Enfuvirtide Antiviral Activity despite Rebound Viremia and Resistance Mutations: Fitness Tampering or a Case of Persistent Braking on Entering?

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(See the article by Deeks et al., on pages 387–91.)

Combination antiretroviral therapy has revolutionized the care of HIV-1–infected individuals, producing profound improvements in morbidity and mortality. Therapy does not, however, cure HIV infection, and the goal of combination therapy remains the suppression of HIV-1 replication below the limit of detection. Despite a growing array of antiretroviral therapy options, virologic suppression is difficult for many patients to achieve, and treatment of drug-resistant virus is a critical challenge confronting HIV therapeutics.

Resistance emerges as a result of both virologic and clinical factors. HIV-1 replication is rapid and error prone, yielding a large, genetically diverse virus population. As a consequence, many single amino-acid changes conferring drug resistance may preexist as low frequency polymorphisms before the initiation of antiviral therapy [1, 2]. Individuals who received their diagnosis of HIV infection before the widespread use of combination antiretroviral regimens often received serial therapy with 1 or 2 agents, resulting in the accumulation of additional drug-resistance mutations to each new approved agent. Poor adherence to therapy has been associated with higher rates of virologic failure and the emergence of drug resistance, and sequential regimens for drug-resistant virus fail in patients [3–6] more often than initial regimens in drug-naive individuals [7–9].

Current therapeutic regimens to treat highly drug-resistant HIV-1 remain inadequate. The recommendation that regimens to treat drug-resistant HIV-1 should include at least 2 new drugs to which patients have not been exposed [10] is often impossible to fulfill if patients have extensive prior therapy experience. Recently, several studies have suggested the presence of residual virologic activity for some antivirals even in the presence of mutations [11–14]. In this issue of the Journal of Infectious Diseases, Deeks et al. [15] report the presence of virologic benefit of enfuvirtide (T-20) in the presence of rebound viremia and enfuvirtide resistance mutations.

Enfuvirtide is the first of a new class of antiretrovirals targeting membrane fusion, an essential energy-requiring step in HIV infection. CD4 receptor and coreceptor binding by glycoprotein (gp) 120 triggers conformational changes in gp41. The rearrangement of specific gp41 heptad-repeat regions 1 and 2 (HR-1 and -2, respectively) into a 6-helix bundle functions as a spring loaded mechanism to provide the energy necessary for membrane fusion. Enfuvirtide is a synthetic 36-aa peptide that binds to HR-1, disrupting interactions with HR-2 and interrupting the fusion reaction [16].

The clinical efficacy of enfuvirtide was demonstrated in 2 phase III studies, which demonstrated its superiority with an optimized antiretroviral background over optimized background alone (the T-20 vs. Optimized Regimen Only [TORO] studies) in highly treatment-experienced patients. Groups receiving regimens that contained enfuvirtide had significantly greater proportion of patients with a ≥1-log₁₀ decrease in HIV-1 RNA levels, <400 copies HIV-1 RNA/mL plasma, and <50 copies HIV-1 RNA/mL plasma. CD4+ T cell increases were significantly greater in patients receiving regimens that contained enfuvirtide, compared with patients receiving optimized regimens only [17, 18]. Additional studies have documented that week-12 data predicted durable viral suppression at 24, 48, and 96 weeks of therapy [19, 20]. Enfuvirtide activity extends to HIV-1 group M (A, B, C, H, A/G, B/H,
Enfuvirtide is an injectable antiretroviral with a number of drawbacks: drug reconstitution can require up to 45 min–1 h, and twice-daily subcutaneous administration may be difficult for lipodystrophic individuals with limited available subcutaneous fat. Enfuvirtide is associated with significant side effects, notably injection-site reactions, and it is expensive. Because enfuvirtide has not been studied extensively in antiretroviral drug–naive patients, it received accelerated Food and Drug Administration approval in March of 2003 for use in treatment-experienced patients only.

Like all antiretrovirals, resistance emerges on therapy with enfuvirtide. HR regions have structural constraints that are genetically well conserved. Despite the relatively constant nature of HR-1 and HR-2, baseline susceptibility to enfuvirtide varies considerably; unlike pro-pol HIV-1 drug targets, which have a relatively narrow (<10-fold) variation in drug susceptibility in HIV-1, baseline susceptibility to enfuvirtide varies by >1000-fold in IC_{50} among untreated HIV-1 isolates [24, 25]. During therapy, a number of mutations (singly or in combination) in a region of HR-1 at 36–45 aa result in rebound viremia, including G36V, N42D or T, N43D, L44M, and L45M [21, 25–30]. The time frame of the emergence of drug resistance in mono-therapy studies (2–3 weeks) suggests that such a number of single mutations pre-existed in the virus population and were simply selected by therapy [2, 29]. Although the bulk of enfuvirtide resistance may be attributable to the region at 36–45 aa [28], sensitivity may be affected by regions outside heptad repeats [26, 28, 30, 31] and by receptor density and fusion rates [32]. It is not clear whether coreceptor sensitivity affects enfuvirtide resistance; the results of in vitro studies have suggested R5 viruses are intrinsically less sensitive to enfuvirtide; Melby et al. [33] reported a shift from dual-tropic to R5-tropic viruses in treated patients in the TORO-1 and -2 studies, which suggests that enfuvirtide may have greater activity against R4-tropic viruses.

