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Change in Vitamin D Levels Smaller and Risk of Development of Severe Vitamin D Deficiency Lower Among HIV-1-Infected, Treatment-naïve Adults Receiving TMC278 Compared with Efavirenz: 48-week Results from the Phase III ECHO Trial

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Background

- **Vitamin D insufficiency and deficiency is highly prevalent among HIV-infected individuals[1,2]**
- **EFV is associated with a reduction in vitamin D levels through induction of CYP450 enzymes[2–4]**
- **In the MONET trial, vitamin D levels increased in HIV-infected patients who switched from EFV-containing regimens to DRV/r[5]**

EFV = efavirenz; CYP = cytochrome
DRV/r = darunavir/ritonavir

[1]Wasserman P, et al. AIDS Patient Care STDs 2010;24:223–7
[2]Dao CN, et al. Clin Infect Dis 2011;52:396–405
[3]Herzmann C, et al. AIDS 2009;23:274–5
[4]Brown TT, et al. Antivir Ther 2010;15:425–9
[5]Fox J, et al. AIDS Res Hum Retroviruses 2011;27:29–34

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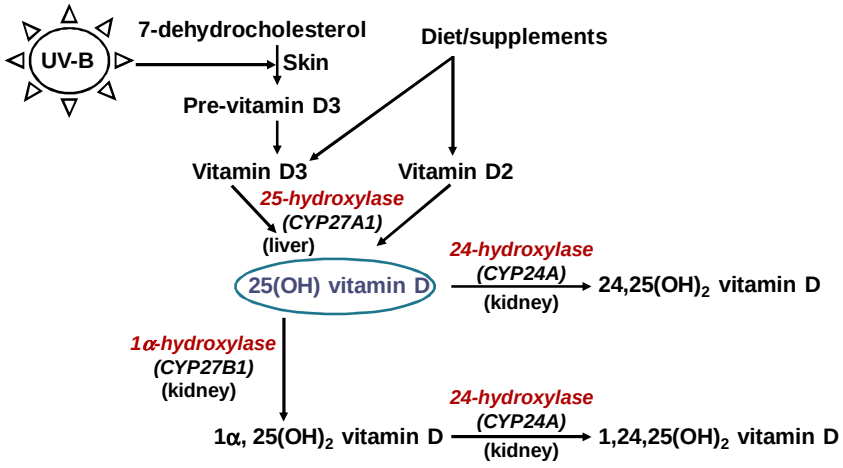
Vitamin D metabolism



Modified from Van Den Bout-van den Beukel C, et al. Academic Thesis, Nijmegen University 2000

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Vitamin D deficiency and clinical implications[1]

- **Decreased bone mineral density and potentially:**
  - **Muscle weakness**
  - **Immune dysfunction**
  - **Decreased myocardial contractility**
  - **Hypertension**
  - **Diabetes**
  - **Cancer**

[1]Holick MF. N Eng J Med 2007;357:266–81

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Objectives of the analysis

- **To compare TMC278 (rilpivirine) vs EFV in the Phase III ECHO* trial over 48 weeks, for changes in:**
  - **Serum levels of 25-hydroxyvitamin D [25(OH)D], a standard indicator of vitamin D status[†,1]**
  - **25(OH)D deficiency status**
- **To compare the proportions of patients with 25(OH)D insufficiency/deficiency at baseline who progress to severe deficiency at Week 48**

[†]Serum levels of 25(OH)D reflect vitamin D produced cutaneously and that obtained from food and supplements, and 25(OH)D has a long circulating half-life of 15 days

