Canadian consensus recommendations for the optimal use of enfuvirtide in HIV/AIDS patients

Anita Rachlis MD MEd FRCPC[1], Jonathan Angel MD[2], Marianne Harris MD CCFP[3], Richard Lalonde MD FRCPC[4], Fiona Smaill MB ChB[5], Cecile Tremblay MD FRCPC[6], Chris Tsoukas MD[7], Sharon Walmsley MD[8]

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BACKGROUND AND OBJECTIVES: An eight-member group consisting of Canadian infectious disease and immunology specialists and a family physician with significant experience in HIV management was convened to update existing recommendations, specifically intended for use by Canadian HIV-treating physicians, on the appropriate use of enfuvirtide in HIV/AIDS patients with resistance to other antiretroviral drugs.

METHODS: Evidence from the literature and expert opinions of the group members formed the basis of the guidelines. Comments on the draft guidelines were obtained from other physicians across Canada with HIV expertise. The final guidelines represent the group's consensus agreement.

RESULTS AND CONCLUSIONS: The recommendations were developed to guide physicians in optimal practices in patient selection for enfuvirtide treatment and subsequent patient management. The issues considered include positive predictors of response to enfuvirtide, stage of disease, optimization of the background regimen, early indicators of enfuvirtide response, and patient education and support.

Key Words: *AIDS; HIV; Recommendations; Treatment*

Les recommandations consensuelles canadiennes pour l'utilisation optimale d'enfuvirtide chez les patients atteints du VIH-sida

HISTORIQUE ET OBJECTIFS : Un groupe de huit personnes composé de spécialistes canadiens de l'infectiologie et de l'immunologie et d'un médecin de famille ayant une vaste expérience de la prise en charge du VIH s'est réuni pour mettre à jour les recommandations existantes, conçues notamment pour les médecins canadiens traitant le VIH, au sujet de l'usage convenable d'enfuvirtide chez les patients atteints du VIH-sida résistants à d'autres antirétroviraux.

MÉTHODOLOGIE : Les données probantes tirées des publications et les avis spécialisés des membres du groupe ont formé le fondement des lignes directrices. D'autres médecins du Canada possédant des connaissances spécialisées en matière de VIH ont commenté la version provisoire des lignes directrices. Les lignes directrices définitives représentent le consensus du groupe.

RÉSULTATS ET CONCLUSIONS : Les recommandations ont été élaborées pour orienter les médecins dans des pratiques optimales pour sélectionner des patients qui recevront un traitement à l'enfuvirtide et une prise en charge subséquente. Les enjeux abordés sont les prédicteurs d'une réaction positive à l'enfuvirtide, le stade de la maladie, l'optimisation de la posologie de fond, les indicateurs précoces d'une réaction à l'enfuvirtide ainsi que l'éducation et le soutien des patients.

DEVELOPMENT PROCESS FOR GUIDELINES

The purpose of the present guidelines is to update existing recommendations (1) on the appropriate use of enfuvirtide in HIV/AIDS patients with resistance to other antiretroviral drugs. An eight-member group of infectious disease and immunology opinion leaders from across Canada and a family physician with significant experience in HIV management was convened by Roche Canada in March 2005. The group identified areas relevant to the use of the enfuvirtide in advance as topics for the guidelines. Group members identified the relevant literature by search and review, and presented their findings to the group for discussion. The expert opinions of the group members were included as evidence. The strength of each recommendation was categorized according to a standard rating system (Table 1). Comments on the draft guidelines were obtained from the group, as well as from primary care physicians and other specialists across Canada with HIV expertise. The final guidelines represent the group's consensus agreement.

