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Journal of AIDS

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Health**

Topic: *DBS - NSW HCV/HIV Testing Pilot*

HIV/Sexual Health Clinical Education Session: Journal Club Journal of Acquired Immunodeficiency Syndrome

Sian Goddard, Registrar, Sydney Sexual Health

21st February 2018

- “Seeks to end the HIV epidemic by presenting important new science across all disciplines that advance our understanding of the biology, treatment and prevention of HIV infection worldwide”
- Monthly publication
- Impact factor 2015: 3.28

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JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROME

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Full Text
OVID

Wolters Kluwer

People born in non-main English speaking countries are less likely to start HIV treatment early in Australia: A national cohort analysis, 2014-15

Gunaratnam P et al on behalf of ACCESS collaboration

(J Acquir Immune Defic Syndr 2017; 77 (4) ; e31)

- **Aim:**
 - Estimate the proportion of patients born in non-main English speaking countries, newly diagnosed with HIV in Australian sexual health clinics, who initiated treatment 6 months after diagnosis, compared with other patients.
- **Methods:**
 - Data from ACCESS network (NSW/WA, Victoria, Queensland and NT).
 - South Africa was included with non-main English speaking countries. English speaking countries included Australia, UK, NZ, Canada, US.
 - HIV diagnoses between Jan 2014 and end-June 2015
- **Results:**
 - 290 people (104 born in non-main English speaking countries; more likely to be younger/female/live in cities/be heterosexual/lower CD4).
 - Treatment at 6 months: 44.2% of people born in non-main English speaking countries, compared to 58.6% for those born in English speaking countries ($p=0.011$)
 - Multivariate analysis adjusted for CD4 count and MSM status: patients born in non-English speaking countries were 47% less likely to have initiated treatment by 6 months (41% less likely if MSM)
- **Conclusion:**
 - Birth in a non-main English speaking country is a barrier to early initiation of HIV ART
 - Authors believe stigma, visa concerns, linguistic barriers, low levels of knowledge re Australian healthcare system, indirect costs may be contributory factors, less so access to ART given PBS subsidy and compassionate access schemes.
 - We must work to reduce financial barriers, increase health literacy, communicate in a culturally and linguistically appropriate way

Bone mineral density declines twice as quickly in HIV-infected women compared with men

Erlandson et al (J Acquir Immune Defic Syndr 2017; 77 (3); 288-294)

- **Background/Aim:**

- HIV positive individuals have an increased fracture risk. Nearly all ART initiation trials demonstrate decline in bone mineral density (BMD), but most studies in men
- Aim to compare long term changes in BMD in cohort of HIV positive men and women and determine sex specific factors

- **Method**

- Retrospective analysis of patients attending an HIV metabolic clinic in Italy from 2004. DEXA scans every 6 months
- Multivariate modelling with many co-variates. Excluded those taking a bisphosphonate

- **Results**

- 839 women and 1759 men, 82% less than 50 years old, all caucasian
- $\frac{3}{4}$ virologically suppressed.
- Nearly 1/3 HCV co-infected
- Median 6.7 year follow up
- Femoral (not lumbar) BMD significantly lower in women than men
- Associations with lower femoral neck BMD: longer TDF exposure, age 46 +, no physical activity, hypogonadism, post-menopausal, vitamin D insufficiency, HCV. Longer duration of integrase inhibitor/higher BMI associated with higher BMD
- Rate of decline significantly higher in women than men

- **Conclusion**

- Age associated change in BMD most pronounced after age 45 – screening from age 50
- Integrase inhibitors appear protective
- HCV equivalent to 5 years of aging

Incidence of Tuberculosis among HIV positive individuals initiating ART at higher CD4 counts in the HPTN 071 (PopART) Trial in South Africa

Bock et al. (J Acquir Immune Defic Syndr 2017; 77 (1); 93-101)

- **Background/Aim:**

- Prevalence of TB at ART initiation is higher with lower CD4 counts
- RCTs have demonstrated lower TB incidence if ART started when CD4>500
- Aim to define incidence of TB in routine care setting

