

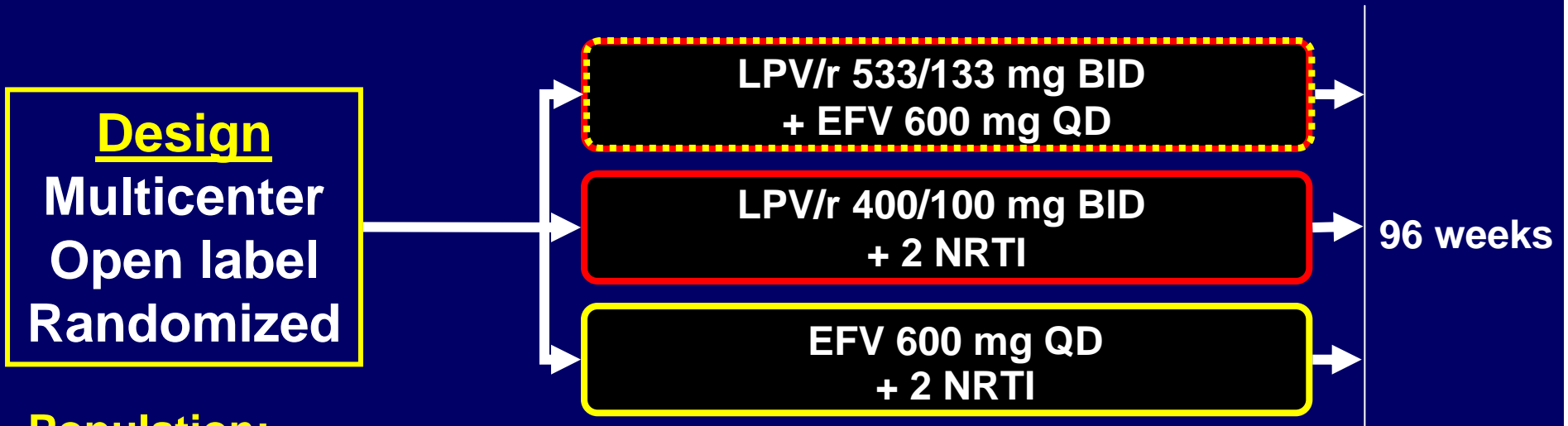
## First Line Antiretroviral Therapy: Five Questions ( and 5 answers)

1. How does a boosted PI (kaletra) compare to NNRTI (efavirenz) for first line therapy?
2. Are NRTIs necessary in first line therapy?
3. Does NNRTI (efavirenz) perform worse at very high viral loads and low CD4?
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5. Is a boosted PI alone (kaletra) a viable treatment strategy?

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# A5142 Study Design



## Population:

ARV-naïve  
HIV RNA >2,000 c/mL  
Any CD4 count

## Stratification:

HIV RNA > 100,000 c/ml  
Hepatitis infection  
Selection of NRTI

**2 NRTI = 3TC  
+ Investigator Selection of  
ZDV or d4T XR or TDF**

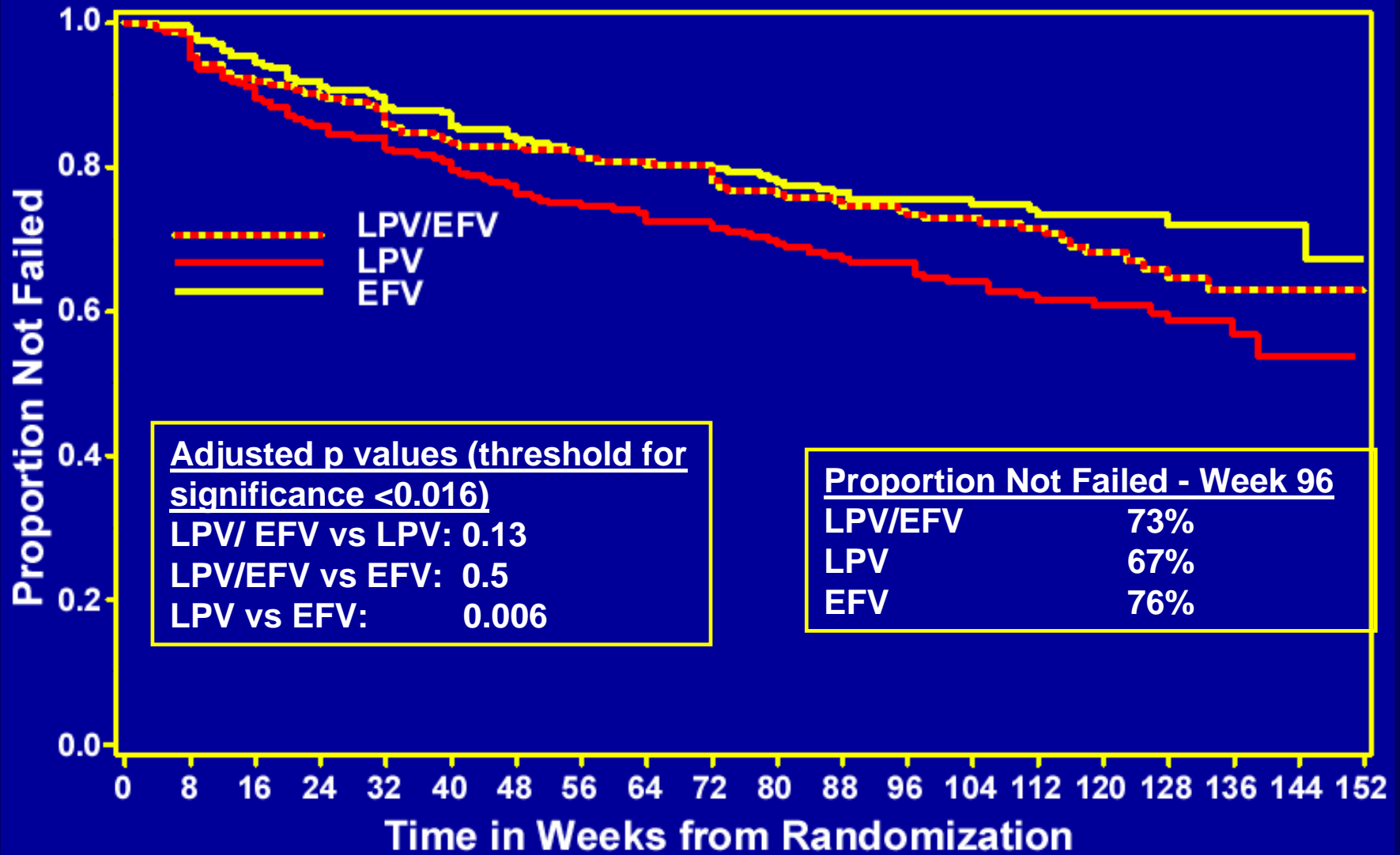
## Objectives

- Compare time to virologic failure
- Compare time to regimen completion

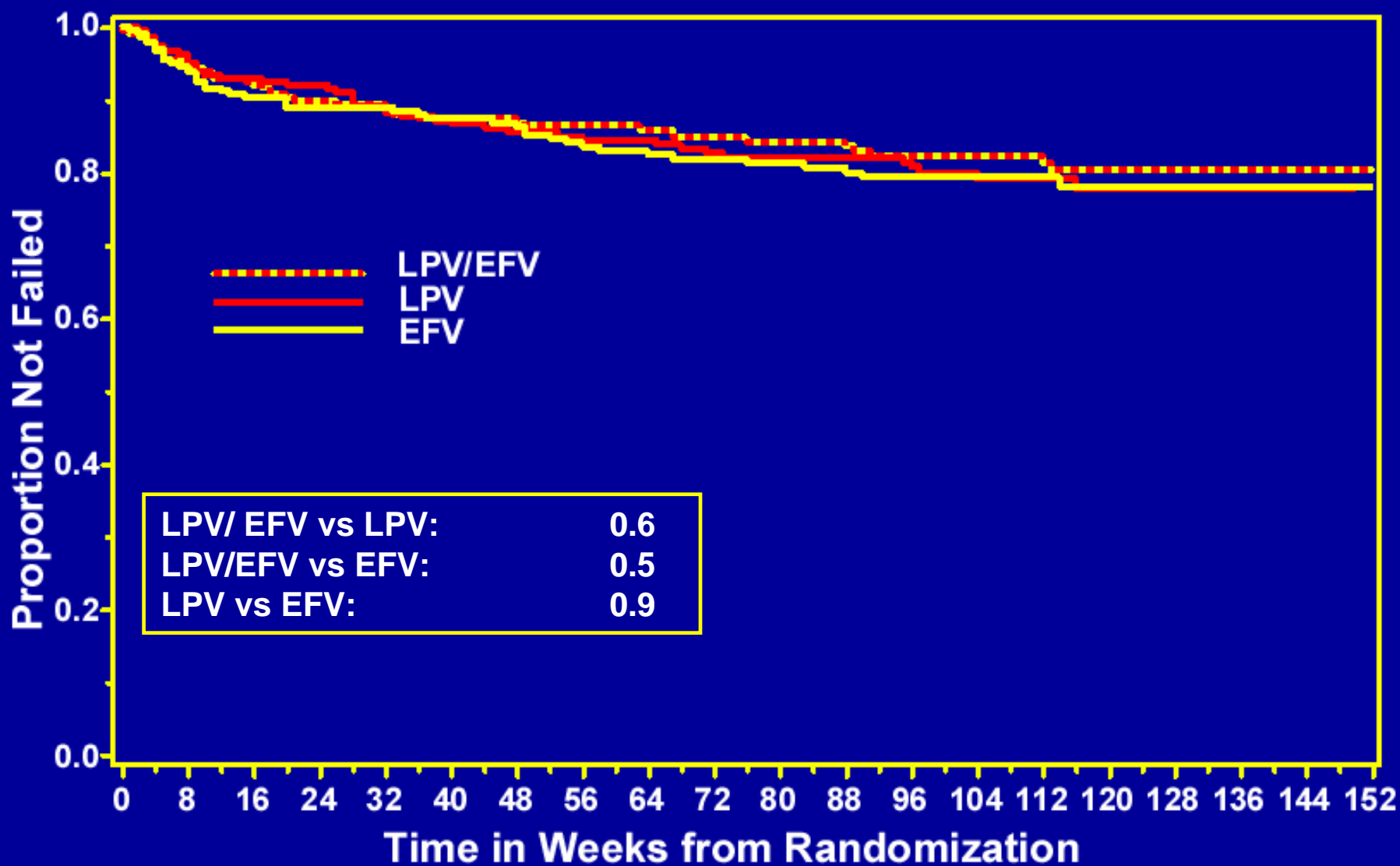
## Baseline Characteristics

	<b>LPV/EFV</b> <b>N=250</b>	<b>LPV</b> <b>N=253</b>	<b>EFV</b> <b>N=250</b>	<b>Total</b> <b>N=753</b>
<b>Female (%)</b>	<b>18</b>	<b>23</b>	<b>19</b>	<b>20</b>
<b>Non-white (%)</b>	<b>65</b>	<b>65</b>	<b>60</b>	<b>64</b>
<b>Age (median)</b>	<b>38</b>	<b>37</b>	<b>39</b>	<b>38</b>
<b>CD4 (median)</b>	<b>181</b>	<b>178</b>	<b>190</b>	<b>182</b>
<b>HIV RNA &gt;10<sup>5</sup></b>	<b>51</b>	<b>51</b>	<b>52</b>	<b>51</b>
<b>Selected NRTI (%)</b>				
<b>ZDV</b>	<b>42</b>	<b>42</b>	<b>42</b>	<b>42</b>
<b>d4T XR</b>	<b>24</b>	<b>25</b>	<b>24</b>	<b>24</b>
<b>TDF</b>	<b>34</b>	<b>34</b>	<b>34</b>	<b>34</b>

