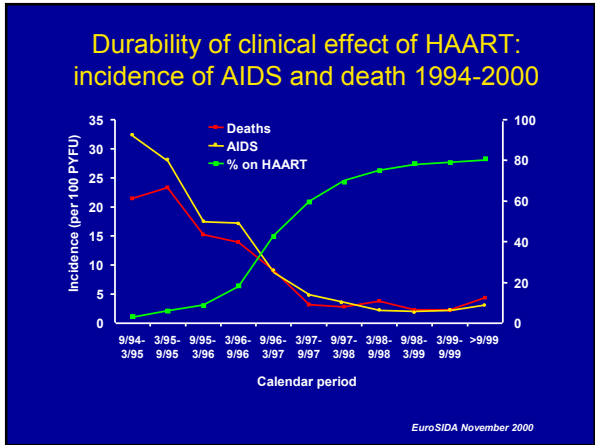
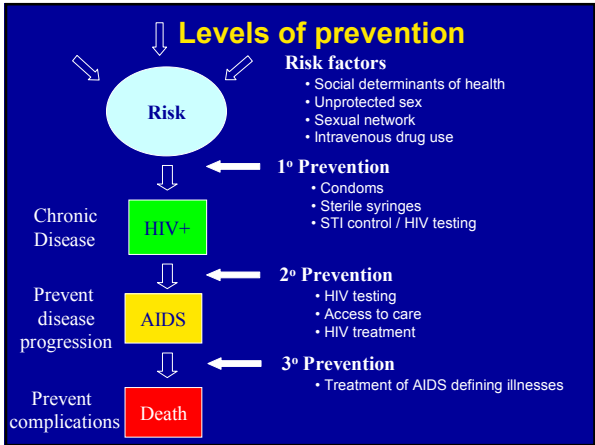
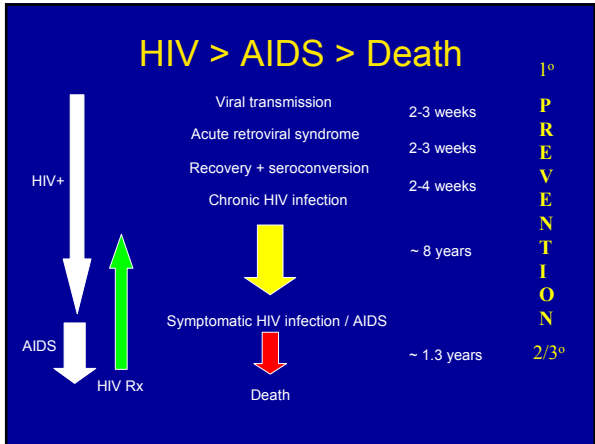


HAART in 2008: What and when to start

Dr Anatole S Menon-Johansson
Chelsea & Westminster Healthcare
8th May, 2008
BIS Trainees' Day



HIV Survival

- Median survival at 25 yo
 - General pop. = 51.1 yrs (M: 50.8, F: 54.8 yrs)
 - HIV+ = 19.9 yrs (M: 17.5, F: 24.2 yrs)
 - 2000-2005 = 32.5 yrs (M: 32.1, F: 32.3 yrs)
 - 2004-2005 HCV- = 38.9 yrs (M: 37.8, F: 40.1 yrs)

Survival of persons with and without HIV infection in Denmark, 1995-2005
Lohse et al.
Ann Intern Med 2007; 146: 87-95

- Expected survival at 5, 10 & 15yrs
 - Pre-1996: 87%, 50% & <28% respectively
 - 2000-2006: 99%, 94% & 89% respectively

Survival following HIV infection of a cohort followed up from seroconversion in the UK
Ewings et al.
AIDS 2008; 22: 89-95

What to start with?

Drugs available for HIV therapy

NRTIs	NNRTIs	Protease Inhibitors	New Classes
<ul style="list-style-type: none"> Abacavir Didanosine Emtricitabine Lamivudine Stavudine Tenofovir Zidovudine 	<ul style="list-style-type: none"> Delavirdine Efavirenz Nevirapine Etravirine 	<ul style="list-style-type: none"> Atazanavir Darunavir Fos-Amprenavir Indinavir Lopinavir Nelfinavir Ritonavir Saquinavir Tipranavir 	<ul style="list-style-type: none"> Fusion Inhibitors <ul style="list-style-type: none"> Enfuvirtide R5 Inhibitors <ul style="list-style-type: none"> Maraviroc Integrase Inhibitors <ul style="list-style-type: none"> Raltegravir

