Perspectives concernant les Inhibiteurs Non Nucléosidiques de la Transcriptase Inverse (INNTI)

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HIV CYCLE

- Fusion inhibitors
- co-receptors inhibitors
- integrase inhibitors
- protease inhibitors
- RT inhibitors

BINDING
UNCOATING
INTEGRATION
TRANSCRIPTION
TRANSLATION
ASSEMBLY
BUDDING

- Genomic RNA
- Double stranded DNA
- Viral proteins
- Cell membrane
- Cell nucleus

RT Inhibitors N/R TIs NNRTIs

Protease Inhibitors
NNRTIs: Common Properties

- Direct on site enzymatic inhibition (non-competitors)
- Substrates and inducers of CYP 3A
- Low genetic barrier
- Long elimination half-life
- Responsible of cutaneous rash
**NNRTIs: Pharmacological features**

<table>
<thead>
<tr>
<th></th>
<th>Mol. weight (g/mol)</th>
<th>Oral bioav. (%)</th>
<th>VD</th>
<th>Protein binding (%)</th>
<th>Plasma T/2 (h)</th>
<th>Clearance (main route)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV</td>
<td>315.68</td>
<td>nd</td>
<td>2.4 L/Kg</td>
<td>&gt; 99</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>NVP</td>
<td>266.3</td>
<td>93</td>
<td>1.21 L/Kg</td>
<td>60</td>
<td>25-30</td>
<td></td>
</tr>
<tr>
<td>ETR</td>
<td>435.28</td>
<td>nd</td>
<td>nd</td>
<td>99.9</td>
<td>41</td>
<td></td>
</tr>
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</table>
# Antiretroviral Therapy for Treatment-Naïve Patients

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred NNRTI</td>
<td>Efavirenz (AI)</td>
</tr>
<tr>
<td>Alternative NNRTI</td>
<td>Nevirapine (BI)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>PI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred PIs</td>
<td>ATV/r QD (AI)</td>
</tr>
<tr>
<td></td>
<td>DRV/r QD (AI)</td>
</tr>
<tr>
<td></td>
<td>fosAPV/r bid (BI)</td>
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<tr>
<td></td>
<td>LPV/r QD or bid (AI)</td>
</tr>
<tr>
<td>Alternative PIs</td>
<td>ATV QD (BI)</td>
</tr>
<tr>
<td></td>
<td>fosAPV/r QD or fosAPV bid (BI)</td>
</tr>
<tr>
<td></td>
<td>SQV/r bid (BI)</td>
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</table>

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Dual N/NtRTIs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred dual N/NtRTIs</td>
<td>TDF-FTC (AI)</td>
</tr>
<tr>
<td>Alternative dual N/NtRTIs</td>
<td>ABV-3TC (BI)</td>
</tr>
</tbody>
</table>

*Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*
NNRTIs:

New drugs under development
TMC278-C204: Rilpivirine vs EFV in Treatment-Naive Patients

Stratified by NRTI backbone and location
(Asia/Africa, US/Europe/Russia, or Latin America)

Week 48:
primary analysis

Week 96:
current analysis

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Description</th>
<th>Week 48: Primary Analysis</th>
<th>Week 96: Current Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>EFV 600 mg QD (open label) + ZDV/3TC or TDF/FTC (n = 89)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine 25 mg QD (blinded) + ZDV/3TC or TDF/FTC (n = 93)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine 75 mg QD (blinded) + ZDV/3TC or TDF/FTC (n = 95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rilpivirine 150 mg QD (blinded) + ZDV/3TC or TDF/FTC (n = 91)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Results at 96 Weeks

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Viral load &lt; 50 copies/mL, %</th>
<th>Mean Δ in CD4+ count, cells/mm³</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rilpivirine 25 mg (n = 93)</td>
<td>76</td>
<td>146</td>
</tr>
<tr>
<td>Rilpivirine 75 mg (n = 95)</td>
<td>72</td>
<td>172</td>
</tr>
<tr>
<td>Rilpivirine 150 mg (n = 91)</td>
<td>71</td>
<td>159</td>
</tr>
<tr>
<td>EFV 600 mg (n = 89)</td>
<td>71</td>
<td>160</td>
</tr>
</tbody>
</table>

