P057

Improving Methods for Patient-Reported Outcome (PRO) Analyses in Observational HIV Studies

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Background

- Patient-reported outcomes (PROs), such as patient satisfaction and tolerability provide a unique opportunity to tailor clinical care and therapeutic pathways to patients' needs[1].
- They are important differentiators between treatment regimens, increasingly used to support the interpretations of clinical outcomes[2].
- Pharmaceutical analyses often utilise simplistic methods such as paired difference tests to compare data obtained at pre-defined follow-up periods to baseline [2-5], using likely implausible missing data assumptions and providing limited longitudinal information on PROs.

Objective

- To evaluate statistical methods used for the analysis of PROs, through their application to a real-world HIV-1 dataset.

Methods

- Firstly, four statistical approaches were evaluated on the treatment-naïve (TN) subgroup of the TAFNES observational cohort of HIV-1 patients (Table 1). Each method was applied to the analysis of the SF-36 [a] mental component score (MCS) and physical component score (PCS). Data were collected at approximately 0, 3, 6, 12, 18 and 24 months after antiretroviral therapy initiation. Each method was compared with a categorical-time variable.
- Secondly, the use of a continuous-time variable was evaluated with the weighted generalised estimating equation, and three non-linear modelling methods (Table 2).

Table 1. Statistical Methods evaluated (Categorical-time variable)

Approach	Details
1) Paired difference (PD) test	♦ Paired Wilcoxon rank sum test ♦ Test for each follow-up visit vs. treatment-initiation ♦ Bonferroni correction for multiple testing
2) Repeated-Measures ANOVA (RM-ANOVA)	♦ Friedman's ANOVA [b]
3) Linear Mixed Model (LMM)	♦ Controlling for covariates: Age, sex, ongoing mental comorbidities, ongoing physical comorbidities, presentation with advanced HIV [c], log_{10} HIV RNA ♦ Analysed on transformed scale to satisfy normality assumptions: -log(100-score)
4) Weighted Generalised Estimating Equation (wGEE)	♦ Covariates as for LMM ♦ Analysed on untransformed scale (no distributional assumptions)

a) Generic PRO tool that measures mental and physical health-related quality of life (HRQoL). Each score ranges 0-100. Higher scores indicate better HRQoL;
b) Non-parametric ANOVA;
c) Presenting for care with a CD4 cell count ≤200/ul or presenting with an AIDS-defining event, regardless of the CD4 cell count [6];
d) Using the wGEE approach.

Table 2. Non-linear modelling methods evaluated (Continuous-time variable) [d]

Approach
Polynomial Transformation
Fractional Polynomial Transformation
Piecewise Linear Splines

Results

Study Population

- 286 TN HIV-1 patients provided evaluable SF-36 data at ≥1 visit: majority male (93.7%), mean age = 38.6 (sd 11.1), median baseline log_{10} HIV RNA = 10.3 (IQR 9.1 – 11.7).

Approach 1) Paired difference test

- Showed significant improvement in MCS & PCS from Month 0 (M0) to each follow-up visit (Table 2).
- Patients with SF-36 data at both visits, N = 155 - 178 (54.2% - 62.2% of total population).
- Incorrectly assumed missing data were missing completely at random (MCAR).

Table 2. PWRS test change in median scores

M0 vs:	Analysis population N	Change in median MCS (P-value)	Change in median PCS (P-value)
M3	177	+3.9 (<0.001)	+1.0 (0.010)
M6	178	+5.1 (<0.001)	+1.2 (0.006)
M12	158	+4.6 (<0.001)	+0.6 (0.010)
M18	155	+3.4 (<0.001)	+1.1 (0.010)
M24	155	+5.1 (<0.001)	+1.3 (0.015)

Approach 2) Repeated-Measures ANOVA

- Showed a significant difference in MCS (p =0.01), but not PCS (p = 0.30) across visits.
- Patients with balanced SF-36 data (observation at all visits), N = 73 (25.5% of total pop.).
- Incorrectly assumed missing data were MCAR.

Approach 3) Linear Mixed Model and 4) Weighted Generalised Estimating Equation

- Both approaches showed significant improvements in MCS & PCS between treatment initiation and each follow-up visit. Both identified covariates associated with MCS & PCS and their change over time (Table 3).

Table 3. LMM and wGEE estimates for the associations between the candidate model predictors and mean MCS and PCS

	wGEE		LMM	
	MCS	PCS	MCSt [a]	PCSt [a]
Visit				
M0 to M3 [b]	+ 3.9	+1.5	+0.07	+0.02
M0 to M6 [b]	+4.2	+1.8	+0.08	+0.03
M0 to M12 [b]	+4.8	+1.3	+0.08	+0.02
M0 to M18 [b]	+2.9	+1.6	+0.06	+0.03
M0 to M24 [b]	+4.8	+1.6	+0.07	+0.02
Higher Age (decades)		-1.6		-0.03
Sex				
Higher Nº of Mental Comorbidities	-6.8		-0.12	
Higher Nº of Physical Comorbidities		-0.8		-0.01
Presentation with Advanced HIV (yes) [c]				
At M0		-5.2		-0.09
Difference in M0 to M3 change		+3.2		+0.06
Difference in M0 to M6 change		+5.1		+0.10
Difference in M0 to M12 change		+5.1		+0.11
Difference in M0 to M18 change		+4.6		+0.09
Difference in M0 to M24 change		+4.0		+0.08
Higher baseline HIV viral load (log_{10} c/ml)				
At M0	-0.9	-0.5	-0.02	-0.01
Difference in M0 to M3 change	+0.8	+0.7	+0.01	+0.01
Difference in M0 to M6 change	+0.8	+0.5	+0.02	+0.01
Difference in M0 to M12 change	+0.7	+0.7	+0.01	+0.01
Difference in M0 to M18 change		+0.6		+0.01
Difference in M0 to M24 change		+0.9		+0.02

Positive effect | Negative effect | Insignificant effect (p>0.05)

a) Transformed MCS & PCS: -log(100-score); b) MCS: For patients with the population average log_{10} HIV RNA. PCS: For patients who did not present with advanced HIV and with the population average log_{10} HIV RNA; c) Person presenting for care with a CD4 cell count ≤200/ul or presenting with an AIDS-defining event, regardless of the CD4 cell count [6].

