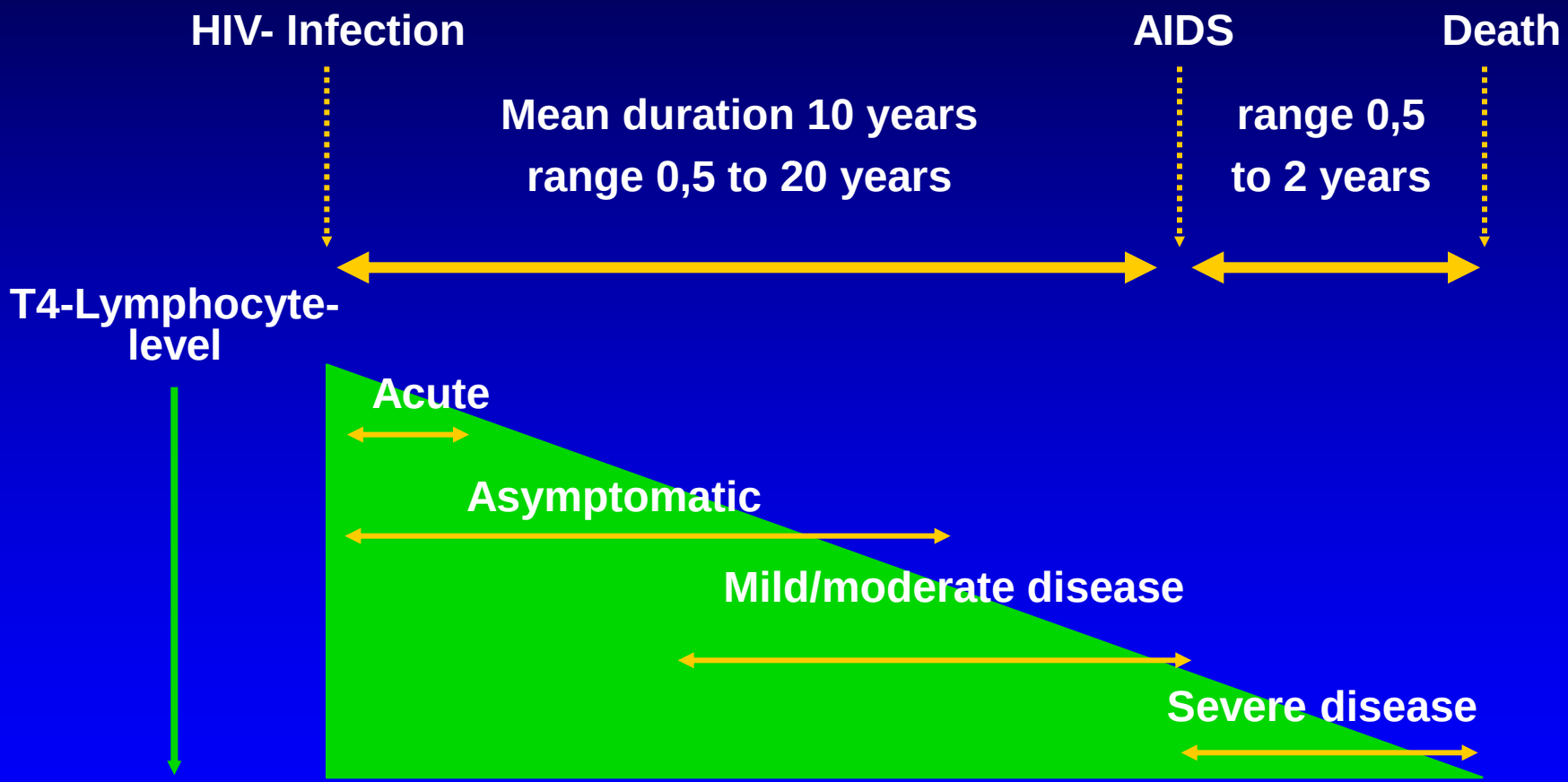
universitäts klinikum bonn

Management of ARV

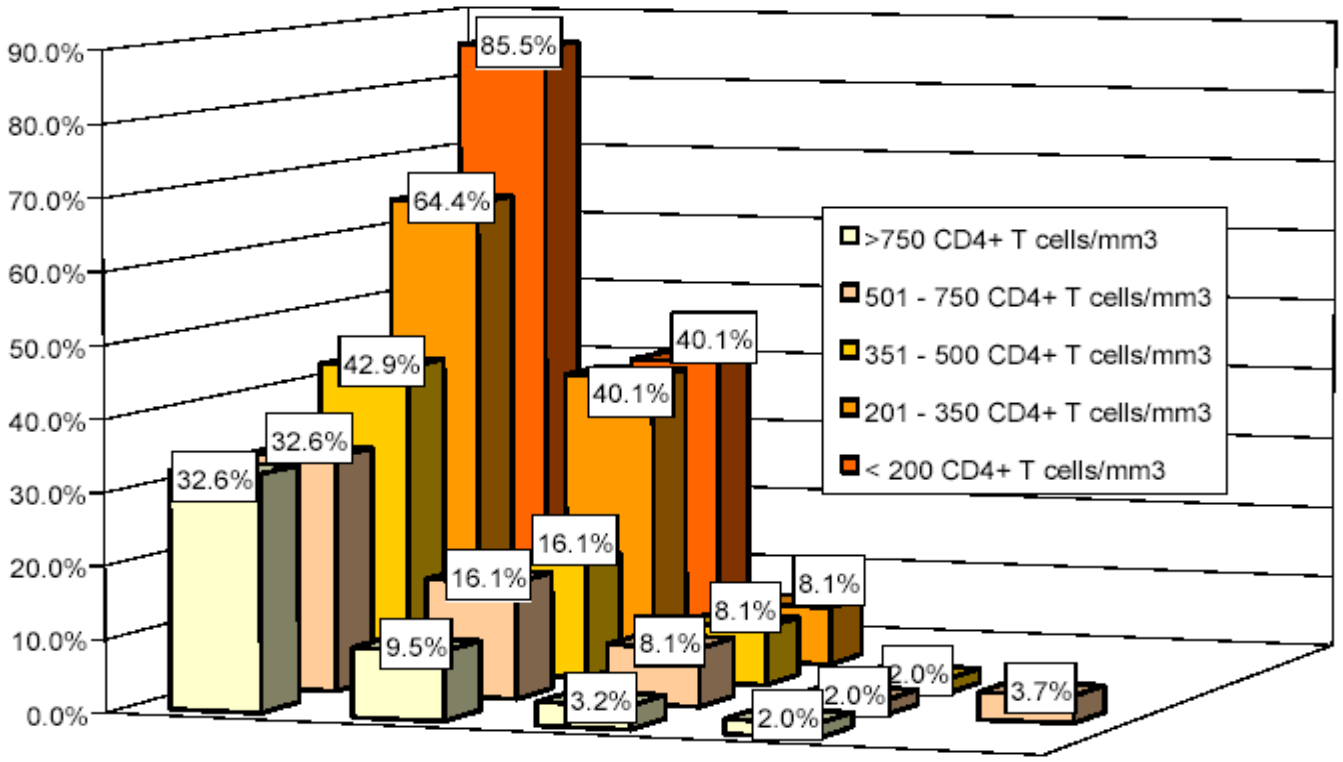
6th Advanced HIV Course, Montpellier, September 3-5, 2008

Jürgen Rockstroh, Department of Medicine I, University of Bonn, Germany

Natural course of HIV in adults

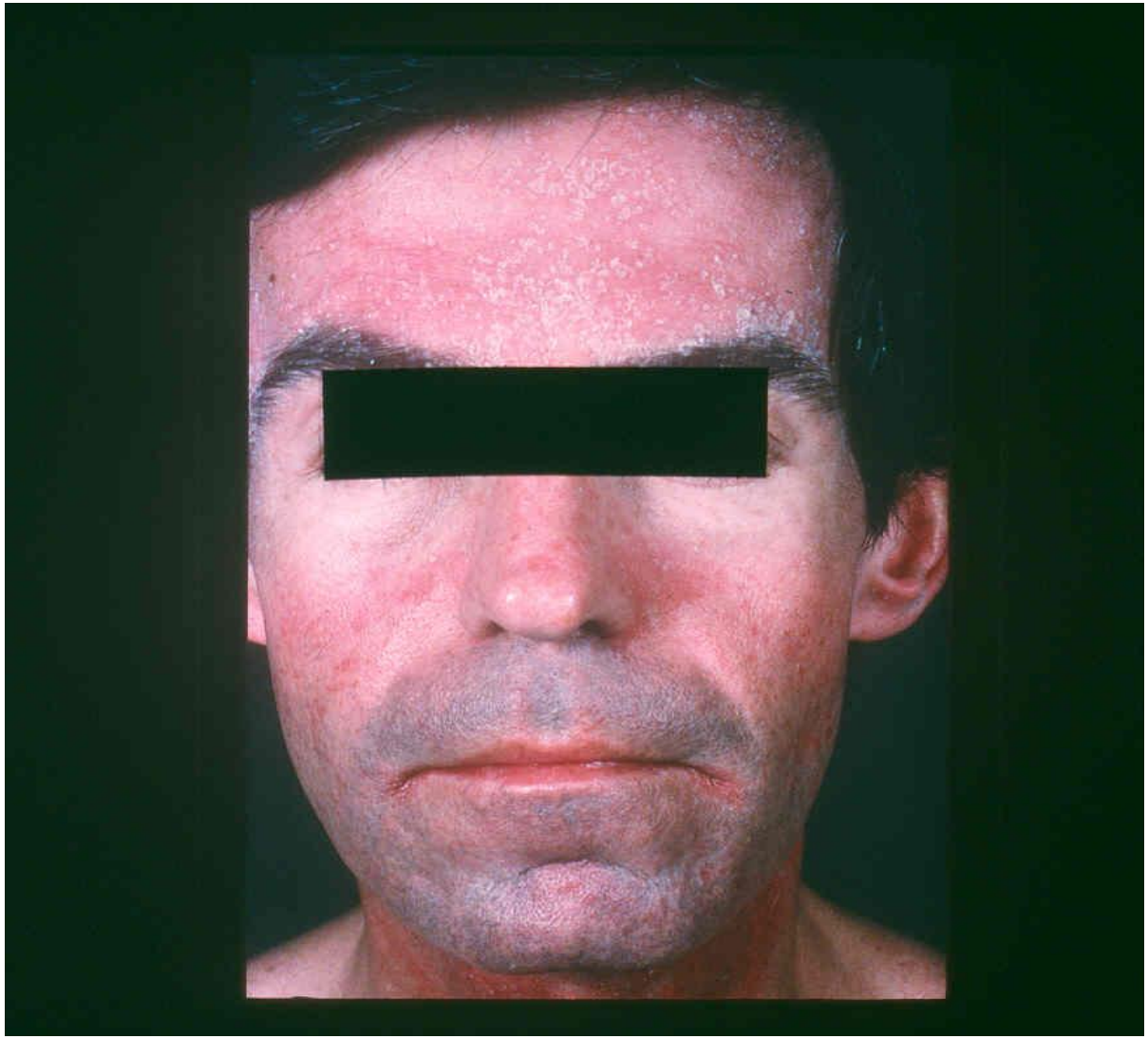


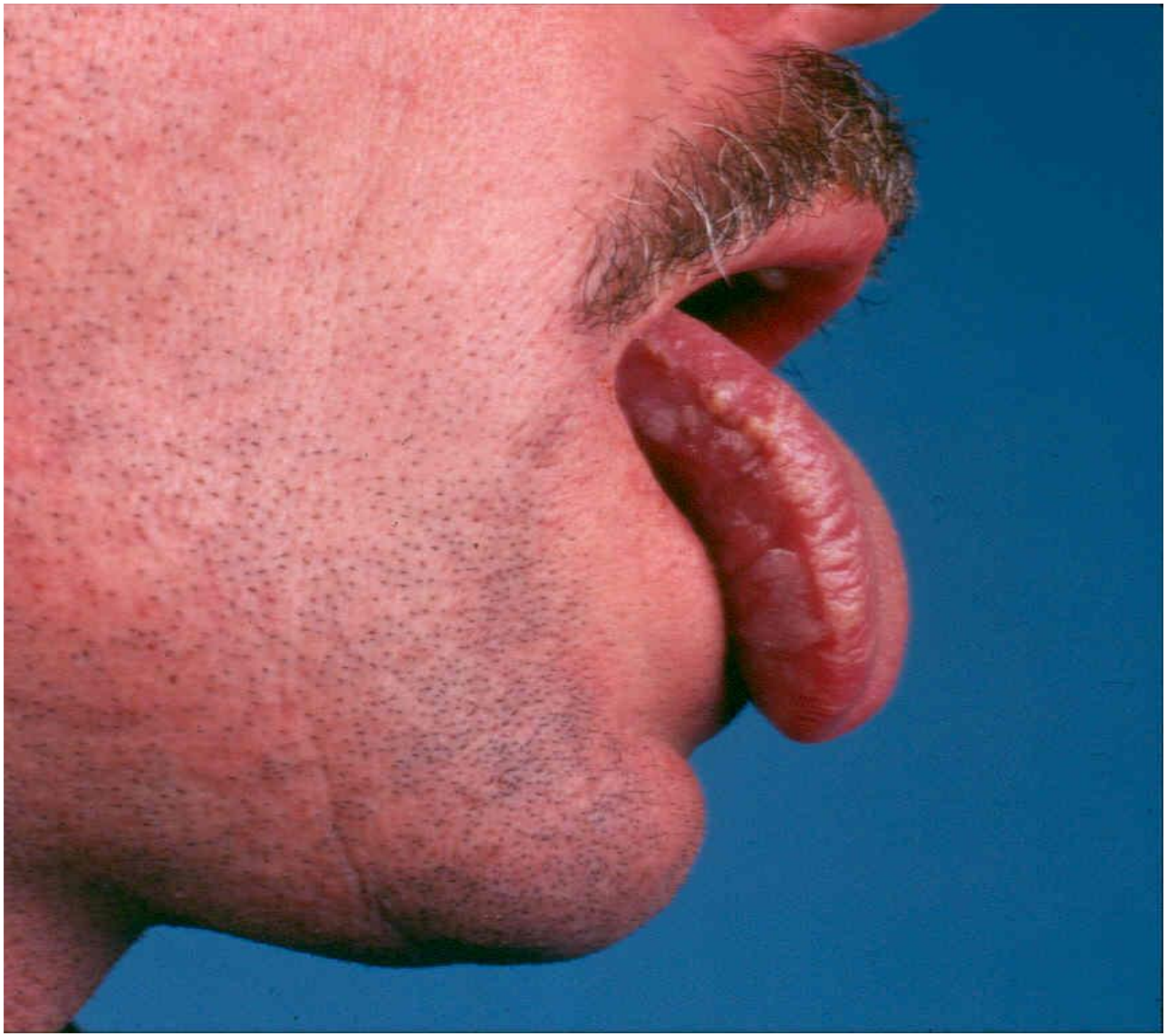
Likelihood of developing AIDS by 3 years after becoming infected with HIV-1

