Is a simple self-rating or visual analogue scale more accurate than prescription refill data, as an indicator of non-adherence in a resource-limited setting in South Africa?

Meyer JC, Summers B, Lentsoane PP, Mokoka MV, Nyingwa J, Teffu SM

7th International Conference on HIV Treatment and Prevention Adherence, Miami
3-5 June 2012

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Adherence - important predictor of antiretroviral treatment (ART) success

Methods to measure adherence
- Each method has advantages & limitations
- No gold standard to measure adherence

Measures of adherence
- Patient self-report
- Dispensing-based (refill)

Associated with clinical outcomes

(Chesney, 2006; Henry, 2011)

(Berg et al., 2010; Bisson et al., 2008; Chalker et al., 2010; Henry, 2011; Nachega et al., 2006; Ross-Degnan et al., 2010)
Valid, inexpensive, rapid assessment of adherence
- Essential to monitor ART in resource-limited settings

Functional computer systems
- Not always available in resource-limited settings to facilitate reliable and easily-traceable pharmacy refill data

**Challenges:**
- Rapid **scaling-up** of ART
- **Down-referral** of stabilised patients to nurse-managed clinics
- **Nurse-initiated** ART

Essential to identify validated methods to measure and monitor adherence, and predict clinical outcomes
OBJECTIVES

- To measure adherence for patients attending Tshepang ART Clinic at Dr George Mukhari Hospital using three different methods
  - Self-report 6-level rating scale
  - Self-report ‘visual analogue scale’ (VAS)
  - Prescription refill data
- To examine agreement between adherence measures and association with clinical markers
- To validate the adherence measures against standards for treatment failure
METHODOLOGY: Study site

Dr George Mukhari Hospital
- Public sector academic hospital
- Ga-Rankuwa, west of Pretoria
- Gauteng Province

Tshepang ART clinic = Place of Hope
Approximately 6 500 patients initiated on ART since 2005
target population

- Live in surrounding semi-urban and rural areas
- Obtain ART from Tshepang Clinic at 4-weekly intervals

ethics considerations

- Medunsa Campus Research and Ethics Committee
- CEO Dr George Mukhari hospital Clinic Head of Tshepang Clinic
- Written consent from patients

inclusion criteria

- HIV positive adults ≥18 years
- On ART for at least 6 months
- Setswana or English speaking

permission to conduct the study
METHOD
Data collection

- Data collection
  - Period of 4 weeks in June 2011
  - Four final year BPharm students

- Data collection training
  - Standardise data collection and interview techniques

- Data collection instruments
  - Structured questionnaire in English and Setswana
  - Retrospective dispensing form

Pilot study
- Feasibility of study
- Test data collection instruments
Patients attending clinic for repeat prescriptions: n=253 (convenience sample, ±20 patients/day, 3 days/week)

Face-to-face structured interview - preferred language of conversation

- Adherence self-report past 4 weeks
  - Rating scale
  - ‘VAS’

- Demographic data

Retrospective file review

- Adherence past 6 months: Prescription refill data
- Clinical markers
- CD4 count within last 6 months
- Viral load within last 6 months

Sub-sample (n=164)

Sub-sample (n=184)
METHOD
Adherence measures: Self-report past 4 weeks

Prospective: ‘Visual analogue scale’ (VAS)

Antiretroviral medication left after one month (4 weeks)

Very few
A
B
C
D
E
F
Half
G
H
I
J
K
All
L

Converted to % adherence

Prospective: 6-item rating scale

Excellent
Very good
Good
Fair
Poor
Very poor

Category of adherence

Adapted from: Ereng, 2011; Polejack, 2007
### METHOD

**Adherence measures: Prescription refill past 6 months**

- **Retrospective: Prescription refill**

<table>
<thead>
<tr>
<th></th>
<th>Date ARVs dispensed</th>
<th>Number of days ARVs dispensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ART initiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 1 (index visit)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Visit 6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Average % of days covered by ARVs over 6 months period
METHOD
Data entry & analysis

Data entry: Microsoft Office Excel™ spreadsheet
- Cross-checked for correctness and completeness

