Factors Associated With Noncompletion of Latent Tuberculosis Infection Treatment: Experience From the PREVENT TB Trial in the United States and Canada

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Online Data Supplement

Supplementary Content

Method Details

In the PREVENT TB trial, unrestricted randomization was stratified by enrollment site and the participant's human immunodeficiency virus (HIV) status. Participants enrolled in 28 sites were followed-up for 33 months after enrollment. Follow-up of the last participant was completed on November 2010. Enrollment of participants in this analysis started at 22 North American sites in 2001; 2 sites were added in 2002 and 1 each in 2003 and 2008.

For the first 322 participants enrolled in each study arm, liver function tests were obtained at baseline before treatment was started, after 1 month of therapy if aspartate aminotransferase at baseline was elevated, and at any time during treatment if hepatitis symptoms were present. Subsequently, liver function tests at baseline were obtained for participants considered by site investigators to be at risk for hepatitis and during treatment for any participant who experienced symptoms of hepatitis.

Table S1. Proportion of Noncompletion of Latent Tuberculosis Infection Treatment

Cohort	9H-SAT	3HP-DOT	P-value
Combined[a] (n=6232)	838/3002 (28%)	568/3230 (18%)	<.001
NCT-AE[b] (n=5143)	135/2299 (5.9%)	182/2844 (6.4%)	.23
NCT-O[c] (n=5915)	703/2867 (24.5%)	386/3048 (12.7%)	.02

Abbreviations: 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); NCT-AE, noncompletion of treatment attributed to an adverse event; NCT-O, noncompletion of treatment attributed to reasons other than an AE

a Combined cohort for analysis includes participants who completed treatment (n = 4826) plus those who did not complete treatment (n = 1406).

b Includes participants who did not complete treatment attributed to an adverse event (n = 317) plus those who completed treatment (n = 4826).

c Includes participants who did not complete treatment attributed to reasons other than an adverse event (n = 1089) plus those who completed treatment (n = 4826).

Table S2A. Adverse Events Among Participants Who Did Not Complete Latent Tuberculosis Infection Treatment Attributed to an Adverse Event, by Regimen

	3HP-DOT (n = 3230) No. (%) [a]	9H-SAT (n = 3002) No. (%) [a]
Influenza-like syndrome	110 (3.4)	12 (0.4)
Oher drug reaction	47 (1.5)	34 (1.1)
Rash only	16 (0.5)	12 (0.4)
Hepatotoxicity	13 (0.4)	76 (2.5)
Other not related adverse event	11 (0.3)	20 (0.7)
Medical error	0	3 (0.1)
Tuberculosis [b]	0	1 (0.03)
Death	1 (0.03)	1(0.03)
Total of adverse events	198 (6.1)	159 (5.3)

357 Adverse events occurred among 317 participants.

Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg).

[a] Percentages are related to the total number of participants enrolled by regimen.

[b] Three participants developed tuberculosis during 9H-SAT treatment; 1 was excluded from this analysis because of being aged <18 years; 1 did not complete treatment after developing hepatotoxicity; and 1 did not complete treatment because of tuberculosis disease (displayed in this table). None developed tuberculosis during 3HP-DOT treatment.

Table S2B. Adverse Events Among Participants Who Did Not Complete Latent Tuberculosis Infection Treatment Attributed to an Adverse Event, by Regimen and by Attribution

Adverse events	**3HP-DOT (n = 3230) No. (%) [a]**	**9H-SAT (n = 3002) No. (%) [a]**
Attributed to study drug(s)	n = 186	n = 131
Influenza-like syndrome	110 (3.4)	12 (0.4)
Oher drug reaction	47 (1.5)	34 (1.1)
Rash only	16 (0.5)	12 (0.4)
Hepatotoxicity	13 (0.4)	73 (2.4)
Not attributed to study drug(s)	n = 12	n = 28
Other not related adverse event	11 (0.3)	20 (0.7)
Hepatotoxicity	0	3
Medical error	0	3
Tuberculosis [b]	0	1 (0.03)
Death	1 (0.03)	1(0.03)
Total of adverse events	199 (6.2)	159 (5.3)

357 adverse events occurred among 317 participants.

Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg).

[a] Percentages are related to the total number of participants enrolled by regimen.

[b] Three participants developed tuberculosis during 9H-SAT treatment; 1 was excluded from this analysis because of being aged <18 years; 1 did not complete treatment after developing hepatotoxicity; and 1 did not complete treatment because of TB disease (displayed in this table). None developed tuberculosis during 3HP-DOT treatment.

Table S3. Number of Participants Who Did Not Complete Latent Tuberculosis Infection Treatment Because of Reasons Other Than an Adverse Event (NCT-O), by 3HP-DOT and 9H-SAT Doses Received

3HP-DOT		9H-SAT	
Number of Doses	Participants Who Did Not Complete Treatment, n = 3230 No. (%)	Number of Doses	Participants Who Did Not Complete Treatment, n = 3002 No. (%)
0	71 (2.2)	0	77 (2.6)
1	61 (1.9)	1–30	124 (4.1)
2	43 (1.3)	31–60	69 (2.3)
3	33 (1.0)	61–90	76 (2.5)
4	30 (0.9)	91–120	60 (2.0)
5	27 (0.8)	121–150	68 (2.3)
6	16 (0.5)	151-180	56 (1.9)
7	15 (0.5)	181–210	52 (1.7)
8	15 (0.5)	211–239	60 (2.0)
9	13 (0.4)	≥240[c]	61 (2.0)
10	4 (0.1)		
11[a]	10 (0.3)		
12[b]	48 (1.5)		

Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg).

[a] 11 doses in <10 weeks (n = 3); 11 doses in >16 weeks (n = 7).

[b] 12 doses in <10 weeks (n = 21); 12 doses in >16 weeks (n = 27).

[c] ≥240 doses in >52 weeks (n = 60).

Table S4. Proportion of Noncompletion of Latent Tuberculosis Infection Treatment Attributed to an Adverse Event (NCT-AE) and Attributed to Reasons Other than an Adverse Event (NCT-O), by Enrollment Site

Site	Treatment Noncompletion Attributed to an Adverse Event (NCT-AE) (n = 317) No. (%)	Treatment Noncompletion Attributed to Reasons Other Than an Adverse Event (NCT-O) (n = 1089) No. (%)	Enrollments (n = 6232) No. (%)
G	49 (15.46)	239 (21.95)	1133 (18.18)
K	29 (9.15)	74 (6.80)	314 (5.04)
L	27 (8.52)	40 (3.67)	270 (4.33)
I	26 (8.20)	27 (2.48)	295 (4.73)
M	25 (7.89)	42 (3.86)	228 (3.66)
W	25 (7.89)	75 (6.89)	494 (7.93)
P	18 (5.68)	106 (9.73)	502 (8.06)
Z	16 (5.05)	90 (8.26)	346 (5.55)
H	14 (4.42)	7 (0.64)	84 (1.35)
R	13 (4.10)	19 (1.74)	185 (2.97)
J	12 (3.79)	17 (1.56)	172 (2.76)
N	12 (3.79)	15 (1.38)	117 (1.88)
T	8 (2.52)	14 (1.29)	168 (2.70)
C	7 (2.21)	19 (1.74)	211 (3.39)
Q	7 (2.21)	1 (0.09)	45 (0.72)
X	6 (1.89)	31 (2.85)	154 (2.47)
F	5 (1.58)	26 (2.39)	300 (4.81)
O	5 (1.58)	50 (4.59)	197 (3.16)
S	3 (0.95)	11 (1.01)	94 (1.51)
U	3 (0.95)	25 (2.30)	111 (1.78)
B	2 (0.63)	46 (4.22)	323 (5.18)
D	2 (0.63)	35 (3.21)	113 (1.81)
A	1 (0.32)	6 (0.55)	32 (0.51)
E	1 (0.32)	67 (6.15)	286 (4.59)
V	1 (0.32)	7 (0.64)	57 (0.91)
Y	0 (0.00)	0 (0.00)	1 (0.02)

