

Low Sensitivity of Self-Report to Identify Sub-Optimal Adherence in Patients with Multidrug-Resistant Tuberculosis and HIV in South Africa

Allison Wolf, MPH, Rubeshan Perumal, Jennifer Zelnick, Boitumelo Seepamore, Mbali Zulu, Kevin Guzman, Bhavna Maharaj, Ken Cheung, K. Rivet Amico, Gerald Friedland, Amrita Daftary, Kogieleum Naidoo, Max O'Donnell



Yale University



BACKGROUND

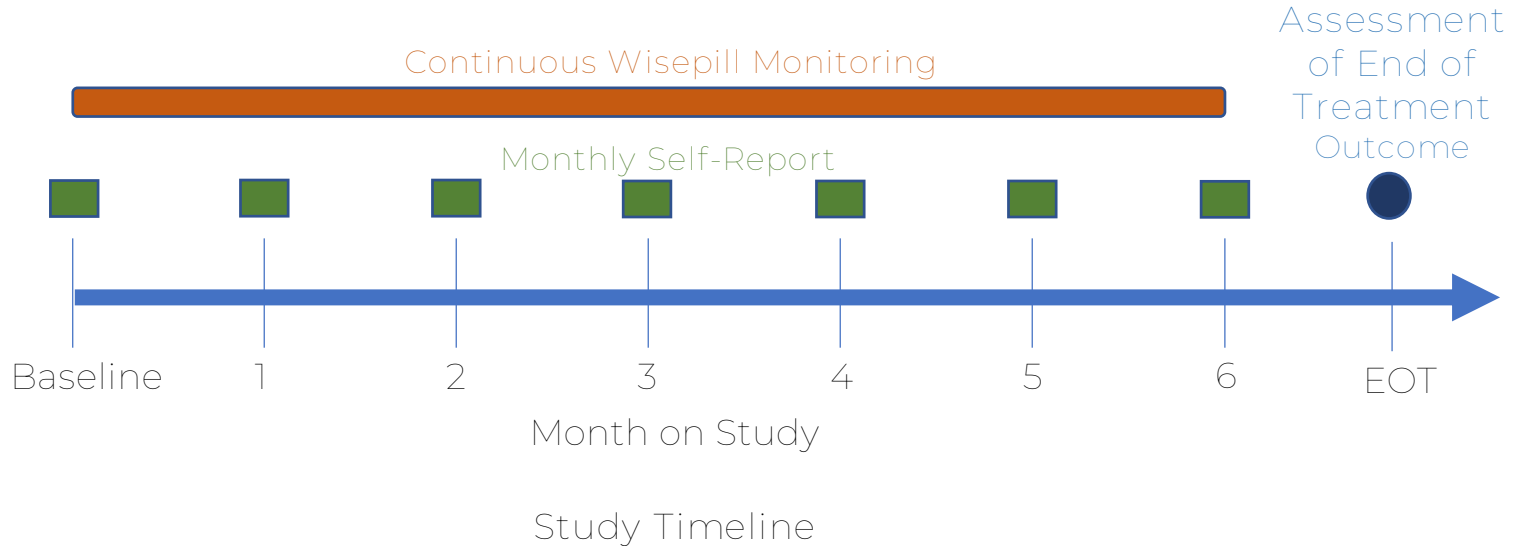
- South Africa continues to be an epicenter of the global TB epidemic, defined by high rates of drug-resistance (DR-TB) and HIV co-infection.
- Bedaquiline has enhanced DR-TB treatment, but low adherence and loss to retention in care remains a challenge.
- Medication Monitoring:
 - Patient self-report is a commonly used tool in research and clinical practice for monitoring medication adherence. It is easily implemented.
 - Electronic dose monitoring (EDM) devices have been introduced to measure adherence in real-time. EDM is less subject to recall and social desirability bias, but they are expensive.
- The purpose of this analysis was to evaluate the accuracy and correlation of self-reported adherence compared to EDM-measured adherence in patients with DR-TB and HIV in the setting of KwaZulu-Natal, South Africa.

METHODS

The PRAXIS Study

Patients with drug-resistant tuberculosis and HIV co-infection initiating a bedaquiline-containing regimen were recruited at a TB-referral hospital in Durban, KwaZulu-Natal, South Africa, 2016-2020 (N=283).

