ASHM Journal Club: Sexual Health

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Sexual Health

- Australian based journal
- Impact factor: 1.238
- Volume 16 1,2 & 3
  2019 + online early

*Publishing on sexual health from the widest perspective*
City of love: group sex is associated with risks for HIV and other sexually transmissible infections among gay and bisexual men in Paris, France

Callander et al (2016, 16 (Apr), 192-194)

Background:
• Relationships identified between group sex and risk of HIV & STI’s among gay men
• Association with group sex and CLAI, substance use associated with sex, sex work & STI diagnosis
• Aim of study - extending current evidence with European perspective

Methods:
• October 2016 - anonymous online survey – gay men in Paris
• Popular geospatial app used (for sex and dating)
• CIS and transgender men aged ≥ 18 years – incentivised
• 52 items which included socio-demographics, sexual experiences & practices, drug use, PrEP
• At least one encounter of group sex in last 3/12 was mandatory for inclusion
• Logistical regression used to assess for recent group sex experience and risk factor association
City of love: group sex is associated with risks for HIV and other sexually transmissible infections among gay and bisexual men in Paris, France

Results:
• 935 individuals started survey with a 62% completion (n=576) – median age was 35 years (18-66)
• 66% reported group sex at most recent encounter 38% reported CLAI – number involved in encounter ranged from 3 to 100 (mean=5)
• Multivariate - PrEP use and HIV status, recent group sex significantly associated with CLAI (receptive: aOR 1.6, insertive: aOR 2.0)

Conclusion:
• Recent group sex associated with CLAI, substance use and STI’s
• Findings suggest closer attention needed in epidemiological networks of group sex participants
• Participation in group sex provides a useful marker for HIV/STI risk
• Safer sex and risk reduction strategies should focus holistically on STIs not just HIV
An automated, electronic, client-centred results delivery system saves time and improves workflow
Knight et al (2019, 16 (Feb), 88-89)

**Background:**
- Increase in HIV testing = increase in result management
- Traditional result notification methods are time consuming
- Electronic methods are acceptable to most people but a more personalised approach such as phone or F2F remains popular
- 2013 cross-sectional survey to identify client preference (n=477) for receiving results - study suggested several methods be available

**Methods:**
- SSHC EMR contains electronic pathology ordering – allows for quality control when importing results (known as result-robot module- RRM)
- Only standard tests were included in automated program - positive, indeterminate and non-standard tests were managed manually
- RRM can determine whether SMS or email result to be sent to client
- During development, questions imbedded to prompt clinician to record client’s preferred result method
An automated, electronic, client-centred results delivery system saves time and improves workflow

Results:
• Between 21 Jan 2016 to 31 Dec 2017 – 19,564 negative SMS/email results sent out
• Prior to RRM implementation result calls were median 2 minute duration
• Automated system potentially saves 652 nursing time hours
• Pre-implementation > 5,454 calls vs 3,204 calls post implementation
• 41% reduction in result calls
• Median of 3 days for clients to receive results

An automated, electronic, client-centred results delivery system saves time and improves workflow

Conclusion:
• RRM provides a more efficient results management flow from lab to client
• Time saving measure for staff and resources to be re-directed to other core services
Effect of an express testing service for gay and bisexual men on HIV testing frequency in Sydney, Australia: a cohort study
Knight et al (2019, 16 (Apr), 124-132)

Background:

• HIV testing frequency is an important intervention for HIV prevention among gay and bisexual men (GBM)
• Increasing testing frequency is crucial to detecting HIV as close to acquisition as possible
• Fast track screening method introduced at SSHC in 2010 – Xpress clinic availability increased testing
• Study aim - to assess the effect of the Xpress clinic on repeat HIV testing in high risk GBM (6 month retest)

Methods:

• Time period 1 Oct 2009 to 31 Dec 2013 (1 year pre-Xpress and 3 years post-Xpress introduction)
• Two observational methods used to assess whether Xpress clinics were associated with increased retesting among GBM and sub group of higher risk GBM
• Inclusion criteria - asymptomatic GBM tested for HIV, HIV +ve , PEP and Vax consults excluded
• Method 1: Before and after analysis to assess 6 month retesting, by quarter (Poisson regression model to calculate average annual testing trend)
• Method 2: Retrospective cohort – higher risk GBM (>5 partners in previous 3/12 to assess Xpress clinic attendance and repeat HIV testing in 6 months
• Outcome - repeat testing within 6 months defined as test >30 days and ≤180 days
Effect of an express testing service for gay and bisexual men on HIV testing frequency in Sydney, Australia: a cohort study

