New Hope for Treatment Experienced HIV (+) Patients

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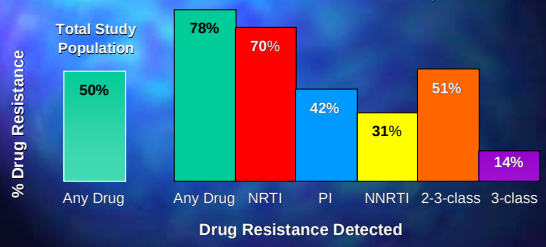
Drug Resistance: Estimated Prevalence

HCSUS: Results representative of the 132,442 (63%) of 209,000 patients under care in early 1996 who survived until 1999 with HIV RNA > 500 copies/mL



Main Objective of Salvage Therapy:

If possible, salvage patients should not be exposed to monotherapy of any kind, or to "virtual monotherapy", where one new drug is added to a failing regimen for any appreciable length of time.

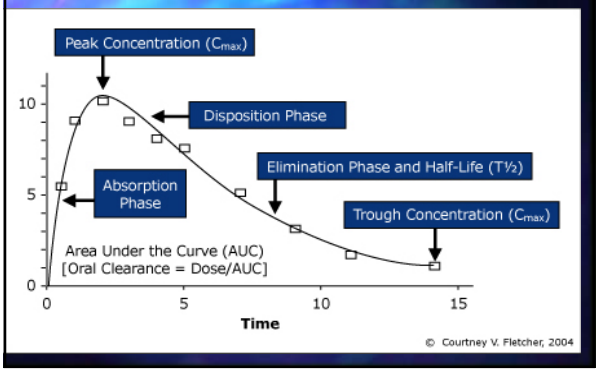
HIV Reverse Transcriptase Inhibitors	HIV Protease Inhibitors
NRTIs ▪ Zidovudine (ZDV, AZT) ▪ Didanosine (ddI) ▪ Zalcitabine (ddC) ▪ Stavudine (d4T) ▪ Lamivudine (3TC) ▪ Abacavir (ABC) ▪ Emtricitabine (FTC)	▪ Saquinavir (SQV) ▪ Ritonavir (RTV) ▪ Indinavir (IDV) ▪ Nelfinavir (NFV) ▪ Amprenavir (APV) ▪ Lopinavir/ritonavir (LPV/RTV) ▪ Atazanavir (ATV)
Nucleotide RTIs ▪ Tenofovir (TDF)	**HIV Entry Inhibitors**
NNRTIs ▪ Nevirapine (NVP) ▪ Delavirdine (DLV) ▪ Efavirenz (EFV)	▪ Enfuvirtide (T-20)

HIV Reverse Transcriptase Inhibitors	HIV Entry Inhibitors
NRTIs ▪ Alovudine (MIV-310, FLT) ▪ Amdoxovir (DAPD) ▪ D-d4FC (DPC 817) ▪ D-FDOC ▪ Racivir ▪ SPD 754 (-dOTC) **Nucleotide RTIs** ▪ GS 7340 (tenofovir prodrug) **NNRTIs** ▪ Calanolide A ▪ Capravirine ▪ GW 8248 ▪ TMC 125	**CD4 Attachment Inhibitors** ▪ BMS-806 ▪ PRO 542 ▪ TNX-355 **Chemokine Receptor Inhibitors** *CCR5 Inhibitors* ▪ AK 602 ▪ PRO 140 ▪ SCH 351125 ▪ SCH 417690 ▪ TAK-220 ▪ UK-427,857 *CXCR4 Inhibitors* ▪ AMD 070 **Fusion Inhibitors** ▪ T-1249
HIV Protease Inhibitors	**HIV Integrase Inhibitors**
▪ Ag 1859 ▪ Fosamprenavir (GW 433908, 908, amprenavir prodrug) ▪ GW 0385 ▪ P-1946 ▪ Ro-033-4649 ▪ Tipranavir (TPV) ▪ TMC 114	▪ L-870810

