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?

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INTRODUCTION & BACKGROUND

- Adherence - important predictor of antiretroviral treatment (ART) success

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

    (Chesney, 2006; Henry, 2011)

- Measures of adherence
  - Patient self-report
  - Dispensing-based (refill) } Associated with clinical outcomes

  (Berg et al., 2010; Bisson et al., 2008; Chalker et al., 2010; Henry, 2011; Nachega et al., 2006; Ross-Degnan et al., 2010)

INTRODUCTION & BACKGROUND (2)

- 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

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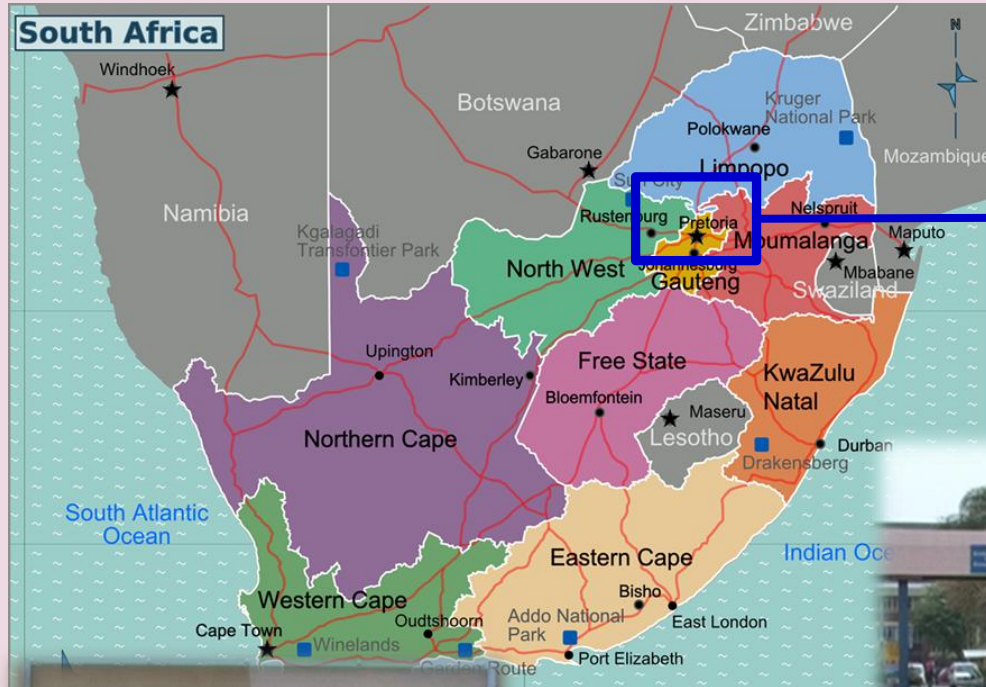
Dr George Mukhari Hospital
- Public sector academic hospital
- Ga-Rankuwa, west of Pretoria
- Gauteng Province

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

METHOD
Target population & ethics

Target population

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

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

Ethical considerations

- Medunsa Campus Research and Ethics Committee
- CEO Dr George Mukhari hospital Clinic Head of Tshepang Clinic ⎤ Permission to conduct the study
- Written consent from patients
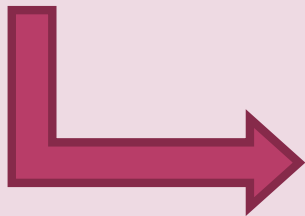
METHOD
Data collection

- **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
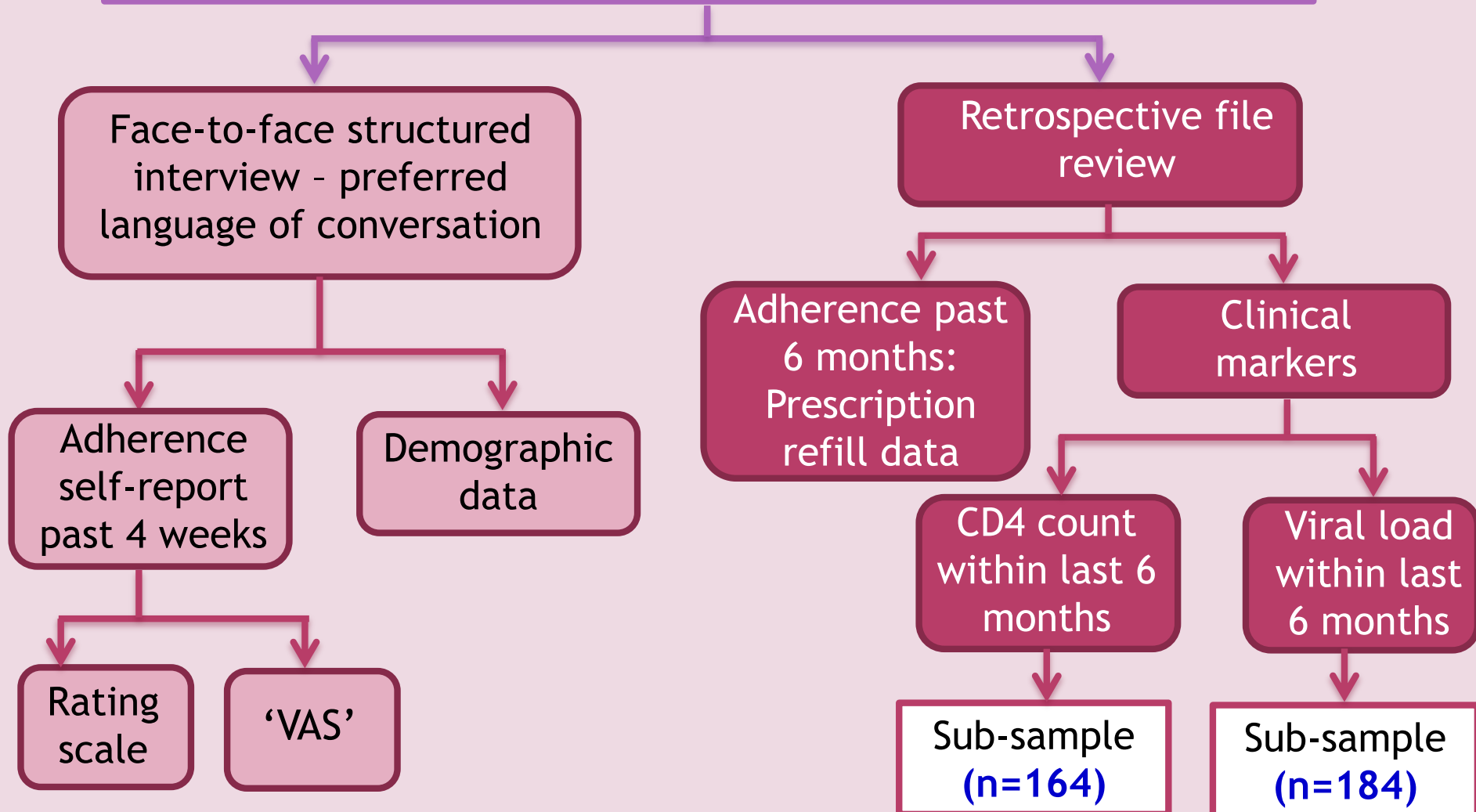 - Retrospective dispensing form

Pilot study
  - Feasibility of study
  - Test data collection instruments

METHOD
Study design: Cross-sectional study

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

Retrospective file review

Adherence self-report past 4 weeks

Demographic data

Adherence past 6 months: Prescription refill data

Clinical markers

Rating scale

'VAS'

