BHIVA Workshop: When to Start

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Aims

- To use cases to:

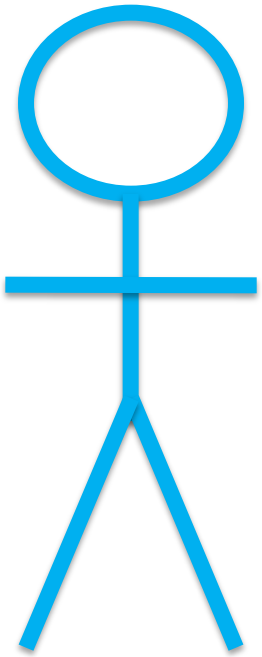
Review new BHIVA guidance

Explore current data around when to start

- To discuss:

Medical decisions, pros and cons

Luigi



Case 1: Luigi

- 27 year old Caucasian MSM
- New HIV diagnosis at annual GU check-up
- Well
- PMH, DH nil of note; NKDA
- SH:
  - Retail manager
  - 10-15 cigarettes/day, 20-30 units EtOH/week
  - Cocaine ‘now & then’

Luigi: Results

CD4	278 (18%) cells/mm ^{3}
HIV-RNA	345,000 copies/ml
HCV antibody	Negative
HBV serology	Natural immunity (sAb 125)
Other bloods/uPCR	Normal range

Keypad Question

BHIVA Guidelines 2012

- …recommend that patients with chronic infection start ART if the CD4 count is < 350 cells/ml (1A)

Luigi: Results

CD4	278 (18%) cells/mm ^{3}
HIV-RNA	345,000 copies/ml
HCV antibody	Negative
HBV serology	Natural immunity (sAb 125)
Other bloods/uPCR	Normal range
STAHRS	**INCIDENT**

What next?

- Review in 3 months
- Start antiretroviral therapy
- Recruit to trial

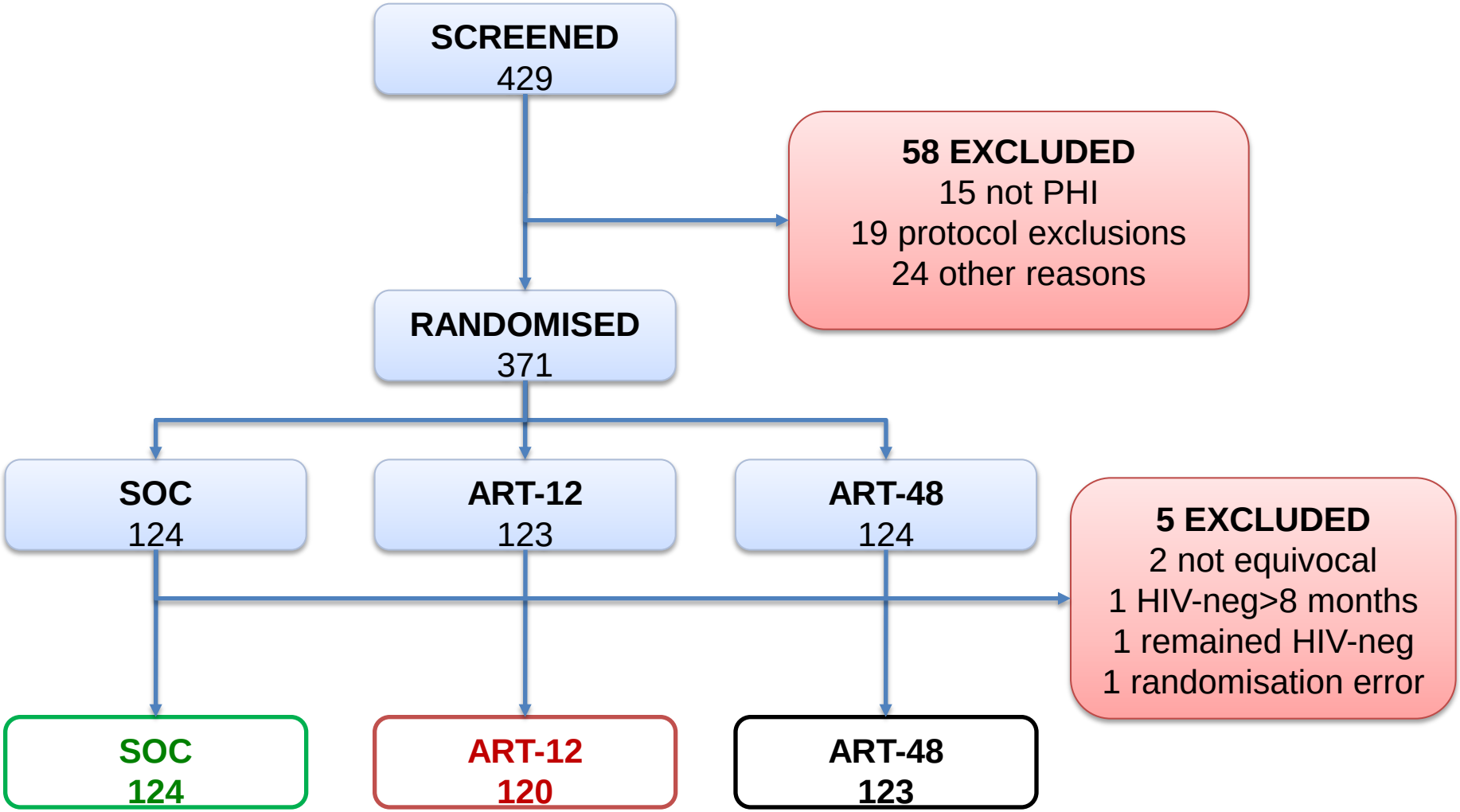
SPARTAC
Treating recent HIV infection

Trial Design

- Definition of PHI
  - laboratory evidence of infection within 6 months of a previous negative test, <3 bands WB, RITA incident, antibody negative PCR+
- Randomisation to one of three arms:
  - 48-week short course ART (ART-48)
  - 12-week short course ART (ART-12)
  - No therapy (Standard of Care SOC)
- Primary end point
  - time to CD4 <350 cells/mm^3 or long-term ART initiation
- Sample size
  - 360 providing 90% power to detect relative reduction in risk of time to CD4 <350 cells/mm^3 of 50% and 25% in ART-48 and ART-12 compared to SOC respectively over an average follow-up of 4 years

