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Update on HIV treatments

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Disclosures

Body Positive NZ have paid to get me here

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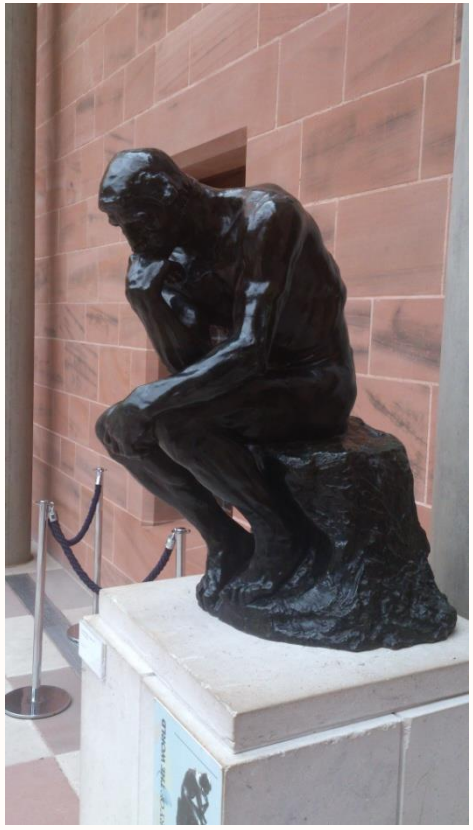
Australia beats NZ in something

Always of interest:



- When to start
- What to use

WHO 2013: Updated Treatment Guidelines

- Expanded ART eligibility
  - Treatment initiation threshold: CD4+ ≤ 500 cells/mm^3
  - Prioritize severe or advanced HIV or CD4+ ≤ 350 cells/mm^3
- Viral load testing preferred for monitoring ART
- Preferred initial regimen: fixed-dose TDF + 3TC (or FTC) + EFV
  - Discontinue use of d4T due to toxicity

WHO Consolidated Treatment Guidelines. June 2013.

Major Guidelines for Initiation of Antiretroviral Therapy

Guideline	AIDS or HIV-Related Symptoms	CD4+ Cell Count < 200/mm^3	CD4+ Cell Count 200-350/mm^3	CD4+ Cell Count 350-500/mm^3	CD4+ Cell Count > 500 cells/mm^3
DHHS-USA, 2013	Yes	Yes	Yes	Yes[1]	Yes[2]
International AIDS Society-USA, 2012	Yes	Yes	Yes	Yes[1]	Yes[2]
British HIV Association, 2012	Yes	Yes	Yes	Consider [3]	Defer[3]
European AIDS Clinical Society, 2012	Yes	Yes	Yes	Consider[3]	Defer[3]
World Health Organization, 2013	Yes	Yes	Yes	**Yes[4]**	Defer[5]

(1) Strong strength recommendation based on observational data (A-II)
(2) Moderate strength recommendation based on expert opinion (B-III).
(3) But treat all HIV+ pregnant women, HBV co-infection, HCV co-infection, HIVAN, HIV related neurocognitive disorders, ITP, non-AIDS cancers and serodiscordant couples
(4) Individuals with CD4 < 350 as a priority.
(5) But treat all HIV+ pregnant women ,TB co-infection with active disease and HBV co-infection with severe liver disease, and serodiscordant copuls

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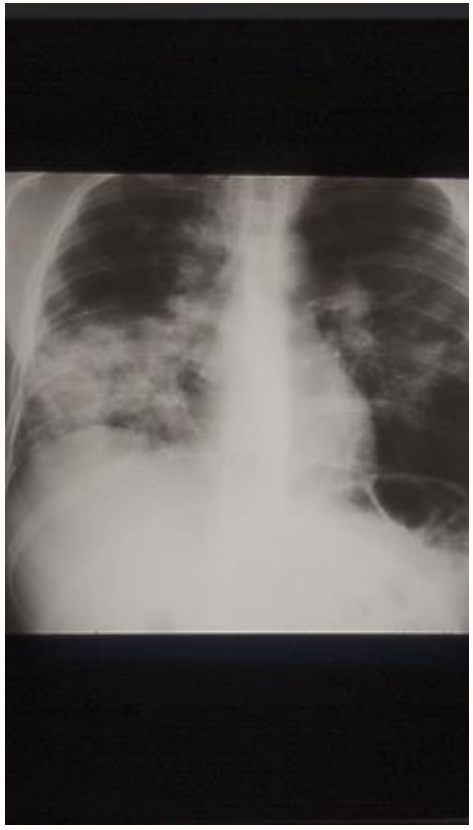
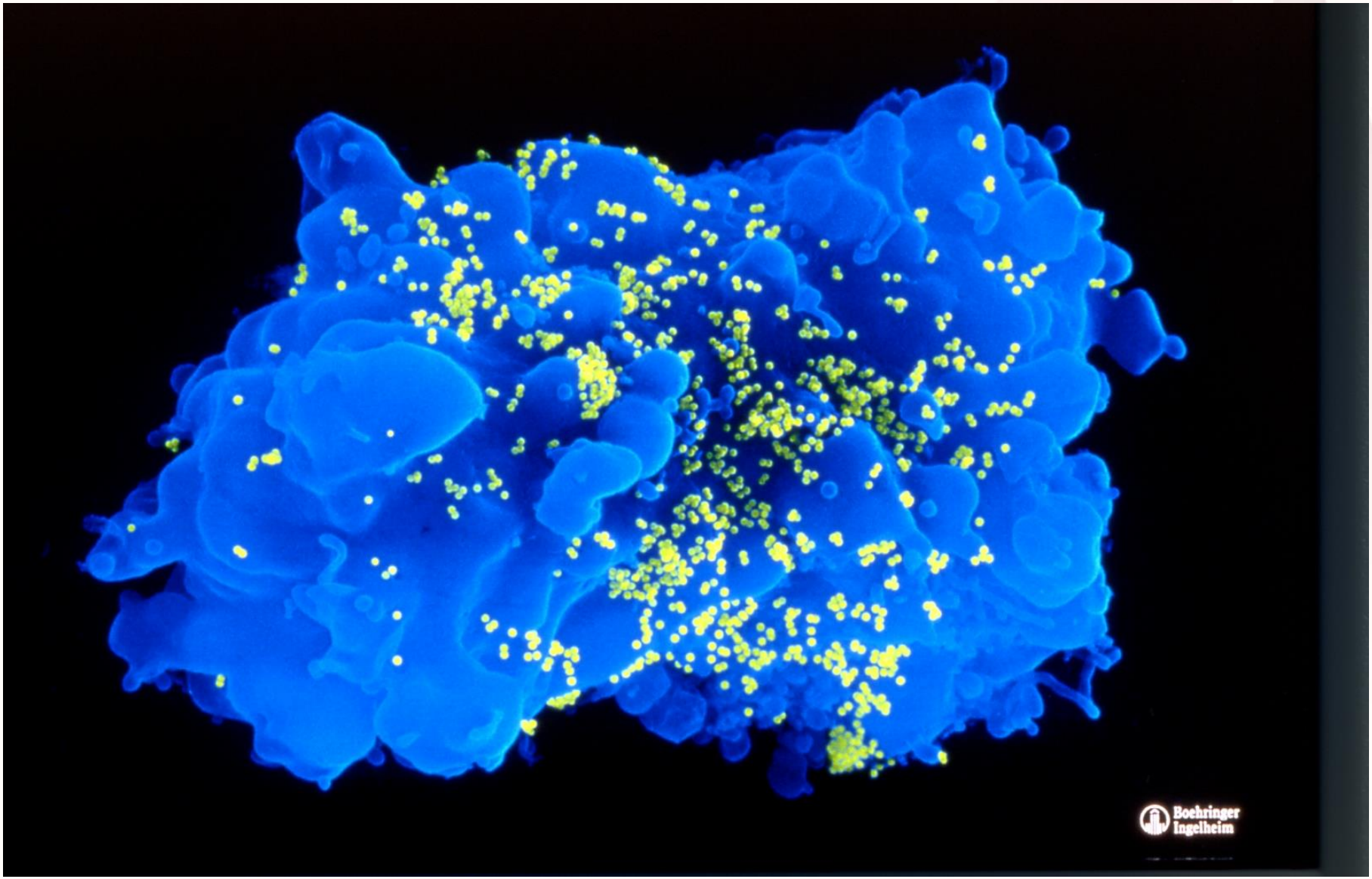
Basics of infectious disease; when to start



