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# Efficacy and safety of NRTI's switch to tenofovir plus emtricitabine (Truvada®) vs. abacavir plus lamivudine (Kivexa®) in patients with virologic suppression receiving a lamivudine containing HAART: The BICOMBO study

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# Background

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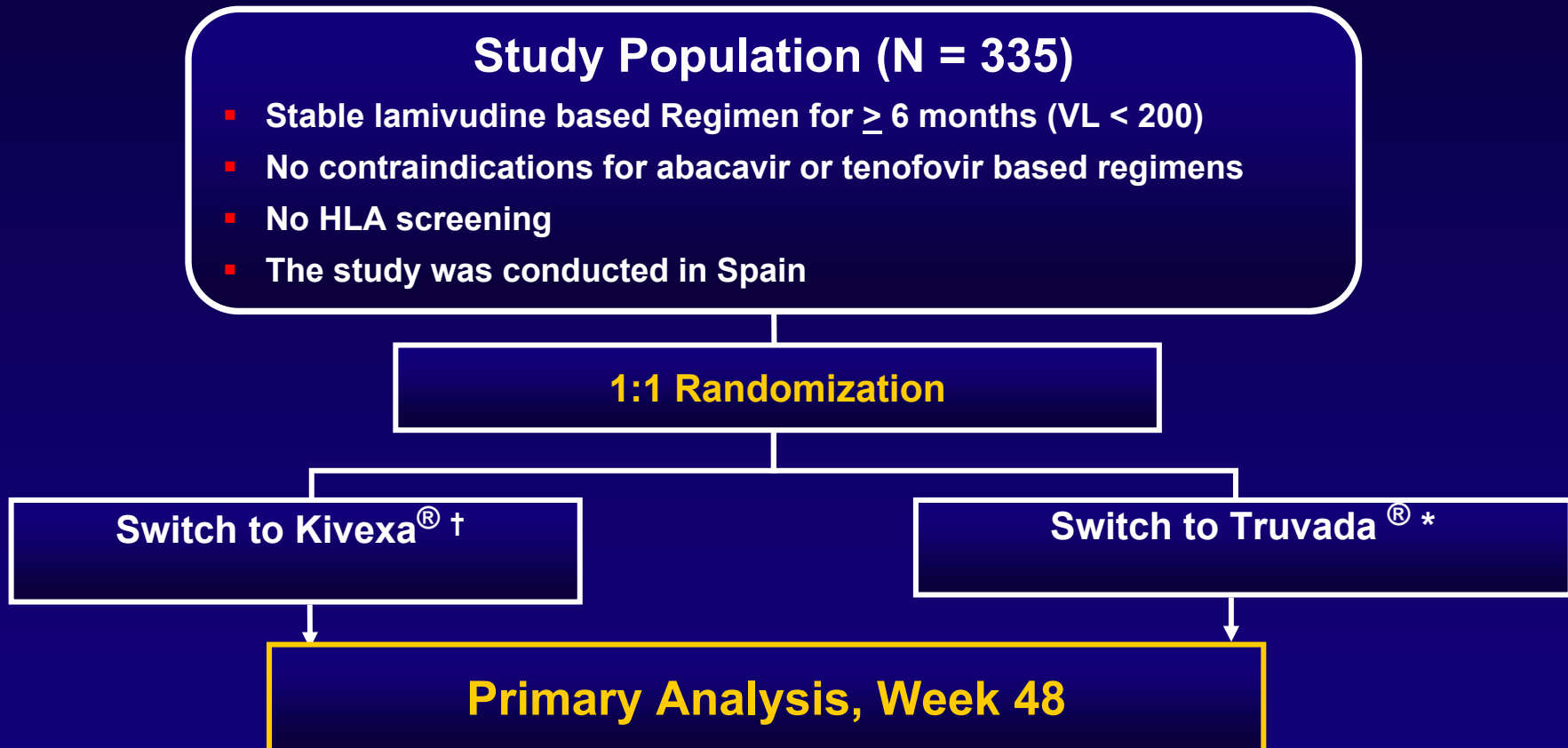
- **Tenofovir (TDF) plus emtricitabine (Truvada®) and abacavir (ABC) plus lamivudine (Kivexa®) are fixed dose combinations and the most commonly recommended and used nucleoside analogs backbone for initial antiretroviral therapy**
- **Kivexa® has favourably compared with zidovudine plus lamivudine (Combivir®) while Truvada® has demonstrated superiority.**
- **However, no head to head comparison has been performed so far between Truvada® and Kivexa®.**

# Objective

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- **To compare the efficacy and safety of Truvada® vs. Kivexa® in patients with virologic suppression and receiving a lamivudine containing regimen.**

# Study Design



\* Tenofovir 300 mg plus emtricitabine 200 mg + unchanged NNRTI or PI.

† Abacavir 600 mg plus lamivudine 300 mg + unchanged NNRTI or PI.

# Primary end-point

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- **The proportion of patients with treatment failure for any reason through Week 48**
  - **Includes virologic rebound ( $> 200$  cp/mL), discontinuation of study therapy or lost to follow-up, progression to a new CDC category C event or death.**
  - **Non-inferiority study of Kivexa<sup>®</sup> vs Truvada<sup>®</sup>. Upper limit of 95% CI of estimated difference  $< 12.5\%$ .**

## Secondary end-points

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- **The proportion of patients with virologic failure at or prior to week 48**
  - **Confirmed on-study HIV RNA  $\geq$  200 copies/mL or last on-study HIV RNA  $\geq$  200 copies/mL followed by discontinuation**
- **Time to treatment failure and to virologic failure**
- **CD4 changes**
- **Safety**
- **Changes of fasting plasma lipids, body fat, bone mineral density and renal function**

# Baseline Characteristics

	<b>KIVEXA<sup>®</sup></b>	<b>TRUVADA<sup>®</sup></b>
	<b>N = 167</b>	<b>N = 166</b>
<b>Median Age, y</b>	<b>43</b>	<b>43</b>
<b>Gender, N (%)</b>		
<b>Male</b>	<b>130 (78)</b>	<b>127 (77)</b>
<b>Risk group, N (%)</b>		
<b>Heterosexual trans.</b>	<b>55 (35)</b>	<b>55 (35)</b>
<b>MSM</b>	<b>55 (35)</b>	<b>51 (32)</b>
<b>IDUs</b>	<b>47 (30)</b>	<b>53 (33)</b>
<b>AIDS, N (%)</b>	<b>63 (38)</b>	<b>65 (39)</b>
<b>Glomerular filtration rate (CG) ml/mit</b>	<b>102</b>	<b>97</b>
<b>Creatinine, mg/dL</b>	<b>1</b>	<b>0.9</b>
<b>CD4 &lt; 200, cells/ mm<sup>3</sup></b>	<b>13 (9)</b>	<b>15 (10)</b>
<b>Median CD4, cells/mm<sup>3</sup></b>	<b>520</b>	<b>508</b>

