Week-12 Response to Therapy as a Predictor of Week 24, 48, and 96 Outcome in Patients Receiving the HIV Fusion Inhibitor Enfuvirtide in the T-20 versus Optimized Regimen Only (TORO) Trials

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Background. Early virological response to antiretroviral therapy is predictive of long-term treatment outcome in therapy-naive patients. In treatment-experienced patients, such correlations are less well defined, because initial responses may be less pronounced and transient because of accumulated cross-resistance to prior therapies. Our objectives were to explore how the virological and immunological status of experienced patients at an early time point (week 12) during enfuvirtide-based therapy predicted their responses at weeks 24, 48, and 96 in the T-20 versus Optimized Regimen Only (TORO) trials.

Methods. Post hoc, modified, on-treatment and intent-to-treat analyses were performed to determine whether the relationship between virological and immunological outcomes at weeks 24, 48, and 96 were predicted by the patients’ week-12 responses to therapy.

Results. Using a modified on-treatment analysis for patients who, by week 12, achieved a decrease in their HIV-1 RNA load of ≥1 log10 copies/mL, 39.2% (95% CI, 33.6%–44.8%) and 59.5% (95% CI, 53.8%–65.1%) achieved a viral load of <50 copies/mL or <400 copies/mL at week 96, respectively, compared with 1.3% (95% CI, 0%–3.8%) and 2.6% (95% CI, 0%–6.1%) of patients, respectively, who did not achieve an early virological response. Using the same modified on-treatment analysis method for patients who, at week 12, achieved a CD4 cell count increase of ≥50 cells/mm3, 87.2% (95% CI, 82.6–91.8) maintained or improved this response through week 96, compared with 56.6% (95% CI, 47.5–65.8) of patients who did not achieve this early categorical immunological response.

Conclusion. Enfuvirtide-based treatment regimens are associated with a rapid and durable response. Week-12 virological and immunological responses to treatment with enfuvirtide are predictive of subsequent outcomes in triple-class treatment–experienced patients.

Enfuvirtide is a 36–amino acid synthetic peptide inhibitor of HIV cell membrane fusion, and it is the first clinically available antiretroviral in this new class of entry inhibitors [1]. In combination with a resistance-guided optimized background (OB) of other antiretroviral agents, enfuvirtide demonstrated significant and durable virological and immunological efficacy over 96 weeks in a patient population with triple-class antiretroviral (ARV) treatment experience [2–5].

The dynamics of early viral load responses in the phase III T-20 versus Optimized Regimen Only (TORO) studies showed that HIV-1 RNA load responses occurred early in treatment-experienced patients who received an enfuvirtide-based regimen, with a median time of 8 days to achieve a viral load reduction of ≥1 log10 from baseline, compared with 92 days for patients receiving an OB regimen alone (according to intent-to-treat analysis) (95% CI, −144 to −65; P<0.0001) [6]. Four baseline predictors of virological response to enfuvirtide-based antiretroviral therapy at weeks 24 and 48 have been identified from the phases III TORO studies: a viral load <5 log copies/mL, a CD4...
cell count $\geq$ 100 cells/mm$^3$, prior treatment with $\leq$ 10 prior ARVs, and $\geq$ 2 active ARVs in the current OB regimen [7, 8]. Although this predictive model is useful, TORO studies have also shown that patients do derive benefit from adding enfuvirtide to optimized antiretroviral therapy, whatever their baseline parameters.

Enfuvirtide is a product that requires reconstitution prior to subcutaneous injection and is therefore not a simple drug to administer. Typically, enfuvirtide is self-administered and requires training and support to minimize any potential negative impact on patient lifestyle and therapy adherence [9]. For these reasons, physicians and patients may be initially reluctant to start enfuvirtide therapy. Establishing appropriate patient and physician expectations during the first weeks of enfuvirtide-based antiretroviral therapy could have a significant influence on patient acceptance and adherence. Therefore, knowledge of how early virological and immunological response to enfuvirtide-based antiretroviral therapy may predict long-term therapeutic success or failure will be instrumental to improving the acceptability of enfuvirtide treatment for both patient and clinician.