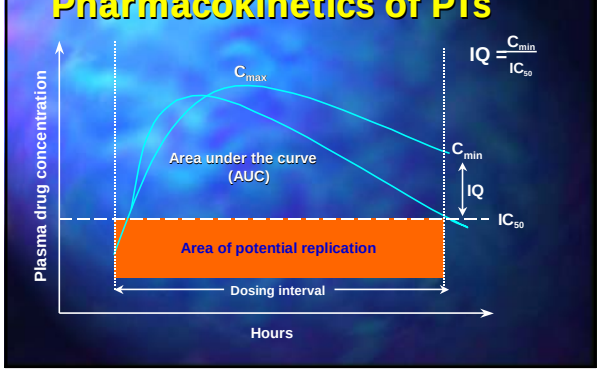
Salvage Patients in the US- Estimate

- 1 million people with HIV in the US
- Approx. 400, 000 under treatment
- 3 Drug Class Resistance (GS=0): 14 % or 56,000 people
- 2 Drug Class Resistance(GS=2): 51 % or 204,000 people
- 30 % may be co-infected with Hep C, and another 10 % with Hep B
- Long term survivors (monotherapy nuke era) vs new salvage patients
- Up to 14% of new infections may have multi-drug resistant (MDR) virus

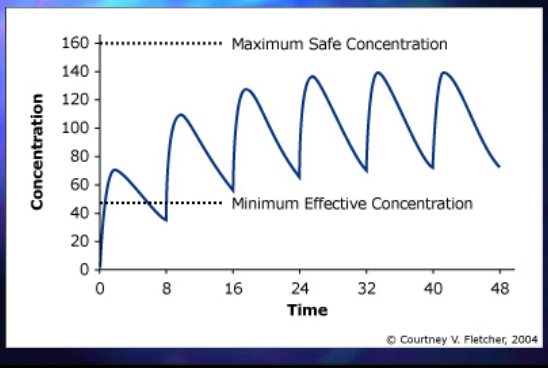
Drug Metabolism



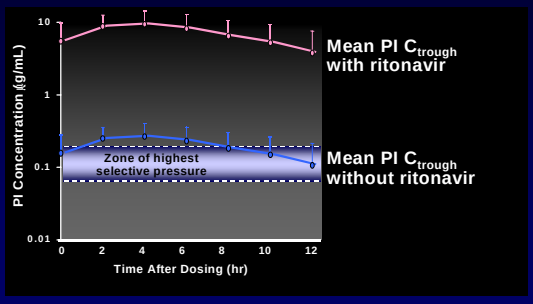
Improving Pharmacokinetics of PIs



Do You Have Enough Medication in your Blood?



Boosting With Ritonavir to Improve the Pharmacokinetics of PIs



Be Aware of Interactions Between PIs

Regimen	Summary of Interactions *	
LPV/RTV + APV	LPV ↓	APV ↓
LPV/RTV + FPV	LPV ↓	FPV ↓
LPV/RTV + SQV	LPV ↔	SQV ↔
LPV/RTV + NFV	LPV ↓	NFV ↔
LPV/RTV + IDV	LPV ↔	IDV ↔ †
ATV + RTV + SQV-hgc	ATV ↔	SQV ↑
FPV + RTV + SQV-hgc	FPV ↔	SQV ↔ ‡

* Compared with single-boosted regimens (in some cases, historical data)

† Small studies with variable findings

‡ If RTV dosed 200 mg/day, SQV if RTV dosed 100 mg/day

APV, amprenavir; ATV, atazanavir; FPV, fosamprenavir; hgc, hard-gel capsule; LPV, lopinavir; RTV, ritonavir; SQV, saquinavir

Norvir Boosted Protease Inhibitors

Boosted Protease Inhibitor Regimen	Dosage
Lopinavir/ritonavir Kaletra	400/100 mg (3 pills) twice daily
Saquinavir/ritonavir Invirase+Norvir	1000/100 mg (6 pills) twice daily 1600/200 mg (10 pills) once daily
Amprenavir/ritonavir Agenerase+Norvir	600/100 mg (5 pills) twice daily
Fosamprenavir/ritonavir Lexiva+Norvir	1400/200 mg (4 pills) once daily 700/100 mg (2 pills) twice daily
Indinavir/ritonavir Crixivan+Norvir	800/100 mg (3 pills) twice daily 400/100 mg (2 pills) twice daily
Atazanavir/ritonavir Reyataz+ Norvir	300/100 mg (3 pills) once daily

Commonly Used Doses for Double Boosted PI combinations

Regimen	Suggested Dosages
LPV/RTV + APV	400/100/750 mg twice daily
LPV/RTV + FPV	533/133/1400 mg twice daily
LPV/RTV + SQV	400/100/1000 mg twice daily
LPV/RTV + NFV	400/100/1000 mg twice daily
LPV/RTV + IDV	400/100/600 mg twice daily
ATV + RTV + SQV-hgc	300/100/1600 mg once daily
FPV + RTV + SQV-hgc	700/200/1000 mg twice daily

Note: See text for discussion of specific regimens. Limited data and experience exist for most regimens. Consider therapeutic drug monitoring, especially among patients with extensive protease resistance.