Results

• 6,971 unique clients had total of 15,980 asymptomatic screens
• Higher risk men - retesting increased by 50% between before and after periods (p<0.01)
• No significant trend in proportion of high risk /GBM retesting in 6/12 in pre-Xpress but significant upward trend in retesting post Xpress
• GBM 1.44-fold more likely to retest in after Xpress period compared to before Xpress
• Younger men more likely to retest within 6 months compared to older men (>30yrs old)
• Overall 106% increase in HIV tests from 2,908 before Xpress to 6,004 in final year of Xpress study period
• In 3 years after Xpress implemented – 44 new HIV infections diagnosed from 9,121 tests

Effect of an express testing service for gay and bisexual men on HIV testing frequency in Sydney, Australia: a cohort study

Conclusion:

• This study was the first to demonstrate Xpress clinic attendance was associated with HIV retesting in higher-risk GBM
• HIV retesting 2.8-fold more likely in high-risk men compared to high-risk men attending routine clinic for screening
• Shorter consults, less F2F questions and same day appointments thought to contribute to increase in testing
• Limitations – not an RCT but a before and after analysis to account for effect of external factors
• Xpress was associated with increase in retesting and total number of HIV tests done at the clinic doubled with more HIV infections detected
Trends in diagnosis of pelvic inflammatory disease in an Australian sexual health clinic, 2002-16: before and after clinical audit feedback

**Background:**
- Guidelines recommend low threshold for PID diagnosis - can be difficult due to non-specific nature of presentations
- 2006 audit showed there was wide variability in PID diagnosis among doctors
- Feedback and QI implemented to increase PID diagnosis and reduce variability – e.g. triage checklist among CT & MG +ve women attending for treatment (NG diagnosis rare at time of study)
- Study investigated trends in PID diagnosis before and after feedback

**Methods:**
- PID diagnosis trends over time of women aged 16-49 years attending clinic from July 2002-June 2016 assessed by doctor
- Electronic attendance data collects demographic, self-reported symptoms & risk info, investigations and diagnoses
- Minimal criteria – cervical motion/uterine or adnexal tenderness in young women experiencing lower abdominal pain
- 2006 audit feedback: MOs told own PID diagnosis rate compared to overall rate
- Primary outcome – PID (only first diagnosis counted for any woman)
- Annual PID diagnosis rate calculated per 100 female consults
- Generalised linear mixed effects model for before and after audit time period (incidence rate ratios reported)
Trends in diagnosis of pelvic inflammatory disease in an Australian sexual health clinic, 2002-16: before and after clinical audit feedback

Results:
• 84,476 consults, 1,755 diagnosed with PID (2.1% 95% CI: 2.0-2.2)
• Doctor specific diagnosis rate ranged from 0-13%
• Diagnosis rate increased over time from 0.8% (2002-3) to 1.7% (2007-8), 2.3% (2010-11 then 2.9% (2015-16)
• Women reporting symptoms at triage increased from 35% to 47%
• Increase in CT and NG diagnoses post feedback audit (57% symptomatic women)
• Self report of symptoms at triage – strongest association with PID diagnosis

Conclusion:
• PID diagnoses increased post feedback audit - marked increase in risk profile of women with symptoms
• Less variability in MO-specific diagnosis rates
• PID checklist improved identification of symptoms suggestive of PID
• Emphasis on diagnostic sensitivity - potential to over diagnose (less experienced MOs)
• Lack of specific diagnostics - ongoing need for tools, training and systems to support clinicians
• Checklist a useful tool for primary health services
ADOPTing a new method of partner management for genital chlamydia in NSW: findings from a pilot implementation program of patient-delivered partner therapy
Lorch R et al (early online 24 May 2019)

Background:
- Partner-delivered partner therapy for chlamydia an effective alternative
- Index case given treatment for partner/s - aim to reduce re-infection
- Lacking implementation guidance - several jurisdictions tried to initiate but hampered by practical implementation
- Study describes a pilot implementation program (ADOPT) in several PFSHS (NSW) and FP NSW for partners of heterosexual patients

Methods
- Programmatic pilot commenced development in 2014 – 3 components:
  - Clarification of NSW PDPT legal and policy framework
  - Service delivery model with resources and data collection
  - Evaluation of PDPT uptake
- 9 sites recruited, eligibility criteria developed – study period: 2016
ADOPTing a new method of partner management for genital chlamydia in NSW: findings from a pilot implementation program of patient-delivered partner therapy

Results:
- Service models developed for prescription or direct supply of PDPT
- Monthly uptake and qualitative feedback reports from pilot sites
- RN standing orders + included in RN administration and supply PD
- Feedback > staff forgetting to offer

