Discontinuation of Enfuvirtide in Heavily Pretreated HIV-Infected Individuals

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Background: Enfuvirtide was shown to be highly effective in treatment-experienced patients. Data on discontinuation of enfuvirtide and switch to new antiretroviral drugs are scarce. We aimed to evaluate the efficacy and the impact of discontinuing and/or switching enfuvirtide on virologic and clinical parameters in clinical practice. **Methods:** All HIV-infected individuals participating in the Swiss HIV Cohort Study who were treated with enfuvirtide for at least 4 weeks in combination with an optimized background antiretroviral regimen were included in this study. **Results:** A total of 151 patients were analyzed. The median baseline CD4 cell count was 108 cells/μL (interquartile range [IQR] 50–206) and HIV RNA was 4.7 $\log_{10}$ copies/mL (IQR 4.1–5.2). Virologic suppression, defined as a viral load below 50 copies/mL at 12 months, was achieved by 57.6% of patients. Overall, a median CD4 cell increase of 121 cells/μL (IQR 50–189) from baseline was noted. Up to 50% of patients discontinued enfuvirtide within the first year of treatment, mainly because of the patient's choice. After discontinuation of enfuvirtide, high rates of virologic failure and clinical progression were observed, notably when CD4 cell count at stopping enfuvirtide was below 100 cells/μL and no switch to new potent antiretroviral drugs such as darunavir, maraviroc, or raltegravir was performed. **Conclusions:** Enfuvirtide provides high virologic and immunologic response in treatment-experienced patients in the setting of clinical practice. Enfuvirtide should not be discontinued but should be replaced by new potent antiretrovirals, particularly in case of severe immunosuppression.
Key words: *discontinuation of enfuvirtide, enfuvirtide, highly active antiretroviral therapy, HIV infection, T-20, treatment-experienced patients*

Enfuvirtide, the first fusion inhibitor, represents an important advance in the treatment of HIV-infected individuals with virologic failure and limited therapeutic options due to multiple resistances and/or drug toxicity. Enfuvirtide has been shown to provide durable virologic suppression and immunological recovery in randomized clinical trials with triple-class treatment-experienced HIV-infected individuals.[1–5] A significant delay of time to virological failure in all patients treated with enfuvirtide was demonstrated in the TORO 1 and 2 trials, even if no active drug was included in the antiretroviral background regimen.[6] Moreover, this drug has been used as part of an optimized background therapy with other new agents, such as tipranavir, darunavir, and raltegravir.[7–12] Nevertheless, the twice-daily subcutaneous administration route and the high frequency of injection site reactions may compromise daily activities and quality of life, leading to drug discontinuation, particularly if potent alternatives become available.[2,3,13] In this context, data on long-term outcome of patients discontinuing enfuvirtide, most notably if switched to new antiretroviral drugs, are certainly needed.

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HIV Clin Trials 2009;10(4):207–214

www.thomasland.com

doi: 10.1310/hct1004-207

Aims of this study were to evaluate the efficacy of enfuvirtide in heavily pretreated HIV-infected individuals and the impact of discontinuing enfuvirtide and switching to new antiretroviral drugs on virological and clinical parameters in the setting of a large cohort study.

METHODS

Study Design

This study was an analysis of the Swiss HIV Cohort study (SHCS) database,[14] a large prospective cohort study with continuous enrollment of HIV-infected individuals aged 16 years or older. Basic sociodemographic characteristics, data on the clinical course (occurrence of opportunistic infections, cardiovascular diseases, death), co-infection with hepatitis B and C, antiretroviral therapy, and immunologic and virologic parameters are collected at enrollment into the study and every 6 months thereafter on standardized data collection forms. AIDS-defining diseases are recorded using the 1993 revised clinical definition of AIDS from the Centers for Disease Control and Prevention.[15] The cause of death is reported using the 10th revision of the International Classification of Diseases and Related Health Problems (ICD-10).[16] For the present analysis, we used the SHCS database extract of June 2008.

Study Population

All HIV-infected individuals participating in the SHCS who were treated with enfuvirtide for at least 4 weeks in combination with an optimized background antiretroviral regimen between March 2001 and April 2007 were included in this study.

