Etravirine (*Intelence*)

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Etravirine (*Intelence*)

**Intelence**
[in-tel-ence]

Dose: 200 mg twice daily following a meal
Etravirine (*Intelence*)

- **Class**  
  - non-nucleoside reverse transcriptase inhibitor

- **Approval**  
  - FDA-approved January 22, 2008

- **Indication**  
  - Combined with other ARVs for treatment-experienced adults

- **FDA-Approved Dose**  
  - 200 mg twice daily following a meal

- **Metabolism**  
  - Primarily in liver via cytochrome P450 enzymes

- **Adverse Events**  
  - Nausea, rash, peripheral neuropathy
### Etravirine Summary of Key Studies

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## Etravirine

### Summary of Key Studies

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<td>SSAT-029</td>
<td>Switch from Efavirenz to Etravirine</td>
</tr>
</tbody>
</table>
INITIAL THERAPY

Etravirine
Once Daily Etravirine versus Efavirenz in Treatment-Naive
SENSE Trial
Once Daily Etravirine *versus* Efavirenz in Treatment-Naive
SENSE: Study Design

### Study Design: SENSE Study

- **Background**: Randomized, controlled, double-blind, phase 2 trial evaluating efficacy of once-daily etravirine compared with efavirenz in treatment-naïve persons with HIV

- **Inclusion Criteria (n = 157)**
  - Age ≥18 years
  - Antiretroviral-naïve
  - HIV RNA >5000 copies/mL
  - No resistance to study drugs

- **Treatment Arms**
  - ETR 400 mg daily + 2NRTIs*
  - Efavirenz 600 mg daily + 2NRTIs*

* NRTIs = tenofovir DF-emtricitabine, abacavir, lamivudine, or zidovudine-lamivudine

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**Etravirine 400 mg once daily + 2 NRTIs**  
(n = 79)

**Efavirenz 600 mg once daily + 2 NRTIs**  
(n = 78)

SENSE = Study of Efavirenz Neuropsychiatric events versus Etravirine

Once Daily Etravirine *versus* Efavirenz

SENSE: Results

Week 48: Virologic Response (ITT-TLOVR*)

<table>
<thead>
<tr>
<th>Baseline HIV RNA Level</th>
<th>Etravirine Arm</th>
<th>Efavirenz Arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>60/79</td>
<td>58/78</td>
</tr>
<tr>
<td>≤100,000 copies/mL</td>
<td>40/52</td>
<td>40/51</td>
</tr>
<tr>
<td>&gt;100,000 copies/mL</td>
<td>20/27</td>
<td>18/27</td>
</tr>
</tbody>
</table>

HIV RNA <50 copies/mL (%)

76 74
77 78
74 67

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response

Once Daily Etravirine *versus* Efavirenz

**SENSE: Result**

<table>
<thead>
<tr>
<th>Grade 1-4 Neuropsychiatric Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Efavirenz Arm</strong></td>
</tr>
<tr>
<td>Prevalence (%)</td>
</tr>
<tr>
<td>0 Week of Study:</td>
</tr>
<tr>
<td>4 Week of Study:</td>
</tr>
<tr>
<td>8 Week of Study:</td>
</tr>
<tr>
<td>12 Week of Study:</td>
</tr>
<tr>
<td>16 Week of Study:</td>
</tr>
<tr>
<td>20 Week of Study:</td>
</tr>
<tr>
<td>24 Week of Study:</td>
</tr>
<tr>
<td>28 Week of Study:</td>
</tr>
<tr>
<td>32 Week of Study:</td>
</tr>
<tr>
<td>36 Week of Study:</td>
</tr>
<tr>
<td>40 Week of Study:</td>
</tr>
<tr>
<td>44 Week of Study:</td>
</tr>
<tr>
<td>48 Week of Study:</td>
</tr>
<tr>
<td>52 Week of Study:</td>
</tr>
</tbody>
</table>

Conclusion: “First-line treatment with etravirine 400mg once daily and two nucleoside reverse transcriptase inhibitors (NRTIs) led to similar rates of HIV RNA suppression, compared with efavirenz and two NRTIs. None of the patients with virological failure in the etravirine arm developed resistance to nonnucleosides.”