- Patients with SF-36 data at ≥1 visit and complete covariate data, N = 285 (99.7% of total population).
- Assumed missing data were missing at random (MAR). Sensitivity analysis showed results were largely robust to missing not at random (MNAR).
- LMM normality assumptions required analysis on a transformed scale, wGEE did not.

Continuous-time analyses (wGEE)

- Estimated the nature of the change in scores, demonstrating steep improvements in MCS and PCS after treatment initiation followed by a plateau (Figure 1).
- The same covariate associations were identified as in the categorical models (Table 3).
- Average model estimates at each visit were similar to the observed averages (Figure 2).
- Similar model fit across continuous-time models. All better fit than categorical models.

Figure 1. Continuous-time wGEE model estimates for change in MCS and PCS, in order of model fit [a].

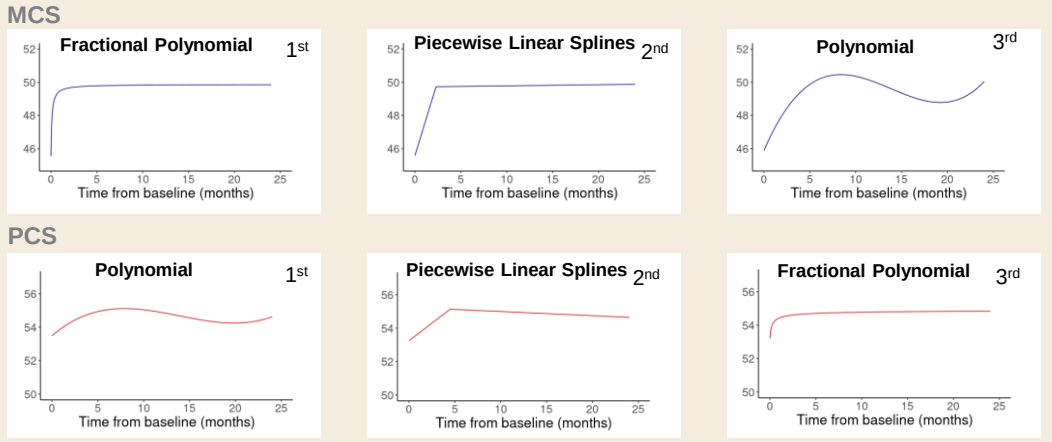
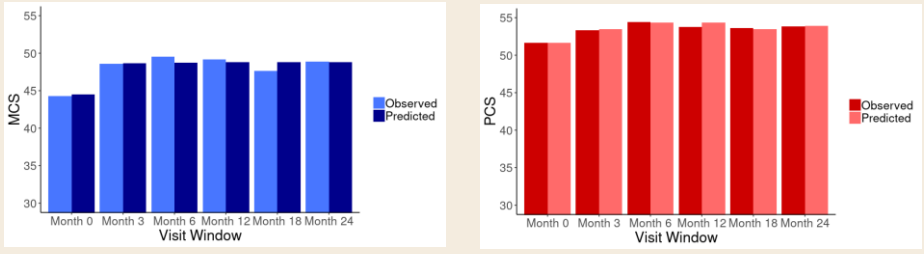


Figure 2. Observed values and predicted estimates for mean MCS and PCS at each visit [b]



a) Estimates for an individual with the population-average characteristics – male, no comorbidities, not presenting with advanced HIV, mean log_{10} HIV RNA, mean age; b) Predicted values are the mean estimates from the best-fitting continuous-time models (MCS – fractional polynomial, PCS - Polynomial), for each patient at each visit.

Discussion

Approach	Strengths	Limitations
1) PD test	♦ Easily performed	♦ Simplistic conclusion ♦ Inappropriate missing data assumption
2) RM-ANOVA	♦ Compares all visits	♦ Required balanced data ➔ reduced statistical power and biased results ♦ Inappropriate missing data assumption
3) LMM	Both LMM and wGEE: ♦ Can handle unbalanced data ♦ Large analysis population ➔ greater statistical power ♦ Additional covariate information ♦ Appropriate missing data assumption ♦ Can analyse continuous variables ♦ Can analyse interactions ♦ No outcome transformation required	♦ Outcome transformation required ➔ reduced interpretability
4) wGEE		♦ Weighting required for appropriate missing data assumption ♦ Lower precision than LMM

Conclusions

Multivariate statistical models for the analyses of PRO in HIV-1 patients show significant advantages over simplistic comparisons:

They help to identify patient focus groups:
- Older patients
- Patients with comorbidities

And showed:
- significant improvements of scores within the first few months of treatment (TN)
- stable plateauing of scores during the follow-up period (treatment-experienced)

which enables cost-effective study resource planning.

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