
What an
old man thinks...

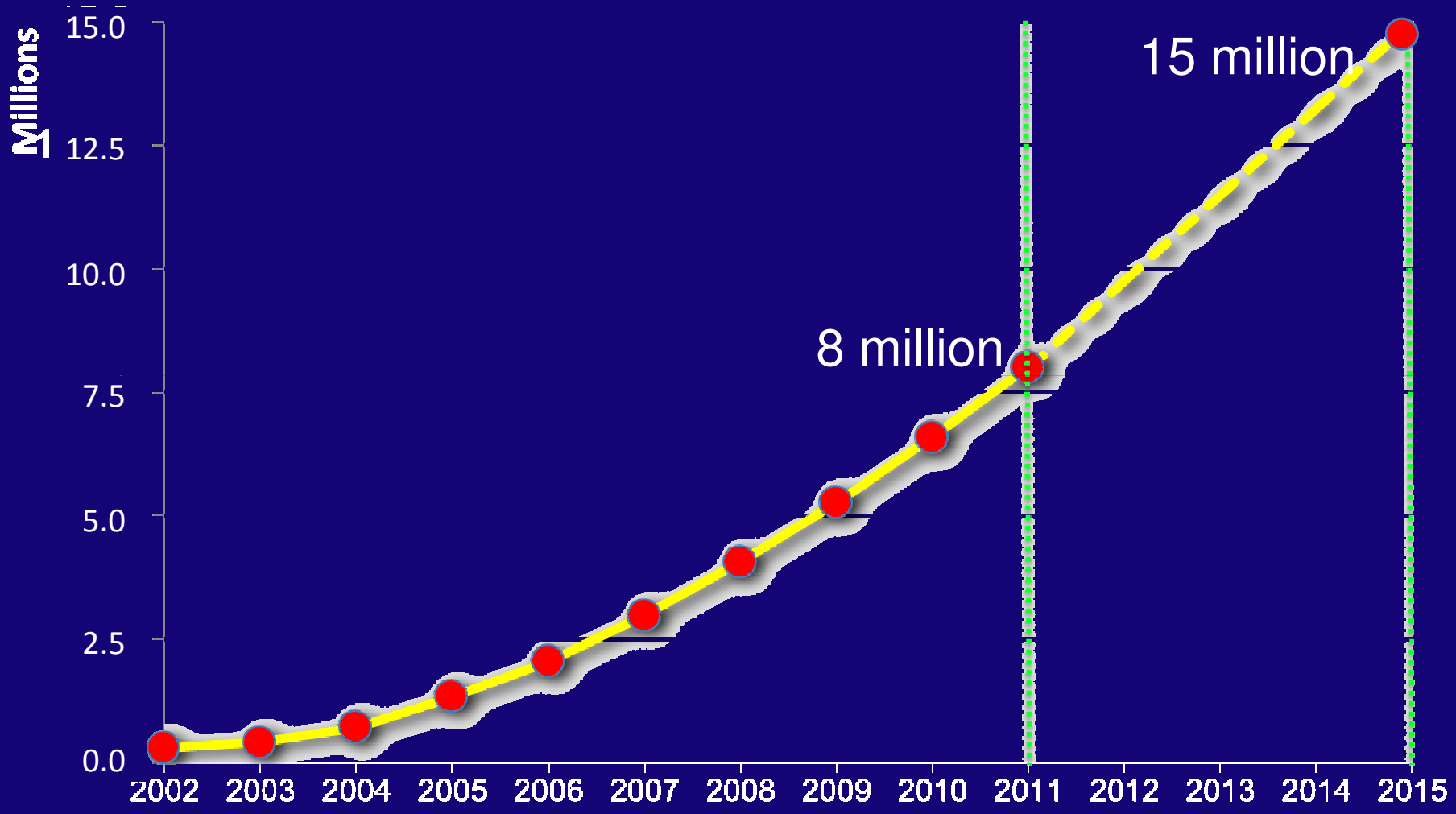
Thoughts

Much of what we discuss is trivial.

NEED:

1. **Logistics**
2. **Costs**
3. **Sustainability**

8 million on ART by end 2011
…15 million is achievable !



Significant variation in ART eligibility thresholds among countries

CD4 count for ART initiation	≤200-350	≤300	≤350	≤350 + TasP	≤500	≤500 + TasP
Number of countries	1	1	43	12	1	3

Results of a WHO survey (2011, n= 61 countries)

WHO Treatment Guidelines 2010

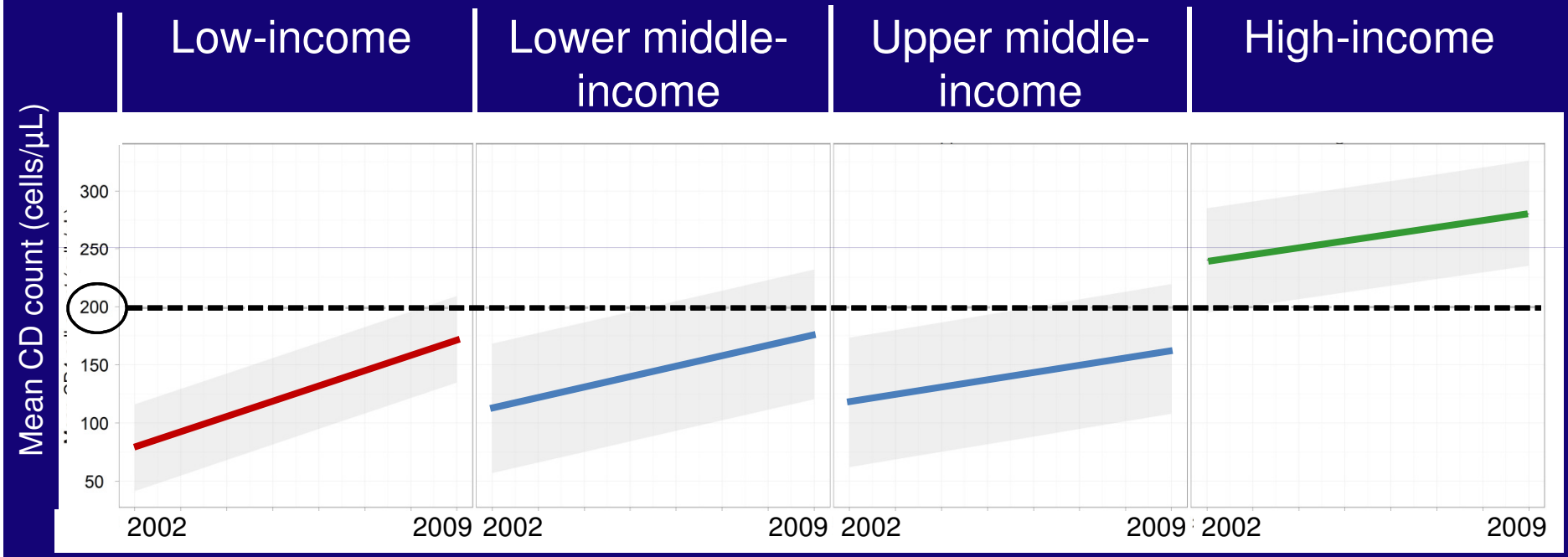
Treat all patients with CD4+ cell counts < 350 cells/mm^3

Treat regardless of CD4+ count if:

- **WHO stage 3 or 4 disease, active TB disease, HBV if HBV therapy indicated**

WHO. Available at: http://whqlibdoc.who.int/publications/2010/9789241599764_eng.pdf.

Mean CD4 count at ART initiation is below 200 in LMIC



Estimates from random-effects model adjusted for age, sex and year of starting ART, 2002-2009

Source: Egger M. CROI 2012

When to Start ART: IAS–USA Recommendations 2012

Patient readiness should be considered when deciding to initiate antiretroviral therapy (ART)

ART should be offered regardless of CD4 cell count (increasing strength of the recommendation as CD4 decreases)

- CD4 ≤ 500 cells/µL (AIa)
- CD4 > 500 cells/µL (BIII)
- Pregnancy (AIa)
- Chronic HBV (AIIa)
- HCV (may delay until after HCV treatment if CD4 > 500) (CIII)
- Age older than 60 (BIIa)
- HIV-associated nephropathy (AIIa)
- Acute phase of primary HIV infection, regardless of symptoms (BIII)

Earlier ART Associated with Decreased Mortality and Disease Progression: Observational Studies

Study	Published	N	Endpoint	Relative Hazard or Hazard Ratio	P or 95% CI
NA-ACCORD	NEJM, 2009	8,362	Death	1.69 CD4 <350 vs 350-500	< 0.001
NA-ACCORD	NEJM, 2009	9,155	Death	1.94 CD4 <500 vs > 500	< 0.001
When to Start Consortium	Lancet, 2009	24,444	AIDS or Death	1.28 (HR) CD4 251-350 vs 351-400	1.04-1.57
HIV-CAUSAL	Ann Int Med, 2011	20,971	AIDS or Death	1.38 (HR) CD4 <350 vs <500	1.23-1.56
CASCADE	Arch Int Med, 2011	9,455	Death	0.51 (HR) CD4 350-499 vs deferred	0.33-0.80
COHERE	Plos Med, 2012	75,336	AIDS or Death	0.74 (HR) CD4 350-<500 on ART 0.96 (HR) CD4 ≥ 500 on ART	0.58-0.80 0.92-0.99

HPTN 052

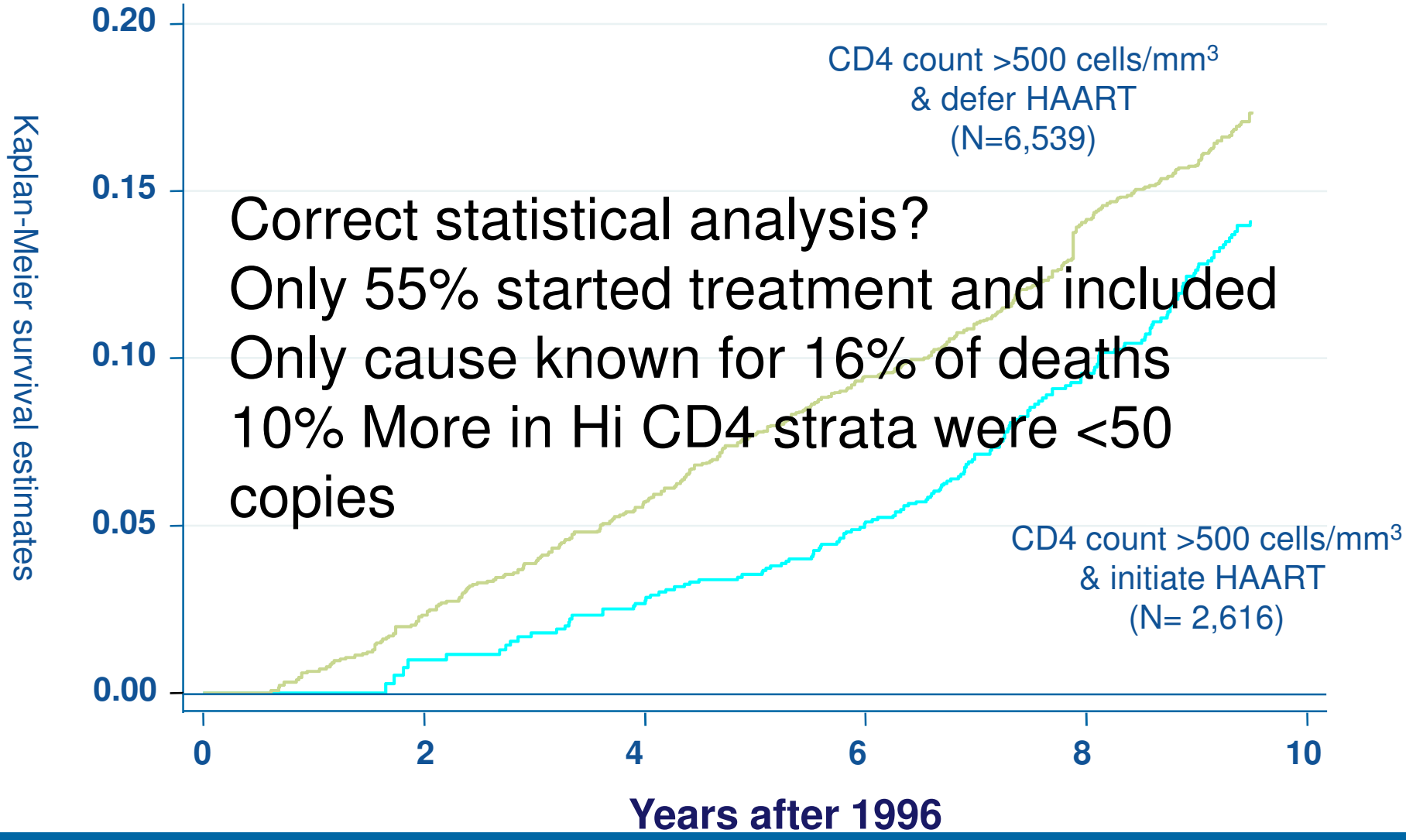
1,750 heterosexual serodiscordant couples in resource-constrained countries randomized to receive ART early (CD4 350-550 cells/μL) or defer until CD4 < 250 cells/μL

Event Rates	Early ART	Deferred ART	HR	P-value
Transmission Rate per 100 pt-years (95% CI)	**0.3 (0.1-0.6)**	**2.2 (1.6-3.1)**	**0.11 (0.04-0.32)**	**< 0.001**
Clinical Event Rate per 100 pt-years (95% CI)	**2.4 (1.7-3.3)**	**4.0 (3.5-5.0)**	**0.59 (0.40-0.88)**	**<0.001**

