

# Predictive Value of IGRAs in HIV-Infected Individuals

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# Background (1)

## HIV and TB

- TB is the most prevalent opportunistic disease in HIV-infected individuals.
- The incidence of TB is increased among HIV-infected patients.
- The rate of progression from latent to active TB is increased.\*
- The course of active TB is often more aggressive.
- HIV-disease is accelerated after active TB.\*\*

\*Lawn SD et al., *AIDS* 2005

\*\*Whalen C et al., *Am J Respir Crit Care Med* 1995

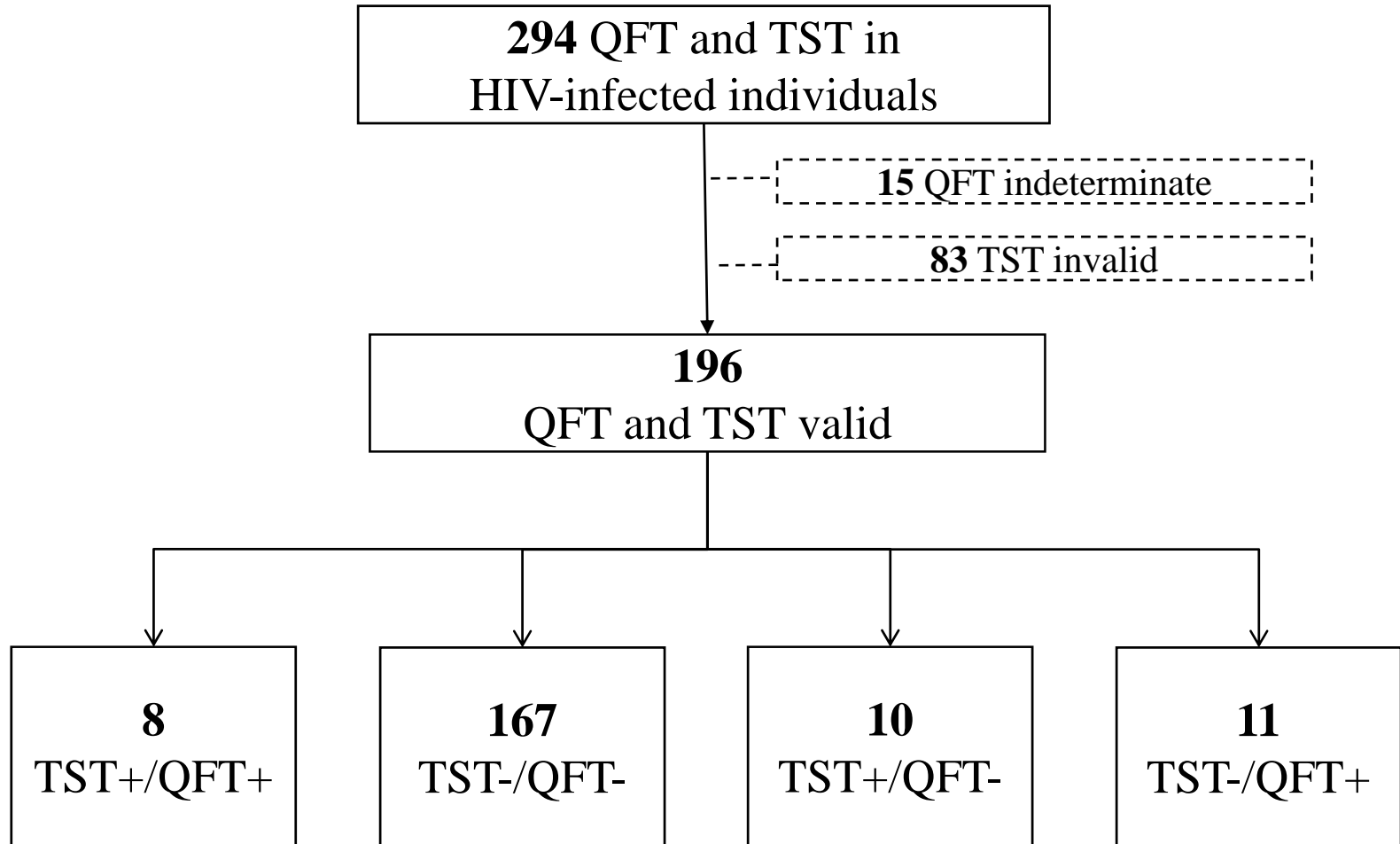
# Background (2)

## TB Screening

- There is no gold standard for the diagnosis of latent tuberculosis infection (LTBI).\*
- Screening Tests:
  - Tuberkulin Skin Test (TST)
  - Interferon- $\gamma$  Release Assays (IGRAs):
    - T-SPOT.*TB*
    - QuantiFERON<sup>®</sup>-TB Gold In-Tube Test (QFT)
- Do IGRAs perform equally well or better than the TST for the detection of LTBI in HIV-infected patients?