- **Methods:**

- Retrospective. Age 18 years+. Starting ART between Jan 2014-Nov 2015. Follow-up until May 2016
- 3 Primary health care clinics in Western Cape South Africa. Antenatal HIV prevalence 14-20%. TB incidence 596-880/100,000
- PopART trial: community random allocation to testing and care of HIV/TB and STIs
- Censored if TB, death, lost to follow-up

- **Results:**

- 2423 people started ART Jan 14- Nov 15. Mean baseline CD4 328. 68% women.
- 12% diagnosed with TB at baseline (5% if CD4 >500)
- Incidence of TB decreased with increasing CD4 count – 9.6/100 PY if CD4 0-200, 1.26/100PY if CD4 >500.
- Hazard ration 0.27 (95% CI 0.12-0.62) comparing those with CD4>500 and CD4<500

- **Conclusion:**

- TB incidence lower among those starting ART at CD4>500. Scale up ART can reduce TB incidence, in addition to general TB prevention strategies

Newly acquired infection with multi-drug resistant HIV-1 in a patient adherent to PrEP

Markowitz et al. (J Acquir Immune Defic Syndr 2017; 76 (4); e104-e106)

- Case report
- 26 year old MSM
- HIV serodiscordant relationship: partner VL undetectable for 4 years
- Condomless RAI with partner and condomless IAI with others
- Circumcised
- Negative HIV test in 2013, March 2015, 18th December 2015
- Prescribed PrEP 18th December 2015
- Started PrEP Jan 1 2016

TABLE 1. Summary of Pertinent Laboratory Results

Test	December 18, 2015	May 3, 2016	May 17, 2016	June 7, 2016	June 9, 2016
Fourth-generation HIV Combo Ag/Ab assay	Nonreactive	Reactive	Reactive		Reactive
HIV nucleic acid amplification assay (qualitative)		Reactive	Reactive		Nonreactive
Multispot HIV-1/2		Nonreactive	Nonreactive		Nonreactive
Roche Cobas TaqMan HIV-1 Test v2.0 (copies/mL)	<20 no signal detected	ND	<20 signal detected		<20 no signal detected
CD4 ⁺ T-cell count (cells/mm ³)			1123		
CD4/CD8 ratio			1.53		
TFV-DP level in DBS (fmol/punch)				1478*	
TFV-DP level in hair (ng/mg)				0.0448*	
Genosure Archive test				Failed	
Genotype of RT from patient proviral DNA					K65R and M184V; K103S, E138Q, and Y188L

*Consistent with daily dosing.

ND, not done; RT, reverse transcriptase.

- Dolutegravir added May 26 2016
- Reported excellent adherence: Hair and DBS on June 7th confirmed daily adherence over preceding 6-8 weeks
- Genotyping: mutations at K65R, M184V – resistance conferring mutations to TDF and FTC, plus other mutations to NNRTI: therefore multi-drug resistant virus
- Cobicistat-boosted darunavir added

Conclusion:

- Multispot HV1/2 remained negative. Delayed seroconversion previously reported in when combination ART given in acute infection/repeated courses of PEP. Critical to use sensitive HIV tests with PrEP
- Testing with low viral load burden complicates testing efficacy
- Rare event: 2 cases of MDR HIV-1 and one wild type through CAI in USA, where 86000 using PrEP.
- Unknown efficacy if virus resistant to TDF and FTC. Need surveillance of resistance among people becoming HIV positive after taking PrEP

Acute alcohol consumption directly increases HIV transmission risk: A randomised controlled experiment

Shuper et al (J Acquir Immune Defic Syndr 2017; 76 (5); 493-500)

- **Background:**

- Cross-sectional studies suggest less condom use if alcohol intoxication, but causal nature of alcohol-condomless sex association not known. ? Risk relevant traits that underly alcohol consumption and condomless sex.
- Aim: assess the impact of acute alcohol consumption on condomless sex intention in MSM