Data analysis: IBM SPSS Statistics 20®
- Evaluation of adherence measures
  - Gold standard: Virologic (VL>400 copies/ml) and immunologic (CD4<100 cells/µL) treatment failure
  - Responses to rating scale: converted to numbers
  - Numbers (%): converted to categories

<table>
<thead>
<tr>
<th>Rating</th>
<th>VAS</th>
<th>Refill</th>
<th>Adherence cut-off</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excellent</td>
<td>95-100%</td>
<td>95-100%</td>
<td></td>
</tr>
<tr>
<td>Very good</td>
<td>90%</td>
<td>85&lt;95%</td>
<td>&lt;95%</td>
</tr>
<tr>
<td>Good</td>
<td>80%</td>
<td>75&lt;85%</td>
<td>&lt;85%</td>
</tr>
<tr>
<td>Fair</td>
<td>70%</td>
<td>65&lt;75%</td>
<td>&lt;75%</td>
</tr>
<tr>
<td>Poor</td>
<td>60%</td>
<td>55&lt;65%</td>
<td></td>
</tr>
<tr>
<td>Very poor</td>
<td>50%</td>
<td>&lt;55%</td>
<td></td>
</tr>
</tbody>
</table>
RESULTS AND DISCUSSION
Mean age: 39.9 (SD±10.8) years; Median age: 38.2 years
Educational level (n=253)

- None: 56%
- Primary: 40%
- Secondary incomplete: 12%
- Secondary: 6%
- Tertiary / vocational: 5%

Demographic information: Educational level
Unemployment rate in South Africa = 25%  
(Statistics SA, 2011)
Antiretroviral treatment (ART)

Time on ART (n=253)

- 55%: 6-24 months
- 22%: 25-48 months
- 23%: >48 months

Mean: 30 months (SD±21.9); Median: 21.6 months

Mostly:
- Lamivudine
- Stavudine or Tenofovir
- Efavirenz or Nevirapine

Regimen 1: 201 (79%)
Regimen 2: 52 (21%)
Self-report past 4 weeks
Distribution of patients by adherence % score

Distribution of patients by adherence % score: VAS (n=253)

Distribution of patients by adherence % score: Rating scale (n=253)

Excellent
Very good
Good
Fair
Poor
Very poor
Refill data past 6 months
Distribution of patients by adherence % score

Distribution of patients by adherence % score: Refill (n=253)
Adherence measures compared
% of patients per category of adherence

- Excellent: Rating (n=253) - 17%, VAS (n=253) - 45%, Refill (n=253) - 53%
- Very good: Rating (n=253) - 24%, VAS (n=253) - 30%
- Good: Rating (n=253) - 6%, VAS (n=253) - 14%, Refill (n=253) - 36%
- Fair: Rating (n=253) - 9%, VAS (n=253) - 13%
- Poor: Rating (n=253) - 2%, VAS (n=253) - 4%
- Very poor: Rating (n=253) - 0.4%, VAS (n=253) - 0.4%

- ≥95% adherence
- ≥85% adherence
- ≥75% adherence
Adherence measures compared for different cut-off points
% of patients per category of adherence

<table>
<thead>
<tr>
<th>Adherence cut-off</th>
<th>Refill (n=253)</th>
<th>VAS (n=253)</th>
<th>Rating (n=253)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥95%</td>
<td><strong>53%</strong></td>
<td><strong>45%</strong></td>
<td><strong>17%</strong></td>
</tr>
<tr>
<td></td>
<td><em>P=0.13050</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥85%</td>
<td>91%</td>
<td>69%</td>
<td>47%</td>
</tr>
<tr>
<td>Excellent &amp; very good</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75%</td>
<td>97%</td>
<td><strong>83%</strong></td>
<td><strong>83%</strong></td>
</tr>
<tr>
<td>Excellent, very good &amp; good</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fisher’s Exact test
Adherence measures compared
Mean adherence score (%)