Table S5. Proportion of Early Discontinuation by Regimen

Discontinuation	**3HP-DOT**	**9H-SAT**
NCT-AE (n=317)		
During the first Month	113 (113/182 = 62%)	--
During the first 3 Months	--	75 (75/135 = 55.6%)
NCT-O (n=1089)		
During the first Month	287 (287/386 = 74.4%)	--
During the first 3 Months	--	376 (376/703 = 53.5%)

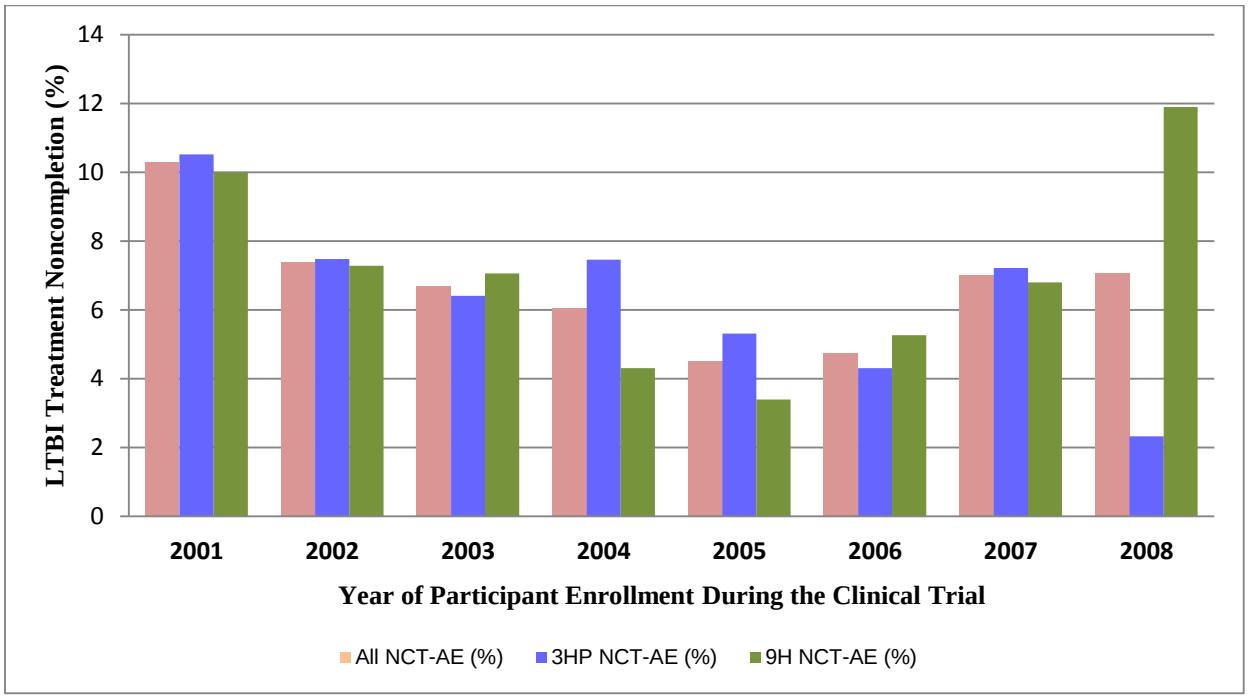
Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); LTBI, latent tuberculosis infection; NCT-AE, noncompletion of LTBI treatment attributed to an adverse event; NCT-O, noncompletion of LTBI treatment attributed to reasons other than an adverse event.

