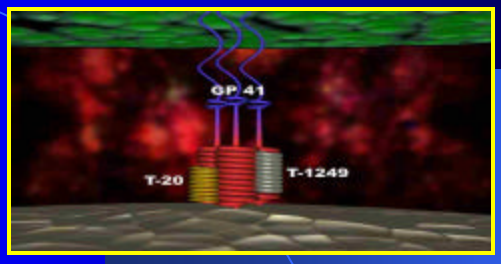
Evaluating the Patient for Fusion Inhibitors



Corklin R. Steinhart, MD, PhD
Senior Attending Physician
Mercy Hospital
Miami, FL

Causes of HIV *Treatment* Failure

Resistant Variants
- Pre- exisitng
- Selected
- Transmitted

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

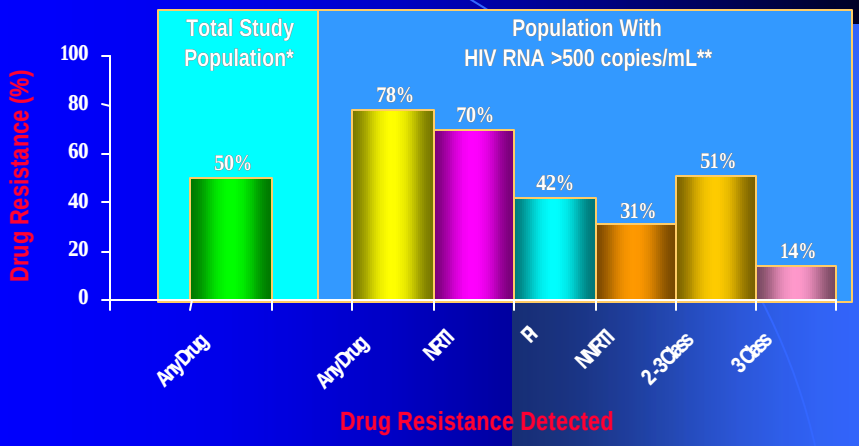
Host Failure?
- CD4+ function
- CTL activity
- Chemokines

