Rilpivirine-Emtricitabine-Tenofovir DF (Complera)

Dose: 1 tablet once daily with food
Rilpivirine-Tenofovir DF-Emtricitabine (Complera)

- **Complera Components:**
  - Rilpivirine 25 mg
  - Tenofovir disoproxil fumarate (DF) 300 mg
  - Emtricitabine 200 mg

- **Dosing:**
  - 1 tablet once daily with food

- **Common Adverse Events (≥2%)**
  - Depression, insomnia, headache

Rilpivirine-Tenofovir DF-Emtricitabine
Summary of Key Phase 3 Studies

• Trials in Treatment-Naïve Adults
  – ECHO: RPV + TDF-FTC versus EFV + TDF-FTC
  – THRIVE: RPV + 2NRTIs versus EFV + 2NRTIs
  – STaR: RPV-TDF-FTC versus EFV-TDF-FTC

• Switch Trials in Adults with Virologic Suppression
  – SPIRIT: Switch to RPV-TDF-FTC from ritonavir-boosted PI + 2NRTIs
  – Near-Rwanda: Switch to RPV-TDF-FTC from NVP-based regimen

**Abbreviations:** RPV = rilpivirine; TDF-FTC = tenofovir DF-emtricitabine; EFV = efavirenz; NRTIs = nucleoside reverse transcriptase inhibitors; EFV-TDF-FTC = efavirenz-tenofovir DF-emtricitabine; RPV-TDF-FTC = rilpivirine-tenofovir DF-emtricitabine; PI = protease inhibitor; NVP = nevirapine
Rilpivirine-Tenofovir DF-Emtricitabine

Trials in Treatment Treatment-Naïve Adults
Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

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

**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 ≥5,000 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: Results

48 Week Virologic Response (Intention-to-Treat)

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

ECHO: Results

48 Week Virologic Failure and Discontinuations (Intention-to-Treat)

Virologic Failure

<table>
<thead>
<tr>
<th></th>
<th>Rilpivirine + TDF-FTC</th>
<th>Efavirenz + TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (%)</td>
<td>11</td>
<td>4</td>
</tr>
</tbody>
</table>

Adverse Event Leading to Discontinuation

<table>
<thead>
<tr>
<th></th>
<th>Rilpivirine + TDF-FTC</th>
<th>Efavirenz + TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants (%)</td>
<td>2</td>
<td>7</td>
</tr>
</tbody>
</table>

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

Incidence of NNRTI Resistance Associated Mutations (RAMs)

The percentages represent the number of participants who developed each specific NNRTI RAM out of the number of participants who developed any NNRTI RAM in that arm of the trial (the n listed at the top of the graph).

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

Incidence of NRTI Resistance Associated Mutations (RAMs)

The percentages represent the number of participants who developed each specific NRTI RAM out of the number of participants who developed any NRTI RAM in that arm of the trial (the n listed at the top of the graph).

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

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

THRIVE Trial
Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

THRIVE: Study Design

- **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 adult with HIV

- **Inclusion Criteria (n = 690)**
  - Antiretroviral-naïve adults
  - Age ≥18 years
  - HIV RNA ≥5,000 copies/mL
  - No resistance to any study drugs

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

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC

THRIVE: Results

48 Week Virologic Response

HIV RNA <50 copies/mL (%)

Rilpivirine + TDF-FTC: 86%
Efavirenz + TDF-FTC: 83%

Rilpivirine + TDF-FTC versus Efavirenz + TDF-FTC
THRIVE: Results

48 Week Virologic Failure and Discontinuations

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

Incidence of NNRTI Resistance Associated Mutations (RAMs)

The percentages represent the number of participants who developed each specific NNRTI RAM out of the number of participants who developed any NNRTI RAM in that arm of the trial (the n listed at the top of the graph).

Incidence of NRTI Resistance Associated Mutations (RAMs)

The percentages represent the number of participants who developed each specific NRTI RAM out of the number of participants who developed any NRTI RAM in that arm of the trial (the n listed at the top of the graph).

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.”

