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

British HIV Association BHIVA

Dr Ed Wilkins

North Manchester General Hospital

6-8 April 2011, Bournemouth International Centre

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COMPETING INTEREST OF FINANCIAL VALUE ≥ £1,000:	
Speaker Name	**Statement**
Dr Ed Wilkins:	Dr Wilkins has received educational grants, honoraria for lectures and advisory boards from the following companies: ViiV, Abbott, Gilead, MSD, Janssen, and BMS
Date	1 April 2011

6-8 April 2011, Bournemouth International Centre

What to start?

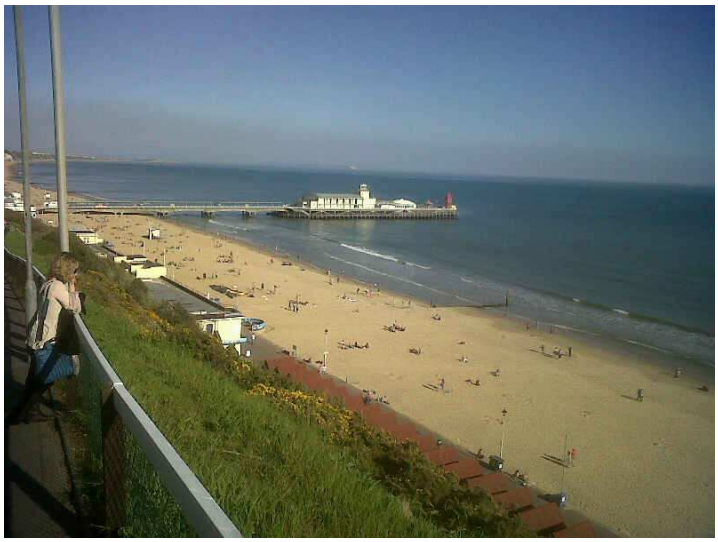
2011

Is it time to change?

Why are you still here?

- To update your knowledge?
- To hear a summary of the guidelines?
- For training purposes?
- To determine treatment regimens for your patients?
  - Thinking of now?
  - Thinking of their future?
- To check your doing everything right?
- To hopefully win a prize?
- To stay for the beer festival?

To have a w/e in Bournemouth?



Relative importance

What to Start?

Getting people tested

Getting people tested

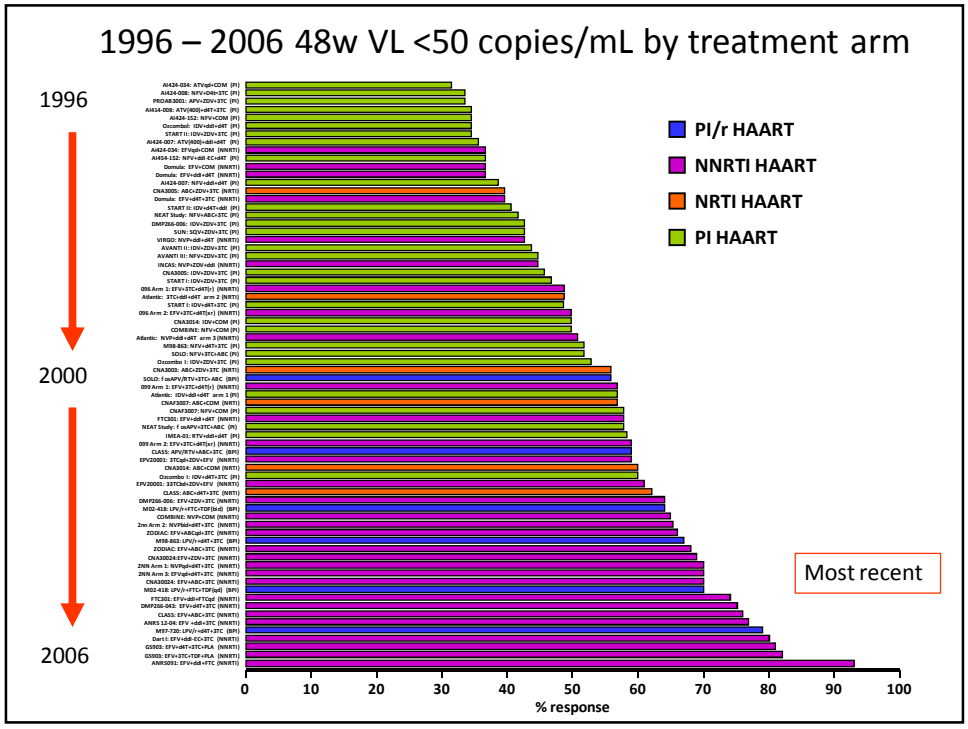
Halve It
EARLY TESTING SAVES LIVES.

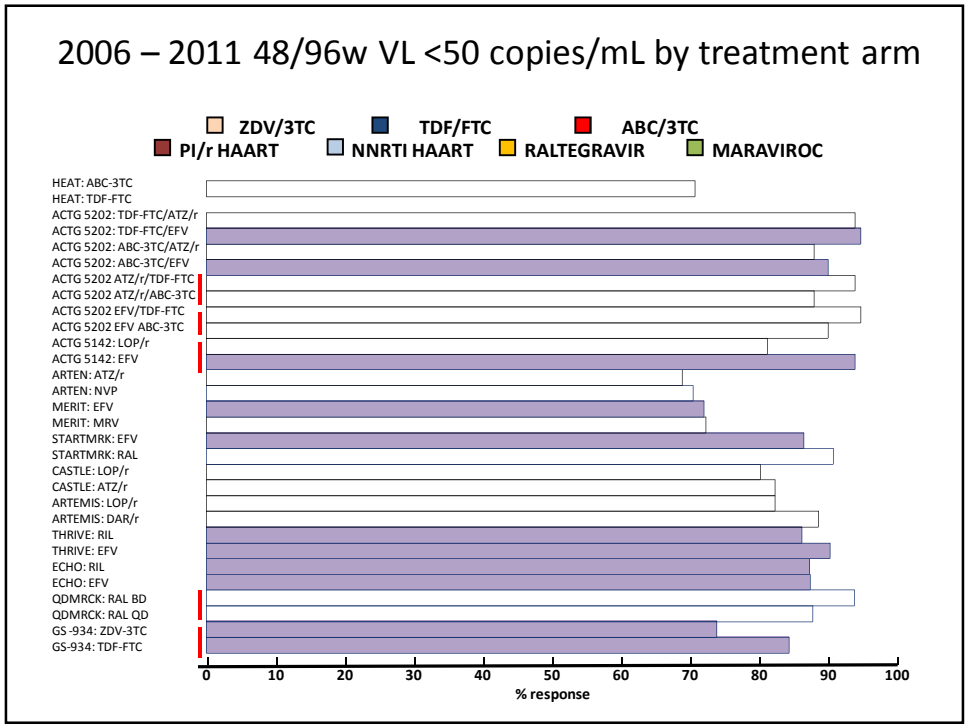
EARLY TESTING SAVES LIVES
HIV is a public health priority

What to start?

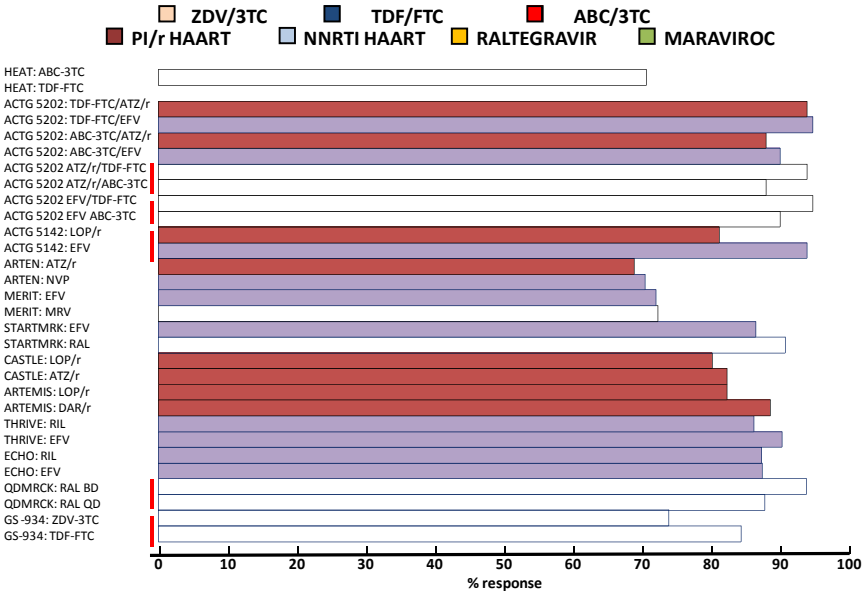
All drugs are active

Proportionality

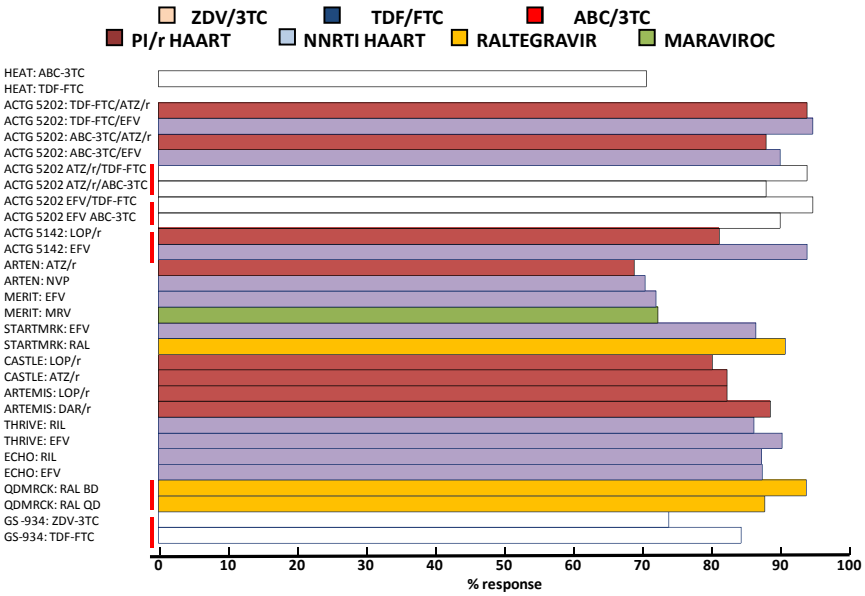

1996 – 2006 48w VL <50 copies/mL by treatment arm
1996
2000
2006
PI/r HAART
NNRTI HAART
NRTI HAART
PI HAART
Most recent
0
10
20
30
40
50
60
70
80
90
100
% response


2006 – 2011 48/96w VL <50 copies/mL by treatment arm
ZDV/3TC
TDF/FTC
ABC/3TC
PI/r HAART
NNRTI HAART
RALTEGRAVIR
MARAVIROC
HEAT: ABC-3TC
HEAT: TDF-FTC
ACTG 5202: TDF-FTC/ATZ/r
ACTG 5202: TDF-FTC/EFV
ACTG 5202: ABC-3TC/ATZ/r
ACTG 5202: ABC-3TC/EFV
ACTG 5202 ATZ/r/TDF-FTC
ACTG 5202 ATZ/r/ABC-3TC
ACTG 5202 EFV/TDF-FTC
ACTG 5202 EFV ABC-3TC
ACTG 5142: LOP/r
ACTG 5142: EFV
ARTEN: ATZ/r
ARTEN: NVP
MERIT: EFV
MERIT: MRV
STARTMRK: EFV
STARTMRK: RAL
CASTLE: LOP/r
CASTLE: ATZ/r
ARTEMIS: LOP/r
ARTEMIS: DAR/r
THRIVE: RIL
THRIVE: EFV
ECHO: RIL
ECHO: EFV
QDMRCK: RAL BD
QDMRCK: RAL QD
GS -934: ZDV-3TC
GS-934: TDF-FTC
0
10
20
30
40
50
60
70
80
90
100
% response

