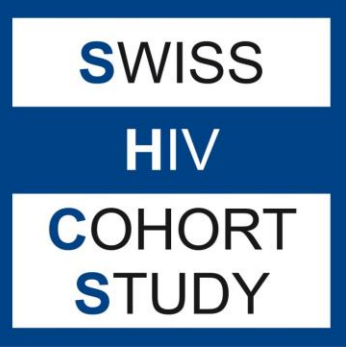


Modelling Waist-Hip Ratio increase in HIV-infected individuals starting antiretroviral therapy



Catalina Barceló (1), Monia Guidi (1,2), Thierry Buclin (1), Philip Tarr (3), Chantal Csajka (1,2) and the Swiss HIV Cohort Study

(1) University Hospital Centre of Lausanne, Switzerland
(2) School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, Switzerland
(3) Infectious Diseases Service, Kantonsspital Baselland, University of Basel, Switzerland



Background and Objectives

Abdominal fat accumulation is common among HIV-infected individuals.¹ Waist-hip ratio (WHR, waist circumference/hip circumference) is an indicator of body fat distribution complementing body mass index (BMI) to identify individuals at increased risk of obesity-related morbidity.²

The aims of this study were to develop a population model characterizing WHR trajectory after antiretroviral therapy (ART) initiation and to quantify the demographic, clinical and pharmacological factors associated with the increase in abdominal obesity.

Methods

- Participants from the Swiss HIV Cohort Study with genetic consent:
 - ART started after 2005 and ≥ 1 WHR measurements before ART start and ≥ 1 WHR measurements after 2011
- Piecewise-linear mixed-effects model (NONMEM 7.4, FOCE-I)
- Covariates tested: age, gender, ethnicity, BMI, CD4 nadir, smoking habit, intravenous drug use, diabetes, HCV, ART regimen and genetic risk score.
- Genetic risk scores calculated from 46 single nucleotide polymorphisms significantly associated with higher WHR in a recent GWAS meta-analysis conducted in the general population.³
- Using the bootstrap models estimates, we simulated WHR values over time for 10'000 individuals and classified them according to WHO cut-offs for abdominal obesity (>0.9 and >0.85).²

Results

- 1000 participants with 8.2 years median follow-up (range 4 to 12) Piecewise-linear model with 3 slopes best described the data. ($\Delta\text{OFV} = -568.8$ and -333.2 , compared to one and two-slope models)

Baseline characteristics	WHR model (n=1000)
Sex (male), n (%)	798 (80)
Age (years), median (range)	40 (19-75)
WHR, median (range)	0.89 (0.56-1.45)
Men >0.9 , n (%)	432 (54)
Women >0.85 , n (%)	87 (43)
BMI (kg/m ²), median (range)	23.24 (14.9-63.36)
Underweight, n (%)	50 (5)
Normal weight, n (%)	637 (64)
Overweight, n (%)	255 (25)
Obesity, n (%)	58 (6)
Ethnicity, n (%)	
Caucasian	857 (86)
African-American	82 (8)
Hispanic	31 (3)
Asian	30 (3)
Nadir CD4 cell count, n (%)	
≤ 99	106 (10)
100-199	207 (21)
≥ 200	687 (69)
Intravenous drug use, n (%)	71 (7)
HCV co-infection, n (%)	143 (14)
Diabetes mellitus, n (%)	34 (3)
Current smoking habit, n (%)	543 (54)
ART (0 to 2.5 years, n=707)	
Protease inhibitors	281 (40)
Nonnucleoside reverse transcriptase inhibitors	398 (56)
Integrase inhibitors	19 (3)
Maraviroc	4 (0.5)
Others	5 (0.5)
Genetic risk score, n=575	
Additive	46 (35-56)
Weighted	0.013 (0.010-0.017)

- Male gender, age and BMI at baseline were associated with a higher WHR before ART initiation (WHR_0).
- During first 2.5 years of ART, individuals with nadir CD4 <100 cells/ μL presented a yearly WHR gain 2.8 times larger ($\text{CI}_{95\%}$: 1.6-3.9) than CD4 nadir ≥ 100 cells/ μL group.
- After 4 years of ART, African and Hispanic individuals presented a yearly WHR gain 2 times larger ($\text{CI}_{95\%}$: 1.1-2.9) than other ethnicities.
- No significant differences were found across ART regimens and genetic risk scores.

