

Supplemental Tables and Figures

Supplemental Table S1. Percent change in BMD at the spine (L1-L4), hip and femoral neck with immediate ART (excluding those who did not start ART) compared with no ART (with follow-up censored in the deferred ART group at last scan prior to ART initiation).

	Immediate ART Group		Deferred ART Group, Censored at ART Start		Immediate - Deferred ART Groups	
	n	Mean (95% CI)	n	Mean (95% CI)	Estimated Difference (95% CI)	p
Spine (L1-L4)						
Baseline to Year 1	189	-2.06 (-2.49, -1.63)	171	-0.05 (-0.46, 0.35)	-2.01 (-2.60, -1.42)	<0.001
Baseline to Year 2	164	-1.72 (-2.27, -1.17)	125	0.45 (-0.10, 1.00)	-2.19 (-2.98, -1.40)	<0.001
Baseline to Year 3	50	-2.42 (-3.40, -1.43)	34	-0.03 (-1.24, 1.17)	-2.37 (-3.93, -0.80)	<0.01
Overall	190	-1.92 (-2.33, -1.51)	174	0.14 (-0.29, 0.58)	-2.08 (-2.68, -1.48)	<0.001
Change from Year 1 to Year 2 (%)	163	0.34 (-0.06, 0.75)	123	0.56 (0.10, 1.03)	-0.24 (-0.86, 0.38)	0.45
Change from Year 2 to Year 3 (%)	49	0.17 (-0.61, 0.95)	34	-0.81 (-1.75, 0.12)	1.02 (-0.22, 2.26)	0.11
Rate of change after Year 1 (% per year)		0.27 (-0.07, 0.60)		0.19 (-0.19, 0.58)	0.09 (-0.42, 0.59)	0.73
Overall rate of change (% per year)		-0.78 (-1.01, -0.56)		0.08 (-0.17, 0.33)	-0.91 (-1.25, -0.57)	<0.001

Total Hip

Baseline to Year 1	188	-2.15 (-2.67, -1.63)	171	-0.22 (-0.60, 0.15)	-1.93 (-2.58, -1.27)	<0.001
Baseline to Year 2	164	-3.02 (-3.71, -2.32)	125	-0.70 (-1.23, -0.17)	-2.29 (-3.21, -1.37)	<0.001
Baseline to Year 3	50	-3.58 (-4.48, -2.68)	34	-1.29 (-2.45, -0.14)	-2.25 (-3.70, -0.80)	<0.01
Overall	189	-2.62 (-3.08, -2.15)	174	-0.44 (-0.93, 0.06)	-2.10 (-2.78, -1.42)	<0.001
Change from Year 1 to Year 2 (%)	163	-0.94 (-1.36, -0.51)	123	-0.31 (-0.80, 0.18)	-0.60 (-1.25, 0.05)	0.07
Change from Year 2 to Year 3 (%)	49	0.07 (-0.60, 0.74)	34	-0.66 (-1.47, 0.14)	0.77 (-0.29, 1.84)	0.15
Rate of change after Year 1 (% per year)		-0.71 (-1.03, -0.39)		-0.38 (-0.76, -0.01)	-0.31 (-0.81, 0.19)	0.23
Overall rate of change (% per year)		-1.35 (-1.61, -1.10)		-0.33 (-0.62, -0.05)	-1.04 (-1.42, -0.65)	<0.001

Femoral Neck

Baseline to Year 1	188	-2.60 (-3.21, -1.99)	171	-0.42 (-0.97, 0.14)	-2.25 (-3.07, -1.42)	<0.001
Baseline to Year 2	164	-3.46 (-4.32, -2.60)	125	-1.50 (-2.22, -0.77)	-1.99 (-3.16, -0.82)	<0.001
Baseline to Year 3	50	-3.64 (-5.08, -2.20)	34	-1.40 (-2.97, 0.17)	-2.23 (-4.40, -0.05)	0.05
Overall	189	-3.09 (-3.68, -2.49)	174	-0.88 (-1.51, -0.25)	-2.18 (-3.04, -1.32)	<0.001

Femoral Neck

Change from Year 1 to Year 2 (%)	163	-0.92 (-1.49, -0.35)	123	-1.04 (-1.69, -0.38)	0.13 (-0.74, 1.00)	0.77
Change from Year 2 to Year 3 (%)	49	-0.13 (-1.17, 0.90)	34	0.32 (-0.92, 1.56)	-0.45 (-2.10, 1.20)	0.59
Rate of change after Year 1 (% per year)		-0.80 (-1.24, -0.37)		-0.71 (-1.21, -0.20)	-0.10 (-0.78, 0.58)	0.77
Overall rate of change (% per year)		-1.57 (-1.91, -1.23)		-0.59 (-0.97, -0.21)	-1.04 (-1.55, -0.53)	<0.001

