Stopping HIV fusion with enfuvirtide: the first step to extracellular HAART

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Introduction: current therapy obstacles

HIV therapeutics has a number of unmet needs, most notably issues of resistance, toxicity and the requirement for chronic therapy. The management of individuals with virus resistant to multiple antiretroviral drug classes is a major challenge in clinical practice. Resistance to one or more approved drug classes may be a consequence of multiple regimen failures, but is increasingly seen in individuals who have recently acquired HIV. Studies of resistance testing indicate advantages, to both genotypic and phenotypic evaluations, over using treatment history alone, in optimizing drug choice for new regimens. However, success in resistance testing studies is also influenced by the availability of treatment options. In the Narval study, performed predominantly in individuals who had received multiple lines of antiretroviral therapy and commonly had virus resistant to all three approved drug classes, the advantages to resistance-optimized therapy that had been reported from the VIRADAPT, GART, VIRA3001 and Havana studies were not evident.

Additionally, interactions between drugs and intracellular targets, most notably the impact of nucleoside analogues on mitochondrial DNA polymerase γ, is thought to be the basis of many treatment toxicities. This underlines the need for new drug classes that will provide the backbone of new regimens and lead to successful long-term management of individuals with virus resistant to approved drug classes.

New drug targets

One focus of new drug development is agents that may inhibit the entry of HIV into infectable cells. Entry of HIV into cells is thought to be, essentially, a three-step process, consisting of attachment, chemokine co-receptor interaction and fusion. Not surprisingly, therefore, specific areas of interest include blocking gp120 binding to CD4 receptors (attachment inhibitors), or blocking the binding site of receptors such as CCR5 and CXCR4 (chemokine co-receptor inhibitors), as well as agents able to disrupt the fusion process (fusion inhibitors).

The entry inhibitor in most advanced clinical development is the fusion inhibitor enfuvirtide (formerly T-20), a 36-amino-acid peptide, being developed jointly by Trimeris and Roche. HIV fusion with CD4 cells is a complex process. It involves a conformational change in the HIV envelope gp120/gp41, leading to an interaction between two helical coils in gp41 that fold into a hairpin shape. This in turn leads to intimate proximity between the HIV envelope and the cell membrane, allowing fusion to occur. Enfuvirtide, and a follow-up compound involving a different amino acid sequence, T-1249, bind to one of these helical regions, preventing the hairpin folding that leads to fusion (Figure 1). These T-compounds are active against both CCR5- and CXCR4-using viruses, although enfuvirtide does not have substantial activity against HIV-2. The fusion process may occur at a range of speeds (‘fast’ to ‘slow’) depending on the concentration of CD4 and co-receptors on cell surfaces. This may influence the activity of fusion inhibitors across cell lineages and between individuals. The lower the receptor/co-receptor concentration on the cell surface the slower the fusion process, and the more time for the inhibitor to bind. Inhibitors of co-receptors slow the fusion process, hence are highly synergic with fusion inhibitors, providing an insight into potential future combination therapies.

