HIV Antiretroviral Drug Regimens and Lung Function Decline in Early HIV Infection

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START Pulmonary Substudy Group

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Conflicts of Interest

- Study funded by NIH
- GlaxoSmithKline consulting (2018)

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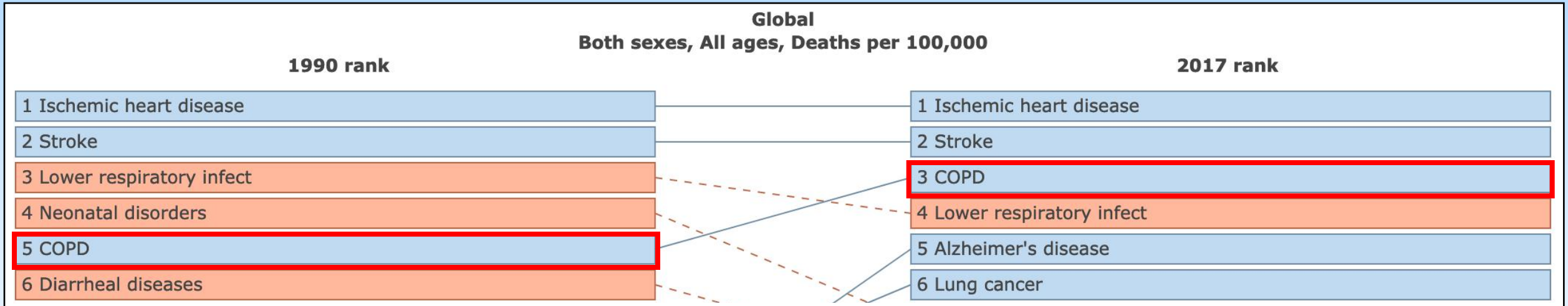
Rationale



Global Burden of Disease. Institute for Health Metrics and Evaluation. *www.vizhub.healthdata.org*. Accessed 10 Mar 2019.

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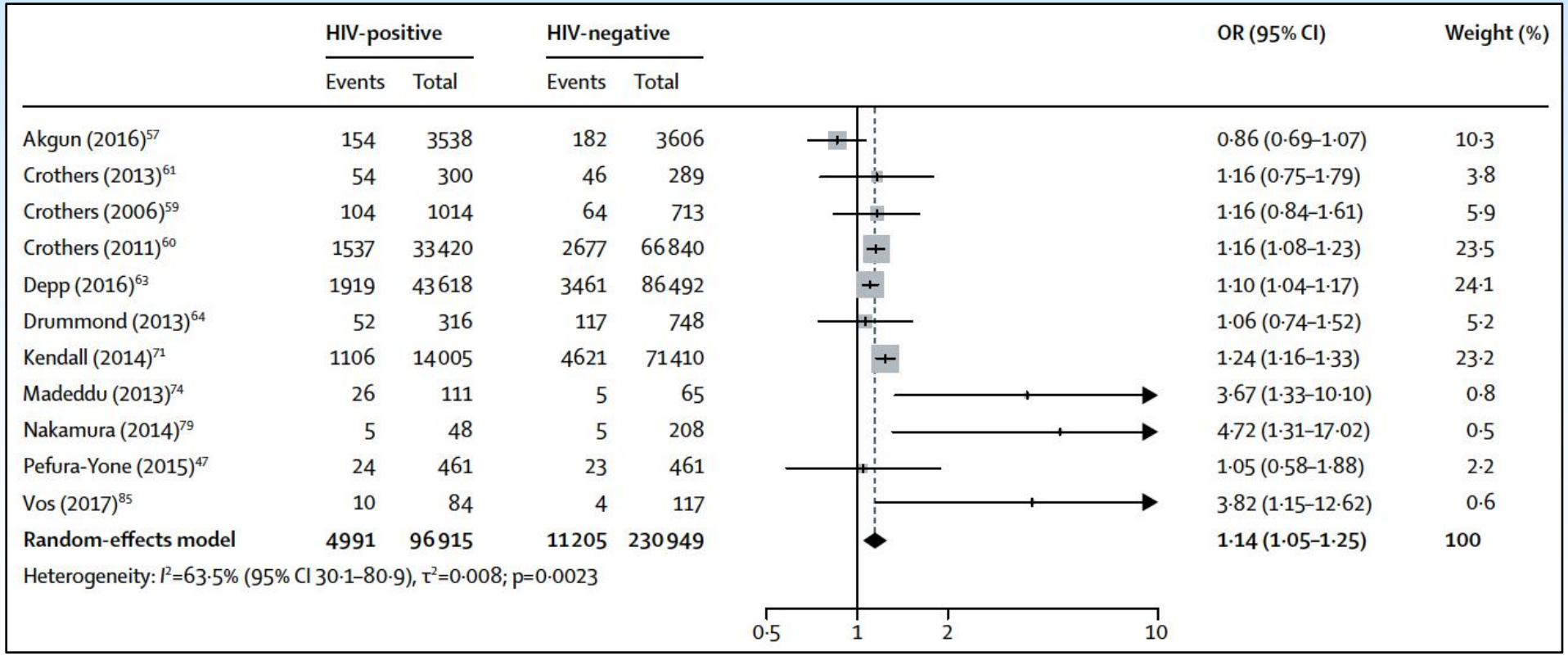
Prevalence of chronic obstructive pulmonary disease in the global population with HIV: a systematic review and meta-analysis

