Dolutegravir with tenofovir disoproxil fumarate-emtricitabine as HIV post-exposure prophylaxis in gay and bisexual men

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Introduction

- Antiretroviral drugs as HIV nonoccupational postexposure prophylaxis (NPEP) is recommended by the World Health Organisation[1]
- Up to one-third of gay or bisexual men (GBM) do not complete 28 days of NPEP[2]
- Adverse events (AEs) are the likely primary cause of NPEP non-completion
- Co-formulated TDF/FTC (Truvada; TVD) is the preferred NRTI backbone for NPEP[3,4]
- Choices for a 3rd drug include PIs, integrase inhibitors, NNRTIs and entry inhibitors[5,6,7,8]
- 3-drug NPEP discontinuation
  - higher with LPVr, DRVr or MVC NPEP
  - lower with raltegravir (RAL), rilpivirine (RPV)[5,6,7,8]
- Limitations of current NPEP regimens
  - PIs: GI side-effects, drug-drug interactions and act after HIV integration[5,6]
  - RAL can cause acute muscle toxicity and twice-daily dosing is required[6]
  - RPV must be taken with food[7]
- Dolutegravir (DTG) is an attractive 3rd drug for NPEP:
  - dosed once-daily
  - potent
  - safe and well tolerated
  - relatively few drug/drug interactions
  - T_{max} 2-4 hours post-dose; and
  - mode of action pre-HIV integration[9,10]
- DTG not previously evaluated for NPEP
- We investigated the completion rate, safety and adherence to TVD + DTG as 3-drug NPEP

Methods

- Open-label, single-arm study at 3 sexual health clinics and 2 emergency departments in Australia
- One hundred HIV-uninfected GBM requiring 3-drug PEP received DTG plus TVD for 28 days
- The primary endpoint was PEP failure (premature cessation or primary HIV infection through Week 12)
- Additional endpoints were: adherence by self-report (n=98); pill count (n=55); plasma tenofovir levels (n=82); plasma DTG levels (n= 80);and safety (clinical and laboratory adverse events [AEs])
- Adherence and adverse events (laboratory & clinical) assessed at Week 1,2 and 4

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Results

Baseline characteristics

- Recruitment 1st August 2014 – 30th October 2015
- Prior NPEP 41%
  - Mean doses 1 (SD 2)
- Risk behaviour
  - receptive anal sex 82%
  - substance use 61%
  - condomless sex 70%
  - HIV+ source 40%
    - HIV RNA detectable 10%
    - HIV RNA not detectable 8%
- Time from exposure (hours)
  - to assessment 25 (IQR 14-39)
  - to 1st NPEP dose 27.5 (IQR 17-40)

Completion

468 GBM eligible for 3-drug PEP
(mean age 33, SD 9, range 18-62 years)

↓

104 GBM consented
(mean age 33, SD 10, range 17-62 years)

↓

4 GBM excluded

source tested HIV negative	2
unable to commit to study visits	1
eGFR < 60 mL/min/1.73m2	1

↓

100 GBM enrolled
(mean age 33, SD 9 range 17-62 years)

↓

Completed 28 days of NPEP n=90

Did not complete NPEP n=10
(median 9, IQR 2-16 days)

lost to follow-up	9
adverse event	1

Adherence

Self-report % (n=98)		Pill count % (n=55)		Day-28 plasma drug level ≥ inhibitory quotient (TDF ≥40ng/mL; n=82) (DTG ≥64ng/mL; n=80)	
TVD	98%	TVD	98%	TNV	85%
DTG	98%	DTG	98%	DTG	99%

measured a mean 15 (SD 8) hrs after last dose of DTG or TVD

Safety / adverse events

Clinical AEs (n=98)

- 67 (68%) reported 144 subjective AEs possibly attributable to study drug
- 98% of AEs were grade 1-2
- There were no unexpected AEs and no serious AEs
- 1 pt ceased NPEP because of grade-3 headache

Subjective AEs possibly related to NPEP occurring in ≥5%

Subjective AEs	Percent
Fatigue	26%
Nausea	25%
Diarrhoea	21%
Headache	10%
Abdominal pain/cramps	9%
Flatus	9%
Vivid dreams	7%

Laboratory AEs

Laboratory test	Grade 1 – Grade 2		Grade 3 – Grade 4	
Chemistries [n (%)]				
↑Creatinine	10/93	(11)		
Hyperglycaemia	1/91	(1)		
Hypophosphataemia	5/91	(5)		
↑Bilirubin	4/93	(4)	1/89	(1)
↑Alanine aminotransferase	22/89	(25)	1/93	(1)
↑Creatine kinase	8/92	(9)	1/92	(1)
↑Lipase	7/92	(8)	1/84	(1)
↑Amylase	7/92	(8)	1/85	(1)
Hyperlactataemia	8/91	(9)	1/89	(1)
Urinalysis [n (%)]				
Proteinuria	10/88	(11)		
Haematuria	1/88	(1)		
Glycosuria	2/88	(2)		

- No pt ceased NPEP for any lab AE
- Most common laboratory AE was raised alanine aminotransferase (25%)
  - only 1 pt had a Grade 3 or 4 ALT
  - no clinical hepatitis
  - no pt with serum bilirubin ≥2xULN had abnormal level of conjugated or unconjugated bilirubin
- Mean eGFR decrease at Day 28 was 14 mL/minBSAc (SD 17, p=0.001)
  - eGFR <60 mL occurred in 3 pts

HIV infection

- No HIV infection through Week 12

Conclusions

- **DTG + TVD were well tolerated as NPEP with high levels of completion (90%) and adherence**
  - **Rates similar to those using single-tablet NPEP with TDF-FTC-RPV**
- **Adherence 98% by self report and pill count, but only 85% had plasma tenofovir ≥40ng/mL at Day 28**

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