Cohen et al, *NEJM*, 2011

NA-ACCORD study:

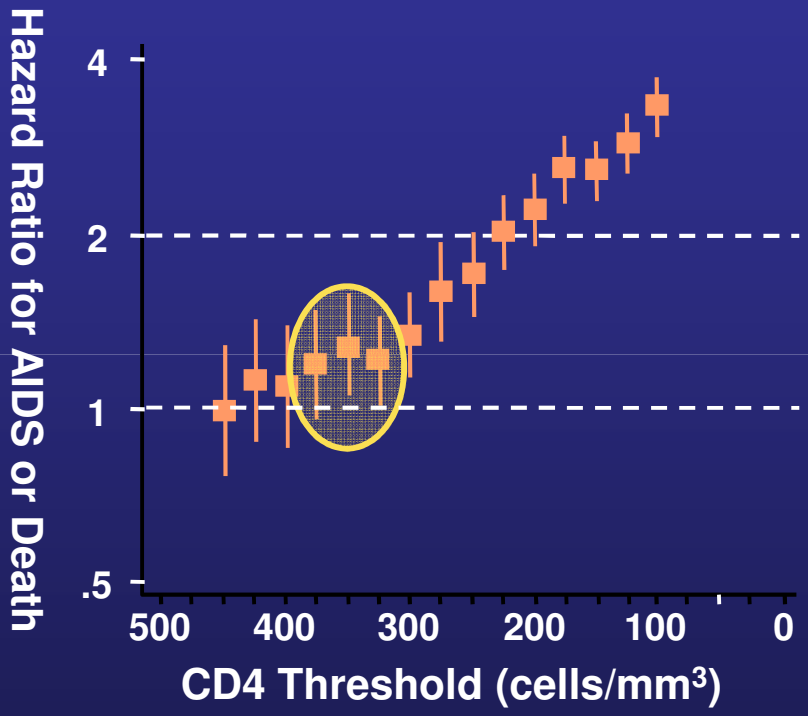
Higher mortality when deferring treatment



Kitahata M, et al CROI 2009. Abstract 71

ART-CC: Delay in starting ART is associated with an increased risk of AIDS or death

Hazard ratios for AIDS or death, adjusted for lead time/unseen events



Comparison	Hazard Ratio (95% CI)
276–375 vs 376–475	1.19 (0.96 to 1.47)
251–350 vs 351–450	1.28 (1.04 to 1.57)
226–325 vs 326–425	1.21 (1.01 to 1.46)

Delaying ART to <350 (but not <375) cells/mm^3 is associated with an increased risk of AIDS or death

Adapted from: Sterne J *et al. 16th CROI* 2009; Montreal, Canada. Oral abstract 72LB.

CASCADE: Absolute Risk Difference and Number Needed to Treat 3 Yrs From BL

CD4+ Cell Count, cells/mm³	Cumulative Risk for AIDS/Death, %		Cumulative Risk Diff at 3 Yrs (95% CI)	Number Needed to Treat at 3 Yrs to Prevent 1 AIDS Event or Death (95% CI)
	Defer	Initiate		
0-49	46.6	16.6	-30.0 (-45.1 to -15.0)	3 (2-7)
50-199	20.7	5.7	-15.0 (-19.7 to -10.3)	7 (5-10)
200-349	10.3	5.5	-4.8 (-7.0 to -2.6)	21 (14-38)
350-499	6.3	3.4	-2.9 (-5.0 to -0.9)	34 (20-115)
500-799	**4.9**	**5.2**	0.3 (-3.7 to 4.2)	∞
CD4+ Cell Count	**Cumulative Risk for Death Alone, %**		**Cumulative Risk Diff at 3 Yrs (95% CI)**	**NNT at 3 Yrs to Prevent 1 Death**
0-49	26.8	8.6	-18.2 (-32.0 to -4.4)	6 (3-23)
50-199	9.1	1.9	-7.2 (-10.1 to -4.4)	14 (10-23)
200-349	4.1	2.7	-1.4 (-3.0 to 0.3)	**74 (33-∞)**
350-499	2.1	0.7	-1.4 (-2.2 to -0.6)	**71 (45-165)**
500-799	1.7	1.2	-0.4 (-2.0 to 1.2)	**239 (49-∞)**

Funk, MJ, et al. AIDS 2010. Abstract THLBB201..

Current CD4 count and mortality in virologic responders to ART

SMART and ESPRIT: N=3280

Non-IDU virologic responders to ART

- CD4 >500: death rate same as general population
- CD4 350-500: death rate higher than general population

AQUITAINE cohort[2]: Mortality same as that of general population in patients with CD4 >500 after 6th year of ART

Rodger A, et al. Abstract 638. 19th CROI, Seattle 2012. Seattle.
Lewden C, et al. *J Acquir Immune Defic Syndr*. 2007;46:72-7.

But what is a normal population when we are controlling for our HIV cohort?

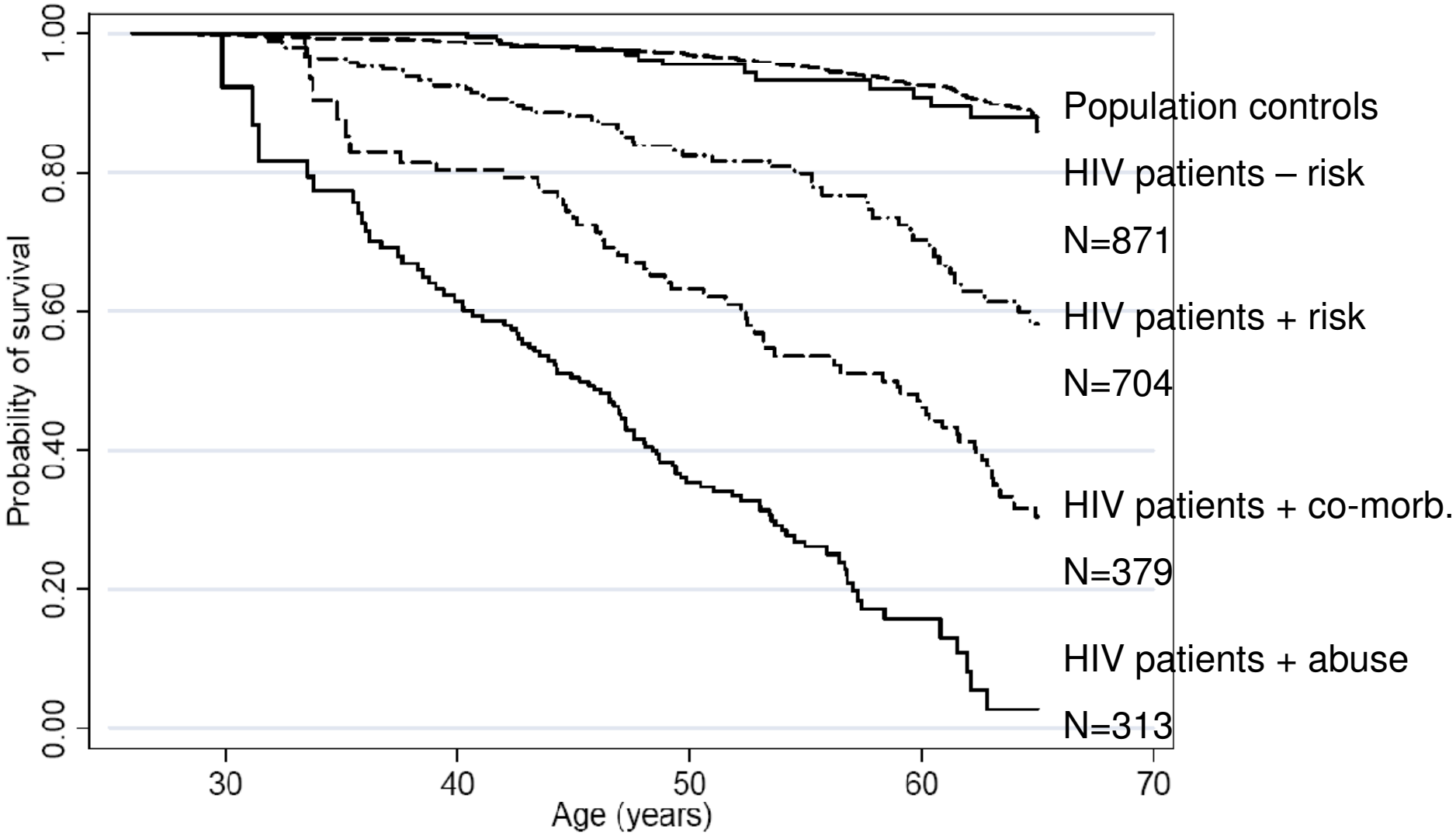
Life expectancy at birth (men)

Glasgow (deprived area)	54
Australian Indigenous	59
India	61
Philippines	65
Lithuania	66
US	75
UK	76
Australian average	77
Glasgow (affluent area)	82

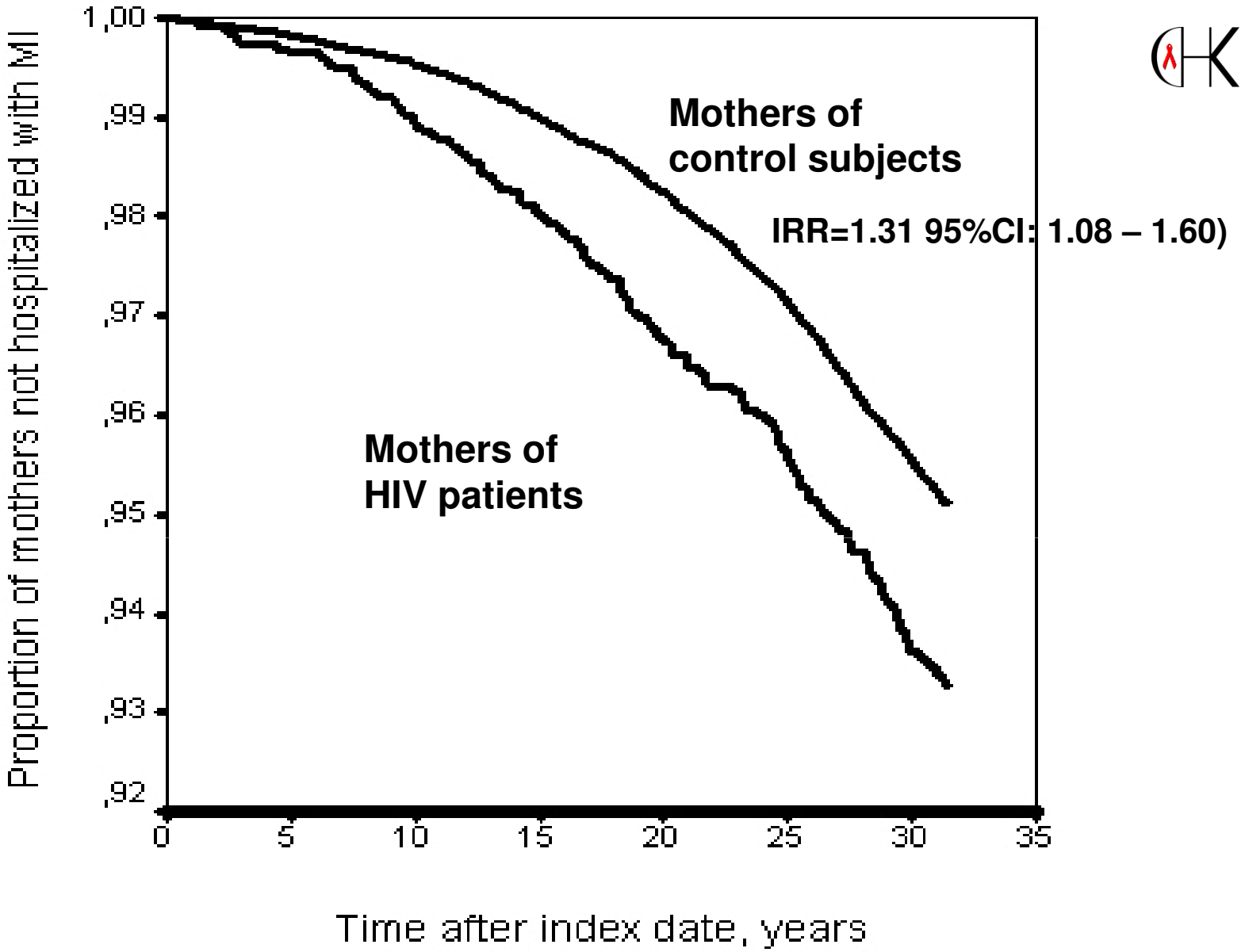
- ***World Health Report 2006, Hanlon et al 2006, AIHW 2008***

Mortality in HIV patients starting HAART after 1 January 1998 N=2267

And population controls, N=9068



Obel et al., PLoS One 2012



Rasmussen et. al, BMC Infectious Diseases, 2011

Why are we treating earlier?

Simpler regimens

Higher efficacy

Less adverse events

Less resistance development

But also .....

Cohort studies

Fear of non-AIDS events

Treatment for prevention

Should we start Treatment Earlier?

