Update: linee guida e novità sui regimi terapeutici per il trattamento della TB latente

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Metodologie di screening per LTBI: quale è la migliore?

- Questionario anamnestico a score?→ Solo casi attivi e sintomatici o con storia nota di contatto
- Rx torace? → Solo soggetti con lesioni in esito probabilmente attribuibili a Tb pregressa mai trattata
- TST? →Interferenza del BCG in quasi tutti i Paesi degli immigrati. Rischio di negatività in immunodepressi
- QFT? → Alti costi. Prelievo sgradito a molte popolazioni (specie Africa Occidentale). Rischio di negatività in immunodepressi

Metodologie di screening per LTBI: quale è la migliore?

- Necessaria valutazione delle diverse popolazioni “a rischio”.
- Ricordarsi che “intention to test is intention to treat”
- Ergo:
  - Immunodepressi (pazienti individuali) : fare tutto subito per aumentare la sensibilità (TST+QFT+Rx torace)
  - Rifugiati e senza fissa dimora (interventi sociali): grandi numeri e problemi organizzativi, necessaria gradazione degli interventi
    - TST→ Rx Torace?
    - QFT→ Rx Torace?
    - TST→ QFT → Rx Torace?

Metodologie di screening per LTBI: quale è la migliore?

- Popolazioni a rischio: come valutare l'ampiezza dell'intervento?
  - Numeri delle popolazioni
  - Provenienza geografica (Paesi ad alta endemia?)
  - Tipologia:
    - Richiedenti asilo/rifugiati
    - Senza fissa dimora
  - Distribuzione sul territorio
    - CARA, CAS
    - SPRAR
    - Dormitori

Metodologie di screening per LTBI: quale è la migliore?

- Popolazioni a rischio: come valutare l'ampiezza dell'intervento?
  - Qual è il livello di "alta endemia" per ritenere utile l'intervento di ricerca della LTBI in una popolazione?
    - >200/100.000 come in alcuni Paesi nordici?
    - > 100/100.000 (WHO)?
    - > 50 (o 40)/100.000?
  - Fino a che età del soggetto positivo siamo disposti a trattarlo per la LTBI?
    - Solo fino a 5 aa?
    - Solo fino a 18 aa
    - Solo fino a 35 aa?
    - Tutti ?

Metodologie di screening per LTBI: quale è la migliore?

- Popolazioni a rischio: come valutare l'ampiezza dell'intervento?
  - Organizzazione dell'accesso
    - Individuale
    - A gruppi (chi li gestisce?)
  - Risorse umane e strutturali disponibili
  - Organizzazione sanitaria
    - Interventi "esterni" (unità mobili?)
    - Interventi nelle strutture sanitarie del Territorio (esistono ancora?)
    - Interventi nelle strutture ospedaliere
    - Capacità di risposta rapida
    - Capacità di gestire popolazioni particolari

Metodologie di screening per LTBI: quale è la migliore?

- POSSIAMO PERMETTERCI DI EFFETTUARE LA RICERCA DELLA LTBI SEPARATAMENTE DALLA RICERCA DELLA TB ATTIVA?
  - NEGLI IMMUNODEPRESSI?
    - NO
  - NEI SENZA FISSA DIMORA?
    - NO
  - NEI MIGRANTI?
    - SI ALLO SBARCO (SOLO TB ATTIVA)
    - NO DOPO LA DISTRIBUZIONE NELLE VARIE REGIONI

INTENTION TO TEST IS INTENTION TO TREAT

Ethical considerations

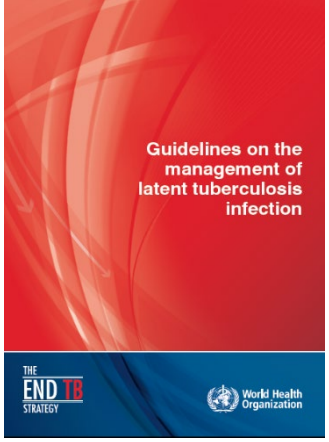
Strong moral justification for an LTBI policy, particularly in vulnerable groups, but specific ethical issues to consider:

- latent TB is an asymptomatic state and lacks immediate risk of transmission
- challenges in communication due to uncertainty regarding accurate assessment of individual risk for development of active TB
- affects individuals and groups that are already socially and medically vulnerable.

