Modelling body mass index trajectory in HIV-infected individuals

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SWISS HIV COHORT STUDY

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Background and Objectives

Weight gain is common following antiretroviral therapy (ART) initiation, especially during the first years, and might be associated with an increased risk of diabetes and cardiovascular disease[1,2]. There are no current specific recommendations regarding weight counseling and management of HIV-infected patients.

The aims of this study were to develop a population model characterizing body mass index (BMI) evolution before and after ART initiation, and to quantify the relative contribution of demographic and clinical factors.

Methods

✦ Population selection from the Swiss HIV Cohort Study (SHCS):
  ✦ ≥ 5 years of follow-up in the SHCS and ART started after 2005.
  ✦ ≥ 1 BMI measurements before ART start and ≥ 1 BMI measurements after 2011.
  ✦ Genetic consent.

✦ Piecewise-linear mixed-effects model (NONMEM 7.3 and FOCE-I method).

✦ Age, gender, ethnicity, CD4 nadir, smoking and physical activity habits, educational degree, diabetes and HCV diagnostic were tested as covariates using the linearized stepwise covariate model building + cross-validation (PsN 4.2).

Results

✦ 1303 participants with 10 years (range 5 to 31) median follow-up and 26594 BMI measurements (13875 person-years of follow-up).

✦ Residual error autocorrelation was observed (**Fig. 1**). The greater the distance between observations (h) the less correlation between residuals. Autoregressive time series (AR(1)) model was used to account for that (**Eq. 1**)[3].

✦ Structural model included a pre-ART slope (SL0) and two post-ART slopes, one for the first 2.5 years (SL1) and another for the following years (SL2).