- **Start at any CD4?** May have health benefits and only increase lifetime therapy by a few years.
- **Wait for the CD4 to fall to around 350?-**would mean a few extra years off therapy
- Cohorts can't agree but most physicians would start early **if there is a co morbid condition or to prevent transmission**

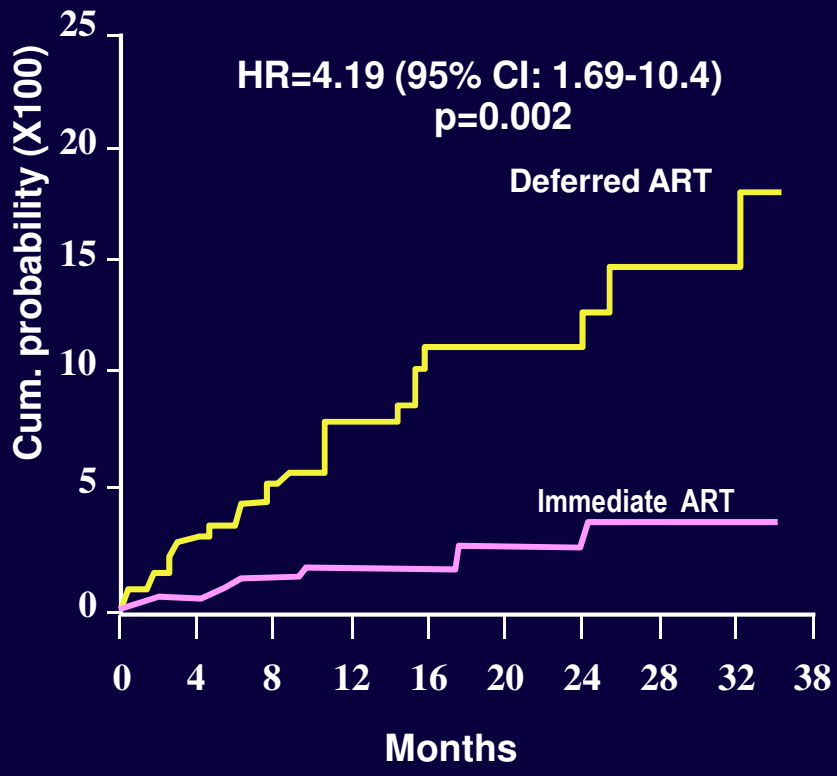
- **Should we wait for a randomised trial?**

Personal point of view

SMART Study

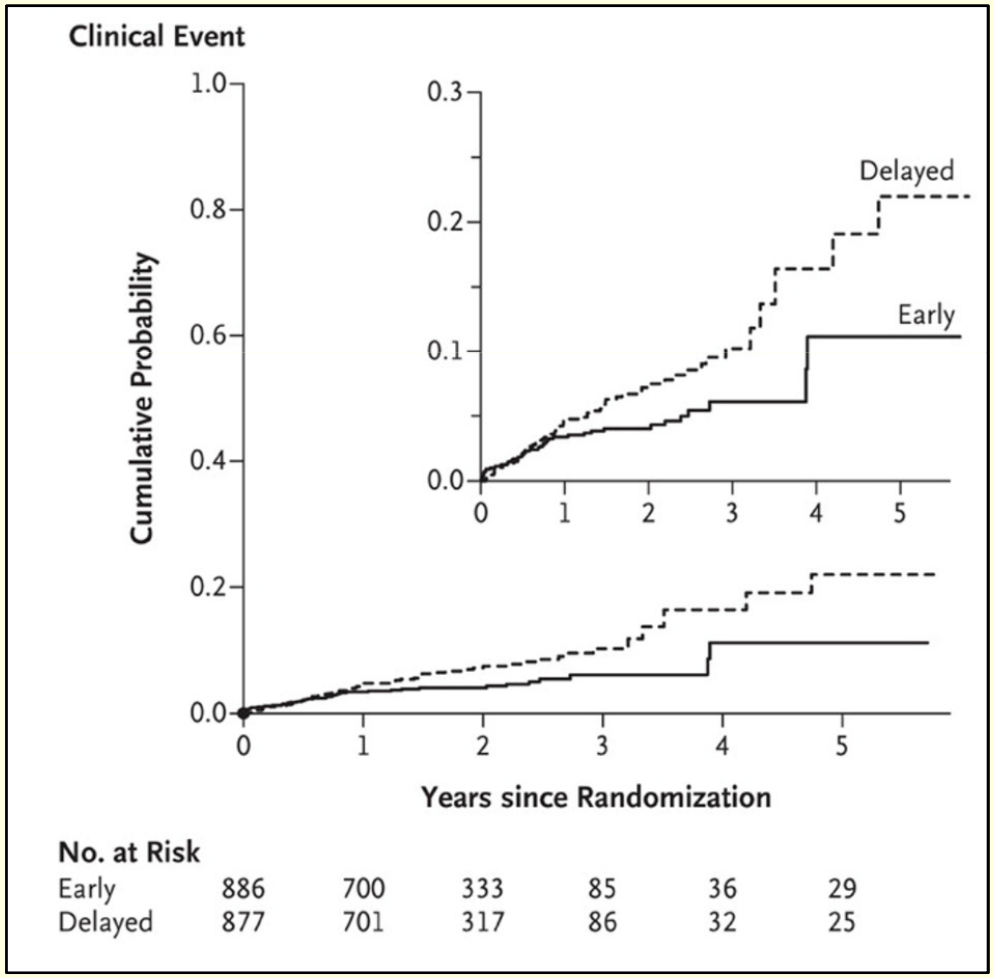
Patients not on ART at Randomization

- Subset: ART-naïve or not on ART at randomization
  - Immediate ART: n=249 (131 naïve)
  - Deferred ART: n=228 (118 naïve)
- > 4-fold increased risk of OD, OD/death, serious non-AIDS event with deferred ARV



1. Emery S, et al. JID 2008;197:1133-44

HTPO52


Clinical Event
Cumulative Probability
1.0
0.8
0.6
0.4
0.2
0.0
0.3
0.2
0.1
0.0
Delayed
Early
0
1
2
3
4
5
Years since Randomization
No. at Risk
Early 886 700 333 85 36 29
Delayed 877 701 317 86 32 25

START-A Randomised trial of Early v Late

HIV-infected adults, ART-naive with CD4+ cell counts > 500 cells/mm^3

Early ART Group

Immediately initiate ART

N=2,000

Deferred ART Group

Defer ART until CD4+ <350 cells/mm^3 or symptoms develop

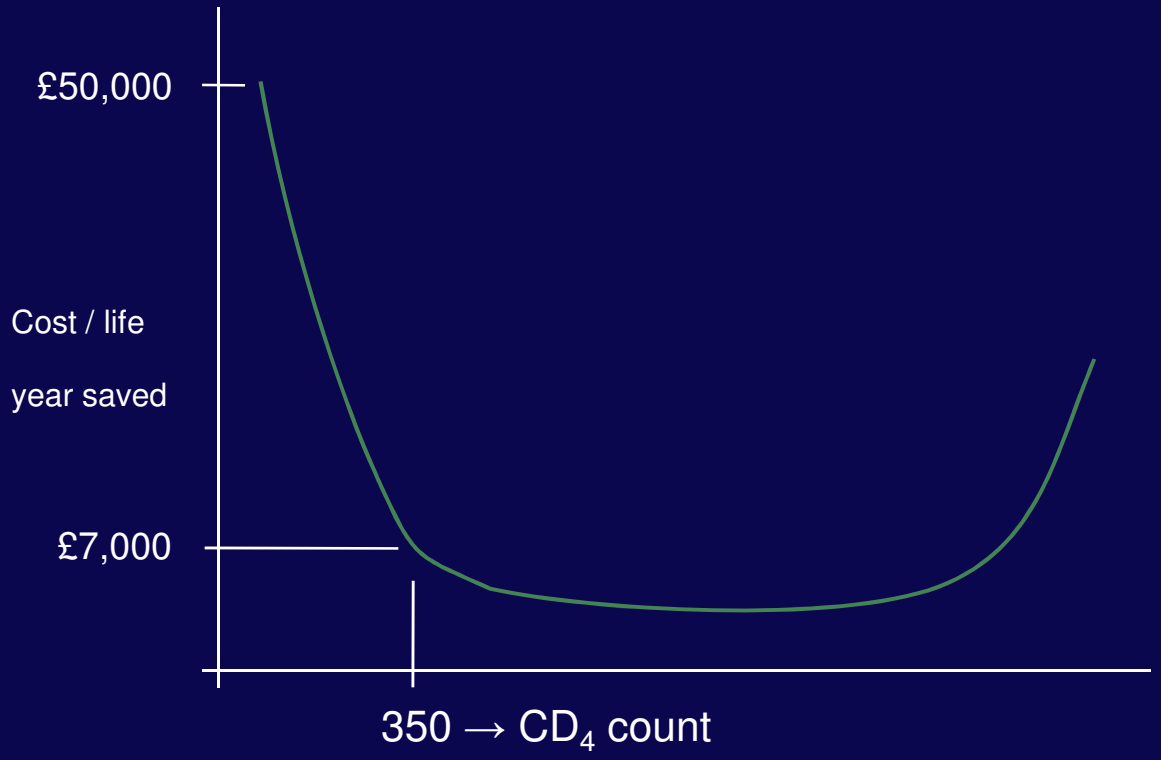
N=2,000

Primary endpoint: Serious AIDS & serious non-AIDS disease (375)

Current Status: **1200 randomised; randomisation finished ≤ 2012 and study ≤ 2015.**
Substudies assessing various organ dysfunction incl. arteries, neuro-system & lungs.

INSIGHT study group and collaborators

Idealised Curve of Cost Effectiveness



<u>2 cost drivers</u>

1. Drugs
2. Hospital admission

REVIEW ARTICLE HIV/AIDS

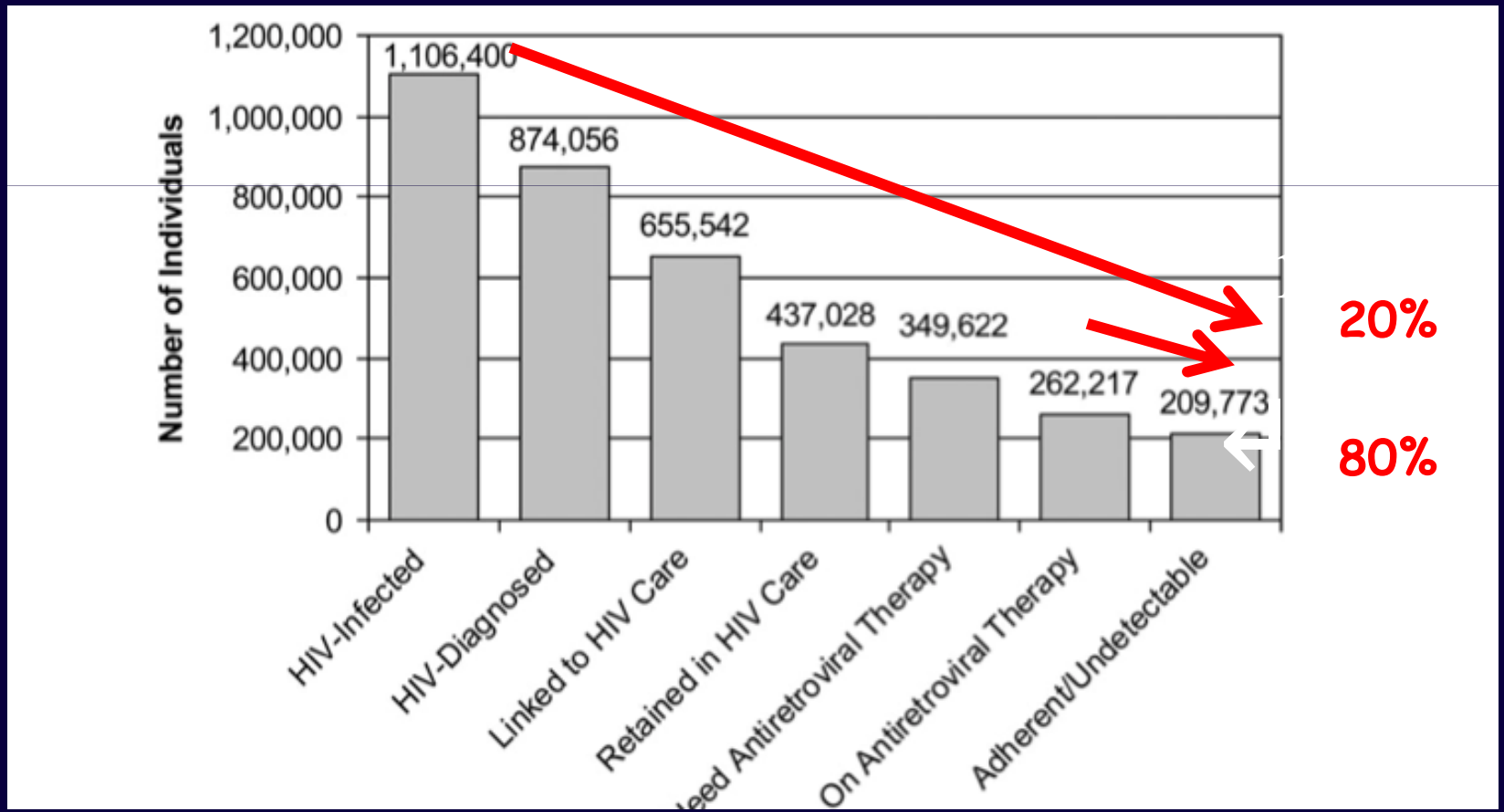
The Spectrum of Engagement in HIV Care and its Relevance to Test-and-Treat Strategies for Prevention of HIV Infection

Edward M. Gardner,[1,3] Margaret P. McLees,[1,3] John F. Steiner,[2] Carlos del Rio,[4,5] and William J. Burman[1,3]

[1]Denver Public Health and [2]Kaiser Permanente Colorado, Denver, [3]University of Colorado Denver, Aurora, Colorado, and [4]Rollins School of Public Health of Emory University, and [5]Emory Center for AIDS Research, Atlanta, Georgia