Follow-up was censored at the start of osteoporosis therapy for 2 participants (both in the deferred group, month 24). Mean changes in BMD from baseline to each year were calculated without adjustments, differences at each year were estimated in regression models adjusted for baseline BMD, and overall changes in BMD were estimated and compared using longitudinal mixed models adjusted for both baseline BMD and visit. Rates of changes in BMD (overall and after year 1) were estimated in longitudinal mixed models using annual BMD changes as response.

Supplemental Table S2: Association of time-updated ART use with percent change in BMD for participants in the immediate ART group (N=190). Participants who did not start ART within the first year were excluded. For example, the coefficient of -0.20 for EFV and total spine BMD denotes that per year of EFV use, spine BMD declined by an estimated 0.20% more than the average BMD decline. None of the associations were significant.

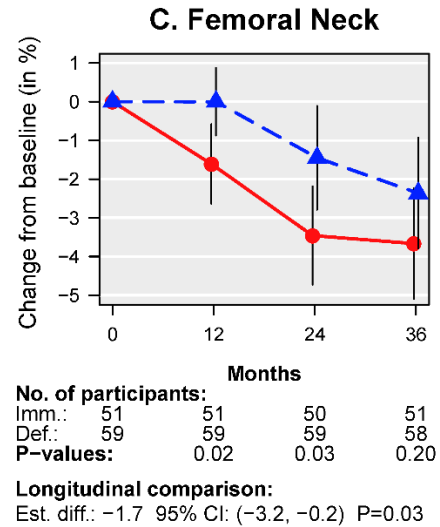
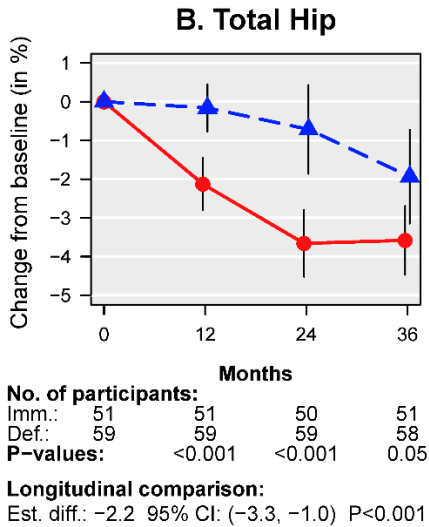
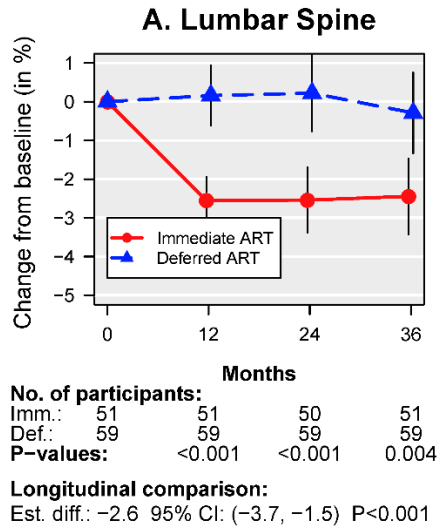
Antiretroviral Drug Used	n (%) in subgroup	Spine (L1-L4) BMD		Total Hip BMD		Femoral Neck BMD	
		Est. Coefficient (95% CI)	p ⁺	Est. Coefficient (95% CI)	p ⁺	Est. Coefficient (95% CI)	p ⁺
EFV	148 (77.9)	-0.20 (-0.79, 0.40)	0.52	-0.12 (-0.78, 0.54)	0.72	-0.36 (-1.22, 0.51)	0.42
TDF	157 (82.6)	0.03 (-0.77, 0.83)	0.94	-0.64 (-1.56, 0.29)	0.18	-0.69 (-1.86, 0.49)	0.25
PI	25 (13.2)	-0.53 (-1.18, 0.12)	0.11	-0.42 (-1.13, 0.30)	0.25	-0.07 (-1.02, 0.88)	0.89
NNRTI	156 (82.1)	-0.27 (-0.87, 0.33)	0.38	-0.04 (-0.73, 0.64)	0.91	-0.23 (-1.12, 0.66)	0.61
Any ART	190 (100.0)	-0.92 (-4.27, 2.43)	0.59	-1.17 (-5.32, 2.97)	0.58	-2.25 (-7.42, 2.92)	0.39