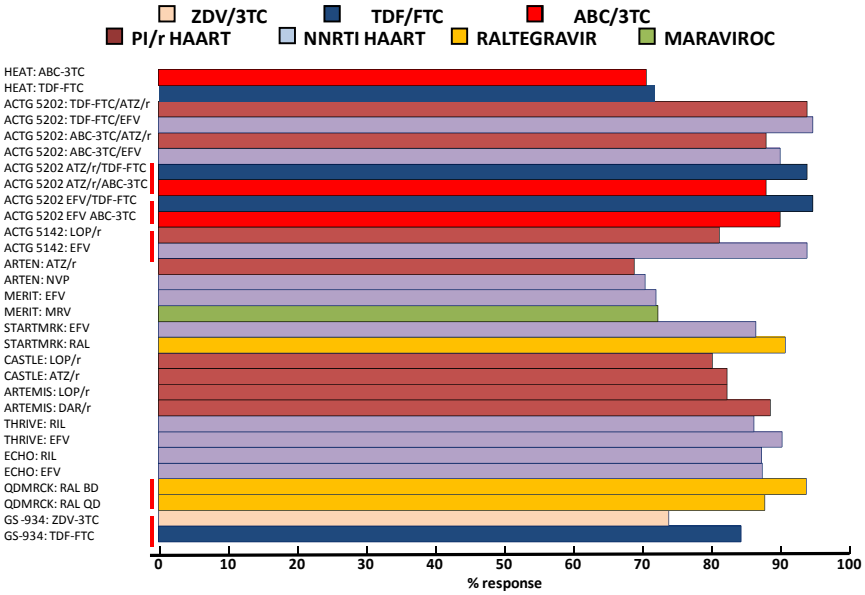
2006 – 2011 48/96w VL <50 copies/mL by treatment arm



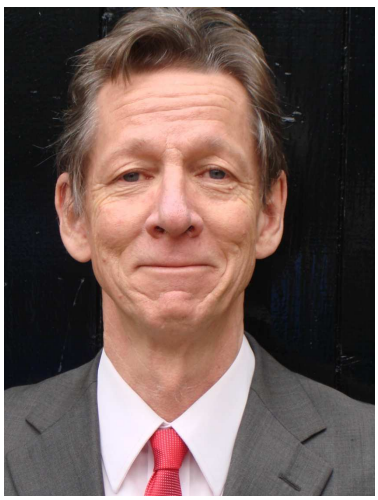
2006 – 2011 48/96w VL <50 copies/mL by treatment arm



2006 – 2011 48/96w VL <50 copies/mL by treatment arm



So ‘What to start’ for today and for tomorrow?



My problem is I'm fallible

I am persuaded by cohort studies

but I know they cannot *prove* the association

- DAD
- UK-CHIC
- NA-ACCORD
- CASCADE
- ART-CC
- SHCS
- KP
- HOPS
- MACS
- ATHENA
- HIV-CAUSAL
- CHORUS
- EuroSIDA
- ICONA
- etc……..

I am persuaded by the concept of RCT

?but I know this is *not* real life

- Completely independent
  - NIH
  - MRC
  - ANRS
  - ACTG
  - GESIDA
  - etc
- Drug registrational studies
  - FDA
  - EMEA

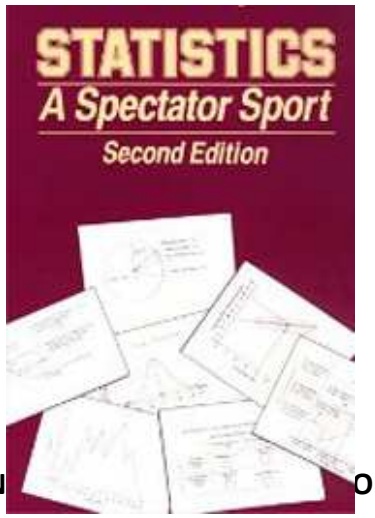
- But they don't represent real clinical practice

I struggle with statistics

Meta-analysis

Systematic reviews

I struggle with statistics



N **OR**

I am impressionable – I need a superhero team

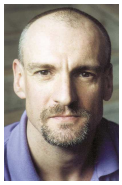
Facto

Force

Logico

Supremo

Miss Conscience



Maverick

Costa

Industangelica

I can convince myself

- Yes - I did see more failures on abacavir with high baseline viral loads before ACTG 5202?
- Yes - more of my patients on abacavir were having MI's before DAD?
- Yes - more of my patients on tenofovir were getting chronic renal failure before EuroSIDA?

None of us are superheroes

We need our Guidelines

1990 Guidelines

NIH STATE-OF-THE-ART CONFERENCE

State-of-the-Art Conference on Azidothymidine Therapy for Early HIV Infection

Sponsored by the National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Public Health Service

This State-of-the-Art Conference, which was sponsored by the National Institute of Allergy and Infectious Diseases (NIAID), National Institutes of Health, was convened to evaluate available scientific information and to resolve safety and efficacy issues related to the use of zidovudine in the treatment of HIV-infected persons with few or no symptoms of disease. The resultant statement is intended to advance understanding of this issue and to be useful to health professionals and the public.

The statement was prepared by a nonadvocacy, non-Federal panel of experts based on (1) presentations during a 1-day public session by investigators working in areas relevant to the questions; (2) questions and statements from conference attendees, including those presented during an open discussion period that was part of the public session; (3) closed deliberations by the panel during the remainder of the first day and the entire second day. This statement is an independent report of the panel and is not a policy statement of NIAID or the Federal Government.

INTRODUCTION

With the spread of the acquired immunodeficiency syndrome (AIDS) epidemic and the realization that between 800,000 and 1.5 million Americans are infected with the human immunodeficiency virus (HIV), physicians in every part of the United States are being called upon to provide primary care for persons with HIV infection. Since there is more information about the length of time a person can be infected with HIV before symptoms begin to occur, physicians are seeking guidelines for HIV antibody testing and counseling, patient monitoring, and treatment of persons presenting in the early stages of disease.

Advances in AIDS research, especially the development of zidovudine (azidothymidine/AZT; Retrovir®) for the treatment of persons with advanced HIV disease, and demonstration of effective prophylaxis against *Pneumocystis carinii* pneumonia (PCP), have brought major changes in clinical practice. Currently, zidovudine is the only antiretroviral drug approved by the Food and Drug Administration. In August 1989, NIAID announced the results of two studies conducted by the AIDS Clinical Trials Group (ACTG), showing that zidovudine can delay disease progression with minimal side effects in HIV-infected persons with fewer than 0.20×10^9 CD4 (T4) cells/L, whether asymptomatic or mildly symptomatic. On March 2 of this year, the Food and Drug Administration approved expanded zidovudine label indications to include these groups.

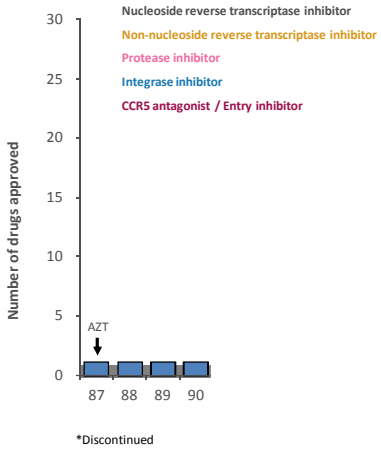
On March 3, NIAID convened the State-of-the-Art Conference on AZT Therapy for Early HIV Infection. A panel of experts, including clinical investigators, community physicians, statisticians, and community representatives with a special interest in AIDS treatment issues, was charged with formulating recommendations for facilitating the transfer of results of the recently completed clinical trials into the practice of medicine to benefit the largest possible number of persons who are infected with HIV. The panel concluded that a large proportion of the asymptomatic and mildly symptomatic HIV-infected population are candidates for early therapy with zidovudine.

This document presents the recommendations made at this conference. The panelists are fully cognizant that these recommendations are made at a time of rapid advances in our knowledge of many aspects of HIV disease and that new scientific developments may alter the state of the art at any time. Periodic state-of-the-art conferences to update recommendations for patient care will be convened as new data on therapies for HIV infection become available.

Moreover, the panelists are fully aware that the recommendations to expand the use of zidovudine have major social and economic implications and will further intensify current problems in securing adequate health care, including diagnosis and treatment, for disadvantaged and underserved popula-

From the Division of AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland.
Requests for reprints should be addressed to Office of Communications, Building 31, Room 7A32, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland 20892.

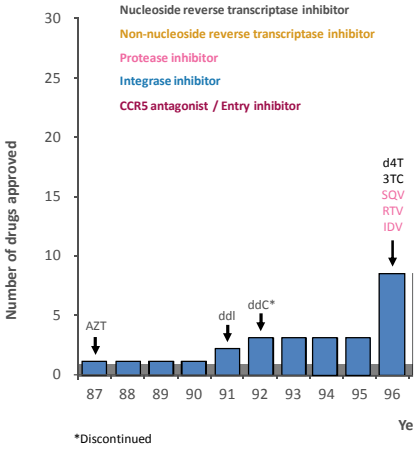
Drug development



Data available at: http://www.ema.europa.eu. Accessed March 2011

Vancouver 1996

Drug development



Data available at: http://www.ema.europa.eu. Accessed March 2011

Guidelines start to mean something

Reprinted from the Journal of the American Medical Association
July 10, 1996, Volume 276
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Consensus Statement

Antiretroviral Therapy for HIV Infection in 1996

Recommendations of an International Panel

Charles C. J. Carpenter, MD; Margaret A. Fischl, MD; Scott M. Hammer, MD; Martin S. Hirsch, MD; Donna M. Jacobsen; David A. Katzenstein, MD; Julio S. G. Montaner, MD; Douglas D. Richman, MD; Michael S. Saag, MD; Robert T. Schooley, MD; Melanie A. Thompson, MD; Stefano Vella, MD; Patrick G. Yeni, MD; Paul A. Volberding, MD; for the International AIDS Society–USA

Objective.—To provide clinical recommendations for antiretroviral therapy for human immunodeficiency virus (HIV) disease with currently (mid 1996) available drugs. When to start therapy, what to start with, when to change, and what to change to were addressed.

Participants.—A 13-member panel representing international expertise in antiretroviral research and HIV patient care was selected by the International AIDS Society–USA.

Evidence.—Available clinical and basic science data, including phase 3 controlled trials, clinical endpoint data, virologic and immunologic endpoint data, interim analyses, studies of HIV pathophysiology, and expert opinions of panel members were considered. Recommendations were limited to drugs available in mid 1996.

Process.—For each question posed, 1 or more member(s) reviewed and presented available data. Recommendations were determined by group consensus (January 1996); revisions as warranted by new data were incorporated by group consensus (February-May 1996).

Conclusions.—Recent data on HIV pathogenesis, methods to determine plasma HIV RNA, clinical trial data, and availability of new drugs point to the need for new approaches to treatment. Therapy is recommended based on $CD4^+$ cell count, plasma HIV RNA level, or clinical status. Preferred initial drug regimens include nucleoside combinations; at present protease inhibitors are probably best reserved for patients at higher progression risk. For treatment failure or drug intolerance, subsequent regimen considerations include reasons for changing therapy, available drug options, disease stage, underlying conditions, and concomitant medication(s). Therapy for primary (acute) infection, high-risk exposures to HIV, and maternal-to-fetal transmission are also addressed. Therapeutic approaches need to be updated as new data continue to emerge.