Antiviral Activity With Varying Doses of UK-453,061

- **In vitro characteristics**
  - IC$_{90}$ of ~12 nM against WT HIV
- **Phase I pharmacokinetics**
  - Elimination half-life: 7-11 hours
  - Metabolized by CYP3A and glucuronidation

![Chemical structure of UK-453,061](image)

Novel NNRTI IDX899 Safe, Effective In HIV-Infected, Treatment-Naive Patients

- IDX899, a novel NNRTI with potent, selective activity against wild-type and NNRTI-resistant HIV in vitro
  - High genetic barrier to resistance in vitro
  - QD dosing feasible

- Current proof-of-concept study assessed safety, activity, and PK of IDX899 monotherapy vs placebo for 7 days in treatment-naive HIV-infected patients

- Adverse events mild and similar to placebo-treated group
- Mean HIV-1 RNA level declined by ~1.8 $\log_{10}$ copies/mL from BL to Day 8 with all 3 doses tested

Novel NNRTI RDEA806 Safe, Effective in Pilot Study in HIV-Infected Patients

- RDEA806, an investigational NNRTI with in vitro activity against NNRTI-resistant mutants, including K103N
  - Preclinical studies show high barrier to resistance
  - No reproductive toxicity in animals
  - Does not inhibit/induce of CYP450

- Current study explored safety, efficacy, and PK of RDEA806 monotherapy vs placebo in treatment-naive HIV-infected pts

- No serious, grade 3/4 adverse events, significant laboratory toxicities or discontinuations
  - Potentially drug related AEs of moderate severity reported in 6 of 36 pts receiving RDEA806 vs 1 of 12 receiving placebo

- Median -1.3 to -1.8 log_{10} copies/mL VL reduction at Day 8

NNRTIs:

Update on existing drugs

EFV
Virologic Response, According to Study Group

ACTG 5142

Percent of patients with virological failure*

Successful Efavirenz dose reduction in HIV Type 1-Infected Individuals with Cytochrome P450 2B6 *6 and *26

CYP2B6 genotypes determined in 456 HIV-1-infected EFV recipients

*CYP2B6 516G>T was identified in the *6 allele (17.9% of patients) and a novel allele, *26 (1.3% of patients).

Genotype-based dose reduction of EFV

EFV-associated CNS symptoms improved in 10/14
**FOTO: 5-Days-On, 2-Days-Off vs Daily Therapy in Suppressed Pts (week end interruption)**

HIV-infected pts on TDF/FTC + EFV with HIV-1 RNA < 50 c/mL (N = 60)

- **Wk 24**
  - Primary endpoint*
  - TDF/FTC + EFV FOTO (n = 30)

*Cross-over from daily to FOTO arm if HIV-1 RNA < 50 c/mL

- **Wk 48**
  - TDF/FTC + EFV FOTO (n = 23)
  - Switch to TDF/FTC + EFV FOTO (n = 27)

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FOTO: 48-Wk Results of 5-Days-On, 2-Days-Off vs Daily Therapy

- Pts on FOTO strategy maintained virologic suppression through Wk 48
- No virologic failure noted in either arm
- 10 pts stopped before Wk 48 (all HIV-1 RNA < 50 c/mL at d/c); 5 on FOTO; 4 on daily (1 before randomization)
  - n = 5 lost to follow-up
  - n = 4 withdrew consent
  - n = 1 pregnancy
- 54 pts reported strong preference for FOTO schedule at 4 wks following switch to FOTO

*After Wk 24, all pts on FOTO.
†P < .001 to reject inferiority of FOTO vs daily strategy to maintain suppression.

NNRTIs:

Update on existing drugs

ETR
Pooled DUET: more etravirine patients with viral load < 50 copies/mL at week 48

*Logistic regression model

CI = confidence interval; TLOVR = time to loss of virological response.