Once Daily Etravirine in Treatment-Naïve Adults

08-2070 Trial
### Once Daily Etravirine in Treatment-Naïve Adults 08-2070: Design

#### Study Design: 08-2070

- **Background**: Phase 2, single-arm trial assessing activity, safety, and tolerability of once-daily etravirine with tenofovir DF-emtricitabine in treatment-naïve adults with HIV

- **Inclusion Criteria** (n = 79)
  - Age ≥18 years
  - HIV RNA >1000 copies/mL
  - Treatment-naïve
  - No resistance to etravirine or TDF-FTC

- **Treatment Arms**
  - Etravirine 400 mg QD + tenofovir-emtricitabine QD

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>Etravirine QD + Tenofovir-emtricitabine QD (n = 79)

*ITT: Intent-to-Treat, M=F: missing equals failure

Once Daily Etravirine in Treatment-Naïve Adults
08-2070: Result

Week 48: Virologic Response (all patients taking ETR + TDF-FTC)

HIV RNA <50 copies/mL (%)

<table>
<thead>
<tr>
<th>HIV RNA Threshold</th>
<th>ITT, M=F*</th>
<th>As Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 copies/mL</td>
<td>61/79</td>
<td>61/69</td>
</tr>
<tr>
<td>&lt; 200 copies/mL</td>
<td>65/79</td>
<td>65/69</td>
</tr>
</tbody>
</table>

*ITT: Intent-to-Treat, M=F: missing equals failure

Once Daily Etravirine in Treatment-Naïve Adults
08-2070: Result

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rash (any grade)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Any grade 2 or higher event</td>
<td>18 (22.8)</td>
</tr>
<tr>
<td>New/worsened grade 3 or 4 sign/symptom</td>
<td>10 (12.7)</td>
</tr>
<tr>
<td>AST or ALT elevation (Grade 2 or higher)</td>
<td>5 (6.3)</td>
</tr>
<tr>
<td>Grade 2 creatinine elevation</td>
<td>2 (2.5)</td>
</tr>
<tr>
<td>New/worsened grade 3 or 4 laboratory abnormality</td>
<td>6 (7.6)</td>
</tr>
<tr>
<td>Etravirine discontinued due to toxicity</td>
<td>3 (3.8)</td>
</tr>
</tbody>
</table>

Conclusions: “In this study of ARV-naive HIV-positive adults, once-daily ETR with TDF/FTC had acceptable antiviral activity and was well-tolerated. Once-daily ETR may be a plausible option as part of a combination ARV regimen for treatment-naive individuals.”
TREATMENT EXPERIENCED

Etravirine
Etravirine in Treatment Experienced
DUET-1 (TMC125-C206)
Study Design: DUET-1

• **Background**: Randomized, controlled, double-blind, placebo-controlled phase 3 trial evaluating the long-term efficacy, tolerability, and safety of etravirine in treatment-experienced adults with HIV.

• **Inclusion Criteria** (n = 612)
  - Age ≥18 years
  - On stable ARV regimen for ≥8 weeks
  - HIV RNA >5000 copies/mL
  - ≥3 primary PI mutations
  - ≥1 NNRTI resistance-associated mutation

• **Treatment Arms**
  - Etravirine 200 mg BID + OBT*
  - Placebo + OBT*

*OBT = NRTIs, Darunavir/r, +/- Enfuvirtide

Week 24: Virologic Response (ITT-TLOVR*)

<table>
<thead>
<tr>
<th>HIV RNA &lt;400 copies/mL</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine + OBT</td>
<td>74/304</td>
</tr>
<tr>
<td>Placebo + OBT</td>
<td>51/308</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HIV RNA &lt;50 copies/mL</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine + OBT</td>
<td>56/304</td>
</tr>
<tr>
<td>Placebo + OBT</td>
<td>39/308</td>
</tr>
</tbody>
</table>

