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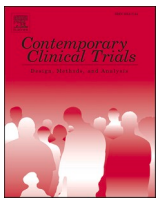

Using a medication event monitoring system to evaluate self-report and pill count for determining treatment completion with self-administered, once-weekly isoniazid and rifapentine

Nigel A. Scott [a,*], Claire Sadowski [a,b], Andrew Vernon [a], Bert Arevalo [c], Karlyn Beer [a], Andrey Borisov [a], Joan A. Cayla [d], Michael Chen [a], Pei-Jean Feng [a], Ruth N. Moro [a], David P. Holland [e], Neil Martinson [f], Joan-Pau Millet [g,h], Jose M. Miro [i,j], Robert Belknap [k]

[a] U.S. Centers for Disease Control & Prevention, Atlanta, GA, USA
[b] Oak Ridge Institute for Science and Education, Oak Ridge, TN, USA
[c] Westat, Rockville, MD, USA
[d] Foundation of TB Research Unit of Barcelona, Barcelona, Spain
[e] Emory University, Atlanta, GA, USA
[f] Perinatal HIV Research Unit (PHRU), University of the Witwatersrand, South Africa and Johns Hopkins University Center for TB Research, Baltimore, MD, USA
[g] Agència de Salut Pública de Barcelona, Spain
[h] CIBER de Epidemiologia y Salud Pública (CIBERESP), Madrid, Spain
[i] Infectious Diseases Service, Hospital Clinic-IDIBAPS, University of Barcelona, Barcelona, Spain
[j] CIBERINFEC, Instituto de Salud Carlos III, Madrid, Spain
[k] Public Health Institute at Denver Health, Denver, CO, USA

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ABSTRACT

Background: Treatment completion is essential for the effectiveness of any latent tuberculosis infection (LTBI) regimen. The Tuberculosis Trials Consortium (TBTC) Study 33 (iAdhere) combined self-report and pill counts – standard of care (SOC) with a medication event monitoring system (MEMS) to determine treatment completion for 12-dose once-weekly isoniazid and rifapentine (3HP). Understanding the performance of SOC relative to MEMS can inform providers and suggest when interventions may be applied to optimize LTBI treatment completion.

Method: iAdhere randomized participants to directly observed therapy (DOT), SAT, or SAT with text reminders in Hong Kong, South Africa, Spain and the United States (U.S.). This post-hoc secondary analysis evaluated treatment completion in both SAT arms, and compared completion based on SOC with MEMS to completion based on SOC only. Treatment completion proportions were compared. Characteristics associated with discordance between SOC and SOC with MEMS were identified.

Results: Overall 80.8% of 665 participants completed treatment per SOC, compared to 74.7% per SOC with MEMS, a difference of 6.1% (95%CI: 4.2%, 7.8%). Among U.S. participants only, this difference was 3.3% (95% CI: 1.8%, 4.9%). Differences in completion was 3.1% (95% CI: −1.1%, 7.3%) in Spain, and 36.8% (95% CI: 24.3%, 49.4%) in South Africa. There was no difference in Hong Kong.

Conclusion: When used for monitoring 3HP, SOC significantly overestimated treatment completion in U.S. and South Africa. However, SOC still provides a reasonable estimate of treatment completion of the 3HP regimen, in U.S., Spain, and Hong Kong.

1. Background

Newly diagnosed and reported tuberculosis (TB) cases remained high at 9.9 million in 2020 worldwide [1]. Treatment for latent TB infection (LTBI) may help to reduce TB cases, particularly within the United States (U.S.) and similar low TB incidence countries, where most cases are due

* Corresponding author at: Division of TB Elimination, National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention, Centers for Disease Control and Prevention, 1600 Clifton Road, NE, MS-E10, Atlanta, GA 30329, USA.
E-mail address: NScott@cdc.gov (N.A. Scott).

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to reactivation of latent infection [2]. Adherence to LTBI treatment is key in accomplishing this goal. The World Health Organization (WHO) recently noted the importance of accurately measuring adherence within clinical trials [3,4], and within TB programs. Better understanding of how patients self-administer medication and identification of predictors of non-adherence are needed to develop interventions to improve adherence [5]. This knowledge can enable TB programs to improve LTBI treatment completion. [6]

The most common non-biologic measure of self-administered treatment completion globally is patient self-report [7,8]. Other measures include pill count and digital systems including medication event monitoring systems (MEMS). Self-report includes asking patients how many pills they take with each dose, when they take their medications, and if they have missed any doses. Pill count involves patients returning unused medication and packaging, with remaining pills counted by program personnel. MEMS and other similar devices involve an electronic medicine bottle cap which records each date and time that the cap is removed from the bottle and assumes a dose is consumed with each opening. Self-report and pill count are often used together, and is popular among U.S. TB programs. Each measure has deficiencies, but they can be complimentary when used in combination [9,10]. The addition of MEMS to self-report and pill count is considered by some to be the most reliable non-biologic measure of self-administered treatment completion [7,8,11].

