *et al.* 2013 [42]	1996–2007	267	1428	6 months	Adjusted HR for OS = 1.9 (1.6–2.2)
Hoffmann *et al.* 2013 [59]	2000–2010	72	N/A	13 months	Worse survival associated with lower PS, low CD4 and IVDU route of HIV infection
Suneja *et al.* 2013 [54]	1995–2009	337	156593	–	Adjusted HR for lung cancer-specific mortality = 1.34 (95% CI 1.15–1.56) Adjusted HR for lung cancer-specific mortality including treatment 1.25 (95% CI 1.06–1.47)

ART, antiretroviral therapy; CI, confidence interval; HR, hazard ratio, IVDU, intravenous drug use; OS, overall survival; PS, performance status; SMR, standardize

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Prevention – Early Lung CT

- Early detection of lung cancer using chest computed tomography (CT) is being increasingly adopted for smokers in the general population, and recent studies suggest that it may be safe and efficacious in HIV infected smokers
- Initial study in 2011 – aimed to replicate findings of 6% reduction in overall mortality and 20% reduction in lung ca mortality
- Two trials to date involving PLWHIV – Baltimore and ANRS with very different results and different populations / protocols

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lung cancer and HIV

risk factors - traditional

- incidence reported > HIV+ in USA
- age
  - smoking
  - COPD

risk factors - HIV specific

- immunosuppression
- inflammation
- viral oncogenesis
- ART

- Disparities exist in treatment HIV+ receive less rx

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Editorial: New HIV drugs: 2018 and beyond

Gillick, Roy

- two drugs vs 3
- one tablet co formulated DRV/C/TAF : First STR with PI
- Next generation NNRTI : Doravarine
- Bictavay new INSTI
- long acting: RPV/Carbotegravir : oral and injectables, ART and PrEP
- HIV broadly neutralizing mAbs (BNAbs)
- The seventh mechanistic class of antiretroviral drugs is a third type of entry inhibitor, the CD4 attachment inhibitors. Fostemsavir
- Ibalizumab is a monoclonal Antibody -binds to the second domain of the host CD4 receptor, FDA approved for heavily treatment-experienced patients with multidrug-resistant HIV failing their current antiretroviral regimen.

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Broadly neutralising antibodies

Cohen YZ, Caskey M.

- single-cell antibody cloning techniques—have led to the isolation and characterization of antibodies from people with HIV infection that can neutralize many variants .
  - referred to as broadly neutralizing antibodies (bnAbs).
  - Such antibodies can be detected in about 25% of persons with untreated HIV-1 infection
- Early clinical trials demonstrated bNAbs are well tolerated, half-lives of approximately 2–3 weeks, and reduce viremia by approximately 1.5 log10 copies/ml.
- Combinations of bNAbs with extended half-lives and increased potency are a promising novel approach to the prevention, treatment, and possibly cure of HIV1 infection.
- only VRCO1 reached efficacy trials to date but many in pipeline

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Broadly neutralising antibodies

Cohen YZ, Caskey M.

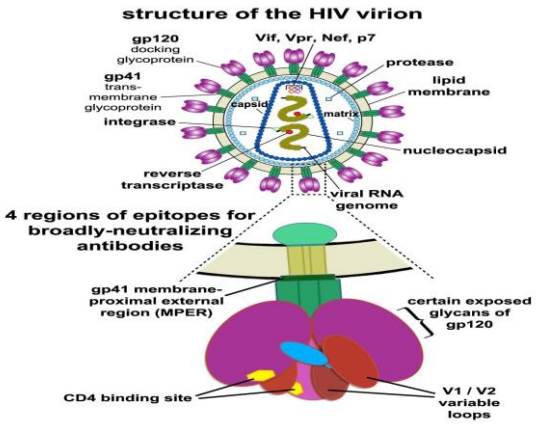

Image designed by Matt Arnegard using an open access figure downloaded from Wikimedia Commons and an adaptation of Fig. 2 in Haynes et al. (2012. Nature Biotechnology 30:423-433)

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Broadly neutralising antibodies

Cohen YZ, Caskey M.

- HIV-1 bnAbs administered through intermittent blood infusions, providing both circulating and mucosal concentrations of antibodies at levels that might be able to block HIV-1 acquisition (genitourinary and rectal mucosal epithelia are the sites of HIV-1 acquisition).
- The bnAbs isolated so far target proteins expressed on the HIV-1 envelope :
  - the critical CD4 binding site (which HIV-1 uses, via its glycoprotein gp120, to enter cells);
  - glycan-coated viral loops, including the V1-V2 glycan and V3 glycan

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Broadly neutralising antibodies

Cohen YZ, Caskey M.

- PK and safety differences vs traditional ART
- both have resistance in monotherapy
- BNABS work with immune system - potential role in cure and PREVENTION
  - macaque models after acute HIV, infusions leading to viral suppression for 8-25 weeks and some
- PREP studies “Antibody mediated Prevention” (VRC01)prevention of HIV-1 infection 4500 heterosexual women in sub-Saharan Africa and in men and transgender people who have sex with men in the Americas and Switzerland. infusions every 8 weeks

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Ibalizumab

Bettiker RL, Koren DE, Jacobson JM

- HIV-1 entry: begins with the envelope protein gp120 binding to domain 1 of the CD4 receptor. Conformational changes in gp120 allow it to bind simultaneously to either the co-receptor CXCR4 or CCR5 then further conformational changes lead to fusion of the HIV-1 envelope with the cellular membrane, allowing viral entry into the cell.
- IgG4 monoclonal antibody a noncompetitive, allosteric inhibitor of HIV-1 cell entry without cross-resistance to existing cell entry inhibitors

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Ibalizumab

Bettiker RL, Koren DE, Jacobson JM

- phase III clinical trial in participants with multiclass antiretroviral drug resistance, IV administration of ibalizumab led to declines in plasma HIV-1 RNA more than 0.5 log in 83% of participants at 1 week.
  - An optimized background antiretroviral regimen was then added, and plasma HIV-1 RNA became less than 50 copies/ml in 43% of participants at 24 weeks.
- dosing is frequent – weekly infusions
- Adverse effects of ibalizumab were uncommon and generally low grade
- resistance can occur, short half life
- FDA approved

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Ibalizumab

Bettiker RL, Koren DE, Jacobson JM

- future directions:
- changes in structure can improve half life
- potential for PrEP – 2 monthly injections evaluated

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summary

- future directions:
- cardiovascular screening involving imaging and risk calculators
- screening for lung cancer
- adherence using innovative methods to assist specific patient groups
- engagement with populations for testing and prevention through seamless online experience
- new medications – options for multi drug resistant HIV, injectables – long acting, new classes BNABS and MCABS

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