Methods

Firstly, four statistical approaches were evaluated on the treatment-naïve (TN) subgroup of the TAFINES observational cohort of HIV-1 patients (Table 1). Each method was applied to the analysis of the SF-36 * 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 (Categorical-time variable)

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<tr>
<th>Approach</th>
<th>Details</th>
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<tr>
<td>1) Paired difference (PD)</td>
<td>Paired Wilcoxon rank sum test</td>
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<tr>
<td>2) Repeated-Measures ANOVA (RM-ANOVA)</td>
<td>Friedman’s ANOVA *</td>
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<tr>
<td>3) Linear Mixed Model (LMM)</td>
<td>Controlling for covariates: Age, sex, ongoing mental comorbidities, ongoing physical comorbidities, presentation with advanced HIV, log10 HIV RNA Analysed on transformed scale to satisfy normality assumptions: log10(100 - score)</td>
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<tr>
<td>4) Weighted Generalised Estimating Equation (wGEE)</td>
<td>Covariates as for LMM Analysed on untransformed scale (no distributional assumptions)</td>
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</table>

Table 2. Non-linear modelling methods evaluated (Continuous-time variable) a

<table>
<thead>
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<th>Approach</th>
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<tr>
<td>Polynomial Transformation</td>
<td>Fractional Polynomial Transformation Piecewise Linear Splines</td>
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Objective

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

Results

Study Population

286 TN HIV-1 patients provided evaluable SF-36 data at 12 visit: majority male (93.7%), mean age = 38.6 (sd 11.1), median baseline log10 HIV RNA = 10.3 (IQR 9.1 – 11.7).

Approach 1) Paired difference test

- Showed significant improvement in MCS & PCS from Month 0 (PD) to each follow-up visit (Table 2).
- Patients with SF-36 data at both visits, N = 155 - 176 (58.2%- 62.2% of total population).
- Incorrectly assumed missing data were missing completely at random (MCAR).

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).

Approach

- Friedman’s ANOVA
- Controlling for covariates: Age, sex, ongoing mental comorbidities, ongoing physical comorbidities, presentation with advanced HIV, log10 HIV RNA Analysed on transformed scale to satisfy normality assumptions: log10(100 - score)
- Covariates as for LMM Analysed on untransformed scale (no distributional assumptions)
- Preparing for care with a CD4 cell count ≥350 at or presenting with an AIDS-defining event, regardless of the CD4 cell count*.
- Using the wGEE approach.

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 steeper 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.

Discussion

Approach

- PD test
- Easily performed
- Simplicistic conclusion
- Inappropriate missing data assumption
- Required balanced data
- Reduced statistical power and biased results
- Inappropriate missing data assumption
- Outcome transformation required

RM-ANOVA

- Comparing at visits
- Weighting required for appropriate missing data assumption
- Lower precision than LMM

LMM

- 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

wGEE

- Weighting required for appropriate missing data assumption
- No outcome transformation required

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 (experienced)