Screening and latent TB

Marc Lipman

BHIVA, 10 October 2014

Why test people living with HIV for TB?

The New England
Journal of Medicine

Volume 320 MARCH 2, 1989 Number 9

A PROSPECTIVE STUDY OF THE RISK OF TUBERCULOSIS AMONG INTRAVENOUS DRUG USERS WITH HUMAN IMMUNODEFICIENCY VIRUS INFECTION

PETER A. SELWYN, M.D., M.P.H., DIANA HARTEL, M.P.H., VICTOR A. LEWIS, M.D., ELLIE E. SCHOENBAUM, M.D., STEN H. VERMUND, M.D., ROBERT S. KLEIN, M.D., ANGELA T. WALKER, M.D., AND GERALD H. FRIEDLAND, M.D.

Abstract To determine the risk of active tuberculosis associated with human immunodeficiency virus (HIV) infection, we prospectively studied 520 intravenous drug users enrolled in a methadone-maintenance program. Tuberculin skin testing and testing for HIV antibody were performed in all subjects.

Forty-nine of 217 HIV-seropositive subjects (23 percent) and 62 of 303 HIV-seronegative subjects (20 percent) had a positive response to skin testing with purified protein derivative (PPD) tuberculin before entry into the study. The rates of conversion from a negative to a positive PPD test were similar for seropositive subjects

period ($P<0.002$). Seven of the eight cases of tuberculosis occurred in HIV-seropositive subjects with a prior positive PPD test (7.9 cases per 100 person-years, as compared with 0.3 case per 100 person-years among seropositive subjects without a prior positive PPD test; rate ratio, 24.0; $P<0.0001$).

We conclude that, although the prevalence and incidence of tuberculous infection were similar for both HIV-seropositive and HIV-seronegative intravenous drug users, the risk of active tuberculosis was elevated only for seropositive subjects. These data also suggest that in HIV-infected persons tuberculosis most often results from

	HIV seropositive	HIV seronegative
Number in cohort	217	203
Number TST +	49 (23%)	62 (31%)
Cases active TB	8	0

Screening

- Used in a population to identify an unrecognised disease in individuals without symptoms or signs

- Enables *earlier interventions & management* in the hope of reducing mortality and suffering from a disease

This is not contact tracing of recently exposed people

(which assumes that in the UK most TB reflects reactivation not new infection)

Latent tuberculosis

Evidence of *immunological sensitisation* to mycobacterial proteins (positive Tuberculin Skin Test or blood Interferon Gamma Release Assay, IGRA)

No symptoms, signs, radiology or microbiology suggesting active disease

UK (BHIVA) approach to LTBI

Risk of active TB

vs

Risk of drug induced hepatotoxicity*

* Serious hepatotox estimated as 0.3%

UK (BHIVA) approach to LTBI

- Use data from low incidence countries
  - UK CHIC*
  - Swiss HIV cohort study**
- Risk based on
  - Country of origin
  - Blood CD4 count
  - Use & duration of ART
  - Blood IGRA result

*AIDS 2009;23:2507

**CID 2007;44:94

UK CHIC data

- Collaborative HIV Cohort Study Group
- Observational cohort: 22,833 between 1996-2005
  - Active TB 376 (1.7%) episodes
- Risk factors for TB:
  ethnicity, low blood CD4, high plasma HIV viral load
- TB incidence decreased after starting ART