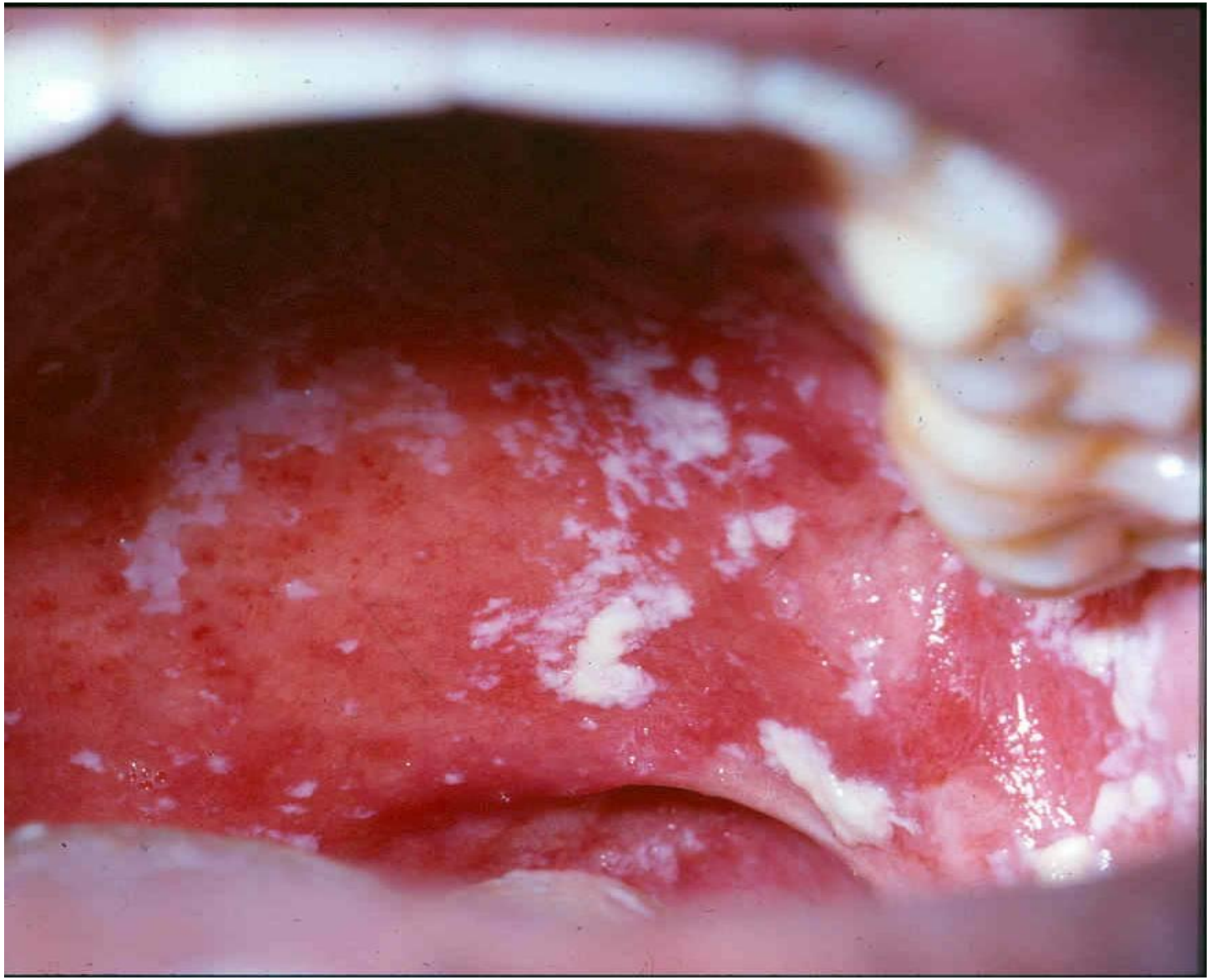


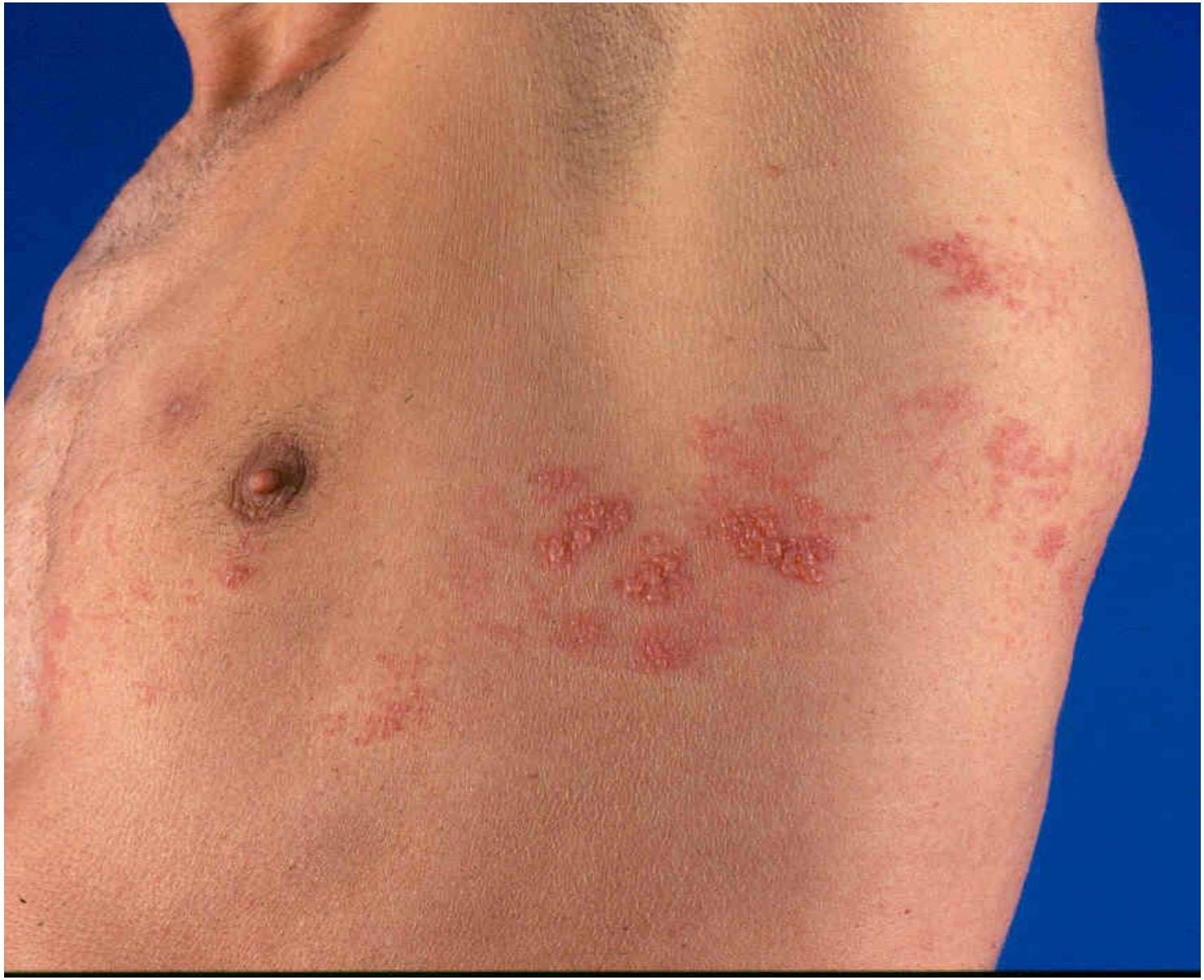
bDNA*	>30K	10K-30K	3K-10K	501-3K	<500
RT-PCR**	>55K	20K-55K	7K-20K	1.5K-7K	<1500

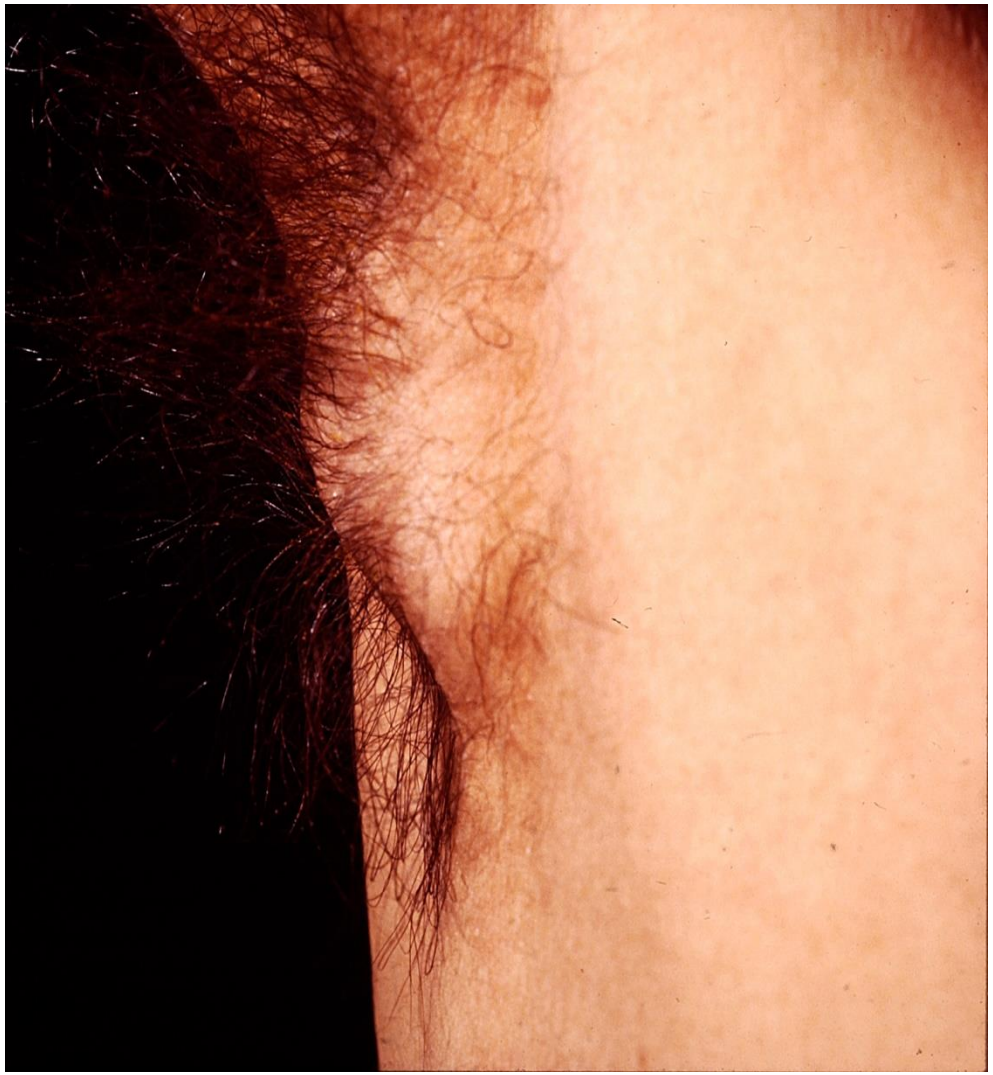
Mellors JW et al., Ann Intern Med 1997;126:946-954



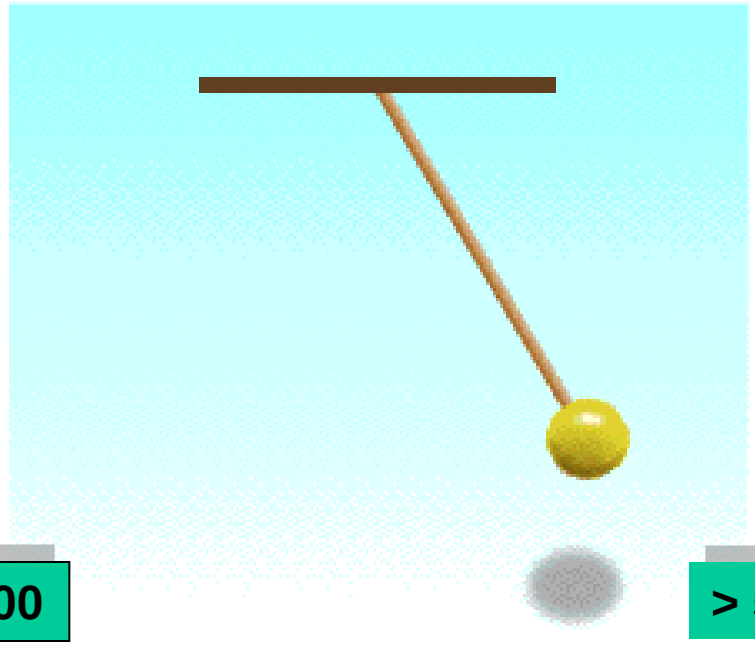








When to start with antiretroviral therapy?