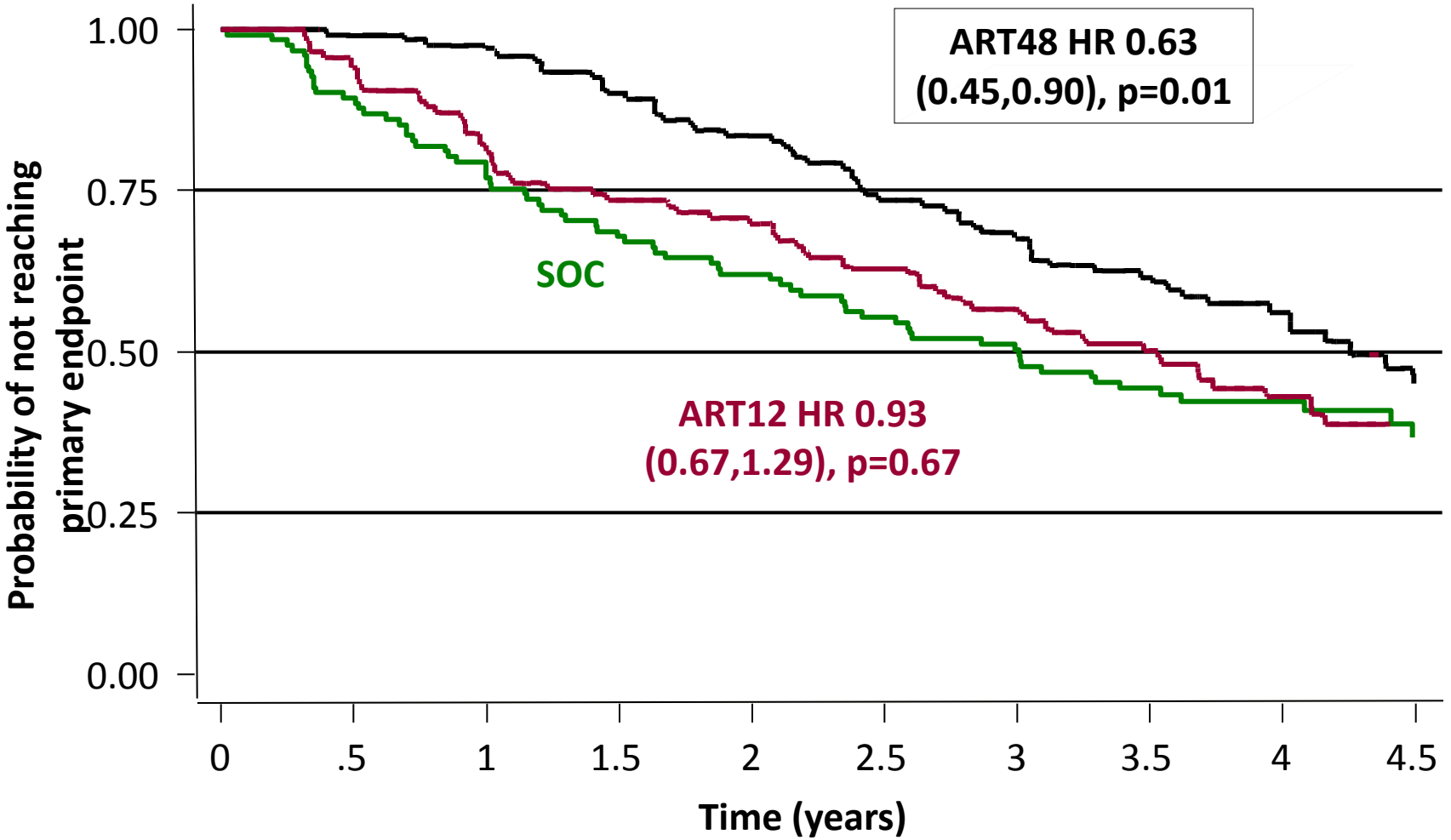
SPARTAC
Treating recent HIV infection

Enrolment & Exclusions



SPARTAC
Treating recent HIV infection

Time to primary endpoint



SOC	123	109	93	82	75	66	59	46	30	18
ART-12	120	110	95	84	79	71	63	49	32	21
ART-48	123	121	117	109	100	88	80	63	41	19

SPARTAC
Treating recent HIV infection

Time to primary endpoint

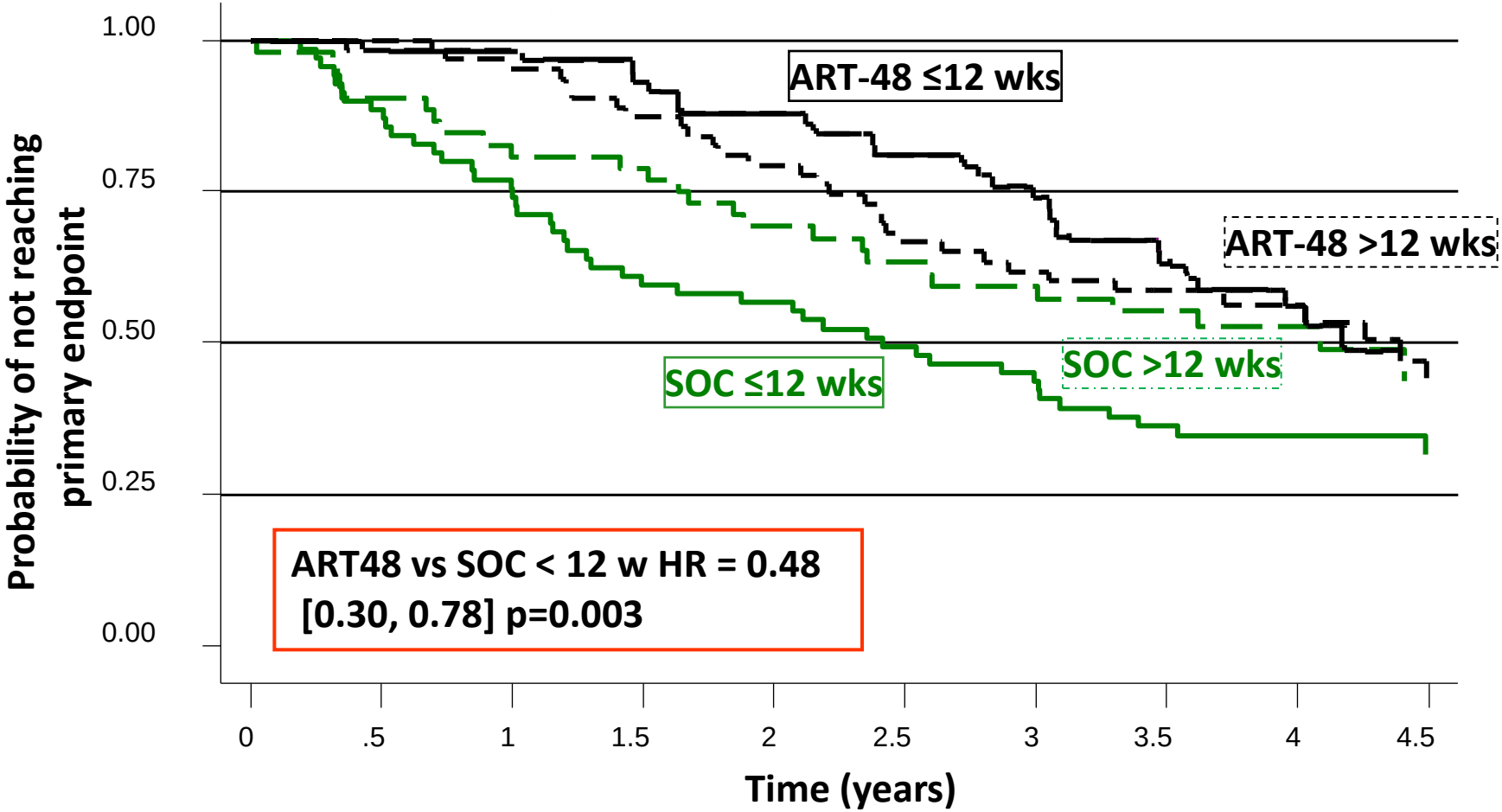
Time to primary endpoint	SOC	ART12	ART48
Median, weeks (95% CI)	157 (114,213)	184 (140,214)	222 (189,270)
Difference vs. SOC	-	27 (-25,79)	**65 (17,114)**
Difference vs. ART12	-	-	38 (-3,79)

	Hazard ratio	95% CI	p
ART12 vs. SOC	0.93	0.67 - 1.29	0.67
ART48 vs. SOC	0.63	0.45 - 0.90	0.01
ART48 vs. ART12	0.68	0.48 - 0.96	0.03

Keypad Question

SPARTAC
Treating recent HIV infection

Duration of infection and time to Primary Endpoint



SOC >12 wks	53	47	42	41	36	32	29	24	14	8
SOC ≤12 wks	70	62	51	41	39	34	30	22	16	10
ART-48 >12 wks	64	63	60	55	50	42	38	32	20	11
ART-48 ≤12 wks	59	58	57	54	50	46	42	31	21	8

Luigi

- What if he presented with seroconversion meningitis?