JAMA. 1996;276:146-154

From Brown University School of Medicine, Providence, RI (Dr Carpenter); Miami Veterans Affairs Medical Center and University of Miami School of Medicine (Dr Fischl); Harvard Medical School, Boston, Mass (Drs Hammer and Hirsch); The International AIDS Society–USA, San Francisco, Calif (Ms Jacobsen); Stanford (Calif) University Medical Center (Dr Katzenstein); University of British Columbia (Dr Montaner); University of California, San Diego, and San Diego Veterans Affairs Medical Center (Dr Richman); the University of Alabama at Birmingham (Dr Saag); the University of Colorado School of Medicine, Denver (Dr Schooley); the AIDS Clinical Consortium of Atlanta (Ga) (Dr Thompson); Istituto Superiore di Sanità, Rome, Italy (Dr Vella); Hôpital Bichat-Claude Bernard, Paris, France (Dr Yeni); and the University of California San Francisco (Dr Volberding).

Financial disclosures appear at the end of this article.

Reprints: International AIDS Society–USA, 350 Hayes St, San Francisco, CA 94102

IMPORTANT ADVANCES in understanding the biology and treatment of human immunodeficiency virus (HIV) infection have occurred during the past 18 months. As a result, new scientifically sound approaches to therapy have been developed that offer new options for persons with HIV infection. The most recent advances fall into 4 major categories: (1) a better understanding of the replication kinetics of HIV throughout all stages of disease; (2) the development of assays to determine the viral load in individual patients; (3) the availability of several new effective drugs; and (4) the demonstration that combination therapy is more effective than nucleoside monotherapy.

In light of these advances, the recommendations of earlier state-of-the-art guidelines[1,2] are no longer applicable to clinical decision making in 1996. Therefore, an international panel of clinical investigators experienced in HIV patient care was selected and convened by the International AIDS Society–USA to develop current recommendations for the clinical management of HIV-infected individuals.

The panel addressed 4 central questions about antiretroviral therapy: when to initiate therapy, which types of drugs to use, when to change therapy, and which types of drugs to use when a change in therapy is indicated. In addition, the treatment of primary HIV infection, prevention of vertical transmission, and postexposure prophylaxis were addressed. The recommendations are not solely based on the results of controlled clinical trials with well-defined clinical endpoints. Developing clinical guidelines in the HIV field at this time requires an approach firmly anchored in data from controlled, double-blind clinical trials when available, but must also include information from trials in progress and available virologic and immunologic endpoint data, as well as extrapolations from studies of the pathophysiology of HIV infection. Clinical decisions must be made for best use of up to 8 available antiretroviral drugs, at a time when long-term studies with clinical endpoints have been completed for only a few possible combinations.

The recommendations herein reflect the panel's agreement on the importance of plasma HIV RNA measurements for predicting risk of clinical progression as well as of the recent demonstration from clinical trials of combination therapies that reductions in plasma HIV RNA

THE LANCET

Consensus statement

British HIV Association guidelines for antiretroviral treatment of HIV seropositive individuals

*BHIVA Guidelines Co-ordinating Committee**

Only incomplete data are available to guide decisions on anti-HIV treatment. A British HIV Association consensus is that guidance must draw on other evidence besides the randomised trial. Marker studies, work on disease pathogenesis and viral dynamics, and expanding knowledge of resistance patterns mean that the approach to therapy is constantly evolving. There is a need for well-informed dialogue between HIV-infected patient and physician to achieve rational, individualised treatment. However, the following broad principles have a wide consensus amongst HIV-treating physicians in the UK: (1) treatment should be offered before substantial immunodeficiency ensues; (2) initial treatment should include combinations of at least two drugs; (3) switches in therapy should involve substitution or addition of at least two new agents; (4) viral load and CD4 measurements are essential; (5) reduction in viral load to below the detection level of a sensitive assay represents the optimal treatment response and failure to achieve or sustain this control should prompt consideration of therapy modification. This response seems to be achieved most reliably with combinations of two nucleoside analogues plus a third agent (a protease inhibitor, a non-nucleoside reverse-transcriptase inhibitor, or a third nucleoside analogue) or of two protease inhibitors.

Recent developments have greatly altered the management of HIV-infected patients and we can expect further expansion in the range of treatments and in the complexity of treatment regimens and the arrival of new or more sensitive laboratory tools, such as plasma viral load assays, that permit greater individualisation of patient management. Our knowledge of the pathogenesis and viral dynamics of and the immune response to HIV infection is also increasing, demanding constant reassessment of treatment strategies. Panel 1 lists the antiretroviral agents that were licenced in the UK as of Feb 28, 1997, or were at an advanced stage of clinical development.

Five large randomised clinical trials[1-5] suggest that combination antiretroviral therapy is superior to nucleoside analogue monotherapy and that short-term changes in viral load (and also in CD4 count) predict much of the treatment effect of these combinations. Smaller, short-term studies of triple-drug combinations or combinations of two protease inhibitors have revealed reductions in HIV plasma viral load by a factor of over 100, suggesting that these therapies may be clinically more beneficial than two nucleoside analogues in combination. However, dilemmas remain. When should treatment begin, which agent(s) should be used, and when should therapy be changed?

On Sept 21, 1996, over 200 HIV physicians and others met in London under the auspices of the British HIV Association (BHIVA) and tried to arrive at a consensus on some of these issues. To provide detailed prescriptive

Lancet 1997; **349:** 1086–92
See Commentary page 1042

*B G Gazzard, G J Moyle, J Weber, M Johnson, J S Bingham, R Brettle, D Churchill, M Fisher, G Griffin, D Jefferies, King E, Gormer R, C Lee, A Pozniak, J R Smith, G Tudor-Williams, I Williams

Correspondence to: Dr Brian Gazzard, Chelsea and Westminster Hospital, London SW10 9TH, UK.

Panel 1: **Antiretroviral agents**

Nucleoside analogues	Protease inhibitors	Non-nucleoside reverse transcriptase inhibitors
Zidovudine (ZDV, AZT)	Saquinavir	Nevirapine*
Zalcitabine (ddC)	Ritonavir	Delavirdine*
Didanosine (ddI)	Indinavir	Loviride*
Stavudine (d4T)	Nelfinavir*	
Lamivudine (3TC)	VX-478*	

*Not yet licenced in Europe (nevirapine is licenced in USA).

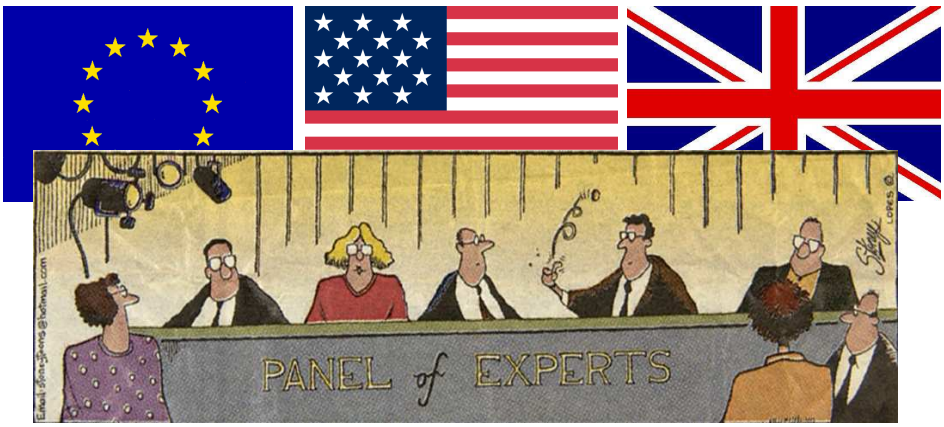
guidelines, such as those published by a US group,[6] would be repetitive and rapidly outdated. The meeting's philosophy was that both patients and doctors should be pointed towards the recent evidence, which should be discussed in detail before individual decisions about therapy are made. However, since HIV treatment budgets are under considerable pressure in the UK (and worldwide) it was felt that broadly agreed principles governing current choices should be included for the benefit of those purchasing HIV health care.

Antiretroviral therapy is just one strand of care for people with HIV infection. Other aspects which require our attention include psychological and social care, management and prevention of opportunistic infections, and prevention of transmission of HIV. The expansion of HIV therapies and viral-load monitoring are likely to increase costs in the short-term but this expenditure must be viewed in the context of the maintenance of health among young, productive members of society, the effects of therapy in reducing the costs of hospital admission and the management of opportunistic disease, and, potentially, the benefits of reducing the transmission of HIV.

Quality of evidence

The best standard of evidence for a particular treatment is agreement between the results of two separate randomised trials. However, the range of treatments for HIV has expanded so rapidly that this quality of evidence

Guideline committees

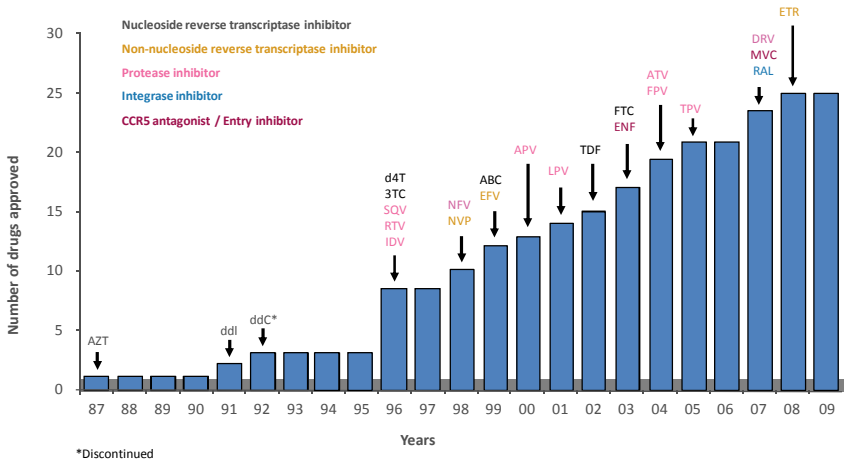


Choice 1998

NRTI/NtRTI	NNRTI	Protease inhibitor	Others
AZT 3TC ddI Abacavir ddC d4T Adefovir*	Nevirapine Efavirenz Delavirdine	Saquinavir Ritonavir Indinavir Nelfinavir Amprenavir Lopinavir/r*	Hydroxyurea