Post hoc analyses of patients receiving enfuvirtide in the TORO trials and in other studies have demonstrated sustained CD4^{+} T cell responses even in patients who did not achieve a ≥1-log reduction in viral RNA levels, which suggests an immunologic benefit of continued therapy despite persistent viremia [20, 34]. Deeks et al. hypothesize that, if persistent virologic effect is present, discontinuing enfuvirtide would lead to an increase in HIV-1 viremia. Similar short-term (“shortstop”) or long-term discontinuation strategies have been used to study the efficacy of the nucleoside reverse-transcriptase inhibitor, nonnucleoside reverse-transcriptase inhibitor, and protease inhibitor components of combination antiretroviral therapy [11–14, 35]. In the study by Deeks et al., patients receiving enfuvirtide for at least 24 weeks with persistent viremia >400 HIV copies/mL plasma were invited to enroll and discontinue enfuvirtide for 12 weeks. Those with >0.5-log increases in viral RNA levels or those with CD4^{+} T cell decreases of >50% were encouraged to restart enfuvirtide either in the context of a new or an existing drug background. Outcome measures included viral RNA levels, sequential genotypic and phenotypic analyses, and CD4^{+} T cell counts in peripheral blood.

Overall, patients who discontinued the enfuvirtide portion of their regimen had a significant increase in viral RNA levels; the greatest increases were detected within 4 weeks after discontinuation but were sustained over the course of 24 weeks (increase of 0.19 log_{10} HIV RNA copies/mL, repeated-measures regression model). In the majority of patients, virologic rebound occurred before phenotypic assays detected a shift in IC_{50}, which suggests that enfuvirtide had suppressive activity against resistant virus. Patients were viremic during therapy and, overall, had decreasing CD4^{+} T cell counts. Slopes after the discontinuation of enfuvirtide were also negative but were not significantly different from the negative slope before therapy. In this pilot study, therefore, it is not known whether the modest but significant virologic effect had clinical or immunologic consequences.

These data are provocative in suggesting that enfuvirtide may have partial antiviral activity in the presence of strong drug resistance mutations. The study poses 2 broad questions that converge on essential drug resistance issues.

What is the virologic and molecular basis for continued drug efficacy in the presence of resistance mutations? In vitro assays presented by Deeks et al. and by other researchers have suggested that enfuvirtide-resistant envelopes exhibit delayed viral entry kinetics or reduced replicative capacity [36]. Other possibilities, including coreceptor shift [33] and replication or fitness differences [37], may help explain the observation, although studies of some enfuvirtide-resistant env suggest high replicative capacity [38].

What is contribution of enfuvirtide drug levels to persistent antiviral effects? In Phase II studies, trough levels varied by 6-fold and exceeded the IC_{50}s of wild-type virus by 8–10 fold [39–41]. In the TORO studies, resistant virus emerged with IC_{50} values in range of 4 to >200-fold [25]. It is possible that enfuvirtide levels in vivo approximate the IC_{50}s of some resistant isolates, which accounts for partial antiviral activity.

The clinical benefit of continuing enfuvirtide in the presence of rebound viremia remains uncertain. Persistence pays off, but for whom? Does the virologic improvement demonstrated in this trial translate into an immunologic or clinical benefit, or is it simply an opportunity for continued drug pressure to select progressively more resistant mutants? At present, these data and those presented elsewhere are not sufficiently compelling to expand indications for the use of enfuvirtide or to amend guidelines regarding its use. The temptation to regard this virologic effect as “intermediate” activity is not
supported with the same robust clinical trial data that established enfuvirtide’s activity, and it should be avoided for the purposes of reporting standard genotyping and phenotyping.

As Deeks et al. point out, larger trials are necessary to evaluate clinical and immunologic responses, the duration of the potential benefit, and the profile of adverse effects of continued enfuvirtide therapy in the setting of rebound viremia. Clinical end-point studies may be feasible in patients with advanced HIV-1 disease who are considering the use of enfuvirtide. Balanced against the cost, inconvenience, and potential adverse effects of continuing enfuvirtide in the setting of resistance, randomized trials, appropriately designed with a focus on sample size, inclusion criteria, and outcome measures, are warranted.

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References