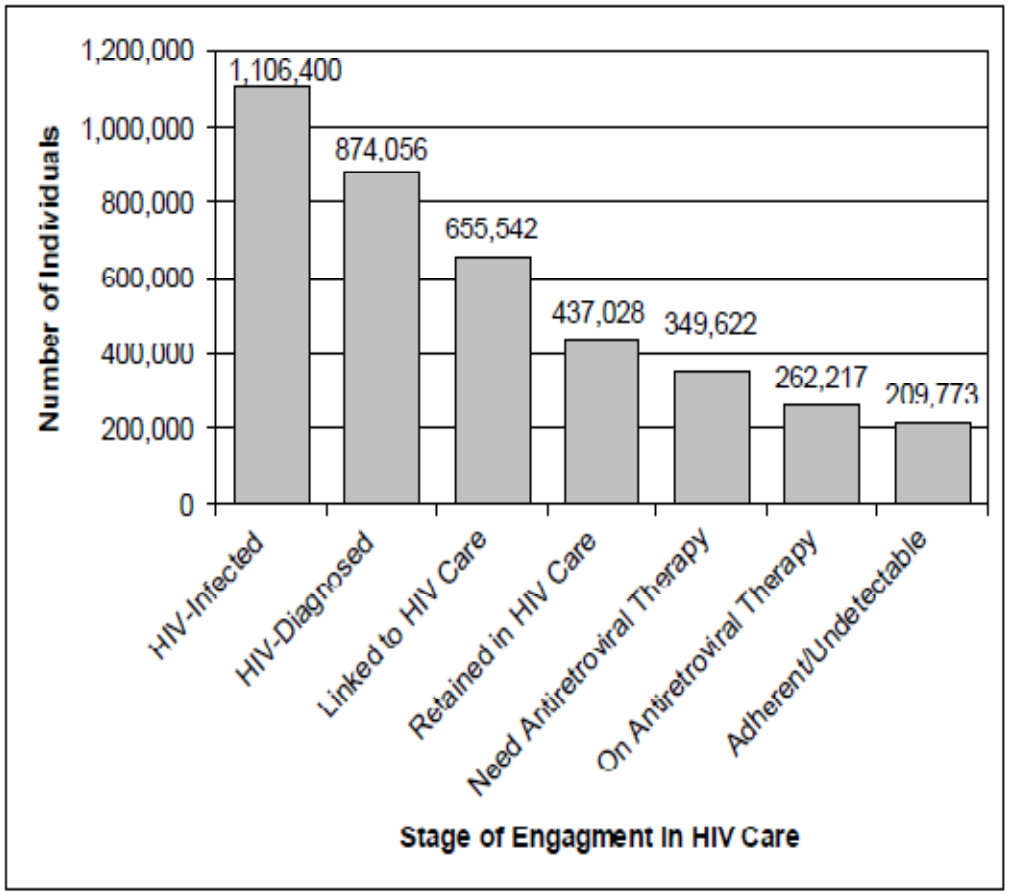
(See the editorial commentary by Lange, on pages 801–802.)

What's happening in Real Life



Gardner EM et al. The spectrum of engagement in HIV care and its relevance to "Test and Treat" strategies for prevention of HIV infection. Clin Infect Dis 2011;52:793-800.

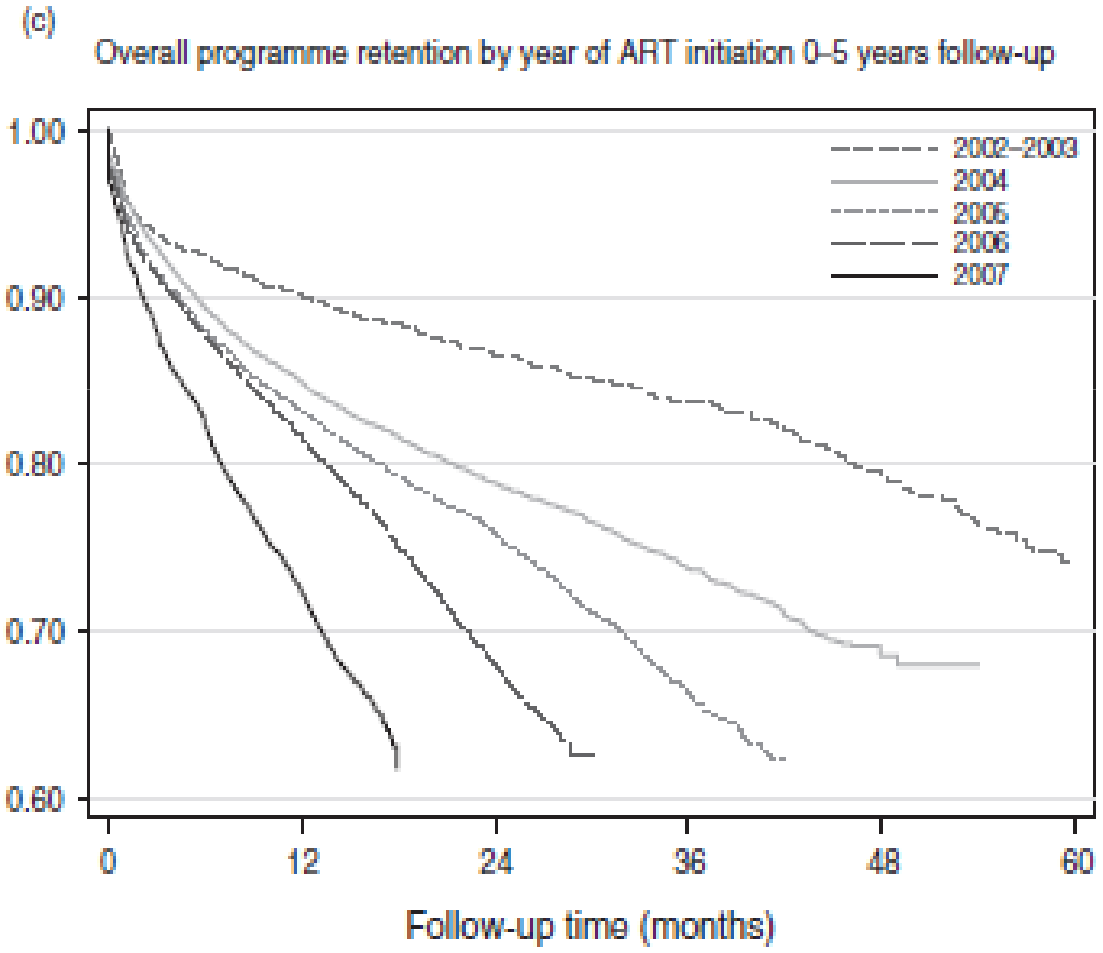
Figure 2. The spectrum of engagement in HIV care in the United States spanning from HIV acquisition to being fully engaged in care, receiving antiretroviral therapy and achieving complete viral suppression. We estimate that only 19% of HIV infected individuals in the United States have an undetectable HIV viral load.



CARE IN UK

- 62 OOO PATIENTS
- 59 800 IN CARE
- 53 OOO ON TREATMENT
- 49 000 UNDETECTABLE

Temporal changes in programme outcomes among adult patients initiating antiretroviral therapy across South Africa



Cornell M, et al. (IeDEA-SA Collaboration). AIDS 2010;24:2263–70.

what

- Generic market
- Potency the same
- COST
- Individualise therapy(adherence toxicity)

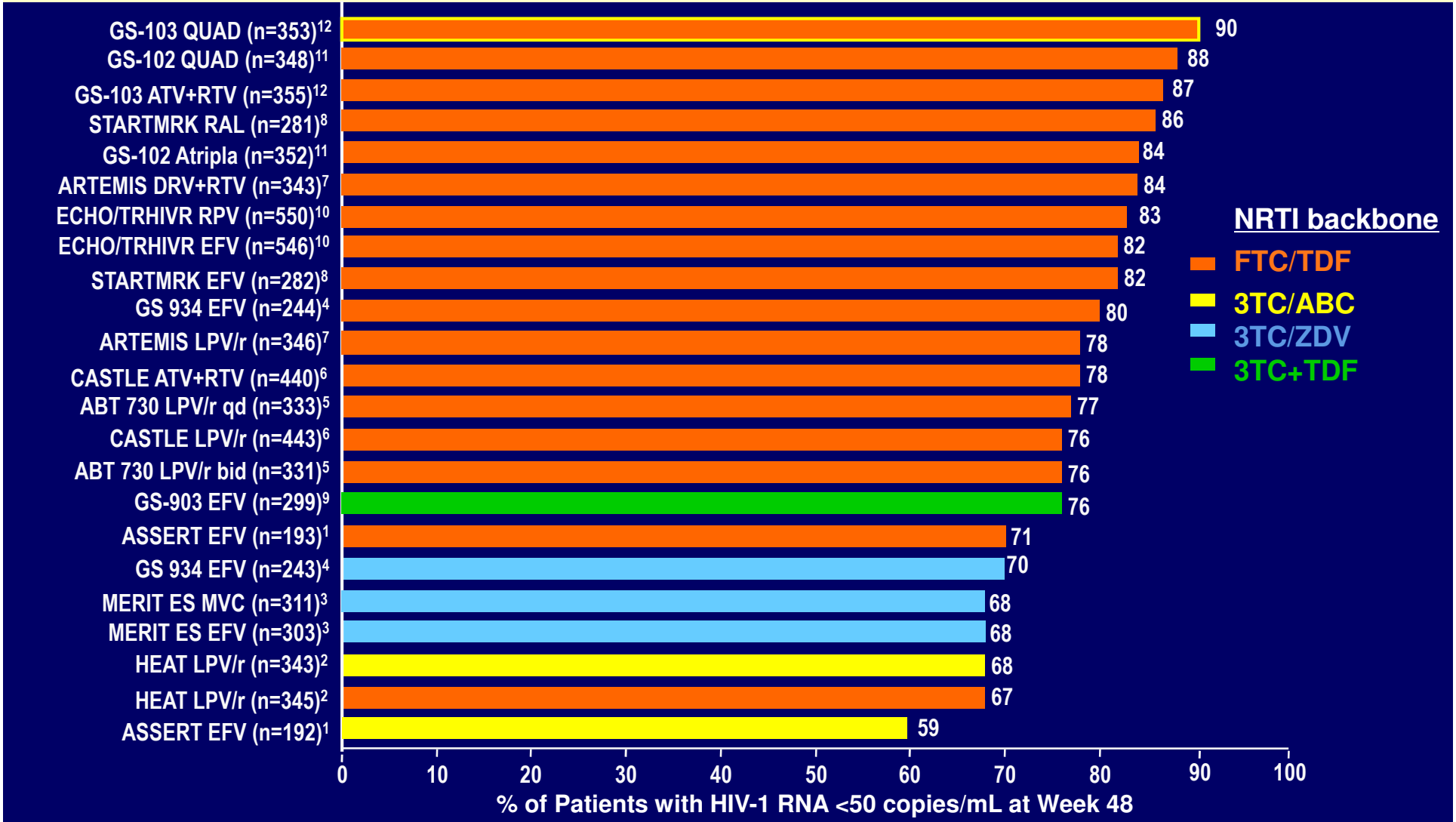
What to Start: Comparison of Guidelines

Regimen	DHHS[1]	IAS[2]	EACS[3]
EFV/TDF/FTC	**Preferred**	**Recommended**	**Recommended**
ATV/RTV + TDF/FTC	**Preferred**	**Recommended**	**Recommended**
DRV/RTV + TDF/FTC	**Preferred**	**Recommended**	**Recommended**
RAL + TDF/FTC	**Preferred**	**Recommended**	**Recommended**
LPV/RTV + TDF/FTC	Alternative	Alternative	Recommended
EFV + ABC/3TC	Alternative	Alternative	Recommended
ATV/RTV + ABC/3TC	Alternative	Alternative	Recommended
DRV/RTV + ABC/3TC	Alternative	Alternative	Recommended
NVP + TDF /FTC	Acceptable	Alternative	Recommended
MVC + TDF/FTC	Acceptable	Alternative	Alternative
RPV + TDF /FTC	Alternative	No recommendation	No recommendation
RAL + ABC/3TC	Alternative	No recommendation	No recommendation

1. DHHS Guidelines, March 2012. 2. Thompson MA, et al. JAMA. 2010;304:321-333.
3. EACS Guidelines, November 2011.

Background: Cross-Study Comparison of Treatment-Naive Clinical Trials

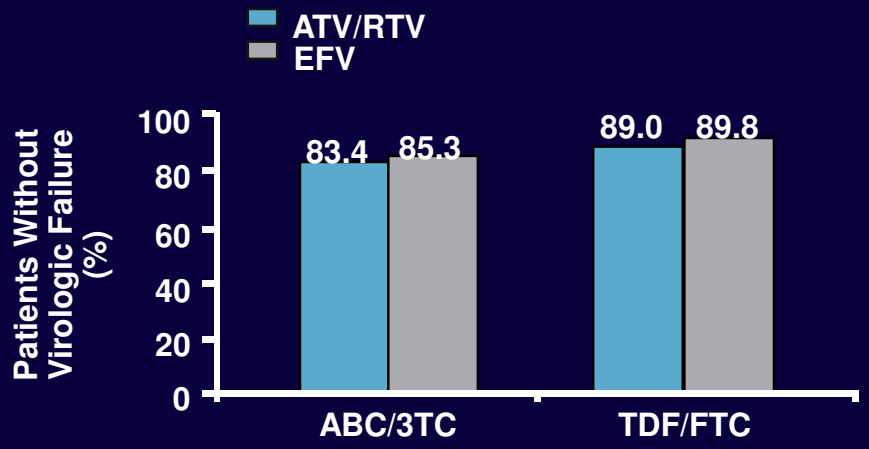
HIV RNA <50 copies/mL at Week 48



This slide depicts data from multiple studies published from 2004-2012. Not all regimens have been compared head-to-head in a clinical trial

Efavirenz-based Regimens

Advantages	Disadvantages
▪ Long history of use; much clinical trial data ▪ Current gold standard for first-line therapy ▪ As effective or more effective than other compators in head-to-head comparisons ▪ Low pill count: coformulated into 1 pill QD regimen ▪ Long half-life	▪ Low genetic barrier to resistance—single mutation ▪ Higher risk of NRTI resistance with NNRTI failure (compared with bPIs) ▪ CNS adverse effects ▪ Teratogenicity ▪ Potential drug interactions (CYP450)



Daar ES, et al. Ann Intern Med. 2011;154:445-456.

