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Consensus Recommendation from a Group of German Experts for the Use of Enfuvirtide in Heavily Pretreated HIV Patients*

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Abstract

Background: The EU approval of enfuvirtide (Fuzeon®) was granted in May 2003 on the basis of the 48-week data from the TORO 1 and TORO 2 studies. Enfuvirtide is licensed for use in pretreated HIV patients experienced with three classes of drugs who exhibited treatment failure or who have shown intolerance to previous antiretroviral treatment regimens.

Recent studies with the new protease inhibitors tipranavir and darunavir (RESIST and POWER studies) showed that a high proportion of heavily pretreated HIV patients achieve a viral load reduction to below the limit of detection when treated with enfuvirtide plus one of these new ritonavir-boosted protease inhibitors and an optimised background treatment regimen [1].

The International AIDS Society (IAS-USA Panel) has recently updated its treatment guidelines in view of these new data and recommends the use of an antiretroviral treatment regimen containing at least two active drugs, one of which that has a new mechanism of action, for HIV patients who have been heavily pretreated. A new treatment goal has also emerged for heavily pretreated patients with advanced HIV disease: reduction of the viral load to below the detection limit of 50 copies/ml. The IAS concluded that the likelihood of achieving this treatment goal is higher when enfuvirtide is selected as one of the two active drugs [2].

Objective: A panel of German experts convened to discuss the currently available data and to incorporate them into the updated German consensus recommendations for the use of enfuvirtide when switching treatment in heavily pretreated HIV patients.

Methods: The consensus recommendations are based on published data from controlled, randomised clinical studies and on the expert opinions of the discussants.

Results and conclusions: The consensus recommendations were developed to provide practice-relevant standardised recommendations for selecting suitable candidates for enfuvirtide therapy and for their management. Aspects including predictive prognostic factors, disease stage, selection of the optimised background regimen, early indicators of a response to enfuvirtide, as well as accompanying educational measures treatment were considered. New protease inhibitors or other remaining active drugs should be used together with enfuvirtide in heavily pretreated patients in order to enable at least two active drugs to be included in such a salvage regimen.

1. Introduction

Despite the advances in antiretroviral therapy, treatment failure and drug resistance pose significant clinical problems in the treatment of patients with HIV infection. Data from 64 studies in antiretroviral-naïve patients carried out between 1994 and 2004 show that treatment failure occurs in approximately 36–56% of patients up to Week 48 [3]. Following several treatment failures, multiple resistant HIV strains are de-

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tectable in many patients and such patients are at a greater risk of disease progression or death [6]. Therefore, new antiretroviral drugs are becoming increasingly important in the management of heavily pretreated HIV patients.

Management of Patients with Multiple Resistant HIV

There are several options available for patients who have failed to achieve a virological response to therapy and have multiple HIV drug resistance:

1. Switching to a new treatment regimen containing as many active drugs as possible (based on the results of genotypic/phenotypic resistance tests),
2. Mega- or giga-HAART regimens (salvage regimens containing six or more antiretroviral drugs, some of which may be only partially active),
3. Continuation of the failing regimen or switching to a partially virus-suppressing regimen to maintain the reduced viral replication efficiency (viral fitness) and residual immunological capacity for as long as possible, until new active treatment options become available.

While these options are usually considered for heavily pretreated patients with virological failure, in rare cases, multiple resistant HIV strains can be harboured by treatment-naïve patients [5, 6].

When selecting from these options, a number of aspects need to be considered: antiretroviral pretreatment, including adherence and toxicities and the results of resistance studies [7, 8], comorbidities and comedications that could influence the response to treatment (for example, hepatitis B and C coinfection, cardiovascular diseases and diabetes, rifampicin, St. John's wort); pharmacological and pharmacodynamic profiles; adherence and drug selection; current CD4 cell count and nadir (absolute and percentage); current viral load and its changes; currently available drugs and those likely to be available in the near future as well as remaining treatment options if the combination selected should fail.

2. Strategic Procedures in the Event of Treatment Failure and Definition of Treatment Goals in Heavily Pretreated HIV Patients

2.1 General considerations when switching treatments

All possible advantages and disadvantages should be taken into account when deciding whether to switch treatment. This involves the evaluation of objective factors (such as the resistance status) and of subjective factors (such as whether the patient is willing to undertake a new treatment). Switching treatment is based not on one drug alone, but always under consideration of the entire antiretroviral treatment regimen. In principle, it is advisable to perform a resistance test prior to making any treatment switch as a result of treatment failure.