PDPT uptake:
- PFSHS: 993 diagnoses in heterosexual population with 445 eligible for PDPT
- In PFSHS’s 30% offered PDPT > 89% accepted
- Proportion of patients offered PDPT increased during 12 month period

Conclusion
- Successfully developed and implemented a model for delivery of PDPT
- Study has led to recommendations to expansion into standard of practice
- For maximum benefit needs to be adopted in GP practice
Gonorrhoea gone wild: rising incidence of gonorrhoea and associated risk factors among gay and bisexual men attending Australian sexual health clinics
Callander D (online early, 9 November 2018)

**Background:**
- NG notifications on the rise among GBM
- More information needed on infection trends e.g. demographics and risk practices
- Calculating incidence is one way to assess rising notifications and changing rate of infection
- Study presents longitudinal analysis of NG incidence in GBM attending PFSHS

**Methods:**
- Retrospective cohort using routine testing data from 47 clinics (ACCESS) from 1 Jan 2010 to 31 Dec 2017
- Males ≥16 years who reported sexual contact with men at any point during 8 year study period
- Incidence calculated using repeat testing - defined as initial –ve followed by +ve and time of risk - time between tests
- Stratified by anatomical site and risk factors (e.g. no of partners)
Gonorrhoea gone wild: rising incidence of gonorrhoea and associated risk factors among gay and bisexual men attending Australian sexual health clinics

Results:
- 75,723 unique GBM with 62% had at least 2 tests
- 14% HIV+ve & 61% Australian born
- Overall incidence any anatomical site was 20.0/100PY (95%CI 19.7-20.3)
- Incidence for symptomatic GBM was 40.7/100py vs 19.0/100py for asymptomatic
- Annual incidence increased from 14.1/100py in 2010 to 24.6/100py in 2017
- Pharyngeal incidence tripled, GBM on PrEP 36.9/100py vs no PrEP 18.6/100py
- Independent factors associated with increased incidence – Hazard ratio (HR): HIV+ve (1.4), <30years (1.4), IDU (1.7), ad hoc condom use (1.4) & >20 partners (1.9)

Conclusion:
- NG incidence increased dramatically over time especially pharyngeal infection
- Several unsurprising factors associated, however, IDU significantly associated
- Importance of throat swabs - may be missed in public health clinic settings
- Broader consideration of risk beyond sole focus on PrEP, condoms and AI
New treatment options for *Neisseria gonorrhoeae* in the era of emerging antimicrobial resistance

Lewis D (online early, 11 July 2019)

**Background:**

- Was initially easy to treat but over time NG acquired a variety of antimicrobial resistance
- Emergence of multi-drug resistant (MDR) & extensively drug resistant (XDR) strains
- No longer presume AB’s will cure NG on every occasion
- WHO –NG listed as a priority pathogen for research and development of new AB’s
- Review to discuss new approaches for treatment

**New treatment options for Neisseria gonorrhoeae in the era of emerging antimicrobial resistance**

**Review:**

- Longest treatment efficacy before resistance emergence - ceftriaxone (30yrs)
- Data suggest injectable AB agents last longer
- Oropharynx - increasingly recognised as site of antimicrobial resistance
- Mutations in genes - generate gonococci with sufficiently high minimum inhibitory concentrations (MIC) > treatment failure
- Emergence of H041 & F89 NG strains with extremely high MIC’s to both ceftriaxone and cefixime - international concern over potential untreatable NG
- Many countries adopted dual treatment despite lack of clinical trial data - intention was to reduce further emergence of ceftriaxone resistant strains
- Emergence and increase in azithromycin and ceftriaxone NG strains
- UK guidelines now Ceftriaxone monotherapy (higher dose of 1g IMI)
New treatment options for *Neisseria gonorrhoeae* in the era of emerging antimicrobial resistance

**Recycling previous treatment:**
- Use of antimicrobial susceptibility testing crucial for effective management of MDR or XDR NG with non-ceftriaxone based treatment
- Ciprofloxacin potential treatment in settings where fluoroquinolone resistance <50%
- Ciprofloxacin single dose therapy - highly effective for oropharynx - new diagnostic assays developed for ciprofloxacin susceptibility
- Research into dual therapy - UK G-TOC trial: comparing gentamicin + azithromycin to ceftriaxone + azithromycin
- 91% clearance in gentamicin arm (lower in oropharynx infections) compared to 98% clearance in ceftriaxone arm

