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SSHC / ASHM Journal Club

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Journal of Infectious Diseases

Dr Nicholas Comninos  RPA Sexual Health

Journal of Infectious Diseases

• Since 1904
• Oxford University Press
• Official publication of Infectious Diseases Society of America
• Impact factor: 6.273 (7/84 for Infectious Diseases)
• Editors welcome major articles and brief reports
• Microbiology, Immunology as well as Epidemiology
• Pathogenesis, diagnosis and treatment
Prevalence, Magnitude, and Correlates of HIV-1 Genital Shedding in Women on Antiretroviral Therapy.

King CC, Ellington SR, Davis NL et al

Background & Aims

- Genital secretions \( \rightarrow \) HIV transmission; Genital Viral Load (GVL) may predict m-t-c transmission independent of plasma VL

- Ongoing HIV genital shedding (HGS) can occur with cART, inconsistent study findings re role of STIs

Aim: understand prevalence & correlates of genital shedding for women overall, on cART & on cART with UD VL

Methods

- Data from 3 prospective HIV transmission studies (Partners in Prevention, Couples Observation Study, Partners PrEP study)

- 1114 HIV Infected African Women

- Plasma HIV RNA (UD=\(<40\) copies/ml) and endocervical HIV RNA (UD=\(<240\) copies/swab) samples at <6, 6-12 and >12 months
2017 Dec 19, 216(12):1534-1540

Prevalence, Magnitude, and Correlates of HIV-1 Genital Shedding in Women on Antiretroviral Therapy.

Results

- Significant correlation between plasma and genital VL.
- Genital RNA (shedding) detected at 5.8% of 1433 visits with undetectable plasma RNA & in 23.6% of visits with detectable plasma RNA.
- Where UD plasma HIV RNA, shedding rates fell over time but mean genital VL remained stable at 3.1 log copies/swab.
- Where detectable plasma HIV RNA, shedding rates did not vary over time but genital VL magnitude increased with time.
- Independent predictors of shedding if plasma RNA undetectable: higher WHO stage, genital ulcers (aOR 3.26), cervical tenderness (not STIs) (aOR 3.54).

Conclusion & Discussion

- Although not seen, women with undetectable plasma RNA may still be at some risk of transmitting, esp. if advanced disease/immunosuppression.
- HIV prevention: may be a role in addressing STIs, co-infections and HIV-related conditions.
- Explaining findings: ? incomplete penetration of cART in female genital tract / compartmentalization.

2018 Jan 15, 217; 208-212

A Prospective Study of the Incidence of Juvenile Onset Recurrent Respiratory Papillomatosis After Implementation of a National HPV Vaccination Program

Novakovic D, Cheng AL, Zurynski Y et al
A Prospective Study of the Incidence of Juvenile Onset Recurrent Respiratory Papillomatosis After Implementation of a National HPV Vaccination Program

Novakovic D, Cheng AL, Zurynski Y et al

Aims
JORRP rare but high paediatric morbidity and the need for recurrent surgery.

Australian 4-v HPV vaccine coverage rates are high

Key risk factor for JORRP: maternal genital warts at delivery.

Aimed to determine if Australian School based HPV immunisation has decreased JORRP incidence

Methods
Prospective surveillance study, 5-year period (2011-2016) after including ENT surgeons in APSU

Each JORRP case → detailed report form incl. parent & child demographics, vaccination history

Incidence rates using ABS estimated residence populations & statistical tests (Poison regression)

If reporting JORRP → offered HPV genotyping (fresh/FFPE tissue sample + sample adequacy measure)

Results

Estimated annual incidence 0.068 per 100,000
Incidence significantly declined from 1.016 per 100,000 in 2012 to 0.022 per 100,000 in 2016 (P=0.034) ie 0.614 decrease in incidence per calendar year (p<0.001)

15 new ‘suspected’ cases in the 5 year period (September 2011 -October 2015) with 11 / 15 ‘confirmed’ (histologically)
7 cases were genotyped (4 cases were HPV -6 and 3 were HPV- 11)

• 60% children were male
• 93% Australian Born (7% UK)
• 60% were first born
• 87% vaginal delivery

Median age at symptom onset = 24 months (most commonly hoarseness, stridor, dyspnoea)
Median age at diagnosis 50 months (range 0-11.5 years)

Conclusion and Discussion

1- JORRP significantly declining in Australia in the 5 year period following 4-v HPV vaccination
2- Australian incidence lower than US estimates (0.5 - 1 per 100,00 as per insurance claims databases)
Serum Albumin as a Prognostic Marker for Serious Non-AIDS Endpoints in the Strategic Timing of Antiretroviral Treatment (START) Study.