The Tuberculosis Trials Consortium (TBTC) Study 33 (iAdhere) [12] compared completion of three months (12 doses) of once-weekly isoniazid (H) and rifapentine (P), (3HP) treatment, among participants randomly assigned to 3 separate treatment arms: directly observed therapy (DOT), self-administered therapy (SAT) without text message reminders and SAT with text message reminders (SAT-r). Both SAT arms included the use of MEMS, as an additional measure of treatment completion. To better understand treatment completion for the 3HP regimen, we evaluated treatment completion of 3HP overall and by country; compared differences in the treatment completion metric when standard of care (SOC) was enhanced by MEMS (SOC with MEMS); and identified characteristics of participants with a SOC-MEMS discordance.

2. Methods

2.1. Design and analysis populations

This analysis was performed using iAdhere data from Hong Kong, South Africa, Spain and U.S. Participants enrolled in the iAdhere study were aged 18 years or older. The iAdhere primary study report [12] provides additional details on the study population. Participants enrolled into all three arms were included as part of the analysis

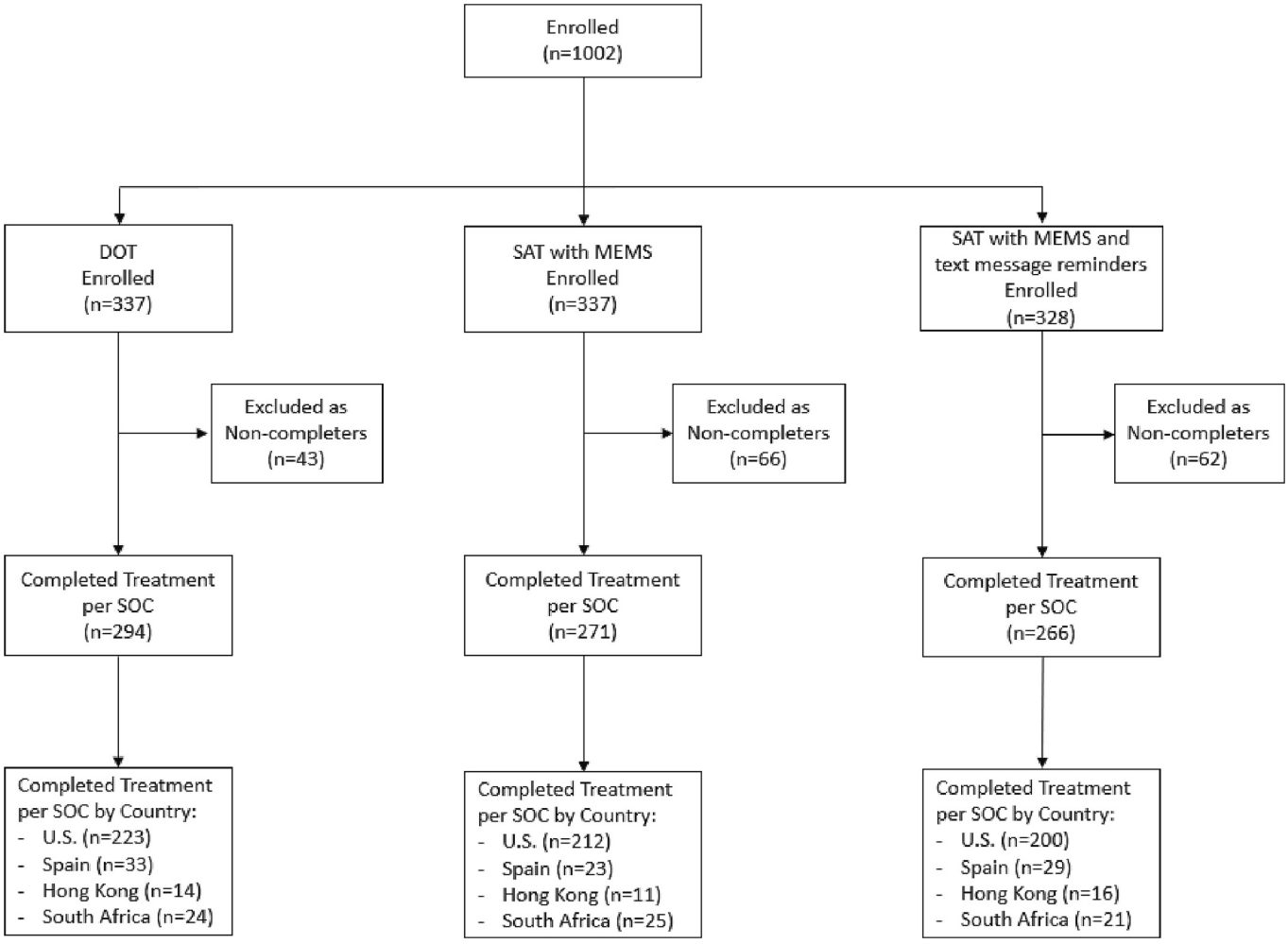

Fig. 1. CONSORT diagram of analyses populations.
DOT – Directly Observed Therapy.
SAT – Self-Administered Therapy.
SOC – Standard of Care.
MEMS – Medication Event Monitoring System.

population (Fig. 1). The study's DOT arm provided a concurrent reference of treatment completion.

The primary study permitted participants from the same household to enroll in the trial. Households were limited to a maximum of 3 persons. Only the first person enrolled was randomized, and other household members were assigned to the same treatment group as the first person randomized.

2.2. Measurement of treatment completion

In all arms of the iAdhere study, treatment completion was defined as taking at least 11 of 12 weekly doses of the 3HP regimen within 16 weeks of first dose taken. Treatment completion in the SAT arms was measured by SOC, where SOC is defined as the combination of self-report and pill count. Participants in the SAT arms were monitored during treatment using SOC with MEMS. MEMS caps replaced the original H bottle caps, and recorded bottle openings. Each H bottle contained 30, 300 mg H pills. Each P box contained 4 blister strips, with 8, 150 mg P pills in each blister strip. One H bottle and one P box was dispensed each month for 3 months, to participants in the SAT arms. The expectation was that each opening of the H bottle, corresponded to a participant taking three (3) H pills and six (6) P pills. Both participants and research staff were blinded to the