- **Method:**

- Random allocation to body weight specified dose of alcohol, placebo alcohol or water.
- Randomly presented with video clips to induce either moderate sexual arousal or no sexual arousal.
- Asked to report intentions to engage in sexual acts +/- condom with hypothetical partners.
- Recruited from a clinic in Toronto Canada providing care for HIVP and MSM, Feb 2012 to March 2015.
- Included if 19 years or older, anal sex with a man in last 6 months, consumed ≥ 5 drinks per week on average and ≥ 5 drinks in one episode in last 6 months, no hx of alcohol/substance misuse in last 5 years, no medical contraindication to alcohol
- Target BAC 0.080%. If assigned to etoh: 0.7g alcohol/kg body weight of 1:3 vodka tonic. Placebo: flat/normal tonic mix with small amount of vodka floated on top/rubbed around glass rim (target BAC 0.000%). Or water. 15 minutes to drink, 13 minute absorption period.
- Shown 2 video clips with either sexual/non sexual content
- Shown 18 hypothetical partners – picture, text with HIV serostatus and condom use preference. Participants reported intention to engage in condom or condomless sex with each partners
- Paid \$50 and \$15 per hour to detox!

Acute alcohol consumption directly increases HIV transmission risk: A randomised controlled experiment

Shuper et al (J Acquir Immune Defic Syndr 2017; 76 (5); 493-500)

• Results

- 283 participants – mean age 42.6, majority white/college educated/employed. $\frac{3}{4}$ reported condomless sex in last 6 months, $\frac{1}{3}$ reported serodiscordant condomless sex. For HIV positive participants: 85% on art
- Significantly stronger intention to engage in condomless sex if given alcohol.
- HIV positive participants indicated significantly stronger condomless sex intention than HIV negative participants
- The effect of alcohol on condomless sex intentions was similar for HIV positive and HIV negative participants
- Participants scoring higher on sexual sensation seeking, compulsivity and sex related alcohol expectancies reported stronger intention to engage in condomless sex, but the impact of alcohol on condomless sex intention was not moderated by these factors.
- The impact of alcohol was consistent, regardless of level of sexual arousal
- Suggest smartphones might be able to deliver HIV prevention messages when entering an alcohol establishment or when attaining a specified BAC!

HIV and age do not synergistically affect age-related t-cell markers

Farhadian et al (J Acquir Immune Defic Syndr 2017; 77 (3); 337-345)

Background:

- Similarities exist among T cell phenotypes in chronic HIV and aging, suggesting that HIV and aging act synergistically on the immune system. Does HIV accelerate the process of immune aging? Could this explain the higher prevalence of inflammatory non-AIDS defining conditions?
- Aim to explore impact of HIV and age on t-cell immune phenotypes

Methods:

- Cross-sectional analysis of men in Veterans Aging Cohort Study. Longitudinal, prospective multisite observational study of HIV infected veterans seen in ID clinics and site-matched uninfected controls from general medicine clinics between 2005 and 2007
- Included if: HIV positive 3+ years before initiation of ART, t-cell nadir<350, VL<400 twice a year for 3+ years and no VL >1000 in 3+ years.
- Uninfected matched by age, alcohol and smoking. Excluded if other reasons for immunosuppression

Results:

- Median age 55. 111 HIV positive, 114 HIV negative (median nadir 167)
- After adjusting for race/ethnicity/smoking/alcohol, each 10 year increase in age saw proportion of naïve CD8 T cells decrease by 6.3% and the proportion of CD4 T cells decrease by 2.7%.
- HIV infection did not have a significant effect on either.
- Age associated a rise in proportion of effector memory cells.
- No effect of age on levels of activated CD4 or CD8 t cells.
- Proportion of activated CD8 cells was 1.4x higher in HIV infected compared with controls.
- For each t cell phenotype measure, there was no significant interaction between age and HIV infection

Conclusion:

- No significant interaction between HIV and age in their effect on any of the T-cell phenotypes examined
- No evidence of increased rate of aging of the adaptive immune system among virally suppressed HIV infected individuals.
- Both age and HIV associated with progression from naïve to mature t cell phenotypes and HIV also associated with t cell activation

Effect of immediate initiation of anti-retroviral therapy in HIV-positive individuals aged 50 years or older

Lodi et al. (J Acquir Immune Defic Sydr 2017; 76 (1); 311-318)