Table S6. Proportion of Participants Who Missed an Early Visit by Regimen

Cohort	**3HP-DOT**	**9H-SAT**	**Total**
Completers (n=4826)	61 (61/2662=2.3%)	136 (136/2164= 6.3%)	197 (4.1%)
NCT-AE (n=317)	5 (5/182=2.3%)	5 (5/135= 3.7%)	10 (3.2%)
NCT-O (n=1089)	18 (18/386= 4.7%)	179 (179/703= **25.5**%)	197 (18.2%)

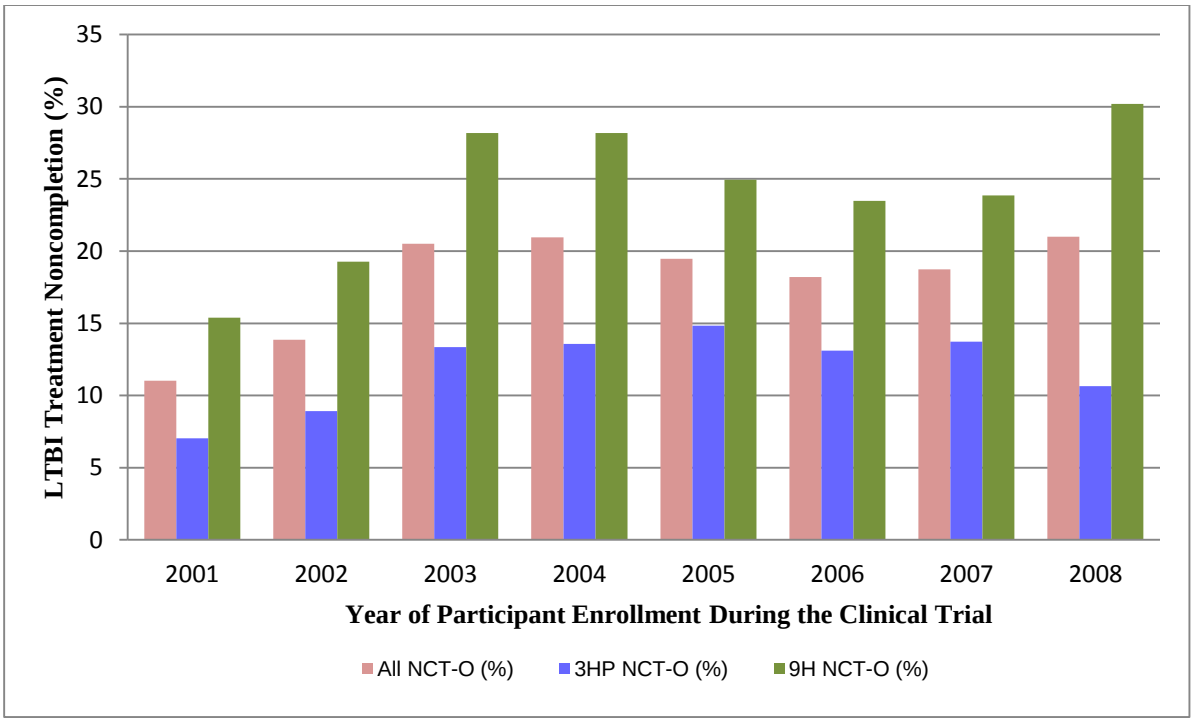
Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); LTBI, latent tuberculosis infection; NCT-AE, noncompletion of LTBI treatment attributed to an adverse event; NCT-O, noncompletion of LTBI treatment attributed to reasons other than an adverse event.
Persons who missed an early visit but returned later were seen at a median time of 12 days (IQR: 9 – 30) in the 3HP-DOT regimen and 38 days (IQR: 30 -68) in the 9H-SAT regimen after the missed visit.