Test and treat at-risk only or all those who are infected?

With current tools most of those treated would not need it. Benefits and harms trade-out unfavourable

- ➔ limit testing and treatment to high-risk groups
- ➔ reduce Number Needed to Treat by improving testing
- ➔ reduce treatment duration and side effects



Treatment options

The following treatment options are recommended for the treatment of latent TB infection:

- 6 months isoniazid (6H)
- 9 months isoniazid (9H)
- 3 months weekly rifapentine plus isoniazid (3HP)
- 3 to 4 months isoniazid plus rifampicin (3-4HR)*
- 3 to 4 months rifampicin alone (3-4R)**

(Strong recommendation, moderate to high quality of evidence)

* Voted by 53% of panel and ** voted by 60% of panel as equivalent optionsfor 6H

Treatment options

3RH should be offered as an alternative to 6H for children and adolescents aged < 15 years. (New)

3HP treatment may be offered as an alternative to 6H for both adults and children in countries with a high TB incidence.(New)

	Intervention	Comparator	N	Active TB	Mortality	AEs	Hepatotoxicity	Completion rate
Adults with HIV	3HP	6H or 9H	2	0.73 (0.23- 2.3)	0.75 (0.44 - 1.27)	0.63 (0.43 - 0.92)	0.26 (0.12 - 0.55)	1.25 (1.01-1.55)
	3HP	continuous INH	1	1.50 (0.69-3.27)	1.06 (0.47-2.41)	0.20 (0.12-0.32)	0.05 (0.02-0.13)	1.59 (1.40-1.80)
Adults without HIV	3HP	9H	1	0.44 (0.18-1.07)	0.75 (0.47-1.19)	0.87 (0.73-1.04)	0.16 (0.10- 0.27)	1.19 (1.16- 1.22)
Children and adolescents	3HP	9H	1	0.13 (0.01-2.54)	0.18 (0.01-3.80)	0.88 (0.32-2.40)	-	1.09 (1.03-1.15)

Adverse events monitoring

- Systematic review shows no direct evidence
- **The Panel agreed on:**
  - Patient education on side effects
  - Routine regular clinical monitoring through a monthly visit to health care provider
  - Baseline laboratory testing based on individual risk assessment

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Latent tuberculous infection among foreign-born individuals applying to shelters in the metropolitan area of Milan

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SUMMARY

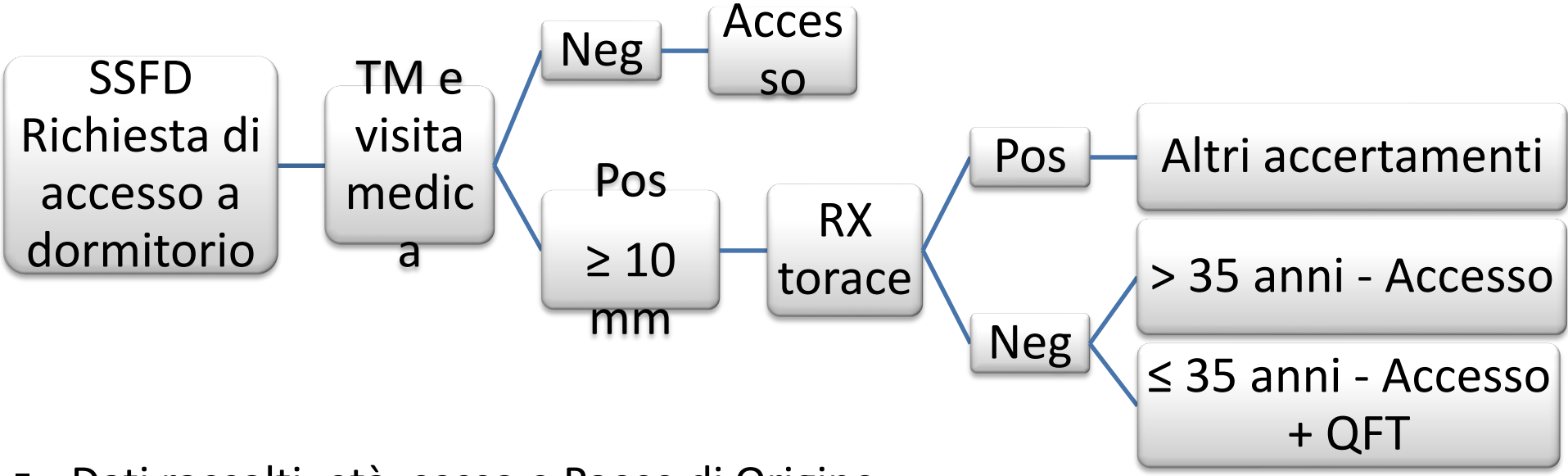
SETTING: Screening for latent tuberculous infection (LTBI) of groups at high risk of active tuberculosis (TB) is a key component of the End TB Strategy.