⁺ P-value for associations between the time-updated use of the specific drug and annual percent change in BMD, estimated in separate longitudinal mixed models which contained the following predictors: percent of time the drug was used in the preceding year, age, gender, race, location and season of enrolment, smoking status, alcohol abuse, drug use, diabetes, BMI, hepatitis B, hepatitis C, previous fragility fracture, eGFR, mode of HIV infection, time since HIV diagnosis, baseline CD4 and CD8, CD4:CD8 ratio, log₁₀ HIV RNA, calcium or vitamin D supplements, baseline BMD and visit. The subject-specific time-updated ART use at years 1, 2 and 3 was calculated as the proportion of time that the specific drug was used during the preceding year.

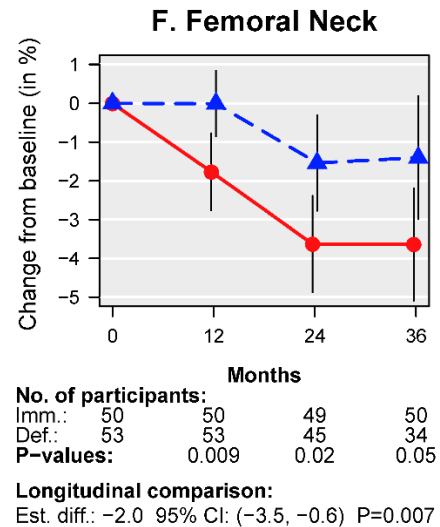
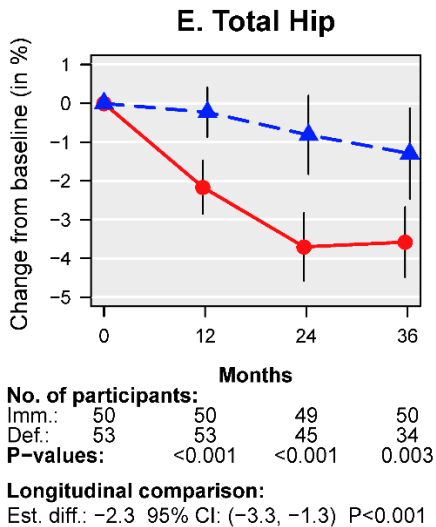
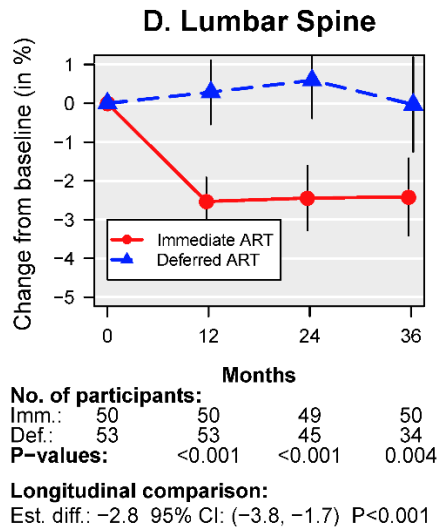
EFV=efavirenz; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; TDF=tenofovir disoproxil fumarate

Supplemental Figure S1. Mean percent change (95% CIs) in BMD by treatment group, restricted to the 110 participants with Year 3 follow-up data. Panels A-C show intent-to-treat comparisons. In panels D-F follow-up in the deferred group is censored at ART start, and in the immediate group participants not taking ART in Year 1 are excluded. (A and D) Lumbar spine (L₁-L₄) BMD, (B and E) total hip BMD, (C and F) femoral neck BMD.