# Baseline Characteristics

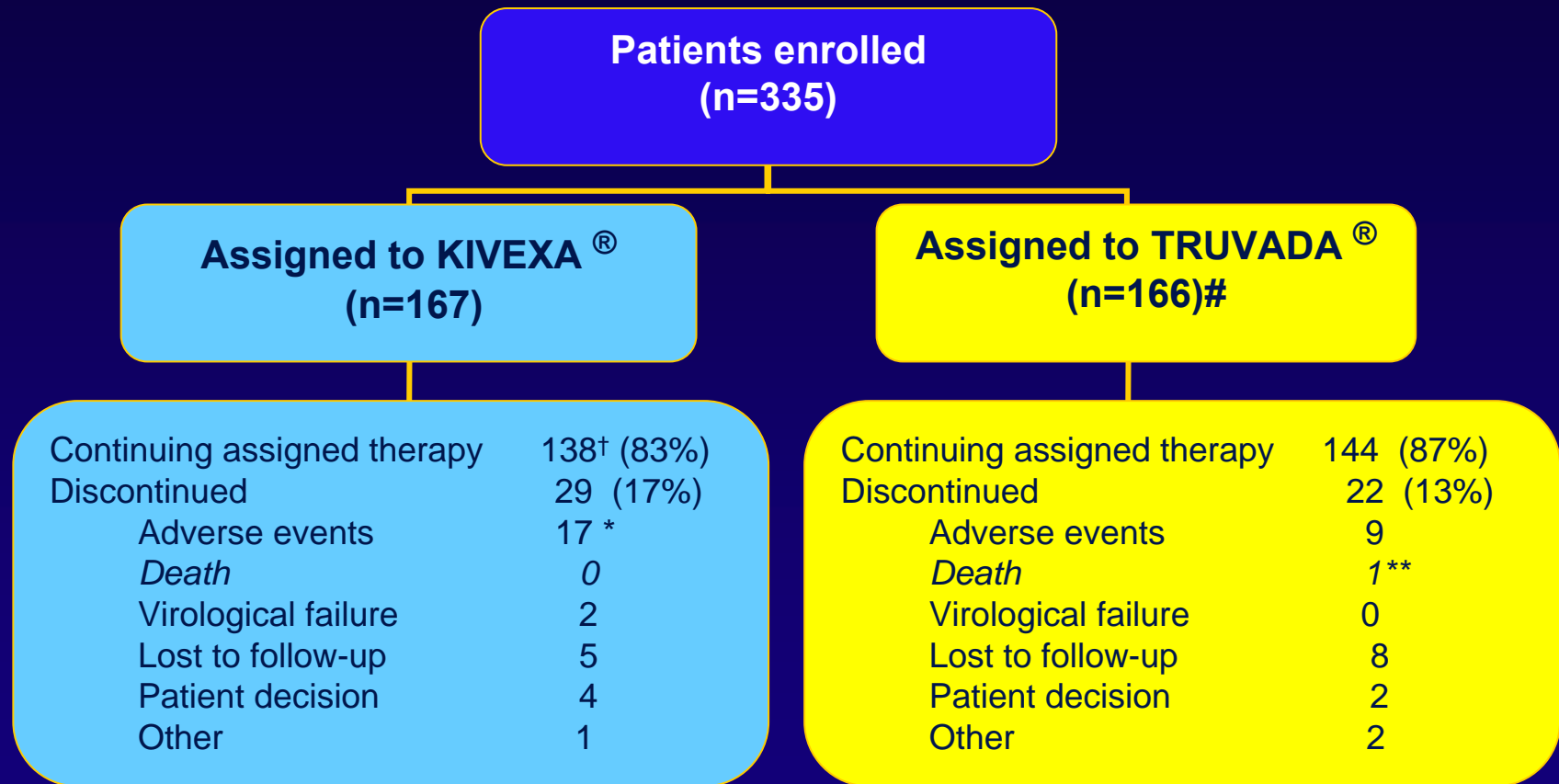
	<b>KIVEXA<sup>®</sup></b>	<b>TRUVADA<sup>®</sup></b>
	<b>N = 167</b>	<b>N = 166</b>
<b>TG &gt; 500 mg/dL, N (%)</b>	<b>1 (1 %)</b>	<b>3 (2 %)</b>
<b>Cholesterol &gt; 240 mg/dL, N (%)</b>	<b>22 (14%)</b>	<b>25 (16%)</b>
<b>LDL &gt; 130 mg/dL, N (%)</b>	<b>51 (38%)</b>	<b>49 (37%)</b>
<b>HDL &lt; 40 mg/dL, N (%)</b>	<b>26 (18%)</b>	<b>29 (20%)</b>
<b>ALT &gt; 40 iu/ml, N (%)</b>	<b>23 (16 %)</b>	<b>36 (25 %)</b>
<b>AST &gt; 40 iu/ml, N (%)</b>	<b>48 (31 %)</b>	<b>54 (35 %)</b>
<b>ALT or AST &gt; 40 iu/ml, N (%)</b>	<b>49 (32%)</b>	<b>62 (40 %)</b>

# Baseline Therapy

	<b>KIVEXA<sup>®</sup></b>	<b>TRUVADA<sup>®</sup></b>
	<b>N = 167</b>	<b>N = 166</b>
<b>ARV exposure, yr.</b>	<b>4.2</b>	<b>3.7</b>
<b>1st. ARV regimen, N (%)</b>	<b>48 (29)</b>	<b>29 (17)*</b>
<b>Efavirenz</b>	<b>94 (56)</b>	<b>88 (53)</b>
<b>Nevirapine, N (%)</b>	<b>56 (34)</b>	<b>62 (37)</b>
<b>PI, N (%)</b>	<b>17 (10)</b>	<b>16 (10)</b>
<b>Previous NRTI</b>		
<b>ZDV+3TC, N (%)</b>	<b>59 (35)</b>	<b>48 (29)</b>
<b>d4T +3TC, N (%)</b>	<b>21 (13)</b>	<b>27 (16)</b>
<b>ddl +3TC, N (%)</b>	<b>31 (19)</b>	<b>23 (14)</b>
<b>TDF +3TC, N (%)</b>	<b>44 (26)</b>	<b>56 (34)</b>
<b>ABC +3TC, N (%)</b>	<b>12 (7)</b>	<b>18 (11)</b>

