Evaluating the Patient for Fusion Inhibitors

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Causes of HIV Treatment Failure

- Resistant Variants
  - Pre-existing
  - Selected
  - Transmitted
- Host Failure?
  - CD4+ function
  - CTL activity
  - Chemokines
- Persistent Viral Replication
- Evolution of Drug Resistance
- Drug Failure

- Subinhibitory Drug Levels
- Limited potency
- Incomplete adherence
- Poor absorption
- Rapid clearance
- Protein binding
- Non-activation
- Drug-Drug interactions
Prevalence of HIV Drug Resistance

Drug Resistance Detected

* Assumes no resistance in samples with HIV RNA <500 copies/mL.
** Represents 63% of total study population.

Richman DD. 41st ICAAC; 2001; Chicago, Ill.

Resistance to > 2 drug classes is a powerful risk-marker of death

Zaccarelli et al., 2nd European HIV Drug Workshop, March 11-13, 2004, Rome; Abstract 49-P4.7

P log-rank < 0.001
N = 627

Note: A switch here is defined as any change to the regimen for any reason, i.e. not only due to virological failure

“We need more drugs!”
Antiretrovirals as of May, 2004:
4 Drug Classes

NRTIs/NtRTI
AZT  d4T*  ddC  ddI  3TC  ABC  TDF  FTC

NNRTIs
EFV  NVP  DLV

Pls
SQV  RTV  IDV  NLF  APV  LPV  ATV  FAPV

Fusion Inhibitors
ENF

*Stavudine XR: FDA Approved 12/31/02, but not yet available in pharmacies.

Targets for HIV Inhibition

Entry Inhibitors

Revers transcriptase Inhibitors

Integrate Inhibitors

Protease Inhibitors
HIV Attachment and Fusion: Targets for Inhibition

Targets for Inhibition

- CD4 Binding
- Coreceptor Binding
- Virus-Cell Fusion

Chemokine Antagonists: eg, SCH D, T-20 (Fuzeon®)

FUZEON profile

- 36-amino acid peptide
- Inhibits gp41-mediated fusion
- Administered by twice-daily subcutaneous injections
- Active against multi-drug resistant virus, regardless of co-receptor usage*

*Greenberg et al, 9th CROI, Chicago, 2001, Poster 470
TORO 1 & TORO 2: Treatment-experienced patients

- **Population:**
  - HIV infected patients with ≥3-6 months prior treatment with ≥1 NRTI, >1 NNRTI and >1-2 PI or documented viral resistance
  - HIV RNA ≥5,000 copies/mL
  - No entry CD4 criteria
- **Design:**
  - Open Label, Randomized, Multi-Center, International
- **Regimen:**
  - Optimized Background (OB)
    - 3-5 ARVs based on prior treatment history and baseline genotype and phenotype (determined prior to randomization)
  - FUZEON (90 mg sc bid) + OB
TORO 1 & TORO 2: Protocol study Design

Randomized 2:1, then start ENF+OB or OB

Screening period
Sample for GT/PT*

Stable regimen

ENF+OB
Switch permitted at virological failure** or at week 48

OB

Weeks
BL 8 16 24 48

GT = Genotypic Testing; PT = Phenotypic Testing

TORO 1 & TORO 2: BL Characteristics and Prior ARV Experience

<table>
<thead>
<tr>
<th></th>
<th>ENF+OB (N=661)</th>
<th>OB (N=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL RNA (median, log_{10} copies/mL)</td>
<td>5.2</td>
<td>5.1</td>
</tr>
<tr>
<td>BL CD4+ cell count (median, cells/mm^3)</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>Number of prior ARVs (median)</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>Years since initiating ARVs (median)</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Prior NRTI (median, years)</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Prior NNRTI (median, years)</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Prior PI (median, years)</td>
<td>3.8</td>
<td>4.0</td>
</tr>
</tbody>
</table>
The treatment benefit seen at week 24 is maintained at week 48:

All comparisons ENF+OB vs. OB P<0.0001

The treatment benefit seen at week 24 is maintained at week 48:

All comparisons ENF+OB vs. OB P<0.0001
CD4+ Cell Count
Change from Baseline

<table>
<thead>
<tr>
<th>Study week</th>
<th>ENF+OB</th>
<th>OB</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>71</td>
<td>35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>48</td>
<td>91</td>
<td>45</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Fuzeon®
(Enfuvirtide, T-20)