Ronit A, Sharma S, Baker JV et al

Background & Aims
- Established inverse relationship between serum albumin and range of adverse health outcomes
- Only 1 study among PLHIV (US Veterans): lowest albumin quartile (25-29) $\rightarrow$ 12 x risk of heart failure, 3 x risk vascular events
- Albumin may provide prognostic information beyond the limited value that VL and CD4 count provide
- Aimed to determine relationship between serum albumin and serious non-AIDS events and mortality, especially where CD4>500

Methods
- START study, 2009-2013. Randomized, blinded trial of early vs delayed ART therapy. N=4576 with 14312 person-years of follow up
- Primary endpoint: serious non-AIDS events: CVD (AMI,CVA,PCI/Stent), ESKD, Decompensated liver disease, non-AIDS cancer (excl BCC/SCC) or death from any of the above or any other non-AIDS/non violent/non-accidental causes.
- Multivariable Cox PH models. DAGs to select potential confounders for analysis
Serum Albumin as a Prognostic Marker for Serious Non-AIDS Endpoints in the Strategic Timing of Antiretroviral Treatment (START) Study.

Results
- In 14312 person-years, 71 participants experienced serious non-AIDS event (immed start group n=24; delayed start group n=47)
- lower Serum albumin associations: older age, African ethnicity, smoking, higher BMI, heterosexual, lower Hb, higher lipids and HIV viral load, HBV, HCV, higher urinary protein but also higher eGFR
- immediate ART initiation significantly associated with higher albumin over follow up period
- per 1g/dL increase -> adjusted HR: 0.39 (0.20-0.79, P=0.009) -> significant, independently lower risk of serious non-AIDS events

Conclusion & Discussion
Lower serum albumin levels -> higher risk of serious non-AIDS events, adjusting for CD4 count, VL and all other included factors.
- Effect size is so large that serum albumin likely to capture more than inflammatory state / immune activation.
- Serum albumin likely a cost effective, useful way to triage non-AIDS event risk, perhaps particularly in lower resource settings.
- Candidate for inclusion in risk stratification indices (not currently included).

Distinct Relapse Rates and Risk Predictors After Discontinuing Tenofovir & Entecavir Therapy
Su T, Yang H, Tseng T et al
Distinct Relapse Rates and Risk Predictors After Discontinuing Tenofovir and Entecavir Therapy

Su T, Yang H, Tseng T et al

Background & Aims

Identifying candidates for therapy discontinuation and predicting outcomes are unmet clinical needs.

Predictors of clinical and virological relapse already reported: HBV DNA level, Genotype, treatment duration and EOT sAg level.

Host genetic factors eg SNPs, HLA loci may have an impact.

Aims to determine the patterns and predictors of relapse and outcomes after NUC discontinuation.

Methods

Prospective cohort study. n=100. Enrolled and followed up patients discontinuing ETV or TDF.

Follow up: (ALT+HBV DNA): 1 month, 3 months and 3 monthly to 2 years.

Endpoint:

• eAg loss or seroconversion (eAg→eAb)
• Undetectable HBV DNA >12 months

Results

Significantly earlier virological and clinical relapse among those discontinuing TDF.

3 and 6 month cumulative V & C relapse rates significantly higher in TDF group, shorter time to V relapse.

12 month sustained clinical response rate not significantly different (TDF V ETV discontinuers).

Overall second year relapse was significantly lower than first year relapse.

Significant independent predictors of:

Virological relapse: 4 wk DNA (>ALT), TDF cessation, EOT sAg (>200 IU/ml), CTLA4 non-GG genotype.

Clinical relapse: EOT sAg level (>200 IU/ml) and CTLA4 non-GG genotype.

