Efavirenz (**Sustiva**)

**Sustiva**  
[sus-TEE-vah]

Dose: 600 mg once daily on empty stomach, preferably at bedtime
INITIAL THERAPY

Efavirenz
### Efavirenz

#### Summary of Key Studies

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Efavirenz Summary of Key Studies

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<tr>
<th></th>
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<td>006: EFV + IDV, EFV + ZDV-3TV versus IDV + ZDV-3TC</td>
</tr>
<tr>
<td></td>
<td>ACTG 388: Efavirenz versus Nelfinavir, both with 3TC-ZVD + IDV</td>
</tr>
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<td><strong>Switch/Simplification Trials</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>ACTG 5116 (and 5125s): PI-sparing versus NRTI sparing regimens</td>
</tr>
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TREATMENT EXPERIENCED

Efavirenz
EFV versus ATV + RTV, both with ABC-3TC or TDF-FTC

ACTG 5202
EFV versus ATV/r, both with ABC-3TC or TDF-FTC

ACTG 5202: Study Design

Study Design: ACTG 5202

- **Background**: Randomized, phase 3b equivalence trial to evaluate open-label efavirenz against atazanavir + ritonavir, each with either double-blinded abacavir-lamivudine or tenofovir DF-emtricitabine, for initial treatment of HIV.

- **Inclusion Criteria** (n = 1857)
  - Age >16 years
  - Antiretroviral-naive
  - No major resistance mutations

- **Treatment Arms** (all medications once daily)
  - EFV 600 mg + ABC-3TC 600-300 mg
  - ATV 300 mg + RTV 100 mg + ABC-3TC 600-300 mg
  - EFV 600 mg + TDF-FTC 300-200 mg
  - ATV 300 mg + RTV 100 mg + TDF-FTC 300-200 mg

EFV versus ATV/r, both with ABC-3TC or TDF-FTC

ACTG 5202: Results

Week 48: Virologic Response

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Results

Week 96: Free of Virologic Failure

*Virologic failure = HIV RNA ≥1000 copies/mL between 16 and 24 weeks, or HIV RNA ≥200 copies/mL after 24 weeks.

EFV versus ATV/r, both with ABC-3TC or TDF-FTC

ACTG 5202: Results

Week 48: Analysis of Lipids

<table>
<thead>
<tr>
<th></th>
<th>EFV + ABC-3TC</th>
<th>ATV/r + ABC-3TC</th>
<th>EFV + TDF-FTC</th>
<th>ATV/r + TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>40 (mg/dL)</td>
<td>29 (mg/dL)</td>
<td>10 (mg/dL)</td>
<td>22 (mg/dL)</td>
</tr>
<tr>
<td>LDL</td>
<td>21 (mg/dL)</td>
<td>13 (mg/dL)</td>
<td>10 (mg/dL)</td>
<td>10 (mg/dL)</td>
</tr>
<tr>
<td>HDL</td>
<td>12 (mg/dL)</td>
<td>8 (mg/dL)</td>
<td>8 (mg/dL)</td>
<td>5 (mg/dL)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>15 (mg/dL)</td>
<td>13 (mg/dL)</td>
<td>14 (mg/dL)</td>
<td>14 (mg/dL)</td>
</tr>
</tbody>
</table>

EFV versus ATV/r, both with ABC-3TC or TDF-FTC
ACTG 5202: Results

Week 48: Change in Creatinine Clearance

Conclusion: “Atazanavir plus ritonavir and efavirenz have similar antiviral activity when used with abacavir-lamivudine or tenofovir DF-emtricitabine.”
Efavirenz 400 mg versus 600 mg, with TDF-FTC

ENCORE1 Trial
Efavirenz 400 mg versus Efavirenz 600 mg, with TDF-FTC

ENCORE1: Study Design

**Study Design: ENCORE1**

- **Background:** Randomized, double-blind, placebo-controlled study comparing the safety and efficacy of two doses of efavirenz, in combination with co-formulated tenofovir DF and emtricitabine