Persistent Viral Replication

Evolution of Drug Resistance

Drug Failure

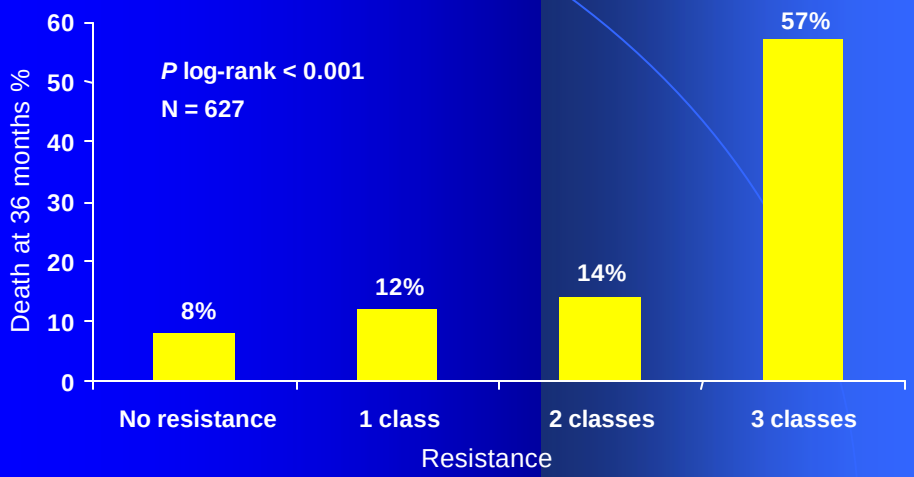
Prevalence of HIV Drug Resistance



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

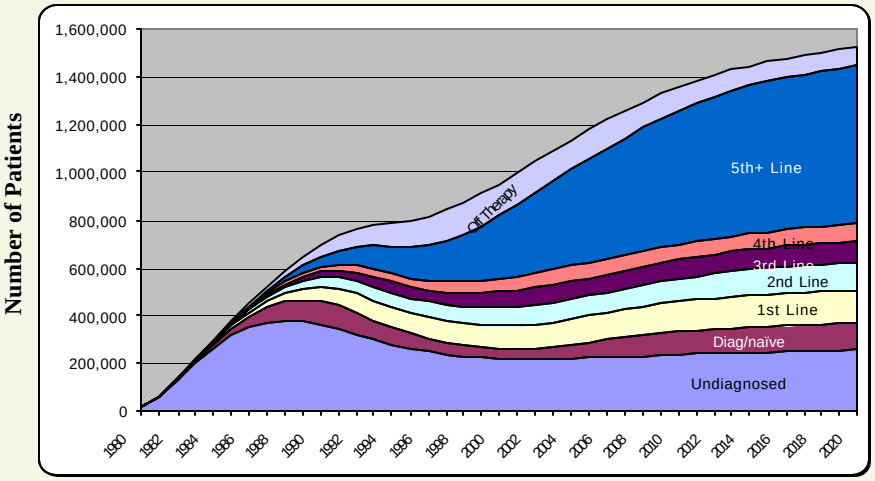
Richman DD. 41st *ICAAC*; 2001; Chicago, Ill.

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

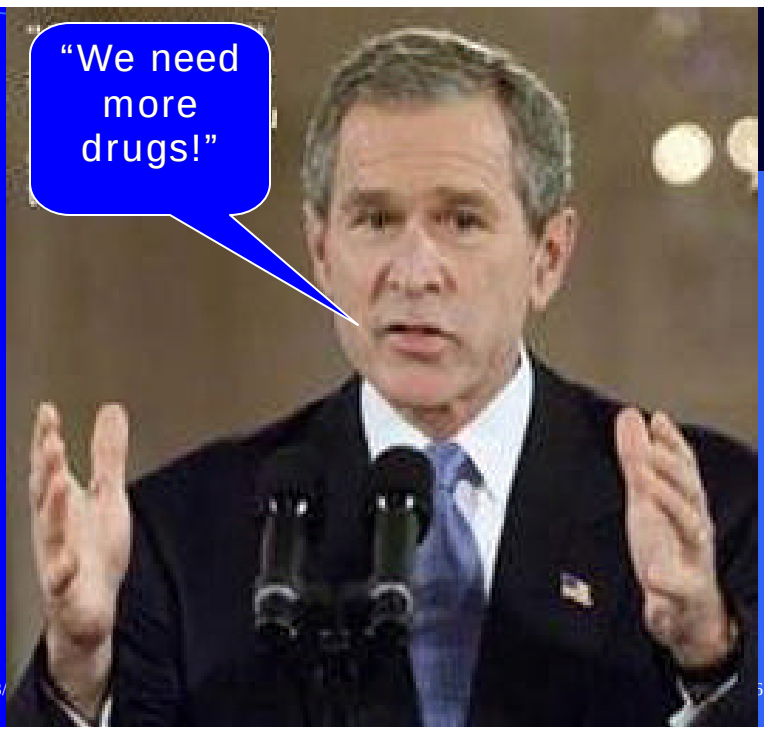


Zaccarelli et al., 2nd European HIV Drug Workshop, March 11-13, 2004, Rome; Abstract 49:P4.7