Jean Joel Bigna, Angeladine Malaha Kenne, Serra Lem Asangbeh, Aurelie T Sibetcheu

Lancet Glob Health 2018; 6: e193–202



	HIV-positive		HIV-negative		OR (95% CI)	Weight (%)
	Events	Total	Events	Total		
Akgun (2016)[57]	154	3538	182	3606	0·86 (0·69–1·07)	10·3
Crothers (2013)[61]	54	300	46	289	1·16 (0·75–1·79)	3·8
Crothers (2006)[59]	104	1014	64	713	1·16 (0·84–1·61)	5·9
Crothers (2011)[60]	1537	33420	2677	66840	1·16 (1·08–1·23)	23·5
Depp (2016)[63]	1919	43618	3461	86492	1·10 (1·04–1·17)	24·1
Drummond (2013)[64]	52	316	117	748	1·06 (0·74–1·52)	5·2
Kendall (2014)[71]	1106	14005	4621	71410	1·24 (1·16–1·33)	23·2
Madeddu (2013)[74]	26	111	5	65	3·67 (1·33–10·10)	0·8
Nakamura (2014)[79]	5	48	5	208	4·72 (1·31–17·02)	0·5
Pefura-Yone (2015)[47]	24	461	23	461	1·05 (0·58–1·88)	2·2
Vos (2017)[85]	10	84	4	117	3·82 (1·15–12·62)	0·6
Random-effects model	**4991**	**96915**	**11205**	**230949**	**1·14 (1·05–1·25)**	**100**

Heterogeneity: I^2=63·5% (95% CI 30·1–80·9), τ^2=0·008; p=0·0023

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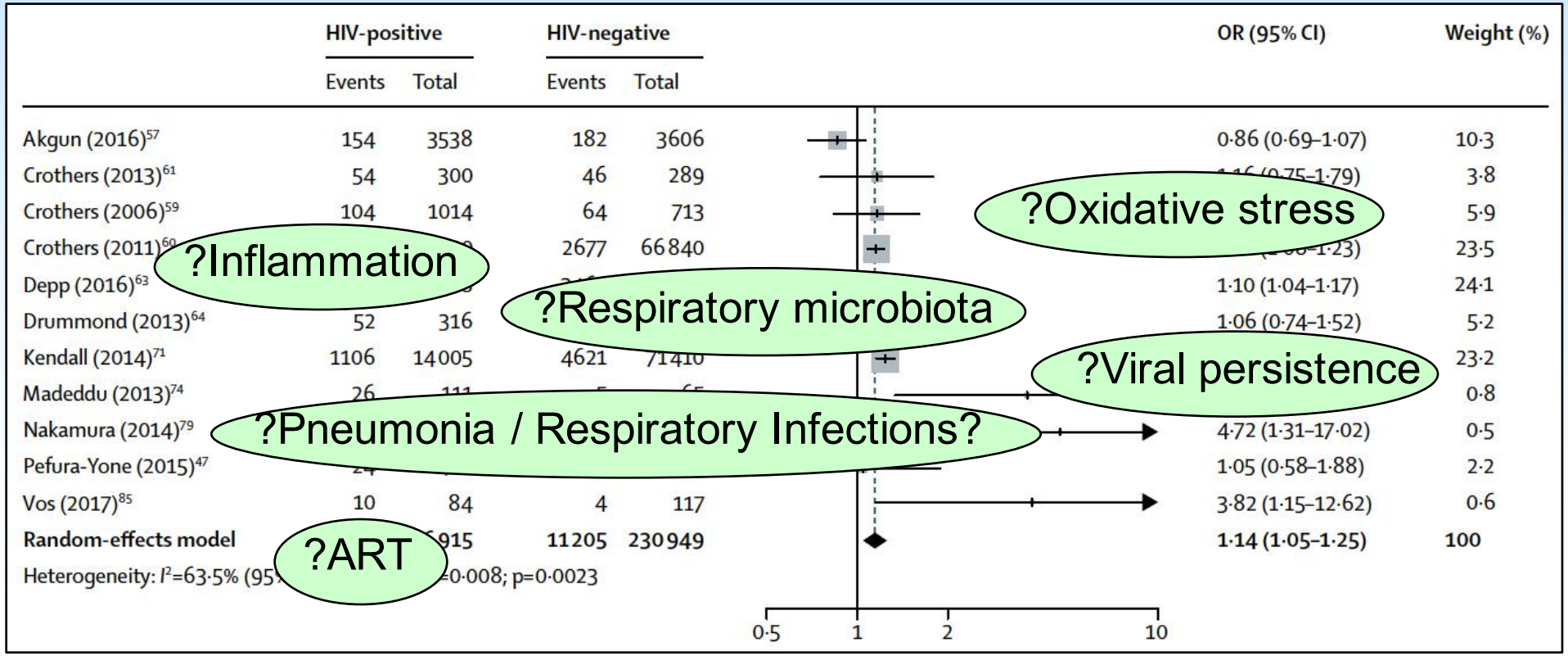