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Etravirine in Treatment Experienced
DUET-2: Results

Week 24: Virologic Response (ITT-TLOVR*)

HIV RNA <50 copies/mL (%)

<table>
<thead>
<tr>
<th>Number of Active Background Antiretrovirals</th>
<th>Etravirine + OBT</th>
<th>Placebo + OBT</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>21/45</td>
<td>4/46</td>
</tr>
<tr>
<td>1</td>
<td>62/105</td>
<td>23/95</td>
</tr>
<tr>
<td>2</td>
<td>68</td>
<td>57/93</td>
</tr>
<tr>
<td>≥3</td>
<td>66</td>
<td>65</td>
</tr>
</tbody>
</table>

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Etravirine in Treatment Experienced
DUET-1: Results

Week 24: Virologic Response (ITT-TLOVR*)

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Etravirine in Treatment Experienced DUET-1: Results

Week 24: Virologic Response (ITT-TLOVR*)

**Interpretation**: “In treatment-experienced patients with NNRTI resistance, treatment with TMC125 (etravirine) achieved better virological suppression at week 24 than did placebo. The safety and tolerability profile of TMC125 (etravirine) was generally comparable with placebo.”

Etravirine in Treatment Experienced

DUET-2 (TMC125-C216)
Etravirine in Treatment Experienced
DUET-2: Study Design

Etravirine in Treatment Experienced DUET-2: Results

Week 24: Virologic Response (ITT-TLOVR*)

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Etravirine in Treatment Experienced DUET-2: Results

Week 24: Virologic Response (ITT-TLOVR*)

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Week 24: Virologic Response (ITT-TLOVR*) in Patients Re-using or Not Using Enfuvirtide

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Interpretation: “In treatment-experienced patients, treatment with TMC125 (etravirine) led to better virological suppression at week 24 than did placebo. The safety and tolerability profile of TMC125 (etravirine) was generally comparable with placebo.”
Etravirine in Treatment Experienced
DUET-1 and DUET-2 (Pooled Analysis)
Etravirine in Treatment Experienced
DUET-1 and DUET-2 Pooled Analysis: Study Design

**Study Design: DUET-1 and DUET-2**

- **Background**: Pooled analysis of 2 randomized, controlled, double-blind, placebo-controlled phase 3 trial evaluating the long-term efficacy, tolerability, and safety of etravirine in treatment-experienced adults with HIV.

- **Inclusion Criteria (n = 1203)**
  - Age ≥18 years
  - On stable ARV regimen for ≥8 weeks
  - HIV RNA >5000 copies/mL
  - ≥3 primary PI mutations and ≥1 NNRTI resistance-associated mutation

- **Treatment Arms**
  - Etravirine 200 mg BID + OBT*
  - Placebo + OBT*

*OBT = NRTIs, Darunavir/r, +/- Enfuvirtide

Etravirine in Treatment Experienced DUET-1 and DUET-2 Pooled Analysis: Results

Week 48: Virologic Response (ITT-TLOVR*)

![Graph showing virologic response at Week 48](image)

- **Etravirine + OBT**: 61 out of 365/599 (16.7%) achieved HIV RNA <50 copies/mL
- **Placebo + OBT**: 40 out of 242/604 (13.2%) achieved HIV RNA <50 copies/mL

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.*

**Source:** Katlama C, et al. AIDS. 2009;23:2289-300.
Etravirine in Treatment Experienced DUET-1 and DUET-2 Pooled Analysis: Results

Week 48: Virologic Response (ITT-TLOVR*), by Number of Active ARVs

*ITT-TLOVR = Intention to Treat-Time to Loss of Virologic Response.