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 | | | | | | Half | | | | | All |
| A | B | C | D | E | F | G | H | I | J | K | L |
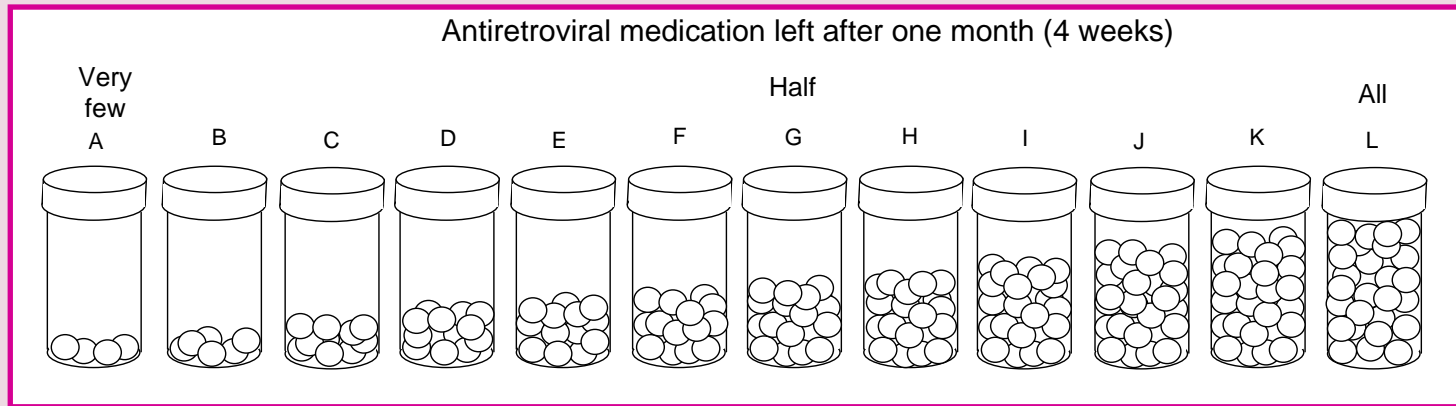
Converted to % adherence

Adapted from: Ereng, 2011; Polejack, 2007

Prospective: 6-item rating scale

Excellent	
Very good	
Good	
Fair	
Poor	
Very poor	

Category of adherence

Retrospective: Prescription refill

	Date ARVs dispensed	Number of days ARVs dispensed
ART initiation		
Visit 1 (index visit)		
Visit 2		
Visit 3		
Visit 4		
Visit 5		
Visit 6		

Average % of days covered by ARVs over 6 months period

METHOD
Data entry & analysis

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

Data analysis: IMB 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
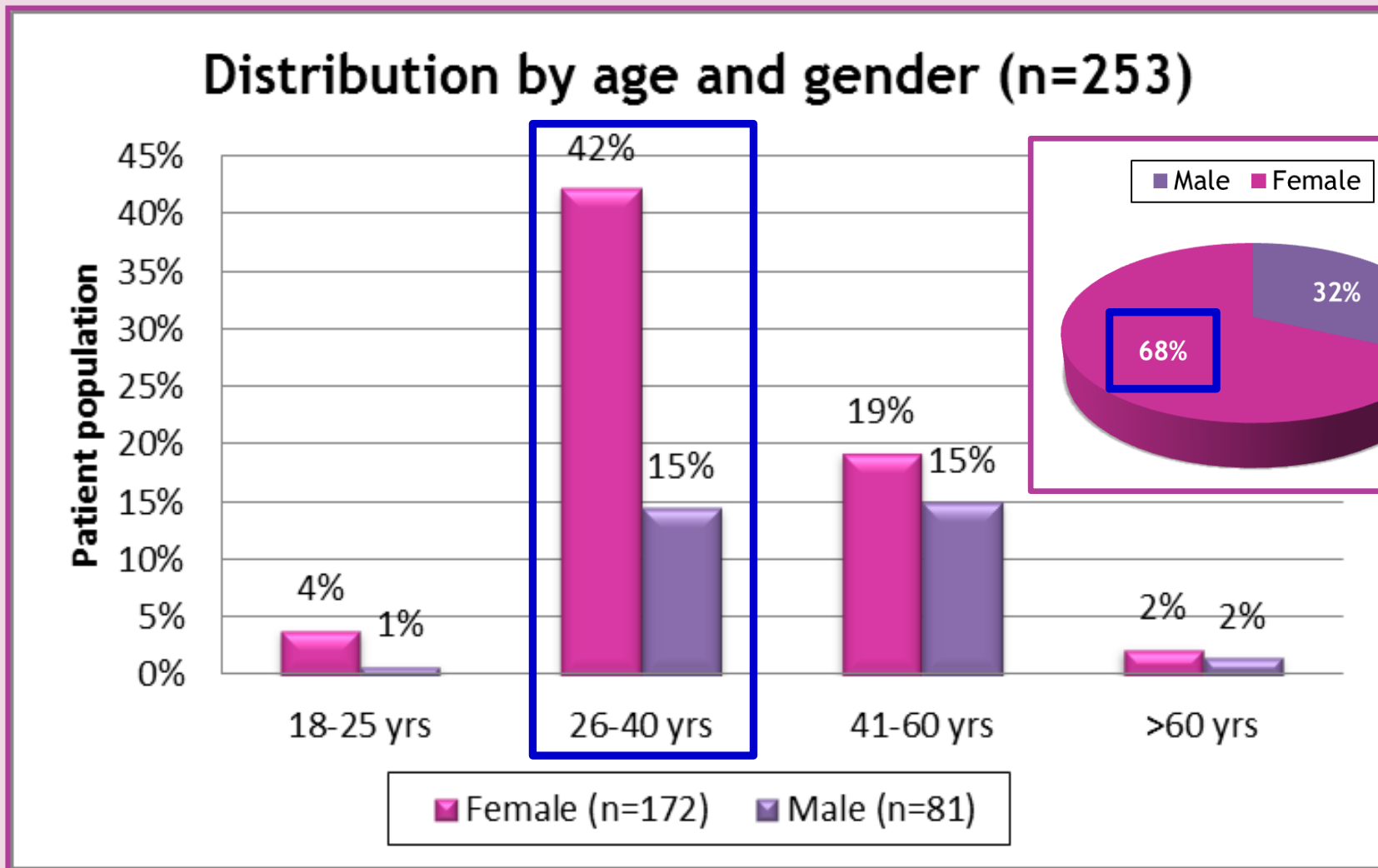 - Numbers (%): converted to categories

Rating	VAS	Refill	Adherence cut-off
Excellent	95-100%	95-100%	
Very good	90%	85<95%	<95%
Good	80%	75<85%	<85%
Fair	70%	65<75%	<75%
Poor	60%	55<65%	
Very poor	50%	<55%	

