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Randomized pilot study of immediate enfuvirtide-based therapy vs. a treatment interruption followed by enfuvirtide-based therapy in highly treatment-experienced patients

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INTRODUCTION

In a previous study, subjects undergoing a structured treatment interruption and subsequently resuming therapy containing one and only one new active drug often achieved a durable viral suppression (viral load < 200 for 72 weeks) (AIDS 2003 17:361-70). This is in contrast to the common observation that salvage regimens containing only a single active agent most often result in rapid virologic failure (Lalezari, NEJM 348:2175).

Based on these observations, we hypothesized that treatment interruptions as a strategy may be most beneficial in a carefully selected cohort of individuals whose virus was resistant to most available drugs yet sensitive to an emerging new therapeutic class (e.g., the fusion inhibitors).

STUDY DESIGN and METHODS

This is a prospective randomized pilot study of enfuvirtide-naïve patients with highly resistant HIV (defined as having genotypic or historical evidence of resistance to ≥ 2 PIs, ≥ 2 NRTIs and ≥ 1 NNRTI).

Thirty subjects were randomized to immediate enfuvirtide plus "optimized background" drugs versus a 16 week structured treatment interruption followed by enfuvirtide/optimized background.

The primary outcome was proportion < 50 copies RNA/mL 48 weeks after initiation of an enfuvirtide based regimen.

Phenotypic assays RT/protease phenotypic susceptibility was measured at baseline using PhenoSense (ViroLogic, Inc). The phenotypic susceptibility score (PSS) was calculated as follows: if the drug was sensitive (< lower fold change cutoff), score = 1; if the drug was partially effective (between the lower and upper cutoff) score = 0.5; if the drug was resistant (> upper fold change), score = 0.

Enfuvirtide drug susceptibility and viral tropism were measured using single cycle replication entry assay in which patient-derived pol env genes was co-transfected with a luciferase-containing env-defective HIV genomic vector; infectivity is assessed by measuring the production of relative light units (RLUs) in cell lines expressing CCR5 or CXCR4.

Genotypic assays. A segment of the gp41-coding region was also amplified, and at least 8 independent clones were sequenced to assess resistance mutations.

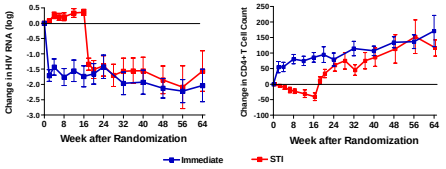
RESULTS

TABLE 1: Baseline characteristics.

Characteristic	Immediate therapy (n=15)	STI (n=15)	All patients (n=30)
HIV-1 RNA (log_{10} copies/mL)	4.62 (4.47 – 5.02)	4.79 (4.53 – 5.13)	4.72 (4.51 – 5.18)
CD4 (cells/mL)	26 (7 – 139)	47 (13 – 94)	39 (12 – 135)
Abacavir fold-change in IC50	6.8 (4.0 – 9.0)	4.6 (3.0 – 8.2)	5.5 (3.2 – 8.5)
Lopinavir fold-change in IC50	41 (1.4 – 124)	69 (5.3 – 179)	51 (2.6 – 171)
Phenotypic sensitivity score	1.5 (1.0 – 3.0)	2.5 (1.0 – 3.0)	2.0 (1.0 – 3.0)
ENF IC50 µg/mL	0.021 (0.015 – 0.032)	0.037 (0.030 – 0.049)	0.031 (0.016 – 0.043)

The median duration of STI was 15.9 (IQR 12.3 to 16) weeks. During the STI, X subjects showed complete reversion to wild-type, y showed partial reversion and z showed no change. CD4 decreased by a median of 27 cells/mm (IQR –59 to –7) and HIV RNA increased by 0.40 (IQR +0.13 to +0.57) log copies/mL during the treatment interruption phase. Two patients discontinued therapy with enfuvirtide due to intolerance of mild injection site reactions. One patient developed bacterial pneumonia and sepsis and died 4 weeks after initiating enfuvirtide.

FIGURE 1: Effect of STI On Outcome.