Available on expanded access 1999

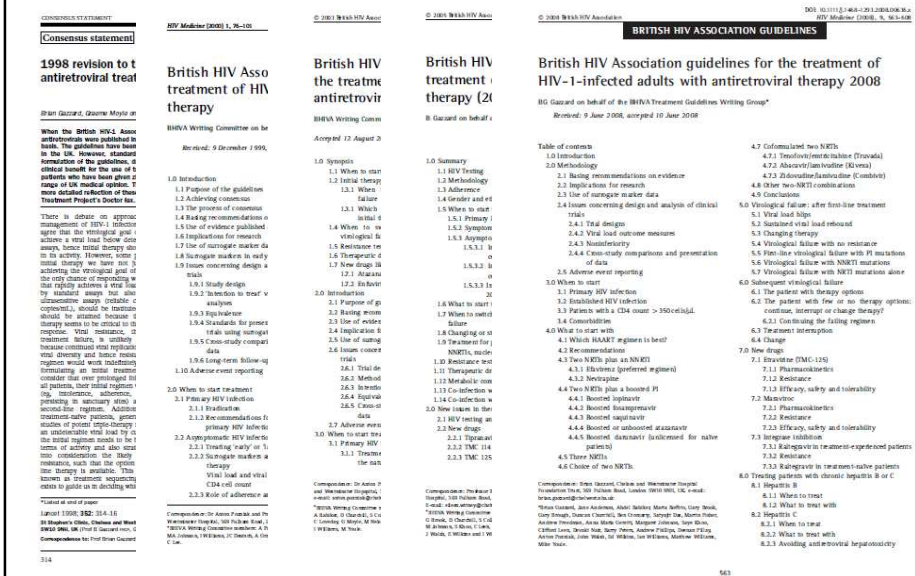
Drug development



*Discontinued

Data available at: http://www.ema.europa.eu. Accessed March 2011

Guideline development



Consensus statement

1998 revision to t
antiretroviral treat

British HIV Asso
treatment of HIV
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treatment
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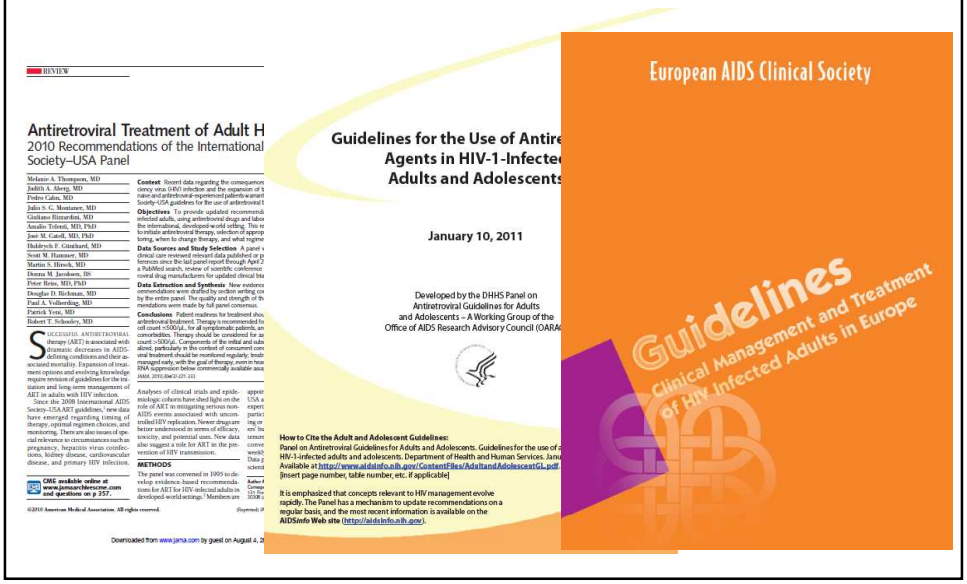
BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008

2010/11 Guidelines



REVIEW

Antiretroviral Treatment of Adult H
2010 Recommendations of the International
Society–USA Panel

Guidelines for the Use of Antire
Agents in HIV-1-Infecte
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 (OARA

European AIDS Clinical Society

Guidelines
Clinical Management and Treatment
of HIV Infected Adults in Europe

So what about the BHIVA guidelines?

- Always been different
- Always been right??
- Nothing since 2008!

	1990	2000	2008
DHHS	AZT	2RT+PI	2RT+PI/r 2RT+NNRTI
IAS	AZT	2RT+PI	2RT+PI/r 2RT+NNRTI
EACS			2RT+PI/r 2RT+NNRTI
BHIVA		2RT+NNRTI 2RT+PI	2RT+NNRTI (2RT+PI/r)

ACTG 5142: Study design

- Randomised, multicentre, open-label trial
- ARV-naïve (n=753)
- ≥13 years of age
- HIV-1 RNA ≥2,000 copies/mL
- Study duration: 96 weeks
- Stratified at randomisation:
  - HIV-1 RNA <100,000 vs ≥100,000 copies/mL
  - Chronic Hepatitis B/C infection
  - NRTI selection

EFV 600 mg 2 NRTIs	n=250
LPV/r 400/100 mg BD + 2 NRTIs	n=253
EFV 600 mg LPV/r 533/133 mg BD	n=250

1st NRTI (all patients): 3TC (150 mg BD or 300 mg OD)
†2nd NRTI (investigator selection): ZDV 300 mg BD, TDF 300mg OD or d4T XR OD

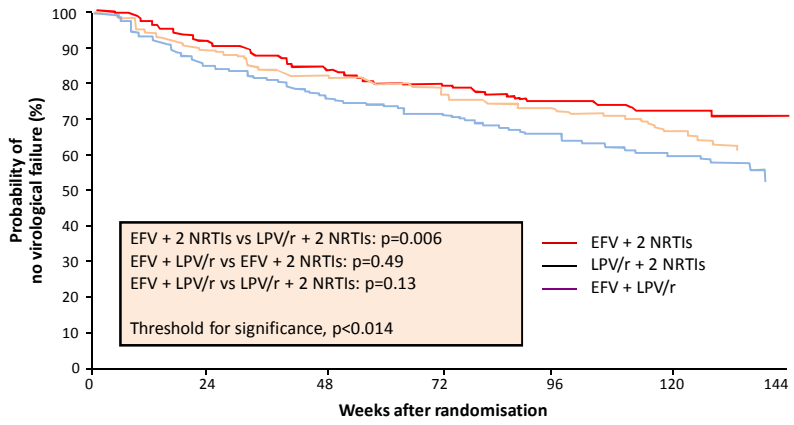
†d4T XR was an investigational formulation of stavudine that is not commercially available
Dosing was 100 mg OD or 75 mg OD if subject weighed <60kg

Riddler SA, Haubrich R, DiRienzo AG et al. N Engl J Med 2008;358:2095–106.

Considerations for an effective ARV regimen – efavirenz ticked the boxes

- **Durable activity**
- **Convenient**
- **Pretty well tolerated**
- **Free of long-term side effects**
- **Limited drug-interaction potential**

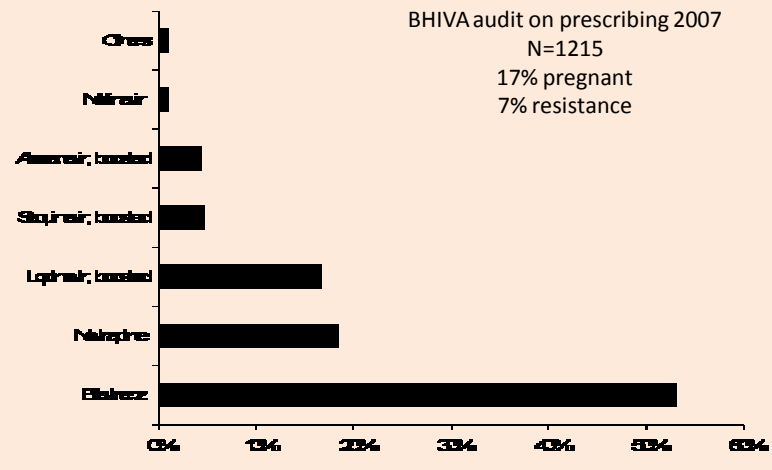
ACTG 5142: Significantly longer time to virological failure with EFV compared to LPV/r



EFV+2NRTIs n=	250	210	186	173	142	73	19
LPV/r+2NRTIs n=	253	210	185	168	140	74	14
EFV+LPV/r n=	250	215	189	181	149	73	17

Adapted from Riddler SA, Haubrich R, DiRienzo AG et al. N Engl J Med 2008;358:2095–106

The most preferred regimens UK 2007



How robust are the guidelines?

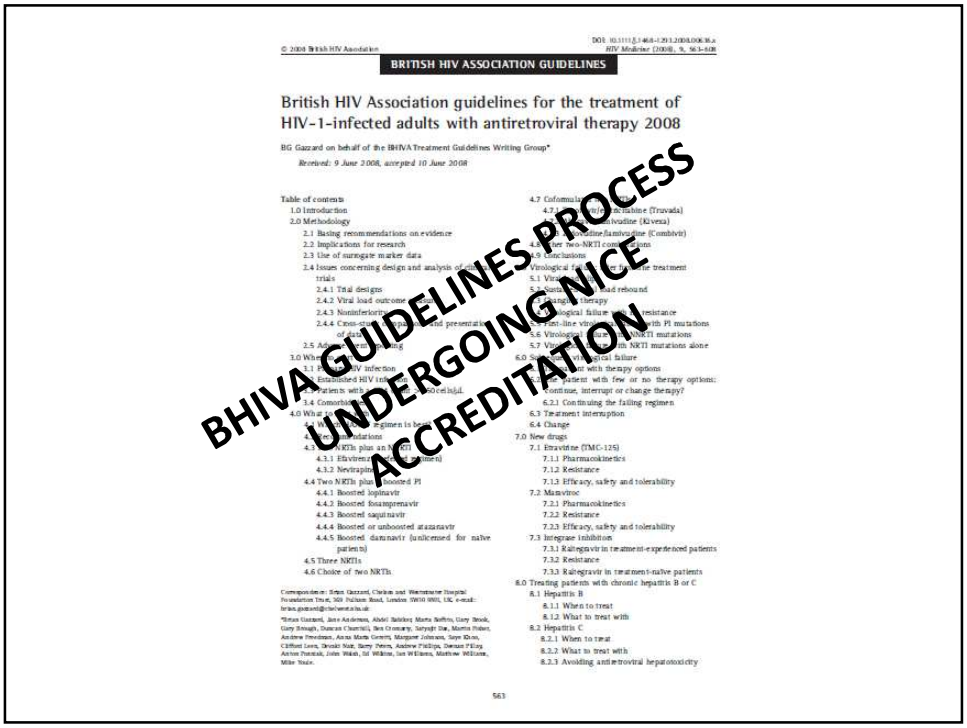
Not enough maybe!

Guidelines process

	Guideline				
	DHHS	IAS	BHIVA	EACS	GESIDA
Last published	2011	2010	2008	2011	2011
Member No.	39	16	25	13	29
Community rep.	√	X	√	X	X
Conflict of interest given	√	√ - forbidden*	√	X	X
Roles of members	√	√	X	X	X
Web consultation period	√	X	√	X	√
Process of recommendations given	√	√	√	X	√
Graded recommendations	√	√	X/√	X	√

Guidelines process

	Guideline				
	DHHS	IAS	BHIVA	EACS	GESIDA
Data collection process given	√	√	X	X	√
Update frequency	Yearly	1-2 yearly	1-3 yearly	Yearly	1-2 yearly
Page numbers	166	12	45	25	239
Reference numbers	936	145	335	1	992
Focussed	√	√	√	Broad	√
Detail	Full	Reviewed data	Reviewed data	Summarised	Full
Review process given	√ - Internal	√ - Internal	X	X	√ - Internal
Drug costs considered	X	X	X	X	√



DOI: 10.1111/j.1468-1293.2008.00636.x
HIV Medicine (2008), 9, 563–608

BRITISH HIV ASSOCIATION GUIDELINES

British HIV Association guidelines for the treatment of HIV-1-infected adults with antiretroviral therapy 2008

BG Gazzard on behalf of the BHIVA Treatment Guidelines Writing Group*

Received: 9 June 2008, accepted 10 June 2008

Table of contents

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*Brian Gazzard, Jane Anderson, Abdel Babiker, Maria Boffito, Gary Brook, Gary Brough, Duncan Churchill, Ben Cromarty, Satyajit Das, Martin Fisher, Andrew Freedman, Anna Maria Geretti, Margaret Johnson, Saye Khoo, Clifford Leen, Deenaz Nair, Barry Peters, Andrew Phillips, Duncan Pleeing, Anton Pozniak, John Walsh, Ian Williams, Ian Williams, Matthew Williams, Mike Youle.

BHIVA GUIDELINES PROCESS UNDERGOING NICE ACCREDITATION

Nevertheless there is reasonable consistency!