MEMS data until the study was completed. By design, participants categorized as non-completers by SOC could not be changed to completers based on MEMS data only. The separate collection of SOC and MEMS data established separate approaches for estimating treatment completion: treatment completion per SOC; and treatment completion per SOC with MEMS. Detailed criteria to estimate how the number of doses were calculated for treatment completed for each approach (SOC and SOC with MEMS) are provided in Supplementary Figs. 1a and 1b.

To standardize the information that clinicians provided to trial participants regarding how to take the medication and use MEMS, a standardized flipchart was developed and translated to languages used in each country and used to coach participants.

2.3. Statistical analyses

The proportion of participants who completed treatment (for SAT and SAT-r arms) was calculated by enrollment country and overall. Where possible, treatment completion was calculated by study site. Treatment completion proportion by SOC was compared to treatment completion proportion by SOC with MEMS. Since the same participants were included when measuring treatment completion for both approaches (SOC vs SOC with MEMS), participants were analyzed as their own matched pair. Wald 95% confidence intervals (95% C.I.) for the differences in proportions between treatment completion were computed by fitting a repeated measures linear probability model that adjusted for the correlation within each matched pair. A secondary analysis compared treatment completion between self-report only and SOC. The results of this secondary analysis are provided in the supplementary appendix.

Univariable and multivariable penalized logistic regression analyses [20 – 22] were performed to identify characteristics of participants (among SAT and SAT-r arms) who had a SOC-MEMS discordant treatment completion outcome. This SOC-MEMS discordance was defined as a mismatch in completion of 3HP treatment, where participants were deemed to have completed treatment per SOC but were found to have not completed treatment according to SOC with MEMS. Participant demographic variables, along with treatment arm, and country specific variables were included as covariates. We applied a p-value of <0.2 to determine which factors from the univariable analyses would be included in the multivariable analyses. Results of the multivariable analyses were reported using Odds Ratios (OR) and corresponding 95% C.I. Analyses were conducted by country level and overall.

The count and percentage of baseline characteristics are also presented by country, arm, and overall. Results are provided in the supplementary appendix.