2.2 Reasons for switching treatment

There are two main reasons to consider switching treatment:

1. Manifest or imminent clinical deterioration based on the symptoms and/or measured by the reduction in CD4 cell count.
2. Continued or new-onset viral replication despite antiretroviral therapy with imminent loss of treatment options due to development of resistance.

2.3 Treatment goal

The ultimate goal of treatment should be reduction of viral load below the detection limit (<50 HIV RNA copies/ml) since this is the best way to avoid further development of resistance and hence clinical or immunological progression.

Although reduction of the viral load to below the detection limit is the ideal goal of treatment, this cannot be attained in all cases. In patients with very advanced HIV disease and resistant HIV strains, immunological stability and the prevention of clinical disease progression may be more realistic goals than complete viral suppression [9]. However, through the use of new drugs, attainment of this goal appears to be increasingly possible, even in heavily pretreated patients.

3. Enfuvirtide (ENF)

3.1 Mechanism of action of enfuvirtide

Enfuvirtide (Fuzeon®) – a peptide containing 36 amino acids – is the first representative of a new class of drugs known as fusion inhibitors. Fusion inhibitors are the fourth therapeutic class of antiretroviral drugs to be developed following the introduction of nucleoside reverse transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs) and the protease inhibitors (PIs). Whereas the other three previously approved antiretroviral drug classes act against "intracellular" viral targets, enfuvirtide works extracellularly, blocking the fusion of HIV and CD4 cells by specifically binding to a surface protein of HIV (the HIV-1 gp41) [10]. While previously available antiretroviral medications all act by inhibiting viral replication in already infected cells, enfuvirtide is able to prevent new infection of target cells. Enfuvirtide, an analogue of the HR-2 (heptad repeat) domain in the gp41 glycoprotein of HIV-1, binds to gp41 in the region of the HR-1 domain and prevents a conformational change of the molecule. Enfuvirtide specifically inhibits HIV-1 and is effective against both CXCR4 and CCR5 as well as against dualtropic viral isolates, but not against HIV-2.

3.2 Efficacy of enfuvirtide

The efficacy and tolerability of enfuvirtide were investigated in the two randomised Phase III studies TORO 1 and TORO 2 (T-20 versus Optimised Background Only). These studies involved a total of 995

heavily pretreated patients at an advanced stage of disease. Patients were randomised to receive either an optimised background regimen only (OB) from the pool of available antiretroviral drugs in accordance with the current resistance analysis, previous therapy and tolerability, or OB plus enfuvirtide. Several evaluations and subanalyses of the TORO studies have been presented [11, 12, 13]. Other large clinical studies with similar patient demographics, design and subanalyses were the Phase III RESIST and POWER studies of the PIs tipranavir and darunavir. The studies consistently demonstrated that enfuvirtide, in combination with one of the new active boosted PIs, improved treatment efficacy compared with an OB alone or a comparator PI [1] (see Fig. 1).

- At Week 24 of the TORO studies, 60% of the patients who were previously ritonavir-boosted lopinavir (LPV/r)-naïve and received LPV/r as a component of a regimen with enfuvirtide achieved a viral load <400 copies/ml compared with 30% of patients who received a regimen with LPV/r without enfuvirtide [1].
- At Week 24 of the RESIST studies, 70% of the patients who were previously enfuvirtide-naïve and received boosted tipranavir (TPV/r) plus enfuvirtide achieved a viral load reduction of ≥1 log compared with 37% of patients who received only TPV/r [14]. Of the patients who received TPV/r plus enfuvirtide, 54% achieved a viral load <400 copies/ml compared with 30% of those who received TPV/r without enfuvirtide [1]. At Week 48, 52% of all patients treated with TPV/r (with or without enfuvirtide) achieved a viral load <400 copies/ml and 30% achieved <50 copies/ml, compared with 30% and 23% of patients, respectively, who received TPV/r without enfuvirtide.
- At Week 24 of a combined evaluation of the POWER studies, 64% of the patients achieved a viral load <50 copies/ml with the use of darunavir/r with enfuvirtide compared with 46% of patients who received darunavir without enfuvirtide [16].