Sustained clinical response: 4 week DNA, eAg positivity, lower sAg levels, HLA DPA1 AA genotype.

Distinct Relapse Rates and Risk Predictors After Discontinuing Tenofovir and Entecavir Therapy

Su T, Yang H, Tseng T et al

Conclusion:

Despite 3 years of NUC with >2 years of consolidation, VR and CR not uncommon

TDF cessation (cf ETV cessation ) may pose a higher risk of V and C relapse

V and CR risk: 4 week HBV DNA level, EOT sAg level may serve as early predictors or warnings

CTLA4 GG predicts VR and CR whereas HLA DPA1 non-GG predicts SCR

More research needed as to optimal consolidation periods, other genomic / genetic predictors of relapse

2018 Mar 28, 217(8):1184-1192

Interferon Treatment Duration in Patients With Chronic Delta Hepatitis and its Effect on the Natural Course of the Disease.

Yurdaydin C, Keskin O, Kalkan Ç et al
Interferon Treatment Duration in Patients With Chronic Delta Hepatitis and its Effect on the Natural Course of the Disease.

Yurdaydin C, Keskin O, Kalkan Ç et al

Background & Aims

Interferon is the only treatment available for chronic delta hepatitis (CDH) and has limited efficacy in some 12 month treatment confers virologic response 6 months after EOT in 25-30% of individuals

Unknown if extended treatment (2 years) confers additional benefit

Aimed to explore effect of IFN duration on HDV viral response and Hep B sAg clearance and determine predictors of treatment response

Methods

Retrospective cohort study, 18yr period
n=99/333 IFN naïve CDH: 99 patients who received IFN (at clinician's discretion) >/=6 months (+/- NUC) and f/up Those discontinuing <6 months excluded. One who discontinued at 6 months (side effects) was included
excluded HCV and HIV co-infection, acute delta hepatitis, HCC (incident) and those lacking baseline data or lost to f/up

Primary outcome: maintained virologic response ‘MVR’ (negative HDV RNA for 2 or more years after EOT)
2-6 month interval follow up during IFN and post EOT Cirrhotic status documented (histological &/or clinical)

Results

Mean age=40, 70% were male. Cumulative median Rx duration=24 months. Cirrhosis in 19% overall

MVR/Virological response in 35% (similar in IFN alone VS IFN + NUC), 16% after 6-12 months Rx

Cumulative probability of MVR increased with treatment duration:
27% at 3 years IFN Rx duration, 50% at 5 years and 75% at more than 5 years

Predictors of MVR after adjustment: lower baseline HBsAg level, higher baseline platelet count
MVR: tended (P=0.52) not to develop HCC, significantly less likely to die, decompensate, need liver transplant
MVR was the only independent predictor of HBsAg clearance (OR 14.3, 95% CI 1.72-142) 33% at 10 years

Conclusion:
MVR to IFN treatment may favourably affect CDH natural history and confer prospect of HBsAg clearance

Certain factors (baseline platelet count, HBsAg level) may predict MVR

New treatments are urgently needed
Anti-Human Immunodeficiency Virus Antibodies in the Cerebrospinal Fluid: Evidence of Early Treatment Impact on Central Nervous System Reservoir?

Burbelo PD, Price RW, Hagberg L et al

Background & Aims
Antibody levels (serum, CSF) may reflect chronic antigen stimulation and immune system activation

Aim: Compare HIV-1 Ab levels in serum & CSF among uninfected & infected subjects (early HIV, chronic HIV on ART, untreated HIV)

Hypotheses:
- That CSF antibody levels serve as a parallel index of active CNS infection during early and chronic infection and of persistent CNS infection whilst on ART
- That the emergence of CNS antibodies early in HIV infection allows an assessment of CNS reservoir compared with the periphery

Methods
Retrospective study-cross sectional design using archived samples University clinic sites: Wisconsin, California and Gothenburg Sweden

Samples from 45 individuals (included 12 uninfected volunteers as controls)

33 with HIV included:
- 10 with ‘Chronic HIV’ (clinical and CD4 parameters) ART treatment was initiated during chronic infection. Median Rx duration 12.5 yrs
- 22 with ‘Early HIV’ (diagnosed 20-132 days of exposure)
- 8 were treated within 3 weeks of diagnosis
- 10 were untreated
- 1 was the ‘Berlin patient’. Sampled 4 years after stem cell transplantation as a comparative benchmark for functional cure
Anti-Human Immunodeficiency Virus Antibodies in the Cerebrospinal Fluid: Evidence of Early Treatment Impact on Central Nervous System Reservoir?