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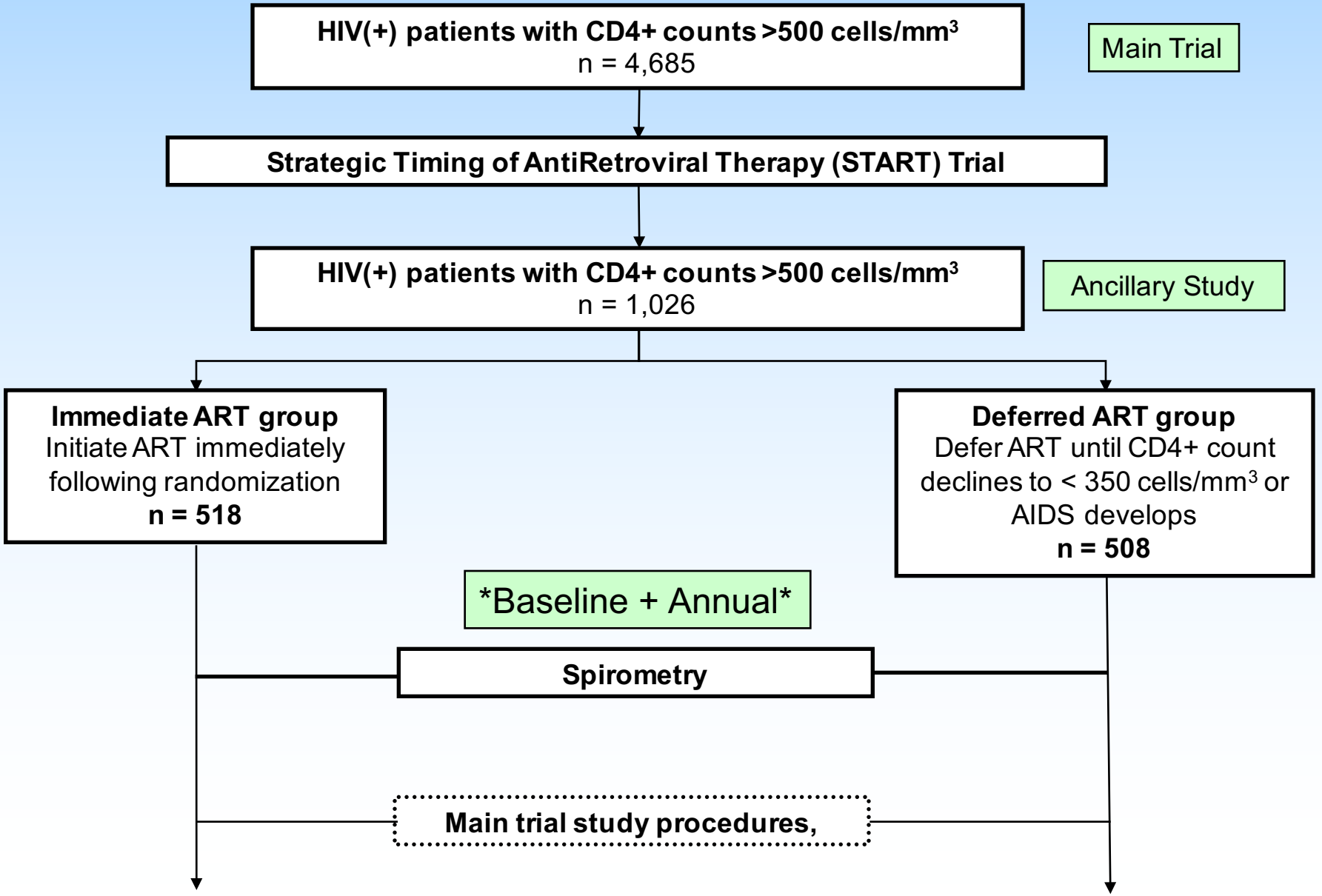
Rationale