Late clinical stages

Early clinical stages

< 200

> 500

200

350

Any viral load

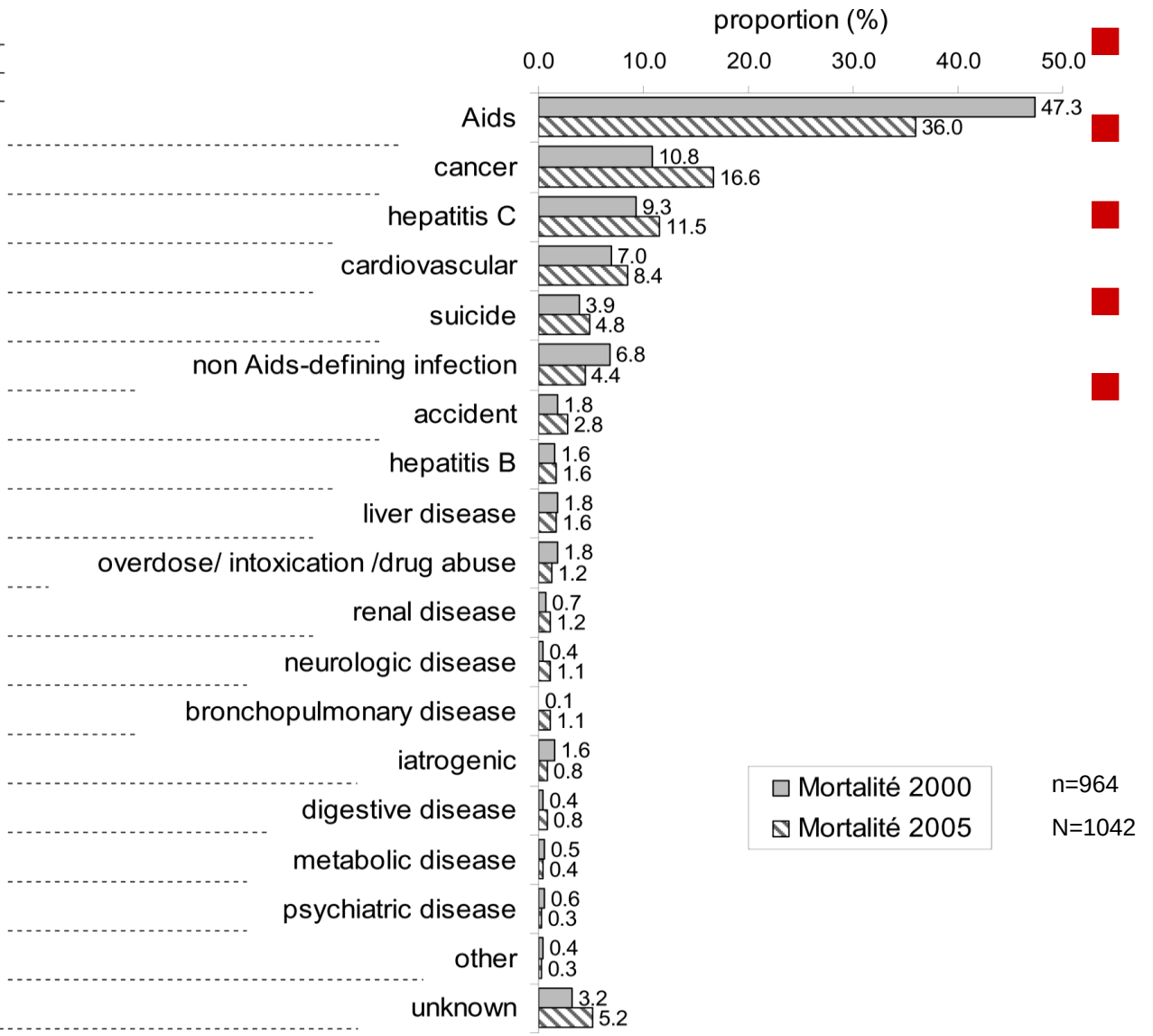
High viral load

CD4

Schechter, 2004 (JID 2004;190:1043-1045)

GERMAVIC: Underlying cause of death in HIV-1 infected adults

Median CD4 cell count (10-90% range)			
2000		2005	
27	(3-210)	42	(4-302)
195	(40-556)	205	(35-500)
184	(44-475)	227	(36-480)
250	(30-671)	338	(77-775)
309	(108-1109)	337	(111-805)
112	(7-545)	156	(13-710)
265	(30-595)	457	(195-956)
145	(50-489)	241	(30-521)
179	(11-387)	154	(10-331)
450	(92-696)	270	(99-739)
27	(0-538)	178	(32-348)
170	(150-528)	364	(153-730)
111	(111-111)	167	(34-524)
126	(21-661)	331	(97-965)
227	(7-404)	235	(36-950)
117	(1-360)	312	(12-690)
157	(50-1030)	372	(259-576)
125	(44-703)	270	(200-571)
254	(30-765)	271	(56-684)



Lewden C et al., J AIDS 2008

Guidelines: When to Start Treatment

Clinical category	CD4 cell count (cells/μL)	Viral load (copies/mL)	DHHS guidelines[1]	IAS-USA guidelines[2]
AIDS-defining illness or severe symptoms[a]	Any value	Any value	Treat	Treatment recommended
Asymptomatic	<200	Any value	Treat	Treatment recommended
Asymptomatic	200–350	Any value	Offer treatment	Consider treatment
Asymptomatic	>350	≥100 000	Consider treatment	Consider treatment
Asymptomatic	>350	<100 000	Defer therapy	Treatment not recommended

[a]Severe symptoms = unexplained fever or diarrhoea >2 to 4 weeks, oral candidiasis, or >10% unexplained weight loss

1. DHHS Guidelines. Revision Oct. 10, 2006. Available at: http://aidsinfo.nih.gov;
2. Hammer S, et al. JAMA 2006;296:827–843

Revised DHHS Guidelines

Indication for initiating ART for the chronically HIV-1-infected patient

Clinical condition and/or CD4 count	Recommendations
• History of AIDS-defining illness (AI) • CD4 count <200 cells/μL (AI) • CD4 count 200–350 cells/μL (AII) • Pregnant women (AI) • Persons with HIV-associated nephropathy (AI) • Persons coinfected with hepatitis B virus (HBV), when treatment is indicated (Treatment with fully suppressive antiviral drugs active against both HIV and HBV is recommended) (BIII)	Antiretroviral therapy should be initiated
Patients with CD4 count >350 cells/μL who do not meet any of the specific conditions listed above	The optimal time to initiate therapy in asymptomatic patients with CD4 count >350 cells/μL is not well defined. Patient scenarios and comorbidities should be taken into consideration

AI, a strong recommendation based on evidence from at least 1 randomised clinical trial with results
AII, a strong recommendation based on evidence from clinical trials with laboratory results
BIII, a moderate recommendation based on expert opinion

DHHS Guidelines. Revision Jan. 29, 2008. Available at: http://aidsinfo.nih.gov

Recommendations for Initiation of Therapy in Naïve HIV-Infected Patients

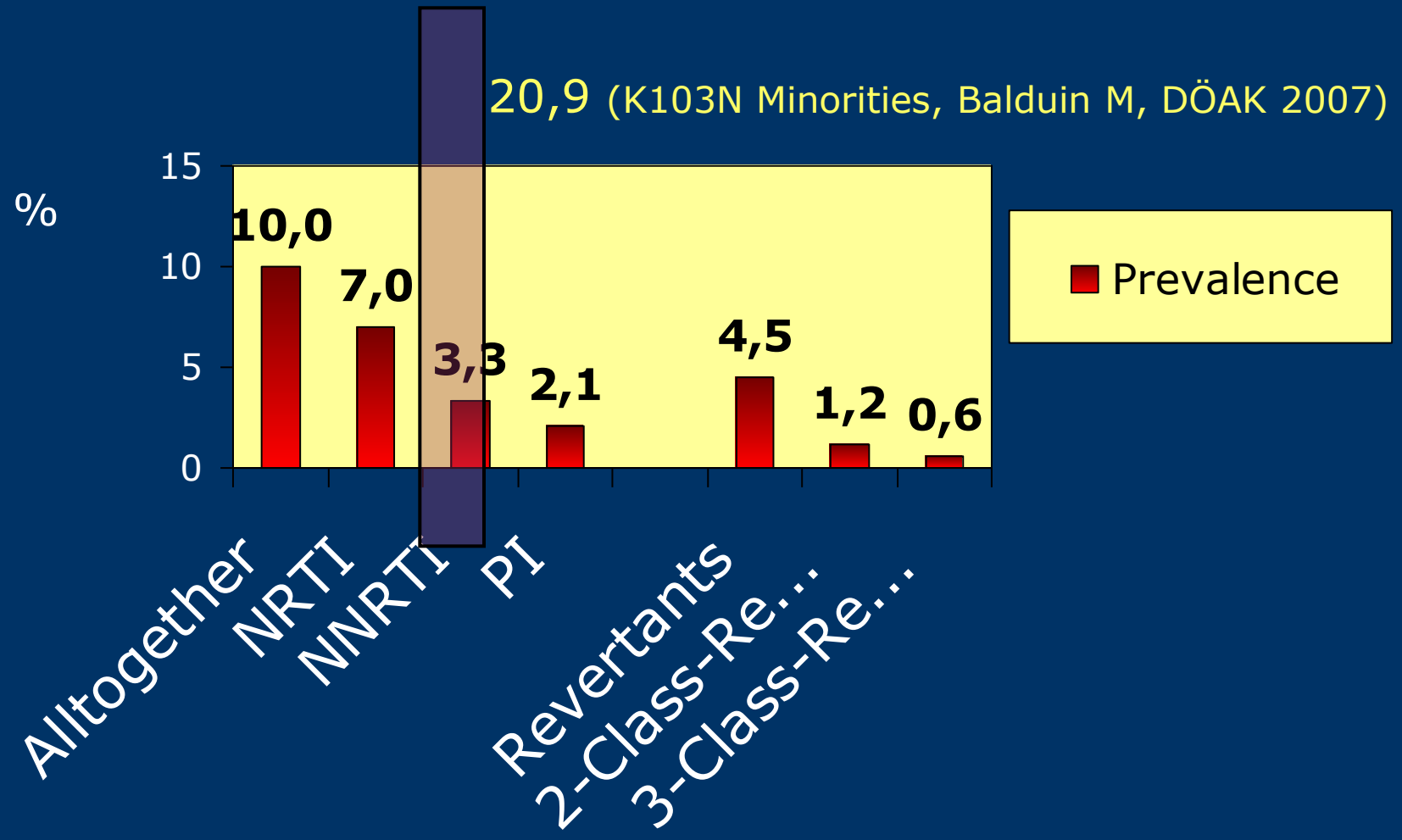
Symptomatic	Asymptomatic	Resistance testing	Additional remarks
• CDC stage B and C: Treatment recommended • If OI, initiate as soon as possible[a]	• CD4 <200: Treatment recommended, without delay • CD4 201–350: Treatment recommended • CD4 350–500: Treatment may be offered if VL >10^5 c/mL and/or CD4 decline >50–100/µL/year or age >55 or hepatitis C coinfection • CD4 >500: Treatment should be deferred, independently of plasma HIV RNA; closer follow-up of CD4 if VL >10^5 c/mL Whatever CD4 and plasma HIV RNA, treatment can be offered on an individual basis, especially if patient seeking and ready for ARV therapy	Genotypic testing and subtype determination recommended, ideally at the time of HIV diagnosis, otherwise before initiation of first-line regimen. If genotypic testing is not available, a ritonavir-boosted PI could be preferred in the first-line regimen	• Before starting treatment, CD4 should be repeated and confirmed • Time should be taken to prepare the patient, in order to optimise compliance and adherence

CDC, Centre for Disease Control and Prevention

[a]Pay particular attention to drug–drug interactions, drug toxicities, immune reconstitution syndrome and adherence, etc.

EACS Guidelines. Revision Dec, 2007. Available at: http://www.eacs.eu/guide/index.htm

RESINA 2001-2007 (n=1343)
Prevalence of primary HIV drug resistance



M. Oette, personal communication 2008

RESINA

How to start?

How do I select the best regimen for my individual patient?