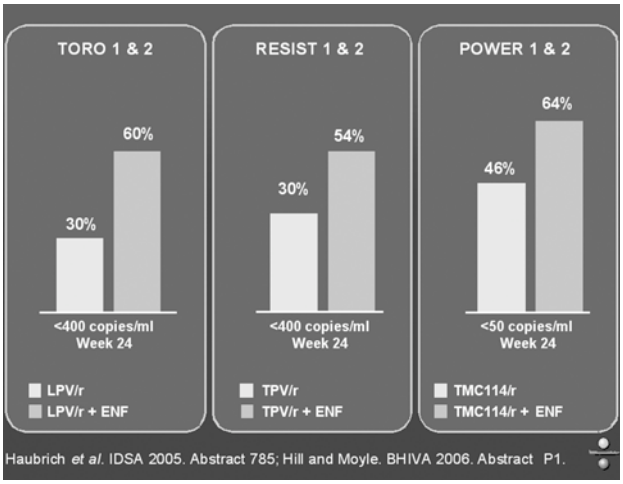


Fig. 1. Attainment of the virological endpoint at Week 24 in the TORO, RESIST und POWER studies.

Data from another study (MK-0518 005) showed that when the integrase inhibitor MK-0518 is combined with enfuvirtide, 90–95% of patients achieved a viral load below the detection limit (<400 HIV RNA copies/ml) compared with 60–70% of patients who received MK-0518 without enfuvirtide [17].

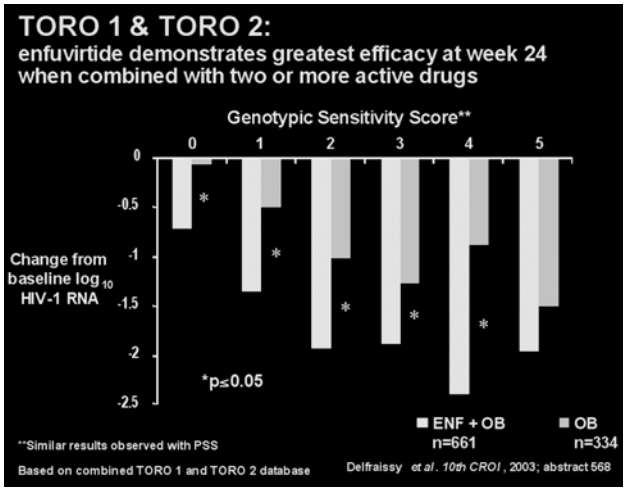


Fig. 2. In the TORO studies, patients were randomised to receive either only an optimised background regimen (OB) from the pool of available antiretroviral drugs in accordance with current resistance analysis, previous therapy and tolerability, or OB plus enfuvirtide.
Result: Treatment with enfuvirtide was superior to treatment with OB alone. Enfuvirtide showed the best effects in combination with two or more active drugs, as evident here from the Genotypic Sensitivity Scores (GSS).

3.3 Resistance to enfuvirtide

Mutations associated with a reduced efficacy of enfuvirtide are located in the HR-1 region of gp41 between amino acids 36–45. The most common mutations observed after treatment failure during enfuvirtide therapy are G36A/D/E/S/V, V38A/E/K/M, N43D, L44M or combinations of N42T + N43H/K/R/S and Q40H/K/P/T + L45M/Q.

If the V38A/E mutation is present, continuation of treatment with enfuvirtide despite resistance can be associated with an immunological response, whereas other mutation patterns are more likely to be associated with a loss of CD4 cells [18, 19].

4. Switching Treatment and Initial Use of Enfuvirtide in Heavily Pretreated HIV Patients and/or HIV Patients with Multiple Resistant HIV (Enfuvirtide-naïve Patients)

4.1 Provisional algorithm – a possible option as a guide for practice

The following algorithm is intended as a suggestion and possible guide for the use of enfuvirtide in clinical practice (see Fig. 3). The algorithm cannot comprehensively cover every individual treatment decision