Grant. AIDS 2009; 23:2507

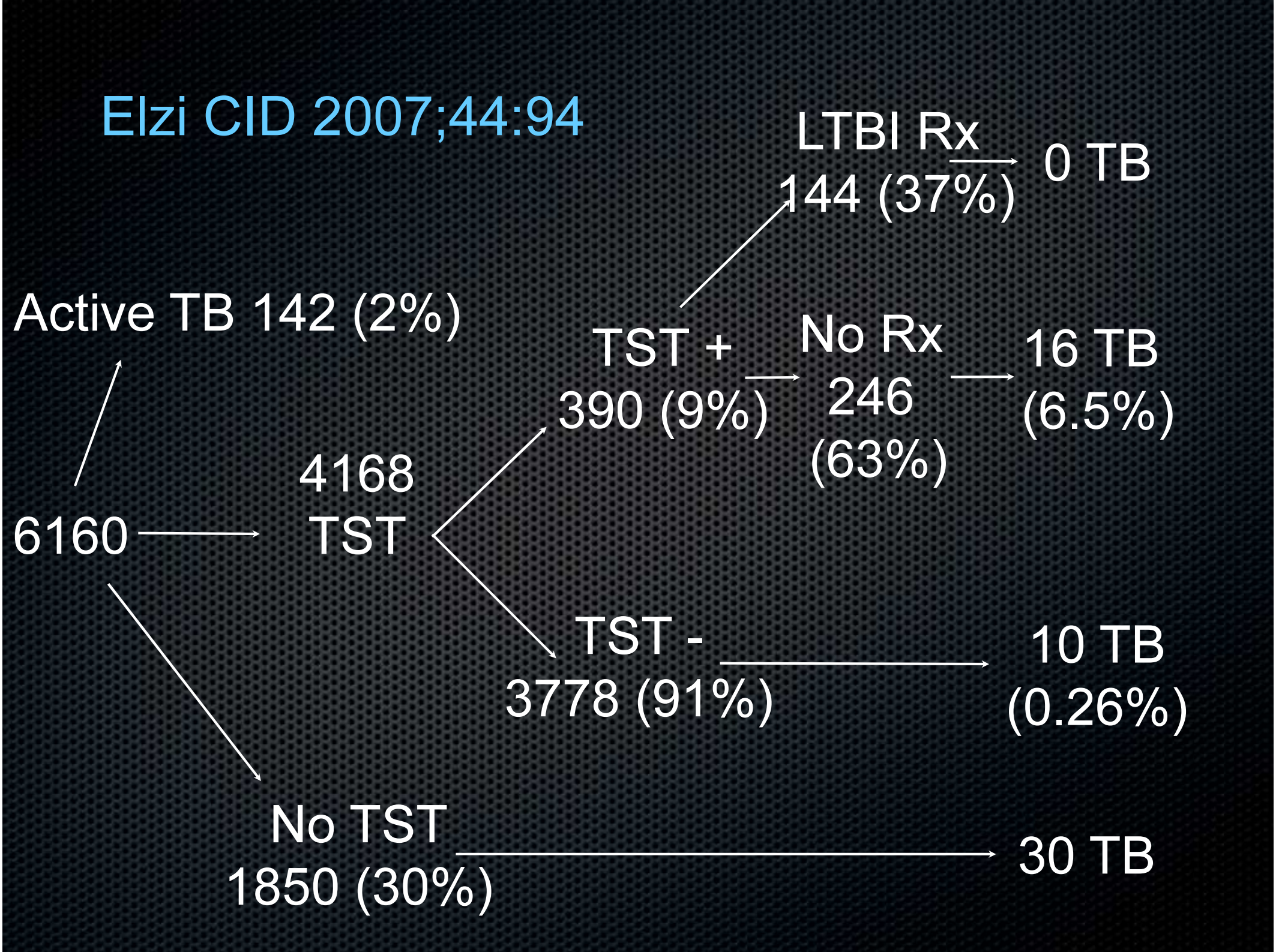
Blood CD4	Adjusted rate ratio (95% CI)
<50	10.65 (6.11, 18.57)
50-199	3.4 (2.05, 5.65)
200-349	1.77 (1.06, 2.96)
350-499	1.84 (1.09, 3.12)