\*Pai M et al., *Lancet Infect Dis* 2007

# Concordance Between QFT and TST



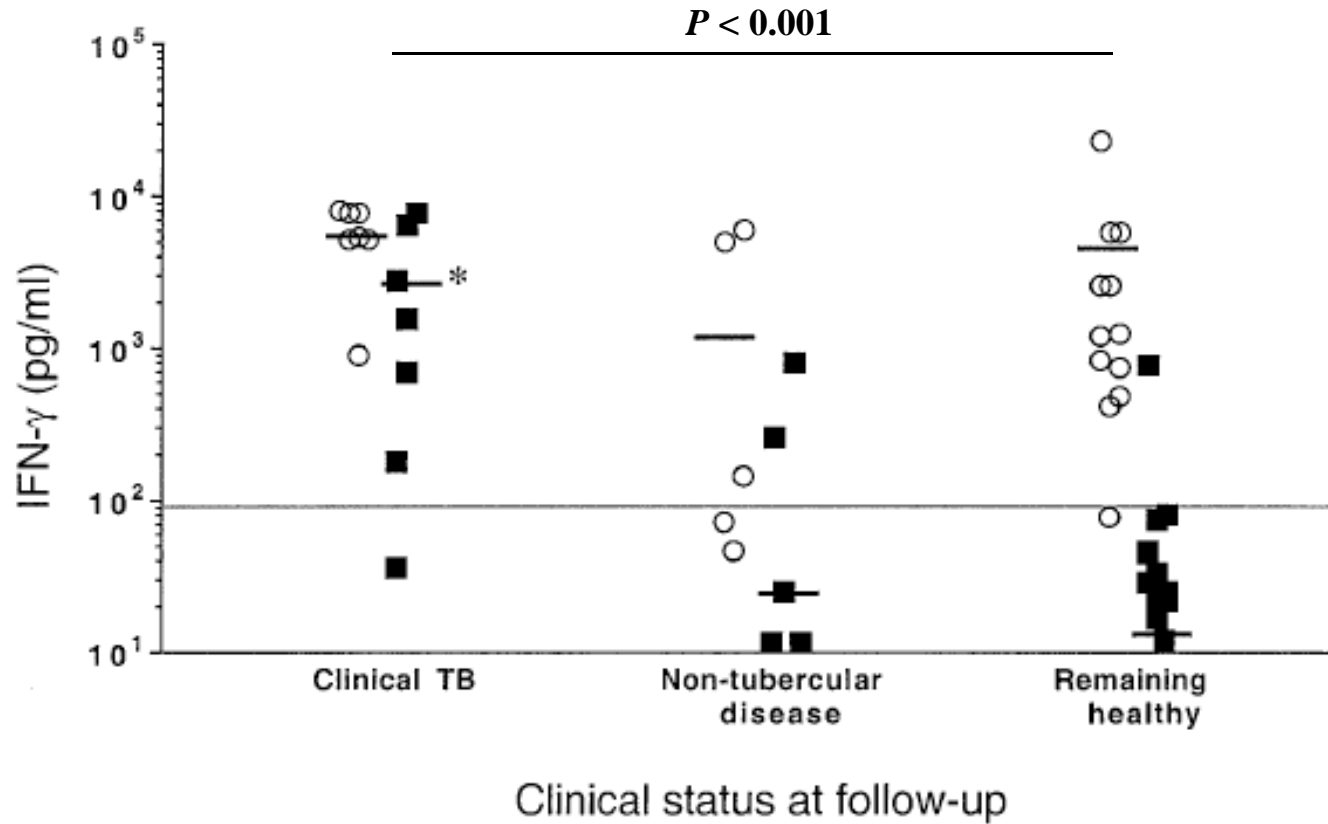
# **Predictive Value of IGRAs**

Do IGRAs predict the subsequent development of active tuberculosis disease?