*ClinicalTrials.gov registry number NCT00540449

[1]NIH dietary supplement website: http://ods.od.nih.gov/factsheets/vitamind/

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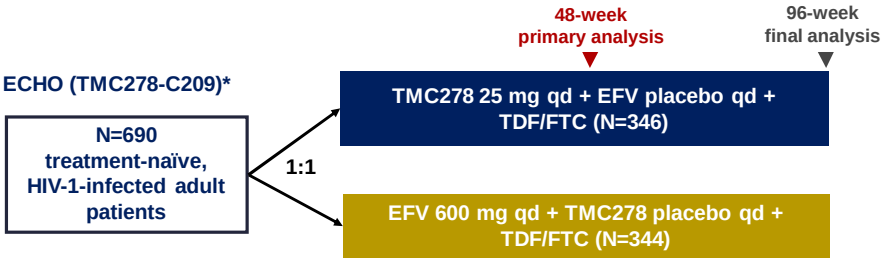
ECHO study design and Phase III Week 48 results

- ECHO and THRIVE are randomised, double-blind, double-dummy, Phase III clinical trials[1]



- In ECHO and THRIVE, TMC278 was non-inferior to EFV in confirmed response (viral load <50 copies/mL, ITT-TLOVR) at Week 48 (primary objective)[1]
- TMC278 had a more favourable safety and tolerability profile than EFV[1]
- A once-daily single-tablet regimen of TMC278 and TDF/FTC is under development[2]

*Countries (4 regions): 13 in region USA, Canada, Europe and Australia; 3 in Asia; 4 in Latin America; and South Africa
ITT = intent-to-treat; TLOVR = time-to-loss of virologic response

[1]Cohen CJ, et al. XVIIIth IAC 2010. Abstract THLBB206
[2]Mathias A, et al. XVIIIth IAC 2010. Abstract LBPE17

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ECHO 25(OH)D analysis: methods

- 25(OH)D was measured in stored serum samples available from ECHO patients at baseline, Week 24 and Week 48*
- Proportions of patients with 25(OH)D levels within defined categories[1–3] were calculated

Optimal/sufficient	(≥30 ng/mL)
Insufficient	(21–29 ng/mL)
Deficient	(10–20 ng/mL)
Severely deficient	(<10 ng/mL)

*Data presented only for patients with paired baseline and Week 48 data

[1]Hyppönen E and Power C. Am J Clin Nutr 2007;85:860–8
[2]Dawson-Hughes B, et al. Osteoporos Int 2005;16:713–6
[3]Holick MF. Mayo Clin Proc 2006;81:353–73

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ECHO 25(OH)D analysis: baseline characteristics*

Median baseline parameter, unit (min–max)	TMC278 N'=292	EFV N'=290
Age, years	36 (18–78)	37 (19–67)
Female	23%	18%
Racial group,†		
Black/African-American	23%	21%
Non-Black/Non-African-American	75%	77%
Log_{10} viral load, copies/mL	4.9 (2.2–6.5)	5.0 (3.0–6.5)
BMI,‡ kg/m^2	24 (16–44)	24 (17–42)
CD4 cell count, cells/mm^3	245 (1–888)	250 (1–693)
Calcium level, mmol/L	2.4 (2–3)	2.4 (2–3)
Phosphorus level, mmol/L	1.1 (1–2)	1.1 (1–2)
25(OH)D level, ng/mL	23.6 (6.4–74.8)	24 (6.4–100.4)

- The geographical distribution of patients covered all four regions, and was similar in the two treatment groups
- 14% and 12% of patients in the TMC278 and EFV groups, respectively, took vitamin D supplements during the study

*Data presented only for patients with paired baseline and Week 48 data; †In some countries reporting of race was disallowed; ‡N'=291 for TMC278, N'=288 for EFV; BMI = body mass index