- Infectious disease that leads to significant illness and death
- Public health risk to others
- Target organ can be assessed for damage
- Combination therapy required with significant drug interactions and some toxicity

HIV release from infected CD4 lymphocyte



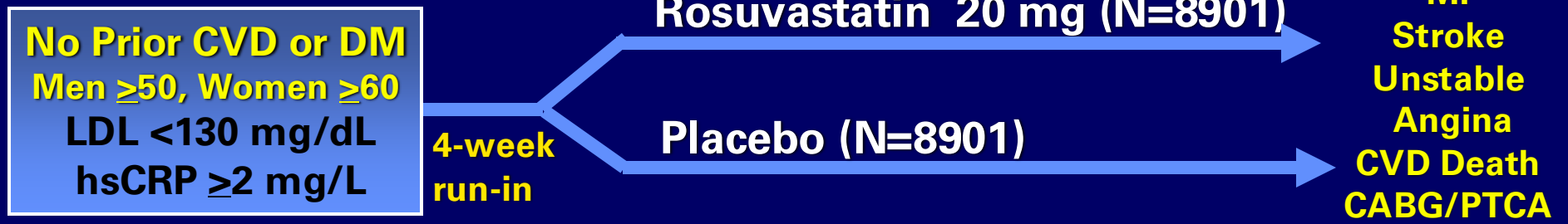
Why don’t we have good evidence of clinical benefit from early ARV?

Because we stopped doing clinical endpoint studies in 1996

JUPITER
Trial Design

JUPITER

Multi-National Randomized Double Blind Placebo Controlled Trial of Rosuvastatin in the Prevention of Cardiovascular Events Among Individuals With Low LDL and Elevated hsCRP



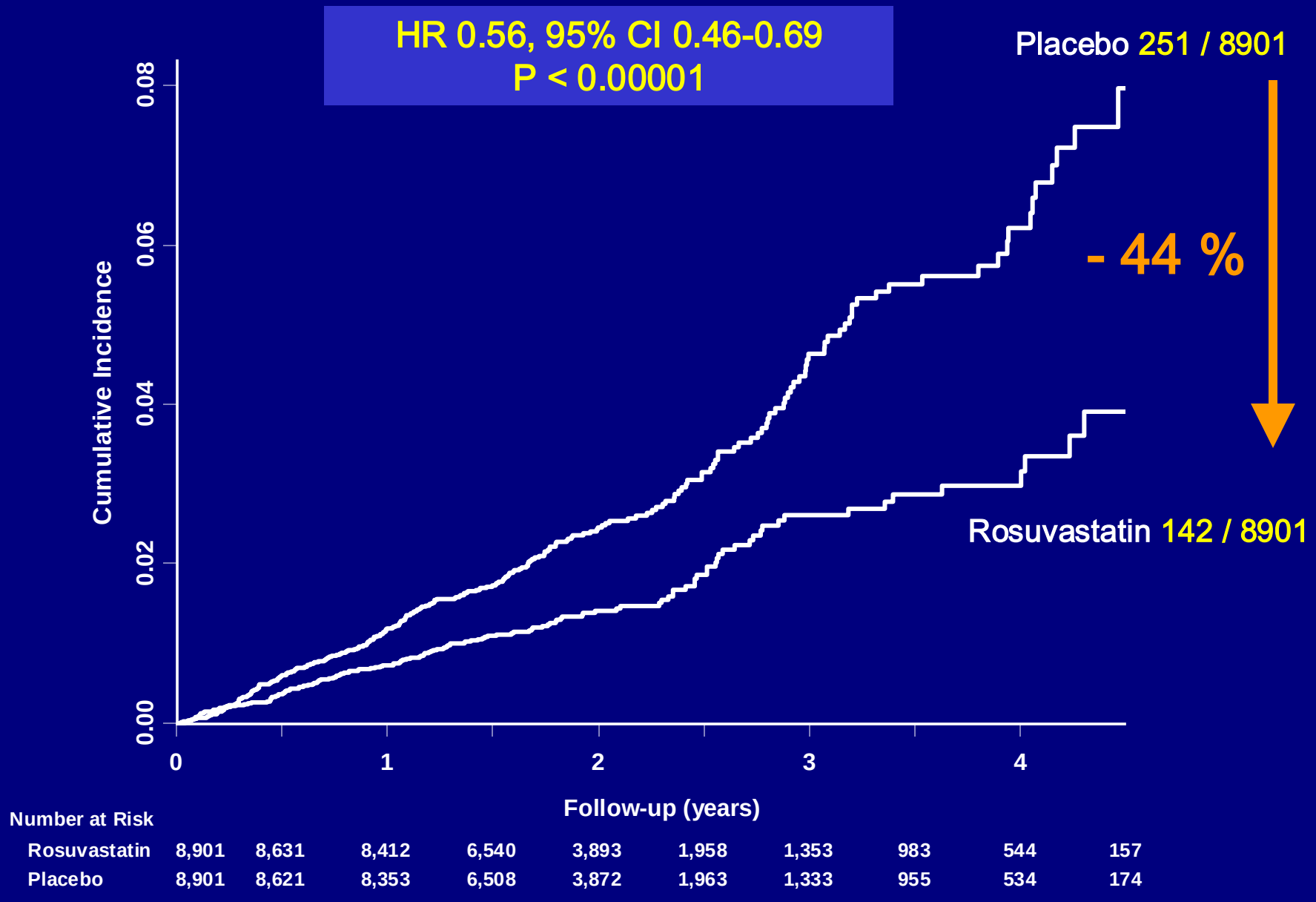
Argentina, Belgium, Brazil, Bulgaria, Canada, Chile, Colombia, Costa Rica, Denmark, El Salvador, Estonia, Germany, Israel, Mexico, Netherlands, Norway, Panama, Poland, Romania, Russia, South Africa, Switzerland, United Kingdom, Uruguay, United States, Venezuela

Ridker et al, Circulation 2003;108:2292-2297.