| Characteristics	Baseline	Last follow-up
Sex (male), n (%)	1037 (79.6)	1037 (79.6)
Age (years), median (range)	36 (10.1, 17-74)	48 (10.0, 25-82)
BMI (kg/m^2), median (range)	22.9 (3.8, 14.5-61.5)	24.5 (4.5, 13.29-61.5)
Underweight (BMI <18.5), n (%)	56 (4.3)	55 (4.2)
Normal weight (BMI 18.5-24.9), n (%)	899 (69.0)	669 (51.4)
Pre-obesity (BMI 25-29.9), n (%)	276 (21.2)	425 (32.6)
Obesity (BMI ≥30), n (%)	72 (5.5)	154 (11.8)
Ethnicity, n (%)		
Caucasian	1120 (86)	1120 (86)
African-American	103 (7.9)	103 (7.9)
Hispanic	39 (3)	39 (3)
Asian	39 (3)	39 (3)
Other	2 (0.1)	2 (0.1)
CD4 nadir category, n (%)		
≥100 cells/µL	143 (11)	143 (11)
100-199 cells/µL	266 (20.4)	266 (20.4)
≥200 cells/µL	894 (68.6)	894 (68.6)
Educational degree, n (%)		
Low (mandatory school)	233 (17.9)	233 (17.9)
Medium (apprenticeship)	609 (46.7)	609 (46.7)
High (bachelor or more)	445 (34.2)	445 (34.2)
Unknown	16 (1.2)	16 (1.2)
Intravenous drug use, n (%)	100 (7.7)	100 (7.7)
HCV co-infection, n(%)	40 (3.1)	77 (5.9)
Diabetes, n(%)	22 (1.7)	47 (3.6)
Smoking habits, n (%)		
Current	760 (58.3)	542 (41.6)
Never	528 (40.5)	528 (40.5)
Past	15 (1.2)	233 (17.9)
Physical activity habits, n (%)		
Low	360 (27.6)	326 (25.0)
Moderate	728 (55.9)	721 (55.3)
Highly active	215 (16.5)	256 (19.7)
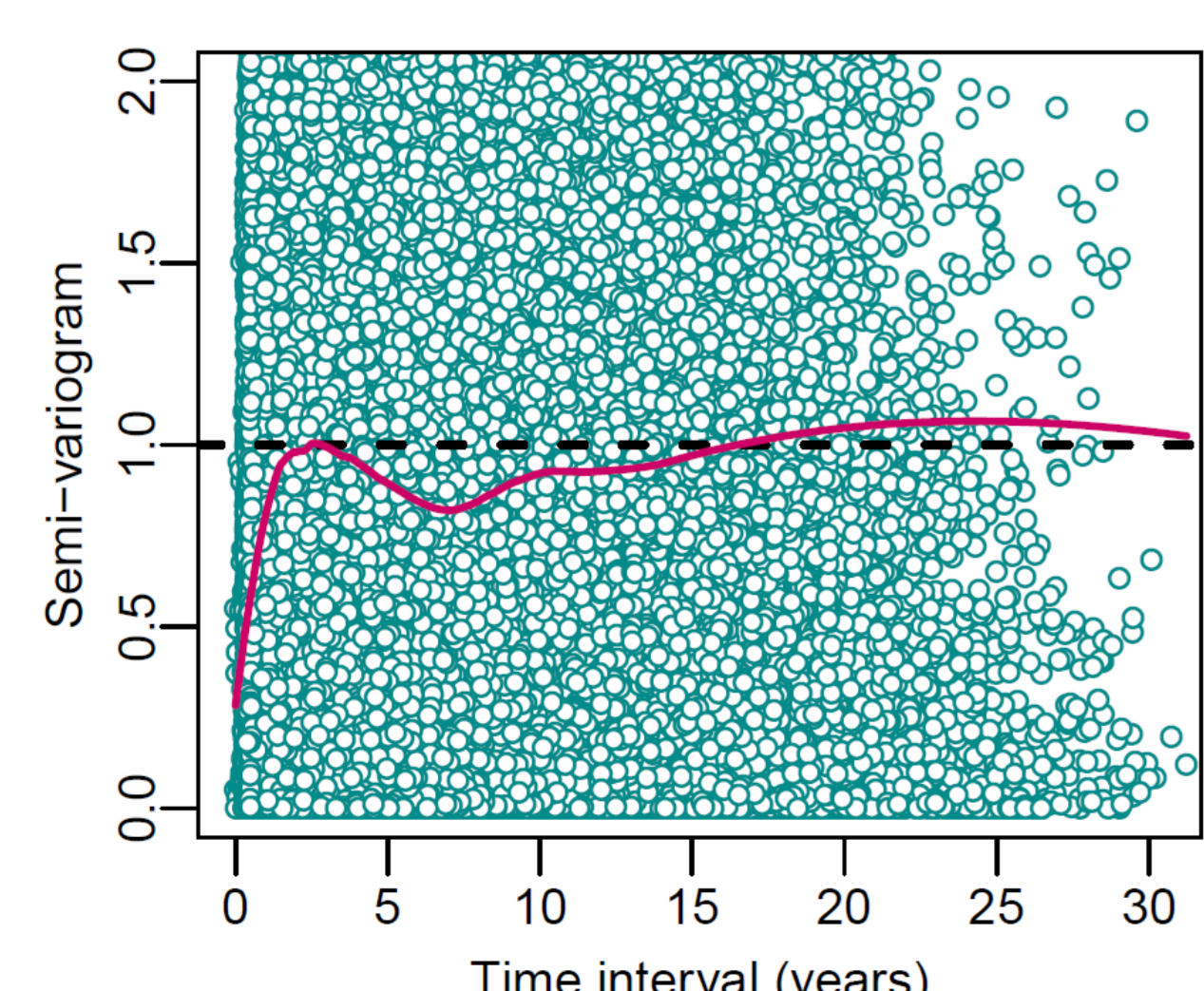
Fig 1. Semi-variogram of structural model IWRES vs time elapsed between corresponding observations (h). Open circles represent one-half the averaged squared difference between pairs of IWRES of observations h units apart for the same individual. The magenta line corresponds to the *lowess* curve for the empirical semi-variogram. The IWRES of a correctly specified model should be centred at 1 (black dashed line) and display no systematic trend.

$$corr(\varepsilon_1, \varepsilon_2) = e^{\frac{-|t_1 - t_2|}{t_{corr}}}$$

Eq 1. Positive correlation between two errors, ε_1 and ε_2, decreases exponentially with the distance between two observations (h). t_{corr} is a constant illustrating how fast the correlation decreases with h.