Keypad Question

BHIVA Guidelines 2008

- …treatment in primary infection (outside a prospective study) should only be routinely considered in those with:
  - Neurological involvement
  - Any AIDS-defining illness
  - A CD4 cell count persistently <200 (i.e. for ≥3M)

BHIVA Guidelines 2012

- We recommend patients presenting with primary HIV infection and meeting any one of the following criteria start ART:
  - Neurological involvement [1D]
  - Any AIDS-defining illness [1A]
  - Confirmed CD4 cell count <350 cells/µL (1C]

BHIVA Guidelines 2012

- We recommend patients presenting with primary HIV infection and presenting any one of the following
  - Neu
  - Any
  - Conf 1C]

This means START & CONTINUE. Although SPARTAC did not continue ART, based on SMART, ART should not be interrupted

Luigi: 3 months later

CD4	500 (38%) cells/mm ^{3}
HIV-RNA	121,000 copies/ml
HCV antibody	Negative
ALT	471
Other bloods/uPCR	Normal range

Luigi: Results

CD4	500 (18%) cells/mm ^{3}
HIV-RNA	345,000 copies/ml
HCV antibody	Negative
ALT	471
Other bloods/uPCR	Normal range
HCV-RNA	**5,752,100 IU/l**
Syphilis serology	Negative

Keypad Question

Acute hepatitis C in HIV-infected individuals: recommendations from the European AIDS Treatment Network (NEAT) consensus conference

The European AIDS Treatment Network (NEAT) Acute Hepatitis C Infection Consensus Panel

AIDS 2011, **25**:399–409

European Consensus Recommendations

1. HCV-RNA levels should be measured at initial presentation and 4 weeks later (BII)
2. Treatment should be offered to:
   a) Individuals without a 2 $\log_{10}$ reduction at week 4 compared with baseline
   b) Persistent serum HCV-RNA 12 weeks after diagnosis of acute HCV

4 weeks later

ALT	85
HCV-RNA	**9987 IU/l**
Syphilis serology	Negative

12 weeks later

ALT	52
HCV-RNA	**<30 IU/l**
Syphilis serology	Negative

What if…..12 weeks later??

ALT	52
HCV-RNA	**2,700,298 IU/l**
CD4	540 (29%)

Keypad Question

BHIVA: When to Start 2012

- *"We recommend patients with HIV and hepatitis C virus co-infection and CD4 count between 350-500 cells/µL start ART:*
  - *i) immediately if HCV treatment is deferred,*
  - *ii) after initiation of HCV treatment if this is starting immediately. (1C)"*

EACS v6: When to start

	CURRENT CD4	
	350-500	>500
HCV for which anti-HCV treatment is being considered or given	**R**	**D**
HCV for which anti-HCV treatment not feasible	**R**	**C**

R = Recommend
C = Consider
D = Defer

Luigi: 3 months later

- Well
- New RMP who is HIV-negative
- Wants to discuss transmission…….and wants to start ART
- What do you say?

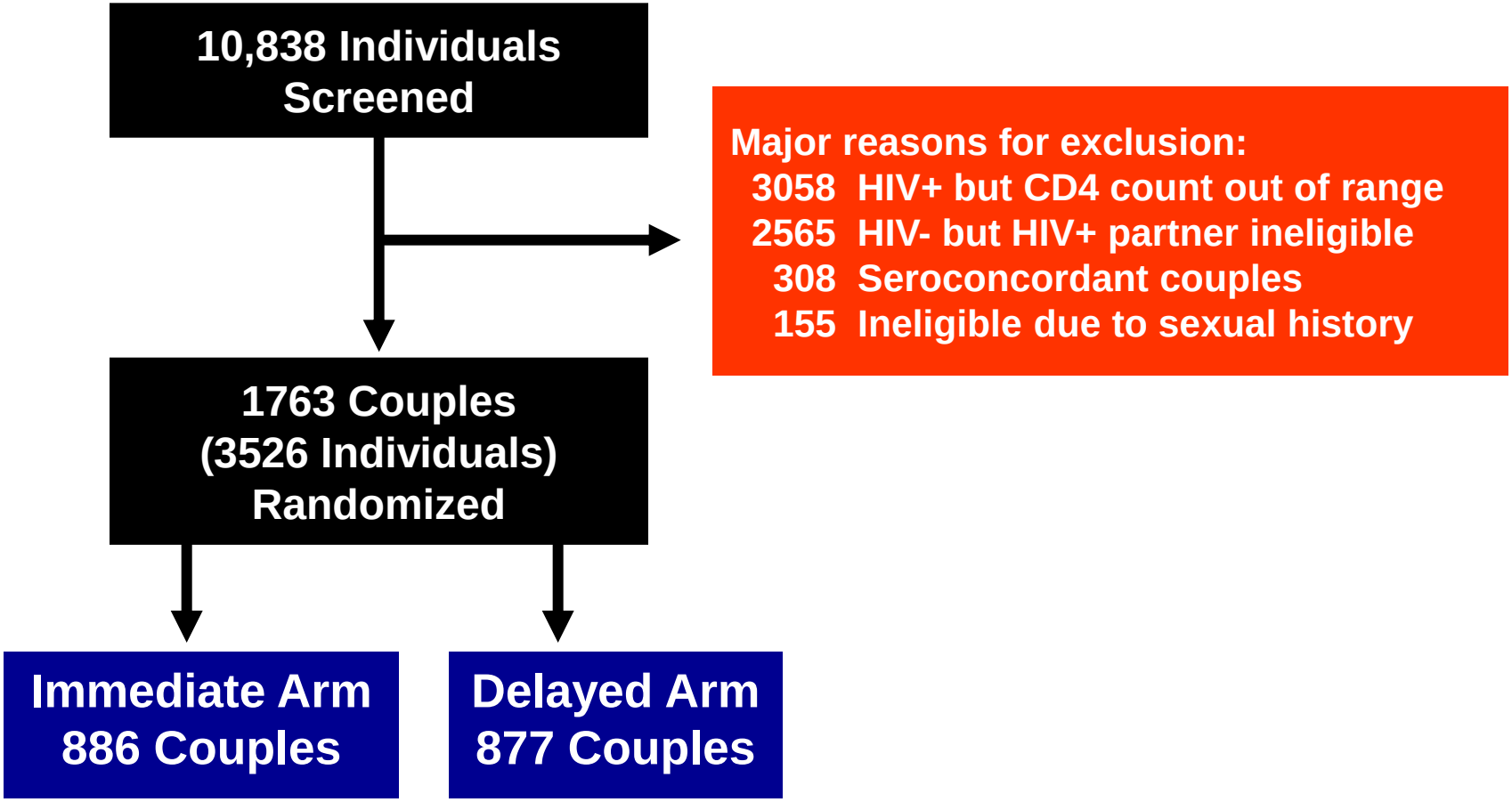
Keypad Question

BHIVA

"We recommend t
that treatment w
the risk of transm
discussed with a
assessment of th
transmission to
the time of this

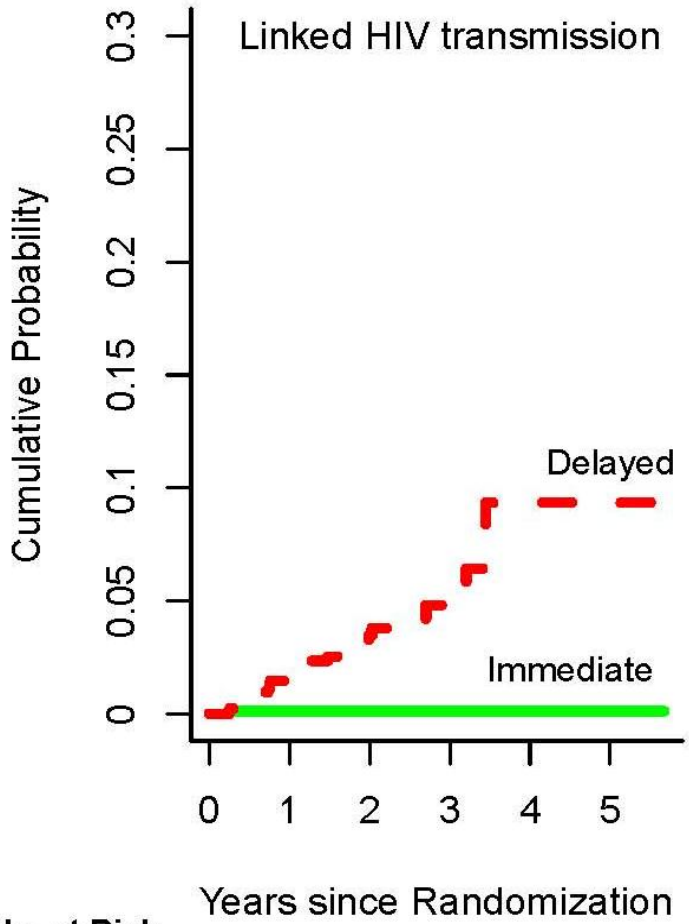
"We recommend following discussion, if a patient with a CD4 count above 350 cell/µL wishes to start ART to reduce the risk of transmission to partners, this decision is respected and ART is started. (GPP)"