- **Inclusion Criteria (n = 636)**
  - Antiretroviral-naïve
  - Age ≥16 years
  - HIV RNA ≥1000 copies/mL
  - CD4 count >50 and <500 cells/mm³

- **Treatment Arms**
  - Efavirenz 400 mg QD + TDF-FTC QD
  - Efavirenz 600 mg QD + TDF-FTC QD

Efavirenz 400 mg versus Efavirenz 600 mg, with TDF-FTC
ENCORE1: Results

Week 48: Virologic Response (Modified Intention-to-Treat)

## Overall Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>EFV 400 mg n (%)</th>
<th>EFV 600 mg n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of adverse events</strong></td>
<td>1173 (49.8%)</td>
<td>1182 (50.2%)</td>
</tr>
<tr>
<td><strong>Serious adverse events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total number of serious adverse events</td>
<td>31 (46.2%)</td>
<td>36 (53.7%)</td>
</tr>
<tr>
<td>Number with serious adverse events</td>
<td>23 (7.17%)</td>
<td>22 (7.12%)</td>
</tr>
<tr>
<td>Number with serious adverse events related to study drug</td>
<td>3 (0.93%)</td>
<td>4 (1.29%)</td>
</tr>
<tr>
<td><strong>Adverse events probably related to study drug</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients with adverse events related to study drug</td>
<td>118 (36.8%)</td>
<td>146 (47.2%)</td>
</tr>
<tr>
<td>Patients stopping drug due to drug related adverse event</td>
<td>6 (1.9%)</td>
<td>18 (5.8%)</td>
</tr>
</tbody>
</table>

Interpretation: “Our findings suggest that a reduced dose of 400 mg efavirenz is non-inferior to the standard dose of 600 mg, when combined with tenofovir and emtricitabine during 48 weeks in ART-naive adults with HIV-1 infection. Adverse events related to the study drug were more frequent with 600 mg efavirenz than with 400 mg. Lower dose efavirenz should be recommended as part of routine care.”
Triple NRTIs versus Efavirenz + 2-3 NRTIs

ACTG 5095 Trial
**Triple NRTIs versus Efavirenz + 2-3 NRTIs**

**ACTG 5095: Study Design**

### Study Design: ACTG 5095

- **Background**: Randomized, double-blind, placebo-controlled, phase 3 trial comparing 3 protease inhibitor-sparing antiretroviral therapy regimens in antiretroviral-naïve patients.

- **Inclusion Criteria** (n = 1147)
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA ≥400 copies/mL

- **Treatment Arms**
  - Triple NRTI: ABC-3TC-ZDV
  - Combined Efavirenz: ZDV-3TC + Efavirenz*
  - Combined Efavirenz: ABC-3TC-ZDV+ Efavirenz*

*Efavirenz arms combined for analysis

---

Triple NRTIs versus Efavirenz + 2-3 NRTIs
ACTG 5095: Results

Week 48: Virologic Failure

*Virologic failure = two successive HIV-1 RNA values ≥200 copies/mL ≥16 weeks after randomization

Triple NRTIs versus Efavirenz + 2-3 NRTIs

ACTG 5095: Results

Week 48: Virologic Response

![Bar chart showing virologic response at Week 48 compared to Triple NRTI Group and Combined EFV Groups.]

- **Triple NRTI Group**:
  - <200 copies/mL: 74%
  - <50 copies/mL: 61%

- **Combined EFV Groups**:
  - <200 copies/mL: 89%
  - <50 copies/mL: 83%

Conclusions: “In this trial of the initial treatment of HIV-1 infection, the triple-nucleoside combination of abacavir, zidovudine, and lamivudine was virologically inferior to a regimen containing efavirenz and two or three nucleosides.”

Class-Sparing Regimens for Initial Treatment of HIV

ACTG 5142
EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV

Study Design: ACTG 5142

- **Background**: Randomized, phase 3 trial comparing the efficacy, safety, and tolerability of 3 different class-sparing ARV regimens in antiretroviral naïve adults and adolescents with HIV.