RESULTS AND DISCUSSION

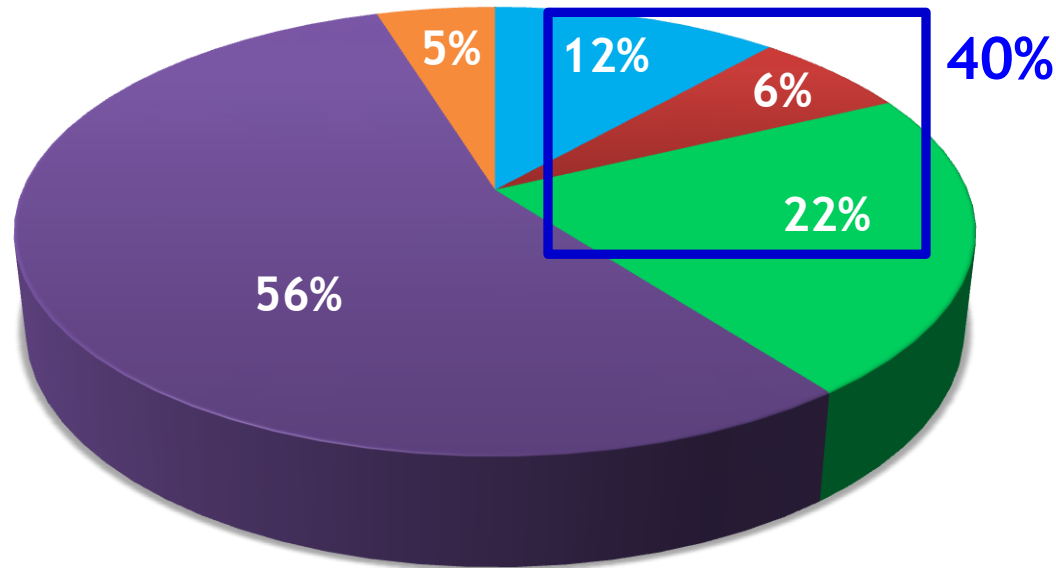# Demographic information: Age and gender

Distribution by age and gender (n=253)

Mean age: 39.9 (SD±10.8) years; Median age: 38.2 years

Demographic information: Educational level

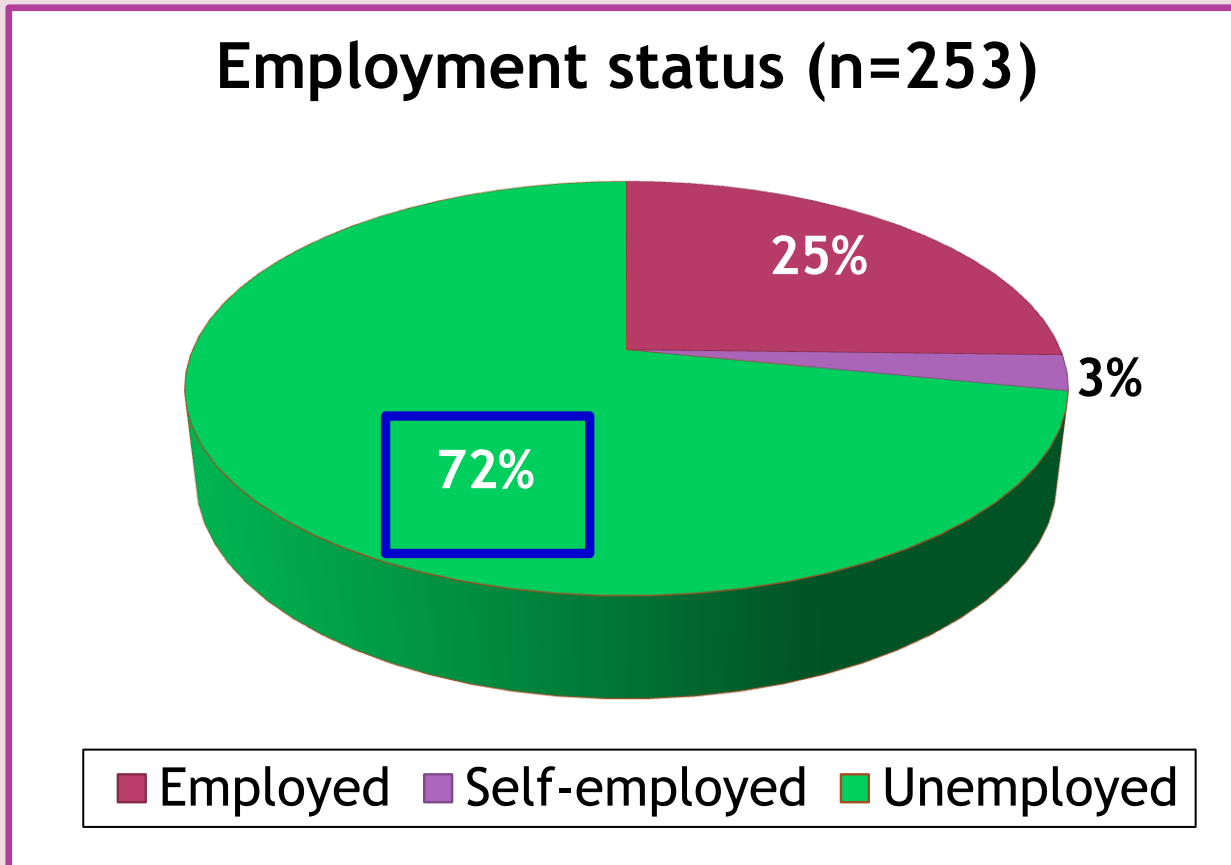
Educational level (n=253)

- 12% None
- 6% Primary
- 22% Secondary incomplete
- 56% Secondary
- 5% Tertiary / vocational

40%

Legend:
- None
- Primary
- Secondary incomplete
- Secondary
- Tertiary / vocational

Demographic information: Employment

Employment status (n=253)

- Employed: 25%
- Self-employed: 3%
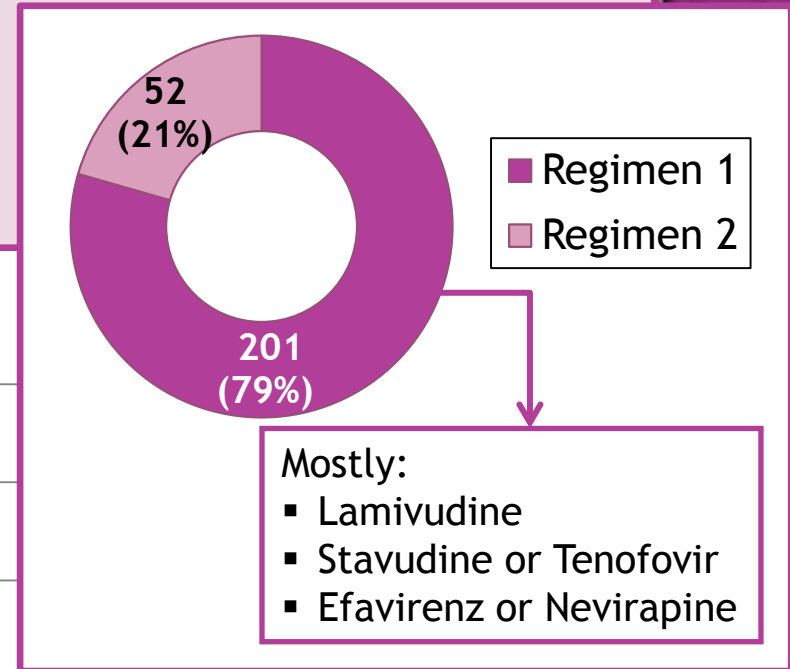- Unemployed: 72%

Unemployment rate in South Africa = 25% (Statistics SA, 2011)

Antiretroviral treatment (ART)

Time on ART (n=253)

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

Patient population / Months

Regimen 1: 201 (79%)
Regimen 2: 52 (21%)