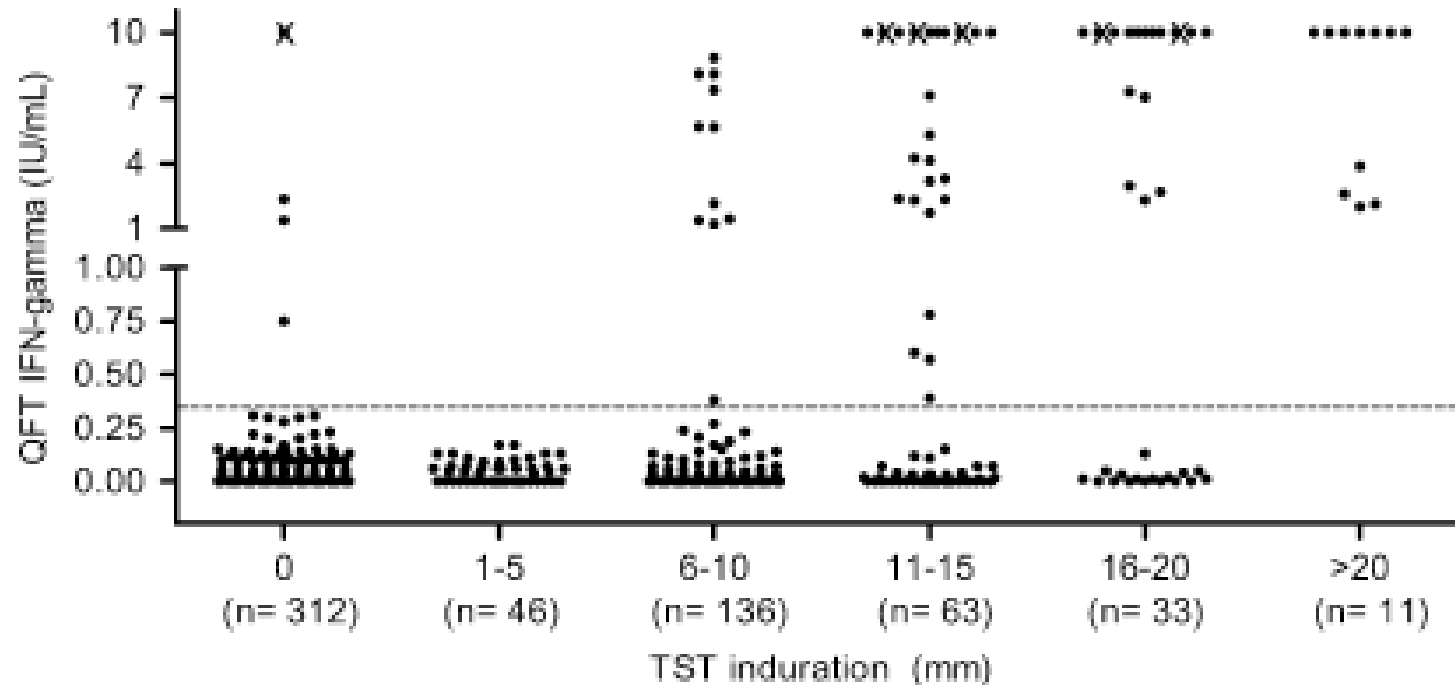
# Predictive Value of IGRAs

- 24 healthy household contacts of sputum-positive TB patients in Ethiopia
- IFN- $\gamma$  release upon exposure to ESAT-6 and PPD in-vitro
- clinical examination after 2 years:
  - 7 patients with active TB
  - 5 patients with non-tuberculous disease
  - 12 individuals remained healthy

# ESAT-6 (■) Is Distinctive, Whereas PPD (○) Is Not



# The Development of TB (x) According to QFT and TST Results



# Detection and Prediction of Active Tuberculosis Disease by a Whole-Blood Interferon- $\gamma$ Release Assay in HIV-1–Infected Individuals

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# Study Objectives

- prevalence of QFT positive patients in a multiethnic cohort of HIV-infected individuals in a low-incidence country
- determination of epidemiological and clinical risk factors for positive QFT results
- sensitivity of the QFT assay for the detection of active TB
- predictive value of the QFT results for the development of active TB during follow-up

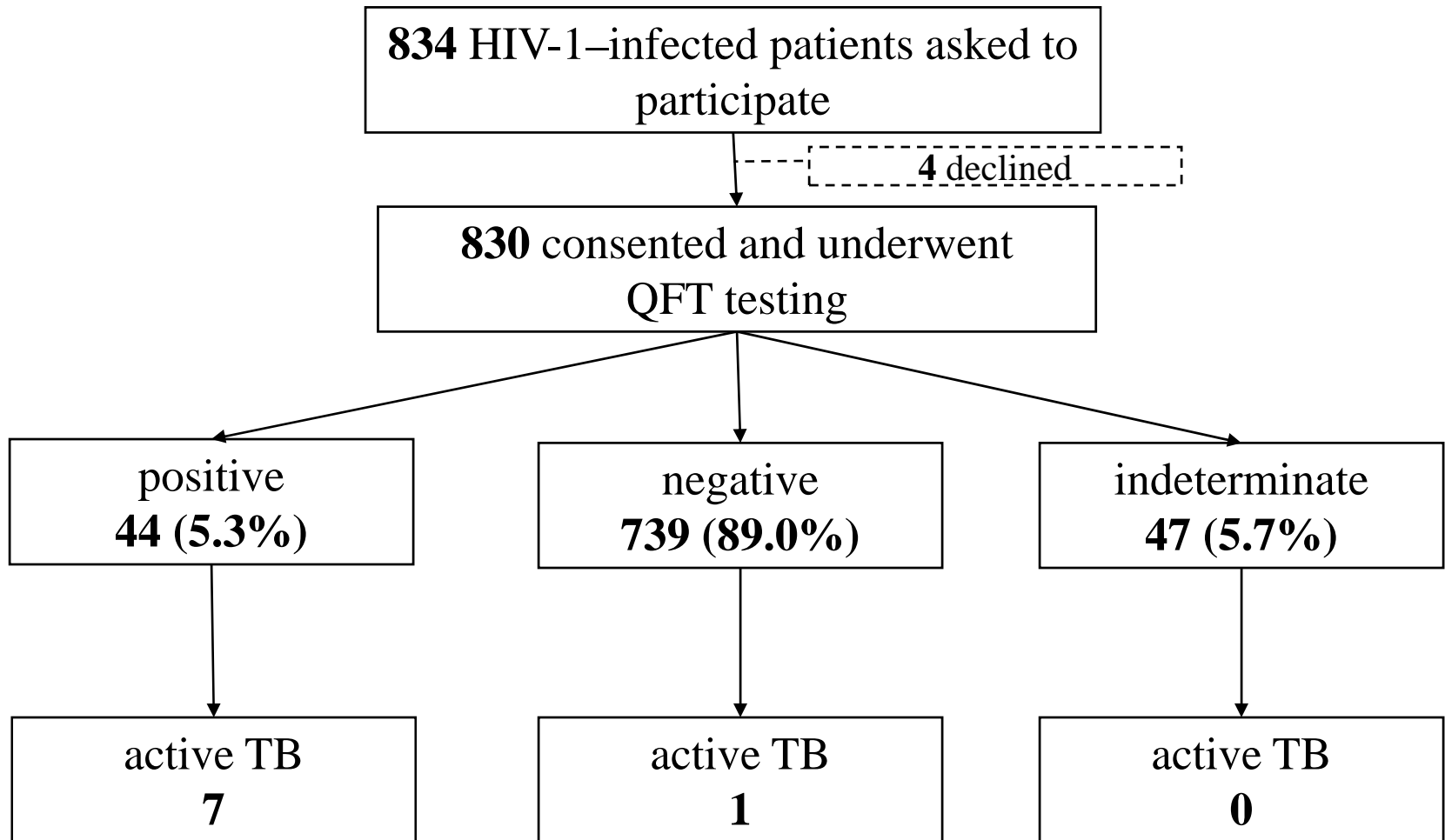
# Study Design

- prospective, longitudinal, single-center
- QFT assay at baseline
- history of LTBI-related risk factors
- monitoring for TB-related clinical symptoms at least every 3 months
- in case of a positive QFT assay result:
  - chest radiography and/or CT-Thorax/Abdomen
  - Ziehl-Neelson staining of sputum or BAL
  - culture and PCR of sputum, blood, urine and stool samples
  - Tuberculin Skin Test