There have been a number of studies demonstrating that short-term (1–12 weeks), induced virological decay rates are predictive of longer-term virological outcomes [10–16]. However, the patient populations in these studies were either previously drug naive or had limited prior treatment experience. The predictive value of early virological responses is less clear in patients who change their antiretroviral therapy regimen after virological failure with a triple-class ARV regimen, for whom initial virological responses may be slower, less pronounced, and transient because of accumulated cross-resistance to prior therapies.

It is, therefore, important to determine whether long-term response can be predicted early on. We explore here, within the TORO data set, early virological and immunological responses at a time point of 12 weeks from therapy commencement and the impact of these responses on long-term virological and immunological outcomes.

**METHODS**

The TORO trials are randomized, phase III studies of enfuvirtide plus an OB regimen versus an OB regimen alone that were performed with triple-class antiretroviral treatment–experienced patients in North and South America (TORO 1) and in Europe and Australia (TORO 2) [4, 5]. A total of 995 triple-class treatment–experienced patients were randomized in a ratio of 2:1 to receive a regimen of enfuvirtide together with an OB (hereafter referred to as the enfuvirtide arm; $n = 661$) or a regimen of OB alone (hereafter referred to as the OB arm; $n = 334$) and had at least 1 follow-up measurement.

To determine whether an early response to an enfuvirtide-based regimen was predictive of subsequent response, we examined the patients’ virological and immunological responses to therapy during the first 12 weeks and identified the impact of these early responses on durability through weeks 24, 48, and 96. A 12-week rather than a 4- or 8-week time point was chosen as the earliest moment for analysis, because treatment responses (i.e., reductions in viral load) were still occurring during the first 12 weeks of the study. Also, from a pragmatic although somewhat arbitrary perspective that is relevant to patient management, a 12-week time-point assessment typically corresponds to when treatment response (virological and/or immunological) is usually assessed after a change in an ARV regimen [17].

Because of the high rate of patients (69%) in the OB arm who experienced protocol-defined virological failure over the study period (the median time to failure was 16 weeks), the analyses reported here investigate only patients originally randomized to the enfuvirtide arm.

Considering the advanced clinical nature of the patients enrolled in the TORO studies, and consequently the relatively small number of patients able to achieve an undetectable viral load, the week-12 virological response category was defined as those who achieved a reduction in HIV-1 RNA load from baseline of $\geq$ 1 log$_{10}$ copies/mL. Those who achieved a CD4 cell count increase of $\geq$ 50 cells/mm$^3$ defined the immunological response category, because it has been demonstrated that a CD4 cell count increase of 25–49 cells/mm$^3$ at 1 year in patients with viremia was associated with a significantly reduced risk of disease progression or death [18, 19]. Consequently, an increase

**Table 1. Baseline demographic characteristics of the combined population in the T-20 versus Optimized Regimen Only (TORO) 1 and 2 studies.**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Enfuvirtide arm ($n = 661$)</th>
<th>OB arm ($n = 334$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV-1 RNA load, 1 log$_{10}$ copies/mL</td>
<td>5.2</td>
<td>5.1</td>
</tr>
<tr>
<td>CD4 cell count, cells/mm$^3$</td>
<td>88</td>
<td>97</td>
</tr>
<tr>
<td>No. of prior ARVs taken</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>No. of years since initiating antiretroviral treatment</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Percent of subjects with prior AIDS-defining events</td>
<td>79</td>
<td>86</td>
</tr>
<tr>
<td>Duration of prior NRTI use, years</td>
<td>6.3</td>
<td>6.3</td>
</tr>
<tr>
<td>Duration of prior NNRTI use, years</td>
<td>1.4</td>
<td>1.5</td>
</tr>
<tr>
<td>Duration of prior PI use, years</td>
<td>3.8</td>
<td>4.0</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median values, unless otherwise indicated. Participants in the enfuvirtide arm were randomized to receive a regimen of enfuvirtide together with an OB. Participants in the OB arm were randomized to receive a regimen of OB alone. ARV, antiretroviral; NNRTI, nonnucleoside reverse-transcriptase inhibitor; OB, optimized background; NRTI, nucleoside and/or nucleotide reverse-transcriptase inhibitor; PI, protease inhibitor.
of \( \geq 50 \) cells/mm\(^3\) was chosen to conservatively represent a clinically relevant improvement in immune function.