3. Results

3.1. Treatment completion analyses

Of 337 participants enrolled in the DOT arm, 294 (87.2%) completed 3HP treatment. In the SAT and SAT-r arms respectively, 271 (80.4%) and 266 (81.1%) participants completed treatment based on SOC (Fig. 1 and Table 1). In the combined SAT arms, overall and by enrollment country, the proportion of treatment completion by SOC was consistently greater than the proportion by SOC with MEMS (Table 1 and Fig. 2). Overall, there was a 6.1% [95% C.I. (4.2, 7.8)] difference between SOC and SOC with MEMS. In the U.S., SOC treatment completion was 3.3% [95% C.I.: (1.8, 4.9)] greater than that based on SOC with MEMS. SOC treatment completion in South Africa was 36.8% [95% C.I. (24.3, 49.4)] greater than treatment completion using SOC with MEMS. The difference of 3.1% [95% C.I. (−1.1, 7.3)] for participants enrolled in Spain was not significant. There was no difference (0.0%) among participants enrolled in Hong Kong. The numbers enrolled in non-U.S. countries were small (each <10% of total enrolled). Differences in treatment completion proportions between self-report only and SOC, overall and by country, were small (Supplementary Table 3).

At the study site level, proportions were calculated and reported only for the U.S. sites, since only the U.S. enrolled at multiple sites ($n = 9$). There was only one enrolling study site in Hong Kong, South Africa, and Spain. For the U.S. site level analyses, the difference between SOC and SOC with MEMS was not significant at any individual site, and ranged from 0% to 4.8% [95% C.I. (−0.5, 10.2)]. (Supplementary Table 1 and Supplementary Fig. 2).

In the combined SAT study population ($N = 665$), 40 participants had SOC-MEMS discordances. Of these discordances, 17 were from the U.S., 2 from Spain, 21 from South Africa, and none from Hong Kong. Among the combined SAT study population, being part of a household cluster, being 35 years or older, reporting Black or African-American race, enrollment in South Africa, being born outside of the country of enrollment, being unemployed, having a history of alcohol abuse, being a current smoker or having ever smoked, being HIV-infected and using concomitant medications at baseline were all factors significantly associated with a discordance in univariable analysis. Being part of a household cluster [OR = 3.02; 95% C.I. (1.09, 8.38)], country of enrollment [South Africa: OR = 13.55; 95% C.I. (6.49, 28.29)] and being a current smoker [OR = 2.75; 95% C.I. (1.35, 5.63)] were factors that remained statistically significant in multivariable logistic regression (Table 2).

The baseline characteristics by country, showed that 73.7% of South African participants were unemployed, compared to 38.5%, 16.7% and 36.3% of participants from Spain, Hong Kong and U.S. respectively. Additionally, 43.1% and 43.9% of participants from Spain and South Africa were current smokers, compared to 10.0% and 20.5% of participants from Hong Kong and U.S. respectively (Supplementary Table 4).

For the study site analyses (U.S. only), individuals who were part of a household cluster were 5 times more likely to have a discordance (OR: 5.21; 95% C.I. [1.62, 16.73]). Those who reported alcohol use were 75% less likely to have the discordance (OR: 0.25; 95% C.I. [0.08, 0.75]), while individuals who identified themselves as current smokers were over four times more likely to have the SOC-MEMS discordance (OR: 4.45; 95% C.I. [1.47, 13.47]) (Table 3). In the South African only analyses, there were several characteristics with p-values <0.2, but not significant in the final multivariable analyses. OR were >2 with wide 95% C.I. (Supplementary Table 2).

4. Conclusion

The measurement of self-administered treatment completion is

Table 1
Percentage treatment completion by standard of care vs. standard of care with MEMS by arm and enrollment country.

Enrollment Country	Treatment Completion							
	DOT[1]	SOC[1,2]			SOC with MEMS[1]			% Difference of Total in SAT SOC vs. SOC with MEMS (95%CI)[3]
		SAT	SAT-r	Total in SAT	SAT	SAT-r	Total in SAT	
United States	223/261	212/262	200/251	412/513	204/262	191/251	395/513	3.3 (1.8, 4.9)
	(85.4)	(80.9)	(79.7)	(80.3)	(77.9)	(76.1)	(77.0)	
Spain	33/35	23/32	29/33	52/65	22/32	28/33	50/65	3.1 (−1.1, 7.3)
	(94.3)	(71.9)	(87.9)	(80.0)	(68.75)	(84.8)	(76.9)	
Hong Kong	14/15	11/14	16/16	27/30	11/14	16/16	27/30	0.0[4]
	(93.3)	(78.6)	(100.0)	(90.0)	(78.6)	(100.0)	(90.0)	
South Africa	24/26	25/29	21/28	46/57	11/29	14/28	25/57	36.8 (24.3, 49.4)
	(92.3)	(86.2)	(75.0)	(80.7)	(37.9)	(50.0)	(43.9)	
Total	**294/337**	**271/337**	**266/328**	**537/665**	**248/337**	**249/328**	**497/665**	**6.1 (4.2, 7.8)**
	(87.2)	**(80.4)**	**(81.1)**	**(80.8)**	**(73.6)**	**(75.9)**	**(74.7)**	

1 iAdhere primary treatment completion results by country.
2 Treatment completion numerators based on Fig. 1; denominators based on iAdhere primary results by country. (See Table 1 of primary iAdhere manuscript $n = 1002$).
3 Wald 95% confidence interval for the difference in proportion between SOC and SOC with MEMS.
4 Wald 95% confidence interval for the difference in proportion cannot be calculated.
DOT – Directly Observed Therapy.
SAT – Self-Administered Therapy.
SAT-r – Self-Administered Therapy with text message reminders.
SOC – Standard of Care.
MEMS – Medication Event Monitoring System.