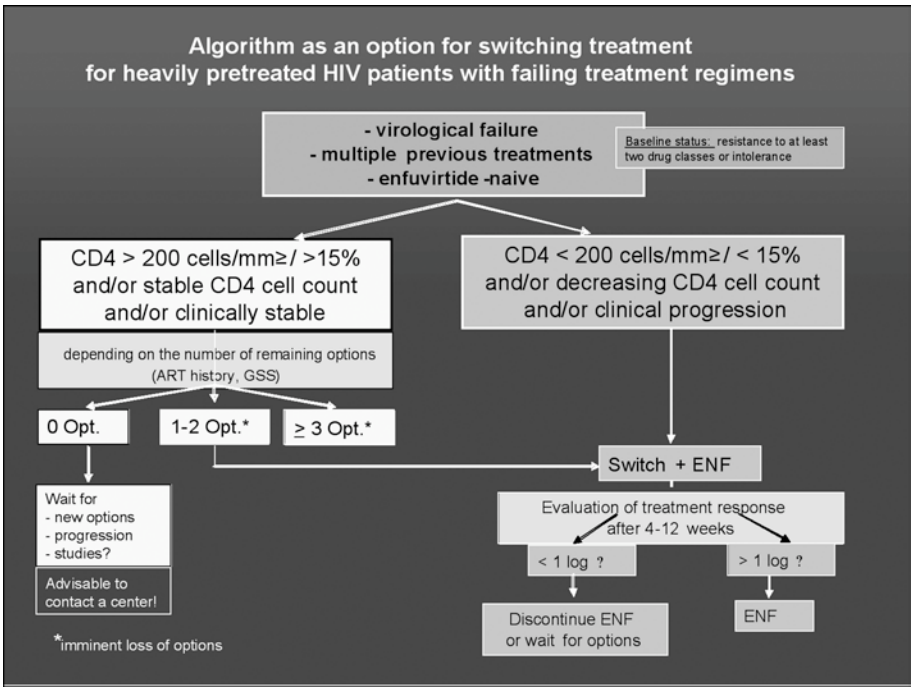


Fig. 3. Algorithm as an option for switching treatment for heavily pretreated HIV patients with failing treatment regimens.

that must be made in practice in this late treatment phase – there will always be cases in which it does not apply[A]. It is always advisable to contact a specialist HIV clinic, not only in these sorts of cases.

HIV patients for whom a switch to enfuvirtide can be considered

A switch in treatment should be considered for heavily pretreated HIV patients with treatment failure who were previously treated with several failing regimens including different antiretroviral drug classes, and/or for patients whose HIV exhibits multiple resistance to at least two antiretroviral drug classes (including treatment-naïve patients) or who show intolerance to the drugs currently used. As part of switching treatment, enfuvirtide should be used if the patient has a chance of achieving a therapeutic response with the new treatment regimen. Patients with multiple resistant HIV should receive enfuvirtide only if the treatment goal described in Section 2.3 can be achieved.

The decision is made depending on the immunological or clinical status of the patient.

➤ **If the CD4 count is stable at >200 cells/mm³ (>15%) and/or the patient is clinically stable,** the number of drugs options available is an important factor to consider. The previous antiretroviral therapy, current resistance analysis – if applicable, the GSS[B] – or the clinical estimate of the cumulative effects of the background therapy can serve as a basis for orientation. Possible guidelines can be derived from a subgroup analysis of the TORO studies:

- If **1–2** active drugs remain as available options, the addition of enfuvirtide as part of a switch in treatment is advantageous.
- If **≥3** active drugs remain as available options, the benefit of adding enfuvirtide is rather small.
- If there are **no** remaining options for an effective background therapy, whenever possible one should wait until new options are available, until clinical progression occurs or until study enrolment for new drugs is possible.

➤ **In the event of a CD4 count <200 cells/mm³ (<15%) or decreasing CD4 count[C] and/or clinical progression**, treatment should be switched to enfuvirtide with the aim of achieving a viral load <50 copies/ml.

4.2 Positive predictive factors for a response to enfuvirtide therapy

Post hoc analysis of the 48-week data from the TORO 1 and 2 studies revealed predictive factors for a treatment response to enfuvirtide that are also indicative of a more favourable prognosis and less intensive previous therapy of HIV infection:

A The algorithm does not cover the ratio of the viral load and CD4 cell count (at a viral load of 300 copies/ml and a CD4 cell count that has already been stable for a long time, it is recommended not to switch but to continue therapy and monitor closely at regular intervals).

B A GSS of "0" should be regarded critically: on one hand, this parameter makes sense in clinical studies if the effect of a drug is being evaluated in comparison with the control arm. On the other hand, a GSS of "0" is not necessarily identical with "no options": if it is possible to recycle an antiretroviral drug, a new option may exist.

C The term "decreasing CD4 cell count" does not require that the patient had a CD4 count <200 cells/mm³. – it can also mean, for example, that the CD4 cell count decreases from 500 to 300 cells/mm3 within months. Therefore, the CD4 count should also be reported as a percentage.

1. Lower plasma viraemia at study entry (baseline HIV RNA <5 log10 copies/ml),
2. Higher CD4 cell count (baseline CD4 count ≥100 cells/μl),
3. Less intensive previous therapy (≤10 antiretroviral drugs) and higher percentage of active drugs (at least two) and enfuvirtide in the backbone [20].