OBJECTIVE: To conduct a retrospective descriptive analysis of LTBI rates among foreign-born individuals applying to shelters in the metropolitan area of Milan, Italy.

DESIGN: All foreign-born individuals registering for years who underwent LTBI confirmation testing, 1322 (49.6%) tested negative, 1339 (50.2%) were positive and five (0.2%) had indeterminate results. In the multivariate analysis, TB incidence in the country of origin and age were significantly associated with QFT-GIT positivity. Although estimated TB incidence in Eritrea, Morocco and Romania was ⩽100/100 000 person-years (py), the probability of being QFT-GIT-positive in individuals

SCREENING NEI SFD-PIANO FREDDO

Criteri di inclusione: tutti i SFD richiedenti accesso ai dormitori con TM positivo, RX torace negativa e di età inferiore ai 35 anni.



- Dati raccolti: età, sesso e Paese di Origine
- ITL intesa come positività al QFT-GIT

- I Paesi di origine sono stati suddivisi in regioni geografiche
- I dati di incidenza dei Paesi di origine sono stati suddivisi in classi (100–150/100,000; 151/100,000–250/100,000; 251/100,000– 350/100,000, e ≥350/100,000 ab anno)

PPD da Nov 2009 a Apr 2017

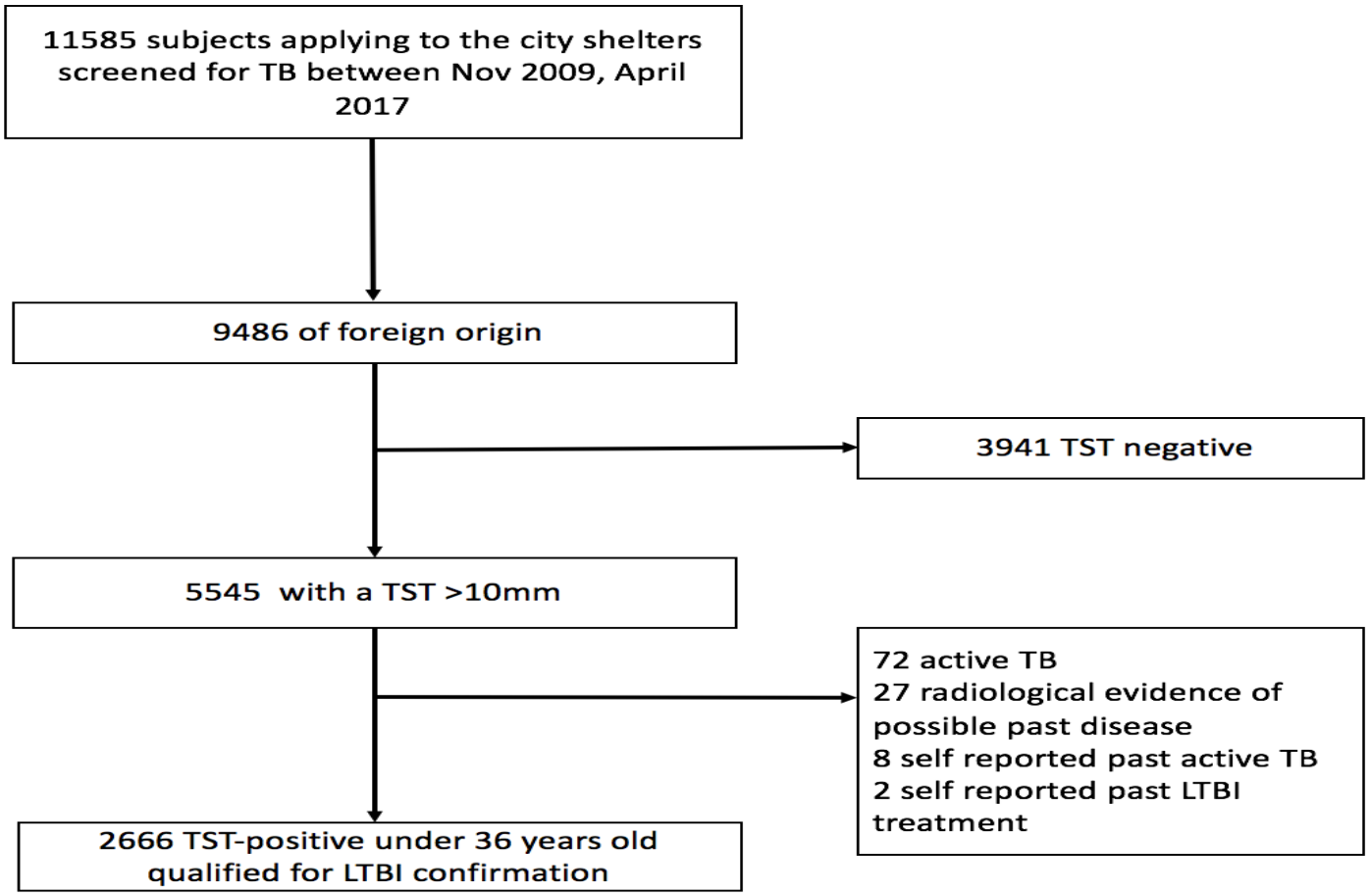


Table 3. TB incidence and % of QFT positive by country of birth

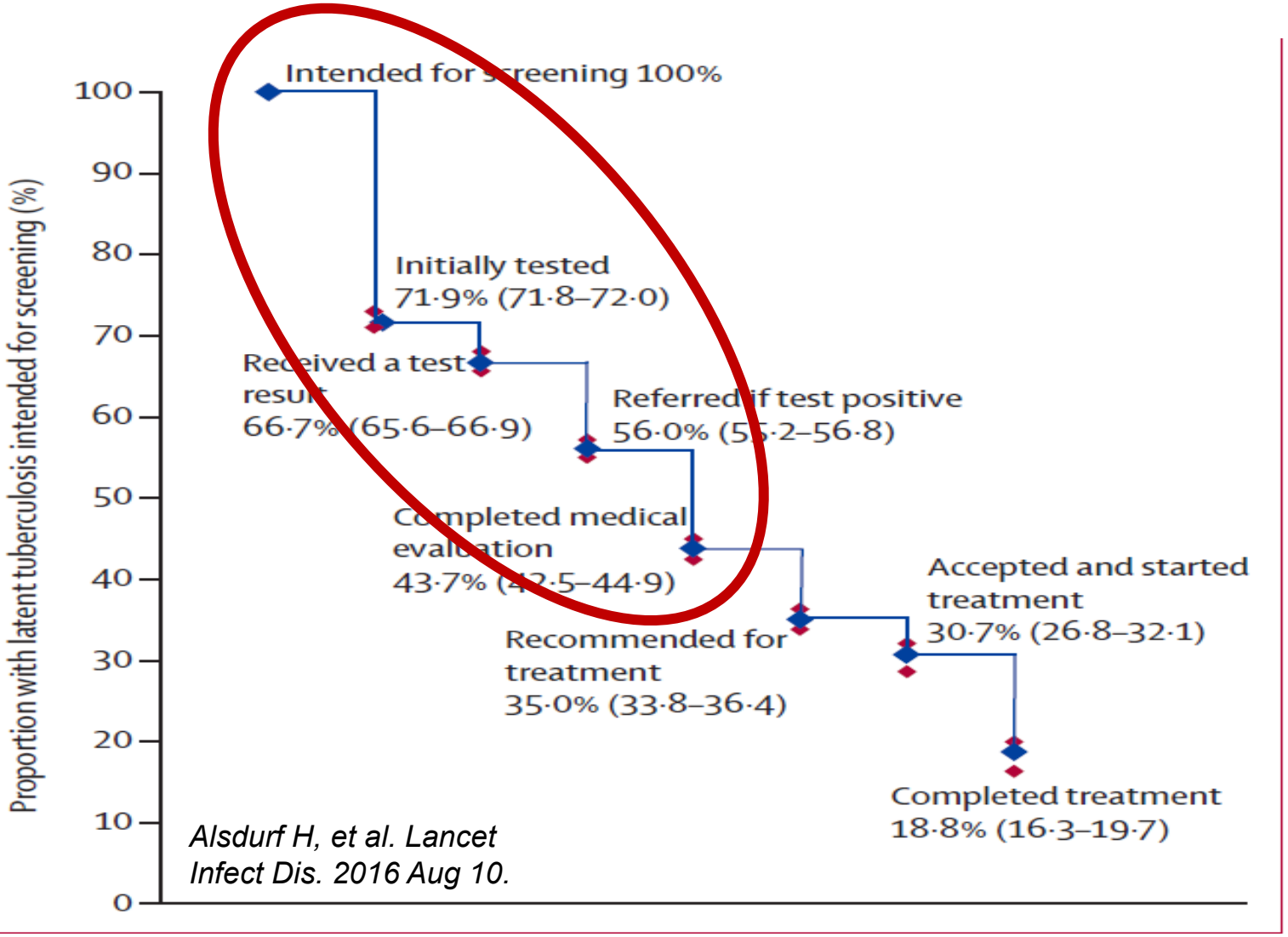
Country*	TB Incidence	Number tested	% QFT Positive
Ethiopia	247	40	82.50%
Somalia	286	198	73.74%
Eritrea	93	141	64.54%
Senegal	137	107	64.49%
Morocco	103	191	64.40%
Guinea	178	66	63.64%
Nigeria	108	172	63.37%
Gambia	284	114	60.53%
Romania	94	137	59.12%
Camerun	238	46	58.70%
Ivory Coast	172	121	52.07%
Mali	60	103	51.46%
Afganistan	189	144	48.61%
Pakistan	231	125	47.20%
Ghana	72	59	40.68%
Bangladesh	225	120	38.33%
Tunisia	31	65	30.77%
Serbia	23	42	21.43%
Egypt	17	228	16.23%
Albania	16	70	11.43%