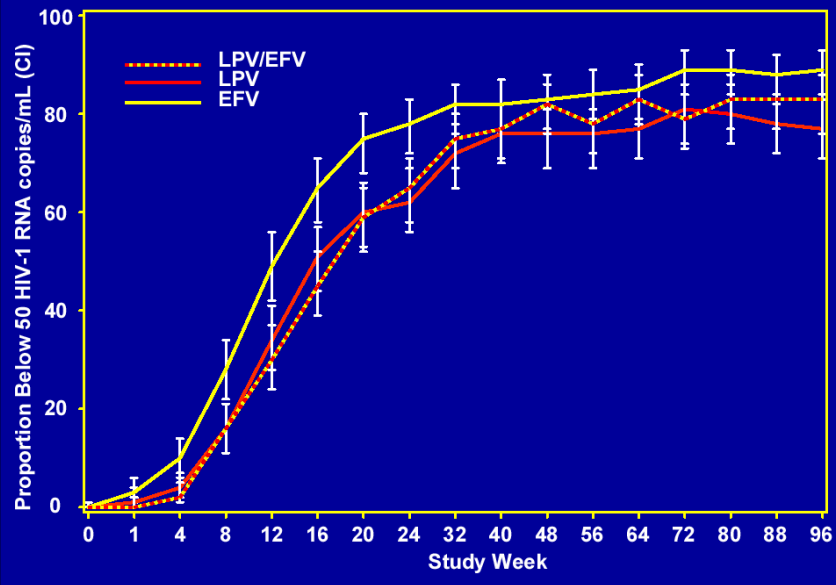
# Time to Virologic Failure



# Time to First Treatment Limiting Toxicity



# HIV RNA <50 copies/mL



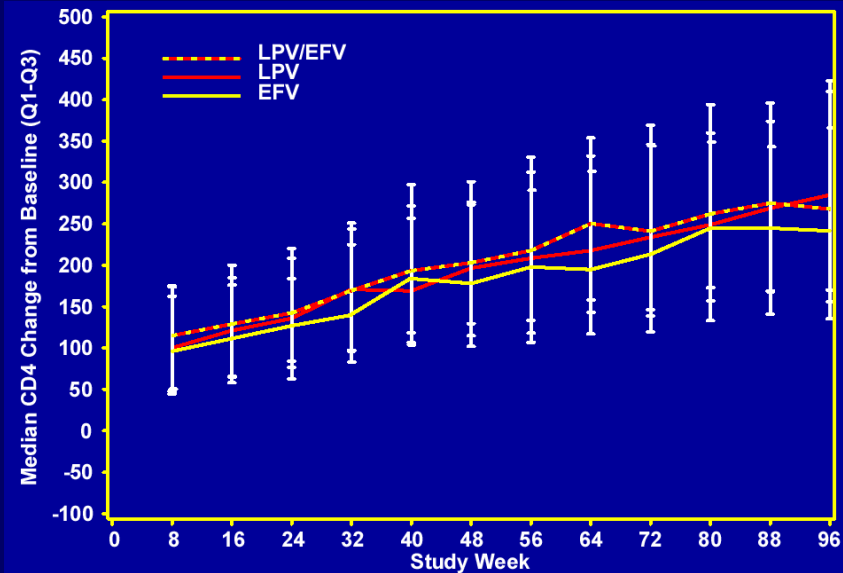
## Proportion <50 Week 96

LPV/EFV 83%  
 LPV 77%  
 EFV 89%

## Week 96

LPV/EFV vs. LPV 0.183  
 LPV/EFV vs. EFV 0.123  
 LPV vs. EFV 0.003

# CD4 Change



## Median change week 96

LPV/EFV +268  
 LPV +285  
 EFV +241

## Week 96

LPV/EFV vs. LPV 0.96  
 LPV/EFV vs. EFV 0.01  
 LPV vs. EFV 0.01

## Preliminary Data of Drug Resistance Mutations

	LPV/ EFV	LPV	EFV
# Observed VF	73	94	60
# Genotypic assays <sup>+</sup>	39	52	33
# NRTI mutations	4(10%)	8(15%)	11(33%)
M184I/V	1	7	8
K65R	0	0	3
# NNRTI mutations	27(69%)	2(4%)	16(48%)
K103N	21	0	9
# Major PI mutations <sup>++</sup>	2	0	0
Mutations in 2 classes	2	2	10

# Conclusions

- Compared with a regimen of EFV + 2 NRTI, LPV+2 NRTI had a significantly shorter time to virologic failure and tended to have a shorter time to regimen completion.
- The NRTI-sparing regimen of LPV + EFV had similar virologic efficacy and similar time to treatment limiting toxicity as EFV+2 NRTI.
- Preliminary resistance analyses show a trend toward more NNRTI resistance in the LPV/EFV arm compared with EFV + 2 NRTI.
- Resistance mutations in 2 drug classes (M184I/V + K103N) were more common in the EFV + 2 NRTI arm. Major PI mutations were rare.

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3. Does NNRTI (efavirenz) perform worse at very high viral loads and low CD4?
4. How do boosted PI regimens (kaletra and fosamprenavir) compare to each other?
5. Is a boosted PI alone (kaletra) a viable treatment strategy?

## **A5095: Study Objectives**

- **To compare the effect of baseline VL and CD4 cell count on virological and immunological responses in EFV+ZDV+3TC treated subjects in A5095**
- **To assess whether adding a fourth drug (abacavir) improved responses in any subgroup.**

# Study Subjects

- N = 765 subjects enrolled in the 2 EFV arms
- Median follow-up of 144 weeks (~3 years)
- 19% women, 81% men
- 21% Hispanic, 35% black, 41% white, 2% other
- Baseline parameters:

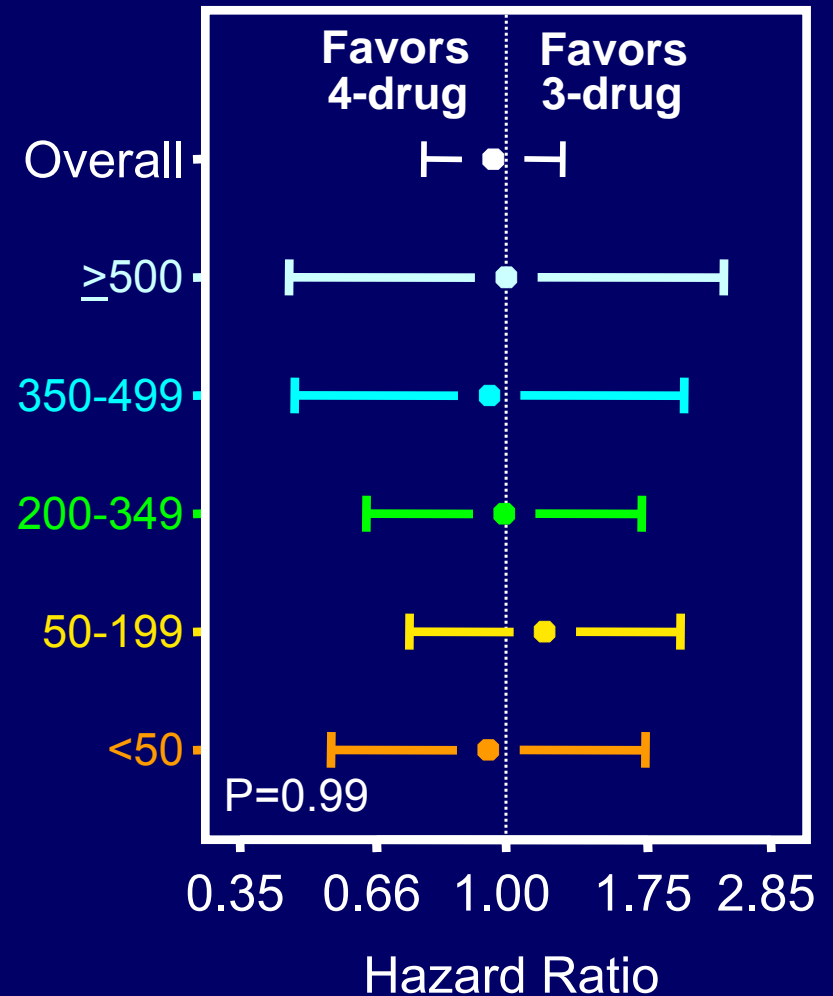
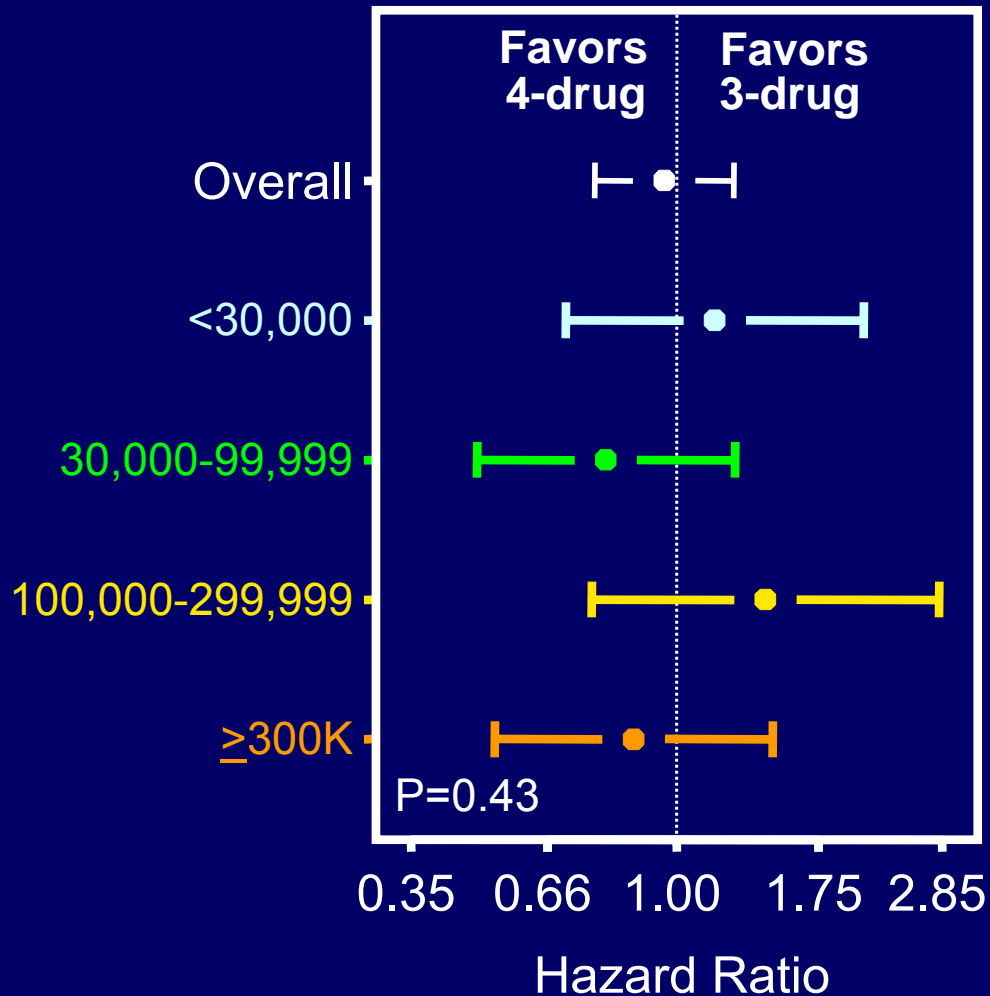
<b>VL (c/ml)</b>	<b>N (%)</b>	<b>CD4 (cells/mm<sup>3</sup>)</b>	<b>N (%)</b>
<30,000	220 (29%)	<50	155 (20%)
30,000-99,999	226 (30%)	50-199	206 (27%)
100,000-299,999	132 (17%)	200-349	228 (30%)
≥300,000	187 (24%)	350-499	105 (14%)
		≥500	71 ( 9%)

