Presenter Disclosure Information

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disclosed no conflict of interest.

Antiretroviral therapy and body weight in the Strategic Timing of Antiretroviral Treatment (START) trial

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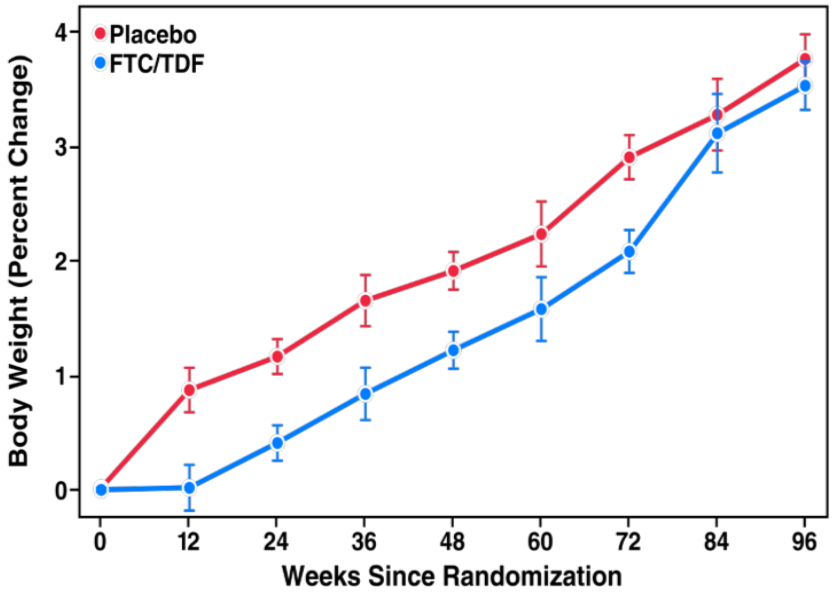
Introduction: ART causing difference in weight change

iPrEx



- Placebo (n=1225)
- Emtricitabine (FTC) and tenofovir diproxil fumarate (TDF) (n=1226)

  Delayed weight gain in treatment group

Preexposure chemoprophylaxis for HIV prevention in men who have sex with men.
Grant RM et al.
N Engl J Med 2010 ;363:2587-99.
DOI: 10.1056/NEJMoa1011205.

