CUMULATIVE TENOFOVIR EXPOSURE IS ASSOCIATED WITH DECREASED BMD IN YOUNG AND OLD HIV-INFECTED ADULTS ON TENOFOVIR BASED REGIMENS

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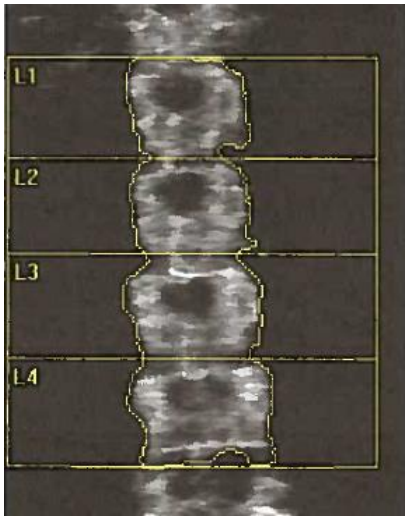
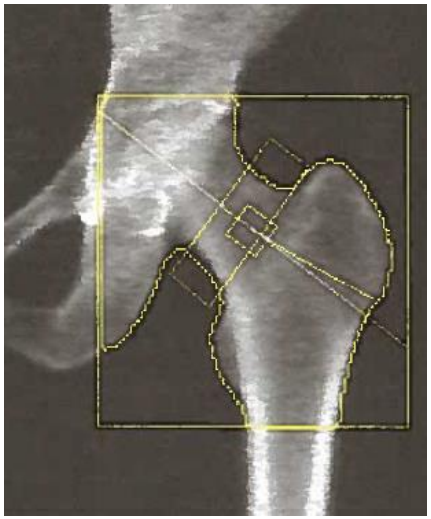
TDF and BMD

- In ART-naive HIV-infected adults BMD decreases roughly 4-6% during the first year of ART
- Use of TDF is responsible for 1-3% greater BMD loss compared to other antiretrovirals
- Effect may be worse when TDF is used with a boosted PI, suggesting a concentration-effect relationship





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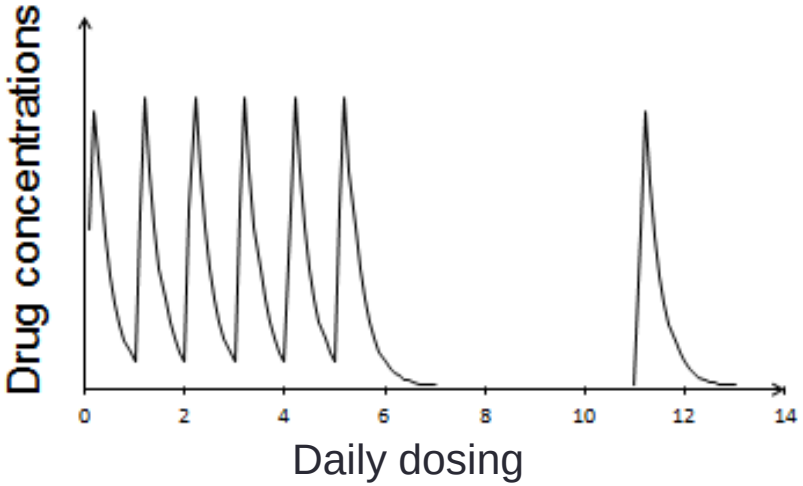
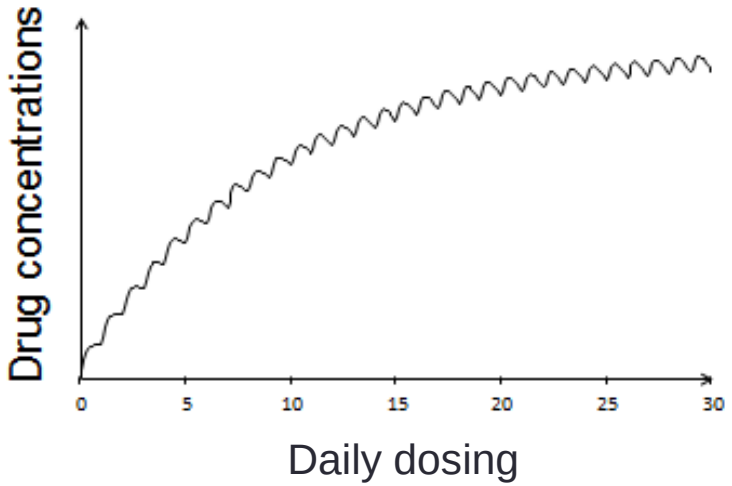
Gap in knowledge

- Are measures of cumulative exposure to tenofovir associated with BMD?