ITBL Quale Terapia? SFD

	Nr Tot	Nr conclusioni	%
Tot SFD	2596	1644	63,3
INH x 6 mesi	1679	926	55
RMP x 4 mesi	10	6	60
RMP+INH x 3 mesi	388	297	76,5
Rifinah x 3 mesi	519	415	79,9

The Union

Focusing on the cascade of care in LTBI



Alsdurf H, et al. Lancet Infect Dis. 2016 Aug 10.

SORVEGLIANZA TB E ITBL
NEI RICHIEDENTI PROTEZIONE INTERNAZIONALE
SUL TERRITORIO MILANESE, 2016-2017

Relatore: Prof. Mario C. RAVIGLIONE
Correlatore: Prof.ssa Mirella M. PONTELLO

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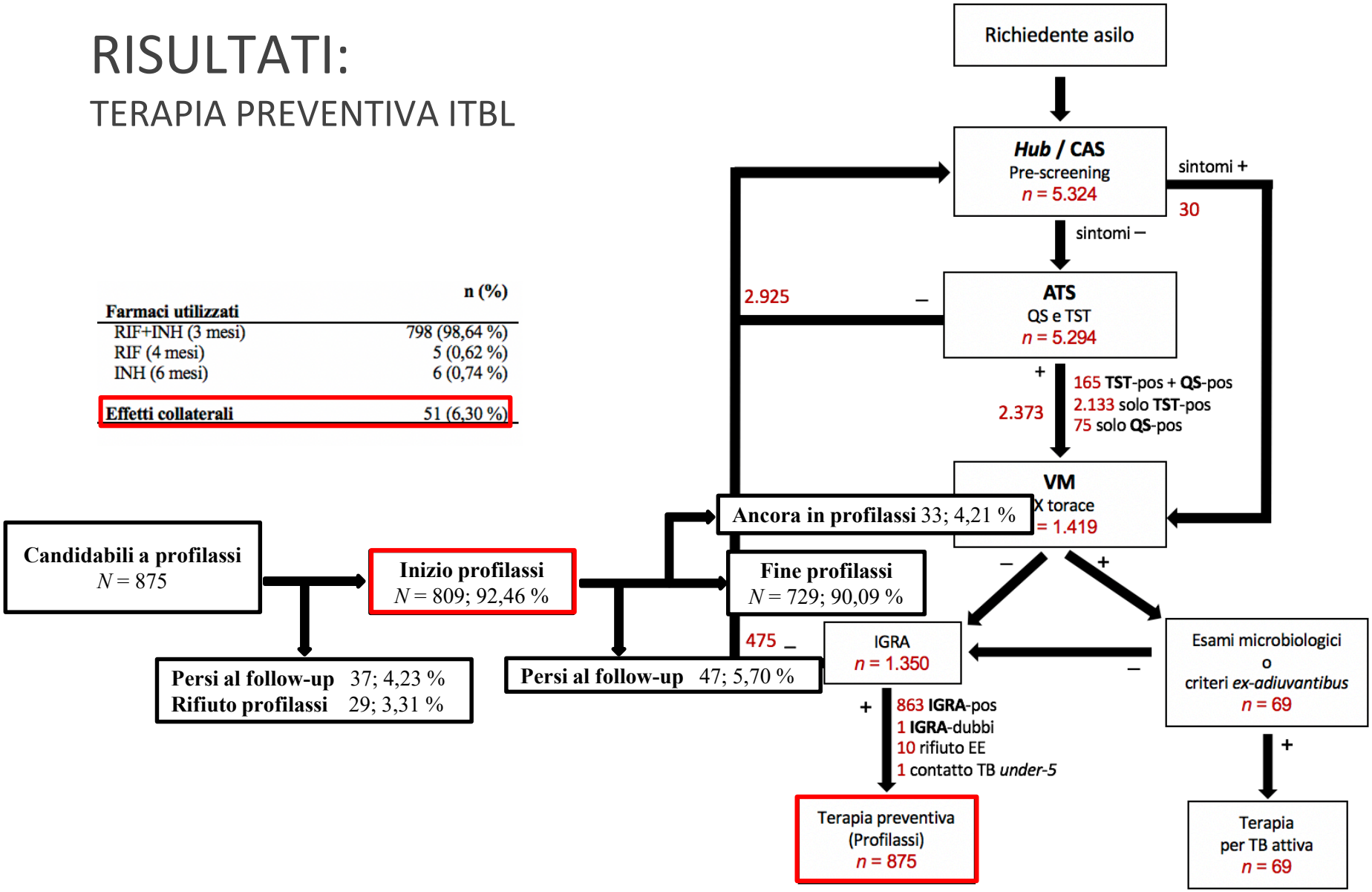
RISULTATI:

TERAPIA PREVENTIVA ITBL

Farmaci utilizzati	n (%)
RIF+INH (3 mesi)	798 (98,64 %)
RIF (4 mesi)	5 (0,62 %)
INH (6 mesi)	6 (0,74 %)
Effetti collaterali	51 (6,30 %)



ONE MONTH OF RIFAPENTINE/ISONIAZID TO PREVENT TB IN PEOPLE WITH HIV: BRIEF-TB/A5279

Brief Rifapentine-Isoniazid Efficacy for TB Prevention

NCT01404312

Susan Swindells[1], Ritesh Ramchandani[2], Amita Gupta[3], Constance Benson[4], Jorge Leon-Cruz[2], Ayotunde Omoz-Oarhe[5], Marc Antoine Jean Juste[6], Javier Lama[6], Javier Valencia[6], Sharlaa Badal-Faesen[7], Laura Moran[9], Courtney V. Fletcher[1], Eric Nuermberger[3], Richard E. Chaisson[3], and the AIDS Clinical Trials Group A5279/BRIEF TB Study Team

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Hypothesis and Primary Objective

Hypothesis:

Four weeks of daily rifapentine and isoniazid will be non-inferior to nine months of isoniazid for preventing TB in people with HIV infection

Primary Objective:

To compare the efficacy of a 4-week daily regimen of rifapentine and isoniazid (1HP) with a 9-month daily regimen of isoniazid (9H) for the prevention of TB in adults and adolescents with HIV infection

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Endpoints

- Primary Endpoint:
  - Incidence rate of first diagnosis of active TB, TB death, or death due to an unknown cause
- Secondary Endpoints
  - Safety and tolerability
  - All-cause and non-TB mortality
  - Adherence to the treatments
  - Pharmacokinetics and drug-drug interactions of RPT/INH with EFV and NVP
  - Rate and pattern of antibiotic resistance