Table 2. Studies examining effects of antiretroviral therapy on risk of chronic obstructive pulmonary disease among patients with HIV infection. All studies adjusted for smoking variables

Author	Setting	On ART (*n*)	No ART (*n*)	Design	Conclusions
George [11]	USA, single center (Los Angeles, CA, USA)	195	20	Cross-sectional study	ART use associated with lower FEV_1/FVC ratio in linear regression analysis (β coefficient −3.2; $P=0.04$).
Gingo [12]	USA, single center (Pittsburgh, PA, USA)	134	33	Cross-sectional study	ART use with higher odds COPD (OR 6.22; 95% CI: 1.19–32.43)
Crothers [22▪]	USA, national healthcare system database	~21 700	~11 700	Prospective, administrative data analysis	ART use with lower incident COPD without smoking adjustment (incidence rate ratio [IRR] 0.90; 95% CI: 0.82–0.99). Smoking adjustment resulted in wider CI (IRR 0.93; 95% CI: 0.73–1.18)
Drummond [25▪]	USA, single center (Baltimore, MD, USA)	169	134	Cross-sectional study	ART use not associated with COPD (OR 0.60; 95% CI: 0.29–1.22). However, viral load at least 200 000 copies/ml associated with COPD (OR 3.41; 95% CI: 1.24–9.39)
Drummond [10▪▪]	USA, single center (Baltimore, MD, USA)	172	144	Prospective, observational cohort	ART use not associated with differences in FEV_1 rate of decline. However, viral load at least 75 000 copies/ml associated with faster rate of FEV_1 decline compared with viral load less than 75 000 copies/ml (69 ml/year faster decline; 95% CI: 15.3–123.0 ml/year; $P=0.012$).
Madeddu [14]	Italy, single center (Sassari, IT)	87	24	Cross-sectional study	ART not associated with COPD, but CI very wide (OR 0.59; 95% CI: 0.06–5.93)

From Kunisaki KM. *Curr Opin HIV AIDS* 2014;9(1):27-33.

Study Design



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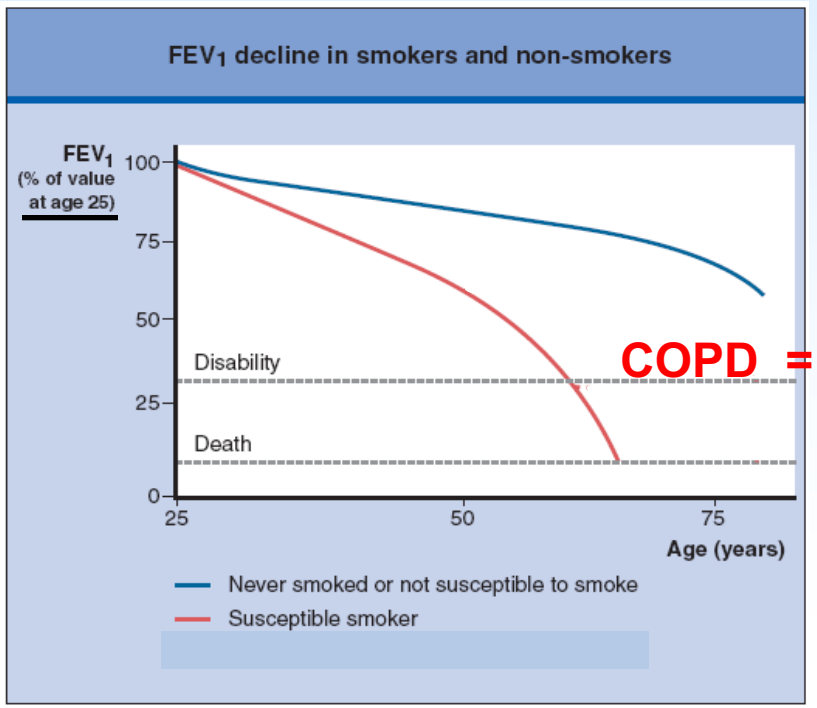
Primary Outcome: Lung Function Decline