JUPITER

Ridker et al NEJM 2008

Primary Trial Endpoint : MI, Stroke, UA/Revascularization, CV Death



HIV clinical endpoint study: CAESAR

1840 HIV+ patients with CD4 counts 25-250,
On AZT or AZT+ddI/ddC,
Placebo controlled trial of 3TC+/- loveride

group		placebo	3TC	3TC +loveride
AIDS/death		20%	9%	9%

Outcome: 50% improvement in survival over 1 year

CAESAR Coordinating Committee. The Lancet, 349, p1413 - 1421, 1997

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ACTG 175 study; clinical endpoint study

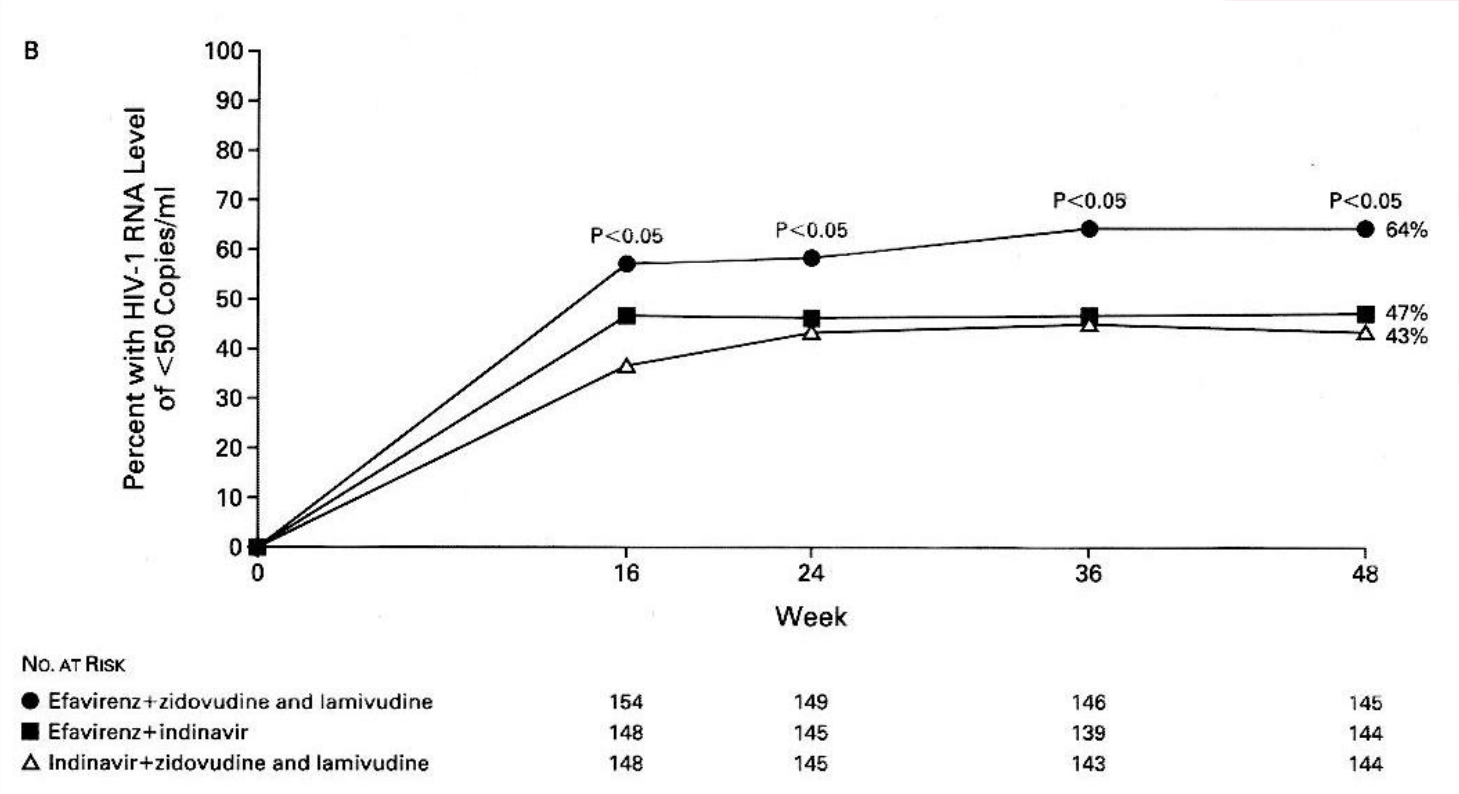
2746 HIV+ patients with CD4 counts 200-500,
Treatment naïve and AZT experienced,
Placebo controlled trial

group	AZT	ddI	AZT+ddI	AZT+ddC
AIDS/death (HR)	1 (ref)	0.69	0.64	0.77

Outcome: significant improvement in delayed clinical progression.
Conclusion: "Antiretroviral therapy can improve survival in patients with 200 to 500 CD4 cells per cubic millimeter."

Hammer SM et al. N Engl J Med. 1996 Oct 10;335(15):1081-90

Dupont 006 Study[1]



At 48 weeks, 90% of patients taking AZT + 3TC + EFZ attained viral load < 50 copies/mL compared to <80% patients in the other 2 treatment arms.

No significant differences in CD4 count changes across all groups.

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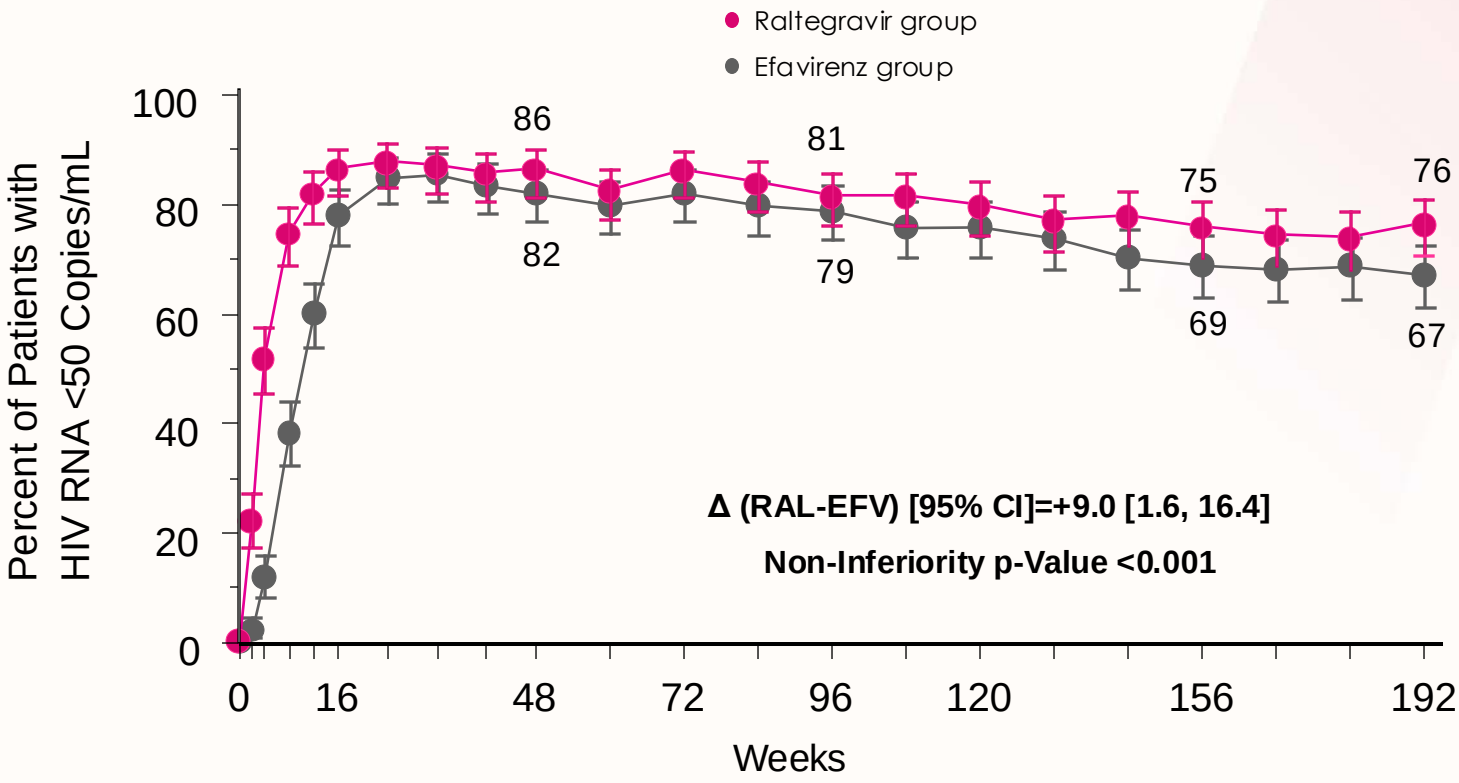
Staszewski S, et al. NEJM 1999;341(25):1863-3.