Rilpivirine vs. Efavirenz in ARV-Naive
ECHO and THRIVE Pooled Data: Study Design

**Rilpivirine: 25 mg qd + TDF/FTC**
(n = 346)

**Efavirenz: 600 mg qd + TDF/FTC**
(n = 344)

**Rilpivirine: 25 mg qd + *2NRTIs**
(n = 340)

**Efavirenz: 600 mg qd + *2NRTIs**
(n = 338)

*2 NRTIs: Tenofovir + Emtricitabine; Zidovudine + Lamivudine; Abacavir + Lamivudine

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 48 Results

Week 48 Virologic Response Stratified by Baseline HIV RNA

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 48 Results

Week 48 Virologic Response Stratified by Baseline CD4 Count

<table>
<thead>
<tr>
<th>Baseline CD4 count (cells/mm$^3$)</th>
<th>2NRTIs + Rilpivirine</th>
<th>2NRTIs + Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>All 576/686 559/682</td>
<td>84</td>
<td>82</td>
</tr>
<tr>
<td>CD4 &lt;50 20/34 29/36</td>
<td>59</td>
<td>81</td>
</tr>
<tr>
<td>CD4 50-200 155/194 144/175</td>
<td>80</td>
<td>82</td>
</tr>
<tr>
<td>CD4 200-350 272/313 252/307</td>
<td>87</td>
<td>82</td>
</tr>
<tr>
<td>CD4 &gt;350 130/144 136/164</td>
<td>90</td>
<td>83</td>
</tr>
</tbody>
</table>

### Treatment-Emergent Adverse Events (AEs)

<table>
<thead>
<tr>
<th>Event</th>
<th>Rilpivirine (n = 686)</th>
<th>Efavirenz (n = 682)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment-related AE ≥ grade 2, n (%)</td>
<td>109 (16)</td>
<td>212 (31)</td>
</tr>
<tr>
<td>AE leading to permanent discontinuation, n (%)</td>
<td>23 (3)</td>
<td>52 (8)</td>
</tr>
<tr>
<td>Any neurologic AE, n (%)</td>
<td>117 (17)</td>
<td>258 (38)</td>
</tr>
<tr>
<td>Any psychiatric AE, n (%)</td>
<td>102 (15)</td>
<td>155 (23)</td>
</tr>
<tr>
<td>Rash, n (%)</td>
<td>21 (3)</td>
<td>93 (14)</td>
</tr>
</tbody>
</table>

Interpretation: “At week 48, rilpivirine 25 mg once daily and efavirenz 600 mg once daily had comparable response rates. Rilpivirine had more virologic failures and improved tolerability versus efavirenz.”

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 96 Results

Week 96 Virologic Response Stratified by Baseline HIV RNA

Rilpivirine vs. Efavirenz in ARV-Naïve ECHO and THRIVE Pooled Data: Week 96 Results

Week 96 Virologic Response Stratified by Baseline CD4 count

HIV RNA <50 copies/mL (%)

<table>
<thead>
<tr>
<th>Baseline CD4 count (cells/mm³)</th>
<th>2NRTIs + Rilpivirine</th>
<th>2NRTIs + Efavirenz</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>535/686</td>
<td>532/682</td>
</tr>
<tr>
<td>CD4 &lt;50</td>
<td>19/34</td>
<td>25/36</td>
</tr>
<tr>
<td>CD4 50-200</td>
<td>138/194</td>
<td>131/175</td>
</tr>
<tr>
<td>CD4 200-350</td>
<td>254/313</td>
<td>243/307</td>
</tr>
<tr>
<td>CD4 &gt;350</td>
<td>122/144</td>
<td>130/164</td>
</tr>
</tbody>
</table>

### Virologic Failure & Resistant Associated Mutations (RAMs)

<table>
<thead>
<tr>
<th></th>
<th>Rilpivirine (n = 686)</th>
<th>Efavirenz (n = 682)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure, n (%)</td>
<td>96 (14)</td>
<td>52 (8)</td>
</tr>
<tr>
<td>Any emergent NNRTI RAM, n (%)</td>
<td>51 (59)</td>
<td>23 (55)</td>
</tr>
<tr>
<td>Most frequent emergent NNRTI RAM</td>
<td>E138K</td>
<td>K103N</td>
</tr>
<tr>
<td>Any emergent NRTI RAM, n (%)</td>
<td>48 (56)</td>
<td>11 (26)</td>
</tr>
<tr>
<td>Most Frequent NRTI RAMs</td>
<td>M184I</td>
<td>M184V</td>
</tr>
</tbody>
</table>