Grant. AIDS 2009; 23:2507

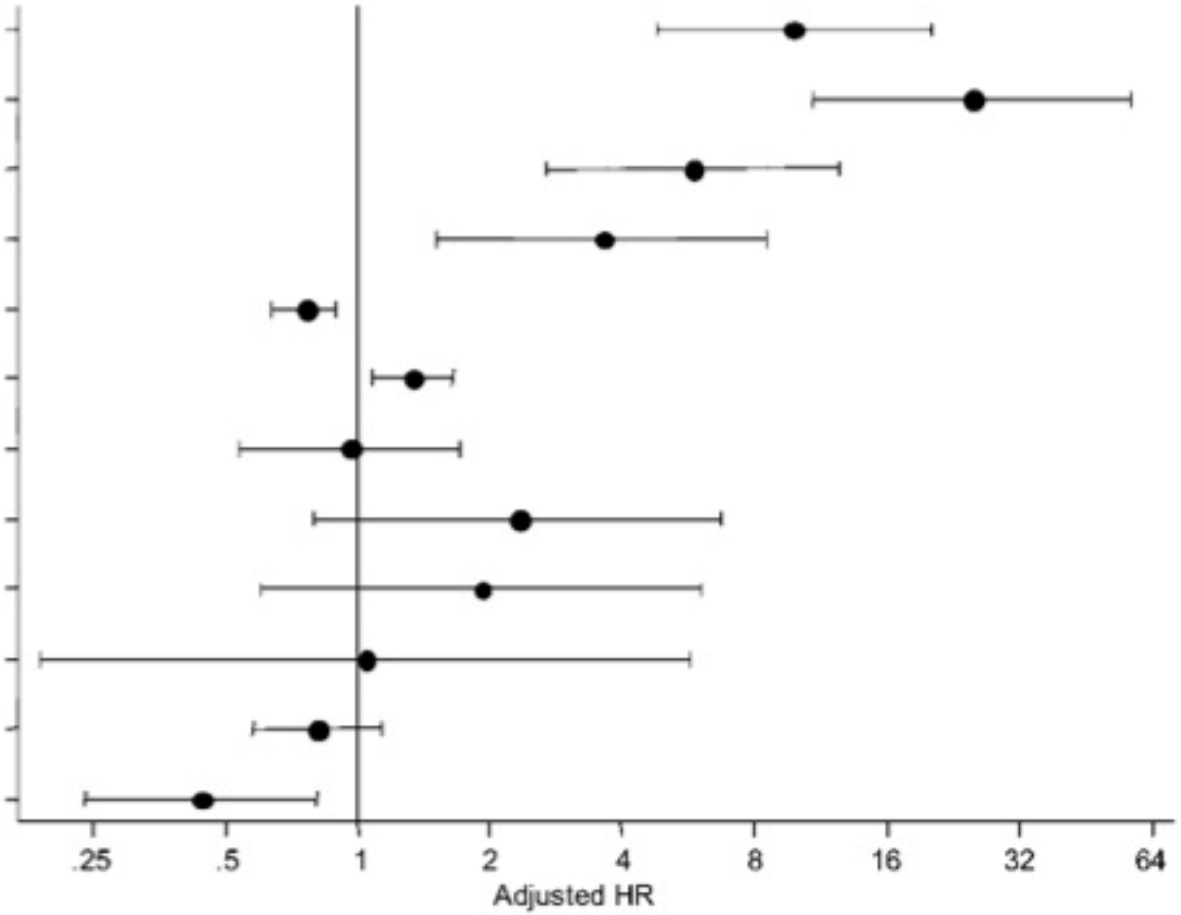
Swiss cohort data

- Observational cohort study 1996-2006, N = 6,018
- Overall TB incidence 200/100 000 PY
- 69% had TSTs, 9.4% positive
- 56 /6018 (0.9%) developed TB
- Number Needed To Treat for preventive therapy = 15 (8 for high TB burden country)

Elzi CID 2007;44:94


Elzi CID 2007;44:94
LTBI Rx
144 (37%)
0 TB
Active TB 142 (2%)
TST +
390 (9%)
No Rx
246
(63%)
16 TB
(6.5%)
4168
TST
6160
TST -
3778 (91%)
10 TB
(0.26%)
No TST
1850 (30%)
30 TB

Parameter	Adjusted HR (95% CI)	*P*
TST result missing (as compared with negative TST result)	9.9 (4.8-20.3)	<.001
TST result positive (as compared with negative TST result)	25 (10.8-57.4)	<.001
Sub-Saharan Africa (as compared with low-risk region)	5.8 (2.7-12.5)	<.001
Medium-risk region (as compared with low-risk region)	3.6 (1.5-8.6)	.003
Baseline CD4$^+$ cell count (per 100 cells/μL increase)	0.76 (0.65-0.89)	.001
Baseline plasma HIV RNA level (per $\log_{10}$ increase)	1.33 (1.08-1.7)	.007
Female sex	0.96 (0.54-1.7)	.9
Heterosexual HIV transmission (as compared with MSM)	2.32 (0.80-6.7)	.1
IDU HIV transmission (as compared with MSM)	1.91 (0.61-6.0)	.3
Other/unknown HIV transmission (as compared with MSM)	1.05 (0.19-5.7)	1.0
Age per 10-year increase	0.81 (0.58-1.13)	.2
Start of triple ART	0.44 (0.24-0.81)	.008