- Getting ranked as 'Recommended'?
  - ITT analysis RCT 48/96w showing overall non-inferiority / superiority with EFV or best of class with equivalent rates of virological failure ***AND***
  - No serious type B/C AE whether:
    - Causality to drug certain (e.g., hypersensitivity with NVP, anaemia with ZDV)
    - Causality to drug uncertain (e.g., MI with abacavir) but sufficient evidence to suspect significant

Recommended in Guidelines for naïve patients without restriction

	BHIVA 2008	EACS 2011	DHSS 2011	IAS 2010	Spanish GESIDA 2011
3rd Drug					
Atazanavir/r		√	√	√	√
Darunavir/r		√	√	√	√
Efavirenz	√	√	√	√	√
Raltegravir		√	√	√	
Lopinavir/r		√			√
Saquinavir/r		√			
Fosampren./r					
Nevirapine		√			
2NRTI					
TDF/FTC	√	√	√	√	√
ABC/3TC					

Recommended in Guidelines for naïve patients without restriction

3rd Drug	NRTIs	Key studies 2008-2011	Excepting
Efavirenz	TDF/FTC	ECHO, THRIVE, STARTMRK, 2NN, ACTG 5202, ASSERT, 934, MERIT, ACTG 5142	1TM pregnancy, active ψ illness, eGFR↓
Darunavir/r	TDF/FTC	ARTEMIS	eGFR↓
Atazanavir/r	TDF/FTC	CASTLE, ACTG 5202, ARTEN	PPI, eGFR↓
Raltegravir	TDF/FTC	STARTMRK	eGFR↓
Lopinavir/r	TDF/FTC	ARTEMIS, 730, CASTLE, GEMINI, OCTANE II, HEAT, ACTG 5142	Lipids, high CV risk, eGFR↓
Nevirapine	TDF/FTC	ARTEN, OCTANE II	CD4 restrictions
Efavirenz	ABC/3TC	ACTG 5202	HLAB57, CD4 >10^5, high CV risk, 1TMp, active ψ
Atazanavir/r	ABC/3TC	ACTG 5202, ASSERT, CNA30024	HLAB57, CD4 >10^5, high CV risk
Lopinavir/r	ABC/3TC	KLEAN, HEAT	HLAB57, CD4 >10^5, high CV risk
Efavirenz	AZT/3TC	934, CNA30024, MERIT	1TM pregnancy, active ψ illness, eGFR, Hb↓
Maraviroc	AZT/3TC	MERIT	R5 tropic, Hb↓

ACTG 5202: study design

HIV-1 RNA ≥1000 c/mL
Any CD4+ count
≥ 16 years of age

ART- naïve
1858 enrolled
Randomized 1:1:1:1

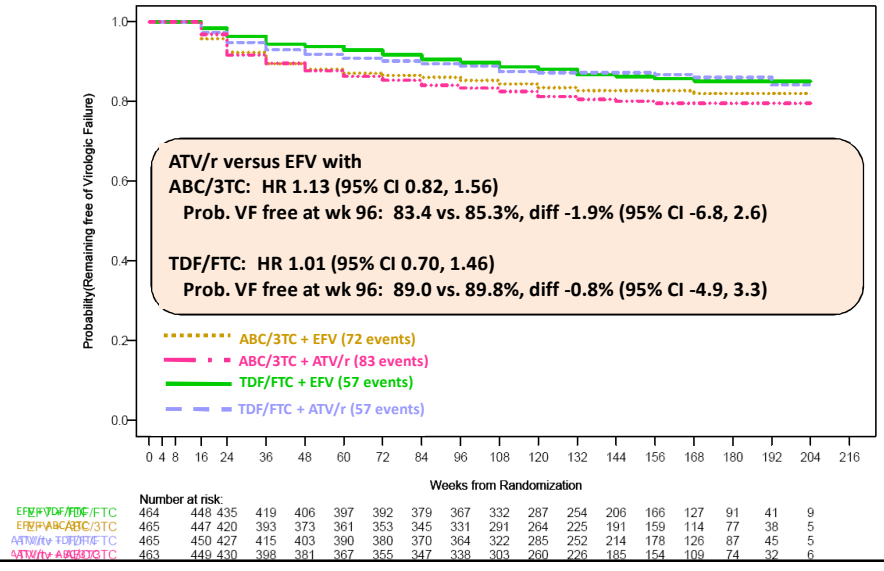
Stratified by HIV-1 RNA
(< or ≥ 100,000 copies/mL)

Arm			
A	TDF/FTC QD	ABC/3TC Placebo QD	EFV QD
B	ABC/3TC QD	TDF/FTC Placebo QD	EFV QD
C	TDF/FTC QD	ABC/3TC Placebo QD	ATV/r QD
D	ABC/3TC QD	TDF/FTC Placebo QD	ATV/r QD

Sax PE et al. IAS 2008 Abstract THAB0303

A5202: Overall

ACTG 5202: no difference in time to virological failure: ATV/r vs. EFV



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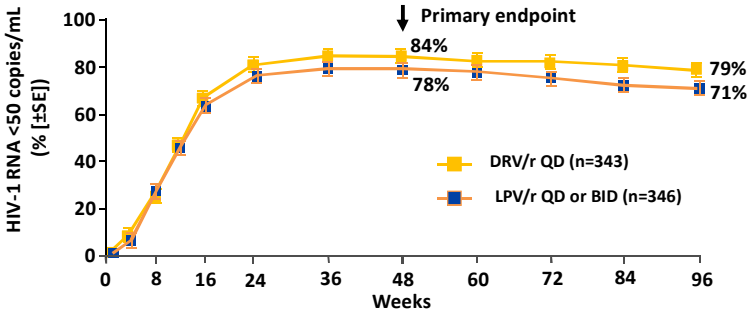
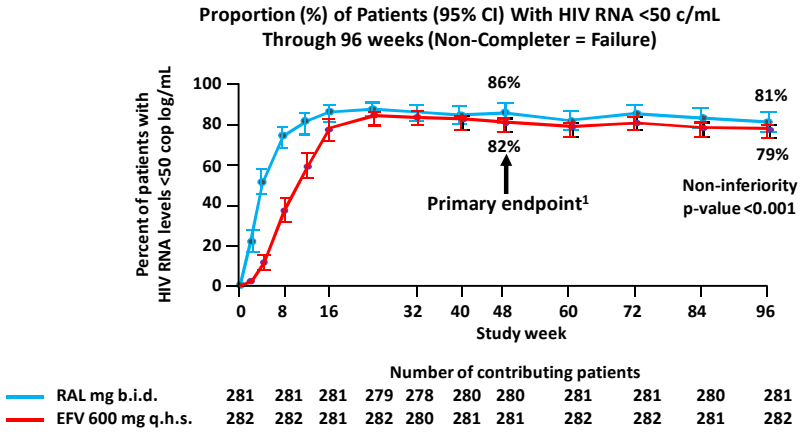


- Superiority at Week 96 also observed when DRV/r (n=343) was compared with a subset of patients treated with LPV/r BID (n=258) only (p=0.038)
- DRV/r was associated with fewer VFs than LPV/r (12% vs 17%; p=0.0437) fewer discontinuations due to AEs (4% vs 9%)

Week 96:
Estimated difference in response vs. LPV/r for noninferiority:
PP: 8.4% (95% CI: 1.9% to 14.8%; p<0.001)
Estimated difference in response vs. LPV/r for superiority:
ITT: 8.3% (95% CI: 1.8% to 14.7%; p=0.012)

Adapted from Mills A et al., *AIDS* 2009, 23:1649–1688.

STARTMRK: virological efficacy at week 96



- Proportion (%) of patients with HIV RNA <400 c/mL at 96 weeks (Non-Completer = Failure)
  - RAL group 85% vs. EFV group 81%
  - Non-inferiority p<0.001

Adapted from Lennox J et al., 49th ICAAC 2009, San Francisco, California, USA. Poster H924b.

Guidelines

- Getting ranked as 'alternative':
  - ITT analysis 48/96w showing reduced efficacy against comparator in certain settings:
    - Restricted by baseline viral load (e.g., abacavir/3TC)
  - Cohort studies show stronger association with serious AE under specific settings:
    - Restricted by CD4 count (e.g., NVP) or co-morbidity (abacavir)

Alternative option in Guidelines for naïve patients

	BHIVA 2008	EACS 2011	DHSS 2011	IAS 2010	Spanish GESIDA 2011
3rd Drug					
Atazanavir/r		√	√	√	√
Darunavir/r		√	√	√	√
Efavirenz	√	√	√	√	√
Raltegravir		√	√	√	
Lopinavir/r		√			√
Saquinavir/r		√			
Fosampren./r					
Nevirapine		√			
2NRTI					
TDF/FTC	√	√	√	√	√
ABC/3TC					

Alternative option in Guidelines for naïve patients

3rd Drug	NRTIs	Key studies 2008-2011	Comments
Efavirenz	TDF/FTC	ECHO, THRIVE, STARTMRK, 2NN, ACTG 5202, ASSERT, 934, MERIT, ACTG 5142	1TM pregnancy, active ψ illness, eGFR↓
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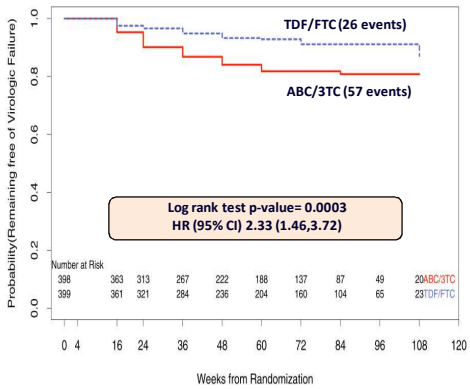
Maraviroc	AZT/3TC	MERIT	R5 tropic, Hb↓

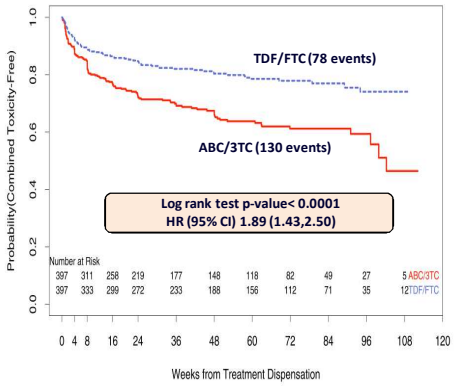
ABC/3TC vs. TDF/FTC
Primary Virologic and Safety Endpoints
(High Viral Load Stratum at DSMB Action)

N=797; median (25th, 75th) follow-up = 60 weeks (28, 84)

Time to Virologic Failure



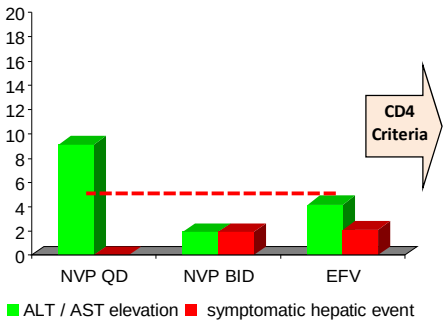
Time to Safety Endpoint



Sax PE, et al. NEJM 2009; 361:2230-2240

Applying CD4 criteria to 2NN study

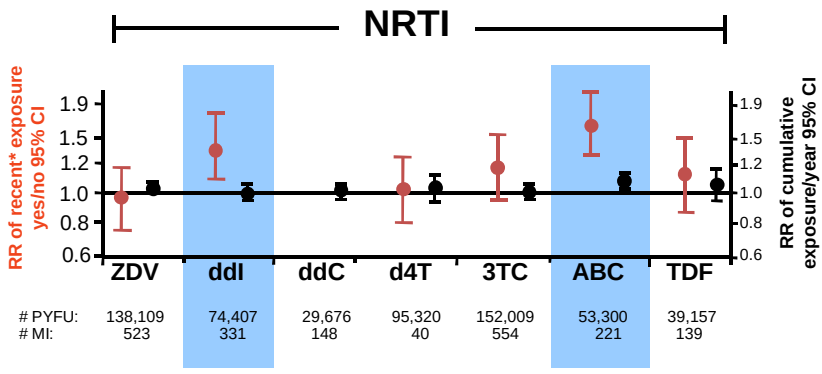
Hepatic events in North America, Europe, Australia