There was no difference in virologic outcomes at week 24 (53 and 36% were < 75 in immediate and STI arms, respectively, P = NS). Similar trends were observed at week 48. In multivariate analysis, only baseline phenotypic susceptibility score was predictive of treatment response at week 24 (P = 0.03). Baseline susceptibility to enfuvirtide did not predict outcome.

FIGURE 2: Virologic Failure Outcomes.

The majority of patients failing enfuvirtide experienced a rapid viral rebound, with HIV RNA levels often approaching pre-treatment levels within 4 to 16 weeks (Panels A and B). Despite rapid virologic failure (defined as return to < 0.5 log of baseline by week 12), CD4+ T cell counts increased and remained above baseline, at least through week 24 (Panel C and D).

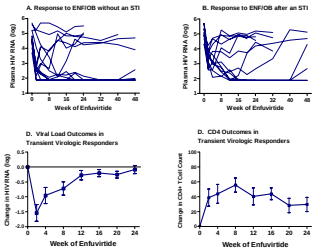
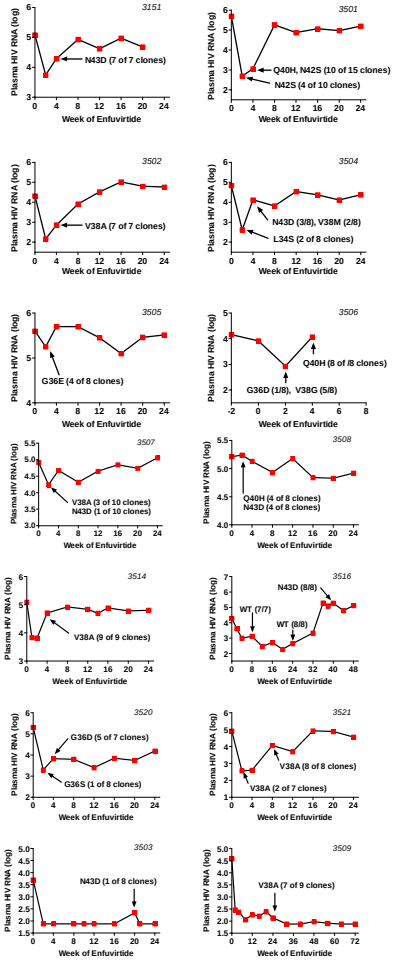


FIGURE 3: Early emergence of resistance



Clonal analysis of HR-1 and HR2 sequences was performed at baseline and at multiple time points after starting enfuvirtide. Genotypic evidence of enfuvirtide resistance was routinely detected at earliest virologic failure time point (which was week 2 to 4 for many subjects). Two subjects with low to intermittent viremia had minority variants containing new enfuvirtide-associated mutations (3503 and 3509).

DISCUSSION

Interrupting therapy prior to initiating salvage therapy with enfuvirtide did not result in an improved virologic response at 48 weeks.

The collective predictive activity of an enfuvirtide-containing regimen (as defined by the phenotypic susceptibility score), but not enfuvirtide baseline susceptibility, was important in predicting treatment response. All subjects with a PSS of ≤ 1 failed to achieve a durable virologic response; in contrast, 63% of subjects with a PSS of > 1 achieved had an undetectable viral load through week 24.

Virologic failure of an enfuvirtide-based regimen was often associated with a rapid increase in viremia back toward pre-treatment levels. However, CD4+ T cell counts often increased and remained elevated in such patients, at least through 24 weeks of observation.

In contrast to experience with protease inhibitors and most nucleoside analogues, genotypic evidence of enfuvirtide resistance was evident at the earliest virologic failure time points. Resistance was evident by week 2 in many subjects, and could be detected in two subjects with intermittent viremia.

Collectively, these data indicate that a low "genetic barrier" to enfuvirtide resistance exists *in vivo*, and that variants containing a single resistance mutation have greater fitness that wild-type HIV (as measured in presence of drug). Our observation that these mutations wane rapidly in absence of continued drug pressure (poster #680) suggests that these same mutations reduce replicative capacity.

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