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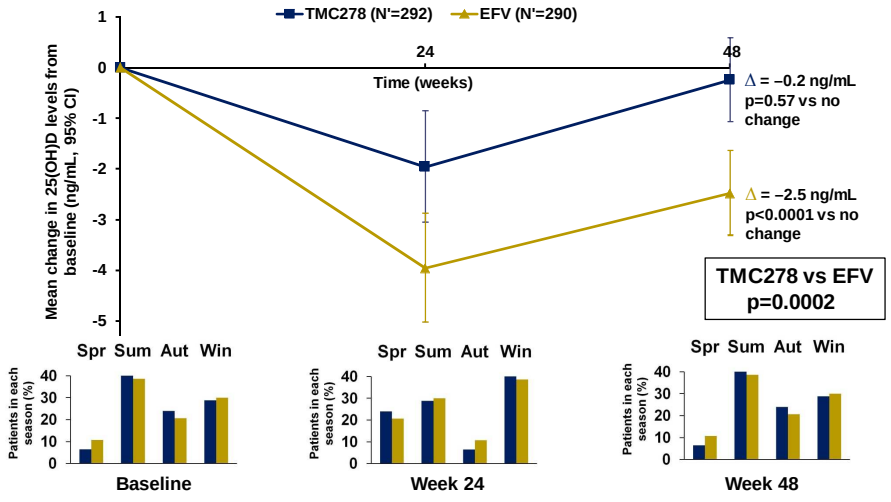
ECHO: mean 25(OH)D changes from baseline



- At baseline the majority of patients were at their (natural) 25(OH)VD replete status
- The dip at 24 weeks can be attributed to reduced Vitamin D stores associated with seasonal change

CI = confidence interval; N'=291 (TMC278), N'=289 (EFV) at Week 24

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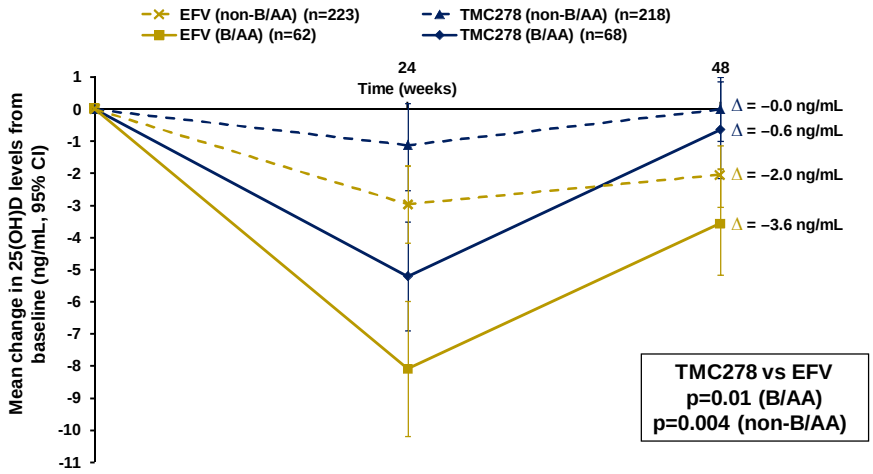
ECHO: mean 25(OH)D changes from baseline by race*



*In some countries reporting of race was disallowed; B/AA = Black/African American
non-B/AA = Non-Black/Non-African-American; n=217 (TMC278), n=222 (EFV) non-B/AA at Week 24

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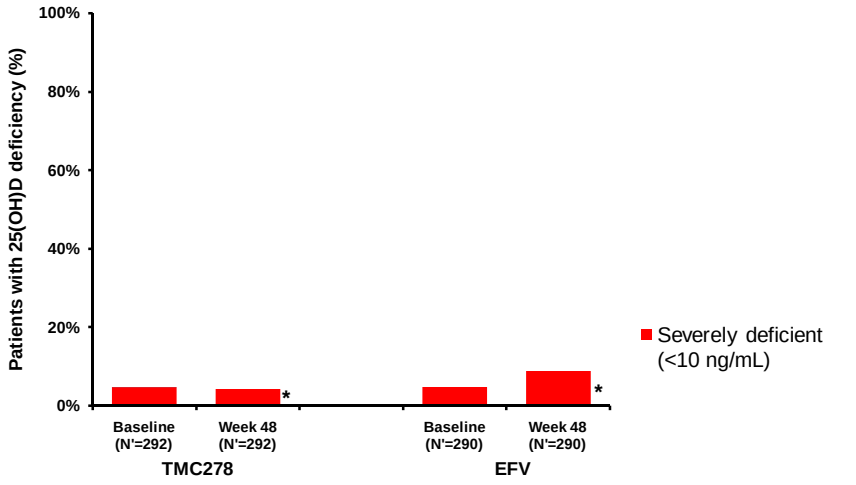
ECHO: changes in 25(OH)D deficiency status from baseline to Week 48