4.3 Use of enfuvirtide in combination with active antiretroviral concomitant medications

Administration of enfuvirtide in addition to other active antiretroviral medications is essential to prevent early development of resistance. Resistance occurs relatively rapidly during enfuvirtide monotherapy and can arise via point mutations. Therefore, when treatment is switched, it is critical to use enfuvirtide together with the most active antiretroviral medication so that enfuvirtide does not lose its activity. The TORO studies showed that patients with advanced HIV disease require treatment with several active antiretroviral drugs. Enfuvirtide showed best efficacy in combination with two or more active drugs (see Fig. 2).

A "fully active" antiretroviral drug is one that demonstrates activity based on the treatment history of the patient and on the results of resistance tests. The interpretation of this concept is critically dependent on which options remain available to the patient. Thus, there is also the possibility of constructing an active nucleoside backbone despite the presence of resistance (M184V, K65R mutation, etc.). In addition to selection of the drugs predicted to be active, two other factors are important: firstly, making use of residual drug effects (e.g., M184V mutation) and secondly, making use of favourable interactions between different resistance mutations which can still provide a degree of activity of the antiretroviral combination even in the presence of resistance mutations (M184V or K65R with thymidine analogue mutations [TAMs]).

5. Additional Aspects when Considering Enfuvirtide Therapy

5.1 Adherence

The TORO studies demonstrated that patient adherence during enfuvirtide therapy was comparable to that seen with the orally administered tablets or capsules of the concomitant therapy [21].

5.2 Acceptance of treatment with enfuvirtide – results of the OpenMind study

Because enfuvirtide is administered subcutaneously and is associated with injection site reactions, physicians tend to underestimate the acceptance of enfuvirtide by patients and their likely compliance. When estimating the likely acceptance of an offer of enfuvirtide therapy there is a discrepancy between physicians and patients: patients are more often prepared to accept treatment with enfuvirtide than the treating physicians expect [22]. This was demonstrated by the results of the OpenMind study in which 499 physicians [23] from HIV clinics and practices and 603 treatment-experienced HIV patients who were clinical candidates for enfuvirtide [24], were interviewed by questionnaire. The study found that 76% of the patients would consider injection therapy if their physician recommended it. However, only about one quarter of the patients (28%) who would be eligible for enfuvirtide treatment had discussed this treatment option with their physicians. Only 10% of these patients received enfuvirtide, although enfuvirtide had already been recommended in the DHHS guidelines [25] and continues to be incorporated into other guidelines (e.g., IAS-USA Guidelines [2], French [26] and Canadian [27] treatment recommendations).

5.3 Patient motivation

Possible reservations a patient may have about treatment with enfuvirtide can be overcome by appropriate motivation and education of the patient and, in particular, through positive experiences with the medication. As a motivational factor for the initial use of enfuvirtide, it is advisable to focus initially on short-term treatment goals and agree on a treatment duration of 3 months with the patient ("3-month plan"), decide whether to continue treatment in Month 3 (Week 12), and then discuss further treatment (see Section 5.5).

5.4 Evaluation of the treatment response up to Week 12

Early monitoring of the viral load – no later than Week 12 – is used to identify a response to enfuvirtide. In the TORO studies, 72.3% of patients who received enfuvirtide plus an OB demonstrated a response to treatment (≥1 $\log_{10}$ reduction in viral load versus baseline) by Week 4, compared with 43.4% of patients

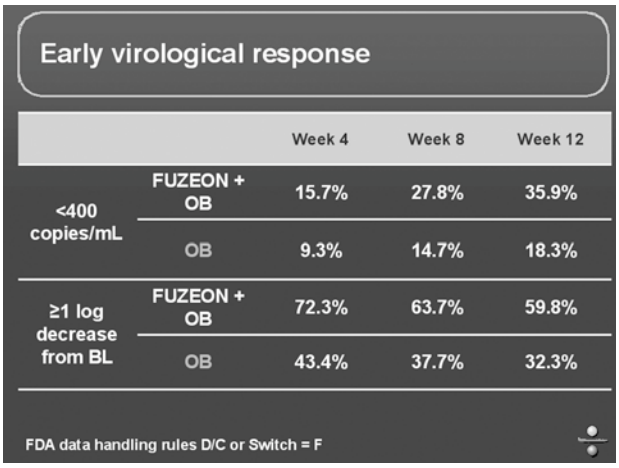
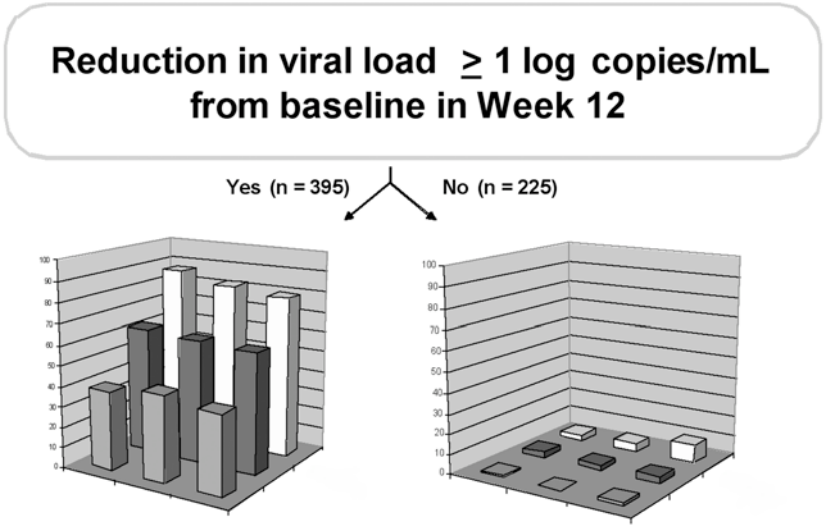