**NOTE:** A majority of virologic failure instances occurred within the first 48 weeks in both arms.

Interpretation: “Rilpivirine 25 mg q.d. and efavirenz 600 mg q.d. had comparable responses at week 96. Rilpivirine had more virologic failures but improved tolerability versus efavirenz. The majority of virologic failures occurred in the first 48 weeks.”
Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR Trial
Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR Study: Design

**Background:** Randomized, open-label, phase 3b trial comparing safety and efficacy of two single-tablet regimens, RPV-TDF-FTC and EFV-TDF-FTC, in treatment-naïve adults with HIV

**Inclusion Criteria (n = 786)**
- Antiretroviral-naïve adults
- Age ≥18 years
- HIV RNA ≥2,500 copies/mL
- No resistance to EFV, RPV, TDF, or FTC

**Treatment Arms**
- Rilpivirine-tenofovir DF-emtricitabine
- Efavirenz-tenofovir DF-emtricitabine

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR: Result

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

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR: Results

48 Week Virologic Outcomes

### Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

#### STaR: Common Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>RPV-TDF-FTC (n = 392)</th>
<th>EFV-TDF-FTC (n = 394)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dizziness</td>
<td>6.6%</td>
<td>22.2%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>9.6%</td>
<td>14.0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.5%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Headache</td>
<td>12.4%</td>
<td>13.5%</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>5.8%</td>
<td>24.5%</td>
</tr>
<tr>
<td>Depression</td>
<td>6.6%</td>
<td>8.9%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>5.1%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Folliculitis</td>
<td>5.3%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Rash</td>
<td>6.1%</td>
<td>12.0%</td>
</tr>
</tbody>
</table>

Conclusion: “In treatment-naïve participants, RPV/FTC/TDF demonstrated noninferior efficacy and improved tolerability compared with EFV/FTC/TDF, as well as a statistically significant difference in efficacy for participants with baseline HIV-1 RNA 100,000 copies/mL or less at week 48.”
Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC

STaR Trial: Week 96 Resistance Data
Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR Resistance Analysis: Result

Development of Genotypic Resistance at Week 48

<table>
<thead>
<tr>
<th>Resistance Type</th>
<th>RPV-TDF-FTC</th>
<th>EFV-TDF-FTC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resistance to study drugs</td>
<td>4.3%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Any NNRTI resistance</td>
<td>4.1%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Any NRTI resistance</td>
<td>4.1%</td>
<td>0.3%</td>
</tr>
</tbody>
</table>

Rilpivirine-TDF-FTC versus Efavirenz-TDF-FTC
STaR Resistance Analysis: Result

Development of Resistance to Study Drugs at 48 weeks, by Viral Load

**Conclusions**: “Among subjects in the primary resistance associated populations (RAP), resistance development to RPV/FTC/TDF consisted of NNRTI and NRTI mutations and was more frequent than resistance development to EFV/FTC/TDF. In subjects with baseline viral load ≤ 100,000 copies/mL, resistance development was low (<2%) for both RPV/FTC/TDF and EFV/FTC/TDF arms and less frequent compared with subjects with baseline viral load >100,000 copies/mL, for RPV/FTC/TDF.”
Rilpivirine-Tenofovir DF-Emtricitabine

Switch Studies in Adults with Virologic Suppression
Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen

SPIRIT STUDY
Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen

SPIRIT: Study Design

**Background:** Open-label, randomized, phase 3b trial evaluating switching from ritonavir-boosted PI plus 2 NRTIs to single-tablet regimen of rilpivirine-tenofovir DF-emtricitabine once daily

**Inclusion Criteria**
- Age ≥18 years
- HIV RNA <50 copies/mL for ≥6 months
- On PI with ritonavir ≥6 months
- No known resistance to study drugs

**Treatment Arms**
- Rilpivirine-tenofovir DF-emtricitabine
- PI with ritonavir (PI/r) + 2 NRTIs x 24 weeks, then rilpivirine-tenofovir DF-emtricitabine