Parameters	Final WHR model		Bootstrap (n=2000 samples)	
	Estimate	RSE (%)	Estimate	CI 95%
WHR_0	0.84	0.4	0.84	0.83, 0.85
$\text{SL}_{0-2.5\text{y}}$ (units y^{-1})	0.0039	19	0.0040	0.0025, 0.0054
$\text{SL}_{2.5-4\text{y}}$ (units y^{-1})	0.0038	28	0.0038	0.0017, 0.0059
$\text{SL}_{>4\text{y}}$ (units y^{-1})	0.0029	14	0.0029	0.0021, 0.0037
Age_{WHR0}	0.09	8	0.09	0.08, 0.10
BMI_{WHR0}	0.16	7	0.16	0.14, 0.18
Men_{WHR0}	0.08	6	0.08	0.07, 0.09
$\text{CD4}_{\text{Nadir}} < 100$ cells/ μL $\text{SL}_{0-2.5\text{y}}$	1.76	33	1.73	0.86, 3.31
African or Hispanic $\text{SL}_{>4\text{y}}$	0.99	46	1.00	0.23, 2.05
Exponential residual error (%)	4.0	4	4.0	3.8, 4.1
BSV_{WHR0} (CV%)	5.5	5	5.4	4.9, 6.0
$\text{BSV}_{\text{SL}_{0-2.5\text{y}}}$ (CV %)	396	6	393	326, 543
$\text{BSV}_{\text{SL}_{2.5-4\text{y}}}$ (CV %)	629	9	630	486, 1192
$\text{BSV}_{\text{SL}_{>4\text{y}}}$ (CV %)	269	7	270	241, 327
Correlation WHR_0 - $\text{SL}_{0-2.5\text{y}}$ (%)	-32.7	21	-32.8	-59.0, -16.5
Correlation WHR_0 - $\text{SL}_{2.5-4\text{y}}$ (%)	-26.1	50	-25.2	-76.3, -3.4
Correlation WHR_0 - $\text{SL}_{>4\text{y}}$ (%)	0		0	
Correlation $\text{SL}_{0-2.5\text{y}}$ - $\text{SL}_{2.5-4\text{y}}$ (%)	-26.6	36	-26.8	-62.6, -5.7
Correlation $\text{SL}_{0-2.5\text{y}}$ - $\text{SL}_{>4\text{y}}$ (%)	-24.8	30	-25.0	-51.1, -7.9
Correlation $\text{SL}_{2.5-4\text{y}}$ - $\text{SL}_{>4\text{y}}$ (%)	-18.1	47	-18.6	-49.9, -1.1

Final WHR model

$$\text{WHR} = \text{WHR}_0 + \text{SL}_{0-2.5\text{y}} + (\text{SL}_{2.5-4\text{y}} - \text{SL}_{0-2.5\text{y}}) \times (\text{time}-2.5)_+ + (\text{SL}_{>4\text{y}} - \text{SL}_{2.5-4\text{y}}) \times (\text{time}-4)_+$$

$$\text{WHR}_0 = 0.84 \times (1 + 0.09 \times \frac{\text{Age}-40}{40}) \times (1 + 0.16 \times \frac{\text{BMI}-23}{23}) \times (1 + 0.07\text{men})$$

$$\text{SL}_{0-2.5\text{y}} (\text{y}^{-1}) = 0.0039 \times (1 + 1.76\text{CD4}_{\text{Nadir}} < 100 \text{ cells}/\mu\text{L});$$

$$\text{SL}_{2.5-4\text{y}} (\text{y}^{-1}) = 0.0038; \text{SL}_{>4\text{y}} (\text{y}^{-1}) = 0.0029 \times (1 + 0.99\text{African or Hispanic})$$

Fig 1. pcVPC of WHR final model

Purple dots represent WHR observed measurements. Black lines represent the 5th, 50th and 95th percentiles of observed data. Magenta lines and areas represent the 5th, 50th and 95th percentiles and corresponding 95% confidential intervals of simulated data. PI, prediction interval.