- **Under consideration of the high number of currently available ARVs, an individual choice should be preferred based on the following factors:**
  - **Patient characteristics**
  - **Drug properties of each respective drug within a given regimen**
- **Considerations:**
  - **Potency**
  - **Adherence issues**
  - **Tolerability**
  - **Drug-drug interactions**
  - **Results from a genotypic resistance testing**
  - **Pregnancy wish**
  - **Comorbidities (particularly cardiovascular and hepatitis coinfection)**
  - **Practical considerations (i.e. refrigeration possible)**
  - **Cost issues**

HIV-drugs 2008

NRTI/NtRTI	NNRTI	Proteaseinhibit.	Fusionsinhibit.
AZT[1]	Nevirapine	Saquinavir	Enfuvirtide
3TC[2]	Efavirenz[6]	Indinavir	
ddI	Emtrivarine	Nelfinavir	Integraseinhibit.
~~DDC~~		Ritonavir	Raltegravir
Abacavir[3]		Fosamprenavir	
Tenofovir[4]		Lopinavir/r	CCR5-Inhibitor
FTC[5]		Atazanavir	Maraviroc
		Tipranavir	
		Darunavir	

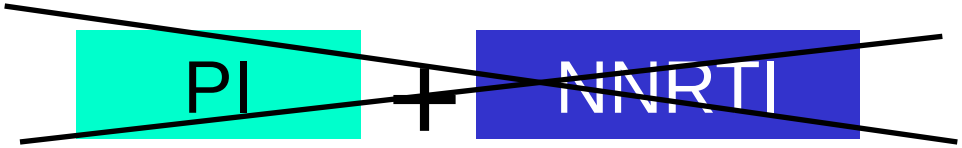
Combivir[1,2], Trizivir[1,2,3], Kivexa[2,3], Truvada[4,5], Atripla[4,5,6]

Options for firstline HAART

PI-containing

NNRTI-containing

NRTI-saving



PI and NNRTI-saving

Recommended Regimens for Treatment-Naive Patients: IAS 2008

Recommended Components of Initial Antiretroviral Therapy[a]

NRTIs	NNRTIs	PIs
TDF/FTC[b] **ABC/3TC[c,d]**	**EFV**	**LPV/RTV** **ATV/RTV** **FPV/RTV** **DRV/RTV** **SQV/RTV**

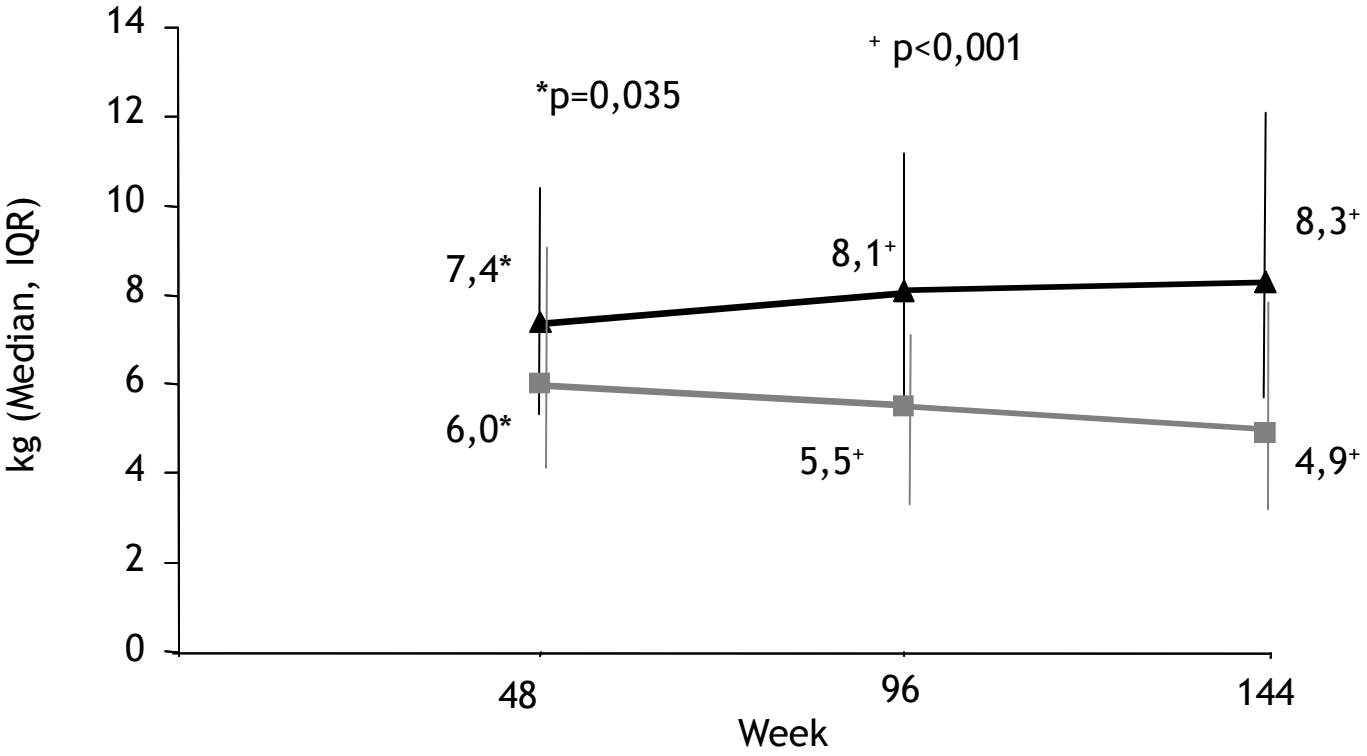
[a]Therapy should consist of 2 NRTIs + either efaviranz or a PI/r. NVP is an alternative (CD4 restrictions)
[b]Or 3TC.
[c]Or FTC.
[d]May have less activity in patients with a viral load > 1000.000 copies/ml; may be associated with increased risk for myocardial infarction

Hammer S et al. *JAMA.* 2008;300:555-570

Choice of Initial Regimen (cont'd)

Component	Recommended Drugs	Comments
NNRTI component	**efavirenz**	**EFV: teratogenic in 1st trimester** **NVP (alternative): increased risk of hepatotoxicity in women with CD4 >250/µL and men with CD4 >400/µL**
PI/r component	**lopinavir/r,** **atazanavir/r,** **fosamprenavir/r,** **darunavir/r,** ***or*** **saquinavir/r**	**ATV/r: diminished hyperlipidemic potential; care with antacids** **DRV/r: important role in Tx-exp pts (reserve?)**
Dual nRTI component	**tenofovir/emtricitabine** ***or*** **abacavir/lamivudine**	**ZDV/3TC: alternative** **ABC: Screen for HLA-B*5701** **to ↓ HSR risk; ↑ risk of CVD?** **ABC/3TC: ?efficacy when viral load >100,000 c/mL**

GS-934: TDF/FTC vs. AZT/3TC – Analyses after 144 Weeks : Total limb fat



TDF/FTC+EFV n=	51	49	48
AZT/3TC+EFV n=	49	44	38

Arribas JR, et al. J Acquir Immune Defic Syndr 2007;Oct 25 [EPub ahead of print]


The NEW ENGLAND JOURNAL of MEDICINE

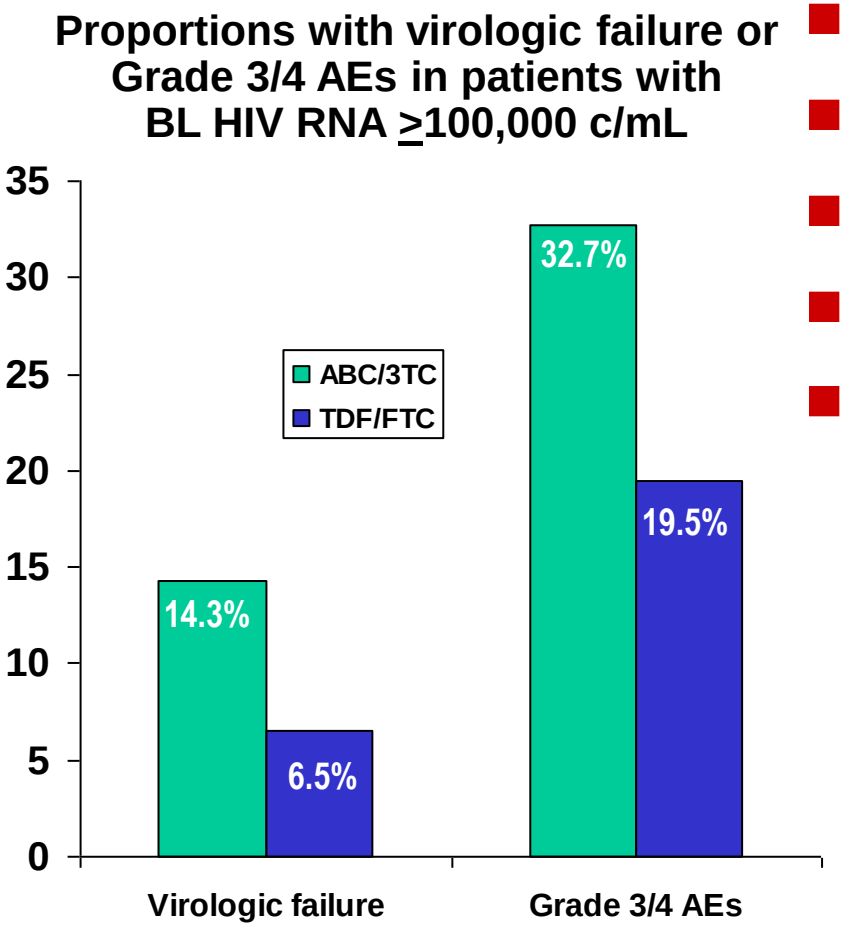
ORIGINAL ARTICLE

Tenofovir DF, Emtricitabine, and Efavirenz vs. Zidovudine, Lamivudine, and Efavirenz for HIV

Joel E. Gallant, M.D., M.P.H., Edwin DeJesus, M.D., José R. Arribas, M.D., Anton L. Pozniak, M.D., Brian Gazzard, M.D., Rafael E. Campo, M.D., Biao Lu, Ph.D., Damian McColl, Ph.D., Steven Chuck, M.D., Jeffrey Enejosa, M.D., John J. Toole, M.D., Ph.D., and Andrew K. Cheng, M.D., Ph.D., for the Study 934 Group*

ACTG A5202: Results of DSMB review (January 2008)

- Time to virologic failure significantly shorter in ABC/3TC versus TDF/FTC arms in subjects with screening HIV RNA >100,000 c/mL
  - HR 2.33 (95% CI, 1.46-3.72; p=0.0003) ITT
- Proportion of subjects with HIV RNA <50 c/mL at Week 48:
  - ABC/3TC = 75% (69–80%)
  - TDF/FTC = 80% (74–85%)
  - p=0.20
- Shorter time to Grade 3/4 adverse events among ABC/3TC group
  - HR 1.87, 95% CI 1.43-2.43; p<0.0001
  - Predominantly body aches and triglyceride elevations
- HSR occurred in 7% of each NRTI group



Sax P, *et al. XVII IAC,* Mexico City 2008, #THAB0303

ACTG 5142: Study Design

- Randomized, multicenter, open-label trial
- ARV-naïve (N=753)
- ≥13 years of age
- HIV-1 RNA ≥2,000 copies/mL
- Study duration: 96 weeks
- Stratified at randomization:
  - HIV-1 RNA <100,000 vs ≥100,000 copies/mL
  - Chronic Hepatitis B/C infection[a]
  - NRTI selection

EFV 600 mg at bedtime + 2 NRTIs	n=250
LPV/r 400/100 mg twice daily + 2 NRTIs	n=253
EFV 600 mg at bedtime + LPV/r 533/133 mg twice daily	n=250

- LPV/r given as soft gel capsules
- 2 NRTIs included 3TC (150 mg twice daily or 300 mg once daily) + investigator selection of:
  - ZDV 300 mg twice daily or
  - d4T XR[b] 100 mg[c] once daily or
  - TDF 300 mg once daily

[a]Based on the presence of hepatitis C antibody or hepatitis B surface antigen, or both
[b]d4T XR was an investigational formulation of stavudine that is not commercially available
[c]75 mg if subject weighed <60 kg

Riddler SA, et al. *N Engl J Med.* 2008;358:2095-2106.