# Risk of Virologic Failure

## Treatment effect by Baseline subgroup

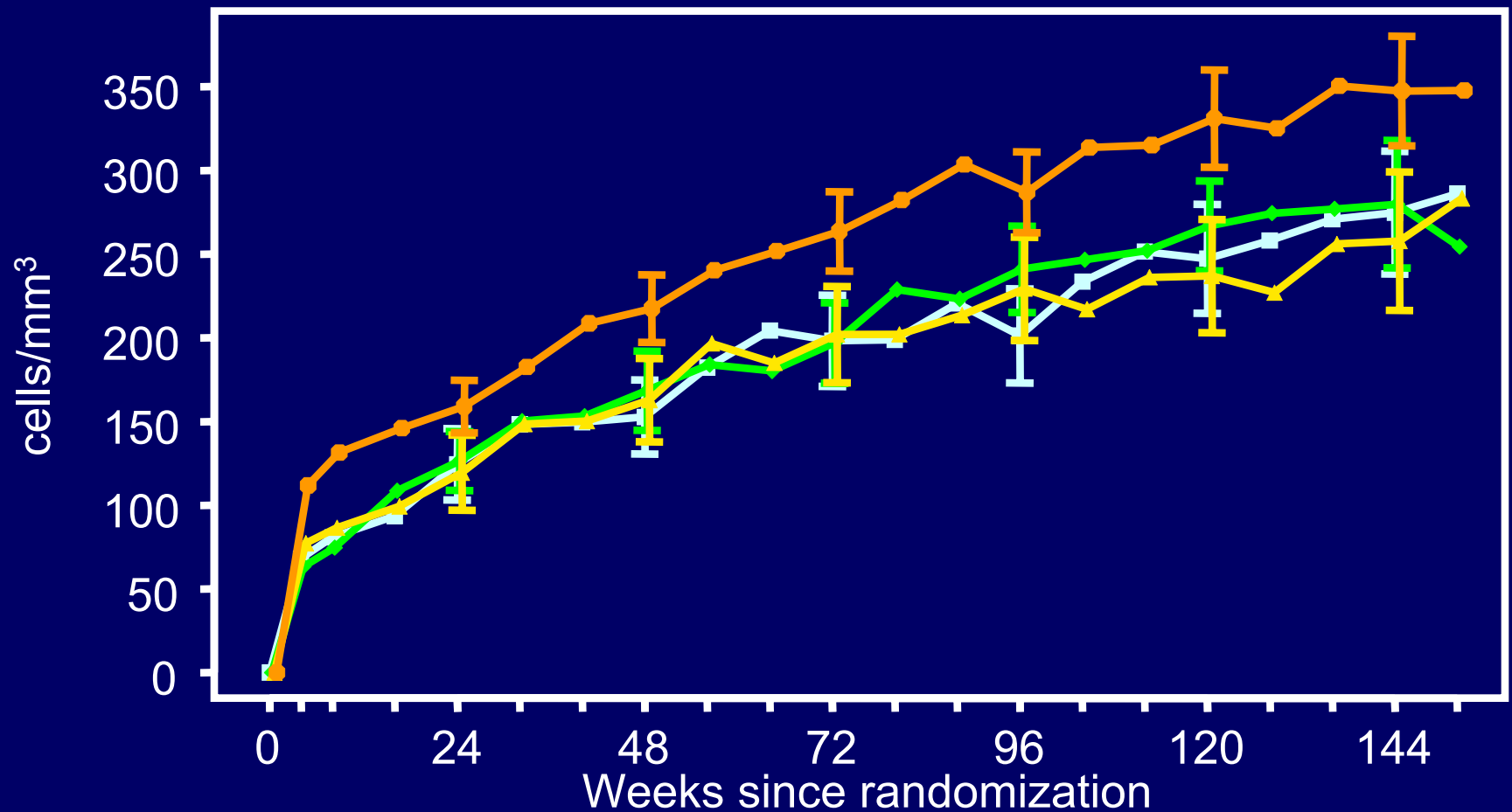
By pre-treatment VL (c/ml)

By pre-treatment CD4 (cells/mm<sup>3</sup>)



# CD4 Change from Baseline

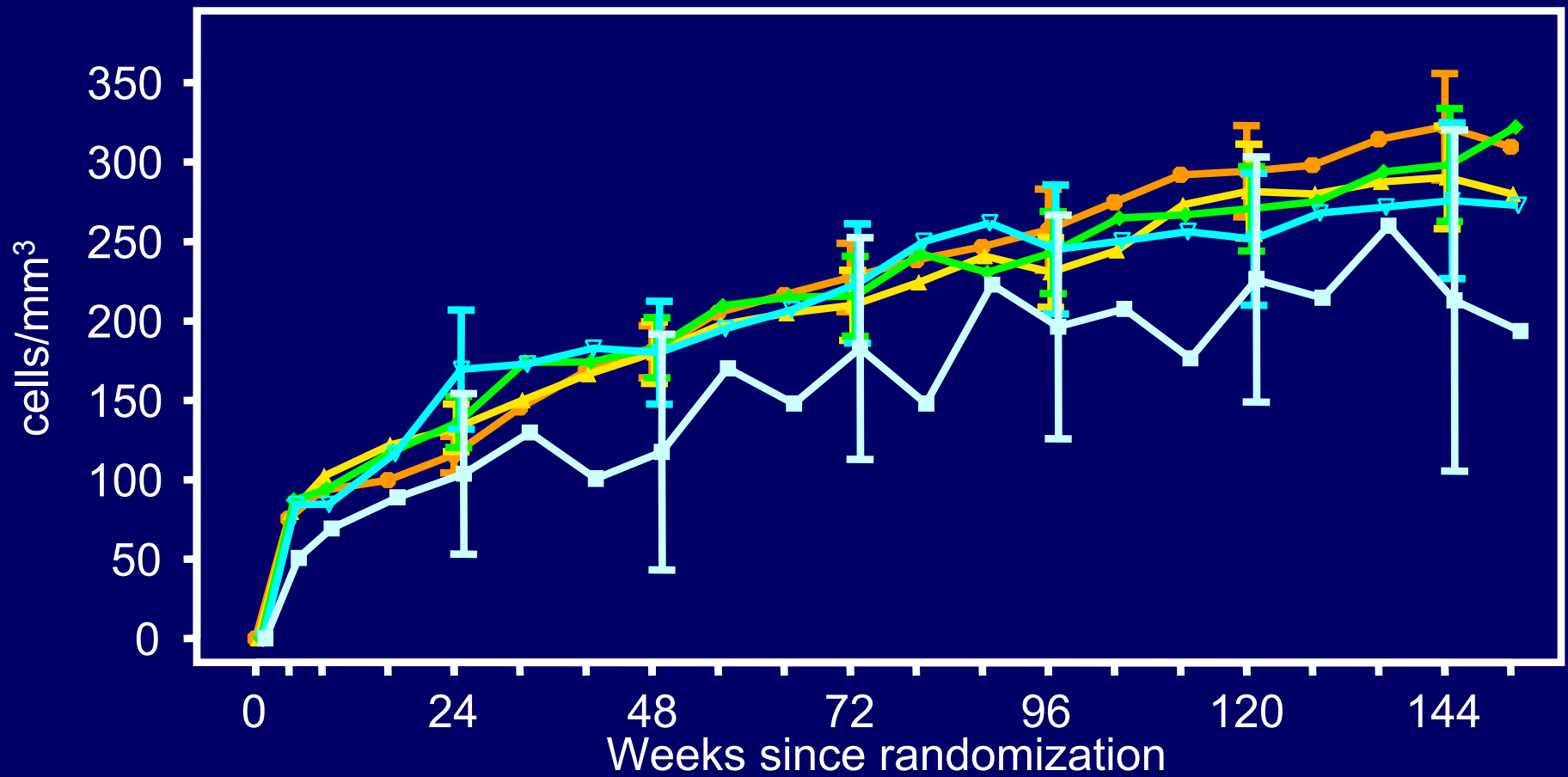
By Baseline VL - ITT



	0	24	48	72	96	120	144
<30,000	220	187	180	169	167	160	108
30,000-99,999	226	212	201	189	181	181	121
100,000-299,999	132	112	108	101	101	94	67
≥300K	187	170	162	155	142	136	95