- **Inclusion Criteria (n = 753)**
  - Age ≥13 years
  - Antiretroviral naïve
  - HIV RNA ≥2,000 copies/mL
  - No CD4 restrictions

- **Treatment Arms**
  - EFV 600 mg QD + 2 NRTIs
  - LPV/r 400/100 mg BID + 2 NRTIs
  - LPV/r 533/133 mg BID + EFV 600 mg QD

- **Plasma Viral-Integrase Inhibitor** (PI)-Sparing Group
  - Efavirenz + 2 NRTIs
  - (n = 250)

- **Non-nucleoside Reverse Transcriptase Inhibitor** (NNRTI)-Sparing Group
  - Lopinavir-ritonavir + 2 NRTIs
  - (n = 253)

- **Nucleoside Reverse Transcriptase Inhibitor** (NRTI)-sparing Group
  - Lopinavir-ritonavir + Efavirenz
  - (n = 250)

EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV

ACTG 5142: Results

Virologic or Regimen Failure

Virologic failure = lack of suppression of plasma HIV-1 RNA by 1 log10 or rebound before week 32 or a lack of suppression to <200 copies/mL or rebound after week 32.

Regimen failure = first of either virologic failure or toxicity-related discontinuation

## EFV + NRTIs versus LPV/r + NRTIs versus LPV/r + EFV

### ACTG 5142: Results

### Summary of Resistance Mutations at Time of Virologic Failure*

<table>
<thead>
<tr>
<th>Variable</th>
<th>EFV + 2 NRTIs (%)</th>
<th>LPV/r + 2NRTIs (%)</th>
<th>LPV/r + EFV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure events</td>
<td>24</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Any mutation</td>
<td>48</td>
<td>21</td>
<td>70</td>
</tr>
<tr>
<td>NRTI-associated mutation</td>
<td>30</td>
<td>19</td>
<td>11</td>
</tr>
<tr>
<td>M184V</td>
<td>17</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>K65R</td>
<td>7</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>NNRTI-associated mutation</td>
<td>43</td>
<td>3</td>
<td>66</td>
</tr>
<tr>
<td>K103N</td>
<td>24</td>
<td>0</td>
<td>55</td>
</tr>
<tr>
<td>Any protease mutation</td>
<td>85</td>
<td>78</td>
<td>80</td>
</tr>
<tr>
<td>Major protease mutation</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>Mutation associated with 2 classes</td>
<td>26</td>
<td>1</td>
<td>7</td>
</tr>
</tbody>
</table>

*Percentages of patients with mutations were calculated for those who had an available genotype at the time of virologic failure.

Conclusions: “Virologic failure was less likely in the efavirenz group than in the lopinavir-ritonavir group. The virologic efficacy of the NRTI-sparing regimen was similar to that of the efavirenz regimen but was more likely to be associated with drug resistance.”
EFV + TDF + FTC versus EFV + ZDV-3TC

Study 934
Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC

Study 934: Study Design

**Study Design: STUDY 934**

- **Background**: Randomized, open label phase 3 study comparing efavirenz plus either tenofovir DF and emtricitabine or fixed-dose zidovudine-lamivudine

- **Inclusion Criteria** (n = 509)
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥10,000 copies/mL
  - CD4 >50 cells/mm³
  - No AIDS conditions in prior 30 days

- **Treatment Arms**
  - Efavirenz + tenofovir DF + emtricitabine
  - Efavirenz + zidovudine-lamivudine

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC

Study 934: Result

Week 48: Virologic Response (< 400 copies/mL)

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC

Study 934: Result

Week 48: Virologic Response (<50 copies/mL)

ITT = Intention-to-Treat; NNRTI-R = Patients with baseline NNRTI mutations.