What We’ve Learned During the Past Year
Diversity of the TORO Patient Population

Baseline Disease State

Baseline CD4 (cells/mm³)

- >200: 25%
- 51-200: 35%
- 0-50: 40%

Baseline Treatment Experience

- 11-13: 53%
- 5-10: 34%
- 14-16: 13%

Number of Prior ARVs
Diversity of the TORO Patient Population
Baseline Resistance (Active Drugs)

Number of ARVs with genotypic sensitivity on baseline resistance test report

Combined TORO 1 & TORO 2: Virological and Immunological Responses at Week 48 by Demographic Subgroups (Proportion of Patients with VL <400 copies/mL)

* P < .05
In Clinical Trials, the Majority of Patients Taking Fuzeon®-based Regimens Were Able to Maintain a High Level of Adherence

![Data Chart]

Analysis of Virological Response of Enfuvirtide in TORO: Implications for Patient Management*

- To explore the effect of demographic, baseline, and treatment factors on virological response after 24 weeks of treatment on enfuvirtide-containing regimens
- To formulate guidance for the best use of enfuvirtide based on the results from the TORO studies in triple class experienced patients

*Montaner et al. 2nd IAS, Paris, July 2003
Clinically Relevant Parameters for Patients Initiating Enfuvirtide (Fuzeon®) Treatment*

**Disease stage**

**Treatment history**

**Activity of background regimen**

Of the multiple factors in the full model, the above were considered the most relevant because they are the ones commonly used in clinical practice.

Simplified Model for Patients Initiating Fuzeon® Treatment*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Odds ratio</th>
<th>95% C. I.</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BL CD4+ count (&gt;100 cells/mm³)</td>
<td>2.4</td>
<td>(1.6, 3.5)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>BL plasma HIV-1 RNA (&lt;100K)</td>
<td>1.8</td>
<td>(1.2, 2.6)</td>
<td>&lt;.0022</td>
</tr>
<tr>
<td>Treatment history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of prior ARVs (≤10)</td>
<td>1.8</td>
<td>(1.2, 2.6)</td>
<td>0.0058</td>
</tr>
<tr>
<td>Activity of background regimen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥2 active ARVs in background</td>
<td>2.8</td>
<td>(2.0, 4.0)</td>
<td>&lt; 1E-04</td>
</tr>
</tbody>
</table>

*HIV RNA<400 copies/ml at week 24
Conclusions

- ENF added to an OB provided significant benefit across all studied sub-groups of triple-class experienced patients in TORO 1 and TORO 2
- Greatest benefit associated with ENF:
  - CD4 ≥100 cells/mm³
  - Viral load <100,000 copies/mL
  - Up to 10 prior ARVs
  - Two or more active ARVs in background
- Patients with all 4 positive prognostic factors: 80% <400 copies/ml at week 24

“So maybe we should not wait so long to use Fuzeon®!”
“Cost” of not using Fuzeon® when switching for Virological Failure

<table>
<thead>
<tr>
<th>At least 1 active drug by genotyping</th>
<th>Number pts failing OB</th>
<th>Number losing drugs in OB at VF</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>160</td>
<td>80 (50%)</td>
</tr>
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Plasma HIV-1 RNA Change from BL

9/13/2004
Clinical Prognosis and Cost-effectiveness of Enfuvirtide (Fuzeon®) in the United States*

*Hornberger et al. 41st ICAAC, Chicago 2003

$43,607 Per QALY gained
$32,795 Per life year gained

|$51,556 | $154,136 | $102,580 |
| **Total** | **Enfuvirtide** | **– $618** | **$18,038** | **$18,656** |
| OB pre-VF | $8,560 | $16,248 | $7,688 |
| OB post-VF | $42,149 | $55,360 | $13,211 |
| ADE | $18,656 | $18,038 | $618 |
| Enfuvirtide | | $24,041 | $24,041 |
| **Total** | $102,580 | $154,136 | $51,556 |
| **Cost-effectiveness** | | | $32,795 |
| Per life year gained | | | **$43,607** |
| Per QALY gained | | | |