# CD4 Change from Baseline

By Baseline CD4 - ITT



Baseline CD4 Category	0	24	48	72	96	120	144
<50	155	139	133	131	120	119	83
50-199	206	181	174	163	160	149	104
200-349	228	205	196	183	173	171	114
350-499	105	95	89	86	87	81	59
≥500	71	61	59	51	51	51	31

## Conclusions

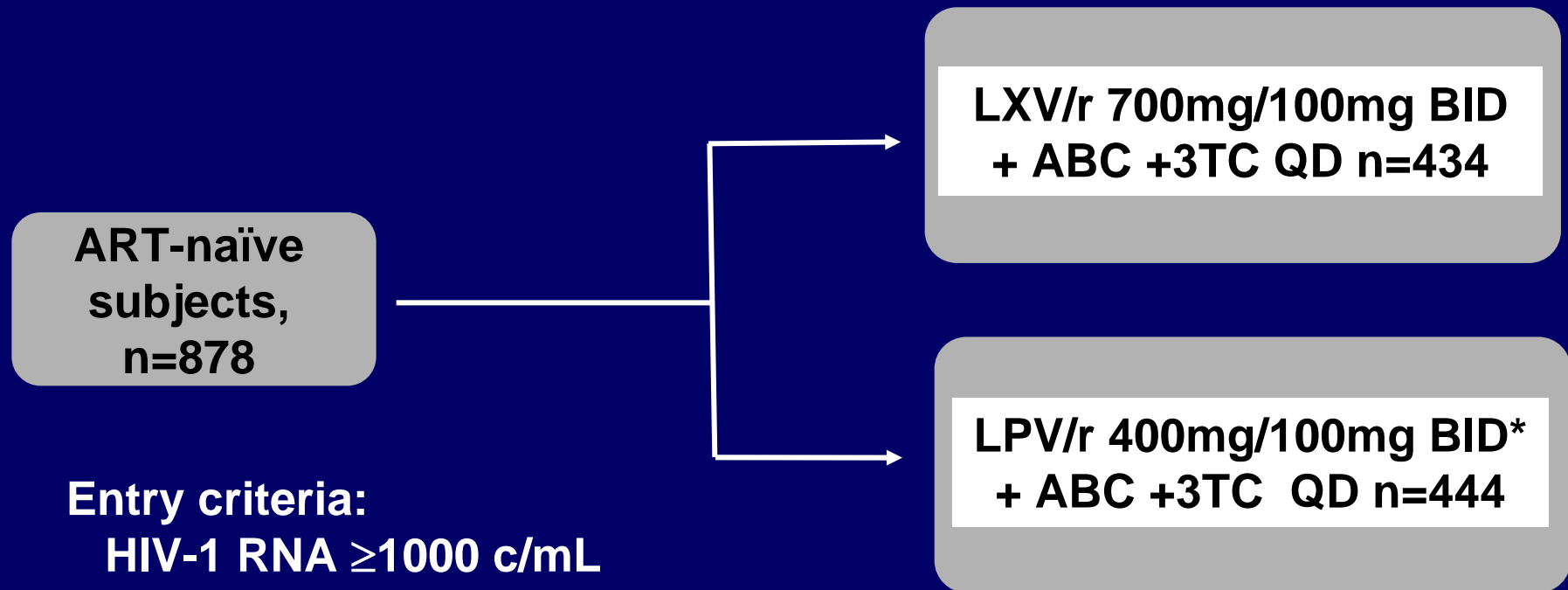
- **After a median follow-up of 3 years:**
  - Over 80% of patients with VL<50 c/ml
  - Median CD4 rise of 278 cells/mm<sup>3</sup>
- **Baseline VL and CD4 cell count were not associated with treatment outcome**
- **These results demonstrate the potency of EFV-based regimens across a wide range of CD4 cell counts and VL**
- **Addition of a fourth drug did not enhance responses in any subgroup**

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2. Are NRTIs necessary in first line therapy?
3. How does NNRTI (efavirenz) perform among persons with very high viral loads and low CD4?
4. How do boosted PI regimens (kaletra and fosamprenavir) compare to each other?
5. Is a boosted PI alone (kaletra) a viable treatment strategy?