Two methods of analysis were employed. The first was a modified on-treatment analysis, in which virological and immunological responses at weeks 24, 48, and 96 were assessed according to week-12 response categories in patients who were still being treated at these specified time points. In addition, a modified intent-to-treat analysis was performed, in which virological and immunological responses at weeks 24, 48, and 96 were assessed according to week-12 response categories, but in which missing data beyond week 12 was categorized as failure.

**Logistic regression.** Logistic regression analysis (using data from both week 12 and specified analysis time points) was used to compare patients who, at 12 weeks, had a decrease in HIV-1 RNA load from baseline of \( \geq 10^0 \) copies/mL with those patients who had a viral load decrease of \( < 10^0 \) copies/mL, according to their categorical virological response at 24, 48, or 96 weeks (the 3 responses are a decrease in viral load \( \geq 10^0 \) copies/mL from baseline, a viral load \( < 400 \) copies/mL, or a viral load \( < 50 \) copies/mL). Similarly, analyses were performed to compare patients with a CD4 cell count increase \( \geq 50 \) cells/mm\(^3\) from baseline at 12 weeks with those who had an increase \( < 50 \) cells/mm\(^3\) on the basis of their immunological response at 24, 48 or 96 weeks (the responses are increases in CD4 cell count from baseline of \( \geq 50 \), \( \geq 100 \), or \( \geq 150 \) cells/mm\(^3\)). The model included response status at week 12 (for patients who achieved a virological response, a status of “yes” is defined as a viral load decrease \( \geq 10^0 \) copies/mL from baseline; for patients with an immunological response, a status of “yes” is defined as a CD4 cell count increase \( \geq 50 \) CD4 cells/mm\(^3\) from baseline, baseline CD4 cell count (per 100 cells/mm\(^3\)), baseline HIV-1 RNA load (per 1 \( 10^0 \) copies/mL), baseline phenotypic sensitivity score, number of previous ARVs taken, and number of ritonavir-boosted protease inhibitors in the patient’s OB regimen (this last parameter was included on the basis of additional subgroup analysis results).
Efficacy of enfuvirtide-based regimens. Data from the phase III TORO 1 and TORO 2 studies have demonstrated the durable efficacy of enfuvirtide in traditionally difficult-to-treat, triple-class ARV treatment–experienced HIV patients through 24, 48, and 96 weeks [2, 4, 5] (figure 1).

Early virological and immunological responses in TORO. At week 12, the least-squares mean change from baseline in HIV-1 RNA load was $-1.67 \log_{10}$ copies/mL for subjects randomized to the enfuvirtide arm, compared with $-0.85 \log_{10}$ copies/mL for subjects randomized to the OB arm ($P < .0001$). The least-squares mean change from baseline in CD4 cell count was +63 cells/mm$^3$ for patients randomized to the enfuvirtide arm, compared with +45 cells/mm$^3$ for patients randomized to the OB arm ($P < .05$).

Categorical virological responses at week 12 for patients in the enfuvirtide arm and OB arm (analyzed with intent-to-treat method) are shown in figure 2. All responses were greater for patients receiving enfuvirtide, compared with those patients randomized to receive only OB. At this early time point, 13% and 36% of patients receiving enfuvirtide achieved HIV-1 RNA loads $<50$ copies/mL and $<400$ copies/mL, respectively (analyzed with the intent-to-treat method, in which treatment discontinuation is considered failure), which was almost double for the TORO 1 and TORO 2 studies [4, 5]. Consequently, data from the 2 trials were pooled for analysis. Table 1 shows combined baseline demographic characteristics of the 2 trials.

RESULTS

As prospectively planned and previously reported, the study design and baseline demographic characteristics were similar for the TORO 1 and TORO 2 studies [4, 5]. Consequently, data from the 2 trials were pooled for analysis. Table 1 shows combined baseline demographic characteristics of the 2 trials.

