Zoledronic acid is superior to TDF-switching for increasing bone mineral density in HIV-infected adults with osteopenia: a randomised trial

Jennifer Hoy[1,2], Robyn Richardson[3], Peter Ebeling[2], Jhon Rojas[4], Nicholas Pocock[3], Stephen Kerr[3], Esteban Martinez[4], Andrew Carr[3]; ZEST study investigators

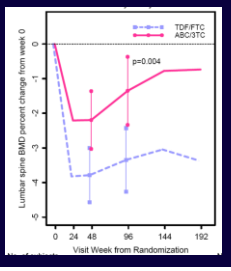
Alfred Hospital, Melbourne, Australia[1]; Monash University, Melbourne[2]; St Vincent's Hospital, Sydney, Australia[3]; Hospital Clinic, Barcelona, Spain[4]

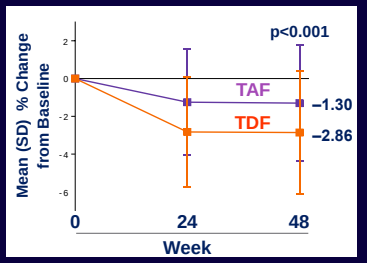
- **Potential conflicts of interest**

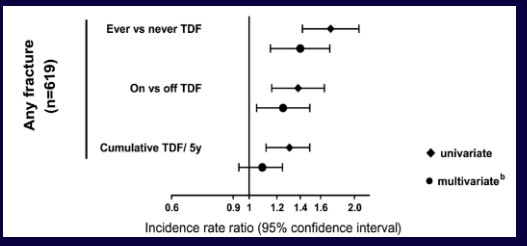
  The Alfred has received reimbursement for my involvement in Advisory Boards for Gilead, ViiV Healthcare, Merck Sharp & Dohme

ZOL vs TDF switch for low BMD

TDF lowers BMD and increases fracture risk





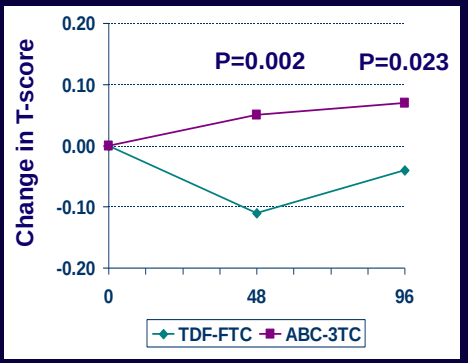


McComsey et al, AIDS 2011; Sax et al, CROI 2015
Borges et al, Clin Infect Dis 2017

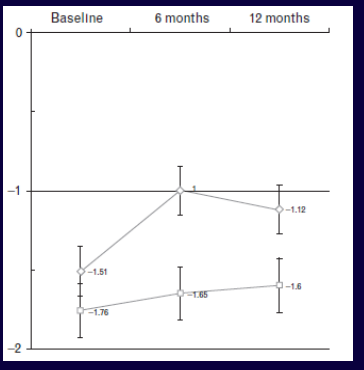
ZOL vs TDF switch for low BMD

TDF switching and bisphosphonates both improve BMD – unknown which is superior

NRTI to abacavir or TDF



Zoledronic acid vs. Placebo



Martin et al, CID 2009; Huang et al, AIDS 2009

ZOL vs TDF switch for low BMD

Hypothesis and primary outcome

- **Hypothesis**
  - bisphosphonate therapy with zoledronic acid (ZOL) will increase BMD more effectively over 2 years than switching TDF to another antiretroviral drug
- **Primary outcome**
  - Mean % change in lumbar spine (L1-L4) BMD by DXA – spine chosen in preference to hip as:
    - measurement of lumbar spine BMD and hip BMD have similar variability, but
    - lumbar spine BMD responds more rapidly to pharmaceutical intervention than hip BMD

