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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Prof Caroline Sabin	Professor Sabin has provided educational courses and materials for Gilead Sciences, Bristol-Myers Squibb, Janssen-Cilag and Viiv Healthcare, has acted in a Consultancy capacity for Glaxo-Smithkline, and has been a speaker at company-sponsored events for Gilead Sciences, Bristol-Myers Squibb, Abbott Pharmaceuticals and Janssen-Cilag.
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When to start ARV treatment – why the difference in guidelines recommendations?

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Background

- Current BHIVA guidelines do not recommend *routine* initiation of cART at CD4 counts >350 cells/μL in *asymptomatic* individuals
- However, other international guidelines committees have made different recommendations regarding initiation of cART in this group
- All guidelines claim to be 'evidence-based' – so why is there a difference?

Topics to be covered

- What processes do each guidelines committee follow?
- What is GRADE?
- Examining the strength of evidence using GRADE
- Examining the strength of evidence using other systems

When to start – CD4 350-500 cells/μL

Guideline committee	Recommendation
DHHS[1]	Start
IAS-USA[2]	Start
WHO[3]	Start, lower priority
BHIVA[4]	Defer unless other clinical condition is present or patient wishes to take TasP
EACS[5]	Consider and actively discuss with patient

[1]http://aidsinfo.nih/gov/guidelines; [2]Thompson MA et al. *JAMA* 2012;308: 387-402; [3]WHO HIV/AIDS Programme June 2013; [4]Williams I et al. HIV Med 2012;13(Supp 2):1-85; [5]www.eacsociety.org.

When to start – CD4 >500 cells/μL

Guideline committee	Recommendation
DHHS[1]	Start
IAS-USA[2]	Start
WHO[3]	Do not start, unless patient meets other criteria
BHIVA[4]	Defer unless other clinical condition is present or patient wishes to take TasP
EACS[5]	Consider and actively discuss with patient

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Department of Health and Human Services (DHHS)

- Panel of >30 voting members with expertise in HIV care and research
- Financial disclosures provided annually
- Target: Adults and adolescents in the US
- Members of each working group synthesise evidence based on available data from peer-reviewed journals and, occasionally, unpublished data (safety signals)
- Panel votes on each recommendation

http://aidsinfo.nih/gov/guidelines

Department of Health and Human Services (DHHS)

Strength of Recommendation	Quality of Evidence for Recommendation
A: Strong recommendation for the statement	I: One or more randomized trials with clinical outcomes and/or validated laboratory endpoints
B: Moderate recommendation for the statement	II: One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes
C: Optional recommendation for the statement	III: Expert opinion

http://aidsinfo.nih/gov/guidelines

IAS-USA

- Recommendations developed by independent panel of experts in HIV research and clinical care
- No participation in industry promotional activities
- Target: HIV+ve adults in resource-rich settings with ART available or in late-stage development
- Systematic literature review (PubMed/EMBASE) to identify relevant published evidence as well as evidence from conferences and safety reports
- Full panel consensus required

Thompson MA et al. *JAMA* 2012;308: 387-402.

IAS-USA

Category, Grade	Definition
Strength of recommendation	
A	Strong support for the recommendation
B	Moderate support for the recommendation
C	Limited support for the recommendation
Quality of evidence	
Ia	Evidence from 1 or more randomized controlled clinical trials published in the peer-reviewed literature
Ib	Evidence from 1 or more randomized controlled clinical trials presented in abstract form at peer-reviewed scientific meetings
IIa	Evidence from nonrandomized clinical trials or cohort or case-control studies published in the peer-reviewed literature
IIb	Evidence from nonrandomized clinical trials or cohort or case-control studies presented in abstract form at peer-reviewed scientific meetings
III	Recommendation based on the panel's analysis of the accumulated available evidence

Thompson MA et al. *JAMA* 2012;308: 387-402.

EACS

- Recommendations developed by panels of experts in HIV research and clinical care
- All panel members complete financial disclosure form
- Target: HIV+ve adults in European resource-rich settings
- Each panel extracts relevant literature – no formal systematic reviews required
- No formal voting system, but content of guidelines is modified until consensus is reached

www.eacsociety.org; Ryom Worm L (personal communication).