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC

Study 934: Result

Week 48: Immunologic Response

Efavirenz + TDF + FTC + versus Efavirenz + ZDV-3TC

Study 934: Result

Adverse Events through 48 Weeks

### Treatment Emergent Adverse Events in ≥ 5% of Subjects in Either Arm

<table>
<thead>
<tr>
<th></th>
<th>EFV + TDF + FTC (n = 257)</th>
<th>EFV + ZVD-3TC (n = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>8%</td>
<td>6%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>7%</td>
<td>4%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Depression</td>
<td>4%</td>
<td>7%</td>
</tr>
<tr>
<td>Headache</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Rash</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Anemia</td>
<td>&lt;1%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Interpretation: “Through week 48, the combination of tenofovir DF and emtricitabine plus efavirenz fulfilled the criteria for noninferiority to a fixed dose of zidovudine and lamivudine plus efavirenz and proved superior in terms of virologic suppression, CD4 response, and adverse events resulting in discontinuation of the study drugs.”

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO Trial
Study Design: ECHO Study

- **Background**: Randomized, double-blind, phase 3 trial comparing rilpivirine and efavirenz in combination with a fixed background regimen consisting of tenofovir DF-emtricitabine in treatment-naïve adults with HIV.

- **Inclusion Criteria (n = 690)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥5000 copies/mL
  - No resistance to any study drugs

- **Treatment Arms**
  - Rilpivirine + Tenofovir DF-Emtricitabine
  - Efavirenz + Tenofovir DF-Emtricitabine

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Result

48 Week Virologic Response (ITT-TLOVR)

HIV RNA <50 copies/mL (%)

<table>
<thead>
<tr>
<th>Baseline HIV RNA (copies/mL)</th>
<th>Rilpivirine + TDF-FTC</th>
<th>Efavirenz + TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>83/346</td>
<td>83/344</td>
</tr>
<tr>
<td>≤100,000</td>
<td>90/181</td>
<td>83/163</td>
</tr>
<tr>
<td>100,000-500,000</td>
<td>79/131</td>
<td>83/134</td>
</tr>
<tr>
<td>&gt;500,000</td>
<td>62/34</td>
<td>81/47</td>
</tr>
</tbody>
</table>

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Result

48 Week Virologic Failure and Discontinuations (ITT-TLOVR)

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Resistance Results

Incidence of NNRTI Resistance Associated Mutations (RAMs)

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
ECHO: Conclusions

**Interpretation**: “Rilpivirine showed non-inferior efficacy compared with efavirenz, with a higher virological-failure rate, but a more favourable safety and tolerability profile.”

Rilpivirine versus Efavirenz, with 2 NRTIs

THRIVE Study
Rilpivirine versus Efavirenz, with 2 NRTIs

THRIVE: Study Design

**Study Design: THRIVE**

- **Background**: Randomized, double-blind, phase 3 trial comparing rilpivirine and efavirenz in combination with two nucleoside reverse transcriptase inhibitors in treatment-naïve adults with HIV

- **Inclusion Criteria (n = 680)**
  - Antiretroviral-naïve
  - Age ≥18 years
  - HIV RNA ≥5000 copies/mL
  - No resistance to any study drugs

- **Treatment Arms**
  - Rilpivirine + 2 NRTIs*
  - Efavirenz + 2 NRTIs*

*Investigator-selected 2 NRTIs:
Tenofovir DF plus emtricitabine; zidovudine plus lamivudine; or abacavir plus lamivudine

Rilpivirine versus Efavirenz, with two background NRTIs

THRVIE: Result

48 Week Virologic Response (ITT-TLOVR)

Rilpivirine versus Efavirenz, with two background NRTIs

THRVIE: Result

48 Week Virologic Failure and Discontinuations

**Virologic Failure**
- Rilpivirine + 2 NRTIs: 27/340 (8%)
- Efavirenz + 2 NRTIs: 20/338 (6%)

**Discontinuation due to Adverse Event or Death**
- Rilpivirine + 2 NRTIs: 9/340 (3%)
- Efavirenz + 2 NRTIs: 24/338 (7%)

*Virologic failure includes those without emerging mutation at failure

Rilpivirine versus Efavirenz, with two background NRTIs
THRIIVE: Resistance Results

Incidence of NNRTI Resistance Associated Mutations (RAMs)