- **Background:**

- Recommended immediate initiation of combined ART for all HIV positive individuals
- But mainly young participants in trials
- Increasing number of people diagnosed at older age
- Higher risk of co-morbidities and polypharmacy in older people

- **Methods:**

- Included: HIV positive, ART naïve, AIDS free, age 50-70, at least one CD4 and HIV-RNA VL within 3 months, from the HIV-CAUSAL Collaboration of HIV cohorts from Europe and the Americas
- From 2005
- General population and US veterans (veterans aging cohort study) had differing background mortality.
- ART defined as triple therapy including at least 2 NRTI.
- Compared mortality (all cause and non-AIDS) if started ART within 3 months of baseline, with those commenced within 3 months of AIDS or CD4 <500 or CD4<350.

- **Results:**

- 9596 included. Median age 55 and CD4 336.
- 5 year all-cause mortality 5.3% in immediate initiation in general population; 14.4% in US vets.
- 5 year all-cause mortality 0.4% lower for general HIV population and 1.61% lower for US veterans when comparing immediate initiation vs initiation at CD4<350.
- Therefore 4-16 deaths per 1000 patients would be prevented over 5 years.
- 5 year risk of non-AIDS mortality was 0.17% lower for general HIV population and 1% lower for US veterans
- For CD4>500 in general population, all cause mortality was 2.8% if immediate ART, 3.7% if CD4<500 and 4.4% if CD4<350.
- Benefit likely higher still, as more than half of patients included had <350 cells at baseline; If only include those with >500 at baseline, 1.6% reduction in mortality if immediate versus start CD4<350.

Weight gain in persons with HIV switched from Efavirenz-based to integrase strand transfer inhibitor-based regimens

Norwood et al. (J Acquir Immune Defic Syndr 2017; 76; 527-531)

- **Background:**

- Anecdotal observation by clinicians at a large HIV clinic in Nashville of weight gain among patients switched from Atripla to Triumeq

- **Methods:**

- Retrospective observational cohort study among adults virologically suppressed for 2 years + on Atripla.
- Assessed weight change over 18 months in those switched from Atripla to an integrase inhibitor or PI, versus those that continued Atripla. Excluded if viral load ever >1000 copies during the study period.

- **Results:**

- 495 patients included.
- 136 switched from Atripla to integrase inhibitor containing regimen
- Average 2.9kg weight gain at 18 months compared with 0.9kg for those remaining on Atripla.
- 34 switched to a PI containing regimen gained 0.7Kg.
- Those switched to Triumeq gained more weight than regimens containing raltegravir/elvitegravir (5.3Kg versus 2.8kg, but not statistically significant).
- Non-statistically significant rise in HbA1C from 6.4-6.9% for integrase inhibitor regimens.

- **Conclusion:**

- Needs further research. ?Due to coming off Atripla or due to Integrase inhibitor combinations.
- Contradictory evidence in other studies.

Changes in Kidney Function Associated with Daily Tenofovir Disoproxil Fumarate/Emtricitabine for HIV PrEP in the US Demonstration Project
Tang et al (J Acquir Immune Defic Syndr 2017; 76; 527-531)

Background:

- HIV infected patients treated with Tenofovir (TDF) containing regimens have shown evidence of decline in creatinine based eGFR.
- Small clinical trials of PrEP daily use found elevations in creatinine and/or reduction in eGFR.
- iPrEs demonstrated a mean decline in creatinine clearance (CrCl) of 2.9% over 18 months of use. Predictors of CrCl<70 were age and lower CrCl at baseline,. But this was a clinical trial and not a 'real world setting' with co-morbidities/diversity.
- The aim was to provide safety information and identify potential risk factors for the development of kidney impairment in the real world setting of expanding PrEP roll-out

Method

- Participants enrolled in US PrEP Demonstration Project
- HIV negative at risk MSM and TW
- 2 STD clinics in San Francisco and Miami; Community Health Centre in Washington DC.
- Eligible if creatinine clearance >60 mL/min and urine dipstick negative or trace for protein
- Given 48 weeks of TDF/FTC for daily PrEP
- Serum creatinine and urine protein dipstick every 12 weeks
- Subset of participants underwent dried blood spot testing to determine adherence