\* P=0.01

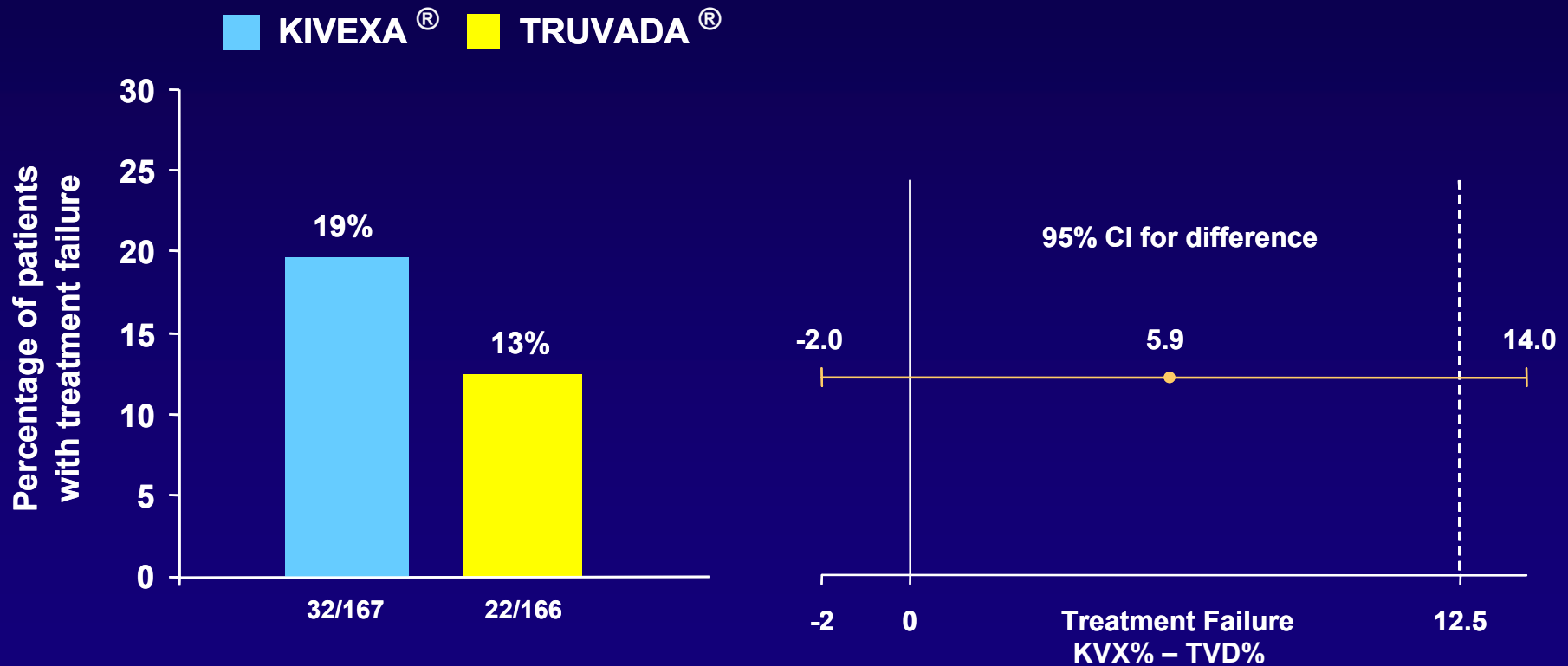
# Patient Disposition at week 48



† 2 subjects with virological failure and  
1 with a new CDC event (cervix carcinoma)  
\* 3 subjects lost to follow-up and 1 new CDC event  
(Cryptosporidiosis)

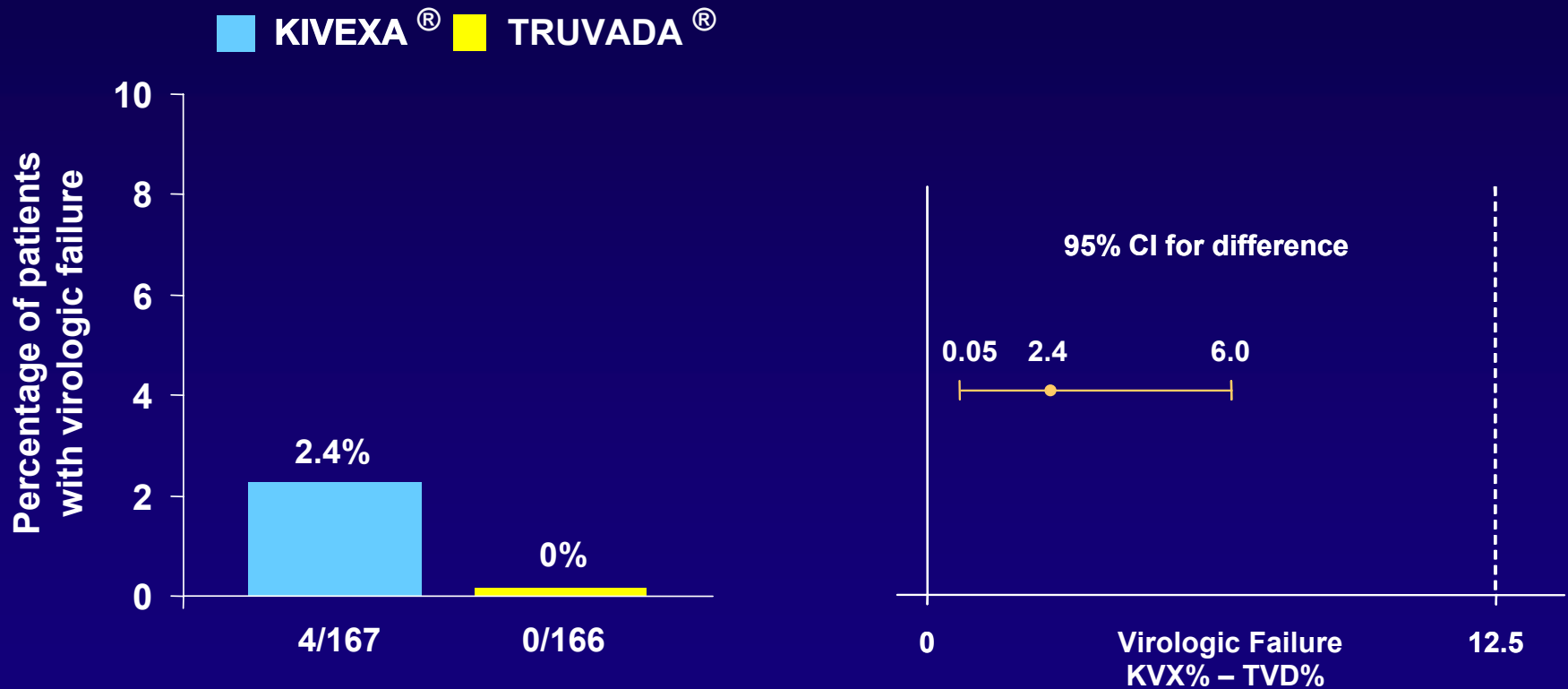
# 2 additional were not eligible  
\*\* Cerebral hemorrhage

# Primary Endpoint Treatment Failure through Week 48



# Secondary Endpoint

## Virologic Failure ( $\geq 200$ c/mL) through Week 48



## Secondary Endpoint

# Virologic Failure ( $\geq 200$ c/mL) through Week 48

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## 4 patients developed VF in the Kivexa arm