HIV Projected Patient Population (U.S.) 1980-2020



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



Antiretrovirals as of May, 2004: 4 Drug Classes

NRTIs/NtRTI

- AZT
- d4T*
- ddC
- ddI
- 3TC
- ABC
- TDF
- FTC

NNRTIs

- EFV
- NVP
- DLV

PIs

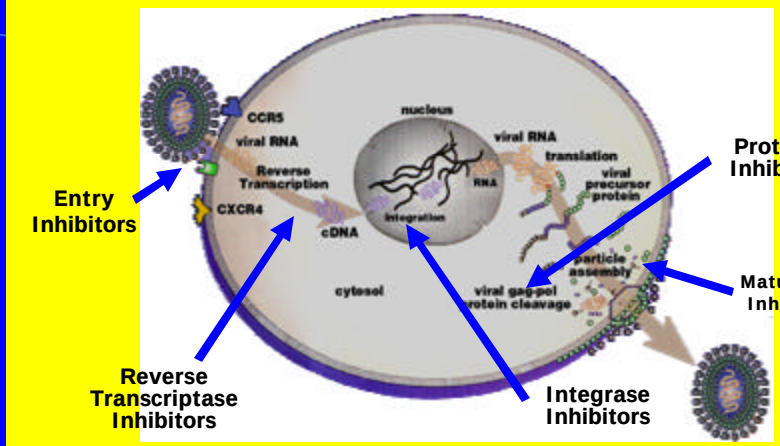
- SQV
- RTV
- IDV
- NLF
- APV
- LPV
- ATV
- FAPV

Fusion Inhibitors

- ENF

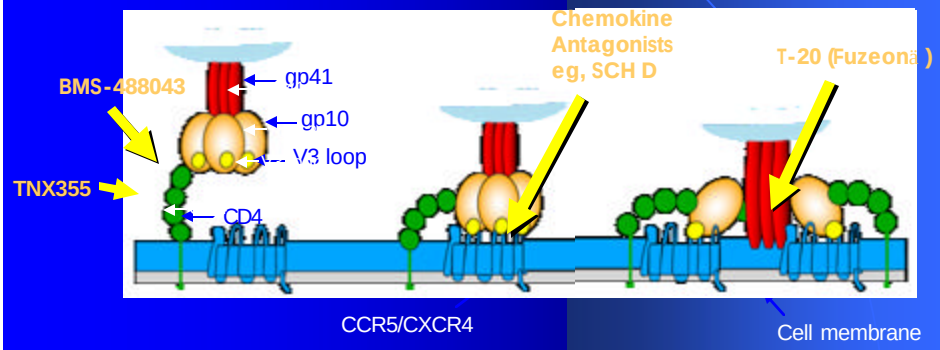
*Stavudine XR: FDA Approved 12/31/02, but not yet available in pharmacies.

Targets for HIV Inhibition



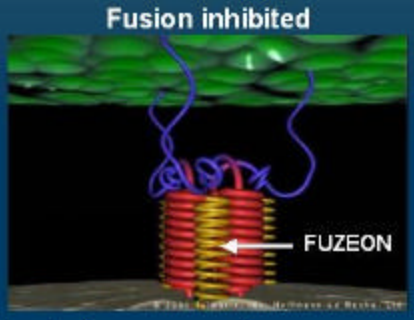
HIV Attachment and Fusion: Targets for Inhibition

CD4 Binding → Coreceptor Binding → Virus-Cell Fusion



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. 8th CROI. Chicago, 2001. Poster 473

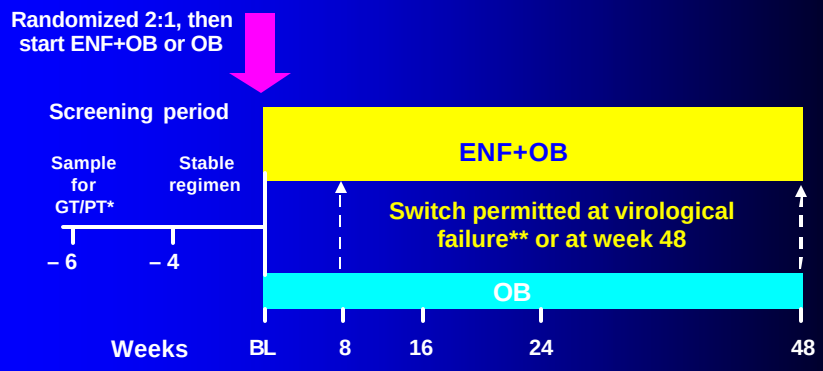
FUZEON

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 PIs 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