Mostly:
- Lamivudine
- Stavudine or Tenofovir
- Efavirenz or Nevirapine
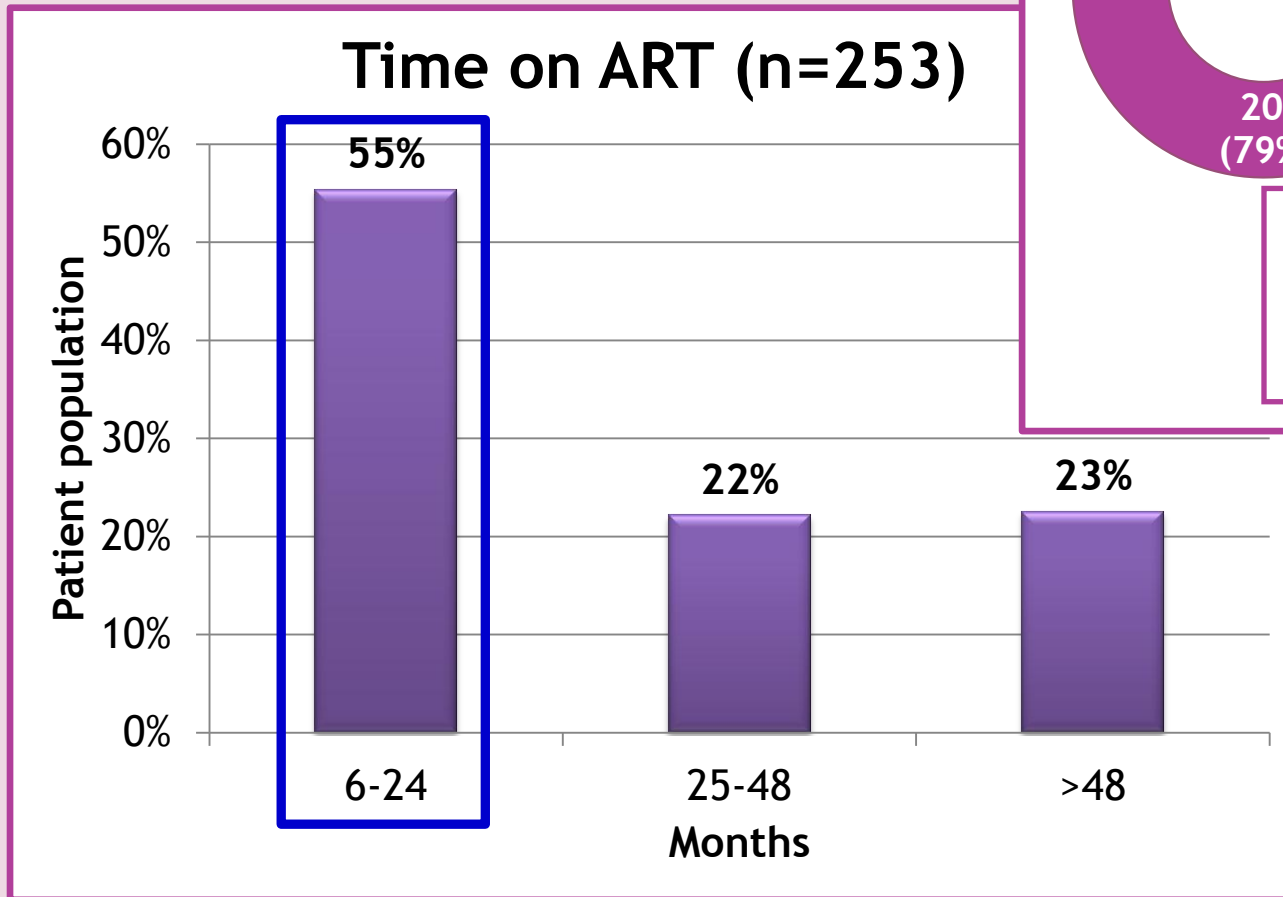
Mean: 30 months (SD±21.9); Median: 21.6 months

Self-report past 4 weeks
Distribution of patients by adherence % score

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

Antiretroviral medication left after one month (4 weeks)
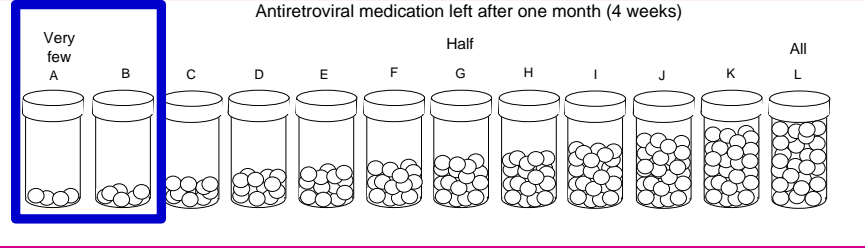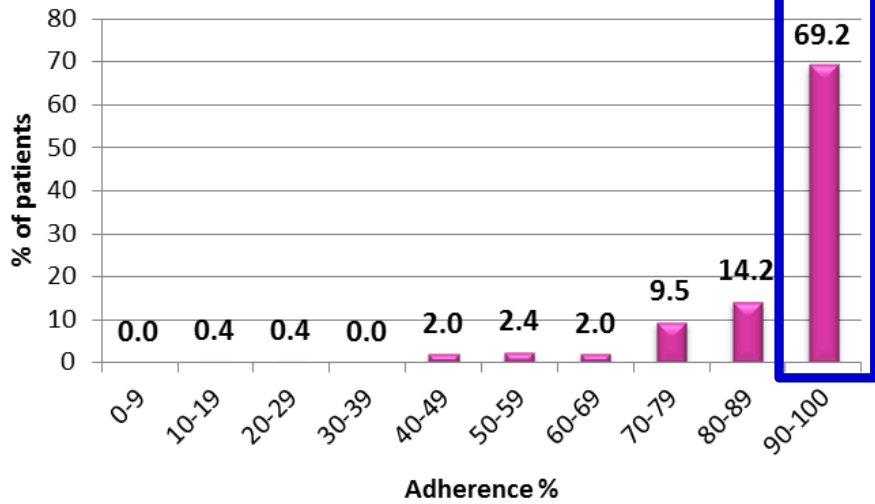
Distribution of patients by adherence % score: Rating scale (n=253)
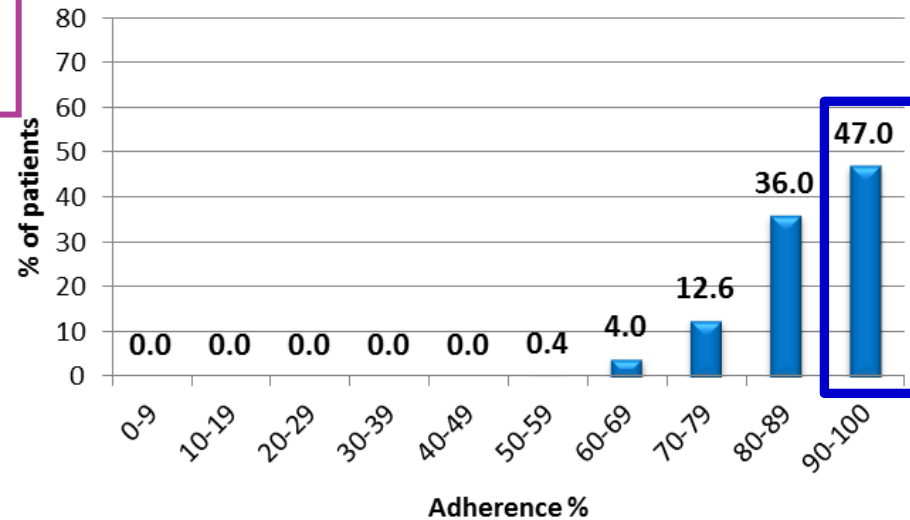
Excellent	
Very good	
Good	
Fair	
Poor	
Very poor	