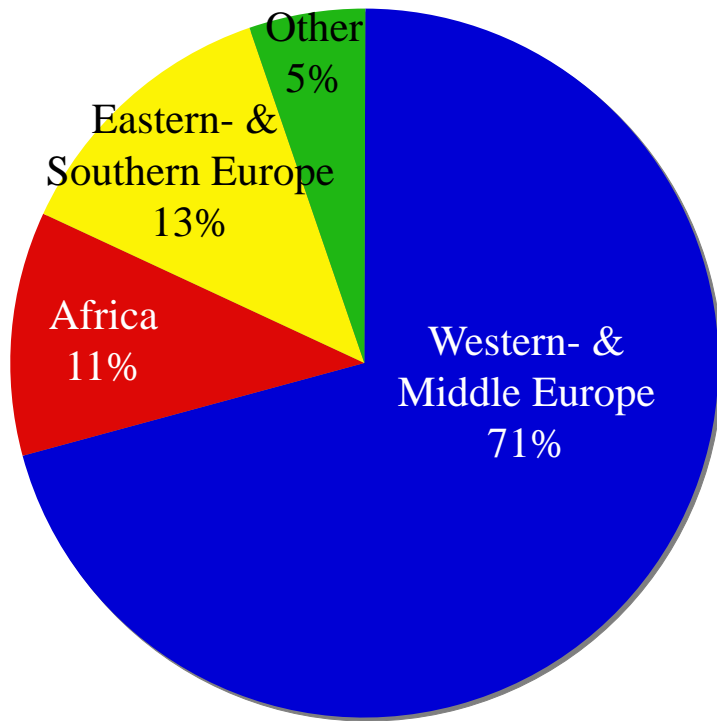
# Study Participants

- 830 HIV-1–infected subjects
- ♂: 581 (70%); ♀: 249 (30%)
- median age [IQR]: 39 years [32-47]
- HIV and AIDS:
  - median CD4<sup>+</sup> T cell count: 393 cells/mm<sup>3</sup> [264-566]
  - median CD4<sup>+</sup> T cell nadir: 194 cells/mm<sup>3</sup> [81-300]
  - median HIV-1 RNA level: 1.7 log copies/ml [1.7-4.4]
  - on antiretroviral therapy: 495 (60%)
  - HIV-1 RNA level < 50 copies/ml: 439 (53%)
  - AIDS: 191 (23%)
- prior active TB: 29 (4%)

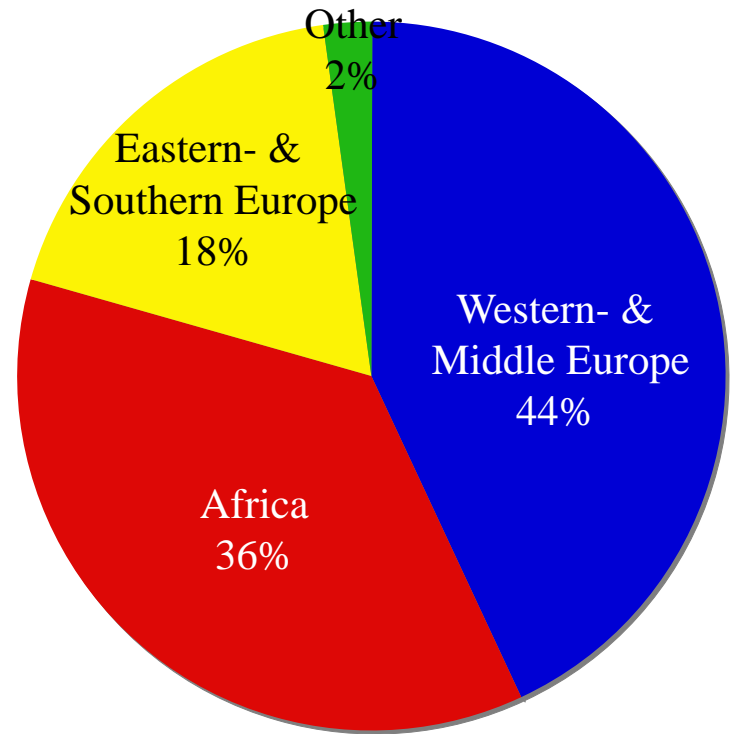
# Detection of Active TB at Baseline According to the QFT-Defined Subgroups



# Country of Origin



all individuals (n=830)