Figure S1. Noncompletion of Latent Tuberculosis Infection Treatment Attributed to an Adverse Event (NCT-AE) Among All Participants and Stratified by Study Regimen Throughout the Trial, June 2001–February 2008 (n = 5143)



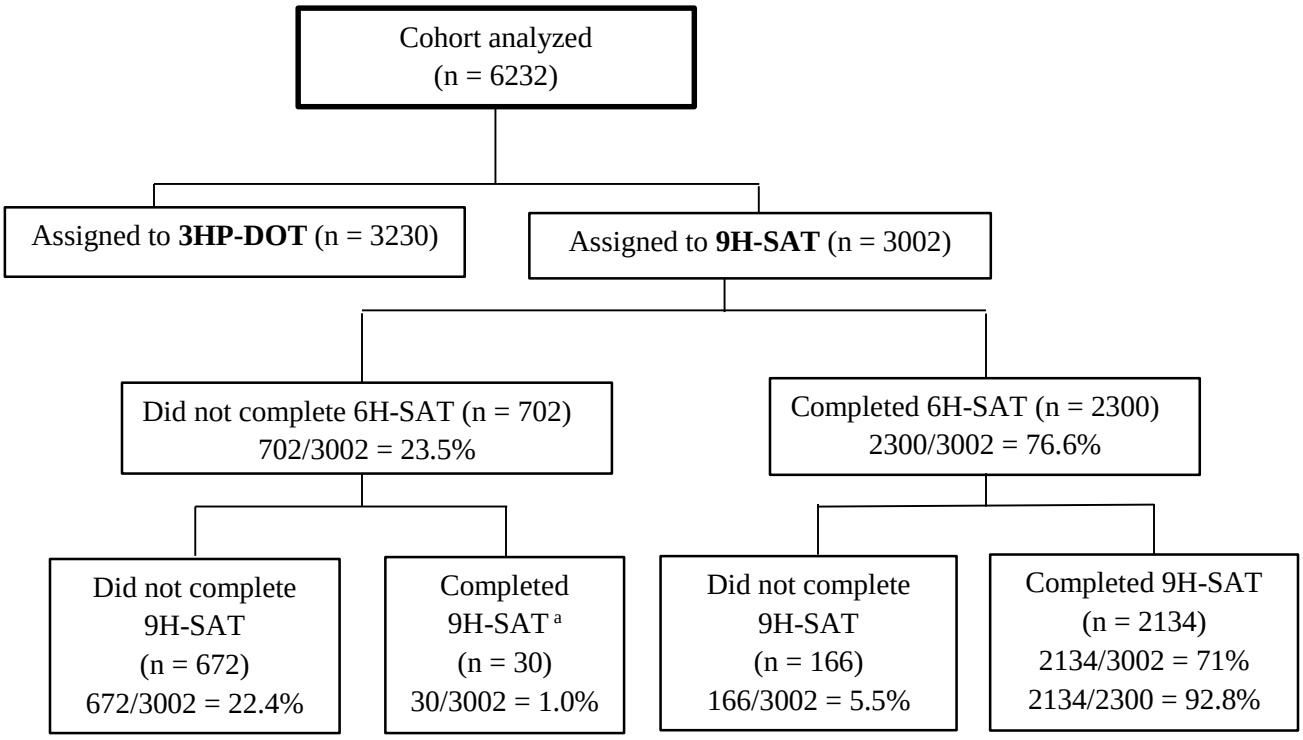
Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); LTBI, latent tuberculosis infection; NCT-AE, noncompletion of LTBI treatment attributed to an adverse event

Figure S2. Noncompletion of Latent Tuberculosis Infection Treatment Attributed to Reasons Other Than an Adverse Event (NCT-O) Among All Participants and Stratified by Study Regimen Throughout the Trial, June 2001–February 2008 (n = 5915)



Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg); LTBI, latent tuberculosis infection; NCT-O, noncompletion of LTBI treatment attributed to reasons other than an adverse event.