Enfuvirtide: efficacy data

Several small, dose-ranging studies have demonstrated dose-dependent efficacy of enfuvirtide, with activity independent of prior exposure, or evidence of resistance to other approved antiretroviral agents. Positive 24 week results from the two
pivotal Phase III studies of enfuvirtide (TORO 1: T20–301, conducted in North America and Brazil\textsuperscript{11} and TORO 2: T20–302, conducted in Australia and multiple European countries\textsuperscript{12}) have recently been reported, and will form the basis of regulatory authority approvals expected in 2003. Both TORO studies had similar designs. HIV-1-positive patients who were treatment-experienced, and/or had documented resistance to each of the three classes of currently available antiretrovirals, first underwent genotypic and phenotypic resistance testing. Then, together with consideration of treatment history, an individualized antiretroviral treatment regimen was chosen, consisting of three to five drugs, including, if feasible, up to two newly approved or investigational drugs. Patients were then randomized 2:1 to receive either enfuvirtide administered with the combination, or the individualized antiretroviral treatment regimen alone [what might be called ‘current standard of care’ (SOC)]. Enfuvirtide was dosed at 90 mg twice daily. TORO 1 involved 491 patients (326 on enfuvirtide, 165 on SOC), and TORO 2 involved 504 patients (335 on enfuvirtide, 169 on SOC). At baseline,
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patients in both studies had a median HIV viral load level of >5 log_{10} copies/mL, and extensive prior exposure to multiple anti-HIV drugs. In TORO 1, enfuvirtide recipients achieved a reduction in viral load at 24 weeks [using the conservative intent to treat (ITT) last observation carried forward approach] of 1.7 log_{10} copies/mL, compared with 0.76 log_{10} copies/mL in the SOC arm. In TORO 2, the reduction was 1.43 log_{10} copies/mL with enfuvirtide, and just 0.65 log_{10} copies/mL with SOC. In both studies, the primary efficacy endpoint, the difference in the magnitude of the decrease in HIV between the two arms (0.93 log_{10} copies/mL in TORO 1 and 0.78 log_{10} copies/mL in TORO 2), statistically significantly favoured the enfuvirtide group (P < 0.0001). Rises in the CD4 cell count also favoured enfuvirtide, increasing by 76 cells/mm³ in TORO 1 compared with 32 cells/mm³ for SOC, and 65 versus 38 cells/mm³ in TORO 2 (P = 0.0001 for TORO 1 and P = 0.023 for TORO 2).

Enfuvirtide was well tolerated from both a clinical and laboratory standpoint. Over 24 weeks, the incidence of laboratory abnormalities and clinical adverse events was similar between the enfuvirtide and SOC arms. Additionally, treatment discontinuation at 24 weeks was ~10% overall and was similar between the enfuvirtide and SOC arms.

Administration issues

Enfuvirtide is currently given as a small volume, subcutaneous injection. In the TORO studies, whereas most patients on the enfuvirtide arms experienced localized injection site reactions, only 3% of patients discontinued the study as a consequence. These reactions generally involve the formation of subcutaneous nodules, which may take many months

![Figure 1](image1.png)

**Figure 1.** Mechanism of action of T-drug fusion inhibitors. Entry of HIV into infectable cells involves attachment, co-receptor binding and fusion. CD4+ T lymphocytes (a) express both CD4 and suitable co-receptors on their surface. Viral envelope glycoprotein gp120 attaches to the CD4 receptor (b). Following initial attachment, a conformational change occurs in gp120, allowing its further association with cellular chemokine co-receptors CCR5 and/or CXCR4 (c). A further conformational change, this time in the viral envelope glycoprotein gp41, allows it to insert the hydrophobic N-terminus into the host cell membrane (d). In the absence of a fusion inhibitor, the helical HR2 domain folds back upon itself and associates with a second helical structure, the HR1 domain (e). This process (called gp41 zipping) leads to fusion of the viral and host cell membranes and hence infection of the cell (f). In the presence of a T-drug fusion inhibitor, binding of the fusion inhibitor to gp41 (g) prevents the successful completion of gp41 zipping (h), preventing the intimacy between viral and cellular membranes needed for fusion (i). For use with permission by TRIMERIS, INC. Copyright owned by TRIMERIS, INC.
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to resolve. Similar nodules may be seen during interleukin-2 (IL-2) therapy. Massaging the nodules may encourage resolution. They are rarely painful or obvious. Patients surveyed in the TORO studies found the injections were ‘easy’ or ‘very easy’ to self-administer in 67% of cases, and found aspects of drug storage (81%), medication preparation (71%), and needle and vial disposal (94%) also ‘easy’ or ‘very easy’. Daily activities were also not substantially affected. For example, patients surveyed responded with ‘not at all’ or ‘a little’ when asked about the impact of injections on recreational activities (79%), managing privacy (75%), socializing (89%), intimacy with their partner (81%) or sleeping (90%). Even considering travelling away from home, 72% reported being ‘not at all’ or ‘a little’ affected.13