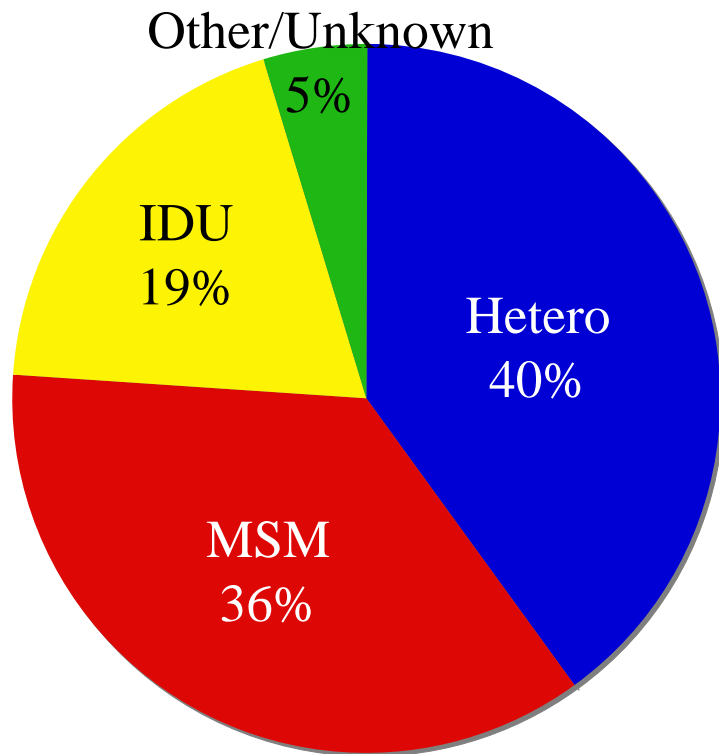


QFT positive individuals (n=44)

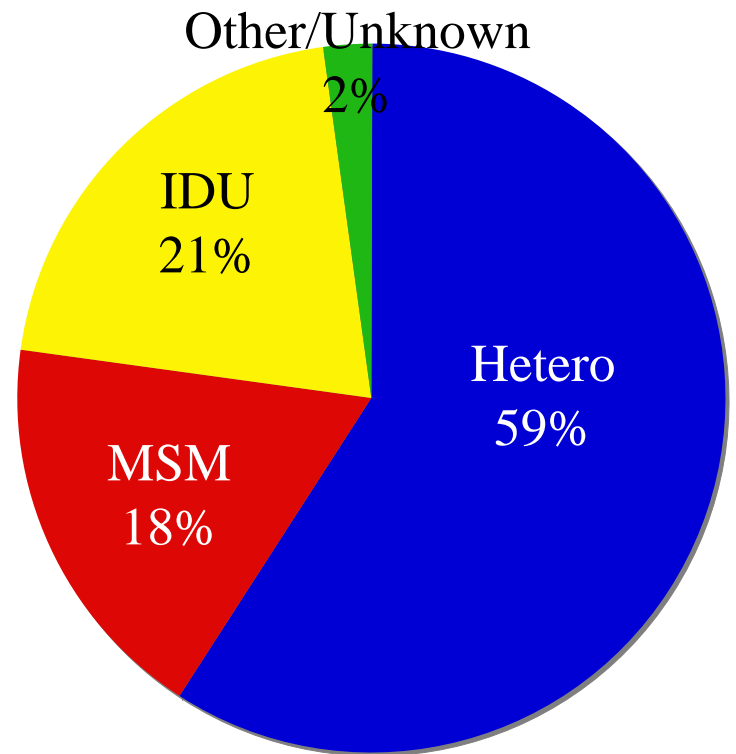
## Epidemiological Factors Associated with a Positive QFT Result

	OR (95% CI)	<i>P</i>
<b>Ethnicity</b>		
White	1.00	
Black	4.84 (2.25-9.97)	< 0.001
<b>Country of origin</b>		
Austrian	1.00	
African	6.57 (2.99-14.25)	< 0.001
<b>TB burden (WHO)</b>		
< 25/10 <sup>5</sup>	1.00	
> 100/10 <sup>5</sup>	5.86 (2.41-13.44)	< 0.001

# Mode of Infection with HIV-1



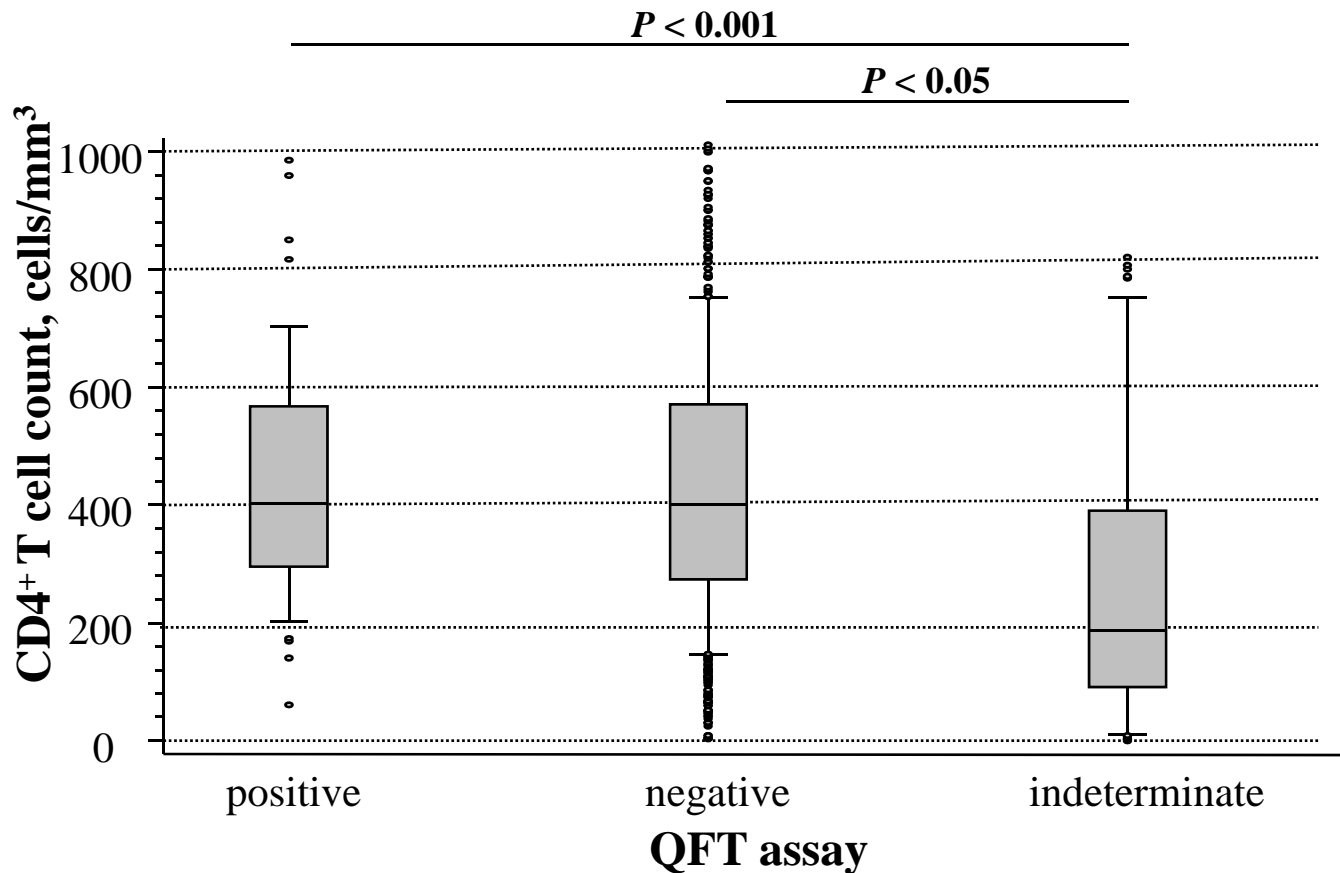
all patients (n=830)