Each participant received continuous EDM with Wisepill device, and self-reported adherence at monthly visits with three methods: Visual Analogue Scale (VAS), 7-day Recall, and 30-Day Recall



ASSESSING 'SUB-OPTIMAL ADHERENCE'

Previous research demonstrated bedaquiline treatment adherence measured by EDM and treatment outcome for MDR-TB and HIV are linearly related.

No specific adherence threshold was identified for positive outcome.

Every missed bedaquiline dose increased the risk for a negative outcome.

STUDY DEFINITIONS

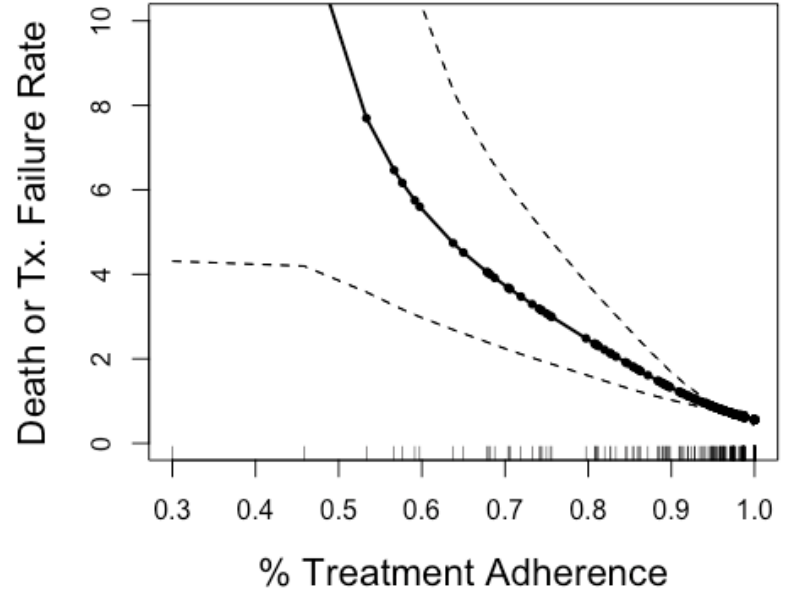
Sub-Optimal Adherence

Self-Report:

Any number of doses reported as missed during a specified time period

EDM:

Any number of recorded missed pill box openings during a specified time period

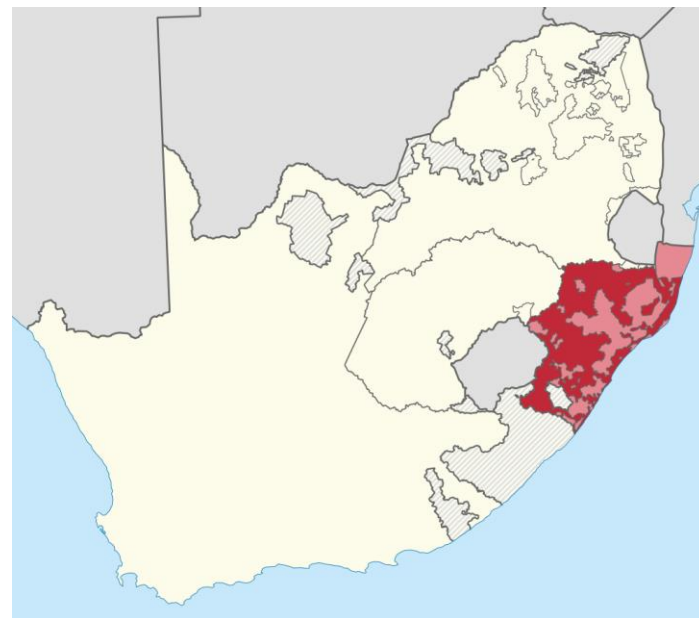


Cox model with penalized splines. Rug plot represents patient observations, dots are predicted observations, dashed lines are 95% CI's. P-for-linearity = 0.15 and p-for-association <0.001.

O'Donnell, MR, et al. JAIDS, 2022.