FUZEON enfuvirtide

TORO 1 & TORO 2: Protocol study Design

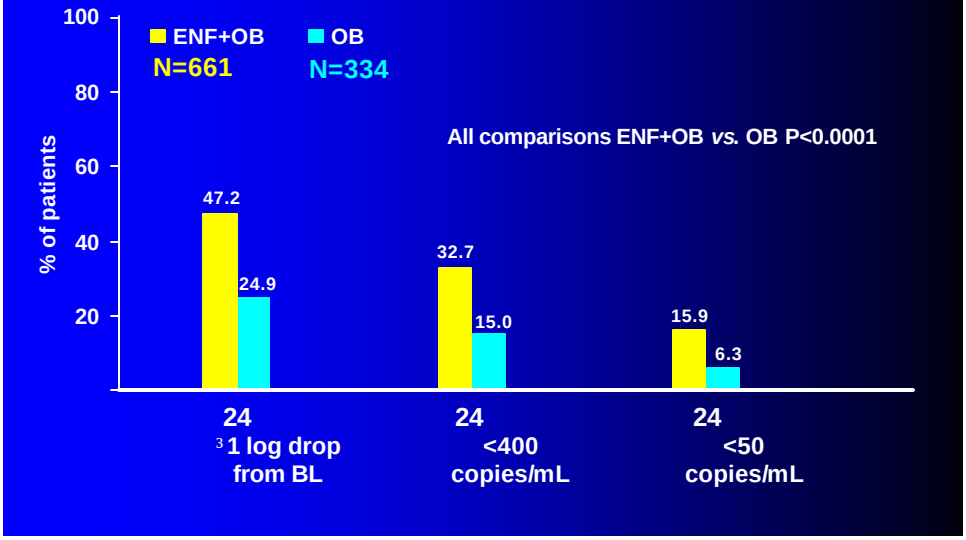


GT = Genotypic Testing; PT = Phenotypic Testing

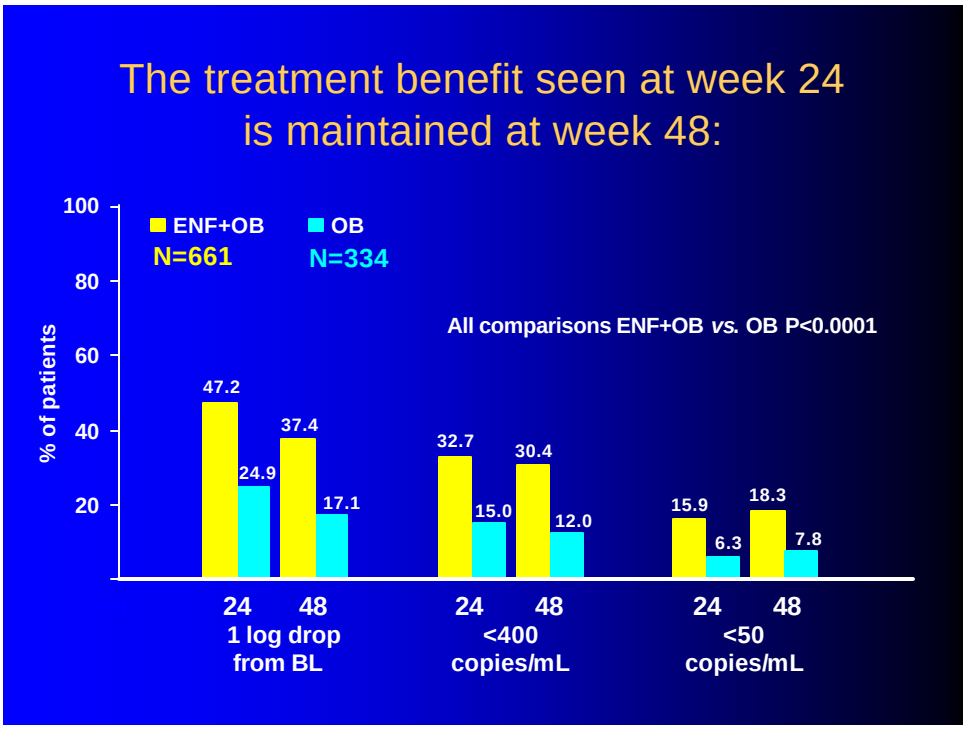
TORO 1 & TORO 2: BL Characteristics and Prior ARV Experience