APV, amprenavir; ATV, atazanavir; FPV, fosamprenavir; IDV, indinavir; LPV, lopinavir; NFV, nelfinavir; RTV, ritonavir; SQV-hgc, saquinavir hard-gel capsules.

Double PI Studies in Treatment Experienced Patients

Cohort	N	Study Type and Regimen	Virologic Outcome (ITT Analysis)
PIN	20	▪ Nonrandomized observational cohort ▪ PI-naive patients ▪ Lopinavir/ritonavir + saquinavir	65% < 50 copies/mL at 48 wks
LOPSAQ	126	▪ Nonrandomized observational cohort ▪ PI-experienced patients ▪ Lopinavir/ritonavir + saquinavir, following STI	Median 3.53 $\log_{10}$ VL reduction at 48 wks
CRIXILOP	32	▪ Nonrandomized observational cohort ▪ PI-experienced patients ▪ Lopinavir/ritonavir + indinavir	Median 1.9 $\log_{10}$ VL reduction at 24 wks
Puzzle-1	37	▪ Prospective, randomized study ▪ PI-experienced patients ▪ Lopinavir/ritonavir + amprenavir ± additional ritonavir	Median 2.0 and 1.1 $\log_{10}$ VL reductions at 52 wks in +ritonavir and –ritonavir arms, respectively

ITT, intent to treat; VL, viral load

How Do Salvage Patients Access Drugs in the US?

- **Treatment IND**
  - Pros: Very early access for those who need it. Physician chooses best combo.
  - Cons: Difficult paper work- local IRBs involved. Patients may be exposed to unknown toxicities . Death vs Risks
- **Phase II- Safety/Dose**
  - Inclusion/exclusion barriers (genotype, allowed OBT,liver, etc)- Optimum dose/safety not established
- **Phase III - Efficacy**
  - Inclusion/exclusion (genotype, allowed OBT, liver,etc) barriers
- **Open Label Safety Study (pre- approval)**
  - Just like Phase III- protocol requirements plus CD4 limits
- **Expanded Access (pre- approval)**
  - No CD4/genotype limits but possible liver exclusions. Physician chooses best OBT freely.

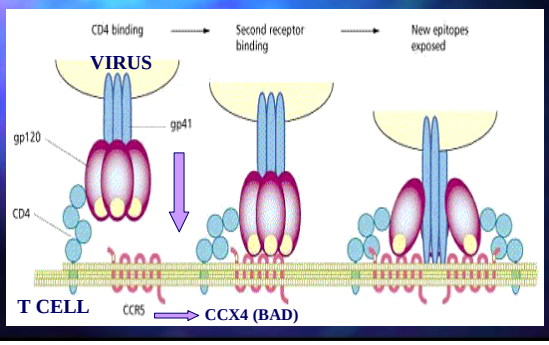
Drugs for Treatment Experience Patients

- **Upcoming Phase II:**
  - Pfizer CCR5 Entry Inhibitor UK-427,857
  - Schering CCR5 Entry Inhibitor
  - Tanox TNX 355 CD4 attachment inhibitor
- **Phase II (now enrolling)**
  - GW873140 (CCR5 Antagonist)
  - Tibotec's TMC 114 Protease
  - Tibotec's TMC 125 NNRTI
- **Phase III :**
  - Boeringher Ingelheim's Protease Tipranavir (closed to enrollment). Currently available through Open Label Safety Study for those under 100 T cells.
  - Pfizer Capravirine (NNRTI) - Closed