Measuring exposure

- Plasma
  - TFV concentrations only provide information regarding exposure from very recent dosing events (past 3-7 days)
- Intracellular
  - TFV-DP in DBS offers information of cumulative exposure over the previous 1-2 months





$T_{1/2}$ of TFV in plasma≈15 hours

$T_{1/2}$ of TFV-DP in DBS≈17 days

Study aim

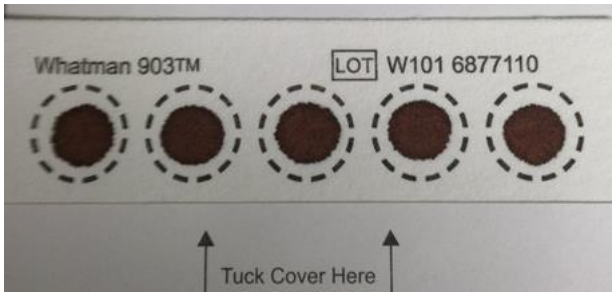
- Investigate the association between concentrations of TFV-DP in DBS and BMD in younger versus older HIV-infected adults

Study design

- Participants:
  - Two cohorts of HIV-infected adults: 18-35 years or >60 years of age
  - Consistent ART with a qualifying regimen that includes TDF for at least one year
  - Suppressed HIV-RNA load (<48 copies/mL on consecutive visits)
  - eGFR > 50 ml/min/1.73 m^2, and no concomitant nephrotoxic agents
- Blood was collected from participants for assessment of tenofovir pharmacology
- Participants underwent a dual-energy x-ray absorptiometry (DXA) scan of their hip and lumbar spine
  - The same machine was used for all study participants

Methods

- 25 µl of whole blood was spotted onto Protein Saver Cards for DBS analysis
  - TFV-DP was quantified in a 3-mm DBS punch using validated LC/MS-MS methods
    - (3-mm punch=12 million RBCs)



- Statistical analyses:
  - Comparisons between two groups were made using either unpaired t-tests or Chi-square tests
  - Univariate and multivariable regression models were used to assess the association of TFV-DP in DBS with spine and hip BMD
  - A p-value of less than 0.05 was considered significant

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N(%) or Mean(SD)	Younger cohort (N=23)	Older cohort (N=22)	P-value
Age (yrs)	31 (3)	64 (4)	…
Sex *Female* *Male*	 2 (9%) 21 (91%)	 2 (9%) 20 (91%)	1.0
Race *Afr-Amer* *Non Afr-Amer*	 2 (9%) 21 (91%)	 4 (18%) 18 (82%)	0.4
Lean mass (g)	51829 (6593)	56709 (10809)	0.07
eGFR (ml/min/1.73 m^2)	100 (13)	71 (17)	**<0.01***
Current smoker	12 (52%)	6 (27%)	0.1
Current HCV infection	0 (0%)	2 (9%)	0.2
PI use	5 (22%)	9 (41%)	0.2
TDF use (yrs) *1 year* *>1 year*	 2 (9%) 21 (91%)	 0 (0%) 22 (100%)	0.5
BMD (g/cm^2) Lumbar spine Hip	 1.0 (0.1) 0.9 (0.1)	 1.0 (0.1) 0.9 (0.1)	 0.6 0.4

T-score analysis

- T-score
  - Compares BMD of participant to that of a healthy young adult
  - Used clinically to define normal, osteopenia, and osteoporosis categories