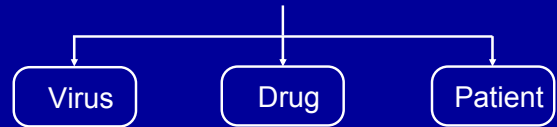
Timeline of HAART development

Time	NRTI	NNRTI	PI	EI / FI	II	FDC
1987	AZT					
1994	ddl					
1996	3TC d4T		RTV SQV			
1998		NVP	NFV			
1999	ABC					
2000			APV/r			AZT+ABC+ 3TC
2001			IDV LPV/r			
2002	TDF	EFV				
2003	FTC			ENF		AZT+3TC
2004			ATV/r FPV/r			ABC+ 3TC
2005			TPV/r			TDF+ FTC
2007		ETV	DRV/r	MVC	RTG	TDF+ FTC+ EFV

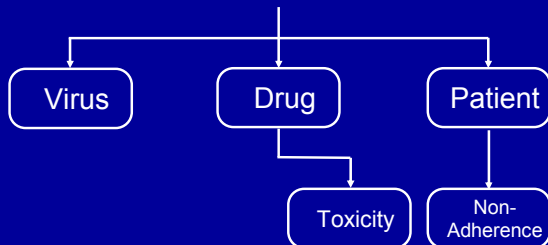
Drugs available for first line HIV therapy: In practice

NRTIs	NNRTIs	Protease Inhibitors
<ul style="list-style-type: none"> Emtricitabine Tenofovir 	<ul style="list-style-type: none"> Efavirenz 	<ul style="list-style-type: none"> Atazanavir / RTV Darunavir / RTV Lopinavir / RTV Saquinavir / RTV
<ul style="list-style-type: none"> Abacavir Lamivudine Zidovudine 	<ul style="list-style-type: none"> Nevirapine 	<p><i>Ritonavir (= RTV)</i></p>

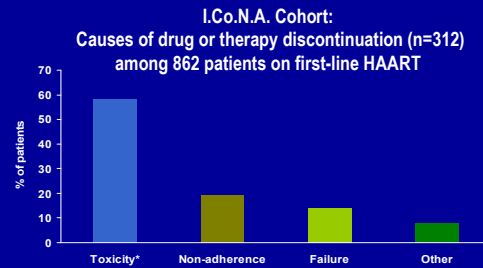
Why do therapies fail?



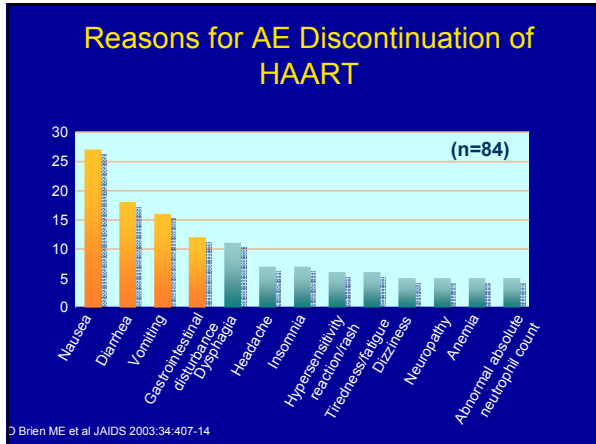
Why do therapies fail?



Drug Toxicity and Non-adherence Are More Common Reasons for Discontinuing ART than Therapeutic Failure



* Toxicity is itself a major cause of non-adherence.