Barriers in Entering Salvage Drug Protocols

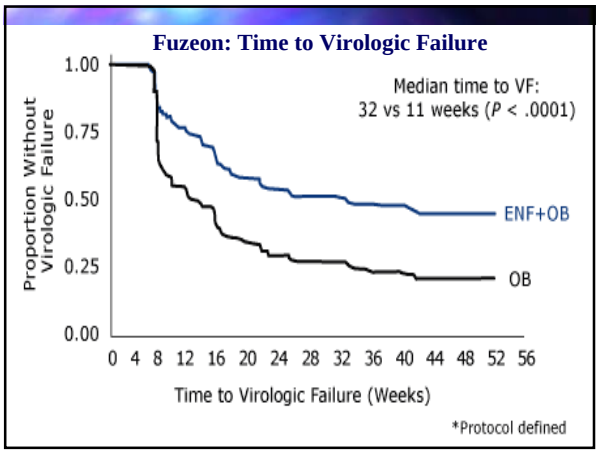
Do you have the right mutations?
Do you have Hep B or C coinfection?
Do you have high liver enzymes?
Have you taken T-20?

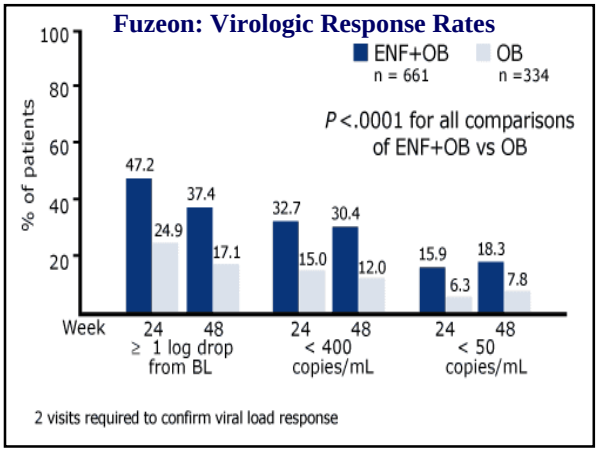
CD4 Receptors- Entry Ports to the T cell