[1]*Division of Infectious Diseases, Department of Medicine, Sunnybrook Health Sciences Centre, University of Toronto, Toronto;* [2]*Division of Infectious Diseases, Department of Medicine, Ottawa Hospital and University of Ottawa, Ottawa, Ontario;* [3]*AIDS Research Program, St Paul's Hospital, Vancouver, British Columbia;* [4]*Immunodeficiency Service and Division of Infectious Diseases, McGill University Health Centre, Montreal, Quebec;* [5]*Department of Pathology and Molecular Medicine, Faculty of Health Sciences, McMaster University, Hamilton, Ontario;* [6]*UHRESS, Centre Hospitalier de l'Université de Montréal;* [7]*Department of Medicine, McGill University Health Centre, Montreal, Quebec;* [8]*Division of Infectious Diseases, Department of Medicine, Toronto General Hospital, University of Toronto, Toronto, Ontario*

Correspondence: Dr Anita Rachlis, A226, Sunnybrook Health Sciences Centre, 2075 Bayview Avenue, Toronto, Ontario M4N 3M5. Telephone 416-480-4689, fax 416-480-5808, e-mail a.rachlis@utoronto.ca

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TABLE 1
Categories reflecting the strength of each recommendation for or against use and the quality of evidence on which the recommendations are based

Category	Definition
Strength of recommendation	
A	Good evidence in support of a recommendation for use
B	Moderate evidence to support a recommendation for use
C	Poor evidence to support a recommendation for or against use
D	Moderate evidence to support a recommendation against use
E	Good evidence to support a recommendation against use
Grade	**Definition**
Quality of evidence	
I	Evidence from at least one properly randomized, controlled trial
II	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one centre), from multiple time-series studies, or from dramatic results in uncontrolled experiments
III	Evidence from opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees

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The recommendations contained in these guidelines are intended for use by health care providers who treat patients with HIV infection. These recommendations are not a substitute for the judgement of a physician experienced in treating these patients.

INTRODUCTION

The effective management of people living with HIV improves clinical outcomes (2,3). The current treatment standard is to initiate antiretroviral combination therapy with two nucleoside reverse transcriptase inhibitors (NRTI) and either a protease inhibitor (PI) (boosted with ritonavir, or unboosted) or a non-NRTI (4,5). With this approach, most patients can achieve sustained virological suppression to less than 50 copies/mL and substantially increase their CD4 cell counts. Furthermore, the prevalence of drug resistance has declined (6-8).

Despite these advances, treatment failure still occurs and drug resistance remains an important clinical problem (6-8). Data from 64 trials in antiretroviral-naive patients between 1994 and 2004 (9) indicated that treatment failed in approximately 36% to 56% of patients by week 48. After the introduction of highly active antiretroviral therapy (HAART), many patients acquired multidrug-resistant viral strains, and patients with drug-resistant virus have a greater risk of disease progression and death (10). Therefore, new agents continue to be important in the management of patients with HIV/AIDS.

THE MANAGEMENT OF PATIENTS WITH MULTIDRUG-RESISTANT HIV

A physician caring for a patient on HAART with a detectable viral load and multidrug-resistant HIV has several options: first, a switch to a new regimen with as many active agents as possible (based on viral resistance genotyping); second, mega- or giga-HAART regimens (salvage regimens that contain six or more antiretroviral drugs, some of which may be partially active); third, treatment interruption before initiation of a new salvage regimen (ie, first or second option); or fourth, continuing a failing regimen or switching to a partially suppressive regimen in an attempt to maintain poor viral fitness and reduced viral replication while waiting until new, active treatment options are available. These options usually apply to treatment-experienced patients with virological failure, but treatment-naive patients may also exhibit multidrug resistance, although rarely (11,12).

There are a number of issues to consider in selecting one of these options: antiretroviral treatment history, taking into account adherence and toxicities, in concert with resistance testing results (13,14); comorbidities that may affect treatment response, adherence and drug selection (eg, hepatitis B and C virus coinfection, cardiovascular disease and diabetes); current and nadir CD4 cell count and fraction; viral load and trends; agents currently available and those likely to be available within two years; and, therapeutic options if this combination fails.