START

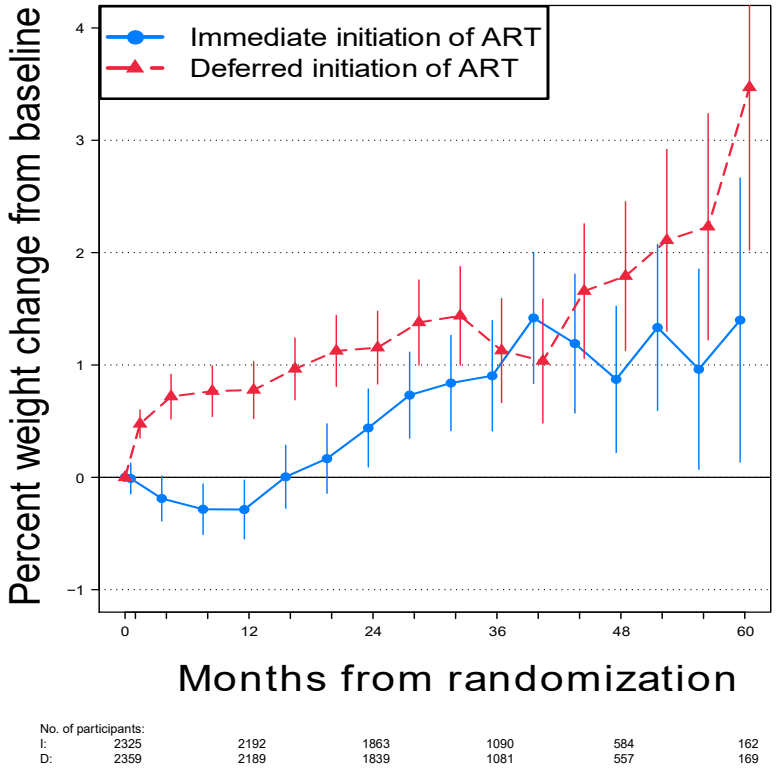


Figure updated from previously published

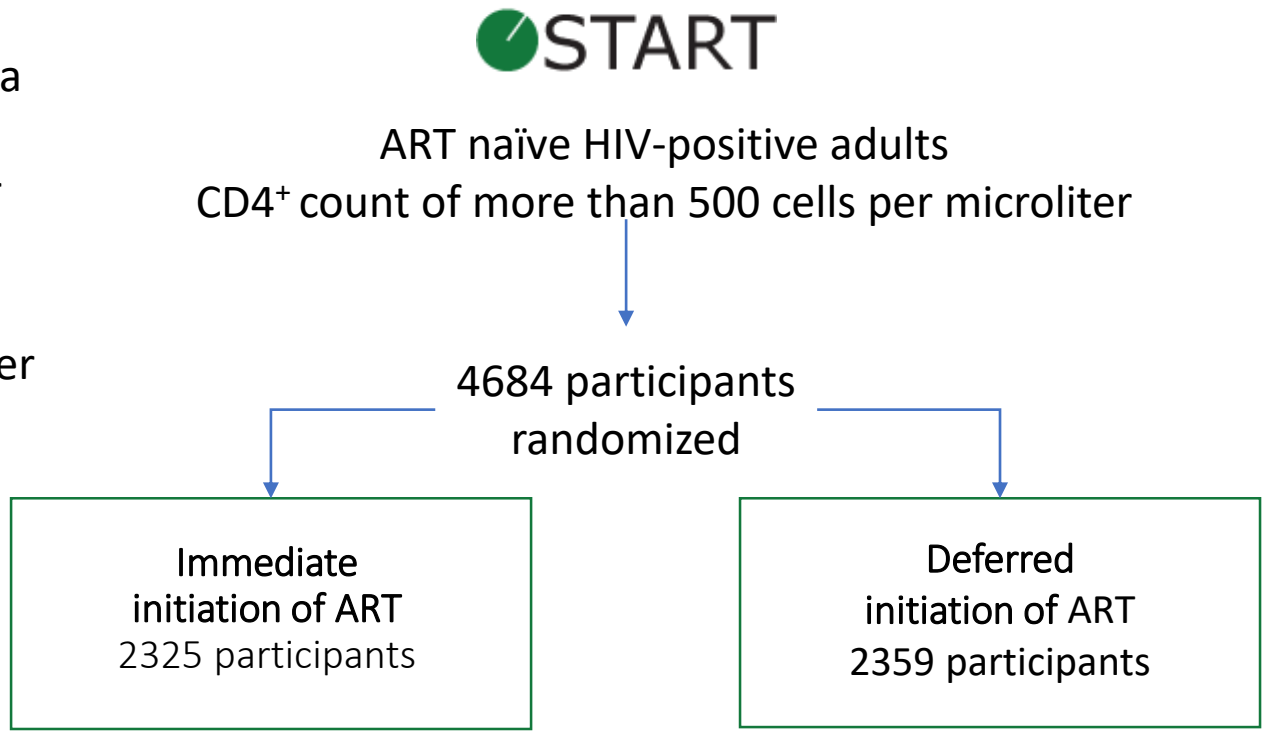
Changes in Cardiovascular Disease Risk Factors With Immediate Versus Deferred Antiretroviral Therapy Initiation Among HIV-Positive Participants in the START (Strategic Timing of Antiretroviral Treatment) Trial Jason V. Baker et al. https://doi.org/10.1161/JAHA.116.004987 , Journal of the American Heart Association. ;6:e004987

Aims

To explore how the treatment difference in weight change varied across subgroups defined by characteristics at study entry: participant demographics, HIV disease state, smoking status and pre-specified ART regimen

Design of the START trial

- Inclusion of ART naïve HIV-positive adults who had a $CD4^+$ count of more than 500 cells per microliter
- Randomized to initiate ART immediately or to defer treatment
- Defer treatment until
  - $CD4^+$ count decreased to 350 cells per microliter
  - Development of AIDS
  - Another condition that dictated the use of antiretroviral therapy
- ART regimen was pre-specified by clinician before randomization
- Participants had visits at baseline, month 1, month 4 and every 4 month.



