Factors Associated with Non-completion of Latent Tuberculosis Infection (LTBI) Treatment: Reasons other than Adverse Events (AE) The TB Trials Consortium PREVENT TB – Study 26

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Background

- LTBI prophylactic treatment plays an important role in the US strategy for tuberculosis (TB) elimination.

- Treatment completion is a challenge since LTBI is asymptomatic and often not perceived as a real threat.

- Low completion rate of LTBI treatment compromises effectiveness and lowers protection against TB.

- Non-completion rate for 9INH has been reported as high as 53% by a study in 68 clinics in the US and Canada (Horsburgh et al).

- PREVENT TB (*NEJM 2011*) was a randomized open-label trial of 3 months once-weekly rifapentine (900 mg) plus isoniazid (900 mg) (3HP-(DOT)) versus 9 months daily isoniazid (300 mg, 9H-(SAT)). Overall rates of treatment non-completion were:

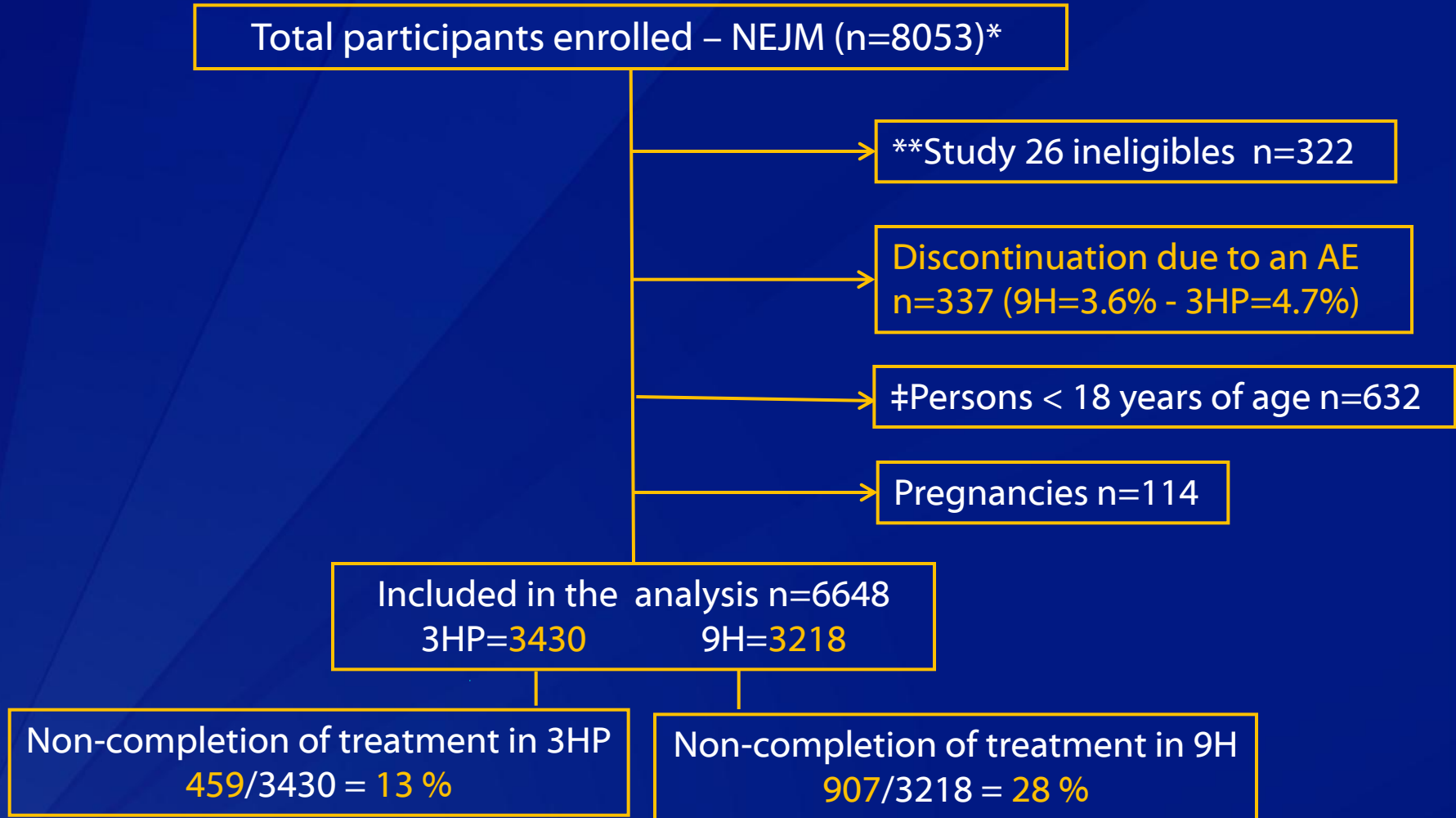 | | |
  |------|--------|
  | 3HP | 18 % |
  | 9H | 31 % |

Objectives

❖ To identify factors, other than AE, associated with non-completion of study 26 LTBI treatment, categorized by regimen.