**New uses for existing agents**
- Ertapenem - broad based activity against NG - was used to treat XDR cases in UK and Australia
- Gemifloxacin> 99.5% cure for predominately macrolide sensitive strains
- Sitafloxacin - good activity against ciprofloxacin-resistant strains but not suitable for mono therapy
- Delafloxacin - recent study showed single dose delafloxacin had 85% cure rate
New treatment options for *Neisseria gonorrhoeae* in the era of emerging antimicrobial resistance

New agents in clinical trials:

• **Solithromycin:**
  – Highly active against most NG strains including XDR, H041 & F89
  – Treatment trial being conducted in the US in comparison with ceftriaxone treatment
  – Failed to demonstrate non-inferiority margin when compared - progress now stalled

• **Zoliflodacin:**
  – Displays activity against NG - has received fast track US FDA approval development
  – Clinical trial 98% cure in participants who received 2g oral Tx, 100% cure in participants who received 3g Tx
  – Cure rates of oropharyngeal infection were lower than those treated with ceftriaxone
  – Being progressed to a phase 3 trial

• **Gepotidacin**
  – First in class triazaacenaphthylene antimicrobial agent
  – Phase 2 clinical trial showed good efficacy, tolerability and safety
  – End point – culture confirmed eradication of urogenital NG 4-8 days post treatment
  – Pre-protocol analysis – 97% cure of 30 participants who received 1.5g dose & 95% cure of 39 participants who received 3g dose
  – Overall 96% cure rate
  – Low number of concomitant rectal or oropharyngeal infection > 2 oropharyngeal infections failed therapy (fluoroquinolone resistant strains)

**Conclusion:**

• Important public health initiative is to stem global rise of new cases
• Dual treatment still recommended but on basis of weak evidence and expert opinion
• Monotherapy – need to optimise dosing strategies to avoid resistance
• R & D required to generate more antimicrobial agents
Should we still be using azithromycin for gonorrhoea treatment?
Mensforth S (online early, 18 June 2019)

Background:
• Need to maintain ceftriaxone as an effective treatment
• Dual therapy with azithromycin widely used as thought to protect ceftriaxone but not proven
• Extended drug resistant NG (XDR) – both ceftriaxone and azithromycin
• Paper reviews evidence of azithromycin use (both mon and dual therapy)

Azithromycin (in a nutshell):
• NG resistance programs reporting upward trend in azithromycin MIC’s - in UK low level resistant strains >5%
• High level resistant strains being reported globally since 2001

Monotherapy for NG
• Differs globally – UK includes azithromycin 2g stat as alternative, European guidelines - must have sensitivity testing
• Not recommended in Australia, US or WHO
• Azithromycin 2g can be effective >95% cure rate but azithromycin1g failing to meet this criteria
• Interpretation of efficacy from older studies - NG culture used to access cure – may have overestimated treatment efficacy due to culture low sensitivity
Should we still be using azithromycin for gonorrhoea treatment?

Dual treatment for NG

- Widely recommended – European guidelines recommending higher dose of 2g
- Postulated if ceftriaxone resistance present, azithromycin will treat infection
- Major contributor to cephalosporin resistance is the mutation in the \textit{penA} gene
- 2018: 1\textsuperscript{st} case of ceftriaxone + high level azithromycin resistance reported from UK, followed by 2 cases in Australia
- New NG infection acquired 14 days post treatment will be subjected to sub-therapeutic levels of azithromycin - possible resistance developing rapidly

Should we still be using azithromycin for gonorrhoea treatment?

Azithromycin and other STIs

- Single dose azithromycin - macrolide resistance for \textit{M. genitalium} (occurs in 30-100\% patients)
- Several global guidelines no longer recommended for chlamydia and NGU treatment
- Move away from azithromycin use to slow down future resistance to variety of STI pathogens
Should we still be using azithromycin for gonorrhoea treatment?
Mensforth S (online early, 18 June 2019)

Conclusion
• Azithromycin has good activity against NG - achieves high tissue levels which are maintained for a long time
• NG has the potential to develop high level resistance to azithromycin - affect on dual therapy on development of ceftriaxone resistance remains uncertain
• 2g dose more likely to be effective at genital sites but is poorly tolerated (GI Sx’s)
• Extent of which wide spread azithromycin use determines NG resistance is uncertain but azithromycin single dose is associated with rapid development of MG resistance
• Several guidelines updated to ceftriaxone mono-therapy
PrEP
New drugs
PrEP
2D ART
outbreak
LTFU
Delivery of drugs

Reminder

- New infections outpace treatment initiations.
- Prevention tools are not being provided on an adequate scale.
- Women and girls continue to be disproportionately affected.
- Stigma and discrimination impede prevention for men who have sex with men, sex workers and transgender persons.