Etravirine in Treatment Experienced DUET-1 and DUET-2: Pooled Analysis

Week 48: Virologic Response in Etravirine Group, by Weighted Genotypic Score

**Conclusion**: “At 48 weeks, treatment-experienced patients receiving etravirine plus background regimen had statistically superior and durable virologic responses (viral load less than 50 copies/ml) than those receiving placebo plus background regimen, with comparable tolerability and no new safety signals reported since week 24.”
ETV+ DRV/r + RAL in Treatment-Experienced Patients

TRIO Trial
Etravirine + Darunavir/r + Raltegravir
TRIO: Study Design

**Study Design: TRIO**

- **Background**: Phase 2, non-comparative trial assessing safety and efficacy of an antiretroviral regimen containing etravirine, darunavir boosted with ritonavir, and raltegravir in adults with HIV and multidrug-resistant virus
- **Inclusion Criteria (n = 103)**
  - Age ≥18 years
  - On stable ARV regimen for ≥8 weeks
  - HIV RNA >1000 copies/ml
  - Mutations allowed: ≥3 PI, ≥3 NRTI, ≤3 NNRTI
  - Naïve to etravirine, darunavir, and raltegravir
- **Treatment Arms**
  - Etravirine 200 mg bid + Darunavir 600 mg BID + Ritonavir 100mg bid + Raltegravir 400 mg bid + optimized background regimen (OBR)

*T = NRTIs +/- Enfuvirtide

**Trio Regimen**
Etravirine + Darunavir + Ritonavir + Raltegravir + OBT (n = 103)

Etravirine + Darunavir/r + Raltegravir
TRIO: Result

Week 24 and 48: Virologic Response (Intention-to-treat Analysis)

Etravirine + Darunavir/r + Raltegravir
TRIO: Result

Week 24: Virologic Response (ITT Analysis), by Baseline HIV RNA

Conclusion: “In patients infected with multidrug-resistant virus who have few remaining treatment options, the combination of raltegravir, etravirine, and darunavir/ritonavir is well tolerated and is associated with a rate of virologic suppression similar to that expected in treatment-naive patients.”

Etravirine in Treatment-Experienced Patients
Study TMC125-C223
Etravirine (formerly TMC125) in Patients with Highly Resistant HIV Study TMC125-C223: Study Design

**Study Design: TMC125-C223**

- **Background**: Randomized, controlled, partially-blind, phase 2b trial evaluating the safety and efficacy of phase 2b formulation of etravirine combined with optimized background therapy (OBT) compared with a standard-of-care regimen.

- **Inclusion Criteria (n = 199)**
  - Adults with HIV
  - HIV RNA >1,000 copies/mL
  - ≥3 NNRTI resistance mutations

- **Treatment Arms**
  - OBT + *Etravirine 400 mg bid* (old formulation*) (n = 77)
  - OBT + *Etravirine 800 mg bid* (old formulation*) (n = 78)
  - OBT + Control (included at least 3 ARVs: NRTIs, PIs, and/or Enfuvirtide) (n = 40)

*Old formulation of etravirine 800 mg equivalent to 200 mg of FDA-approved formulation of etravirine*

Etravirine (formerly TMC125) in Patients with Highly Resistant HIV Study TMC125-C223: Results

Week 48: Change in HIV RNA Level

Etravirine (formerly TMC125) in Patients with Highly Resistant HIV
Study TMC125-C223: Results

Week 48: Change in HIV RNA, by Baseline Etravirine Mutations

Number of Baseline Etravirine Resistance-Associated Mutations

Mean Change in HIV RNA from Baseline (Log10 copies/mL)

Etravirine (formerly TMC125) in Patients with Highly Resistant HIV
Study TMC125-C223: Results

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

**Conclusion**: “Etravirine demonstrated higher efficacy than control, irrespective of the number of detectable nonnucleoside reverse transcriptase inhibitor resistance-associated mutations.”