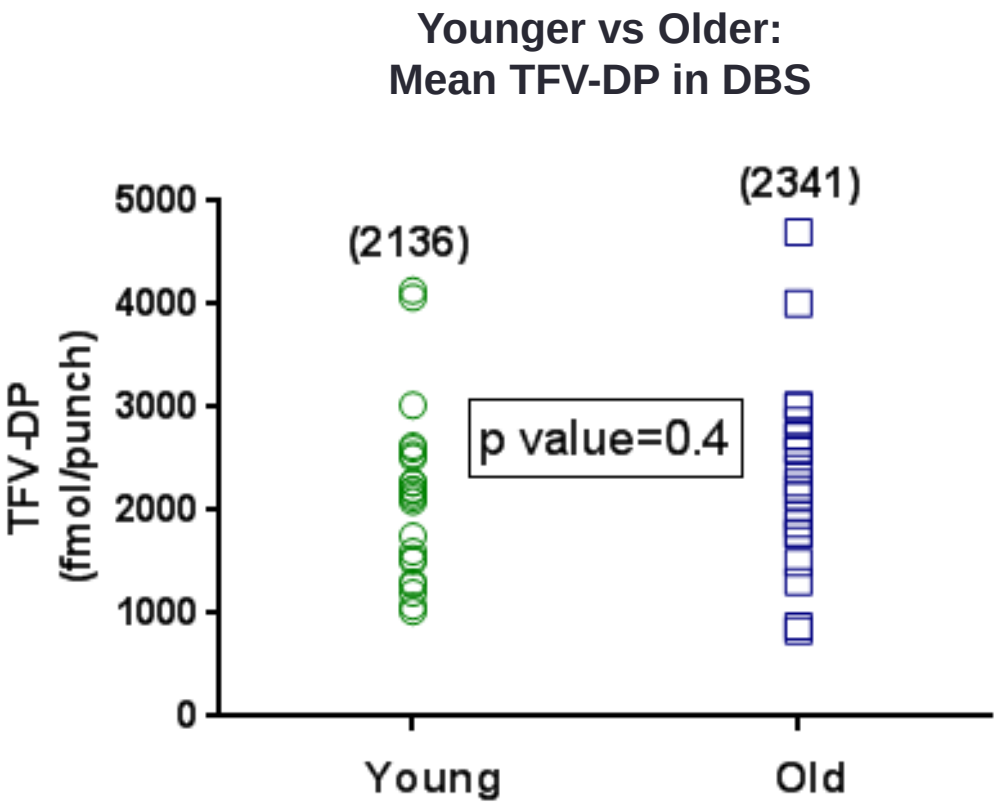
- Lumbar Spine

	Younger	Older
Normal	13 (56%)	10 (45%)
Osteopenia	8 (35%)	11 (50%)
Osteoporosis	2 (9%)	1 (5%)
p-value	0.6	

- Hip bone

	Younger	Older
Normal	13 (57%)	12 (55%)
Osteopenia	10 (43%)	8 (36%)
Osteoporosis	0 (0%)	2 (9%)
p-value	0.3	

Results: TFV-DP in DBS

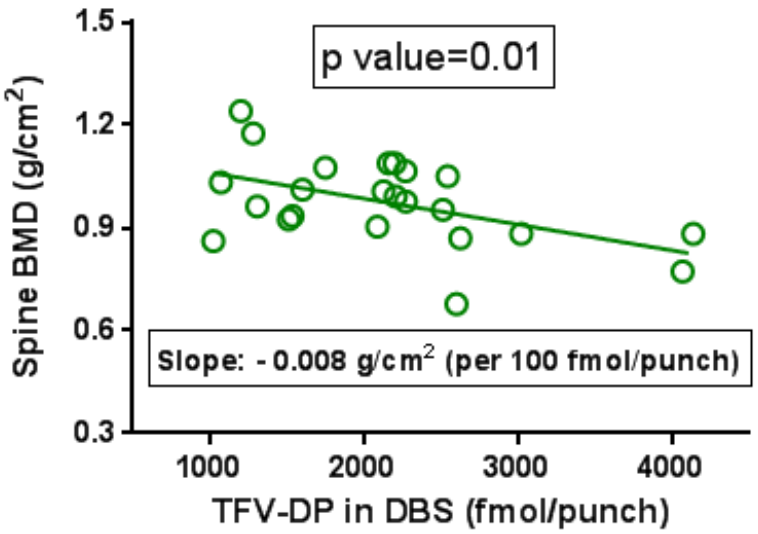


- One participant was excluded due to extremely high TFV-DP levels (43,614 fmol/punch)
  - MacBrayne: Abst#_O_19

Results: Younger Cohort

- Lumbar spine BMD regression analysis:

Univariate:



Multivariable: Adjusting for age and lean mass, relationship between spine BMD and TFV-DP differed significantly by age (p=0.01)

Spine BMD decreased an avg of 0.007 (-0.002, -0.013) g/cm^2 per 100 fmol/punch increase in TFV-DP in the young cohort (p=0.009)

- No significant association was observed for hip BMD (p=0.2) in the younger cohort

Results: Older Cohort

- No significant associations were found between TFV-DP and BMD in spine (p=1.0) or hip (p=0.1)

- No difference in TFV-DP according to PI-use (p=0.1), however the association between PI-use and hip BMD varied significantly by age (p=0.02)
- Adjusting for lean mass and TFV-DP in DBS, older participants taking a PI had lower hip BMD by 0.11 (0.03, 0.2) g/cm^2 relative to those not taking a PI (p=0.008)

Conclusions

- Higher cumulative tenofovir exposure associated with lower lumbar spine BMD in younger participants
  - Consistent with iPrEX results in HIV-negative participants
    - Average BMD decline inversely related to TFV-DP in PBMC
- Although PI-use not associated with TFV-DP (p=0.1), it was associated with lower hip BMD in older participants
  - Consistent with previous studies in HIV-infected adults
- Measures of cumulative tenofovir exposure may be predictive of BMD in virally suppressed HIV-infected patients taking TDF

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Mechanisms

- Intracellular concentrations of TFV-DP in DBS are indicative of adherence
  - Greater concentrations reflect better adherence and greater cumulative exposure to drug
- Intracellular TFV-DP in osteoblasts may be the mechanism for lower BMD
  - TFV-DP in DBS may be a surrogate marker for intracellular phosphorylation activity

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Limitations

- Small n, non-diverse population
  - Limited number of covariates included in regression models
  - Need to study this effect in larger, more diverse groups

- Clinical relevance of low BMD is undetermined
  - Few studies have shown that use of TDF increases risk for fractures
  - Long term follow up is needed
    - Participants from this study are being followed to assess changes in BMD associated with tenofovir pharmacology (NCT02304263)

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Acknowledgements

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