Plasma HIV-1 RNA was measured centrally using the Roche ampli
cor monitor, version 1.5. CD4 cell count was measured using conventional flow cytometry techniques.

Figure 2. Week-12 plasma HIV-1 RNA load response in patients randomized to receive a regimen of enfuvirtide with an optimized background (OB), compared with patients randomized to receive an OB regimen only. Food and Drug Administration data handling rules state that discontinuation or switch equals failure.

Figure 3. Virological responses at weeks 24, 48, and 96 in patients receiving enfuvirtide therapy who did and did not experience a viral load decrease $\geq 1 \log_{10}$ copies/mL from baseline at week 12. ITT, intent-to-treat analysis; OT, on-treatment analysis.
the proportion of patients who achieved these end points in the control group.

Additional analyses were restricted to TORO study patients who were randomized to the enfuvirtide arm. Of these 661 patients, 620 (93.8%) had a week-12 viral load measurement. Of these 620 patients, 575 patients also had a CD4 cell count measurement at week 12.

**Predictive values of an early virological or immunological response.** Using the modified on-treatment analysis, 39.2% (95% CI, 33.6%–44.8%) and 59.5% (95% CI, 53.8%–65.1%) of patients with an HIV-1 RNA load decrease ≥1 log10 copies/mL from baseline at week 12 achieved a viral load <50 copies/mL and <400 copies/mL, respectively, at week 96 (28.9% and 43.8% of patients achieved these respective viral loads, by the modified intent-to-treat analysis). Furthermore, of these patients, 79.4% (95% CI, 74.7%–84.0%) maintained the decrease of ≥1 log10 copies/mL from baseline to 96 weeks (achieved by 58.5% of patients, by modified intent-to-treat analysis) (figure 3). Conversely, the number of patients who achieved undetectable viral loads (<50 or <400 copies/mL) at 96 weeks was greatly reduced (<3%) in the group of patients who did not achieve a viral load reduction ≥1 log10 copies/mL at week 12 (according to both the modified on-treatment and the intent-to-treat analysis) (figure 3).

Of patients in the enfuvirtide arm who showed at a CD4 cell count increase ≥50 cells/mm3 at 12 weeks, 87.2% (95% CI, 82.6%–91.8%) maintained this response to week 96 (55.3% maintained this response, by the modified intent-to-treat analysis). In addition, 59.6% of patients (95% CI, 52.9%–66.4%) who achieved this early immunological response showed an increase of at least 150 cells/mm3 at week 96 (37.8% of patients, by modified intent-to-treat analysis).

**Logistic regression analysis.** The logistic regression analysis is shown in table 2. Patients who achieved a virological response (defined as an HIV-1 RNA load decrease ≥1 log10 copies/mL) at week 12 were far more likely to subsequently achieve a categorical virological response by week 24, 48, or 96 than were those patients whose viral load had decreased by <1 log10 copies/mL at week 12. For example, patients with a decrease in viral load ≥1 log10 copies/mL at week 12 were 43 times more likely to reach an undetectable viral load (defined as <50 copies/mL) by week 96 (OR, 43.7; 95% CI, 5.9–324.2).

Similarly, patients with a CD4 cell increase ≥50 cells/mm3 from baseline at week 12 were more likely to maintain or improve this response by week 24, 48, or 96, than were those with an increase <50 cells/mm3 (table 3). Those with a ≥50 cells/mm3 increase at week 12 were 3 times more likely to have an increase in CD4 count of at least 150 cells/mm3 by week 96 (OR 3.4; 95% CI, 2.1–5.8).

**Predictive values of combined early virological and immunological responses.** The predictive values of combined virological and immunological responses to enfuvirtide-based

### Table 2. Logistic regression analysis of adjusted ORs (95% CIs) for comparing patients who achieved a viral load decrease ≥1 log10 copies/mL at week 12 with patients who achieved a viral load decrease <1 log10 copies/mL at week 12.