Proportion (%) of Patients (95% CI) with HIV RNA < 50 copies/mL (Non-Completer = Failure)



Number of Contributing Patients

Raltegravir group	281	281	280	281	281	277	281	281
Efavirenz group	282	281	281	282	282	281	282	282

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DeJesus et al. Presented at IDSA 49th Annual Meeting October 20-23, 2011Boston, MA. Abstract 30623, Poster H.405

Surrogate marker studies (viral load or CD4)

Good bits:

Patients don't need to die to generate results

Fewer subjects needed,

Results available faster,

Preliminary FDA approval on 48 week data.

Bad bits:

Don't collect enough clinical endpoints to achieve significant results.

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So what's the risk of treating early

Patient may not be ready to start and stuff things up,

Longer exposure to drugs; causing problems with kidneys or cholesterol or Vit D.

Better drugs might come available later

Costs money

So what's the risk of **not** treating early

Permanent damage to lymphoid organs,

Loss of some immune responses, CD4 recovery,

Accelerated aging; brain, heart, bones, kidneys, liver.

Diseases of chronic inflammation (similar risk to smoking)

But, you are not likely to get AIDS (18 AIDS cases in Australia in 2012)

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Long term survival in HIV patients on treatment

Compared mortality in AHOD cohort with Standardised Mortality Ratio (SMR), from Australian Bureau of Statistics. General population =1.

		SMR	(95% CI)
CD4	<350	8.6	(7.2-10.2)
	350-499	2.1	(1.5-2.9)
	>500	1.5	(1.1-2.0)
Viral load	<400	2.1	(1.7-2.5)
	>400	9.0	(7.5-10.9)

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Australian HIV Observational Database annual report .13;1 2013

Fine tuning ARV drugs (what to use)

What's happening over the ditch?

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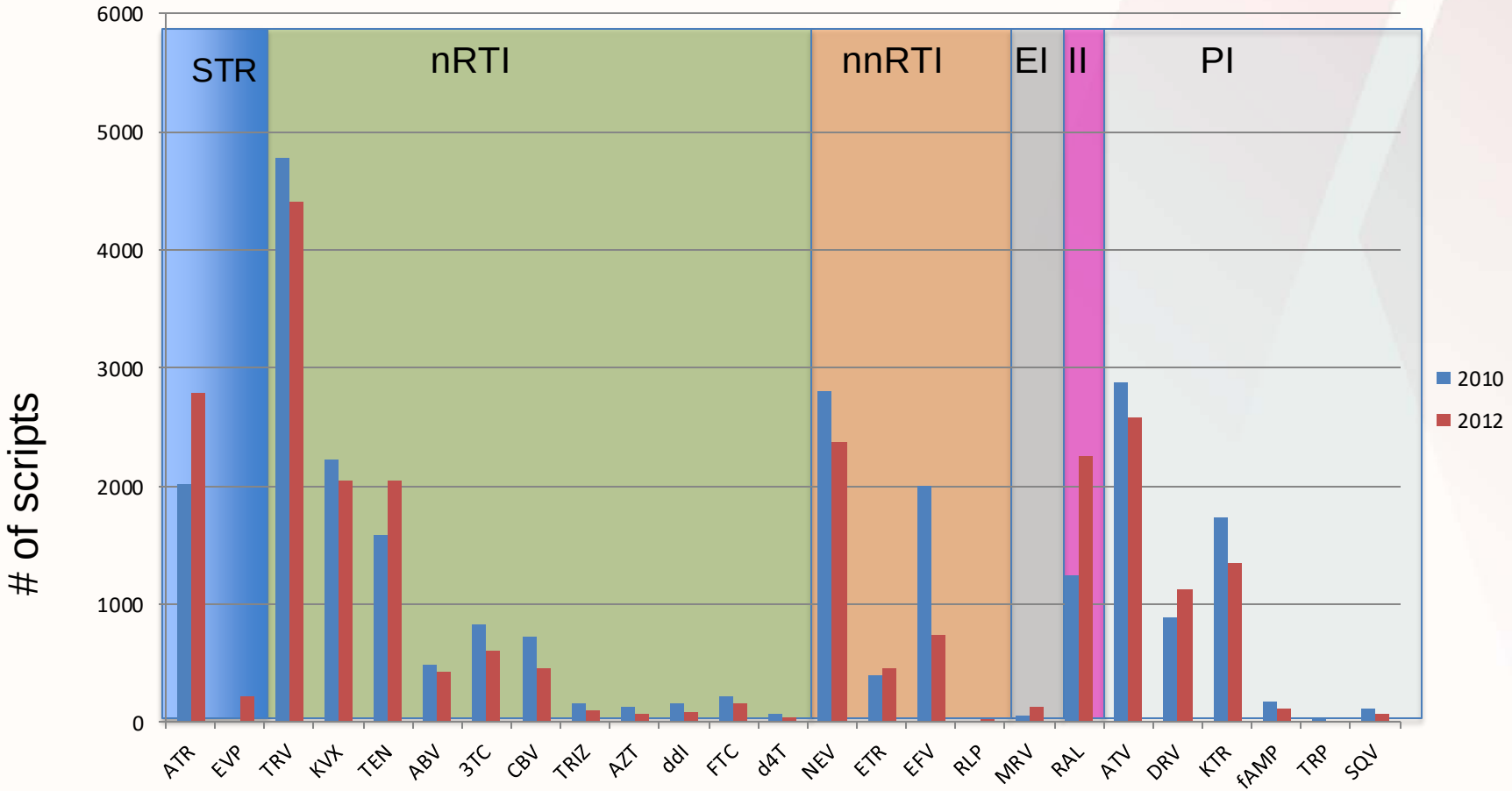
Antivirals dispensed in Australia

(12,800 patients estimated)