WHO

- Four Guideline Development Groups and external peer review group of >100 individuals
- All participants declare competing interests
- Those with exclusive engagement with single pharmaceutical company, and/or a major role in completed, ongoing or planned trials are excluded from discussions

WHO HIV/AIDS Programme June 2013.

WHO

- Target: HIV+ve adults and adolescents - focus on settings with limited capacity and resources in the health system
- Guidelines based on a public-health approach to scaling up the use of ARV drugs for HIV treatment and prevention – balance between best-proven standard of care and feasibility in resource-limited settings
- GRADE system used for most guidelines

WHO HIV/AIDS Programme June 2013.

BHIVA

- Recommendations developed by panel of experts in HIV research and clinical care
- Financial disclosures reported at start of process
- Target: HIV+ve adults in resource rich settings
- GRADE system used with summary of findings tables constructed where appropriate
- Guidelines published online for public consultation and undergo external peer review

Williams I et al. HIV Med 2012;13(Supp 2):1-85.

Topics to be covered

- What processes do each guidelines committee follow?
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The need for a systematic approach

- Traditional methods for guidelines development were often opaque:
  - terms for literature review
  - method of evidence synthesis
  - balance of evidence from different types of studies
  - weighting given to different outcomes of treatment
- Possible for different guidelines committees to make different recommendations on basis of same evidence, or vice versa

What is GRADE?

- **G**rading of **R**ecommendations **A**ssessment, **D**evelopment and **E**valuation
- Transparent, structured process for developing and presenting summaries of evidence for systematic reviews and treatment guidelines
- Results of systematic review of literature *relating to the question* determine strength/evidence *for that recommendation*

http://www.gradeworkinggroup.org/

Identifying the question

- Use of PICO (**P**atient /**I**ntervention /**C**omparator /**O**utcome) to define question of interest
- Outcomes should be important to patients; use of surrogate markers may lead to a down-rating of quality of evidence
- Initial rating of importance of outcomes should precede review of evidence

Guyatt GH et al. *J Clin Epidemiol* 2011;**64**:395-400.

Identifying the question - BHIVA

Patient:	HIV-infected naïve to antiretroviral therapy
Intervention:	Starting ART early: i) at CD4 count >350 cells/μL, ii) at CD4 count >500 cells/μL, iii) immediate at time of diagnosis
Comparator:	Starting ART at CD4 count <350 cells/μL (standard-of-care)
Outcome:	Death AIDS Non-AIDS co-morbidities Drug adverse events Drug resistance HIV transmission/incidence

Assessing quality of evidence

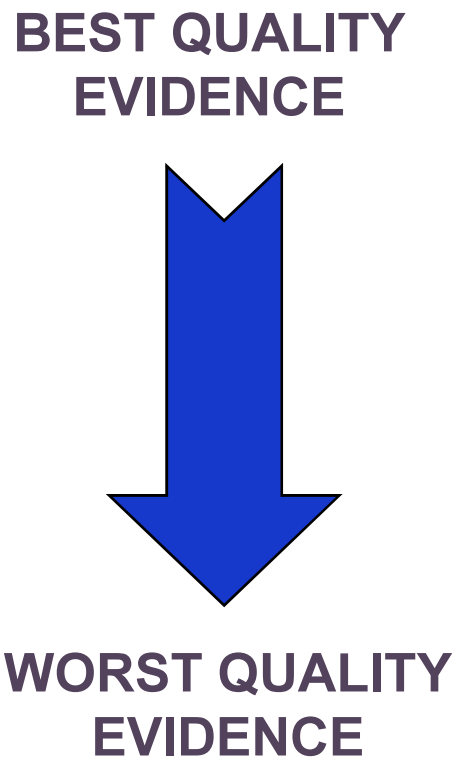
- Four categories for quality of a 'body of evidence'
  - High (⨁⨁⨁⨁)
  - Moderate (⨁⨁⨁◯)
  - Low (⨁⨁◯◯)
  - Very low (⨁◯◯◯)

High	**Very confident** that true effect lies close to that of the estimate
Moderate	**Moderately confident** in effect estimate: true effect is likely to be close to estimate, but there is a possibility that it may be substantially different
Low	Confidence in effect estimate is **limited**: true effect may be substantially different from estimate
Very low	**Very little confidence** in effect estimate: true effect is likely to be substantially different from estimate

Balshem H et al. *J Clin Epidemiol* 2011;**64**:401-6.