Etravirine versus Protease Inhibitor in ARV-Experienced

TMC 125-C227
Etravirine *versus* Protease Inhibitor in ARV-Experienced TMC125-C227: Study Design

**Study Design: TMC125-C227**

- **Background**: Randomized, controlled, open-label phase 2 trial evaluating the safety and efficacy of etravirine (formerly TMC125) in PI-naïve patients with NNRTI resistance

- **Inclusion Criteria** (n = 116)
  - Age >18 years
  - HIV RNA >1,000 copies/mL
  - Documented genotypic NNRTI resistance
  - PI naïve

- **Treatment Arms**
  - Etravirine 800 mg bid + 2NRTIs
  - Investigator-selected PI + 2NRTIs

*Note: Old formulation of 800 mg bid equivalent to FDA-approved etravirine dose of 200 mg bid. Initial study planned for 48 weeks, but enrollment stopped prematurely and etravirine treatment discontinued after median 14.3 weeks due to suboptimal virologic response.*
Etravirine versus Protease Inhibitor in ARV-Experienced TMC125-C227: Study Design

Prevalence of Baseline NNRTI Resistance Mutations

Etravirine in Patients with Highly Resistant HIV
TMC125-C223: Results

Weeks 12 and 24: Change in HIV RNA

<table>
<thead>
<tr>
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<th>Week 12</th>
<th>Week 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Etravirine 800 mg bid</td>
<td>-1.39</td>
<td>-1.51</td>
</tr>
<tr>
<td>Control</td>
<td>-2.16</td>
<td>-2.13</td>
</tr>
</tbody>
</table>

Etravirine *versus* Protease Inhibitor in ARV-Experienced TMC125-C227: Results

Week 24: Mean Change of HIV RNA From Baseline (observed data)

![Graph showing mean change in plasma viral load (log_{10} copies/mL ± SE) over weeks 0 to 24 for Etravirine 800 mg bid (old formulation) and Control (investigator selected PI).]

Etravirine *versus* Protease Inhibitor in ARV-Experienced TMC125-C227: Results

Week 24: Proportion of Patients with HIV RNA Less than 50 copies/mL

![Graph showing the proportion of patients with HIV RNA less than 50 copies/mL over 24 weeks for Etravirine 800 mg bid (old formulation) and Control (investigator selected PI).]

**Conclusions**: “In a PI-naive population, with baseline NRTI and NNRTI resistance and NRTI recycling, TMC125 (etravirine) was not as effective as first use of a PI. Therefore the use of TMC125 (etravirine) plus NRTIs alone may not be optimal in PI naive patients with first-line virological failure on an NNRTI-based regimen. Baseline two-class resistance, rather than pharmacokinetics or other factors, was the most likely reason for suboptimal responses.”

Etravirine in Treatment-Experienced Children and Adolescents

PIANO Trial
**Study Design: PIANO**

- **Background**: Phase 2, single-arm trial assessing safety and efficacy of etravirine in treatment-experienced, HIV-infected patients.

- **Inclusion Criteria (n = 101)**
  - Children ≥6 and <12 years
  - Adolescents ≥12 and <18 years old
  - Treatment-experienced
  - No resistance to etravirine

- **Treatment Arms**
  - Etravirine 5.2 mg/kg bid + Investigator-selected optimized background regimen (OBR)

*OBT = ≥ 2 active ARVs, including a ritonavir-boosted PI and NRTIs +/- Enfuvirtide +/- Raltegravir

**Etravirine 5.2 mg/kg bid + OBR (n = 101)**

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Etravirine in Treatment-Experienced Children & Adolescents

PIANO: Result

Week 24 and 48: Virologic Response (ITT Analysis, N=F)*


*ITT: Intent-to-Treat, N=F: Noncompleter=Failure
Etravirine in Treatment-Experienced Children & Adolescents