Definitions

Discontinuation of enfuvirtide was defined as stopping treatment for at least 30 days or switching to another antiretroviral regimen. The main reason for stopping enfuvirtide was classified according to five categories: patient's wish, physician's decision, virologic failure, toxicity or intolerance, or other reason.

As in the TORO trials, early virologic response to enfuvirtide was shown to be predictive of long-term outcome[17]; response to treatment was assessed by the proportion of patients achieving virologic suppression, defined as an HIV RNA below 50 copies/mL, and by the change in CD4 cell count from baseline to 12 months after starting enfuvirtide.

A clinical event was defined as the occurrence of a new AIDS-defining disease or HIV-related death during the first year of treatment and at 6–12 months after discontinuation of enfuvirtide. In patients with a previous AIDS diagnosis, we considered only new AIDS-defining disorders and excluded recurrences.

Statistical Analysis

Basic sociodemographic characteristics, CD4 cell count, HIV viral load, and antiretroviral therapy were compared using the chi-square test for categorical variables and the Mann-Whitney test for continuous variables. Logistic regression was used to estimate the odds ratios of achieving virologic suppression at 12 months after starting enfuvirtide. Cox regression was used to estimate the hazard ratios of new AIDS-defining diseases and HIV-related deaths within the first year after starting enfuvirtide and at 6–12 months after discontinuation of enfuvirtide, excluding those patients who died within 30 days after discontinuing enfuvirtide ($n=4$). Clinical progression was displayed using Kaplan-Meier plots. All patients were censored at 1 year if no clinical event had occurred. All analyses were performed using STATA™ software version 9.2 for Windows (Stata Corp., College Station, Texas, USA).

RESULTS

Study Population

A total of 151 HIV-infected individuals participating in the Swiss HIV Cohort Study who were treated with enfuvirtide for at least 4 weeks were included in this study. Thirty-nine individuals (25.8%) had participated in the TORO 2 trial. Baseline characteristics are shown in **Table 1**.

Virologic Suppression and Immunologic Recovery

A total of 57.6% heavily pretreated HIV-infected individuals treated with enfuvirtide in combination

Table 1. Characteristics of 151 HIV-infected individuals starting enfuvirtide within the framework of the Swiss HIV Cohort Study between 2001 and 2007

Characteristic	*n* (%)	Median (IQR)
Age, years		45 (40–52)
Male gender	130 (86.1)	
BMI, kg/m^2		21.8 (19.7–24.2)
Caucasian	139 (92.1)	
Level of schooling		
Mandatory	29 (19.2)	
Apprenticeship	62 (41.1)	
Higher education	48 (31.8)	
Unknown	12 (7.9)	
Transmission risk		
MSM	87 (57.6)	
Heterosexual	36 (23.8)	
IV drug use	26 (17.2)	
Other[a]	2 (1.3)	
Co-infection with hepatitis B (HBs-antigen positive)	9 (6.0)	
Co-infection with hepatitis C (anti-HCV positive)	34 (22.5)	
Prior AIDS-defining condition	34 (22.5)	
Baseline CD4 cell count, cells/μL		108 (50–206)
Baseline HIV RNA, $\log_{10}$ copies/mL		4.7 (4.1–5.2)
Previous number of antiretrovirals		11 (9–13)
Background antiretroviral regimen		
Lopinavir	54 (35.8)	
Tipranavir or darunavir	44 (29.1)	
Other	53 (35.1)	

Note: BMI = body mass index; MSM = men who have sex with men; IV = intravenous.
[a]Transmission through blood products, perinatal, or unknown.

with an optimized background regimen achieved a viral load below 50 copies/mL at 12 months after starting treatment. The proportion of patients who maintained a HIV RNA below 50 copies/mL on treatment was 61.3% and 64.9% at 24 and 36 months, respectively. In the intention-to-treat analysis, in which discontinuation of enfuvirtide was considered as a failure, a viral load below 50 copies/mL was attained by 39.6%, 37.7%, and 27.2% of patients at 12, 24, and 36 months, respectively. Overall, the median CD4 cell count at 12 months was 254 cells/μL (interquartile range [IQR] 153–349), corresponding to a median increase of 121 cells/μL (IQR 50–189) from baseline.