Parameter	Structural model Estimate	Structural model RSE (95% CI)	Final model Estimate	Final model RSE (95% CI)
BMI$_{Baseline}$ (kg m^{-2})	**23.5**	0.4% (23.3,23.7)	**23.7**	0.4% (23.5,23.9)
SL0$_{pre-ART}$ (kg m^{-2} y^{-1})	**0.07**	17.2% (0.05,0.10)	**0.10**	13.9% (0.08,0.13)
SL1$_{≤2.5yART}$ (kg m^{-2} y^{-1})	**0.28**	7.4% (0.24,0.33)	**0.20**	9.8% (0.16,0.24)
SL2$_{>2.5yART}$ (kg m^{-2} y^{-1})	**0.09**	11.0% (0.07,0.11)	**0.11**	10.2% (0.08,0.13)
1/t$_{corr}$(y^{-1})	**1.49**	39.8% (0.33,2.70)	**1.43**	40.8% (0.29,2.60)
RE$_{prop}$ (%)	**4.4**	6.2%	**4.4**	6.5%
BSV$_{BASE}$ (CV%)	**14.5**	5.9%	**13.6**	5.6%
BSV$_{SL0}$ (CV %)	**270**	33.4%	**177**	38.2%
BSV$_{SL1}$ (CV %)	**193**	15.4%	**263**	16.9%
BSV$_{SL2}$ (CV %)	**274**	20.7%	**223**	23%
Age (10y)$_{BASE}$			**0.03**	12.5% (0.02,0.04)
Diabetes$_{BASE}$			**0.15**	25.3% (0.08,0.23)
African$_{BASE}$			**0.06**	30% (0.03,0.1)
Asian$_{BASE}$			**-0.09**	20.2% (-0.13,-0.06)
Nadir<100 cells/µL$_{SL0}$			**-1.9**	24.3% (-2.9,-1.0)
Nadir<200 cells/µL$_{SL0}$			**-1.0**	23.8% (-1.5,-0.5)
Nadir<200 cells/µL$_{SL1}$			**1.0**	25.3% (0.5,1.5)
African$_{SL1}$			**1.0**	31.5% (0.4,1.6)
Hispanics$_{SL1}$			**-0.8**	42.3% (-1.4,-0.1)
HCV$_{SL2}$			**-0.8**	30.6% (-1.4,-0.3)

Final BMI model

BMI$_{Baseline}$ (kg m^{-2}) = 23.7 x (1+0.15^{diabetes}) x (1+0.06^{African}) x (1 -0.09^{Asian}) x (1 +0.003 x (Age-Age$_{median}$))

SL0$_{pre-ART}$ (kg m^{-2}y^{-1}) = 0.1 x (1 -1.9$^{nadir<100cells/µ}$) x (1 -1$^{nadir<200cells/µ}$)

SL1$_{≤2.5yART}$ (kg m^{-2}y^{-1}) = 0.2 x (1+1$^{nadir<200cells/µ}$) x (1 +1^{African}) x (1 -0.8^{Hispanic})