## 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  $\geq 1000$  c/mL

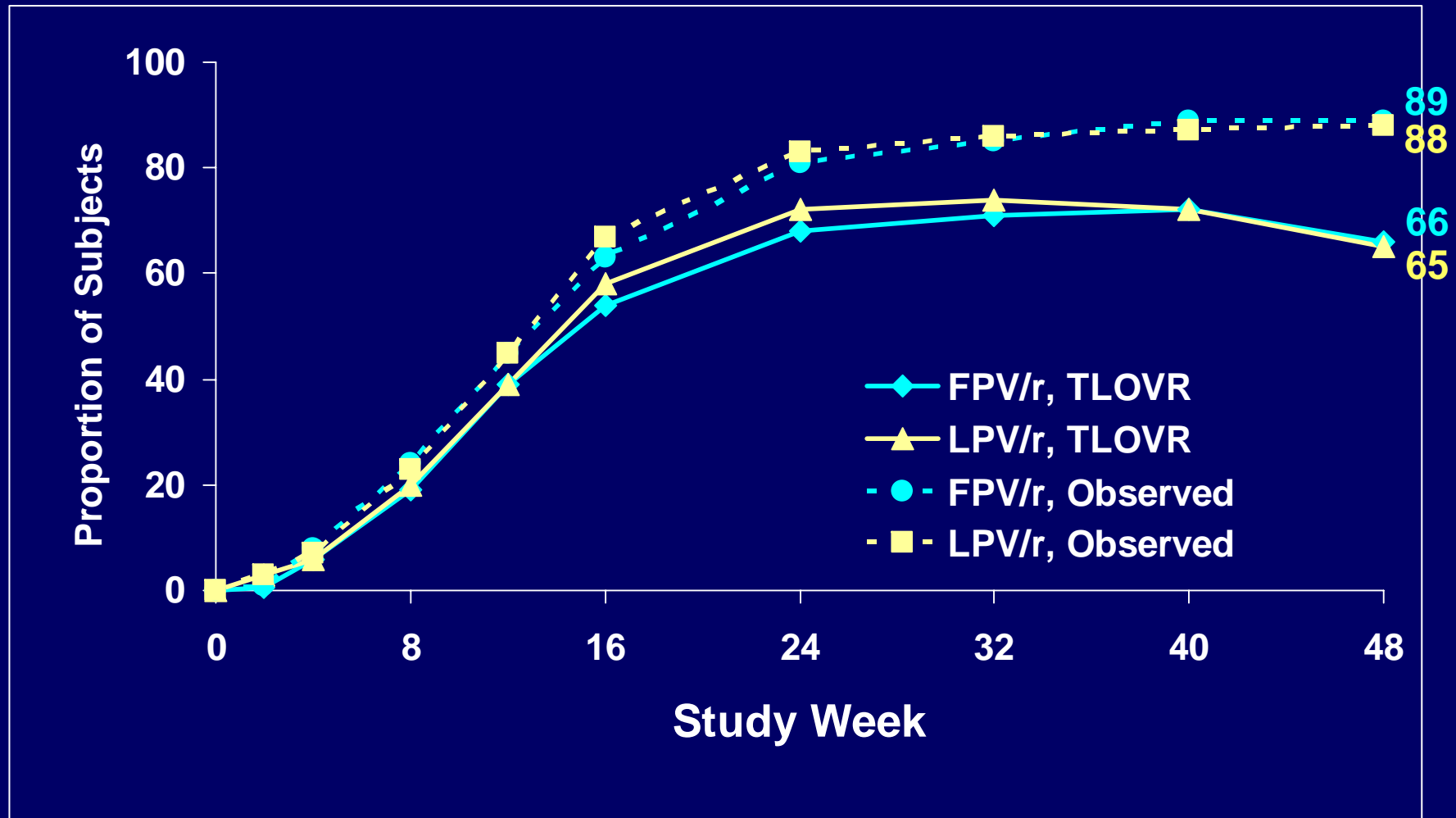
No CD4 cell count restrictions

Stratified by entry HIV-1 RNA  $< 100,000$  c/mL or  $\geq 100,000$  c/mL

\*LPV/r 400/100mg Capsules

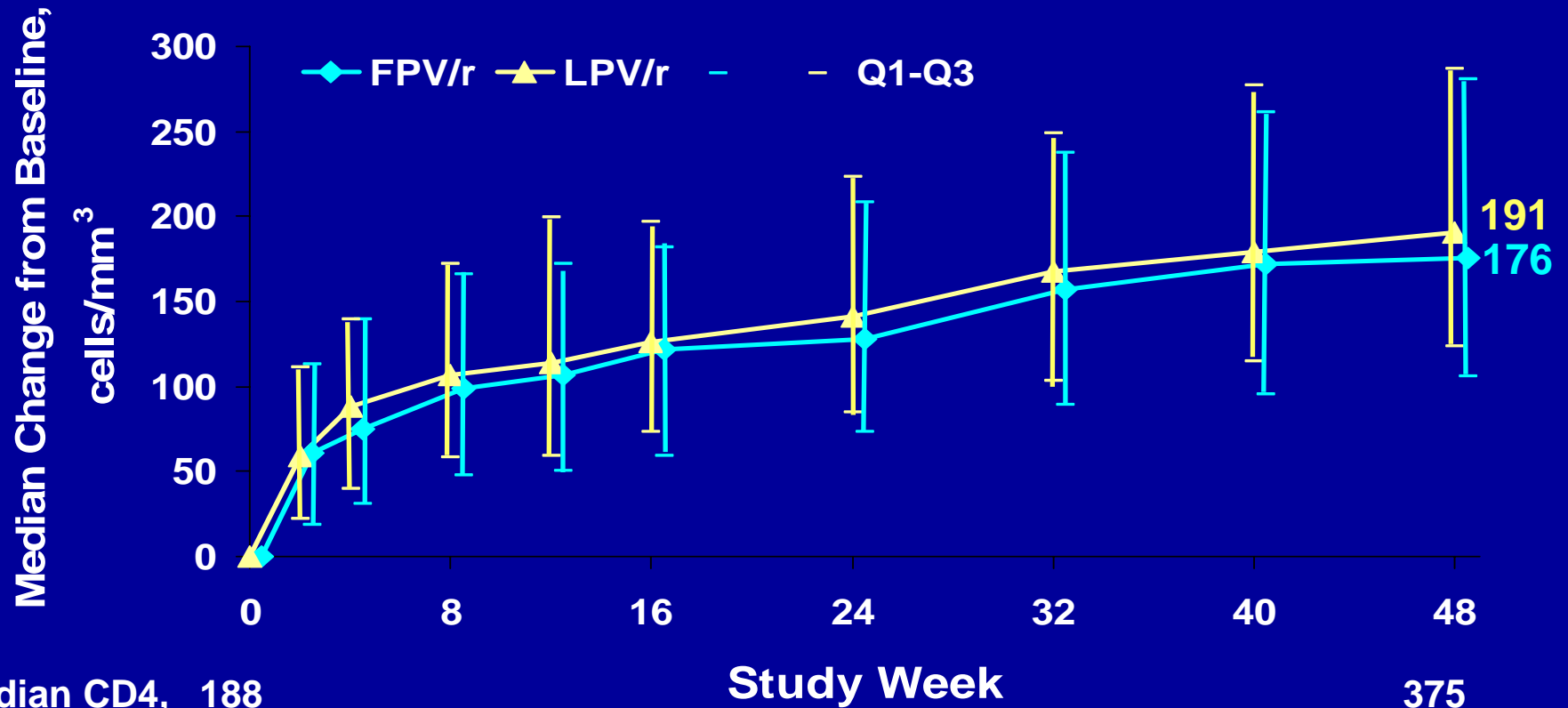
Eron, THLB0205

## HIV-1 RNA &lt;50 c/mL



KLEAN

# Change from Baseline in CD4 Cell Count



Median CD4, 188  
cells/mm<sup>3</sup> 194

Study Week

375  
397

KLEAN

## Clinical Treatment-Related Grade 2-4 AEs $\geq 2\%$

	LXV/r BID (N=436)	LPV/r BID (N=443)	Total (N=879)
Diarrhea	55 (13%)	50 (11%)	105 (12%)
Nausea	28 ( 6%)	24 ( 5%)	52 ( 6%)
Suspected HSR to ABC	27 ( 6%)	17 ( 4%)	44 ( 5%)
Headache	13 ( 3%)	5 ( 1%)	18 ( 2%)
Fatigue	10 ( 2%)	6 ( 1%)	16 ( 2%)
Vomiting	8 ( 2%)	8 ( 2%)	16 ( 2%)
Rash	11 ( 3%)	2 (<1%)	13 ( 1%)

# Resistance Through 48 Weeks

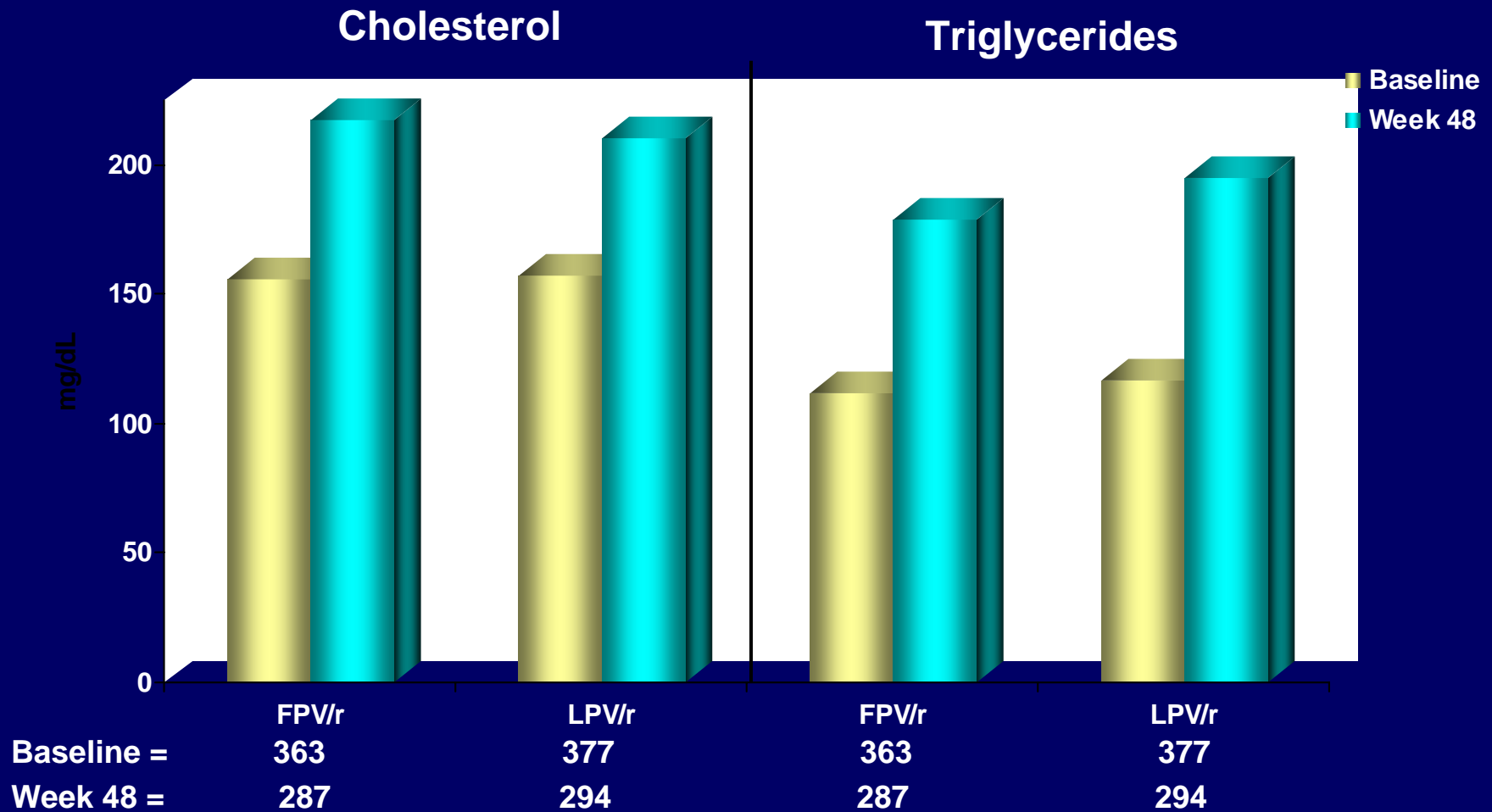
	FPV/r BID (n=14)*	LPV/r BID (n=21)*
<b>Treatment-emergent mutations (n)<sup>†</sup></b>		
TAM-associated mutations (M41M/L)	0	1
3TC-associated mutations (M184I, M184V, M184M/V)	3	4
NNRTI –associated mutations (V106V/A)	0	2
PI-associated mutations (I54I/L, I93I/L, K20K/R, I62I/V)	3	2

\*3 patients (FPV/r:1; LPV/r:2) did not have on-treatment genotypes available for analysis

<sup>†</sup>No treatment-emergent reduced phenotypic susceptibility to FPV/r or LPV/r was detected. No treatment-emergent, International AIDS Society-USA defined, major PI mutations were acquired.

KLEAN

# Median Fasting Lipids (mg/dL) at Baseline and Week 48



Use of lipid-lowering medications was similar in the FPV/r and LPV/r groups (11%)

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# KALETRA as Initial Monotherapy

- Randomized trial comparing kaletra to kaletra + combivir
- Inclusion: CD4 > 100, VL < 100K, no resistance, treatment naïve
- Primary endpoint VL < 400 at week 24 and VL < 50 at week 48

# Results: MONARK

OUTCOME	Kaletra	Kaletra + Combivir
	N=83	N=53
PRIMARY ENDPOINT	65%	75%
RNA<50, on treatment	84%	98%
DRUG RESISTANCE	2% (PI) M46I, L10F, V82A	1% (M184V)

## Conclusions

- Monotherapy with Kaletra could achieve sustained suppression in majority of patients meeting entry criteria
- Viral suppression rates lower, more intermittent viremia, drug resistance with monotherapy
- Need to identify predictors of success of this strategy before it can be recommended

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# AIDS 2006– TIME TO DELIVER : REPORT CARD FOR ANTIRETROVIRAL THERAPY



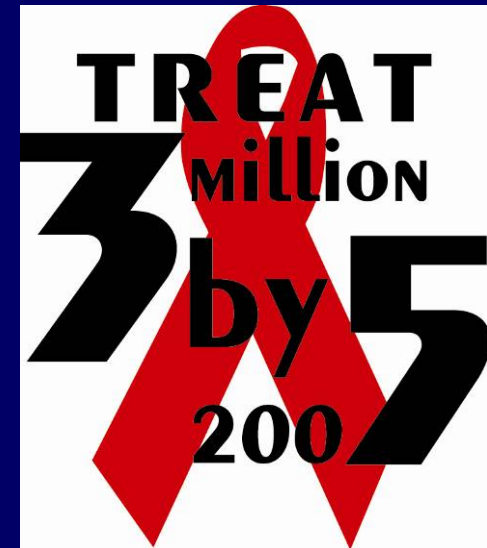
Haitian Patient, before and after Receiving Free Treatment for HIV Infection and Tuberculosis.

The photograph on the left was taken in March 2003, and that on the right in September 2003. Many impoverished patients in rural Haiti and Rwanda now receive comprehensive medical care through public-private partnerships.

