17TH ANNUAL CONFERENCE OF THE BRITISH HIV ASSOCIATION (BHIVA)

British HIV Association BHIVA

Dr Nick Paton

MRC Clinical Trials Unit, London

6-8 April 2011, Bournemouth International Centre

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Nick Paton:	None declared
Date	1 April 2011

6-8 April 2011, Bournemouth International Centre

Time to change?
…. when to start

Nick Paton MD FRCP
MRC Clinical Trials Unit
BHIVA conference, April 2011

Current BHIVA guidelines (1)

Presentation	
Primary HIV infection	Treatment in clinical trial or neurological involvement or CD4 <200 cells/μL >3/12 or AIDS-defining illness
Established HIV infection	
CD4 <200 cells/μL	Treat
CD4 201–350 cells/μL	Treat as soon as possible when patient ready
CD4 351–500 cells/μL	Treat in specific situations with higher risk of clinical events – see section 3.3
CD4 >500 cells/μL	Consider enrolment into 'when to start' trial
AIDS diagnosis	Treat (except for tuberculosis when CD4 >350 cells/μL)

BHIVA Treatment Guidelines, 2008HIV Medicine (2008), 9, 563–608

Current BHIVA guidelines (2)

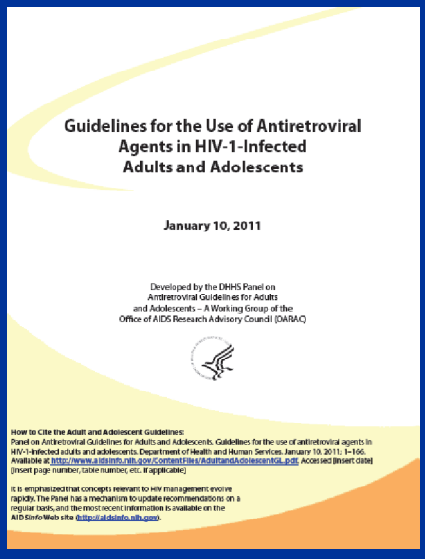
Consider in the following specific situations:

- AIDS diagnosis (e.g. Kaposi's sarcoma); any HIV-related comorbidity;
- hepatitis B infection, where treatment of hepatitis B is indicated (see hepatitis guidelines);
- hepatitis C infection in some cases, where treatment for hepatitis is deferred;
- low CD4 percentage (e.g. <14%, where PCP prophylaxis would be indicated);
- established CVD or a very high risk of cardiovascular events (e.g. Framingham risk of CVD >20% over 10 years).

+ discordant couples where partner has high VL

BHIVA treatment guidelines, 2008

What do others do?


Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents

January 10, 2011

Developed by the DHHS Panel on Antiretroviral Guidelines for Adults and Adolescents – A Working Group of the Office of AIDS Research Advisory Council (OARAC)

How to Cite the Adult and Adolescent Guidelines:
Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. January 10, 2011; 1-166. Available at http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf. Accessed [insert date] [insert page number, table number, etc. if applicable]

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Web site (http://aidsinfo.nih.gov).

- "The Panel emphasizes its recognition of the importance of clinical research in generating evidence to address unanswered questions related to the optimal safety and efficacy of antiretroviral therapy (ART). "
- "The Panel encourages both the development of protocols and patient participation in well-designed, Institutional Review Board (IRB)-approved clinical trials".

DHHS guidelines

Based on the cumulative weight of evidence described above, the Panel recommends that:

- ART should be initiated in all patients with a history of an AIDS-defining illness or with a CD4 count of <350 cells/mm^3 **(AI)**.
- ART is also recommended for patients with CD4 counts between 350 and 500 cells/mm^3 **(A/B-II)**.*
- ART should also be initiated, regardless of CD4 count, in patients with the following conditions: HIVAN **(AII)** and HBV coinfection when treatment of HBV is indicated **(AIII)**.
- A combination ARV drug regimen is also recommended for pregnant women who do not meet criteria for treatment with the goal to prevent perinatal transmission **(AI)**.
- For patients with CD4 counts >500 cells/mm^3, 50% of the Panel members favor starting ART (B); the other 50% of members view treatment as optional (C) in this setting (B/C-III).
- Patients initiating ART should be willing and able to commit to lifelong treatment and should understand the benefits and risks of therapy and the importance of adherence **(AIII)**.
- Patients may choose to postpone therapy, and providers, on a case-by-case basis, may elect to defer therapy based on clinical and/or psychosocial factors.

*The Panel is divided on the strength of this recommendation: 55% of Panel members voted for strong recommendation (A) and 45% voted for moderate recommendation (B).