Pooled DUET 96-Wk Results: ETR + DRV/RTV-Containing OBR in Exp’d Pts

- Randomized trial of ETR vs placebo, both with DRV/RTV-containing OBR in multiclass-resistant pts
  - Superior virologic suppression with ETR at Wks 24 (primary endpoint) and 48
- Superior virologic suppression maintained at Wk 96 in ETR vs placebo arm[1]
  - Higher response with ETR irrespective of number of active agents, baseline ETR FC, weighted score, sex, race, and age
- Greater mean change in CD4+ cell count with ETR vs placebo
  - +123 vs +86 cells/mm³ ($P < .0001$)

- No new safety signals in Wks 48-96[2]
  - New rash in < 1% of pts
  - CNS adverse effects similar between arms in Wks 48-96

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NNRTIs:

Update on existing drugs

NVP
The ARTEN study

- Open-label (due to hyperbilirubinaemia)
- Treatment-naive patients with CD4+ T cells < 400/mL (male) or 250 (females)

Genotype report

- Week 2: up-titration to 400 mg NVP/day

<table>
<thead>
<tr>
<th>n=188</th>
<th>Screening</th>
<th>Nevirapine bid + FTC/TDF = 188</th>
<th>Cont. or new</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=188</td>
<td>Screening</td>
<td>Nevirapine qd + FTC/TDF = 188</td>
<td>Cont. or new</td>
</tr>
<tr>
<td>n=193</td>
<td>Screening</td>
<td>Atazanavir/r qd + FTC/TDF = 193</td>
<td>Cont. or new</td>
</tr>
</tbody>
</table>

Week -4 0 2 48 144 or EOT Post-trial

Primary endpoint

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.
ARTEN included a more stringent primary endpoint

![Study period diagram]

**Primary endpoint**
HIV RNA <50:
- Week 0
- Week 24
- Week 36
- Week 48

**TLOVR algorithm:**
HIV RNA <50:
- Sensitivity analysis

**Primary analysis:** 95% CI for difference between the combined NVP groups and ATZ/r in proportion of responders (primary endpoint); non-inferiority margin -12%

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.
ARTEN: ITT analyses (Week 48)
Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07

Treatment response by primary endpoint (ITT) (two visits prior Wk 48)

95% CI = -5.9% to 9.8%; p = 0.63

67 65 020 40 60 80 100 ATZ/r NVP qd + bid

Treatment response by sensitivity analysis: TLOVR algorithm (ITT)

Suppression to HIV-RNA <50 copies/mL at two visits prior to Week 48 (e.g. suppression at weeks 24, 36 and 48)

95% CI = -10.4% to 4.5%; p = 0.44

74 70 020 40 60 80 100 ATZ/r qd + bid

Suppression at two visits up to Week 48 (including week 48; eg at weeks 36 and 48, based on the TLOVR algorithm)
Nevirapine qd and bid were similarly effective

Treatment response by primary endpoint (ITT):
by nevirapine dose schedule

Nevirapine qd vs ATZ/r
95% CI = -6.5% to 11.5%; p=0.58

Nevirapine bid vs ATZ/r
95% CI = -7.7% to 10.7%; p=0.75

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.
OT analysis over time (single measurement)

HIV-RNA <50 copies/mL over time (OT)

HIV-RNA <50 copies/mL at 48 weeks, n (%)

<table>
<thead>
<tr>
<th></th>
<th>NVP qd</th>
<th>NVP bid</th>
<th>NVP qd + bid</th>
<th>ATZ/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-RNA &lt;50 copies/mL at 48 weeks, n (%)</td>
<td>132/144 (91.7)</td>
<td>124/130 (95.4)</td>
<td>256/274 (93.4)</td>
<td>154/175 (88.0)</td>
</tr>
</tbody>
</table>

Total excluding missing data, based on pre-defined time windows, numbers differ from TLOVR endpoint values.

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.

CD4 cell count improvement to Week 48

<table>
<thead>
<tr>
<th></th>
<th>NVP qd + bid (n=269)</th>
<th>ATZ/r (n=173)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ increase (mean)</td>
<td>170</td>
<td>185</td>
</tr>
<tr>
<td>95% CI</td>
<td>-39.3 to 7.4</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>0.18</td>
<td></td>
</tr>
</tbody>
</table>
Response according to baseline viral load

Response by screening viral load (primary endpoint analysis; Wk 48)

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.
Non-inferiority was reached despite a higher premature discontinuation rate in the NVP arm up to Week 48.