Hierarchy of evidence

- Randomized controlled trial
- Cohort study
- Case-control study
- Cross-sectional study
- Case series/case note review
- ‘Expert’ opinion



GRADE and randomized trials

- Evidence from randomized trials – initially determined to be of **high** quality
- Five reasons for down-rating quality of evidence
  - Risk of bias
  - Inconsistency
  - Indirectness
  - Imprecision
  - Publication bias
- GRADE does not guarantee consistency in assessing strength of recommendations

Balshem H et al. *J Clin Epidemiol* 2011;**64**:406-6.

GRADE and observational studies

- Evidence from observational studies – initially determined to be of **low** quality
- Three primary reasons for up-rating quality of evidence
  - Large magnitude of effect (2/5-fold increase)
  - Dose-response gradient
  - All plausible confounders or other biases increase confidence in estimated effect
- As with randomized trials, quality of evidence can also be down-graded for lack of consistency and for indirectness

Guyatt GH. *J Clin Epidemiol* 2011;**64**:1311-16.

Strength of recommendation

- Confidence that desirable effects of intervention outweigh undesirable effects
- **Strong** recommendation: most informed patients would choose the recommended management
- **Weak** recommendation: patients' choices will vary according to their values and preferences

Guyatt GH et al. *BMJ* 2008;**336**:1049-51.

Strength of recommendation

- Strength of recommendation determined by:
  - balance between desirable/undesirable consequences of different strategies
  - quality of evidence
  - variability in values and preferences
  - resource use

Guyatt GH et al. *BMJ* 2008;**336**:1049-51.

Topics to be covered

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BHIVA – question of interest

Patient:	HIV-infected naïve to antiretroviral therapy
Intervention:	Starting ART early: i) at CD4 count >350 cells/μL, ii) at CD4 count >500 cells/μL, iii) immediate at time of diagnosis
Comparator:	Starting ART at CD4 count <350 cells/μL (standard-of-care)
Outcome:	Death AIDS Non-AIDS co-morbidities Drug adverse events Drug resistance HIV transmission/incidence

BHIVA – question of interest

- No published RCT that directly assesses this question
- HPTN 052[1] – clear benefit of cART at CD4 >350 cells/μL compared to <250 cells/μL
- But we know that deferring to this level is detrimental to health – thus, this trial provides only indirect evidence for the question
- Whilst several observational studies have attempted to answer the question, most are affected by 'lead-time' bias

[1]Cohen MS. *NEJM* 2011;**365**:493-505.

Summary of findings from cohorts (deferred vs. immediate)

	Comparison	Death	AIDS/death
NA-ACCORD[1]	<500 vs. >500	1.94 (1.37, 2.79)	n/a
	<350 vs. 351-500	**1.69 (1.26, 2.26)**	**n/a**
When to Start[2]	351-450 vs. 451-550	0.93 (0.60, 1.44)	0.99 (0.76, 1.29)
	251-350 vs. 351-450	**1.13 (0.80, 1.60)**	**1.28 (1.04, 1.57)**
CASCADE[3]	<500 vs. 500-799	0.98 (0.47, 2.04)	0.91 (0.56, 1.49)
	<350 vs. 350-499	**1.96 (1.25, 3.03)**	**1.33 (0.88, 2.04)**
HIV-CAUSAL[4]	**<350 vs. 351-500**	**1.01 (0.84, 1.22)**	**1.38 (1.23, 1.56)**

1. Kitahata M. *NEJM* 2009;**360**:1-12; 2.When to Start Consortium. *Lancet* 2009;**373**:1352-63; 3. CASCADE Collaboration. *Arch Int Med* 2011;**171**:1560-9; 4. HIV-CAUSAL Collaboration. *Ann Int Med* 2011;**154**:509-15.