Refill data past 6 months
Distribution of patients by adherence % score
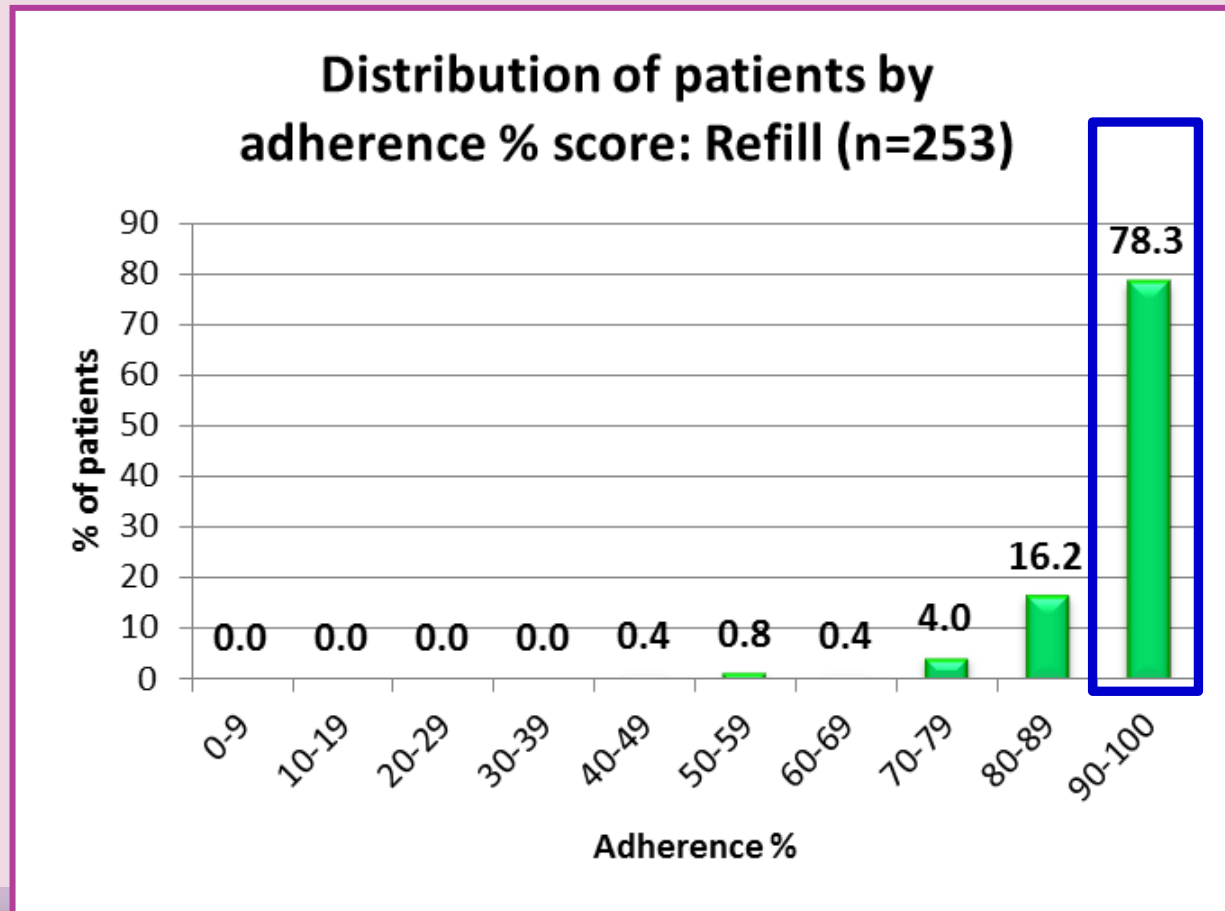
Adherence measures compared
% of patients per category of adherence

Category	Rating (n=253)	VAS (n=253)	Refill (n=253)
Excellent	17%	45%	53%
Very good	30%	24%	38%
Good	36%	14%	6%
Fair	13%	9%	2%
Poor	4%	2%	1%
Very poor	0.4%	5%	0.4%

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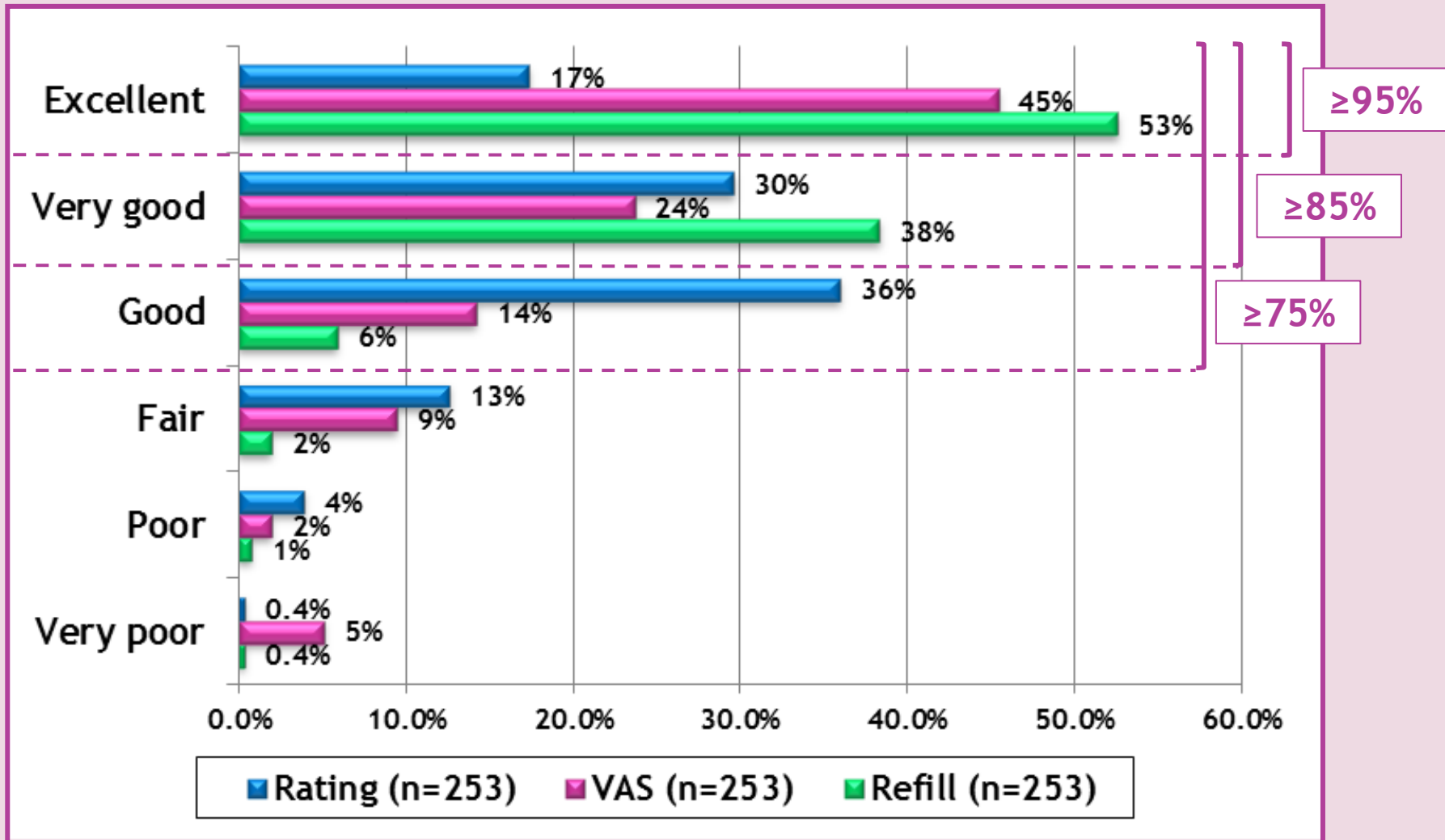
Adherence measures compared for different cut-off points
% of patients per category of adherence