Source: UNAIDS/WHO estimates

38 million infected
23 million on treatment
1.7 million newly infected
Development of broadly neutralising antibodies

WHAT IS THIS ANTIBODY?
This antibody is a broadly neutralizing antibody to HIV. Its name is VRC01. It stops HIV from binding to human T-cells by attaching to the virus and preventing it from infecting the T-cell.

1. The VRC01 antibody is able to bind onto HIV at the (2) CD4 binding site on the gp120 protein. (3) This neutralizes HIV and prevents HIV from being able to attach to cells and infect them.
Can a passively infused monoclonal antibody prevent HIV-1 infection in high risk adults?

Two harmonized protocols:

The AMP Studies:

**HVTN 704/HPTN 085**
(2700 MSM and TG in the Americas, Europe)

**HVTN 703/HPTN 081**
(1900 Women in sub-Saharan Africa)

Chairs – L Corey, M Cohen
Co-Chairs – S Edupuganti, N M Mgodi

**AMP Study design**

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>MSM &amp; TG in the Americas</th>
<th>Women in sub-Saharan Africa</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>VRC01 10 mg/kg</td>
<td>900</td>
<td>634</td>
<td>1534</td>
</tr>
<tr>
<td>VRC01 30 mg/kg</td>
<td>900</td>
<td>634</td>
<td>1534</td>
</tr>
<tr>
<td>Control</td>
<td>900</td>
<td>634</td>
<td>1534</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>2700</strong></td>
<td><strong>1900</strong></td>
<td><strong>4600</strong></td>
</tr>
</tbody>
</table>

- Two different infusion doses: important to know if lower dose of 10 mg/kg can protect
  - Powered to associate mAb serum level with protection
  - All subjects provided an HIV prevention package

Study duration: ~22 months
Next generation mAbs - Summary

• If virus is targeted by multiple or trispecific bNAbs, then escape is difficult.
• Studies will use trispecific bNAbs or combinations of mAbs
  – improve efficacy through better coverage
  – higher potency.
• aim to a licensure trial.
HPTN 083 and 084: Phase 3 for CAB LA PrEP

Objective:
To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV-uninfected MSM/TGW (083) and cisgender women (084)

Long-Acting Agents: Good, Bad, or Ugly?

When administering agents with long $t_{1/2}$ in non-removable method
• May require an oral lead-in to assess toxicity before administering LA formulation
• May have a prolonged sub-therapeutic tail

Markowitz et al, Lancet HIV 2017;4:e331-40
Implants and transdermal drug delivery systems for HIV prevention

Charles Flexner, MD
Johns Hopkins University

Share your thoughts on this presentation with #IAS2019
Drug delivery systems

• Consider contraception
  – Non biodegradable implants – early studies
  – Bioerodable – less advanced
  – Transcutaneous patches

Long Acting ARV Implants

• Potential advantages over injectables
  – Removable (inert, or early bioerodable forms)
  – More consistent and predictable drug release
  – PK not dependent on injection site
  – May remain in place for years (inert, non-degradable subcutaneous versions)

• Potential disadvantages over injectables
  – Specialized device required for insertion
  – Minor surgical procedure to remove
  – Should be removed (if not bioerodable)
  – Regulated as both a drug and a device
  – Difficulty moving to a generic marketplace
Transcutaneous ARV Delivery Systems

advantages vs IMI

- Removable
  - Can be applied by the patient or family member
  - PK not dependent on placement site (?)
  - May remain in place for days or weeks
  - Also appropriate for short-duration drug delivery (per day or week)

disadvantages vs IMI

- Limited number of drug candidates
  - Complex manufacturing
  - Expensive to manufacture
  - Regulated as both a drug and a device
  - Difficulty moving to a generic marketplace
Topical PrEP: long-acting and on-demand

Symposium: New prevention products in the pipeline

Jared Baeten MD PhD

Vice Chair, Department of Global Health
Professor, Departments of Global Health, Medicine, and Epidemiology
Director, UW/Fred Hutch Center for AIDS Research (CFAR)
Co-Director, International Clinical Research Center
University of Washington
Affiliate Investigator, Vaccine and Infectious Disease Division, Fred Hutchinson Cancer Research Center
Co-Principal Investigator, Microbicides Trials Network
Dapivirine vaginal ring: across the life cycle

Through an intentional series of studies, the dapivirine vaginal ring is being evaluated across the reproductive life cycle:

**Conception & Contraception**
(Balkus et al. JAIDS 2018; Makanani et al. JAIDS 2018; MTN-020/025; IPM 027/032)

**Pregnancy & Lactation**
(MTN-041, MTN-042 & MTN-043)

**Adolescents & Post-menopausal Women**
(MTN-023, MTN-024, MTN-034)

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**MPTs**

- **Idea:** Many women at risk of HIV also want family planning. Why not combine HIV prevention with contraception?