❖ To identify potential predictors for non-completion of assigned treatment.

Methods

❖ Participants enrolled, June 2001 - February 2008 (n= 8053)
Participant sites: 27 clinics in USA, Canada, Brazil, and Spain

    a) 3HP: Directly Observed every week with monthly evaluation visits
    b) 9H: Self-administered daily with monthly evaluation visits

❖ Non-completion of treatment definition by regimen:
    a) 3HP: Failure to complete at least 11 of 12 doses in 10-16 weeks
    b) 9H: Failure to complete at least 240 of 270 doses in 35-52 weeks

❖ Missed early clinic visit:
    a) 3HP: Missing any of the first 3 of the 12 weekly DOTs
    b) 9H: Missing any of the first 3 of the 9 monthly visits

PREVENT TB Study Participants Included in the Analysis of Reasons for Non-completion of LTBI Treatment

Total participants enrolled – NEJM (n=8053)*

**Study 26 ineligibles n=322

Discontinuation due to an AE n=337 (9H=3.6% - 3HP=4.7%)

‡Persons < 18 years of age n=632

Pregnancies n=114

Included in the analysis n=6648
3HP=3430   9H=3218

Non-completion of treatment in 3HP
459/3430 = 13 %

Non-completion of treatment in 9H
907/3218 = 28 %

*Reported in the 2011 NEJM publication   **Source case resistant to INH/RIF (50%), source case culture negative (31%), other (19%).
‡This analysis considers adults age 18 or older.

Reasons for Non-completion of LTBI treatment, Other than AE (n=6648)

	3HP (n=3430)		9H (n=3218)	
	Frequency (n=459)	%(3430)	Frequency (n=907)	%(3218)
Lost for more than 3 months	58	1.7	280	8.7
Patient refused therapy	210	6.1	212	6.6
Non-compliant with schedule	60	1.7	121	3.8
Patient withdrew consent	52	1.5	64	2
Rx canceled by physician	17	0.5	47	1.5
*Other:	62	1.9	183	5.7

*3HP other: Moved out of state or to another country (13), incarcerated (10), unknown (39).
*9H other: Moved out of state or to another country (36), incarcerated (15), error in dosages (7), schedule and legal issues (3), unknown (122).

Univariate Analysis of Factors Associated with Non-completion of LTBI Treatment - The PREVENT TB Study (n=6648) (1 of 2)

	OR	95% CI	p-value
Regimen (9H vs 3HP)	2.5	2.24, 2.88	<0.001
Age (median=37) (ref $\geq$ 37)	1.1	0.97, 1.23	0.132
Sex (ref = female)	1.1	0.98, 1.24	0.118
Race (ref=white)			
African American	1.1	0.95, 1.26	0.236
Asian	0.7	0.61, 0.91	0.004
Other*	0.8	0.65, 0.95	0.012
HIV status (ref=HIV-non infected)			
Unknown	0.8	0.73, 0.93	0.002
Infected	0.9	0.66, 1.33	0.725
Country of origin (ref=born in US)	0.8	0.67, 0.86	<0.001
Education (ref $\geq$ college)			
$\leq$ 8 grade	1.1	0.92, 1.39	0.245
8 grade – some college	1.4	1.14, 1.61	0.001
$\geq$ 1 month incarceration (ref=no)	2.0	1.59, 2.48	<0.001

*American Indian and others in US/non-US

Univariate Analysis of Factors Associated with Non-completion of LTBI Treatment - The PREVENT TB Study (n=6648) (2 of 2)

	OR	95% CI	p-value
Missed early clinic visit (ref=no)	6.5	5.64, 7.42	<0.001
Any unscheduled clinic visit (ref=no)	2.0	1.71, 2.24	<0.001
Homeless (ref=no)*	1.6	1.30, 1.97	<0.001
Injecting drug use ever (IDU) (ref=no)	1.6	1.20, 2.07	0.001
Cirrhosis (ref=no)**	1.5	1.12, 1.96	0.006
Current smoker (ref=no)	1.5	1.32, 1.69	<0.001
Unemployment $\geq$ 1 year (ref=no)	1.4	1.17, 1.65	<0.001
Alcohol (ref=no)			
Use (only 1 'yes' to CAGE)	1.3	1.15, 1.48	<0.001
Abuse ($\geq$ 2 'yes' to CAGE)	2.0	1.63, 2.50	<0.001
Need of interpreter (ref=no)	0.9	0.74, 0.98	0.028

*Homeless or living in shelter > 6 months. **Medical history reported by patient.