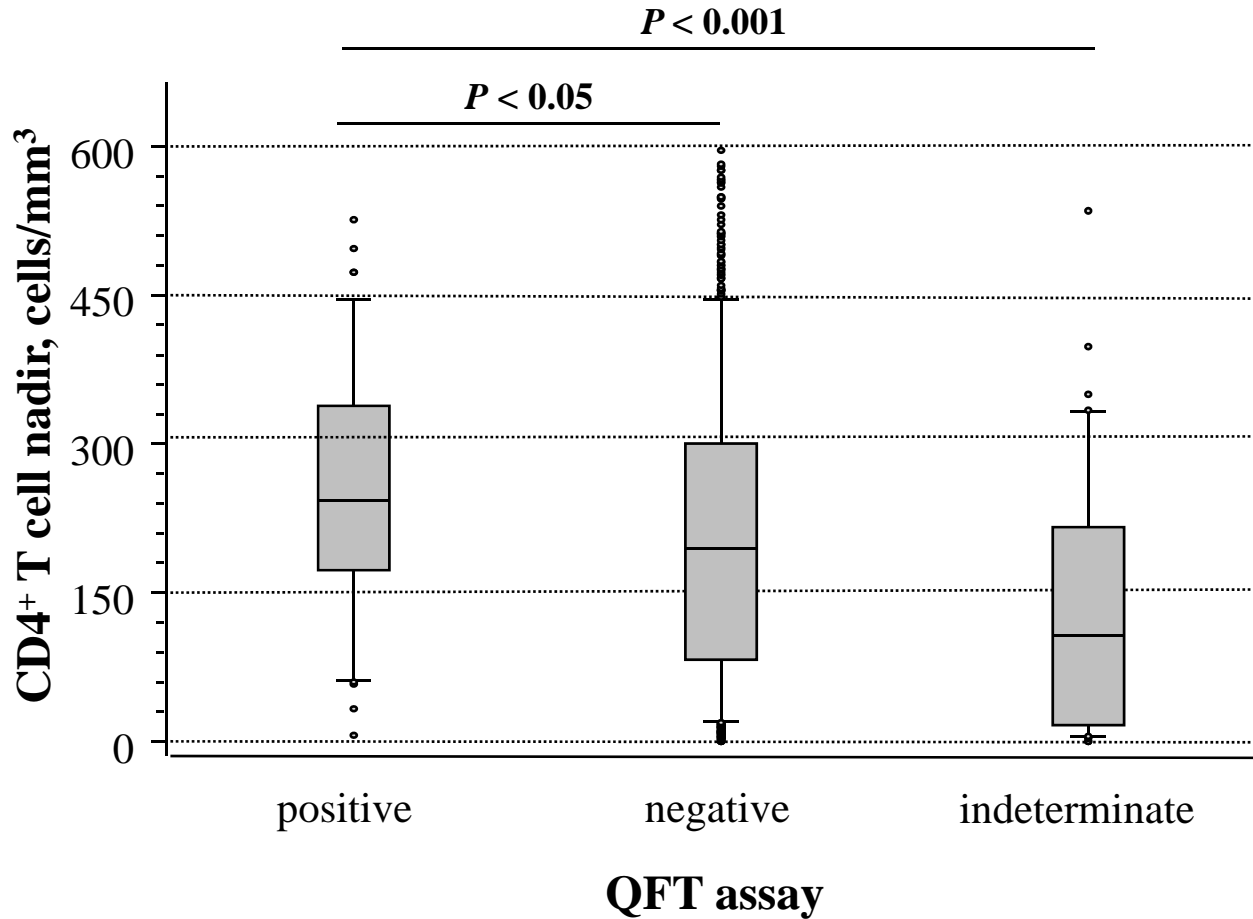
QFT positive patients (n=44)