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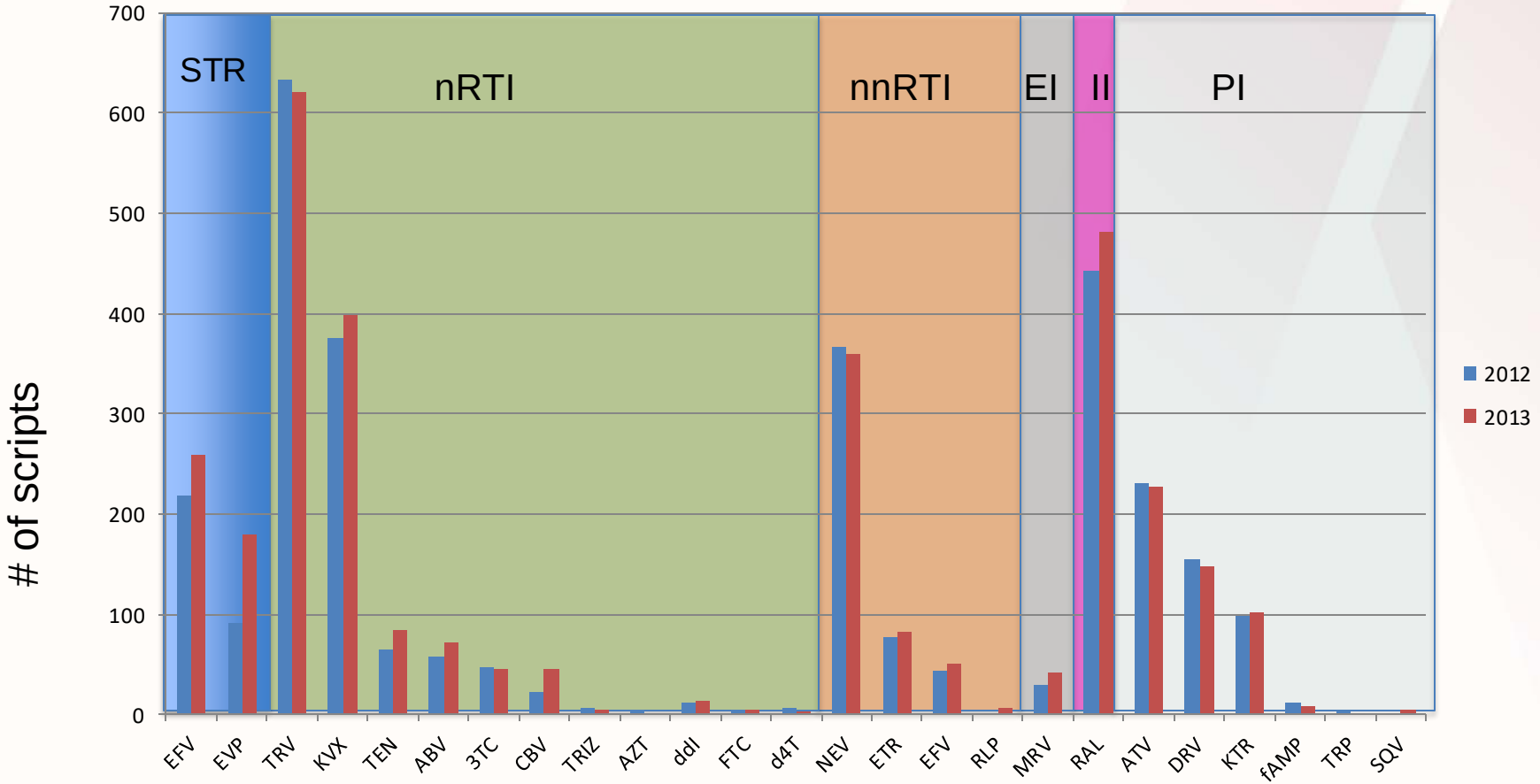
Highly specialised drugs (S100) program, $210 M

Scripts dispensed in a 2 month period

ASC pharmacy (3,791 scripts)



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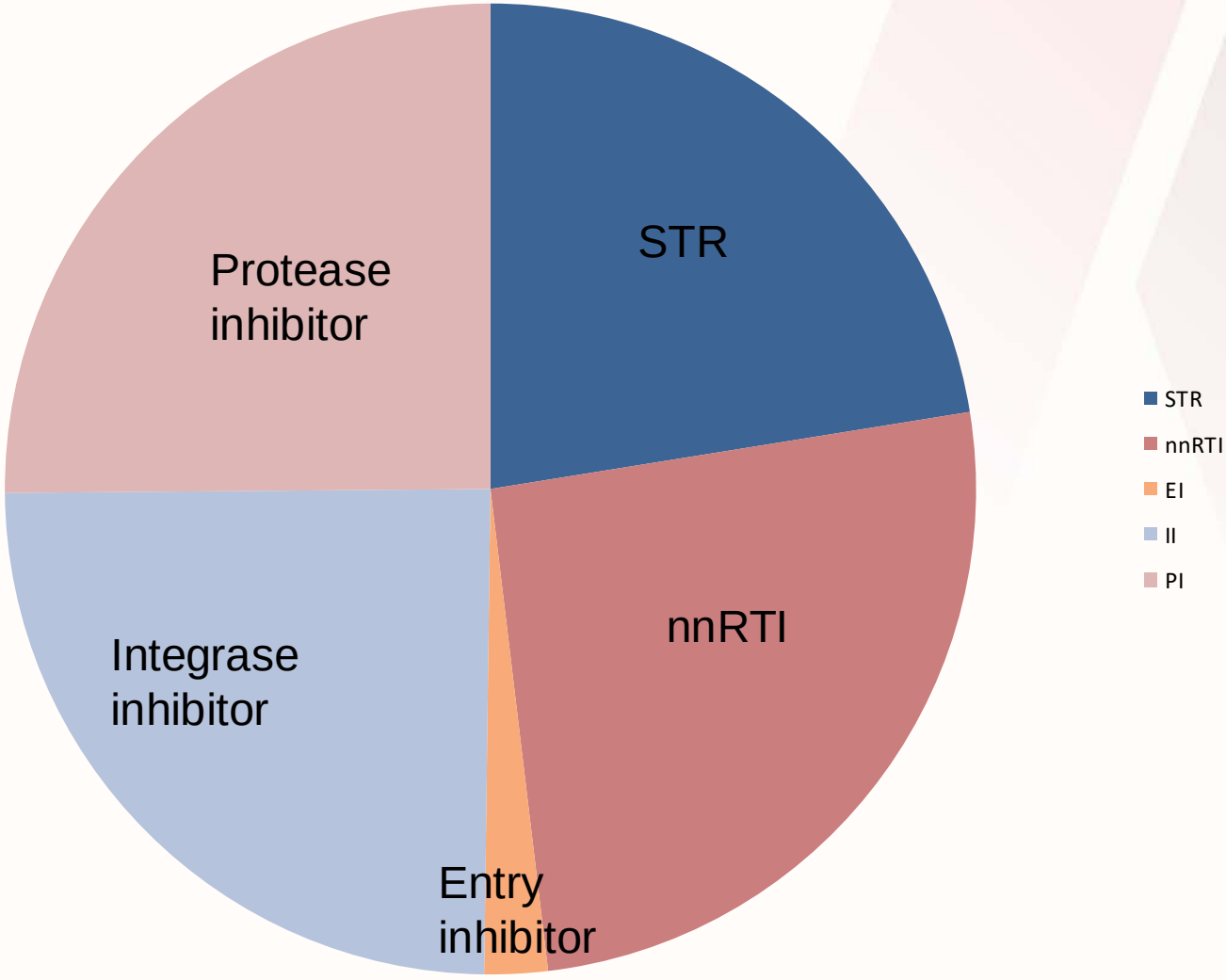
Cost 4.2 million $AU

ARV class use (ASC audit)



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Meta-analysis of Efficacy of Initial ART Regimens in Prospective Trials

- Meta-analysis of 216 treatment arms from prospective trials of initial ART, 1994-2010 (N = 40,124 pts)
- Mean rate of undetectable HIV-1 RNA: 60% overall
  - 66% at Wk 48, 60% at Wk 96, 52% at Wk 144
  - 25% discontinued before end of study
- Better mean efficacy with more recent year of initiation
  - 43% in 1994 vs 78% in 2010

Lee FJ, et al. IAS 2013. Abstract WEAB0104.