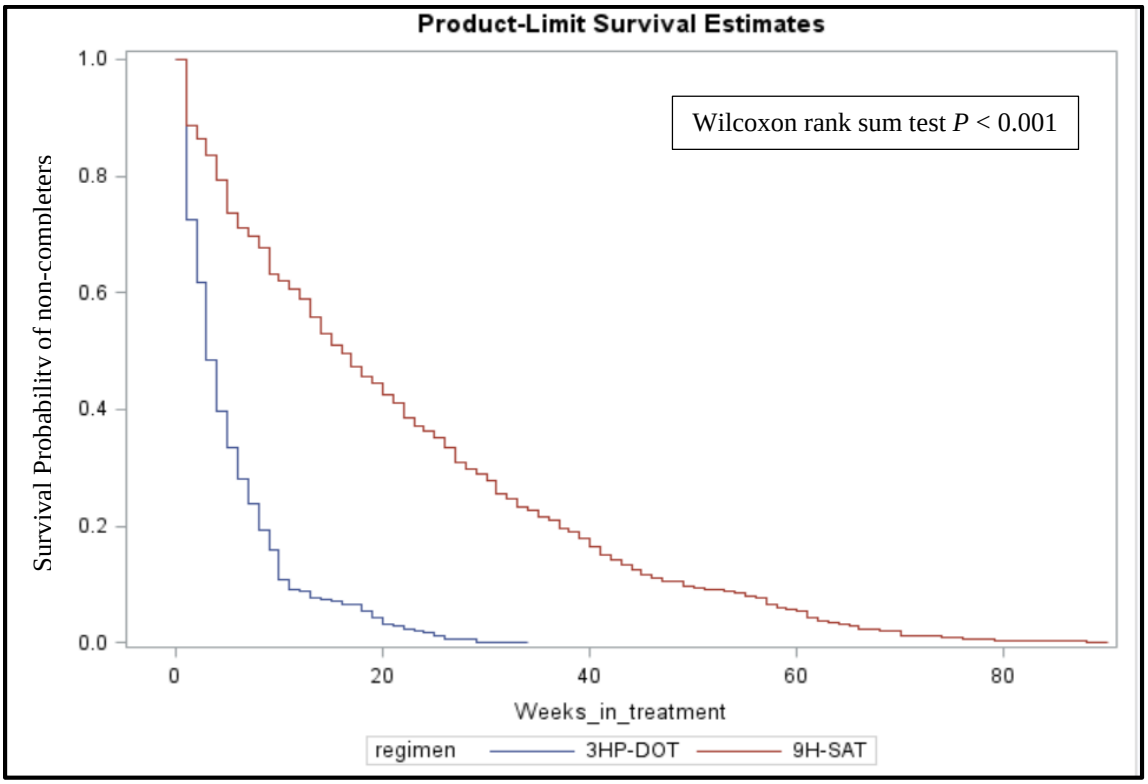
Figure S3. Latent Tuberculosis Infection Treatment Noncompletion at 6 and 9 Months Among Participants Assigned to Receive Isoniazid Only (n = 3002)



Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 6H-SAT or 9H-SAT, 6 or 9 months, respectively, of daily self-administered isoniazid (maximum dose, 300 mg).

[a] Did not receive ≥162 doses in 23–36 weeks; however, participants continued treatment and were able to complete 9 months of treatment by taking 240 of 270 doses in 35–52 weeks of 9H-SAT.

Figure S4. Kaplan-Meier Curve Among Participants Who did not Complete Latent Tuberculosis Infection Treatment, Stratified by Regimen



Abbreviations: 3HP-DOT, 3 months of directly observed once-weekly rifapentine (maximum dose, 900 mg) plus isoniazid (maximum dose, 900 mg); 9H-SAT, 9 months of daily self-administered isoniazid (maximum dose, 300 mg).
Participants received treatment up to 34 (3HP-DOT) and 90 (9H-SAT) weeks.