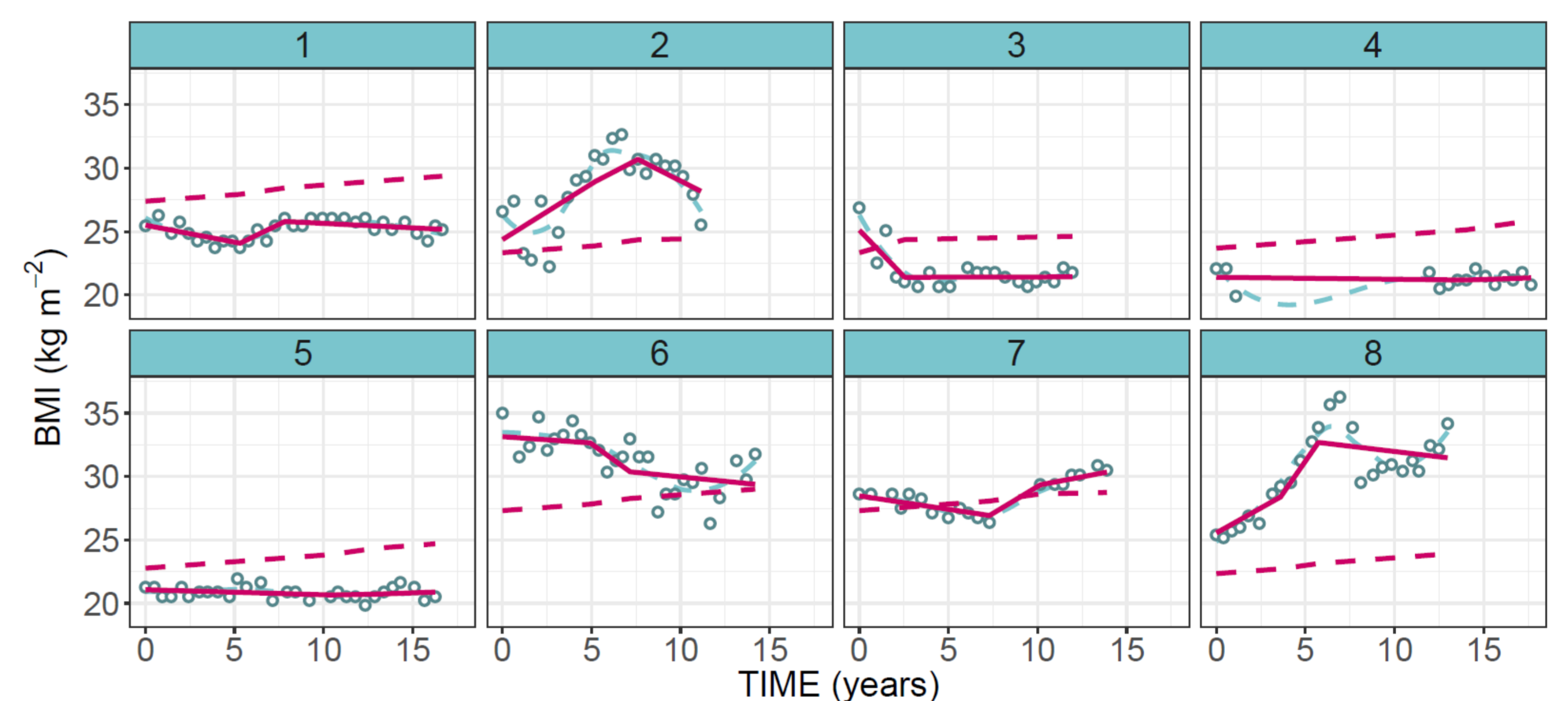**SL2$_{>2.5yART}$** (kg m^{-2}y^{-1}) = 0.11 x (1 -0.8^{HCV})