DHHS guidelines 2011

Reasons to defer at high CD4

- Significant barriers to adherence
- Temporary reasons e.g. transient requirement for drugs with interactions
- Pending surgery with prolonged fasting needed.
- Patients with exceedingly poor prognosis e.g. non-HIV-related malignancy or end-stage liver disease (not considered for transplantation).
- Elite controllers (unclear whether benefit)

Differences with BHIVA guidelines

- DHHS recommend at 350-500 vs BHIVA only in specific conditions
- DHHS split but overall recommend at >500 vs BHIVA support more research

Evidence favouring start at < 350

- Two RCTs

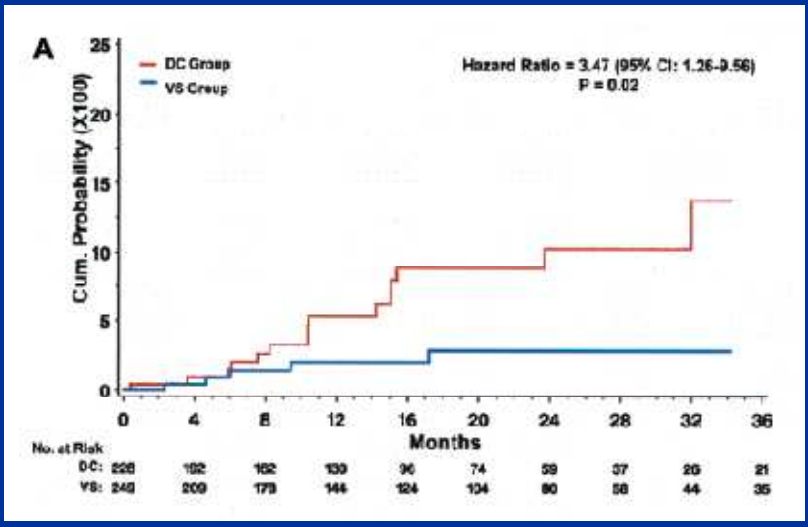
SMART naïve analysis

Start immediately (at > 350) vs < 250
477 ART naïve at enrollment

Event, n (Rate per 100 Person-Yrs)	Deferred Arm (n = 228)	Immediate Arm (n = 249)	HR (DC/VS)	95% CI	*P* Value
OD/death	15 (4.8)	5 (1.3)	3.5	1.3-9.6	.02
OD only	11 (3.5)	4 (1.1)	3.3	1.0-10.3	.04
Serious non-AIDS events	12 (3.9)	2 (0.5)	7.0	1.6-31.4	.01
Composite	21 (7.0)	6 (1.6)	4.2	1.7-10.4	.002

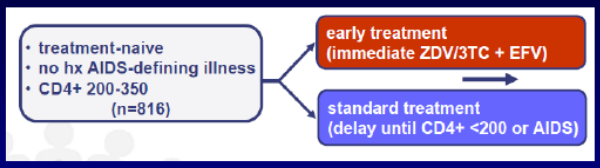
Emery S, et al. J Infect Dis. 2008;197:1133-1144.

SMART naïve: OI or death



CIPRA HT001

- Randomized controlled trial in Haiti of early vs. deferred therapy in HIV-infected patients with CD4 count 200-350

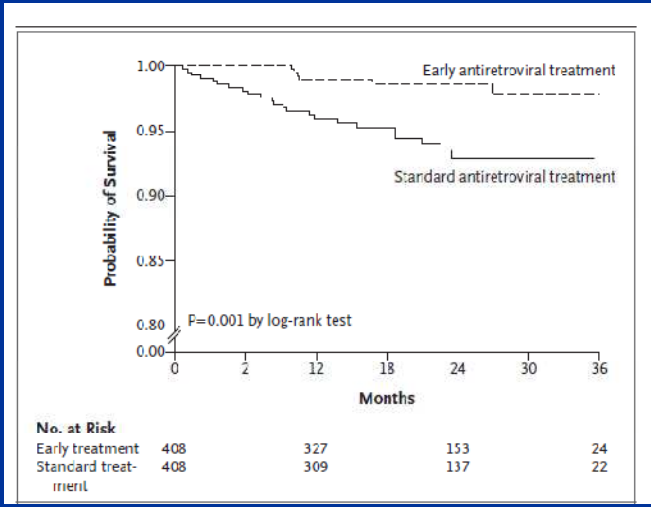


- DSMB stopped trial after median follow-up of 21 months because of excess mortality in the standard of care arm

	Early	Standard	HR (p-value)
Death	6	23	4.0 (0.0011)
Incident TB	18	36	2.0 (0.0125)