Statistics

- Clinically significant change in creatinine defined as $>0.2\text{mg/dL}$ and creatinine clearance $>25\%$
- eGFR calculated using Chronic Kidney Disease Epidemiology Collaboration equation
- Regression model to establish mean change from baseline creatinine/CrCl at each follow-up visit
- End-points: CrCl <60 and <70
- Univariate logistic regression to identify correlates of incident eGFR <70 (including enrolment site, age, race/ethnicity, DM, HTN (self report and/or BP $>140/90$ in clinic), use of diabetic or antihypertensive medications, NSAIDs, recreational drugs, baseline CrCl/eGFR).
- Multivariate logistic regression for co-variables with $p<0.10$
- Additional univariate analysis of drug levels in dried blood spot as predictors of eGFR <70 and CrCl
- Worsening proteinuria defined as increase from baseline value.
- Correlated worsening proteinuria with change in creatinine and CrCl (Kruskal-Wallis test)
- Correlate drug level with worsening proteinuria (Fisher's exact)

Results

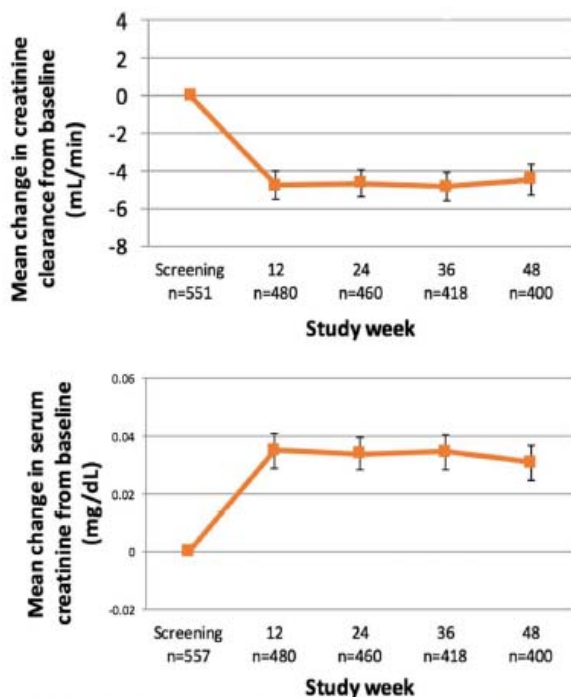
- October 2012 – January 2014
- 557 MSM and TW enrolled
- Median age 33 (range 18-65)
- No participant with CrCl<70 at baseline

TABLE 1. Baseline Characteristics of Cohort of All Participants Enrolled in Study

Participant Characteristics at Baseline (N = 557)	N or Median (% or IQR)
Study Site	
San Francisco	300 (53.9%)
Miami	157 (28.2%)
Washington, DC	100 (18.0%)
Age, yr	
18–29	205 (36.8%)
30–39	181 (32.5%)
40+	171 (30.7%)
Gender	
Male	548 (98.4%)
Transgender women	7 (1.3%)
Other	2 (0.4%)
Race/ethnicity	
White	266 (47.8%)
Latino	192 (34.5%)
Black/African-American	40 (7.2%)
Asian	26 (4.7%)
Other	32 (5.8%)
Hypertension	
No	494 (88.7%)
Yes	63 (11.3%)
Diabetes mellitus	
No	548 (98.4%)
Yes	9 (1.6%)
Antihypertensive or diabetic medication use	
No	520 (93.4%)
Yes	37 (6.6%)
Recreational drug use	
No	133 (26.7%)
Yes	366 (73.4%)
Nonsteroidal anti-inflammatory drug use	
No	480 (86.2%)
Yes	77 (13.8%)
Weight (kg)	76 (70–88)
Baseline serum creatinine, mg/dL	0.92 (0.83–1.01)
Baseline CrCl, mL/min	124 (108–144)
≥90	504 (91.5%)
≥70–<90	47 (8.5%)
Baseline eGFR, mL/min/1.73 m ²	108 (96–119)
≥90	463 (83.1%)
≥70–<90	85 (15.3%)
≥60–<70	7 (1.3%)
<60	2 (0.4%)