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Primary Endpoints

First Outcome	Randomized Treatment		Total
	9H	1HP	
All Outcomes	33	32	65
Active TB, Confirmed	14 (42%)	18 (56%)	32 (49%)
Active TB, Probable	10 (30%)	11 (34%)	21 (32%)
Death Related to TB	2 (6%)	0 (0%)	2 (3%)
Death from Unknown Cause	7 (21%)	3 (9%)	10 (15%)

	9H	1HP	IRR Difference
Events/PY of follow up	33/4896	32/4926	0.023
Incidence per 100 PY	0.67	0.65	(95% CI -0.30-0.35)

Non-Inferiority margin = 1.25 per 100 PY

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Incident rate differences by selected baseline covariates

Stratum	Incidence Rate 9H	Incidence Rate 1HP	Incidence Rate Difference 9H – 1HP (95% Confidence Interval)
Female sex	0.692	0.801	-0.109 (-0.577, 0.359)
Male sex	0.654	0.478	0.177 (-0.259, 0.612)
CD4 $\leq$ 250/mm^3	1.275	1.931	-0.656 (-2.061, 0.749)
CD4 > 250/mm^3	0.586	0.465	0.121 (-0.186, 0.428)
Not on ART at entry	0.718	0.747	-0.029 (-0.501, 0.443)
On ART at entry	0.628	0.546	0.082 (-0.353, 0.517)
IGRA/TST Negative/missing	0.585	0.576	0.009 (-0.334, 0.352)
IGRA/TST Positive	0.967	0.903	0.064 (-0.736, 0.864)

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Safety – Grade ≥3 Adverse Events

	Treatment Group							
	9H (N=1498)				1HP (N=1488)			
	Grade				Grade			
Sign/Symptom/Lab Event	3	4	5	Number subjects	3	4	5	Number subjects
Any General Body	123	12	0	135	101	9	1	111
Any Hematology	36	21	0	57	41	22	0	63
Any Hematology, Coagulation	4	1	0	5	0	3	0	3
Any Hematology, RBC	8	18	0	26	6	14	0	20
Any Hematology, WBC/Differential	16	2	0	18	28	8	0	36
Any Liver/Hepatic	24	18	0	42	19	9	0	28
Any Gastro-Intestinal	22	2	0	24	29	1	1	31
Any Skin	11	0	0	11	8	0	0	8
Any Neurological	25	4	1	30	12	2	0	14
ANY EVENT	213	59	2	274	198	47	5	250

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Conclusions

- 1HP is non-inferior to 9H for preventing TB, TB death or death from unknown cause in adults and adolescents with HIV infection
- Rates of TB were higher in those with +TST/IGRA or CD4 ≤250
- Rates of endpoints were higher in 1HP recipients with CD4 ≤250 vs 9H
- Safety was good and similar in both arms, with more hematologic toxicity with 1HP and more liver and neuro- toxicity with 9H
- Completion of treatment was excellent in both arms but better with 1HP
- 1HP provides a highly-effective, ultra-short course regimen for the prevention of TB in people with HIV
- 1HP could contribute to improvements in global control of TB and should be studied in other high-risk groups

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Preventive treatment for MDR-TB contacts

In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. (New)

Outcomes	Reference	Intervention	Control	Relative effect (OR) (95% CI)	Difference (95% CI)	Follow-up
Incidence of active TB	*68*	2/41 (4.9%)	13/64 (20.3%)	0.20 (0.04-0.94)	154 fewer per 1000 (273 fewer to 36 fewer)	30 months
	69	0/93 (0%)	3/15 (20%)	0.02 (0.00-0.39)	200 fewer per 1000 (403 fewer to 3 more)	36 months
	70	0/21 (0%)	0/10 (0%)	-	0 more per 1000 (138 fewer to 138 more)	12 months
	71	0/30 (0%)	0/166 (0%)	-	0 more per 1000 (45 fewer to 45 more)	≤ 9 years
Incidence of MDR-TB	*69*	0/93 (0%)	3/15 (20%)	0.02(0.00-0.39)	200 fewer per 1000 (403 fewer to 3 more)	36 months
	70	0/21 (0%)	0/10 (0%)	-	0 more per 1000 (138 fewer to 138 more)	12 months
	71	0/30 (0%)	0/166 (0%)	-	0 more per 1000 (45 fewer to 45 more)	≤ 9 years

Grazie e sostenete Stop TB Italia!
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