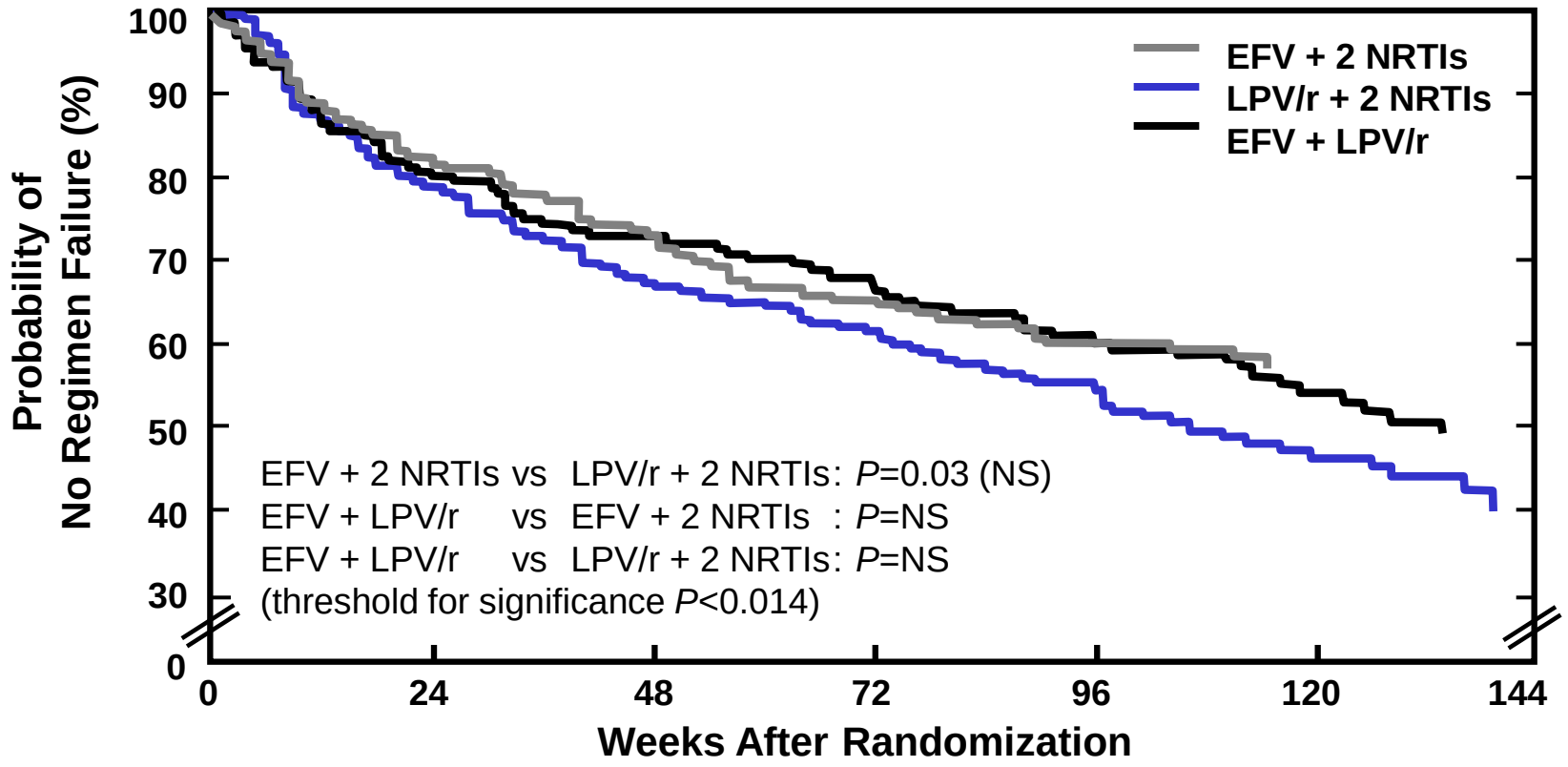
Baseline Characteristics

	EFV + 2 NRTIs n=250	LPV/r + 2 NRTIs n=253	EFV + LPV/r n=250	Total N=753
Male (%)	81%	77%	82%	80%
Non-white (%)	60%	65%	65%	64%
Age, years (median)	39	37	38	38
CD4+ cell count, cells/mm^3 (median)	195	190	189	191
<200 cells/mm^3 (%)	51%	53%	51%	52%
<100 cells/mm^3 (%)	34%	33%	36%	35%
HIV-1 RNA, $\log_{10}$ copies/mL (median)	4.8	4.8	4.9	4.8
≥100,000 copies/mL (%)	36%	37%	41%	38%
Selected NRTI (%)				
ZDV	42%	42%	42%	42%
d4T XR[a]	24%	25%	24%	24%
TDF	34%	34%	34%	34%

[a]d4T XR was an investigational formulation of stavudine that is not commercially available

Adapted from: Riddler SA, et al. *N Engl J Med.* 2008;358:2095-2106.

Co-Primary Endpoint: Time to Regimen Failure (RF)

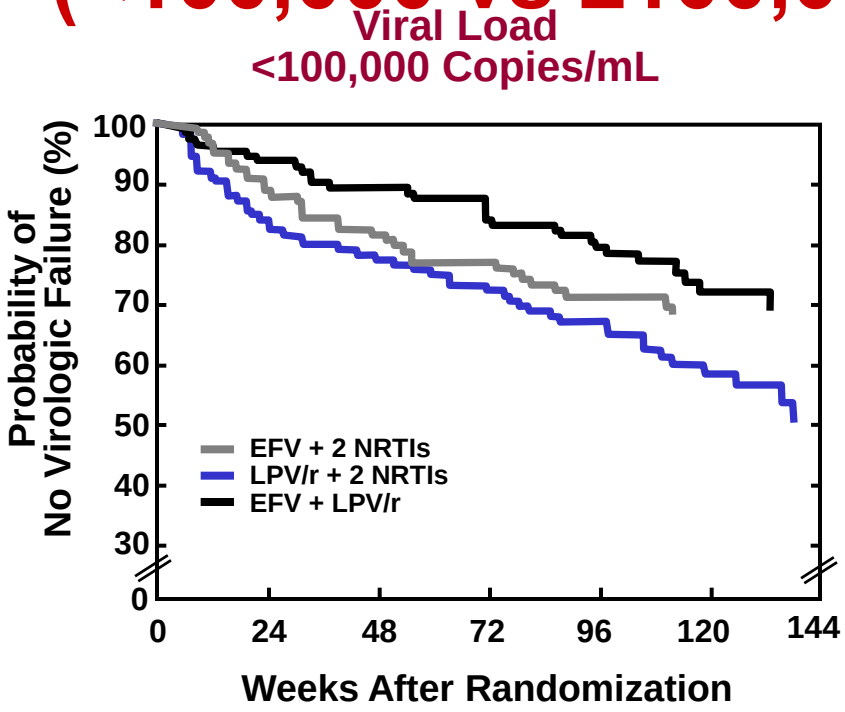


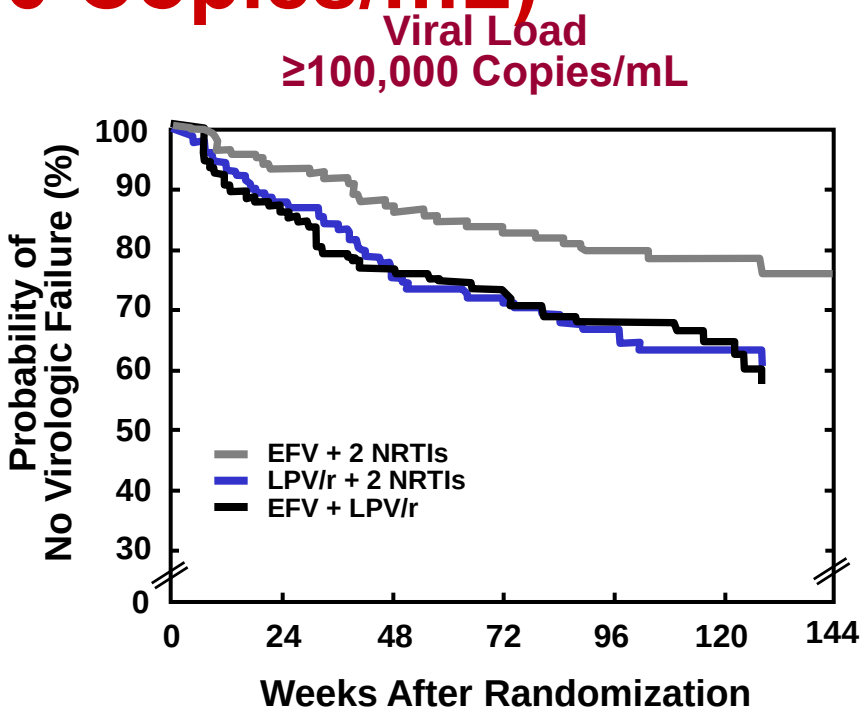
Number of Patients

EFV + 2 NRTIs	250	188	160	142	113	55	13
LPV/r + 2 NRTIs	253	193	159	143	116	52	11
EFV + LPV/r	250	195	169	155	126	59	14

Adapted from: Riddler SA, et al. *N Engl J Med.* 2008;358:2095-2106.

Time to VF by Viral Load Stratification (<100,000 vs ≥100,000 Copies/mL)





Number of Patients

EFV + 2 NRTIs	129	102	90	83	66	33	8
LPV/r + 2 NRTIs	130	105	95	87	73	42	8
EFV + LPV/r	128	113	103	100	83	38	8

	121	108	96	90	76	40	11
	123	105	90	81	67	32	6
	122	102	86	81	66	35	9

Adapted from: Riddler SA, et al. *N Engl J Med.* 2008;358:2095-2106.

ACTG 5142
Preliminary analysis of mutations associated with resistance

	LPV/EFV	LPV	EFV
Pat. With virological failure	73	94	60
Number of genotypic resistance tests*	39	52	33
Number of NRTI mutations M184I / V K65R	4 (10%) 1 0	8 (15%) 7 0	11 (33%) 8 3
Number of NNRTI mutations K103N	27 (69%) 21	2 (4%) 0	13 (43%) 9
Number of primary PI mutations**	2	0	0
Mutations in 2 drug classes	2	2	10

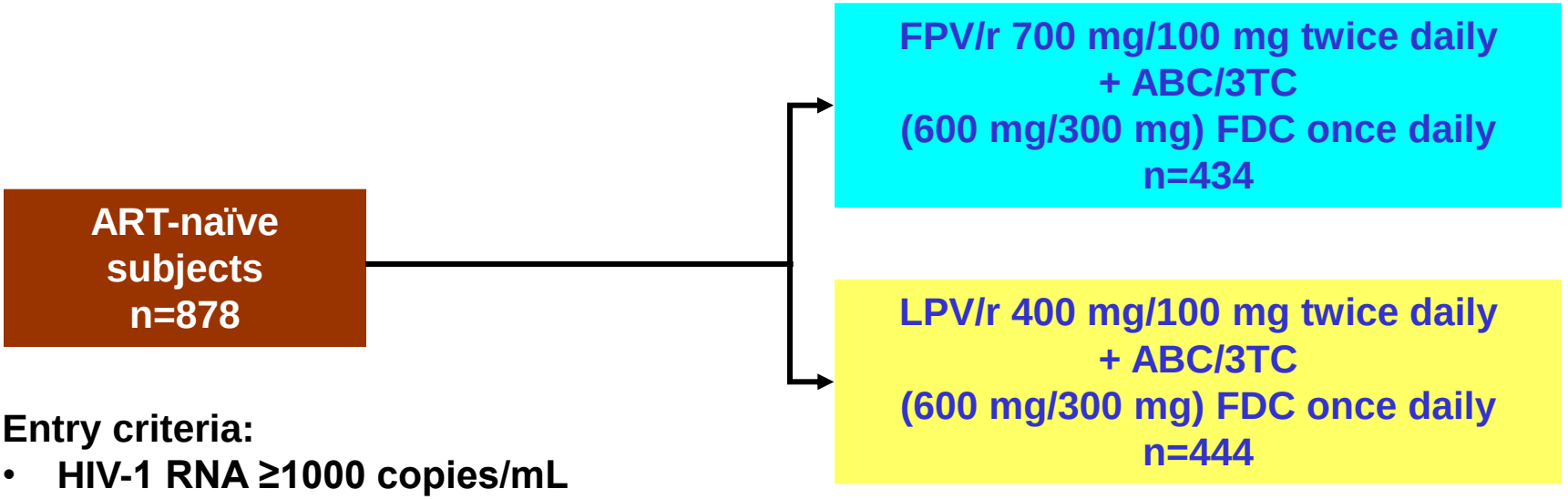
* Some results are still pending

** 30N, 32I, 33F, 46I, 47A/V, 48V, 50L/V, 82A/F/L/S/T, 84V, 90M

Adapted from Riddler et al., XVI International AIDS Conference, Toronto 2006, THLB0204

KLEAN: Study Design

Phase IIIb randomized (1:1) open-label, 48-week study conducted at 131 sites in the US, Europe, and Canada



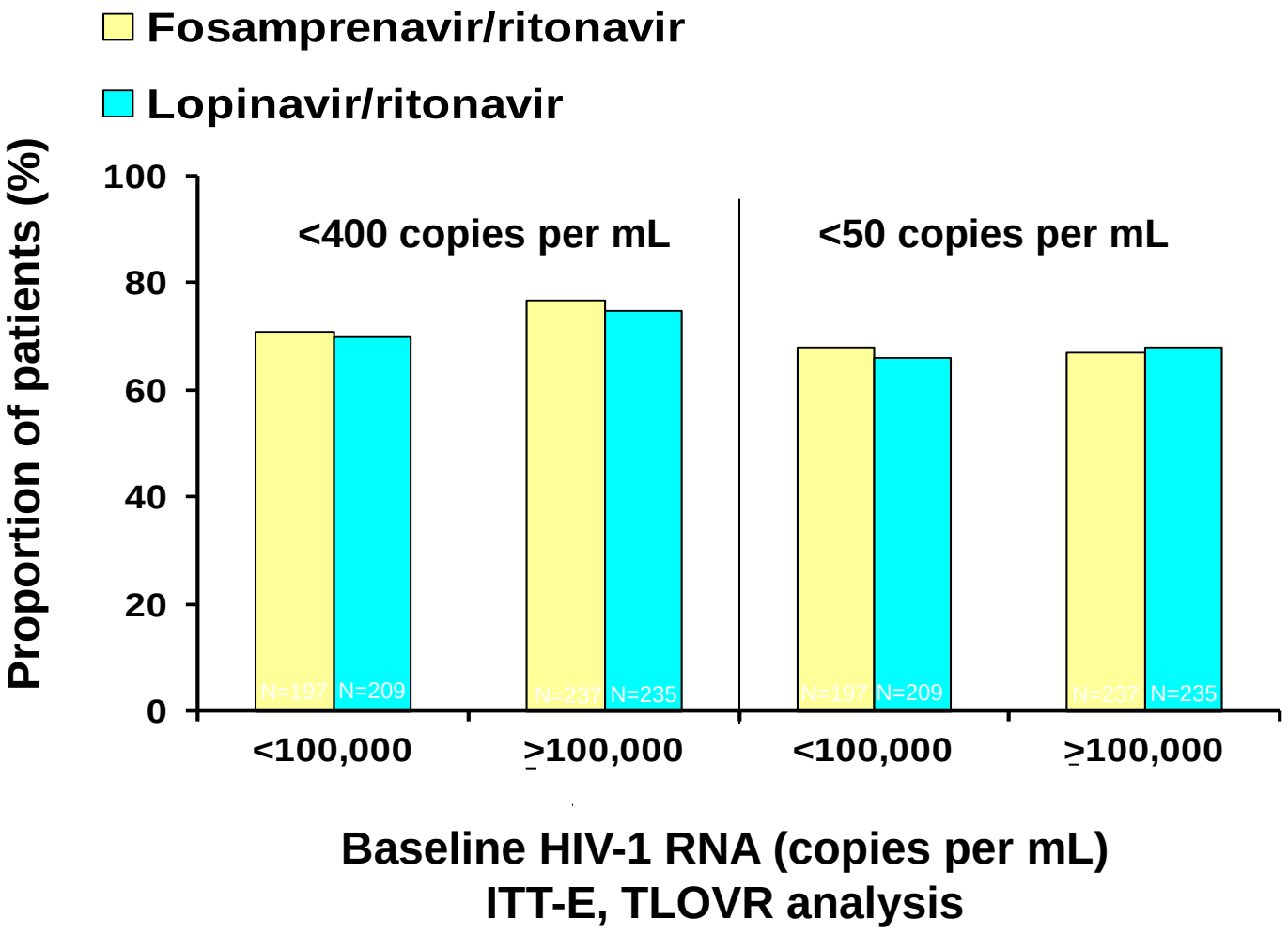
Entry criteria:

- **HIV-1 RNA ≥1000 copies/mL**
- **No CD4+ cell count restrictions**

- **Stratified by entry HIV-1 RNA <100,000 copies/mL or ≥100,000 copies/mL**
- **KLEAN had 90% power to detect non-inferiority of FPV/r to LPV/r within a 12% difference**

Eron J Jr, Yeni P, Gathe J Jr, et al. Lancet. 2006;368:476-482.

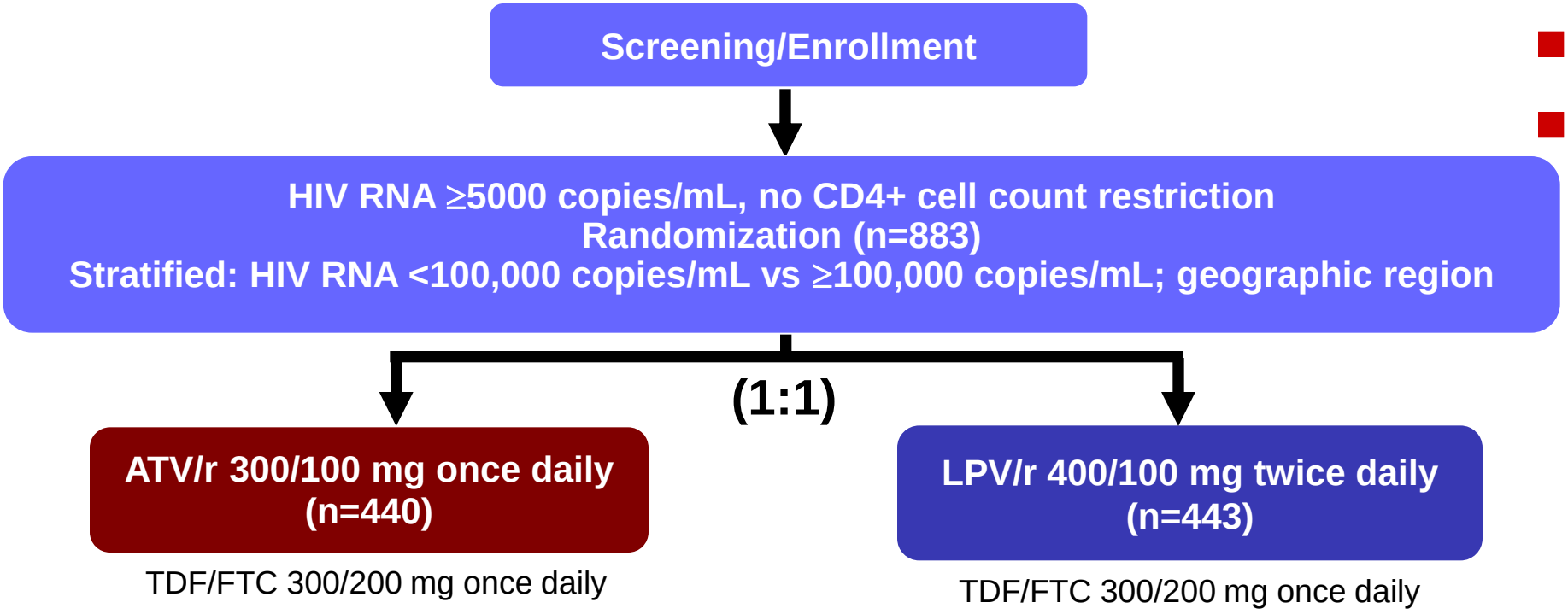
KLEAN: 48-Week Response Rates by Base Line Viral Load



Eron J, et al. *Lancet*. 2006; 368:476-482.

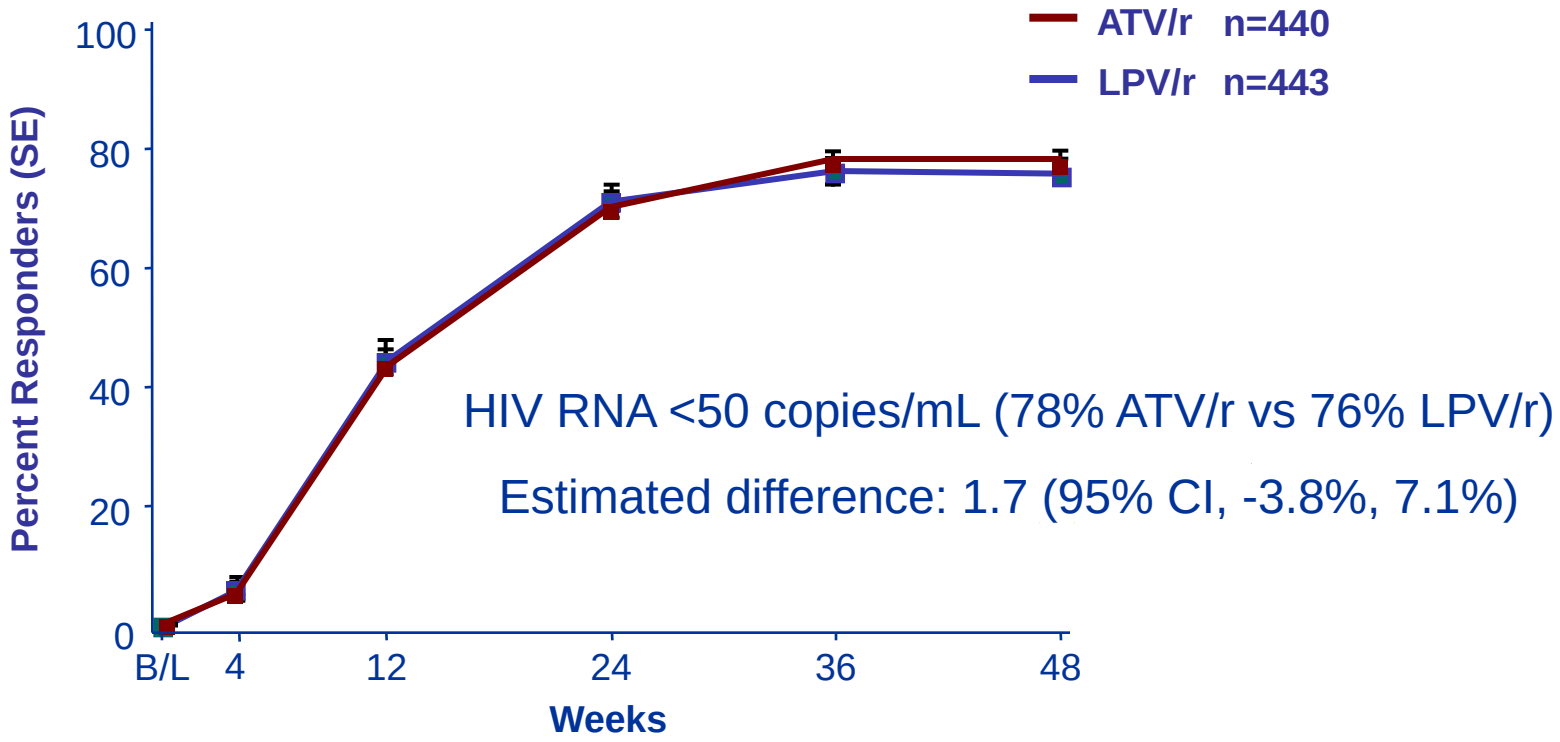
CASTLE: Study Design

International, multicenter, open-label, randomized, 96-week study to determine the comparative clinical efficacy and safety of ATV/r and LPV/r in treatment-naïve HIV-1 infected subjects



Molina et al. Efficacy and Safety of Boosted Once-daily Atazanavir and Twice-daily Lopinavir Regimens in Treatment-Naïve HIV-1 Infected Subjects (CASTLE): 48-Week Results. Presented at CROI 2008.

Primary Efficacy Endpoint: ITT-Confirmed Virologic Response (NC=F)



ATV/r has noninferior antiviral efficacy compared with LPV/r

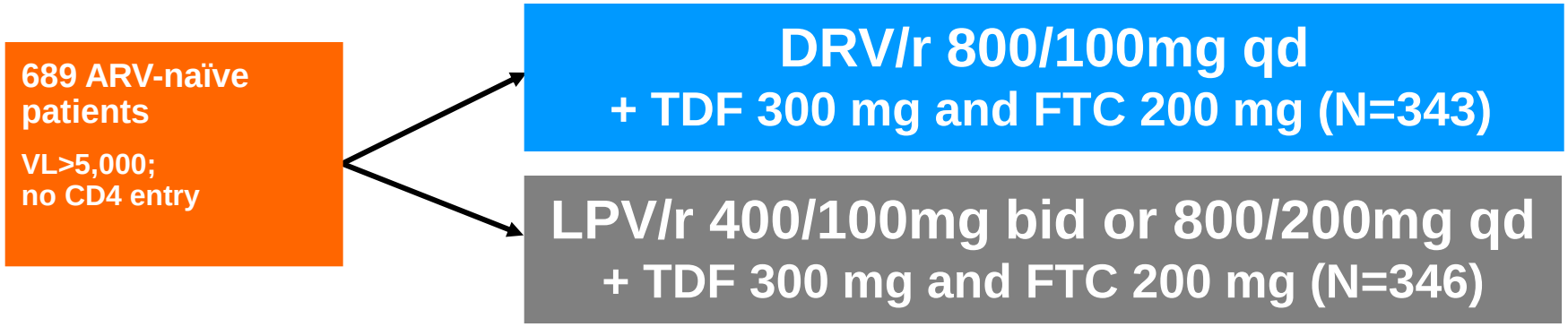
Supporting Analyses:

TLOVR: HIV RNA <50 copies/mL: ATV/r 78%, LPV/r 76%; 1.9 (-3.6, 7.4)

OT-VROC: HIV RNA <50 copies/mL: ATV/r 84%, LPV/r 87%; -3.5 (-8.7, 1.8)

Molina et al. Efficacy and Safety of Boosted Once-daily Atazanavir and Twice-daily Lopinavir Regimens in Treatment-Naïve HIV-1 Infected Subjects (CASTLE): 48-Week Results. Presented at CROI 2008.