Fig 2. Example of individual profiles using BMI final model. Open circles represent real observations while the turquoise dashed-line corresponds to the *lowess* curve. The dashed and continuous magenta lines correspond to the model population (PRED) and individual (IPRED) prediction respectively.
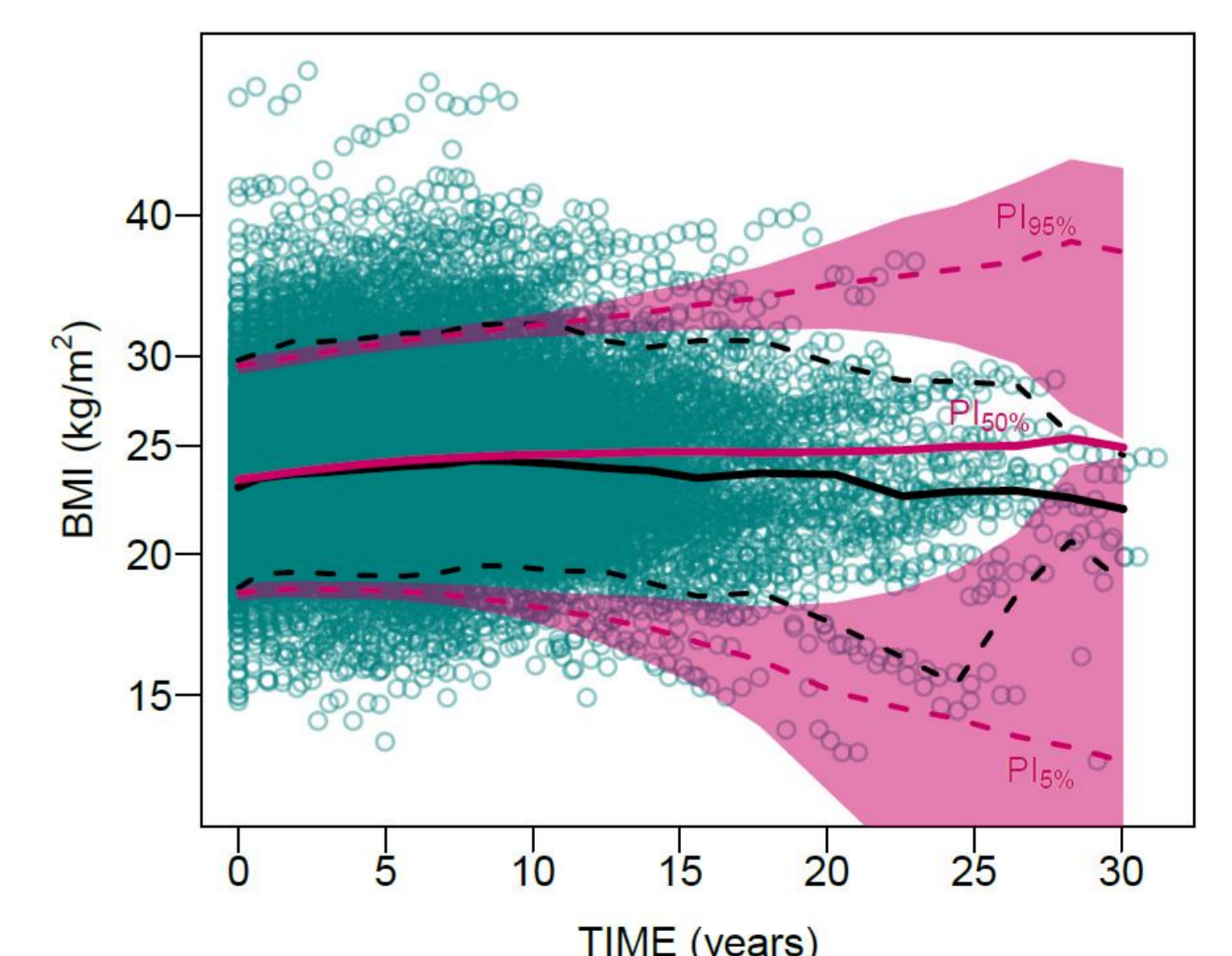

Fig 3. prediction-corrected Visual Predictive Check of BMI final model. Open circles represent BMI measurements. Black lines represent the 5th, 50th and 95th percentiles of observed data. Magenta lines represent the 5th, 50th and 95th percentiles of simulated data.

Conclusions

✦ The first 2.5 years of ART are characterized by a significant increase in BMI (+0.7 kg m^{-2} in average), further influenced by CD4 nadir and ethnicity.

✦ After a relatively steep slope during the first 2.5 years of ART, weight gain seems to return to an average level comparable with the general population, being lessened by HCV co-infection[4].

✦ This model will be further refined with obesity-associated genetic markers and ART regimens in order to create a useful tool to inform metabolic risk factor management in the HIV-infected population.

1. Achhra AC, Mocroft A, Reiss P et al. Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study. *HIV Med* 2016; 17: 255-68.
2. Hasse B, Iff M, Ledergerber B et al. Obesity Trends and Body Mass Index Changes After Starting Antiretroviral Treatment: The Swiss HIV Cohort Study. *Open Forum Infect Dis* 2014; 1: ofu040.
3. Karlsson MO, Beal SL, Sheiner LB. Three new residual error models for population PK/PD analyses. *J Pharmacokinet Biopharm* 1995; 23: 651-72.
4. Collaboration NCDRF. Trends in adult body-mass index in 200 countries from 1975 to 2014: a pooled analysis of 1698 population-based measurement studies with 19.2 million participants. *Lancet* 2016; 387: 1377-96.