	ENF+OB (N=661)	OB (N=334)
BL RNA (median, $\log_{10}$ copies/mL)	5.2	5.1
BL CD4+ cell count (median, cells/mm^3)	88	97
Number of prior ARVs (median)	12	12
Years since initiating ARVs (median)	7	7
Prior NRTI (median, years)	6.3	6.3
Prior NNRTI (median, years)	1.4	1.5
Prior PI (median, years)	3.8	4.0

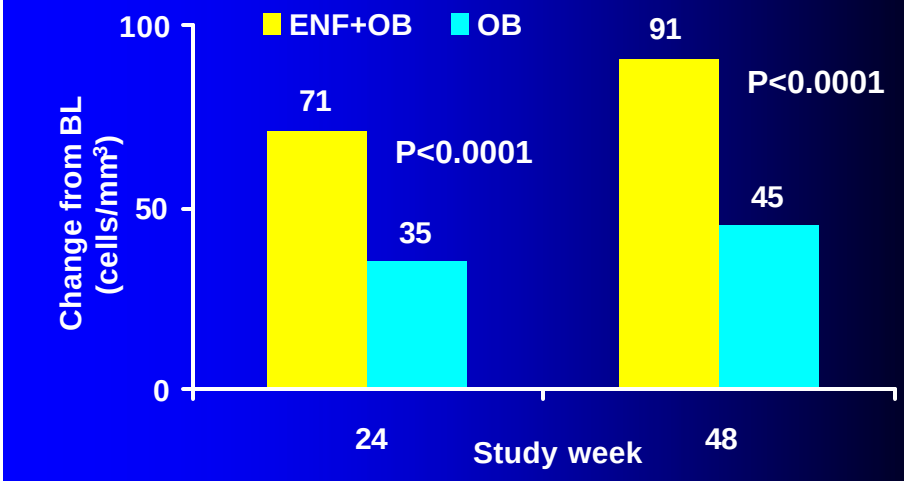
The treatment benefit seen at week 24 is maintained at week 48:



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

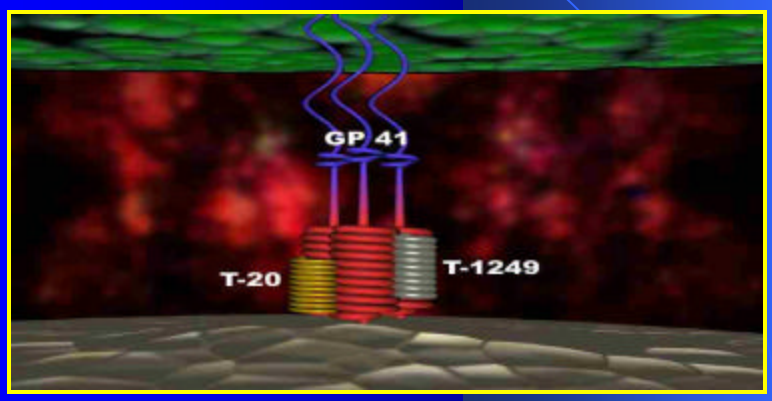


CD4+ Cell Count
Change from Baseline



Fuzeon®
(Enfuvirtide, T-20)

What We've Learned During the Past Year

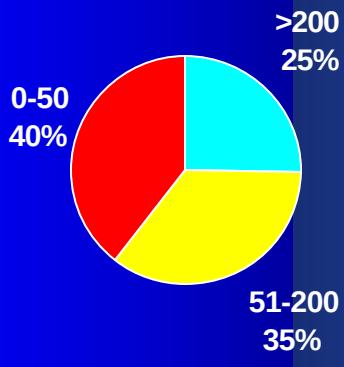


Duff F. 8th ECCATHI, Athens, 2001.