Fig. 4.

who received an OB without enfuvirtide [28] (see Fig. 4).



Raffi, R. et al. „Week-12 Response to Therapy as a Predictor of Week 24, 48, 96 Outcome in Patients Receiving the HIV Fusion Inhibitor Enfuvirtide in the T-20 versus Optimized Regimen Only (TORO) Trials ", CID 2006, 42 p. 870 -877

Fig. 5.

5.5 Additional treatment planning at Week 12

The Week 12 reduction in viral load on an enfuvirtide-containing regimen is highly predictive of the long-term (i.e., Week 96) success of therapy. This factor can substantially contribute toward motivating the patient to use enfuvirtide.

- If after 12 weeks the reduction in viral load is ≥1 log, a response during continued treatment over 24, 48 and 96 weeks is highly likely (see Fig. 5).
- If after 12 weeks the reduction in viral load is <1 log, the likelihood of an additional response is low (see Fig. 5) [29].

5.6 Management of enfuvirtide therapy

The provision of professional nursing support can be of considerable benefit in facilitating the integration of enfuvirtide into patients' lives. Since local injection site reactions can lead to treatment interruption, nursing assistance should start prior to initiation of enfuvirtide treatment and provide support regarding the preparation of the dosing solution, where and how the injection should be given, and how to manage injection anxiety. The provision of educational measures allows enfuvirtide to be considered for an increasing number of patients, particularly those who have been difficult to treat in the past due to noncompliance. It may also be helpful for patients initiating therapy with enfuvirtide to be accompanied by a friend or relative when visiting the practice/outpatient clinic. In this way, preparation and storage of the solution, drawing up the medication into the syringe, and the subcutaneous injection can be learned together in a private setting before being implemented over the long term [30].

5.7 Selection of the injection site and management of local injection site reactions

Suitable injection sites for enfuvirtide include the abdominal region, upper thighs and upper arms. The region around the waistband as well as a 2–3 cm diameter circle around the navel should be avoided. With the help of a care-giver the back may also be considered as a potential injection site. There are extensive recommendations and suggestions regarding the injection site, and it is therefore advisable to develop individualised solutions for each patient. Prior to injection, the injection site should be palpated with the hand to avoid any site with a preexisting injection reaction. Gentle massage of the injection site is favoured by some patients. The injection should be given slowly, if possible over a period of several minutes. The site must be changed for every injection. Slow administration of the injection and change in the injection site can help to avoid the occurrence of injection reactions.

If local injection site reactions occur, a topical antihistamine can be applied. Other patients prefer the application of warming compresses.

5.8 Safety and tolerability of enfuvirtide

The peptide structure of enfuvirtide necessitates parenteral administration – as a subcutaneous injection. The most frequently observed adverse reaction during enfuvirtide therapy is a local injection site reaction. Such reactions were experienced by 98% of all patients in the TORO studies. However, only 7% of the patients discontinued treatment within 2 years for this reason. Over the 96-week observation period of the TORO studies, neither the number or severity of injection site reactions nor the rate of pneumonia increased; furthermore, no latent toxicities were identified during the second year of the trials. After 96 weeks, 362 of 663 patients (55%) remained on treatment.13 This indicates that the majority of patients were successfully managing this treatment and were

able to integrate the subcutaneous injections into their everyday routine without significant problems. Professional nursing assistance and education of the patient can make the use and handling of enfuvirtide much easier (see Section 5.6).