Although suppression of viral replication to less than 50 copies/mL is the ideal goal of therapy, it may not always be achievable. In patients with advanced disease and drug-resistant virus, immunological stability and the prevention of clinical disease progression may be more realistic goals of therapy than is complete viral suppression (15). However, it is important to not prematurely reduce expectations about achieving virological suppression when viable treatment options are still available (16).

OVERVIEW OF ENFUVIRTIDE

Enfuvirtide, also known as T-20, is the first member of a new class of antiretroviral drugs called fusion inhibitors. It is a 36-amino acid synthetic peptide inhibitor of gp41-mediated fusion between HIV and the membrane of the target CD4 lymphocyte (17). Because it is a large peptide, enfuvirtide must be administered by subcutaneous injection at a dose of 90 mg twice daily (18). The extracellular mode of action and unique antiviral target results in several benefits, including the absence of cross-resistance with other antiretroviral agents, as well as decreased risk of systemic toxicity and drug interactions (18,19). Treatment response to enfuvirtide is not affected by viral tropism for CCR5 and CXCR4 coreceptors (17).

Enfuvirtide efficacy

The importance of enfuvirtide in the management of treatment-experienced patients was initially demonstrated in the T-20 versus Optimized Regimen Only 1 (TORO 1) study and the TORO 2 study (20,21). Treatment-experienced adult patients from Europe, Australia and the Americas with at least three or six months previous experience with NRTI, non-NRTI and one to two PIs, and/or resistance to each of these classes of agents, were enrolled in these studies (n=995). Patients were randomly assigned to treatment for 48 weeks with either enfuvirtide plus optimized background therapy or optimized background alone, followed by a 48-week optional extension period of enfuvirtide plus optimized background therapy (52% of patients entered the extension). Optimized background selection was guided by genotypic and phenotypic resistance testing, as well as previous antiretroviral treatment and tolerance history.

The key efficacy results from the combined intent-to-treat meta-analysis of the TORO studies at 48 weeks of treatment

TABLE 2
Summary of key efficacy results from the T-20 versus Optimized Regimen Only 1 (TORO 1) and TORO 2 studies* (22)

Parameter	Enfuvirtide plus optimized background	Optimized background alone	P
Least squares mean change in plasma HIV RNA from baseline (log_{10} copies/mL)	–1.48	–0.63	<0.0001
Viral load <400 copies/mL (% of patients)	30.4	12.0	<0.0001
Viral load <50 copies/mL (% of patients)	18.3	7.8	<0.0001
Median time to virological failure (weeks)	32	11	<0.0001
Least squares mean CD4 count increase (cells/μL)	+91	+45	<0.0001
Baseline subgroups with maximal benefit of enfuvirtide			
• Higher CD4 cell counts			
• Lower viral loads			
• Less treatment experience			
• Resistance to fewer agents			

**These data are from the intent-to-treat population, with the patients who switched to enfuvirtide therapy excluded from the analysis*

(22) are summarized in Table 2. Long-term follow-up of these patients to 96 weeks of treatment showed durability in patient response (23). The majority of patients who were responders (virological or immunological) at weeks 24 and 48 continued to respond at 96 weeks; 26.5% continued to have HIV RNA levels under 400 copies/mL and 31.5% continued to have a CD4 count increase of 100 cells/μL or higher (intent-to-treat analysis).

In the TORO trials, patients who failed therapy with the optimized background therapy alone (control arm) had the opportunity to switch after eight weeks to a new, optimized background therapy that included enfuvirtide. Therefore, it was possible to evaluate the impact of the drug when used later in the treatment course. In the patients in whom enfuvirtide was introduced later, both the decline in viral load and the increase in CD4 count were substantially less (23), likely due to the acquisition of new resistance and the re-emergence of pre-existing resistance due to lack of complete virological suppression (24).