Efficacy of Initial ART Associated With NRTI Backbone, Third Drug, Other Factors

- Mean efficacy 70% vs 62% with baseline VL < vs ≥ 100,000 copies/mL
- Mean efficacy 75% vs 65% with DHHS "preferred" vs "alternative" ART
- Number of pills or doses per day did not predict overall efficacy
- Specific NRTI backbones, third drugs associated with efficacy

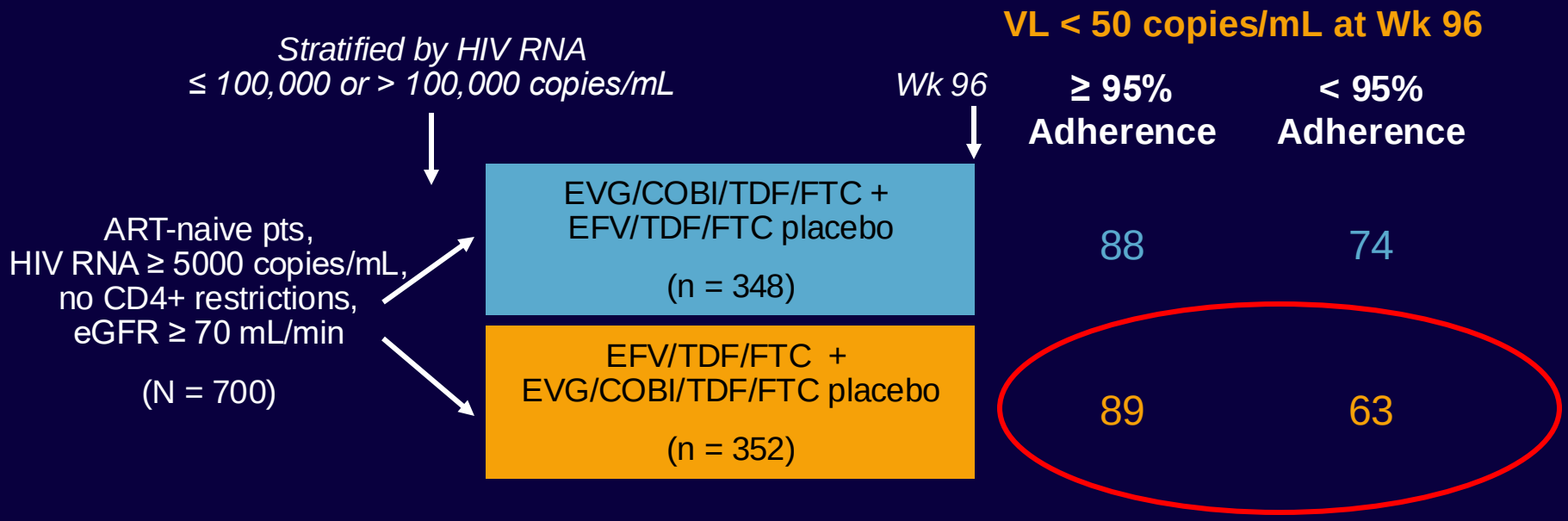
	Efficacy, % (SD)	Coefficient (95% CI)	*P* Value
NRTI backbone			
TDF/FTC	73 (10)	Ref	
ABC/3TC	63 (7)	-7.6 (-12.7 to -2.6)	.003
Third drug class			
NNRTI	61 (15)	Ref	
INSTI	84 (5)	11.9 (4.6-19.2)	.002
Boosted PI	67 (9)	-0.9 (-4.7 to 3.0)	.660

Adjusted for multivariable analysis including year of commencement, other drugs received, baseline patient characteristics, and duration of follow-up.

Lee FJ, et al. IAS 2013. Abstract WEAB0104.

Efficacy of EVG/COBI/TDF/FTC (Stribild) vs EFV/TDF/FTC when Adherence < 95%

- Preplanned adherence analysis at Wk 96 of Study GS-US-236-0102

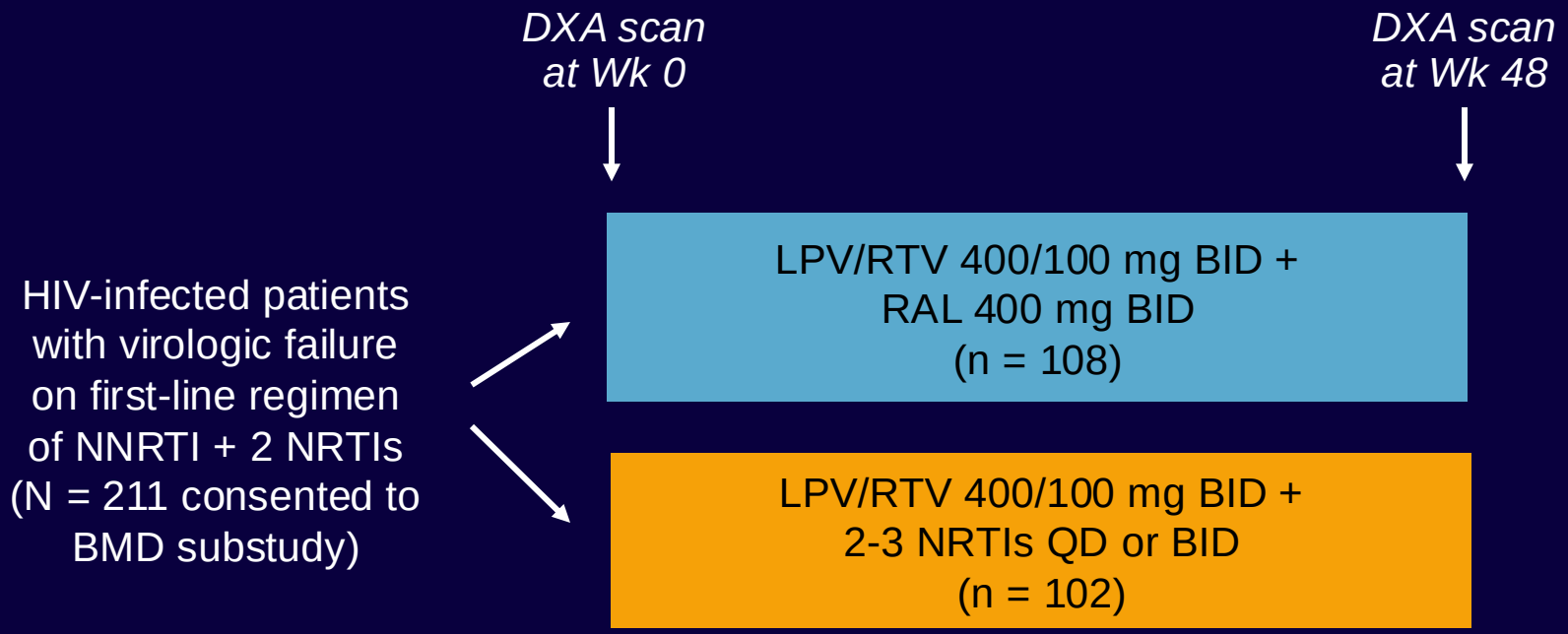


- ≥ 90% adherence in 93% with EVG/COBI/TDF/FTC, 89% with EFV/TDF/FTC
- Significantly greater improvement in CD4+ cell counts with EVG/COBI/TDF/FTC vs EFV/TDF/FTC (317 vs 245; *P* = .039)

Shalit P, et al. IAS 2013. Abstract TUPE293.