Initiation of Antiretroviral Therapy in Early Asymptomatic HIV Infection
The INSIGHT START Study Group
N Engl J Med 2015; 373:795-807
DOI: 10.1056/NEJMoa1506816

Statistical Methods

- Subgroups were defined using data from baseline
- Longitudinal repeated measures models used to:
  - Compare the mean percent change in weight from baseline for the immediate vs. deferred groups within subgroups
  - Test for treatment group * subgroup interaction
    - Interaction p-value for age, CD4 and HIV RNA from model with continuous variable.
  - Models adjusted for
    - baseline weight, visit and further adjusted for age, gender, region, CD4 and HIV RNA, as appropriate.

Subgroup defined from baseline data
Age
Geographic region : Low-mid-income (Africa, Asia, Latin America) High income (US, Europe, Australia)
Smoking status
Gender
CD4
HIV RNA
Pre-specified ART regimen (INSTI, PI, NNRTI)
Pre-specified NRTI regimen (TDF vs. other)

Results:

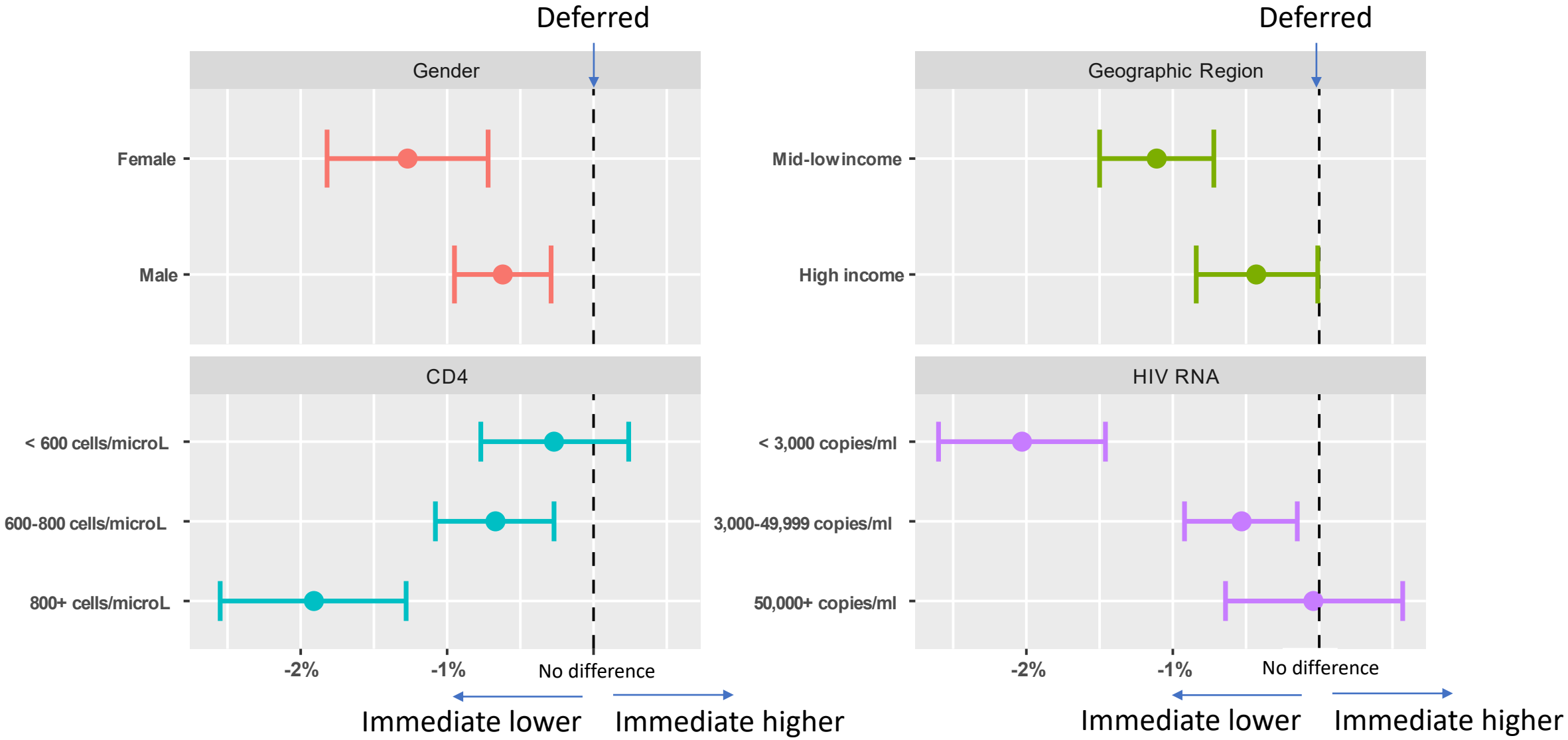
- 4684 participants from 215 sites in 35 countries
- Followed for a mean of 3.0 years
- Mean percent change in weight from baseline:
  - Immediate: 1.1% (95% CI :0.9, 1.5)
  - Deferred: 1.9% (95% CI: 1.7, 2.2)
  - Imm-Def: -0.8% (95% CI: -1.1,-0.5)