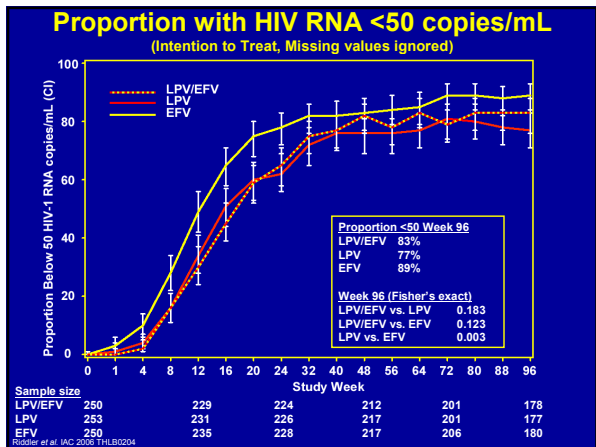
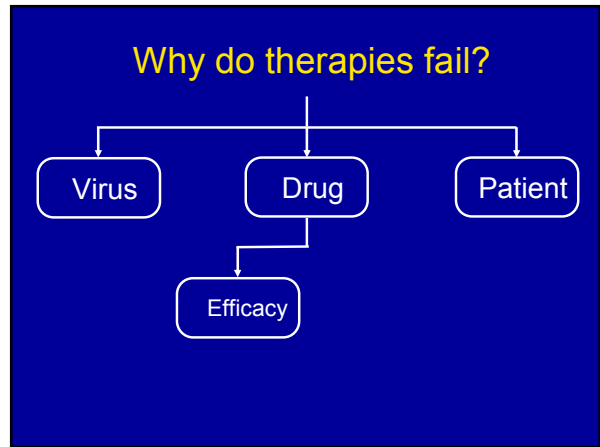
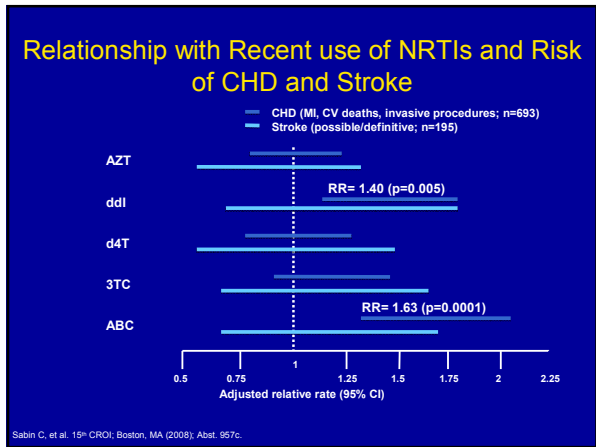


ART Toxicity Related to CD4+ Cell Count at ART Initiation

- Retrospective analysis of 3050 pts in CPCRA trials Dec 1996 - August 2001
 - ZDV, ddI, d4T use common
- Increasing risk of grade 4 toxicity and AIDS events with decreasing CD4+ at time of HAART initiation
- Most common grade 4 events: liver toxicity, neutropenia, pancreatitis, and anemia

Entry CD4+, cell/mm ³	AIDS Events, %	Grade 4 Toxicity, %
< 200	19.7	30.1
200-399	6.1	26.0
> 400	0.9	19.6

Reisler RB, et al. CROI 2002. Abstract 36.



ACTG 5202

- 4 arms:
 - Blinded ABC/3TC or TDF/FTC
 - With ATV/r or EFV
- 96 weeks with additional 48 week follow-up
- N=1858

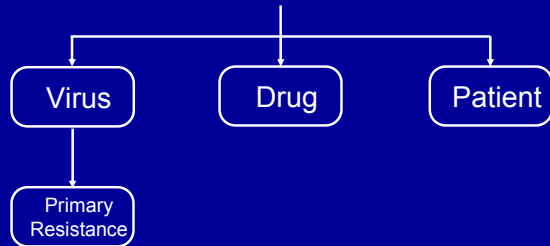
ACTG 5202 – Primary End-points

- Time to virological failure, defined as
 - HIV viral load ≥ 1000 copies/ml at or after week 16 and before week 24
 - or ≥ 200 copies/ml after week 24
- Time from treatment initiation to first grade 3 or 4 adverse event that is at least 1 grade higher than baseline
- Time from treatment initiation until discontinuation

ACTG 5202 – Planned data review Jan/Feb 2008

- Virological failure rates significantly higher in the ABC/3TC arms
- This excess occurred in patients with high baseline viral load ($\geq 100,000$ copies/ml)
- Hazard Ratio 2.33 (95% CI 1.46, 3.72), $p=0.0003$
- Difference not seen in patients with baseline viral load $< 100,000$ copies/ml

Why do therapies fail?