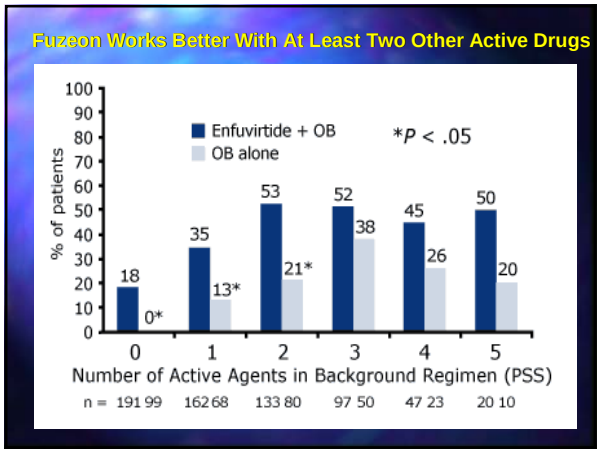


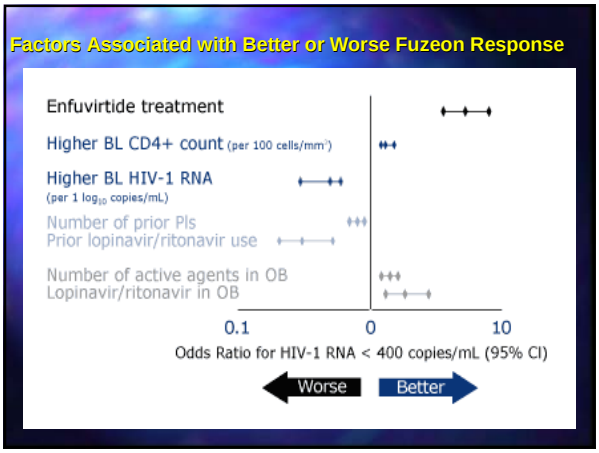
Fuzeon: Mechanism of Action

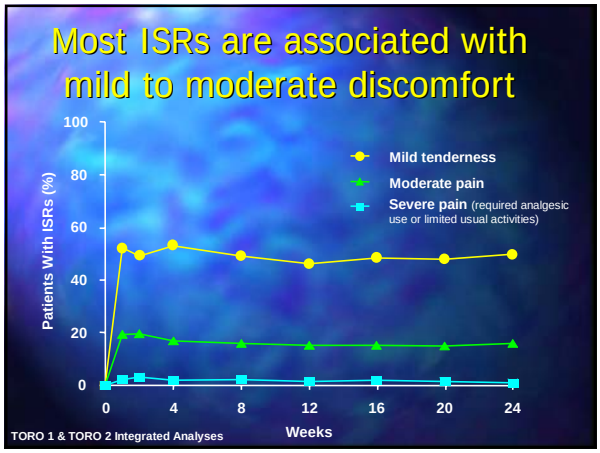
Video











Fuzeon- 2 Year Follow Up Data

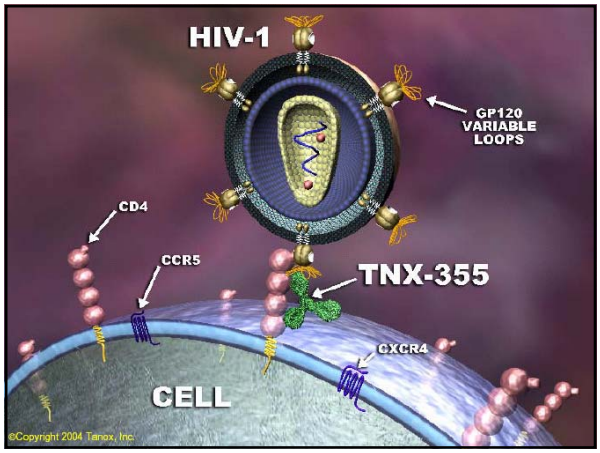
	Fuzeon + OBT	OBT Alone
Mean CD4 increase	166	10
Mean Viral Load Decrease	- 2.56 log	-0.3 log
% Patients with CD4 increase over 50 cells	39 % wk 96 51 % wk 48	16 % Wk 48
% Patients with Viral Load under 400	26 % wk 96 34% wk 48	13% wk 48

Fuzeon- 2 Year Follow Up

- At week 96, 47% of patients withdrew:
  - 10.2% for insufficient therapeutic response;
  - 7.2% for injection site reactions;
  - 12.1% for adverse events (OB related)

FUZEON 2 YEAR FOLLOW UP: SIDE EFFECTS

	Year 1	Year 2	Total
Upper respiratory tract infection	12%	7%	19%
Sinusitis	8%	3%	11%
Bronchitis	7.6%	3%	10.7%
Cough	8.7%	3%	12.7%
Diarrhea	32%	5%	37%
Pyrexia (increased temp)	12%	4%	17%
Arthralgia (joint pain)	8%	3%	11%
Oral candidiasis	8%	3%	11%
Fatigue	20%	3%	24%
Dermatitis	10%	3%	12%



TNX-355 by Tanox Pharmaceutical

- Acts by inhibiting viral fusion after virus-CD4 binding
- After a single infusion of TNX-355:
  - Gradual dose-related HIV RNA reduction (–1.09 $\log_{10}$ c/mL at day 21 at highest dose)
  - Immediate CD4 increase (approximately 100 cells/mm^3)
  - No SAEs reported
- Further, multiple dosing studies planned, with infusions every 7–14 days

Kuritzkes DR, *et al. 10th CROI*, Boston 2003, #13

Anti-CD4 monoclonal antibody, TNX-355

- Inclusion Criteria
  - Cumulative HAART experience of a minimum of 6 months, with triple-class experience (NRTI, NNRTI, PI)
  - Viral susceptibility to OBT during screening, determined by PhenoSense GT or similar assay
  - Stable viral load >5,000 within 8 weeks prior to randomization while on stable HAART regimen for minimum 4 weeks prior to screening.
  - CD4+ count >50 cells/mL
- Exclusion Criteria
  - Prior use of Fuzeon (T 20), LIVER ENZYMES > 2.5 UPPER LIMIT

Kuritzkes DR, *et al. 10th CROI*, Boston 2003, #13

TANOX MEETING THIS THURSDAY AT THE CENTER FOR AIDS

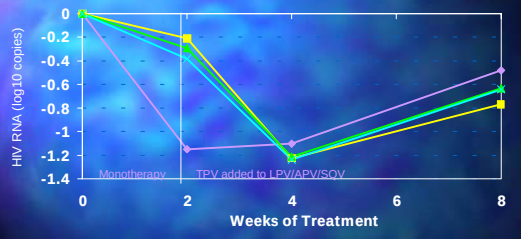
Thursday, July 22, 2004
6:00 to 8:00 pm
Space is limited.
RSVP to Floyd 713.527.8219
x106 or
floyd@centerforaids.org