Efavirenz equivalent

Boosted Atazanavir (not formally proven)

Raltegravir

Quad (cobicistat)

Dolutegravir

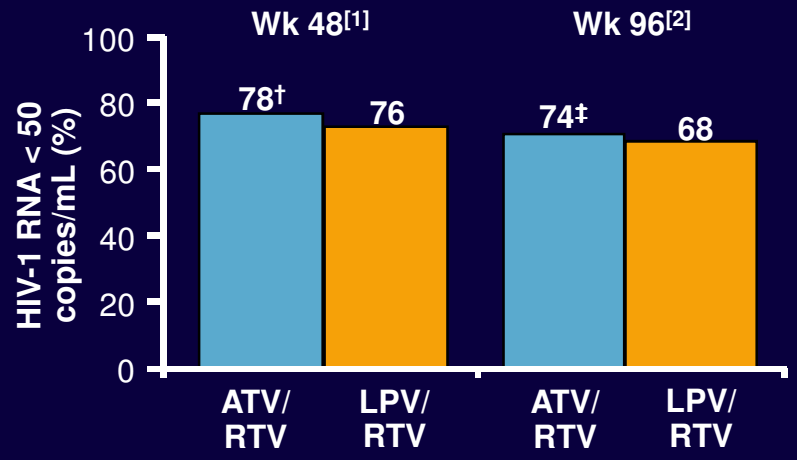
Etravirine (not formally proven)

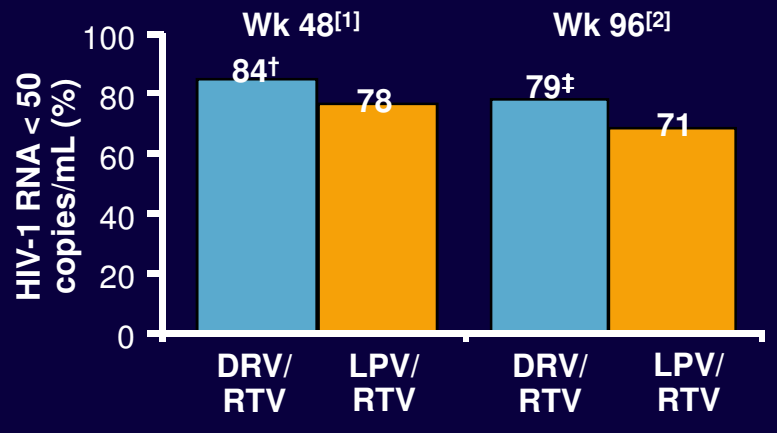
Pregnancy registry

- NO excess risk of teratogenesis

Preferred Boosted PIs

PI	Advantages	Disadvantages
ATV/RTV	▪ Efficacy comparable to efavirenz through 96 weeks ▪ Favorable lipid profile ▪ Low risk of resistance at failure ▪ Lowest pill burden of boosted PIs (2/day) ▪ Daily dose requires only RTV 100 mg/day	▪ Absorption impaired with acid-reducing agents ▪ Associated with rise in unconjugated bilirubin and scleral icterus in 4-9% of pts ▪ Food requirement for dosing
DRV/RTV	▪ Favorable lipid profile ▪ Low risk of resistance at failure ▪ Relatively low pill burden ▪ Daily dose requires only RTV 100 mg/day	▪ Rash in ~ 3% of pts; use with caution in pts with sulfa allergy ▪ No coformulations with other classes



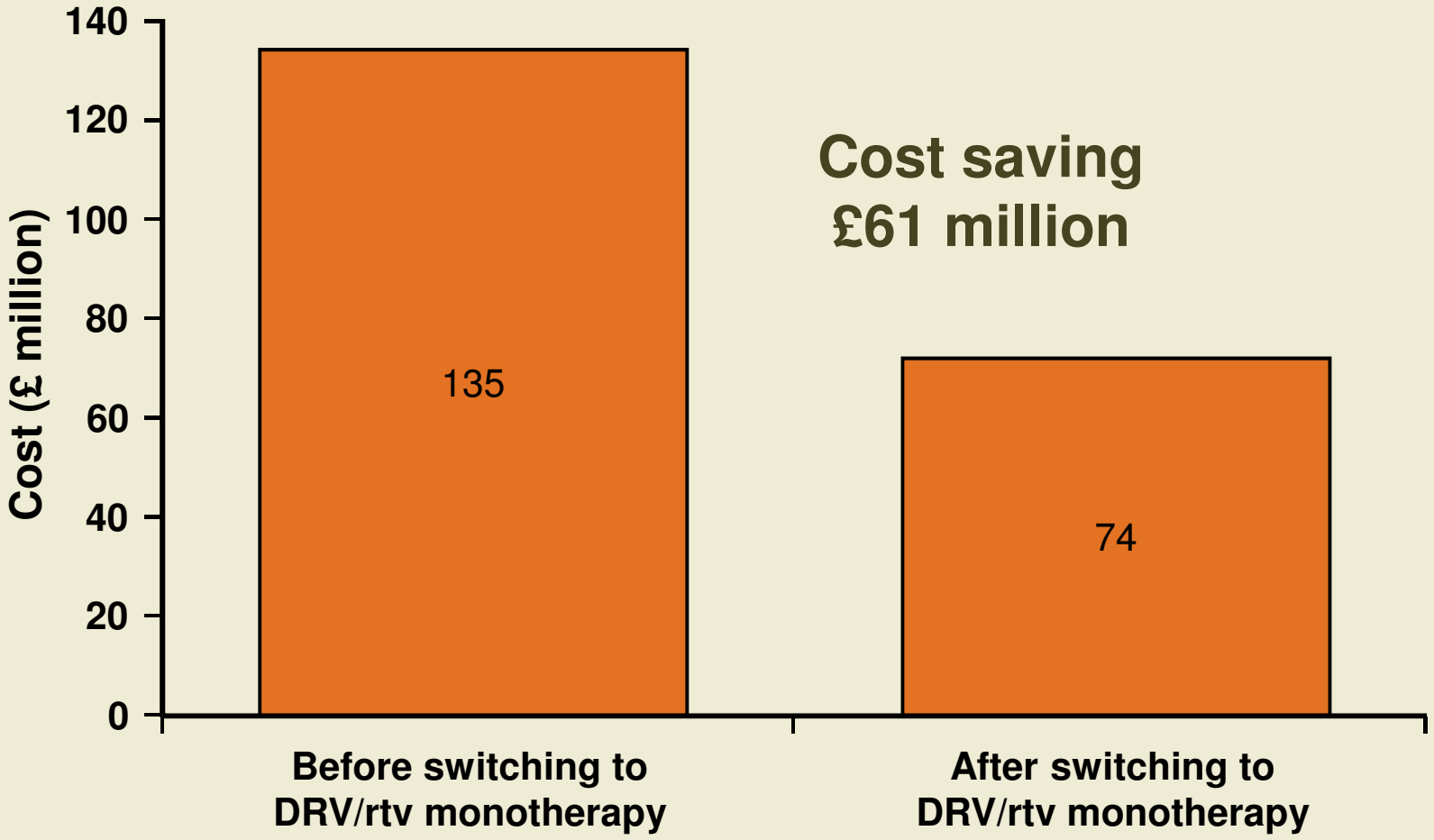


. Molina JM, et al. Lancet. 2008;372:646-655. Ortiz R, et al. AIDS. 2008;22:1389-1397.

Major downside of PIs

- Cost of goods is high

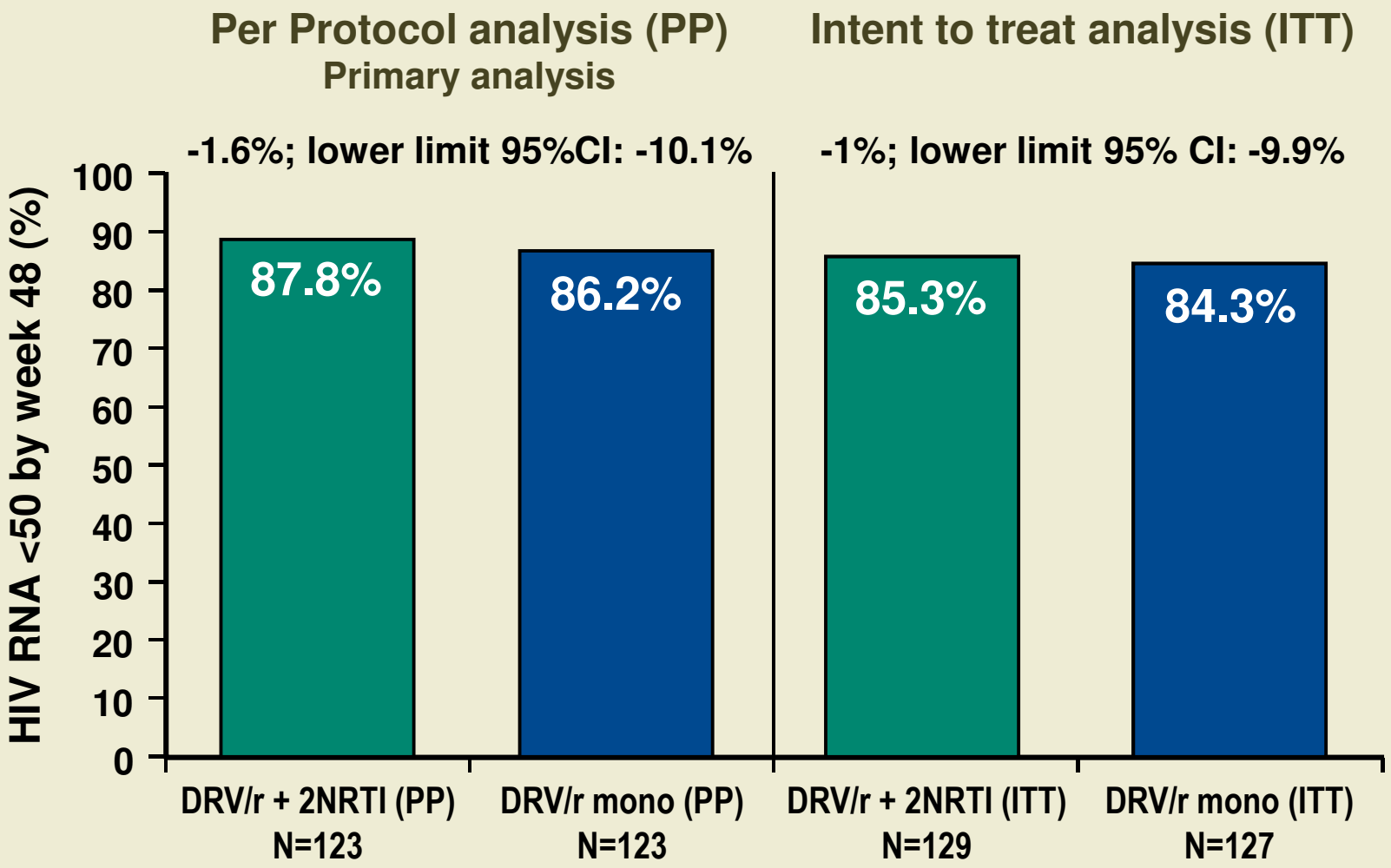
Cost impact of DRV/r monotherapy in the UK