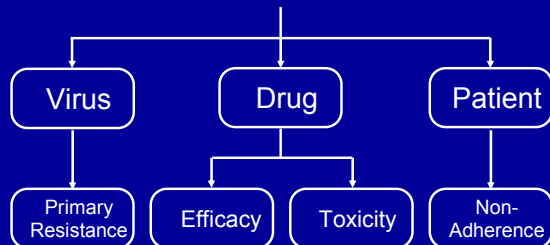


CDC Survey: Drug-resistant HIV among newly diagnosed patients

Resistance to:	Prevalence of drug resistance (%)				
	1998 ¹ (n=238)	1999 (n=240)	2000 (n=245)	2003-2004 ² (n=787)	2003-2006 ³ (n=3130)
Any drug	3.8	10.0	9.0	14.5	10.4
NRTI	3.4	8.3	6.9	7.1	3.6
NNRTI	0.4	2.1	1.2	8.4	6.9
PI	0.0	1.7	2.0	2.8	2.4
≥ 2 drug class	0.0	1.7	1.2	3.1	1.9

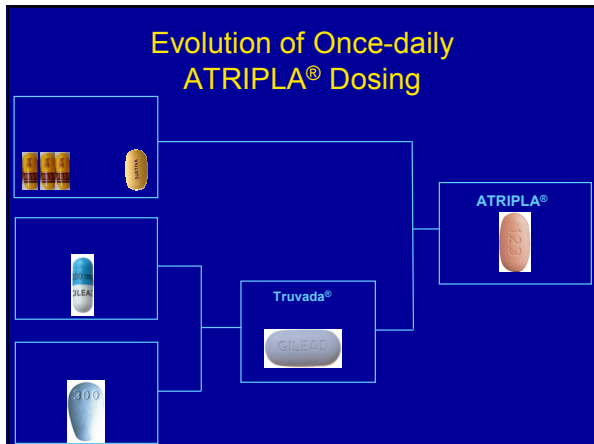
1. Bennett D, et al. 9th CROI, Seattle, 2002; Abst. 372.2.
 2. Bennett D, et al. 12th CROI, Boston, 2005; Abst. 674.
 3. Wheeler W, et al. 14th CROI, Los Angeles, 2007; Abst. 648

Why do therapies fail?

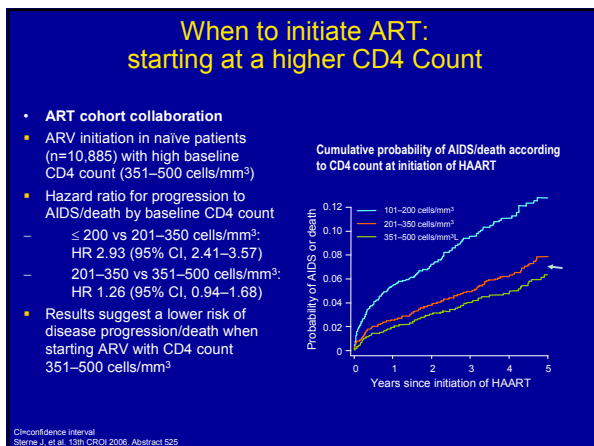
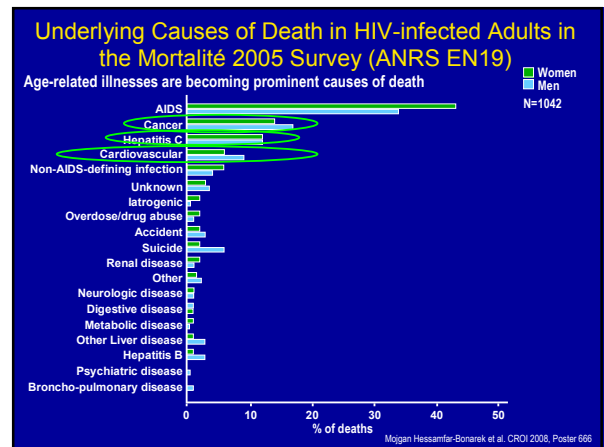
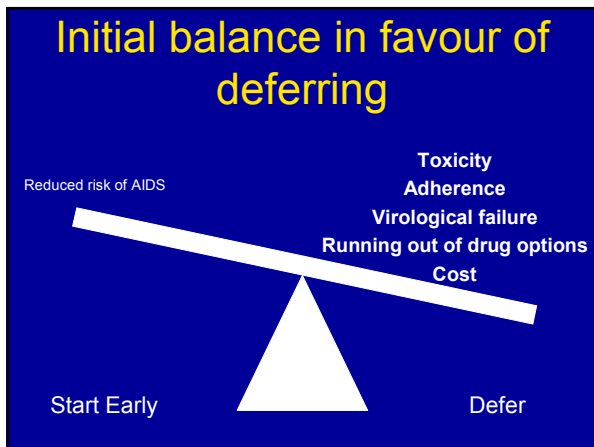


HAART: A decade ago





When to start?