4 / 4 no resistance tests before any ART regimen

4 / 4 two or more previous ART regimens for 1-5 years. Never exposed to ABC

1 / 4 previous virologic failure. Wild type virus

### VF developed between months 4-8 of the study

4 / 4 were receiving Kivexa + Nevirapine or Efavirenz

2 / 4 genotypic test available at failure

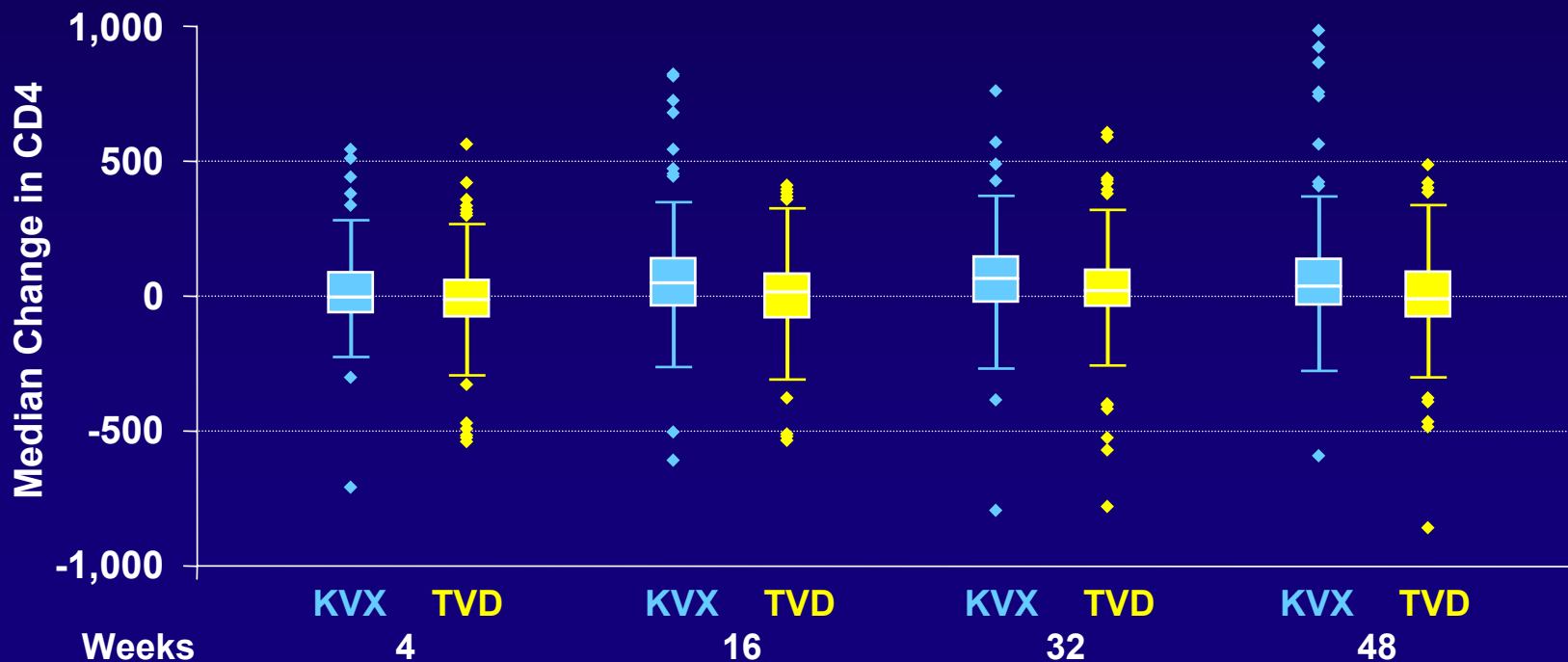
75I, 184V, 219E, 101E, 181E

74V, 100I, 103, 63S

4 / 4 VL became undetectable with same (n=1) or different ART (n=3)

## CD4 Changes

- Median changes in CD4 cell count were: +44 cells/mm<sup>3</sup> (KIVEXA<sup>®</sup>) and – 2.7 cells/mm<sup>3</sup> (TRUVADA<sup>®</sup>) through Week 48 (p=0.032)



# Adverse Events

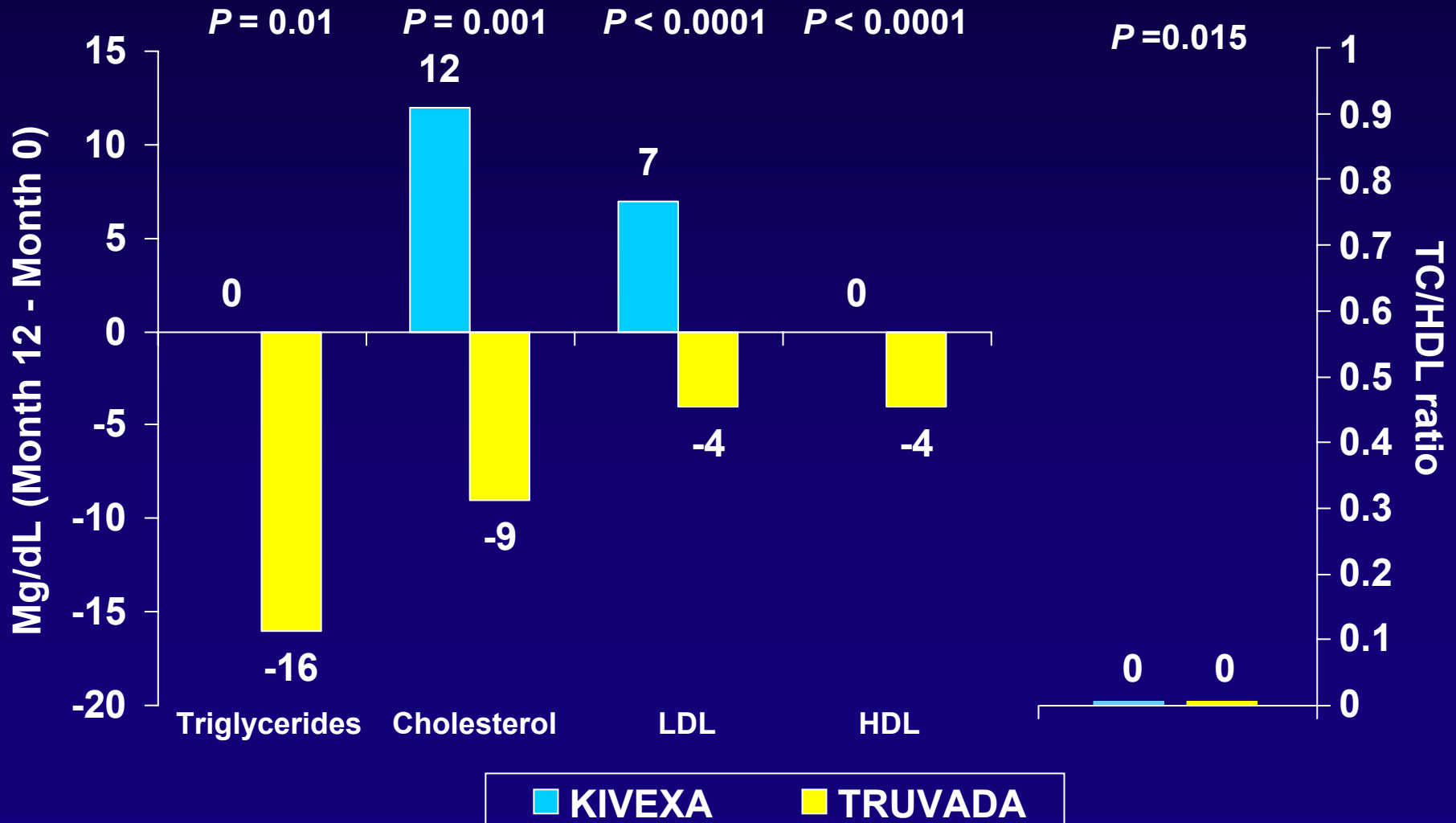
	<b>KIVEXA<sup>®</sup></b>	<b>TRUVADA<sup>®</sup></b>
	<b>N = 167</b> <b>N (%)</b>	<b>N = 166</b> <b>N (%)</b>
<b>Death</b>	<b>0 (0)</b>	<b>1 (1) &amp;</b>
<b>Any AE</b>	<b>109 (65)</b>	<b>89 (54)*</b>
<b>AE leading to discontinuation: Total</b>	<b>17 (10)</b>	<b>9 (5) **</b>
<b>Suspected ABC hypersensitivity</b>	<b>9 (5)</b>	<b>0 (0)</b>
<b>Cefalea, fever, asthenia, diarrhoea</b>	<b>4 (2)</b>	<b>0 (0)</b>
<b>CNS</b>	<b>1 (1)</b>	<b>3 (2)</b>
<b>GI</b>	<b>1 (1)</b>	<b>2 (1)</b>
<b>Rash</b>	<b>0 (0)</b>	<b>1 (1)</b>
<b>Kidney</b>	<b>0 (0)</b>	<b>2<sup>†</sup> (1)</b>
<b>Lipodystrophy</b>	<b>1 (1)</b>	<b>1 (1)</b>
<b>Liver</b>	<b>1<sup>#</sup> (1)</b>	<b>0 (0)</b>