***p=0.032** (Fisher's Exact test) for treatment comparison in severe 25(OH)D deficiency at Week 48, irrespective of baseline

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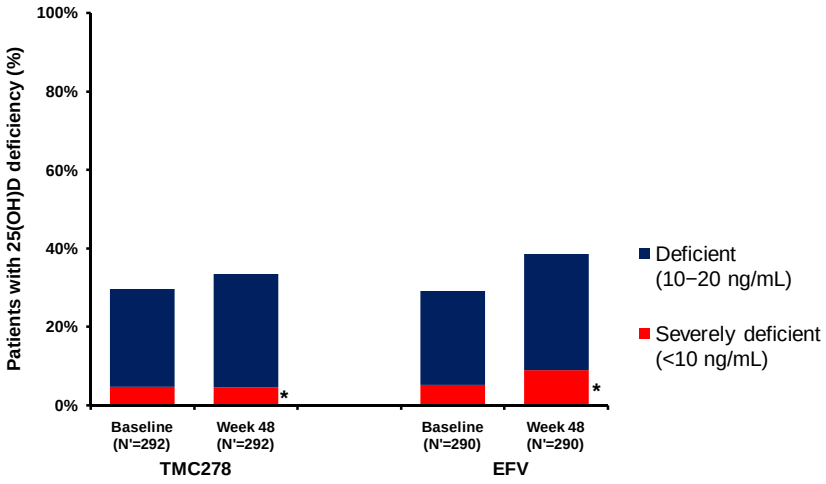

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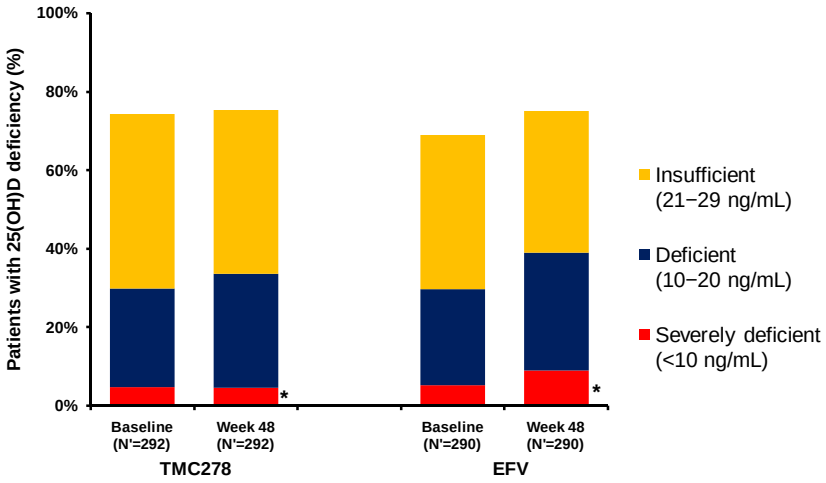