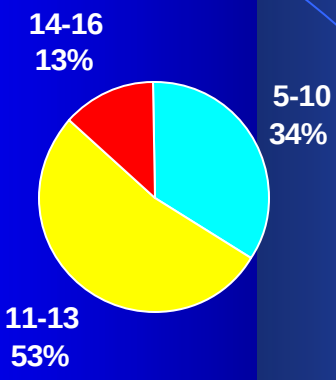
Duff F. 8th ECCATHI, Athens, 2001.

Diversity of the TORO Patient Population
Baseline Disease State

Baseline CD4 (cells/mm^3)

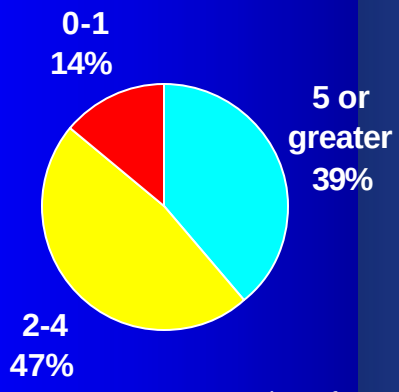


Diversity of the TORO Patient Population
Baseline Treatment Experience



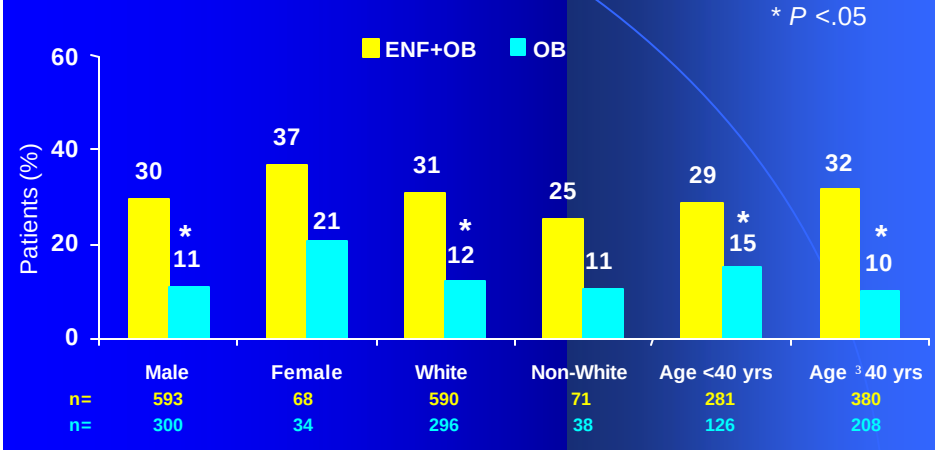
Number of Prior ARVs

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

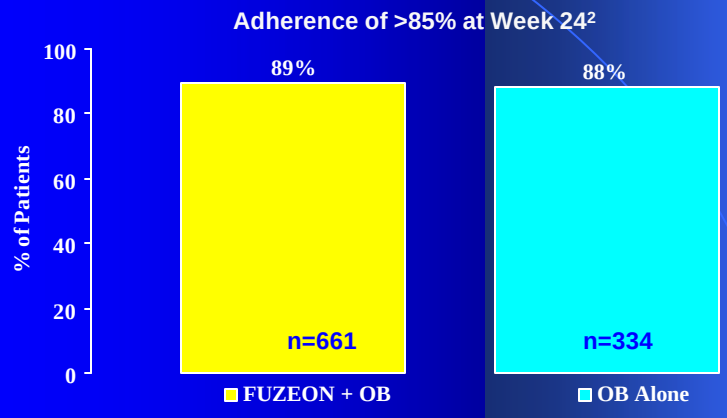


Number of ARVs with genotypic sensitivity on baseline resistance test report

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



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



TORO 1 and TORO 2 Integrated Analyses

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*