Studies of newer protease inhibitors, such as tipranavir and darunavir (TMC 114), provide further evidence of the efficacy of enfuvirtide in treatment-experienced patients. In the Randomized Evaluation of Strategic Intervention in Multi-Drug ReSistant Patients with Tipranavir 1 (RESIST-1) trial (25), a 24-week viral load reduction to under 400 copies/mL was seen in 47% of patients treated with an optimized background regimen plus tipranavir/ritonavir (TPV/r) plus enfuvirtide versus 34.7% who received an optimized background regimen plus TPV/r only. Similarly, 22% of patients that received enfuvirtide had viral load suppression in the comparator group (an optimized regimen that included a ritonavir-boosted PI) versus 16.5% of patients in the comparator group that did not receive enfuvirtide. In the combined RESIST-1 and RESIST-2 trials, 35.8% of patients treated with an optimized background regimen plus TPV/r plus enfuvirtide had viral load reduction to less than 50 copies/mL at 48 weeks versus 14.4% who received an optimized background regimen plus comparator-boosted PIs plus enfuvirtide (25,26). At week 24 of the Performance Of TMC114/r When Evaluated in triple-class-experienced patients with PI Resistance 1 (POWER 1) and POWER 2 studies, 63% and 64% (respectively) of enfuvirtide-naive patients who received enfuvirtide plus darunavir/ritonavir (TMC 114/r) as part of their regimen achieved viral load reductions of less than 50 copies/mL, versus 56% and 30% (respectively) of patients who received the same regimen without enfuvirtide (27,28).

Enfuvirtide safety

Enfuvirtide is generally well tolerated. In clinical trials, most adverse events have been mild to moderate in intensity. No exacerbation of other common antiretroviral toxicities by enfuvirtide has been observed. Treatment discontinuations for safety reasons occurred in 14.0% of patients in the TORO studies after 48 weeks – 4.4% for injection site reactions, 8.9% for adverse events of any cause, 0.3% for laboratory anomalies and 0.5% for deaths (29).

The most common adverse event associated with enfuvirtide is injection site reaction, characterized by tender erythematous nodules at the injection site that may persist. For the majority of patients, injection site reactions are mild and tolerable, with few individuals requiring drug discontinuation or analgesics to control them (23,29). Although injection site reactions occurred in 98.3% of enfuvirtide-treated patients in the TORO trials in the initial 48-week treatment period, these reactions limited treatment in less than 5% of patients (29). The incidence of injection site infections, including abscesses and cellulitis, was 2.4 per 100 patient-years (18).

Constitutional adverse events, especially gastrointestinal events, were less common in the enfuvirtide-treated patients in the TORO studies versus those treated with optimized background alone. These events included diarrhea, nausea and fatigue. Changes in fat distribution were equally common in enfuvirtide-treated patients and in those not treated with enfuvirtide (30). Systemic hypersensitivity to enfuvirtide occurred in less than 1% of patients in the TORO trials (29).

Pneumonia was more common in the enfuvirtide-treated patients in the TORO studies (23,29). The incidence of pneumonia in this group (2.7% at week 48 and 1.2% at week 96) was similar to the expected range in patients with advanced HIV infection from the literature, while the optimized background alone arm of the study had a lower incidence than expected. The drug relationship of this finding has not been established, and the reason for the difference is currently unknown (29). The risk factors for pneumonia were low baseline CD4 cell count, intravenous drug use, prior or current tobacco use, and a prior history of lung disease.

Antibodies to gp41, an HIV-1 envelope glycoprotein (a fragment of which is identical to enfuvirtide), are produced

soon after HIV infection and may affect enfuvirtide response. Data from the TORO studies showed that enfuvirtide cross-reactive gp41 antibody did not affect patient safety or efficacy (31).

Recommendations for patient safety considerations during enfuvirtide therapy:

- Educate the enfuvirtide-treated patient about pneumonia symptoms and counsel him to contact his physician if symptoms appear (IIB).
- Pneumococcal immunization should be provided and repeated every five years as part of standard care of HIV patients (IIIC).