FEV_1: Forced expiratory volume in 1 second





Normal:
(-25 to -30 mL/yr)

COPD = (-50 to -60 mL/yr)

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Previously Published Main RCT Results

	FEV_1 slope (95% CI), mL/year	p value
Baseline smokers		
Immediate ART (n=135)	−32·9 (−58·5 to −7·4)	..
Deferred ART (n=155)	−29·7 (−54·3 to −5·0)	..
Difference	−3·3 (−38·8 to 32·2)	0·86
Baseline non-smokers		
Immediate ART (n=383)	−27·8 (−44·2 to −11·4)	..
Deferred ART (n=353)	−22·2 (−39·6 to −4·9)	..
Difference	−5·6 (−29·4 to 18·3)	0·65
Pooled analysis adjusted for baseline smoking status		
Immediate ART (n=518)	−29·1 (−42·9 to −15·4)	..
Deferred ART (n=508)	−24·5 (−38·6 to −10·3)	..
Difference	−4·7 (−24·4 to 15·1)	0·64
Pooled analysis adjusted for smoking status at each study visit		
Immediate ART (n=518)	−28·8 (−42·6 to −14·9)	..
Deferred ART (n=508)	−23·6 (−37·8 to −9·3)	..
Difference	−5·2 (−25·1 to 14·6)	0·61

Data are from groups of patients randomly assigned to either immediate or deferred ART initiation. ART=antiretroviral therapy.

Table 2: Primary outcome of FEV_1 slope comparisons

Kunisaki KM. *Lancet Respir Med* 2016;4:980-989.

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Current Analysis

- **<u>Secondary analysis of relationship between ART regimen and FEV_1 slope</u>**
- Analysable ART regimens: NNRTI, PI, INSTI
  - All on dual-NRTI (88% TDF/FTC; 7% ZDV/3TC; 4%ABC/3TC)
  - Includes both immediate and deferred ART strategies
- Through all of follow-up
  - Unblinding May 2015
  - Follow-up through Dec 2016

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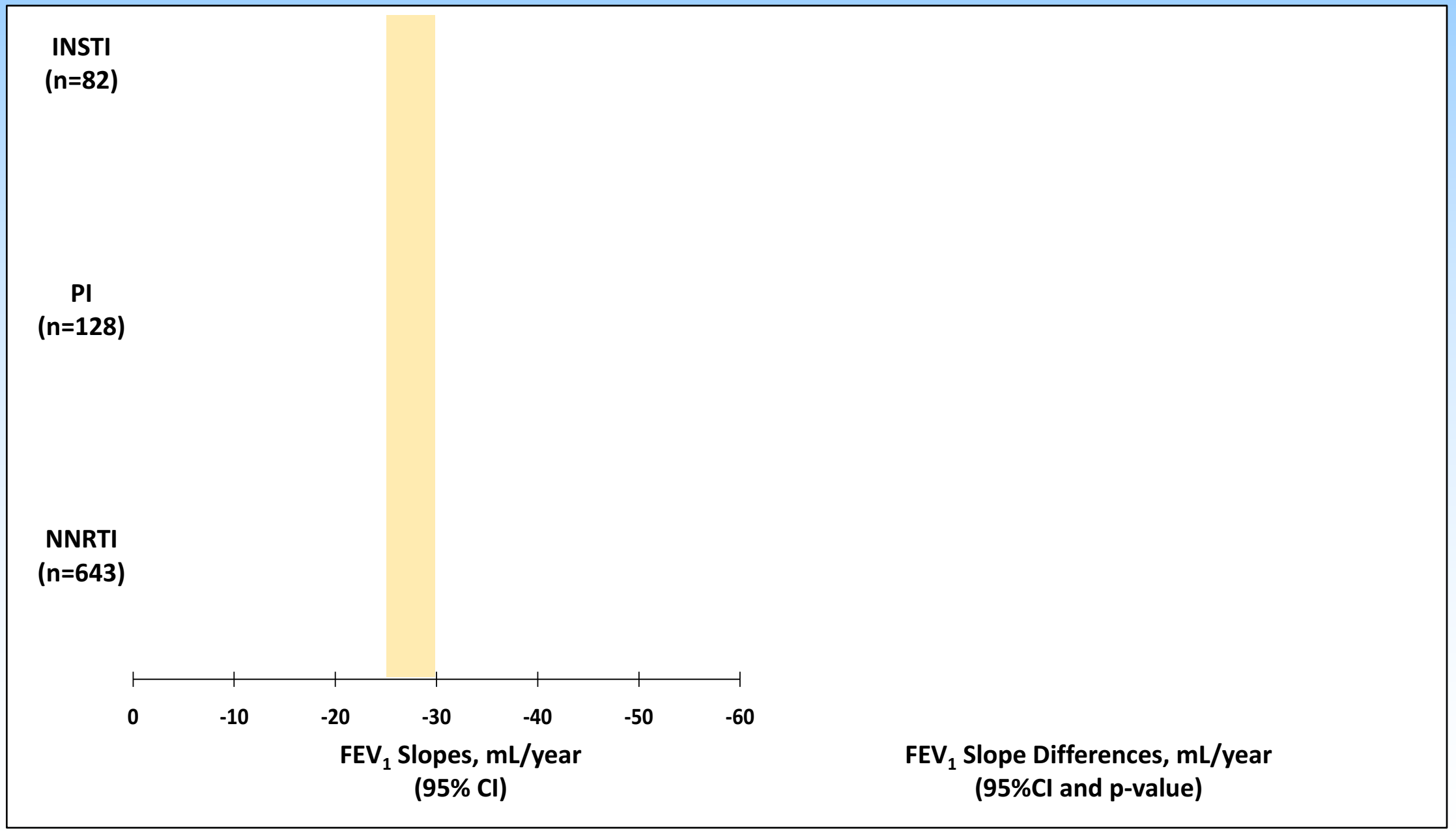