HPTN 052

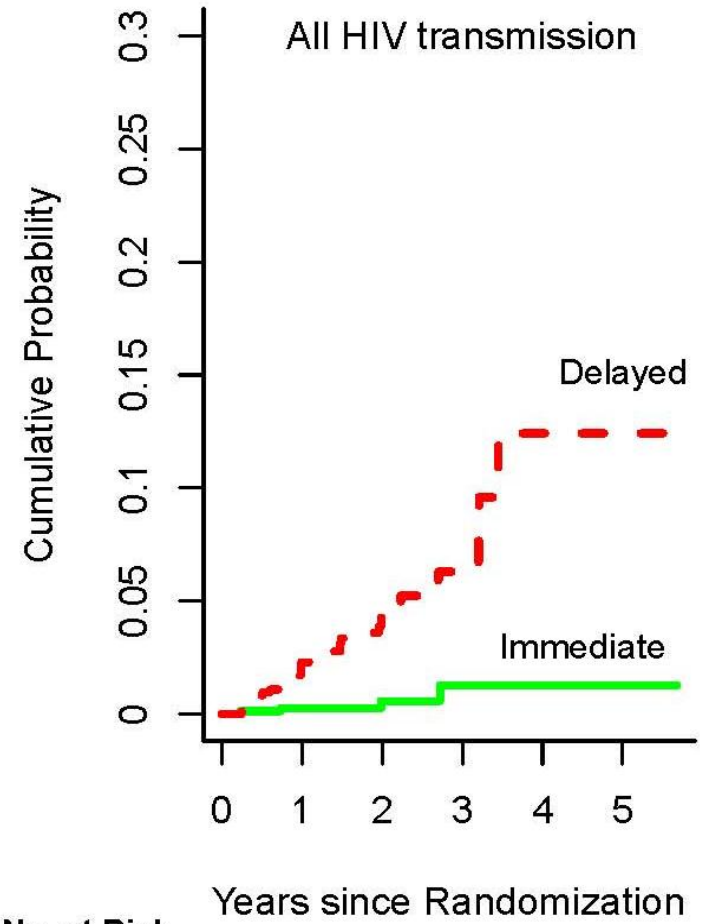


Cohen M. 6th IAS Rome 2011

HPTN 052



No. at Risk						
Immediate	893	658	298	79	31	24
Delayed	882	655	297	80	26	22



No. at Risk						
Immediate	893	658	298	79	31	24
Delayed	882	655	297	80	26	22

Cohen M. 6th IAS Rome 2011

What about anal sex?

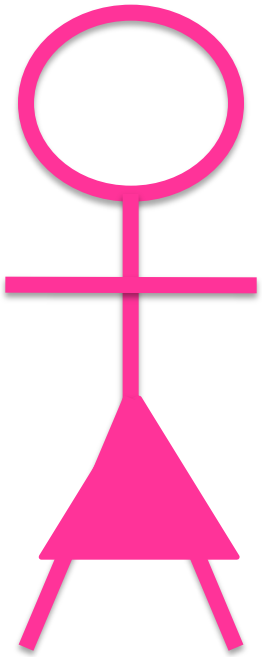
- HPTN052
  - Included only 37 MSM couples **<u>but</u>**
  - Heterosexuals have anal sex too:
    - US 16-20% recent [1,2] 35% lifetime [3]
      - 16% 15-21 year olds last 3 months[2]
    - 10% of women and 14% men in South African survey of >4500 individuals [4]
- Case report of MSM transmission in setting of undetectable VL [5]

[1] Khawcharoenporn T et al. ICAAC 2011 #H1-1148 [2] Lescano et al. Am J Public Health 2008 [3] Mosher et al. Adv data 2005.
[4] Kalichman SC et al. STI 2009 [5] Stumer at al. Antivir Ther 2008.

Luigi: 1 month later

- Luigi and his partner have both attended for gonorrhoea treatment
- Decision made to commence ART

Agnes



Agnes

- 58 year old Caribbean woman
- Diagnosed by GP March 2011
- Hypertensive, impaired glucose tolerance
- DH:
  - Amlodipine 10mg daily
- SH
  - Divorced, not sexually active currently
  - Non-smoker, minimal EtOH

Agnes: Results

CD4	440 (28%) cells/mm ^{3}
HIV-RNA	7,420 copies/ml
HCV antibody	Negative
HBV serology	Vaccinated (sAb 125)
Creatinine/eGFR	132/55
Other bloods/uPCR	Normal range

Agnes: Results

Total-chol	6.9
HDL-chol	1.2
Triglycerides	4
Blood pressure	150/98
JBS-2 CV risk	**23%**

Keypad Question

BHIVA 2008

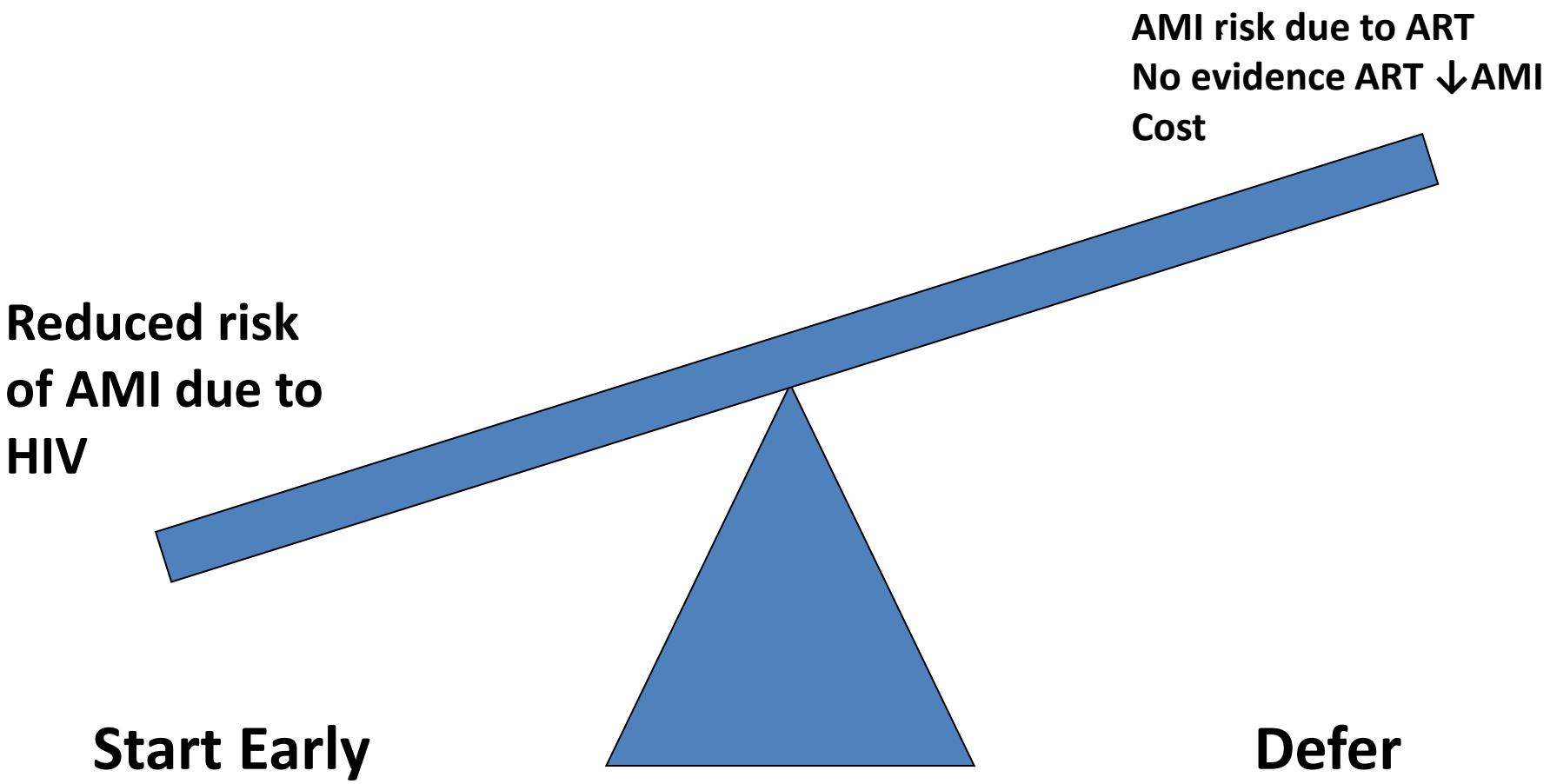
"..treatment may be started or considered before the CD4 count is below 350 cells/mL……. established CVD or a very high risk of cardiovascular events (e.g. Framingham risk of CVD >20% over 10 years)."