Without CD4 cut-offs

55

D:A:D: Recent and/or cumulative antiretroviral exposure and risk of MI



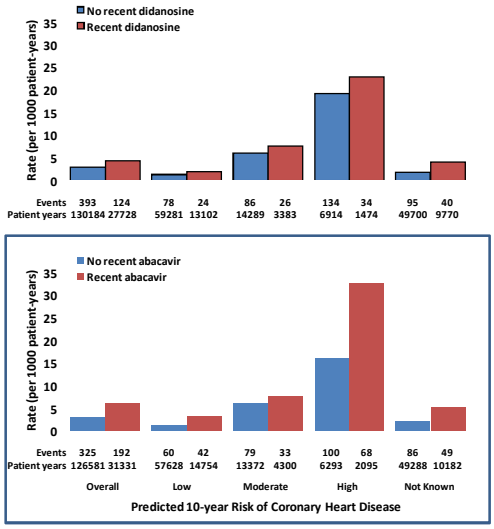
*Current or within last 6 months. †Approximate test for heterogeneity: $P = 0.02$

Lundgren JD, et al. CROI 2009. Abstract 44LB; DAD Study Group Lancet 2008

Only >30,000 PY of follow up

NRTIs and MI Risk in D:A:D

- Increased risk from ABC and ddI most marked in those at "high" risk
  (6% of D:A:D)
- Numbers needed to harm/5 years
  - ABC = 11
  - ddI = 20

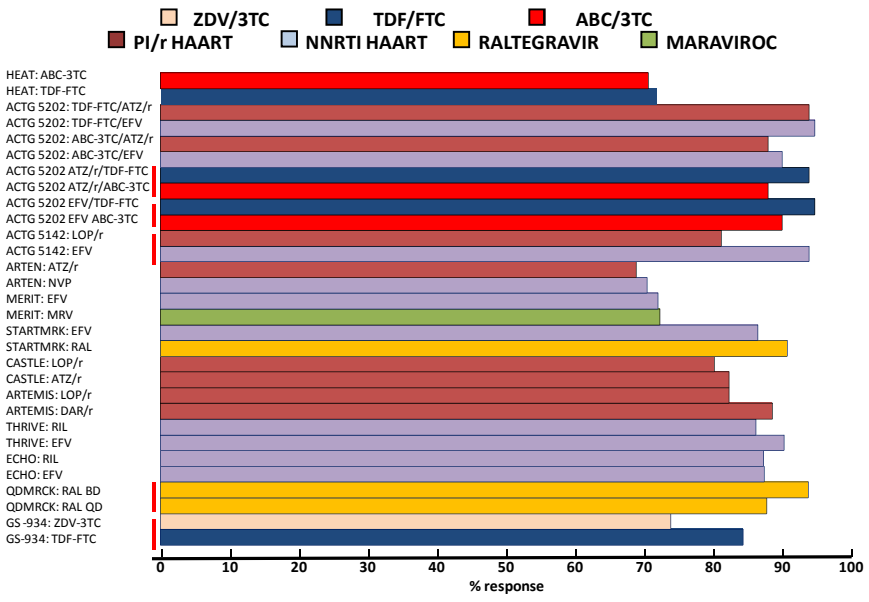


Chronic disease – drug links with varying evidence of significance

Organ system	HIV effect		Studies linking drug	Drugs
Cardiac	Significant		DAD ANRS SMART	Abacavir DDI
Renal	Significant		EuroSIDA	Tenofovir Atazanavir Lopinavir
Bone	Evident		ACTG 5142 ACTG 5202 Several small studies	Tenofovir

So how significant are the differences between drugs?

2006 – 2011 48/96w VL <50 copies/mL by treatment arm



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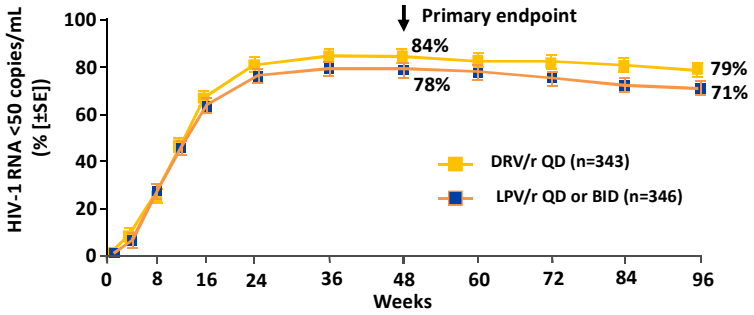

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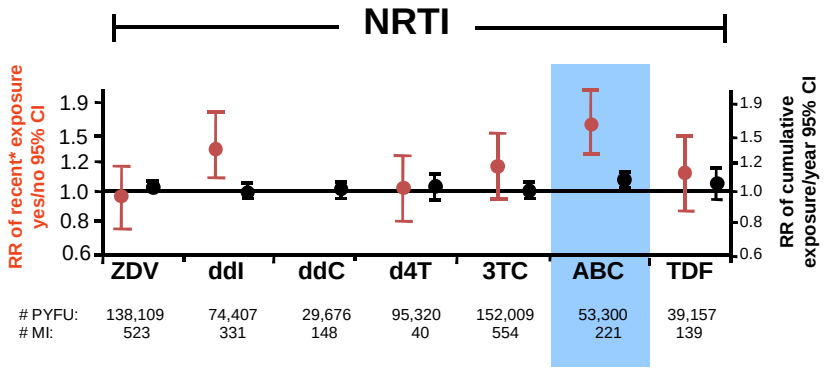
Adapted from Mills A et al., *AIDS* 2009, 23:1649–1688.

How certain are we that the drug is the cause of a s/e?

D:A:D: Recent and/or cumulative antiretroviral exposure and risk of MI



*Current or within last 6 months. †Approximate test for heterogeneity: $P = 0.02$

Lundgren JD, et al. CROI 2009. Abstract 44LB; DAD Study Group Lancet 2008

Only >30,000 PY of follow up

Observational cohort vs. randomised studies

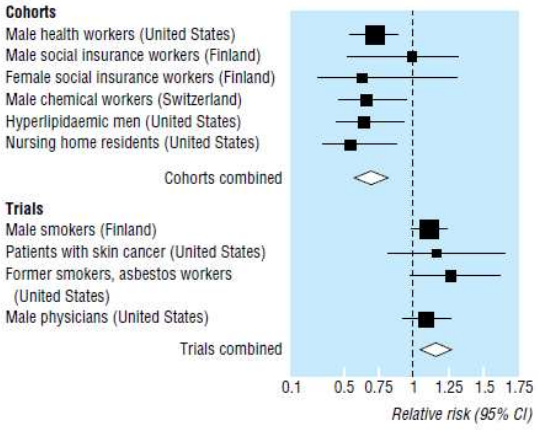
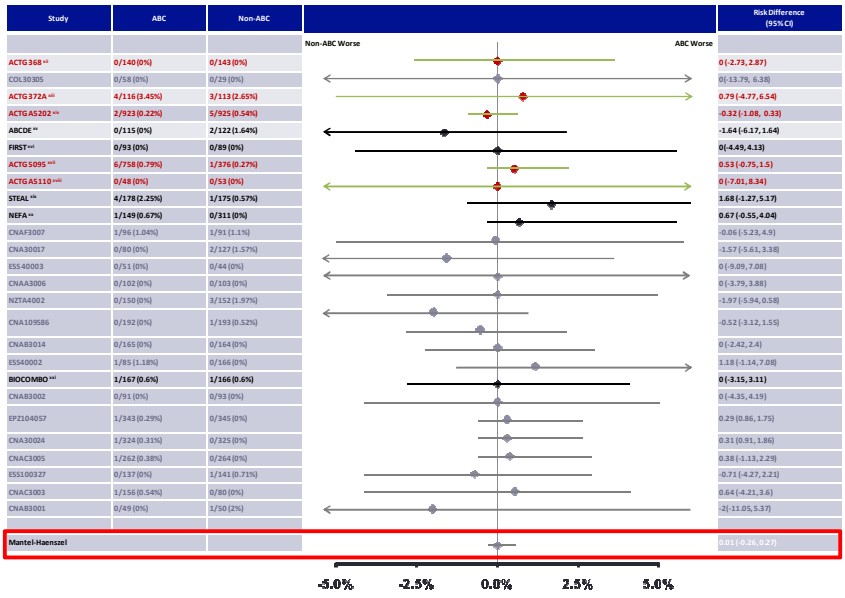


Fig 2 Meta-analysis of association between β carotene intake and cardiovascular mortality: results from observational studies show considerable benefit, whereas the findings from randomised controlled trials show an increase in the risk of death. Meta-analysis is by fixed effects model

FDA Meta-Analysis of ABC in naïve patients:

No association between ABC and MI

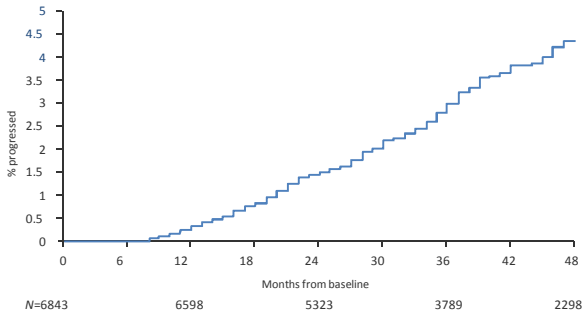


Ding X, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 808.

EuroSIDA: Rate of chronic kidney disease and exposure to ARV

6843 patients, 75% male, median 43 years,
90% on cART CD4 450, 22% hypertension,
5% diabetes. Median f/u 3.7 yrs

Incidence :1.1 (0.9-1.2/100 PYFU

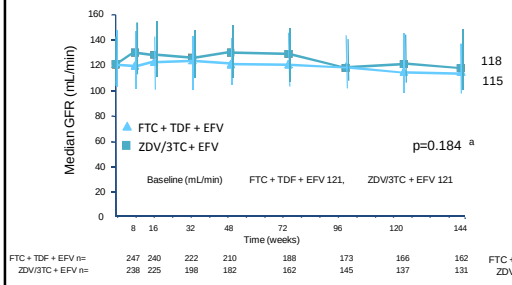


	Multivariable	
	IRR/yr	95% CI
Tenofovir	1.16	1.06 – 1.25
Indinavir	1.12	1.06 – 1.18
Atazanavir	1.21	1.09 – 1.34
Lopinavir	1.08	1.01 – 1.16

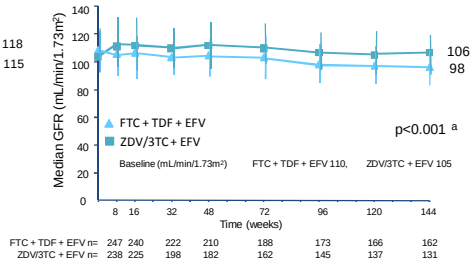
Adapted from Mocroft A et al. *AIDS* 2010; 24:1667–1678

Slide 934: Median (IQR) Glomerular Filtration Rate

Cockroft–Gault formula



Modification of diet in renal disease formula



[a]Wilcoxon rank sum test

Adapted from Arribas JR et al. IAS 2007 Poster #WEPEB 029

ATRIPLA® is not indicated for treatment-naïve patients in the EU

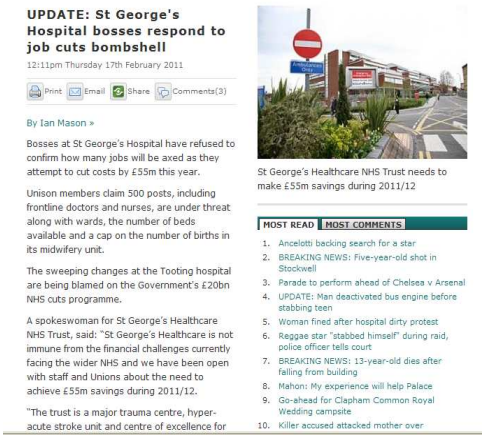
Chronic disease – drug links with varying evidence of significance

Organ system	HIV effect		Studies linking drug	Drugs	Not found in RCT
Cardiac	Significant		DAD ANRS SMART	Abacavir DDI	FDA - meta Cruciani - meta
Renal	Significant		EuroSIDA	Tenofovir Atazanavir Lopinavir	934 903-E
Bone	Evident			Tenofovir	ACTG 5142 ACTG 5202 Several small studies

What about costs and will guidelines become less important?