Fitzgerald D, NEJM, 2010

CIPRA HT001



Severe NEJM 2010, 363, 257

CIPRA HT001

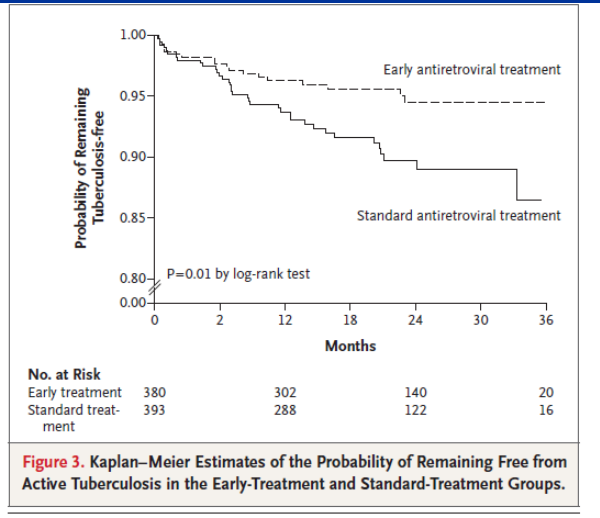
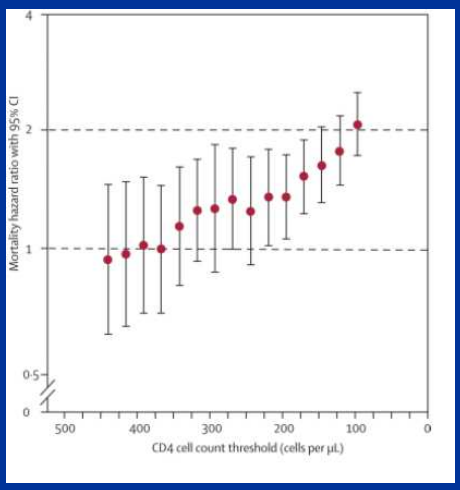


Figure 3. Kaplan–Meier Estimates of the Probability of Remaining Free from Active Tuberculosis in the Early-Treatment and Standard-Treatment Groups.

Severe NEJM 2010, 363, 257

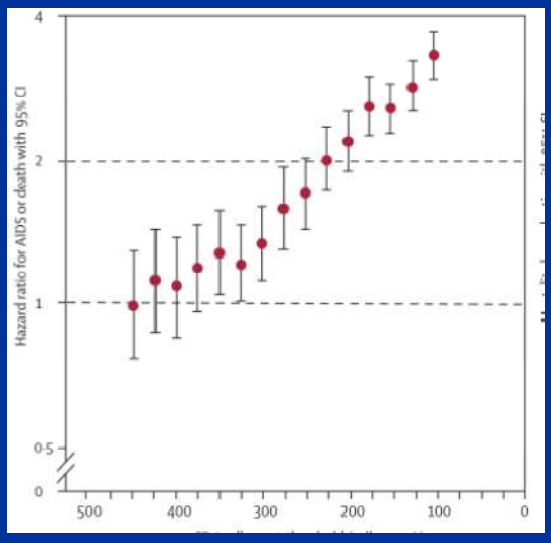
Evidence favouring start at higher than 350

- Randomised clinical trials – NONE
- Cohort studies:
  - ART-CC
  - NA ACCORD



- 18 cohorts
- 21,247 patients
- Deferred vs immediate treatment at different CD4 strata
- Adjusted for lead times and unseen AIDS / death events

When to start consortium; Lancet 2009; 373; 1352-1363



When to start consortium; Lancet 2009; 373; 1352-1363

NA-ACCORD

- Collaboration of 22 HIV research cohorts in the US and Canada, representing more than 60 sites
- 17,517 asymptomatic treatment-naïve HIV+ patients who received medical care during 1996 to 2005
- Patients stratified by CD4 count: 350-500 or >500
- Compared the relative risk of death for patients who started ART when CD4 count was above the threshold vs. those who deferred therapy until the CD4 count was below the threshold

Kitahata M, et al. NEJM 2009.

Table 3. Risk of Death Associated with Deferral of Antiretroviral Therapy, According to CD4+ Count at Baseline, with Adjustment for HIV RNA Level, Age, and Sex.*