Multivariate Analysis – Final Model - Reasons for Non-completion of LTBI Treatment - The PREVENT TB study (n=6648)

	OR	95% CI	p-value
Regimen (9H vs. 3HP)	2.1	1.5, 2.9	<0.001
Education (ref ≥ college)			
≤ 8 grade	1.1	1.05, 1.76	0.020
8 grade – some college	1.3	1.1, 1.63	0.004
≥ 1 month incarceration (ref=no)	1.5	1.11, 1.99	0.008
Alcohol (ref=no)			
Use (only 1 'yes' to CAGE)	1.1	0.97, 1.31	0.112
Abuse (≥ 2 'yes' to CAGE)	1.7	1.3, 2.25	<0.001
Site (ref=20)			<0.001
Current smoker x *regimen*			0.049
3HP	0.98	0.76, 1.27	
9H	1.4	1.11, 1.63	
Age x *regimen*			0.016
3HP (age<37)	0.9	0.76, 1.19	
9H (age<37)	1.3	1.13, 1.59	
Country of origin x *regimen*			<0.001
3HP (US)	0.7	0.6, 0.98	
9H (US)	1.3	1.1, 1.6	

	OR	95% CI	p-value
Missed early clinic visit x *regimen*			<0.001
3HP	8.5	6.7, 10.66	
9H	4.3	3.57, 5.17	
IDU ever x *regimen*			0.003
3HP	3.4	1.91, 6.03	
9H	1.2	0.73, 2.04	
Any unscheduled clinic visit x *regimen*			<0.001
3HP	2.0	1.48, 2.74	
9H	0.9	0.73, 1.06	
Homeless x IDU ever			0.012
Homeless	1.4	0.73, 2.65	
No homeless	3.4	1.9, 6.03	
Need of interpreter x *regimen*			0.024
3HP	0.7	0.49, 0.9	
9H	1.0	0.79, 1.28	

Number of doses taken at the time participants stopped 3HP (%) (n=459)