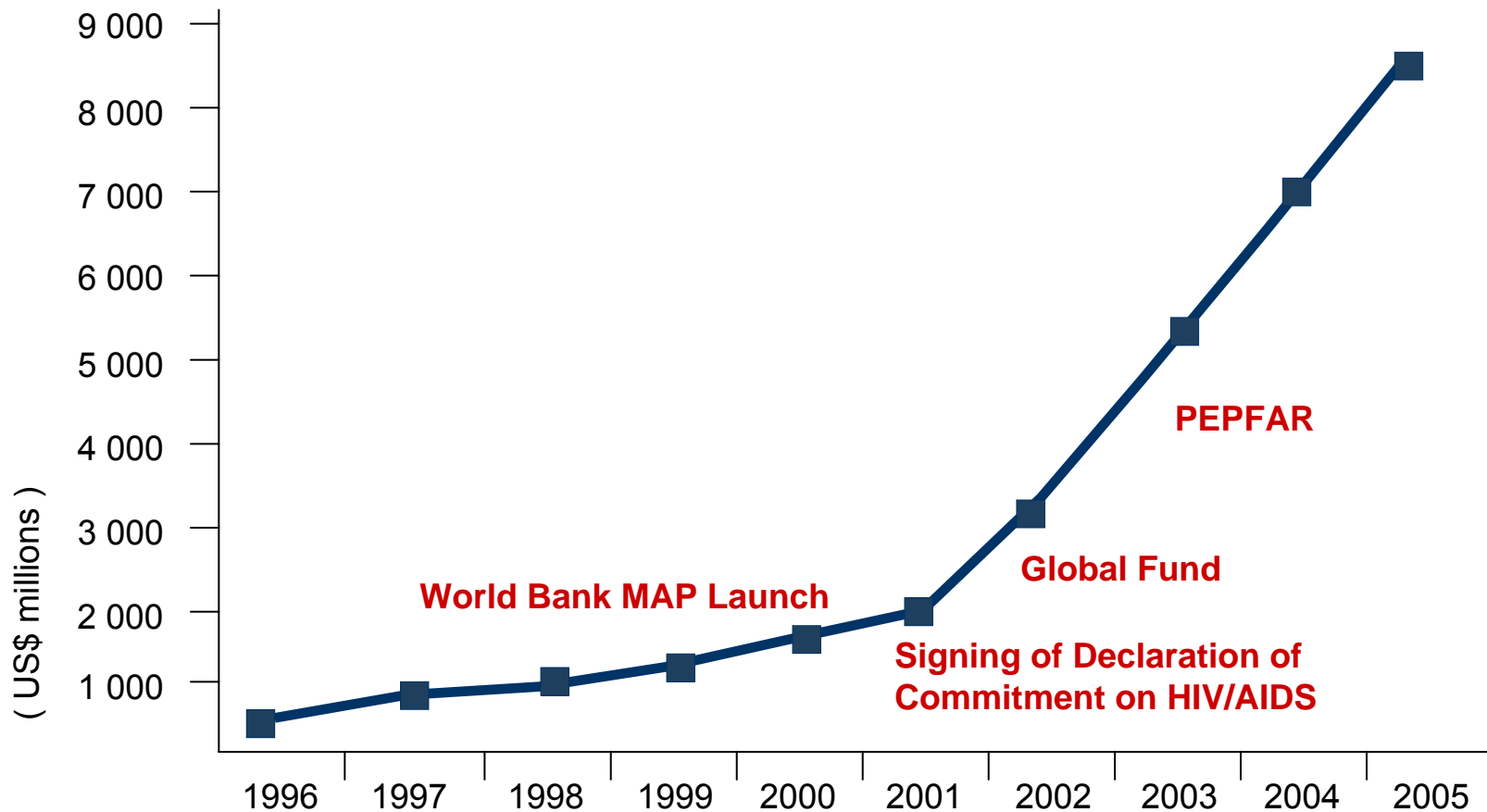
**Jim Kim and Paul Farmer, NEJM, 2006**



Dr LEE Jong-Wook  
1945-2006



# Estimated total annual resources available for AIDS, 1996–2005



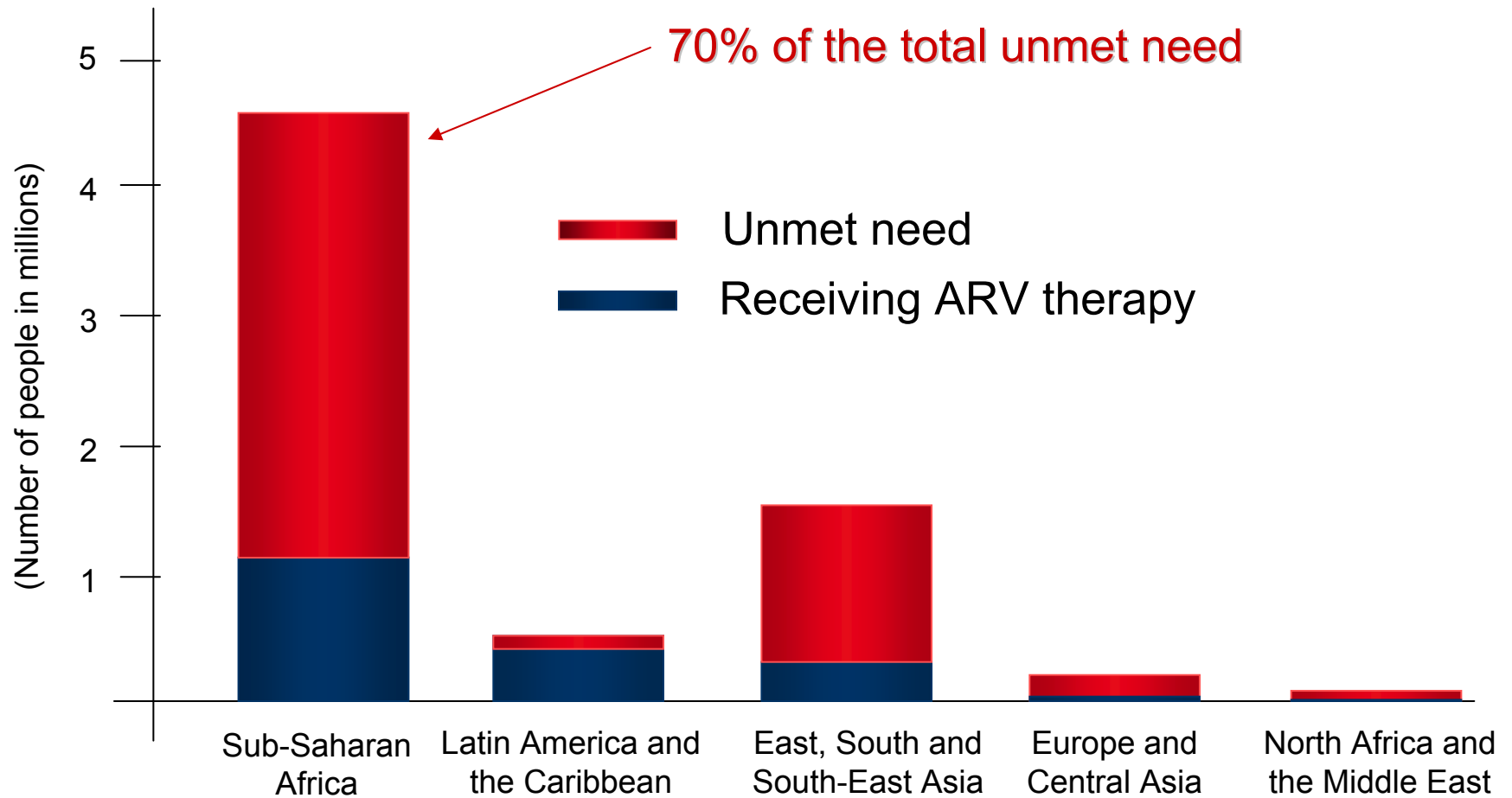
Source: *Lancet*, 2006; 368: 526–30

# Access June 2006

Geographical region	Number of people receiving ARV therapy	Estimated need	Coverage
Sub-Saharan Africa	1 040 000	4 600 000	23%
Latin America and the Caribbean	345 000	460 000	75%
East, South and South-East Asia	235 000	1 440 000	16%
Europe and Central Asia	24 000	190 000	13%
North Africa and the Middle East	4 000	75 000	5%
<b>Total</b>	<b>1 650 000</b>	<b>6 800 000</b>	<b>24%</b>