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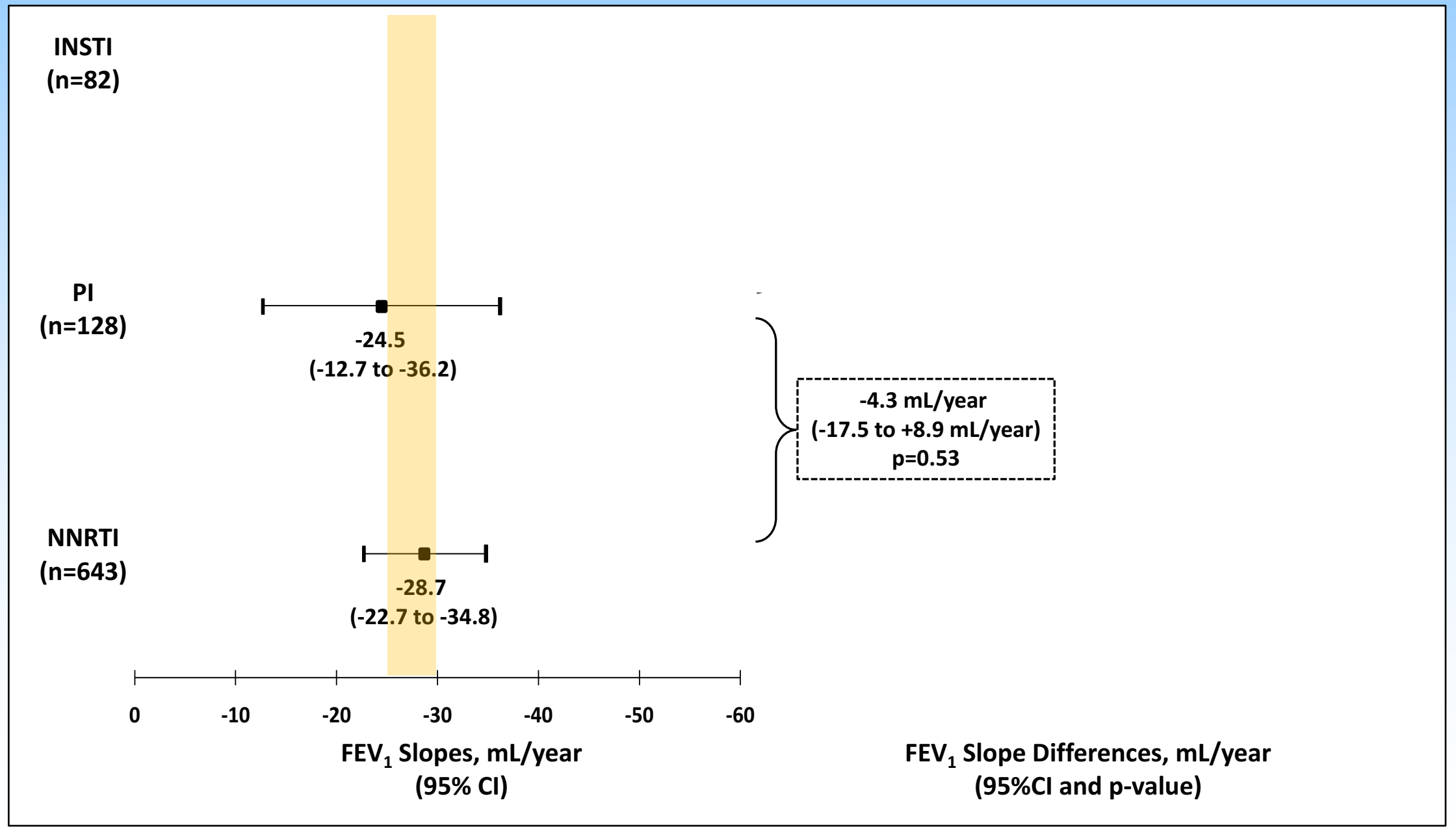