PARTICIPANTS

N=283		
Gender		
	Female	150 (53.0)
	Male	133 (47.0)
Age, Median (IQR)		36 (29 – 44)
Education		
	No Secondary	49 (17.3)
	At least some Secondary	234 (82.7)
Housing Type		
	Single Family	44 (15.6)
	Multi-Family	225 (79.5)
	Informal	39 (13.8)
History of TB		
	DS-TB	179 (63.3)
	DR-TB	52 (18.4)
	Any	192 (67.8)
On ART at Baseline		
	For >30 days	246 (86.9)
CD4 Count*		
	>200	156/271 (57.6)
	≤200	115/271 (42.4)
	Median (IQR)	246 (108 – 445)
Undetectable Viral Load*		167/271 (61.5)



*Data available for 271 participants

RESULTS - MONTHLY ADHERENCE

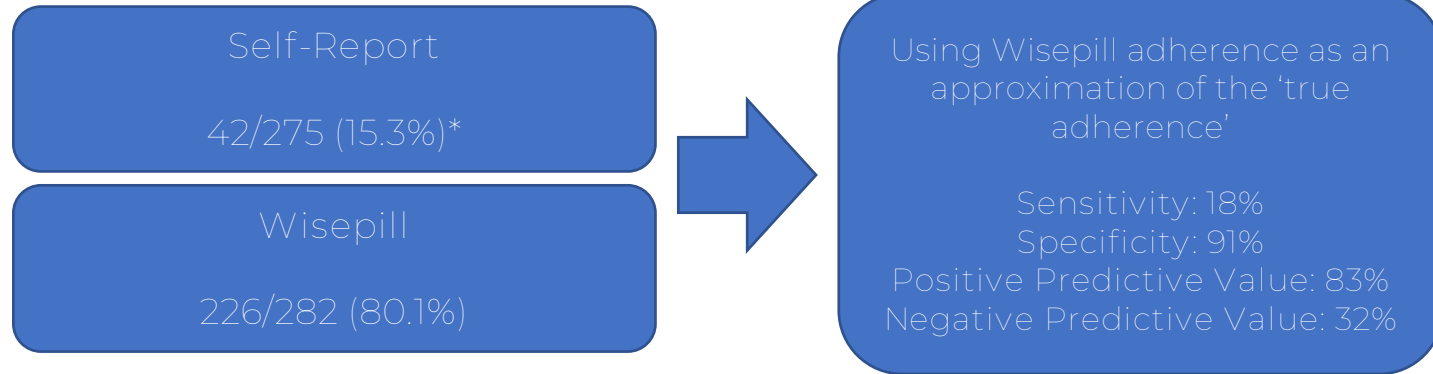
Proportion of sub-optimally adherent participants at each monthly visit by method

Monthly Visit	Visual Analogue Scale (VAS)	7-day Recall	30-day Recall	Wisepill (7-days)	Wisepill (30-days)
1	0/193 (0%)	0/195 (0%)	1/195 (0.5%)	13/194 (6.7%)	60/195 (30.8%)
2	3/265 (1.1%)	11/270 (4.1%)	11/271 (4.1%)	31/264 (11.7%)	92/269 (34.2%)
3	1/184 (0.5%)	6/187 (3.2%)	3/188 (1.6%)	22/182 (12.1%)	55/183 (30.1%)
4	2/176 (1.1%)	6/183 (3.3%)	5/183 (2.7%)	20/171 (11.7%)	50/176 (28.4%)
5	1/175 (0.6%)	2/180 (1.1%)	0/181 (0%)	33/165 (20.0%)	63/172 (36.6%)
6	5/235 (2.1%)	4/249 (1.6%)	8/249 (3.2%)	49/174 (28.2%)	98/223 (44.0%)
Mean	0.9%	2.2%	2.5%	15.1%	34.0%
	Reported (Self-Report)			Monitored (Wisepill)	

Each self-report method performed similarly from month-to-month, failing to detect a majority of episodes of sub-optimal adherence compared to Wisepill. 30-day monitoring captured the greatest number of adherence lapses.

RESULTS - CUMULATIVE 6-MONTH ADHERENCE

Cumulative proportion of participants with at least one missed dose by self-report or missed pill box opening by Wisepill



Cumulative 6-month Self-Report reveals more participants with <100% adherence during the study compared to the monthly analysis, but significantly less than by Wisepill ($p < .0001$).

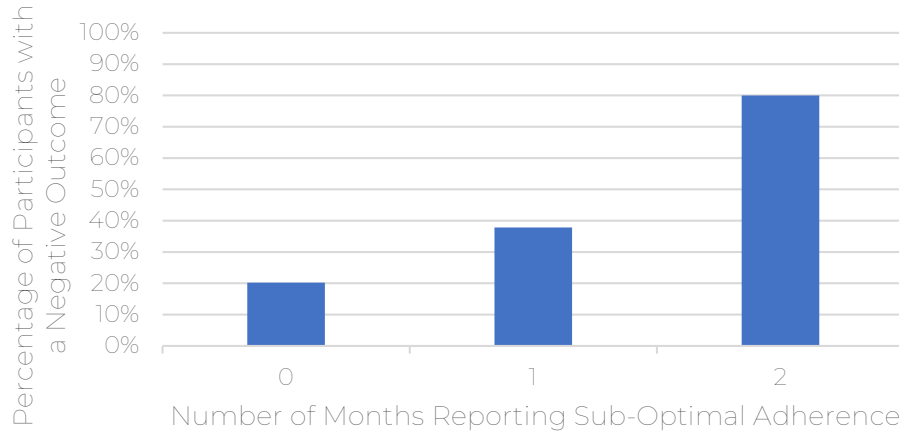
Self-report is a specific, but not sensitive measure of sub-optimal adherence