Factor	Odds ratio	95% C. I.	P-value
Disease stage			
BL CD4+ count (>100 cells/mm^3)	2.4	(1.6, 3.5)	<.0001
BL plasma HIV-1 RNA (<100K)	1.8	(1.2, 2.6)	<.0022
Treatment history			
No. of prior ARVs (≤10)	1.8	(1.2, 2.6)	0.0058
Activity of background regimen			
≥2 active ARVs in background	2.8	(2.0, 4.0)	<.0001

*HIV RNA<400 copies/ml at week 24

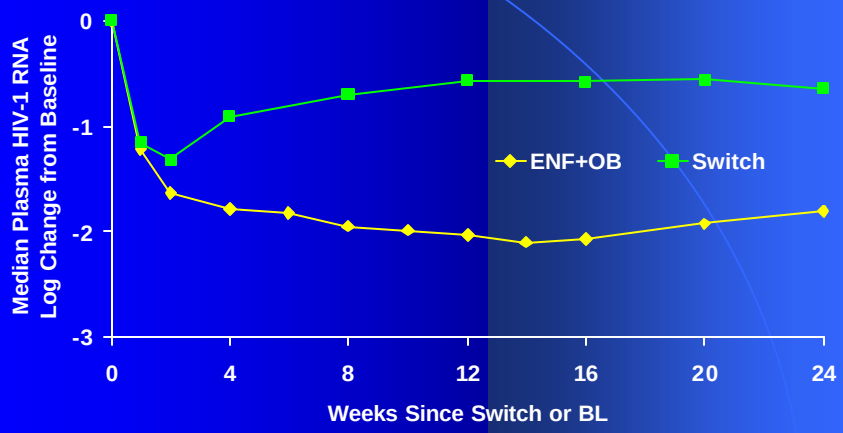
Conclusions

- 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/mm^3
  - 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

"Cost" of not using Fuzeon® when switching for Virological Failure

	Number pts failing OB	Number losing drugs in OB at VF
At least 1 active drug by genotyping	160	80 (50%)