Elzi CID 2007;44:94

EACS/BHIVA guidelines for screening (& hence offering treatment)

	Sub-Saharan Africa	Medium TB incidence country	Low TB incidence country
Blood CD4 count	Any	<500	<350
Duration of ART use	<24 months	<24 months	<6 months
Blood IGRA	+	+	+

HIV Med 2011;12:517

NICE HIV & TB Guidance 2010

- Blood CD4 <200: TST & IGRA
  - Either positive ASSESS FOR ACTIVE TB & CONSIDER Rx FOR LTBI
- Blood CD4 200-500: IGRA OR TST/IGRA
  - Either positive ASSESS FOR ACTIVE TB & CONSIDER Rx FOR LTBI
- Blood CD4 >500: CONSIDER AS IMMUNOCOMPETENT

NO DISTINCTION BETWEEN IGRA TEST TYPES

How do the strategies compare in the UK?

What is the impact of longterm ART on risk of active TB?

Antiretroviral treatment

- 9 observational cohort studies - reduction by 67%
- ~80% (Brazil, USA, Italy)
- Most benefit in those with low CD4 counts
- Lifelong treatment (hence longterm benefit)

Badri Lancet 2002; 359:2059
Jones IJTLD 2000 ;4:1026
Girardi AIDS 2000;14:1985

Is IGRA testing helpful?