Failure to complete at least 11 of 12 doses in 10 to 16 weeks
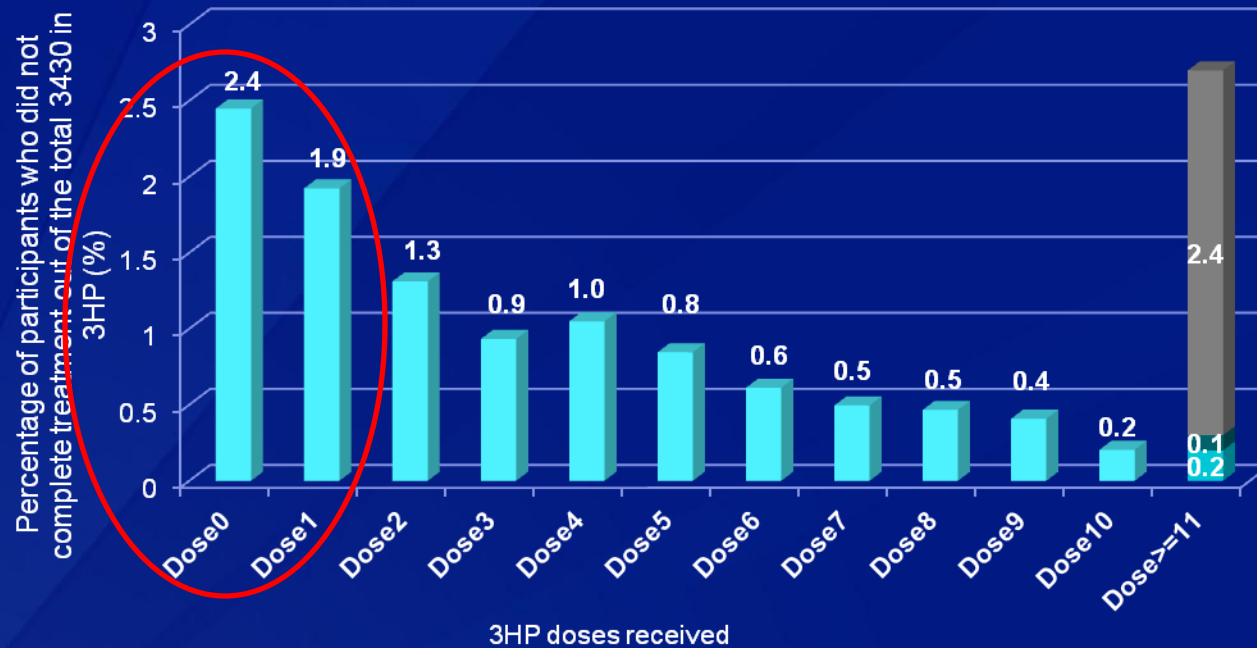
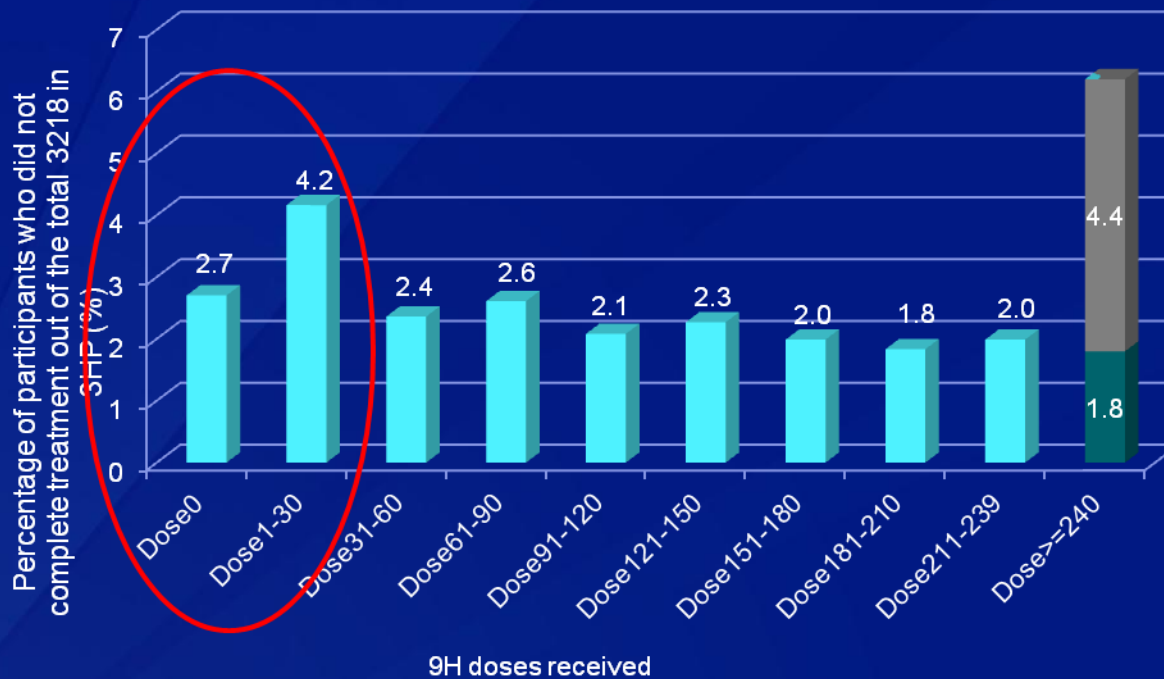<10 doses: 367
≥11doses in >16 weeks: 81(2.4%)
≥11doses in <10weeks: 7(0.2%)
13 doses in 10-16week: 4(0.1%)

Number of doses taken at the time participants stopped 9H (%) (n=907)

Failure to complete at least 240 of 270 doses in 35 to 52 weeks

<240doses: 708
>240 doses in >52 weeks: 142 (4.4%)
>240 doses in <35 weeks: 0
>270 doses in 35-52 weeks: 57 (1.8%)

Limitations

- ❖ 3HP was an open-label clinical trial subject to bias

- ❖ 3HP was directly observed weekly, with more frequent interaction between providers and participants which probably improved compliance

- ❖ Variability among sites participating in the clinical trial not feasible to accurately evaluate individually

Summary

- ❖ Among 6648 adults, the factors associated with non-completion of treatment were 9H regimen, education less than a college degree, being incarcerated, alcohol consumption, or enrollment site

- ❖ In 9H arm: current smokers, participants younger than 37, born in the US, with history of injecting drugs, or missed at least 1 of the first 3 monthly visits were more likely not to complete treatment

- ❖ In the 3HP arm: participants with history of injecting drugs, missed at least 1 of the first 3 DOT, or had at least 1 unscheduled visit were more likely not to complete treatment

Conclusions

- ❖ 3HP: less non-completion of treatment for reasons other than AEs

- ❖ 3HP and 9H share some common but also have some distinct predictors

Acknowledgments

Disclaimer: Presentation reflects authors' opinion and not official position of CDC