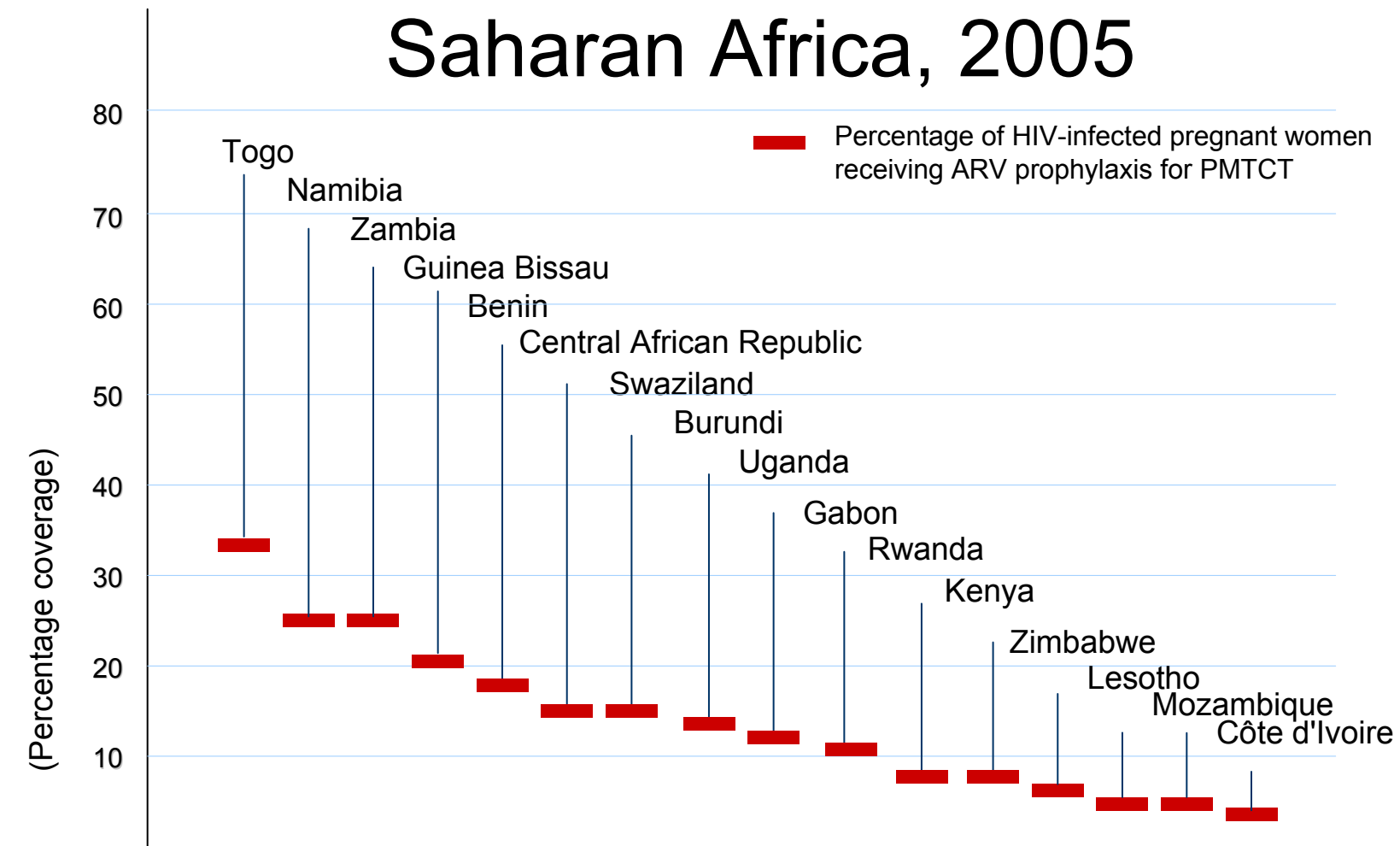


# ARV Therapy: global need, June 2006

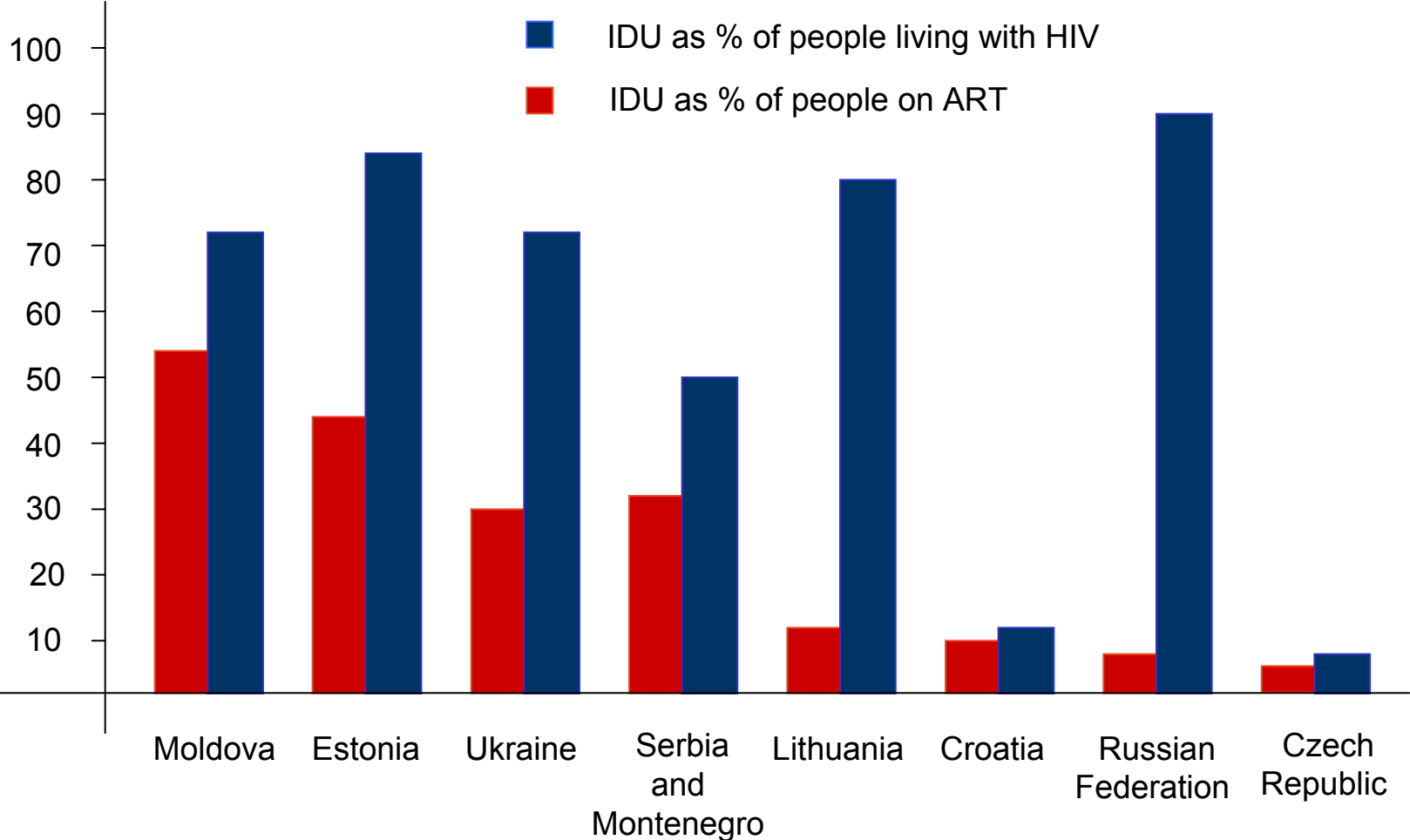


**UNAIDS, 2006**

# Access to PMTCT services in sub-Saharan Africa, 2005



# Treatment access among IDU in Eastern Europe



# Children's Access to Antiretroviral Therapy



Africa

8%

Asia

5%

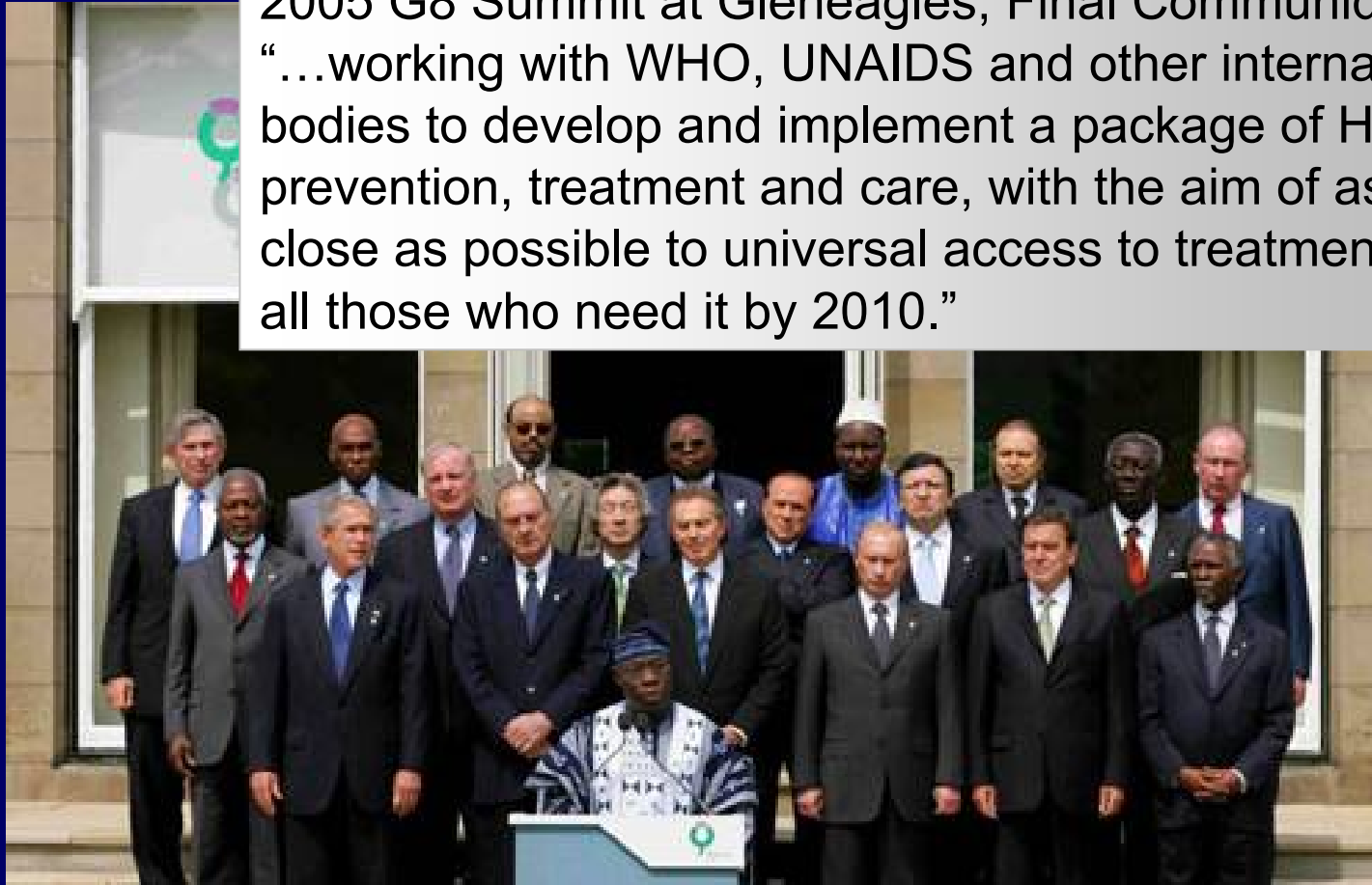
Latin America

8%

UNAIDS, 2006

# Universal Access

2005 G8 Summit at Gleneagles, Final Communiqué:  
“...working with WHO, UNAIDS and other international bodies to develop and implement a package of HIV prevention, treatment and care, with the aim of as close as possible to universal access to treatment for all those who need it by 2010.”