Adherence cut-off		Refill (n=253)	VAS (n=253)	Rating (n=253)
≥95%	Excellent	53% _P=0.13050_	45%	17%
≥85%	Excellent & very good	91%	69%	47%
≥75%	Excellent, very good & good	97%	83%	83%

Fisher's Exact test

Adherence measures compared
Mean adherence score (%)
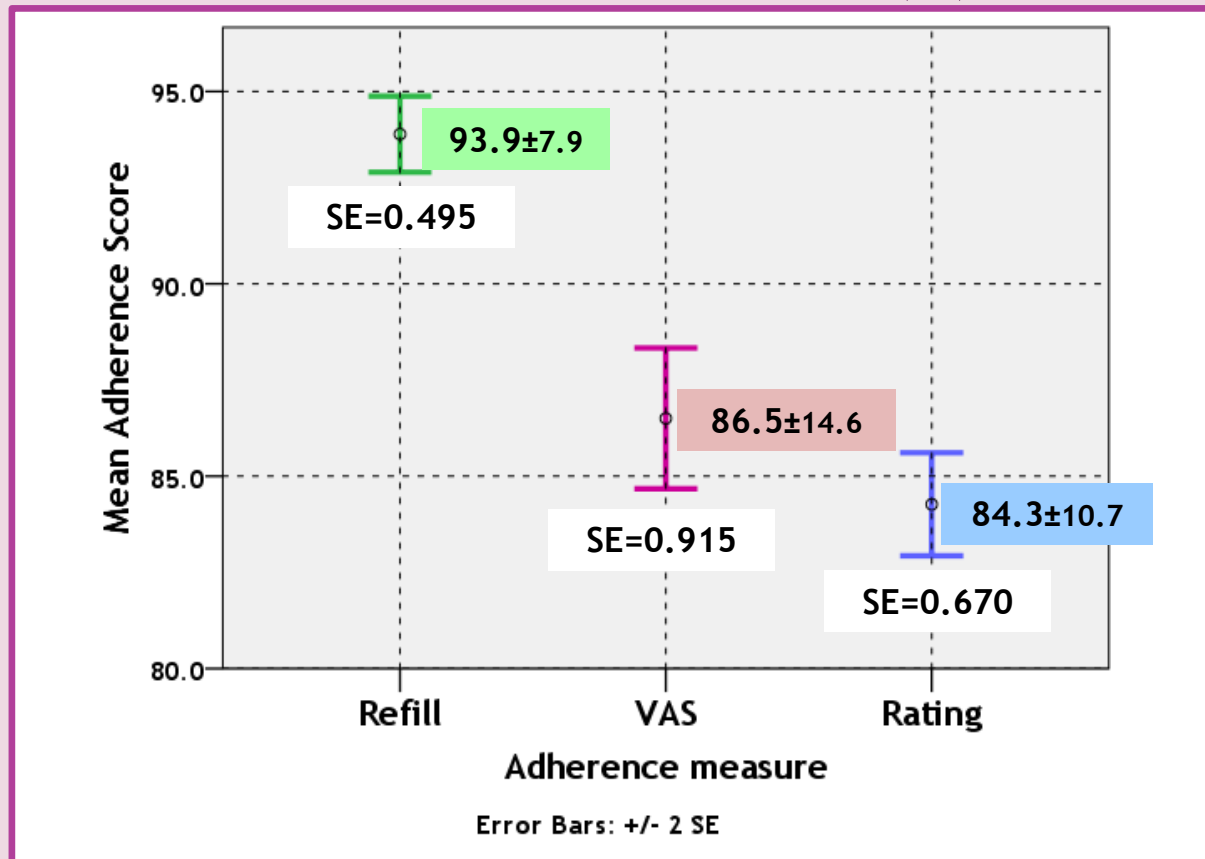
One-Way ANOVA Pairwise Comparison	Measure	Measure	Mean diff	SE	P	95% CI	
	Refill	VAS	7.3881	1.0405	.000	4.893	9.883
		Rating	9.6213	0.8324	.000	7.627	11.616
	VAS	Refill	-7.3881	1.0405	.000	-9.883	-4.893
		Rating	2.2332	1.1342	.141	-.485	4.951

Adherence (% score): Association between measures

		Rating	VAS	Refill
Rating	rho	1	0.632	0.113
	P (2-tailed)	-	<0.001	0.073
	n	253	253	253
VAS	rho		1	0.048
	P (2-tailed)		-	0.45
	n		253	253
Refill	rho			1
	P (2-tailed)			-
	n			253

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)

65 (35%)

119 (65%)
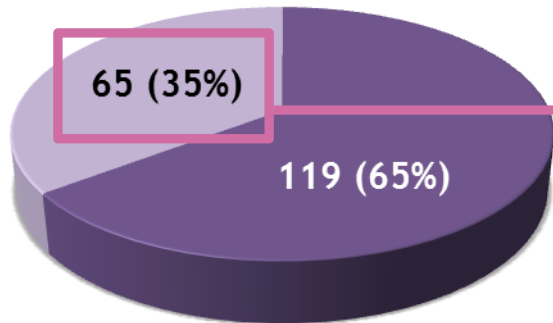
- ≤400 copies/ml
- >400 copies/ml

Median VL: 40 cells/μl

	Time on ART (months)						Total
	6-24 months		**25-48 months**		**>48 months**		
VL≤400 copies/ml	83 (80%)		16 (42%)		20 (48%)		119 (65%)
VL>400 copies/ml	21 (20%)	34%	22 (58%)	34%	22 (52%)	32%	65 (35%)
Total	104		38		42		184

Percentage of patients with ≥95% adherence by time on ART (n=184)

- Refill (P=0.622)
- VAS (P=0.507)
- Rating (P=0.065)

6-24 (n=104): Refill 56%, VAS 45%, Rating 20%
25-48 (n=38): Refill 47%, VAS 40%, Rating 8%
>48 (n=42): Refill 50%, VAS 52%, Rating 29%