BHIVA 2012

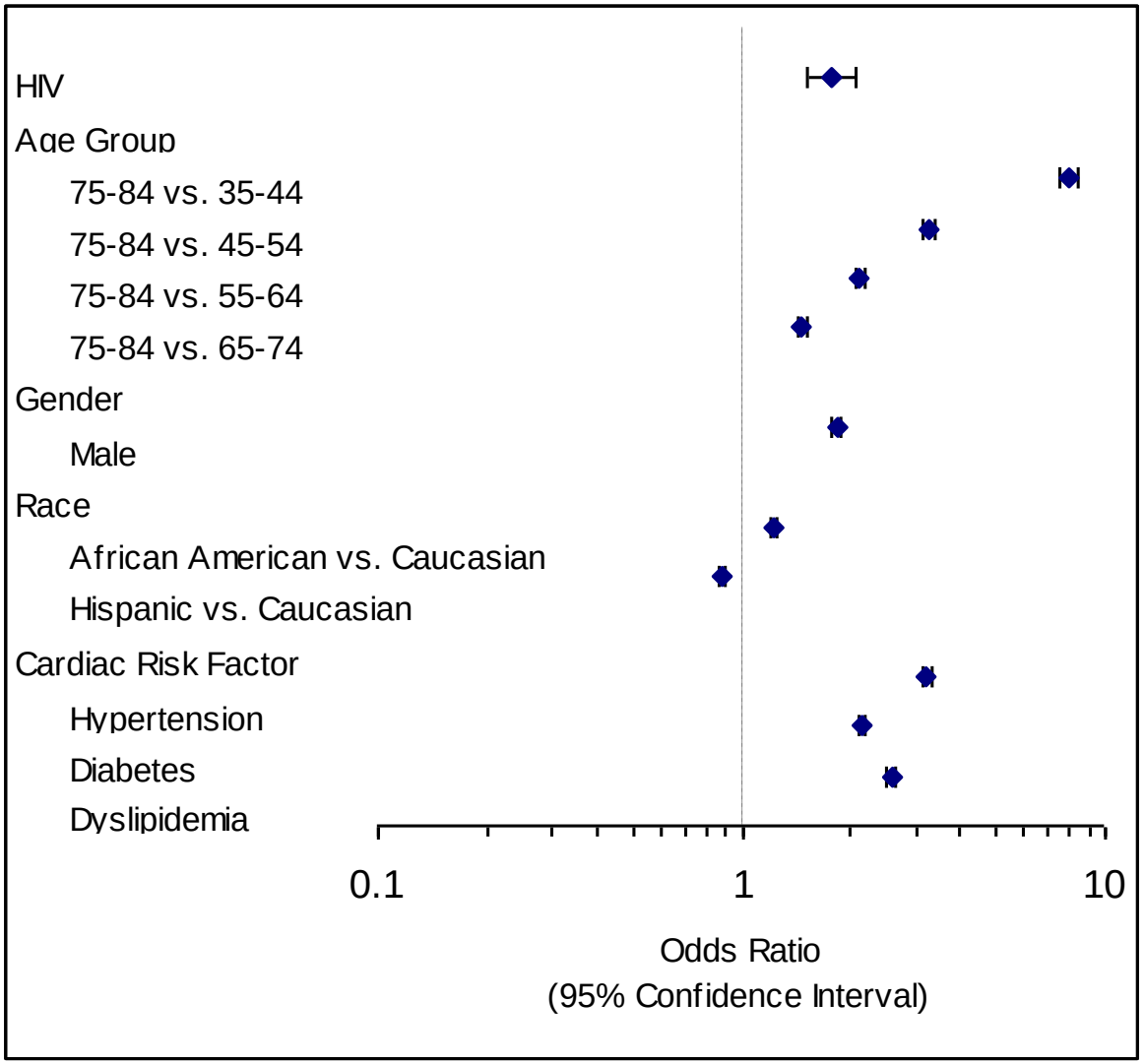
"..treatment may b
considered befo
below 350 cells/
established CVD
of cardiovascula
Framingham risi
over 10 years)."

"There are insufficient data to inform whether CVD risk should affect the decision to start ART"