Date of Preparation April 2010

Gazzard B and Hill A, Poster 3 BHIVA 2010

The MONET trial:
PI: ARRIBAS Jose

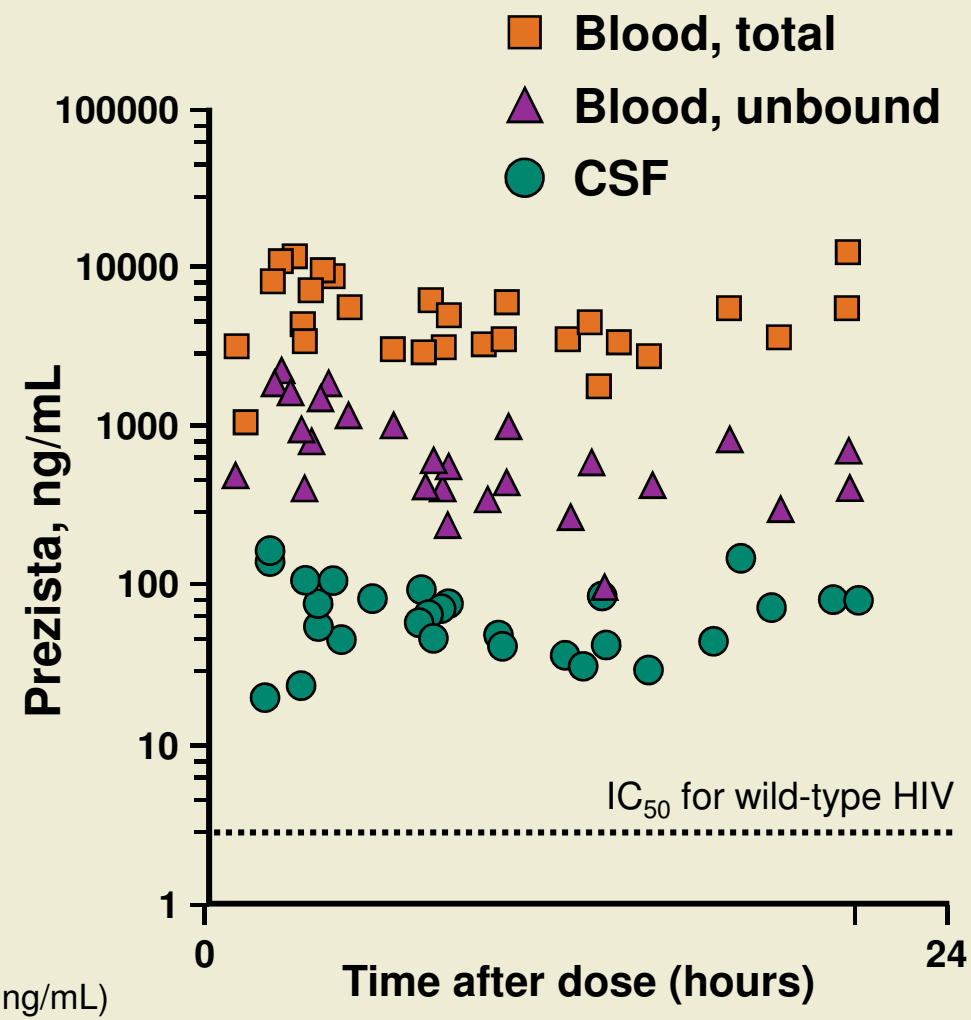


Date of Preparation April 2010

Arribas J., WAC 2009, Cape Town TUAB106-LB

Darunavir concentations in blood and in CSF

- **Darunavir concentrations in CSF exceeded the IC_{50} of wild-type HIV in all samples**
- **Darunavir CSF concenrations did not correlate with post-dose sampling time**



CSF, cerebrospinal fluid
IC_{50}, inhibitory correlation for wild-type HIV (2.75 ng/mL)

Date of Preparation April 2010

Letendre S et al. ICAAC 2009 Poster 45

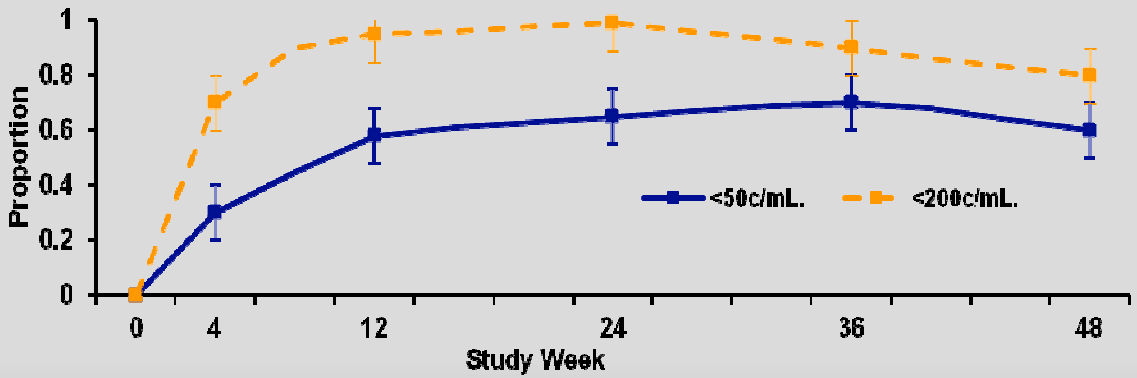
Ernest Study- second line

- Boosted PI
- Boosted PI plus nucs
- Boosted PI plus Integrase

Darunavir/r + Raltegravir: NRTI Sparing Regimen for ARV-naïve Patients-ACTG A5262

Single arm study of DRV/r (800/100 mg) QD + RAL (400 mg BID) (N=112)		
Age (years)	Median (Q1,Q3)	36 (27, 45)
Sex	Male	98 (88%)
Race	White	49 (44%)
CD4 cell count (cells/mm^3)	<200 200<350 ≥350	40 (36%) 32 (29%) 40 (36%)
HIV-1 RNA (copies/mL)	≤100,000 ≥100,000	63 (56%) 49 (44%)

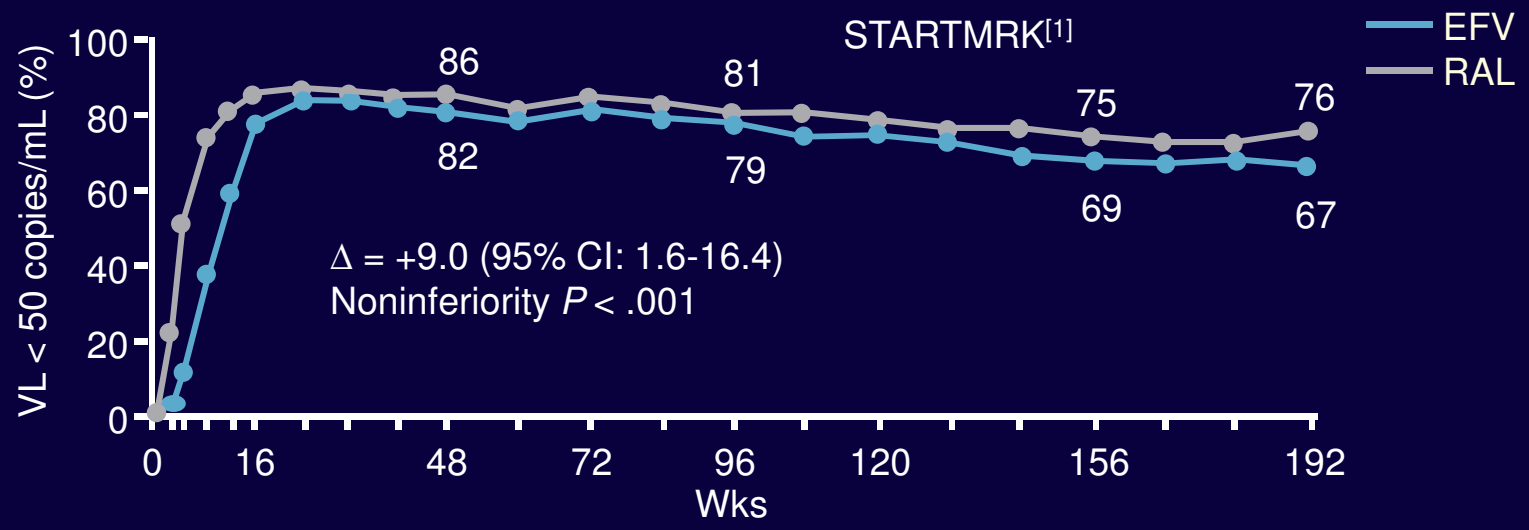
Proportion Of Subjects With HIV-1 RNA <200 and <50 copies/mL
(ITT analysis, missing/off study= ignored



Taiwo B, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 551.

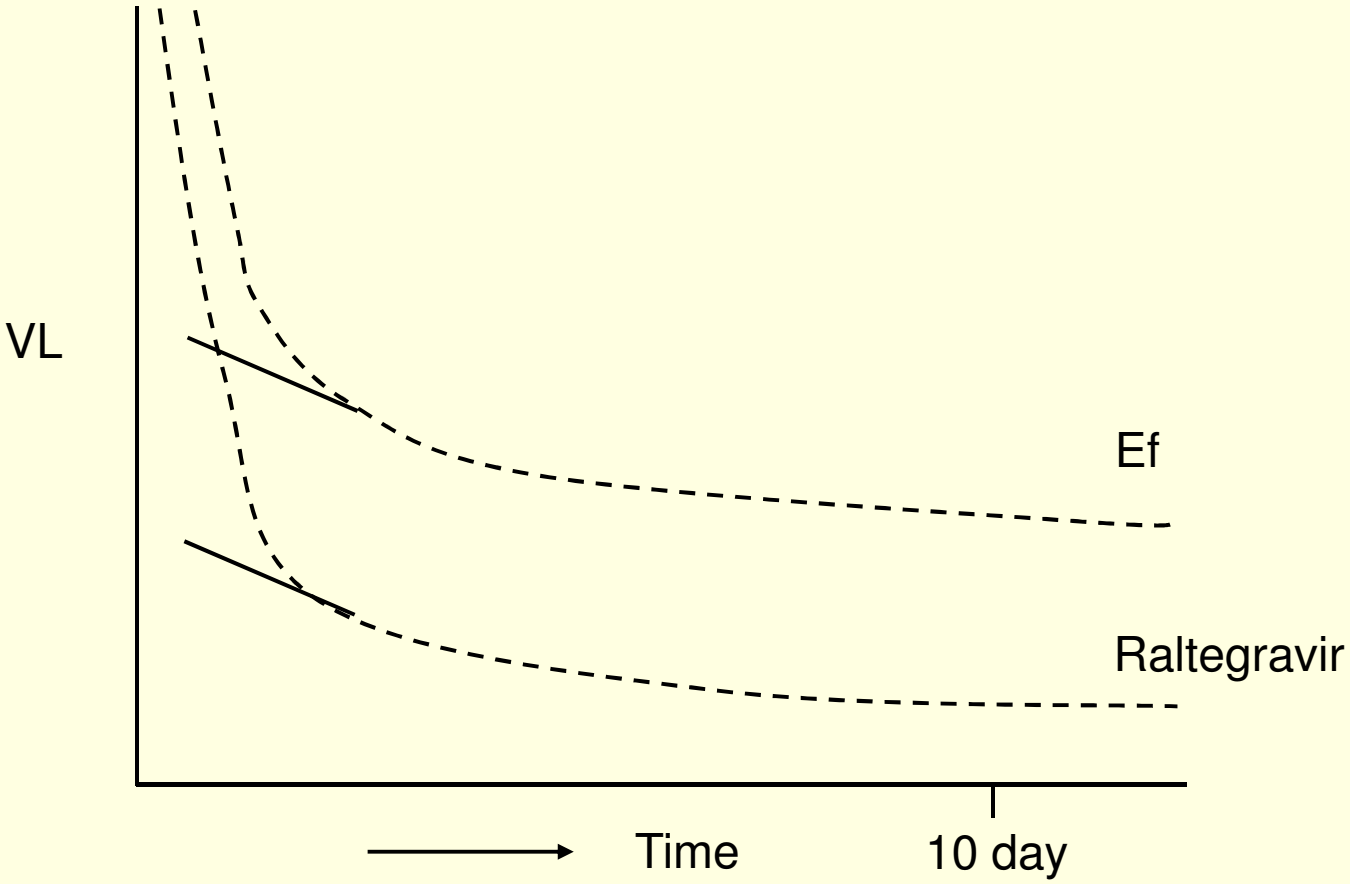
Raltegravir-Based Regimens

Advantages	Disadvantages
▪ 4-yr efficacy comparable to efavirenz regardless of baseline VL or CD4+ count ▪ Few adverse events[2] ▪ Few drug-drug interactions ▪ Neutral effect on lipids ▪ Greater CD4+ increase than with EFV[2]	▪ Twice-daily administration ▪ Low genetic barrier to resistance[▪ Risk of NRTI resistance with failure ▪ No coformulations with other classes ▪ Potential for skin reactions ▪ Little data with other NRTIs than TDF/FTC



Rockstroh J, et al. EACS 2011. Abstract PS 1/1

Why Raltegravir works quicker

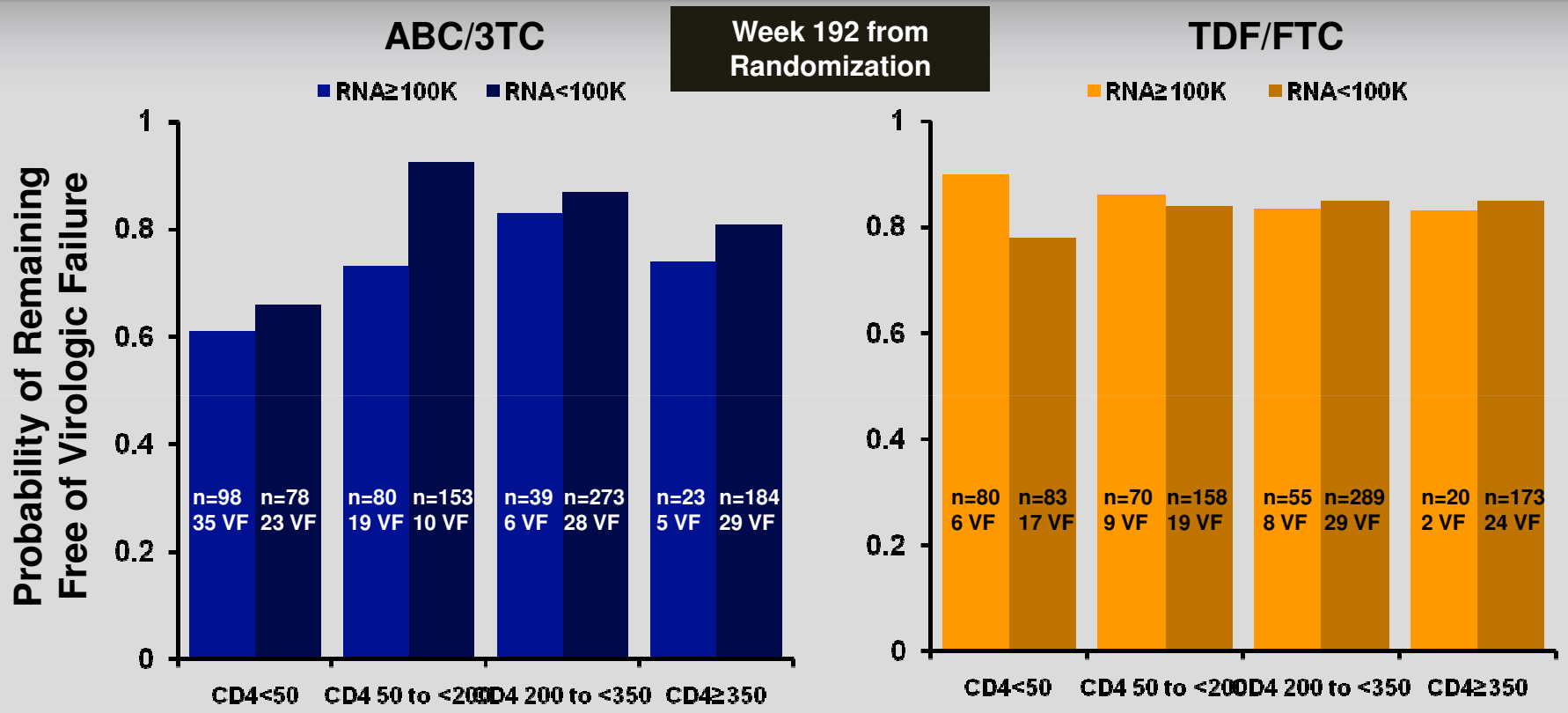


Abacavir ,Rilpivirine, lopinavir High Viral Load and Low CD4 count

It appears that there are more VFs in the high VL strata and if CD4 is low

Where do we place Abacavir ,rilpivirine and lopinavir in our treatment strategies?