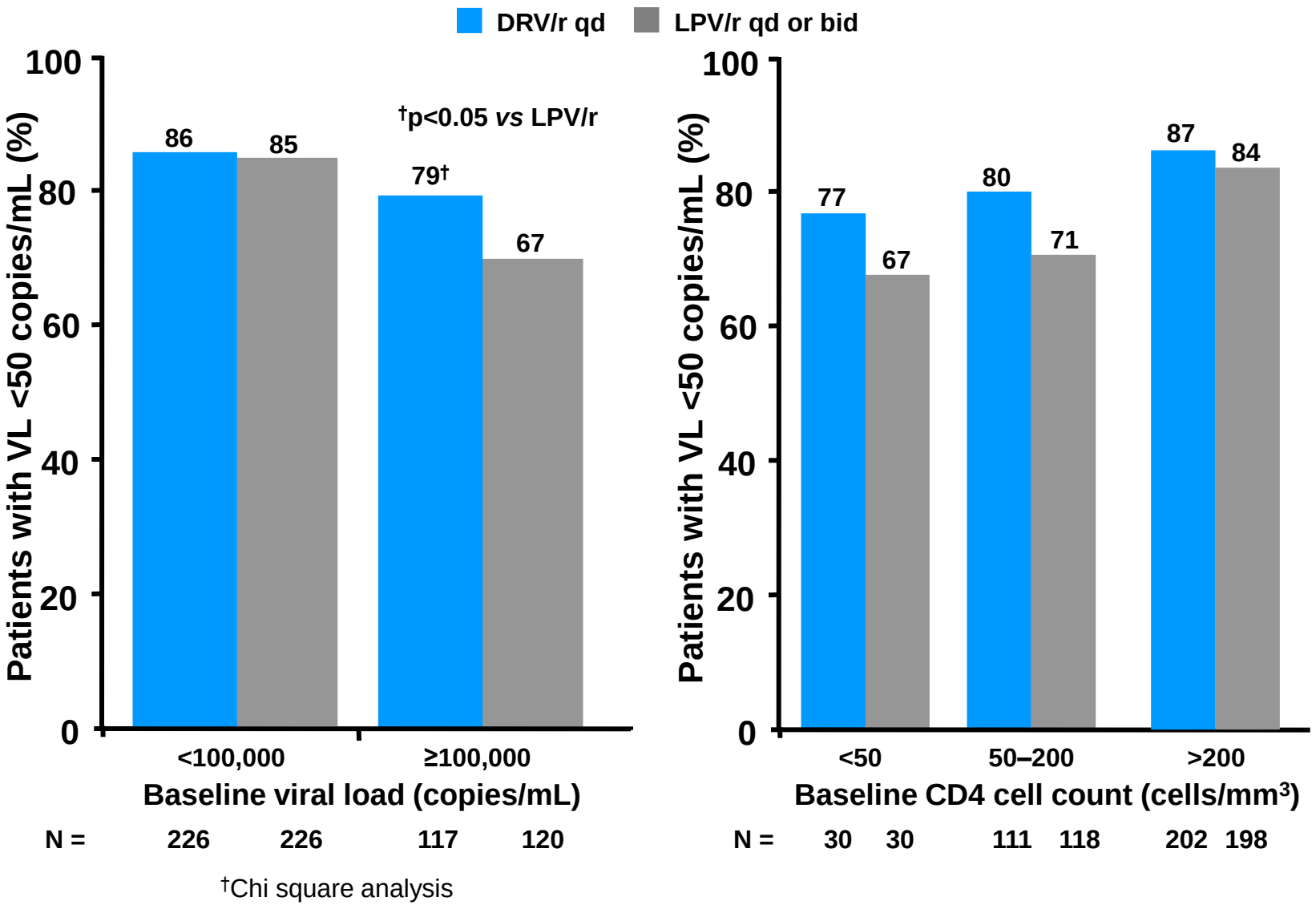
ARTEMIS: Phase III study design



LPV dosing		LPV formulation	
qd =	15%	Capsule only =	15%
bid =	77%	Tablet only =	2%
bid/qd =	7%	Capsule/tablet switch =	83%

Dosing was based on regulatory approval; switch was made according to local regulatory approval and drug availability

ARTEMIS: Confirmed response by baseline VL or CD4 at Week 48 (ITT-TLOVR)



†Chi square analysis

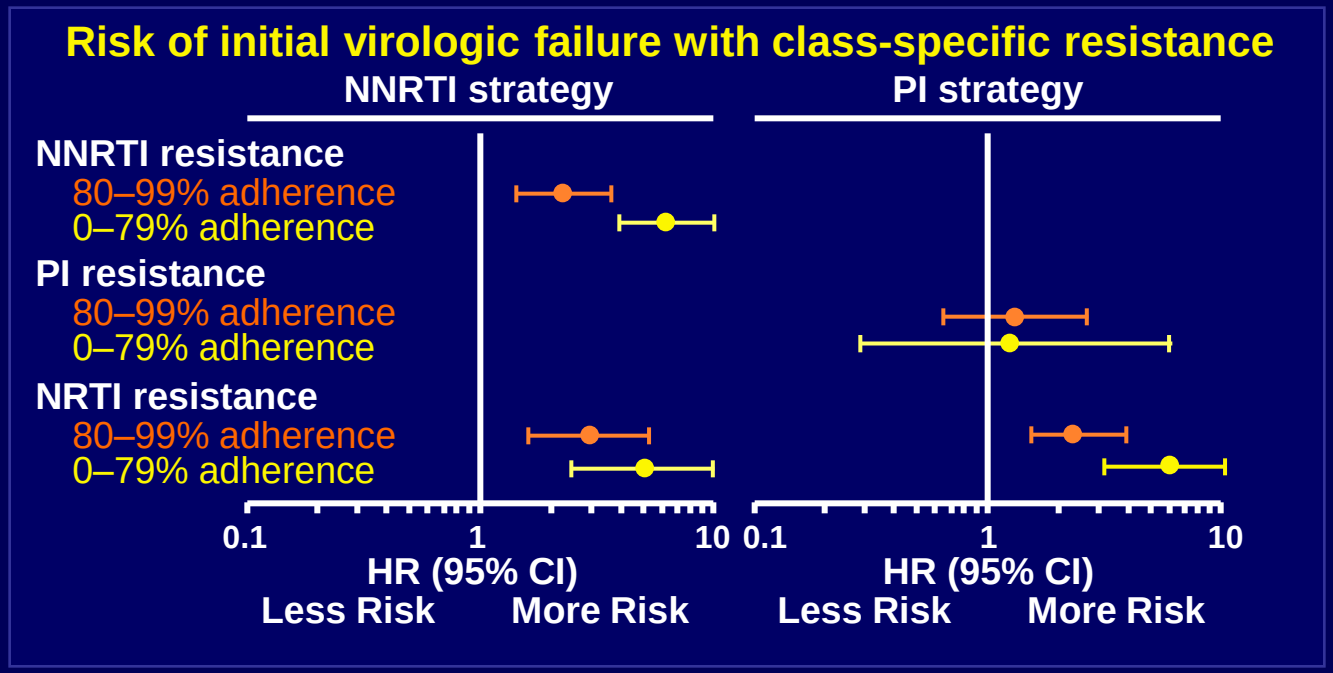
FIRST study (CPCRA 058): Relationship between adherence and class-specific resistance

Study design

- Treatment strategies:
  - PI strategy (PI + NRTIs): n=457
  - NNRTI strategy (NNRTIs + NRTIs): n=446
- Median follow-up = 5 yrs

Implications

- For both strategies: black ethnicity and, to a lesser extent, higher viral load also associated with more frequent resistance



What is the treatment goal in HIV ?

Decline of viremia below limit of detection

(HIV-RNA<50copies/ml)

How to monitor treatment success?

- **Toxicity control after 2 weeks (check adherence and for rash)**
- **First control of CD4 count and viral load after 4 weeks**
- **In case no > 2 log-drop in HIV-RNA has occurred 4 weeks after treatment initiation check adherence level (TDM) and perform resistance testing**

welcome to the
www.hiv-druginteractions.org
website

THE UNIVERSITY of LIVERPOOL

This informative and educational HIV pharmacology resource is valuable for healthcare professionals, scientific researchers or anyone with an interest in HIV therapy. You can find reports on recent news and hot topics in HIV, discover comprehensive information and advice on drug interactions, read about advances in therapeutic drug monitoring (TDM), and much more!

LATEST NEWS

Hot Topics

Meeting Report - Pharmacogenetics at the 6th International Workshop on Clinical Pharmacology of HIV Therapy, Quebec, April 2005.

Drug Metabolism - Review on Cytochrome P450 induction.

Drug Interactions - Coadministration of protease inhibitors and acid reducing agents.

Recent Publications

Pharmacokinetics - Recent publications on the metabolism of drugs of abuse.

PK - Predictors of response to lopinavir in PI-experienced patients.

Drug Metabolism - Renal transporters and antiviral drugs.

DRUG INTERACTION CHARTS

Access a wealth of information on HIV drug interactions by visiting our drug interactions page. The dynamically driven process allows you to build your own customised drug interaction chart, giving detailed information on predicted interactions of specified multiple drug combinations.

HIV-CHARTS2GO

Click here to register and download the latest version of HIV-Charts2go for you PDA device.

SITE NEWS

Dynamic Interaction Charts

Added: Friday 11th March 2005

The latest site update is a substantial redevelopment of the Interaction Charts. The new chart interface provides you with a greater level of flexibility, allowing you to select the specific interactions you need to review.

more...

EMAIL UPDATES

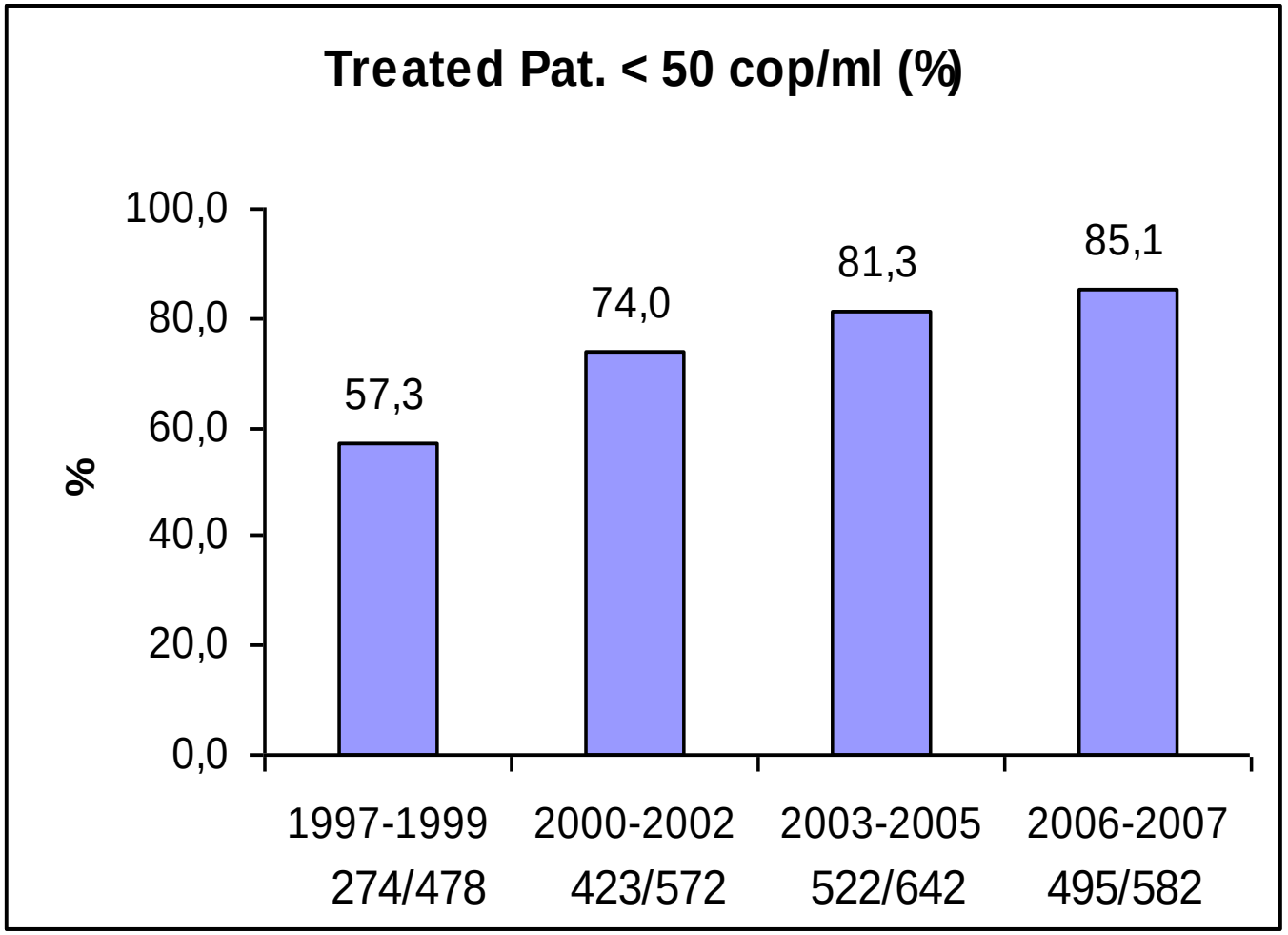
Click here to register for the latest site updates via email.

Keep up-to-date with all the latest developments in HIV clinical pharmacology by registering for our regular email update service.

Last reviewed: 15 March 2005

How successful is HIV-therapy today?