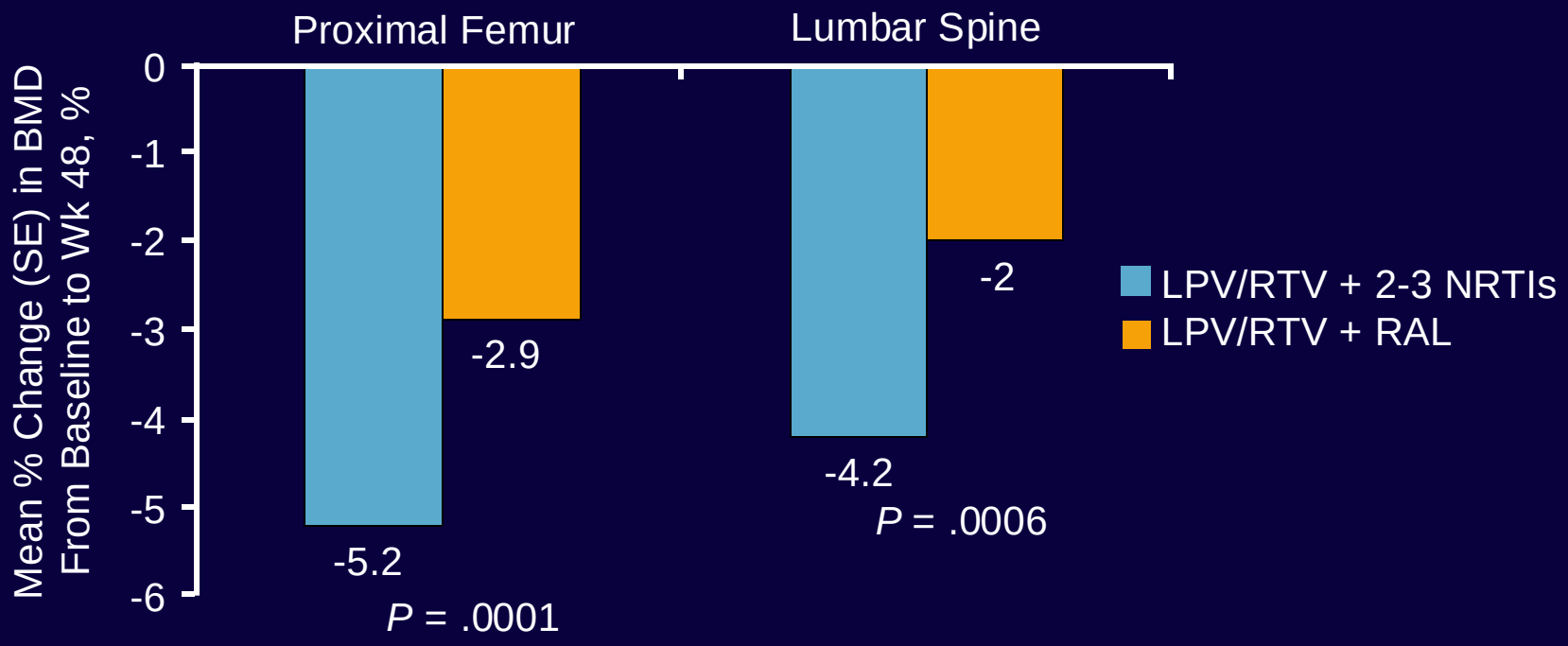
SECOND-LINE Subanalysis: BMD Loss With LPV/RTV + NRTIs vs LPV/RTV + RAL

- Subanalysis of randomized, open-label, multicenter, international trial



Martin A, et al. IAS 2013. Abstract WELBB05.

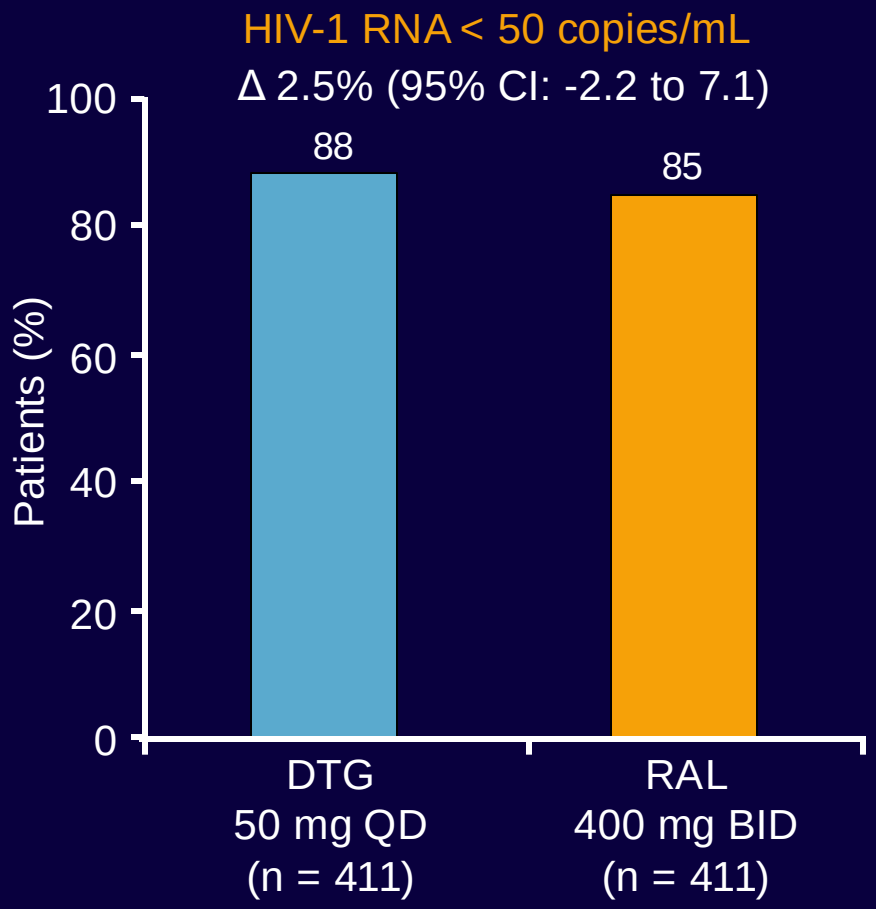
SECOND-LINE: Greater Mean BMD Loss With NRTI-Based Regimen at Wk 48

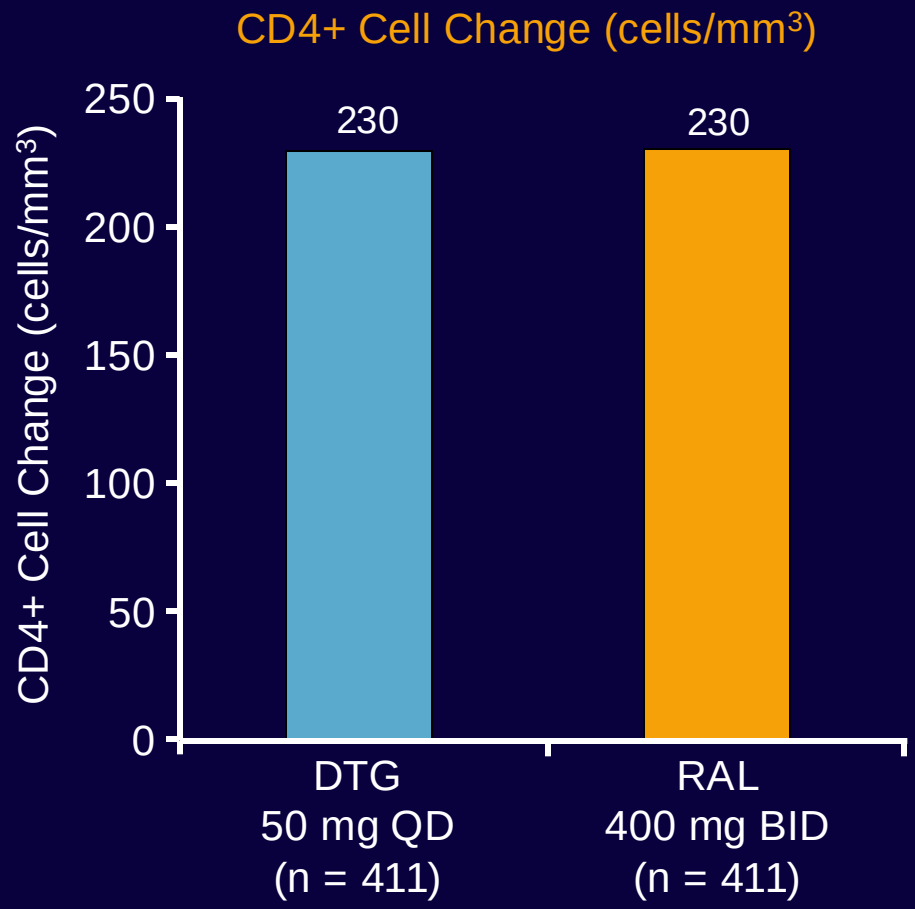


- No significant difference in frequency of new osteopenia, osteoporosis
- Greater decline in lumbar spine BMD associated with lower BMI, no TDF before study, and TDF initiation on study

Martin A, et al. IAS 2013. Abstract WELBB05.