- **Multipurpose vaginal rings in development – phase I / early phase II:**
  - Tenofovir / levonorgestrol ring (CONRAD)
  - Dapivirine / levonorgestrol ring (IPM, MTN044/IPM-053/CCN019)
  - Pod rings containing ARVs, contraceptives and anti-STI drugs
Films, inserts, lubricants, douches

- Small, easy to store & hide, inexpensive, stable

- Private to use, quick to reach preventive concentrations, also quick to reverse
  - (right drug, right place, right time)

- End-user studies = high interest

On-demand topical can mean both immediate and sustained protection

- Rapid release
- Extended local concentrations, without loss with sex or menses
- Low systemic exposure
- No impact on microbiome

(Rohan et al. R4P 2018 – NH model)
There gaps are wide, and many

- The science
- The reality

PrEP choices of the future

Options → choices → coverage → impact

Slide adapted from Thes Palanee-Phillips
Multifaceted contraceptive decision-making

- Effectiveness does not drive all decision-making
- Perception of safety is similarly important
- Many other factors are important too

Figure 1. Contraceptive features by importance to adolescent and young women.

(Walker et al. J Adolesc Health 2019)
2DR

- Islatravir plus doravirine may offer new dual therapy option
- Islatravir (MK-8591) 1st in class NRTTI (nucleoside reverse transcriptase) translocation inhibitor
  - Phase 2 study: doravirine + 3TC + islatravir (0.25, 0.75 or 2.25mg) vs doravirine/TDF/3TC for 24 weeks, then drop 3TC in islatravir arms
  - Good viral suppression to W48, promising 2DR
- DTG/3TC
  - N-of-1 and switch (Gemini) 96 week data
Upcoming/ongoing CAB/RPV studies for HIV treatment

**CAB + RPV**

- **2 monthly IM: ATLAS 2M** \(n=1200\)
- **Children/Adolescents: MOCHA 12-18** \(n=150\)
- **Poor Adherers ACTG 5359** \(n=350\)
  - VL >200 at entry
  - No RPV or INSTI mutations
  - Phase 1: 24 weeks SOC (incentivised)
  - Then open label switch CAB/RPV 48 wks
  - 52 week tail if discontinue
- **LATTE 1 rollover POLAR** \(n\sim 100\)
- Implementation study (US): CUSTOMIZE
  - \(N=135\)
  - One year single arm study

**CAB**

- **ACTG 5357** CAB LA + bNab VRC01LS
  - \(n=75\)
  - Single arm study
  - Endpoint is to maintain viral suppression

**FIRST-IN-HUMAN TRIAL OF MK-8591-ELUTING IMPLANTS**

Demonstrates concentrations suitable for HIV prophylaxis for at least one year

Randolph Matthews, MD, PhD
Sr. Principal Scientist
Translational Pharmacology, Merck & Co., Inc., Kenilworth, NJ, USA

Islatravir (ISL) Clinical Development Overview

- Oral ISL administered to ~264 individuals to date
  - 144 healthy study participants, 30 treatment-naive persons living with HIV (PLWH) in Phase 1
  - ~90 PLWH in Phase 2
    - Daily doses ≤2.25 mg for 48+ weeks
- Oral Phase 1 development program
  - Generally well tolerated
  - Linear PK for both parent (plasma) and active triphosphate (TP) in PBMCs over a broad range
    - Half-life of parent ISL: 50-60 hr
    - Half-life of active ISL-TP in PBMCs: 120-177 hr

ISL Implant Design Similar to Nexplanon®

- ISL implant based on Implanon®/Nexplanon®
  - Uses same polymer
  - Removable (not bioerodible)
Conclusions

• ISL prototype implants were generally well tolerated, with no discontinuations due to an AE and no severe implant-related AEs
  – No laboratory or other signs of systemic reactions
  – Local tolerability (erythema, induration) generally mild and possibly dose dependent

• Both implants (54 and 62 mg) had concentrations above PK threshold at 12 weeks
  – 62 mg implant projected to be well above threshold at 12 months and likely for several months beyond

**Supports potential of the ISL implant as a once-yearly PrEP option**
ART is being initiated earlier and earlier, sometimes during Acute HIV Infection.