Limitations - unmeasured confounding

- Under current treatment guidelines, few patients start cART at high CD4 counts
- Those who start cART may differ to those who defer in several respects
- Direction of bias unpredictable; may differ in different settings
- Most cohort studies were not *designed* to address this comparison, and therefore do not capture high-quality prospective data on potential confounders or on any harms of cART

Strength of observational evidence

- Well-designed non-randomized trial?
  Studies not generally designed to answer this question, all relevant information may not be captured
- Large magnitude of effect (2/5-fold increase)?
  No – all RH estimates <2
- Plausible confounders/biases increase confidence in estimated effect
  No – unpredictable confounding and unclear whether all other sources of bias (e.g. loss-to-follow-up) adequately addressed
- Consistency?
  No – estimates differ widely, possibly due to differences in analytical methods

BHIVA recommendations

Recommendation: CD4 350-500 cells/μL	Level/strength of evidence
Defer unless other clinical condition is present or patient wishes to take TasP	Insufficient data to make recommendation

Recommendation: CD4 >500 cells/μL	Level/strength of evidence
Defer unless other clinical condition is present or patient wishes to take TasP	Insufficient data to make recommendation

WHO – 350-500 cells/μL

- Impact on HIV transmission strongly supported by evidence, but quality of evidence for clinical benefit only moderate as mainly from observational studies
- Pooled analysis of 21 observational studies: lower risk of death with earlier ART in 13 studies, lower risk of progression to AIDS or death in 9 studies
- Pooled analysis of 3 RCTs: low-quality evidence in support of ART initiation at higher CD4 counts for reducing mortality and disease progression

WHO HIV/AIDS Programme June 2013.

WHO – >500 cells/μL

- Guidelines Development Group did not find evidence and/or favourable risk-benefit profiles to support recommendations for initiating ART at CD4 cell count >500 cells/mm^3…”

WHO HIV/AIDS Programme June 2013.

WHO

Recommendation: CD4 350-500 cells/μL	Level/strength of evidence
Start, lower priority	Strong recommendation, moderate quality evidence

Recommendation: CD4 >500 cells/μL	Level/strength of evidence
Do not start, unless patient meets other criteria	Insufficient data to make recommendation

WHO HIV/AIDS Programme June 2013.

Topics to be covered

- What processes do each guidelines committee follow?
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EACS

Recommendation: CD4 350-500 cells/μL	Level/strength of evidence
Consider	N/A

Recommendation: CD4 >500 cells/μL	Level/strength of evidence
Consider	N/A

EACS

"Use of ART should be **considered** and **actively discussed** with the HIV-positive person; under these circumstances, some experts would recommend starting ART whereas others would consider deferral of ART; this **clinical equipoise** reflects that whereas certain data, such as **hypotheses** on **pathophysiology** and **chronic immune activation**, supports starting ART, this needs to be **balanced** against the risk of known or undiscovered **adverse drug reactions** from use of ART, and hence the **risk/benefit ratio** for use of ART under these circumstances has not yet been well defined."

DHHS

Recommendation: CD4 350-500 cells/μL	Level/strength of evidence
Start	Strong recommendation, data from well-designed, nonrandomized trials or observational studies with long-term clinical conditions

Recommendation: CD4 >500 cells/μL	Level/strength of evidence
Start	Moderate recommendation, expert opinion

http://aidsinfo.nih/gov/guidelines

IAS-USA

Recommendation: CD4 350-500 cells/μL	Level/strength of evidence
Start	Strong recommendation, evidence from ≥1 RCT

Recommendation: CD4 >500 cells/μL	Level/strength of evidence
Start	Moderate recommendation, based on panel's analysis of evidence

Thompson MA et al. *JAMA* 2012;308: 387-402.

The evidence for earlier cART initiation

- Increasing evidence of potential benefit of cART at higher CD4 counts
- Greater understanding of harms of untreated HIV
- Potential role of CD4 nadir as predictor of adverse outcomes
- Potential for cART to prevent HIV transmission

Sax P. New HIV Treatment Guidelines: Who should be treated? http://www.medscape.com/viewarticle/76712

Summary (1)

- Although much has been made of the fact that BHIVA guidelines differ from other international guidelines, the differences are not as large as might be expected
- ALL guidelines allow for the initiation of ART in asymptomatic individuals with a CD4 count >350 cells/μL, should person want treatment for the prevention of transmission to partners
- It is only in the relatively small group of asymptomatic patients with a CD4 count >350 cells/μL who do not wish to take ART for this reason that the guidelines deviate slightly

Summary (2)

- Whilst GRADE provides a transparent process for developing and presenting summaries of evidence, it does not guarantee consistency in the way that evidence is interpreted
- The choice of studies included in systematic reviews can have a major impact on estimates of effect
- Recommendations also take into account the context in which guidelines will be used, which may partly explain some inconsistencies