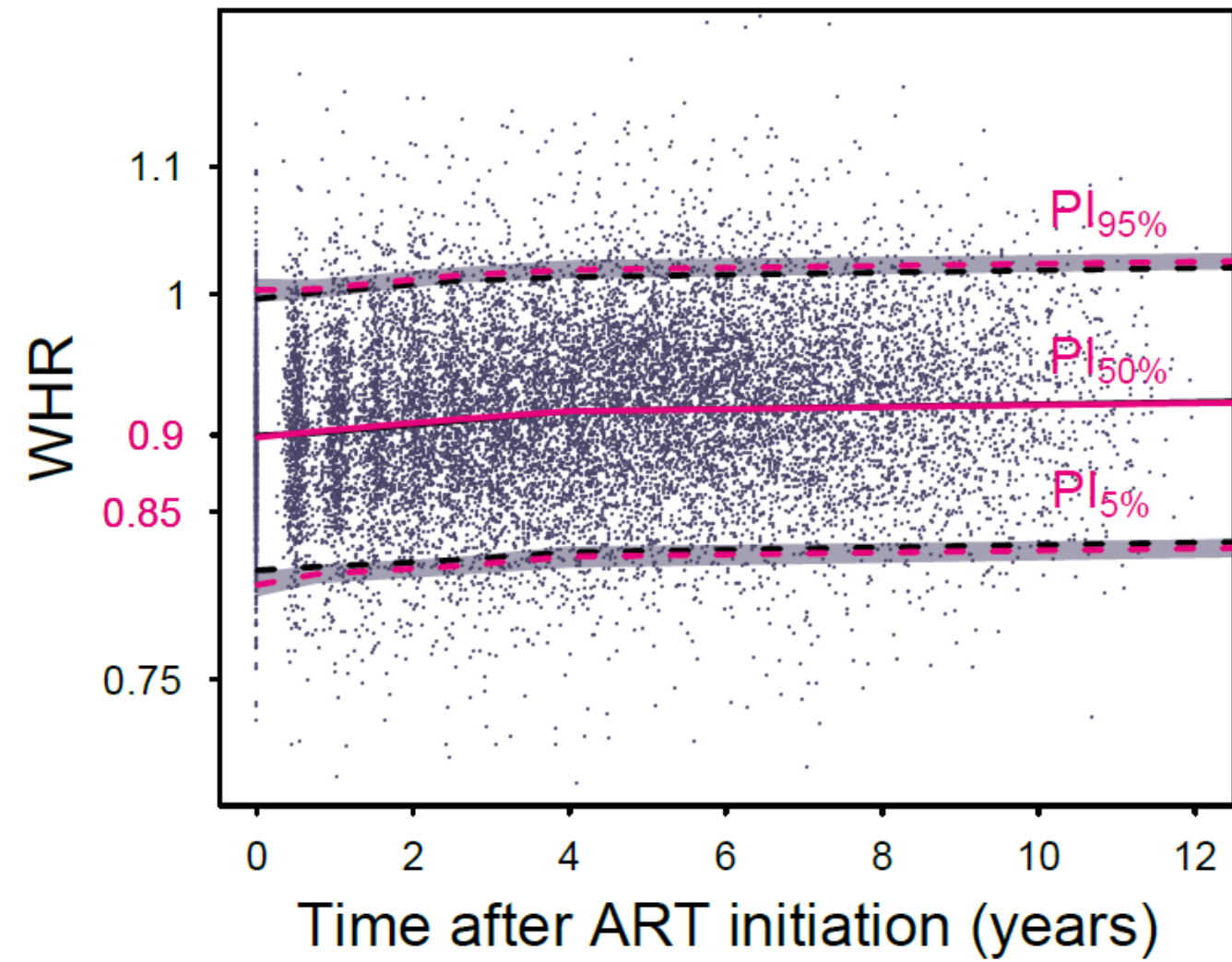
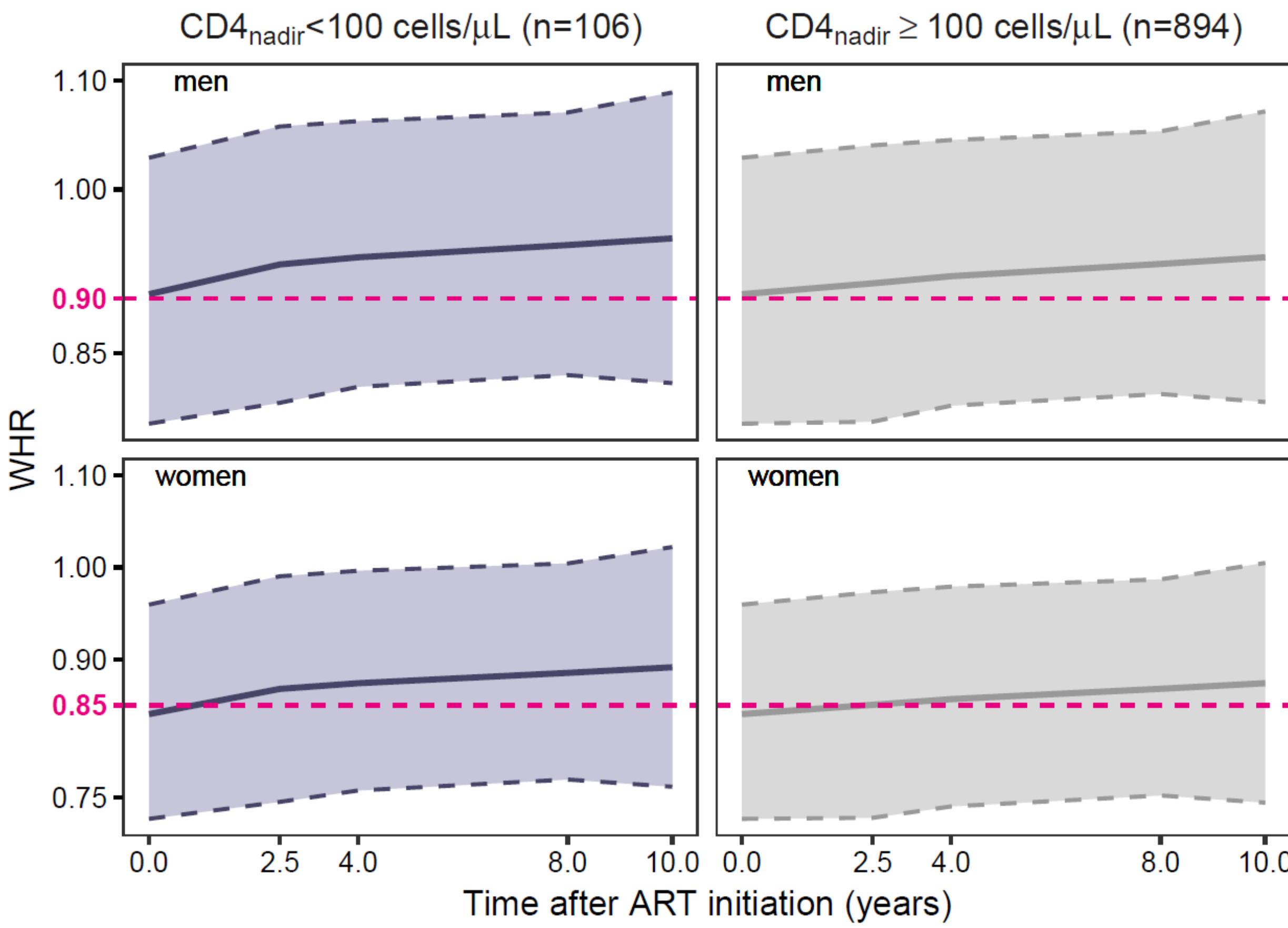


Fig 2. Model-based WHR simulations over time by gender and CD4 nadir categories. Rest of covariates fixed at median or reference value. Colored areas represent 95% prediction intervals.



- Model simulations, using the bootstrap models estimates, showed that individuals in the nadir CD4 cell count <100 cells/ μL group have a higher risk of presenting abdominal obesity at 2.5 years after ART initiation, compared to the nadir CD4 cell count ≥ 100 cells/ μL group ($\text{OR}=1.20$, $\text{CI}_{95\%}$ 1.10-1.31 and $\text{OR}=1.22$, $\text{CI}_{95\%}$ 1.11-1.34, men and women respectively).

Conclusions

- WHR before ART initiation was associated with age and BMI and significantly higher in men.
- WHR gain was larger during the first 2.5 years after ART initiation. Individuals with CD4 nadir <100 cells/ μL showed a 1.8-fold higher gain in WHR and a higher risk to present abdominal obesity after 2.5 years of ART, compared to CD4 nadir ≥ 100 cells/ μL .
- Based on the predicted high prevalence of abdominal obesity, regular WHR monitoring and implementation of weight management interventions is advised after ART initiation, especially in individuals with low nadir CD4 cell count.

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