Balance **in favour** of treating early for CVD Risk

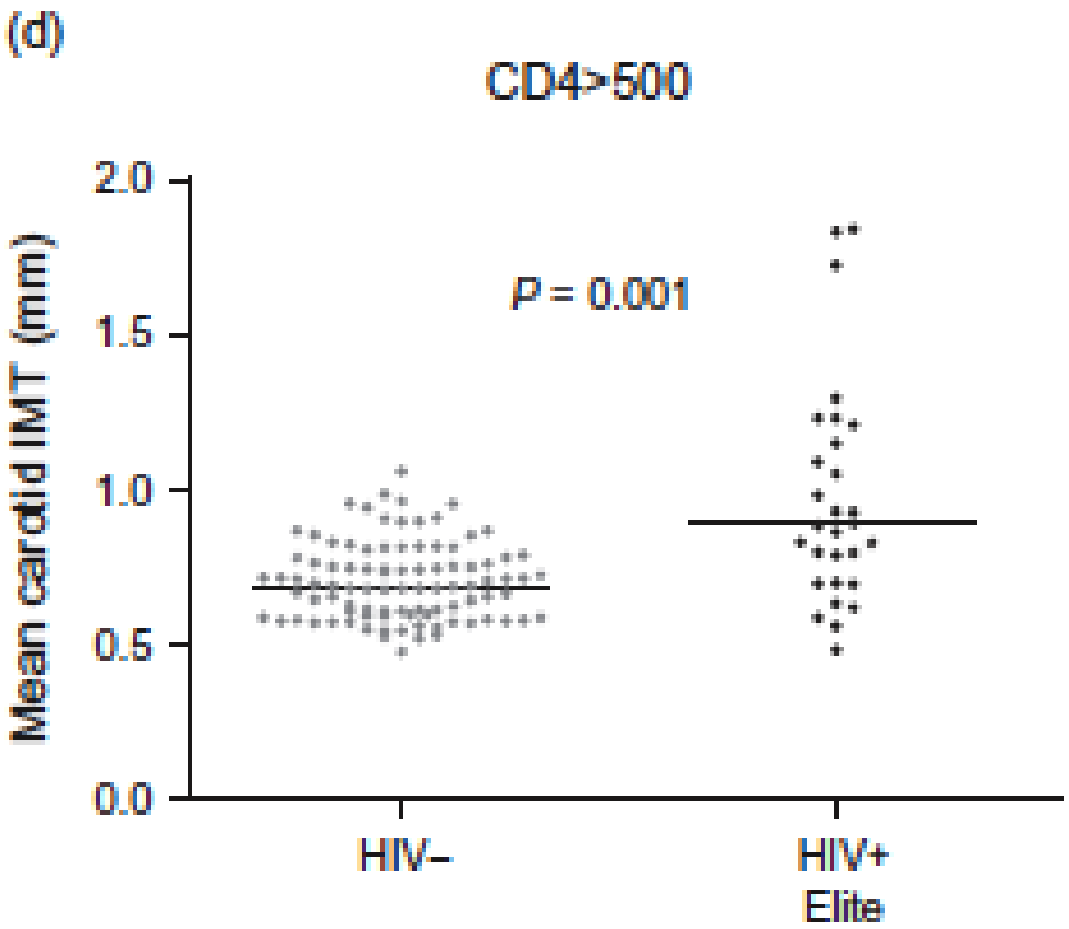


HIV Confers AMI Risk Comparable to Traditional CVD Risk Factors



Adapted from Triant V, et al. J Clin Endocrinol Metabol 2007:92(7)2506-12.

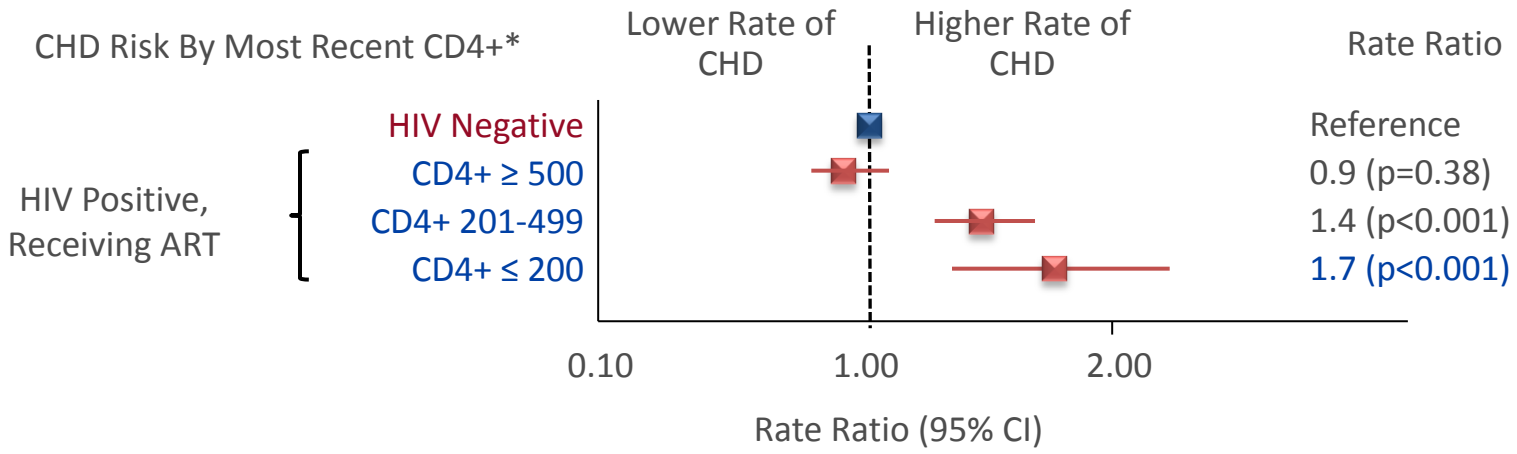
Carotid IMT is Increased in HIV Elite Controllers



Hsue AIDS 2009

CD4+ cell count and CHD risk in HIV-infected patients

- Cohort study of 20,775 patients HIV+ matched to 215,158 patients HIV- Kaiser Permanente members for age, sex and center (1996–2008)
- Overall, increased risk of CHD: 1.2 ($P < 0.001$), MI: 1.4 ($P < 0.001$) in HIV+ vs HIV-

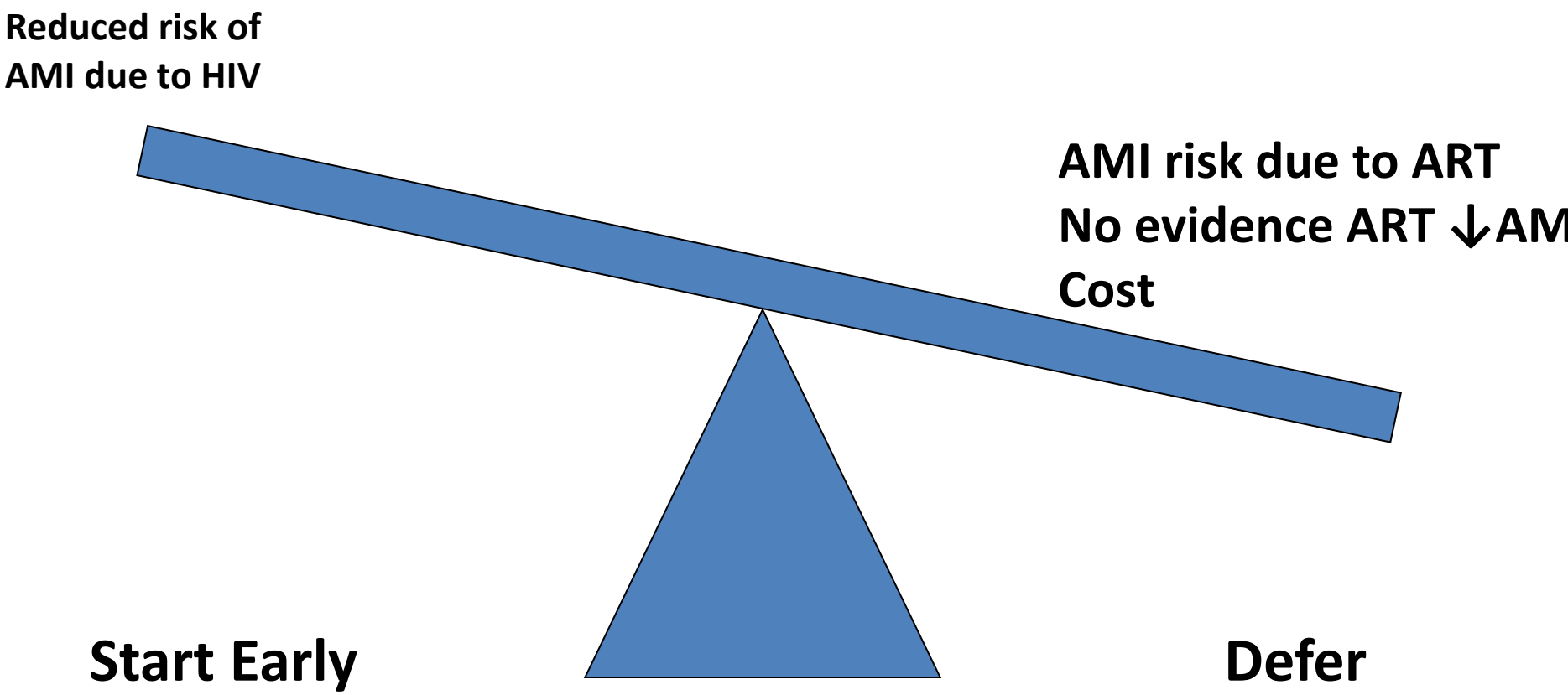


- Increased risk of CHD in HIV+ patients with lowest recorded CD4+ < 200 cells/mm^3