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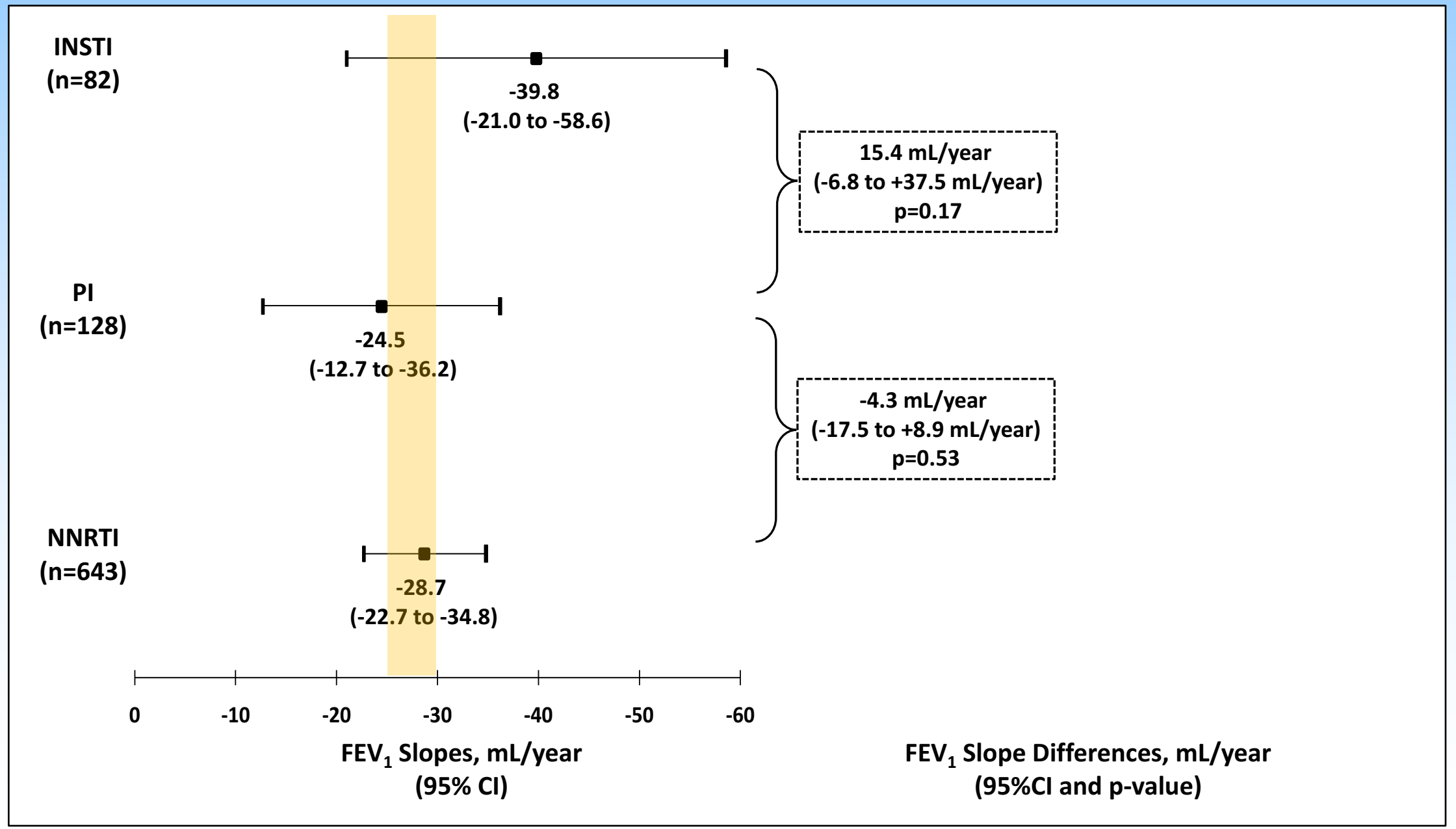