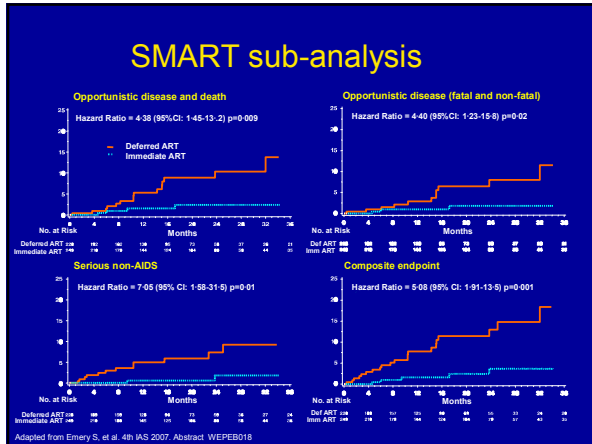


SMART: intermittent versus continued ART

	Intermittent ART (DC) group		Continued ART (vs) group		
	N	Rate	N	Rate	
OD or death (primary endpoint)	120	3.3	47	1.3	2.6 [1.9, 3.7] <0.001
CV, renal, liver disease	65	1.8	39	1.1	1.7 [1.1, 2.5] 0.009
CV disease	48	1.3	31	0.8	1.6 [1.0, 2.5] 0.05
Renal disease	9	0.2	2	0	4.5 [1.0, 20.9] 0.05
Liver disease	10	0.3	7	0.2	1.4 [0.6, 3.8] 0.46

Copenhagen HIV programme
SMART study group. NEJM 2006;355:2283-96

N = 5,472



SMART Naïve Subset: Clinical Events (Composite Endpoint) by Treatment Arm and Proximal CD4+ Cell Count

Proximal CD4+ cell count (cells/mL)	Deferred ART			Immediate ART		
	Person-years ^A (%)	Events ^B	Rate ^C	Person-years ^A (%)	Events ^B	Rate ^C
<250	19 (6.4)	3 (2)	16.0	10 (2.6)	1	10.4
250-349	65 (21.7)	6 (3)	9.2	30 (7.9)	2	6.7
350-499	118 (39.5)	9 (7)	7.6	109 (28.8)	2	1.8
≥500	97 (32.4)	3 (2)	3.1	230 (60.7)	0	0.0
Overall	299 (100)	21 (14)	7.0	379 (100)	5	1.3

^A Time spent in the CD4+ cell count category censored at event.
^B First events only. Numbers in parentheses are numbers of events that occurred before (ie-) initiation of ART.
^C per 100 person years.
 Emery S, et al. IAS 2007/Abstract WEPEB018.

When to Initiate ARV Therapy: BHIVA, DHHS, & European Guidelines*

Clinical Category	CD4 cells/mm ³	HIV RNA copies/mL	BHIVA ¹ guidelines	DHHS ^{2,4} guidelines	European ³ guidelines
AIDS-defining illness or severe symptoms	Any value	Any value	Treat	Treat	Treat
Asymptomatic	<200	Any value	Treat	Treat	Treat
Asymptomatic	201-350	Any value	Treat	Treat	Treat
Asymptomatic	350-500*	≥100,000	Consider treatment	Consider treatment	Consider treatment*
Asymptomatic	>350	<100,000	Monitoring	Defer treatment	N/A

DHHS=Department of Health and Human Services; BHIVA= British HIV Association. *Start treatment, taking into account viral load, rate of CD4 decline, patient's wishes, presence of hepatitis C (CV).
 1. Gazzard B et al. HIV Medicine 2005; 7:487-503.
 2. DHHS Guidelines. 10 October 2006. Available at: <http://www.aidsinfo.nih.gov>. Accessed Nov 5th 2007.
 3. European guidelines 2007. Clumeck EAACS 2007. Madrid P86. Final version to be posted on <http://www.eacs.eu/guidelines.htm>
 4. DHHS Guidelines December 2007. Available at <http://www.aidsinfo.nih.gov>. Accessed Dec 24th 2007.

- ### Summary
- What to start with?
 - Efavirenz + (Truvada / Kivexa / Combivir)
 - Boosted PI + (Truvada / Kivexa / Combivir)
 - Guided by genotypic resistance testing
Review toxicity / adherence
 - When to start?
 - AIDS diagnosis
 - Symptomatic
 - CD4 < 350 cells / mm³

- ### Acknowledgements
- Professor Brian Gazzard
 - Dr Mark Nelson
 - Dr Laura Waters