Table 3. Predicted times to clinical outcomes and costs

<table>
<thead>
<tr>
<th></th>
<th>OB alone</th>
<th>ENF + OB</th>
<th>Difference (ENF + OB – OB)</th>
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<tr>
<td>Mean time to VF (years)</td>
<td>0.5</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Mean time to IF (years)</td>
<td>1.3</td>
<td>2.9</td>
<td>1.6</td>
</tr>
<tr>
<td>Overall ADE free time (years)</td>
<td>3.3</td>
<td>4.8</td>
<td>1.5</td>
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<tr>
<td>Overall life expectancy (years)</td>
<td>4.6</td>
<td>6.2</td>
<td>1.6</td>
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<tr>
<td>Quality adjusted life expectancy (years)</td>
<td>3.3</td>
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<tr>
<td>Non-ARV medical costs (per year)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Pre ADE</td>
<td>$16,364</td>
<td>$23,838</td>
<td>$7,464</td>
</tr>
<tr>
<td>Post ADE</td>
<td>$16,851</td>
<td>$16,612</td>
<td>$239</td>
</tr>
<tr>
<td>Total</td>
<td>$33,215</td>
<td>$40,440</td>
<td>$7,225</td>
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<tr>
<td>Pharmaceutical costs (per year)</td>
<td></td>
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<td>1.2</td>
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Figure 1. Predicted times to clinical outcomes

- ENF+OB
- OB

Mean time to VF: 1.0, 0.5
Mean time to IF: 2.9, 1.3
Total time to a new ADE: 4.8, 3.3
Total life expectancy: 6.2, 4.6

ENF, enfuvirtide; OB, optimized background; VF, virological failure; IF, immunological failure; ADE, AIDS-defining event.

Figure 3. Improvements in Life Expectancy for Other Interventions in Common Diseases

- Enfuvirtide added to an optimized background regimen
- M. avium/fungal infection/CMV prophylaxis in HIV
- PCP/toxoplasmosis prophylaxis in HIV
- Chemotherapy in small-cell lung cancer
- Ticlopidine for stroke risk
- Implantable defibrillator for arrhythmia
- TPA for infarction

Gain in life expectancy (years)

PCP, Pneumocystis carinii pneumonia; TPA, tissue plasminogen activator.

*Adapted from Wright and Weinstein, 1998.
“So how do we evaluate the patient for fusion inhibitors?

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

March 23, 2004

It is emphasized that concepts relevant to HIV management evolve rapidly. The Panel has a mechanism to update recommendations on a regular basis, and the most recent information is available on the AIDSinfo Website: [http://AIDSinfo.nih.gov](http://AIDSinfo.nih.gov)
Treatment Regimen Failure: Assessment

Possible causes:
- Suboptimal adherence
- Toxicity
- Pharmacokinetics
- Suboptimal drug potency
- Viral resistance

Approach depends on cause of regimen failure and remaining antiretroviral options

Therapeutic options:
- Clarify goals: viral suppression may not be possible
- Remaining ARV options
- Base treatment choices on expected tolerability, adherence, future treatment options, past medical history, and resistance testing
Changing Therapy: Treatment Options

Extensive prior treatment:
- Avoid adding single active drug
- Seek expert advice
- If few or no treatment options, consider continuing same regimen. Other possible strategies:
  - PK enhancement
  - Therapeutic drug monitoring
  - Retreatment with prior medications
  - Multidrug regimens (limited by complexity, tolerability)
  - New ARV drugs, e.g. enfuvirtide, investigational drugs
  - Treatment interruptions not recommended

Fuzeon®
Indications

- In combination with other antiretroviral agents for the treatment of HIV-1 infection in treatment experienced patients
- Other patient types
  - Less ARV-experienced pts?
  - Patients who can’t tolerate other meds?
    - Peripheral neuropathy with nucleosides
    - GI intolerance with PIs
  - Patients with lipid issues?
Summary and Conclusions

- Fuzeon® is the first of the entry inhibitors
- Attacks the virus at a different site in its life cycle: should be effective against multi-drug resistant virus
- Post-hoc analysis of the registrational trials
  - Significantly better than OBR when there are no active drugs left
  - Works better when used earlier: lower pVL, higher CD4 counts, when fewer ARVs have been used previously, and when >2 active drugs are available
- So where exactly should it be used?

Only Time Will Tell
Thank you very much!