RESULTS - THE RELATIONSHIP BETWEEN ADHERENCE AND SUBSEQUENT OUTCOMES: SELF-REPORT

OR=2.97 (95% CI: 1.49 -5.92)

If a participant that ever reported sub-optimal adherence the odds of a negative outcome is 2.97 that of a participant that never did.

Frequency of Negative Outcome by Number of Sub-Optimal Self-Report

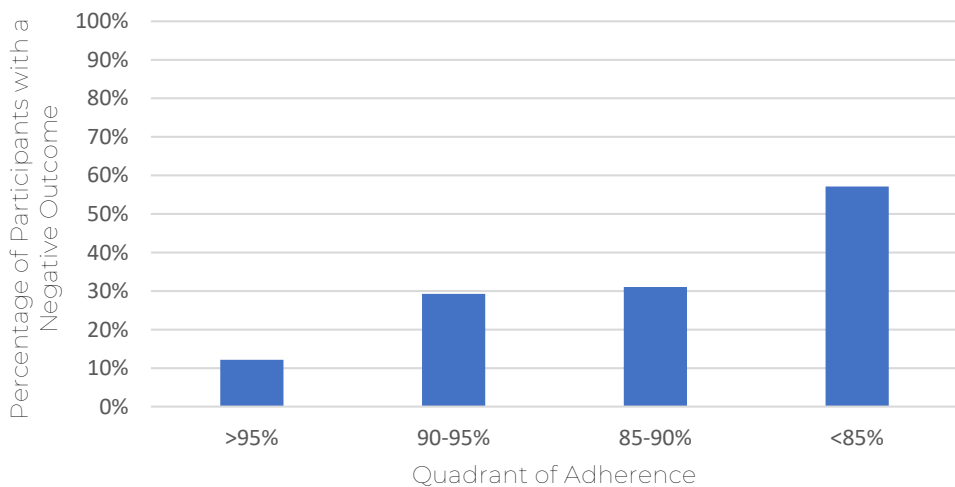


End of Treatment Outcome		Proportion of Participants Self-Reporting Sub-Optimal Adherence
Positive Outcome		24/210 (11.4)
Cured		20/187 (10.7)
Completed	Treatment	4/23 (17.4)
Negative Outcome		18/65 (27.7)
Lost to Follow-up	Treatment	10/27 (37.4)
Failure	Treatment	2/3 (66.7)
	Death	6/35 (17.1)

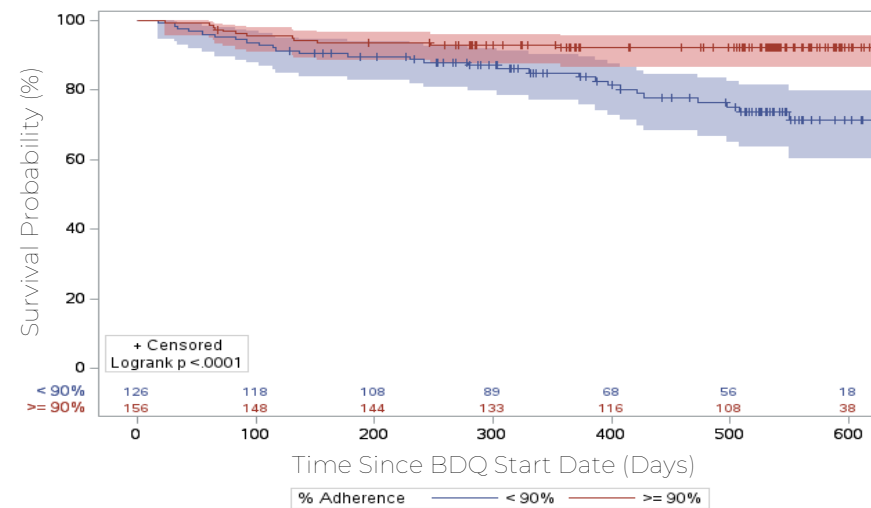
Self-report does allow us to identify participants at risk for a negative outcome, but only 27.7% of them.