<table>
<thead>
<tr>
<th>One-Way ANOVA</th>
<th>Measure</th>
<th>Measure</th>
<th>Mean diff</th>
<th>SE</th>
<th>P</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Refill</td>
<td>VAS</td>
<td>7.3881</td>
<td>1.0405</td>
<td>.000</td>
<td>4.893</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Rating</td>
<td>9.6213</td>
<td>0.8324</td>
<td>.000</td>
<td>7.627</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>Refill</td>
<td>-7.3881</td>
<td>1.0405</td>
<td>.000</td>
<td>-9.883</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>Rating</td>
<td>2.2332</td>
<td>1.1342</td>
<td>.141</td>
<td>-.485</td>
</tr>
</tbody>
</table>
Adherence (% score): Association between measures

<table>
<thead>
<tr>
<th></th>
<th>Rating</th>
<th>VAS</th>
<th>Refill</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rating</td>
<td>rho</td>
<td>1</td>
<td>0.632</td>
</tr>
<tr>
<td></td>
<td>P (2-tailed)</td>
<td>-</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>253</td>
<td>253</td>
</tr>
<tr>
<td>VAS</td>
<td>rho</td>
<td>1</td>
<td>0.048</td>
</tr>
<tr>
<td></td>
<td>P (2-tailed)</td>
<td>-</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td>253</td>
<td>253</td>
</tr>
<tr>
<td>Refill</td>
<td>rho</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>P (2-tailed)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td>253</td>
</tr>
</tbody>
</table>

Spearman’s Rank correlation: significant at the 0.01 level (2-tailed)
Clinical markers: Viral load (VL)

Viral load (copies/ml) within past 6 months (n=184)
- VL≤400 copies/ml: 119 (65%)
- VL>400 copies/ml: 65 (35%)

Median VL: 40 cells/µl

<table>
<thead>
<tr>
<th>Time on ART (months)</th>
<th>6-24 months</th>
<th>25-48 months</th>
<th>&gt;48 months</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>VL≤400 copies/ml</td>
<td>83 (80%)</td>
<td>16 (42%)</td>
<td>20 (48%)</td>
<td>119 (65%)</td>
</tr>
<tr>
<td>VL&gt;400 copies/ml</td>
<td>21 (20%)</td>
<td>34%</td>
<td>34%</td>
<td>65 (35%)</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
<td>38</td>
<td>42</td>
<td>184</td>
</tr>
</tbody>
</table>

Percentage of patients with ≥95% adherence by time on ART (n=184)
- Refill (P=0.622)
- VAS (P=0.507)
- Rating (P=0.065)
Clinical markers: CD4 count (cells/µl)

CD4 cell count (cells/µl) within past 6 months (n=164)

- Mean: 304.8 ± 199.4 cells/µl
- Median: 279.0 cells/µl

<table>
<thead>
<tr>
<th>Time on ART (months)</th>
<th>CD4≥100 cells/µl</th>
<th>CD4&lt;100 cells/µl</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>6-24 months</td>
<td>86 (92%)</td>
<td>7 (8%)</td>
<td>93</td>
</tr>
<tr>
<td>25-48 months</td>
<td>29 (83%)</td>
<td>6 (17%)</td>
<td>35</td>
</tr>
<tr>
<td>&gt;48 months</td>
<td>26 (72%)</td>
<td>26 (28%)</td>
<td>36</td>
</tr>
<tr>
<td>Total</td>
<td>141 (86%)</td>
<td>23 (14%)</td>
<td>164</td>
</tr>
</tbody>
</table>

Percentage of patients with ≥95% adherence by time on ART (n=164)

- Refill (P=0.884)
- VAS (P=0.564)
- Rating (p=0.147)
Association of adherence measures with clinical markers