# Priorities to reduce mortality of HIV/AIDS patients in low-income settings

- Expand HIV testing for earlier diagnosis
- Ensure essential package of care for HIV-infected patients, including TB screening and co-trimoxazole
- Provide ART for Stages 3 and 4 disease as early as possible
- Expand CD4+ testing for earlier initiation of ART
- Abolish user fees

## Recommendations for initiating antiretroviral therapy in HIV-infected pregnant women

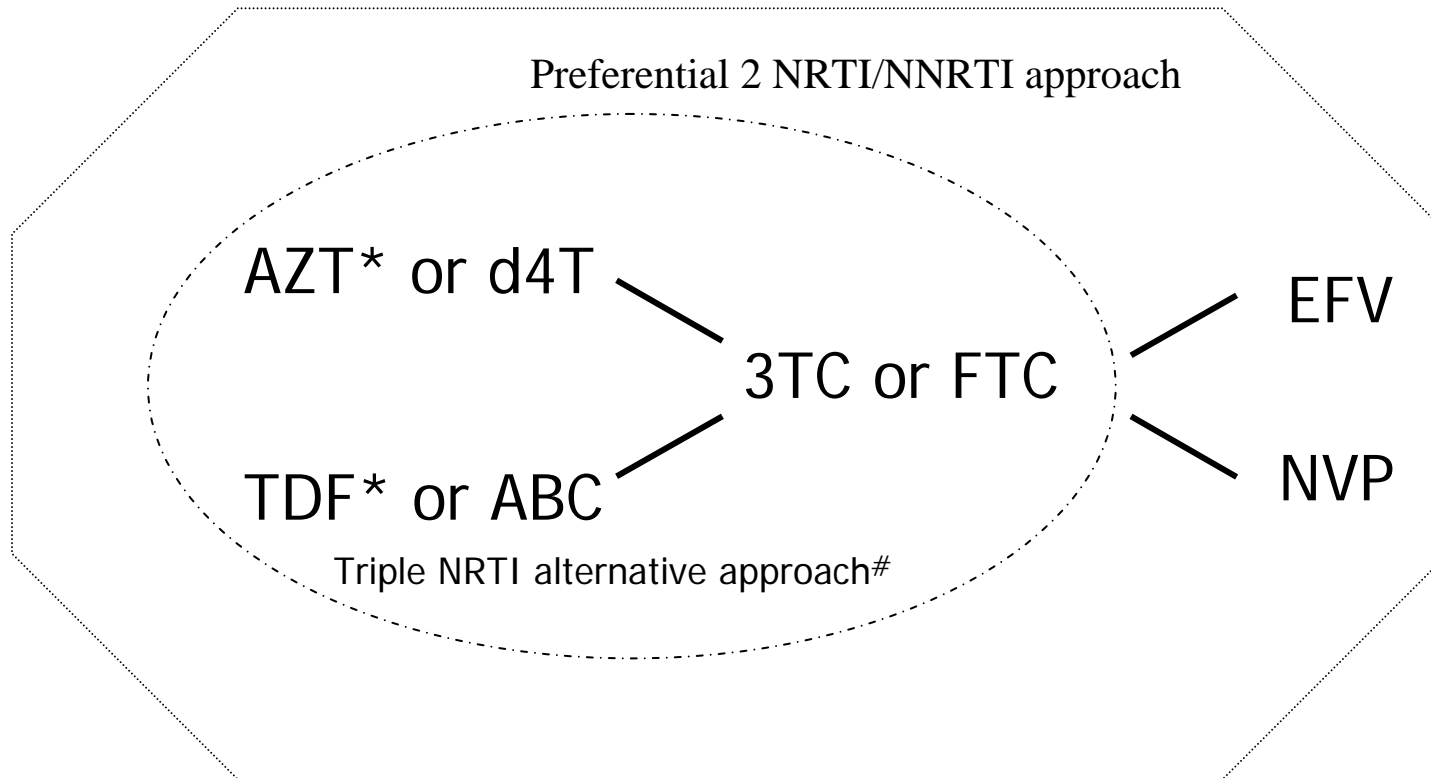
WHO Clinical Staging	CD4 testing not available	CD4 testing available
<b>1</b>	Do not treat	Treat if CD4 cell count < 200/mm <sup>3</sup> (2, 3)
<b>2</b>	Do not treat (1)	
<b>3</b>	Treat	Treat if CD4 cell count < 350/mm <sup>3</sup> (2)
<b>4</b>		Treat irrespective of CD4 cell count

(1) Treatment is recommended if TLC < 1200/mm<sup>3</sup>.

(2) The precise CD4 cell level above this value at which ARV treatment should be started has not been established.

(3) Treatment can be considered if CD4 counts < 350 cells/mm<sup>3</sup>, particularly for women with CD4 values nearing the threshold of 200/mm<sup>3</sup>.

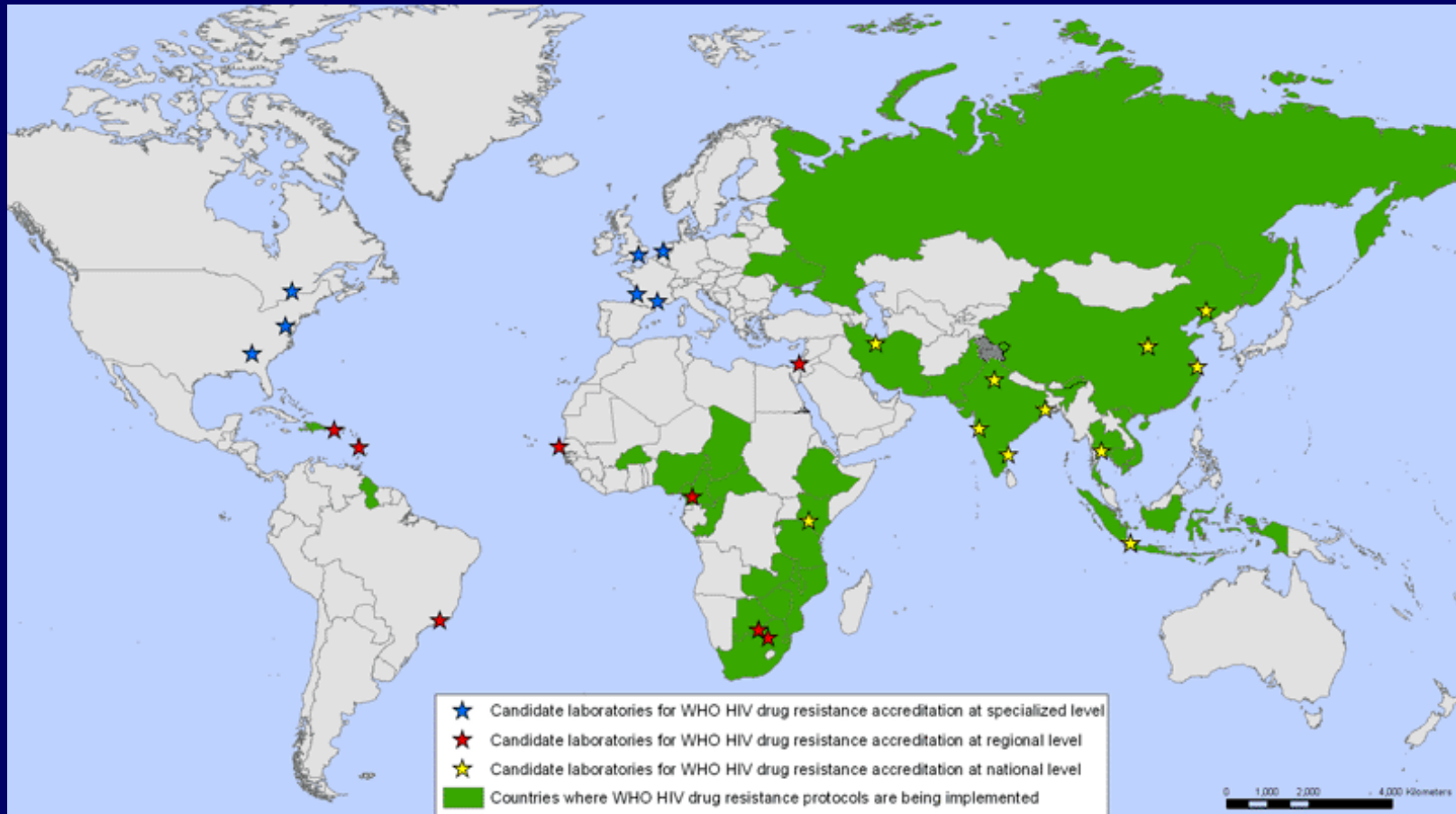
## First Line ARV Drugs in Adults and Adolescents



\* Preferential NRTI to be combined with 3TC or FTC.

# Triple NRTI should be considered as an alternative strategy for first-line in situations where NNRTI options provide additional complications and to preserve the PI class for second line (e.g., pregnancy, viral hepatitis co-infection, TB co-infection, women who wish to fall pregnant or who have CD4 count  $> 250$  cells /mm<sup>3</sup>; severe reactions to NVP or EFV and HIV-2 infection).

# WHO Global Program to Monitor HIV Drug Resistance



# DART STUDY: FIXED TREATMENT INTERRUPTION

- 3314 HIV+ in Uganda and Zimbabwe
- After 48 weeks of treatment if CD4>300 randomize to continuous or 12 weeks on 12 weeks off
- Regimens ZDV+3TC + NVP OR ABC OR TDF
- Approximately 400 subjects in each group

# DART STUDY: RESULTS

- CD4 nadir 132 (1-199)
- CD4 at randomization 358 (300-1054)
- Randomization terminated early after DSMB review
- At this time median followup 51 weeks
- ARV exposure: Continuous 99%, STI 49%
- WHO stage 4 or death 2.6 fold higher in STI vs continuous therapy (8.3/100py vs 32 /100py)

# Events in DART

	CONT	STI
• Esophageal candidiasis	4	17
• Extra pulm TB	1	4
• Cryptococcal disease	2	2
• HSV	1	2
• Death	4	5

## STI in AFRICA

- Patients with low CD4 nadir at risk for faster HIV disease progression with STI
- This strategy is risky in the short term and probably also in the long term
- Transmission/drug resistance other reasons to put this strategy to rest

# MULTIDRUG RESISTANT TB

- Cultures for TB not routinely performed in Africa
- Drug susceptibility for TB not routinely performed
- Clinicians noted very high and rapid mortality rates in patients initiating ART
- Epidemic of MDR TB identified in Kwazulu Natal

## Identifying XDR TB

- Did fingerprinting and drug susceptibility on 1540 patients with known or suspected TB
- 35% (535) culture +
- Of these 221/535 (41%) MDRTB
- Among these 53 had “XDR TB” resistant to all first and second line agents
  - INH, rif, etb, sm, cipro, kanamydin

## XDR TB: OUTCOMES

- 90% XDR TB were the same strain
- 52/53 patients died
- Median survival was 25 days
- 47 had HIV testing, all were HIV+

# IMPLICATIONS

- In this area, MDRTB and XDR TB threatens success of ART programs
- These cases accounted for 67% of the deaths in the program during that time period
- Evidence for both nosocomial and community transmission
- Need to monitor and respond to epidemics