ZOL vs TDF switch for low BMD

Inclusion criteria

- Age ≥18 years
- Stable ART including TDF for preceding 6+ months
- HIV RNA <50 copies/mL for preceding 3+ months
- eGFR >60ml/min
- T-score ≤ -1.0 at spine (L1–L4) or left femoral neck by DXA (i.e. osteopenia)
- No prior virological failure, resistance, intolerance or contraindication to proposed switch ARV drug (including HLA-B*5701+ or prior CVD for abacavir)

ZOL vs TDF switch for low BMD

Exclusion criteria

- Prior bisphosphonate
- On TDF for previously active chronic HBV
- Requiring therapy for low BMD (e.g. fragility fracture)
- Secondary causes of osteoporosis
  - hypogonadism (low total testosterone/oestrogen and LH>25% above ULN)
  - hypothyroidism (low T4 and elevated TSH)
  - hyperparathyroidism (elevated PTH / Ca)
  - inhaled fluticasone in a patient on ritonavir
  - prednisolone ≥7.5mg/day or equivalent
- Contra-indication to ZOL (hypocalcaemia, uveitis, recent or planned dental surgery)
- Concurrent use of any nephrotoxic drug
- Breast-feeding or pregnancy

ZOL vs TDF switch for low BMD

Study design

- Randomised, open-label, 2-year trial
- Eligible patients allocated to either
  - ZOL 5mg IVI at M0 and M12 and continue TDF
    OR
  - Switch TDF to alternate ARV (no ZOL)
- Stratification by
  - radiology facility
  - T-score (< or ≥ -2.0)

ZOL vs TDF switch for low BMD

Study Design

- Calcium 1500mg/day for all participants
- Vitamin D replacement to promote BMD increase and prevent ZOL-induced hypocalcaemia
  - Screening / Month 11: if <25 nmol/L, received vitamin D 100,000IU (2 tablets)
  - Screening / Month 11: if 25-50 nmol/L, received vitamin D 50,000IU (1 tablet)
  - For above patients, if still <50 nmol/L at Month 3 received vitamin D 50,000IU monthly thereafter
  - ZOL given at least 2 weeks after Vitamin D replacement

ZOL vs TDF switch for low BMD

DXA

- Sites
  - lumbar spine (L1-L4)
  - left hip
- Facilities x 3 (Sydney, Melbourne, Barcelona)
  - common protocol
  - central adjustment of BMD values for longitudinal and cross-sectional consistency based on phantom scans
- BMD results unavailable until M24 unless
  - minimal-trauma fracture or
  - BMD decline of >5% or
  - new T-score <-2.5

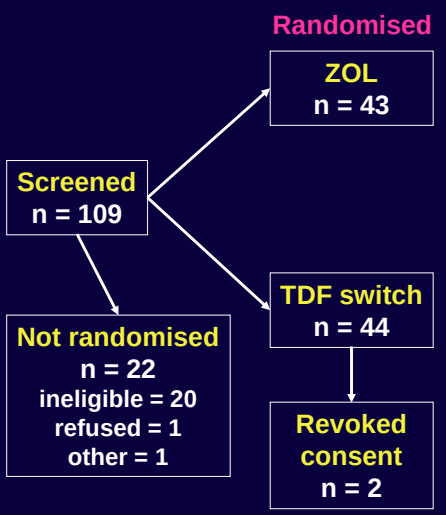
ZOL vs TDF switch for low BMD

Statistical analysis

- **Sample size**
  - prior studies mean 2-year change at lumbar spine
    - 6.1% (SD <4%) with a bisphosphonate
    - 1% (SD 2%) with tenofovir switching
  - if Δ=4% and SD=6%, sample size = 36 / group
  - if LTFU is 15%, n=42 / group
- **DXA and lab parameters**
  - groups compared with t-test
- **Categorical data**
  - groups compared using Fisher's exact test or a Chi-square test as appropriate
- **All presented analyses by ITT**
  - PP analyses yielded similar results