PIANO: Result

Week 48: Measures of Adherence

Etravirine in Treatment-Experienced Children & Adolescents

PIANO: Result

Week 48: Adverse Events

Conclusions: “Results with etravirine 5.2 mg/kg bid (with OBR) in this treatment-experienced paediatric population and etravirine 200 mg bid in treatment-experienced adults were comparable. Etravirine is an NNRTI option for treatment-experienced paediatric patients.”
SWITCH STUDIES

Etravirine
Etravirine plus Darunavir/r as Dual Therapy
INROADS Trial
**Etravirine + Darunavir/r as Dual Therapy**

**INROADS: Design**

<table>
<thead>
<tr>
<th>Study Design: INROADS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong>: Phase 2b, single-arm trial evaluating etravirine with darunavir plus ritonavir in treatment-experienced subjects or treatment-naïve persons with HIV and with transmitted drug-resistant HIV</td>
</tr>
<tr>
<td><strong>Inclusion Criteria (n = 54)</strong></td>
</tr>
<tr>
<td>- Age ≥18 years</td>
</tr>
<tr>
<td>- Treatment-naïve: resistance to either efavirenz or nevirapine, but no resistance to etravirine darunavir</td>
</tr>
<tr>
<td>- Treatment-experienced subjects</td>
</tr>
<tr>
<td>- HIV RNA &gt;500 copies/mL</td>
</tr>
<tr>
<td>- CD4 count ≥50 cells/mm³</td>
</tr>
<tr>
<td><strong>Treatment Arms (all taken once daily)</strong></td>
</tr>
<tr>
<td>- Etravirine 400 mg + Darunavir 800 mg + RTV 100 mg</td>
</tr>
</tbody>
</table>

* INROADS = Intelence aNd pRezista Once A Day Study

Etravirine + Darunavir/r as Dual Therapy
INROADS: Result

Week 48: Virologic Response

CVR = confirmed virologic response; TLOVR = Time to loss of virologic; ITT: Intent-to-Treat. CVR allows patients who are resuppressed after failure to be counted as virologic responders.

Conclusions: “Etravirine 400 mg and darunavir/ritonavir 800/100 mg as a two-drug once-daily regimen in treatment-experienced subjects or treatment-naïve subjects with transmitted resistance was virologically efficacious and well tolerated.”
Switch to Etravirine from PI-Based Regimen

ETRA-SWITCH STUDY
Switch to Etravirine from PI-Based Regimen
ETRA-SWITCH: Design

Study Design: ETRA-SWITCH

- **Background**: Open label, randomized phase 3b trial that enrolled persons with HIV who had suppressed HIV RNA levels while taking a ritonavir-boosted PI plus 2NRTIs and examined the efficacy and safety of switching the ritonavir-boosted PI to etravirine

- **Inclusion Criteria (n = 43)**
  - On PI >12 months
  - HIV RNA <50 copies/mL for >6 months
  - No NRTI or NNRTI resistance
  - No prior virologic failure with prior regimen
  - Patients had dyslipidemia OR use of lipid lowering medication OR GI disturbance OR persistent dissatisfaction with current regimen

- **Treatment Arms**
  - Switch PI in regimen to etravirine 400 mg/day
  - Continue current PI-based ART regimen

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Switch Group
Switch from PI to ETR (n = 22)

Maintain Group
Continue PI-based Regimen (n = 21)

Switch to Etravirine from PI-Based Regimen

ETRA-SWITCH: Result

Week 48: Virologic Response (ITT Analysis, Missing = Failure)

Switch to Etravirine from PI-Based Regimen

ETRA-SWITCH: Result

Week 48: Change in Plasma Lipids from Baseline

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Etravirine Group</th>
<th>PI (Control) Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>-16.4</td>
<td>-54.0</td>
</tr>
<tr>
<td>HDL</td>
<td>-0.1</td>
<td>-1.0</td>
</tr>
<tr>
<td>LDL</td>
<td>-6.1</td>
<td>-29.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Etra-SWITCH: Result