& Cerebrovascular accident; \* P=0.02 \*\* P=0.004; † highest creatinine 1.1 and 6.1; # highest ALT/AST 42/ 59;

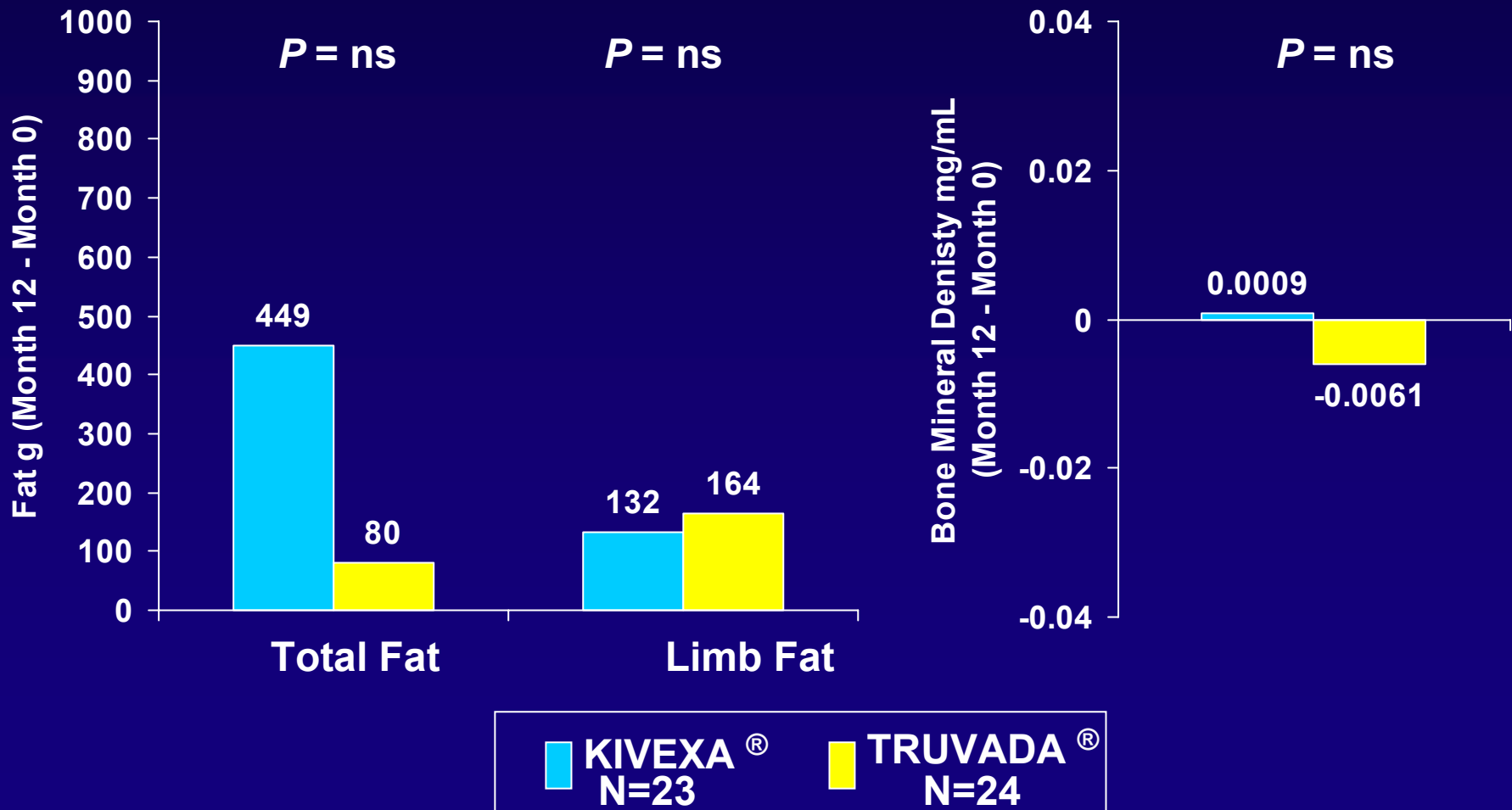
# LAB Abnormalities

Liver Function Abnormalities (ALT/AST > 200)		
	N (%)	
	KIVEXA N = 167	TRUVADA N = 166
ALT	1 (1%)	0 (0%)
AST	1 (1%)	1 (1%)
ALT or AST	1 (1%)	1 (1%)

# Change in Median Fasting Plasma Lipids



# Change in Mean Total and Limb Fat and Bone Mineral Density (n=47)



## RENAL FUNCTION. Median Changes From Baseline (mo. 12 – baseline)

	<b>KIVEXA<sup>®</sup></b>		<b>TRUVADA<sup>®</sup></b>	
	<b>n</b>	<b>Median (IQR)</b>	<b>n</b>	<b>Median (IQR)</b>
<b>Δ Creatinine , mg/dL</b>	<b>124</b>	<b>-0.03 (-0.1,- 0.04)</b>	<b>129</b>	<b>-0.02 (-0.1, 0.03)</b>
<b>Δ GFR (CG), ml/mit</b>	<b>107</b>	<b>1.3 (-5, 7)</b>	<b>129</b>	<b>-0.5 (-5, 9)</b>

Note: Only 1 patient (Truvada arm) developed a plasma creatinine  $\geq$  2 mg/dL

# HLA TYPING

	N (%)	
	HLA-B05701+	HLA-B05701-
<b>CASES (N=9) *</b>	<b>3 (33%)</b>	<b>6 (67%)</b>
<b>CONTROLS (N=14)</b>	<b>1 (7%)</b>	<b>13 (93%)</b>

\* **KIVEXA<sup>®</sup> interruption due to suspected Abacavir hypersensitivity**

# Conclusions

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**In patients switching from a lamivudine containing regimen:**