Tipranavir/RTV in PI-experienced subjects

- Non-peptidic PI, active against WT and PI-resistant viruses
- Phase II safety/dose finding study of TPV/RTV: 500/100, 500/200, 750/200 mg all BID
- 216 patients enrolled:
  - Experience of all 3 ART classes
  - ≥2 PIs and at least one primary PI mutation
  - Any CD4; VL >1000 c/mL
- 500/200 mg dose optimal:
  - Median VL reduction of 0.98 $\log_{10}$ in functional monotherapy at 2 weeks
  - Response not compromised by >20 mutations except when ≥3 of the following PR mutations present: L33I/V/F, V82A/F/L/T, I84V, L90M
  - AEs: diarrhea, 4.2%; ⇧ LFTs, 10%; ⇧ TG, 15.5%; cholesterol, no change

Gathe J, *et al. 10th CROI*, Boston 2003, #179

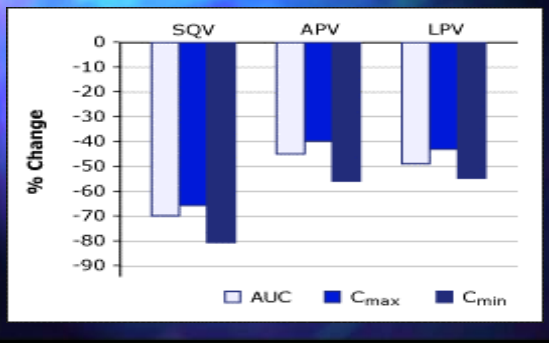
Tipranavir BI 1182.51
HIV RNA median change from baseline



TPV	n = 66	60	60	57
APV	n = 74	64	64	61
SQV	n = 74	67	70	64
LPV	n = 78	74	72	62

TPV/r TPV/APV/r TPV/SQV/r TPV/LPV/r

Tipranavir Brings PI Blood Levels Down



Tipranavir- Lessons Learned

- It is a heavy inducer of the metabolism of all other protease inhibitors (it reduces blood levels of those drugs), even in the presence of 200 mg of Norvir
- It can reduce HIV viral load by 1.2 logs even in patients with multi-drug resistance. The effect only lasts for 4 weeks if no active drug is present in the background.
- We suspect T-20 may add durability to Tipranavir (data not available yet)
- GI and liver side effects do not seem greater than other protease inhibitors
- We will know more by late Oct (ICAAC conf)

Tipranavir Open Label Study Sites in Houston

- Male or Female with HIV diagnosis
- CD4 less than 100 cells
- Viral load greater than 10,000 copies
- Failed or intolerant to currently approved treatments and have limited treatment options
- Expanded access to start in Sept/Oct