Patient Satisfaction Scores

Conclusion: “Switch from a PI-based regimen to a once-daily combination based on ETR maintained undetectable VL during 48 weeks in virologically suppressed HIV-infected patients while lipid profile and patient satisfaction improved significantly.”
Switch to Etravirine from Efavirenz

SWITCH-EE STUDY
Switch from Efavirenz to Etravirine

SWITCH-EE: Design

Study Design: SWITCH-EE

- **Background**: Randomized, double-blind, crossover study comparing the safety and efficacy of etravirine with efavirenz

- **Inclusion Criteria** (n = 58)
  - Age ≥18 years
  - On EFV-containing ART regimen for ≥3 months
  - HIV RNA <50 copies/mL for ≥3 months

- **Treatment Arms**
  - EFV 600 mg daily + NRTI backbone x 6 weeks, then switch EFV to ETR
  - ETR 400 mg daily + NRTI backbone x 6 weeks, then switch ETR to EFV

**“EFV First” Group**
EFV 600 mg QD + NRTIs, then switch EFV to ETR
(n = 28)

**“ETR First” Group**
ETR 400 mg QD + NRTIs, then switch ETR to EFV
(n = 30)

Switch from Efavirenz to Etravirine

SWITCH-EE: Result

Week 12: Treatment Preference

Switch from Efavirenz to Etravirine
SWITCH-EE: Result

Week 12: Treatment Preference, with Significant Order Effect

Switch from Efavirenz to Etravirine
SWITCH-EE: Result

Week 12: Change in Plasma Lipids from Baseline

<table>
<thead>
<tr>
<th>Lipid</th>
<th>Median change from baseline (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td>End of Efavirenz Period: 5.5</td>
</tr>
<tr>
<td></td>
<td>End of Etravirine Period: 4.6</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>End of Efavirenz Period: 1.7</td>
</tr>
<tr>
<td></td>
<td>End of Etravirine Period: 1.4</td>
</tr>
<tr>
<td>HDL</td>
<td>End of Efavirenz Period: 1.1</td>
</tr>
<tr>
<td></td>
<td>End of Etravirine Period: 1.1</td>
</tr>
<tr>
<td>LDL</td>
<td>End of Efavirenz Period: 3.3</td>
</tr>
<tr>
<td></td>
<td>End of Etravirine Period: 2.8</td>
</tr>
</tbody>
</table>

Conclusion: “After substitution of efavirenz by etravirine, patients did not express a significant preference for etravirine. There was no measurable effect on neuropsychiatric symptoms and sleep. Cholesterol decreased.”
Switch to Etravirine from Efavirenz due to CNS Toxicity

SSAT-029 STUDY
Switch to Etravirine from Efavirenz Due to CNS Toxicity

SSAT-029: Design

<table>
<thead>
<tr>
<th>Study Design: SSAT-029</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Background</strong>: Randomized, double-blind, phase IV trial evaluating the impact of switching from etravirine to efavirenz on central nervous system (CNS) symptoms on a stable, fully suppressive efavirenz-based regimen</td>
</tr>
<tr>
<td><strong>Inclusion Criteria (n = 38)</strong></td>
</tr>
<tr>
<td>- On efavirenz plus 2NRTIs &gt;12 weeks</td>
</tr>
<tr>
<td>- Ongoing CNS symptoms</td>
</tr>
<tr>
<td>- HIV RNA &lt;50 copies/mL</td>
</tr>
<tr>
<td>- CD4 count &gt;50 cells/mm³</td>
</tr>
<tr>
<td>- No previous exposure to etravirine or rilpivirine</td>
</tr>
<tr>
<td><strong>Treatment Arms</strong></td>
</tr>
<tr>
<td>- ETR + EFV-placebo + 2NRTI x 12 weeks, then open-label ETR + 2NRTIs</td>
</tr>
<tr>
<td>- EFV + ETR-placebo + 2NRTI x 12 weeks, then switch to open-label ETR + 2NRTIs</td>
</tr>
</tbody>
</table>