IGRA testing in Denmark

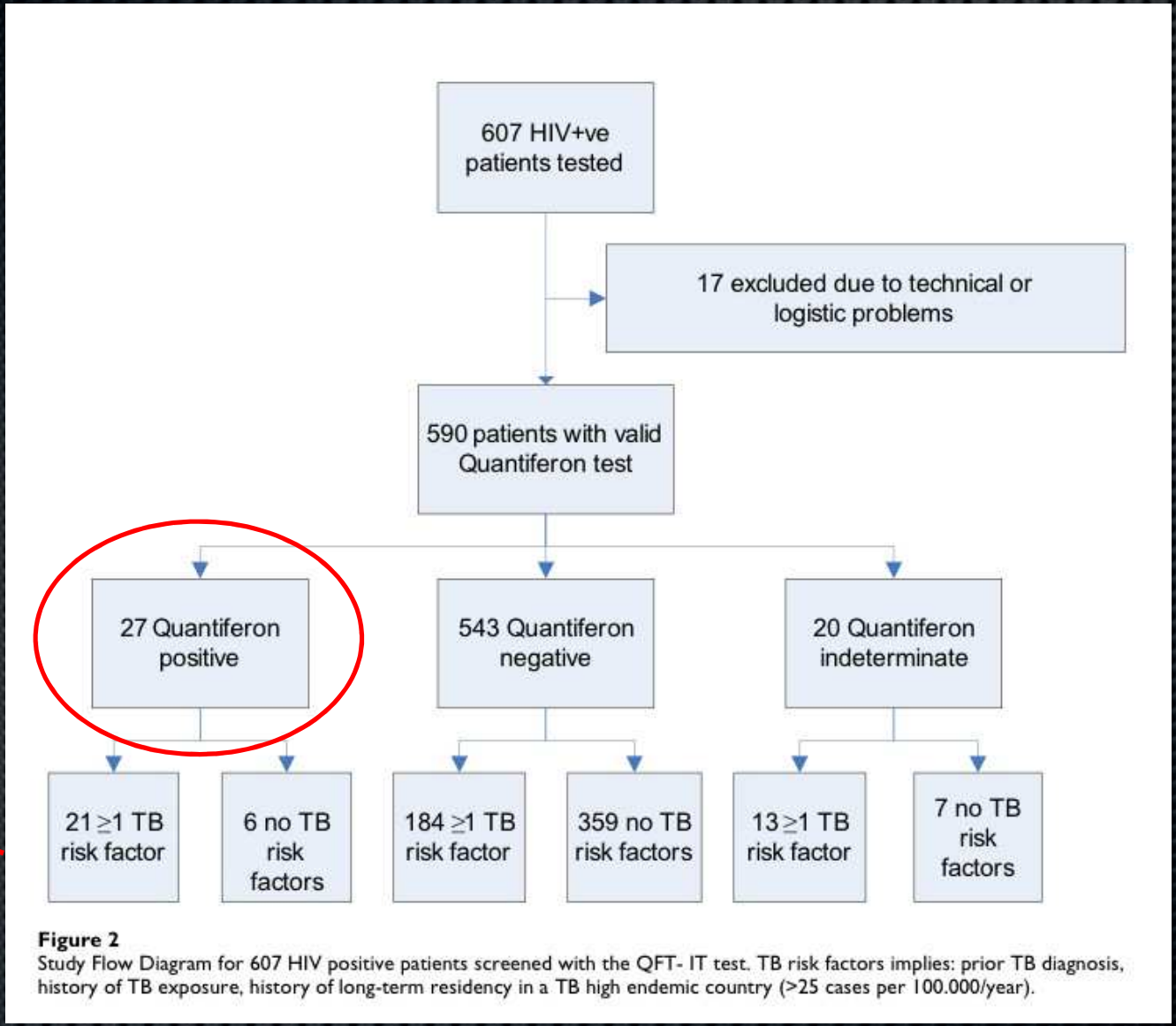


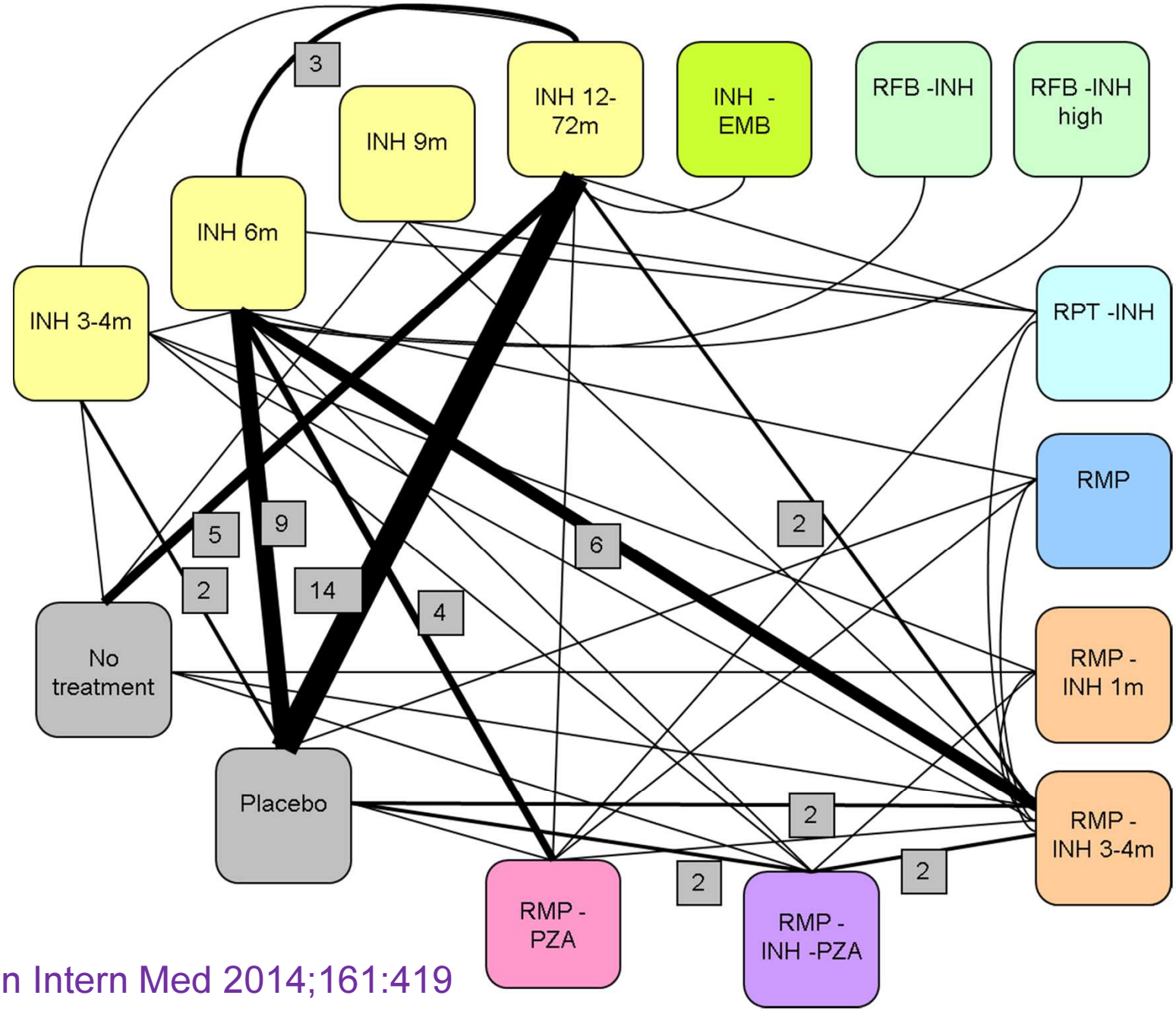
Figure 2
Study Flow Diagram for 607 HIV positive patients screened with the QFT- IT test. TB risk factors implies: prior TB diagnosis, history of TB exposure, history of long-term residency in a TB high endemic country (>25 cases per 100.000/year).