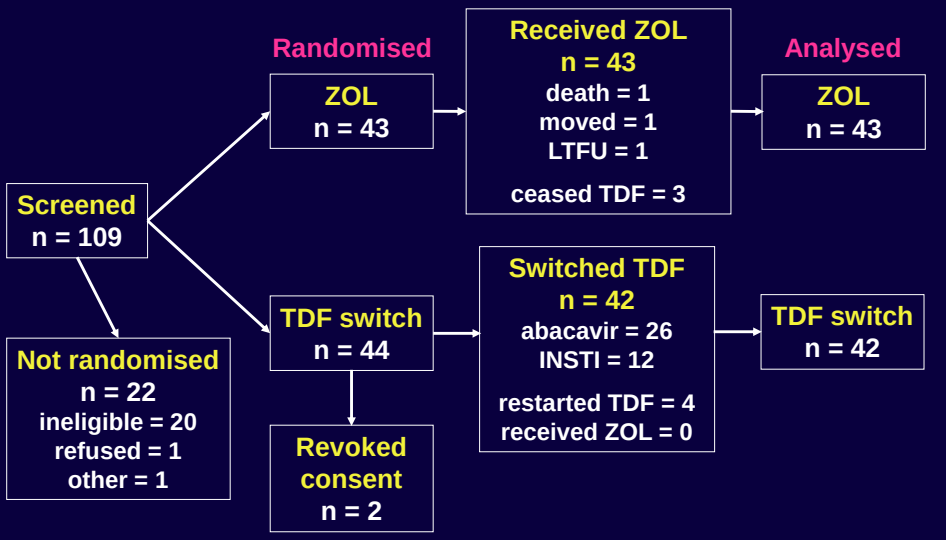
ZOL vs TDF switch for low BMD

CONSORT chart



ZOL vs TDF switch for low BMD

CONSORT chart



ZOL vs TDF switch for low BMD

Screening / baseline characteristics

Variable	ZOL n=43	TDF switch n=42
Age (mean yrs)	49	51
Sex (male %)	93	100
Ethnicity (white, %)	74	81
CD4 count (cells/mm^3)	626	609
TDF duration (mean yrs)	5.7	6.0
Boosted PI (%)	23	21
Weight (mean kg)	75	75

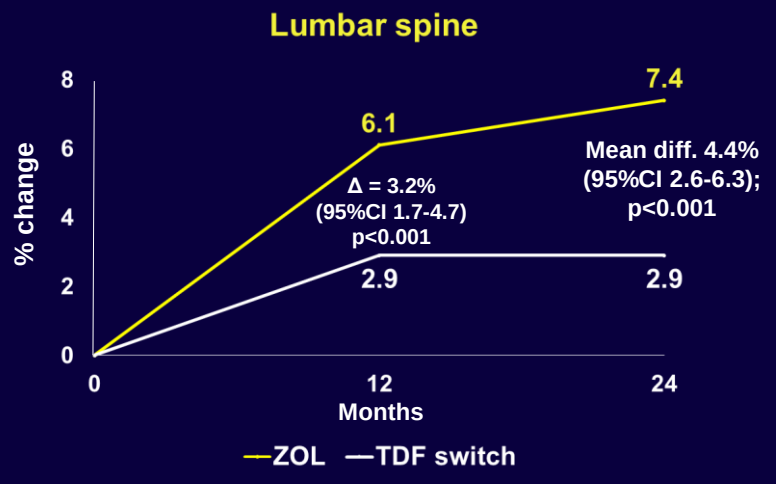
ZOL vs TDF switch for low BMD

Screening / baseline characteristics

Variable	ZOL n=43	TDF switch n=42
T-scores (median)		
spine	-1.7	-1.6
left total hip	-1.4	-1.1
Vitamin D		
<25 nmol/L	12%	20%
25-50 nmol/L	40%	36%
eGFR (mean mL/min)	93	91