<table>
<thead>
<tr>
<th>Viral load</th>
<th>Week 24 (n = 583)</th>
<th>Week 48 (n = 506)</th>
<th>Week 96 (n = 369)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50 copies/mL</td>
<td>98.3 (13.3–723.9)</td>
<td>NA</td>
<td>43.7 (5.9–324.2)</td>
</tr>
<tr>
<td>&lt;400 copies/mL</td>
<td>48.3 (19.0–123.0)</td>
<td>51.1 (15.7–167.0)</td>
<td>45.9 (10.8–195.0)</td>
</tr>
<tr>
<td>≥1 log10 decrease</td>
<td>189.7 (73.5–489.8)</td>
<td>97.4 (37.6–252.4)</td>
<td>42.7 (16.8–108.7)</td>
</tr>
</tbody>
</table>

**NOTE.** The model includes response status at week 12 (a status of “yes” is defined as a viral load decrease ≥1 log10 copies/mL from baseline), baseline CD4 cell count (per 100 cells/mm3), baseline viral load (per 1 log10 copies/mL), baseline phenotypic sensitivity score, number of previous antiretrovirals taken, and number of ritonavir-boosted protease inhibitors in the patient’s optimized background regimen.

### Table 3. Adjusted ORs (95% CIs) for a comparison of patients who had a CD4 cell count increase ≥50 cells/mm3 at week 12 with patients who achieved an increase <50 cells/mm3 at week 12.

<table>
<thead>
<tr>
<th>CD4 count increase, cells/mm3</th>
<th>Week 24 (n = 496)</th>
<th>Week 48 (n = 448)</th>
<th>Week 96 (n = 316)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>8.7 (5.7–13.4)</td>
<td>3.6 (2.3–5.7)</td>
<td>5.4 (3.0–9.8)</td>
</tr>
<tr>
<td>≥100</td>
<td>7.1 (4.4–11.4)</td>
<td>3.7 (2.4–5.6)</td>
<td>4.8 (2.8–8.1)</td>
</tr>
<tr>
<td>≥150</td>
<td>19.4 (7.5–49.8)</td>
<td>5.8 (3.4–9.9)</td>
<td>3.4 (2.1–5.8)</td>
</tr>
</tbody>
</table>

**NOTE.** The model includes response status at week 12 (a status of “yes” is defined as a CD4 cell count increase ≥50 cells/mm3 from baseline), baseline CD4 cell count (per 100 cells/mm3), baseline viral load (per 1 log10 copies/mL), baseline phenotypic sensitivity score, number of previous antiretrovirals taken, and number of ritonavir-boosted protease inhibitors in the patient’s optimized background regimen.
therapy at week 12 for subsequent immune recovery are shown in figures 4 and 5. Patients who achieved both a virological response (HIV-1 RNA load reduction \( \geq 1 \log_{10} \text{copies/mL} \)) and a marked CD4 cell count increase (\( \geq 50 \text{cells/mm}^3 \)) at week 12 showed a high probability of maintaining and increasing their immunological response through 96 weeks (figure 4, left). Even those patients who achieved a virological response but not an immunological response at week 12 showed immune recovery through week 96 (figure 4, right). A clinically meaningful immune response was also—but less reliably—achieved in patients who did not achieve a viral load reduction \( \geq 1 \log_{10} \text{copies/mL} \) from baseline at week 12, but who did show a CD4 cell count increase \( \geq 50 \text{cells/mm}^3 \) at week 12 (figure 5, left).

**DISCUSSION**

The responses to enfuvirtide-based therapy at week 12 in the highly treatment-experienced TORO patient population with a median baseline CD4 cell count of 88 cells/mm\(^3\) were an HIV-1 RNA load decrease of 1.67 \( \log_{10} \text{copies/mL} \) and a CD4 cell count increase of 63 cells/mm\(^3\) (data are given as least-squares mean values). More importantly, patients who achieved good early virological and immunological responses to therapy and who continued therapy had a strong likelihood of maintaining or improving those responses for up to 96 weeks.