Acceptability and adherence to injections have been extensively investigated in Type I diabetes mellitus. In many ways these patients, in being young persons with a chronic illness that is potentially amenable to lifelong therapy, are analogous to HIV patients. Not surprisingly, literature on diabetes adherence describes many of the issues that are familiar to HIV physicians in managing adherence. Confidence and competence with the injection process is one key component of success, but achieving this may also reflect other components of patients’ physical and psychological well being. Education and encouragement are the watchwords for successful injection adherence in adolescents with diabetes,14 and this is likely to be true with injectable antiretrovirals. The backbones of diabetic clinics are the diabetic nurses who educate about the disease, teach injection technique, explain monitoring and its importance, encourage adherence and are generally available on the end of a telephone to advise and assist. Many large HIV clinics now have adherence-dedicated staff who will be able to expand into this role.

Personal experience with individuals with HIV receiving interferon-α, growth hormone (GH) injections, IL-2 or enfuvirtide has been that injectables are readily accepted, even in healthy individuals, when the patient is well educated about the therapy. Its favourable and adverse effects must be understood, and the therapy seen to have effects that are readily observed: decline in hepatitis C viral load with interferon-α, weight gain with GH, CD4 rise with IL-2 and viral load fall with enfuvirtide.

Arguably, enfuvirtide is one of the most well tolerated antiretrovirals, so patients will experience benefit in exchange for little sacrifice in terms of systemic adverse events. For some patients, a simple and well-tolerated injection may be more agreeable than the side-effects of additional oral antiretrovirals.

Resistance

No cross-resistance exists between enfuvirtide and currently approved antiretrovirals. Resistance to enfuvirtide may be selected in vitro, and ViroLogic’s Phensosense technology (Virologic, Oakland, CA, USA) has been modified to provide sensitivity testing in clinical trials and is potentially commercial in the future. Fortunately, in vitro T-1249 appears to be active against most of these enfuvirtide-resistant viruses; however, this drug is only now in early Phase II studies, so is ~3 years behind enfuvirtide. It may also be feasible to combine enfuvirtide with T-1249.

Clinical roles for enfuvirtide therapy

Studies performed for registrational purposes may not reflect the final pattern of use of an antiretroviral agent. Encouraging earlier initiation of enfuvirtide may help to diminish the risk of losing current options, in what might be called ‘first salvage’ therapy, rather than using enfuvirtide, as it was in the TORO studies, against multiclass-resistant virus in ‘deep salvage’. Multiple studies in treatment-experienced patients demonstrate the value of commencing two new drug classes simultaneously. Appreciation of the extent of cross-resistance, with the nucleoside/nucleotide analogue class, has underlined the need (when feasible) to delay therapy-switch until accumulation of several clearly active new agents has been achieved. If we initiate a new regimen with our last available approved drug class, failing to achieve full suppression would mean a fusion inhibitor may also then need to be initiated on a suboptimal backbone. As a result, both remaining classes may be consumed rapidly (through resistance development), for only short-term clinical benefits. If the fusion inhibitors are started in persons embarking on their last conventional drug class, this is likely to substantially increase the number of optimal responders at this line of therapy, increasing the chances of maintaining patients’ health until other options arrive.

There is potential value to be added by including enfuvirtide when other options exist. Rather than saving enfuvirtide until there are no remaining treatment options, its early use will potentially offset its cost and inconvenience, by reducing the number of individuals needing more complex and costly (both financially and in terms of toxicity) ‘mega-HAART’ regimens in the salvage setting.

Conclusions

A range of new drugs targeting viral entry are in clinical development and look set to alter, initially, our approach to treatment of experienced patients. Logical use of the agents argues for their use in individuals with realistic options, rather than in individuals with poor clinical characteristics and extensive resistance to currently approved drug classes. Enfuvirtide, the most advanced of these new agents, is an injectable fusion inhibitor, and has demonstrated potent antiviral activity and excellent tolerability in extensively pre-treated patients.
References