Results: summary

1) Chronic treated HIV: paired pre & post ART levels: modest decreases in Ab levels
   - ART conferred only a modest drop in serum HIV antibody levels, highly variable
   - ART conferred modest decline (approx. 50%) in CSF HIV antibody levels. No significant declined: antibodies to p24

2) Untreated HIV: robust and sustained increase in Ab levels over time
   - Serum Ab levels appeared at day 26-46 after infection and continued to rise to 12 months
   - CSF Ab levels appeared LATER (32-64 days after infection) and increased through 18 months to level of chronic HIV group

3) Early Treatment group: marked and durable attenuation of Ab levels
   - Serum Ab levels 7-fold lower than those with chronic treated HIV after at least 240 days of infection
   - Even more marked attenuation in CSF Ab levels. Earlier the ART, greater the attenuation

Conclusions and Discussion

Serum Ab levels rise before CSF Ab levels: ?delayed CNS vs systemic activity and replication
Early ART vastly blunts the CNS Ab response
Delayed ART (ART initiated in chronic HIV) → modest reductions in serum & CSF Ab levels

Natural Course of Human T-Cell Leukemia Virus Type 1 Proviral DNA Levels in Carriers During Pregnancy

Fuchi N, Miura K, Tsukiyama T et al
Background and Aims

- Infection in childhood likely a risk factor for adult T cell leukaemia, mostly via mother-to-child transmission through breast milk (breastfeeding not advised)
- Proviral DNA may be linked to infectivity and mother to child transmission
- Natural history of HTLV-1 in pregnancy poorly understood. It is unclear how pregnancy impacts on DNA level and how HTLV-1 affects the immune system in pregnancy
- A subset of regulatory T cells (Tregs) maintain maternal tolerance to the foetus but HTLV-1 is frequently detectable in these cells.

Aimed to examine changes in sequential proviral DNA levels in pregnant HTLV-1 carriers in Japan
Aimed to examine changes in specific subset of Tregs both infected with HTLV-1 and responsible for foetal tolerance

Methods

Prospective, longitudinal cohort study over 2 years (2013-2015) Nagasaki prefecture hospital and regional clinics
36 known HTLV-1 positive antenatal carriers and 17 HTLV-1 negative antenatal attendees

DNA levels and flow cytometry for Tregs [CD4+; CD25+; CD127(low)] at: 1st trimester (10-12/40); 2nd trimester (22-24/40); 3rd trimester (34-36/40) and 1 month post-partum

Results: summary

Huge variation individual antenatal proviral DNA levels, so individuals classified as ‘high (50%)’ and ‘low (50%)’ DNA levels

**Proviral DNA:**
- Over course of pregnancy: no significant differences between intra-subject proviral DNA levels for high and low groups
  - At 1 month post partum: significantly higher proviral DNA for high and low groups compared to pregnancy levels

**Tregs (median percentage):**
- Over course of pregnancy: no significant differences in Treg population (%) between HTLV-1 positive and HTLV-1 negative women
- Over course of pregnancy: no significant intra-subject changes in Treg population (%) regardless of HTLV-1 status
  - At 1 month post partum: significantly higher Treg population (%) in HTLV-1 positive compared with HTLV-1 negative women

Conclusion

Regardless of individual proviral DNA level, levels plateau during pregnancy and are elevated at 1 month after delivery

Although Treg (%) populations do not appear to change during pregnancy, HTLV-1 carriers have significantly higher Treg (%) populations than their HTLV-1 uninfected counterparts at 1 month after delivery
The Female Genital Tract Microbiome Is Associated With Vaginal Antiretroviral Drug Concentrations in Human Immunodeficiency Virus-Infected Women on Antiretroviral Therapy.