The TORO studies showed that the quality of life scores during enfuvirtide therapy were better than in the comparator arm without enfuvirtide; furthermore, patients treated with enfuvirtide and OB had significantly less frequent or a similar frequency of adverse reactions in almost all categories compared with patients treated only with OB [31]. The occurrence of fewer adverse reactions during intensified therapy in the enfuvirtide treatment arm was an unexpected result. One explanation could be the favourable immunomodulatory properties of enfuvirtide [32]. Patients treated successfully with enfuvirtide in the TORO studies had reduced T cell activation and T cell apoptosis. As a peptide, enfuvirtide is not metabolised through the cytochrome P-450 system, and so there is a reduced risk of interactions with this enzyme system. The other point of note may be the fact that enfuvirtide has no cross-resistance with other approved antiretroviral drugs. Enfuvirtide has a favourable systemic tolerability profile, without the systemic adverse reactions that are typical of other antiretroviral drugs.

5.9 Discontinuation of enfuvirtide

Possible reasons for discontinuation of enfuvirtide include virological nonresponse to treatment, noncompliance or adverse reactions. In such cases, a decision should be made, based on the clinical immunological status, the current resistance analysis as well as whether and which other (experimental, if applicable) treatment options are available.

6. Enfuvirtide in Special Situations

6.1 Pregnancy

There is insufficient experience and a lack of well-controlled studies of enfuvirtide in pregnant women. Animal experiments showed no harmful effects with respect to foetal development. During pregnancy, enfuvirtide should be used only when the potential benefits outweigh the potential risk for the foetus. It is not known whether enfuvirtide is transferred into breast milk. Because of the risk of HIV transmission and potential adverse reactions in nursing infants, mothers should be instructed not to breastfeed when being treated with enfuvirtide [33].

To date, few case reports have been published in the international scientific literature. A 38-year-old pregnant patient receiving antiretroviral therapy (lamivudine, tenofovir, ritonavir-boosted lopinavir) who was also treated with enfuvirtide and nevirapine beginning 3 weeks prior to a scheduled caesarean section delivered a healthy girl who remained HIV-negative for at least 6 months after delivery. Despite the extremely limited experience at this time, the authors emphasized the possible importance of using enfuvirtide to prevent maternal transmission of HIV to the fetus [34]. More recently published experiences with enfuvirtide have focussed on perinatal transmission of the infection in pregnant women infected by multiple resistant HIV-1 [35]. Two other reports described the prevention of mother-to-child transmission of multiple drug resistant HIV-1 with enfuvirtide [36] and enfuvirtide plus tipranavir, respectively [37].

6.2 Patients with HIV strains exhibiting primary resistance

"Primary resistance" of a virus is defined as the existence of resistance mutations to antiviral drugs in patients without previous contact to these drugs. This results from transmission of viruses already resistant in the donor host. This phenomenon has been observed with increasing frequency in the last few years. The licensing of enfuvirtide specifically mentions the three-drug-class experience of the patient; however, this applies not only to the characteristic of the patient but also to the three-drug-class experience of HIV. In clinical practice, an HIV patient may already be infected with a three-drug-class-experienced/resistant virus without having received treatment with any of the three drug classes [38]. Therefore, enfuvirtide should be included in differential therapeutic considerations as part of individual treatment decisions in patients who have been less intensively pretreated and, in particular, if no other options are available or the viral resistance profile seems to indicate that this would be beneficial.

6.3 Intolerance

A possible indication for the use of enfuvirtide is the presence of intolerance to other drugs, e.g., lipodystrophy syndrome or other mitochondrial toxicities. In studies to date, no characteristic metabolic adverse reaction profile of enfuvirtide has been evident, so that it can be assumed that enfuvirtide does not lead to the development of lipodystrophy. However, because of the subcutaneous administration, it can often be difficult to use enfuvirtide in patients with marked lipoatrophy.

6.4 Postexposure prophylaxis (PEP)

The extracellular mechanism of action of enfuvirtide suggests that it is theoretically possible to use it promptly as part of postexposure prophylaxis (PEP), e.g., after needlestick injuries or after exposure to multiple resistant viruses. However, its use as part of PEP should be evaluated with extreme caution since there are no scientific results available for this indication. It should also be kept in mind that enfuvirtide and all other antiretroviral drugs are not currently approved for prophylactic use.

[D] Note: The intermittent use of enfuvirtide must be strictly distinguished from the aforementioned "3-month plan" strategy, i.e., initially using enfuvirtide for 3 months and deciding in Week 12 whether to continue treatment.