The Effect of Same-Day Observed Initiation of Antiretroviral Therapy on HIV Viral Load and Treatment Outcomes in a US Public Health Setting
Christopher D. Pilcher, MD,* Clarissa Chipene-Norvell, FN-PhD,* Aditi Dasgupta, BS,* Diane Jones, RN,* Wendy Hartogson, PhD,* Sandra Torres, MSW,* Fabiola Calderon, MSW,* Erin Demarco, MPH,* Edrin Geog, MD,* Motica Gandhi, MD,* Dance Y. Harrell, MD,* and Hiroshi Hatanaka, MD,*
(J Acquir Immune Defic Syndr 2017;74:44-51)

High Feasibility of Empiric HIV Treatment for Patients With Suspected Acute HIV in an Emergency Department
Kathleen R. Jacobson, MD, Sanjay Aneja, MD, Kristin B. Walsh, MD, Meredith Lora, MD, Stephen Merajver, MD, Sharara Livermore, MPH, and Michael Menchine, MD, MPH
(J Acquir Immune Defic Syndr 2016;72:242-245)

**Antibody Response to HIV (without treatment)**

**Effect of ART during Acute HIV**

- Keating et al CID, 2016
• 234 patients enrolled in AHI study Bangkok, Thailand
  - 41 Fiebig I (NAT+/Ag-/IgM-, IgG-, WB-)
  - 72 Fiebig II (NAT+/Ag+/IgM-, IgG-, WB-)
  - 92 Fiebig III (NAT+/Ag+/IgM+, IgG-, WB-)
  - 19 Fiebig IV (NAT+/Ag+/IgM+, IgG-, WB ind)
  - 10 Fiebig V (NAT+/Ag+, IgM+, IgG+, WB+ without p31)

HIV testing in era of PrEP/ Acute HIV

• 3rd generation may be better than 4th generation assays in the setting of acute HIV on PrEP – all tests have potential to be negative despite HIV infection!!!!!

• Higher reliance of RNA for diagnosis – although often negative in this setting!

• Retest with other HIV tests if possible

• Diagnosis no longer straight forward – reflects GP41/P24 and impacts of ART

• Consider what PoCT used overseas

• Future : new POCT HIV RNA eg GeneXpert
Multiple Causes of HIV Positive Tests in PrEP Users

Rare events which need thorough investigations

- PrEP discontinuation or low adherence
- HIV-infection before PrEP initiation
- Breakthrough infection with a resistant virus
- Breakthrough infection with a susceptible virus
- False-positive HIV test

How to Manage Ambiguous HIV Test Results during PrEP

More experience needed to manage ambiguous tests results

To resolve false-positive results:
- Repeat testing, discussion between clinicians and virologists
- Seek expert opinion

PrEPline toll-free 855-448-7737 (11 am – 6 pm EST)

Continue PrEP if PrEP adherence
- Maintains protection
- Risk for resistance

Stop PrEP Reassess HIV status
- Facilitate diagnosis
- Risk of infection

Initiate ART if no PrEP adherence
- Drug-related AEs
- Confirm diagnosis

Smith DK et al OFID 2018; Stekler JD et al. OFID 2018; Saag M et al. IAS-USA 2018 guidelines JAMA 2018
Reminder of why we need PrEP innovation

25% discontinuation in PrEP and its predictors in Australia

<table>
<thead>
<tr>
<th></th>
<th>HR (95%CI)</th>
<th>aHR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16-29</td>
<td>1.82 (1.53-2.16)</td>
<td>1.73 (1.47-2.09)</td>
</tr>
<tr>
<td>30-39</td>
<td>1.41 (1.19-1.68)</td>
<td>1.39 (1.17-1.65)</td>
</tr>
<tr>
<td>40+</td>
<td>Ref</td>
<td>Ref</td>
</tr>
<tr>
<td>Trans or gender diverse</td>
<td>1.73 (1.04-2.87)</td>
<td>1.45 (0.87-2.42)</td>
</tr>
<tr>
<td>PrEP naïve at baseline</td>
<td>1.51 (1.28-1.79)</td>
<td>1.44 (1.21-1.71)</td>
</tr>
<tr>
<td>Injecting drug use</td>
<td>1.55 (1.20-2.01)</td>
<td>1.64 (1.23-2.19)</td>
</tr>
<tr>
<td>Methamphetamine use</td>
<td>1.33 (1.02-1.74)</td>
<td>1.34 (1.11-1.61)</td>
</tr>
<tr>
<td>Enrolled at clinician discretion</td>
<td>1.39 (1.09-1.79)</td>
<td>1.27 (1.04-1.59)</td>
</tr>
</tbody>
</table>