Bonn HIV-cohort 1/2008



Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analyses

	1996–99	2000–02	2003–05	1996–2005
Mortality rates (per 1000 person-years)				
Overall	16·3 (14·9–17·8)	12·4 (11·5–13·2)	10·0 (9·3–10·8)	12·0 (11·5–12·5)
Between the ages 20 and 44 years	13·1 (11·7–14·7)	10·3 (9·4–11·2)	7·5 (6·8–8·3)	9·7 (9·1–10·2)
Potential years of life lost before age 65 years (per 1000 person-years)				
20–64 years	365·9	260·4	189·4	247·0
Life expectancy (years; adjusted)				
At exact age 20 years	36·1 (SE 0·60)	41·2 (SE 0·52)	49·4 (SE 0·54)	43·1 (SE 0·33)
At exact age 35 years	25·0 (SE 0·42)	30·1 (SE 0·31)	37·3 (SE 0·37)	31·7 (SE 0·21)
Percent surviving from 20 to 44 years	75·5%	79·5%	85·7%	81·1%

Mortality rates are deaths per 1000 person-years (95% CI). [A[redacted]]

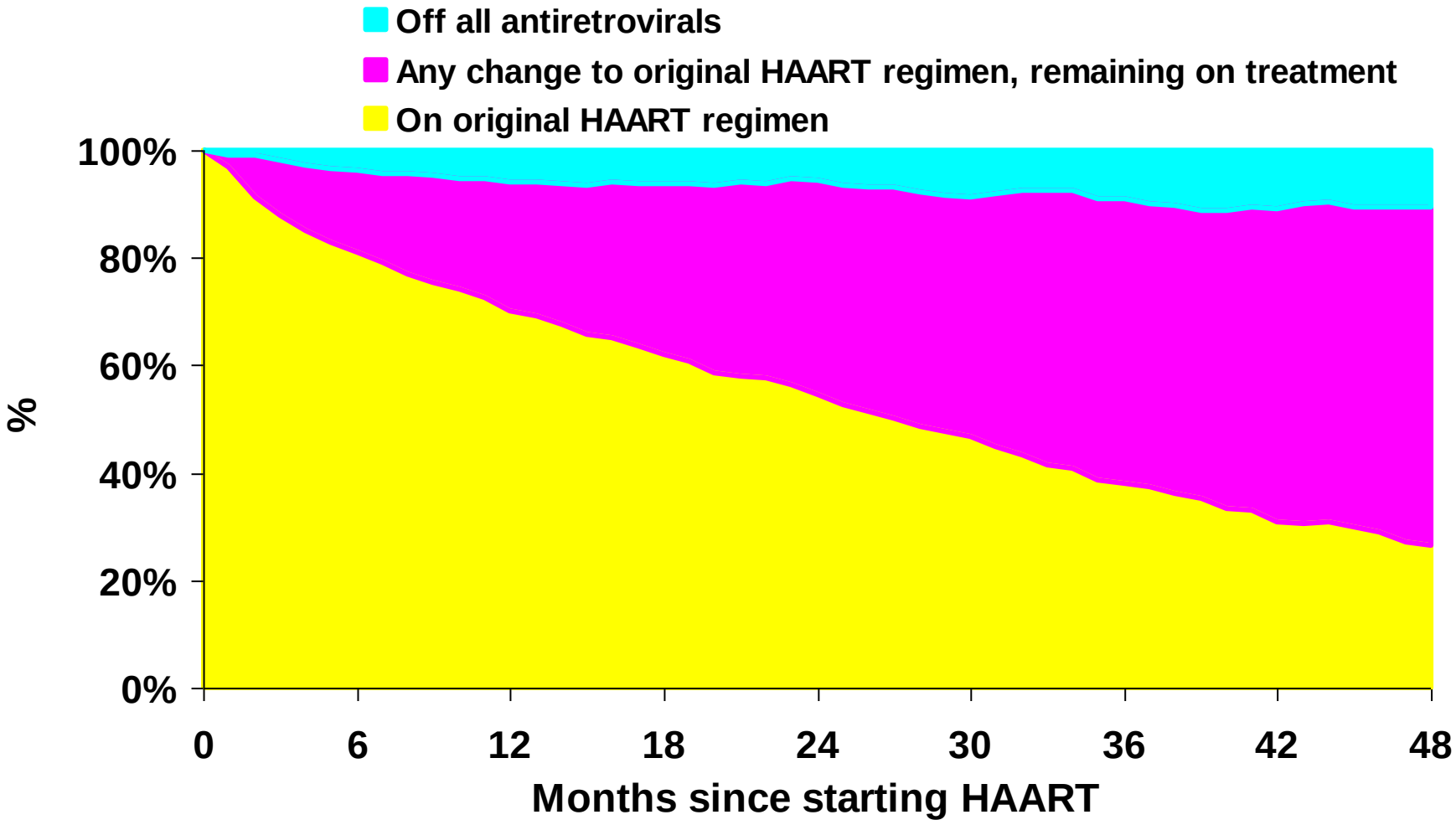
Table 2: Health indicators for overall (20 years or older) population by period of follow-up

The Antiretroviral Therapy Cohort Collaboration, Lancet 2008;372:293-299

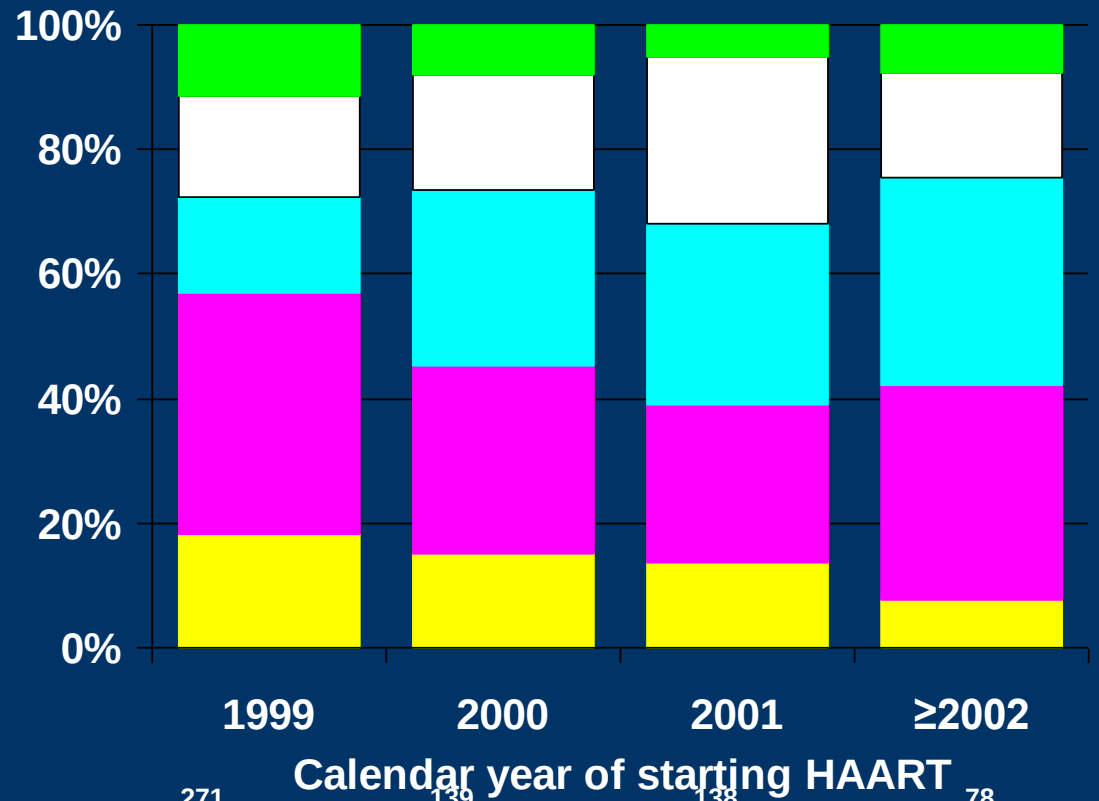
Which challenges remain?

HAART Era, The Latest News…

Changes to a first HAART regimen



Changes to a First HAART Regimen



Reason	N	CD4	VL
Unknown	49	312	2.26
Other	112	391	2.60
Choice	189	364	2.60
Toxicities	190	386	2.28
Failure	86	328	3.78

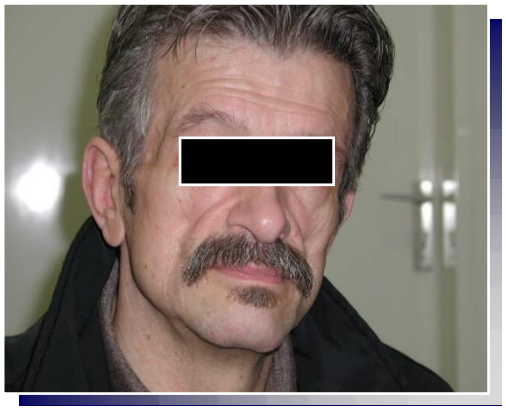
N	271	139	138	78	p=0.27 p<0.0001
Median CD4	382	348	355	336	p=0.36
Median VL	2.60	2.60	2.60	2.72	p=0.37

Mocroft A, Phillips A, Soriano V, Rockstroh J et al. AIDS Res Hum Retroviruses 2005

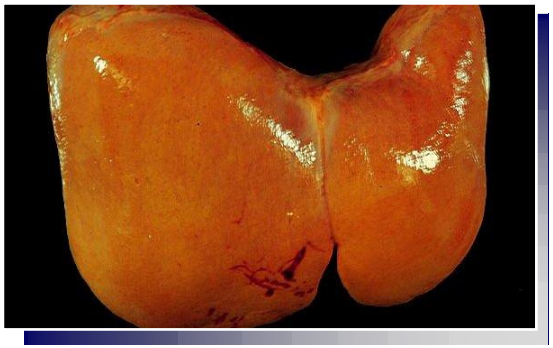
HAART: Not Without Toxicity

Dyslipidemia/CHD

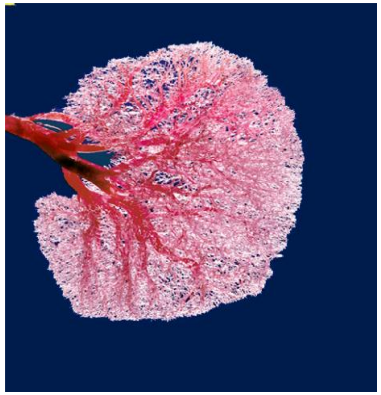
Lipoatrophy



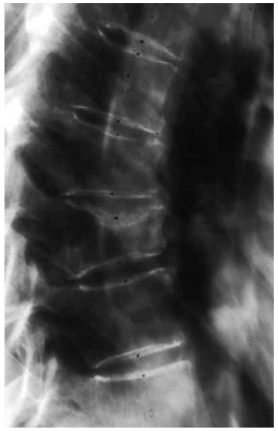
hepatic

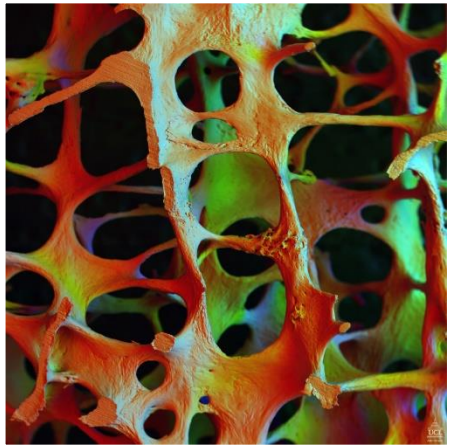


Renal



Bone density ?

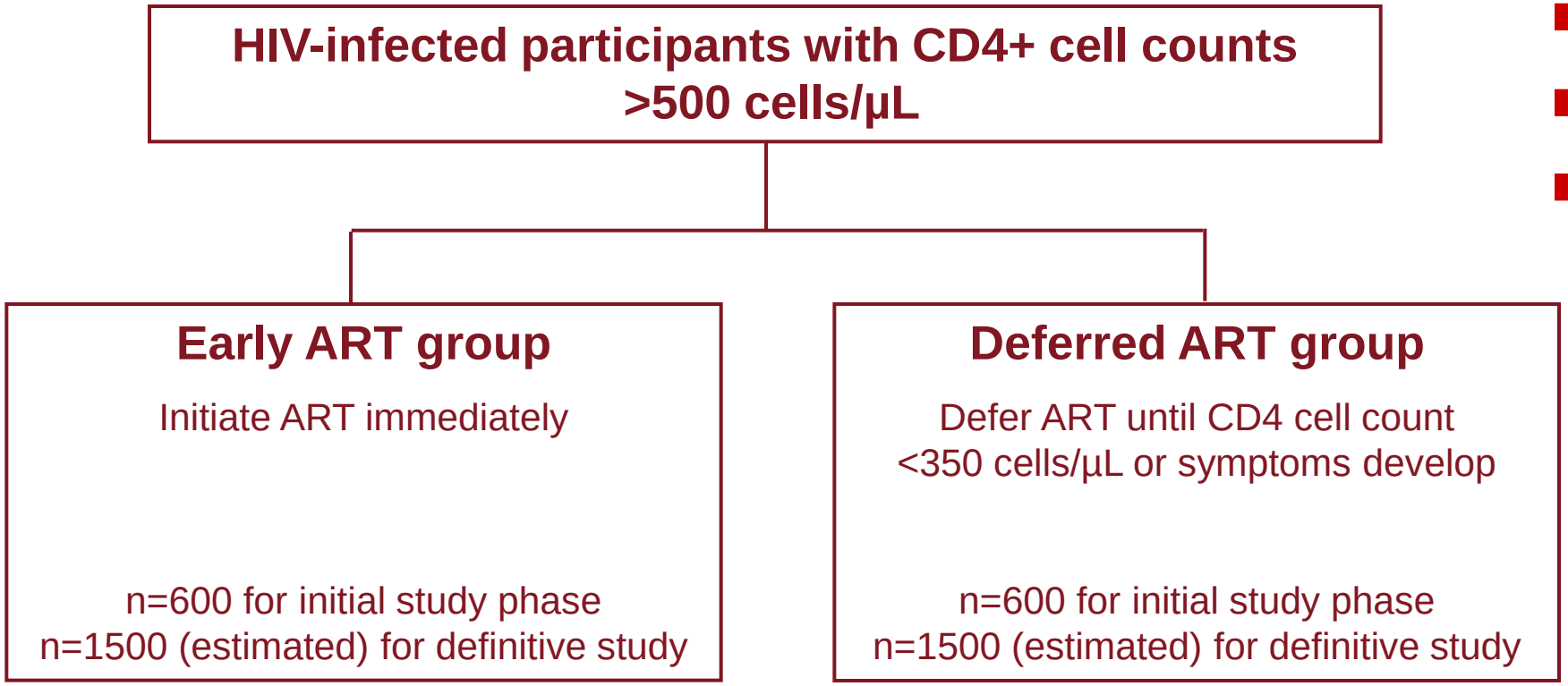




Gastrointestinal

INSIGHT: The START Trial

(Strategic Timing of Antiretroviral Treatment)



Gordin et al. IAS 2007, MOSY205 oral presentation