Plasma HIV-1 RNA Change from BL



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

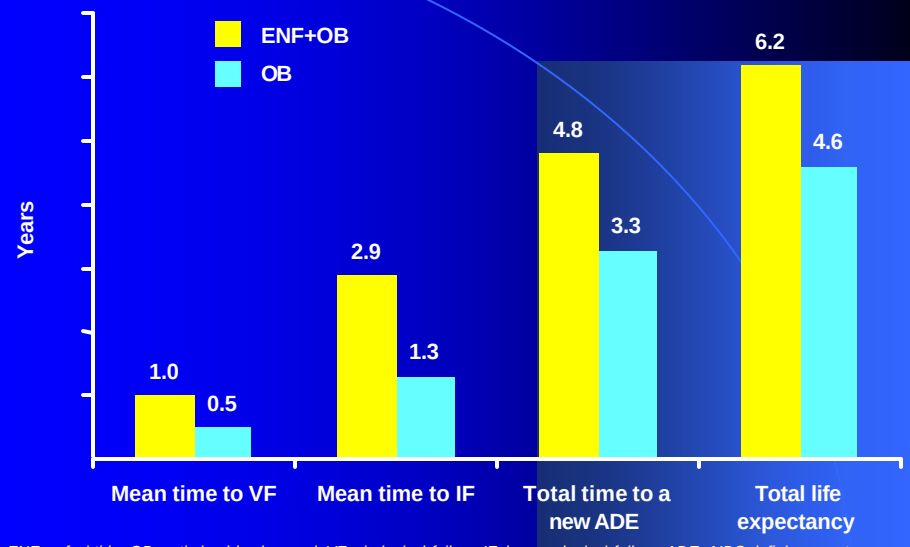
$ $ $ $ $ $ $

*Hornberger et al. 41st ICAAC, Chicago 2003

Table 3. Predicted times to clinical outcomes and costs

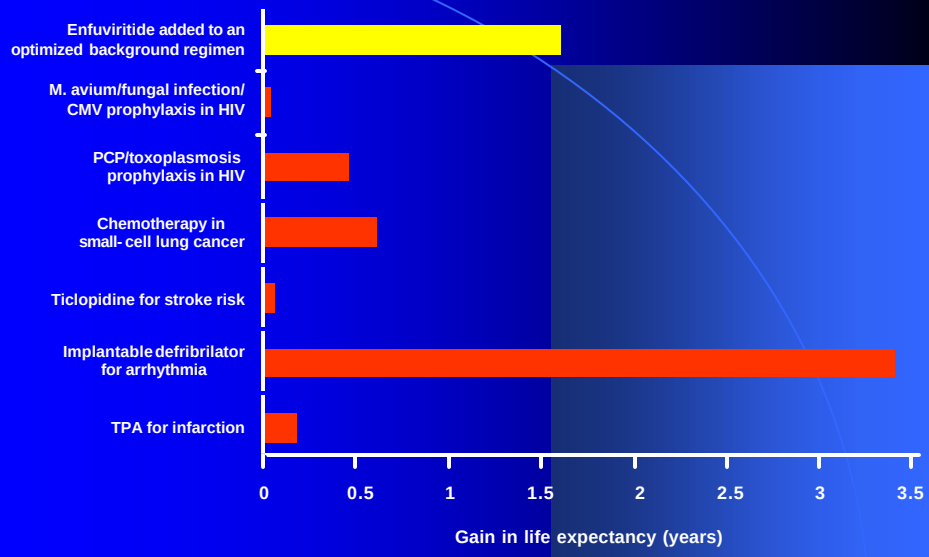
	OB alone	ENF + OB	Difference (ENF + OB) – OB
Mean time to VF (years)	**0.5**	**1.0**	**0.5**
Mean time to IF (years)	**1.3**	**2.9**	**1.6**
Overall ADE free time (years)	**3.3**	**4.8**	**1.5**
Overall life expectancy (years)	**4.6**	**6.2**	**1.6**
Quality adjusted life expectancy (years)	**3.3**	**4.5**	**1.2**
Non-ARV medical costs (per year)			
Pre ADE	**$16,364**	**$23,838**	**$7,464**
Post ADE	**$16,851**	**$16,612**	**–$239**
Total	**$33,215**	**$40,440**	**$7,225**
Pharmaceutical costs (per year)			
OB pre-VF	**$8,560**	**$16,248**	**$7,688**
OB post-VF	**$42,149**	**$55,360**	**$13,219**
ADE	**$18,656**	**$18,038**	**–$618**
Enfuvirtide		**$24,041**	**$24,041**
Total	**$102,580**	**$154,136**	**$51,556**
Cost-effectiveness			
Per life year gained			**$32,795**
Per QALY gained			**$43,607**

Figure 1. Predicted times to clinical outcomes



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*



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

**Adapted from Wright and Weinstein, 1998.*

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

March 23, 2004

Developed by the Panel on Clinical Practices for Treatment of HIV Infection convened by the Department of Health and Human Services (DHHS)

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)

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

Treatment Regimen Failure: Assessment

Therapeutic options:

- Clarify goals: viral suppression may not be possible
- Remaining ARV options
- Base treatment choices on expected tolerability, adherence, future treatment options, past med 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!