Enfuvirtide resistance

A wide range of baseline susceptibilities to enfuvirtide have been identified, but no consistent relationship to viral load response has been found (32). Mutations in amino acid positions 36 to 45 on the gp41 sequence are associated with reduced in vitro susceptibility to enfuvirtide (33-35). Data from Canadian patients failing enfuvirtide therapy indicate that mutations at G36D, V38A, V38M, N42T and N43D were most frequently associated with enfuvirtide resistance (35). Some enfuvirtide-resistant isolates have also been found to decrease replicative capacity (17,36,37) and fitness (38).

CCR5 inhibitors are currently being evaluated as antiretroviral drugs. No information is currently available on the impact of enfuvirtide resistance on response to CCR5 inhibitors.

Recommendation for enfuvirtide resistance testing:

- Resistance testing for enfuvirtide is not currently recommended (or available) (IIC).

SELECTION OF PATIENTS FOR ENFUVIRTIDE THERAPY

Treatment-experienced patients

Most of the data available for enfuvirtide support its use in treatment-experienced patients (eg, TORO [20-22], RESIST [25,26,39,40] and POWER [27,28] studies).

Some patients are more likely to benefit from enfuvirtide treatment. Independent positive predictive factors for virological response to enfuvirtide were identified from a logistic regression analysis of the TORO 48-week data (41):

- Baseline CD4 cell count of at least 100 cells/μL;
- Baseline plasma HIV-1 RNA level under 5 $\log_{10}$ copies/mL;
- A history of 10 or fewer prior antiretrovirals; and,
- Two or more active antiretrovirals in optimized background regimen.

One study (41) found a positive correlation between the number of these predictive factors and response rate. In patients receiving enfuvirtide plus optimized background, 67% with all four factors had HIV-1 RNA levels under 400 copies/mL at week 48 of treatment versus 20% with only one predictive factor (41).

Although enfuvirtide treatment is beneficial at later stages of disease (42), patients have improved outcomes with the earlier use of enfuvirtide. In the TORO studies, patients who received enfuvirtide from the start of the study had better outcomes than those who added enfuvirtide later, after virological failure with optimized background regimen alone (24). Patients with less treatment experience and more active agents in the optimized background regimen (agents given concomitantly with enfuvirtide) had a greater benefit from the inclusion of enfuvirtide in their regimens (22,41). A less-than-optimal salvage regimen and failure to maximally suppress viral replication allows for the accumulation of resistance mutations, which limits future optimized background choices to be used with enfuvirtide (43,44). These findings suggest that enfuvirtide should be considered earlier in the management of HIV as part of salvage regimens that include other active agents, and that it should not be reserved until late in the disease when its use may effectively be limited to monotherapy.

In pediatric patients, the pharmacokinetics, safety and efficacy of enfuvirtide are similar to those in adults, although the number of children studied to date is small (18,45,46).

Issues such as toxicity, costs and the impact on the response to subsequent therapies are considerations in the use of enfuvirtide therapy.

Treatment-naive patients and those with less treatment experience

Although enfuvirtide is recommended for treatment-experienced patients (usually those with multidrug resistance), it may have a role in certain treatment-naive patients. Although rare, treatment-naive patients can have significant drug resistance due to transmission of antiretroviral-resistant strains (13). A 2005 report from New York City (12) identified a treatment-naive patient with a highly resistant strain of HIV that had in vitro resistance to multiple classes of antiretroviral drugs but was susceptible to enfuvirtide. A finding of primary multiple class resistance may put patients in the same position as treatment-experienced patients in terms of the expected benefit of enfuvirtide treatment, but no supporting data are currently available. A recent report of a small number of patients less experienced with antiretrovirals suggested clinical benefit with the use of enfuvirtide (47).