<table>
<thead>
<tr>
<th></th>
<th>NVP qd (n=188)</th>
<th>NVP bid (n=188)</th>
<th>ATZ/r (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any premature discontinuation, up to Week 48, n (%)</td>
<td>41 (21.8)</td>
<td>53 (28.2)</td>
<td>18 (9.3)</td>
</tr>
<tr>
<td>Discontinuations due to AEs, n (%)</td>
<td>20 (10.6)</td>
<td>27 (14.4)</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Lost to follow-up, n (%)</td>
<td>6 (3.1)</td>
<td>2 (1.1)</td>
<td>4 (2.1)</td>
</tr>
<tr>
<td>“Lack of efficacy”*, n (%)</td>
<td>11 (5.9)</td>
<td>21 (11.2)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Other, n (%)</td>
<td>4 (2.1)</td>
<td>3 (1.6)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>*As defined by the investigator</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>NVP qd (n=188)</th>
<th>NVP bid (n=188)</th>
<th>ATZ/r (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virologic failure, n (%)</td>
<td>21 (11.2)</td>
<td>24 (12.8)</td>
<td>27 (14.0)</td>
</tr>
<tr>
<td>“Lack of efficacy” (investigator defined VF)</td>
<td>11 (5.9)</td>
<td>21 (11.2)</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>No confirmed response at Wk 48=VF</td>
<td>10 (5.3)</td>
<td><strong>3 (1.6)</strong></td>
<td>24 (12.4)</td>
</tr>
</tbody>
</table>
Overall incidence of adverse events was similar between groups

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.
Low rate of rash or hepatic events with NVP used as in label

<table>
<thead>
<tr>
<th>%</th>
<th>Any degree</th>
<th>Grade 3—4</th>
<th>Leading to discontinuation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NVP qd</td>
<td>NVP bid</td>
<td>ATZ/r</td>
</tr>
<tr>
<td><strong>Rash</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(including during lead-in phase)</td>
<td>14.9</td>
<td>17.0</td>
<td>12.4</td>
</tr>
<tr>
<td><strong>Hepatitis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(excl. viral)</td>
<td>1.6</td>
<td>2.1</td>
<td>0.0</td>
</tr>
<tr>
<td><strong>LEE</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(coded as AE, excluding hyperbilirubinaemia)</td>
<td>5.9</td>
<td>7.4</td>
<td>1.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DAIDS Grade (% patients)</th>
<th>NVP qd</th>
<th>NVP bid</th>
<th>ATZ/r</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT</td>
<td>3.2</td>
<td>2.7</td>
<td>4.3</td>
</tr>
<tr>
<td>AST</td>
<td>4.3</td>
<td>1.6</td>
<td>4.3</td>
</tr>
<tr>
<td>Total bilirubin</td>
<td>1.1</td>
<td>1.6</td>
<td>2.1</td>
</tr>
</tbody>
</table>
ARTEN: lipid profile (week 48)

Change in lipid and cardiovascular risk parameters from baseline to Week 48

Soriano et al. IAS 2009, Cape Town, South Africa, Poster LBPE07.
Summary

• Nevirapine is a potent first-line choice
  – Efficacy non-inferior to ATZ/r
  – Effective in combination with Truvada®
  – Effective in patients with high screening viral load (>100,000 c/mL)
  – Efficacy of qd and bid NVP/Truvada® regimens similar

• Nevirapine/Truvada® demonstrates a more favourable lipid profile than ATZ/r

• Low rate of hepatic adverse events in ARTEN in which the CD4 count guidance was applied

• Most rashes occurred in the early treatment phase when patients are being closely monitored (thus avoiding grade 4 events)
154 HIV-infected patients
- All taking 3-drug ART
- HIV RNA in blood <50 c/mL

HIV RNA measured using a more sensitive assay (2.5 c/mL)
- NVP: 60% <2.5 c/mL
- EFV: 42% <2.5 c/mL
- LPV/r: 29% <2.5 c/mL

NVP was the only factor associated with undetectable HIV RNA on multivariate analysis

Conclusions

• NNRTIs remain the most successful and recommended treatment choice after more than 10 years of clinical use, and new options are in development

• NNRTIs have unique pharmacologic properties accounting for the possibility of QD dosing and a reasonable degree of forgiveness in clinical practice, thus well combining the highest standard of antiretroviral efficacy with a reduced interference with normal life activities and long-term toxicity

• Specific features like co-formulation (e.g. EFV), good penetration into sanctuaries (e.g. NVP), reduced lipid impact (e.g. NVP) and activity in treatment-experienced patients (e.g. ETR) make NNRTIs a truly attractive choice for long-term antiretroviral therapy