In the multivariate analysis, a low baseline HIV viremia <5.0 $\log_{10}$ copies/mL and a backbone regimen containing boosted darunavir or tipranavir were independently associated with higher odds of virologic suppression after adjustment for age, HIV transmission risk, baseline CD4 cell count, HIV RNA, and antiretroviral treatment.

Clinical Progression on Treatment

During a total follow-up period of 126 person-years (py), 13 individuals experienced a new AIDS-defining disease and 9 patients died. Of these, two deaths were reported to be HIV-related (non-Hodgkin's lymphoma and pneumonia). Six additional patients who had been censored at the occurrence of a new AIDS-defining disease died within the first year after starting enfuvirtide. The rate of clinical progression amounted to 11.7 events (95% CI 7.1–19.4) per 100 py if only AIDS-defining diseases and HIV-related deaths were considered and 16.9 events (95% CI 11.1–25.7) per 100 py if deaths from all causes were included. The most frequent AIDS-defining diseases were esophageal candidiasis (30.8%) and *Pneumocystis jiroveci* pneumonia (15.4%), followed by Kaposi's sarcoma, non-Hodgkin's lymphoma, primary lymphoma of the brain, and cytomegalovirus retinitis. In the multivariate analysis, after adjustment for age, baseline

CD4 cell count, and HIV RNA, severe immunosuppression with CD4 cell count lower than 50 cells/μL was the strongest risk factor of clinical progression (hazard ratio [HR] 5.04, 95% CI 1.39–18.35, $p = .014$; compared to CD4 ≥200 cells/μL).

Discontinuation of Enfuvirtide

During a follow-up period of 173 py, 82 patients discontinued enfuvirtide for at least 1 month or switched to another antiretroviral regimen after a median of 345 days (IQR 176–686). Of these, 45 discontinuations occurred during the first year of treatment, corresponding to a discontinuation rate of 32.6 (95% CI 24.1–44.1) per 100 py. The most frequent reasons for stopping enfuvirtide were the patient's choice (49.1%), followed by the physician's decision (15.5%), virologic failure (5.3%), and toxicity (15.1%). After stopping enfuvirtide, 36 out of 82 (43.9%) patients switched to new antiretroviral drugs; of those, 7 received new drugs including darunavir, maraviroc, or raltegravir, and 18 (22%) patients discontinued all antiretrovirals without switch to other regimens. Among all sociodemographic factors investigated, higher education was associated with lower risk of treatment discontinuation (**Table 2a**).

At stopping enfuvirtide, 31 out of 82 (37.8%) patients had achieved a viral load below 50 copies/mL, and the median CD4 cell count was 169 cells/μL (IQR 84–332). Among 56 patients with available data at 6 months after stopping enfuvirtide, 35.7% had a viral load below 50 copies/mL at stopping enfuvirtide and 6 months later. The median CD4 cell count was 187 cells/μL (IQR 49–333) at 6 months after stopping enfuvirtide, and the rate of clinical progression was 32.2 (95% CI 20.0–51.8) events per 100 py in the first year after stopping enfuvirtide. Twelve patients experienced a new AIDS-defining disease and 9 patients died; of these deaths, 5 were reported to be HIV-related (non-Hodgkin's lymphoma in 2 patients, wasting in 2 patients, and pneumonia in 1 patient). Eight additional patients, who had been censored at the occurrence of an AIDS-defining condition, died within the first year after stopping enfuvirtide.

In the multivariate analysis, after adjustment for age, CD4 cell count, virologic suppression at stopping enfuvirtide, and new antiretroviral regimen, the strongest risk factor of clinical progression was severe immunosuppression with a CD4 cell count of less than 100 cells/μL at discontinuation of enfuvirtide (HR 5.1, 95% CI 1.45–18.0, $p = .011$, compared with CD4 cells ≥200), whereas switch to new antiretroviral drugs such as boosted tipranavir, darunavir, raltegravir, or maraviroc was clearly associated with lower risk of clinical progression (HR 0.07, 95% CI 0.01–0.53, $p = .010$) (**Table 2b, Figure 1**).