## Rilpivirine versus Efavirenz, with two background NRTIs

**THRIVE: Result**

### Resistance Associated Mutations (RAMs)

<table>
<thead>
<tr>
<th></th>
<th>Rilpivirine (n = 340)</th>
<th>Efavirenz (n = 338)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic Failure with Resistance Data</td>
<td>27 (8%)</td>
<td>20 (6%)</td>
</tr>
<tr>
<td>Emergent NNRTI RAMs</td>
<td>59%</td>
<td>47%</td>
</tr>
<tr>
<td>Most Frequent NNRTI RAMs</td>
<td>E138K</td>
<td>K103N</td>
</tr>
<tr>
<td>Emergent NRTI RAMs</td>
<td>64%</td>
<td>33%</td>
</tr>
<tr>
<td>Most Frequent NRTI RAMs</td>
<td>M184I/V</td>
<td>M184V</td>
</tr>
</tbody>
</table>

Interpretation: “Despite a slightly increased incidence of virological failures, a favourable safety profile and non-inferior efficacy compared with efavirenz means that rilpivirine could be a new treatment option for treatment-naive patients infected with HIV-1.”
Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC

LAKE Trial
Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC

LAKE: Study Design

**Study Design: LAKE**

- **Background**: Randomized study to compare the long-term efficacy and safety of efavirenz and lopinavir-ritonavir, each in combination with co-formulated abacavir-lamivudine, in antiretroviral-naïve adults with HIV

- **Inclusion Criteria (n = 126)**
  - Age ≥18 years
  - Antiretroviral-naïve
  - No recent opportunistic infection
  - No CD4 count or HIV RNA restrictions
  - HLA*B5701 testing not available at time of study

- **Treatment Arms**
  - Efavirenz 600 mg QD + ABC-3TC QD
  - Lopinavir-RTV 400/100 mg BID + ABC-3TC QD

---

**Efavirenz + ABC-3TC**

(\(n = 321\))

**Lopinavir/r + ABC-3TC**

(\(n = 309\))

Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC
LAKE: Results

Week 48: Virologic Response

![Bar chart showing virologic response at Week 48 for Efavirenz + ABC-3TC and Lopinavir-Ritonavir + ABC-3TC.]

On-treatment analysis:
- Efavirenz + ABC-3TC: 87%
- Lopinavir-Ritonavir + ABC-3TC: 91%

Intention-to-treat analysis (M=F):
- Efavirenz + ABC-3TC: 57%
- Lopinavir-Ritonavir + ABC-3TC: 63%

Efavirenz versus Lopinavir-Ritonavir, with ABC-3TC

LAKE: Results

Week 48: Virologic Response, by Baseline CD4 count (OT analysis)

**Conclusions**: “Similar virological efficacy was observed for efavirenz and lopinavir/r, when administered with abacavir-lamivudine in antiretroviral-naïve patients, while immunological improvement was slightly superior for efavirenz. The higher rate of discontinuation due to toxicity in the efavirenz group was related to a higher incidence of hypersensitivity reaction. Nowadays, the use of the new formulation of lopinavir/r and the HLA-B*5701 genotype test before starting abacavir should improve the safety profiles of these regimens.”
Fosamprenavir + ritonavir versus Efavirenz, with ABC-3TC

SUPPORT Trial
FPV/r versus EFV, both with ABC-3TC

**SUPPORT: Study Design**

<table>
<thead>
<tr>
<th>Study Design: SUPPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background:</strong> Randomized, open-label pilot study comparing ritonavir-boosted fosamprenavir versus efavirenz, both in combination with abacavir-lamivudine, in minority adults with HIV</td>
</tr>
<tr>
<td><strong>Inclusion Criteria (n = 101)</strong></td>
</tr>
<tr>
<td>- Age ≥18 years</td>
</tr>
<tr>
<td>- Antiretroviral-naïve</td>
</tr>
<tr>
<td>- HIV RNA &gt; 5000 copies/mL</td>
</tr>
<tr>
<td>- HLA-B*5701 negative</td>
</tr>
<tr>
<td>- Minority race or ethnicity</td>
</tr>
<tr>
<td><strong>Treatment Arms</strong> (all medications once daily)</td>
</tr>
<tr>
<td>- Fosamprenavir 1400 mg + Ritonavir 100 mg + Abacavir-lamivudine 600-300 mg</td>
</tr>
<tr>
<td>- Efavirenz 600 mg + ABC-3TC 600-300 mg</td>
</tr>
</tbody>
</table>