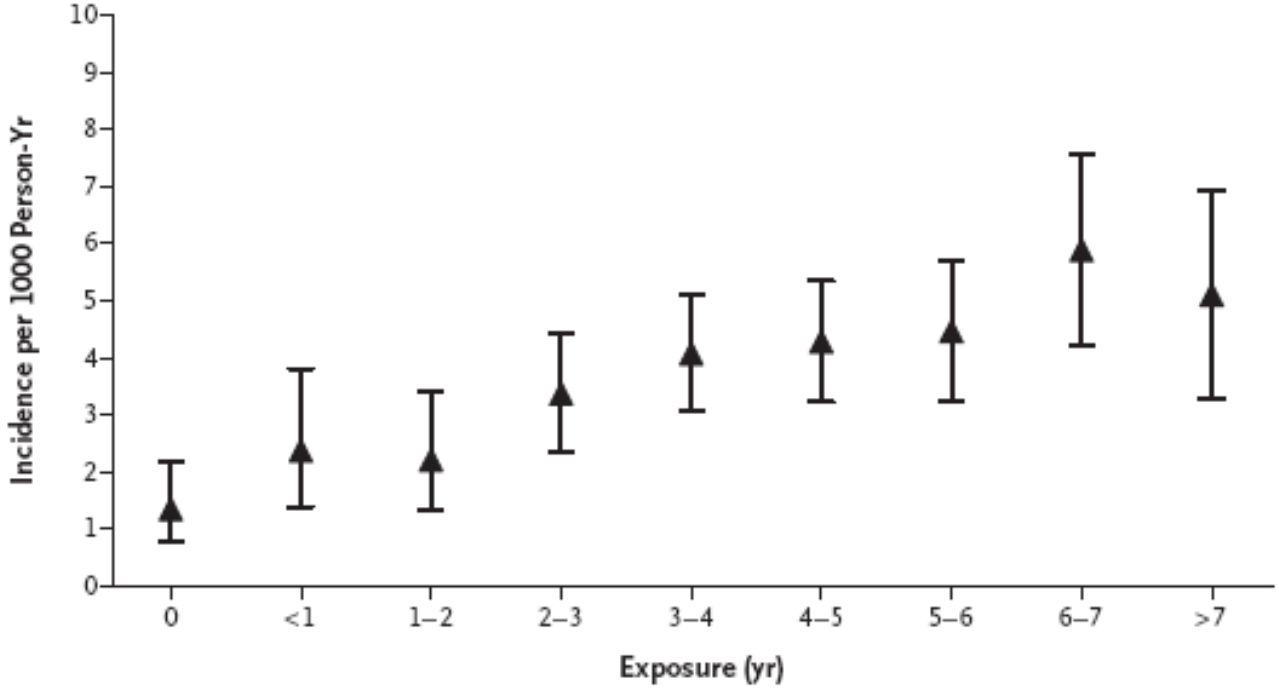
*Adjusted for age, race, sex, tobacco use, alcohol/drug abuse, obesity, diabetes, and use of lipid-lowering and antihypertensive therapy.
The following factors were time varying in the analysis: ART, CD4+ count, age, diabetes, lipid-lowering therapy, antihypertensive therapy, remaining factors were fixed variables.

Klein D, et al. 18th CROI; 2011 Feb 27-Mar 2; Boston, MA, USA: Poster 810.

Balance **against** treating early for CVD Risk



D.A.D



	0	<1	1–2	2–3	3–4	4–5	5–6	6–7	>7	Total
No. of Events	16	17	20	41	61	62	51	47	30	345
No. of Person-Yr	11,815	7105	9027	12,098	14,892	14,394	11,351	7935	5853	94,469

Figure 1. Risk of Myocardial Infarction According to Exposure to Combination Antiretroviral Therapy.

Friis-Moller et al. NEJM 2007.

D.A.D

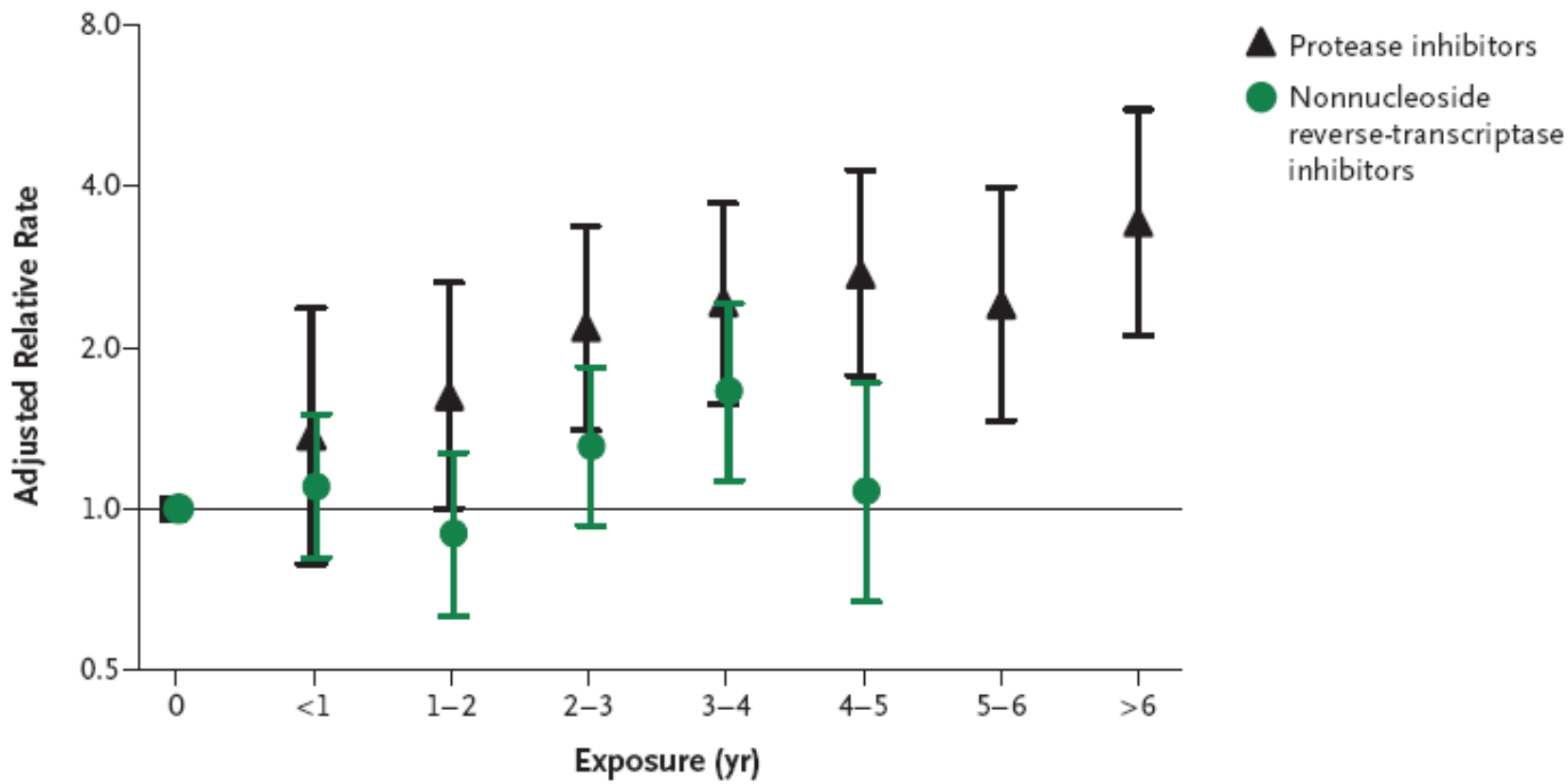


Figure 2. Risk of Myocardial Infarction According to Exposure to Protease Inhibitors and Nonnucleoside Reverse-Transcriptase Inhibitors.