Variable	351-to-500 CD4+ Count		More-Than-500 CD4+ Count	
	Relative Risk (95% CI)	P Value	Relative Risk (95% CI)	P Value
Without inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.69 (1.26–2.26)	<0.001	1.94 (1.37–2.79)	<0.001
Female sex	1.21 (0.89–1.64)	0.24	1.85 (1.33–2.59)	<0.001
Older age (per 10-yr increment)	1.68 (1.48–1.91)	<0.001	1.83 (1.62–2.06)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	1.13 (0.72–1.78)	0.59	0.93 (0.87–0.99)	0.03
With inclusion of HIV RNA data				
Deferral of antiretroviral therapy	1.63 (1.21–2.19)	0.002	1.85 (1.20–2.86)	0.006
Female sex	1.47 (1.02–2.12)	0.04	1.35 (0.85–2.15)	0.20
Older age (per 10-year increment)	1.89 (1.69–2.11)	<0.001	1.81 (1.58–2.07)	<0.001
Baseline CD4+ count (per 100 cells/mm^3)	0.74 (0.55–1.00)	0.06	0.97 (0.89–1.05)	0.45
Baseline HIV RNA level (per $\log_{10}$ copies/ml)	1.11 (0.96–1.28)	0.15	1.13 (0.96–1.33)	0.14

Kitahata, NEJM 2009

NA-ACCORD absolute rates

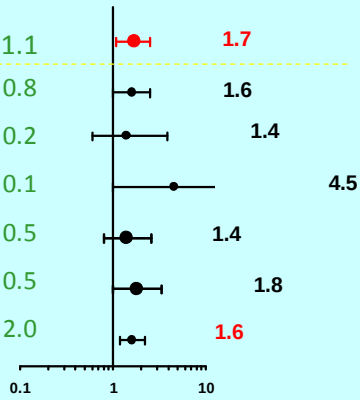
- Crude rates of death in early therapy group:
  - 1.6% per year in 350-500
  - 1.3% per year in >500
- So excess mortality due to deferral =
  - Approx additional 1.0% per year (at 350-500)
  - Approx additional 1.2% per year (at > 500)

Interpretation?

- One cohort suggests no advantage above 350
- The other suggests about 1% survival advantage of treating above 350
- Problem is cannot adjust for unknown confounders.
- Data is supportive of a theoretical advantage, but this magnitude of advantage could easily be explained by errors inherent in the analyses

Serious Non-AIDS Outcomes in SMART

Endpoints	No. of Patients with Events	Rate DC	Rate VS	Relative Risk (95% CI)
Major CVD+, hepatic or renal disease	104	1.8	1.1	1.7
CVD+	79	1.3	0.8	1.6
Hepatic (Cirrhosis)	17	0.3	0.2	1.4
Renal (ESRD)	11	0.2	0.1	4.5
NADM++	47	0.8	0.5	1.4
Other non-OD death	51	0.9	0.5	1.8
Any of the above	186	3.2	2.0	1.6

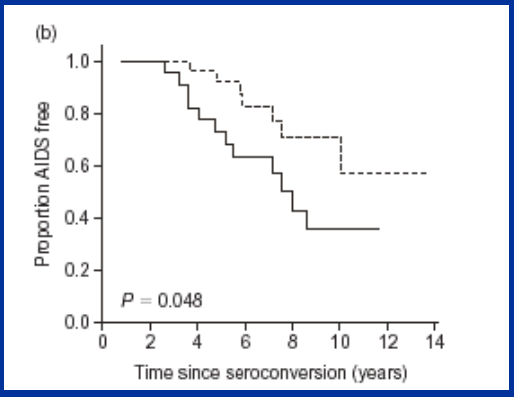


+ MI (clinical or silent), stroke, surgery for CAD
++ Except non-melanoma skin

NEJM 2006; 355:22838-96

Immune Activation and HIV Pathogenesis

- Activation may directly accelerate HIV progression (independent of CD4 loss)



___ T cell activation > median

--- T cell activation < median

Hazenberg, AIDS 2003

SMART biomarkers (all-cause mortality)

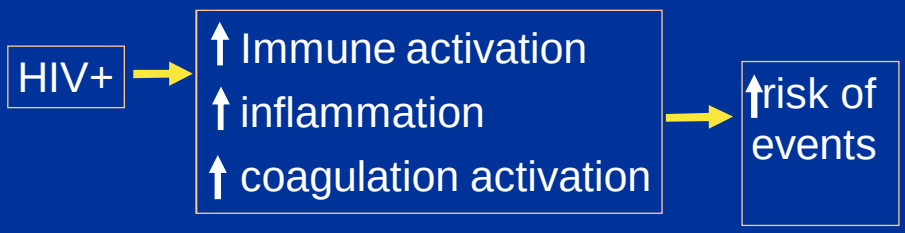
Marker	Adjusted OR ($4^{th}/1^{st}$)	p-value
Hs-CRP	2.8	0.03
Amyloid A	2.6	0.09
Amyloid P	1.1	0.84
IL-6	11.8	<0.0001
D-dimer	26.5	<0.0001
F1.2	1.2	0.66

*OR – per mean difference between 4^{th} and 1^{st} quartile

Similar associations found for CVD (fatal and non-fatal)

Kuller et al, CROI 2008

How does HIV increase Non-AIDS Disease Risk?