Recommendations for the selection of patients for enfuvirtide therapy:

- Current data indicate that predictive factors, such as a baseline CD4 count of at least 100 cells/μL, baseline plasma HIV-1 RNA level under 5 $\log_{10}$ copies/mL, a history of 10 or fewer prior antiretrovirals, and at least two active antiretrovirals in the treatment regimen, are useful in identifying patients in whom enfuvirtide treatment is more likely to be effective (IA).
- Although the TORO trials demonstrated the benefit of enfuvirtide in patients who were triple antiretroviral drug class-experienced (not necessarily multidrug resistant or with virological failure), its benefits may not be limited to these patients. The best response is seen when other active agents are included in the optimized background regimen, preferably from a drug class to which the patient has not been previously exposed (IA).
- Enfuvirtide may also be useful for patients who have intolerance but not necessarily resistance to other agents (IIIC).

- Inclusion of enfuvirtide in a treatment regimen to provide another active drug class should be considered in treatment-naive patients with primary multidrug resistance (IIIB).
- Enfuvirtide is a useful addition to the treatment regimen even in late-stage disease. For patients with advanced HIV infection and no other fully active agents available, enfuvirtide may provide some benefit in combination with partially active agents (IB).
- Pediatric patients with a multidrug-resistant virus may similarly benefit from enfuvirtide treatment (IIIB).

THE MANAGEMENT OF PATIENTS SELECTED FOR ENFUVIRTIDE THERAPY

The role of treatment interruption before the initiation of enfuvirtide therapy

In the TORO studies, patients who had treatment interruptions before enrollment in the study did not have an advantage in long-term virological and immunological response over those who immediately switched to new agents (48). In a study of treatment-experienced patients that compared 24 weeks of enfuvirtide plus optimized background treatment versus 16 weeks of structured treatment interruption followed by enfuvirtide plus optimized background, no significant difference was found between treatment groups in the proportion of patients with a viral load under 75 copies/mL (53% versus 36%, respectively) (49).

Recommendation for the role of treatment interruption in enfuvirtide therapy:

- Treatment interruption before the initiation of enfuvirtide plus optimized background therapy does not improve outcome and is therefore not recommended (IE).

Optimizing the background regimen

A number of trials support the use of resistance testing to guide optimized background therapy selection (50-55). Prior resistance test results are also useful, because a resistance-related mutation that is not currently measurable by standard assays may reappear quickly when antiretroviral therapy is reintroduced (14). Expert advice to interpret the resistance test results significantly benefits the selection of optimal background therapy (50,52).

The use of more active agents in the optimized background regimen, including new boosted PIs (39,41,56), improves virological response to enfuvirtide and limits new mutations, therefore limiting the emergence of further drug resistance (24). In the TORO trials, the time to virological failure correlated positively with the phenotypic susceptibility score (the number of susceptible drugs and, therefore, active agents) in the background regimen (42,57).

Schapiro et al (58) showed that a higher tipranavir mutation score was associated with reduced virological response in patients also treated with enfuvirtide. Prior use of lopinavir/ritonavir was found to be negatively associated with virological response to an enfuvirtide-containing regimen (22). However, lopinavir/ritonavir added as a new agent was associated with improved virological response (22), similar to the improved responses demonstrated in studies evaluating the addition of a new boosted PI (tipranavir/ritonavir in the RESIST studies [39,40] and darunavir/ritonavir [TMC 114/r] in the POWER studies [27,28]).

Selection of concomitant agents is less problematic with enfuvirtide than with other antiretrovirals because drug interactions are unlikely to be an issue (19).

Recommendations for optimizing the background regimen:

- Use resistance testing along with expert interpretation to assist in the selection of optimal background therapy to accompany enfuvirtide. Review prior resistance test results to assess mutations that could re-emerge under selective drug pressure (IA).
- Use as many active drugs as possible concomitantly in the optimal background regimen, including new boosted PIs (IA).