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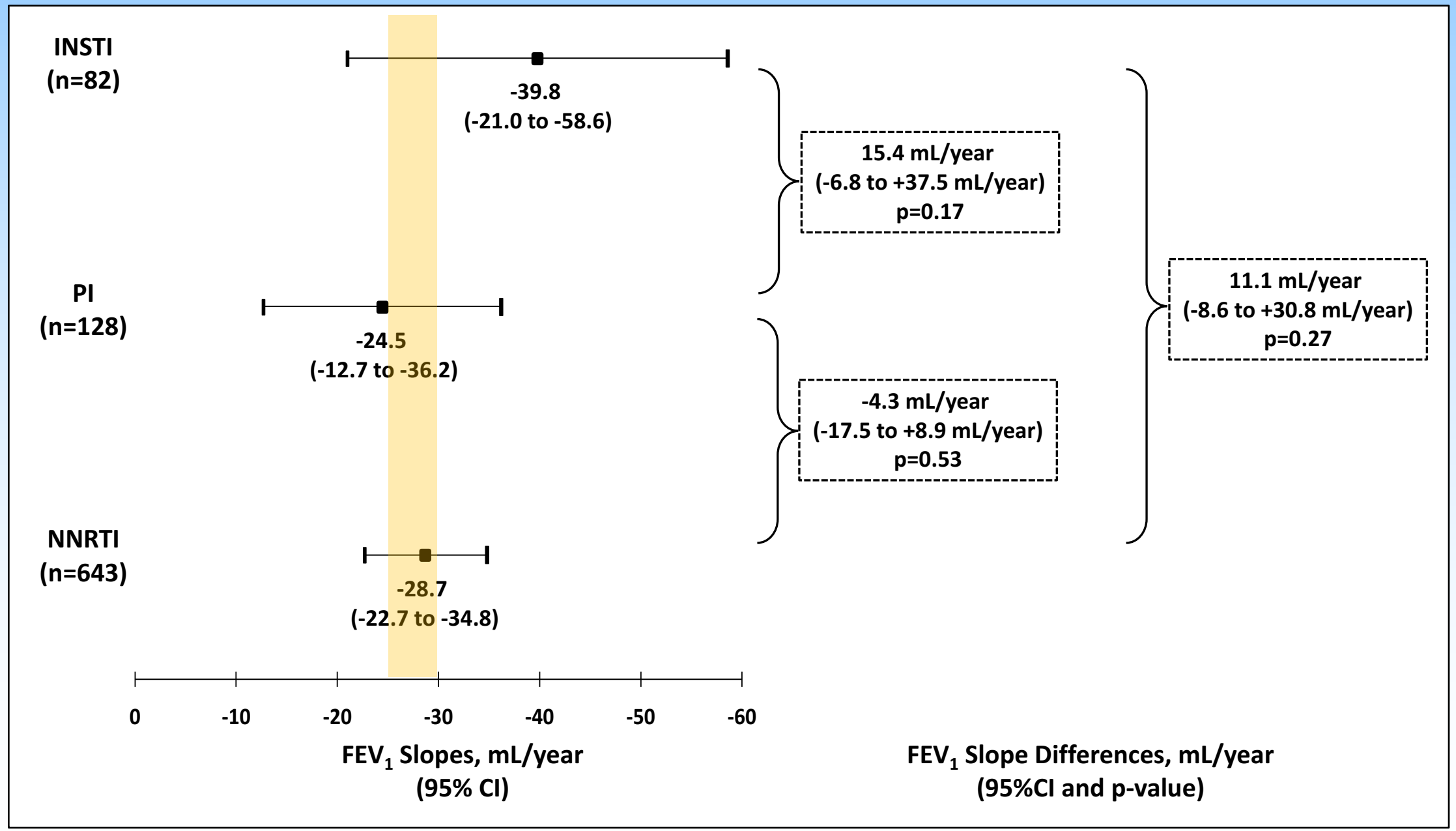

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Conclusions

- Lung function decline is similar for NNRTI and PI drugs
  - Both in the range of normal age-related FEV_1 decline.

- More data are needed to assess the potential effects of INSTIs on lung function decline.

Thank you to the 1,026 START Pulmonary Substudy participants

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MRC Medical Research Council

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