Summary of efficacy considerations

- Risk of AIDS/death modest at high CD4+ cell counts.
- However, when add risk of serious non-AIDS morbidity/mortality and other effects of inflammatory processes, there may be substantial excess morbidity
- Early ART is likely to decrease risk across a spectrum of disease pathogenesis pathways
- The cumulative beneficial impact of early ART is likely to be modest, but we could get a surprise when we look!

Summary of safety considerations

We need evidence to guide decisions on patient management

- Benefit of early HIV treatment on serious clinical events (AIDS & non-AIDS)
- Effect of early HIV treatment on:
  - Adverse events
  - Resistance
  - Adherence & regimen use
  - Metabolic abnormalities
  - Body composition
  - HIV transmission

Evidence Needed to Guide Policy Makers

- All of above +
- Cost effectiveness
  - care for individuals
  - Prevention of new infections
  - (could be massively cost-saving)
- Feasibility

Why do we need RCT evidence?

Because of the potential for bias, modest - *but important* - differences in clinical outcomes between early and deferred ART require large randomized trials to obtain reliable evidence.

Early vs deferred RCTs in progress

- SPARTAC
- TEMPRANO
- HPTN 052
- START

SPARTAC

- Treatment in primary infection
- N = 371
- Randomised into one of three arms:
  - a. Long Course combination Anti-Retroviral Therapy for 48 weeks
  - b. Short Course combination Anti-Retroviral Therapy for 12 weeks
  - c. No Anti-Retroviral Therapy
- Started in 2004,completed recruitment in 2007
- Results in 2011

TEMPRANO

- ANRS TEMPRANO study
  - 1,650 patients
  - Planned end: Aug 2013
  - Randomization: Early (>350) versus deferred (<350 cells/mm^3) ART
  - Primary question: Does early ART reduce risk of AIDS, non-AIDS cancer and non-AIDS invasive bacterial diseases?

HPTN-052

- HPTN 052 study
  - 1,763 couples
  - Planned end: 2013
  - Randomization: Early (>350) versus deferred (<250 cells/mm^3) ART
  - Primary question: Does early ART reduce risk of HIV transmission?

START

HIV-infected individuals who are ART-naïve with CD4+ count > 500 cells/mm^3 (n=4000)

Early ART Group	Deferred ART Group
Initiate ART immediately following randomization	Defer ART until the CD4+ count declines to < 350 cells/mm^3 or AIDS develops

Primary endpoint (time to first event)

- **AIDS* or death from AIDS**
  - Opportunistic events consistent with the 1993 CDC expanded surveillance definition, plus additional events. *Esophageal candidiasis and chronic *Herpes simplex* counted only if they result in death
- **Non-AIDS**
  - Cardiovascular disease (CVD) (MI, angioplasty, CABG, stroke)
  - Chronic end-stage renal disease (ESRD) (initiation of dialysis, renal transplantation)
  - Decompensated liver disease
  - Non-AIDS defining cancers (other than basal and squamous cell skin cancers)
- **Death from any cause**

Secondary endpoints (1)

- Individual components of composite primary endpoint
- Bacterial pneumonia
- Adverse events
- Hospitalization
- Quality of life
- Health care utilization and cost of care
- HIV transmission risk behavior
- HIV drug resistance

Secondary endpoints (2)

- Pulmonary embolism or deep vein thrombosis
- New-onset diabetes mellitus
- Coronary artery disease requiring drug treatment
- Congestive heart failure
- Peripheral arterial disease
- Change in estimated GFR and development of proteinuria
- Blood pressure and blood lipids
- ECG abnormalities
- Use of BP- or lipid-lowering treatment or aspirin