FPV/r versus EFV, both with ABC-3TC

SUPPORT: Results

Week 96: Virologic Response (Intention-to-treat, Missing=Failure)

![Graph showing virologic response at week 96 for FPV/r and EFV with ABC-3TC.]

FPV/r versus EFV, both with ABC-3TC
SUPPORT: Results

Week 96: Analysis of Lipids

FPV/r versus EFV, both with ABC-3TC

SUPPORT: Results

Week 96: Analysis of Cardiovascular Biomarkers

Change from Baseline (%)

FPV/r + ABC-3TC
EFV + ABC-3TC

Conclusions: “In this study of underrepresented patients, treatment with abacavir/lamivudine combined with either fosamprenavir/ritonavir or efavirenz over 96 weeks, produced stable or declining biomarker levels except for hs-CRP, including significant and favorable decreases in thrombotic activity (reflected by d-dimer) and endothelial activation (reflected by sVCAM-1). Our study adds to the emerging data that some cardiovascular biomarkers are decreased with initiation of ART and control of HIV viremia.”

TREATMENT EXPERIENCED

Efavirenz
EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC

006 Trial
Study Design: 006

**Background**: Open-label, randomized, phase 3 trial evaluating safety, efficacy and tolerability of efavirenz plus zidovudine plus lamivudine versus efavirenz plus indinavir versus indinavir plus zidovudine plus lamivudine in persons with HIV.

**Inclusion Criteria** (n = 450)
- Age ≥13 years
- Naïve to lamivudine, NNRTIs, PIs
- CD4 >50 cells/mm³
- HIV RNA >10,000 copies/mL
- No resistance to NRTIs or PIs

**Treatment Arms**
- EFV 600 mg QD + ZDV BID + 3TC BID
- EFV 600 mg QD + IDV 1000 mg q8h
- IDV 1000 mg q8h + ZDV BID + 3TC BID

EFV + ZDV + 3TC vs. EFV + IDV vs. IDV + ZDV + 3TC

006: Results

Week 48: Virologic Response (Intention-to-Treat Analysis)

### 006: Results

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>EFV + ZDV + 3TC</th>
<th>EFV + IND</th>
<th>IDV + ZDV + 3TC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash</td>
<td>34%</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>CNS Effects</td>
<td>58%</td>
<td>53%</td>
<td>26%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15% (combined EFV groups)</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>8% (combined EFV groups)</td>
<td>15%</td>
<td></td>
</tr>
<tr>
<td>Treatment Discontinuation</td>
<td>27%</td>
<td>Not reported</td>
<td>43%</td>
</tr>
</tbody>
</table>

Conclusions: “As antiretroviral therapy in HIV-1-infected adults, the combination of efavirenz, zidovudine, and lamivudine has greater antiviral activity and is better tolerated than the combination of indinavir, zidovudine, and lamivudine.”

4-Drug Regimens versus 3-Drug Regimen

ACTG 388 Trial
## Study Design: ACTG 388

### Background
Randomized, controlled, phase 3 trial comparing the activity, safety, and tolerability of two different 4-drug regimens with a 3-drug regimen in advanced HIV disease.