DISCUSSION

This study, involving 151 heavily pretreated HIV-infected individuals who started enfuvirtide in combination with an optimized antiretroviral background regimen, indicates that high virologic and immunologic response rates to treatment may be achieved in the setting of clinical practice. However, up to 50% of patients discontinued enfuvirtide within the first year of treatment, mainly because of the patient's choice. After discontinuation of enfuvirtide, high rates of virologic failure and clinical progression were observed, if CD4 cell count at stopping enfuvirtide was below 100 cells/μL and no switch to new potent antiretroviral drugs such as darunavir, maraviroc, or raltegravir was performed.

In our study, enfuvirtide was associated with significant virologic suppression and led to immunological recovery in HIV-infected individuals with extensive treatment history, in particular to a rapid increase in CD4 cell count above 200 cells/μL. This confirms findings of randomized clinical trials and small observational studies.[2,4,5,12,16,17] Drug potency, resistance, adverse effects, and interactions may influence the efficacy of antiretroviral therapy. In this study, a baseline HIV RNA below 5.0 $\log_{10}$ copies/mL and an antiretroviral regimen containing new potent antiretroviral drugs like tipranavir and darunavir were independently associated with higher odds of achieving virologic suppression at 12 months. This suggests that individuals with less advanced HIV disease and stronger backbone regimes, reflecting a lower number of drug resistance mutations, are most likely to benefit from a treatment with enfuvirtide. These findings are consistent with results of the TORO 1 and 2 trials where four independent predictors of virologic suppression at Week 24 were identified, namely a baseline CD4 cell count above 100 cells/μL, a viral load below 100,000 copies/mL, at least two backbone antiretrovirals to which the HIV virus

Table 2. Multivariate hazard ratios (HR) of (a) discontinuing enfuvirtide and (b) new AIDS-defining diseases and HIV-related deaths during the first year after stopping enfuvirtide

(a)

Characteristic	HR[a]	95% CI	*p* value
Age, per 10 years older	1.30	0.89–1.88	.171
Female gender	1.57	0.80–4.82	.138
Non-White ethnicity	1.21	0.52–3.46	.536
Level of schooling			
Mandatory	1[b]	–	–
Apprenticeship	0.36	0.17–0.79	**.010**
Higher education	0.34	0.14–0.83	**.017**
Transmission risk			
MSM	1[b]	–	–
Heterosexual	0.98	0.44–2.19	.965
IV drug use	8.49	0.45–161.4	.155

(b)

Characteristic	HR[a]	95% CI	*p* value
Age, per 10 years older	1.03	0.54–1.97	.934
CD4 <100 cells/μL at stopping enfuvirtide	5.12	1.45–18.0	**.011**
HIV RNA <50 copies/mL at stopping enfuvirtide	0.41	0.08–2.09	.286
Switch to new antiretroviral drugs[c]	0.09	0.01–0.53	**.010**

Note: MSM=men who have sex with men; IV=intravenous.
[a]Adjusted for all variables listed in the table.
[b]Reference category.
[c]Tipranavir, darunavir, maraviroc, or raltegravir.