Donahue Carlson R, Sheth AN, Read TD et al

Background & Aims

• cART concentrations in female genital tract not well characterized. Depends upon myriad host and drug specific factors

• Implication for biomedical HIV prevention in women:
  – CAPRISA 004 study South Africa: TFV 1% vaginal gel for PrEP: Female genital tract TFV concentrations varied widely
  – In vitro study: Gardnerella may metabolize TFV

• To examine the relationship between the vaginal microbiome and antiretroviral therapy concentrations in the female genital tract

• Hypothesis: the ability of cART to concentrate within the female genital tract varies according to microbiome community type and by cART type, with increased genital concentrations in Lactobacillus-dominated community types.
The Female Genital Tract Microbiome Is Associated With Vaginal Antiretroviral Drug Concentrations in Human Immunodeficiency Virus-Infected Women on Antiretroviral Therapy.

Donahue Carlson R, Sheth AN, Read TD et al

Microbiome ‘types’ in the study

Low Diversity Microbiome
Lactobacilli 96%

Intermediate Diversity Microbiome
Lactobacilli 50%
Other species, none dominant

High Diversity Microbiome
Lactobacilli 1%
Prevotella, Megaspера, Shuttleworthia
‘Altered flora’
The Female Genital Tract Microbiome Is Associated With Vaginal Antiretroviral Drug Concentrations in Human Immunodeficiency Virus-Infected Women on Antiretroviral Therapy.

Methods
Prospective cohort study, single centre, ethics approval and individual informed consent

20 virologically suppressed (RNA <75c/ml) predominantly African American women (on TDF/F+ATV/rt and on any cART for at least 6 months).

Regular menstrual cycles, no STIs/symptomatic BV/pregnancy or genital lesions (pelvic exam, swabs), no interacting medicines

Trough-timed plasma and genital samples at 6 biweekly visits over one menstrual cycle

Cervico-vaginal lavage ‘Pellets’ from which DNA could be extracted: 16S RNA gene sequencing for microbiome community type according to bacterial taxa

CVL pellets also detected WBC, RBC and Semen presence and allowed for Gram Stain and Nugent Score

Blood tests (oestradiol and progesterone) to characterize follicular and luteal phases or class cycle as ‘anovulatory’

Primary predictor: microbiome community type: low, intermediate & high diversity (→Megasphaera, Prevotella, Shuttleworthia, min Lacto)

Others predictors: age, abiotic use <30 days, BMI, genital tract RBC/WBC, serum E/P level etc)

Primary Outcome: ART concentration (log-transformed)

Results
90% had CD4 count/>= 200 x 10^7, 95% were not on hormonal contraception
Nugent>7 BV was common

57% overall, 9.1% in low diversity microbiome type
67.9% in intermediate diversity microbiome type
91.9% in high diversity microbiome type

Relative abundance of Gardnerellaspp was uncommon (0.8%, 2.68% and 0.44% in low, intermediate and high diversity microbiome community types respectively)

BMI significantly associated with intermediate diversity microbiome community type.
No other secondary predictors associated with microbiome community type

Multivariate models:
FTC: no significant differences in FGT ART concentration of genital:plasma ratios by microbiome community type group but ‘trend toward’ lower ATV concentrations in high diversity microbiome Community Type (p=0.051)

TFV: significantly higher genital ART concentration AND genital:plasma ratio for intermediate microbiome community type compared with high and low diversity types (similar values for latter two types)

ATV: No significant difference in genital ART concentration BUT borderline-significantly higher genital:plasma ratio for intermediate microbiome community type compared with high and low diversity types.
The Female Genital Tract Microbiome Is Associated With Vaginal Antiretroviral Drug Concentrations in Human Immunodeficiency Virus-Infected Women on Antiretroviral Therapy.