A5202: Time to Virologic Failure by Baseline Viral Load and CD4 Count



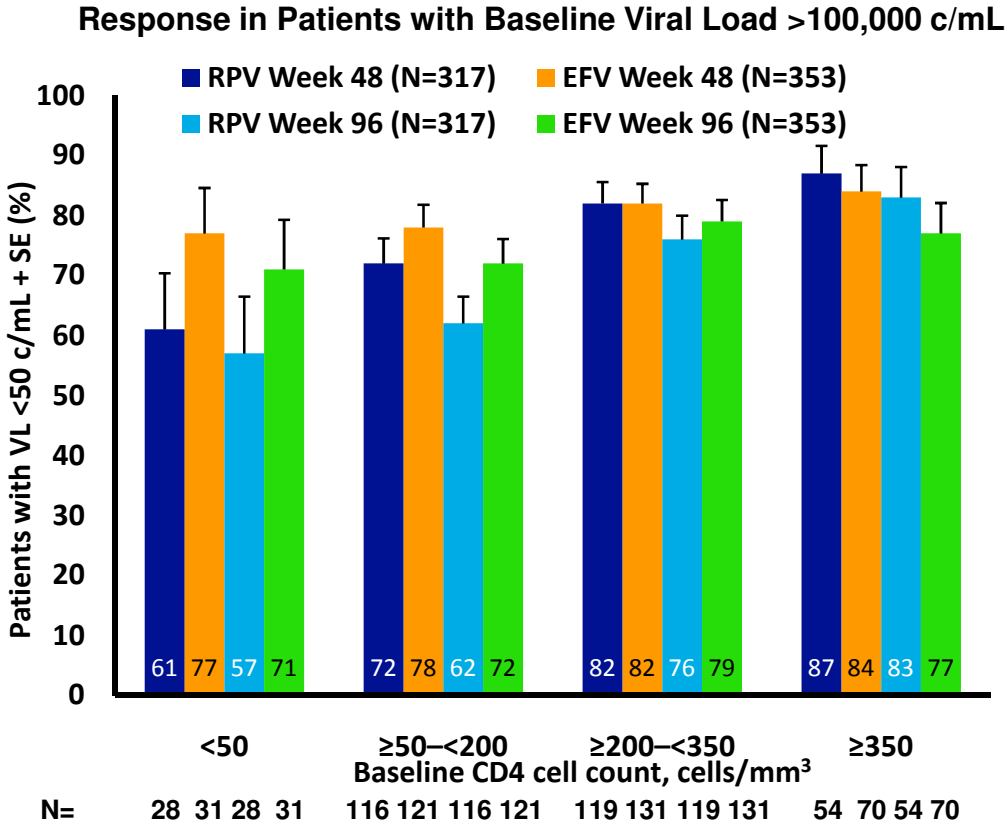
- Increased risk of VF with baseline lower CD4 or higher VL in those assigned ABC/3TC
- Results confirm previously reported analysis based on *screening* viral load

Grant P, et al. 18th CROI; Boston, MA; February 27-March 2, 2011. Abst. 535.

Rilpivirine-caution in low CD4 and high VL

Pooled ECHO and THRIVE:

Response with Baseline Viral Load >100,000 c/mL by Baseline CD4



- For baseline viral load >100,000 c/mL:
  - Virologic failure rates higher for RPV than EFV

Cohen C, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 626.

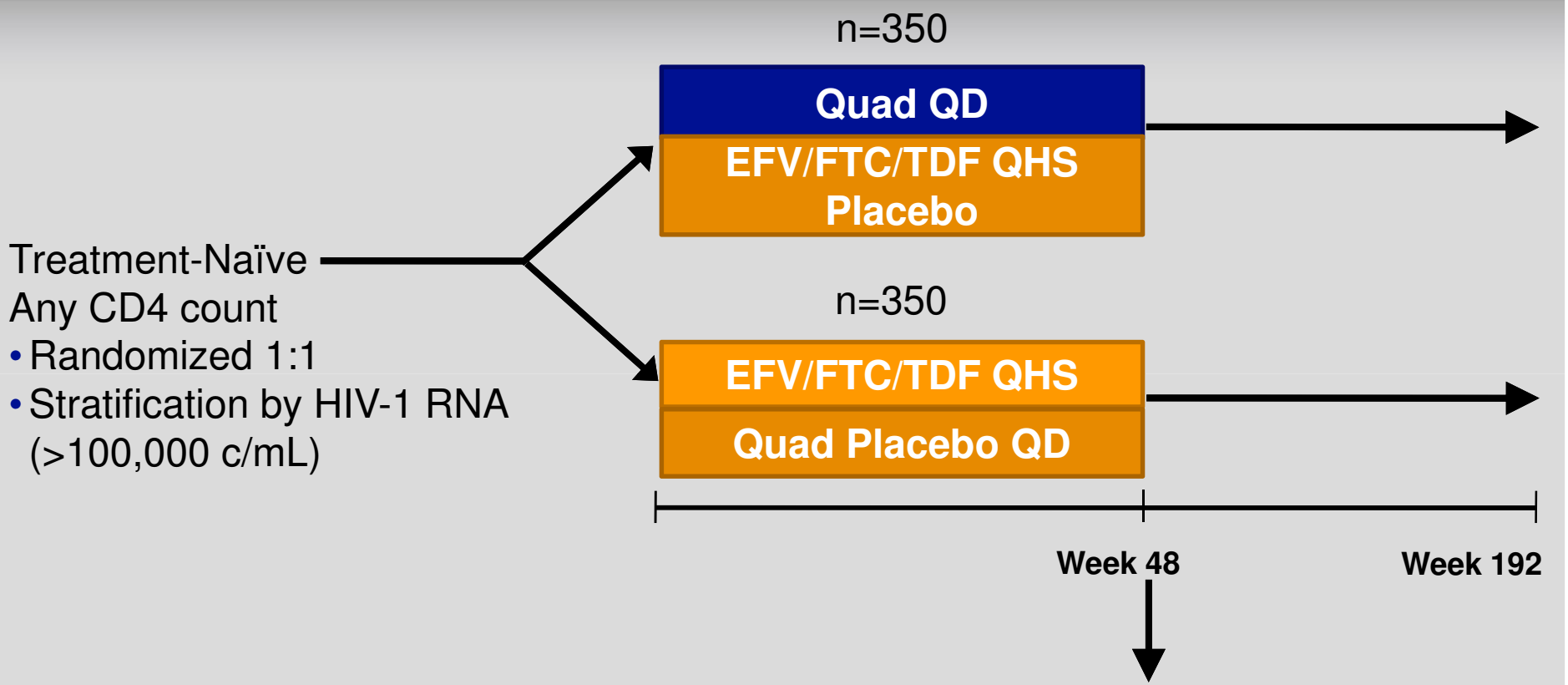
What about South Africa

- Efavirenz is main stay
- Combivir acceptable NOT D4T
- PI montherapy interesting option

What is new

- New drugs
- STR
- Cure

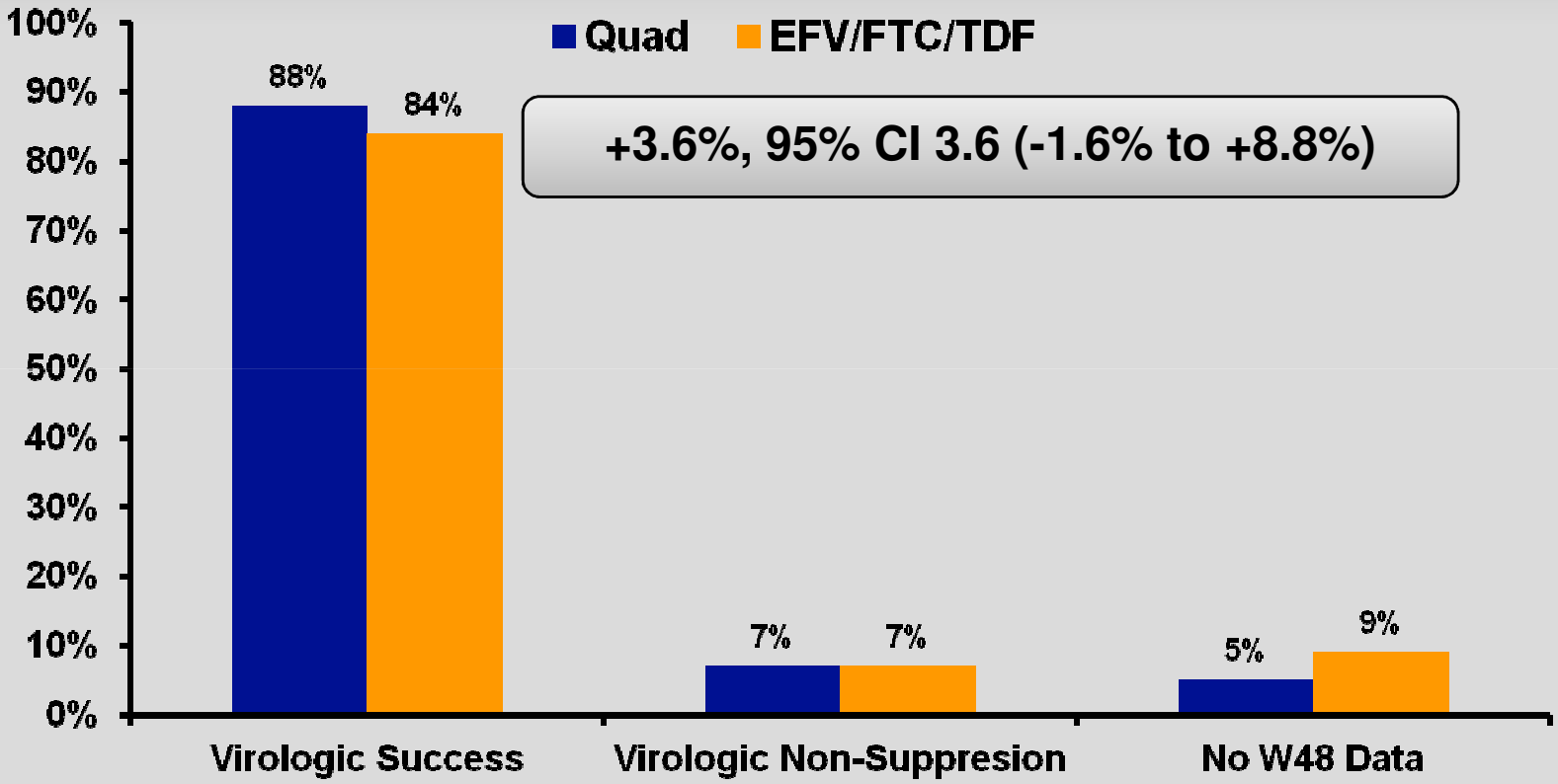
Elvitegravir/Cobicistat/FTC/TDF (Quad) vs. EFV/FTC/TDF (Study 236-102)



Primary Endpoint: Proportion with HIV-1 RNA < 50 copies/mL at Week 48

- FDA snapshot analysis (ITT), 12% non-inferiority margin

Study 236-102: Primary Endpoint: HIV-1 RNA < 50 copies/mL



CD4+ change: Quad +239 vs. EFV +206 c/mm^3 (p=0.009)