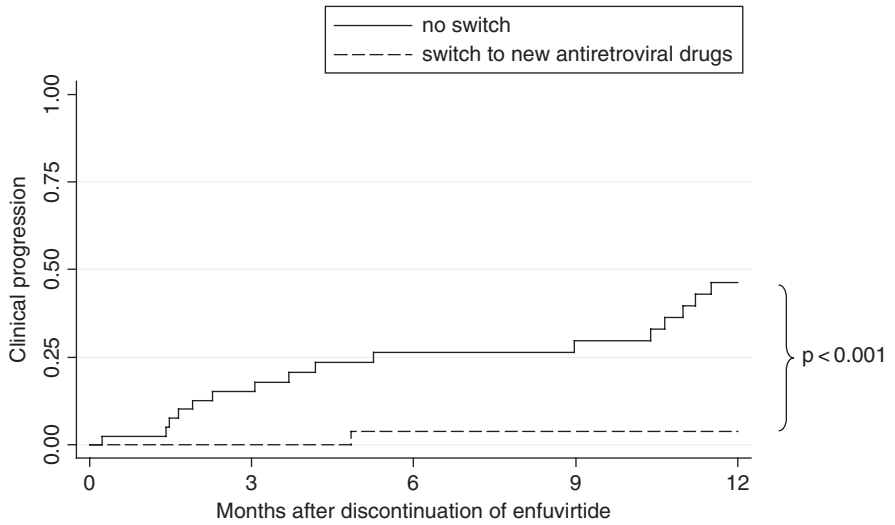

Figure 1. Kaplan Meier plots of clinical progression, that is, new AIDS-defining diseases and HIV-related deaths, after discontinuation of enfuvirtide according to whether patients had been switched to an antiretroviral regimen containing new antiretroviral drugs (tipranavir, darunavir, maraviroc, or raltegravir).

remains susceptible, and prior exposure to less than 10 antiretroviral drugs.[1,2] Moreover, the addition of enfuvirtide to tipranavir, darunavir, or raltegravir in randomized clinical trials was associated with a greater proportion of patients achieving virologic suppression at 24 weeks, which highlights the importance of combining newer drugs with enfuvirtide if virus is highly resistant to most available drugs.[7,9–11,18]

As previously reported in the literature,[19–22] baseline CD4 cell count was the strongest predictor of clinical progression within the first year after starting enfuvirtide, with a linear increase in the hazard ratios of new AIDS-defining diseases and HIV-related deaths with increasing level of immunodeficiency, in particular if CD4 count was below 50 cells/μL. Several additional factors may contribute to the prognosis of HIV-infected patients after starting enfuvirtide, such as management of drug-related side effects and interactions, treatment of opportunistic infections, and co-morbidities such as chronic hepatitis B and C.

Discontinuation of Enfuvirtide

Up to 50% of patients discontinued enfuvirtide, mainly within the first year of treatment. The most frequent reason for stopping enfuvirtide was the patient's choice, followed by the physician's decision including virologic failure and switch to new antiretroviral drugs and toxicity. The discontinuation rate of enfurvitide in our study was markedly higher than in the TORO 1 and 2 trials, where only 26.5% of patients stopped enfuvirtide before Week 48; of those, only 4%–14% discontinued because of injection site reactions such as induration, erythema, pain, and discomfort.[3] This difference may presumably be explained by the increasing availability over the past few years of potent alternative antiretroviral drugs with improved tolerability and safety. Selection bias may also have affected our results, since participants of clinical trials are more likely to be highly motivated and adherent to treatment. It is interesting that, in our study population, lower level of schooling was the strongest risk factor of treatment discontinuation within the first year of treatment, suggesting that socioeconomic factors may play an important role in coping with adverse reactions. Consistently, intravenous drug use tended to be associated with higher risk of discontinuing enfuvirtide, which failed statistical significance due to the low number of patients. Self-administration of enfuvirtide through subcutaneous injections requires training and support in order to minimize any potential negative impact on patient lifestyle and adherence to treatment.

After discontinuation of enfuvirtide, high rates of virologic failure and clinical progression were observed. Severe immunosuppression with a CD4 cell count of less than 100 cells/μL at discontinuation of enfuvirtide was the strongest risk factor of clinical progression, whereas patients who were switched to new antiretroviral drugs such as darunavir, maraviroc, and raltegravir were less likely to experience a new AIDS-defining disease or to die in the first year after stopping enfuvirtide. These findings demonstrate that enfuvirtide should not be discontinued but replaced by new active drugs, particularly in patients with advanced HIV disease. Recently, the integrase inhibitor raltegravir was shown to be a valuable replacement of enfuvirtide, providing similar efficacy in heavily pretreated individuals who switched from enfuvirtide to raltegravir with the advantage of easier oral administration and improved tolerability.[23]