Therapeutic drug monitoring and enfuvirtide dosing

Therapeutic drug monitoring currently does not appear to have a role in enfuvirtide treatment, but could be a useful tool in optimizing the efficacy of enfuvirtide-containing regimens in multidrug-experienced patients. The trough concentration of enfuvirtide after 12 weeks of treatment has been found to be associated with virological suppression at week 12 (59). More research is needed to clarify the potential role of enfuvirtide plasma level monitoring.

Preliminary data have not shown a difference in response to enfuvirtide based on body mass index (60). Although enfuvirtide's pediatric dosage is adjusted by weight, it remains unclear whether enfuvirtide dose should be adjusted for weight in adults.

Use of 12-week response to enfuvirtide in treatment decisions

In the TORO studies, treatment-experienced patients who had good virological and immunological responses to enfuvirtide therapy at week 12 (eg, a decrease of at least 1 $\log_{10}$ HIV-1 RNA copies/mL and an increase of at least 50 CD4 cells/μL, respectively) were very likely to maintain or improve their responses up to week 96 (61). Even though patients without a strong week 12 virological response were unlikely to achieve undetectable viral load, many of these patients who had a good week 12 immunological response had some immune recovery at week 96.

Recommendation for the use of 12-week response to enfuvirtide:

- Evaluate enfuvirtide response at 12 weeks to assess the likelihood of long-term response. A positive response to enfuvirtide after 12 weeks of treatment indicates a greater likelihood of a long-term response. However, a lack of virological response at 12 weeks does not rule out a positive long-term immunological outcome; therefore, evaluation at 12 weeks should include virological, clinical and immunological outcomes (IB).

Enfuvirtide discontinuation

In patients with virological failure despite HAART, there may be an advantage to continuing a failing regimen if it impairs viral fitness and slows immunological deterioration (62). In a study by Morse et al (63), more new mutations resulting in antiretroviral resistance were found in patients treated with

enfuvirtide with rising viremia than in those with persistent low-level viremia. Some evidence indicates that enfuvirtide may impair viral fitness (37,38,64). In a randomized trial of patients who achieved virological suppression for more than nine months with an optimized regimen containing enfuvirtide, the risk of viral rebound was less in those who remained on enfuvirtide versus those who discontinued enfuvirtide (65).

Recommendation for enfuvirtide discontinuation:

- The decision to discontinue enfuvirtide if there is lack of virological suppression or rebound following exposure should be considered in the context of the entire antiretroviral regimen and the immunological response (IIIA).

PATIENT EDUCATION AND SUPPORT

The key to the optimal use of enfuvirtide is good patient education and support at all levels, including physicians, nurses, pharmacists, families and friends.

Initiation of enfuvirtide therapy

The patient and the physician need to be ready and motivated to use enfuvirtide. The patient should understand the need for enfuvirtide, the reasons for use at this point in his/her therapy, the likelihood of its effectiveness, and the time commitment for preparation and administration.

Before initiating enfuvirtide treatment, issues of patient anxiety about needles and injection site reactions need to be considered, along with the risk of triggering relapses in recovering drug addicts. A negative, previous personal or family experience with injections may be overcome with the use of a needle-free injection system such as the Biojector (Bioject Inc, USA). Concerns about self-injection have been found to decrease with Biojector use (66,67). Biojector has also been found to reduce injection site reactions, as well as pain immediately after injection (66,68).

The patient should be made fully aware of the symptoms and expected duration of injection site reactions, and strategies for the prevention and management of injection site reactions should be reviewed, including injection technique and location. Rotation of injection sites, a smaller gauge needle (31G), or a needle-free injection system may prove useful in minimizing injection site reactions (66,68,69). Some patients using standard needles have reported that slow injection, massaging of the site, and the use of hot or cold compresses may lessen reactions (18). In addition, recognition of signs of local infection should be reviewed. Allergic reactions, although rare, should be discussed. Successful desensitization of an enfuvirtide-induced skin hypersensitivity reaction has been reported (70).