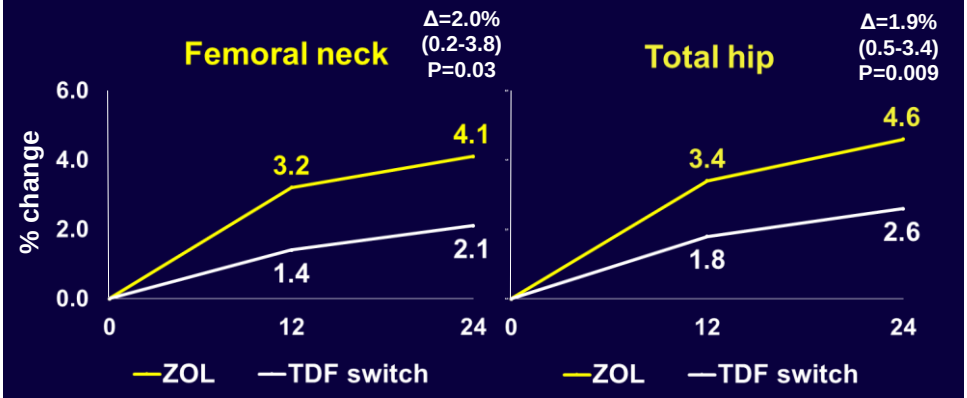
ZOL vs TDF switch for low BMD

Changes in BMD



ZOL vs TDF switch for low BMD

Changes in BMD - hip



- 1 pt in ZOL group had unevaluable hip BMD
- M12 data carried forward for 1 pt/group because of subsequent left hip replacements
- Baseline data carried forward to M12 for 1 patient in TDF switch group

ZOL vs TDF switch for low BMD

Fractures

	ZOL n=43	TDF switch n=42	P
Fractures (n, %)			
events*	1 (2%)	7 (17%)	0.03
wrist		1	
spine	1	1	
ribs		2	
hand / foot		3	
patients	1 (2%)	4 (10%)	0.20

* 1 fracture in each group was deemed a fragility fracture

ZOL vs TDF switch for low BMD

Other adverse events

	ZOL n=43	TDF switch n=42	P
eGFR (mean Δ)	-6.0	3.3	0.003
SAE (n, %)	9 (19%)	6 (14%)	0.57
RNA >50 cp/mL	0	1 (2%)	..

- No SAE was deemed to be related to any study intervention

ZOL vs TDF switch for low BMD

Limitations

- Almost all white, adult men
- Follow-up for 24 months – follow-up ongoing to M36
- Pre-TAF, but switch to TAF unlikely to be superior to switch to ABC or INSTI
- Not powered for fracture events

ZOL vs TDF switch for low BMD

Conclusions

- ZOL (with Ca^{2+} ± vitamin D replacement) is more effective at increasing BMD than switching from TDF, in adult men with low BMD
- Much larger and longer studies are required to determine impact on fracture outcomes
- Clinical significance will likely depend on underlying fracture risk

ZOL vs TDF switch for low BMD

Acknowledgements

- **Participants**
- **Investigators** Mark Bloch, David Baker, Julian Elliott, Beng Eu, Robert Finlayson, Andrew Gowers, Margaret Hellard, Stephen Kent, James McMahon, Marilyn McMurchie, John Mills, Richard Moore, Timothy Read, Norman Roth, Catherine Sheppard, Ban Kiem Tee
- **Site coordinators** Shikha Agrawal, Susan Boyd, Pilar Callau, Cath Downs, Sian Edwards, Shruti Gupta, Helen Kent, Helen Lau, Nicola Mackenzie, Erin McDonald, David Ninham, Katherine Ognenovska, Julie Silvers, Trina Vincent, Lesley Williams
- **Imaging staff** Sherala Gunasekara, Marita Huynh, Amparo Tricas y Ana Rodríguez
- **Pharmacists** Ivette Aguirre, Elisabeth Farré, Linda Hotong, Anne Mak
- **Financial support** National Health and Medical Research Council of Australia APP1022660; Balnaves Foundation

Questions