6 years,
2 cases

Brock, Respir Res 2006;7:56 & Soborg ERJ 2014

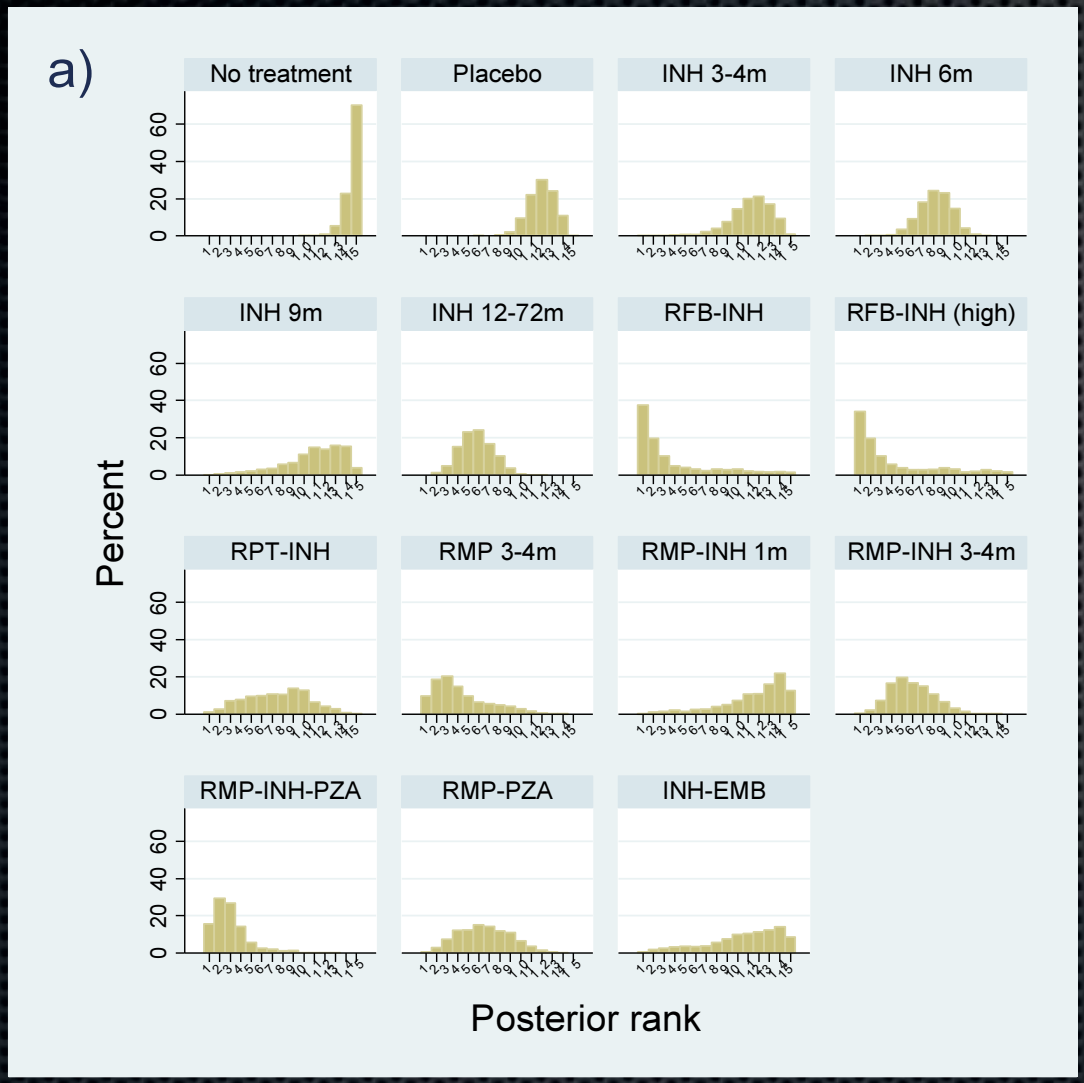
To test is to treat!