Tipranavir Open Label Study Sites in Houston

Dr. Joseph Gathe
Ph: 713-526-9821

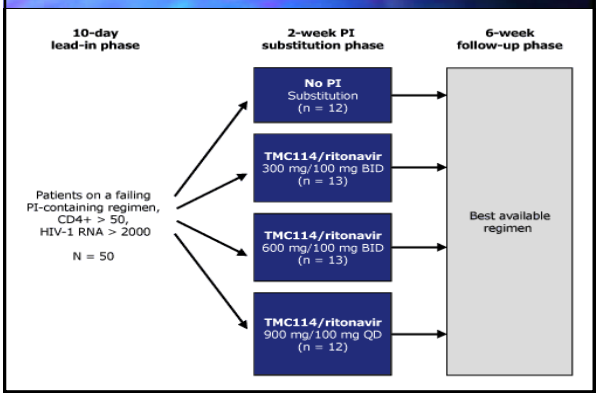
Dr. Shannon Schrader
713-526-1717

TMC-114+Norvir in PI-experienced patients

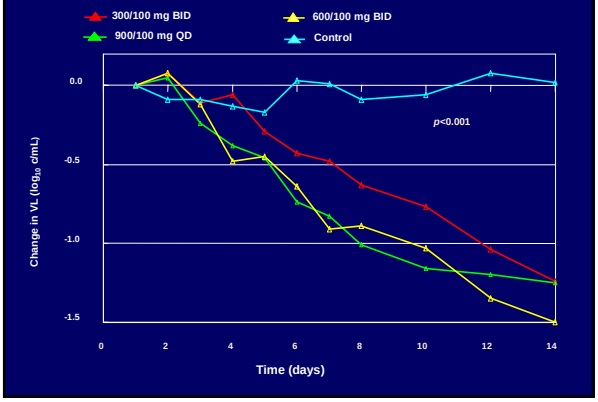
- Open, randomized study in 50 patients failing therapy:
  - CD4 >50 cells/mm^3; HIV RNA >2000 c/mL
  - Prior use of 2–4 PIs for ≥2 months each
- Current PIs:
  - LPV/r 54%, IDV 14%, NFV 6%
  - Boosted PIs 86%
- Resistance:
  - 46% resistant to all PIs
  - 27% sensitive to 1 PI
  - Median fold-change to TMC-114 = 1.7
- PI substitution with 1 of 3 doses of TMC-114 + RTV vs no substitution
- AEs:
  - Diarrhea 30%
  - Rash 5%
  - Headache 15%

Arasteh K, *et al. 10th CROI*, Boston 2003, #8; Koh Y, *et al. ibid*, #549

TMC 114: New PI for Multi Drug Resistant Virus- Study Design



TMC 114- Study Results



TMC 114 study sites in Houston

- University of Texas Health Sciences Center at Houston, Houston, Texas, 77030, United States; Raul Nunez 713-500-5483 raul.nunez@uth.tmc.edu
  Ben Barnett, MD, Principal Investigator

  University of Texas Medical Branch, Galveston, Texas, 77555-0435, United States; Recruiting Cheryl Mogridge, RN 409-772-3991 clmogrid@utmb.edu
  William O'Brien, MD, Principal Investigator

TMC 125- A new NNRTI

- It might work following resistance to Sustiva (EFV) or Viramune (NVP). In a clinical trial conducted in England, 16 HIV-positive who were failing either Sustiva® (efavirenz) or Viramune® (nevirapine) were switched to TMC-125 (in combination with the nucleoside analogues they were taking previously). Twelve of these 16 patients had mutations in their virus known to cause high-level resistance to both Sustiva and Viramune. Eight days after switching to TMC-125, viral load decreased, on average, by 0.86 log and seven patients saw their viral load decrease by more than 1 log.

TMC 125

Inclusion Criteria

- HIV-1 infection, male or female
- Viral load at screening > 1,000 copies/mL
- Documented genotypic evidence of resistance to currently available NNRTIs, either present at screening, or from prior genotypic analysis
- At least 3 primary PI resistance mutations on screening VirtualPhenotype
- Previous NRTI experience for at least 3 months

Exclusion Criteria:

- Acute hepatitis A, B, or C
- Chronic HBV and/or HCV with AST and/or ALT > 3 x ULN

TMC 125 study sites in Houston

- Shannon Schrader, MD
  - Mark Mall, RN 713-830-3018
- Ben Barnett, MD
  - Raul Nunez 713-500-5483

Safety and Effectiveness of the Oral HIV Entry Inhibitor SCH 417690 in HIV Infected Patients

- CCR5 Receptor Inhibitor
- The study will last a maximum of 48 weeks.
- Patients will be randomly assigned to one of 4 groups.
  - -Group 1 will receive placebo;
  - -Group 2 will receive 5 mg SCH 417690 daily;
  - -Group 3 will receive 10 mg SCH 417690 daily;
  - -Group 4 will receive 15 mg SCH 417690 daily.
- All patients will continue their current ART
- After two weeks, patients will receive ART optimized by the results of genotypic/phenotypic testing performed at study screening.

University of Texas, Galveston
Carrie Derkowski, BS 409-747-0241 caderkow@utmb.edu

Internet Resources

- For more information on clinical studies, visit www.clinicaltrials.gov
- Subscribe to a free Internet support group by sending an email to: FuzeonSupport-subscribe@yahoogroups.com
- Nelson Vergel's email powertx@aol.com.
- Visit the upcoming web site www.SalvageTherapies.org
- Save Your Life- Become a Treatment Activist. Visit atac-usa.org

FUZEON RESOURCE CENTER AT THEBODY.COM

http://www.thebody.com/fuzeon/resource/?m54h