# QFT Assay Results and CD4<sup>+</sup> T Cell Counts

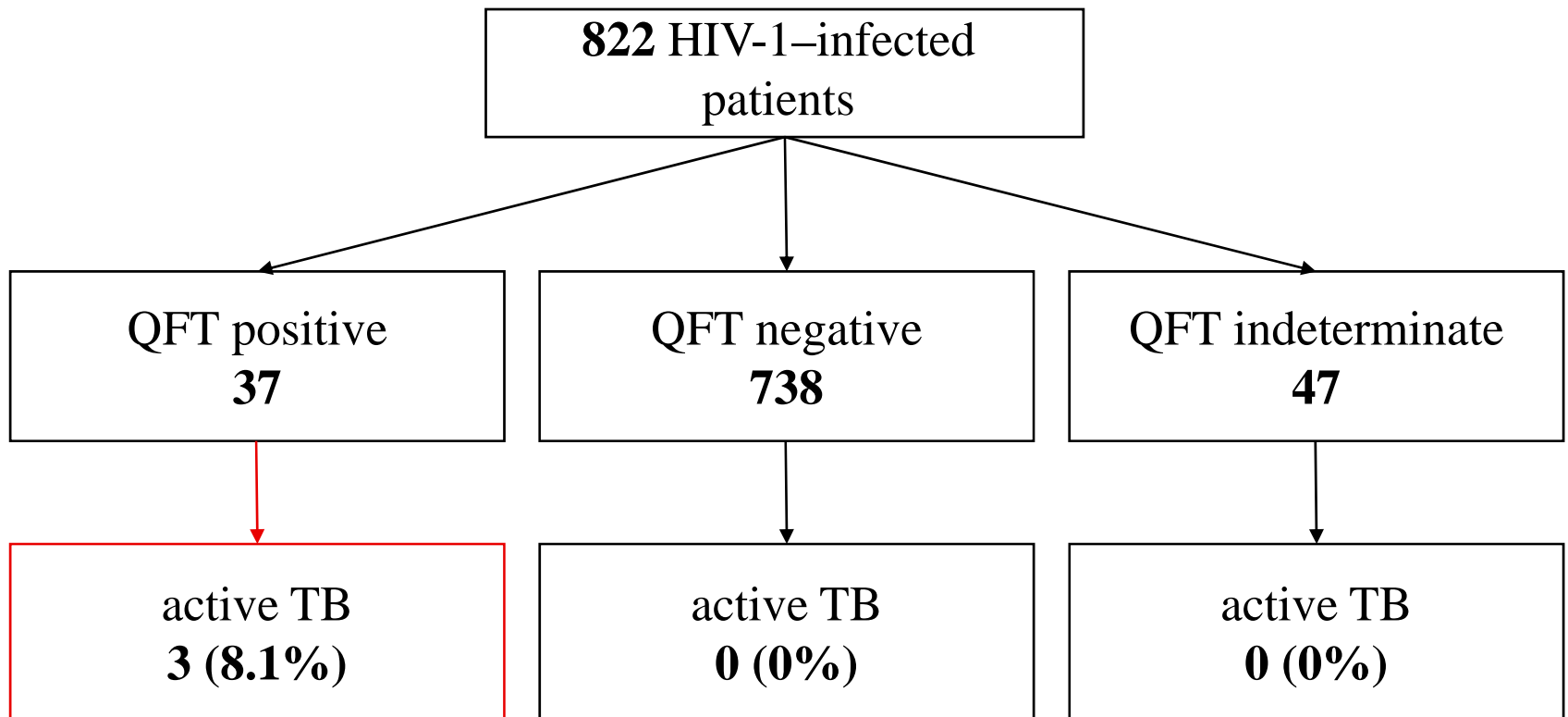
## (1)



# QFT Assay Results and CD4<sup>+</sup> T Cell Nadirs



# Predictive Value of the QFT Assay in HIV-1–Infected Individuals



## Follow-Up

- median follow-up [IQR]: 19 months [12-21]
- follow-up stratified:
  - < 20 days: 37 (5%)
  - 20-365 days: 176 (21%)
  - > 365 days: 609 (74%)

# Active TB Remains a Clinical Diagnosis

**Table 4. Characteristics of patients with latent or active tuberculosis.**

Characteristic	Latent <i>Mycobacterium tuberculosis</i> infection (n = 34)	Active tuberculosis (n = 11)	P
Positive TST result	23 (67.6)	8 (80.0) <sup>a</sup>	
Mean no. of risk factors ± SD	1 ± 0.81	1 ± 0.98	.567
Mean no. of symptoms ± SD	0.5 ± 0.71	2.36 ± 1.29	<.001
Median CD4 <sup>+</sup> T cell count, cells/mm <sup>3</sup> (IQR)	441 (333–586)	231 (153–396.5)	.012
Median CD4 <sup>+</sup> T cell nadir, cells/mm <sup>3</sup> (IQR)	249 (180.5–347)	217 (153–310)	.491
Median HIV-1 RNA level, log <sub>10</sub> copies/mL (IQR)	1.7 (1.7–4.3)	4.9 (4.6–5.2)	<.001
Receiving ART	17 (50.0)	1 (9.1)	
Previous AIDS-defining illness	6 (17.6)	0 (0.0)	

**NOTE.** Data are no. (%) of patients, unless otherwise indicated. ART, antiretroviral therapy; IQR, interquartile range; TST, tuberculin skin test.

<sup>a</sup> Only 10 patients with active tuberculosis underwent a TST.