SPRING-2: Wk 48 Analysis of TDF/FTC or ABC/3TC + DTG vs RAL



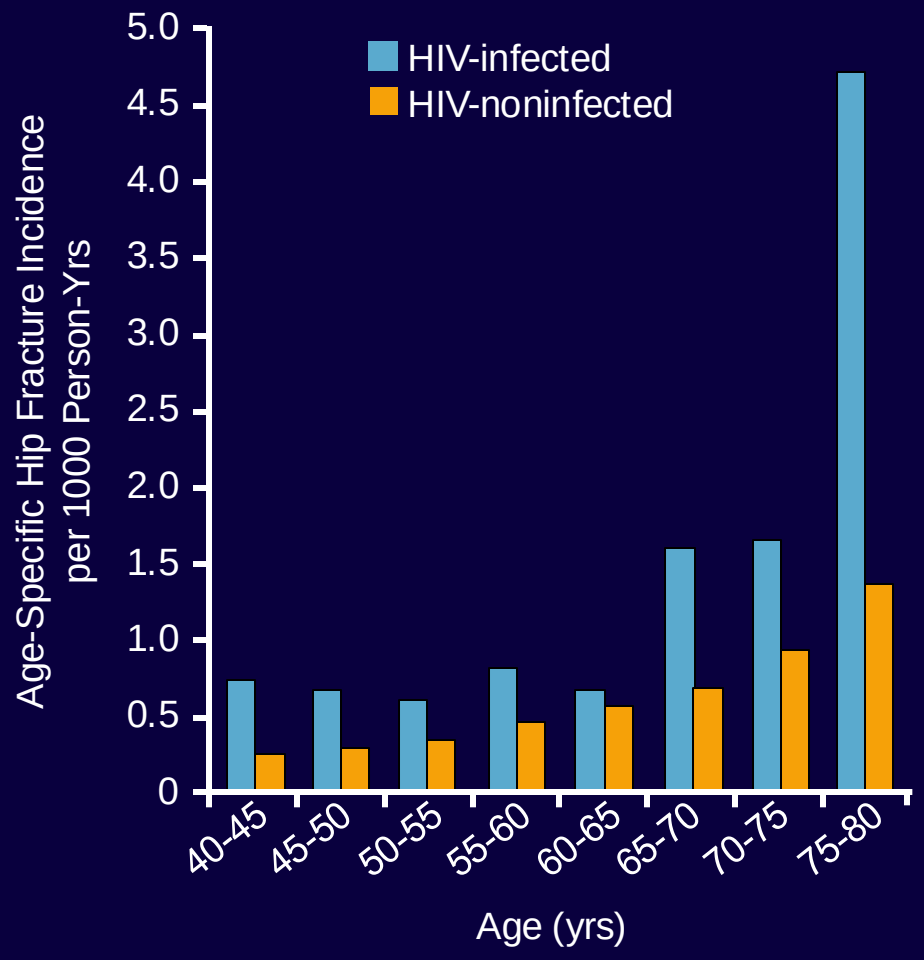


Noninferiority criteria met.

Raffi F, et al. IAC 2012. Abstract ThLBB04.

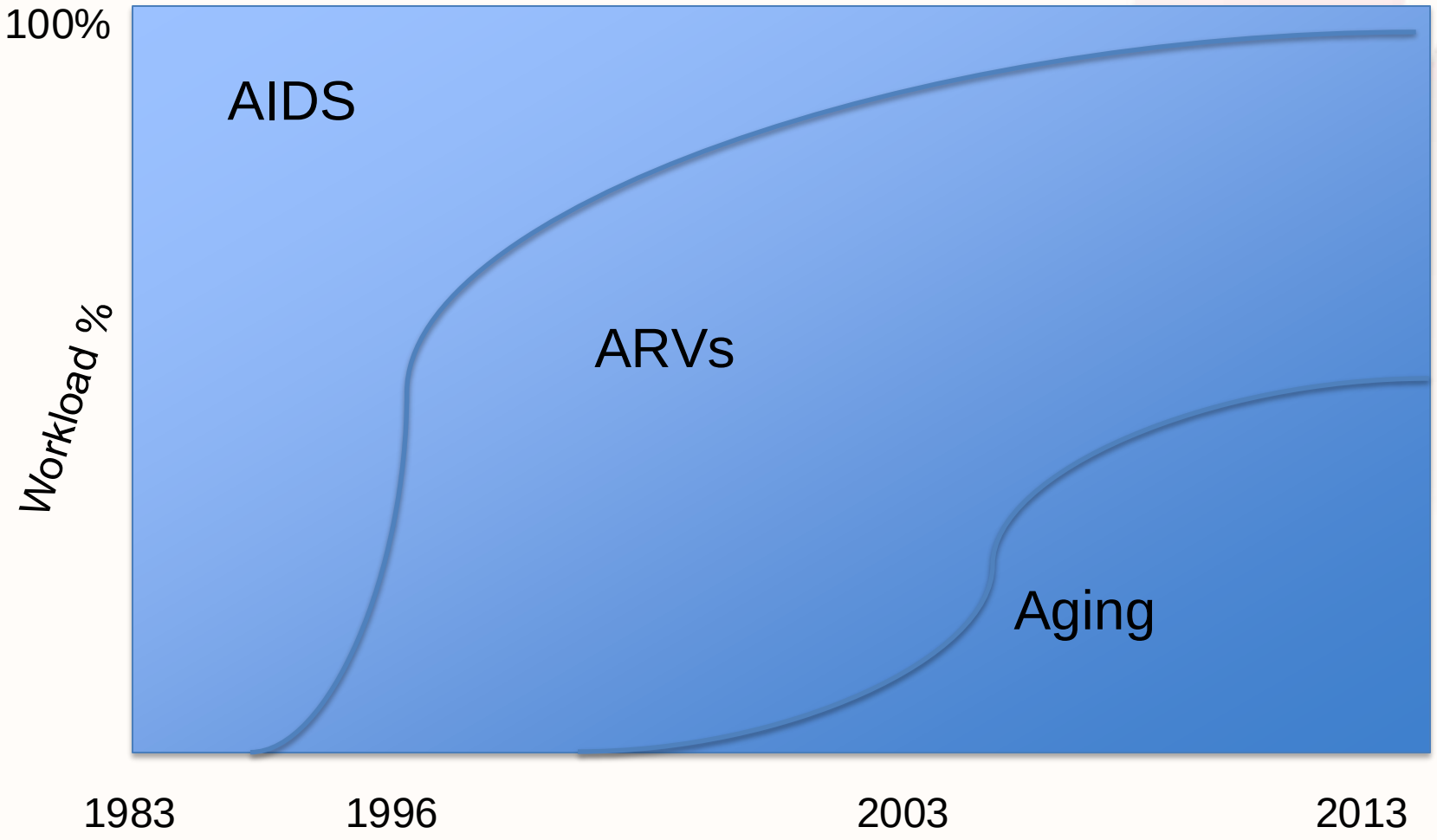
HIV Independently Associated With Increased Risk of Hip Fractures

- Population-based cohort study SIDIAP^{Q} database, 2007-2009; Catalonia, Spain (N = 1,118,587 pts aged ≥ 40 yrs)
  - HIV-infected: 2489 (0.22%)
  - Identified incident major osteoporotic and hip fractures
- HIV infection associated with
  - 4.72-fold ↑ hazard ratio for hip fracture
  - 1.75-fold ↑ hazard ratio for all fractures
  - Independent of age, sex, BMI, smoking, EtOH use



Knobel H, et al. IAS 2013. Abstract WEAB0205.

The 3 ERAs of HIV



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