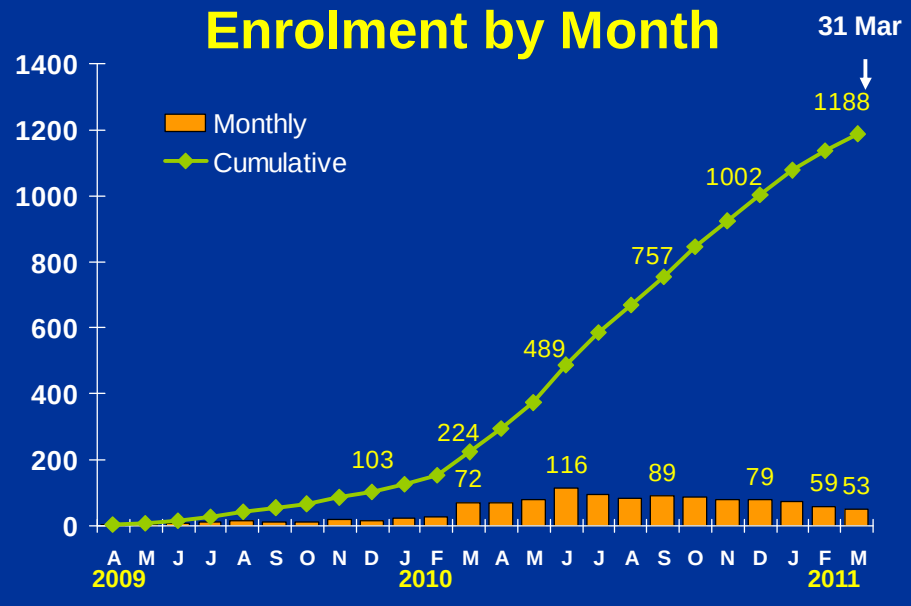
START Sub-studies

- Genomics (NIAID)
- Neurology (NIMH, NINDS)
- Informed Consent (NIH Dept. of Bioethics)
- Arterial Elasticity (NHLBI)
- Pulmonary (NHLBI)
- Bone Mineral Density (NIAMS)

Sample size for START

- 90% power and alpha = 0.05 (2-sided)
- Hypothesized risk reductions with early ART (compared to no ART) are:
  - AIDS* = 43%
  - Serious non-AIDS = 24%
  - Composite of AIDS* (20% of events) and non-AIDS (80% of events) = 28.8%
- Rate in deferred ART group for composite outcome = 2.8 per 100 person years
- 4.5 years average follow-up
- Loss to follow-up rate of 2.7 per 100 person years, equivalent to 15% cumulative lost to follow-up after 6 years
- Hypothesized hazard ratio after considering use of ART in the deferred arm and non-adherence in early ART arm = 0.71
- Target number of primary events = 370, of which 74 are fatal and non-fatal AIDS* and 296 are fatal and non-fatal non-AIDS events

Enrolment by Month



Enrolment, by Region (31-Mar-11)

Location	Open Sites	Enrolling Sites	Enrollment
United States	27	25	177
Europe (+Israel)	52	52	587
South America	13	12	226
Australasia	8	7	100
Africa	3	3	98
Overall Total	103	99	1188

START
Baseline Characteristics

*Data as of 22-Feb-2011

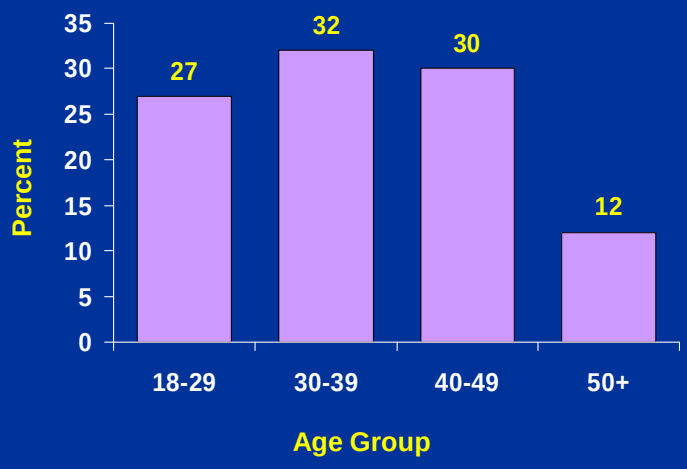
Demographics

Median Age (years, IQR)	37 [29, 44]
Gender (% female)	16
Race (%)	
Asian	6
Black	17
Latino/Hispanic	12
White	62
Other	2

Mode of HIV infection

Likely mode of HIV infection (%)	
sexual contact with same sex	69
sexual contact with opposite sex	27
injection drug use	2
blood products	1
other/unknown	5
Time known to be HIV positive, years (median, IQR)	1 [0, 3]

Age Distribution



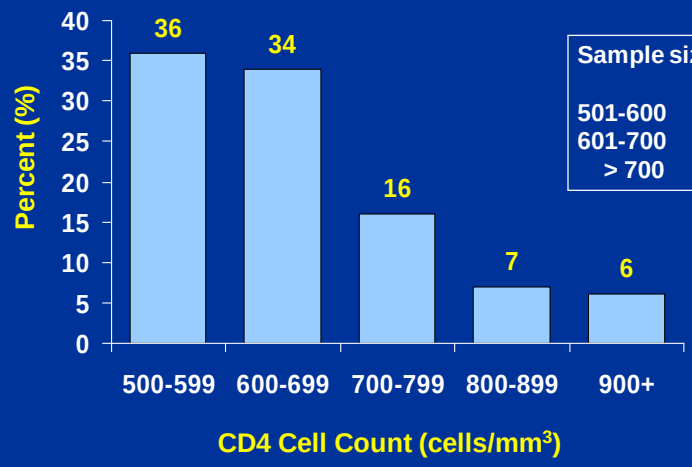
Other Baseline Data

Medical History	
Hepatitis B (%)	2
Hepatitis C (%)	6
Quality of Life	
Current health: 0-100 scale (median, IQR)	85 [75, 90]