Stark reality

- Government strapped for cash
- Financial savings must be made
- Probably no/limited uplift for drug bill
- PBR on its way



UPDATE: St George's Hospital bosses respond to job cuts bombshell

12:11pm Thursday 17th February 2011

Print Email Share Comments(3)

By Ian Mason »

Bosses at St George's Hospital have refused to confirm how many jobs will be axed as they attempt to cut costs by £55m this year.

Unison members claim 500 posts, including frontline doctors and nurses, are under threat along with wards, the number of beds available and a cap on the number of births in its midwifery unit.

The sweeping changes at the Tooting hospital are being blamed on the Government's £20bn NHS cuts programme.

A spokeswoman for St George's Healthcare NHS Trust, said: "St George's Healthcare is not immune from the financial challenges currently facing the wider NHS and we have been open with staff and Unions about the need to achieve £55m savings during 2011/12.

"The trust is a major trauma centre, hyper-acute stroke unit and centre of excellence for

St George's Healthcare NHS Trust needs to make £55m savings during 2011/12

MOST READ | MOST COMMENTS

1. Ancelotti backing search for a star
2. BREAKING NEWS: Five-year-old shot in Stockwell
3. Parade to perform ahead of Chelsea v Arsenal
4. UPDATE: Man deactivated bus engine before stabbing teen
5. Woman fined after hospital dirty protest
6. Reggae star "stabbed himself" during raid, police officer tells court
7. BREAKING NEWS: 13-year-old dies after falling from building
8. Mahon: My experience will help Palace
9. Go-ahead for Clapham Common Royal Wedding campsite
10. Killer accused attacked mother over

Drugs costs in Spain – incorporated into guidelines

Summary of ARV prescribing 'Guidelines' in London

Recommended in Guidelines for naïve patients

	BHIVA 2008	EACS 2011	DHSS 2011	IAS 2010	London consortium
3rd Drug					
Atazanavir/r		√	√	√	√
Darunavir/r		√	√	√	
Efavirenz	√	√	√	√	√
Raltegravir		√	√	√	
Lopinavir/r		√			
Saquinavir/r		√			
Fosampren./r					
Nevirapine		√			√*
2NRTI					
TDF/FTC	√	√	√	√	
ABC/3TC		√*			√*

Mandated in Commissioning guidance

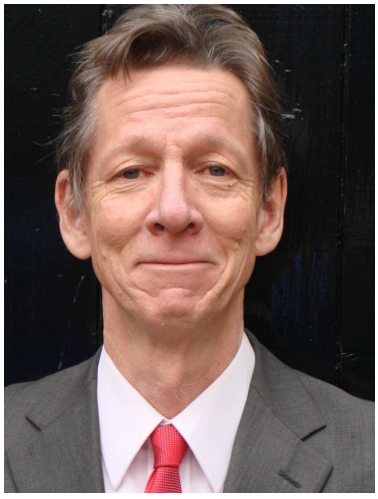
- No drug will be excluded from being prescribed
- The guidelines for use of treatment must be supported by scientific evidence
- Where two options are broadly similar but have a significant difference in costs, the less expensive drug will be preferred
- **Where a drug is used outside the guideline it will not be reimbursed**

The future – the cost risk to us?

- Cost and industry tendering will determine strategies of treatment
- Guidelines will have less impact
- Fixed – dose combinations will become less of a factor

- Less clinical freedom will exist

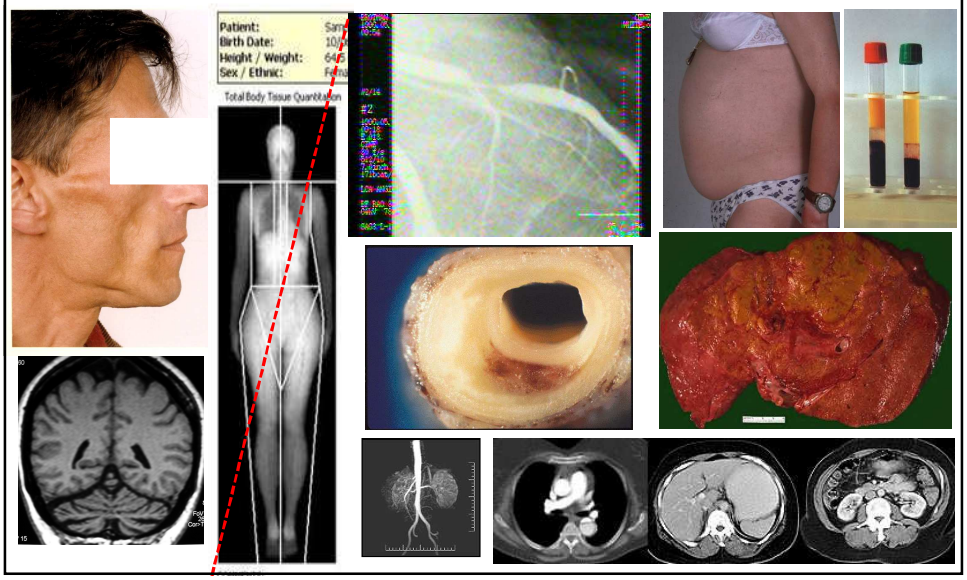
So 'What to start' for tomorrow?



The ARV future?

- Is there a future without efavirenz?

Is there a future without efavirenz?



Why/why not efavirenz?

For

- Long track record
- Familiarity
- Unsurpassed potency
- Convenience
- Forgiveness
- No significant end-organ toxicity?
- HBV co-infected
- HCV on treatment

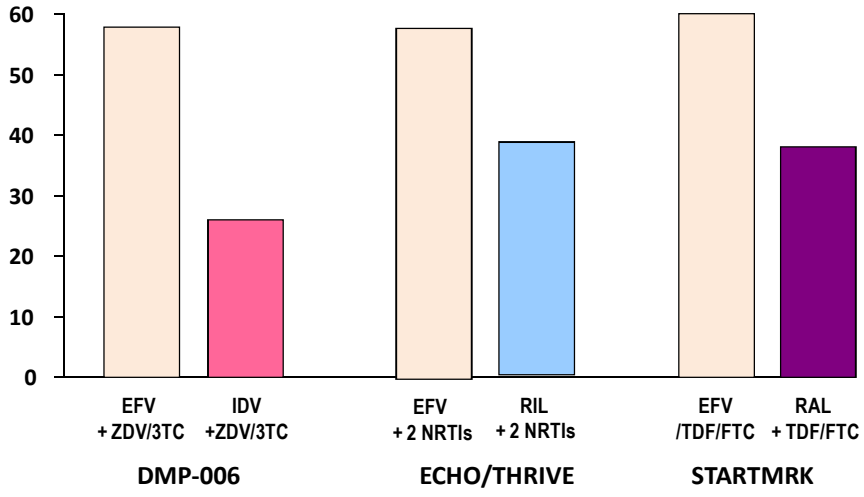
Against

- CNS adverse effects
- Teratogenicity 1st trimester?
- Low resistance barrier
- Risk of resistance with treatment interruption
- Lower CD4+ cell count increase?
- Lipids?
- Vitamin D?

Why choose an alternative?

- NNS intolerability of efavirenz
  - Inevitable consequence?
  - Often long-lived?
  - Often severe?
  - Dangerous in those with a pre-existing/current psychiatric diagnosis?
  - Difficult to manage safely?
- Likelihood of planned/unplanned pregnancy
  - Teratogenicity?

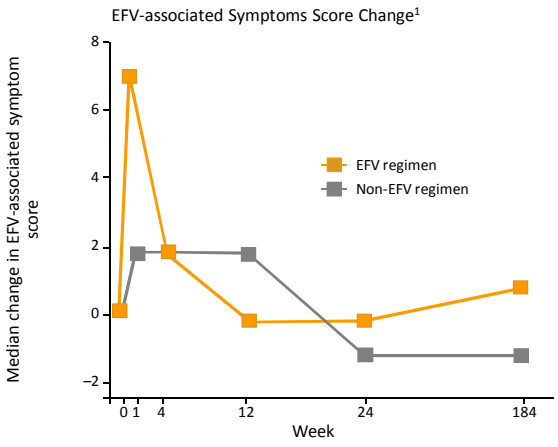
Clinical trials of first-line EFV: 48-week data on NPS adverse events*



*All Grade 1–4 nervous system events

Hill and Gazzard, AIDS Reviews 2010

Symptoms typically resolve by Week 4: Study A5095/5097



n=200 and n=103 at Week 0 for the EFV and non-EFV regimens, respectively

- Randomised, double-blind trial
- Naïve patients with HIV-1 RNA level >400 copies/mL and any CD4 cell count[2]
- Minimal increase in baseline EFV-associated symptoms "of questionable clinical significance"[1]

1. Adapted from Clifford DB, et al. 13th CROI 2006 Poster 773; 2. Gulick RM, et al. N Engl J Med 2004;350:1850–61

ECHO/THRIVE data + pre-existing neurological/psychiatric history

No history		Past history	
Neurological		**Psychiatric**	
Efavirenz BL	Efavirenz 48w	Efavirenz BL	Efavirenz 48w
43%	49%	26%	41%
Neurological		**Psychiatric**	
Rilpivirine BL	Rilpivirine 48w	Rilpivirine BL	Rilpivirine 48w
23%	35%	21%	35%

Antiretroviral Pregnancy Registry 1/89- 1/10

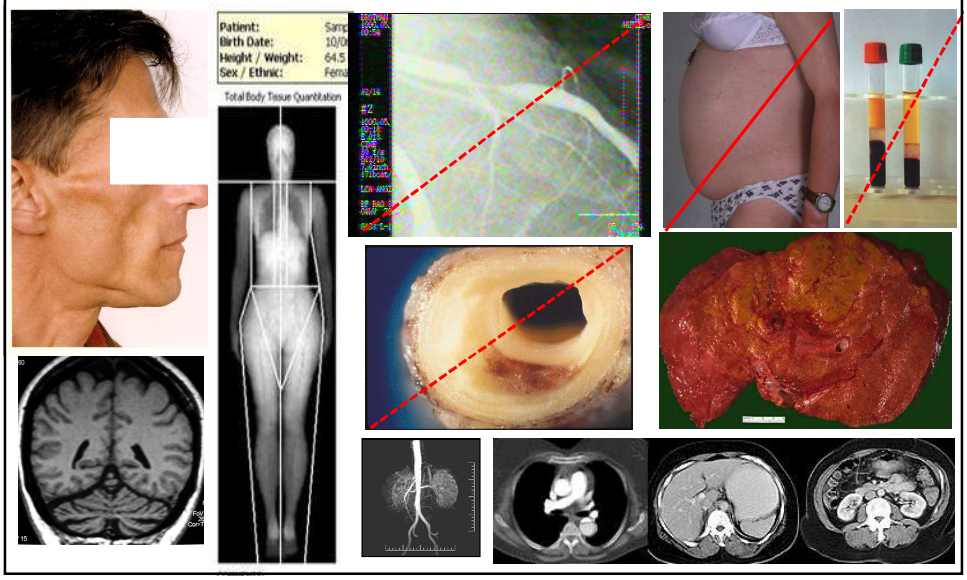
Prospective Cases (http://www.APRegistry.com)

	% Birth Defects
CDC general birth defect surveillance	2.7% (2.7-2.8%)
1st trimester any ARV exposure	2.8% (2.3 - 3.3%)
Atazanavir sulfate-containing (9/393)	2.3% (1.0 - 4.3%)
ABC-containing (19/670)	2.8% (1.7 – 4.4%)
AZT-containing (100/3,289)	3.0% (2.5 - 3.7%)
3TC-containing (99/3,481)	2.8% (2.3 - 3.5%)
d4T-containing (19/795)	2.4% (1.4 – 3.7%)
Efavirenz containing (14/546)	2.6% (1.4 - 4.3%)
FTC containing (12/456)	2.6% (1.4 – 4.6%)
Indinavir-containing (6/276)	2.2% (0.8 - 4.7%)
Nelfinavir-containing (37/1,080)	3.4% (2.4 – 4.7%)
Nevirapine-containing (19/882)	2.2% (1.3 – 3.3%)
Ritonavir-containing (24/1,122)	2.1% (1.4 – 3.2%)
Lopinavir-containing (10/590)	1.7% (0.8 – 3.1%)
Tenofovir-containing (19/879)	2.2% (1.3 – 3.4%)
ddI-containing (17/380)	4.5% (2.6 – 7.1%)

Is there a future without PI's?