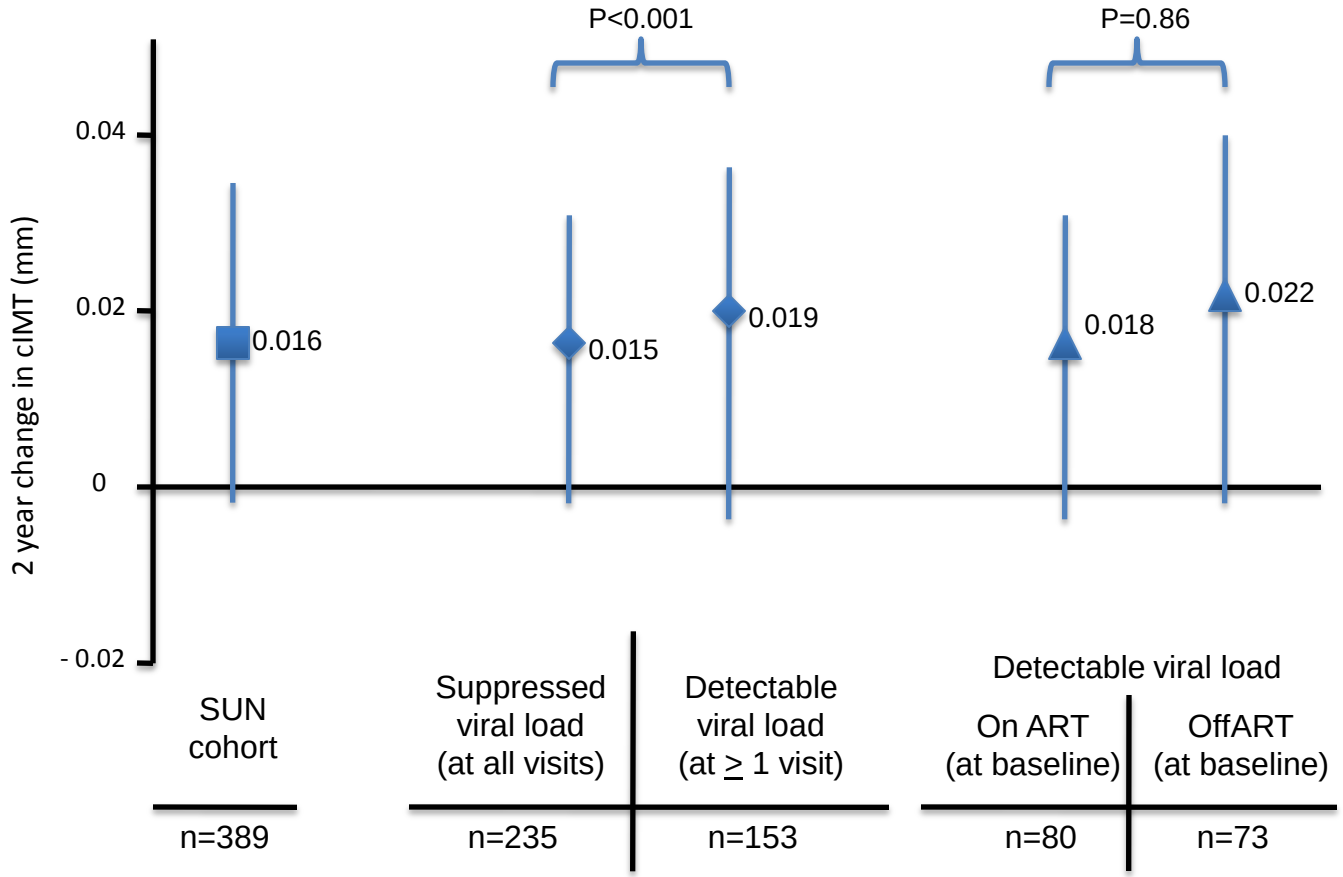
Friis-Moller et al. NEJM 2007.

SMART

FATAL OR NON-FATAL CVD EVENTS					
DC ARM (n=2720)		VS ARM (n=2752)		HR (95%CI)	*P*-value
No.	Rate (per 100 PY)	No.	Rate (per 100 PY)		
48	1.3	31	0.8	1.6 (1-2.5)	0.05

El-Sadr et al. NEJM 2006.

SUN Study



Baker *et al*. JID 2011.

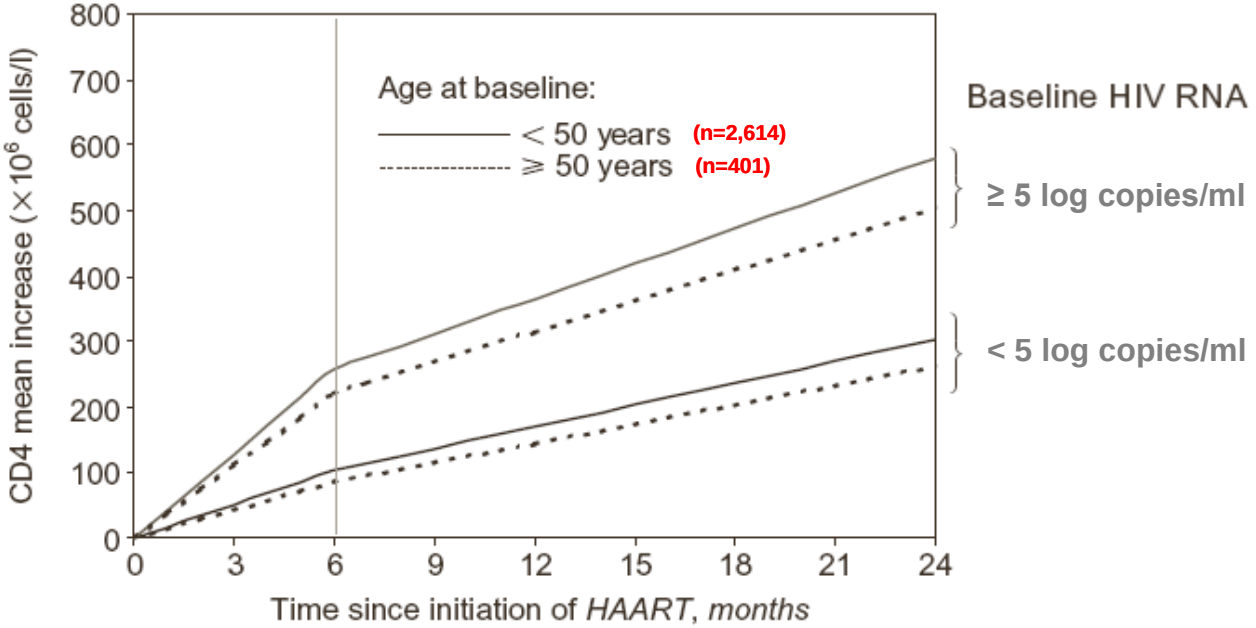
Decision

- No clinical end-point data to support earlier ART in CVD (hence change in guidelines)

Keypad Question

Poorer immunological response in older patients supports earlier ARV therapy

- Studies involving >55,500 ART-naïve patients started on ART therapy show that older age is an independent predictor of lower CD4 count increases[1-4]
  - Significantly poorer immunological response is regardless of baseline HIV RNA levels (p<0.0001)[4]



  - Older patients have poorer clinical outcomes, with significantly faster progression to AIDS (p<0.001) and shorter survival (P<0.001)[2,5]

1. Bosch RJ, et al. J Acquir Immune Defic Syndr 2007;44(3):268-277.
2. COHERE study group. AIDS 2008;22(12):1463-1473.
3. Gandhi RT, et al. J Acquir Immune Defic Syndr 2006;42:426-434.
4. Adapted from Grabar S, et al. AIDS 2004;18:2029-2038.
5. Nogueras M, et al. BMC Infect Dis 2006;6:159.

IAS-USA 2010

"Therapy is recommended regardless of CD4cell count in the following settings …….
……older than 60 years"

BHIVA 2012

"The absolute risk
progression is si
for a given CD4
people (see Tabl
consideration sh
starting at highe
older persons."

"The absolute risk of disease progression is significantly higher for a given CD4 count in older people (see Table 2.1), so consideration should be given to starting at higher CD4 counts in older persons."

Agnes

- Attends 3 months later
- Markers similar
- Has a new HIV-negative partner….

Thank you!

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