**Immediate Switch Arm**
RPV-TDF-FTC QD (n = 317)

**Delayed Switch Arm**
PI/r + 2 NRTIs x 24 weeks, then RPV-TDF-FTC QD (n = 159)

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Study Design

<table>
<thead>
<tr>
<th>Baseline Antiretroviral Regimens</th>
<th>Immediate Switch Arm (n = 317)</th>
<th>Delayed Switch Arm (n= 159)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NRTI at Screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TDF-FTC</td>
<td>80.4%</td>
<td>81.8%</td>
</tr>
<tr>
<td>ABC-3TC</td>
<td>13.2%</td>
<td>13.2%</td>
</tr>
<tr>
<td><strong>Ritonavir-Boosted PI at Screening</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atazanavir</td>
<td>38.5%</td>
<td>34.0%</td>
</tr>
<tr>
<td>Lopinavir</td>
<td>30.6%</td>
<td>36.5%</td>
</tr>
<tr>
<td>Darunavir</td>
<td>19.9%</td>
<td>20.8%</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>7.9%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>1.9%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Results

Week 24 Virologic Response (Intent-to-Treat Analysis)

<table>
<thead>
<tr>
<th>Baseline HIV RNA Level</th>
<th>RPV-FTC-TDF</th>
<th>PI/r + 2NRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>94/90</td>
<td>297/143/159</td>
</tr>
<tr>
<td>≤100,000 copies/mL</td>
<td>95/89</td>
<td>155/83/93</td>
</tr>
<tr>
<td>&gt;100,000 copies/mL</td>
<td>95/92</td>
<td>125/48/52</td>
</tr>
</tbody>
</table>

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen

SPIRIT: Results

Virologic Failure (HIV RNA ≥50 copies/mL) at Weeks 24 and 48

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Results

Week 24: Change in Plasma Lipids from Baseline

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Result

Week 48: Change in Plasma Lipids from Baseline

Switch to RPV-TDF-FTC from Ritonavir-boosted PI Regimen
SPIRIT: Result

Week 48 Virologic Outcomes in Patients with Resistance Mutations*


*Pre-existing NRTI or NNRTI resistance mutations by baseline proviral DNA or historical RNA genotype
Conclusion: “Switching to the STR RPV/FTC/TDF from an RTV-boosted protease inhibitor regimen in virologically suppressed, HIV-1-infected participants maintained virologic suppression with a low risk of virologic failure, while improving total cholesterol, LDL, and triglycerides.”

Switch RPV-TDF-FTC from NVP-Based Regimen

Near-Rwanda Trial
Switch to RPV-TDF-FTC from NVP-Based Regimen Near-Rwanda: Study Design

- **Background**: Randomized, open-label, single-center, noninferiority study conducted in Rwanda to evaluate a switch from a nevirapine (NVP)-based regimen to a single tablet regimen of rilpivirine-tenofovir DF-emtricitabine (RPV-TDF-FTC).

- **Inclusion Criteria (n = 150 enrolled)**
  - Rwandan adults with HIV-1 infection
  - HIV RNA <50 copies/mL within 12 months of screening
  - HIV RNA <50 copies/mL at screening visit
  - On NVP + lamivudine + 2nd NRTI ≥12 months
  - No prior virologic failure
  - No prior ART change except NRTI substitution
  - eGFR >60 mL/min and Hemoglobin >8 g/dL
  - No active TB or pregnancy

- **Treatment Arms (2:1 randomization)**
  - Continue NVP + 2 NRTIs
  - Switch to RPV-FTC-TDF

Switch to RPV-TDF-FTC from NVP-Based Regimen Near-Rwanda: Results

24 Week Virologic Response (FDA Snapshot Analysis)

Switch to RPV-TDF-FTC from NVP-Based Regimen
Near-Rwanda: Results

Week 24: Change in Plasma Lipids from Baseline

![Graph showing mean change from baseline (mg/dL) for different lipid categories: Total Cholesterol, LDL, Triglycerides, and HDL. The graph compares Rilpivirine-Tenofovir DF-Emtricitabine and Nevirapine + 2 NRTI's.]

Conclusions: “A switch from nevirapine-based ART to rilpivirine-emtricitabine-tenofovir disoproxil fumarate had similar virologic efficacy to continued nevirapine-based antiretroviral therapy after 24 weeks with few adverse events.”
The **National HIV Curriculum** is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of a financial assistance award totaling $1,021,448 with 0% financed with non-governmental sources. The contents are those of the author(s) and do not necessarily represent the official views of, nor an endorsement, by HRSA, HHS, or the U.S. Government. For more information, please visit HRSA.gov. This project is led by the University of Washington’s Infectious Diseases Education and Assessment (IDEA) Program.