(0 = worst possible 100 = best possible)

Baseline CD4 Distribution

Median (IQR) 635 (576 - 723)

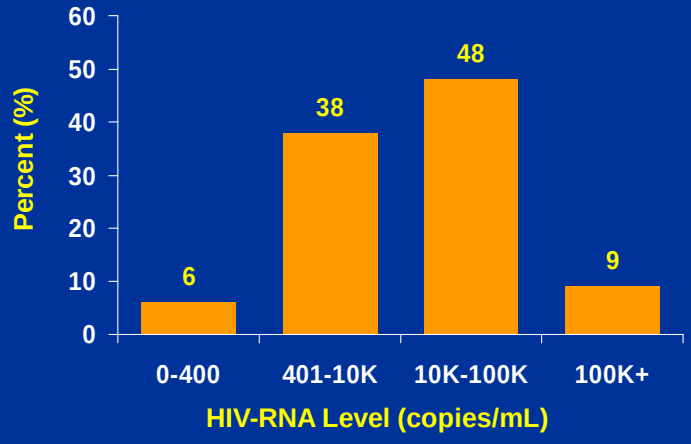


Sample size assumptions:

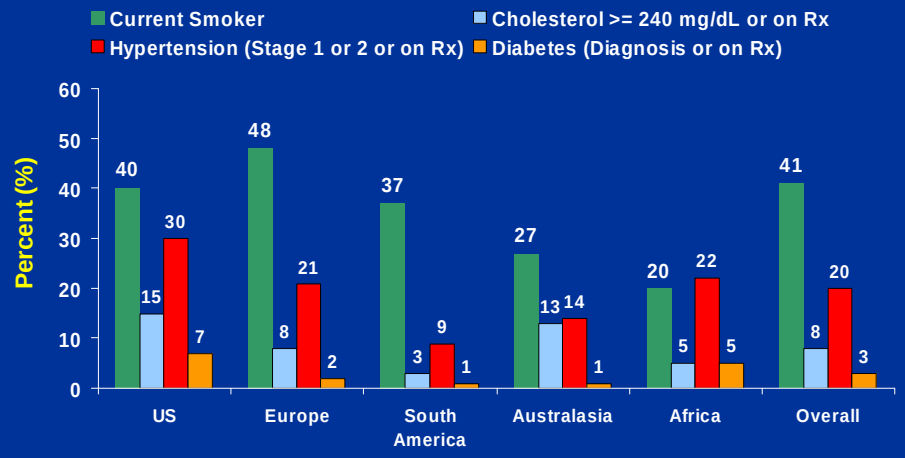
501-600	70%
601-700	20%
> 700	10%

Baseline HIV-RNA Distribution

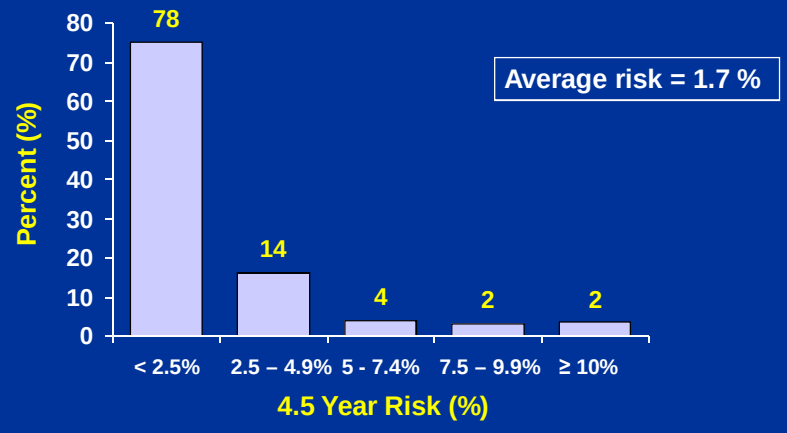
Median (IQR) 14,000 (3,734 – 43,003)



Percent with Clinically Elevated Modifiable CVD Risk Factors, by Region



Distribution of 4.5 Year Risk* of Coronary Heart Disease



* Based on age, gender, smoking, total/HDL cholesterol ratio, SBP, presence of diabetes and ECG left ventricular hypertrophy (LVH)

Looking forward

- 137 new sites to open
  - 14 new countries
- Total 238 sites in 36 countries
- 1188 enrolled and 2812 to go
- Target: complete enrolment by end 2012

Is it time to change now?