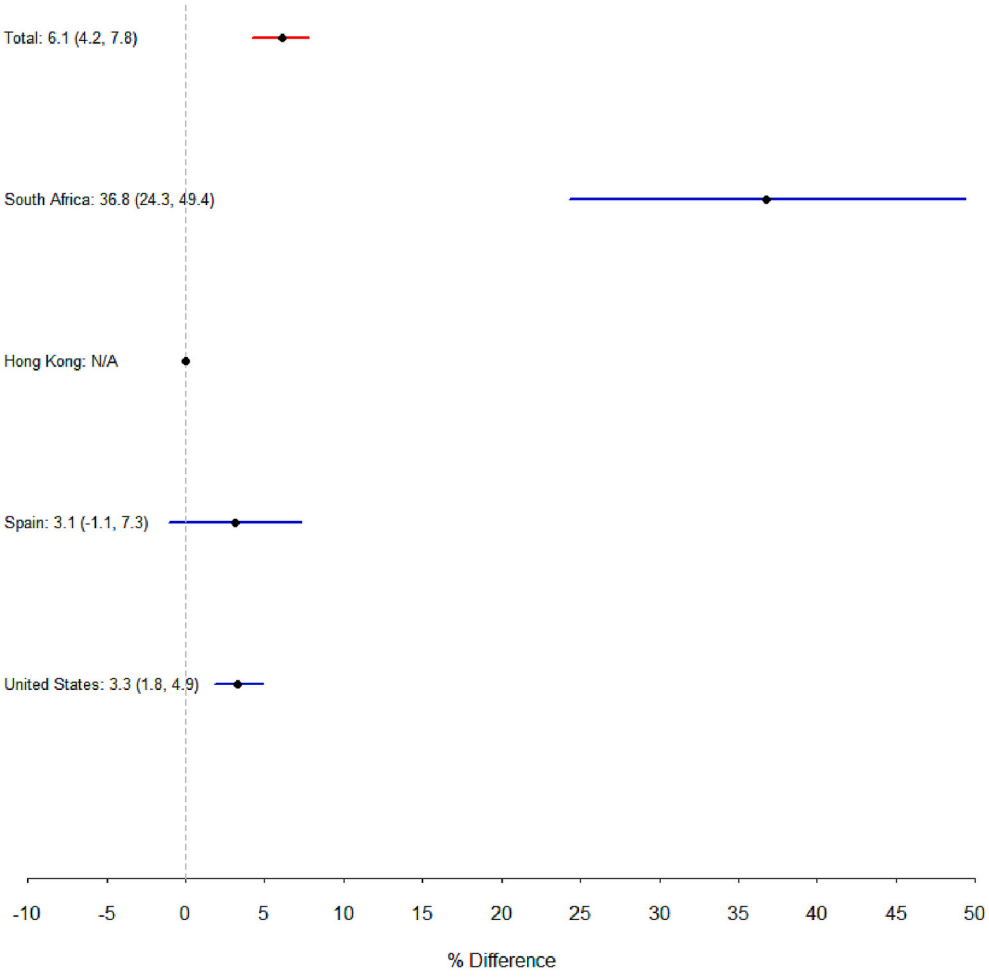

Fig. 2. Percent difference in treatment completion: SOC vs SOC with MEMS by enrollment country with their 95% C.I.

Table 2
Univariable and multivariable analyses of factors associated with self-report and pill count overestimating treatment completion compared with MEMS openings. (Combined SAT/SAT-r Analysis Population – Using Ordinary LR) (Overall Study Population).