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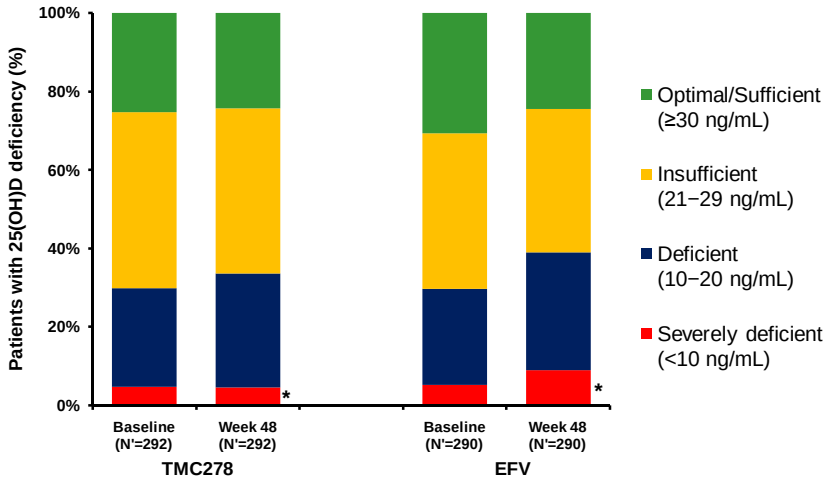

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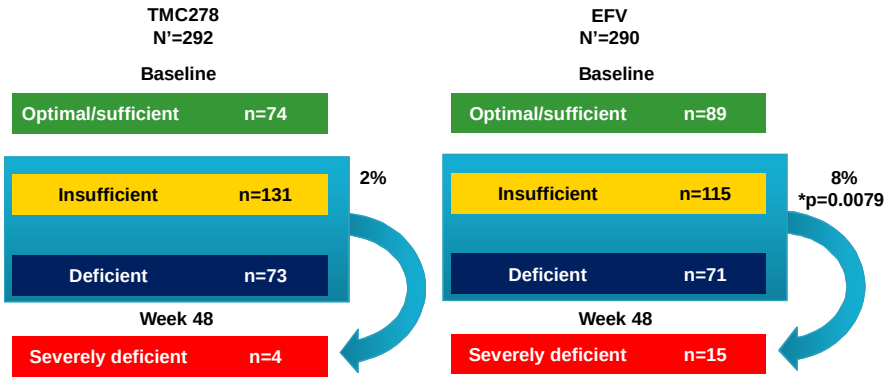
ECHO: effects of NNRTI treatment on progression to severe 25(OH)D deficiency



Optimal/sufficient: ≥30 ng/mL
Insufficient: 21−29ng/mL
Deficient: 10−20ng/mL
Severely deficient: <10ng/mL
*Fisher's exact test versus TMC278 at Week 48

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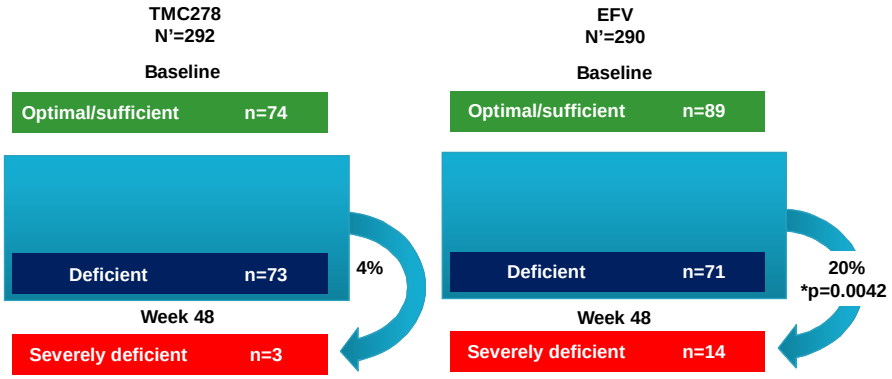
ECHO: effects of NNRTI treatment on progression to severe 25(OH)D deficiency



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Conclusions:

In HIV-1 infected, treatment-naïve adults receiving TMC278 or EFV over 48 weeks in ECHO

- At baseline, 72% of patients had sub-optimal 25(OH)D levels
- Mean 25(OH)D levels after 48 weeks of treatment
  - Remained unchanged with TMC278
  - Were statistically significantly reduced with EFV
  - Declined more in Black/African-American patients than in non-Black/non-African-American patients
- The risk of progression to severe 25(OH)D deficiency (<10 ng/mL) was significantly higher with EFV than with TMC278

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