At week 12, almost two-thirds of the patients receiving enfuvirtide-based therapy had a viral load reduction \( \geq 1 \log_{10} \text{copies/mL} \), a significant proportion of whom achieved an undetectable viral load at week 24 (viral load, \( <50 \text{or} <400 \text{copies/mL} \)) and maintained this response through week 96. Not only are these results unusually high in such a heavily treatment-experienced population, but the strong predictability of the early virological responses on the ability to obtain and maintain an undetectable viral load also confirm that re-establishing viral suppression is an achievable goal that can be assessed early on.

Although patients who did not demonstrate a 1-log\(_{10}\) copies/mL decrease in plasma viremia at week 12 were subsequently much less likely to achieve peak viral suppression at week 48, many of these patients were able to achieve significant increases in the CD4 cell count that were clinically meaningful, especially to those patients who are both profoundly immunosuppressed and in a predicament in which maximal virological suppression may not be feasible because of limitations in available therapeutic options. Clearly, for these patients, a consideration of anticipated clinical and immunological outcomes should also play a role in the decision to use and continue enfuvirtide.

**Figure 4.** Immunological responses at 24, 48, and 96 weeks in patients receiving enfuvirtide therapy who achieved a viral load decrease of \( \geq 1 \log_{10} \text{copies/mL} \), who did or did not experience a CD4 cell count increase \( \geq 50 \text{cells/mm}^3 \) at week 12. ITT, intent-to-treat analysis; OT, on-treatment analysis.

<table>
<thead>
<tr>
<th>CD4 cell count increase</th>
<th>Patients at week 4</th>
<th>Patients at week 8</th>
<th>Patients at week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \geq 50 \text{cells/mm}^3 )</td>
<td>40%</td>
<td>50%</td>
<td>60%</td>
</tr>
<tr>
<td>( \geq 100 \text{cells/mm}^3 )</td>
<td>20%</td>
<td>30%</td>
<td>40%</td>
</tr>
<tr>
<td>( \geq 150 \text{cells/mm}^3 )</td>
<td>10%</td>
<td>20%</td>
<td>30%</td>
</tr>
</tbody>
</table>
therapy when a therapy switch is needed to preserve health and clinical stability [2]. In addition, data from the Medical Outcomes Study–HIV questionnaire used in the TORO studies showed that, even in patients who did not achieve a viral load <400 copies/mL at week 48 (i.e., “nonresponders”), a measurable improvement in their quality of life was observed [20].

There was a proportion of patients who achieved neither a viral load reduction $\geq 1 \log_{10}$ copies/mL from baseline nor a CD4 cell count increase $\geq 50$ cells/mm$^3$. Although resistance to enfuvirtide cannot be ruled out, it is perhaps more likely that this lack of response was caused by these patients not having an active background treatment regimen with which to pair enfuvirtide. For these patients, the decision to cease treatment with enfuvirtide until a new active ARV option becomes available may be prudent.

The strong week-12 responses seen in triple-class treatment–experienced patients receiving enfuvirtide-based therapy and the predictive value of these early responses with regard to subsequent immune recovery and virological outcomes at 2 years may have significant implications for increasing patient motivation and acceptance of therapy. This is a potentially important consideration, given that patient acceptance of enfuvirtide use is best established during the first few weeks of enfuvirtide therapy [21].

In conclusion, the long-term predictive value of early response to enfuvirtide-based therapy was investigated, and patients who achieved early virological or immunological responses to enfuvirtide therapy had a strong likelihood of maintaining or improving these responses through 24, 48, and 96 weeks. Patients with both early virological and immunological responses demonstrated an increased likelihood of durability, and patients who did not show a virological response by week 12 were unlikely to achieve a subsequent undetectable viral load. However, a favorable immunological response alone, which improved over time, was seen in those patients with week-12 immunological response, even in the absence of early virological response. This may be highly beneficial in heavily treatment-experienced patients with limited options whose critical immunological status places them at high risk for rapid clinical complications. Patients who do not benefit from a virological response by week 12 will thus need to consider, under guidance of their physicians, the potential immunological benefits of enfuvirtide therapy when deciding whether to continue treatment beyond this period. Indeed, the cessation of enfuvirtide treatment may not be in the best interest of such patients, given their limited treatment options.

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References