			Univariable				Multivariable			
Characteristics	# With Discordance*	# w/o Discordance*	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI	P-value	OR	Lower 95% CI	Upper 95% CI	P-value
Part of Household Cluster	6	48	2.24	0.92	5.49	0.08	3.02	1.09	8.38	0.03
Female	19	310	0.92	0.49	1.74	0.80				
Age 35 years or older	15	363	0.43	0.23	0.84	0.01				
Race										
White	7	340	ref	ref	ref	ref				
Black/African American	27	139	8.95	3.90	20.58	0.0007				
Asian	6	124	2.37	0.81	6.93	0.84				
Other Race	0	22	1.01	0.05	19.38	0.49				
Country of Enrollment										
U.S.	17	496	ref	ref	ref	ref				
Spain	2	63	1.12	0.29	4.35	0.48				
Hong Kong	0	30	0.47	0.03	8.29	0.24				
South Africa	21	36	16.71	8.15	34.29	<0.0001	13.55	6.49	28.29	<0.0001
Born Outside Country of Enrollment	14	381	0.35	0.18	0.68	0.002				
Indication for LTBI Treatment										
Contact of a person with infectious TB	18	216	ref	ref	ref	ref				
Recent LTBI screening test conversion	3	62	0.66	0.20	2.14	0.21				
Fibrosis	0	1	4.00	0.04	368.57	0.60				
HIV infection	1	3	5.02	0.56	44.85	0.23				
Positive results on LTBI screening test	18	343	0.63	0.32	1.23	0.11				
Occupation-Unemployed	28	230	3.91	1.97	7.76	<0.0001				
Did Not Complete High School										
Complete High	20	402	ref	ref	ref	ref				
Did Not Complete High School	17	191	1.79	0.93	3.48	0.600				
Unknown	3	32	2.11	0.64	7.04	0.443				
Homeless	1	34	0.65	0.12	3.53	0.618				
Drug Use	3	28	1.96	0.60	6.64	0.263				
Resident of Correctional Facility	0	8	0.90	0.04	18.78	0.945				
Alcohol Use	21	327	1.01	0.53	1.89	0.988				
Alcohol Abuse	11	34	6.68	3.10	14.43	<0.0001				
Current Smoker	20	141	3.43	1.80	6.51	0.0002	2.75	1.35	5.63	0.006
Ever smoke	23	256	1.93	1.02	3.67	0.043				
Diabetes	1	51	0.42	0.08	2.25	0.313				
Liver Disease	2	29	1.31	0.34	5.07	0.694				
HIV Positive	2	6	6.19	1.27	30.07	0.024				
Concomitant Medications at Baseline	15	359	0.45	0.24	0.87	0.017				
Treatment Arm										
SAT	23	314	ref	ref	ref	ref				
SAT w/reminders	17	311	0.75	0.39	1.42	0.38				

DOT – Directly Observed Therapy; SAT – Self-Administered Therapy.
* Discordance: a mismatch in treatment completion status, where participants were deemed to have completed treatment per SOC but were found to have not completed treatment according to SOC with MEMS.

important in determining whether a patient has received adequate therapy. No gold-standard for such measurement has been established. Methods such as self-report, pill count and MEMS, used to determine treatment completion each have their own strengths and weaknesses when used individually [7]. Confidence in treatment completion measurement can be increased when methods are used concurrently, to supplement individual weaknesses [9,10]. A strength of the iAdhere study was the use of three different methods in assessing treatment completion. In this post-hoc secondary analysis, SOC (self-report and pill count) consistently overstated the quantity of 3HP doses attributed towards treatment completion when compared to the combination of SOC with MEMS. However, this overstatement was not always severe, and varied by country. Treatment completion was significantly overstated by 3.3% for the U.S. population, non-significantly overstated by 3.1% for Barcelona, Spain, significantly overstated by 36.8% for Soweto, South Africa, and there was no difference in treatment completion for the Hong Kong site (Table 1). With all countries combined, treatment completion was significantly overstated by 6.1%.

In countries such as U.S., Spain, and Hong Kong, overstatement of treatment completion was small compared to South Africa, with point estimates of U.S. and Spain being similar in magnitude, 3.3% compared to 3.1%. The non-significant finding in Barcelona, Spain is likely related to small sample size ($n = 65$), resulting in reduced power to identify a difference as significant. Similar reasoning can be applied to Hong Kong ($n = 30$) and to each individual U.S. site, which all showed either a non-significant difference or no difference (Supplementary Table 1 and Supplementary Fig. 2). While the sample size in South Africa was also small ($n = 57$), the finding was significant because of the large difference being detected.