- **For treatment efficacy, the Kivexa<sup>®</sup> group did not meet the non-inferiority endpoint compared to the Truvada<sup>®</sup> group**
  - **the difference was mainly driven by Kivexa discontinuations due to suspected abacavir hypersensitivity**
- **For the virologic efficacy, Kivexa<sup>®</sup> met non-inferiority criteria compared to Truvada<sup>®</sup>**
  - **however, there were more failures with Kivexa<sup>®</sup> than Truvada<sup>®</sup> (2.4% vs 0%)**

# Conclusions

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On switching from a lamivudine nucleoside backbone to either Kivexa<sup>®</sup> or Truvada<sup>®</sup>:

- Retrospective HLA testing showed B5701+ in 3/9 cases of suspected HSR
- Safety endpoints showed:
  - A more favorable lipid profile (cholesterol, TG and LDL but not HDL) for those switching to Truvada<sup>®</sup> vs Kivexa<sup>®</sup>
  - No differences in renal function or bone mineral density between Truvada<sup>®</sup> and Kivexa<sup>®</sup> treatment arms

# BICOMBO Study Group

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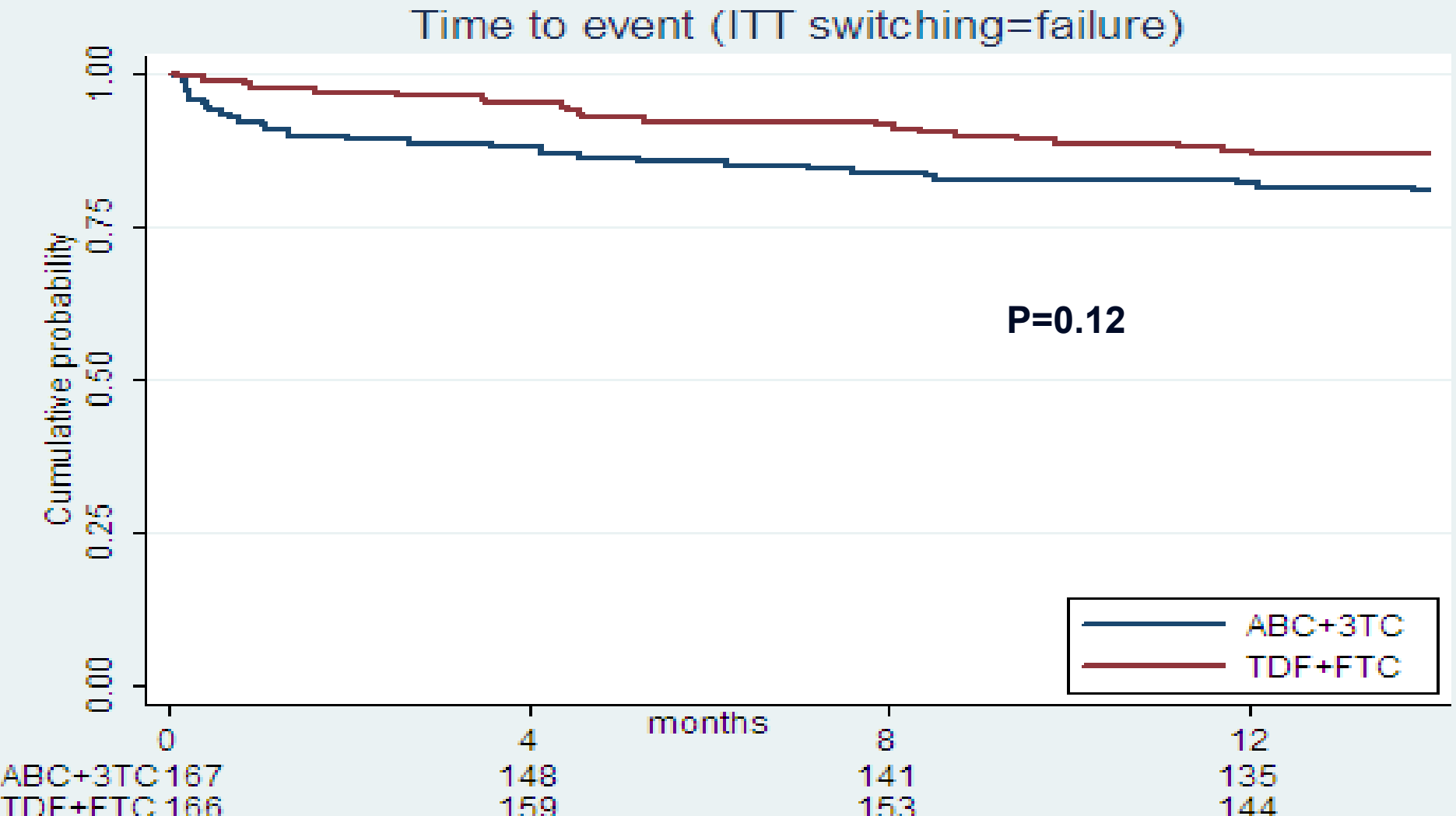
F.G. Peralta

AND 335 PATIENTS !!!!