1. Three month recall
2. Reasons for enrolment not mutually exclusive
Covariates not significant at univariate level include condomless anal sex, Site type

Source: Kathleen Ryan “Results from a large Australian PrEP demonstration study: discontinuation and subsequent HIV and other sexually transmitted infection risk”
**Large HIV outbreak in rural Indiana in 2015**

- Scott County population of 15,000
  - 5 HIV cases from 2004-2013
- 11 cases identified in January 2015
  - First 3 through routine screening
  - Next 8 through contact tracing
- 181 HIV cases by November 2015
  - 88% injected extended-release oxymorphone
  - 92% co-infected with HCV
- 235 HIV cases by June 2019
  - High prevalence
    - Scott County: 1.3%
    - Austin: 7.5%

Conrad et al., MMWR 2015; Peters et al., NEJM 2016

- Multi generational
- Short half life - frequent
- Oxymorphone
- Social issues, 43% female

**Contact tracing and phylogenetic studies**

Peters et al., NEJM 2016
**Study Design, Population, Duration**

- **HPTN 078**: Enhancing Recruitment, Linkage to Care and Treatment for HIV-Infected Men Who Have Sex with Men (MSM) in the United States

<table>
<thead>
<tr>
<th>Screened population</th>
<th>Enrolled participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSM and TGW &gt;= 16 yo</td>
<td>MSM and TGW HIV+, Unsuppressed</td>
</tr>
<tr>
<td>1305</td>
<td>144</td>
</tr>
</tbody>
</table>

**Study Duration**: 12 Month Follow-up

**Deep-Chain Respondent Driven Sampling (DC-RDS)**

AND

**Direct Recruitment**

**Enhanced Case Manager Intervention**

**SOC for Linkage and Treatment**

**Health Status**

<table>
<thead>
<tr>
<th></th>
<th>DC-RDS (N=72)</th>
<th>Direct Recruitment (N=584)</th>
<th>Overall N=1305</th>
<th>Enrolled (N = 144)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Received Treatment for Substance Abuse</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>HIV Positive Suppressed Viral Load</td>
<td>147 (20)</td>
<td>116 (20)</td>
<td>263 (20)</td>
<td>20 (14)</td>
</tr>
<tr>
<td>Syphilis Co-infected with HIV</td>
<td>129 (18)</td>
<td>112 (17)</td>
<td>51 (35)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis C (Antibody Positive)</td>
<td>147 (21)</td>
<td>99 (17)</td>
<td>246 (19)</td>
<td>22 (15)</td>
</tr>
<tr>
<td>Health coverage Yes No</td>
<td>613 (85)</td>
<td>482 (83)</td>
<td>1095 (84)</td>
<td>116 (81)</td>
</tr>
</tbody>
</table>

**Majority had access to health care, most who were HIV+ were virally suppressed, High rates of HCV and syphilis**
Enhanced Case Manager (CM) Intervention

The enhanced CM intervention includes patient choice, motivational interviewing and automated phone/email/text messages.

Viral Suppression (<200) by Arm and Visit

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>CM Arm</th>
<th>SOC Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 3</td>
<td>41 (28%)</td>
<td>20 (28%)</td>
<td>21 (29%)</td>
</tr>
<tr>
<td>Month 6</td>
<td>52 (36%)</td>
<td>26 (36%)</td>
<td>26 (36%)</td>
</tr>
<tr>
<td>Month 9</td>
<td>56 (39%)</td>
<td>28 (39%)</td>
<td>28 (39%)</td>
</tr>
<tr>
<td>Month 12</td>
<td>68 (48%)</td>
<td>30 (42%)</td>
<td>38 (54%)</td>
</tr>
</tbody>
</table>

At baseline, the median viral load was 19,459 copies/mL, and at Month 12, 48% were virally suppressed, with no difference between the CM and SOC arms (OR = 0.615 [p = 0.1526, 95% CI = 0.315, 1.197]).
Key Messages

• Both DC-RDS and DR worked to find the target population
  – ~1300 MSM, mostly Black, poor and educated
• Most were HIV positive (69%) and virally suppressed (78%)
  – Most knew they were positive and successfully engaged in care
• 12% were HIV positive, but unsuppressed
  – Almost all (94%) were willing to enroll (re-engage in care)
  – The vast majority (89%) already knew their HIV+ status
• Despite access to health care, there were high levels of HCV and syphilis

why did intensive case management NOT make a difference?

conclusions

• Innovative drug delivery is close and exciting
• New drugs and new formulations for HIV and PrEP
• Greater focus on marginalised groups to enter clinical trials and populations poorly represented in ART studies
• Diagnosing HIV will be increasingly difficult