One explanation for these differences in performance across countries, especially as it relates to South Africa, is suggested by the logistic model results. The model showed that country of enrollment was significantly associated with discordances between SOC and SOC with MEMS. Compared to U.S. participants, those enrolled in South Africa were 13 times more likely to have discordance observed. This association with country may be attributed to local policy on LTBI treatment during the time the study was being conducted. The iAdhere study began enrollment in 2014, at which time the TB incidence rate in South Africa was 1070 per 100,000 compared to 3.2, 12 and 77 per 100,000 for U.S., Spain and Hong Kong respectively [14]. Treatment for LTBI in the U.S., Spain and Hong Kong was a usual part of contact tracing. However, in South Africa, at the time of the trial, isoniazid preventive treatment for TB contacts, was limited to contacts of TB patients who were under five years of age or those with HIV infection and was not part of national guidelines for the wider population [15]. These differences in guidelines may have played some role in the implementation of treatment for LTBI

Table 3
Univariable and multivariable analyses of factors associated difference between self-report and pill count treatment completion compared with mems-based treatment completion. (Combined SAT/SAT-r Analysis Population – Using Ordinary LR) (U.S. Population Only).

			Univariable				Multivariable			
Characteristics	# With Discordance*	# w/o Discordance*	Odds Ratio (OR)	Lower 95% CI	Upper 95% CI	P-value	OR	Lower 95% CI	Upper 95% CI	P-value
Part of Household Cluster	4	33	4.61	1.48	14.35	0.008	5.21	1.62	16.73	0.006
Female	9	8	1.07	0.41	2.74	0.90				
Age 35 years or older	11	300	1.16	0.43	3.08	0.77				
Race										
White	6	298	ref	ref	ref	ref				
Black/African American	6	99	3.00	0.98	9.14	0.31				
Asian	5	79	3.17	0.99	10.20	0.27				
Other	0	20	1.12	0.06	22.01	0.67				
Born Outside Country of Enrollment	12	329	1.16	0.42	3.21	0.78				
Indication for LTBI Treatment										
Contact of a person with infectious TB	4	110	ref	ref	ref	ref				
Recent LTBI screening test conversion	3	62	1.38	0.33	5.80	0.75				
Fibrosis	0	1	8.31	0.08	833.11	0.37				
HIV infection	0	0	–	–	–	–				
Positive results on LTBI screening test	10	323	0.80	0.26	2.47	0.23				
Occupation-Unemployed	9	177	2.01	0.78	5.18	0.15				
Did Not Complete High School										
Complete High	9	318	ref	ref	ref	ref				
Did Not Complete High School	5	147	1.25	0.43	3.65	0.43				
Unknown	3	31	3.73	1.02	13.58	0.06				
Homeless	1	31	1.34	0.24	7.61	0.74				
Drug Use	0	24	0.55	0.03	9.99	0.69				
Resident of Correctional Facility	0	8	1.64	0.08	35.10	0.75				
Alcohol Use	5	270	0.37	0.13	1.02	0.05	0.25	0.08	0.75	0.01
Alcohol Abuse	0	23	0.58	0.03	10.47	0.71				
Current Smoker	6	99	2.26	0.84	6.08	0.11	4.45	1.47	13.47	0.008
Ever smoke	8	205	1.27	0.49	3.26	0.62				
Diabetes	1	49	0.82	0.15	4.56	0.82				
Liver Disease	2	26	2.86	0.70	11.77	0.14				
HIV Positive	0	0	–	–	–	–				
Concomitant Medications at Baseline	9	306	0.70	0.27	1.79	0.45				
Treatment Arm										
SAT	8	254	ref	ref	ref	ref				
SAT w/reminders	9	242	1.17	0.46	3.01	0.74				

DOT – Directly Observed Therapy.
SAT – Self-Administered Therapy.
* Discordance: a mismatch in treatment completion status, where participants were deemed to have completed treatment per SOC but were found to have not completed treatment according to SOC with MEMS.

in South Africa, which was reflected by the large SOC-MEMS discordance observed in that country. However, as elaborated in the limitations below, this study did not collect specific data to confirm this reasoning. Additionally, the findings of the baseline characteristics by country (Supplementary Table 4), suggest that the population enrolled in South Africa was different from participants in other countries.

While TB programs, in countries including the U.S. and Spain, traditionally use methods such as self-report and pill count to measure treatment completion, the availability of data showing MEMS caps openings allowed us to estimate by how much treatment completion was overestimated when using only the traditional SOC methods. This overestimation was not severe in magnitude (<4%) in U.S., Spain, and Hong Kong enrolling in this study. This information adds to our understanding of treatment completion, and the findings suggests that MEMS may not be needed to obtain reasonable estimates of treatment completion for the 3HP regimen in these countries. In South Africa, SOC with MEMS could be applied to increase accuracy of the treatment completion measurement. Care should be taken in assessing treatment completion differences reported in this analysis, given the small individual country sample sizes. Additionally, these findings observed on a trial setting, may differ in program settings. Interventions [16], such as education in use of the regimen, memory aids, incentives and/or reinforcements, might improve treatment completion when SOC with MEMS is not implemented.