RESULTS – THE RELATIONSHIP BETWEEN ADHERENCE AND SUBSEQUENT OUTCOMES: WISEPILL

Frequency of Negative Outcome by Quartile of Bedaquiline Adherence Measured by Wisepill



Survival Analysis for Mortality Stratified by High Versus Low Cumulative Bedaquiline Adherence



Relatively small reductions in monitored adherence increases the risk for negative outcomes emphasizing the need for a sensitive adherence monitoring system.

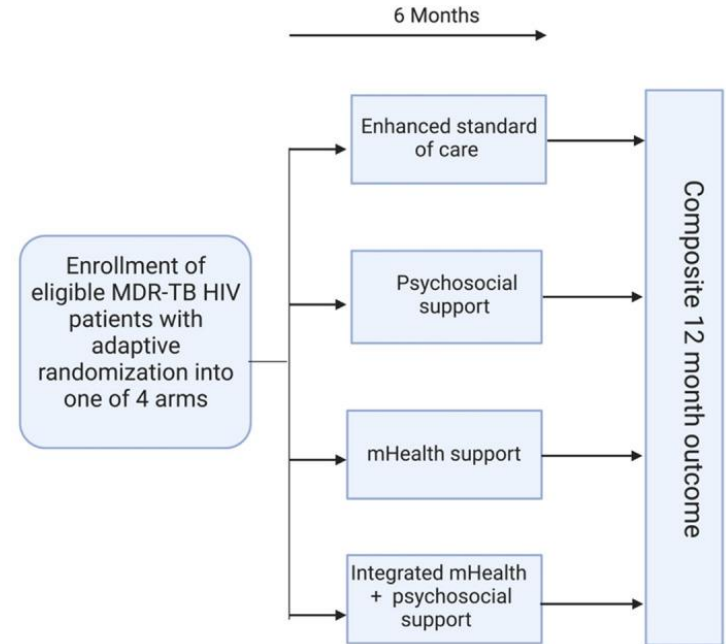
DISCUSSION

- Self-report was highly specific for non-adherence, but too insensitive to identify most episodes of non-adherence.
- Cumulative 6-month self-report measures identified a larger proportion of sub-optimally adherent participants compared to monthly account, but too late to intervene.
- The EDM device identified more episodes of non-adherence compared to the self-report and in 'real-time,' which allows for near-time intervention.
- While EDM devices would require a large investment, they may be a critical component in an adherence support program for DR-TB HIV in the setting of KwaZulu-Natal, South Africa.

NEXT STEPS

ADAP-TIV Study (NCT05633056)

A adaptive randomized control study





Yale University



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CAPRISA

Nesri Padayatchi (PI)
Kogieleum Naidoo
Rubeshan Perumal
Boitumelo Seepamore
Mbali Zulu
Bhavna Maharaj

Columbia University

Max R O'Donnell (PI)
Ken Cheung
Karl Reis
Kevin Guzman

Touro College

Jennifer Zelnick

Yale University

Gerald Friedland

York University

Amrita Daftary

University of Michigan

K Rivet Amico

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RESULTS - CUMULATIVE ADHERENCE VS. OUTCOME

Median 6-Month Cumulative Adherence Measured by Wisepill and Self-Report Compared to End of Treatment Outcome

End of Treatment Outcome	N (%)	Median Cumulative 6-month TB Adherence by Wisepill	Proportion of Participants Self-Reporting 100% Adherence During All 6-months
Positive Outcome	210 (74.5)	97.4 (91.1 – 98.9)	186/210 (88.4)
Cure	187 (66.1)	97.4 (91.3 – 98.9)	167/187 (89.3)
Completed	23 (8.1)	98.9)	19/23 (82.6)
Negative Outcome	72 (25.5)	86.6 (73.6 – 95.1)	47/65 (72.3)
Lost to Follow-up	27 (9.5)	94.8)	17/27 (63.0)
Treatment Failure	3 (1.1)	73.9)	1/3 (33.3)
Death	42 (14.8)	87.5 (81.0 – 95.8)	29/35 (82.9)
Early Termination	1 (0.4)		

Both methods – monitoring and report – detected lower adherence in participants with a negative outcome. 72.3% of participants with a negative outcome reported that they did not miss a single dose during the full 6-month treatment period.