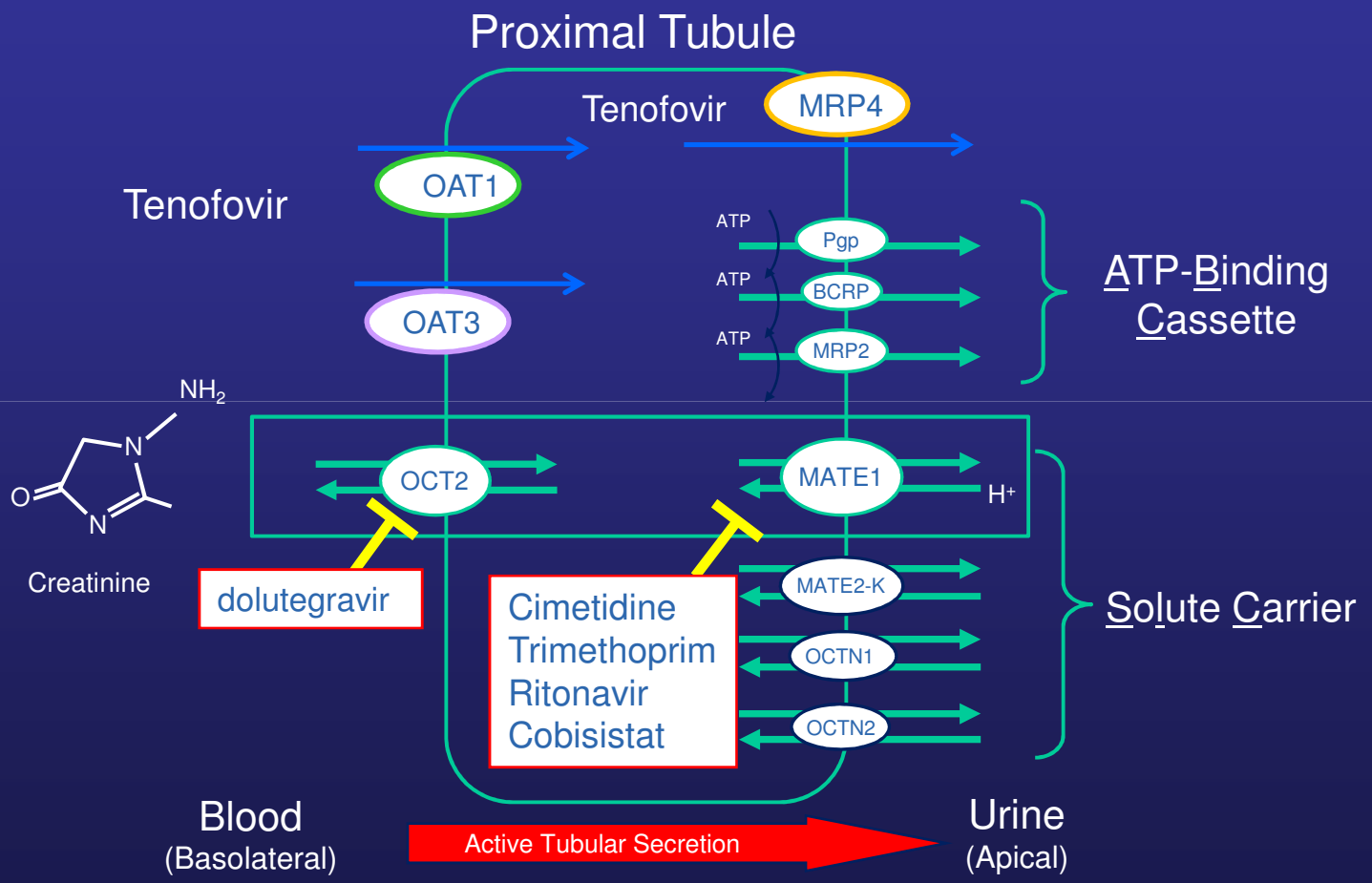
Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

Study 236-102: Integrase and NNRTI Resistance Through Week 48

	Quad (n=348)	EFV/FTC/TDF (n=352)
Subjects Analyzed for Resistance, n (%)	14 (4)	17 (5)
Subjects with Resistance to ARV Regimen, n (%)	8 (2)	8 (2)
Any Primary Integrase-R, n	7	
E92Q	7	
T66I	1	
Q148R	1	
N155H	1	
Any Primary NNRTI-R n		8
K103N		7
V108I		2
Y188Y/F/H/L		1
G190A		1
Any Primary NRTI-R, n	8	2
M184V/I	8	2
K65R	3	2

Sax P, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 101.

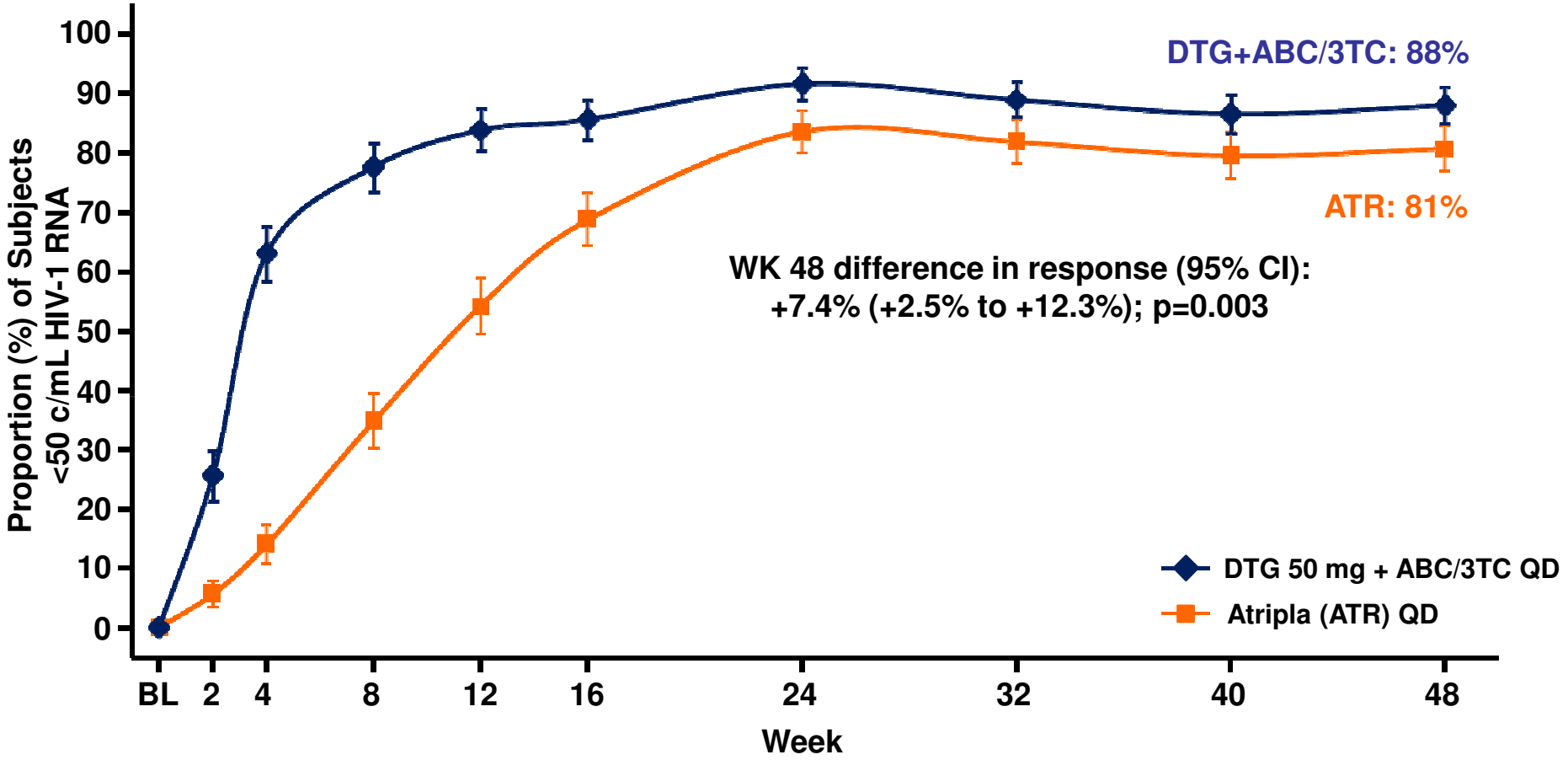
Is Creatinine and eGFR the right model for CKD when on HAART?



MATE: multidrug and toxic compound extrusion

Cihlar T, et al. Antivir Ther. 2007;12:267–72. Tong L, et al. Antimicrob Agents Chemo. 2007;51:3498–504.n Meyer HE, et al. Am J Physiol Renal Physiol. 2010; 298:F997–F1005.

Proportion (95% CI) of Subjects <50 c/mL (FDA Snapshot)

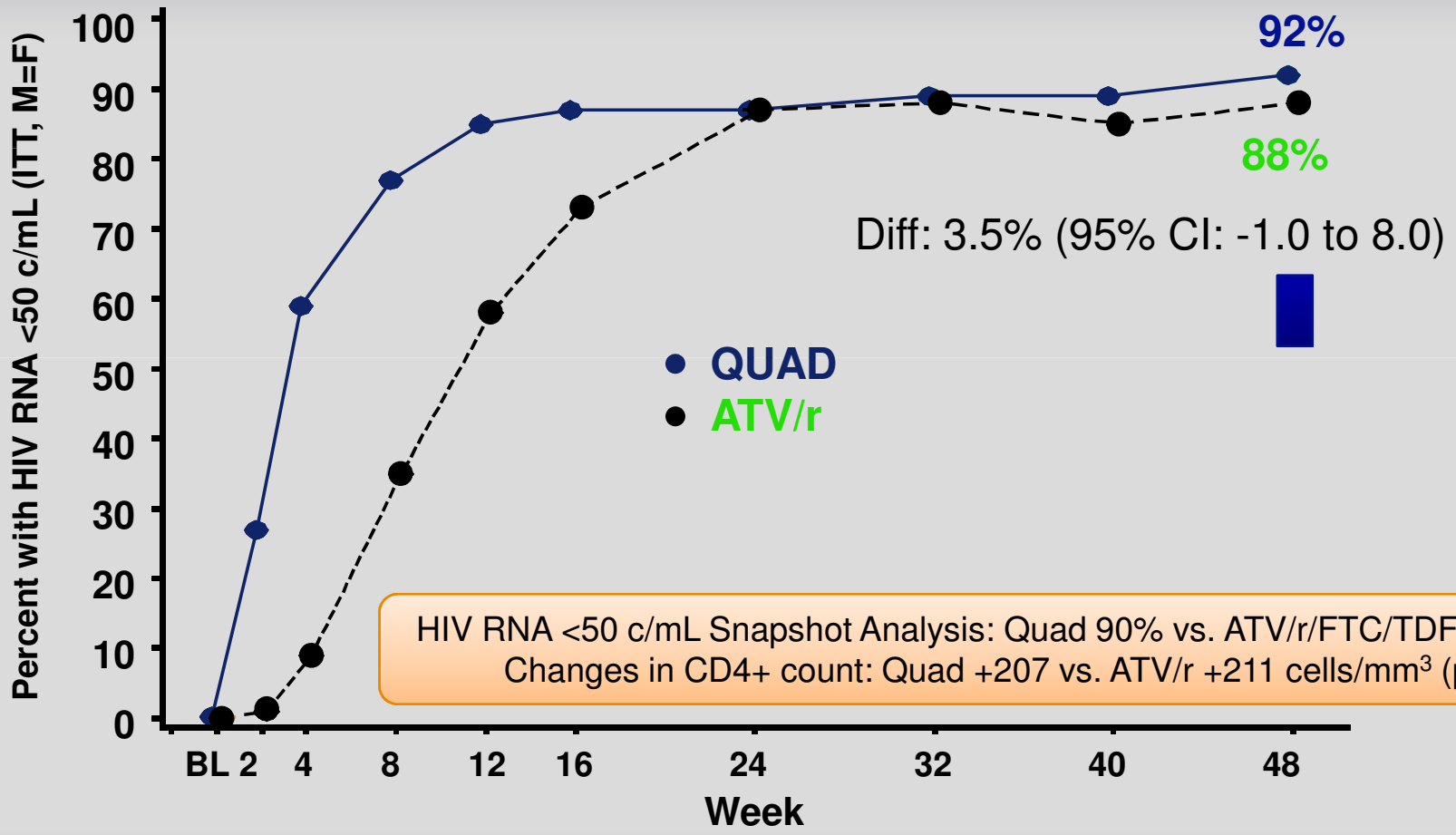


- DTG 50mg +ABC/3TC QD was statistically superior to Atripla at Week 48 (primary endpoint)
- Subjects receiving DTG +ABC/3TC achieved virologic suppression faster than Atripla, median time to HIV-1 RNA <50c/mL of 28 days (DTG +ABC/3TC) vs 84 days (Atripla), P<0.0001

Walmsley S, et al. 52nd ICAAC. 9-12 Sept 2012. Abstract H-556b.

Single Tablet Regimens

Study 236-103: HIV-1 RNA < 50 c/mL Through Week 48
4 v 4 pills and look at the results!



HIV RNA <50 c/mL Snapshot Analysis: Quad 90% vs. ATV/r/FTC/TDF 87% (P=NS)
Changes in CD4+ count: Quad +207 vs. ATV/r +211 cells/mm^3 (p=0.61)

DeJesus E, et al. 19th CROI; Seattle, WA; March 5-8, 2012. Abst. 627.

Uk Study

- Atripla
- Truvada efaverenz
- Tenofovir lamivudine efaverenz

WHO

- Atripla
- Boosted PI plus
- Integrase plus

The Berlin Patient

1. 2 BMT
2. Very severe GVH
3. Was dual tropic

Journal article

ABSTRACT

Persistence of the latent viral reservoir has been recognized as a major obstacle to eradicating human immunodeficiency virus (HIV) in infected individuals receiving antiretroviral therapy. It has been suggested that histone deacetylase inhibitors (HDACis) may purge HIV in the latent viral reservoir. However, the effect of HDACis on the degree and extent of HIV expression in the latent viral reservoir has not been fully delineated. Here we demonstrate that HDACis do not induce HIV production in the latent viral reservoir of aviremic individuals. Therefore, alternative therapeutic strategies may be necessary to eliminate HIV in the latent viral reservoir.

Source: PubMed

conclusions

- How do you deliver a high quality high volume service at low cost?
- Client involvement
- Standard regimens STR adherence and resistance