Strengths and Limitations

The strengths of our study were the high number of patients investigated in the setting of clinical practice, and the availability of data on clinical progression after discontinuation of enfuvirtide. There are some limitations to our study. Data on baseline genotypic and phenotypic resistance testing, which is recommended for selecting a background regimen for enfuvirtide,[24–26] were not available for the present analysis. This may have confounded the association between backbone antiretroviral therapy and virologic suppression, possibly underestimating the potency of newer drugs used as background treatment. Misclassification of the reason for discontinuing enfuvirtide may have occurred, since many factors may play a role in decision making. In particular, patients discontinuing enfuvirtide because of virologic failure may have been coded as "physician's decision." Moreover, no code for treatment simplification exists in the SHCS database as a reason for stopping a specific drug, although these individuals have probably been coded as patient's choice or physician's decision. Finally, our results may have been affected by selection bias following the

longitudinal design with loss to follow-up and the high number of treatment discontinuations. This may have led to an overestimation of the virologic and immunologic response to enfuvirtide, since patients who better tolerate antiretroviral therapy are more likely to have optimal adherence and thus attain higher virologic suppression. It is also possible that individuals who discontinued enfuvirtide and did not switch to other antiretroviral regimens represent a selection of patients with multidrug resistant virus, poorer compliance, and therefore virologic failure.

CONCLUSIONS

Enfuvirtide in combination with an optimized background antiretroviral therapy provides high virologic response rates and immunologic recovery in treatment-experienced HIV-infected individuals, also in the setting of clinical practice. Nevertheless, a high proportion of patients discontinue enfuvirtide mainly because of the patient's choice and availability of new potent antiretroviral regimes with improved tolerability. After discontinuation of enfuvirtide, high rates of clinical progression are observed if no switch to new potent antiretroviral drugs such as darunavir, maraviroc, or raltegravir is performed.

ACKNOWLEDGMENTS

This study has been financed in the framework of the Swiss HIV Cohort Study, supported by the Swiss National Science Foundation (SHCS project no. 446). The members of the Swiss HIV Cohort Study are M. Battegay, E. Bernasconi, J. Böni, HC Bucher, Ph. Bürgisser, A. Calmy, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS, Centre Hospitalier Universitaire Vaudois, CH-1011- Lausanne), H. Furrer (Chairman of the Clinical and Laboratory Committee), C. Fux, M. Gorgievski, H. Günthard (Chairman of the Scientific Board), H. Hirsch, B. Hirschel, I. Hösli, Ch. Kahlert, L. Kaiser, U. Karrer, C. Kind, Th. Klimkait, B. Ledergerber, G. Martinetti, B. Martinez, N. Müller, D. Nadal, M. Opravil, F. Paccaud, G. Pantaleo, A. Rauch, S. Regenass, M. Rickenbach (Head of Data Center), C. Rudin (Chairman of the Mother & Child Substudy), P. Schmid, D. Schultze, J. Schüpbach, R. Speck, P. Taffé, A. Telenti, A. Trkola, P. Vernazza, R. Weber, S. Yerly.

L. Elzi has been supported by an unrestricted grant of the University of Basel (Nachwuchsförderungsprogramm). G. Kaufmann and C. Fux do not have any conflicts of interest. L. Elzi has received an unrestricted grant by Roche Pharma Switzerland. M. Cavassini has received travel grants from Abbott, Gilead, Roche, and Boehringer Ingelheim. B. Hirschel has received travel grants and speakers' honoraria from Abbott, Bristol-Myers Squibb, Gilead, Glaxo, Merck, and Roche. P. Vernazza has received travel grants, grants, or honoraria from Bristol-Myers Squibb, Gilead, GlaxoSmithKline, Roche, Tibotec, Abbott, and Pfizer. E. Bernasconi has received travel grants or honoraria from Gilead, Roche, GlaxoSmithKline, Pfizer, Boehringer Ingelheim, and Tibotec. R. Weber has received travel grants or speakers' honoraria from Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, Hoffman-La Roche, TRB Chemedica, and Tibotec. M. Battegay has received research grants or speakers' honoraria from Abbott, Bristol-Myers Squibb, Boehringer Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme, TRB Chemedica, and Tibotec, and serves as a consultant for Boehringer Ingelheim (Switzerland) and Hoffmann-La Roche (Switzerland).

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