Intent-to-Treat Comparison
Imm. vs. Def. ART Groups

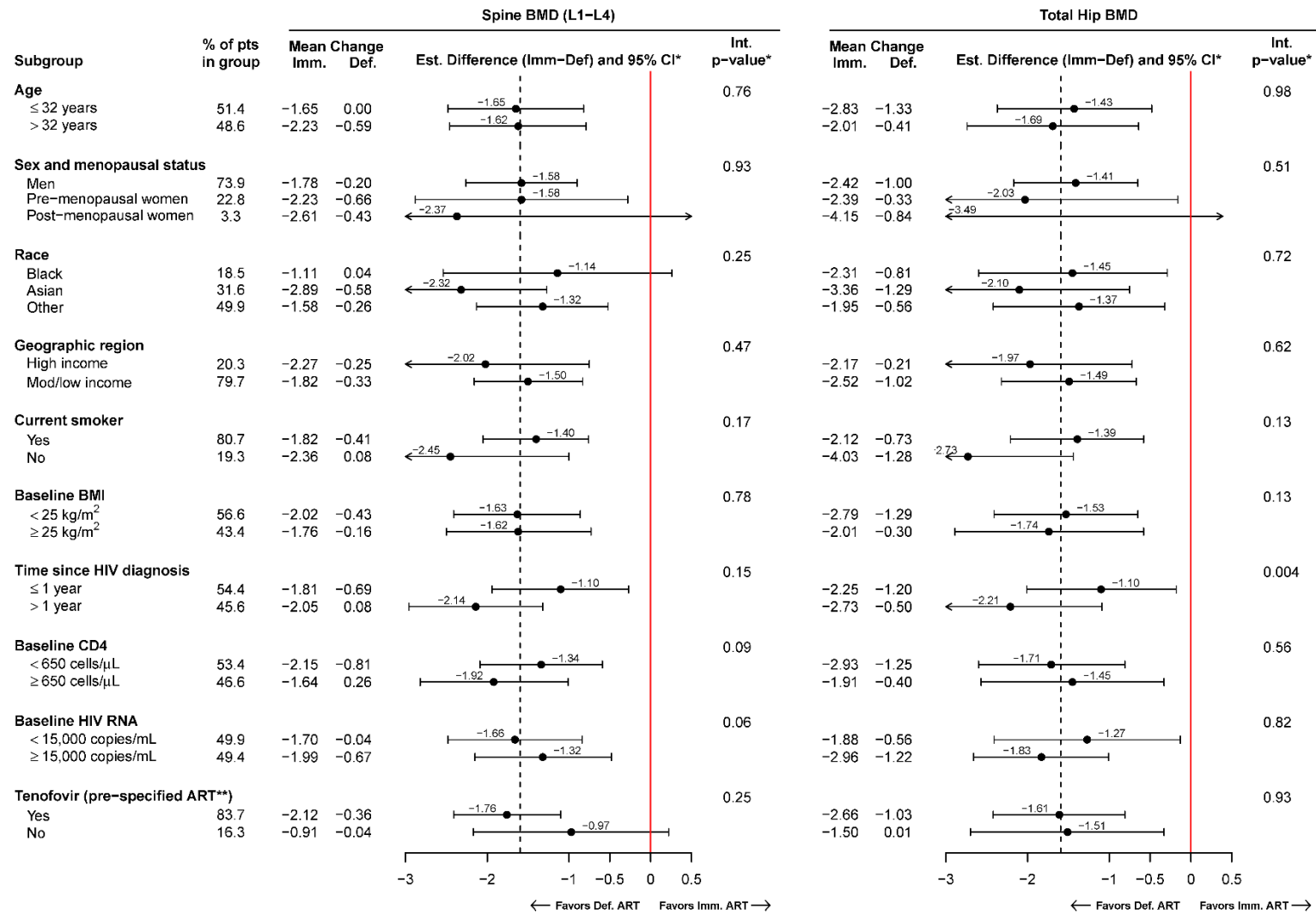


Immediate Group* vs.
Def. Censored at ART Start



* Excluding participants who did not start ART within the first year.

Supplemental Figure S2. Subgroup analyses for spine and hip BMD, restricted to data through Year 2. Mean percent change from baseline, and treatment differences (immediate minus deferred ART groups) in spine (L₁-L₄) and total hip BMD are estimated within subgroups, by intent-to-treat, with 95% confidence intervals. The vertical dashed line shows the overall difference between the immediate and deferred ART groups. P-values are for tests of heterogeneity of the treatment difference across subgroups.



* Estimated in a longitudinal mixed model, adjusted for visit and baseline BMD. The interaction p-value tests for heterogeneity across subgroups, and was calculated using continuous variables for age, BMI, time since HIV diagnosis, CD4 count, and log₁₀ HIV RNA levels.

** In the immediate ART group, a tenofovir-containing ART regimen was selected prior to randomization (“pre-specified”) for 162 participants. Of those who were pre-specified tenofovir and had the corresponding follow-up scans, 155 (96.3%) and 138 (97.2%) used tenofovir at years 1 and 2, respectively.