- Is there a future without efavirenz?
- Is there a future without boosted PI's?

Is there a future without PI/r?



Why/why not a boosted PI?

For

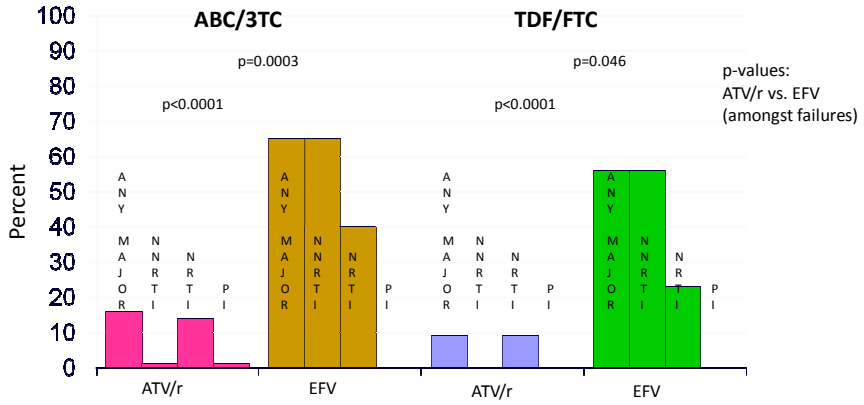
- Long track record
- High resistance barrier
- ATV/r equivalent to EFV
- Greater CD4+ increase?
- Preferred option in pregnancy

Against

- No single-pill regimens
- MI risk for LOP/r?
- Lipohypertrophy?
- Lipids for older PIs
- GI toxicity for older PIs
- Increased TDF renal toxicity?

A5202: Overall ITT

Percent of Failures with Emergence of Major Resistance Mutations*

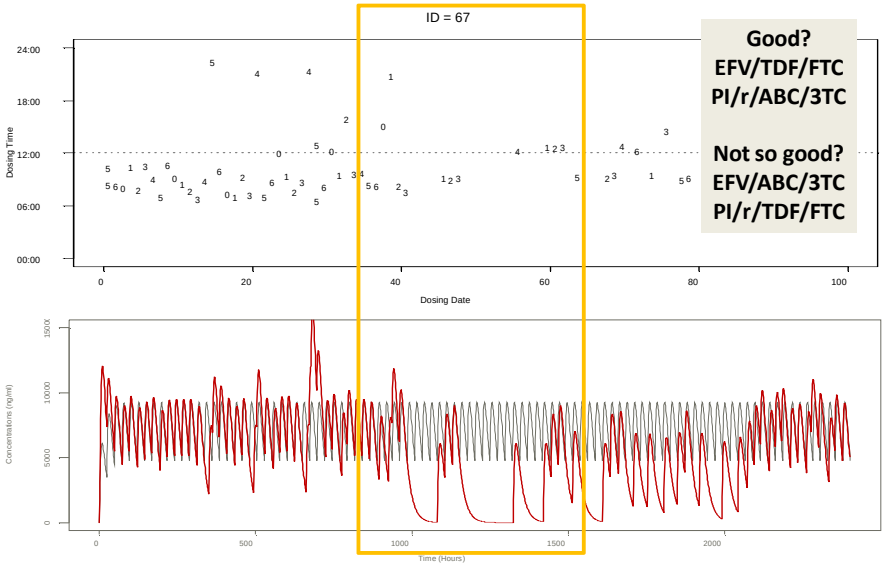


Viral failures

No baseline resistance N=	76	63	54	48

*Major mutations defined by IAS-USA (2008) list plus T69D, L74I, G190C/E/Q/T/V for RT and L24I, F53L, I54V/A/T/S and G73C/S/T/A for PR

Fewer pills means greater impact if pills missed



Pill burden and convenience

Options to choose from							
	EFV	DAR/r	ATZ/r	RAL	LOP/r	NVP	MRV
Factors determining adherence and QOL							
QD	√	√	√		√	√	
BD				√	√	√	√
Total pill burden	1	3	2	2	4	2	2
Convenience	Night	Food	Food PPI's			CD4	
Factors determining resistance development							
Forgiveness	√			√		√	√
Resistance barrier		√	√		√		

Is there a future without NRTI's?

- Is there a future without efavirenz?
- Is there a future without boosted PI's?
- Is there a future without NRTI's?

Why/why not choose TDF vs. ABC

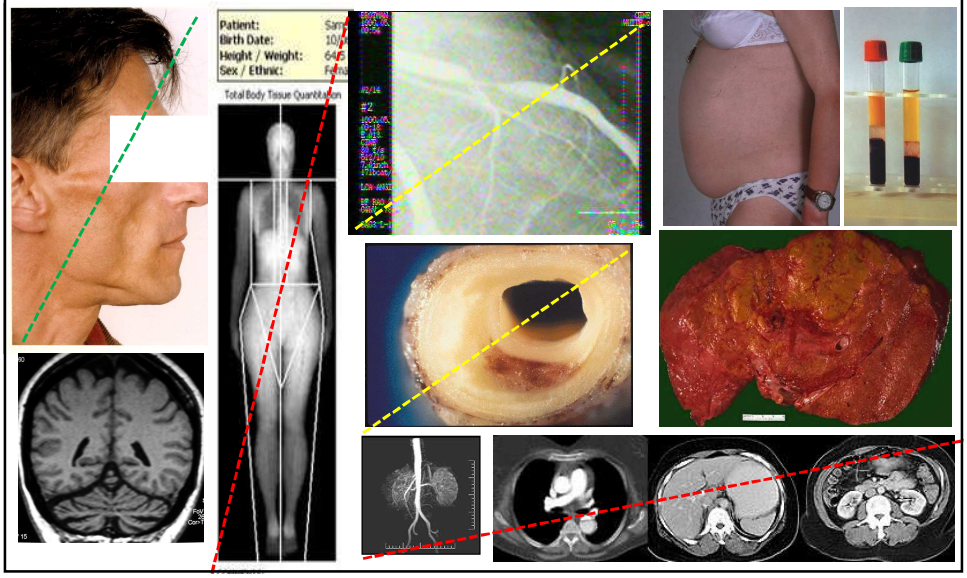
For

- Greater virological efficacy at high viral loads?
- Well tolerated
- No long-term cardiac toxicity
- Good for lipids
- Convenient co-formulation
- Forgiving

Against

- Link with CRF?
- Concerns over long-term bone effect?
- Lack of CNS penetration?

Is there a future without NRTI's?



Is there a future with RAL?

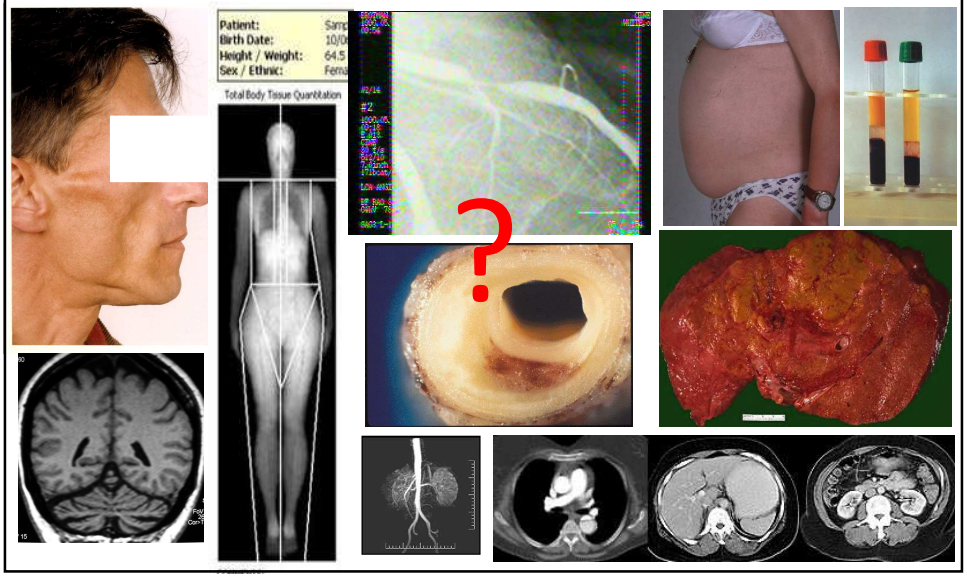
For

- Very well tolerated
- As effective as EFV
- Good tolerability
- No lipid effects
- Few drug-drug interactions
- Not known to be teratogenic
- Rapid virologic suppression?
- Greater CD4+ cell count increase than with EFV?

Against

- No long-term data
- Twice-daily dosing
- Resistance risk at VF similar to EFV
- Cost issues?
- Excellent data in experienced patients
- Signal for rhabdomyolysis?

Is there a future with integrase inhibitors?



RAL studies demonstrating fragility

Study	Type	Arm	Comparator	Virological failure RAL	Virological failure OTHER
QDMRK	Naïve	QD	BD	33.3%	6.7%
SWITCHMRK	Switch	RAL	LOP/r	6.9%	2.5%
SPARTAN	Naïve	RAL/ATAZ	ATAZ/TDF/FTC	18.2%	3.2%
ACTG	Naïve	RAL/DAR/r	-	25%	-

Selecting ART - considerations

Patien

- Rea
- Bas
- Age
- Occ
- Co-
- Pla
- Acc
- Co-
- Like
- HLA

For example

- Evaluate/discuss with patient:
  - Which NRTI backbone to use after evaluating cardiovascular disease risk, risk of chronic kidney disease and considering baseline HIV viral load
  - Whether EFV or PI/r if past mental health illness after and explaining risk of efavirenz or in young woman not contemplating pregnancy wanting simple regimen
  - Etc..etc..

Is there a future without ARV'

- Is there a future without efavirenz?
- Is there a future without boosted PI's?
- Is there a future without NRTI's?

- Is there a future without ARV's?

Is there a future without ARV's?

blood

2011 117: 2791-2799
doi:10.1182/blood-2010-09-309591

Evidence for the cure of HIV infection by CCR5Δ32/Δ32 stem cell transplantation

Kristina Allers, Gero Hütter, Jörg Hofmann, Christoph Loddenkemper, Kathrin Rieger, Eckhard Thiel and Thomas Schneider

We will always need our superheroes!

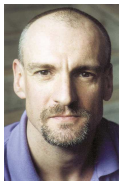
Facto

Force

Logico

Supremo

Miss Conscience



Maverick

Costa

Industrangelica

What to start?

2011

Thanks ?