Network meta-analysis of LTBI treatment RCTs



Stagg. Ann Intern Med 2014;161:419

Active TB



Regimen	Rank (CrI)
No treatment	15 (13-15)
Placebo	12 (10-14)
INH 3-4 m	11 (7-14)
INH 6 m	8 (5-11)
INH 9 m	11 (4-15)
INH 12-72 m	6 (3-9)
RFB-INH	2 (1-14)
RFB-INH (high)	2 (1-14)
RPT-INH	8 (2-13)
RMP	4 (1-10)
RMP-INH 1 m	13 (4-15)
RMP-INH 3-4 m	6 (3-10)
RMP-INH-PZA	3 (1-8)
RMP-PZA	6 (2-11)
INH-EMB	11 (3-15)

Stagg. Ann Intern Med 2014;161:419

	Within-country incidence		Immunocompromised?		HIV study?	
Regimen	Low	High	No	Yes	No	Yes
No treatment	11 (3, 12)	12 (10, 12)	11 (7, 12)	11 (9, 12)	12 (10, 12)	9 (2, 11)
Placebo	11 (8, 12)	8 (6, 11)	9 (6, 12)	9 (7, 11)	9 (7, 11)	9 (7, 11)
INH 3-4 m	9 (3, 12)	11 (4, 12)	8 (4, 11)	-	9 (4, 11)	-
INH 6 m	8 (4, 11)	6 (3, 8)	6 (3, 10)	7 (4, 9)	6 (2, 9)	7 (4, 10)
INH 9 m	7 (2, 11)	-	8 (1, 12)	11 (4, 12)	9 (3, 12)	-
INH 12-72 m	6 (3, 9)	4 (2, 7)	5 (2, 8)	5 (2, 8)	5 (2, 8)	5 (2, 8)
RFB-INH	4 (1, 11)	-	-	2 (1, 11)	-	2 (1, 11)
RFB-INH (high)	4 (1, 11)	-	-	2 (1, 11)	-	2 (1, 11)
RPT-INH	3 (1, 11)	7 (2, 11)	10 (1, 12)	7 (2, 10)	6 (1, 11)	7 (2, 11)
RMP	4 (1, 11)	2 (1, 8)	3 (1, 8)	-	3 (1, 8)	-
RMP-INH 1 m	-	10 (3, 12)	9 (3, 12)	-	10 (4, 12)	-
RMP-INH 3-4 m	4 (1, 10)	4 (2, 8)	4 (1, 9)	5 (2, 8)	4 (1, 8)	5 (2, 9)
RMP-INH-PZA	-	1 (1, 4)	2 (1, 7)	2 (1, 7)	2 (1, 8)	2 (1, 7)
RMP-PZA	5 (2, 10)	6 (2, 10)	4 (1, 11)	6 (3, 9)	2 (1, 10)	6 (2, 10)
INH-EMB	-	9 (2, 12)	-	10 (3, 12)	-	10 (3, 11)

Stagg. Ann Intern Med 2014;161:419

ART & Isoniazid Preventive Therapy

- 1st Brazilian study - 76% reduction in Rio on IPT and ART.
- Follow up – reduction by 17% over ART alone
- 1st SA study - 2 cohorts IPT alone reduced by 27%, ART alone 35%, Combined 85%
- 2nd SA study - IPT 37% extra benefit over ART

Golub AIDS 2007; 21:1441
Golub AIDS 2009; 23:631
Durovni Lancet ID 2013;13:852
Rangaka Lancet 2014;384:682

What is current UK LTBI testing practice in HIV?