<table>
<thead>
<tr>
<th></th>
<th>Rating</th>
<th>VAS</th>
<th>Refill</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CD4 count</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rho</td>
<td>0.323</td>
<td>0.222</td>
<td>0.021</td>
</tr>
<tr>
<td>P (2-tailed)</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>0.794</td>
</tr>
<tr>
<td>n</td>
<td>164</td>
<td>164</td>
<td>164</td>
</tr>
<tr>
<td><strong>Change in CD4</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rho</td>
<td>0.247</td>
<td>0.231</td>
<td>-0.046</td>
</tr>
<tr>
<td>P (2-tailed)</td>
<td>0.003</td>
<td>0.005</td>
<td>0.583</td>
</tr>
<tr>
<td>n</td>
<td>144</td>
<td>144</td>
<td>144</td>
</tr>
<tr>
<td><strong>Viral load</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rho</td>
<td>-0.333</td>
<td>-0.163</td>
<td>-0.154</td>
</tr>
<tr>
<td>P (2-tailed)</td>
<td>&lt;0.001</td>
<td>0.027</td>
<td>0.036</td>
</tr>
<tr>
<td>n</td>
<td>184</td>
<td>184</td>
<td>184</td>
</tr>
</tbody>
</table>

Spearman’s Rank correlation: significant at the 0.01 level (2-tailed)
Sensitivity and specificity of adherence measures for virologic failure (VL > 400 copies/ml) at different adherence cut-offs

<table>
<thead>
<tr>
<th>Adherence cut-off (n=164)</th>
<th>Measure</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>Refill</td>
<td>55% (43-67)</td>
<td>57% (48-66)</td>
<td>41% (32-52)</td>
<td>70% (60-78)</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>66% (54-76)</td>
<td>52% (43-61)</td>
<td>43% (34-53)</td>
<td>74% (64-82)</td>
</tr>
<tr>
<td></td>
<td>Rating</td>
<td>92% (83-97)</td>
<td>26% (19-35)</td>
<td>41% (33-49)</td>
<td>87% (71-94)</td>
</tr>
<tr>
<td>85%</td>
<td>Refill</td>
<td>15% (9-25)</td>
<td>94% (88-97)</td>
<td>59% (36-80)</td>
<td>67% (60-74)</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>46% (35-58)</td>
<td>73% (65-80)</td>
<td>48% (36-61)</td>
<td>71% (63-79)</td>
</tr>
<tr>
<td></td>
<td>Rating</td>
<td>71% (59-80)</td>
<td>61% (52-69)</td>
<td>50% (40-59)</td>
<td>79% (70-86)</td>
</tr>
<tr>
<td>75%</td>
<td>Refill</td>
<td>6% (2-15)</td>
<td>98% (93-99)</td>
<td>57% (25-84)</td>
<td>66% (58-72)</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>29% (20-41)</td>
<td>87% (79-92)</td>
<td>54% (38-70)</td>
<td>69% (61-76)</td>
</tr>
<tr>
<td></td>
<td>Rating</td>
<td>37% (26-49)</td>
<td>94% (88-97)</td>
<td>77% (60-89)</td>
<td>73% (66-80)</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value; NPV: Negative predictive value
Sensitivity and specificity of adherence measures for virologic failure

<table>
<thead>
<tr>
<th>Virologic failure (n=184)</th>
<th>Failure</th>
<th>VL&gt;400 copies/ml</th>
<th>65 (35%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No failure</td>
<td></td>
<td>VL≤400 copies/ml</td>
<td>119 (65%)</td>
</tr>
</tbody>
</table>
Sensitivity and specificity of adherence measures for immunologic failure (CD4<100 cells/ml) at different adherence cut-offs