CrCl, creatinine clearance, calculated using the Cockcroft-Gault equation; eGFR,

Creatinine clearance



- Mean creatinine increased baseline to week 12 by 0.03mg/dL (95% CI 0.02-0.05, $p < 0.0001$) (4.6%) (2.65 micromols/L)
- Creatinine clearance decreased by 4.8 mL/min (95% CI 3.3-6.3, $p < 0.0001$) (3.0%)
- Both stable from week 12 to 48
- 94/499 (18.8%) of participants had an increase of >0.2 mg/dL (=17.7 micromol/L), with 18 confirmed on subsequent testing
- 31/499 (6.2%) had a $>25\%$ loss of CrCl from baseline ->25/31 with repeat testing -> 6 confirmed and 1 persisted until 48 weeks
- 10/499 (2%) had CrCl <70 during study, but using eGFR (25, 5.1%) and 11 persisted on repeat testing

FIGURE 1. Mean change in creatinine clearance (top panel) and serum creatinine (bottom panel) from baseline to 48 weeks in a demonstration project of HIV preexposure prophylaxis among men who have sex with men using daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Number of participants with available data at each study visit is represented by n. Bars represent standard errors. Results were similar when including only participants who returned for all 4 quarterly follow-up visits.

Predictors of eGFR <70 mL/min/1.73m²

- Univariate logistic regression:
 - Age 40+ (P=0.0001)
 - Use of NSAIDs (P=0.027)
 - Recreational drugs (P=0.028)
 - Baseline eGFR <90 (p<0.0001)
 - Increasing weight (p=0.07)
 - TFV-DP level (P trend 0.40)
 - No association with site/ethnicity/HTN/antihypertensive drugs/anti DM drugs)
- Multivariate logistic regression :
 - Age 40+ (OR 3.79, 1.43-10.03)
 - Baseline eGFR <90 (OR 9.59, 3.69-24.94)
- Only 2 people with age <40 and eGFR>90 had a fall to CrCL<70, and not sustained

TDF levels

- 294 participants had 1+ TFV drug level
- Mean change in CrCl from baseline to week 12:
 - +5.0mL/min (+5.6%) (<2 doses/week)
 - -4.4 ml/min (-3.1%) (2-3/week)
 - -6.1 mL/min (-4.1%) (4-7/week i.e. 82% of those tested)
- Statistically significant difference between CrCl at week 12 with those taking 4-7 doses versus <2 (P=0.011), but not 2-3doses (P=0.64)

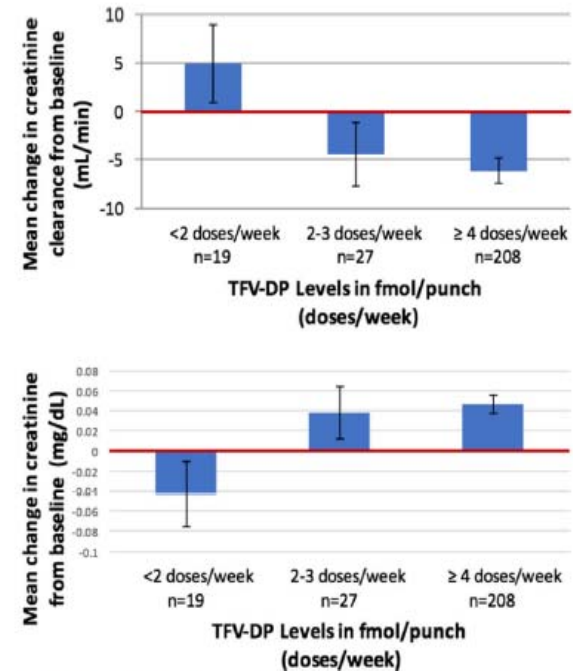


FIGURE 2. Mean change in creatinine clearance (top panel) and serum creatinine (bottom panel) from baseline to week 12 by tenofovir disoproxil level (TFV-DP) in dried blood spots among men who have sex with men in a demonstration project of HIV preexposure prophylaxis using daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Number of participants in each category is represented by n. Bars represent standard errors.