UK LTBI testing in HIV

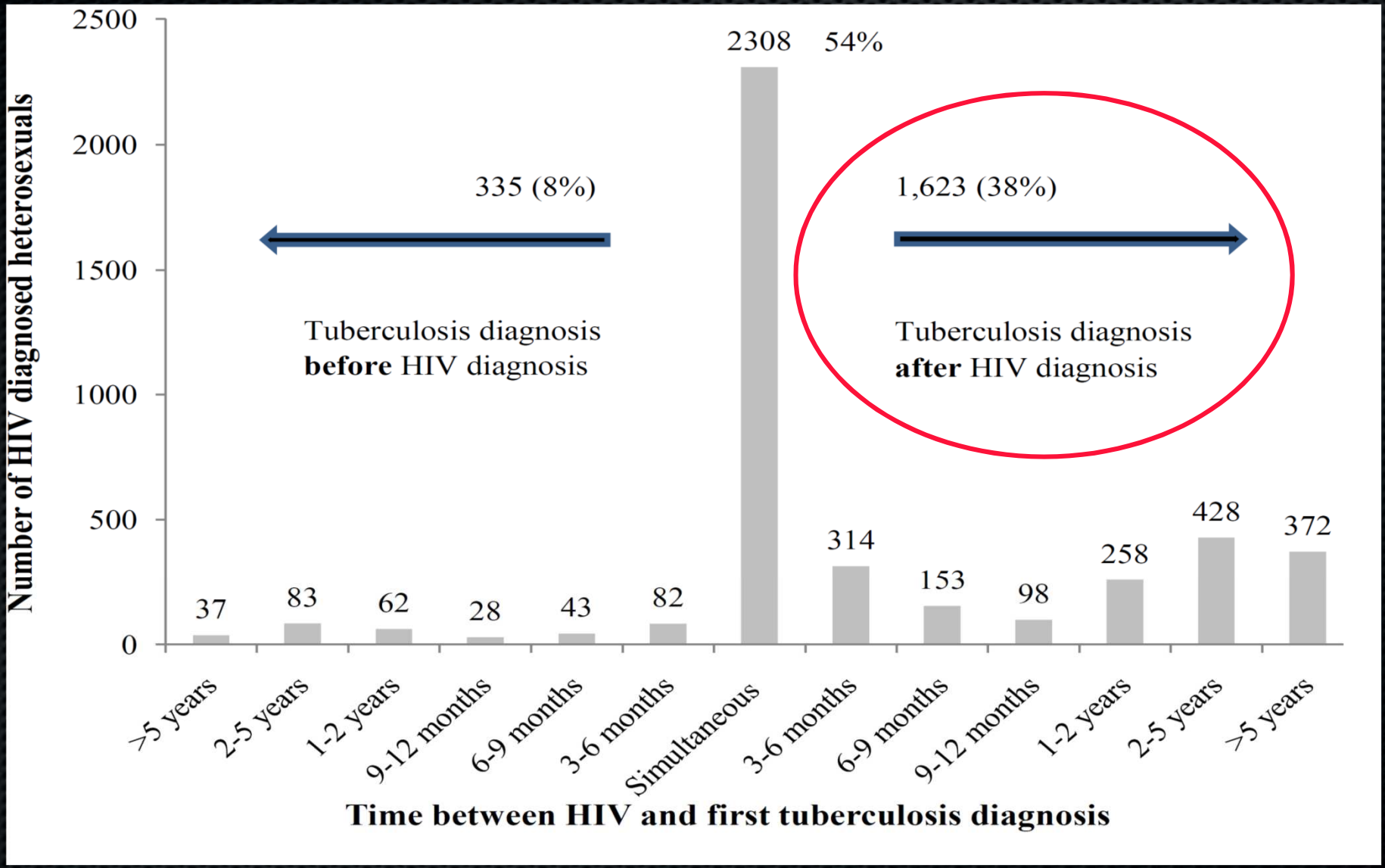
- Internet survey
- Do you screen for LTBI?
- 105/151 replies

Please contact Helena White

Helena.white@uhl-tr.nhs.uk

What is the likely impact of a LTBI testing programme?

HIV & TB diagnosis in heterosexual adults, E & W 2002-10



Rice, AIDS 2013

Summary

- HIV+ individuals are a good population to consider for LTBI screening
- Current guidance is based on limited data and needs re-evaluation in light of widespread use of ART
- If LTBI testing then must consider treating
- Drug treatment for LTBI is effective – though evidence in low TB incidence areas is limited
- Prevention of TB in HIV+ individuals includes offering an HIV test!
- Think about the cost-effectiveness of clinical practice
- Do simple things well