The impact of enfuvirtide administration on daily activities, such as work, social life, travel and privacy, should be addressed with the patient. The effect of injection site reactions on physical appearance may also need to be addressed.

Some patients may have physical limitations that restrict their ability to administer enfuvirtide injections; therefore, the following should be assessed:

- adequacy of vision;
- the ability to use both hands, including issues of strength and tremors;
- mental capacity and memory, specifically, the ability to learn and remember procedures;
- the presence of adequate subcutaneous tissue, as many treatment-experienced patients have subcutaneous fat wasting; and,
- the availability of resources to help with injections and provide psychological support (eg, caregiver, partner, friends, family, support groups, social worker and pharmacist).

The patient should be well educated about enfuvirtide reconstitution and injection technique. Sterile technique should be emphasized. Tools such as videos and patient literature may also be useful.

Special attention should be given to the prevention and management of accidental HIV exposure by the caregiver, if applicable. Caregivers should be counselled to seek medical attention immediately if a needle stick injury occurs. Accidental exposure guidelines are available (71). Correct techniques for the disposal of needles and syringes should be carefully explained and safe containers provided to prevent accidental exposure.

Ongoing support

Ongoing patient support is important for retention on enfuvirtide therapy (72,73). A 24 h contact number of an experienced health care provider should be provided to the patient to address questions and problems.

The patient should be reassessed regularly, for example, weekly for one month, every two weeks in the second month of treatment, and then monthly. During these reassessments, the following should be reviewed:

- injection technique;
- side effects, including injection site reactions;
- adherence, including missed doses and reasons for missing a dose, as well as whether or not counselling should be provided;
- the patient's motivation to continue antiretrovirals and enfuvirtide; and,
- acceptance of treatment: ease of injection and impact on activities of daily living.

Physicians have an opportunity to improve lagging motivation in patients who have either a good virological or immunological response, or both, at week 12, because these patients are likely to have long-term positive benefits from enfuvirtide therapy (61).

Recommendations for patient education and support:

- Assess the appropriateness of enfuvirtide therapy for the individual patient, taking into account issues such as readiness and motivation, anxiety, physical issues that may limit their ability to administer the drug, and the availability of resources to help with injections and psychological support (IIIA).
- Educate the patient (and caregiver, if necessary) thoroughly on injection procedures, including reconstitution, injection technique, disposal of needles and syringes, and drug storage (IIIA).
- Counsel the patient on side effects, including injection site reaction prevention and management, and allergic reactions (IIIA).

TABLE 3
Balance of benefits and barriers in the use of enfuvirtide

Potential benefits	Potential barriers
Decreased viral load	Subcutaneous self-injection
Increased CD4 cell count	Injection site reactions
Fewer gastrointestinal toxicities	Impact on daily routine
Lack of hepatic or other significant laboratory toxicities	Privacy/travel issues
	Cost/payer coverage
Clinical improvements	
Absence of drug-drug interactions	
Improved quality of life	

- Provide ongoing support and regular reassessment (IIIA).
- Provide appropriate documentation to assist the patient in transporting injection supplies during air or international travel (IIIB).

CONCLUSIONS

Enfuvirtide is a first-in-class drug that targets HIV by inhibiting viral fusion with the host cell. It is a useful addition to anti-HIV therapeutic strategies. Thus far, it has provided antiviral, immunological and clinical benefits, has a low toxicity, and contributes to improved quality of life in patients with HIV. The route of administration of this drug (subcutaneous injection) represents a new challenge for HIV/AIDS patients and their treating physicians, but these challenges can be overcome.

Ultimately, the benefits of enfuvirtide need to be balanced against the barriers (Table 3). It is essential that physicians be able to identify patients who are likely to benefit the most from the drug at an optimal time in treatment, rather than waiting until the late stages of the disease, when the benefits are likely to be limited. The present guidelines are intended to assist the treating physician in the appropriate selection and management of patients for the optimal use of enfuvirtide.

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