Values at study entry	
Median weight	74 kg
Median age	36
% female	26.8%
% smokers	32.0%
Median CD4	651
Median HIV RNA	12761
High income country	46.0%
Low-mid income country	54.0%
ART Class (pre-specified)	
NNRTI	78.7%
INSTI	3.9%
PI	17.4%
NRTI class (pre-specified)	
TDF	88.9%
Other	11.1%

Subgroup * treatment interaction

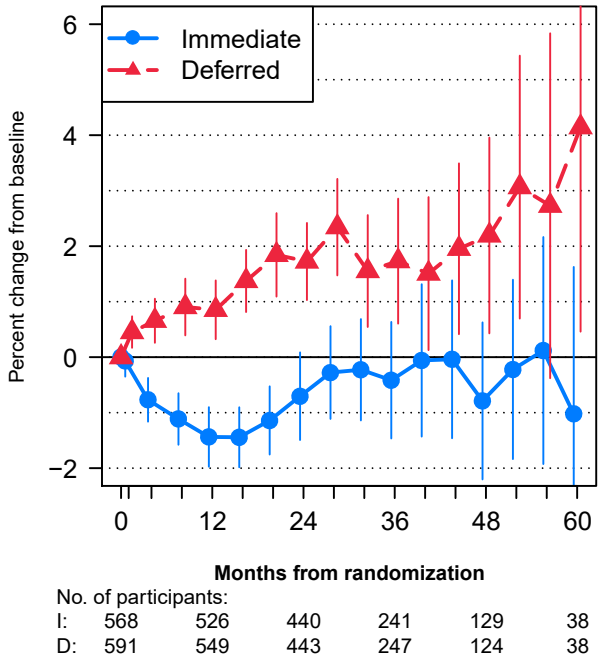
Subgroup	P values	Subgroup	P values
Age	**p = 0.17**	Gender	**p = 0.048**
Smoking status	**p = 0.42**	Geographic Region	**p = 0.019**
Pre-specified ART (INSTI, PI, NNRTI)	**p = 0.06**	$CD4^+$ count	**p < 0.001**
Pre-specified NRTI (TDF vs. others)	**p = 0.63**	HIV-RNA levels	**p < 0.001**

Difference between treatment groups (immediate vs. deferred) in mean percent weight change from baseline



Mean percent change in weight from baseline for immediate and deferred ART group in those with baseline HIV-RNA under 3,000 copies/mL

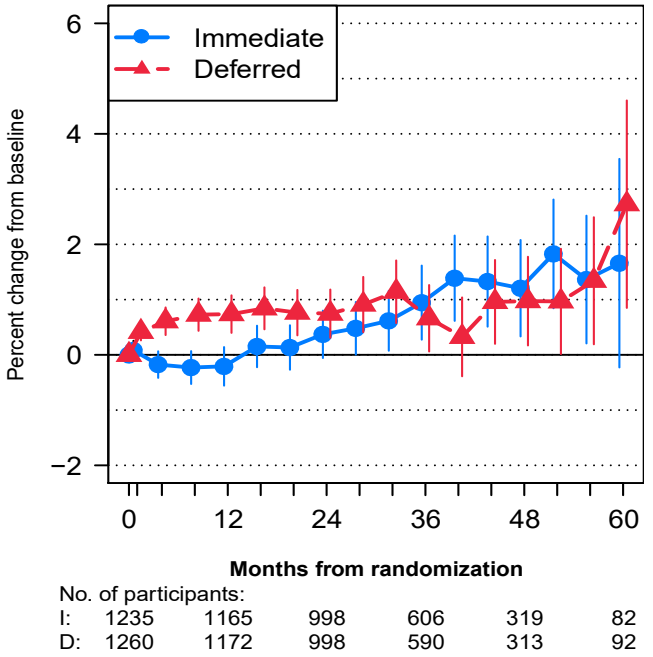
	Mean % Change from Baseline (95% CI)	Imm-Def Difference (95% CI)	Difference P-value
Immediate Group	0.4 (-0.1, 2.4)	**-2.0** (-2.6, -1.5)	<0.001
Deferred Group	2.4 (1.9, 2.9)		