Time on ART (months)
% of patients
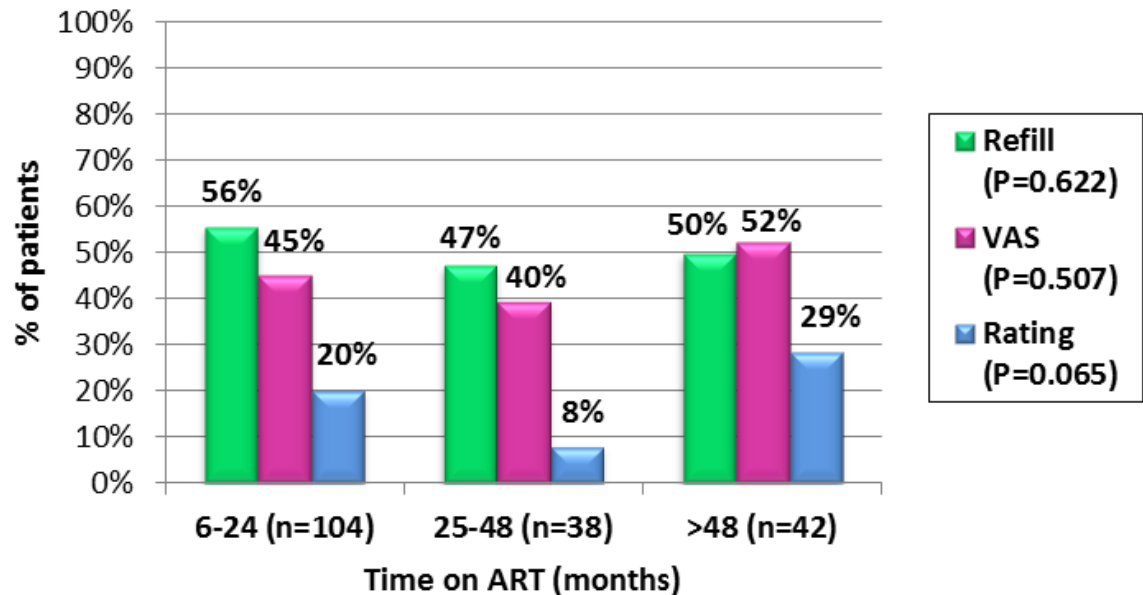
Clinical markers: CD4 count (cells/µl)

CD4 cell count (cells/µl) within past 6 months (n=164)
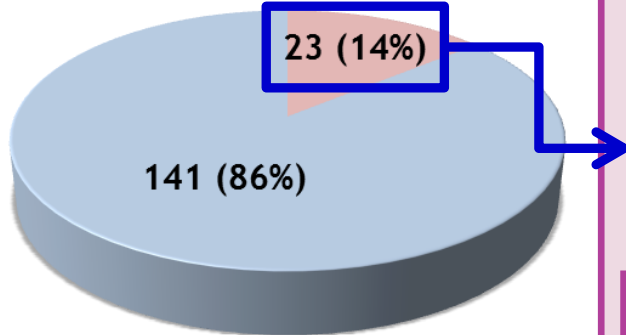
23 (14%)
141 (86%)

Legend:
- <100 cells/µl
- ≥100 cells/µl

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

	Time on ART (months)						Total	
	6-24 months		25-48 months		>48 months			
CD4≥100 cells/µl	86 (92%)		29 (83%)		26 (72%)		141 (86%)	
CD4<100 cells/µl	7 (8%)	30%	6 (17%)	26%	10 (28%)	44%	23 (14%)	
Total	93		35		36		164	

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

Legend:
- Refill (P=0.884)
- VAS (P=0.564)
- Rating (p=0.147)

6-24 (n=93): Refill 56%, VAS 50%, Rating 23%
25-48 (n=35): Refill 51%, VAS 43%, Rating 11%
>48 (n=36): Refill 53%, VAS 56%, Rating 31%
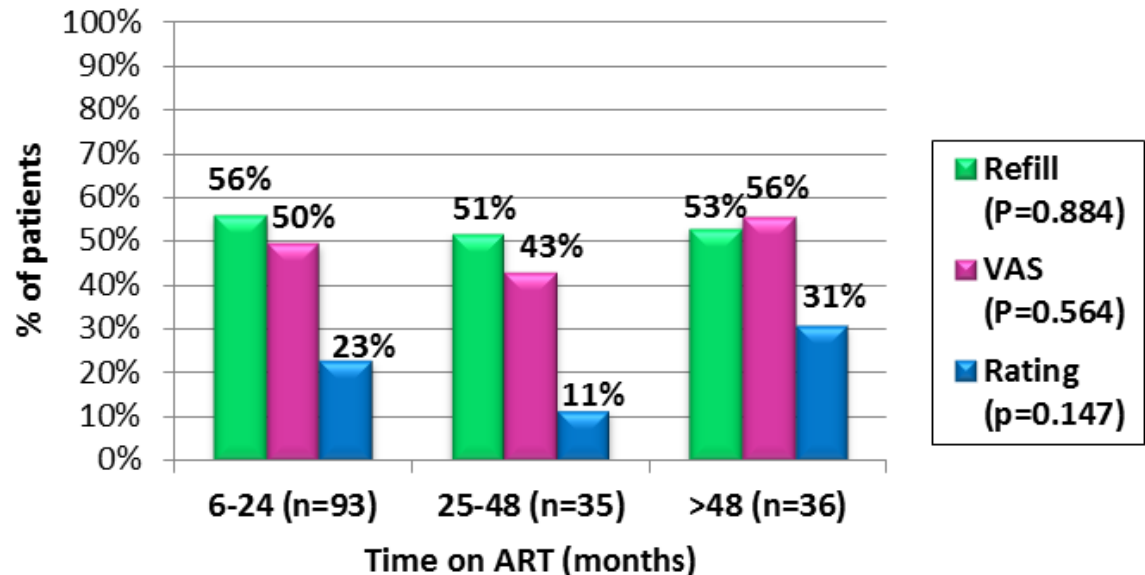
Association of adherence measures with clinical markers

			Rating	VAS	Refill
CD4 count		rho	0.323	0.222	0.021
		P (2-tailed)	<0.001	0.004	0.794
		n	**164**	**164**	**164**
Change in CD4		rho	0.247	0.231	-0.046
		P (2-tailed)	0.003	0.005	0.583
		n	**144**	**144**	**144**
Viral load		rho	-0.333	-0.163	-0.154
		P (2-tailed)	<0.001	0.027	0.036
		n	**184**	**184**	**184**