# **Comparative Study on the Predictive Value of QFT Assay and TST for the Development of Active TB**

# Study Participants

- 305 HIV-1–infected patients
- ♂: 223 (73%); ♀: 82 (27%)
- median age [IQR]: 40 years [32-48]
- HIV and AIDS:
  - median CD4<sup>+</sup> T cell count: 376 cells/mm<sup>3</sup> [253-533]
  - median CD4<sup>+</sup> T cell nadir: 178 cells/mm<sup>3</sup> [72-283]
  - median HIV-1 RNA level: 1.7 log k/ml [1.7-4.4]
  - on antiretroviral therapy: 187 (61%)
  - HIV-1 RNA level < 50 copies/ml: 160 (52%)
  - AIDS: 79 (26%)
- prior active TB: 12 (4%)
- median follow-up [IQR]: 29 months [22-32]

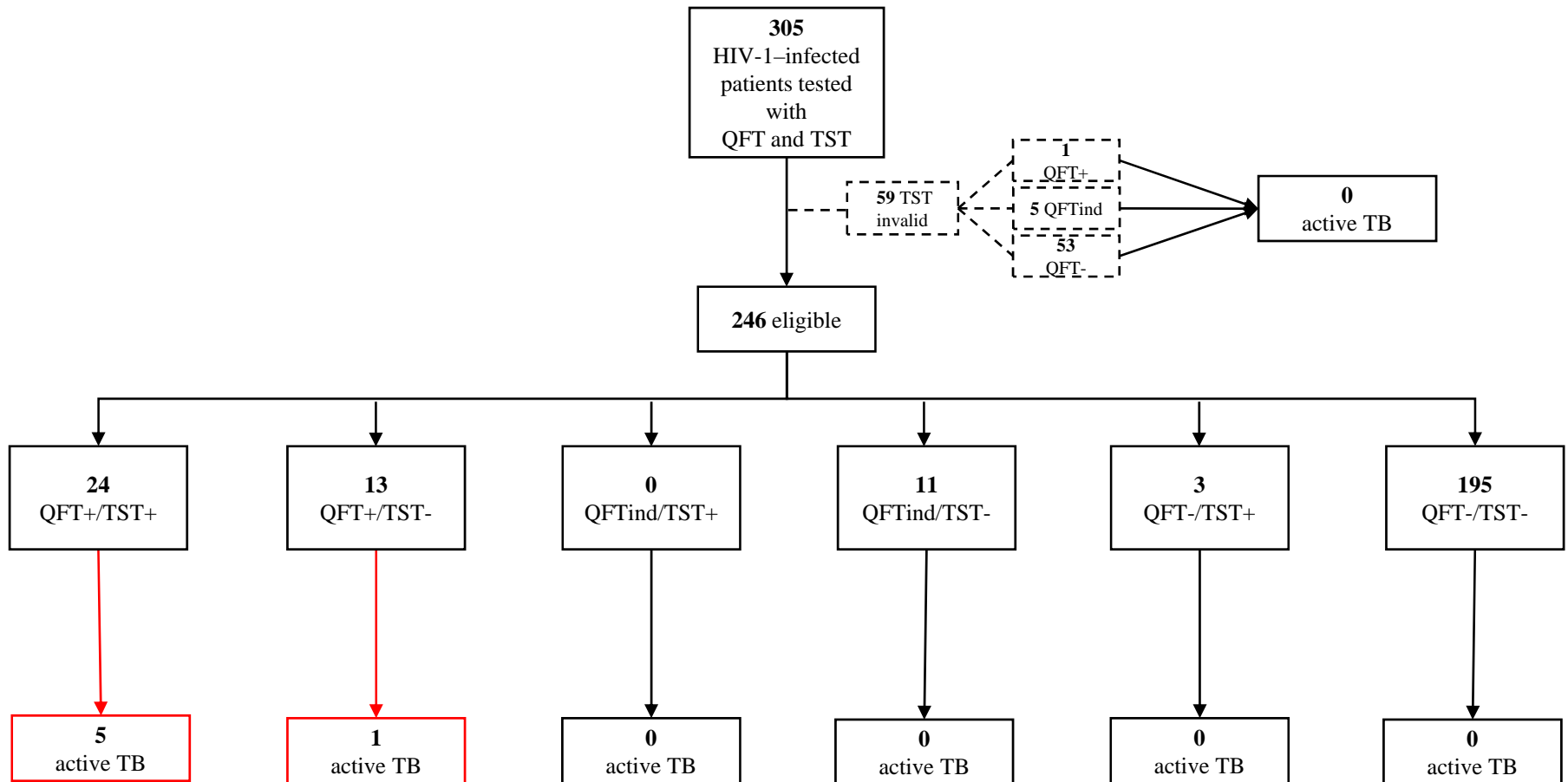
# Concordance Between QFT and TST

TST

QFT

		Positive		Negative		Raw Agreement		$\kappa$	$P$
Cut-off: > 5mm	Positive	24 (10.21%)		3 (1.28%)		219 (93.19%)		.7117	< .0001
	Negative	13 (5.53%)		195 (82.98%)					
Cut-off: > 10mm	Positive	18 (7.66%)		3 (1.28%)		213 (90.64%)		.6102	< .0001
	Negative	19 (8.09%)		195 (82.98%)					
Cut-off: > 15mm	Positive	13 (5.53%)		3 (1.28%)		208 (88.51%)		.4825	< .0001
	Negative	24 (10.21%)		195 (82.98%)					

# Active TB Within the Follow-Up Period



# Summary

- All patients who eventually developed active TB had a positive QFT result at baseline.
- Positive QFT results were predominantly found among patients with ethnic and geographic risk factors.
- The performance of the QFT assay depended on actual and past CD4<sup>+</sup> T cell counts.

## **Conclusion I**

Patients with a positive QFT result are at significantly higher risk to develop active TB as compared to those with a negative QFT result among HIV-infected individuals.

## **Conclusion II**

The QFT assay may be a a more sensitive tool for the identification of those at high risk of developing active TB among HIV–infected patients than the TST.

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