Conclusion & Discussion

After adjusting for known and potential confounders:

Genital:plasma ratios for TFV & ATV were lower in low diversity & high diversity microbiome community types than in intermediate diversity microbiome community type

Important implications for biomedical prevention in women including:

• PrEP
• PEP
• Mother to child transmission
• TasP in settings of suboptimal adherence / ongoing viraemia

Critical Appraisal

Strengths

• First study to examine this question
• Fascinating, understudied area
• Knowledge may guide prevention strategies and efforts
• In many ways more practically useful than an in vitro study
• Adds to a body of knowledge about HIV and the vaginal microbiome
Critical Appraisal

Explaining the study findings:

Genital pH changes: known phenomenon of ‘ion trapping’ where strongly basic (pKa) lipid soluble drugs (TDF, ATV) achieve higher concentrations in acidic environments. The opposite holds for strongly acidic (pKa) drugs (FTC)

Supported by the fact that high diversity microbiome types are likely more alkaline (91.9% had BV by Nugent criteria) but lower [TFV] & [ATV]

BUT...

1. What about low diversity microbiomes? These likely had a lower pH (more acidic) but also had lower [ATV] & [TFV] than intermediate diversity microbiomes! (pH values of microbiome types were not reported!!!)

And

2. Study did not find that FTC was lower in low diversity microbiome community Type or higher in high diversity microbiome community type as one may expect with ‘ion trapping’.

Authors:

- Microbial strains in some microbiome types may inactivate or degrade ART? More research needed
- Transport mechanisms into the female genital tract varying by pH-dependent and pH-independent factors? More study

Confounding?

Unmeasured BV risk factors:

Smoking status was not measured or recorded
Socioeconomic status was not recorded

Unmeasured factors potentially impacting on altered microbiome community type

Diet
Diabetes / other conditions associated with immunosuppression
Critical Appraisal

Other limitations:

- n=20
- Not truly a prospective study-used stored specimens from a parent study cohort
- TDF/F+ATV less used in developed countries
- With outcome: unclear whether genital tract:plasma ratios or mean genital tract [ART] are more useful
- Technology advanced: difficult to replicate or translate to other settings (e.g., Sub-Saharan Africa)
- Generalizability: African American women, single centre East Coast USA
  - Higher incidence of BV.
- All participants reported consistent adherence but not clear on details: impact of inconsistent adherence?
  - Could differences in genital [cART] reflect varying adherence, despite plasma VL<75c/ml?
  - Less likely if cART truly does achieve higher genital [cART] than plasma [cART]?

Thank you 😊

Questions and discussion
SEXOLOGY

A generic term encompassing the scientific study of all aspects of human sexuality.

SEXUAL HEALTH

Sexual health is a state of physical, emotional, mental and social well-being in relation to sexuality; it is not merely the absence of disease, dysfunction or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships, as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected and fulfilled.

(WHO, 2010)
SEXUALITY

Sexuality is a central aspect of being human throughout life and encompasses sex, gender identities and roles, sexual orientation, eroticism, pleasure, intimacy and reproduction. Sexuality is experienced and expressed in thoughts, fantasies, desires, beliefs, attitudes, values, behaviours, practices, roles and relationships. While sexuality can include all of these dimensions, not all of them are always experienced or expressed. Sexuality is influenced by the interaction of biological, psychological, social, economic, political, cultural, ethical, legal, historical, religious and spiritual factors.

PSYCHOSEXUAL THERAPY

SILOS (AND IMPERIALISM)
EX-PLISSIT

- Explicit
- Permission
- Limited Information
- Specific Suggestion/s
- Intensive Therapy

PERMISSION

- Taboo topics
- Allow the client’s permission to have sexual feelings/thoughts/behaviours and relationships.
- Check your values

PERMISSION

- Asking the “right” question
  - Sexual history is more than the five Ps
    1. Partners
    2. Prevention of pregnancy
    3. Protection from STIs
    4. Practices
    5. Past history of STIs
  - Are you happy with your sex life?
  - IS everything going okay in your sex life?
LIMITED INFORMATION

- Provide **limited information**.
- Provide **accurate** information.
  - Dispel myths and correct misconceptions.

SPECIFIC SUGGESTIONS

- Provide **specific suggestions** to assist the client/s with their issues.
- Specific suggestions can include techniques, strategies and coaching.

POSTGRADUATE PROGRAM IN SEXUAL & REPRODUCTIVE HEALTH @ USyd

- Masters/Grad Dip/Grad Cert/Single Units
- Medicine or Science in Medicine
- Four Pathways
  1. STIs & HIV
  2. Psychosexual Therapy
  3. Reproductive Health and Fertility
  4. Public Health