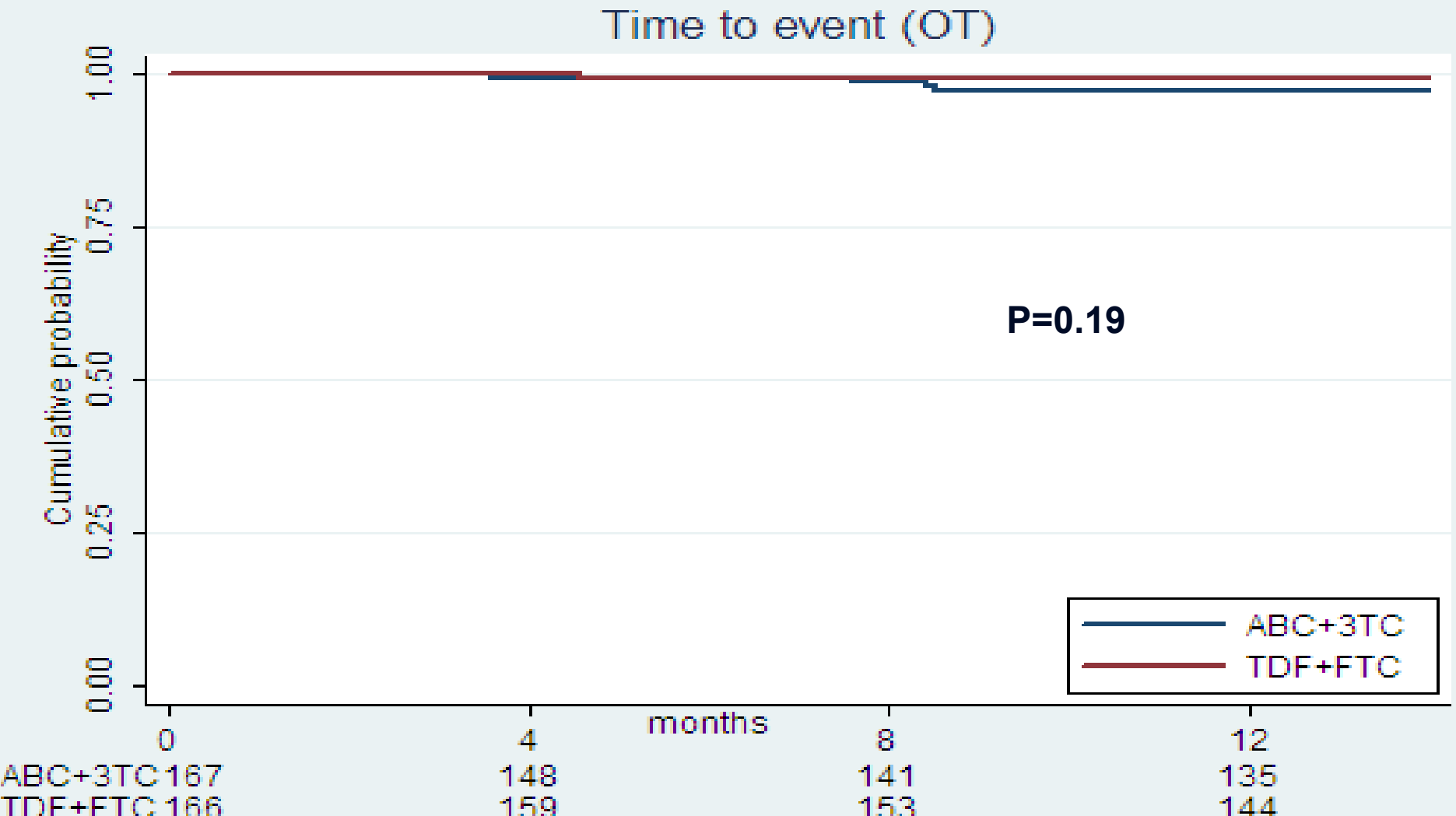


Backup slides

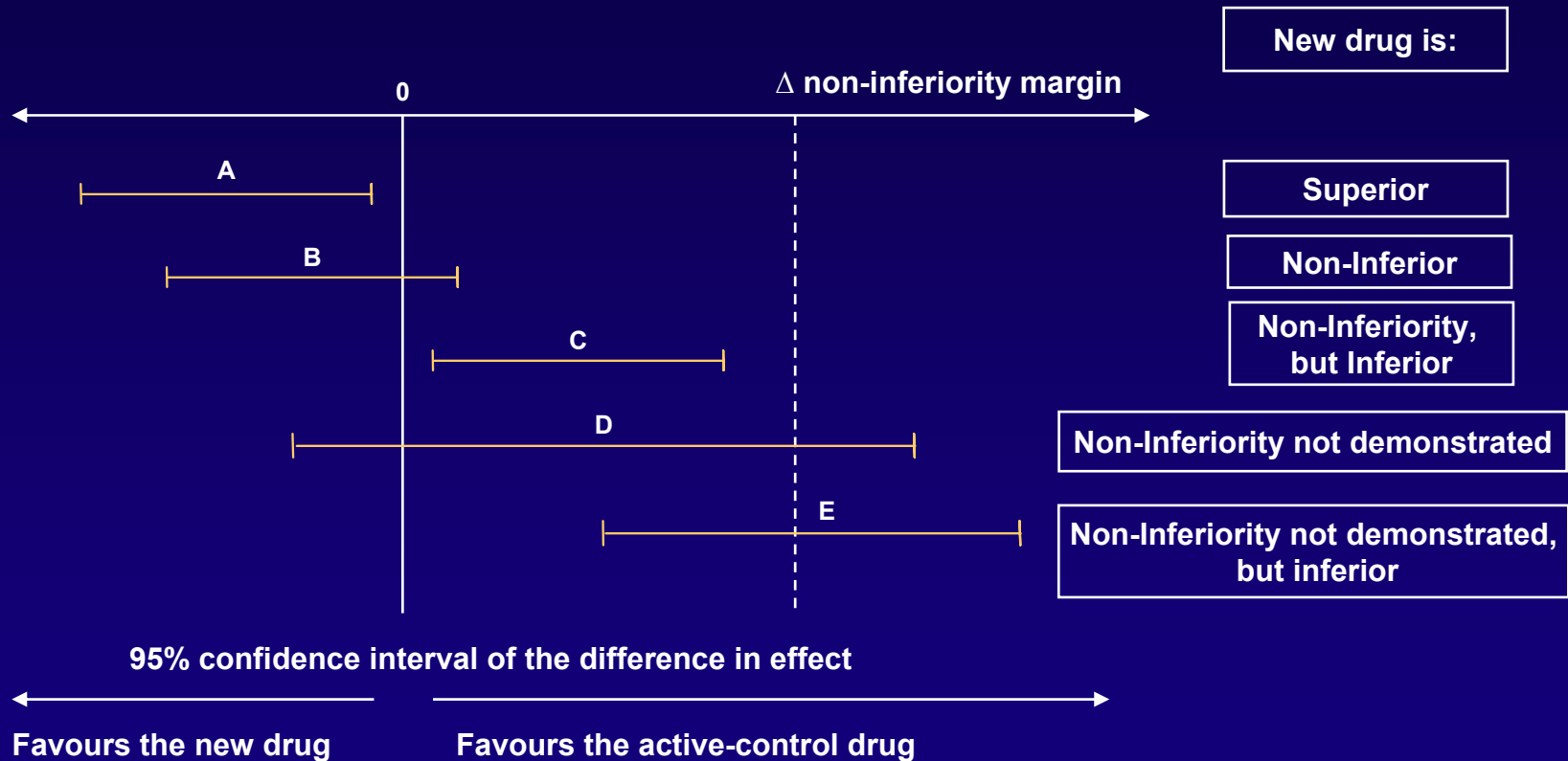
# Time to treatment failure



# Time to virological failure



# Range of Possible Outcomes for Non-inferiority Study Designs



# LAB Abnormalities

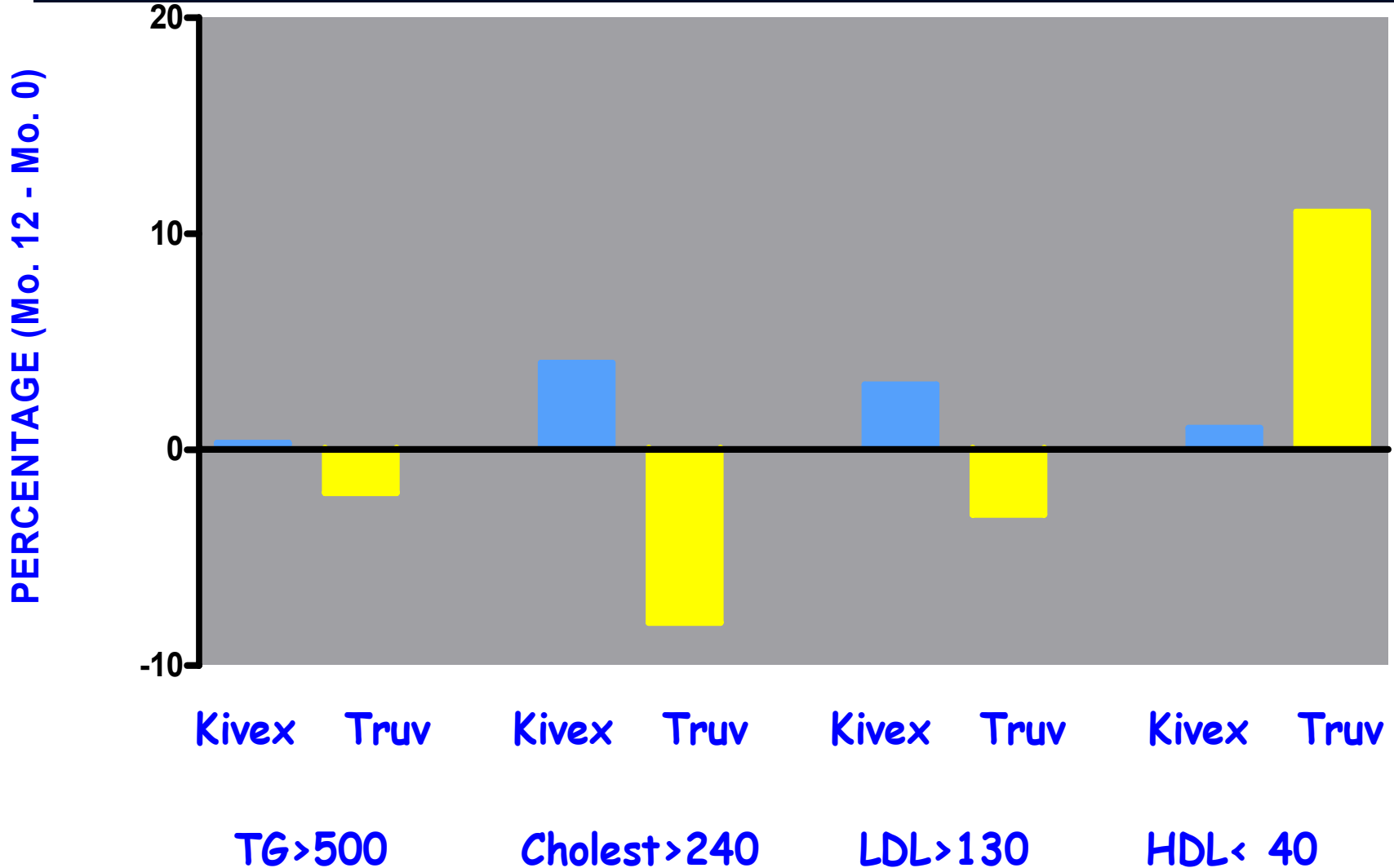
**Liver Function Abnormalities (ALT/AST > 200  
when ALT/AST were > 40 at baseline**

	<b>N (%)</b>	
	<b>KIVEXA N = 49</b>	<b>TRUVADA N = 62</b>
<b>ALT</b>	<b>1 (2 %)</b>	<b>0 (0%)</b>
<b>AST</b>	<b>1 (2%)</b>	<b>1 (2%)</b>
<b>ALT or AST</b>	<b>1 (2%)</b>	<b>1 (2%)</b>

# Lipid lowering agents

	N (%)	
	KIVEXA N = 167	TRUVADA N = 166
Baseline	11 (7)	18 (11)