### Inclusion Criteria (n = 517)
- Prior ART: only ZDV, d4T, DDI, ddC
- CD4 ≤200 cells/mm³
- HIV RNA ≥80,000 copies/mL
- No resistance to NRTIs or PIs

### Treatment Arms
- **IDV 800 mg TID + ZDV-3TC BID**
- **EFV 600 mg QD + IDV 800 mg TID + ZDV-3TC BID**
- **NFV 1250 mg BID + IDV 1000 mg BID + ZDV-3TC BID**

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**Indinavir Group**
- **Indinavir + Zidovudine-Lamivudine**
  - (n = 168)

**Efavirenz + Indinavir Group**
- **Efavirenz + Indinavir + Zidovudine-Lamivudine**
  - (n = 173)

**Nelfinavir + Indinavir Group**
- **Nelfinavir + Indinavir + Zidovudine-Lamivudine**
  - (n = 176)

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4-Drug Regimens versus 3-Drug Regimen
ACTG 388: Results

Week 48: Virologic Failure

<table>
<thead>
<tr>
<th>Group</th>
<th>Patients (%) with Virologic Failure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDV Group</td>
<td>31/168</td>
</tr>
<tr>
<td>EFV + IDV Group</td>
<td>23/173</td>
</tr>
<tr>
<td>NFV + IDV Group</td>
<td>46/176</td>
</tr>
</tbody>
</table>

*Virologic failure = confirmed increase in HIV-1 RNA level greater than baseline or nadir values, failure to achieve HIV RNA <200 copies by week 24, or relapse (2 consecutive HIV-1 RNA levels ≥200 copies/mL after confirmed virologic response (HIV-1 RNA levels <200 copies/mL).

### Clinical Toxicity and Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Variable</th>
<th>IDV only (n = 168)</th>
<th>EFV + IDV (n = 168)</th>
<th>NVF + IDV (n = 168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea (+/- vomiting)</td>
<td>15</td>
<td>7</td>
<td>19</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4</td>
<td>3</td>
<td>16</td>
</tr>
<tr>
<td>Rash</td>
<td>2</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Nephrolithiasis</td>
<td>22</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Serum bilirubin &gt;2.5x ULN</td>
<td>16</td>
<td>0</td>
<td>8</td>
</tr>
<tr>
<td>ANC &lt;750 cells/mm³</td>
<td>8</td>
<td>12</td>
<td>21</td>
</tr>
<tr>
<td>AST &gt;5x ULN</td>
<td>6</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Serum triglycerides &gt;750 mg/dL</td>
<td>7</td>
<td>12</td>
<td>8</td>
</tr>
</tbody>
</table>

Conclusions: “A 4-drug regimen containing efavirenz plus indinavir resulted in a superior virologic response, whereas one containing nelfinavir plus indinavir resulted in an inferior response and a greater likelihood of toxicity.”
NRTI-sparing Regimens following Viral Suppression
ACTG 5116: Study Design

Study Design: ACTG 5116

• **Background**: Randomized, open-label trial to compare NRTI-sparing regimen of lopinavir-ritonavir plus efavirenz versus efavirenz plus 2 NRTIs

• **Inclusion Criteria (n= 236)**
  - Prior ACTG 388 participants: HIV RNA ≤200 copies/mL on a first 3- or 4-drug ARV regimen
  - Non-ACTG 388 participants: stable first 3- or 4-drug NNRTI or PI-based regimen for ≥18 months without viral failure or resistance and HIV RNA ≤200 copies/mL

• **Treatment Arms**
  - Lopinavir-ritonavir 533/133 mg BID + Efavirenz 600 mg QD
  - Efavirenz 600 mg QD + 2 NRTIs

NRTI-Sparing Regimens following Viral Suppression
ACTG 5116: Results

Week 48: Virologic Failure and Treatment-Related Discontinuations

Virologic failure = two successive HIV-1 RNA values > 200 copies/mL

Class-sparing Regimens following Viral Suppression
ACTG 5116: Results

Week 48: Virologic Response (Intent-to-Treat)

![Graph showing virologic response at Week 48 for two treatment regimens. The graph compares Lopinavir-ritonavir + Efavirenz versus Efavirenz + 2 NRTIs.]

**Conclusions**: “Switching to EFV + NRTI resulted in better outcomes, fewer drug-related toxicity discontinuations and a trend to fewer virologic failures compared to switching to LPV/r + EFV.”

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