	Months	12	24	36	48
Percentage on ART	Immediate	92%	93%	93%	94%
	Deferred	7%	17%	24%	46%

Mean percent change in weight from baseline for immediate and deferred ART group in those with baseline HIV-RNA between 3,000-50,000 copies/mL

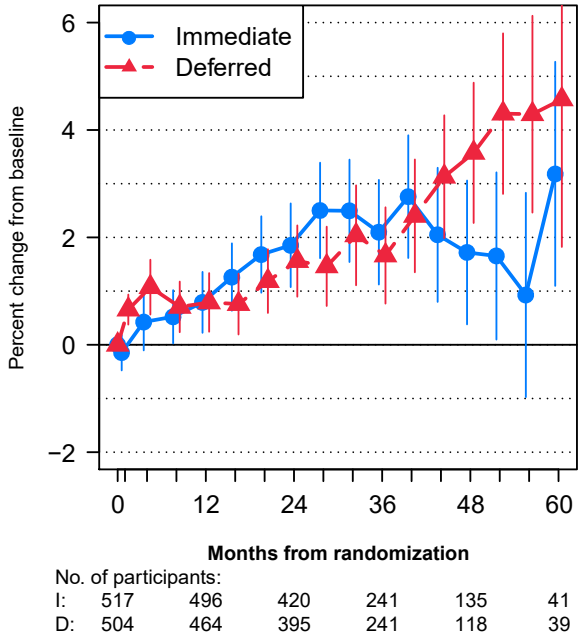
	Mean % Change from Baseline (95% CI)	Imm-Def Difference (95% CI)	Difference P-value
Immediate Group	1.3 (0.9,1.7)	**-0.5** (-0.9, -0.2)	0.006
Deferred Group	1.8 (1.5,2.2)		



	Months	12	24	36	48
Percentage on ART	Immediate	95%	96%	96%	97%
	Deferred	11%	31%	40%	67%

Mean percent change in weight from baseline for immediate and deferred ART group in those with baseline HIV-RNA levels over 50,000 copies/mL

	Mean % Change from Baseline (95% CI)	Imm-Def Difference (95% CI)	Difference P-value
Immediate Group	2.3 (1.8,2.8)	**-0.0** (-0.6,0.6)	0.90
Deferred Group	2.4 (1.9,2.9)		



	Months	12	24	36	48
Percentage on ART	Immediate	96%	97%	97%	98%
	Deferred	27%	51%	64%	80%

Limitations

- The number of participants recieving INSTIs (4%) was too low to consider the effect of INSTIs.
- We were not able to clarify the specific effect of TDF against other NRTIs, since most participants received TDF (89%).

Discussion

- Immediate ART resulted in a delayed weight gain compared to deferral of treatment.
- The effect of ART differed across subgroups by HIV-RNA level, CD4 count, gender and geographic region of the participants. Those with high CD4 counts, of female gender or from low-mid-income countries had a higher difference in weight.
- The difference in weight was pronounced in those with baseline HIV-RNA below 3,000 copies/mL. The weight reduction impact was consistent with the iPrEx study.
- No weight difference was seen between the groups in those with baseline HIV-RNA higher than 50,000 copies/mL.
- We speculate that ART reduces the catabolic effects of HIV-infection in those with high HIV-RNA levels thereby causing a weight increase. Therefore the weight loss effect by ART itself, is no longer evident.

Acknowledgements

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