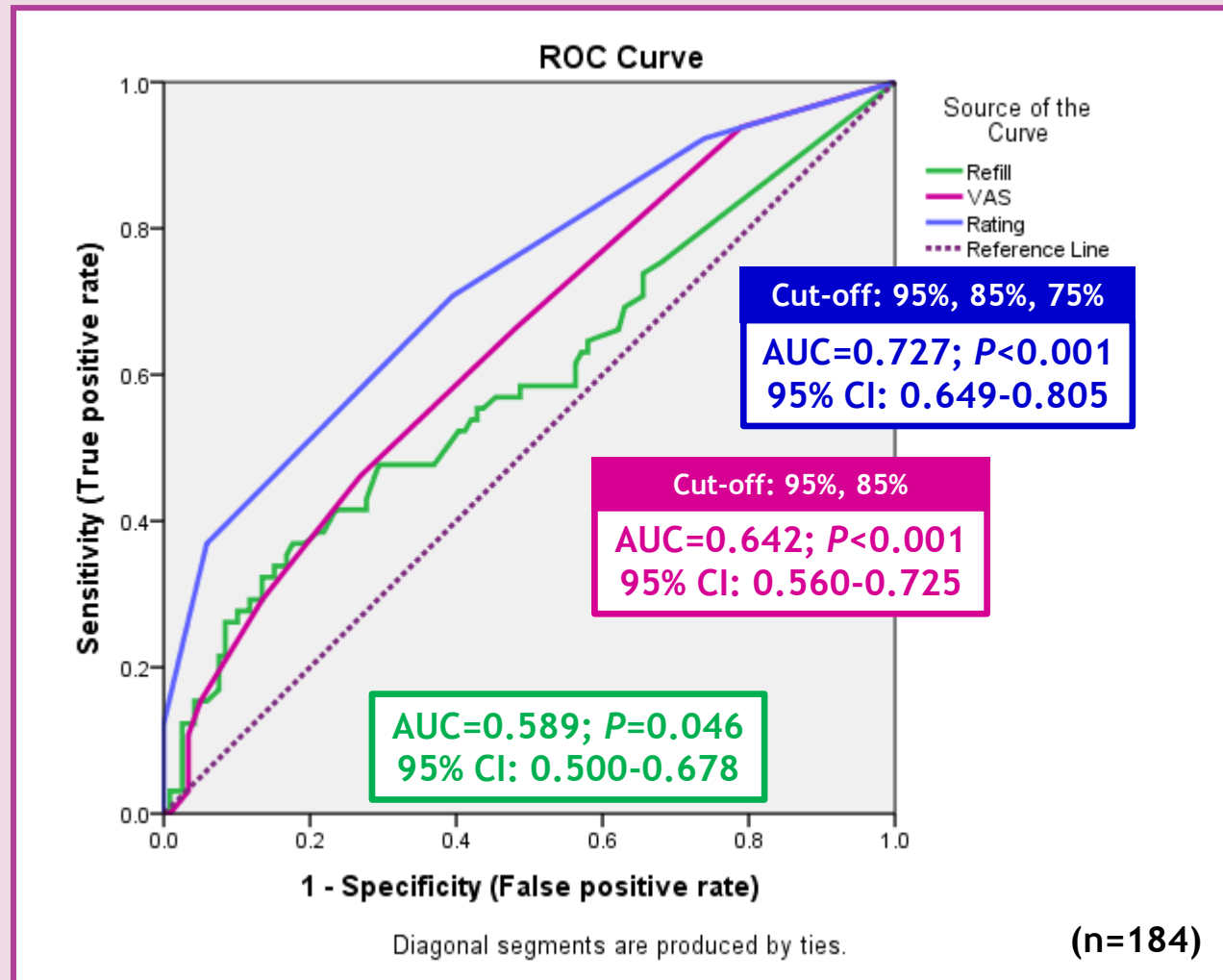Spearman's Rank correlation: significant at the 0.01 level (2-tailed)

Sensitivity and specificity of adherence measures for virologic failure (VL>400 copies/ml) at different adherence cut-offs

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

PPV: Positive predictive value; NPV: Negative predictive value

Sensitivity and specificity of adherence measures for virologic failure

ROC Curve

Source of the Curve
- Refill
- VAS
- Rating
- Reference Line

Cut-off: 95%, 85%, 75%
AUC=0.727; *P*<0.001
95% CI: 0.649-0.805

Cut-off: 95%, 85%
AUC=0.642; *P*<0.001
95% CI: 0.560-0.725

AUC=0.589; *P*=0.046
95% CI: 0.500-0.678

Diagonal segments are produced by ties.

(n=184)

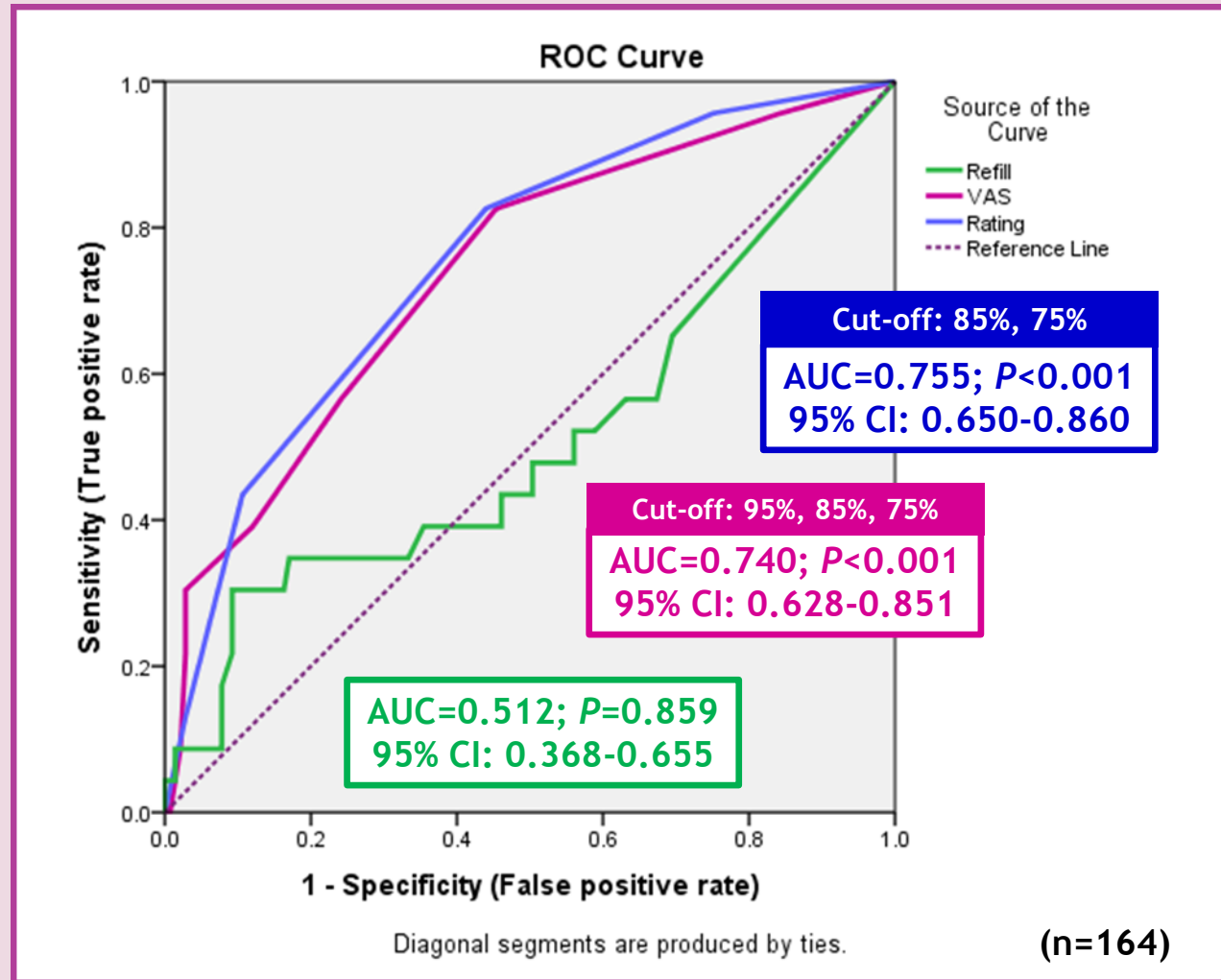| Virologic failure (n=184)	Failure	VL>400 copies/ml	65 (35%)
	No failure	VL≤400 copies/ml	119 (65%)

Sensitivity and specificity of adherence measures for immunologic failure (CD4<100 cells/ml) at different adherence cut-offs

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

PPV: Positive predictive value; NPV: Negative predictive value

Sensitivity and specificity of adherence measures for immunologic failure

ROC Curve

Source of the Curve
- Refill
- VAS
- Rating
- Reference Line

Cut-off: 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

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

Diagonal segments are produced by ties.

(n=164)

Immunologic failure (n=164)	Failure	CD4<100 cells/µl	23 (14%)
	No failure	CD4≥100 cells/µl	141 (86%)

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

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- 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

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