At mo. 12	18 (11)	21 (13)

## PLASMA LIPIDS ABOVE/BELOW NCEP RECOMMENDATION FOR TREATMENT



## Planned sub-studies / subanalysis

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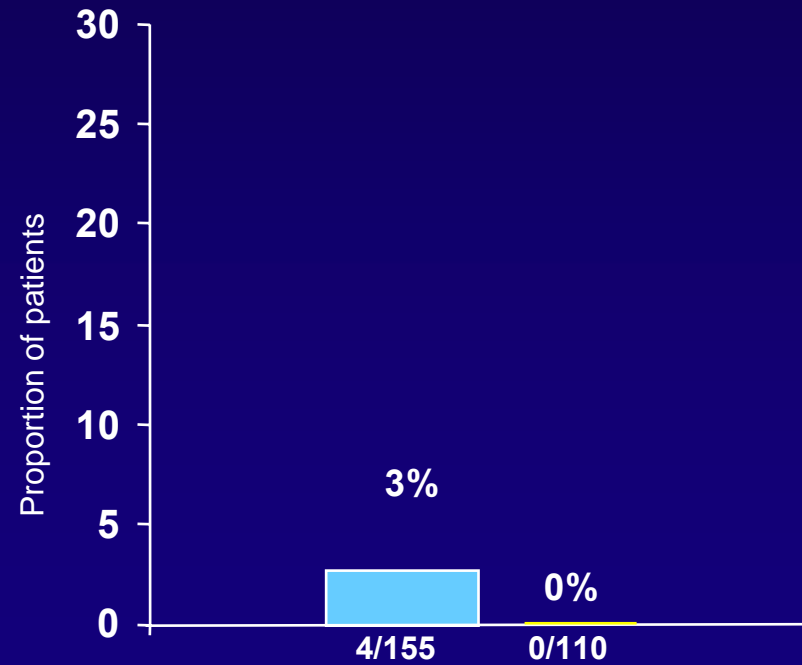
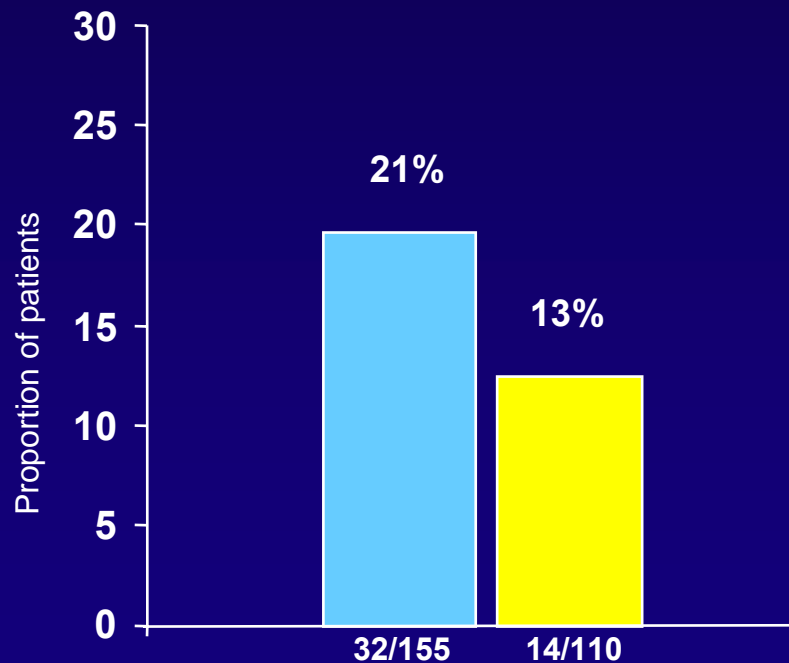
- **Metabicombo**
- **Mitochondrial toxicity**
- **Patients never exposed to abacavir (n=155) or tenofovir (n=110)**

# Treatment Failure and Virologic Failure ( $\geq 200$ c/mL) through Week 48 among patients never exposed to abacavir or tenofovir

## Treatment Failure

## Virologic Failure ( $\geq 200$ c/mL)

■ KIVEXA ■ TRUVADA



Difference Estimate (95% CI) 8% (-1.4%, 16.8%)

2.6% (-0.08%, 6%)