Proteinuria

- 75/478 (15.7%) had worsening proteinuria at week 12 compared with baseline ($P < 0.0001$)
- 49.3% had the finding confirmed at next visit
- Percentage remained stable through week 48
- No association of proteinuria with co-variates
- People with proteinuria had larger increases in creatinine (decrease CrCl 8.9 vs 3.6 mL/min, $P = 0.009$)
- Higher TFV-DP levels associated with proteinuria ($P = 0.03$)
- 2 incidents of 4+ proteinuria, but trace on rpt testing

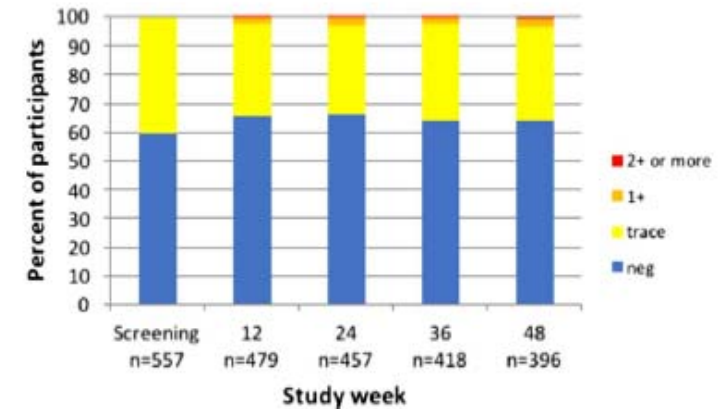


FIGURE 3. Urine protein level from results of urine dipstick by study week among men who have sex with men in a demonstration project of preexposure prophylaxis using daily oral tenofovir disoproxil fumarate/emtricitabine (TDF/FTC). Number of participants in each category is represented by n. Results were similar when including only participants who returned for all 4 quarterly follow-up visits.

Discussion

- Confirms previous study findings of small but statistically significant increase in creatinine/decrease in CrCl after starting PrEP
- Changes stabilise after 12 weeks
- Higher blood levels of TDF had larger elevation in creatinine
- Age 40+ and/or eGFR<90 risk factors for reaching threshold of kidney impairment
- Recommends 6 monthly screening, but more frequent if risk factors
- No additional benefit to monitoring protein if monitoring CrCl
- Unclear clinical significance of small creatinine increases
- Other PrEP trials showed reversibility
- Likely tubular damage rather than glomerular if acute and stabilises, and reversible

Critical appraisal

Study population:

- Appropriate. Cohort study. No placebo group, but RCT not ethical
- No explanation for results presented for 499 people when 557 recruited
- 400 participants at week 48: Why did people drop out? What were the characteristics? Did people with increased creatinine/proteinuria disproportionately drop -out?
- What were the duration/severity of co-morbidities
- Frequency of NSAIDS
- No mention of personal history of renal impairment/other medications, including over the counter medications/supplements
- No measure of types /frequency of recreational drug use

Measurement:

- Definition of clinically significant change in renal function
- Only dipstick for proteinuria and trace proteinuria included
- Worsening proteinuria not stratified by severity
- Diurnal variation of proteinuria not mentioned – instructions regarding exercise

Critical appraisal

Interpretation:

- ?normal fluctuations of proteinuria – did some people actually have underlying renal impairment missed at baseline? Only one measurement prior to starting PrEP.
- What is the likely error for creatinine measurement (Creatinine clearance go up 5% in those not taking PrEP ?!)
- No presentation of sequential results
- Should have sensitivity analysis for those who exited study?
- ?Under-powered to see a difference in renal function according to adherence
- Underpowered to assess effect of PrEP on groups known to be at higher risk of kidney impairment, including co-morbidities ?also for ethnicity. No OR or confidence intervals presented for co-variables at univariate analysis
- Difficult to draw long term conclusions with only 48 weeks follow-up. No discussion re discrepancy between frequency of proteinuria and declining CrCl