We elected to use MEMS as a more objective albeit still indirect measure of adherence, to treatment completion after considering other direct measures including biologic samples. Our findings are consistent with the results of other studies [13,23] showing that self-report and pill count overestimate adherence when compared to MEMS. Specifically, Alili et al. [13], reported that when compared with MEMS, median adherence for self-report and pill count was overestimated by 17% and 8% respectively. MEMS also allowed us to detect variability between countries that was not detected by self-report and pill counts. The cost and complexity of MEMS can be limiting factors, but we would encourage their use in more clinical trials settings whenever feasible. In addition, the paper by Williams et al. [7], provides a robust discussion on MEMS and suggests best practices on when to implement such electronic monitoring devices.

This post-hoc secondary analysis also aimed to determine characteristics of participants for whom a discordance was observed. In the combined SAT study population, which included all enrolling countries, participants who were part of a household cluster, were current smokers and enrolled in South Africa were more likely to have a discordance. In the U.S. specific analyses, participants who were more likely to be discordant were part of a household cluster and current smokers. Being part of a household cluster and a current smoker were identified as risk factors in both the overall analyses and when analysis was restricted to U.S. participants. This suggests that these two characteristics are risk factors that may be common across countries. The finding of current smokers is in line with previous studies [17–19] which have shown that being a current smoker is a predictor for non-completion of treatment. Participants who are part of a household cluster and current smokers,

may be targeted for some of the treatment completion interventions described above. Among the U.S. specific analyses, reported use of alcohol reduced the odds of having a discordance. This finding is counter-intuitive, and it is possible that alcohol use is a marker for an unobserved characteristic of U.S. participants in this study.

There were limitations to our post-hoc secondary analysis. Although we were able to identify factors associated with discordance between SOC and SOC with MEMS, we did not seek to identify participant reasons for not taking medications even when reporting doses as consumed. Further effort is needed to address this discordance between reported doses and true treatment completion. Another limitation was that only one study site enrolled in Hong Kong, South Africa and Spain, so results may not be representative of practices across these individual countries. Additionally, this post-hoc secondary analysis did not collect data on the added costs in implementing MEMS as a measure of treatment completion. As such, TB programs and clinics would need to carefully weigh the cost-to-benefit ratio if considering implementing the SOC with MEMS approach. There was no additional cost associated with the SOC only approach.

A combination of methods tends to improve the measurement of self-administered treatment completion [9,10]. Our findings showed that treatment completion was overstated by 3.3% in U.S., and by 36.8% in South Africa. However, care should be taken when interpreting results from this secondary analyses. The addition of MEMS to SOC provided improved measurement of treatment completion, but SOC by itself still provided a reasonable measurement, for U.S., Spain and Hong Kong, indicating that adequate therapy had been completed by the majority of participants on 3HP. Participants who are current smokers or part of a household cluster, might benefit from being followed closely and other interventions, to ensure treatment completion in the absence of MEMS. The role of digital technology in monitoring and supporting patient treatment completion should be further studied.

Ethical approval

This study was approved by the institutional review board(s)/ research ethics committees at Centers for Disease Control and Prevention (CDC). Additionally, each site followed local review policies and procedures.

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All authors have approved the submitted version. All authors agree both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which they were not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

CRediT authorship contribution statement

Nigel A. Scott: Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Claire Sadowski:** Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing. **Andrew Vernon:** Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Bert Arevalo:** Data curation. **Karlyn Beer:** Writing – original draft, Writing – review & editing. **Andrey Borisov:** Conceptualization, Methodology, Validation, Data curation, Writing – original draft, Writing – review & editing. **Joan A. Cayla:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Michael Chen:** Conceptualization, Methodology, Writing – original draft, Writing – review & editing. **Pei-Jean Feng:** Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing. **Ruth N. Moro:** Methodology, Data curation, Writing – original draft, Writing – review & editing. **David P. Holland:** Writing – original draft, Writing – review & editing. **Neil Martinson:** Investigation, Writing – original draft, Writing – review & editing. **Joan-Pau Millet:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Jose M. Miro:** Investigation, Resources, Writing – original draft, Writing – review & editing. **Robert Belknap:** Conceptualization, Methodology, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authorship team members have declared (below or attached) any potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

Data will be made available on request.

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Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention, the National Institutes of Health, or the authors' affiliated institutions. References in this manuscript to any specific commercial products, process, service, manufacturer, or company do not constitute endorsement or recommendation by the U.S. Government.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cct.2023.107173.

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