6.5 Intermittent use of enfuvirtide[D]

In individual isolated cases and certain exceptional cases, the intermittent use of enfuvirtide might be appropriate, e.g., pregnancy, when severe gastrointestinal absorption disorders are present (e.g., patient with Kaposi's sarcoma in the gastrointestinal tract), or when interactions with another treatment have occurred (e.g., chemotherapy, lymphoma patients).

6.6 Continuation of enfuvirtide therapy when there is a clinical or immunological response despite virological rebound?

Early measurement of viraemia 4 or 12 weeks after the start of treatment can serve as a predictor of the long-term virological response (see Sections 5.4 and 5.5). However, the viral load should not be used as the sole criterion when deciding whether to continue treatment. Thus, despite virologically failing enfuvirtide therapy, a clinical (e.g., reduction in adverse reactions of another treatment) or immunological (increase in CD4 cell count) response to therapy can be present. In such cases, continuation of treatment despite the virological rebound should be considered.

This is based on the observation of reduced viral fitness of enfuvirtide-resistant viruses: in one study, the replicative fitness of the mutated viruses was inversely proportional to the resistance [39, 40]. Two other studies showed that the development of specific mutations (V38A) during enfuvirtide therapy was associated with an increase in CD4 cell count [41, 18].

6.7 Reuse of enfuvirtide in enfuvirtide-experienced patients (recycling)

The term "recycling" refers to the situation where a patient who received enfuvirtide as part of their previous antiretroviral therapy regimen but then discontinued, e.g., because of resistance, was retreated with enfuvirtide later in the course of treatment. The current resistance analysis and the current GSS can serve as starting points. Recycling is considered in the following situations:

1. Despite detected current resistance, drugs used previously are used in the patient because there are no other options available.
2. Despite the history of resistance, the current virus sample from the patient does not show presence of resistance mutations, so that recycling offers a chance to suppress the current virus. Since resistance mutations acquired during enfuvirtide therapy can disappear just a few weeks after discontinuation of enfuvirtide [42], the observed clinical advantage of enfuvirtide therapy despite resistance [42] might be attributable to reduced viral fitness [41]. For this reason, "recycling" of enfuvirtide should be considered as a possible option later in the course of treatment.

7. Discussion and Conclusion

The use of enfuvirtide is intended for previously treated HIV patients with three-drug-class experience who exhibit treatment failure or show intolerance to previous antiretroviral treatment regimens. The term "three-drug-class experience" does not mean that treatment must be switched per se – careful consideration of the advantages and disadvantages may argue against switching antiretroviral therapy. However, there may be situations for switching treatment in which neither three-drug-class experience nor an intolerance exists and yet the use of enfuvirtide should still be considered, e.g., if treatment with one of the other antiretroviral drug classes is ruled out because of adverse reactions so that cumulatively the required "three-drug-class experience" cannot be achieved. Other cases involve the existence of primary resistance (see Section 6.2). Enfuvirtide should be included in differential therapeutic considerations as part of individual treatment decisions (e.g., in patients with primary resistance) and when no other options are available, even for patients who have been less intensively pretreated in order to prevent subsequent suboptimal use of enfuvirtide in very advanced stages of treatment and disease and to keep future treatment options open.

- ➤ **The treatment goal for intensively pretreated patients is maximal suppression of the viral load (reduction of the viral load to below the detection limit of 50 copies/ml).**
- ➤ **A switch in treatment should be considered when there is clinical or immunological deterioration and an imminent loss of available treatment options.**
- ➤ **Enfuvirtide should be used as part of a treatment switch for HIV patients with multiple previous treatments and multiple resistant viruses.**
- ➤ **Whenever possible, enfuvirtide should be used together with two active drugs (e.g., an active boosted protease inhibitor) and an optimised antiretroviral background regimen.**
- ➤ **Possible reservations concerning treatment with enfuvirtide can be overcome by appropriate motivation of the patients and the provision of professional nursing assistance.**
- ➤ **As a motivational factor for the initial use of enfuvirtide, it is advisable to focus initially on short-term treatment goals ("3-month plan").**
  - o **Early monitoring of the viral load – no later than Week 12 – can identify a response or nonresponse to enfuvirtide.**
  - o **Evaluation of the future course of treatment beginning in Week 12 allows predictions to be made about the further immunological response in Weeks 24, 48 and 96 on the basis of the CD4 count increase or viral load reduction.**

Enfuvirtide should be included in differential therapeutic considerations as part of individual treatment decisions (e.g., in patients with primary resistance) and when no other options are available, even in patients who have been less intensively pretreated.

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