- Do we have enough evidence to really be sure?
- Costs – can we afford it?
- Is it the most pressing thing to do in a resource-limited setting?

Costs

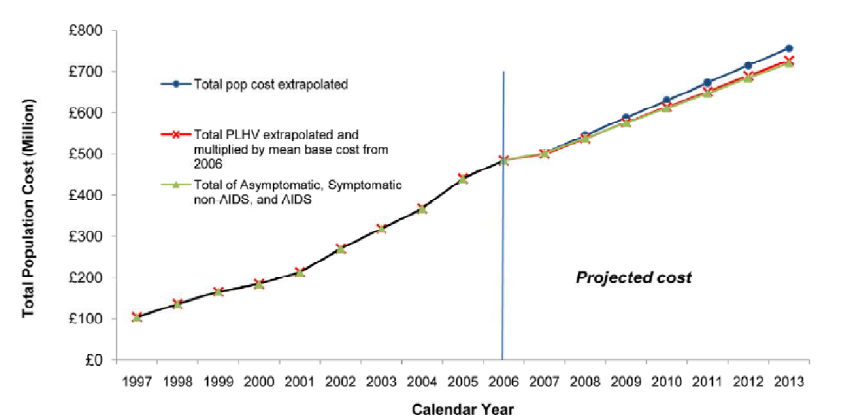


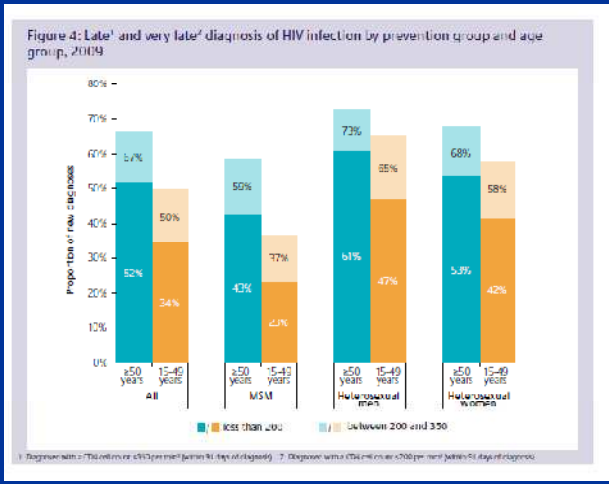
Figure 4. Annual Average UK Direct Population Cost 1997–2006 and Projections 2007–2013 based on three Scenarios (UK 2006 prices).

Mandalia, PLoS One, 2010.
doi:10.1371/journal.pone.0015677

How many additional pts would start if guidelines changed to Rx all?

- 78% of those accessing care in UK in 2009 were on ART (HPA 2010 report)
- Remaining 22%
  - Many are eligible with CD4 < 350 but not taking
  - Some moribund and not started
  - Very few with higher CD4 T-cell counts but not started (<< 10%)
  - Of these many would not start even if recommended
- Impact on costs “limited”
  - <10% increase
  - £60 million
  - Can the NHS afford it?

Is early ART the greatest priority for limited healthcare resources?

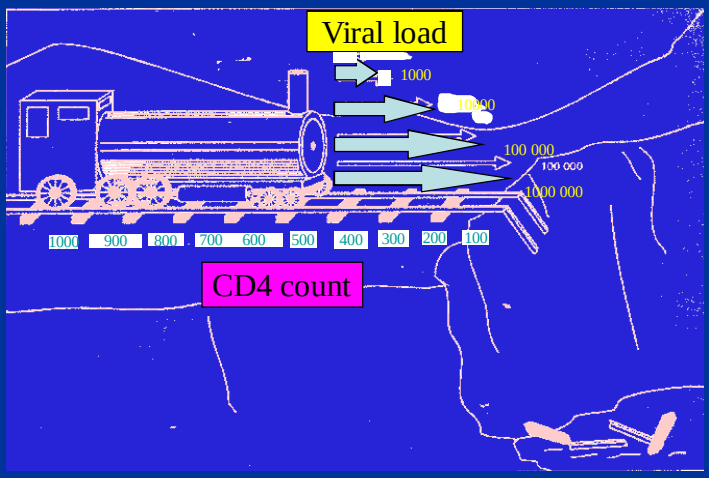


HPA 2010 report

Do we have enough evidence?

- We cannot be certain of net clinical benefit ….possibility of net harm (although small)
- We need to have unequivocal belief in need in order to try to convince patients
- We don't know it's cost effective (and may not be able to convince funders of the need for resources)
- [Changing guidelines may make the trial harder to do]
- [If there is a substantial clinical benefit we may not have to wait too long for results]

Deciding when to treat



When we decide to change direction…