<table>
<thead>
<tr>
<th>Adherence cut-off</th>
<th>Measure (n=164)</th>
<th>Sensitivity (95% CI)</th>
<th>Specificity (95% CI)</th>
<th>PPV (95% CI)</th>
<th>NPV (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>95%</td>
<td>Refill</td>
<td>44% (26-65)</td>
<td>54% (46-62)</td>
<td>13% (7-23)</td>
<td>86% (77-91)</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>83% (63-93)</td>
<td>55% (46-63)</td>
<td>23% (15-33)</td>
<td>95% (88-98)</td>
</tr>
<tr>
<td></td>
<td>Rating</td>
<td><strong>96% (79-99)</strong></td>
<td>25% (18-33)</td>
<td>17% (12-25)</td>
<td>97% (86-100)</td>
</tr>
<tr>
<td>85%</td>
<td>Refill</td>
<td>17% (7-31)</td>
<td>92% (87-96)</td>
<td>27% (11-52)</td>
<td>87% (81-92)</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>57% (37-74)</td>
<td>76% (68-82)</td>
<td>28% (17-42)</td>
<td>92% (85-95)</td>
</tr>
<tr>
<td></td>
<td>Rating</td>
<td><strong>83% (63-93)</strong></td>
<td>56% (48-64)</td>
<td>24% (16-34)</td>
<td>95% (88-98)</td>
</tr>
<tr>
<td>75%</td>
<td>Refill</td>
<td>9% (2-27)</td>
<td>98% (94-99)</td>
<td>40% (12-77)</td>
<td>87% (81-91)</td>
</tr>
<tr>
<td></td>
<td>VAS</td>
<td>39% (22-59)</td>
<td>88% (82-92)</td>
<td>35% (19-54)</td>
<td>90% (84-94)</td>
</tr>
<tr>
<td></td>
<td>Rating</td>
<td><strong>44% (26-63)</strong></td>
<td>89% (83-93)</td>
<td>40% (23-59)</td>
<td>91% (85-95)</td>
</tr>
</tbody>
</table>

PPV: Positive predictive value; NPV: Negative predictive value
Sensitivity and specificity of adherence measures for immunologic failure

<table>
<thead>
<tr>
<th>Immunologic failure (n=164)</th>
<th>Failure</th>
<th>CD4&lt;100 cells/µl</th>
<th>23 (14%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No failure</td>
<td></td>
<td>CD4≥100 cells/µl</td>
<td>141 (86%)</td>
</tr>
</tbody>
</table>

AUC=0.512; P=0.859
95% CI: 0.368-0.655

AUC=0.740; P<0.001
95% CI: 0.628-0.851

AUC=0.755; P<0.001
95% CI: 0.650-0.860

Immunologic failure (n=164)

Failure
CD4<100 cells/µl 23 (14%)
No failure
CD4≥100 cells/µl 141 (86%)

Cut-off: 95%, 85%, 75%
AUC=0.755; P<0.001
95% CI: 0.650-0.860

Cut-off: 95%, 85%, 75%
AUC=0.740; P<0.001
95% CI: 0.628-0.851

Cut-off: 95%, 85%, 75%
AUC=0.512; P=0.859
95% CI: 0.368-0.655

(n=164)
CONCLUSIONS

- Prescription refill data
  - Showed the lowest sensitivity to detect possible virologic and immunologic failure
  - Sensitivity decreased with lower cut-off points for adherence

- Rating scale
  - Showed the highest sensitivity to detect patients with possible virologic failure at 95% cut-off for non-adherence

- Rating scale and the VAS as single measures
  - ‘Fairly’ accurate to discriminate between patients with possible virologic or immunologic failure, and those not
**RECOMMENDATIONS**

- **Rating scale and pictorial VAS** are suited to screen patients in a resource-limited setting with:
  - insufficient human resources for time-consuming adherence assessments
  - unavailability of computer systems to accurately calculate refill adherence

  Targeted **interventions for patients at risk**

  Monitoring of clinical markers could be limited to **patients at risk**

- Further data analysis and studies in larger population to validate measures:
  - If used in combination (models)
  - For specific patient groups (e.g. time on ART, regimen)
  - In repeated measurements of adherence
LIMITATIONS OF THE STUDY

- Different regimens may require different minimum levels of adherence
  - ART regimen was not factored in the analysis

- Results could have been biased by
  - lag times between VL and CD4 test results and adherence measures
  - medication left over from previous months (refill data)
  - interpretation of self-report measures

- Incomplete patient records and limited clinical data
  - Small sample size
ACKNOWLEDGEMENTS

- Patients at Tshepang clinic for their willingness to participate in the study
- Staff of Tshepang Clinic for their willingness to assist us in this research project
- Department of Pharmacy, University of Limpopo, Medunsa Campus for financial support
- Professor H Schoeman for advice on the data analysis
References