Immediate Switch Arm
Etravirine + 2NRTI (n = 20)

Delayed Switch Arm
Efavirenz + 2NRTIs x 12 weeks, then Etravirine + 2NRTIs (n = 18)

Switch to Etravirine from Efavirenz Due to CNS Toxicity

SSAT-029: Result

Week 24 and 48: Virologic Response (on-treatment analysis)

Switch to Etravirine from Efavirenz Due to CNS Toxicity

SSAT-029: Result

Change in CNS Adverse Events, by Study Group

Switch to Etravirine from Efavirenz Due to CNS Toxicity
SSAT-029: Result

Change in CNS Adverse Events: Combined Analyses

Switch to Etravirine from Efavirenz Due to CNS Toxicity

SSAT-029: Result

Lipid Changes After 12 Weeks of Etravirine

Conclusion: “Switching efavirenz to etravirine led to a significant reduction in overall grade 2-4 CNS adverse events, including insomnia, abnormal dreams and nervousness as individual adverse event. Lack of improvement for some events suggests other causative factors.”
Weighted Scores for Etravirine-Associated Mutations Based on Data from Duet 1 & 2

<table>
<thead>
<tr>
<th>Etravirine Mutation Score</th>
<th>Predicted Response Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 2.0</td>
<td>Highest response rate</td>
</tr>
<tr>
<td>2.5 - 3.5</td>
<td>Intermediate response</td>
</tr>
<tr>
<td>&gt;3.5</td>
<td>Progressive reduced response</td>
</tr>
</tbody>
</table>

Weighted Scores for Etravirine-Associated Mutations Based on Data from Duet 1 & 2

Virologic Response at Week 24 in Duet-1 and Duet-2

<table>
<thead>
<tr>
<th>Etravirine Weighted Genotypic Score</th>
<th>Highest Response</th>
<th>Intermediate Response</th>
<th>Reduced Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0-2.0</td>
<td>74.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0-3.5</td>
<td>52.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 3.5</td>
<td>37.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

HIV RNA < 50 copies/ml

Baseline Etravirine Resistance-Associated Mutations Predicting Response to Etravirine; DUET 1 & 2

<table>
<thead>
<tr>
<th>Individual Mutation Weight to Etravirine</th>
<th>Virologic Response at Week 24 in Duet-1 &amp; Duet-2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>V90I</td>
<td>V106I</td>
</tr>
<tr>
<td>A98G</td>
<td>E138A</td>
</tr>
<tr>
<td>K101E</td>
<td>V179F</td>
</tr>
<tr>
<td>K101H</td>
<td>G190S</td>
</tr>
<tr>
<td>V179D</td>
<td></td>
</tr>
<tr>
<td>V179T</td>
<td></td>
</tr>
<tr>
<td>G190A</td>
<td></td>
</tr>
</tbody>
</table>

# Weighted Scores for Etravirine-Associated Mutations Based on Monogram Biosciences Data

<table>
<thead>
<tr>
<th>Individual Mutation Weight to Etravirine (n = 30 mutations)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
</tr>
<tr>
<td>-----------------</td>
</tr>
<tr>
<td>V90I</td>
</tr>
<tr>
<td>K101H</td>
</tr>
<tr>
<td>V106M</td>
</tr>
<tr>
<td>E138Q</td>
</tr>
<tr>
<td>V179D</td>
</tr>
<tr>
<td>V179F</td>
</tr>
<tr>
<td>V179M</td>
</tr>
<tr>
<td>Y181F</td>
</tr>
<tr>
<td>V189I</td>
</tr>
<tr>
<td>G190E</td>
</tr>
<tr>
<td>G190T</td>
</tr>
<tr>
<td>H221Y</td>
</tr>
<tr>
<td>P225H</td>
</tr>
<tr>
<td>K238T</td>
</tr>
</tbody>
</table>

Score

≥ 4 = Reduced Susceptibility

Acknowledgment

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